Christian Raulin
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Editors

Laser and IPL Technology in Dermatology and Aesthetic Medicine

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(Editors)

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ISBN 978-3-642-03437-4 e-ISBN 978-3-642-03438-1
DOI 10.1007/978-3-642-03438-1
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2010937978

Cover design: eStudioCalamar, Figueres/Berlin

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword I

At the publication of this volume, lasers are half a century old, or perhaps it is more accurate to write half a century young. The interplay between light and matter fascinated Albert Einstein, whose $E = mc^2$ expresses the fact that all matter and all energy are equated by only one constant – the speed of light. He also figured out that the only "thing" different observers measure as being constant – is the speed of light. Apparently, we live in a universe not only bathed in light, but defined by it. Einstein's work on quantum electromagnetism is less well-known, but anyone using a laser should appreciate that the device exists because of it. Fundamentally, creation of a photon is the time-inverse of its absorption. In an excited atom, it is possible for photons to stimulate the creation of more photons. Stimulated emission, the S.E. of L.A.S.E.R., is at the heart of every laser. Charles Townes and colleagues made the first device using stimulated emission to amplify (the "A" in L.A.S.E.R.) microwave photons, and in a few years this was done with light (the "L" in L.A.S.E.R.).

Is an understanding of laser operation important to a physician using a laser? Yes! Extreme power, coherence, well-defined wavelength, ability to generate very brief pulses, and to focus tightly, are all properties of lasers important to their medical applications. In dermatology, we use lasers mainly as surgical tools to heat or vaporize cells and tissue with precision and often with selectivity, i.e., preferentially affecting some light-absorbing targets within the skin. This excellent book is a thorough and practical description of those applications, which depend on high-power pulses at well-defined wavelength regions. Sometimes, a xenon flashlamp can be used for selective photothermolysis of large targets such as hair follicles or blood vessels. The selectivity possible with flashlamps is always inferior to that possible with lasers, but in practice, is often sufficient. For very small targets such as the isolated dermal melanocytes of nevus of Ota, or tattoo ink-containing cells, very powerful short pulses are needed to achieve safety and efficacy. Lasers are the only sources able to deliver such pulses.

In other applications, such as fractional photothermolysis, it is necessary to deliver light in a microbeam, or as an array of small foci. Again, lasers are ideal for this application. Fractional laser treatments at present are not selective for some specific target in the skin. However, we can expect that "smart" laser microbeam treatments will be developed that will use imaging to identify which tissue structures the laser should expose. These devices may create another paradigm for laser dermatology, because some of the most important target structures in skin are not pigmented.

The coherence property of lasers is not used much in dermatology, but it will be. Coherence can be thought of as a measure of how much alike photons in a beam are, with respect to each other. High coherence lasers are used to make holograms, and in

medicine to measure blood flow by laser doppler velocimetry. Lasers have revolutionized biological microscopy for research. They will probably revolutionize microscopy of living skin, with further development. A combination of high brightness and low coherence offers the potential for deep, high-speed microscopy of skin. Optical coherence tomography and related approaches used widely in ophthalmology, are entering cardiovascular and endoscopic imaging applications, and have strong potential in dermatology.

Ultimately, it is clinical practice that defines the therapeutic and diagnostic use of lasers. As such, clinical dermatologists have a major role to play in motivating the creation of new applications and new medical lasers. This book offers practical knowledge, practical uses, and a thorough understanding of the risks and benefits posed by a wide spectrum of medical lasers and related technologies.

People are not pastries. If you treat them according to a fixed recipe, they will sometimes be overcooked. The natural variations of skin structure, pigmentation, sun exposure, wound healing, age, and gender are important for not only laser dosimetry, but also for the fundamental decisions of whether to treat and if so, with which device(s). These are also the natural variations that make medicine an art, as well as a science. Enjoy!

Boston, MA, USA Prof. Dr. R. Rox Anderson

Foreword II

When amplified by stimulated emission of radiation, light may have unique properties capable of causing novel reactions in biological materials. In complex multicellular organisms, the host responses to this form of electromagnetic radiation may also be unique resulting in outcomes different from those expected from traditionally described response to injury.

Until the twentieth century, the complex forces guiding the evolution of human responses to injury were never influenced by the collective properties of lasers or IPL technology. By altering the properties of lasers, savvy investigators have explored the creation of selective tissue injury with novel combinations of spatial localization and mechanisms of tissue alteration. The form of injury may be manipulated to stimulate a cascade of repair responses aimed at correcting a variety of lesions in skin and other organs. The precision of tissue alteration can not be achieved by other means. This book contains many examples – written by those who discovered the response pathway and those who have successfully exploited the tissue response to develop and constantly improve the diagnostic and therapeutic use of lasers and IPL technologies.

We expect more rapid growth of the technologies that creates unique energy waves, pulses, and "packets" of energy. We expect advances in molecular biology, pathology, optical diagnostics, and molecular tagging to lead a better understanding of tissue response to radiation. We expect investigators versed in biology, photochemistry, nanotechnology, electronics, and photophysics to continue the rapid development of this technology in subsequent medical and surgical uses.

There will always be those creative investigators who understand both the technical and biological parameters enough to capture selected portions of tissue responses at the right place at the right time in the right organ.

This book may be viewed as an update in the impression progress made to date and a foundation for future advances.

Boston, MA, USA — Prof. Dr. John A. Parrish

Preface

Laser and IPL technology have brought about thorough ongoing changes in the treatment options for many clinical pictures encountered in dermatology during recent years. The specialism of aesthetic medicine has benefited greatly from all this. The rapid technical progress and the frequent emergence of new equipment and indications make it extraordinarily difficult for the interested doctor to get an overview of the research position and the possibilities and the limitations of these procedures. Disconcertingly, popular science publications also have a role in all this, so that the need for factual and objective information is constantly becoming more intense, especially as there are very few evidence-based scientific studies available on the possible applications of new laser techniques. In addition, the time elapsing between current knowledge and developments and their practical implementation is becoming shorter and shorter.

This book is addressed equally to specialists who already have experience in using laser and IPL systems and to doctors and students who harbor the ambition of becoming well-informed about the specific treatment options so as to be in a position to give patients competent advice. Without a precise and structured digest of results from research and technology, including the most recent, it is not possible for the clinician to guarantee up-to-date and correct care of the patient.

We have been able to secure international opinion of leaders for all the chapters of this book. This was the only way to fulfill our own ambition of taking full account of the rapid further development of the specialist area and to give the reader an up-to-date overview of laser therapy in dermatological-aesthetic medicine and its fringe areas, including photodynamic therapy. We have tried consistently to achieve a uniform presentation, with reference also to terminology and the structure of the texts. Where there turned out to be differences in various authors' opinions, both sides had the chance to make their case.

This textbook gives the theoretical bases of laser and IPL technology and reviews the voluminous current knowledge on the various indications. References to unsolved problems or questions that are still under discussion are found in the appropriate text sections. The chapters each have a list of the background literature and further reading matter. It would not have been possible to avoid overlappings and repeats, and they are intentional to ensure that each of the individual texts can be complete in itself.

We are particularly concerned to profile conventional alternatives to laser treatment insofar as they are better based in medicine and more economical. The quality of a method is determined to a decisive degree by careful observation of indications, and laser and IPL technology are far from being a universal panacea – not least because of the potential risks inherent in them. We therefore thought it was important

to sensitize the reader to complications, safety, administration of treatment by persons with no medical qualifications, and forensic considerations.

This book is no more able than any other to be a substitute for first-hand experience with patients. Consultation and critical analysis of diagnosis and therapy options remain an essential component of the doctor's work. For this reason one chapter is devoted entirely to ethical aspects of laser therapy.

Our sincere thanks are due to all the authors for their committed cooperation on this multiauthor work. We thank our staff assistants and colleagues for their constructive criticisms and their many hours of hard work without which it would not have been possible to prepare the book within the planned time frame. All patients who are recognizable in the illustrations have kindly given their consent to this. At this point, we should like to thank them cordially for their support. Our book is not made up solely of theory, but takes life from the many illustrative clinical examples. Not least, we are very grateful to Springer-Verlag, especially the clinical medicine editors Dr Tobias Kemme, Dr Sverre Klemp and Mrs Ellen Blasig, for their efficient project management and the successful structure of the book, and Mr Sreejith Viswanathan for his excellent editorial work.

We are pleased to say we feel confident that this text has presented laser and IPL therapy as used in dermatology and aesthetic medicine in a well-rounded manner and on the basis of comprehensive and up-to-date knowledge of the current scientific status.

Karlsruhe, autumn 2010 Prof. Dr. Christian Raulin
Karlsruhe, autumn 2010 Dr. Syrus Karsai

Contents

Part I

Basics

Basic Laser Physics

1

Rudolf Steiner

Core Messages

- Following the history of lasers and, at the same time, their medical applications demonstrates the continuous improvement of insight into laser reactions and the development of devices.
- Understanding the characteristics of photons and light is the basis for all applications in medical diagnosis and therapy.
- Knowledge about the physical principle of lasers will remove any mystery from laser technology.
- Lasers can be designed in different ways and thus be optimised to the intended use.
- Laser radiation, depending on the wavelength and the mode of operation, is a powerful tool to treat patients, but it also can be dangerous if safety instructions are ignored.
- An overview about the different types of medical lasers on the market facilitates the right choice of a laser system for the specific application.

1.1 History

To invent the LASER (acronym for *L*ight *A*mplification by *S*timulated *E*mission of *R*adiation, coined by Gordon Gould) some understanding of Einstein's ideas about stimulated emission of radiation [5] was necessary. Albert Einstein developed the theoretical concept of light travelling in waves of particles (photons) and of "stimulated emission." Although Einstein did not invent the laser his work laid the foundation for it. He pointed out, considering photon statistics, that stimulated emission of radiation could occur (Fig. 1.1).

The precursor to the laser was the MASER (microwave amplification by stimulated emission of radiation). The impetus for the development of the maser was increasing interest in microwave radiation following the utility of it in radar technology. The first maser [22] was created by Townes (published in 1954) who, along with James Gordon and Herbert Zeiger, succeeded in producing an inverted population by isolating excited ammonia molecules. But the first maser, a system with two energy levels, was incapable of continuous output. To achieve continuous output, new systems with more than two energy levels had to be designed. These systems could release stimulated emission of excited atoms without falling to the ground state, thus maintaining a population inversion. Nikolai Basov and Alexander Prokhorov in Moscow first developed this idea. Basov, Prokhorov, and Townes shared the 1964 Nobel Prize in physics for developing the maser concept (Fig. 1.2).

After masers became a reality, scientists looked at the possibility of stimulated emission in other regions of the electromagnetic spectrum. Arthur Schawlow, together with Townes, at Bell Telephone Laboratories in Murray Hill, New Jersey, began investigating the possibility of optical and infrared (IR) masers. They published in 1958 the first detailed proposal for building an optical maser (later to be renamed a laser) in *Physical Review* [10]. The challenges of creating a working laser were tremendous. The much smaller

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_1,

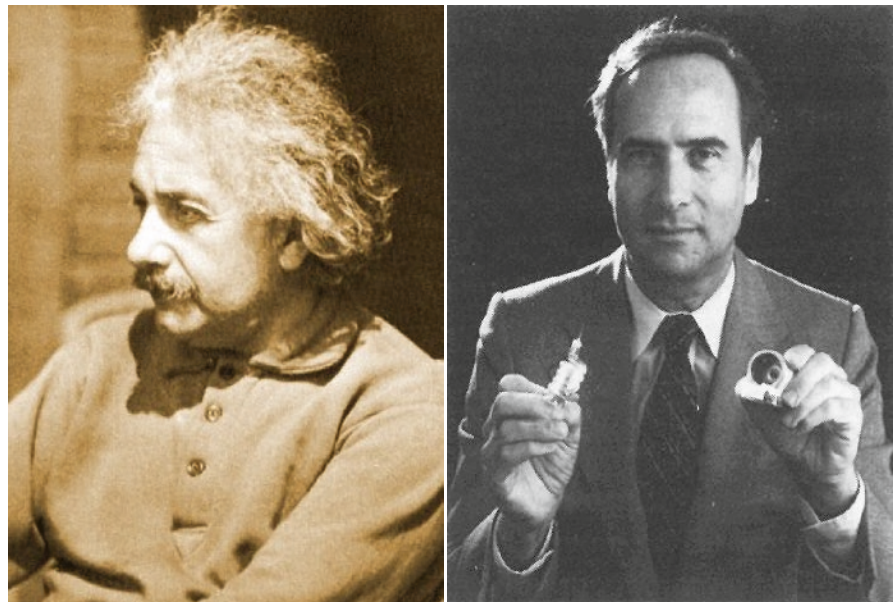

Fig. 1.1 Albert Einstein (*left*) and T.H. Maiman (*right*)

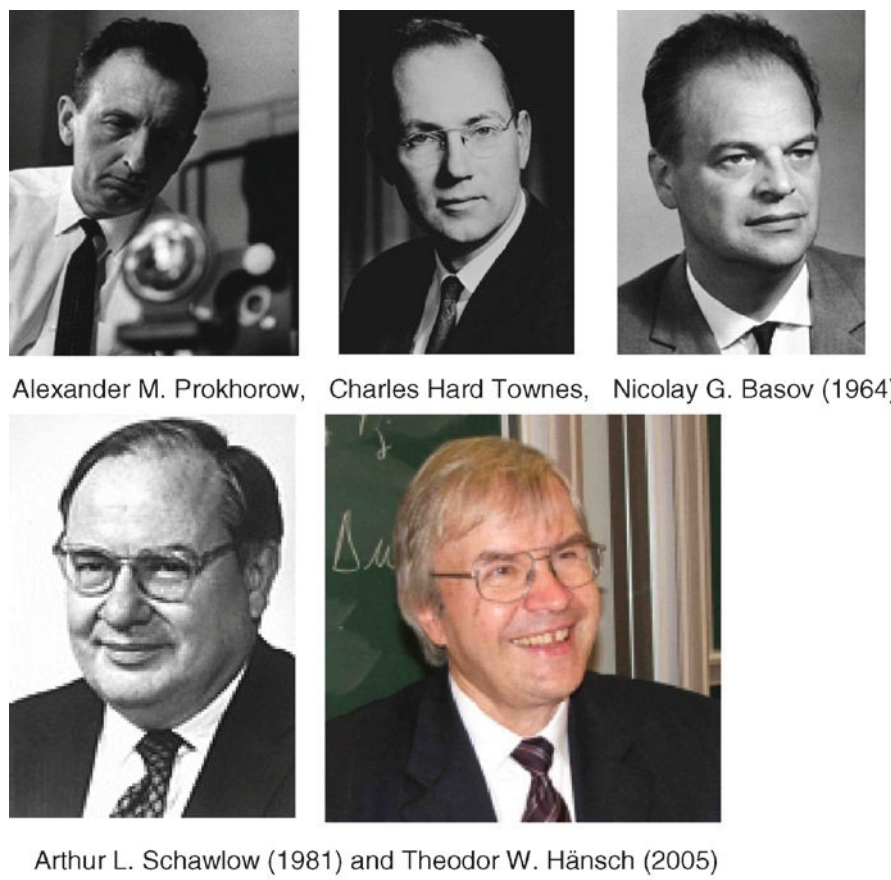

Fig. 1.2 Nobel laureates connected with lasers [Alexander M. Prokhorow, Charles Hard Townes, Nicolay G. Basov (1964), Arthur L. Schawlow (1981), and Theodor W. Hänsch (2005)]

wavelengths of visible light and the difficulty of finding an appropriate laser medium meant that many more experiments had to be performed and that it was much more difficult to adjust an apparatus to function as a laser. It was not until 1960 that Maiman [14, 24] created the first working laser. Maiman's laser was a ruby rod with silver ends that had been placed inside a spring-shaped flashlamp. Maiman's laser, however, was only capable of pulsed operation due to its three energy level transitions. Soon afterwards, in 1960, Peter Sorokin and Mirek Stevenson at IBM Laboratories developed the first four-level laser, which was capable, in theory, of continuous output; however, in solid state a continuous output could not be achieved. Further laser developments followed in a short time: the Nd:YAG laser, CO_2 laser, Argon-ion laser, Excimer laser, and diode laser. A list of milestones in the development of lasers is given in Table 1.1.

1.2 Characteristics of Light

Light is electromagnetic radiation in the visible wavelength region from 400 to 700 nm or extended from 380 to 750 nm. Laser radiation, however, is between 100 nm and 1 mm. The speed of light in a vacuum is c (ms^{-1}), where

$$c = 299,792,485\ ms^{-1} (\text{or } 186,282 \text{ miles per second}).$$

Speed of light, the frequency ν of the electromagnetic wave, and the wavelength λ in a vacuum obey the relation

$$c = \lambda \cdot \nu$$

and in matter they obey the relation

$$c(\lambda) = c_0 / n(\lambda)$$

(n = the wavelength–dependent refractive index).

Table 1.1 Milestones in the history of lasers

1917	Einstein publishes his paper about stimulated emission
1951	Development of the maser by C.H. Townes
1958	C.H. Townes and A.L. Schawlow propose that the maser concept could be extended to optical frequencies
1960	T.H. Maiman at Hughes Labs and his assistant Charles Asawa report on May 16 the first functioning laser: a pulsed ruby laser
1961	First medical laser applications in ophthalmology by Charles J. Campbell
1961	The first continuous wave laser is reported by A. Javan: the helium neon laser
1962	First diode laser is reported by M.I. Nathan et al.
1963	First medical laser applications in dermatology by L. Goldman
1964	Nicolay Basov, Charles Townes, and A.M. Prokhorov get the Nobel prize for their fundamental work in the field of quantum electronics, which has led to the construction of oscillators and amplifiers based on the maser and laser principles
1964	The Argon Laser is developed at Hughes Labs. The continuous wave 488/514 nm argon ion laser is well suited to retinal surgery Kumar Patel invents the CO_2 (carbon dioxide) 10,064-nm (far-infrared) gas ion laser at Bell Labs The Nd:YAG (neodymium doped, yttrium aluminium garnett) 1,064-nm laser also is developed at Bell Labs
1969	The dye laser is introduced at IBM Labs by P. Sorokin and J. Lankard. The pulsed dye laser is the first laser to produce selective light-induced injury
1970	The first excimer laser [based on Xenon (Xe) only] is invented by N. Basov's group at Lebedev Labs, Moscow
1977	J. Madey's group at Stanford University develops the first free electron laser
1980	L. Goldman establishes *The American Society for Laser Medicine and Surgery, Inc,* the world's largest professional organization dedicated to promoting excellence in patient care by advancing laser applications and related technologies
1981	A. Schawlow and N. Bloembergen receive the Nobel prize for "their contribution to the development of laser spectroscopy and nonlinear optics"
1984	D. Matthew's group at Lawrence Livermore Labs demonstrates a "laboratory" x-ray laser
2005	J. Hall and T. Hänsch receive the Nobel prize for contributing to the development of laser-based precision spectroscopy, including the optical frequency comb technique

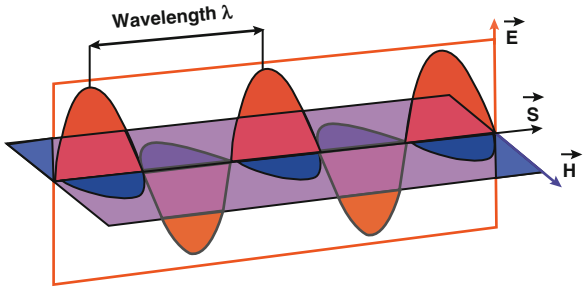

Fig. 1.3 Schematic presentation of an electromagnetic wave with electric, *E*, and magnetic, *H*, field vectors and the Poynting vector, *S*. The planes of the linearly polarised field vectors are perpendicular to each other

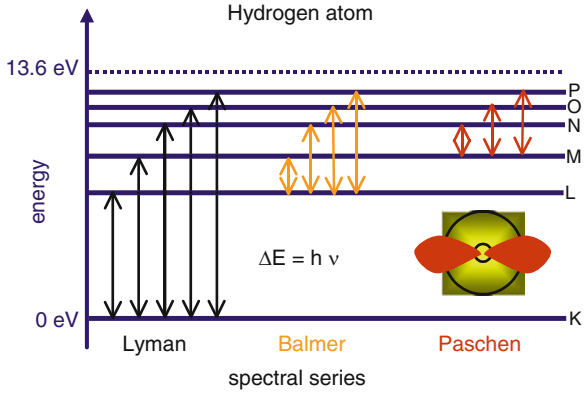

Fig. 1.4 Schematic presentation of the origin of spectral lines of a hydrogen atom

The electromagnetic radiation is characterised by Maxwell's equations of an alternating electric field, with field strength E (V/cm) and magnetic field H (Fig. 1.3). The transported power is described by the Poynting vector S (W/m²) representing the energy flux density

$$S = E \times H.$$

According to Bohr's atomic model, electrons occupy certain fixed orbitals (principal quantum number). Electrons can only jump from orbit to orbit and therefore they can emit energy (emission of radiation) or absorb energy (absorption of radiation). The quantisation of energy is described by ΔE (eV). (Fig. 1.4).

$\Delta E = h{\cdot}\nu$ where h is

(h : Planck's constant;

$h = 6.26617 \times 10^{-34}$ Js; ν = frequency of light.

With this expression, light can be described either as a wave or as a particle (photon) moving at the speed of light, having no mass but carrying energy and momentum. This property is referred to as wave-particle duality [3, 20]

$$\text{Energy} : E_{\text{photon}} = h{\cdot}\nu,$$

$$\text{Momentum} : p = E_{\text{photon}} / c = h{\cdot}\nu / c,$$

$$\text{Power} : P = N_{\text{photon}}{\cdot}h\nu / t \ (N : \text{number of photons}).$$

1.2.1 Stimulated Emission of Radiation

Photons can be absorbed by atoms when the enegy corresponds to an electron transition to a higher energy level (orbit). The atom is then in an excited state with energy E_2. It may spontaneously decay to the ground state, with energy E_1, emitting a photon with the difference in energy between the two states, $\Delta E = E_2 - E_1 = h\nu$, where h is again Planck's constant. The phase of the spontaneously emitted photon and also the direction of travel are random. This is different for stimulated emission (Figs. 1.5 and 1.6).

The interaction of a photon with an atom will affect the atom's state. The atom, acting as a small electric dipole, will oscillate with the external field. Thus, an electron, due to the presence of another photon, is influenced to decay to the lower energy level, releasing a second photon that is in phase with the first photon. The second photon also travels in the same direction and has the same energy and polarisation. This is called *stimulated emission*. As a result, the two photons are totally coherent. This is also the basis for optical amplification to take place.

If the number of atoms in the excited state is given by N_2, the rate at which stimulated emission occurs is given by:

$$\mathrm{d}N_2 / \mathrm{d}t = -B_{21}\rho(\nu)N_2,$$

where B_{21} is a proportionality constant for this particular transition and is also called the Einstein B_{21} coefficient. $\rho(\nu)$ is the radiation density of photons of the frequency ν. The emission rate of photons is therefore proportional to the number of excited atoms, N_2, and the density of the perturbing photons. For spontaneous emission we have $\mathrm{d}N_2/\mathrm{d}t = -A_{21}N_2$ and for induced absorption we have $\mathrm{d}N_1/\mathrm{d}t = -B_{12}\rho(\nu)N_1$.

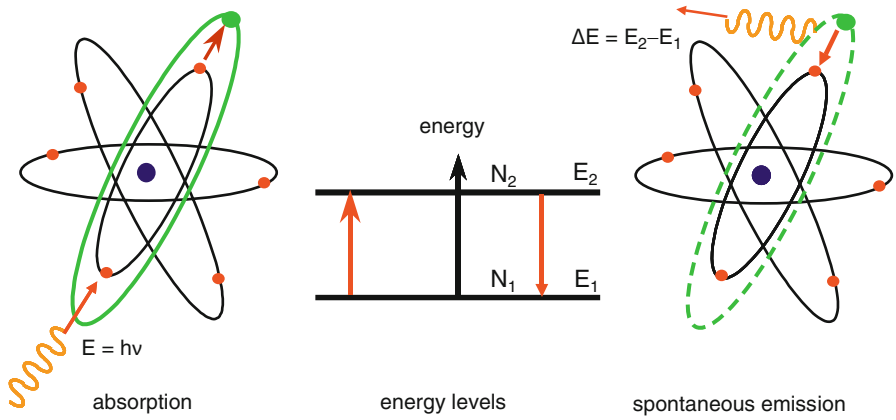

Fig. 1.5 Absorption and spontaneous emission. A photon is absorbed by an atom, lifting an electron into a higer orbit. This excited state lasts only for about 10^{-7} s, then the electron drops into a lower orbit with emission of a photon of energy $\Delta E = E_2 - E_1$

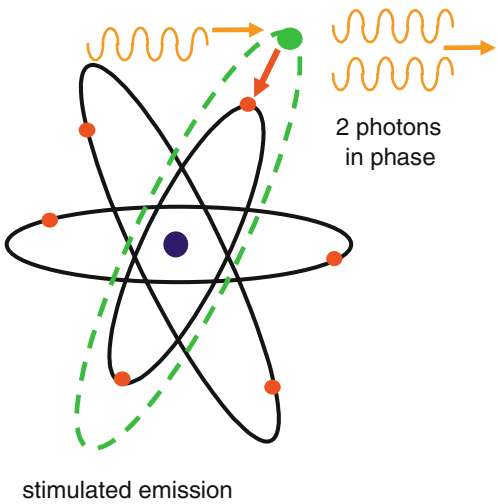

Fig. 1.6 Stimulated emission. A photon induces the decay of an excited energy state. Simultaneously, a second photon is emitted that has the same phase and wavelength

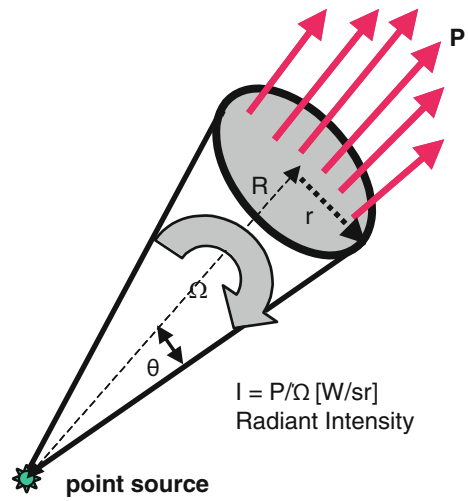

Fig. 1.7 Schematic representation of radiant intensity from a point source

1.2.2 Definitions of Radiation

1.2.2.1 Radiant Power

The power output of a source is described by its *radiant power, P* (W). It is measured with a power or energy metre by photodiode or thermal sensors.

1.2.2.2 Radiant Energy

This is energy emitted, transferred, or received as radiation. A source with a power output P (W), which is turned on for a time duration t (s), will yield a *radiant energy, Q* (J).

$$Q = P \cdot t \text{ (J; Ws)}.$$

1.2.2.3 Radiant Intensity

The power P (W) from a point source that is directed into a particular direction at a solid angle, Ω (steradians or sr), is called the *radiant intensity*, I (W/sr).

For an isotropic source, the whole sphere has 4π (sr) of solid angle. In limit of small angle θ, the solid angle of a cone Ω is (Fig. 1.7):

$$\Omega = 4\pi \cdot \pi r^2 / 4\pi R^2 \text{ (sr)} = \pi r^2 / R^2 \text{ (sr)} = \pi\theta^2 \text{ (sr)}.$$

1.2.2.4 Irradiance

The power P (W) of a continuously emitting source that irradiates a surface area, A (cm²), is called the *irradiance, E*, where

$$E = P / A \text{ (W/cm}^2\text{)}.$$

1.2.2.5 Radiant Exposure

The energy Q (J) of a pulsed light source that reaches a surface A (cm²) due to an irradiance E, and is maintained for a time interval t (s) is called *radiant exposure*, H, where

$$H = Q / A = Pt / A = Et \ (\mathrm{J/cm^2}).$$

1.2.2.6 Fluence Rate

Imagine an isotropic sphere located in biological tissue collecting photons impinging from all angles onto a small region of its surface. Then it measures the *fluence rate*, F (W/cm²). The fluence rate is the total absorbed power by the small sphere divided by its cross-sectional area, A ($A = \pi r^2$). The fluence rate irradiating the target sphere is:

$$F = P_{\mathrm{absorbed}} / A \ (\mathrm{W/cm^2}).$$

In some literature the fluence rate is expressed with the greek symbol Φ.

1.3 Principle of Lasers

A laser is actually an *oscillator* rather than a simple amplifier. The difference is that an oscillator has positive feedback in addition to the amplifier. "Light" is understood in a general sense of electromagnetic radiation with wavelengths from 100 nm to 1 mm. Thus one can have ultraviolet, visible, or IR lasers. In medical applications nearly all types of lasers are used for specific medical treatments or diagnostic applications.

The amplifier of a laser is the laser material that can be a solid, a gas, or a liquid. The feedback mechanism is produced by the resonator, where the light is reflected by two mirrors so that the photons pass several times through the laser material. The number of photons within the resonator increases exponentially due to the stimulated emission (Fig. 1.8).

However, a laser can only work when the stimulated emission of excited atoms of a laser material is larger than the spontaneous emission and the losses within the resonator. In thermal equilibrium, according to the Boltzmann statistics, the number of excited atoms, N_2, with higher energy, E_2, is always smaller than the number, N_1, of atoms in the lower energy level, E_1. Therefore, a two-level laser system cannot exist because there must be the possibility of an *inversion*. This is possible with a three- or four-level laser design.

The rate balance of a two-level system at thermal equilibrium using the Einstein's coefficients is

$$(\text{Induced absorption}) B_{12}\rho(\nu)N_1 = B_{21}\rho(\nu)N_2$$
$$(\text{stimulated emission}) + A_{21}N_2 \ (\text{spontaneous emission}).$$

With the relation of the Einstein coefficients $A_{21}/B_{21} = 8\pi h\nu^3/c^3$, we receive also Planck's law of black body radiation:

$$\rho(\upsilon) = 8\pi h\upsilon^3 / c^3 \times 1/(e^{h\nu/kT} - 1).$$

The premise for a laser activity is the population inversion between the levels where the laser transition should take place. The higher this inversion, the more effective is the laser. To get a high inversion, the Einstein coefficient A_{21} of the upper laser level should be small so that the losses due to spontaneous emission are small as well. This means that the lifetime of the upper laser level τ_2 should be long. The lower laser level should be less populated (Fig. 1.9) and should have a short lifetime.

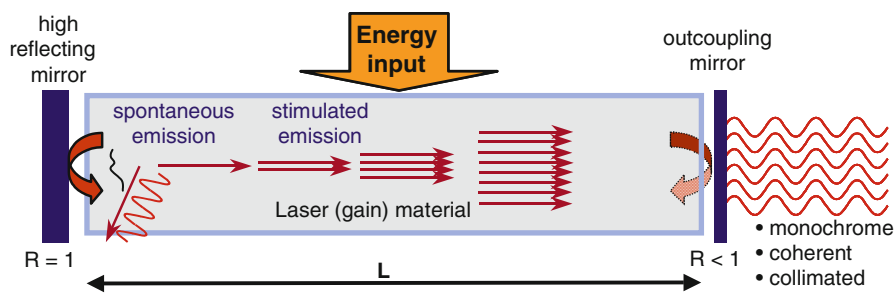

Fig. 1.8 Principle of a laser

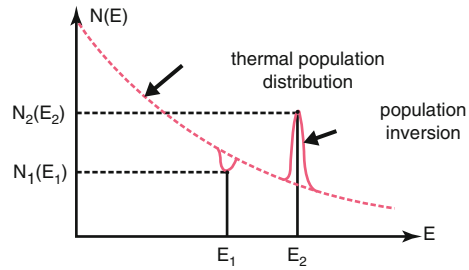

Fig. 1.9 In thermal equilibrium (Boltzmann statistics) the population distribution follows an exponential curve, meaning that the number of excited atoms with higher energy is always less than at lower energy levels ($N_2 < N_1$). Population inversion is the opposite ($N_2 > N_1$)

1.3.1 Laser Design

To produce a population inversion in the laser material of a solid-state laser, one needs a pumping source, which can be a flashlamp or another pumping laser (diode laser). The absorption of the ground state must be sufficiently high. A large Einstein coefficient B is favourable. These conditions are well fulfilled in three-level and four-level systems (see Fig. 1.10).

The first laser, which was demonstrated and produced by Maiman, was a *three-level* ruby laser. Ruby is an Al_2O_3 crystal in which about 0.05% of the Al ions are replaced by Cr^{3+} ions. The problem of a three-level laser is that the lower laser level is the ground state, as shown in Fig. 1.10. It is much more difficult to obtain population inversion in three-level lasers because the lower laser level initially has a very large population, N_0. By turning on the flashlamp pump, dN atoms are excited and lifted to level 1, which then decay quickly to level 2. Thus, the population of level 2 will be dN, and the population of the ground state will be (N_0−dN). Hence, for population inversion we require dN > (N_0−dN), that is, dN > N_0/2. Therefore, to obtain population inversion we have to pump more than half the atoms out of the ground state into the upper laser level. This obviously requires a very large amount of energy, which normally only can be delivered by intensive flashlamps. Therefore, three-level lasers are pulsed lasers. One exception of a three-level continuous wave (cw) laser is the argon ion laser. Here, electrical energy is used to ionise the atoms to become the lower laser level.

Much less energy is required to reach the laser threshold in four-level lasers, in which the lower laser level is empty before the pumping process starts. Although the threshold for population inversion is very high in a three-level system, they can be quite efficient once this threshold is overcome. Ruby lasers pumped by bright flashlamps actually give very high output pulse energies of 20 J easily, and are used in dermatologic applications.

Continuous lasers, like the Nd:YAG laser, normally use four-level systems. Atoms are pumped from the ground state to level 3, which can be composed of different excited states. From there, the upper laser level 2 is populated by fast transition, τ_{32}. This level is long-lived. It is a metastable system because the transition directly to the ground state, τ_{20}, is forbidden. The laser transition occurs to the lower laser level 1 which is short-lived, with fast transition to the ground state. This allows for very efficient pumping.

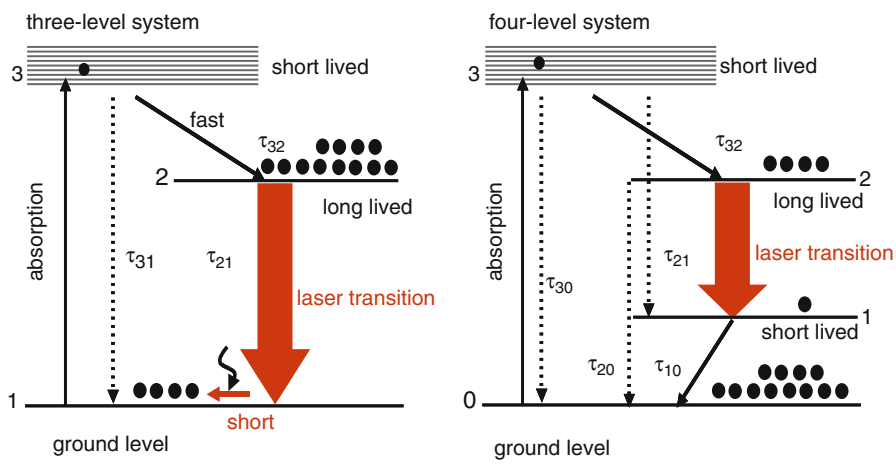

Fig. 1.10 Three- and four-level laser systems

1.4 Optical Resonators

The optical resonator is composed of two mirrors with the laser active medium located between them. The mirrors might either be flat (Fabry-Perot-Resonator) or curved. In case of plane-parallel mirrors, the reflected beam in the resonator is a plane wave. Because mirrors are never ideal plane, this resonator has losses and is slightly unstable. Stable resonator configurations use concave mirrors and are easier to adjust. Oft-used resonator configurations are the symmetric confocal resonator ($R_1 = R_2 = L$), which has the most stable design and least diffraction losses, as well as the spherical type ($R_1 = R_2 = L/2$).

The relation that describes the stability of an optical resonator is determined by the resonator length, L, and the curvatures of the mirrors, R_1 and R_2. With the mirror parameters

$$g_1 = 1 - L / R_1 \text{ and } g_2 = 1 - L / R_2$$

the stability condition is (Fig. 1.11):

$$0 \leq g_1 g_2 \geq 1.$$

The resonator geometry determines the form of the output beam with regard to diameter, divergence, and composition of modes. When we consider a stable Gaussian resonator, the multiple reflected beam is always running back in to itself and the phase of the wave front must match the curvature of the mirrors. Because of the marginal condition of the electromagnetic field on the mirrors, a standing wave results along the axis. Therefore, the standing wave spectrum must fulfil the condition:

$$n \cdot \lambda / 2 = L,$$

with integer $n = 1, 2, 3, 4, \ldots,$;

wavelength λ; and resonator length L.

This results in an axial spectrum of longitudinal modes with frequency spacing:

$$\Delta\nu = c / 2L.$$

As an example, for a resonator length of 0.5 m, neighboring longitudinal modes are separated by $\Delta\nu = 300$ MHz. A laser emits a characteristic mean wavelength according to the atomic resonance frequency, which is broadened due to the Doppler effect. If pumping of the laser exceeds the threshold because of losses in the resonator, then laser radiation is emitted and the number of longitudinal modes (axial eigenfrequencies) is determined by the ratio of the Doppler width, $\Delta\nu_D$, to the separation of the modes, $c/2L$, as demonstrated in Fig. 1.12.

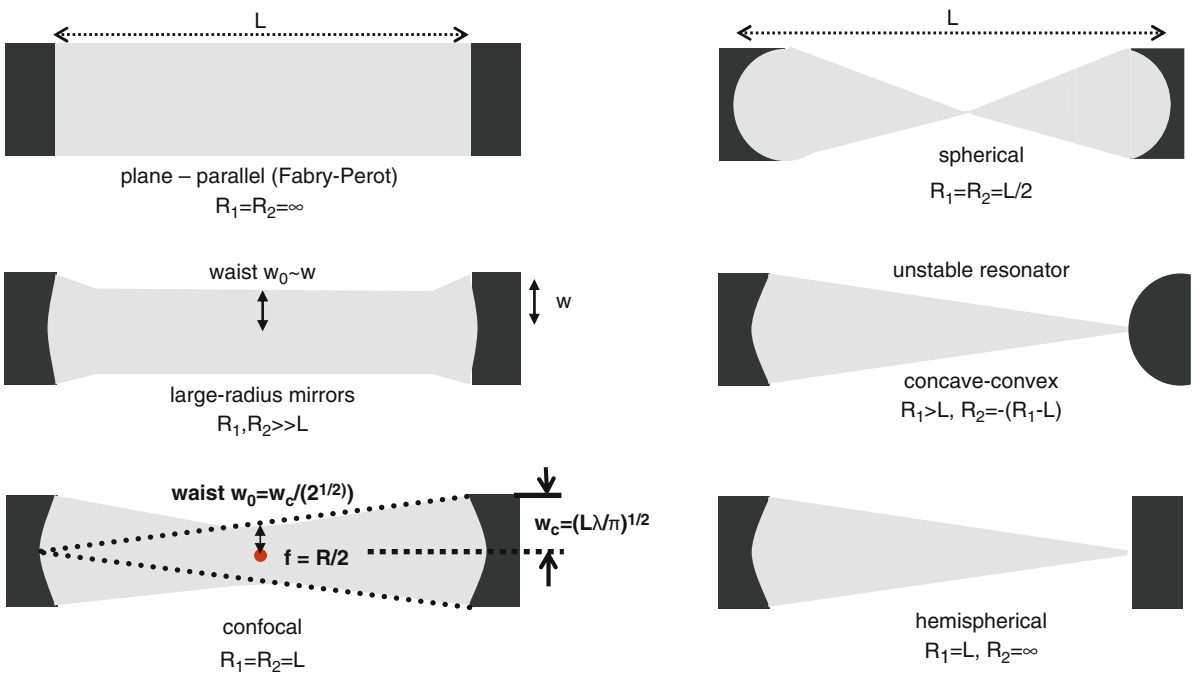

Fig. 1.11 Different stable and unstable resonator configurations

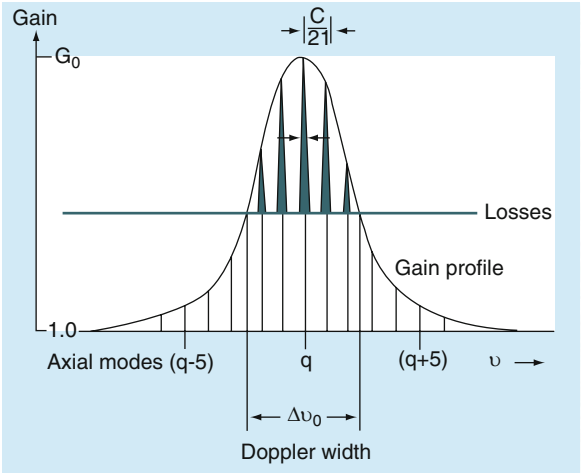

Fig. 1.12 Origin of the longitudinal (axial) modal spectrum. Laser activity is only observed when the gain within the Doppler width exceeds the losses

Practically, only few resonators are working in the stable Gaussian basic mode. Like all systems characterised by marginal conditions, resonators have an entire spectrum of inherent modes. The Gaussian basic mode (Fig. 1.13) represents the oscillation state with the lowest inherent value. Higher modes have a more complex intensity distribution and the transversal expansion of the beam is larger. To increase the output power of a laser, a large amplification volume has to be generated with the assistance of higher transversal modes.

Resonators using spherical mirrors have an output beam with allowed transversal intensity distributions mathematically described by the Hermite-Gaussian modes, the so-called TEM_{nm} modes (transversal electromagnetic modes). Lasers are often designed for the operation in a single transversal mode, the basic Gaussian mode TEM_{00}, which has the smallest beam diameter and the smallest spot size in the focus. Normally they have cylindrical symmetry. In this case the transverse mode patterns are described by a combination of a Gaussian beam profile with a Laguerre polynomial. The modes are denoted TEM_{pl}, where p and l are integers representing the radial and angular mode orders, respectively.

With $p = l = 0$, the TEM_{00} mode is the lowest order, or the fundamental transverse mode of the laser resonator, and has the form of a Gaussian beam (Fig. 1.14). The pattern is a round spot with a constant phase. Modes with increasing p show concentric rings of intensity, and modes with increasing l show angularly distributed lobes. In general there are $2l(p+1)$ spots in the mode pattern. The overall size of the mode is determined by the Gaussian beam radius w, and this may increase or decrease with the propagation of the beam. During propagation the modes preserve their general

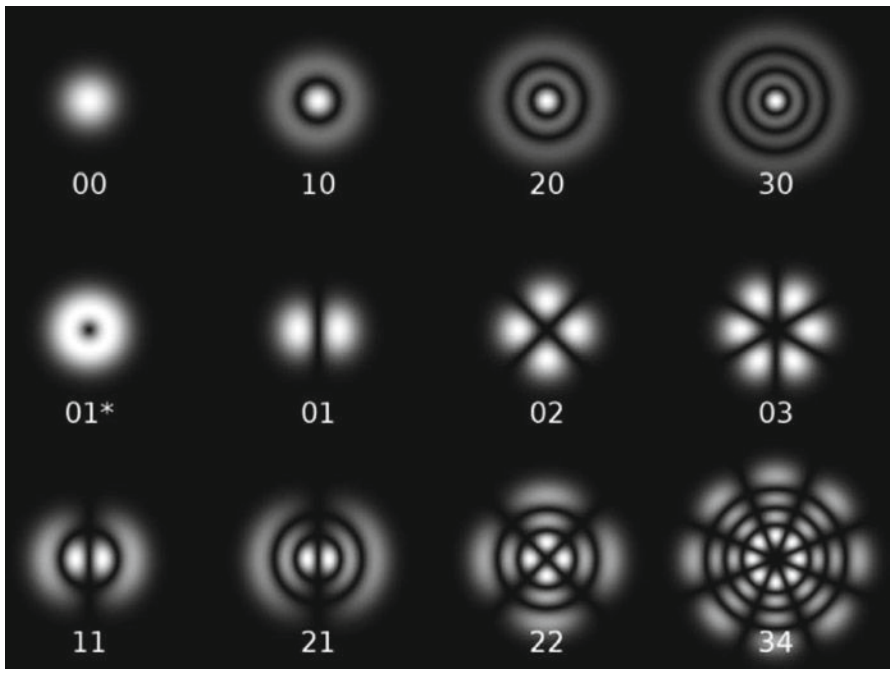

Fig. 1.13 Cylindrical transverse mode patterns TEM_{pl}. TEM_{01^*} represents a special case, the so-called *doughnut mode*, an overlay of the patterns with l = 1, 2, 3

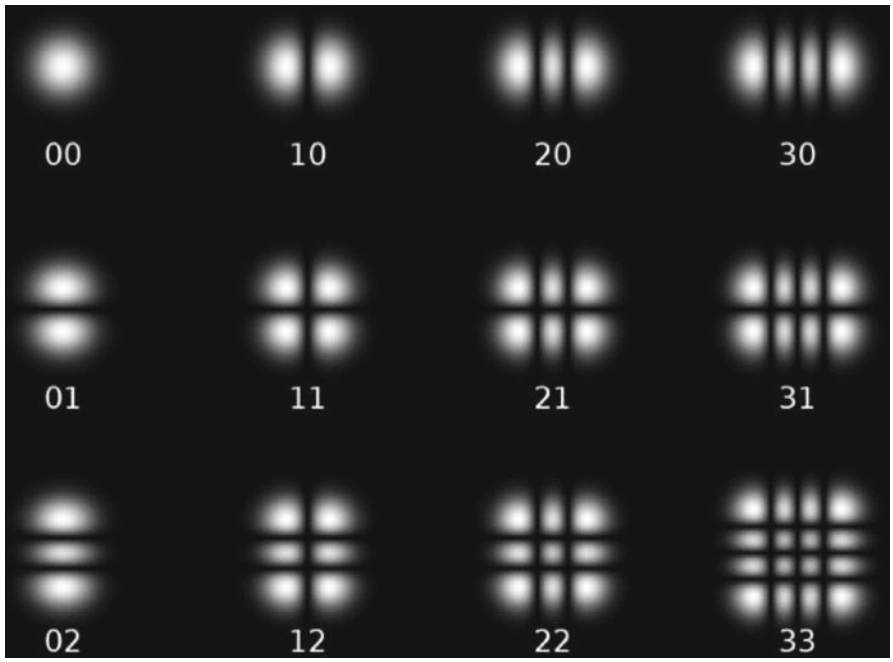

Fig. 1.14 Rectangular transverse mode pattern TEM_{mn} of lasers with Brewster's angle elements

shape. Because higher-order modes are larger compared to the TEM_{00} mode, the fundamental Gaussian mode of a laser may be selected by placing an appropriately sized aperture in the laser cavity that only the fundamental mode can pass through.

The symmetry of optical resonator often is restricted in lasers by polarising elements like Brewster's angle windows, leading to transverse modes with rectangular symmetry. These modes are named TEM_{mn}, with m and n being the horizontal and vertical orders of the pattern. The intensities of the patterns are determined by the order of the Hermite polynomials and demonstrated in Fig. 1.14. The TEM_{00} mode corresponds to the same fundamental mode as in the cylindrical geometry. The number of spots in the intensity patterns is described by the expression $(m+1)(n+1)$. The polarisation of the phase in each spot is offset by π radians with respect to the horizontal or vertical neighbours.

1.5 Laser Radiation

Laser radiation is characterised by its parallelism, the spatial and temporal coherence; its monochromatism, the spatial distribution and divergence (beam quality); and the polarisation, power, and operating mode (pulsed or cw).

The intensity distribution across a Gaussian beam is a bell-shaped Gaussian function. It is a beam of best quality that can be focused to the smallest spot. Lasers emitting in TEM_{00} mode have such a quality. The Gaussian function of the intensity $I(r,z)$ depends on the distance, z, from the beam waist and the radius, w, according to the formula:

$$I(r,z) = I_0(W_0 / W(z))^2 \exp^{-2r^2/W^2(Z)}.$$

The intensity at the beam waist, I_0, can be described in relation to the laser power, P, by the expression:

$$I_0 = 2P / \pi w_0^2 \ (W/cm^2).$$

With distance, z, from the beam waist at z_0, the cross-section and the radius, w, of the beam increases and can be expressed as

$$w(z) = w_0(1 + (z / z_0)^2)^{1/2}.$$

The distance, z, where the cross-section of the beam is twice the area of the focal spot is called the *Rayleigh length* (see Fig. 1.15).

$$\text{Rayleigh length} : z_0 = \pi w_0^2/\lambda$$

where the beam has widened to:

$$w(\pm z_0) = w_0\sqrt{2}.$$

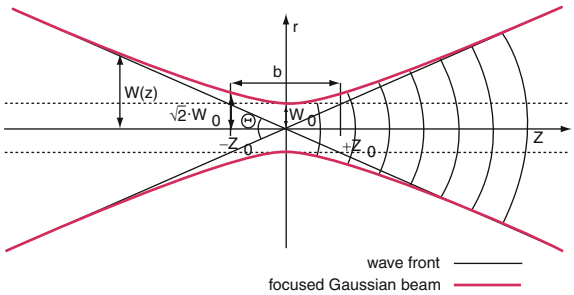

Fig. 1.15 Focused Gaussian beam with spherical wave fronts and the angle of divergence Θ. The radius of the beam waist is w_0 and at a certain distance from the beam waist, $w(z)$. The distance until $\pm z_0$ is twice the Rayleigh length, b

The length between the spots $\pm z_0$, denominated as b, is twice the Rayleigh length and is called the *confocal parameter*. The intensity there is half the intensity at the focal spot.

The quality of multimode laser beams, which have no Gaussian profile, is expressed as M^2, which is independent of λ. It is the relation of the beam parameter product (BPP), which is the product of a laser beam's divergence angle (half-angle) and the radius of the beam at its narrowest point (the beam waist), to that of a Gaussian beam. The BPP quantifies the quality of a laser beam and how well it can be focused to a small spot. M^2 of a Gaussian beam is exactly one. The smaller M^2 of a laser beam is, the smaller is its focal spot.

$$M^2 = w\Theta / (\lambda / \pi)$$

with the divergence of a Gaussian beam,

$$\Theta_0 = \lambda / \pi w_0.$$

If the waist of a laser beam is equal to that of a Gaussian beam, then

$$M^2 = \Theta / \Theta_0.$$

Important laser parameters are summarised in Table 1.2.

Polarisation of the laser beam can be achieved by introducing polarising optical components into the resonator, such as deflecting mirrors in folded resonators or by active laser crystals where the faces have Brewster angles (Fig. 1.16). Such a Brewster resonator produces linear polarised light. The disadvantage may be that the losses of the resonator increase and the output power is reduced.

Table 1.2 Important laser parameters

Wavelength λ (nm or µm)	Photon energy
Power P (W)	For cw lasers
Energy $E = Pt$ (J)	For cw lasers
Peak power P_{max} (W)	For pulsed lasers
Energy E per pulse (J)	For pulsed lasers
Pulse duration t [fs (10^{-15}) to ms (10^{-3})]	For pulsed lasers
Effect on tissue	
Energy density E/A (radiant exposure) (J/cm^2) (A = effective area)	For pulsed lasers
Power density W/A (irradiance) (W/cm^2) (A = effective area)	For cw lasers
Beam quality $L_w = 1/M^2$ (mm mrad^{-1})	General for lasers

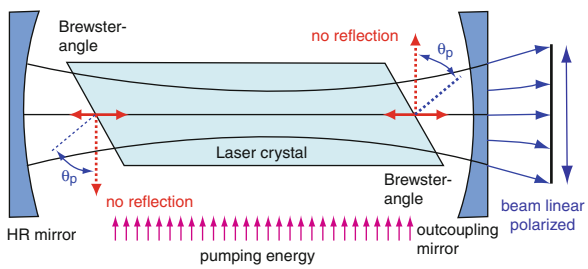

Fig. 1.16 Brewster resonator producing linear polarised laser light [8]

The *operational modes* of lasers are cw, pulsed as interrupted radiation (in ms), pulsed free running (in hundreds of µs), Q-switched (in ns), or mode-locked (in fs).

Interrupted radiation of a cw laser is done by mechanical or electronic switching with modification of the pulse length. The pulse frequency is low to moderate, up to 100 Hz. Flashlamp-pumped solid-state lasers in the free-running mode have pulse lengths of 50 µs up to several hundred microseconds. Pulses of medical dye lasers systems can vary from microseconds to 50 ms.

Shorter pulses with very high intensities in the nanosecond range are produced by Q-switching of the laser. A Q-switch can be introduced into the resonator that reduces the performance factor of the laser resonator. Therefore, the threshold for lasing is very high for a short period of time. During this time, with continuous

pumping, pumping power, P_p, the inversion of the number of excited atoms, can be built up, $\Delta N(t)$ (Fig. 1.17). When the Q-switch opens at $t=0$, the threshold power, $S(t)$, goes down immediately and the amplification is now much higher than the resonator losses. A strong laser pulse is generated with complete depletion of the energy reservoir [21].

The power of the pulse can be estimated according to the expression:

$$P(t) = h\nu T(c/2L)Vn(t)\,(\mathrm{W}),$$

where h is Planck's elementary quantum of action (Planck's constant), ν is the frequency of the laser transition, $T = 1 - R$ is the transmission of the output mirror, V is the resonator volume, $n(t)$ is the photon number density, and L is the resonator length.

Some typical representatives of Q-switches are shown in Table 1.3.

Ultrashort laser pulses are generated by mode-coupling due to the coherence properties of the laser. Compared to Q-switching, where the shortest pulse durations are in the range of the resonator period, mode-coupling can generate even shorter laser pulses. Mode-coupling finally is attained by forcing a fixed phase relationship, $\Phi_{q+1} - \Phi_q = \Phi$, between the longitudinal laser modes having the distance $\Delta\nu_{q,q+1} = c/2L$

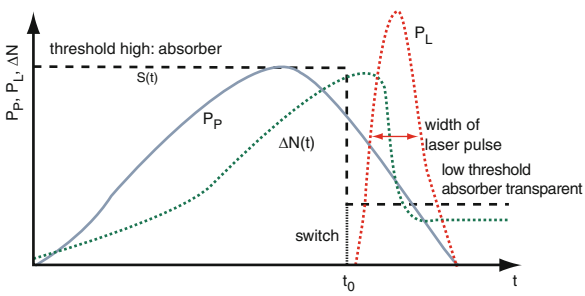

Fig. 1.17 Scheme of a Q-switch: P_p is pumping power, $S(t)$ is threshold power, $\Delta N(t)$ is the inversion, and P_L the laser power

Table 1.3 Typical representatives of Q-switch devices

Type of Q-switch	Switching time
Rotating aperture in resonator	>10 μs
Rotating mirror or prism	<0.1 μs
FTIR Q-switch	<50 ns
Electro-optical switch	<10 ns
Acousto-optical switch	<50 ns
Saturating absorber	<0.1 ns

FTIR frustrated total internal reflection

(see Fig. 1.12). This is associated with interference effects with amplitudes that are larger than those of individual modes. For more information see [4].

1.6 Medical Lasers

Since the invention and commercial availability of lasers, such systems have been widely used for medical applications in the treatment of soft and hard biological tissue, from the Ultraviolet (UV) Excimer laser, ArF at 193 nm, in ophthalmology up to the CO_2 laser in the IR-region at 10,640 nm for surgical interventions. The whole spectrum of lasers is shown in Fig. 1.18.

1.6.1 Solid-State Lasers

1.6.1.1 Nd:YAG Laser

The most important solid-state laser is the Nd:YAG laser, with neodymium as laser ion (Nd^{3+}) doped with 1–1.5% into an yttrium-aluminium-garnet crystal ($Y_3Al_5O_{12}$). Its fundamental wavelength is 1064.2 nm. Frequency doubling with a KTP crystal (potassium titanium oxide phosphate, $KTiOPO_4$) leads to 532 nm (green light). The third and fourth harmonics are 355 and 266 nm, respectively. The Nd:YAG laser is a four-level system (Fig. 1.10). Other, weaker emission wavelengths are 1,320 and 1058.2 nm ($Nd:CaWO_4$). The overall efficiency of a flashlamp-pumped Nd:YAG laser is less than 2%. Therefore, it must be cooled with water. Diode pumped systems (805-nm laser diodes) reach efficiencies of about 15% at output power of about 10–15 W. Nd:YAG lasers are used as cw lasers up to 100 W for surgical applications, e.g., long pulse lasers in dermatology or Q-switch lasers with-to 20-ns pulse length in urology (lithotripsy) and dermatology (tattoo removal).

1.6.1.2 KTP Laser

KTP lasers are frequency-doubled Nd:YAG lasers using KTP crystals inside the cavity or externally with an emission wavelength of 532 nm in the green part of the visible spectrum.

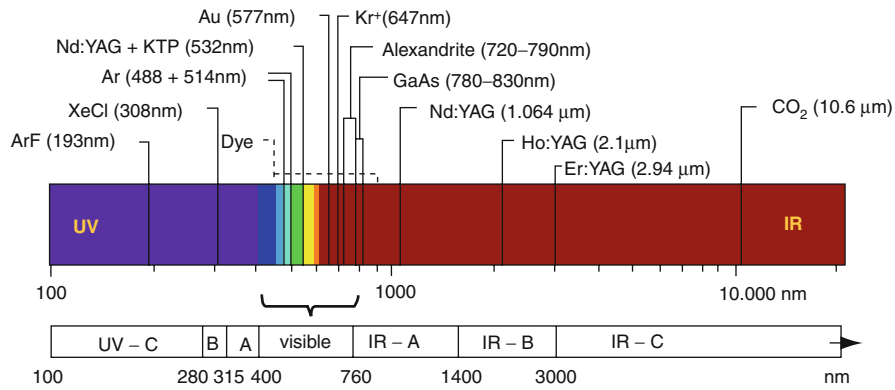

Fig. 1.18 Medical lasers

1.6.1.3 Er:YAG Laser

The Er:YAG laser with a 2.94-µm wavelength is well suited for ablation of soft and hard biological tissue because the wavelength is highly absorbed in water ($\mu_a = 10^4\,cm^{-1}$). Erbium ions are doped in high concentration (~50%) in YAG or other crystals (Er:YSGG: 2.78 µm; Cr:Er:YSGG: 2.80 µm; Cr:Tm:Er:YAG: 2.64 µm). This laser exists only as pulsed laser system because the rather complex energy-level scheme of erbium with important energy-transfer upconversion (ETU; see Fig. 1.19) and cross-relaxation (CR) processes. Laser transition occurs from the energy level $^4I_{11/2}$ to $^4I_{13/2}$. The lower laser level has a longer lifetime of 9 ms compared to the upper laser level. Only by hard pumping and the efficient upconversion processes is lasing possible. The ETU process ($^4I_{13/2}$, $^4I_{13/2}$) → ($^4I_{15/2}$, $^4I_{9/2}$) leads to a fast depletion of the lower laser level. The other advantage of the ETU process is that half of the ions undergoing this process are upconverted to the $^4I_{9/2}$ upper level and, by subsequent multiphonon relaxation, are recycled to the $^4I_{11/2}$ upper laser level, from where they can each emit a second laser photon [18, 19].

Pulsed Er:YAG laser systems (pulse lengths from 100 to 500 µs) have a mean power of up to 30 W and repletion rates of up to 50 Hz, with efficiencies of 1–2%. They are used in dermatological applications for superficial tissue ablation, in dentistry, and in minimal invasive surgery. The laser light is transmitted either by an articulated arm or by fibres. Germanium oxide fibres proved to be stable in clinical routine work.

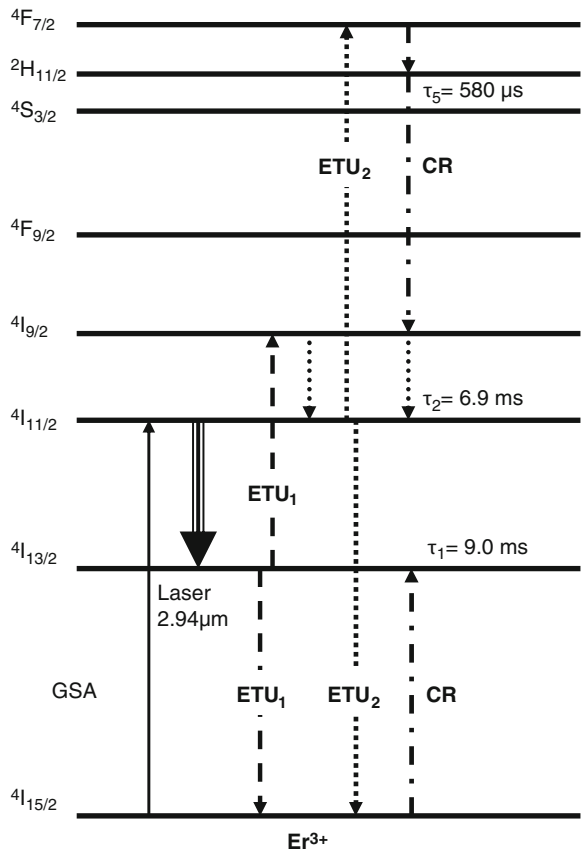

Fig. 1.19 Energy level scheme of the Er:YAG laser. *GSA* ground state absorption; *ETU* energy-transfer upconversion between neighboring erbium ions; *CR* cross-relaxation

1.6.1.4 Holmium:YAG Laser

Flashlamp- or diode-pumped Ho:YAG lasers can be operated in the pulsed or the cw mode. In the pulsed mode, with pulse durations 200–600 µs and energies from 0.2 to 3.5 J, repetition rates up to 50 Hz have a mean power of 30–40 W. Combining several laser heads, high-power systems are also available. The wavelength is 2,080 nm.

Applications with low power first appeared in ophthalmology for refractive surgery procedures called

laser thermal keratoplasty to correct mild to moderate cases of hyperopia and astigmatism. In recent years applications in urology and endourology are more important. Besides stone disintegration, treatment of benign prostate hyperplasia (BPH) by enucleation or vaporisation has become a standard surgical intervention [11, 13].

The most efficient laser material for high-power flashlamp-pumped lasers is Cr,Tm,Ho:YAG. The laser's active ion is Ho^{3+} with a concentration of about 0.5% atomic units (AU) in the host material YAG, co-doped with thulium ions (Tm^{3+}, 6% AU) and for lamp pumping with chromium ions (Cr^{3+}, 1% AU). The scheme of the lamp-pumped holmium system is shown in Fig. 1.20.

The pump light in Fig. 1.20 is absorbed by the broad absorption bands A_2 T_2 of the chromium ions at wavelengths of 420 and 600 nm or directly by energy levels of the Tm^{3+} ions from $^3H_6$ $^3F_4$ by diode pumping. From all the excited levels, rapid radiationless energy transfer occurs to the energy level $^3F_4$ of the holmium ions. The highly excited Tm^{3+} ions are deactivated from the $^3F_4$ to the $^3H_4$ level. The energy difference of the levels $^3F_4$ and $^3H_4$ fit very well with the energy difference between the low energy level $^3H_6$ and the $^3H_4$ level of the Tm^{3+} ion. So the energy of the deactivated Tm^{3+} ion is, with a high probability, resonantly transferred to a neighboring Tm^{3+} ion, which then is excited from the low energy level $^3H_6$ to the $^3H_4$ level. This resonant energy transfer is called cross-relaxation with quantum efficiency raised to two. One pump photon can excite two Tm^{3+} ions to the $^3H_4$ level by this cross-relaxation.

The $^3H_4$ excitation energy migrates between neighbouring Tm^{3+} ions via energy resonant processes. If a holmium ion is reached, the energy can be transferred without radiation to the quasi-resonant upper laser level $^5I_7$ of the Ho^{3+} ion. The laser radiation terminates at the $^5I_8$ level of the Ho^{3+} ion.

The lower laser level of the Ho^{3+} ion has only a small energy difference to the ground state and is therefore highly populated at ambient temperatures. Holmium laser systems operating at room temperature are quasi-three-level laser systems. Consequently, a very high excitation energy is necessary to reach a population inversion. The resulting thermal load to the laser material in lamp-pumped systems allows laser operation only in the pulsed mode. The laser output is very temperature-dependent. It will be reduced by about 3% per degree of rising temperature.

1.6.1.5 Thulium Laser (Tm:YAG)

Laser therapy of symptomatic BPH is a promising, less invasive alternative to the traditional BPH surgery. Besides the holmium laser, the cw thulium laser at a 2-μm wavelength is used as well [6]. Compared to the KTP laser, the thulium laser is more efficient [25]. The absorption coefficients of the mid-IR lasers are compared in Fig. 1.21. Tm:YAG lasers have a slightly higher absorption in water than the Ho:YAG lasers. Therefore, Tm:YAG lasers are well suited for vaporisation of the prostatic tissue.

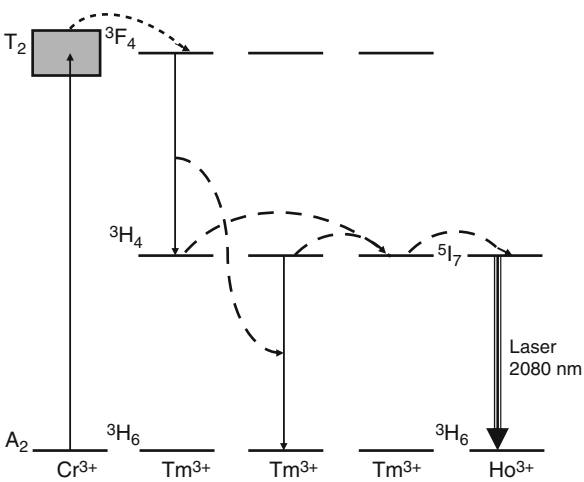

Fig. 1.20 Scheme of the Cr,Tm,Ho:YAG laser system

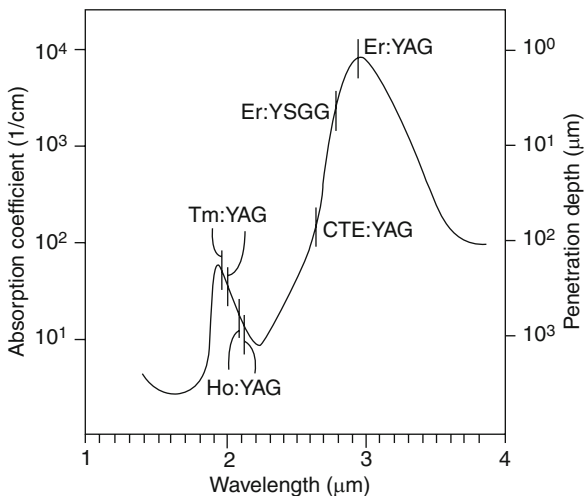

Fig. 1.21 Absorption coefficients and penetration depths in water of mid-infrared laser [7]

1.6.1.6 Alexandrite Laser

This solid-state laser is tunable in the wavelength range 700–830 nm, normally being operated at 750 nm. Alexandrite laser medium is a chromium-doped chrysoberyl (Cr:$BeAl_2O_4$, gemstone alexandrite) and can operate in cw (up to 100 W) or pulsed mode. Because light of this wavelength region is absorbed by melanin and dyes, but not significantly by blood, it can be used for the destruction of melanin-containing structures (hair roots, pigmented lesions). The first applications were reported in the fragmentation of kidney stones [17].

Also not a true four-level laser, the vibronic transition on which this laser usually operates permits operation similar to a four-level laser. The scheme of the energy levels is shown in Fig. 1.22.

The four-level laser depicted in Fig. 1.22 has a ground manifold, a pump manifold, and an upper laser manifold, similar to a three-level laser. But, in contrast to the three-level system, there is a fourth manifold, the lower laser manifold, in which the lower laser level resides, well above the ground manifold. Because the population density of the ground level does not have to be overcome, Cr:$BeAl_2O_4$ operation on a vibronic transition resembles the operation of a four-level laser with a low laser threshold.

1.6.1.7 Ruby Laser (Cr^{3+}:Al_2O_3)

Although the ruby laser was the first laser, which was developed by Maiman in 1961, it was for a long time ignored and not used in medical applications. The emission wavelength is 694 nm. The laser is a three-level laser and therefore more than 50% of the ions in the ground state must be excited to get an inversion. Only strong pumping by powerful flashlamps can produce this inversion. Modern laser systems with advanced technology are able to produce high pulse energies up to 20 J. The laser light is transmitted through fibres or articulated arms. The deep red color of the laser light is absorbed by melanin and dark pigments. Therefore, the medical applications are mostly in dermatology, similar to the alexandrite laser, to remove hairs or tattoos with black or blue color.

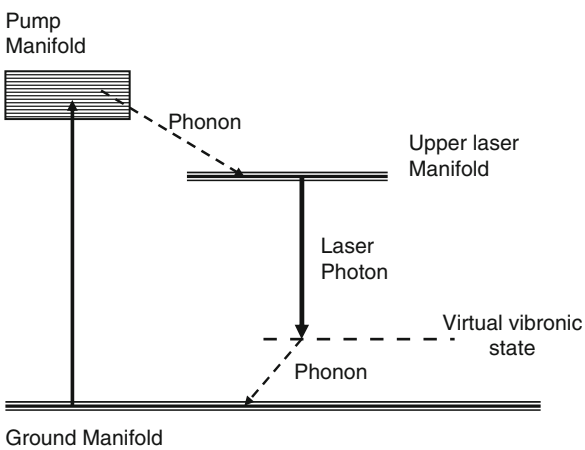

Fig. 1.22 Scheme of the energy levels of the alexandrite laser

The laser active ion is Cr^{3+} replacing Al ions, Al^{3+}, in the host material, sapphire (Al_2O_3), at a doping concentration of 0.05% AU of Cr_2O_3. The two strong absorption bands in the ruby crystal are around 400 and 550 nm. Optical pumping occurs from the ground state, $^4A_2$, to the two excited states of the chromium ion, $^4T_1$ and $^4T_2$, from where, quickly and without radiation, the energy is transferred to the upper laser level, *E*. Laser emission of 694 nm occurs from energy level *E* to the ground state $^4A_2$.

1.6.1.8 Titanium-Sapphire Laser (Ti:Al_2O_3)

The Ti:sapphire laser was developed by Moulton and first reported by him in 1986 [15]. This solid-state laser is pumped by a frequency-doubled Nd:YAG laser and can be tuned between 660 and 1,160 nm. With mode-locking the laser emits ultra-short femtosecond pulses (45–180 fs) at high repetition rates (80–100 MHz) or picosecond pulses. Due to the high power of the laser pulses, Ti:sapphire lasers are used as a light source in two-photon microscopy or in ophthalmology for cutting transparent ocular tissue (flap preparation of the cornea for vision corrections).

1.6.2 Gas Lasers

1.6.2.1 Carbon Dioxide Laser

The carbon dioxide (CO_2) laser is still one of the important lasers used for medical surgery and industrial applications. With a power range from mW to tens of kW in the cw mode and an efficiency of up to 30%, laser systems are compact and economic. The sealed laser tube

is filled with a mixture of gases, CO_2 (1–9%), N_2 (13–45%), and helium (60–85%). Excitation occurs by direct current high-voltage gas discharge or through high frequency (RF). It must be mentioned that only with direct current supply units is the superpulse technique possible; it generates pulses <1 ms and with a peak power about ten times higher than the mean power. The gas components have different reaction mechanisms during the laser process.

The structure of the CO_2 molecule is linear, with the carbon atom in the centre. Such molecule configurations can vibrate in symmetric and asymmetric stretch modes as well as in bending modes (Fig. 1.23). The energies associated with molecular vibration are quantised just like electron energies; therefore, only certain vibrational levels are possible. The possible forms of resonant vibration are referred to as the vibrational modes of a molecule.

During gas discharge free electrons collide with N_2 molecules and excite them. The CO_2 is excited through a collision with excited N_2 molecules. This transfer of energy occurs by a resonant effect. Because the vibrational energy levels of N_2 are metastable and have an energy very close to that of the first energy level of the asymmetric stretch mode of CO_2, they have ample time to transfer their energy and excite the CO_2 molecules. The lasing occurs when CO_2 in the excited asymmetric mode makes the transition to the bending or symmetric stretch modes. The CO_2 then returns to its ground state through another collisional transfer of energy with the helium atoms. With this lasing process the CO_2 laser is a three-level laser with direct pumping into the upper laser level because the lower laser level is depleted very quickly through the presence of helium in high concentration. One receives a bunch of laser lines around the central laser wavelengths at 10.6 and 9.6 µm.

A special variant of the CO_2 laser is the TEA (*T*ransversely *E*xcited *A*tmospheric Pressure) CO_2 laser. High peak powers can only be achieved by increasing the density of the excited CO_2 molecules. To avoid too high voltage necessary to achieve gas breakdown in longitudinal configuration, Beaulieu invented the TEA-laser in 1970 [2]. Mechanical Q-switching of CO_2 lasers to generate <1 µs pulses at kHz repetition rates can be used to cut bone tissue [12].

Transmission of the CO_2 laser light usually is provided by an articulated arm with mirrors. A new fibre technology invented at Massachusetts Institute of Technology, Cambridge, MA, USA, and developed by OmniGuide Inc., a wavelength-scalable hollow optical fibre from 750 nm to 10.6 µm with large photonic bandgaps [23] opens the possibility of flexible CO_2 laser transmission and endoscopic applications.

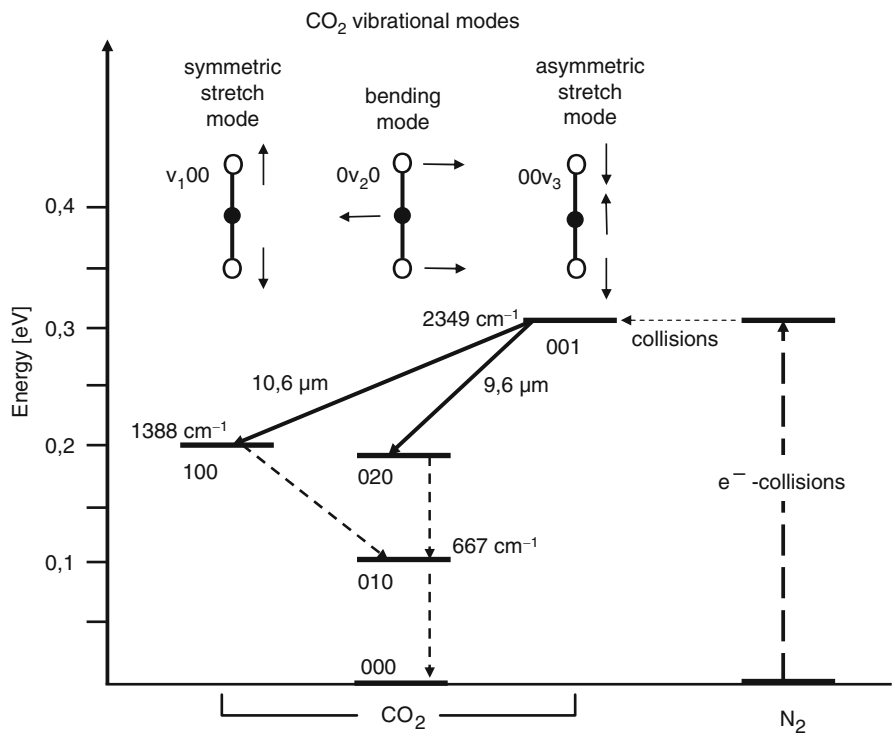

Fig. 1.23 Scheme of the energy levels of a CO_2 laser and the vibration modes of the linear CO_2 molecule

1.6.2.2 Argon Ion Laser

Noble gas ion lasers are cw lasers. Prominent representatives are the Ar^+ laser and Kr^+ laser. The wavelengths of the Argon ion laser are 363,488 and 514.5 nm in the UV, blue, and green spectral regions. Intense lines of the Krypton ion laser are at 530.9nm, 568.2 nm, and in the red region are at 647 and 676.4 nm. The output power in multi-line mode of the Ar^+ laser is between 2 and 100 W; the Kr^+ laser has about 20 W. Only in the UV spectrum is the Ar^+ laser still unrivaled.

Ion lasers are very inefficient: about one-tenth of a percent of electrical current is converted to laser light. They need high electrical current supply and water cooling. Nevertheless, the Ar^+ laser has been used to pump Ti-sapphire and dye lasers. It mostly has been replaced by more efficient frequency-doubled Nd:YAG lasers.

The argon laser consits of a plasma tube filled with argon gas at low pressure, 0.01–0.1 mbar. Plasma discharge current up to 60 A ionises the argon from its Ar ground state, $3p^6$, by successive electron collisions to the ionised Ar^+ ground level, $3p^5$. Further electron collisions excite the argon ion to the Ar^+3p^44p (upper laser) levels. Laser transition occurs from these levels to the lower laser levels, Ar^+3p^44s.

1.6.2.3 Helium-Neon (HeNe) Laser

The best known cw gas laser is the HeNe laser. The active medium is a mixture of helium and neon in proportions of 5:1–10:1 at low pressure (1 mbar) in a glass capillary. The actual laser transition occurs in the neon. The gas discharge tube operates at 1.5–2 kV, maintaining a glow discharge or plasma. Electron collisions excite helium atoms from the ground level to the 2^1S_0 and 2^3S_1 state. The energy of the helium atoms is transferred by collision with the neon atom to the neighboring energy levels of the neon, $3s_2$ and 2s levels. The $3s_2$ level of neon is an example of a metastable atomic state, meaning that it is only after a relatively long period of time – on atomic time scales – that the $Ne^*(3s_2)$ atom de-excites to the $2p_4$ level by emitting a photon with a 632.8-nm wavelength. The excited $Ne^*(2p_4)$ atom rapidly de-excites to its ground state by emitting additional photons or by collisions with the plasma tube walls. Because of the extreme quickness of the de-excitation process, at any time in the HeNe plasma there are more neon atoms in the $3s_2$ state than there are in the $2p_4$ state, and a population inversion is said to be established between these two energy levels.

Further laser lines of the HeNe laser are at 543, 594, 604, and 612 nm in the visible spectrum and at 1,152 and 3,391 nm in the IR spectrum. HeNe lasers are often used as aiming beams, for spectroscopic or diagnostic applications and biostimulation. Maximum output power is 100 mW; small devices have 1–5 mW output power.

1.6.2.4 Excimer Laser

Basov and his colleagues in Moscow first discovered in 1971 the stimulated UV emission of an excited xenon dimer (Xe_2) at 176 nm [1]. Excimer is a short form of the expression "excited dimers." Molecules, such as noble gas halides (ArF, KrF, XeCl, XeF), are stable only in their excited states and not in their ground states. The laser medium consists of such molecules in a buffer gas like helium or neon at a total pressure of 2–3 bar.

Figure 1.24 shows the potential curves of for a halogen rare gas molecule, (RGH) in its excited state and ground state. The electronically excited RGH (XY)* forms the upper laser level with a lifetime of several nanoseconds. The laser radiation occurs during transition from this excited state to the non excited state of rare gas and halogenide. The efficiency of excimer lasers is about 2%. They exist only as pulsed lasers, with pulse widths ranging from several ns to 100 ns. Maximum mean power is 200 W. The repetition rate is up to kHz.

The wavelength of an excimer laser depends on the rare gas and the halogenide. The wavelengths mainly used in the UV spectrum are listed in Fig. 1.25.

1.6.3 Dye Lasers

The invention of the dye laser in 1966 by Fritz P. Schäfer was a chance discovery. When he directed the beam of a ruby laser through a glass cuvette with fluorescing dye he observed a lasing effect. The reflections of the glass walls were sufficient to react as a resonator. Later, T.W. Hänsch used the dye laser with frequency-selective optical elements for spectroscopy. Today, dye lasers are still in use as cw lasers pumped with argon ion lasers or frequency-doubled Nd:YAG lasers. The advantage of the dye laser is its broad tuning range, up to 100 nm with one dye. Numerous dyes are available, covering the whole range in the visible spectrum. However, low-cost diode lasers have become an interesting alternative, specially for photodynamic therapy.

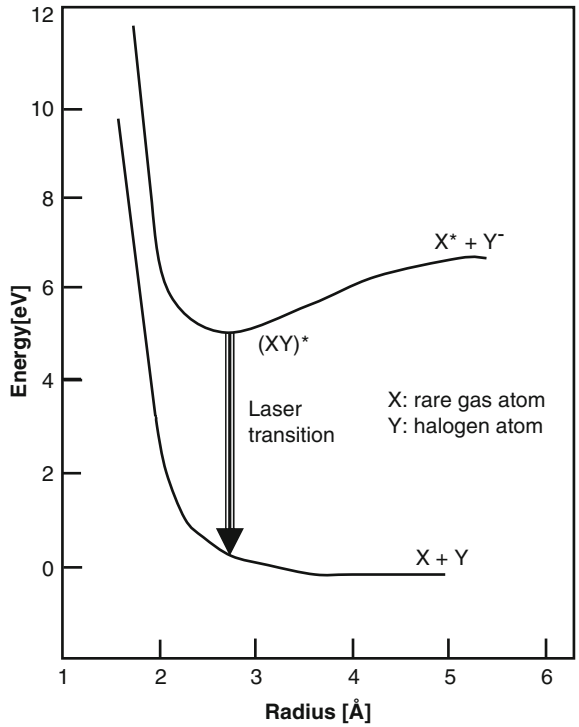

Fig. 1.24 Typical potential curves of rare gas-monohalide excimers

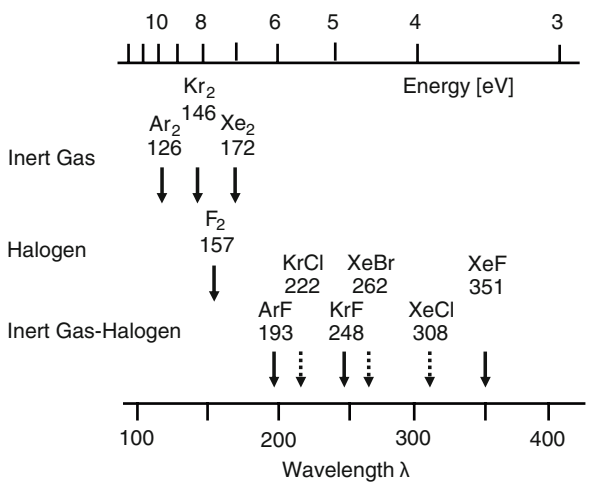

Fig. 1.25 Laser wavelengths of the different excimers in nanometers

Pulsed dye lasers are routinely used in dermatology for treatment of vascular malformations.

Some of the fluorescing dyes used in dye lasers are rhodamine 6G (R6G), fluorescein, coumarin, stibene, umbelliferone, tetracene, and malachite green [16].

The dye laser is a four-level laser. R6G has been chosen as an example in Fig. 1.26. Photon absorption of the R6G molecules excites the molecules from the bottom of the S_0-band to the higher S-bands. All excited states in the higher S-bands contribute to the laser activity because there is a very fast transition (10^{-12} s) of the vibration-rotation energy levels within one S-band to the lowest energy level, where they will have a Boltzmann distribution. Also, transitions from higher S-bands, to the S_1-band, as demonstrated in Fig. 1.26, are very fast (10^{-11} s) compared to the fluorescence lifetime of $\geq 10^{-8}$ s.

Transitions from S_1 to the vibration-rotational energy levels in the S_0-band are responsible for the different laser lines that continuously can be tuned within the range of the dye used.

1.6.4 Diode Laser (Semiconductor Laser)

Hall and his team at General Electric were the first to demonstrate the emission of a semiconductor laser diode in 1962 [9].

Laser diodes are formed by doping very thin layers on the surface of a crystal wafer to produce an *n-type* region (negative, increase of negative free charges – electrons) and *p-type* region (positive, increase of free positive charges – holes), one above the other, resulting in a *p–n* junction. Applying a forward electrical bias causes the two species of charge carriers, holes, and electrons, to be injected from both sides of the *p–n* junction into the depletion zone, situated in the centre of the *p–n* junction. Holes are injected from the *p*-doped semiconductor and electrons from the *n*-doped semiconductor (see Fig. 1.27). Recombination or annihilation of both charges results in a spontaneous emission of a photon, with energy equal to the difference between the electron and hole states involved.

The difference between the photon-emitting semiconductor laser and conventional diodes lies in the use of a different type of semiconductor. Photon-emitting semiconductors are the so-called *direct bandgap* semiconductors. These semiconductors are compound semiconductors, in contrast to silicon and germanium, which are single-element semiconductors that do not emit photons. Compound semiconductors have crystalline Structures that are virtually-identical to silicon or germanium but use alternating arrangements of two different atomic species in a checkerboard-like pattern. Such materials are gallium arsenide, indium phosphide, gallium antimonide and gallium nitride.

In the absence of lasing, holes and electrons can coexist in proximity to one another, without recombining,

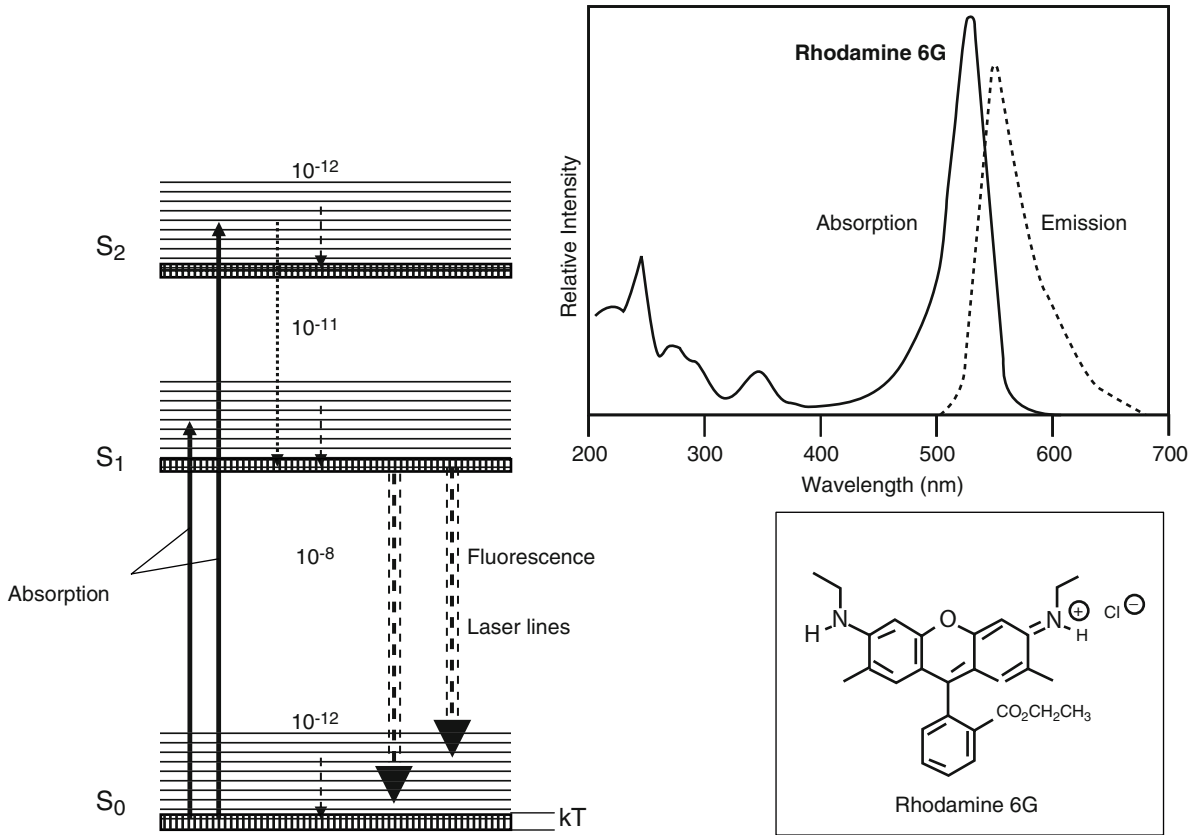

Fig. 1.26 Scheme of a dye laser. Inserts show the structure of rhodamine 6G (*bottom*) with absorption and emission spectra (*top*)

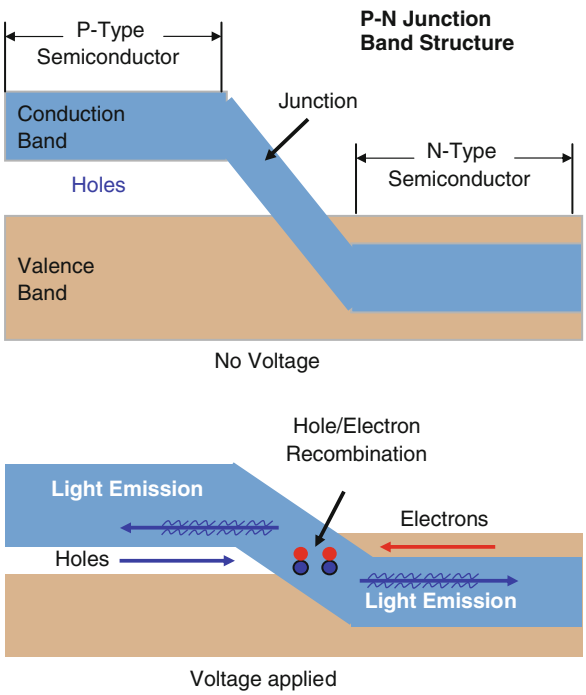

Fig. 1.27 Band gap structure of laser diodes

for a certain time, termed the "upper-state lifetime" or "recombination time," about a nanosecond, before they recombine. A nearby photon with energy equal to the recombination energy can cause recombination by stimulated emission. This generates another photon of the same frequency, travelling in the same direction, with the same polarisation and phase as the first photon. This stimulating emission causes light amplification in the *p*–*n* junction region proportional to the number of electrons and holes being injected.

A simple form of a laser diode consists of an optical waveguide as the optical cavity, made on the crystal surface, such that the light is confined to a relatively narrow line (see Fig. 1.28). When the two ends of the crystal are cleaved to form perfectly smooth, parallel edges, they form a Fabry-Perot resonator. The laser diode will start to lase when the losses (spotaneous emission, absorption, incomplete reflection) are surpassed by the stimulating emission.

Laser diodes are very efficient, with an electrical current to light conversion of up to 60%. Therefore, they are well suited for medical applications because they

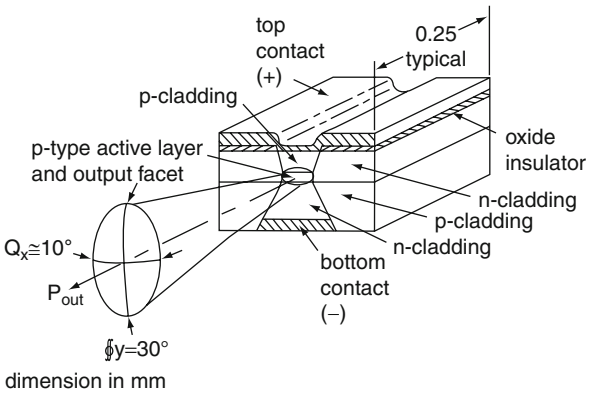

Fig. 1.28 Schematic drawing of a laser diode with asymmetric light emission. Emitting surface is about 1 µm high and 100 µm wide

are very powerful (up to 100 W), they are small devices, and they are flexible in wavelength. Laser diodes are available from the UV spectrum (for chromophore excitation) into the visible spectrum until the near-IR spectrum for surgical applications.

Laser diodes with a single emitter, as demonstrated in Fig. 1.28, may have an optical output of 10 to 40 W. Peltier elements are normally integrated to cool the diodes. Even higher power is obtained by diode bars, where 20–50 single emitters, 100 µm broad, are aligned in one stripe with a fill factor of 50%. Such bars can be mounted one above the other to form a stack of several 100 W output power.

Take Home Pearls

- New developments in laser technology provide higher efficiency in laser light generation and miniaturisation to improve the handling in medical applications.
- Laser light is now available in the range of UV to far IR.
- According to the needs of specific applications, the radiation of laser light can be modulated from cw to femtosecond pulses.
- Experienced dermatologists have now the possibility to select the optimal laser wavelength and pulse regime.

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Laser-Tissue Interactions

2

Rudolf Steiner

Core Messages

- Understanding laser-tissue interactions and using the laser in an optimal way are the most important messages in this chapter.
- The wavelength-dependent penetration depth of laser light into tissue determines heat flow and the thickness of the zone of necrosis.
- The concept of photothermolysis, introduced by Rox Anderson, improved specificity of laser-tissue interactions.
- Thermal lasers are used for tissue coagulation and vaporisation.
- For tissue ablation, high absorption of the laser light by the tissue is necessary, as is high power density of the laser pulse (>100 kW/cm²).
- Keep in mind that the shorter the laser pulse or the laser irradiation on the same spot, the smaller will be the zone of necrosis.
- Consider possible acoustic side effects with short and ultrashort laser pulses.

2.1 Optical Properties of Tissue

To understand the various modalities of laser-tissue interaction, it is necessary to get an overview of how photons penetrate biological tissue and how physics dominates their behaviour. When photons strike the surface of the tissue, because of the refractive index change, a portion (4–10%) of the photons are reflected according to the angle of incidence. Photons penetrating the surface initially are refracted, obeying the law of Snellius, which states that photons entering a medium with a higher refractive index are refracted towards the vertical axis to the surface (Fig. 2.1). The refractive index of tissue (n_{tissue}) is ~1.4. Snellius' law states:

$$\frac{\sin\alpha_1}{\sin\alpha_2} = \frac{n_2}{n_1} = n_{12}.$$

In the tissue, the photons may be scattered, changing their direction of flight according to the probability function expressed as the anisotropy factor, g, or absorbed, exciting the absorbing molecule by an electronic transition.

2.1.1 Absorption

The energy states of molecules are quantized; therefore, absorption of a photon takes place only when its energy, $E=h\nu$, corresponds to the energy difference between such quantized states.

Absorption of a photon by a chromophore causes either a quantized change in the distance between charges (electron transition, ultraviolet or visible spectrum; Fig. 2.2) or a quantized change of vibrational modes of the molecule (vibration transition, near infrared [NIR]; Fig. 2.3).

Absorbing molecular components of the tissue are porphyrin, haemoglobin, melanin, flavin, retinol, nuclear acids, deoxyribonucleic acid (DNA)/ribonucleic acid (RNA), and reduced nicotinamide adenine dinucleotide,

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_2,

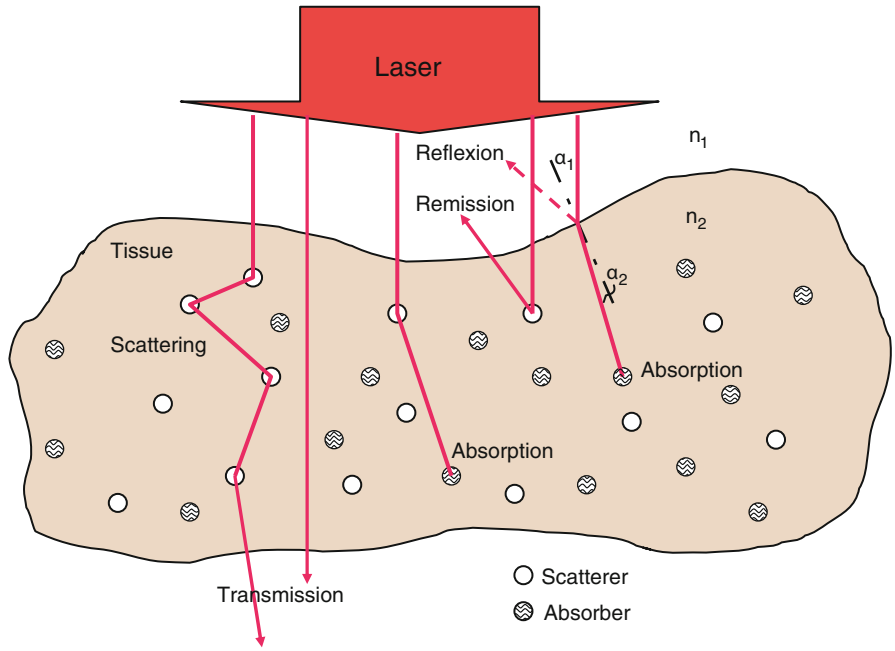

Fig. 2.1 Optical behaviour of a tissue layer during irradiation with laser light

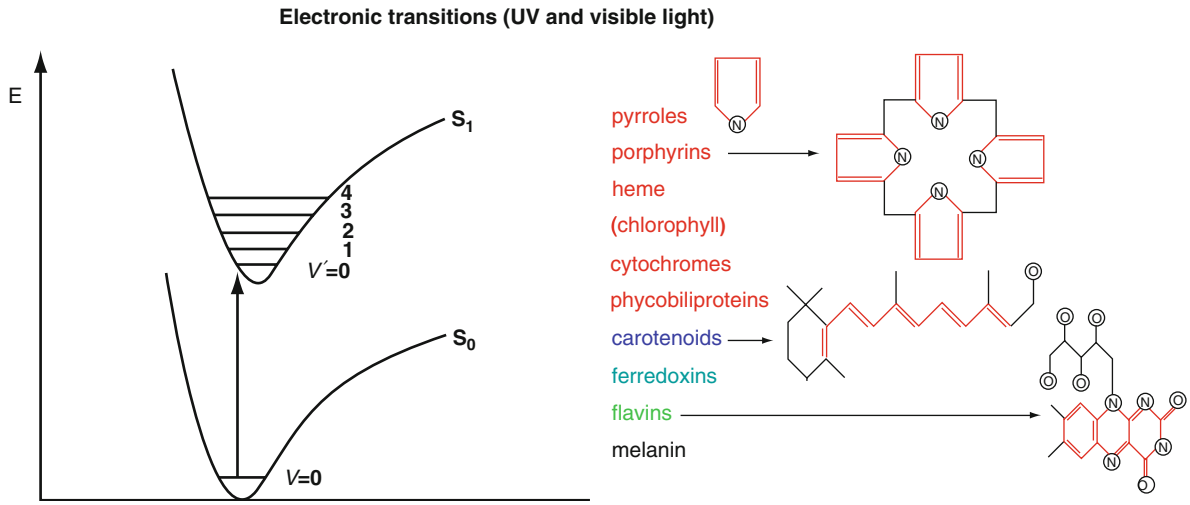

Fig. 2.2 Scheme of electronic excitation after photon absorption and a list of some chromophores in the tissue with the chemical structure. *UV* ultraviolet

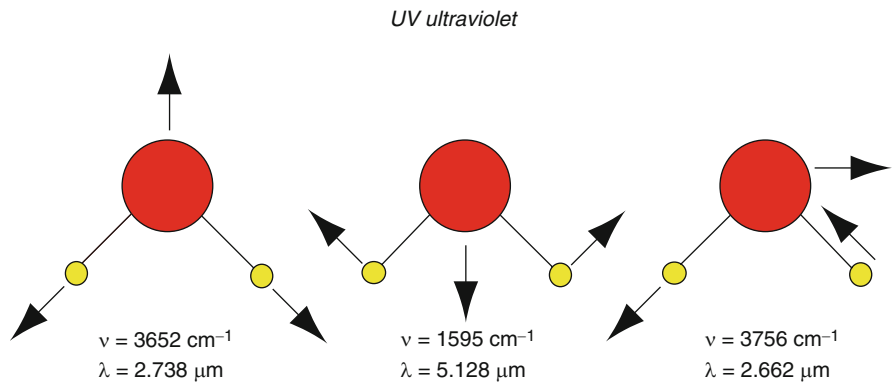

Fig. 2.3 Vibration transitions of a water molecule with its absorption bands

where electronic transitions are excited, leading to discrete and intense (broad) absorption bands. In the NIR and mid-infrared (MIR) region, tissue absorption is dominated by water absorption, with the maximum at 3 μm. The coefficient μ_a (cm^{-1}) characterizes the absorption. The inverse, l_a, defines the penetration depth (mean free path) into the absorbing medium.

To understand the mechanism of absorption, one can imagine a chromophore with a geometrical cross-section of size A (cm²) being placed in a parallel laser beam (Fig. 2.4). The shadow it creates is the effective cross-section σ_a (cm²), which in most cases is smaller than the geometrical cross-section A. When there are a lot of chromophores in a solution with volume density ρ_a (cm^{-3}), then the absorption coefficient is $\mu_a = \rho_a \sigma_a$ (cm^{-1}).

Chemists normally use Beer's law when they calculate the transmission of light through a cuvette of a dimension, d, filled with absorbing liquid. Then the expression for the transmission, T, is

$$T = I / I_0 = 10^{-\varepsilon c d} = 10^{-\rho}$$

where:

- ε: molar extinction coefficient [L/mol·cm]
- c: concentration of chromophores [mol/L]
- l: optical path (cm)
- ρ: optical density (OD) or extinction

Physicists, however, describe the transmission, T, as

$$T = I / I0 = \exp(-\sigma_a N_a l) = \exp(-\mu_a l),$$

where:

- σ_a: effective cross-section of absorption (cm²)
- N_a: density of the absorbing molecules (cm^{-3})
- l : optical path (cm)
- μ_a: absorption coefficient (cm^{-1})

The absorption spectra of different chromophores of biological tissue and water are plotted in Fig. 2.5.

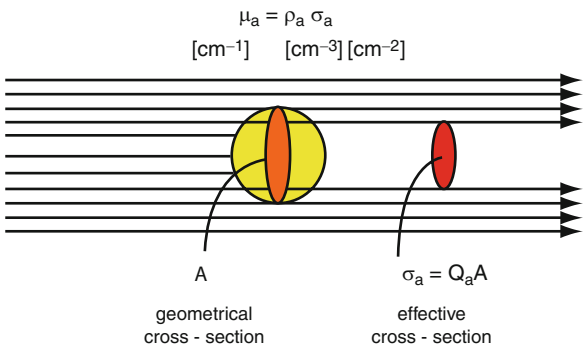

Fig. 2.4 Definition of the absorption coefficient by the cross-section of chromophores and their volume densities

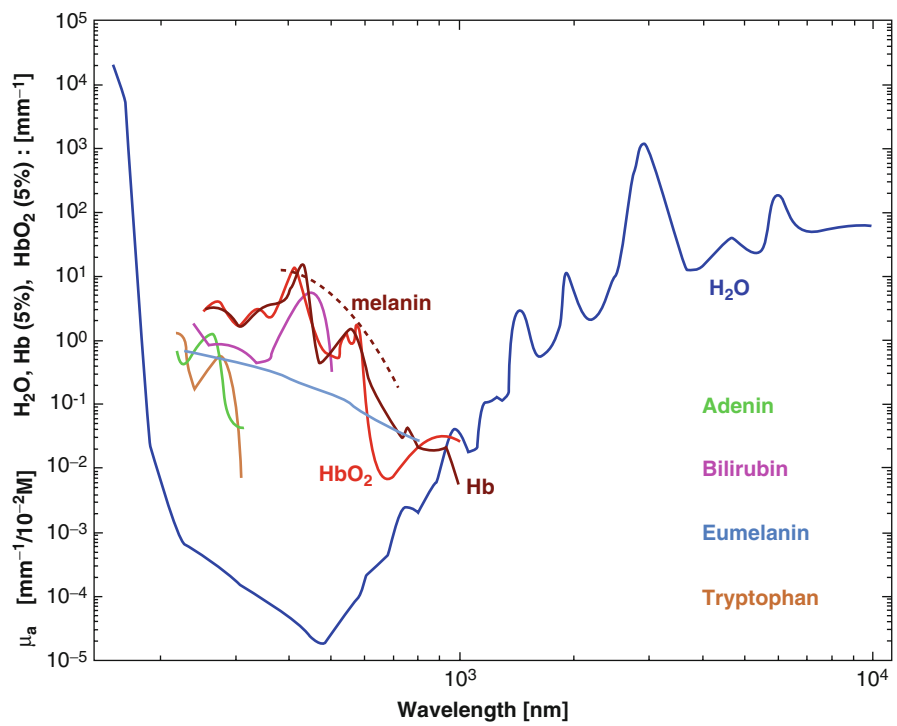

Fig. 2.5 Absorption spectra of chromophores in biological soft tissue

2.1.2 Scattering

The scattering behaviour of biological tissue is also important because it determines the volume distribution of light intensity in the tissue. This is the primary step for tissue interaction, which is followed by absorption and heat generation. Scattering of a photon is accompanied by a change in the propagation direction without loss of energy. Scattering structures of the tissue can be *macroscopic* like muscle fibres, skin layers, or dentin tubules; *microscopic* like cells or intracellular structures; and even *sub-microscopic*, taking into account macromolecules or nanoparticles.

According to the size of the scattering structure, one has to distinguish between Rayleigh scattering, $d << \lambda$, and Mie scattering, $d \geq \lambda$. Scattering of tissue is always a combination of Rayleigh and Mie scattering (see Fig. 2.6), depending on what structures are dominant. Rayleigh scattering is rather isotropic, only depending on the polarisation and the wavelength. The scattering cross-section is inverse to λ^4, which makes the sky "blue." The equation for Rayleigh scattering is:

$$Q_s = \frac{128\pi^4 a^4}{3\lambda^4}\left|\frac{n_s^2 - n^2}{n_s^2 + 2n^2}\right|.$$

Mie scattering, near-field as well as far-field, can be calculated exactly with a Monte Carlo simulation (MCS). Forward scattering is pronounced and is demonstrated in Fig. 2.7, which gives an example of the scattering behaviour of a water droplet of 10 µm in size at a wavelength of 650 nm. Because of the large size of the droplet, one gets interference of scattered light from different locations within the droplet. This results in intensity maxima when measuring the angle-resolved scattering.

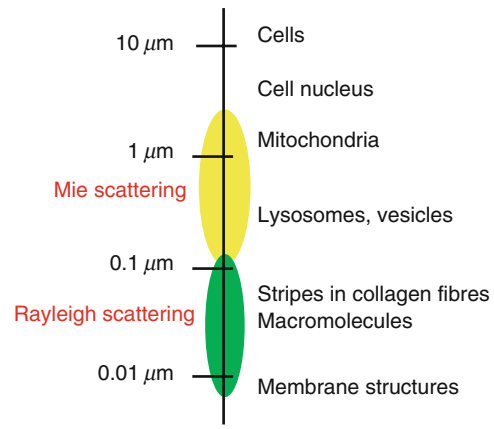

Fig. 2.6 Rayleigh and Mie scattering of tissue structures

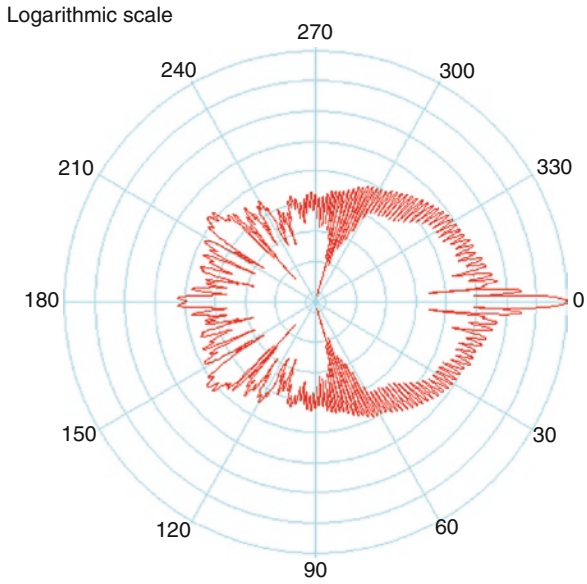

Fig. 2.7 Mie scattering of a water droplet that is 10 µm in size at $\lambda = 650$ nm

The scattering, similar to absorption, is expressed by the scattering coefficient μ_s (cm^{-1}). The inverse parameter, $1/\mu_s$ (cm), is the mean free path length until a next scattering event occurs. As a rule of thumb, one can say that for red light in the human skin, the mean free path length for absorption is 50 µm, and the mean free path length for scattering is 5 mm. This means that, statistically, a photon is scattered 100 times until it is absorbed.

We have seen from Mie scattering that scattering is not isotropic. Forward scattering is predominant in biological tissue. This characteristic is described by the anisotropy factor g. g can have absolute values from 0 to 1, from isotropic scattering ($g = 0$) to forward scattering ($g = 1$). Negative values for g stand for backward scattering. In tissue, g can vary from 0.8 to 0.99.

> Anisotropy factor g: $0 \leq g \leq 1$. $g = 0$: isotropic scattering; $g = 1$: forward scattering.
> Taking into account the g value, a reduced scattering coefficient, μ_s' (cm^{-1}), is defined as
>
> $$\mu_s' = \mu_s(1-g).$$

In MCSs, one has to consider a probability function for g in what direction a photon is scattered. The Henyey-Greenstein phase function [7] $p(\theta)$ is often used to describe the angular distribution of light scattered by tissue. It is characterized by the average cosine <cos θ>

of the scattering angle, θ. Since the Henyey-Greenstein phase function is a probability density function, it is normalized to an area of 1 (Fig. 2.9). This model has been applied to numerous situations, ranging from the scattering of light by biological tissue to scattering by interstellar dust clouds. The angular distribution of scattered light is given by

$$p(\theta) = \frac{1}{4\pi} \frac{1-g^2}{(1+g^2-2g\cos(\theta))^{3/2}}.$$

The parameter g characterizes the normalized distribution. For some values of g, Fig. 2.8 shows the probability of scattering from $-180° \leq \theta \leq +180°$. When g approaches the value 1, then the function is very peaked around $\theta = 0$. In case of isotropic scattering, $g = 0$, there is a constant value of $1/4\pi$ over all scattering angles θ.

The sum of μ_s and μ_a is called the total attenuation coefficient μ_t (cm^{-1}):

$$\mu_t = \mu_s + \mu_a \ (cm^{-1}).$$

Measuring the optical constants of biological tissues is not a simple task. In a configuration where a collimated beam hits a tissue sample of defined thickness and only the transmitted photons (ballistic photons) reach the detector, the attenuation coefficient μ_t can be measured.

In general, the optical parameters of tissue like μ_a, $\mu_{s,}$ and g cannot be measured directly. Very complex measuring and evaluation processes are needed to determine such parameters. When a slice of tissue is placed between two integrating spheres (Ulbricht spheres), then the total transmitted and diffusely reemitted radiation can be measured. MCS helps to extract the values of the optical parameters by iteration procedures.

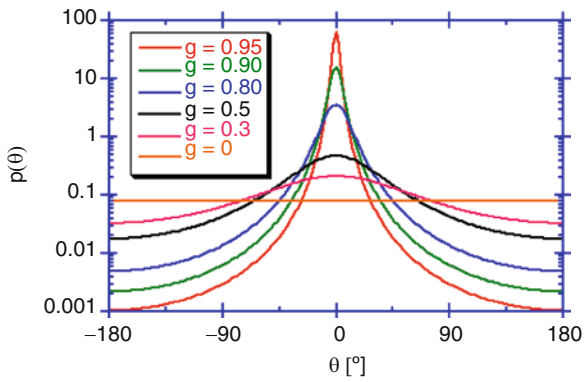

Fig. 2.8 Henyey-Greenstein probability function for different g values

Some other expressions are helpful to describe the optical properties of biological tissue. The fraction of the scattering μ_s over the total attenuation μ_t is called Albedo a:

$$Albedo\ a = \mu_s/(\mu_s + \mu_a)$$

Whereas the effective damping coefficient μ_{eff} is defined as:

$$\mu_{eff} = (3\mu_a(\mu_a + \mu_s'))^{1/2} \ (cm^{-1}).$$

The inverse value $1/\mu_{eff}$, is called the effective penetration depth, d_{eff}, of light into tissue:

$$d_{eff} = 1/\mu_{eff} \ (cm),$$

and the effective mean free path length, X_{eff}, is as follows:

$$X_{eff} = 1/(\mu_a + \mu_s')\,[cm].$$

The equation

$$I(d) \propto I_0 e^{-\sqrt{3\mu_a(\mu_a+\mu_s')}d} = I_0 e^{-\mu_{eff}d}$$

describes approximately the portion of the power of light or photon density, which is transported over a distance d. Photons may propagate undisturbed or may reach the detection surface element after multiple scatterings. If scattering is predominantly in a forward direction, then the transport (reduced) scattering coefficient μ_s' is considerably smaller than μ_s. Single photons arriving at the detector element may have passed a much longer path length (multiple scattering) than distance d.

Photon density penetration into tissue also can be described approximately by the diffusion

$$\frac{\partial}{\partial t}\rho(\vec{r},t) - Dc_m\Delta\rho(\vec{r},t) + \mu_a c_m \rho(\vec{r},t) = q_0(\vec{r},t).$$

With the diffusion constant D,

$$D = \frac{1}{3(\mu_a + \mu_s')}$$

No analytical solution exists, however, for the transport equation modelling the light penetration into biological tissue. Therefore, in most cases, the MCS [18] has to be used to determine the photon distribution in the tissue. Programmes are available on and can be downloaded free from the Internet. MCS is also useful to model laser-tissue interactions. One example was published by Romero et al. [12].

Table 2.1 A summary of penetration depths in muscle tissue at different laser wavelengths

Wavelength (nm)	Penetration depth ($1/\mu_a$ [μm])	Effective optical penetration ($1/\mu_{eff}$ [μm])
193	≈10	≈1
308	50	6
532	830	240
1.064	2.500	1.900
2.060	286	250
2.940	3	3
10.600	17	17

The decision of the appropriate model to calculate the photon distribution and penetration into tissue depends on the values for μ_a and μ_s' [17]. Several cases can be distinguished:

$\mu_a \gg \mu_s'$: Lambert-Beers' law ($\lambda < 300$ nm and $\lambda > 2{,}000$ nm)
$\mu_a \ll \mu_s'$: the diffusion approximation is valid ($650\text{ nm} < \lambda < 1{,}150$ nm)
$\mu_a \approx \mu_s'$: the transport equation with MCS is valid ($300\text{ nm} < \lambda < 650$ nm; $1{,}150\text{ nm} < \lambda < 2{,}000$ nm).

Table 2.1 summarizes the penetration depth in muscle tissue at different laser wavelengths. The mean free path due to absorption and the effective penetration have been considered [3].

It is possible to measure the light distribution inside tissue by introducing a miniaturized probe of 100-μm diameter into the tissue via the hollow needle of a syringe. The measurements confirm the theoretically derived phenomenon that the light intensity directly below the tissue surface is enhanced by a factor of 2–4 as compared with the intensity of the incident beam [15]. The increased fluence rate is caused by scattered photons overlapping with the incident photons. Another observation is that, due to the scattering effect, the penetration depth depends on the irradiated area. Consequently, the penetration depth will double if, for the same irradiance, the beam diameter increases from 1 to 5 mm. For dermatological applications, this effect has to be taken into account. For deep light penetration when treating port wine stains or for hair removal, 10- to 15-mm spot diameters of the laser are recommended.

The measured intensity inside the tissue is called the *fluence rate*. It is the power absorbed by a small sphere divided by the cross-section of the sphere: $A = \pi R^2$.

Fluence rate: $F = P/A$ (W/cm²)

The depth of penetration of laser light into tissue is greatest in the wavelength range of 700–900 nm (optical window). Blood, water, and melanin are the main absorbing components in the tissue (Fig. 2.5). Therefore, Ar^+ lasers, dye lasers, and diode lasers effectively interact with blood, the Alexandrite laser with melanin, and MIR lasers with the water content of the tissue.

2.2 Reaction Mechanisms

The first systematic presentation of the reaction mechanisms of lasers with tissue was by Boulnois [3] in 1986 (Fig. 2.9). Another important finding was the "selective photothermolysis" (SP) by Anderson and Parish in 1983 [1, 2]. SP is the damage confined to the specific tissue structures by selection of laser wavelength, regulation of pulse duration, and repetition rate.

In the following section we consider the different laser-tissue interaction mechanisms.

2.3 Non thermal, Chemical Reactions

In low-dose irradiation of living tissue, photons may have an influence on the proliferation of cells. Much literature has been published in the past about the interaction of photons (633-nm helium-neon laser or an 820-nm diode laser) with in vitro cell cultures [11] and wound healing by biostimulation. Most of the results, however, were not verified or generated under controlled condition.

2.3.1 Biostimulation

It is well accepted that the energy of photons when absorbed in cells or tissue may affect cellular metabolism and signalling pathways. A review is given by Hawkins-Evans and Abrahamse [6].

Molecular targets can be cytochrome c oxidase (with absorption in the NIR) or photoactive porphyrins. Cellular targets are mitochondria with the effects of increased adenosine triphosphate production, modulation of reactive oxygen species, and initiation of cellular signalling [5], as illustrated in Fig. 2.10.

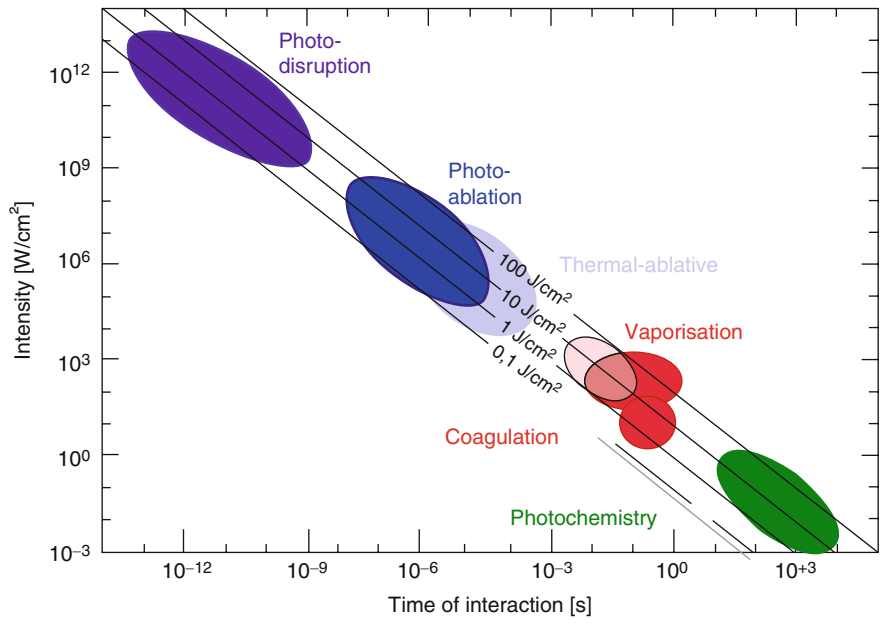

Fig. 2.9 Plot of laser-tissue interaction mechanisms over time of interaction. Modified from Boulnois JL. Photophysical processes in recent medical laser developments: a review. Lasers Med Sci. 1986;1:47–66 [3]

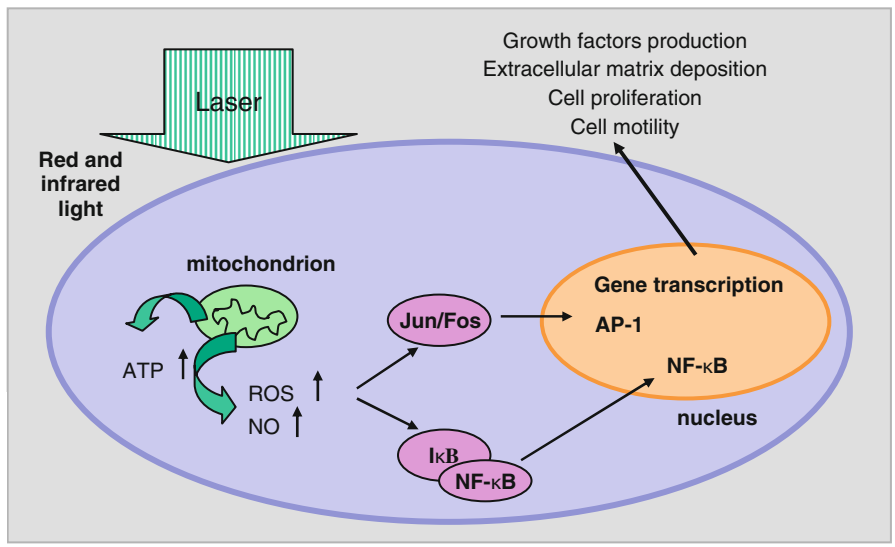

Fig. 2.10 Cell signalling pathways induced by low-level laser therapy. *ATP* adenosine triphosphate, *ROS* reactive oxygen species, *NO* nitric oxide

The results may be:

- Increased cell proliferation and migration (particularly by fibroblasts).
- Modulation in the levels of cytokines, growth factors, and inflammatory mediators.
- Influence on the activity of second messengers (cyclic adenosine monophosphate, Ca^{2+}, nitric oxide).
- Increased tissue oxygenation.
- Increased healing of chronic wounds and improvements in injuries and carpal tunnel syndrome, pain reduction, and impact on nerve injury.

In all cases, the light dose has to be selected carefully because more light is not always better. Spectral regions that show the highest effect of activation are around 633, 690, 820 and 900 nm.

2.3.2 Photodynamic Therapy

Photodynamic therapy (PDT) uses a photochemical reaction with three components: light for activation, sensitizers, and molecular oxygen. The sensitizer molecules

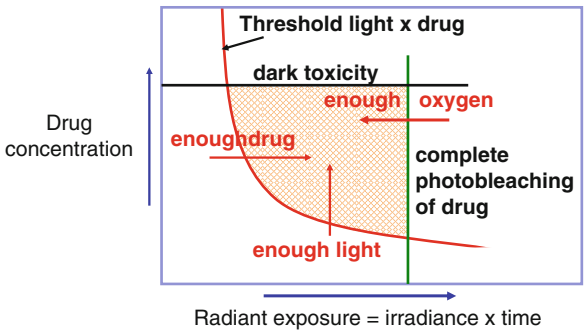

Fig. 2.11 Treatment window for photodynamic therapy

are accumulated in the target cellular structure. They absorb the photons and become excited. After energy transformation from a singlet state to a long-lived triplet state by intersystem crossing, the energy is transferred to oxygen. The excited oxygen (singlet oxygen or radical) destroys the cell. This phototoxic reaction is used in tumour treatment but also in the treatment of precancerous stages or nonmalignant lesions. Sensitizers are also fluorescent. Therefore, they are used for tumour diagnosis and imaging, for example, to visualize bladder tumours in early stages. PDT is described in detail in Chap. 28 of this book.

Here, it is illustrated in the graph of Fig. 2.11 that PDT has a treatment window depending on drug concentration, dark toxicity, radiant exposure of laser light, and sufficient oxygen supply. Therefore, dosimetry is very important for a successful treatment to control all these parameters, especially in deeper layers of the tissue. Sensitizer concentration accumulated in the target tissue and photobleaching during irradiation can be monitored by increase or decrease of the fluorescence intensity.

2.4 Thermal Reactions

The energy of laser irradiation is transferred into heat due to the absorption of the photons by tissue components, DNA/RNA, chromophores, proteins, enzymes, and water. According to the degree of heating, stepwise and selective thermal damage can be achieved:

42–45°C: beginning of hyperthermia, conformational changes, and shrinkage of collagen;
50°C: reduction of enzymatic activity;
60°C: denaturation of proteins, coagulation of the collagens, membrane permeabilisation;
100°C: tissue drying and formation of vacuoles;
>100°C: beginning of vaporization and tissue carbonisation;
300–1,000°C: thermoablation of tissue, photoablation and disruption.

The corresponding pathologic analysis of photothermal effects is well described by Thomsen [16]. Examples of coagulation and tissue vaporization are presented in Fig. 2.12.

The laser irradiation that is absorbed by the tissue will heat the tissue, and the temperature increase, ΔT, is given by the absorbed thermal energy per unit volume, Q (J/cm³), divided by the density, ρ (g/cm³), and the specific heat, c_w [J/g°K]:

$$\Delta T = Q/\rho c_w \ [°K]$$

Thermal diffusion is responsible for heat flow into the tissue. If the exposure time with a laser pulse, t_p, is short compared to the diffusion time, t_d, then we have *"thermal confinement"* and the pulse energy is converted into heat [10, 13, 14] in a tissue volume determined by the inverse absorption coefficient, $1/\mu_a$, and the spot size, d. The diffusion time is

$$t_d = 1/\kappa\mu_a^2 \ [s].$$

The thermal diffusion coefficient κ (m²/s) is determined by the thermal conductivity, Λ [W/m°K], divided by the density and specific heat:

$$\kappa = \Lambda/\rho c_w \ (m^2/s).$$

Table 2.2 summarizes the thermal coefficients for different biological tissue materials.

Thermal diffusion and the extent of tissue necrosis are related. With low laser power and long irradiation time, thermal necrosis is large. Shortening the laser application time reduces the time for thermal diffusion, and the zone of necrosis becomes smaller. Minimum thermal necrosis is reached when the irradiation time is equal to the thermal diffusion time or thermal relaxation time. Nevertheless, it will not be smaller than the wavelength-dependent penetration depth of the laser light into the tissue.

Thermal damage of the tissue is described by the Arrhenius rate equation. The consequence of this equation is that the threshold for tissue damage depends on the laser power and the application time. This threshold can be reached with high laser power in a very short time, resulting in a higher temperature, or with low power but long irradiation, where the threshold is reached with lower temperature. Figure 2.13 explains this relation.

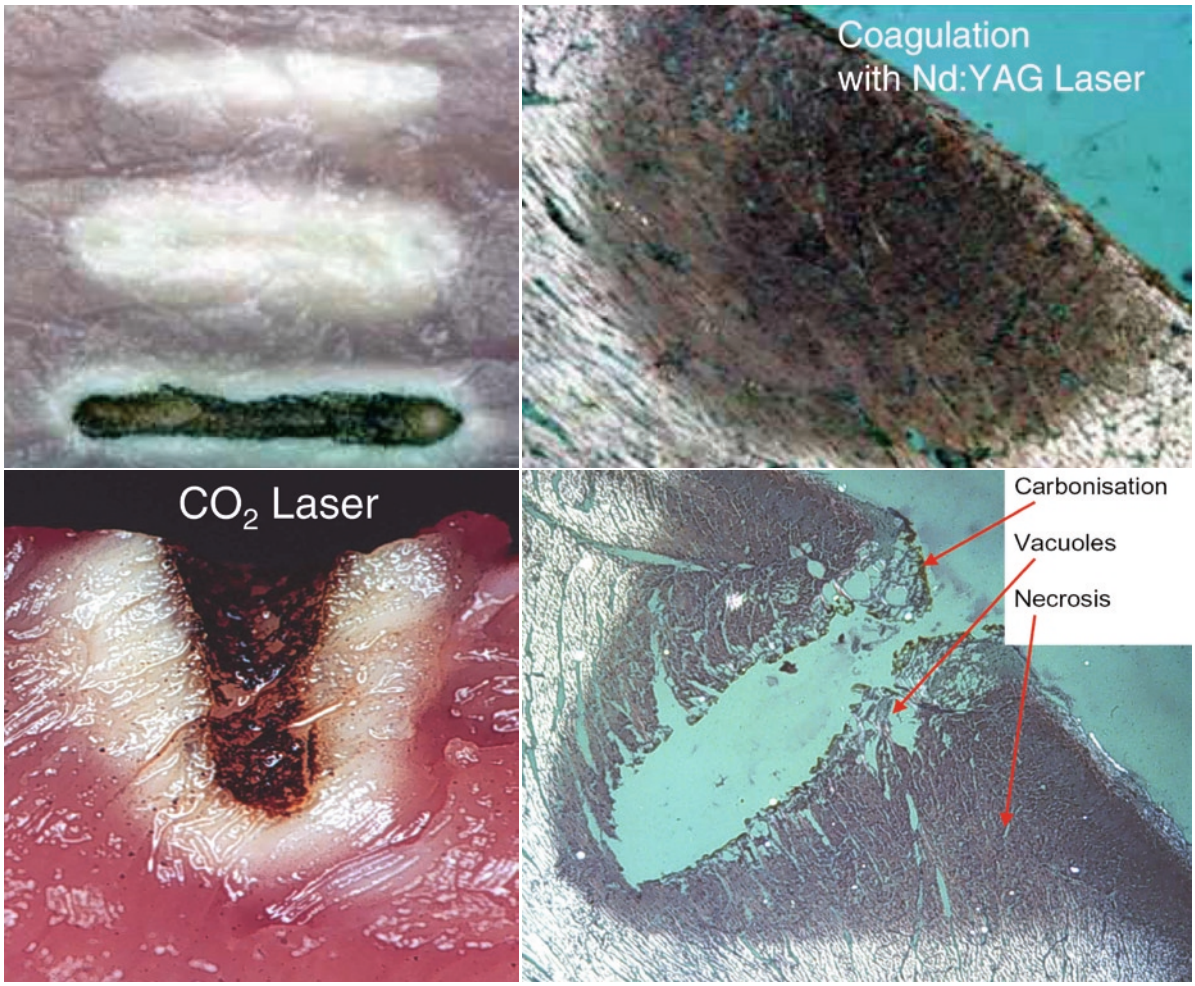

Fig. 2.12 Tissue effects of coagulation and vaporization with corresponding histologies. CO_2 carbon dioxide, *Nd:YAG*, neodymium-doped yttrium aluminium garnet

Table 2.2 Thermal constants for different biological tissues and materials

Material	Density ρ (g/cm³)	Water content (%)	c_w (J/g K)	Λ (W/m K)
Water	1,000	100	4.183	0.58
Blood	900	55	3.22	0.62
Fat	900	–	1.93	0.3
Cartilage	1,225	60–70	3.06	0.36
Liver	1,200	80	3.42	0.44
Aorta	1,000	80	3.76	0.48
Copper	8,933	–	0.383	384
Diamond	3,510	–	0.502	33,000

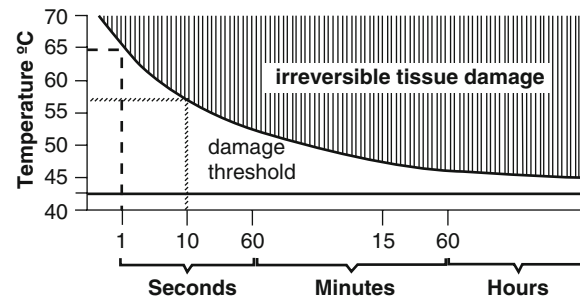

Fig. 2.13 Time-temperature characteristic of tissue damage. The threshold for tissue damage at different temperatures depends on laser power and application time. A 1-s pulse reaches the threshold at 65°C, whereas a 10-s pulse reaches the threshold at 57°C

Example:

The carbon dioxide laser is used in microsurgery for cutting tissue. We want to know the cutting depth by vaporization of the tissue with $p = 60$ W, focused to a spot size diameter of 0.4 mm and moved with a velocity of 2 cm/s [4]. Let E_c be the energy for heating the tissue to the boiling point and E_v the latent energy for vaporization per unit volume.

$$E_c = \rho c_w \Delta T \,[\mathrm{J}],$$

where ρ is the density (here, 1,000 kg/m³ for water), c_w is the specific heat (4,200 J/kg°K), and ΔT is the difference between the boiling point and body temperature (~63°K).

$$E_v = \rho L_v,$$

where L_v is the latent heat for evaporation (2.3×10^6 J/kg). The evaporated volume per unit time is then

$$V = P / \left(E_v + E_c\right) = d \cdot v \cdot d_{cut}.$$

Hence,

$$d_{cut} = P / dv\left(E_v + E_c\right).$$

With the parameters above for laser power, P, spot size, d and velocity, v, one calculates a cutting depth (d_{cut}) of 3 mm.

This value, of course, is overestimated because we neglected reflection, tissue components other than water, reabsorption by evaporating material, and energy dissipation. Nevertheless, it gives an estimation of the laser reaction on cutting tissue.

2.4.1 Relaxation Time

When the thermal diffusion length, L, is equal to the optical penetration depth, then we have the relation:

$$L = \left(4\kappa\tau\right)^{1/2},$$

where κ is the diffusivity with its value for water of 1.4×10^{-3} cm²/s. When $t = 1$ s, then $L = 0.8$ mm. Taking the optical tissue penetration $1/\mu_a$ as characteristic dimension, we get for the relaxation time:

$$\tau_R = 1/(4\mu_a \kappa).$$

For a carbon dioxide laser, wavelength 10.6 μm, with $\mu_a = 500$ cm^{-1} and $\kappa = 10^{-3}$ cm²/s, one gets a relaxation time (τ_R) of 1 ms.

2.5 Tissue Ablation

The preconditions for tissue ablation are high absorption and very short laser pulses. Analogous to the *thermal confinement,* one can define a *stress confinement* when tissue is heated up so fast that the pulse duration is shorter than the propagation time, $t_{m,}$ of the stress wave through the heated volume. The internal stress is described by the *Grüneisen coefficient*, Γ:

$$\Gamma = \alpha/(\rho c_w \kappa_T),$$

where α is the coefficient of thermal expansion, ρ is the density, c_w is the specific heat, and κ_T is the isothermal compressibility. The propagation time, t_m, of the stress wave through the heated tissue volume is

$$t_m = 1 / \left(c_a \mu_a\right)[\mathrm{s}],$$

where c_a is the speed of sound in the medium. When the stress wave with velocity c_a cannot leave the heated volume during the laser pulse, then it is removed with the ablation of the material and the surrounding tissue is not damaged.

For the photoablation process, a simple model has been derived to calculate the ablation depth [8, 17]. It is called the "blow-off" model. To ablate tissue, an ablation threshold must be surmounted. The ablation depth, d, per laser pulse is determined by the pulse energy until a saturation threshold. The assumption is that there exists a threshold $F_s(d)$ for the energy density. Below this threshold, no material is removed.

Ablation threshold: $F_s(d) = F_0 \exp(-\mu_a d)$.

The solution for the ablation depth, d, can simply be derived from this expression:

$$d = \left(1/\mu_a\right) \ln\left(F_0 / F_s\right).$$

Figure 2.14 explains graphically the threshold behaviour, and Fig. 2.15 gives a demonstration of the ablation process with supersonic particle ejection and the ablated crater in dental hard tissue. Only UV lasers (ArF excimer laser) and pulsed MIR lasers have such high tissue absorption that they are effective ablating lasers.

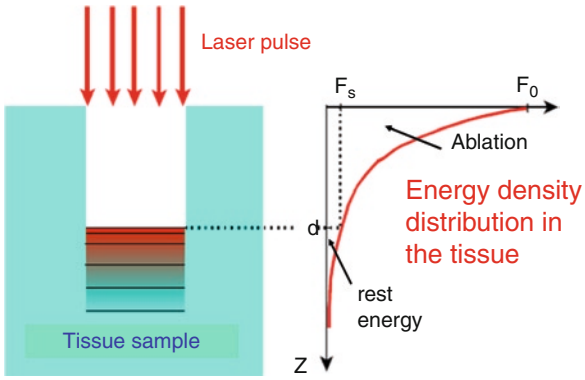

Fig. 2.14 Schematic representation of the blow-off model

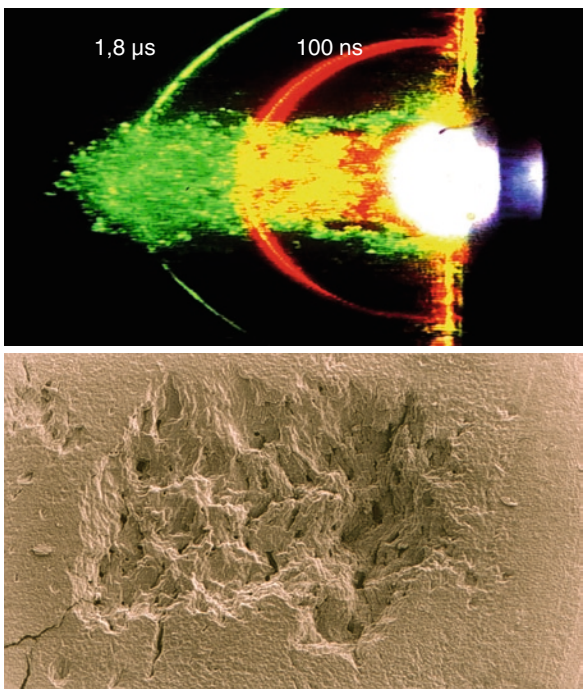

Fig. 2.15 Picture of the ablation process (*top*) and the crater in hard dental material (*bottom*)

The threshold behaviour of highly absorbed laser radiation, e.g., the erbium-doped yttrium aluminium garnet (Er:YAG) laser with a 2,940-nm wavelength, can be used to modulate the thickness of necrosis in soft tissue. Operation of the laser in normal ablation mode does not produce effective thermal necrosis; therefore, no coagulation can stop bleeding. The advantage is that the healing is fast with minimal scarring. However, for precise superficial surgical interventions, it would be helpful if the Er:YAG laser also could coagulate the tissue and stop bleeding. This is possible by applying between the ablating laser pulses a series of high-frequency sub-threshold laser pulses. The energy of such pulses is below the ablation threshold and therefore is transferred into heat. The heat causes thermal necrosis. The thickness of the necrotic tissue layer can be modulated by the number of sub-threshold pulses. Some Er:YAG laser systems have such operation modes, which are well accepted for microsurgery procedures.

In Fig. 2.16, the addition of the laser pulse heating effect is demonstrated. Certain levels of temperature can be attained, producing thermal necrosis.

A good summary and overview of laser-tissue interaction is the graph in Fig. 2.17. Here, the duration of laser application of duration of laser pulses is plotted for different laser types and their corresponding depth of penetration of biological tissue. Areas are marked for normal thermal reactions, thermal confinement – the pulse duration is shorter than the thermal diffusion length or thermal relaxation time – and stress confinement for ultrashort laser pulses.

2.6 Photodisruption

Focused laser pulses in the nanosecond region (e.g., with a Q-switch neodymium (Nd):YAG laser), or with picosecond or femtosecond durations (titanium (Ti) sapphire laser) develop power densities of 10^{12} W/cm² and more. The electric field strength of this focused radiation is high enough to pull electrons out of the atoms, forming a plasma and producing an optical breakdown with shockwaves disrupting the tissue. The process of this photomechanical reaction is described in detail by Boulnois [3] and Vogel and Venugopalan [17].

Above a light intensity of 10^{11} W/cm², an increased and nonlinear absorption of the light occurs, accompanied by an intense white flash and an acoustic signal – an optical breakdown happens with plasma formation. Multiphoton absorption is responsible for the ionization of atoms. The effect is intensity dependent and scales with I^4. The free electrons are accelerated in the intense electromagnetic field (inverse Bremsstrahlung), and secondary electrons are produced through collision ionization (Avalange effect; see Fig. 2.18). The heated electrons and ions form the plasma of 15,000–20,000° K and a pressure of 20–60 bar. It follows

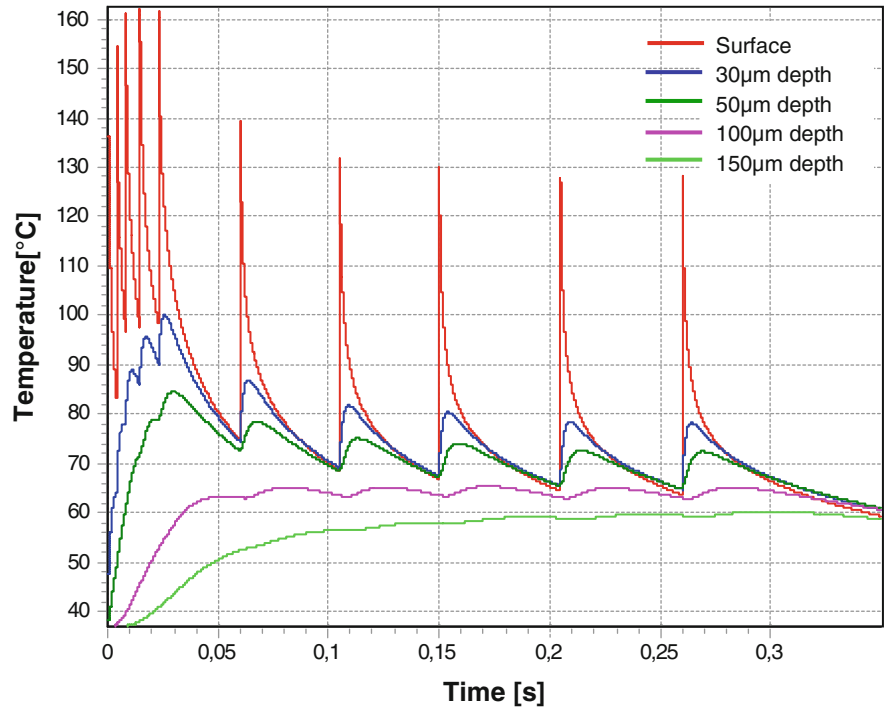

Fig. 2.16 Temperature profiles created by sub-threshold erbium-doped yttrium aluminium garnet laser pulses

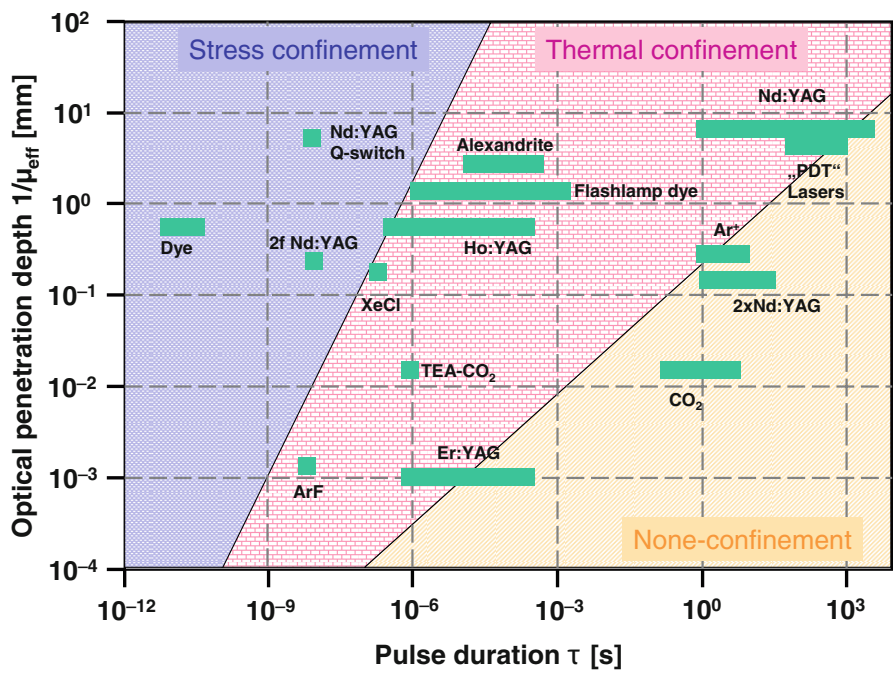

Fig. 2.17 Schematic of laser types, the corresponding tissue reactions, pulse duration, and optical penetration depth

a cavitation bubble of water vapour; the dimension of it depends on the pulse energy and pulse duration. The shorter the pulse, the smaller may be the energy to get an optical breakdown. Hence, the cavitation bubble also will be smaller, and the side effects will be reduced.

The length of the plasma, Z_{max}, created by a focused Gaussian beam, is determined by the Rayleigh length of the focus, Z_R, and the relation of the pulse intensity to the threshold intensity, I_0/I_{th}, for an optical breakdown.

Plasma length: $Z_{max} = Z_R \cdot (I_0/I_{th} - 1)^{1/2}$

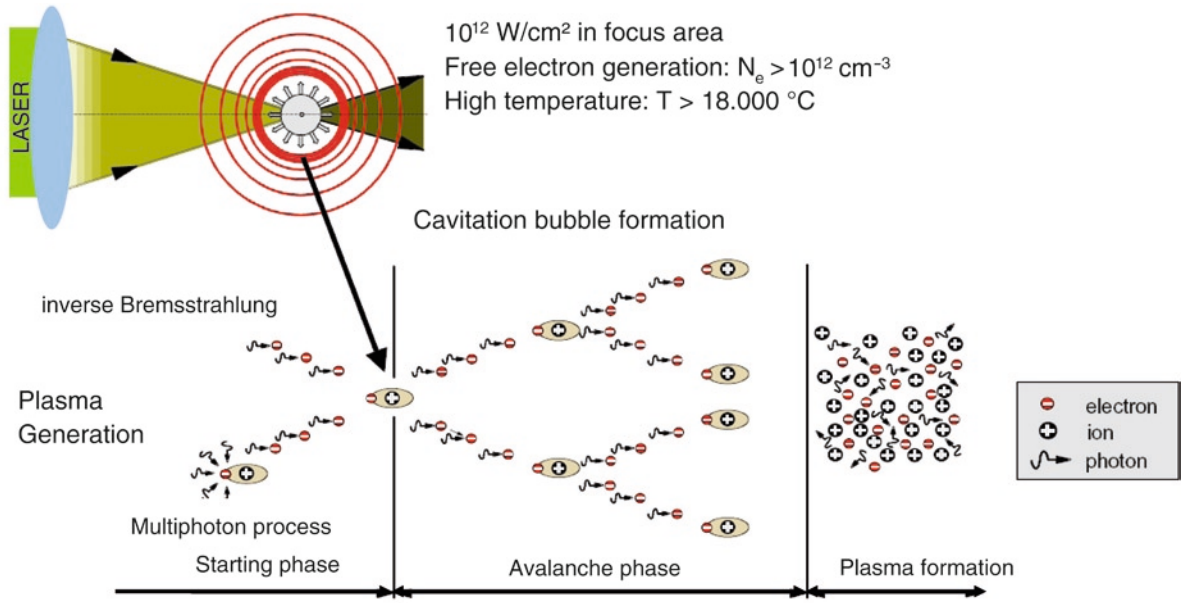

Fig. 2.18 Schematic presentation of the processes responsible for the optical breakdown generated by ultrashort laser pulses

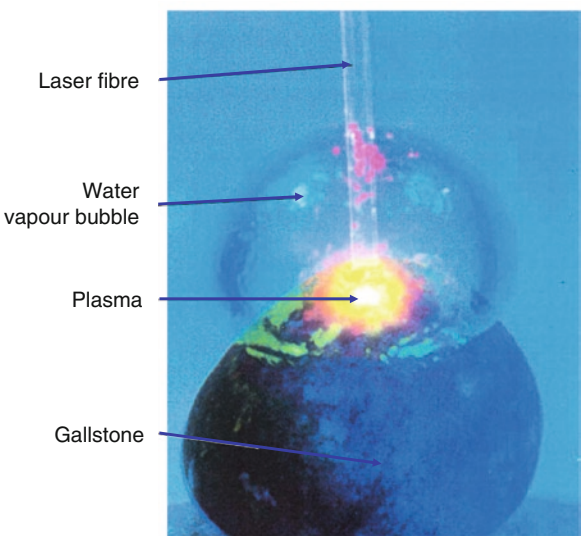

Fig. 2.19 Picture of an optical breakdown with plasma and cavitation bubble [9]

where Z_R is the Rayleigh length, $Z_R = \pi\omega_0^2/\lambda$, with beam waist ω_0 and λ the wavelength in the medium, corrected with the refractive index.

The example of a high-speed camera picture is taken from Ihler [9]. It shows the reaction of a picosecond laser pulse on a gallstone. The laser pulse is guided through a fibre to the stone. The plasma formation and the cavitation bubble are clearly visible. The bubble has its maximum dimension after about 300 µs, then it collapses, and normally a multiple rebound effect occurs (Fig. 2.19).

Medical applications of ultrashort laser pulses (100 fs, Ti:sapphire laser) are found in ophthalmology for cutting flaps of the cornea. Soft and hard tissue removal can be done very precisely, but the efficiency is not very high. Therefore, most applications of multiphoton absorption are in microscopy and tissue diagnostics.

Take Home Pearls

- Be sure to use a laser with the right wavelength, power or energy, and pulse regime for your specific application.
- Consider depth of penetration of the light into the tissue and the quadratic power density dependence with the distance (spot size).
- Take the zone of necrosis for blood coagulation into consideration.
- Less laser power is sometimes better to prevent uncontrollable side effects.
- With only one laser device you are limited in your dermatologic applications; do not try to extend it for other applications because you will fail.

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Intense Pulsed Light Technology

3

Karin Kunzi-Rapp and Rudolf Steiner

Core Messages

- Intense pulsed light (IPL) systems are high-intensity pulsed sources that emit polychromatic light in a broad wavelength spectrum, which can differ between flash lamps and manufacturers.
- IPL can be configured for different emission spectra by varying filtration, lamp type, or current density.
- The waveband of light emitted by IPL is chosen so that it has both the correct penetration depth and the optimal absorption by the target chromophore.
- The broad spectrum will be an advantage of IPL therapy if the parameters of energy, pulse duration, and emission spectrum are chosen in an optimal way.
- The clinical flexibility of the IPL device requires more expert knowledge than laser systems with restricted indications.

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3.1 Intense Pulsed Light Technology

Unlike lasers, intense pulsed light (IPL) systems are high-intensity pulsed sources that emit polychromatic light in a broad wavelength spectrum, which can differ among flash lamps and manufacturers. The xenon flash lamp is a gas-discharged, high-intensity lamp filled with xenon gas that produces bright light when an electrical current passes through the gas. These lamps work in a pulsed mode and convert electrical energy stored in capacitor banks into optical energy. The emitted broadband light is covering the spectrum from ultraviolet (UV) to infrared (IR). The light is filtered by various means to select wavelengths anywhere from the blue/UV through the far IR. However, the most common systems emit radiations between 400 and 1,200 nm, with cuton and cutoff wavelengths, depending upon the indications to be treated. In the short wavelength region of the spectrum, manufacturers use optical filters to cut off the UV and parts of the visible light, depending on the indication. Some of the IPL devices are equipped with a water filter system, which cuts off the wavelength in the absorption spectra of water above 950 nm to prevent thermal damage of the skin. The flash lamp includes mirrors surrounding the xenon lamp and is cooled by water circulating around the quartz envelope.

The flash lamp and the optical filter unit are integrated in the hand piece, and the light is usually coupled into the surface of the skin via a sapphire or quartz block (Fig. 3.1). Some IPL devices enhance the fluence of the therapeutic spectrum by transformation of the filtered unwanted short wavelengths into fluorescent light of a higher wavelength or by re-entry of the reflected light from the skin surface. To enhance patient safety, some modern “high-end” IPLs actively cool the

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DOI: 10.1007/978-3-642-03438-1_3, © Springer-Verlag Berlin Heidelberg 2011

Fig. 3.1 Example of an intense pulsed light (IPL) hand piece with the light emitting quartz block at the right side

surface of the skin. For a particular IPL system, either cryogen spray, forced refrigerated air, or the contact cooling may be integrated into the distal end of the hand piece.

Like lasers, the reaction mechanism of the IPL sources is based on the principle of selective photothermolysis that Anderson and Parrish described for the pulsed dye laser [4]. According to the thermal relaxation time, pulse duration has to fit the size of the target. The pulse durations of IPL are technically restricted to the millisecond range and should be lower than the thermal relaxation time of the target structure so that the surrounding tissue is not damaged. In addition to single pulses, higher fluences can be achieved by generating burst pulses. The intervals between the pulses can be set at values between 1 and 300 ms, which allows the epidermis to cool down between the pulses while heat is retrained in the larger targets like hair follicles or vessels. Short pulse durations in the nanosecond range that result in high light intensities, like those of Q-switch lasers, are impossible.

Along with the pulse duration, the shape of the pulse is essential. Because the energy is measured over the full length of the pulse, it is important that the pulse shape is as square as possible, with instant intensity over the whole pulse duration. For a pulse duration of more than 2 ms, the temperature obtained in the epidermis is proportional to the intensity. Therefore, a square pulse offers the lowest possible intensity for a given fluence and minimizes the risk of side effects such as skin burns [5]. Also, a nonuniform pulse will change the spectral distribution of light emitted (Fig. 3.2) [7]. IPLs are vulnerable to the instantaneous "pumping" voltage of the capacitors. It follows that the spectrum changes as the power ramps up and down. In atypical configuration, the beginning and the end portions of the pulses are red-shifted (less energetic), and the middle of the pulse will be blue-shifted. Most modern systems use a sophisticated computer control system that minimizes this so-called spectral litter [9].

In human skin the target chromophores (hemoglobin, melanin, water) are not uniform in size and depth and show broad absorption spectrums. In addition penetration depth increases with the wavelength in the visible spectral range. Therefore the waveband of light emitted by IPLs will be advantageous compared to lasers if the parameters of energy, pulse duration, and emission spectrum are chosen in an optimal way.

Besides the traditional indications such as reduction of unwanted hair and vascular lesions, IPL devices are also being used for a more diverse range of treatments like photorejuvenation for acne or cellulite and inflamed, hypertrophic scars or keloids. In the last few years, photodynamic therapy with a 5-aminolevulinic acid photosensitizing agent and IPL has proved to be an effective method in treating actinic keratoses as well as acne and sun-damaged skin [2, 6].

Novel, low-fluence, home-use IPL devices for hair removal have entered the consumer market. Initial clinical studies demonstrated a significant reduction of unwanted body hair [3, 10] and did not present an optical hazard, according to currently available international standards [8].

The clinical flexibility of the IPL device requires more expert knowledge than laser systems with restricted indications. Significant differences in clinical outcome have been recorded among different free-discharge and constant-current IPLs despite identical settings. Unlike medical lasers, IPL devices are largely unregulated and unclassified as to degree

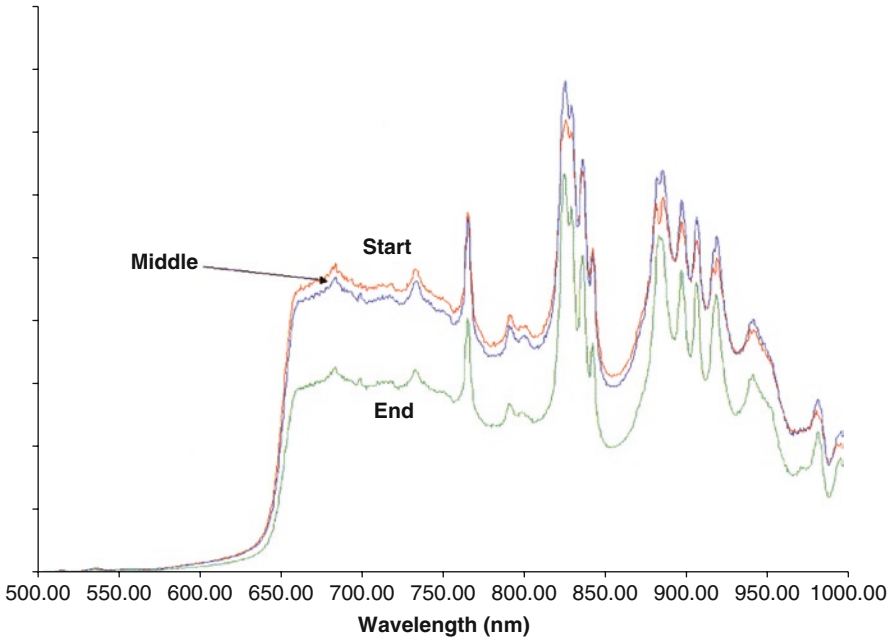

Fig. 3.2 Current is constantly changing throughout the pulse train, and this affects the relative wavelength portions. Notice how the difference between the start and the end of the pulse is greater at 700 nm than at 950 nm, indicating a spectral distribution shift. The units on the *y*-axis are arbitrary. Reprinted with permission

of safety hazard [9]. Up to now, standards imposed on the manufacturers are only for technical performance data and operating tolerance determined by CE-compliance under electrical safety standards of the European Union Medical Device Directive. Currently there is no requirement for the measurement of key IPL performance characteristics, which include fluence, pulse duration, pulse profile, spectral output, and time-resolved spectral output. Scientific measurements showed a shift in spectral distribution between pulses in a pulse train, within a pulse, and at different radiant exposures. There is a direct correlation between the electrical discharge current profile and the output energy profile. The difference between first-generation, free-charge systems and modern square pulse systems may have important clinical consequences in terms of different light-tissue interactions and hence clinical efficiency and safety. Methods to reduce the incidence of adverse effects include lightening of the skin and sun avoidance prior to IPL treatment. Cooling devices are helpful in protecting the epidermis but may not be sufficient to protect tanned or darker-skinned patients. Because all IPLs are designed for deep penetration and strong absorption by hemoglobin or melanin, they have a high potential for eye injury. Treatment in the area near the eye is not recommended unless the eyes are protected with metal lenses, and adequate eye protection goggles are obligatory for all people within the operating room [1].

Take Home Pearls

- Similar to lasers, the basic principle of IPL devices is the absorption of photons by skin chromophores and the thermal damage of the target.
- Short pulse durations in the nanosecond range result in high light intensities, like those of Q-switch lasers, are impossible.
- The combination of particular wavelengths, pulse durations, pulse intervals, and fluences allowes the treatment of a wide spectrum of skin conditions.
- This versatility is advantageous for skilled and experienced physicians, but for untrained users it implies the risk of evoking side effects because of nonspecific thermal damage.
- Unlike medical lasers, IPL devices are largely unregulated and unclassified, and up to now have not been subject to govermental control.

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Part II

Indications

Benign Tumors and Organoid Nevi

4

Stefan Hammes

Core Messages

- The group of indications regarding benign tumors and organoid nevi is very heterogeneous.
- Ablative lasers (carbon dioxide and erbium: yttrium aluminum garnet (YAG) lasers) are mainly used for therapy.
- In case there is an additional vascular component, the (additional) use of vascular-specific lasers makes sense (long-pulsed neodymium: YAG and dye lasers).
- The recurrence rates are often not negligible.
- Sufficient sun protection is especially important after deeper ablations.
- Pretherapeutic biopsies are important.

4.1 Adenoma Sebaceum

Adenoma sebaceum occurs isolated or as one symptom with nevoid systemic diseases, the so-called *phacomatoses* (Pringle's disease, Bourneville's disease/tuberous cerebrosclerosis). Characteristic of phacomatoses are multiple small angiofibromas scattered symmetrically over nose, nasolabial fold, cheeks, and chin. Their number and size increase during the course of life. Excision, electrocoagulation, cryo-methods, and dermabrasion have been the therapy options up to now. Lasers have clearly improved the results and facilitated the treatment, but the recurrence rate remains almost unchanged.

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So far, the carbon dioxide (CO_2) laser (continuous wave [CW]/pulsed) has brought the best results. This is due to its capacity to ablate evenly whole areas of tissue while stopping the bleeding. The argon laser is especially recommended for single red or skin-colored papules. There are, however, worse results with dark skin types due to an increased absorption of melanin. The pulsed dye laser is appropriate exclusively for the treatment of flat (<1 mm), red angiofibromas (Fig. 4.1). Kaufmann and Hibst [52] reported successful application of the erbium:yttrium aluminum garnet (YAG) laser in six cases (three adenoma sebaceum and three isolated angiofibromas). Regarding the tendency of angiofibromas to bleed, experience shows that a combination with a CO_2 laser makes sense to ensure a sufficient ablation depth [6, 13, 41, 81, 82, 89].

Because of the painfulness of laser treatment, and in cases of areal extension and for patients with mental retardation (Bourneville's disease), therapy under a general anesthetic should be considered.

Unfortunately, none of the systems achieve a permanent complete removal, despite multiple treatments. Recurrences occur mostly after 1–2 years. Thus the patients must be comprehensively informed that a laser therapy can only produce a temporary cosmetic improvement.

4.2 Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome, first described in 1977, is an autosomal dominant, inherited disease characterized by the occurrence of multiple cutaneous hamartomas with adnexal differentiation [11]. An association with intestinal neoplasms has been reported [43, 75]. Recently, the cutaneous lesions in this syndrome have

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DOI: 10.1007/978-3-642-03438-1_4, © Springer-Verlag Berlin Heidelberg 2011

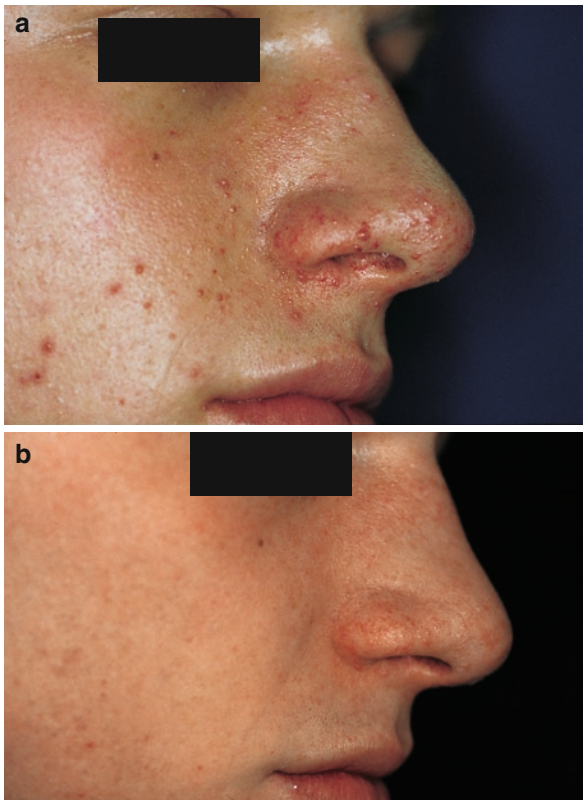

Fig. 4.1 (**a**) Pringle's disease (10/94). (**b**) After three sessions with pulsed dye laser (2/98). Reproduced with permission from Raulin and Greve [68]

been interpreted as different developmental stages of one single hamartoma with sebaceous differentiation, called mantleoma.

The operative removal of individual tumors is restricted by the large number of changes [21, 43]. The mentioned adnexal tumors are all benign, but because of multiple occurrences, especially on face and neck, they pose a considerable cosmetic problem for affected persons.

Successful treatments with an erbium:YAG laser [24], a CO_2 laser [40, 44], and a copper steam laser [25] have been reported. Especially attractive results from the treatment of multiple mantleomas can also be achieved in one to two treatment sessions with the ultra-pulsed CO_2 laser (Fig. 4.2).

4.3 Epidermal/Organoid Nevus

Epidermal nevi are congenital organoid malformations (hamartomas) that result from a circumscribed disturbance in the mixing ratio of otherwise normal skin structures.

Epidermal nevi are mostly situated in a strip-like manner along the Blaschko lines and develop, during the course of life, a more or less strong keratinous surface.

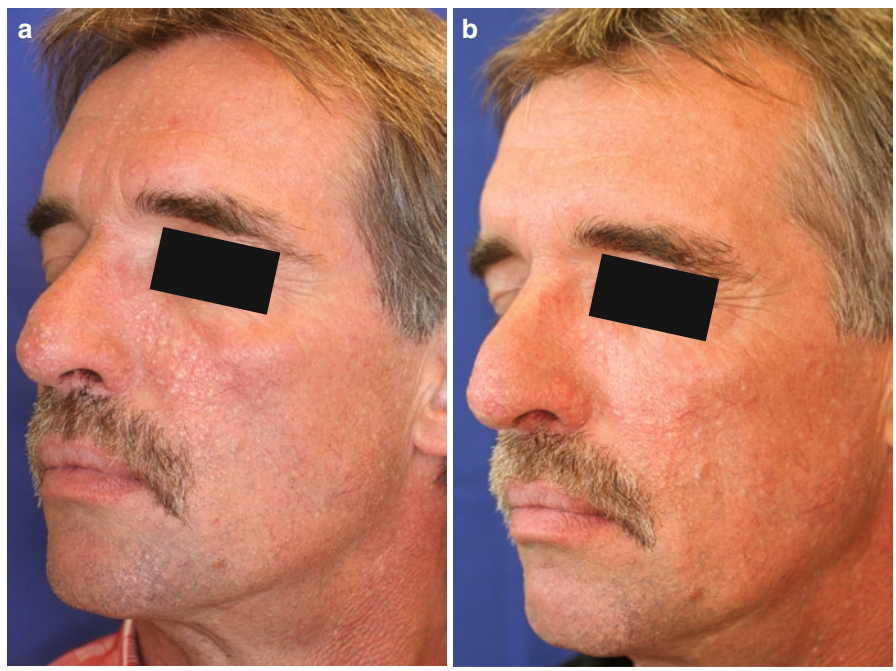

Fig. 4.2 (**a**) Birt-Hogg-Dubé syndrome (8/07). (**b**) After two treatments with ultra-pulsed carbon dioxide laser (8/09)

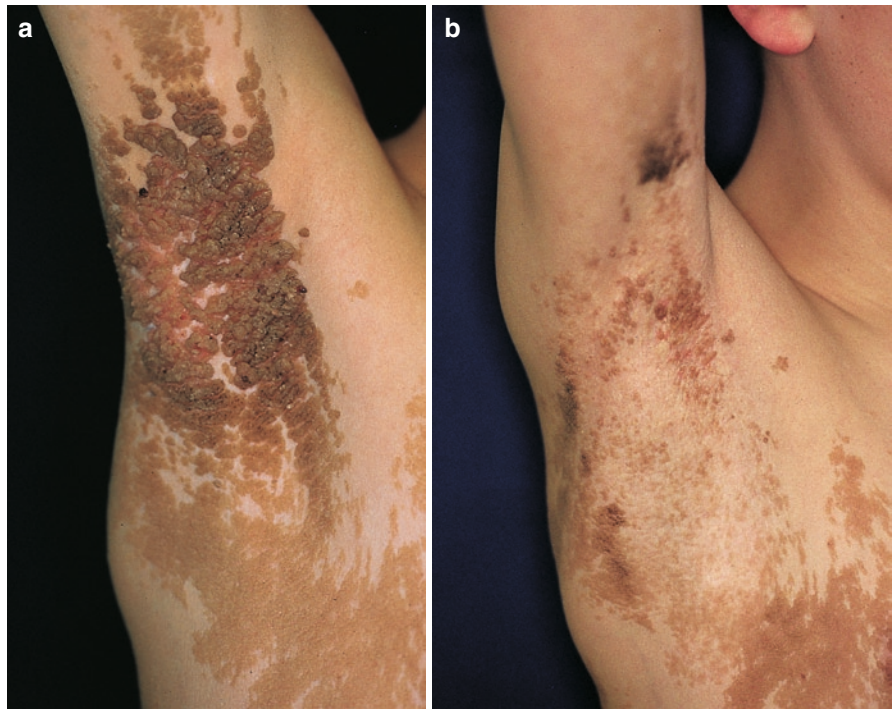

Fig. 4.3 (**a**) Large-area epidermal nevus (1/98). At the patient's request, only the axillary was treated because he could not stand the smell. (**b**) Result after two sessions with the combined erbium:yttrium aluminum garnet/carbon dioxide laser (3/00). This patient had a recurrence-free follow-up period of more than 2 years. Reproduced with permission from Raulin and Greve [68]

A distinction must be made between papillomatous soft and hard/verrucous forms. It is called nevus unius lateralis when only one side is affected. Inflammatory linear verrucous epidermal nevus (ILVEN) is a special case, which is marked by an additional inflammatory component and intensive pruritus.

The CO_2 laser (CW/pulsed) has proved to be a good therapy option in various case reports. It is the best option, especially for verrucous and extended epidermal nevi, because it allows ablation over a large area and with limited bleeding (Fig. 4.3). Because the coagulation that can be achieved with the argon laser is very superficial, it is used mainly for rather soft forms. Recurrence-free follow-up terms after therapy with a CO_2 laser amount to up to 4 years.

The erbium:YAG laser can also be used to ablate epidermal nevi. Empirically, the combination with the CO_2 laser is advantageous in cases of large-area nevi, as well as with a number of other benign tumors and organoid nevi, because bleeding hampers the visibility and thus an exact ablation [16, 37, 38, 52, 57, 67].

Baba et al. [8] treated five patients with heavily pigmented, flat, epidermal nevi using the long-pulsed ruby laser (pulse time 2 ms). Within a maximum of four sessions, the nevi could be either completely removed or clearly brightened. It must, however, be mentioned that one of the cases was a large-area nevus unius lateralis, which was treated in a test treatment; in another case, the papillomatous parts were additionally ablated with electrocautery.

Alster [2] reports that a 5-year-old patient could be freed from agonizing itching caused by an ILVEN within two treatment sessions with the pulsed dye laser. One year after therapy, the result was still unchanged.

4.4 Epithelioma Adenoides Cysticum

Typical of the epithelioma adenoides cysticum of Brooke are numerous small, colorless papules that are located mainly on nasolabial folds and the nasal canthus. Histologically they are hair follicle tumors (trichepitheliomas). Adenoma sebaceum or syringomas must be considered as differential diagnoses. Occasionally, basaliomas can develop, which is why a histological examination should be carried out at the least doubt.

There are reports about successful treatment with the argon and CO_2 lasers in individual cases. Recurrences depend on ablation depth and are part of the nature of the disease [20, 76, 77, 90].

Our experiences with regard to the number of treatments, success rate, and recurrences are mainly the same as those with the adenoma sebaceum.

4.5 Fibrous Papule of the Nose

It has been histopathogenetically discussed whether the fibrous papule of the nose (fibrosis nodularis nasi) is a fibroma or a regressive fibrosed nevus. These small lesions, which occur mostly isolated on the tip of the nose, can become an intensive red and thus be perceived as cosmetically disturbing. Before laser therapy was introduced, excisions and cauterization were the therapy options [36].

Due to the fibrous structure, only ablations with the erbium:YAG or pulsed CO_2 lasers have proved to be of value, in our experience (Fig. 4.4). In individual cases, two treatment sessions were necessary for a complete and scar-free removal. The patients must be comprehensively informed about the possibility of recurrences.

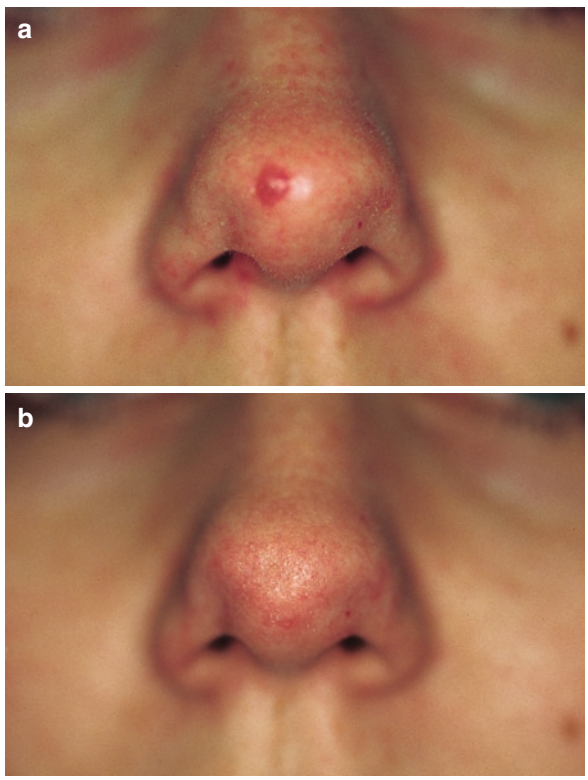

Fig. 4.4 (**a**) Fibrous papule of the nose (12/98). (**b**) Patient after one treatment with the ultra-pulsed carbon dioxide laser (2/99). Reproduced with permission from Raulin and Greve [68]

Contrary to expectations, the application of the pulsed dye laser has brought unsatisfactory results despite high energy density values and after the application of several pulses. As with adenoma sebaceum, the argon laser can be considered as a therapy option. So far, there have been no scientific studies about the laser treatment of fibrous papules of the nose.

4.6 Koenen Tumors

Periungual fibromas associated with tuberous sclerosis, also known as Koenen tumors, are found in approximately 15% of tuberous sclerosis patients [42], although some studies present figures as high as 52% [63]. The onset of lesions usually occurs after puberty. Grossly periungual fibromas appear as smooth, firm, flesh-colored or reddish papular lesions arising from the nail fold. They may cause nail deformities and occasionally pain. Histologically they appear as highly vascular lesions with thin bundles of collagen and dense elastic fibers [53]. Periungual fibromas are most often treated by surgical resection [86] but carry a high recurrence rate. Some authors report successful treatment with less recurrence by shave excision and phenolization [59]. The possible complications of this treatment are necrosis of the proximal nail fold, infection, and deformity of the nail fold and nail plate.

Laser vaporization of Koenen tumors with a CO_2 laser proved to be similar to conventional surgical techniques in terms of cosmetic satisfaction. However, bleeding was negligible and operating time was considerably shorter for laser treatment compared to that of surgery [10]. The cosmetic and functional outcome is good (Fig. 4.5).

4.7 Mastocytosis

Mastocytosis is a group of disorders that are histologically marked by a proliferation of mast cells. Among the cutaneous forms of mastocytoses are isolated mastocytosis or, disseminated (urticaria pigmentosa infantum or adultorum) and diffuse mastocytosis. Clinically, they appear as yellow-brown or brown-reddish papules.

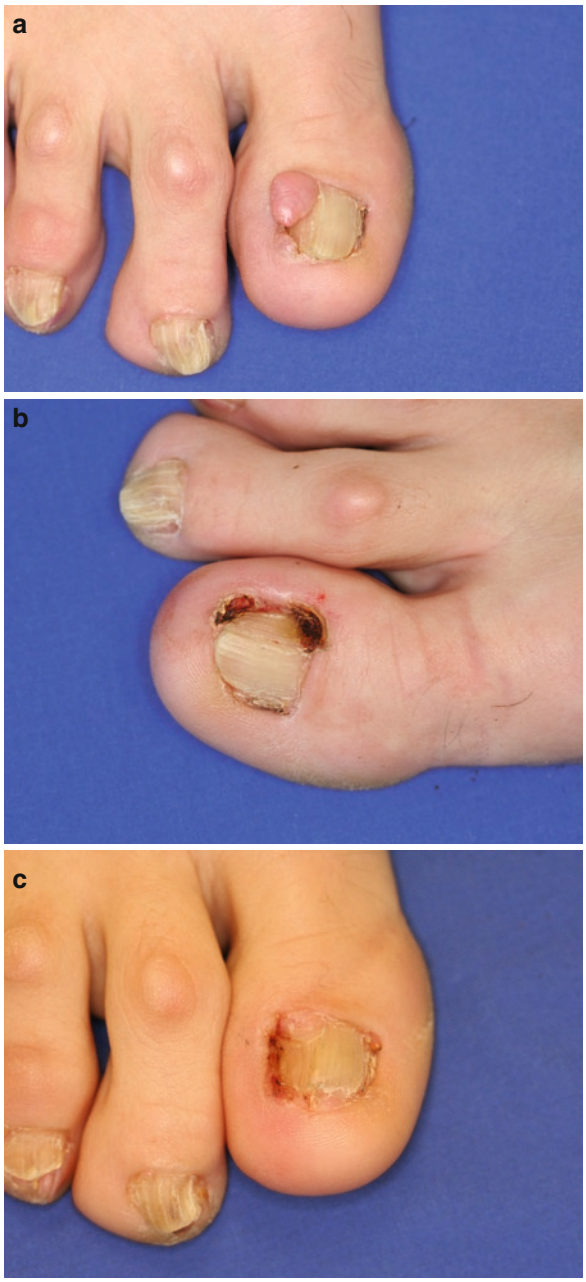

Fig. 4.5 (**a**) Koenen tumor (3/09). (**b**) Directly after treatment with continuous wave (CW) and ultra-pulsed carbon dioxide (CO_2) laser (3/09). (**c**) Two months after one treatment with CW and ultra-pulsed CO_2 laser (5/09)

So far, there have been only experimental observations regarding laser treatment of these skin lesions. Landthaler and Hohenleutner [55] and Ellis [18] describe the application of the pulsed dye laser with urticaria pigmentosa. In both studies, 70% and 100% of the lesions recurred after 12 and 14 months, respectively. Hadshiew et al. [30] treated three patients using the Q-switched ruby laser; all treated areas had repigmented after 4–6 months. Figure 4.6 shows a successful therapy test with the Q-switched ruby laser with urticaria pigmentosa adultorum.

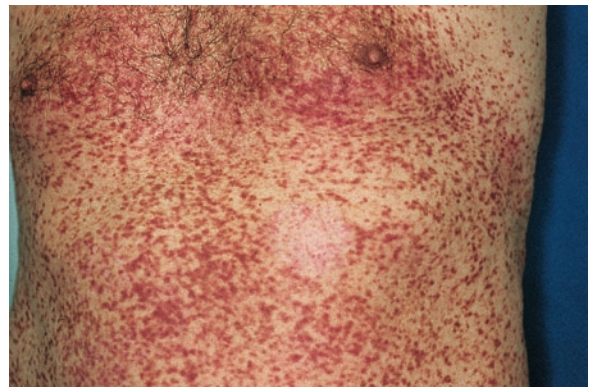

Fig. 4.6 Mastocytosis (urticaria pigmentosa adultorum). Brightening after five test treatment sessions with Q-switched ruby laser on left side of hypogastrium. Follow-up period of 6 months. Test treatments with Q-switched neodymium:yttrium aluminum garnet laser (1,064 and 532 nm) and pulsed dye laser on other place did not produce any success. Reproduced with permission from Raulin and Greve [68]

4.8 Nevus Sebaceous

Like epidermal nevi, the nevus sebaceous is an organoid malformation (hamartoma) and is marked by a proliferation of sebaceous glands, located mostly in the scalp. In a retrospective study with 596 patients, the risk for the development of malignant tumors, especially of basaliomas, within nevi sebacei, is assessed low at <1%. Some authors still recommend surgical removal for prophylactic reasons; this can, however, be difficult in individual cases due to the extension, and scars are inevitable [15].

Regarding dermatological laser therapy, the only options are CO_2 laser or a combination of CO_2 and erbium:YAG laser. With these, we did not achieve convincing results. Complete removal is not possible due to the depth of the nevi down to the central corium; thus, recurrences are preprogrammed. Ashinoff [7], however, could reach a clear and stable improvement with a linear nevus sebaceous of Jadassohn using a CO_2 laser in a 10-year-old boy (follow-up term 1 year).

4.9 Neurofibromas

Neurofibromas rarely occur solitarily, but mostly in large numbers as one of the main symptoms of the autosomal inherited neurofibromatosis (m. Recklinghausen). Other typical skin symptoms of this disorder are café au lait spots and freckle-like hyperpigmentation of the axillas.

During the course of life, the nodules and nodes grow in extent and number; the objective of a therapy can only be remission because relapses and new nodules occur in almost every case.

Treatment of neurofibromas can be done effectively with the continuous CO_2 laser (Fig. 4.7). The solid, colloidal consistency of the nodes requires high performances that cannot be achieved using the pulsed mode. After opening the epidermis, the neurofibroma can be pressed out and ablated. Removal should always be done completely down to the base to prevent quick recurrence. The partly very deep skin lesions can be adjusted to their environment with the pulsed CO_2 laser. The skin lesions heal within 1–2 weeks; scars are inevitable. The evaluations of the cosmetic result as well as the expectations of the patients are rather individual. A test treatment should be done in every case [9, 45, 51, 74].

Kardorff [46] has published case reports about successful therapy of neurofibromas using the erbium: YAG laser in combination with surgical excision.

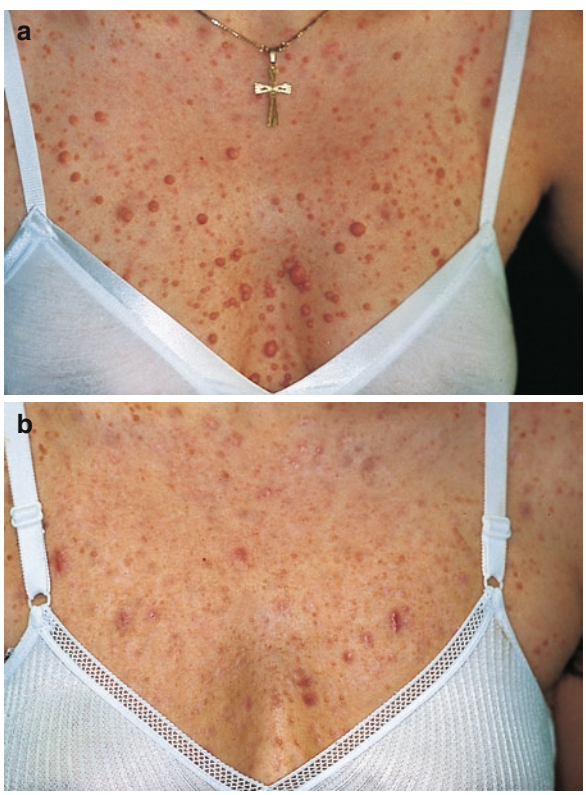

Fig. 4.7 (**a**) Neurofibromatosis Recklinghausen (12/95). (**b**) Satisfactory result for the patient after three treatments with continuous wave and ultra-pulsed carbon dixode lasers (4/96). Reproduced with permission from Raulin and Greve [68]

4.10 Papillomatous Dermal Nevus

It is for didactic reasons that papillomatous dermal nevi are described here, although they are nevi that have become papillary or fibrotic over the course of time. Occurring mostly during the second half of life, these elevated nevi can be removed with good cosmetic results with the erbium:YAG and/or pulsed CO_2 laser (Fig. 4.8). An anecdote tells us that the result with an actor was so good that the actor had to recreate a dermal nevus with makeup for certain roles (Fig. 4.9). The possibility of relapses should be pointed out to each patient. At the least doubt regarding the benignity, a biopsy should be performed [31].

Pigmented dermal nevi should not be treated because melanin-containing cells remain in the skin and because this can, as described in the literature, lead to the development of pseudomelanomas [16, 34, 52, 64].

4.11 Rhinophyma

Rhinophyma, a swelling of the nose caused by sebaceous hypertrophy, occurs in connection with rosacea. Standard therapies are surgical removal with a scalpel, electrocautery, dermabrasion, or cryotherapy. The main reported disadvantages of these methods are insufficient intraoperative hemostasis and the development of demarcation lines, which is why hopes for treatment were pinned on the CO_2 laser.

Contrary to the theoretical advantages, the results do not clearly speak for the application of the laser. Comparative studies with conventional scalpel and electrosurgery show equally good results for both methods with similar profiles of side effects (Fig. 4.10).

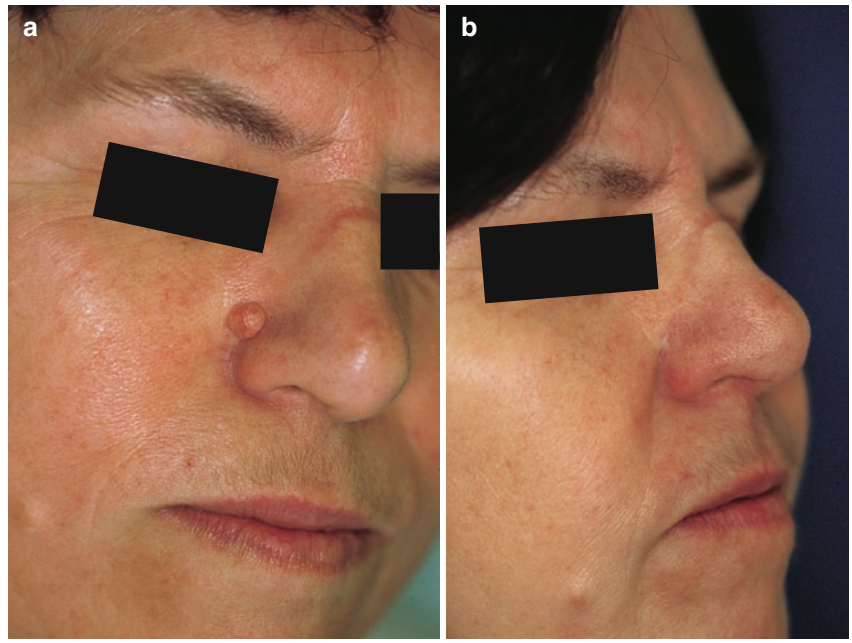

Fig. 4.8 (**a**) Papillomatous dermal nevus (8/97). (**b**) Removal with minimal scarring through ultra-pulsed carbon dioxide laser (3/00). Reproduced with permission of from Raulin and Greve [68]

Fig. 4.9 (**a**) Papillomatous dermal nevus (2/09). (**b**) Removal with minimal scarring with the ultra-pulsed carbon dioxide laser (5/09). (**c**) The result was so good that the actor had to recreate a dermal nevus with makeup for certain roles

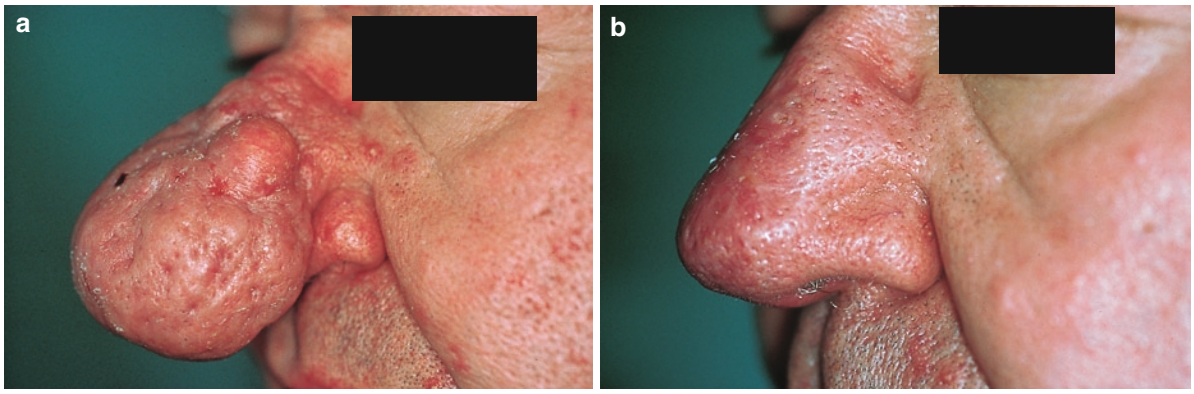

Fig. 4.10 (**a**) Rhinophyma (9/97). (**b**) After ablation with an ultra-pulsed carbon dioxide laser (5/98) (photos courtesy of Dr. T. Hebel, Munich). Reproduced with permission from Raulin and Greve [68]

It is recommended to ablate in CW mode first and then to adjust the marginal areas in the pulsed mode in a second step. Compared to conventional methods, laser therapy is judged to be clearly more time-consuming despite immediate hemostasis. Ablation with the erbium:YAG laser is theoretically possible, but because of bleeding that begins quickly, the procedure must be stopped quite early [12, 26, 29, 32, 47, 80, 91].

4.12 Mucosal Fibroma

Laser systems have been increasingly applied in oral surgery to treat benign tumors of the oral mucosa. The most frequently applied laser is the CO_2 laser, which is used in the continuous as well as in the pulsed mode. With this system, mucosal fibromas can easily be ablated during one treatment session (Fig. 4.11). Relapses are rare [22, 23, 58, 61, 65, 66, 71].

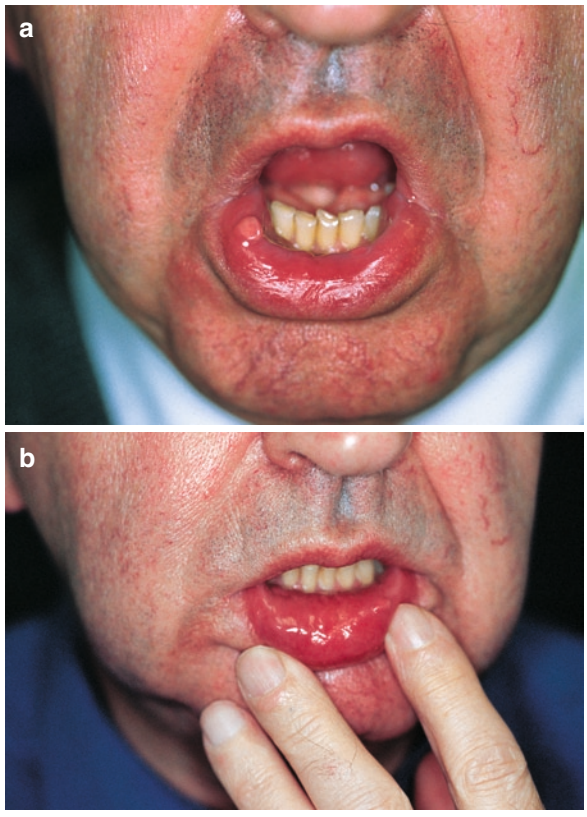

Fig. 4.11 (**a**) Mucosal fibroma (11/99). (**b**) Removal after one treatment with ultra-pulsed CO_2 laser (3/00). Reproduced with permission from Raulin and Greve [68]

4.13 Seborrheic Keratoses

Seborrheic keratoses are common benign, epidermal neoplasms that are very variable in number, size, and color. The simplest and cheapest therapy option is still excochleation. We think that the use of a laser is justified only at exposed localizations (Fig. 4.12) (eyelid, nostril, etc.) or in cases of extensive occurrence (Fig. 4.13). In such cases, pulsed erbium:YAG or CO_2 lasers can be used. The Q-switched ruby or neodymium (Nd):YAG lasers can also be used with good results for the treatment of flat pigmented seborrheic keratoses. It does, of course, depend on the

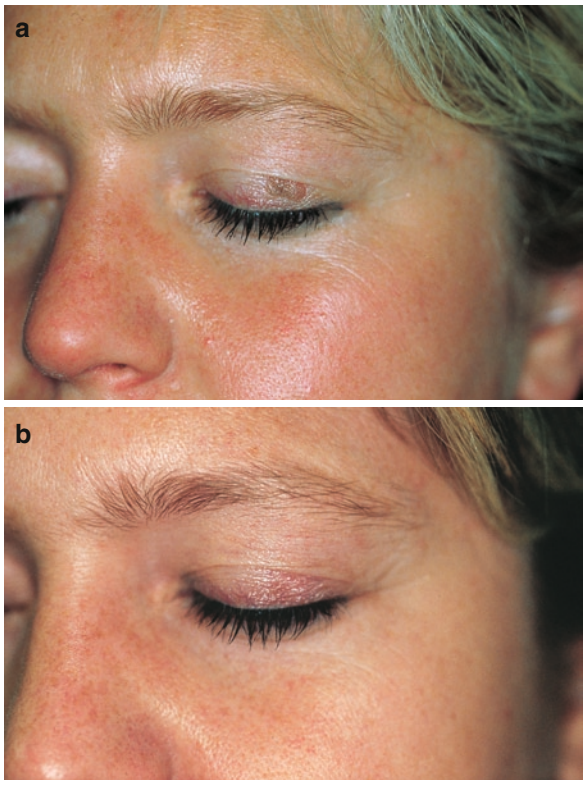

Fig. 4.12 (**a**) Solitary, histologically ascertained seborrheic keratosis (9/99). (**b**) Complete removal through one-time treatment with an erbium:yttrium aluminum garnet laser (3/00). Reproduced with permission from Raulin and Greve [68]

thickness of the lesions, but one or two treatment sessions do in most cases lead to complete removal [16, 19, 69, 87].

4.14 Syringomas

Until some years ago, the therapy of syringomas was difficult because of their disseminated distribution pattern. Surgical excision, electrocautery, and cryotherapy are theoretically possible in some cases, but they lead to unsatisfactory results or are not practicable with extended areas or periocular localizations.

Good results can be achieved with the pulsed CO_2 and erbium:YAG lasers, preferably in combination (Fig. 4.14). In most cases, 1–3 treatment sessions are necessary for removal. In case of recurrence, which is frequent with hidradenomas, the treatment can be repeated. It is recommended that an initial test treatment be performed. In the context of patient information, the danger of scar formation and transient or, in individual cases, even permanent hypopigmentation should be pointed out. Patients with dark circumorbital rings are especially predestined for these side effects [5, 14, 16, 52, 73, 76, 85, 88].

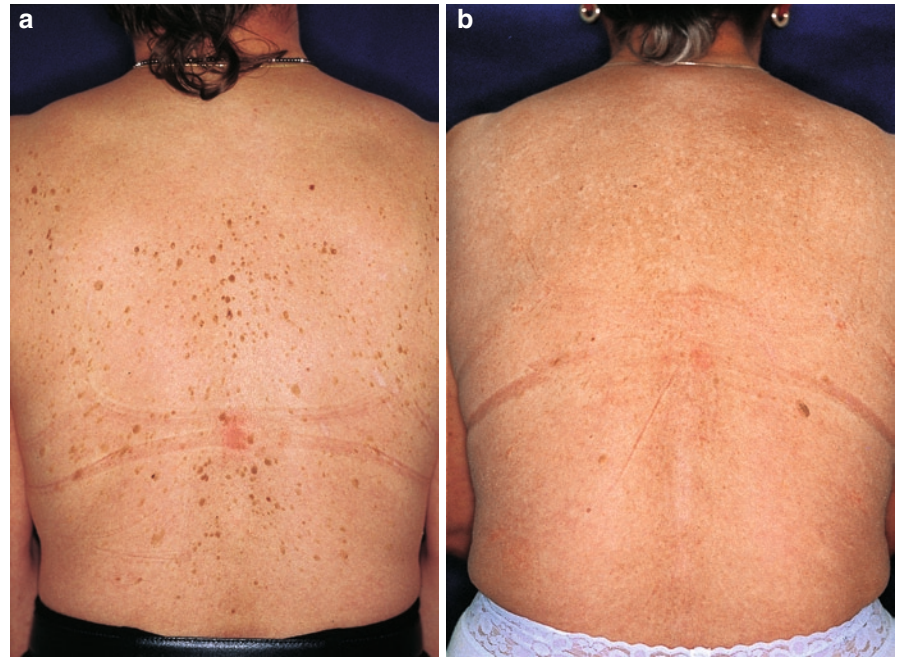

Fig. 4.13 (**a**) Disseminated seborrheic keratoses (5/95). (**b**) Removal (4 partial treatments) with the Q-switched ruby laser with an energy density of 40 J/cm² and a pulse diameter of 2 mm. Follow-up period of more than 4 years (11/99). Reproduced with permission from Raulin and Greve [68]

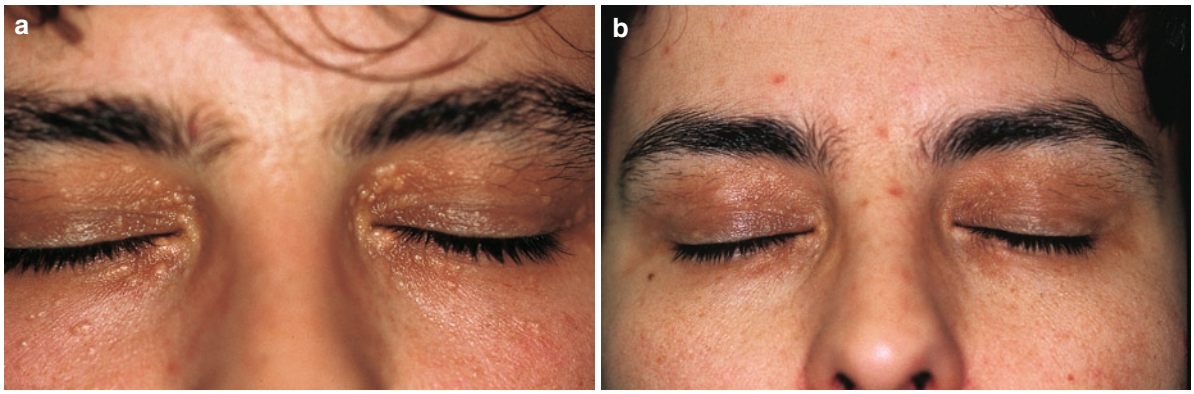

Fig. 4.14 (**a**) Extended syringomas in a 35-year-old patient (8/95). (**b**) The syringomas after three sessions with an ultra-pulsed carbon dioxide laser and a follow-up of more than 4 years (3/00). Reproduced with permission from Raulin and Greve [68]

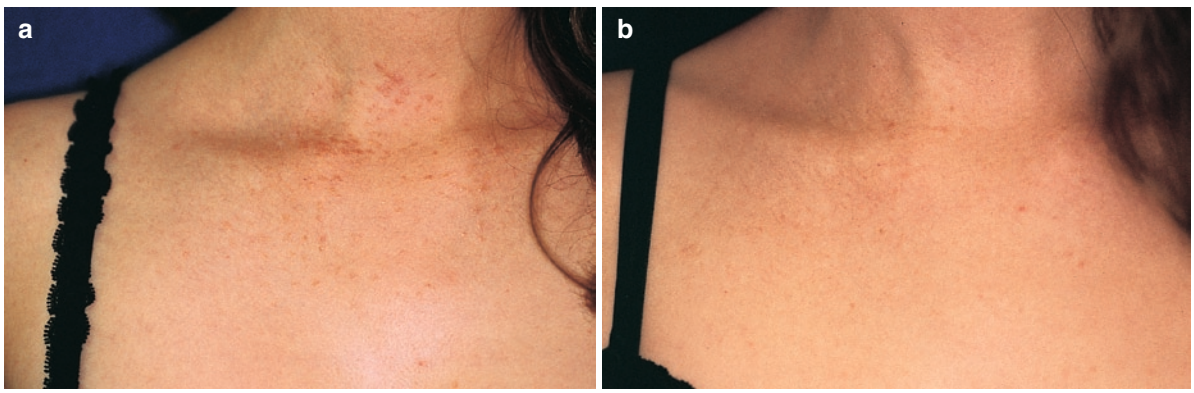

Fig. 4.15 (**a**) Disseminated (eruptive) syringomas (10/98). (**b**) Discrete residuals and hypopigmentation after three treatments with the pulsed dye laser and 15-month follow-up (1/00). No recurrences. Reproduced with permission from Raulin and Greve [68]

We achieved a good cosmetic result in a case of syringomas on the chest area, which we treated with pulsed dye laser; there was, however, slight hypopigmentation (Fig. 4.15). One year after the last of three treatment sessions, the patient was still recurrence-free.

4.15 Sebaceous Hyperplasia

Sebaceous hyperplasia manifests as small, white-yellowish papules with central dents on the forehead, cheeks, and nose. Those affected are particularly men older than 30 years of age who have seborrheic skin types. Apart from the effective, cost-efficient, and uncomplicated cryotherapy, the pulsed dye laser (Fig. 4.16) and ablating laser systems (erbium:YAG and pulsed CO_2 lasers) (Fig. 4.17) also lead to good results. Irrespective of the treatment method, two to three sessions are necessary [28, 72, 79].

4.16 Xanthelasmas

Xanthelasmas are typically, yellowish, flat plaques on the upper and lower eyelids. About half of these patients also have a disorder of the lipid metabolism. The "classic" treatment method is surgical excision, but this method involves scar formation and a high recurrence rate. According to Mendelson and Maason [60], there are recurrences after the first excision in 40% of cases and after the second in 60% of cases. In cases of extended area and difficult localization, this therapy is applicable only with difficulty or with restrictions; in addition, it cannot be repeated at will in the case of recurrences.

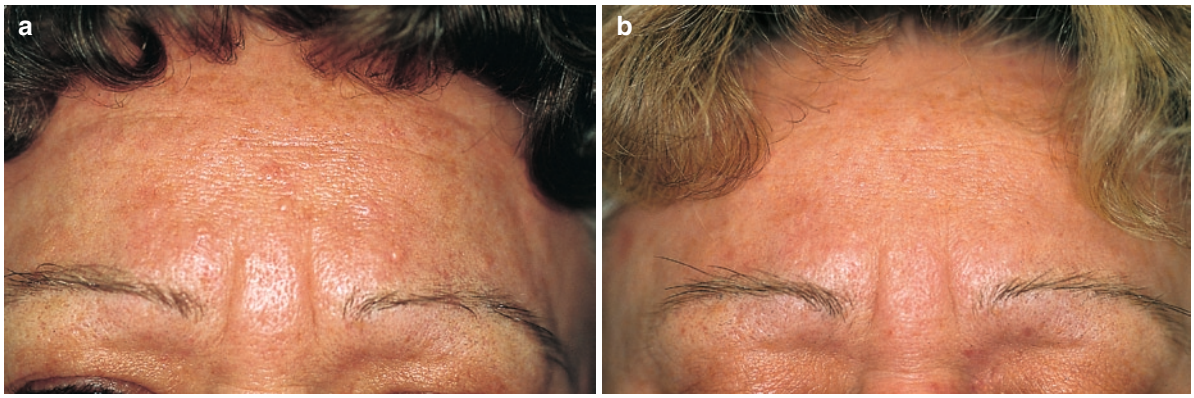

Fig. 4.16 (**a**) Sebaceous hyperplasia (4/95). (**b**) Regression after three treatments with the pulsed dye laser (1/96). Reproduced with permission from Raulin and Greve [68]

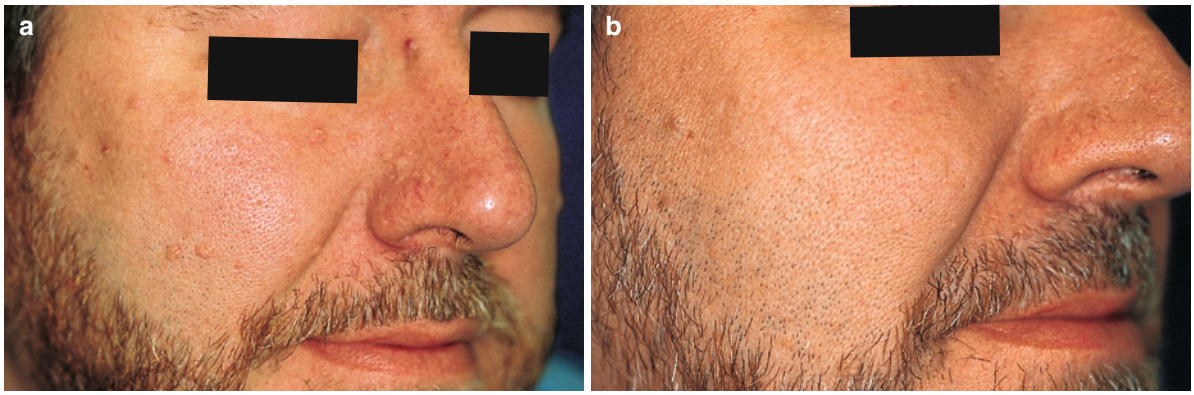

Fig. 4.17 (**a**) Sebaceous hyperplasia (6/98). (**b**) Complete removal after one treatment with combined erbium:yttrium aluminum garnet/carbon dioxide laser and pulsed dye laser (8/99). Reproduced with permission from Raulin and Greve [68]

During the course of the past few years, argon, CO_2, erbium:YAG, and pulsed dye lasers have been used for this indication.

The results after treatment with the argon laser are contradictory. In a study by Hintschich [35] there were very good results without scar formation and good results with slight scar formation after one or two treatment sessions in 13 out of 32 xanthelasmas; in six cases there was only a reduction of size. After 12–18 months, the recurrence rate amounted to 37%. However, Drosner et al. [17] report complete and permanent removal of 21 xanthelasmas after one to two sessions (follow-up time 12 months).

In our experience, the pulsed dye laser is appropriate only for initial, flat lesions, and one must initially be prepared for several sessions (Fig. 4.18) [49].

In studies published in a number of scientific publications, the CO_2 laser has proved to be the most effective method (Fig. 4.19). In a study of 23 patients with a total of 52 xanthelasmas, we could achieve complete removal of all lesions with the Ultrapulse CO_2 laser (Lumenis Aesthetic, Santa Clara, Calif.) after one session [70]. Transient hyperpigmentation occurred in 4% and transient hypopigmentation in 13% of the cases. During a 10-month follow-up, only three patients had recurrences. The treatment with the CO_2 laser can be done under local anesthesia without any problem [84]. The eyes should be protected with eyeshields. The therapy can be repeated in case of recurrence. Its application is limited only with an extended depth of xanthelasmas; therefore, the treatment should take place in an early stage. Remaining deep parts must be removed surgically during a second session. The adjuvant application of the pulsed dye laser has proved to be a good recurrence prophylaxis [3, 4, 27, 60, 78].

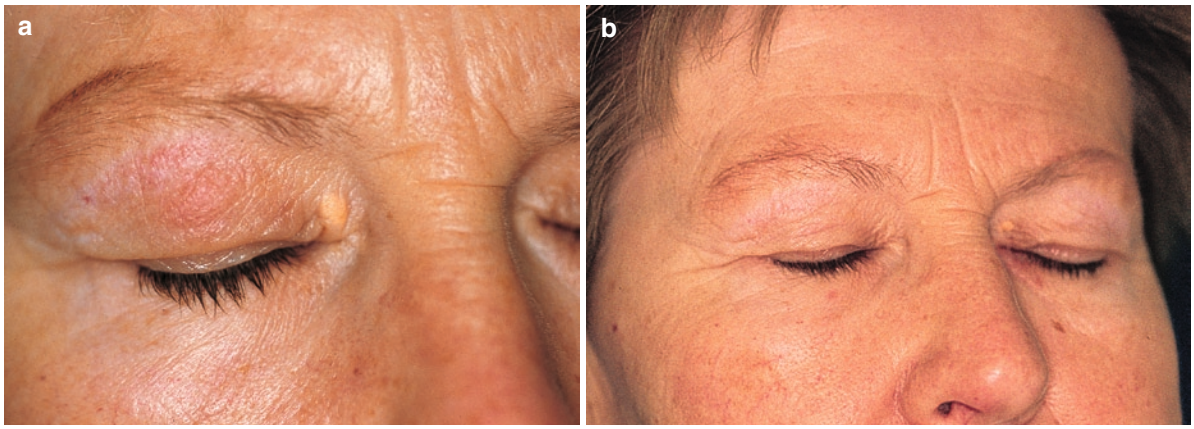

Fig. 4.18 (**a**) Xanthelasma (10/94). (**b**) Removal after three sessions with pulsed dye laser. Recurrence-free follow-up period of nearly 5.5 years (2/00). Reproduced with permission from Raulin and Greve [68]

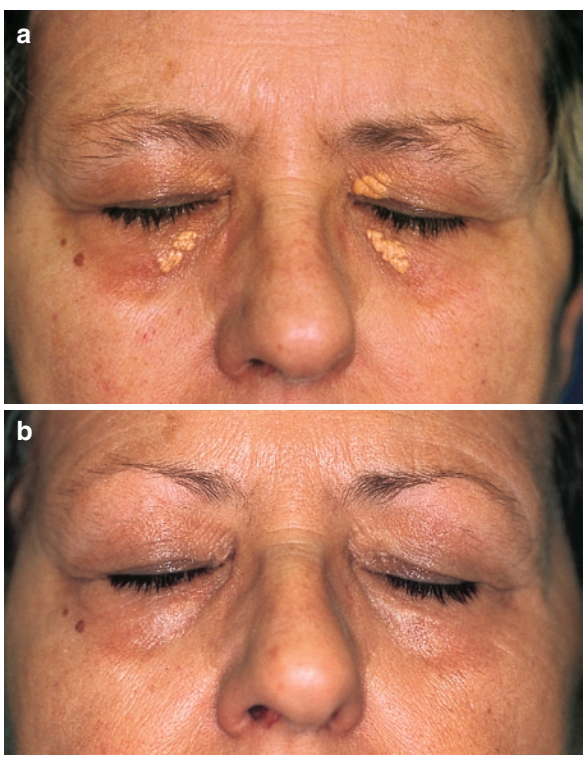

Fig. 4.19 (**a**) Xanthelasmas (11/96). (**b**) Complete removal with slight hypopigmentation after one treatment with the ultra-pulsed carbon dioxide laser (03/02). No recurrence after more than 5 years. Reproduced with permission from Raulin and Greve [68]

Reports about the application of the erbium:YAG laser have been published by Kaufmann and Hibst [52], Dmovsek-Olup and Vedlin [16], and Hartmann et al. [33]. We think that deeply penetrating xanthelasmas certainly cannot be ablated completely with only this type of laser due to the lack of hemostasis. To us, a combined application of both systems seems to be ideal. The application of Q-switched lasers (Nd:YAG and potassium titanyl phosphate/Nd:YAG) is not an effective option [50].

4.17 Tongue Papilloma

Like sebaceous fibromas, benign tongue papillomas can also be ablated with the CW/pulsed CO_2 laser (Fig. 4.20). Several authors have reported advantages compared to scalpel excision: lower postoperative pain and reduced inflammatory reaction. Furthermore, they especially emphasize that the coagulation of small vessels facilitates the work, improves the sight, and produces only slight scar formation [22, 23, 58, 61, 65, 66, 71].

4.18 Cysts

4.18.1 Eccrine Hidrocystoma

These small, benign cystic tumors derive from the eccrine perspiratory glands and commonly occur on the eyelids. Emptying by stitch incision is sufficient in most cases as a temporary therapy measure. To treat recurrences, we have positive experiences with

vaporization or ablation of the cyst wall with erbium:YAG and pulsed CO_2 lasers as an elegant and effective method (Fig. 4.21). Eyeshields are recommended when treating the eyelids.

Tanzi and Alster [83] also report the successful treatment of hidrocystoma on the face of a 54-year-old patient with the pulsed dye laser (585 nm, 7.0–7.5 J/cm²). After a total of four treatment sessions they had achieved nearly complete removal (Fig. 4.22). There were no recurrences within the 18-month follow-up period. The effective mechanism is still unknown.

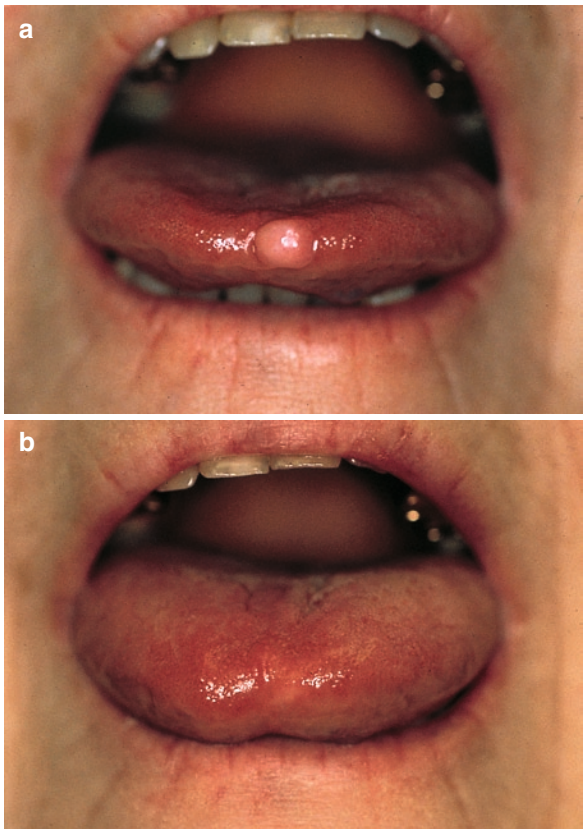

Fig. 4.20 (**a**) A 10-year-old tongue papilloma (9/00). (**b**) Complete removal in 3 months after one treatment with a pulsed carbon dioxide laser (12/00). Reproduced with permission from Raulin and Greve [68]

4.18.2 Eruptive Vellus Cyst

See Sect. 4.18.4, Steatocystoma Multiplex, below.

4.18.3 Mucoid Dorsal Cyst

Laser therapy (erbium:YAG/CO_2) of mucoid dorsal cysts has not proved effective among our patients. After emptying the mucous secretion and despite deep ablation of the wound ground, there were recurrences in most patients within a few weeks. However, Landthaler et al. [48, 56] reported better results (Fig. 4.23).

4.18.4 Steatocystoma Multiplex

Steatocystoma multiplex is a rare, autosomal dominant genodermatosis that is marked by numerous small

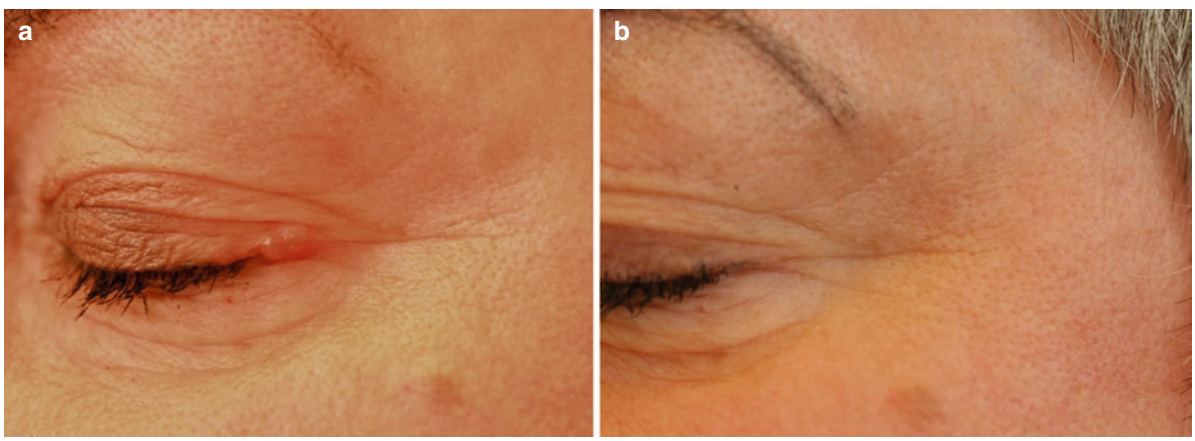

Fig. 4.21 (**a**) Eccrine hidrocystoma (3/09). (**b**) After one session with an erbium:yttrium aluminum garnet laser (8/09)

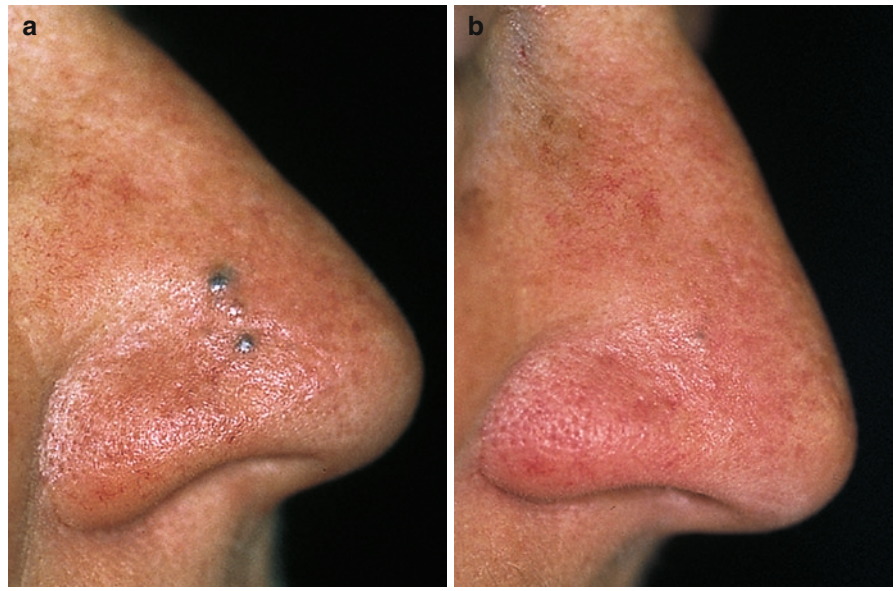

Fig. 4.22 (**a**) Hidrocystomas (5/02). (**b**) Except for one small recurrence, complete removal after three treatments with a pulsed dye laser (10/02). Reproduced with permission from Raulin and Greve [68]

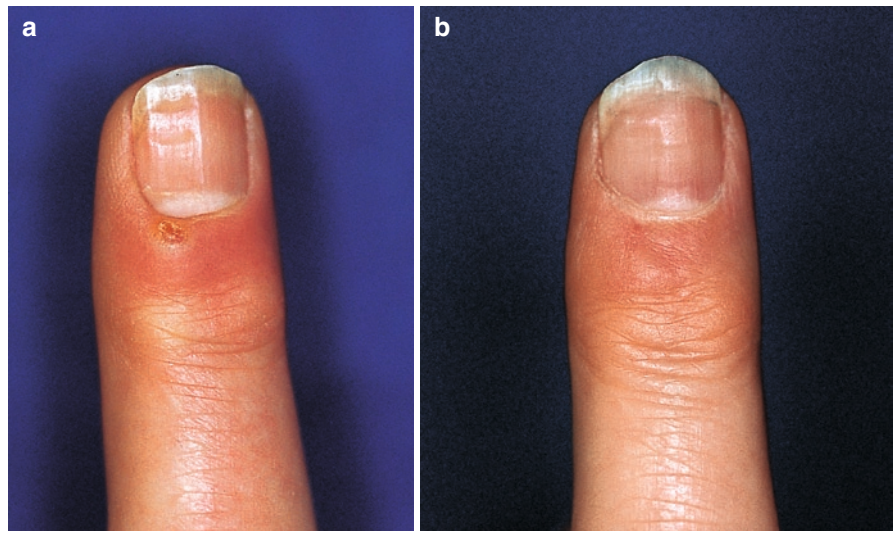

Fig. 4.23 (**a**) Mucoid finger cyst (12/99) after repeated cryotherapy. (**b**) Removal after deep ablation and marsupialization with an erbium:yttrium aluminum garnet and carbon dioxide laser (3/00). Reproduced with permission from Raulin and Greve [68]

cysts on the chest, abdomen, axillaries, back, scrotum, and face. There is a smooth transition to eruptive vellus cysts [39]. In both cases, the lesions reach into the central dermis and therefore cause therapeutic trouble. In one patient treated by us, the surgical strategy consisting of minimal scalpel incision and extraction of the cyst wall resulted in less scar formation than the initial opening and ablation with erbium:YAG and CO_2 lasers. Individual cases report good results with both methods [1, 54].

4.18.5 *Traumatic Mucous Cyst (Traumatic Mucous Retention Cyst, Mucocele)*

Traumatic ruptures of the salivary gland ducts cause these pseudocysts, which are most commonly located on the red of the lips or mucosa of the lower lip. They are the most frequent lesions of the oral mucosa and can later turn into a chronic inflammatory form, the

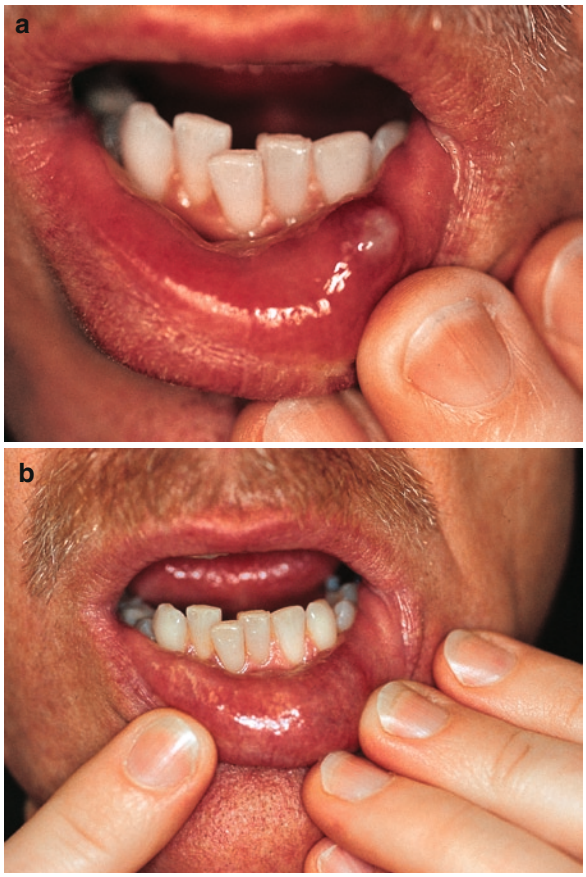

Fig. 4.24 (**a**) Traumatic mucous retention cyst (11/99). (**b**) Removal 1 month after one-time therapy with ultra-pulsed carbon dioxide laser (12/99). Reproduced with permission from Raulin and Greve [68]

mucous granuloma. Removal with the CO_2 laser is uncomplicated and brings good results (Fig. 4.24). The erbium:YAG and coagulating lasers are other therapy options [22, 23, 62].

Take Home Pearls

- At the slightest doubt about the benign nature of a tumor, a biopsy must be taken and examined to exclude malignancy.
- Therapy with ablative lasers (CO_2 and erbium:YAG laser) yields in most cases much better cosmetic results than surgery, but keep in mind the possibility of recurrences.
- The treatment is painful and in most cases has to be carried out under local anaesthesia.

Aknowledgement: I would like to thank Alexandra Hammes for translating this chapter into English and for proofreading.

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5 Facial Rejuvenation and Other Clinical Applications of Intense Pulsed Light

Peter Bjerring and Kaare Christiansen

Core Messages

- Intense pulsed light (IPL) systems basically emit pulses of broad-spectrum visible and near visible infrared light.
- Different optical filtering techniques restrict the bands of wavelengths to match the specific absorptions of the two major skin chromophores hemoglobin and melanin.
- Furthermore, the pulse durations for IPL systems, in contrast to lasers, can be adjusted within a wide range. Therefore, IPL systems are very versatile and highly efficient for treatment of a vast range of skin conditions.
- IPLs are normally the first choice in facial rejuvenation treatment of diffuse redness, telangiectasias, and epidermal pigmentation.
- Fine wrinkles can also be reduced with IPL, and if combined with photodynamic therapy (PDT) it may be as efficient as fractional laser treatment. The combined IPL-PDT treatment has also shown high efficacy in acne treatment.
- Finally, IPL is now the most used equipment for hair removal, with same efficacy as alexandrite and diode lasers.

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5.1 Introduction

The first intense pulsed light (IPL) device was approved by the US Food and Drug Administration (FDA) for treatment of spider veins and leg veins in September 1995. It was based on the principle of selective photothermolysis [4], which indicates that the optical pulse durations should be chosen to be shorter than the thermal relaxation time (TRT) of the target. The variation in target size is several decades for cutaneous vessels (10 μm to 0.5 mm), and therefore the corresponding optimal TRTs vary between 50 μs and 120 ms.

In contrast to most lasers, the light pulse duration of IPL systems can easily be changed to match the TRT of the target. Most lasers emit a single, characteristic wavelength, whereas flash lamps in IPL systems emit the entire visual optical spectrum as well as a part of the near infrared (NIR) spectrum. A band of wavelengths matching the target's absorption spectrum can readily be obtained by selecting an appropriate combination of optical filters. IPL systems have been shown to be clinically superior to laser systems (for pulse durations >2.5 ms) when the primary mode of action is photothermolysis. For very short pulse durations, IPL systems may not deliver the necessary amount of optical energy, and in this case a laser might be a better choice.

Early versions of IPL devices were notorious for having a very narrow therapeutic window, resulting in frequent skin burn reactions due to inappropriate optical filters and light pulse characteristics. Second- generation IPL devices incorporate improved filters, which effectively remove unwanted ultraviolet (UV) and/or NIR light and shape the light pulse to be close to constant over time (squared pulse technology), which render these systems both safe and clinically efficient.

Initially, IPL systems were mainly used as substitutes for pulsed dye lasers and argon ion lasers for the

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_5,

treatment of vascular malformations and hemangiomas, but gradually other indications such as different photorejuvenation modalities and optical hair removal were also successfully addressed with these devices.

Treatment of photodamaged skin can be divided into four categories:

Type I
Photorejuvenation:
- Treatment of pigmented disorders
- Treatment of telangiectasias
- Reduction of diffuse erythema

Type II
Nonablative photorejuvenation:
- Reduction of fine wrinkles (epidermal effect)
- Reduction of rhytids and skin pore size [59] (dermal effect)

Type III
Ablative photorejuvenation:
- Ablative resurfacing using either carbon dioxide (CO_2) laser [18, 42] or erbium:yttrium aluminum garnet laser [69]

Type IV
Photodynamic photorejuvenation:
- Nonablative treatment combining Type I photorejuvenation with photodynamic therapy (PDT-assisted type II photorejuvenation)

5.2 Type I Photorejuvenation

5.2.1 IPL Treatment of Pigmented Disorders

The target chromophore in pigmented lesions is melanin. Melanin is a pigment produced by the melanocytes, situated in the stratum basale. Melanin-loaded packages (melanosomes) are taken up by keratinocytes, which accumulate the pigment in the upper part of the epidermis where the pigment protects the deeper tissues against UV damage.

The biological effect of optical treatment of unwanted pigment is either an optomechanical breakdown or a thermal damage of the pigment with subsequent removal of the damaged tissue by the immune system. Melanin does not have any specific light absorption peaks above 350 nm (Fig. 5.1), but it absorbs visible light as well as NIR light with decreasing absorption for longer wavelengths.

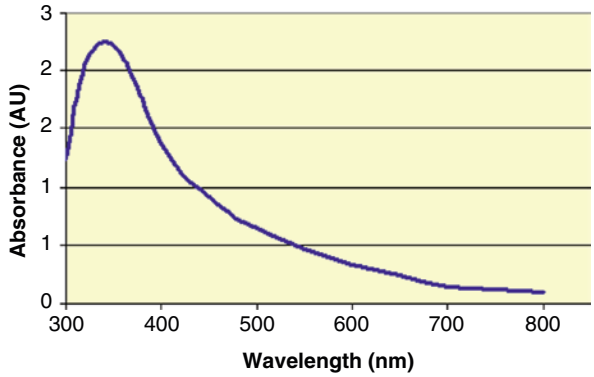

Fig. 5.1 Absorption spectrum for eumelanin

Because melanin absorbs all visible wavelengths, treatment of dyspigmentation such as solar lentigines, poikiloderma of Civatte, and benign melanocytic lesions can be performed with different lasers as well as with broadband IPL systems. Sherwood et al. [65] investigated the effects of 504, 590, 694, 720, and 750 nm and found 504 nm to be optimal, whereas Anderson et al. [5] tested Q-switched lasers with wavelengths of 355, 532, and 1,064 nm and found 532 nm to produce optimal pigment clearance. Both these findings reflect that a compromise between a high absorption in melanin and a lesion-specific penetration depth has to be found.

Treatment of pigmented disorders can also be based on the phenomenon of photoacoustics [71], where the pigment is broken down by shock waves generated in the tissue by very short light pulses from Q-switched lasers operating with pulse durations of 2–50 ns. These short pulse durations correspond to the TRTs of individual melanosomes. Longer pulse duration can also be used according to the theory of selective photothermolysis targeting the entire pigmented lesions. This type of treatment can be performed with normal mode (pulse durations in the millisecond domain) lasers and with IPL systems.

Several comparative split-face studies have been performed to evaluate the best choice of device for pigment treatment. Wang et al. [72] performed a split-face study comparing efficacy and side effects of a Q-switched alexandrite (755 nm) laser and an IPL for freckle and lentigo treatment in Asian skin types. For

patients with freckles, the Q-switch laser was found to be superior to IPL, but for patients with solar lentigines, the IPL treatment was most efficient. Postinflammatory hyperpigmentation developed in one patient (1 of 15) with freckles and eight (8 of 17) patients with lentigines after Q-switch treatment, but in none of the IPL-treated areas.

However, facial freckles on Asian skin types successfully have been treated with an IPL system in multiple sessions by Huang et al. [34], who used a new and objective method for evaluation of the severity of freckling and posttherapy improvement using an UV-sensitive camera and film. Thirty-six patients were IPL-treated with one to three sessions 4 weeks apart (mean, 1.47 sessions). Irradiation was performed with high pass cutoff filters at 550–590 nm and a fluence of 25–35 J/cm^2, and single or double pulses of 4.0-ms duration were used. A statistically significant improvement in mean freckles area and severity index (FASI) score was demonstrated at 6 months after treatment compared with baseline ($n=36$, $p<0.005$). The overall improvement rate, as determined from the difference in mean FASI score, was 63% at 12 weeks and 58% at 6 months.

In another split face study performed by Butler et al. [10] KTP laser treatments (532 nm) were compared to IPL treatments for 17 patients with dyschromias. Photos were blindly evaluated 1 month after a single treatment, and the mean improvement was found to be slightly higher for IPL, 35.1% vs. 30.2% for the KTP laser-treated side. Patients found KTP laser treatment to be slightly more painful (5.3 vs. 4.4 on a 0–10 visual analog scale [VAS]), and greater postprocedure swelling was also registered on the KTP laser-treated side.

In a study performed by Rusciani et al. [58], 175 patients were treated for poikiloderma of Civatte with an IPL using a 550-nm cutoff filter for the first treatment and 515-nm and 590-nm cutoff filters for the subsequent sessions. Double or triple pulses of 2.5- to 3.5-ms duration and delay of 10–20 ms were used with a fluence of 32–36 J/cm^2. Clearance of more than 80% of both the vascular and pigmented components of poikiloderma of Civatte was observed. Minimal and transient side effects occurred in only 5% of the patients. No scarring or pigment disturbances were noted after the treatments.

Melanin placed high in the epidermis, as in solar lentigines and freckles, can be treated very efficiently and safely with IPL (Fig. 5.2). The above mentioned investigations indicate that pigment located deeper, as in the cases of Becker's nevi and dermal melasma, is better treated with longer wavelengths, which have deeper penetration into the skin tissue, as well as with high-intensity, short Q-switched laser light pulses (Table 5.1).

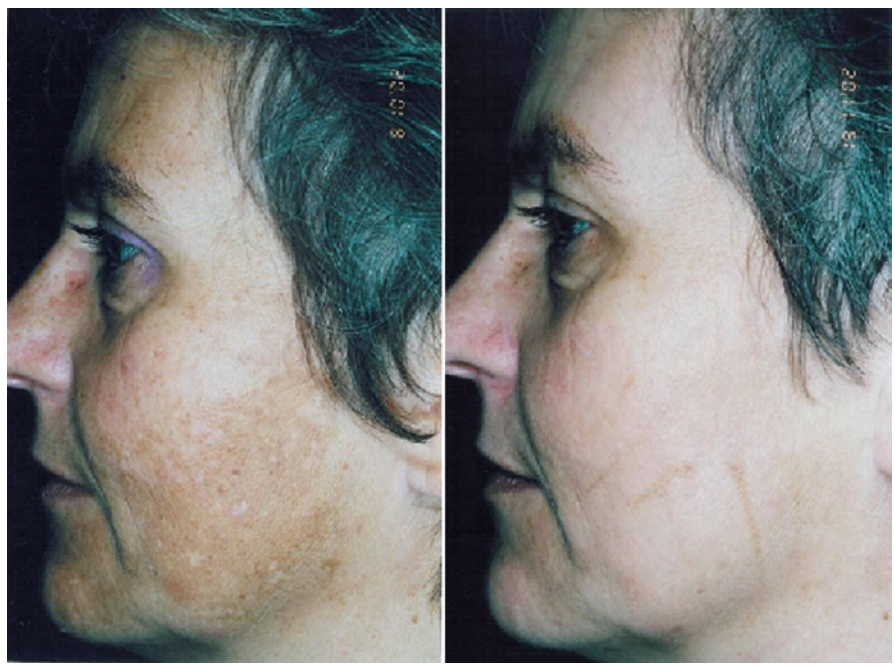

Fig. 5.2 Intense pulsed light treatment of epidermal melasma before and 1 month after a single treatment: double pulse, 2.5-ms pulse duration, 10-ms delay. Note the few missing overlaps

Table 5.1 Recommendation for treatment of epidermal pigment

	Epidermal pigmentation	Dermal pigmentation
Equipment	IPL	Q-switched lasers
Cutoff filters	525–590 to 900 nm	See Chap. 10
Pulse duration	2.5–4 ms	
Number of pulses	2–3	
Pulse delay	>10 ms	
Clinical endpoint	Photo-oxidation of the pigment, resulting in immediate darkening of pigmented spots	
Energy	Depending on filters and specific IPL equipment	

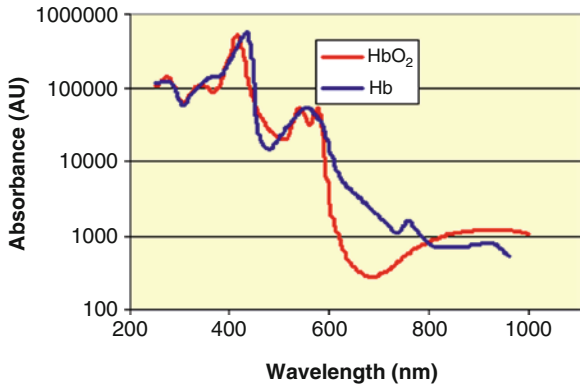

Fig. 5.3 Light absorption spectra for reduced hemoglobin (Hb) and oxyhemoglobin (HbO_2)

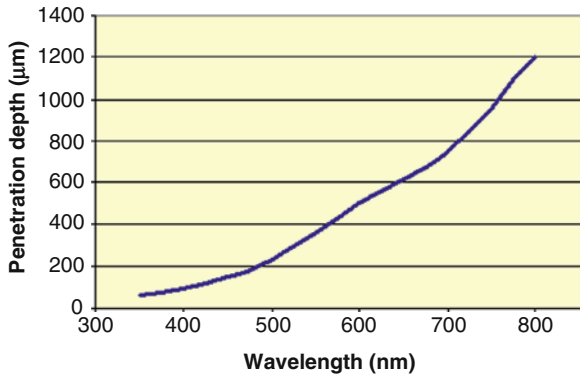

Fig. 5.4 Approximate penetration depth of optical radiation in fair white skin to a value of 1/*e* of the incident energy density

5.2.2 IPL Treatment of Telangiectasias

The ultimate target for optical treatment of ectatic vessels is the lamina intima of the vessel wall, which has to be heated to a temperature of 70°C for more than 1 ms to induce permanent damage. This will lead to formation of a blood clot and eventual disruption and clearance of the vessel. However, the vessel wall is nearly transparent for all wavelengths and cannot act as a light absorber (chromophore) itself. Therefore, the treatment is instead based on light absorption in reduced hemoglobin and in oxyhemoglobin inside the blood vessel. The absorbed light is transformed into heat and subsequently conducted to the lamina intima of the vessel wall.

Reduced hemoglobin has major light absorption peaks at 432 and 556 nm, and oxyhemoglobin has three absorption peaks at 414, 542, and 576 nm [52] (Fig. 5.3). The strongest absorption occurs at 414 nm, but due to the very shallow penetration depth for this relatively short wavelength (Fig. 5.4, [3]) and the high absorption in the competing and overlaying chromophore melanin in the epidermis, this wavelength is not practically usable. The argon laser, emitting light at 488 and 514 nm, was the first laser used for vascular treatments in the 1970s [26], but over time it became technically possible to use longer wavelengths: the KTP laser at 532 nm, the tunable pulsed dye laser (PDL), with even deeper penetrating wavelengths ranging from 577 to 600 nm. Even longer wavelengths from either diode lasers at 810–980 nm or neodymium (Nd): YAG lasers at 1,064 nm are used now for vascular treatments. The penetration depth of Nd:YAG laser light at 1,064 nm is significantly deeper than for dye lasers, up to 2 mm, and its primary use is treatment of leg telangiectasias. The light absorption in hemoglobin and oxyhemoglobin at this wavelength is about 1/10 of that for 576 nm, but the absorption in the competing chromophore melanin is reduced even more. Therefore, this wavelength can successfully be used if skin surface cooling is applied.

In 1995, IPL systems got FDA clearance for vascular treatment. The first IPL systems used 515-nm cutoff filters, and this device emitted light from about 510 nm to more than 1,200 nm [54]. Due to the high absorption in melanin at 510 nm and the relatively low absorption in hemoglobin, the risk of skin burn was high and darker skin types or sun-tanned persons could not be treated with these systems. In later generations of IPL systems,

the emitted band of wavelengths has been restricted to 530, 550, or even 570 nm depending on the skin types treated.

A further development in some newer IPL systems is the use of dual mode filtering, meaning that the emitted light passes both a short wavelength cutoff filter and a thick layer of water, which blocks wavelengths above 900 nm that would otherwise have lead to unwanted, nonspecific heating of the tissue water present in the skin. Dual mode filtering increases the selectivity of the heat delivery and reduces the light energy needed, which in turn reduces surface heating significantly. This filtering system has reduced the risk of adverse effects from IPLs significantly and has abolished the need for surface cooling.

In a comparative IPL split-face study with dual mode filtering, we investigated the clinical efficacy and safety of two different IPL-generated wavelength bands (555–950 nm vs. 530–750 nm) [8]. The restricted 530- to 750-nm wavelength band was found to be superior for treatment of visible telangiectasias where 81.8% vs. 58.8% of the patients obtained fair, good, or excellent improvement (Fig. 5.5). No skin atrophy, scarring, or pigment disturbances were found after the treatments, but acute side effects such as edema and erythema were registered in two-thirds of the facial sides treated with the restricted wavelength band and only in one-third of the other side. Because the used light fluence in general was lower for the restricted wavelength band (13–15 J/cm^2 compared with 11.5–20 J/cm^2), it can be concluded that treatment with the restricted wavelength band is efficient but more aggressive, calling for caution, especially when treating darker skin types than Fitzpatrick skin type III or patients with sun-tanned skin.

According to the theory of selective photothermolysis, the pulse duration for vascular treatments must be equal to or less than the thermal relaxation time (TRT) of the vessels. The TRT for a vessel with a diameter can be calculated by:

$$\mathrm{TRT} = d^2/16 \cdot \kappa, \text{ where } \kappa = 1.3 \times 10^{-7}\, m^2$$

Calculations predict that the ideal pulse duration for the treatment of telangiectasias within a diameter of 30–300 μm is 0.5–40 ms (Fig. 5.6). The cross-sectional dimensions of telangiectatic vessels vary from 10 to 400 μm. The mean diameter of the vessels has been shown to be related to the color of the lesion; diffuse pink lesions generally have smaller diameters (10–20 μm) than purple lesions (50 μm). The larger

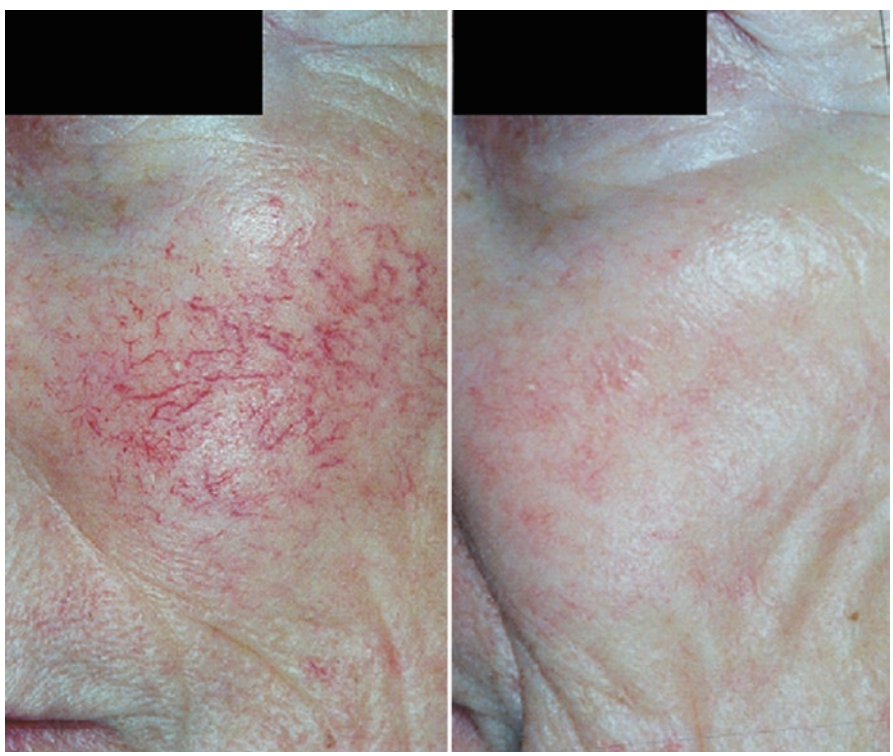

Fig. 5.5 Patient with visible telangiectasias before (*left*) and after (*right*) four intense pulsed light treatments

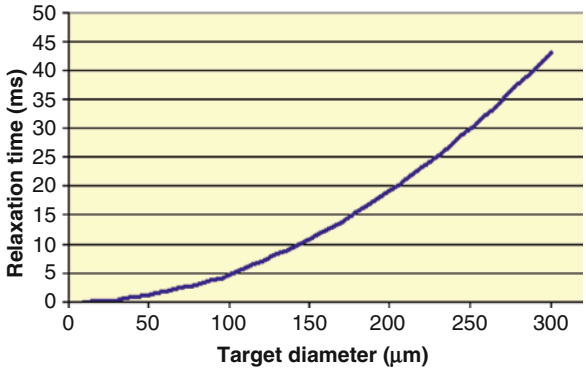

Fig. 5.6 Thermal relaxation time for different vessel diameters

vessels are normally located deeper than pink and red lesions [17]. The diameters of visible telangiectatic vessels vary between 100 and 400 μm. In contrast to most lasers, single light pulses from IPL systems can be varied over a very broad range of time to accommodate variations in vessel diameter [53, 63].

In 2001, Altshuler et al. [2] published the "extended theory of selective photothermolysis" and introduced the concept of "thermal damage time" (TDT) for non-uniformly pigmented targets. For thicker vessels, the TDT is significantly longer than the TRT. The theory provides new recommendations for treatment parameters for both photoepilation and photosclerotherapy. For thicker vessels, the TDT is significantly longer than the TRT. Because facial telangiectasias normally consist of thinner vessels (<200 μm), the use of TRT and not TDT will in most cases be sufficient as a guideline for selection of proper light pulse durations in clinical settings.

For a correctly chosen pulse time and a given laser wavelength or IPL wavelength band, it is necessary to ensure that the correct amount of optical energy is also released to heat the vessel's lamina intima to 70°C for at least 1 ms to denature structural proteins and to start the vessel clearance procedure. If the energy setting is too high, too much heat will be conducted further out into the surrounding tissues (with substantial risk of thermally induced adverse effects), or the blood inside the vessel will start to boil, leading to steam formation, disruption of the vessel wall, and blood leaking into the interstitium with the clinical sign of purpura. However, if the energy setting is too low for the pulse time used, the vessel temperature will not reach a level sufficient to denature proteins, and the expected clinical result will not take place. A correct energy setting is obtained if a rapid color change of the vessels to a blue color can be observed within less than a second after the light pulse. This biological reaction (transient purpura) may rapidly reverse to the original vessel color and is followed by a longer-lasting diffuse erythema and later edema. A lack of skin reaction does not imply that the treatment will be totally ineffective, but usually indicates that a more effective result could have been achieved by increasing the energy slightly. If the skin turns a grayish color, indicating denaturation of the epidermis, the energy setting has been too high and must be reduced or skin surface cooling must be applied.

Today the most commonly used devices for treatment of facial telangiectasias and diffuse redness are IPL systems, followed by PDL (LPDLs). In darker skin and for the treatment of vessels on the legs, the long-pulsed Nd:YAG laser combined with rigorous skin surface cooling seems to be superior. In 2008, Galeckas et al. [22] performed a split-face study comparing a PDL with an IPL system. Ten patients were treated three times at - to 4- week intervals. Follow-up with blinded evaluation took place 1 month after the final treatment. Improvements of dark and light lentigines on the PDL-treated side were 86.5% and 65% vs. 82% and 62.5% on the IPL-treated side. Clearance of vessels <0.6 and >0.6 mm was 85% and 38% for the PDL-treated side, and 78.5% and 32.5% for the IPL-treated side. Improvements in skin texture were 40% vs. 32% at the IPL-treated side. PDL treatments were more painful (5.8 vs. 3.1 on a 0- to 10-point VAS) and the treatment procedure lasted longer (7.7 vs. 4.6 min) and resulted in purpura in 10% of the treatments, whereas the IPL treatments were purpura free.

Also, a side-by-side study was performed by Fodor et al. [19] comparing an IPL system to an Nd:YAG laser for treatment of vascular lesions. Twenty-five patients with telangiectasias, leg veins, or cherry angiomas underwent treatment of the same category of lesion in the same area. At the 1-year follow-up, 72% felt they still had good to excellent results after the Nd:YAG treatment, whereas only 48% felt the same after IPL treatment. The most common side effect after Nd:YAG laser treatment was hyperpigmentation. Patients with telangiectasias, cherry angiomas, or leg veins <1 mm were more satisfied after IPL, whereas those with leg veins >1 mm were more satisfied after

Nd:YAG laser treatment. Overall, satisfaction with treatment of vascular lesions was greater with the Nd:YAG laser, although this method was more painful.

Because IPL systems emit a band of wavelength covering one or more of the absorption peaks of reduced hemoglobin and oxyhemoglobin, these devices are also very efficient for treatment of superficially located vascular malformations (port wine stains) [7, 15] as well as telangiectasias [8] and diffuse redness [7]. Deeply situated and thicker vessels and leg veins are normally better treated with Nd:YAG lasers [19].

5.2.3 Reduction of Diffuse Redness (Erythema)

Erythema is caused by dilation of capillaries, resulting in increased blood content in the skin that is observable as permanent redness or facial flushing. In 30–50% of cases the cause of erythema is unknown, but solar radiation and skin inflammation due to acne, medication, allergies, or rosacea are common causes.

The main difference between optical treatment of visible telangiectasias and diffuse erythema is the pulse duration, which should be shorter in the treatment of diffuse erythema due to the smaller size of the capillaries (10–50 μm). Several treatment options are available: KTP lasers [45] (532 nm) and copper vapor lasers (510 and 578 nm) were used in the past, but today, IPLs and LPDLs are commonly used. Taub [67] reported in 2003 that 83% of patients obtained reduction in redness and 75% noted reduced flushing as well as improved skin texture after 1–7 PDL treatments with 450-μs pulse duration. However, this short pulse duration always lead to purpura formation. The LPDL produces a train of light pulses, and the resulting longer macropulse may last for tens of milliseconds. Bernstein et al. [6] concluded, in an investigation of 20 rosacea patients treated with the LPDL, that rosacea improved with a very favorable safety profile and with significantly less purpura as with earlier generations of short pulsed dye lasers.

Diffuse redness can also be treated effectively with IPL systems without concomitant production of purpura. We found a reduction in diffuse redness in 19 out of 21 patients (90.4%) after IPL treatment with 10-ms pulse duration and a wavelength band of 555–950 nm [7] (Fig. 5.7). In a later comparative study [8] optimizing the wavelength band, we found fair, good, or excellent clearance in diffuse erythema in 72.7% of patients treated with 530–750 nm and in 35% of patients treated with 555–950 nm. This difference was statistically significant ($p = 0.025$). In both cases, 2–3 treatments 3–4 weeks apart were performed with two 2.5-ms pulses with a 10-ms delay.

Neuhaus et al. [49] performed a comparative study using either LPDL or IPL treatment for erythemato-

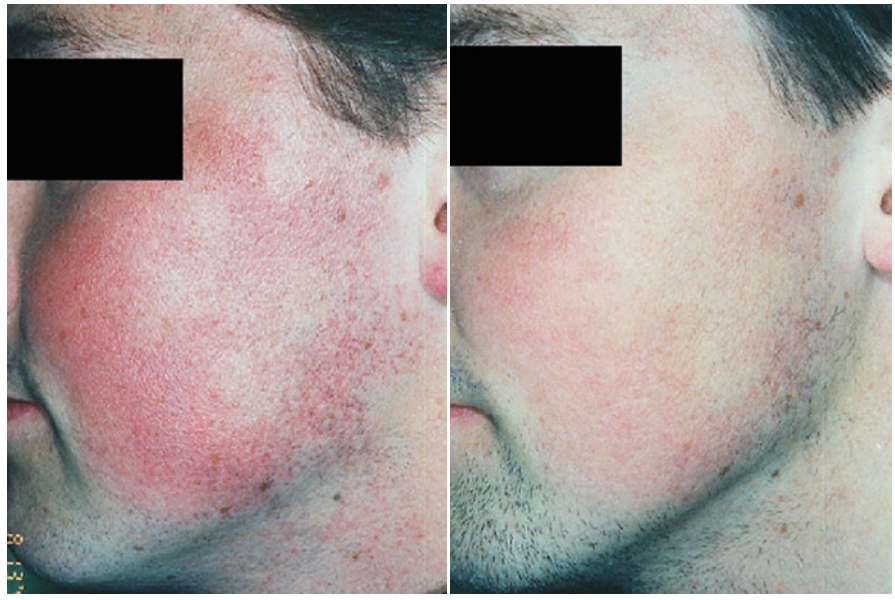

Fig. 5.7 Patient with diffuse erythema without significant visible vessels before (*left*) and after (*right*) four intense pulsed light treatments

telangiectatic rosacea. This was a randomized, controlled, single-blind, split-face trial with non-purpuric treatments in 29 patients. LPDL settings were 10-mm spot size, 7 J/cm^2 fluence, 6-ms pulse duration with cryogen cooling, and the IPL was equipped with a 560-nm filter, a pulse train of a 2.4-ms and a 6.0-ms pulse separated by a 15-ms delay. Significant reduction in cutaneous erythema was obtained with both devices, but no significant difference was noted between the non-purpuric LPDL and the IPL treatments.

In another IPL study, 34 rosacea patients were treated four times at 3-week intervals. Papageorgiou et al. [51] found an average reduction in rosacea severity of 3.5 points on a 10-point VAS. Both patients and physicians rated the overall improvement of rosacea, and more than 50% improvement was rated by 73% of the patients and 83% of the physicians ($p < 0.001$). The IPL treatment of rosacea produced a significant reduction in erythema and telangiectasias of rosacea with minimal side effects, and the improvements were sustained at 6-month follow-up (Fig. 5.8, Table 5.2).

5.2.4 Conclusion Type I Photorejuvenation

IPL photorejuvenation has been performed for more than 10 years now, and as early as in 2002, Weiss et al.

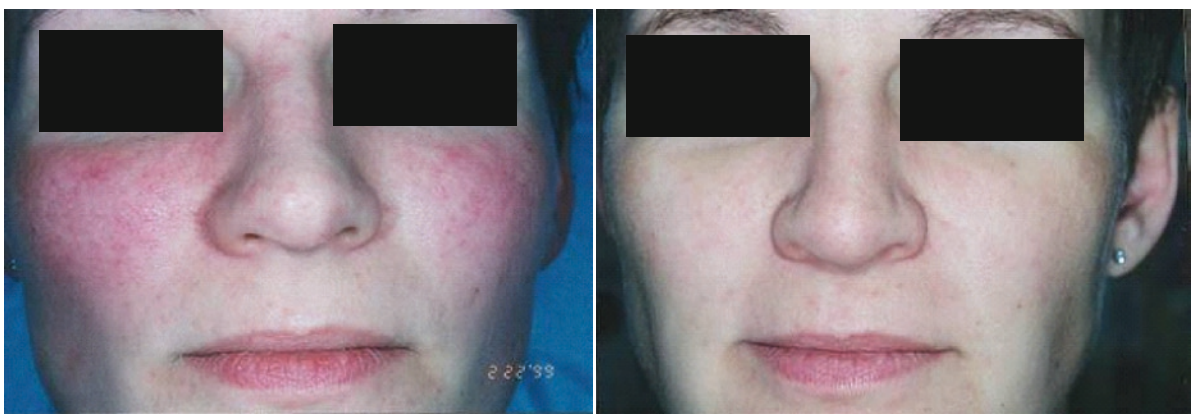

Fig. 5.8 Rosacea patient before (*left*) and 2 months after (*right*) two intense pulsed light treatments

Table 5.2 Recommendation for treatment of telangiectasias and erythema

	Erythema, diffuse redness	Thin vessels just individually visible	Visible thick vessels <1 mm	Visible thick vessels >1 mm
Equipment	IPL	IPL	IPL	Nd:YAG laser
Cutoff filter	Nonpigmented and lightly pigmented skin types I–III: 525–540 to 950 nm			NA
	Pigmented skin types I–III and higher skin types: 550–590 to 950 nm			
Pulse duration	6–8 ms	10–14 ms	15–30 ms	Chap. 16
Number of pulses	1	1	1	
Clinical endpoint	Disappearance of vessels	Bluish response or disappearance of vessels	Bluish response (transient purpura)	
Energy	Depending on optical filters and specific IPL device			

IPL intense pulsed light, *Nd:YAG* neodymium:yttrium aluminum garnet

[73] evaluated long-term clinical results on the face, neck, and chest. Four years after treatment of telangiectasias, with a median of three treatment sessions, improvements still remained visible in 82% of patients. For pigmentation and textural improvement, corresponding improvements were found in 79% and 83% of the patients, respectively. In 2005, Goldman et al. [27] performed a literature review of IPL photorejuvenation and concluded that IPL is an excellent treatment modality for vascular and pigmented manifestations of photoaging.

IPL treatment of sun-damaged skin, including telangiectasias and mottled pigmentation of the face, neck, and chest, is as effective as any other nonablative treatment modality, and it is safe, with no downtime and only minimal adverse effects such as temporary edema and erythema lasting 1–2 days.

5.3 Photorejuvenation Type II – Nonablative Wrinkle Reduction

Nonablative wrinkle reduction has been successfully performed with short PDLs (585–595 nm), IPL systems (525–950 nm), infrared wavelength lasers [20, 32, 33, 50], radiofrequency devices [41, 47], and other optical infrared devices [56, 75]. These treatments resulted in only little or no type I photorejuvenation effects (effects on ectatic vessels and irregular pigmentation).

The theory behind the short pulsed laser and IPL treatment with visible light is based on the fact that short pulses of light are preferentially absorbed in hemoglobin and will produce a transient dilatation of normal capillaries leading to a subliminal damage to the endothelium and to extravasation of thrombocytes. Both phenomena result in the release of humoral mediators, which stimulate fibroblast production of collagens, elastin, and glucosaminoglycans.

The mode of action of the infrared light sources is general and nonspecific heat damage to the dermal tissues due to light absorption in tissue water. Simultaneous cooling of the skin surface protects the epidermis against heat damage. Heating of the dermis initiates a wound-healing response, leading to renewal of the dermal extracellular matrix and ground substance.

Photorejuvenation type II performed with IPL leads to increased collagen production [48] and improvement in skin texture [16, 37], but until now the clinical efficacy of IPL treatment for reduction of facial wrinkles as a monotherapy has been shown to be modest [29, 30, 37] and inferior to other nonablative treatments, especially fractional laser treatments [13, 43, 60].

On the other hand, IPL photodynamic treatment combined with high-concentration (20%) 5-aminolaevulinic acid (ALA) has shown significant reduction in wrinkle appearance; recently we demonstrated that low- concentration (0.5%) liposome encapsulated 5-ALA has good clinical efficacy for reduction of wrinkles [9]. This treatment is called photorejuvenation type IV (see Sect. 55).

5.3.1 Recommendation for Nonablative Treatment of Wrinkles

IPL treatment is now generally not recommended as monotherapy for nonablative wrinkle reduction. However, in 20% of patients this treatment results in minor, visible improvements in skin wrinkling as an additional effect to photorejuvenation type I. Instead, the combination of photodynamic treatment and IPL is now recommended (see Sect. 5.5.1) (Table 5.3).

Table 5.3 Recommendation for nonablative wrinkle reduction

	Stand-alone IPL settings: safe but not very efficient	Recommended non-ablative treatment for wrinkles
Equipment	IPL	Photodynamic photorejuvenation or nonablative fractional treatments. See Chap. 24
Cutoff filter	525–550 to 950 nm	
Pulse duration	2.5–4 ms	
Number of pulses	2–3	
Pulse delay	≥10 ms	
Energy	Depending on filter combinations and specific equipment	

IPL intense pulsed light

5.4 Photorejuvenation Type III – Ablative Wrinkle Reduction

Due to limitations in most IPL systems' optical energy output at short pulse durations, there have been only a few attempt to perform ablative wrinkle reduction. In contrast, ablative treatments can be performed with high clinical efficacy with both Er:YAG and CO_2 lasers, either with classical full-coverage ablation or with fractional ablation. The fully ablative treatment requires meticulous postprocedure wound-healing treatment, and downtime normally lasts from a few days to 2 weeks (see Chap. 21).

5.5 Photorejuvenation Type IV

5.5.1 Photodynamic Photorejuvenation

Cutaneous photodynamic effects were first demonstrated in 1904 by von Tappeiner and Jodblauer [44]. In 1990, Kennedy et al. [39] introduced 5-ALA as a topical photosensitizing agent. 5-ALA is a prodrug, which is transformed into the highly photoactive endogenous protoporphyrin IX (PpIX). When PpIX is present in high concentrations inside the cells, illumination of the skin's surface with light of specific visible wavelengths (407, 510, 542, 578, 630, and 665 nm) will result in the formation of free oxygen radicals, leading to cell death.

PDT has been used for treatment of malignant or premalignant skin conditions since the beginning of the 1990s [24]. Successful application of PDT in the treatment of actinic keratosis (AK) has been reported in more than 100 studies now. Since Ruiz-Rodriguez et al. [57], Gold [23], and Morton et al. [46] in 2002 found improvements in signs of aging skin after IPL treatment of AKs, cosmetic use of 5-ALA as an enhancer for standard photorejuvenation has become common.

The exact mode of action of the pretreatment with 5-ALA leading to increased cosmetic improvements is currently not known. It is hypothesized that the effect might be due to scattered cell destruction amongst normal dermal cells, which generates a biological signal leading to an increased fibroblast production. Also, 5-ALA is a precursor to cytochromes, and therefore supplying 5-ALA to the skin may increase cytochrome capacity, increasing the oxidative metabolism of the cells, and the production of collagen and elastic fibers.

Clinically, the added effect of pretreatment with 20% 5-ALA prior to standard photorejuvenation procedures is well documented. Alster et al. [1] published a comparative split-face study with IPL therapy alone and in conjunction with topical 20% 5-ALA (Levulan, Kerastick, Dusa Pharmaceuticals, Wilmington, Mass., USA). Ten patients with mild to moderate photodamaged facial skin were randomly assigned to treatment with 5-ALA applied for 60 min followed by IPL treatment on one half of the face and IPL alone on the other side. Two treatments were delivered with a 4-week interval between them. Significantly better clinical improvement scores were noted on the areas that were treated with a combination of 5-ALA plus IPL (reduction in severity on a 0–4 scale of 1.82 vs. 1.25 at the 1-month follow-up, 1.77 vs. 1.21 at the 3-month follow-up, and 1.65 vs. 1.28 at the 6-month follow-up). Dover et al. [14] published a randomized, prospective, controlled 5-ALA split-face photorejuvenation study, where 20 subjects participated in a series of three split-face treatments 3 weeks apart, in which half of the faces were pretreated for 30–60 min with 20% 5-ALA (Levulan, Kerastick) followed by IPL treatments. Where as the other facial halves were treated with IPL alone. Pretreatment with 5-ALA followed by IPL treatment was more efficacious than IPL treatment alone, as judged against a global score for photoaging (80% of subjects vs. 45% of subjects; $p=0.008$). Better results were achieved on the side pretreated with 5-ALA compared with the side treated with IPL alone for fine lines (60% of subjects vs. 25% of subjects; $p=0.008$).

Short-contact (30–60 min), full-face 5-ALA (Levulan, Kerastick) photorejuvenation with IPL activation was compared to IPL treatment alone by Gold et al. [25]. Three treatments were given at 1-month intervals with follow-up visits at 1 and 3 months after the final treatment. Thirteen out of 16 patients completed the trial. Three months after the final treatment, improvements were greater in the ALA/PDT/IPL sides than in IPL-alone sides for the following parameters: photodamage/crow's feet appearance (55% vs. 29.5%), tactile skin roughness (55% vs. 29.5%), and telangiectasias (84.6% vs. 53.8%).

Reduction of application time of 5-ALA from 2–3 h to "short" contact (30–60 min) did not result in inferior clinical outcomes. Side effects such as erythema, edema, and crusting are normally considered to be adverse

effects after photorejuvenation with a pretreatment of 2–3 h of 20% 5-ALA, and many patients reported downtime of up to 1 week after treatment [24]. Unfortunately, even with a 30- to 60- min 5-ALA application time, the frequency and severity of adverse effects such as erythema and edema are significant. Dover et al. [14] found intense erythema and edema in 50% of the patients treated with 30- to 60-min 5-ALA application followed by IPL irradiation, compared to 15% in the side treated with IPL only. This difference was statistically significant. Alster et al. [1] found that erythema lasting for 1–4 days, edema, desquamation, and blistering lasting for 2–4 days were seen only in the 5-ALA and IPL-treated side when using 20% 5-ALA.

The transformation of 5-ALA into PpIX can be monitored noninvasively by detecting skin surface fluorescence. In a human in vivo study by Juzeniene et al. [38] using topically applied 5-ALA, methyl-5ALA (MALA), and hexyl-5 ALA, a tight correlation was found between the 5-ALA concentrations used, application time, and endogenously produced photosensitizer. This investigation was based on skin fluorescence measurements of induced PpIX, which fluoresces at 634 nm (with excitation at 407 nm). A linear correlation between skin surface fluorescence and application time of 5-ALA was found for at least the first 8 h of application, and the increased fluorescence was found to be a function of the 5-ALA concentration used. However, the concentration correlation was nonlinear because application of 0.2%, 2%, and 20% 5-ALA resulted in fluorescence intensities of 20%, 50%, and 90, respectively.

We investigated skin fluorescence after 5-ALA application on the backs of ten white volunteers. Fluorescence was monitored with a FluoDerm detector (Dia-Medico ApS, Denmark) 12 h after the end of the application [11]. We found that the skin fluorescence after a 1- to 2-h application of 20% 5-ALA continued to increase for 8 h after the end of application, and the skin fluorescence was still significant after 36 h. This clearly explains why higher 5-ALA concentrations induce a high risk of phototoxic side effects. Due to the low natural permeability of 5-ALA through the stratum corneum, it is not possible to reduce 5-ALA concentrations in standard cream vehicles and still obtain sufficient penetration.

Liposomes have been used as vehicles for transportation of both hydrophilic and hydrophobic compounds across the stratum corneum barrier since 1970 [62]. In 1996, Fresta et al. [21] and Short et al. [66] found that encapsulation of hydrophilic compounds in vesicles of unsaturated phospholipids resulted in increased cutaneous absorption. Liposome encapsulation of 5-ALA allowed for the use of much lower concentrations of 5-ALA, and the optimal concentration of liposome -encapsulated 5-ALA was found to be 0.5% [11]. After approximately 2 h of repeated spraying with a 0.5% liposome-encapsulated 5-ALA spray (Photo Spray, Ellipse A/S, Denmark) at 15-min intervals, skin fluorescence was found to saturate at a safe fluorescence level that was equivalent to the fluorescence normally obtained after a 30- to 60-min application of 20% 5-ALA in a moisturizing cream base – but with a substantially lower total dose of 5-ALA delivered, and hence no prolonged action. This safe and relatively low fluorescence level remains constant for as long as the spraying is maintained and begins to decrease only 15 min after the spraying procedure is terminated.

In a recently published study [9], we found that in white skin the spraying time with Photo and Spray could be reduced to 1 h by decreasing the spraying intervals to 5 min and still obtain equivalent and sufficient facial skin fluorescence levels for photodynamic wrinkle reduction. Thirty-seven healthy, white female patients participated in this randomized, prospective split-face study, and two different IPL treatment modalities were investigated, both of which were preceded by approximately 1 h of spraying with 0.5% liposome-encapsulated 5-ALA (Photo Spray). One of the treatment modalities combined type I photorejuvenation with wrinkle reduction (C-PDT) with an IPL light spectrum from 530 to 750 nm and double light pulses with durations of 2×2.5 ms spaced with a delay of 10 ms (7 J/cm^2). The other modality (PDT alone) emitted a spectrum from 400 to 720 nm. Three low-energy passes were performed with a single pulse of 30-ms duration (total 10.5 J/cm^2). After a series of three C-PDT or PDT-alone treatments, the patients obtained statistically significant ($p < 5 \times 10^{-5}$) reductions in Fitzpatrick wrinkle severity for periorbital wrinkles, with a reduction of 1.2 grades (SD 1.1) and 1.1 (SD 1.1), respectively (Figs. 5.9 and 5.10). The reduction in Fitzpatrick wrinkle severity for perioral wrinkles was a little smaller: 0.8 grades (SD 1.0) and 0.7 (SD 0.9), respectively (Fig. 5.11). These results show that statistically significant improvements in wrinkle reduction and skin texture, which are equivalent to previously reported results obtained with 20% ALA, can be obtained with 0.5% liposome encapsulated 5-ALA

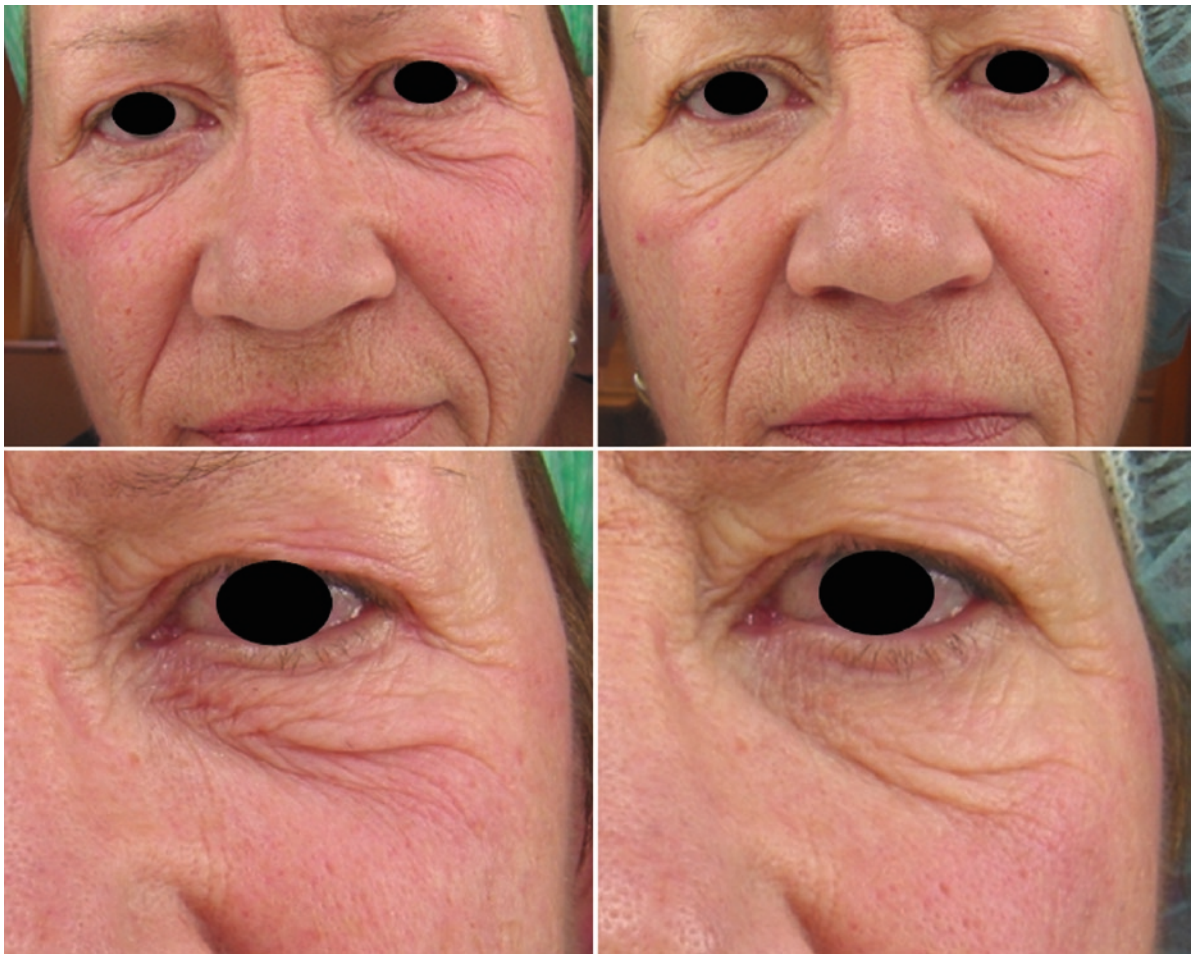

Fig. 5.9 Reduction of wrinkles in a 61-year-old female patient with substantial periorbital wrinkles before and 3 months after three fluorescence-controlled photodynamic photorejuvenation treatments 3 weeks apart

spray. This study also showed that side effects could be avoided or minimized by liposome encapsulating, which allowed for a 40-fold reduction in the 5-ALA concentration.

5.5.2 Fluorescence-Controlled Photodynamic Photorejuvenation

A relatively large interindividual variation exists in treatment efficacy of photorejuvenation treatment with enhancement by 5-ALA. Monitoring of the obtained skin fluorescence also shows large individual differences. In our recent study [9], the individual differences after 1 h of spraying with Photo Spray were between 1 and 11 FluoDerm units (FDU), and Christiansen et al. [11] found a variation in fluorescence of between 1 and 8 FDU after 1 h of facial application of 20% 5-ALA. Our own studies have shown that an added fluorescence of 2 FDU is needed to obtain clinically efficient photodynamic photorejuvenation. In one of our studies [9] we found it necessary to extend the 5-ALA spraying time for half an hour in 26% of patients.

It can be concluded that fluorescence monitoring during pretreatment with 5-ALA (and after IPL treatment) should be performed to improve clinical efficacy, reduce treatment time, and increase safety of photodynamic photorejuvenation treatments (Table 5.4).

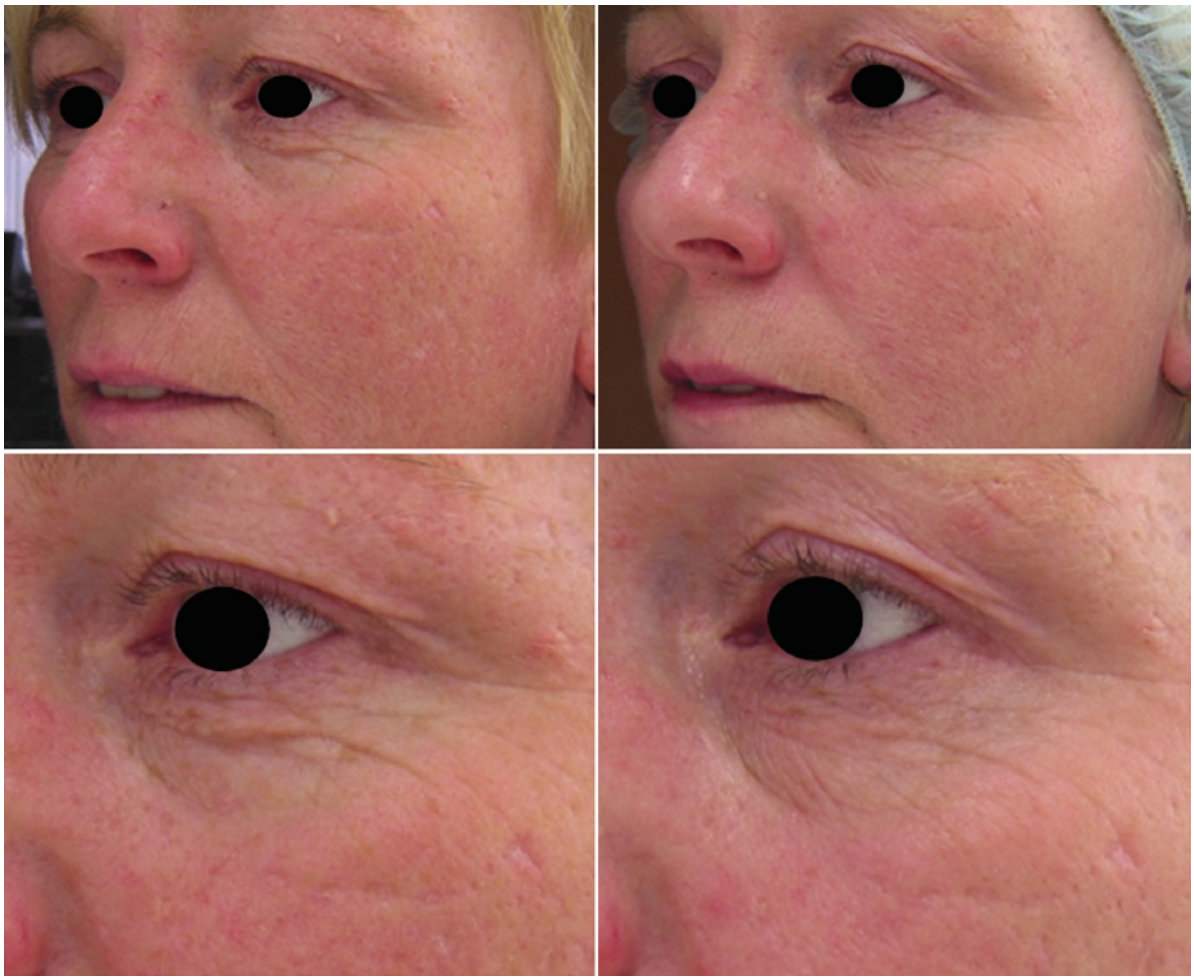

Fig. 5.10 Reduction of wrinkles in a 42-year-old female patient with substantial periorbital wrinkles before and 3 months after three fluorescence-controlled photodynamic photorejuvenation treatments 3 weeks apart

5.6 Other Clinical Applications for IPL Treatment

5.6.1 Acne Vulgaris

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit. The most common site is the face – followed by the shoulders, back, chest, arms, neck, buttocks, and legs. Acne is the most common dermatosis, affecting adolescents as well as young adults in all ethnic groups. The disorder is caused by abnormal desquamation of the follicular epithelium that results in obstruction of the pilosebaceous canal. This obstruction leads to the formation of comedones, which can become inflamed because of overgrowth of propionibacterium acnes. In 75% of patients the disease is mild to moderate. In the remaining 25%, the patients have inflammatory lesions and normally benefit from treatment with benzoyl peroxide, azelaic acid, or topical antibiotics. The main emphasis on management of inflammatory acne is to prevent development of atrophic and hypertrophic scarring.

For poor responders or patients who cannot accept medical treatments, laser-, lamp-, or IPL-light treatments alone or in combination with PDT have been shown to be efficient treatment modalities. The mode of action of light treatment of acne is related to energy

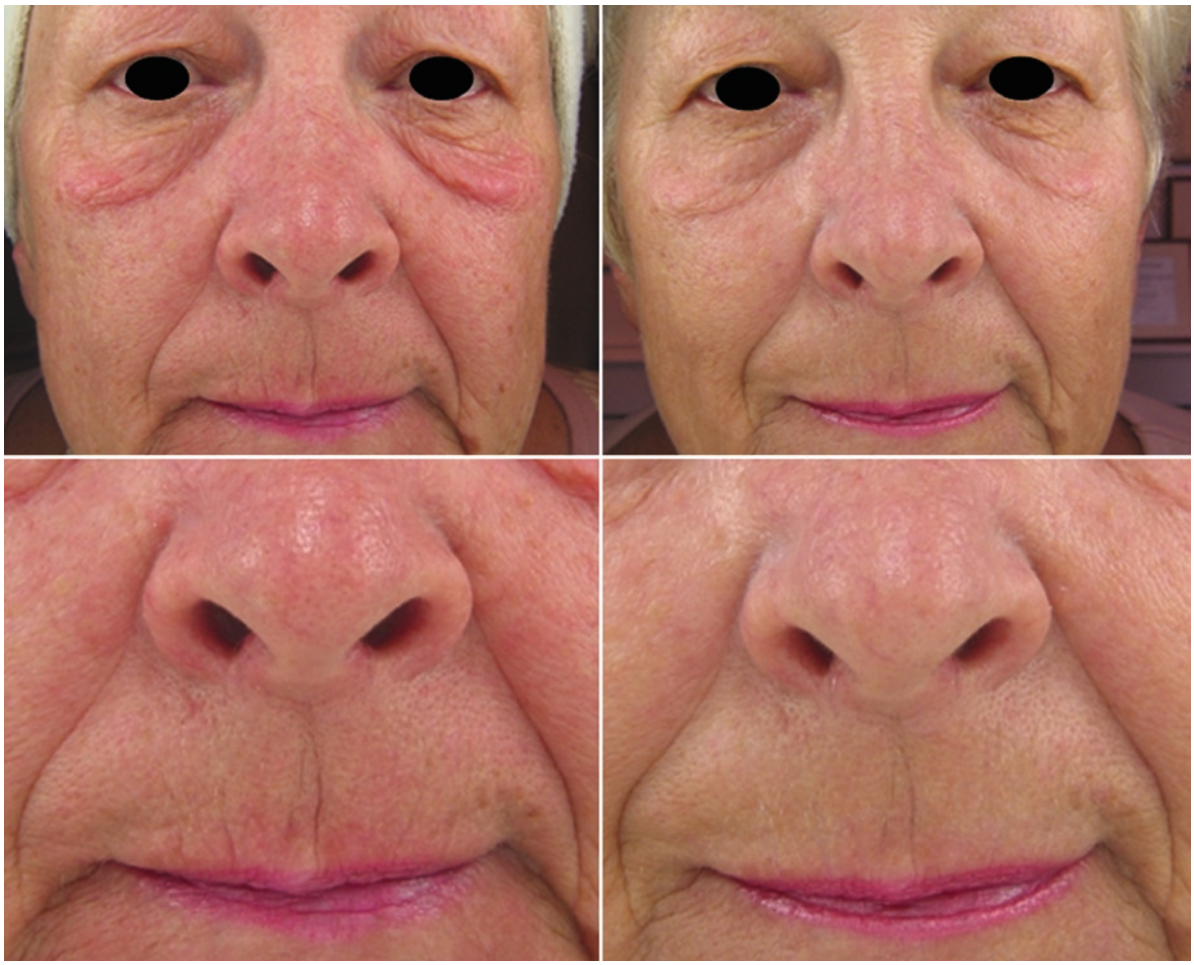

Fig. 5.11 Reduction of wrinkles in a 60-year-old female patient with substantial periorbital wrinkles before and 3 months after three fluorescence-controlled photodynamic photorejuvenation treatments 3 weeks apart

and wavelength. NIR light decreases sebum excretion from the sebaceous glands, visible red light reduces inflammation, visible light reduces cornification and hence opens up the pilosebaceous canal. Most strains of propionibacteria contain PpIX and can be selectively destroyed by exposure to visible light, especially blue light at 415 nm. Because IPL systems, by nature, emit a broad spectrum of wavelengths from 380 to 1,200 nm, all of the above mechanisms can be addressed by using specific optical filters. IPL systems are well-suited light-emitting devices for acne treatments.

5.6.2 Light Treatment of Acne Vulgaris

Seaton et al. [64] compared the efficacy and tolerability of PDL treatment with sham treatment in patients with facial inflammatory acne in a double-blind, randomized, controlled trial. Forty-one adult volunteers with mild to moderate facial inflammatory acne were randomly assigned to PDL ($n=31$) or sham ($n=10$) treatment. Treatment was given at baseline, and patients were seen after 2, 4, 8, and 12 weeks. Assessors and participants were unaware of treatment allocations. Primary outcome measures were acne severity after 12 weeks

Table 5.4 Recommendation for photodynamic photorejuvenation

	Fluorescence-controlled photodynamic photorejuvenation	Photodynamic photorejuvenation
Pretreatment	Liposome encapsulated 0.5% 5-ALA or 20% 5-ALA or 16% MALA	
Endpoint pretreatment	Fluorescence controlled: Increase of ≥2 FDU	0.5% 5-ALA: 60 min 20% 5-ALA: 30 min 16% MALA: 30 min
Equipment	IPL	IPL
Cutoff filter	530–950 nm or 525–555 to 950–1,200 nm	
Pulse duration	2.5–4 ms	
Number of pulses	2–3	
Interpulse delay	10–20 ms	
Clinical endpoint	Photo-oxidation of the pigment, resulting in immediate darkening of pigmented spots; Light erythema	
Energy	Depending on filters and specific IPL equipment	

ALA 5-aminolevolinic acid, *MALA* methyl-5-aminolevolinic acid, *FDU* FluoDerm units, *IPL* intense pulsed light

and adverse events at any time. After 12 weeks, acne severity (measured by the Leeds revised grading system) was reduced from 3.8 (SD 1.5) to 1.9 (SD1.5) in the PDL group and 3.6 (SD1.8) to 3.5 (SD1.9) in the sham group ($p=0.007$). Inflammatory lesion counts were reduced by 49% in PDL patients and by only 10% in controls ($p=0.024$). The most rapid improvements were seen in the first 4 weeks after treatment.

In a previous study we found that IPL light with a wavelength band of 530–750 nm covering most of the Q bands of the hemoglobin absorption spectrum produced the best results in the treatment of inflammatory acne. We performed a randomized split-face study including 11 volunteers (3 men/8 women) aged between 17 and 36 years (average age 25.6 years). All volunteers were instructed to apply adapalene cream or gel 0.1% on the entire face every night throughout the trial period. A randomly selected side of the face was also given IPL treatments 4 times at intervals of 3 weeks. Single passes with very short pulse durations (2×2.5 ms, delay 10 ms) with pulse energy varying from 7–9 J/cm^2 were applied. At 1-month follow-up the side treated with the combination of adapalene and IPL showed clearance of inflammatory lesions by 57.8% vs. 32.8% on the adapalene side only (Figs. 5.12 and 5.13). This difference was found to be statistically significant ($p<0.05$).

Comparison between optical treatments for acne vulgaris with PDL, IPL, and light-emitting diodes (LED) in a blue-red combination was performed by Sami et al. [61]. Forty-five patients with moderate to severe acne were randomly divided into three equal groups. The measured parameter was the number of treatments needed to obtain a reduction in inflammatory acne

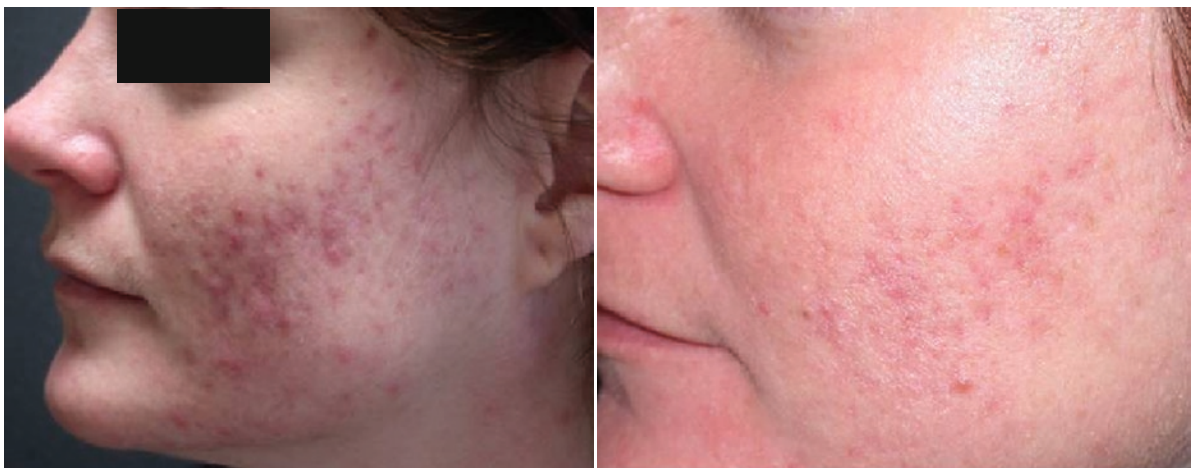

Fig. 5.12 Acne patient before (*left*) and 2 months after (*right*) two intense pulsed light treatments

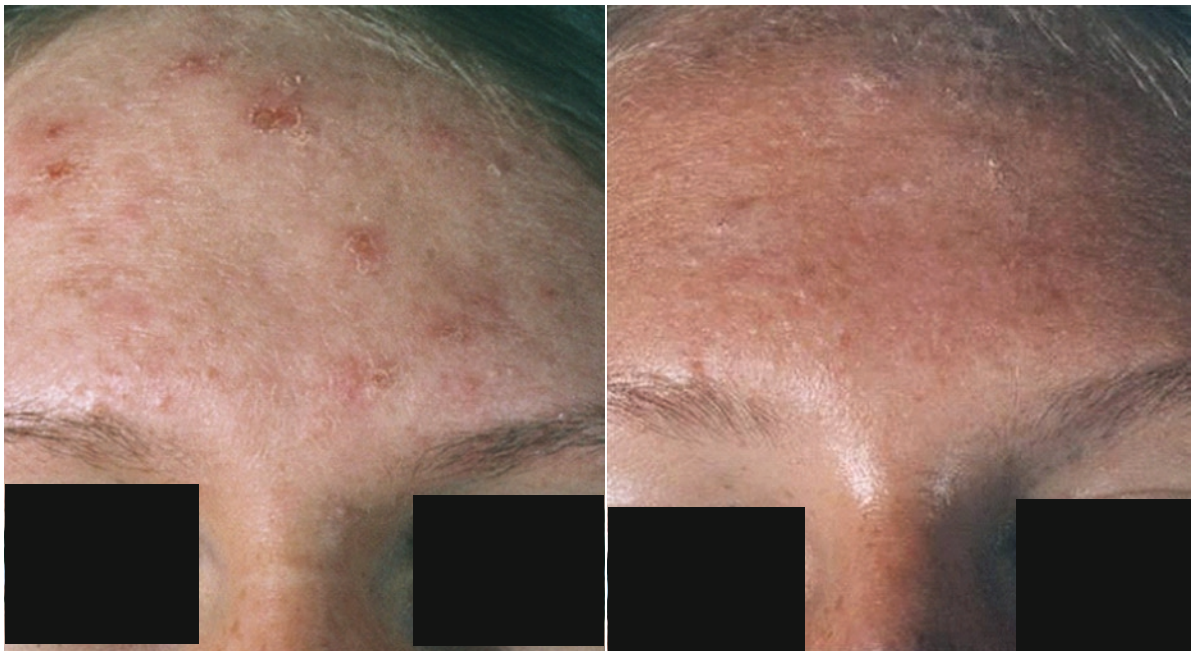

Fig. 5.13 Reduction in active acne in an 18-year-old female patient before (*left*) and 3 months (*right*) after four intense pulsed light treatments 3–4 weeks apart (photo courtesy of Dr. A. Troilius)

greater than 90%. This was reached after 4.1 ± 1.39 treatments of PDL, 6 ± 2.05 treatments of IPL, and 10 ± 3.34 treatments in patients treated with LEDs.

5.6.3 Combined PDT and Light Treatment of Acne Vulgaris

Itoh et al. [36] performed PDT on 13 Japanese patients suffering from acne vulgaris. Twenty percent 5-ALA was applied 4 h prior to exposure with incoherent light (600–700 nm) for approximately 15 min (a total energy dose of 13 J/cm^2). All patients obtained apparent improvement of facial appearance and reduction of new acne lesions at 1, 3, and 6 months after the PDT treatment. The adverse effects were discomfort, burning and stinging during irradiation, edematous erythema for 3 days after PDT, epidermal exfoliation from the fourth to the tenth day, irritation, hypersensitivity to physical stimulation for 10 days after PDT, and pigmentation or erythema after epidermal exfoliation. The treated areas returned to normal condition within 1 month. It was concluded that PDT was beneficial in the treatment of acne and that a photoactivating, polychromatic visible light source was better than laser light because of its cost-effectiveness, uniform illumination field, and time efficiency in treating large areas.

Different therapeutic protocols for PDT treatment of acne vulgaris with three different light sources were investigated by Taub [68]. Twenty-two patients with moderate to severe acne vulgaris were randomly assigned to receive either ALA-PDT with photoactivation by IPL (600–850 nm), a combination of IPL (580–980 nm) and bipolar radiofrequency energy, or blue light (417 nm). All patients received three treatments 2 weeks apart, and follow-ups were performed 1 and 3 months after last treatment. The clinical improvements were highest with IPL activation and lowest with blue light activation, but the differences were not found to be statistically significant. Also, the variability in treatment responses was significantly smaller with IPL than with the other two modalities, and it was further concluded that PDT treatment of moderate and severe acne vulgaris with 5-ALA activated with IPL results in greater, longer-lasting, and more consistent improvement than either radiofrequency/IPL or blue light.

In a split-face study of inflammatory facial acne, Rojanamatin and Choawawanich [55] treated 14 Asian patients 3 times at 3- to 4- week intervals with IPL on one side and a combination of IPL and topical ALA on the other side. At the follow-up visit 12 weeks after the

Table 5.5 Recommendation for optical acne treatment

	Laser treatment of acne vulgaris	IPL treatment of acne vulgaris	Fluorescence-controlled photodynamic photorejuvenation	Photodynamic photorejuvenation
Pretreatment	None	None	Liposome encapsulated 0.5% 5-ALA 20% 5-ALA 16% MALA	
Endpoint pretreatment	NA	NA	Fluorescence controlled ≥2 FDU	0.5% 5-ALA: 60 min 20% 5-ALA: 30 min 16% MALA: 30 min
Equipment	PDL	IPL		
Cutoff filter (IPL only)	NA	530–950 nm or 525–555 to 950–1,200 nm		
Pulse duration	350–450 μs	2.5–4 ms		
Number of pulses	1	2–3		
Delay	NA	10–20 ms		
Clinical endpoint	Transient purpura or nonpurpuric response	Photo-oxidation of the melanin, resulting in immediate darkening of pigmented spots; slight erythema		
Energy	2–7 J/cm^2	Dependent on filters and specific IPL equipment		

IPL intense pulsed light, *ALA* aminolevolinic acid, *MALA* methyl-5-aminolevolinic acid, *FDU* FluoDerm units, *PDL* pulsed dye laser

last treatment, the reduction in lesion counts on the ALA-pretreated side was 87.7% vs. 66.8% on the IPL-alone side. Mild edema and minimal crusting were registered on the combined treatment side, but these were mild and reversible.

However, the clinical reaction to IPL treatment in Asian skin types often differs from that in white skin. In an IPL split-face study evaluating the effect on acne vulgaris of IPL alone or 30-min pretreatment with 16% methyl aminolaevulinate (MAL), Yeung et al. [74] found a reduction of inflammatory lesions that was not statistically significant on either the PDT-treated side ($p=0.06$) or the IPL-treated side ($p=0.82$) 12 weeks after treatment. Surprisingly, significant reductions of noninflammatory lesions were observed in 38% of the MALA/PDT group and 43% in the IPL group 12 weeks after treatment.

In 2008, Haedersdal et al. [28] performed a systematic review of the published evidence-based studies of acne vulgaris treated with optical methods identified through searches in PubMed and the Cochrane Library. A total of 587 patients were involved in these studies, 16 of which were randomized controlled trials, and three were controlled trials. They concluded that IPL-assisted PDT seems to be superior to IPL alone, but that IPL PDT results in more intense side effects such as pain, erythema, edema, crusting, and hyperpigmentation than IPL treatment alone.

5.6.4 Rosacea

Please see treatment of "Type I photorejuvenation": reduction of diffuse redness (Sect. 5.2.2) (Table 5.5).

5.7 IPL Treatment of Unwanted Hair (Optical Depilation)

Worldwide, millions of men and women remove unwanted hair on a daily basis. Many regard this as a normal part of life, but some individuals – for a esthetic or cultural reasons – are looking for more permanent solutions. There are two medical causes of unwanted hair: hirsutism and hypertrichosis. The first affects only women, resulting in hair growth with a normal male pattern, mainly facial hair in the beard and upper lip areas. It is commonly seen as a secondary effect of endocrine disorders or as an adverse effect of medication. Hypertrichosis is the presence of excessive amounts of hair in either normal or abnormal locations. The cause is most commonly genetic or ethnic, but hypertrichosis can also occur as a secondary effect of endocrine disorders and as an adverse effect of medication.

It is now well recognized that long-term hair growth control requires more than destroying the hair in its follicle. The pluripotential stem cells residing along the hair shaft and particularly in the bulb area should also be damaged [12] because these cells are responsible for hair follicle regeneration. The hair follicle itself is transparent at visible light wavelengths and therefore cannot act as the primary target for optical treatments. The primary chromophore in hair removal is the melanin contained in the hair shaft and hair bulb. The melanin absorbs light and converts it into heat, which then is conducted to the hair follicle cells. Permanent damage to the hair follicle will occur only if the outermost cells reach a temperature of 70°C for a minimum of 1 ms. Melanin does not have specific light absorption peak above 350 nm (Fig. 5.1) but absorbs visible light as well as NIR light with decreasing absorption for longer wavelengths. Hair follicle destruction can therefore be obtained by using wavelengths longer than those of the hemoglobin absorption peaks but shorter than wavelengths absorbed in tissue water. IPL cutoff filters of 590–645 nm are suitable for hair removal. High-end IPL systems with dual mode filtering, which blocks both shorter wavelengths and infrared light, are effective and only need relatively low energy levels to be efficacious, which increase the treatment safety significantly. Also, these treatments normally require no skin surface cooling for treatment of skin types I–IV.

Brown, brownish-black, or black hairs contain eumelanin, which has high absorption of visible and NIR light. Blond and red hair contains pheomelanin, which has much lower light absorption. Treatment of red and blond hair is therefore more difficult and requires cutoff wavelengths to be shorter (530–550 nm). However, these wavelengths are also absorbed by hemoglobin, which leads to less treatment selectivity and efficacy. Gray and light blond hairs typically absorb so weakly that they cannot be treated successfully with optical methods.

Optical hair removal and optical treatment of ectatic vessels (Sect. 5.2.2) are based on selective photothermolysis, and the pulse durations were previously selected according to the TRT for the treated hair diameter. For fine (30 μm), medium coarse (70 μm), and large coarse hair (120 μm), the TRTs are 0.6, 3, and 10 ms, respectively. Because the heat generated by light in the melanin has to be conducted from the hair to the surrounding follicular tissue, which takes time, these pulse durations should be extended. The "extended theory of selective photothermolysis" [2] predicts that the TDT for the entire hair follicle for a fixed fluence is independent of the pulse duration over a range up to 10 times the TRT. Because the thermal load of the skin surface for a fixed fluence decreases with extended pulse duration, the treatment safety is improved by treating hairs with prolonged pulse durations.

Shaving, but not waxing because this will remove the target, must be performed prior to treatment. Leaving up to 0.5-mm-long hairs helps to indentify the area to be treated. Skin reaction with perifollicular erythema is a sign of correct energy setting and predicts an efficient treatment. For darker skin types (IV–VI), this reaction may take from 15 min to several hours to develop. If a too-short pulse duration or a too-high fluence has been chosen, epidermal damage may occur and the skin turns a grayish color, indicating denaturation of the epidermis. Also, treatment with too-short pulse durations and too-high energy settings may cause the hair to partially vaporize during the light pulse. In this case, the target disappears before the end of the light pulse, resulting in insufficient heating of the follicle and treatment failure.

The efficacy of IPL-based hair removal has been investigated by Troilius et al. [70] in a study of the bikini lines of ten women with dark hair and skin types II–IV. Four treatments at 1-month intervals with a 600-nm cutoff filter were performed. Based on hair counts before treatment and at 4 and 8 months after the last treatments, a hair reduction of 74.7% (SD ± 18.3%) and 80.2% (SD ± 20.3%) were registered, respectively. No side effects or pain were registered during the treatments.

The treatment safety can be increased in hair removal from darker skin types by selecting cutoff filters with longer wavelengths. In 2006, Lee et al. [31] compared IPL hair removal with a 600- to 950-nm filter and a 645- to 950-nm filter in the axillary area of 55 Asian women. Four treatments were carried out at intervals of 4–6 weeks, and longer pulse widths were used in connection with the darker filter. Follow-ups were conducted 8 months after the last treatment, and average clearances of 52.8% and 83.4% were achieved with the 600- to 950-nm filter and the 645- to 950-nm filter, respectively. It was concluded that shifting the emitted light spectrum 45 nm upwards with the use of longer pulse durations provided a safer and more effective means of photoepilation in Asian patients. Also, Huo et al. [35] obtained efficient hair removal at 3- and 6-month follow-up in 341 Chinese patients after three

Table 5.6 Recommendations for hair removal

	Thin hairs	Medium hairs	Thick hairs
Equipment	IPL, diode, or alexandrite	IPL, diode, or alexandrite	IPL, diode, or alexandrite
Pulse duration for skin types I–III	10–15 ms	20 ms	30 ms
Pulse duration for skin types IV–VI	15–20	30	55 ms
Cutoff filter for skin types I–III	IPL: dark and brown: 580–610 nm; light hair: 530–550 nm Laser: NA		
Cutoff filter for skin types IV–VI	For IPL: 645–720 nm Laser: NA		
Number of pulses	1		
Clinical endpoint	Perifollicular erythema or pain		
Energy	Depending on the laser type and filters for the specific IPL equipment		

IPL intense pulsed light

to five treatments. Only three cases of blistering and one case of infection were registered.

Since melanin absorbs light over a broad band wavelengths, many different lasers have been used successfully in the past for hair removal. Recently, Khoury et al. [40] performed a comparison of a 755-nm alexandrite, a 1,064-nm Nd:YAG, and an 810-nm diode laser in 20 American patients receiving three treatments in four axillary quadrants at 4- to 6-week intervals. Exposures were performed with a 20-ms pulse duration except for the diode laser, where the pulse durations were decreased to 11–14 ms. The obtained hair reductions were 70.3% ± 14.4% for the Nd:YAG laser, 47.4% ± 16.7% for the alexandrite laser, and 59.7% ± 13.6% for the diode laser. A combination of alexandrite and Nd:YAG laser treatments resulted in hair reduction of 67.1% ± 15.1%. The Nd:YAG laser was most painful and the alexandrite was the least painful. This study shows that acceptable hair reduction can be obtained with several laser modalities using long pulse durations (Table 5.6).

5.8 Conclusions

IPL systems are flash lamp-based light treatment devices, which produce broadband visible and NIR light. By using different light-filtering techniques, the spectrum of the emitted light can be matched to the principal light absorption wavelengths of the major skin chromophores hemoglobin and melanin. The mode of action is a selective heating of the chromophore-containing structures of the skin. Selective destruction of either ectatic vessels or mottled pigmentation is thus achieved by both restricting the emitted spectrum of wavelengths and tailoring the pulse duration to match the size of the skin structure to be destroyed.

Technically, IPL systems are simpler than lasers, resulting in less maintenance costs for the user, which may be one of the reasons for the success IPL systems. Also, systems have larger safety margins than most lasers, and many of the most common IPL treatments can be delegated, making IPL treatments cost-effective compared to laser treatments.

Recent developments of IPL systems have shown two distinct directions: (1) very sophisticated, high-end integrated systems with multiple filter combinations intended for the treatment of a broad range of different skin conditions, and (2) small, effective, cheap, and safe devices for home use.

Take Home Pearls

- The intense pulsed light device (IPL) covers a broader range of dermatological light treatments than individual laser systems.
- The broadband, incoherent light output of IPLs is safer than the coherent light output from lasers.
- The pulse duration of IPL systems is highly variable within the millisecond domain, which ensures that skin treatments can be performed with pulse durations selected according to the target's thermal relaxation time.

- IPL systems have demonstrated high efficacy for hair removal and treatment of diffuse redness, facial telangiectasias, rosacea, epidermal pigmentation as well as photorejuvenation.
- Wrinkle reduction performed with IPL treatment combined with a photosensitizer (photodynamic photorejuvenation) may obtain results comparable to fractional skin rejuvenation treatment.
- IPL systems should be the first choice of treatment device whenever possible.

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Inflammatory Dermatoses: Acne

6

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Core Messages

- Light-based acne therapies may act via a variety of mechanisms, including targeting *Propionibacterium acnes* and/or sebaceous gland destruction.
- Light-based therapies potentially offer more rapid onset of action, better patient compliance, and fewer adverse events than traditional therapies.
- Photodynamic therapy may be more effective than light-based treatments alone.
- The optimal treatment parameters for light-based treatments and photodynamic therapy are unknown.
- The efficacy of light-based therapies is not fully established and they currently should be considered second-line acne therapies.

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6.1 Introduction

Acne is an extremely common disorder that predominately occurs among teenagers and young adults. Acne occurs in up to 70% of the population and affects approximately 40 million adolescents and 20 million adults in the United States alone [11, 28, 30]. Acne is capable of causing a significant and detrimental psychosocial impact and is associated with depression, suicide, social isolation, and unemployment [10, 17, 24, 27].

The classic lesions observed in acne include closed and open comedones and inflammatory papules and pustules. The development of these acne lesions is characterized by hypercornification of the pilosebaceous duct with the formation of the microcomedo, increased sebum production, proliferation of *Propionibacterium acnes*, and the development of inflammation.

Traditional medical therapies for acne generally act by modifying one or more of the above pathophysiologic factors. These traditional therapies include topical antimicrobials and retinoids, oral antibiotics, and oral isotretinoin. Though these therapies are efficacious, they have some limitations, including incomplete responses, slow onset of action, and issues with poor patient compliance. In addition, some therapies are associated with potentially serious adverse events, which may limit their use, such as benign intracranial hypertension and lupus-like syndromes with the use of tetracyclines [55]. Systemic isotretinoin is a highly effective and generally safe therapy. However, it carries considerable concerns with potential teratogenicity, which complicates its use and may limit its acceptance by patients and physicians [46].

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_6, © Springer-Verlag Berlin Heidelberg 2011

Table 6.1 Predominant mechanisms of action of various light-based acne therapies

P. acnes photodestruction	Sebaceous gland alteration	*P. acnes* photodestruction and sebaceous gland alteration
Blue light	1,320-nm Nd:YAG laser	Photodynamic therapy
Red light	1,450-nm diode laser	
Intense pulsed light	1,540-nm erbium:glass laser	
Intense pulsed light and heat		
Photopneumatic therapy		
532-nm KTP laser		
585/595-nm PDL		

KTP potassium titanyl phosphate, PDL pulsed dye laser, Nd:YAG neodymium:yttrium aluminum garnet

Light-based therapies are an attractive alternative acne therapy because as they potentially offer more rapid onset and better patient compliance with a low incidence of adverse events. However, optimal treatment methods and the relative efficacy of light-based therapies as compared to traditional therapies remain unclear. Light-based acne therapies are generally thought to act via reducing *P. acnes* proliferation or by targeting the sebaceous gland to reduce sebum production; however, other mechanisms may exist (Table 6.1).

6.2 Light-Based Therapies that May Target *P. acnes*

P. acnes is a microaerophillic gram positive bacterium that is part of the normal skin flora. Increased numbers of *P. acnes* have been reported in acne; however, their number does not correlate with the clinical severity [31]. A number of acne therapies including benzoyl peroxide, azeliac acid, and topical and oral antibiotics act by reducing *P. acnes*, highlighting the important role this micro-organism plays in the pathogenesis of acne. *P. acnes* contributes to the development of acne via colonization of the sebaceous follicle and the promotion of inflammation. This bacterium possesses a number of intrinsic properties that contribute to the pathogenesis of acne, including the production of lipases that promote rupture of the formed comedo and the production of proinflammatory mediators [42, 49].

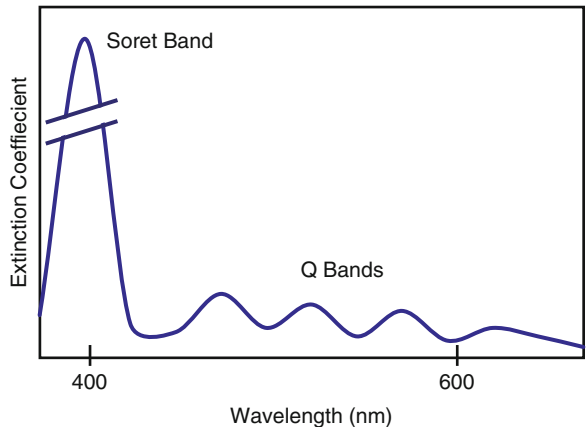

Fig. 6.1 Photoexcitation spectrum of protoporphyrins showing the Soret and Q bands. The Soret band represents the highest peak of absorption and the Q bands weaker absorptions at longer wavelengths

A further feature of *P. acnes* is the endogenous production and accumulation of porphyrins, with coproporphyrin III thought to be the major subtype [29]. These endogenous porphyrins absorb visible light, which induces the formation of singlet oxygen species and other reactive free radicals that subsequently cause bacterial destruction [2]. The absorption of light and the production of free radicals at differing wavelengths are well characterized (Fig. 6.1). Light absorption is most pronounced with blue light (approximately 415 nm); however, the reaction can be initiated at longer wavelengths if enough light is delivered.

6.2.1 Blue Light

P. acnes colonies are reliably destroyed when exposed to blue light in vitro due to the strong absorption and photoactivation of endogenous porphyrins at this wavelength [2, 3]. However, blue light only superficially penetrates human skin due to a high degree of light scattering, which may limit its therapeutic effect. Despite this disadvantage, blue light has been demonstrated to be effective in improving acne.

Tzung et al. [48] investigated a 420-nm light (F-36 W/Blue V, Waldmann, Villingen-Schwenningen,

Germany) in a randomized split-face trial. The blue light was administered twice weekly at a dose of 40 J/cm^2 for 4 weeks. Twenty-eight Taiwanese patients completed the trial, with the blue light therapy resulting in a significant improvement in the Michaelsson acne severity score (52% improvement vs. 12%; $p=0.009$) at 8 weeks. Further evidence is provided by Gold et al. [14] who performed a randomized controlled trial comparing a 417-nm blue light source (Blu-U, DUSA Pharmaceuticals, Wilmington, Mass.) administered twice weekly to self-administered twice daily topical 1% clindamycin. Twenty-five participants completed 4 weeks of treatment, and the clinical response was assessed 4 weeks later. The inflammatory lesion counts improved 36% in the blue light group compared to 14% in the clindamycin group. However, changes in the patients' global improvement scores were similar. Both trials found the blue light treatment to be safe and well accepted by the patients.

6.2.2 Red Light

Though red light is less effective in activating porphyrins than blue light (Fig. 6.1), red light is able to penetrate human skin to greater depths and activate porphyrins in the sebaceous follicle. Red light may also induce anti-inflammatory effects via influencing cytokine release from tissue macrophages [57]. Zane et al. [58] reported the effectiveness of a 600- to 750-nm red light (PDT 1200, Waldmann Medical Division, Villingen-Schwenningen, Germany) administered twice weekly at a fixed dose of 20 J/cm^2 in 15 patients with moderate facial acne. At the end of the 4-week treatment period there was a significant reduction in the global acne grading system score (median score reduced from 16 to 8), which was sustained at a 3-month follow-up visit. The treatments were well tolerated with no significant adverse events. Na and Suh [34] investigated the usefulness of a portable 635- to 670-nm red light source (Softlaser SL30, Beurer GmbH & Co., Ulm, Germany) in a split-face randomized trial of 30 patients with mild to moderate acne. Patients self-administered the light twice daily for 8 weeks and received a cumulative dose of 604.8 J/cm^2 by the end of the treatment period. A 59% reduction in noninflammatory lesions and a 66% reduction in inflammatory lesions on the treatment side compared to a 3% and 74% increase, respectively, on the control side were observed. However, the study was not blinded, making interpretation of the results more difficult.

6.2.3 Blue and Red Light

The simultaneous use of blue and red light attempts to combine the strengths of the two wavelengths – namely the strong photoactivation of porphyrins by blue light and the deeper penetration and possible anti-inflammatory action of red light. Papageorgiou et al. [38] compared the effectiveness of combined 415- + 660-nm light to 415-nm light alone, white light alone, and 5% benzoyl peroxide in a randomized trial of 107 patients with mild to moderate acne. The investigators used fluorescent lamps in reflector fixtures (type HF 885, Osram Sylvania, Brussels, Belgium). After daily treatment for 12 weeks (cumulative blue light dose 320 J/cm^2 and red light dose 202 J/cm^2), the combined blue–red light therapy was found to improve inflammatory lesions by 76%. The blue–red light treatment was significantly superior to the blue light alone at weeks 4 and 8, but not at week 12. It was also superior to benzoyl peroxide alone at weeks 8 and 12 and was superior to white light alone at all time points. The treatments were well tolerated, with no significant adverse events.

6.2.4 Intense Pulsed Light

Pulsed light sources are capable of delivering significantly more photons at peak power than a continuous wave source, which may enhance any therapeutic effect. Chang et al. [8] investigated an intense pulsed light (IPL) source with a 530- to 750-nm filter (I^{2}PL, Ellipse Flex, DDD, Horsholm, Denmark) in 30 Korean women with mild–moderate acne. All patients used benzoyl peroxide gel, and a randomly selected side of the face was treated with IPL. The patients received three IPL treatments, 3 weeks apart using fluences of 8.0 J/cm^2 for skin type III and 7.5 J/cm^2 for skin type IV and a pulse duration of 2.5 ms and a double light pulse with a 10-ms interval. Three weeks after the final IPL treatment, all patients had experienced an improvement in acne lesions on both the IPL and

benzoyl peroxide alone sides of the face, with no significant differences between the two sides. No adverse events were seen.

6.2.5 Intense Pulsed Light and Heat

The principle of chemical reactions proceeding at a faster rate at higher temperatures is utilized in devices, that combine pulsed light with heat. These devices attempt to maximize porphyrin photoactivation and subsequent bacterial destruction. Gregory et al. [16] studied the use of pulsed light and heat energy using the ClearTouch LHE system (Radiancy Inc, Orangeburg, New York). Patients acted as their own controls by forgoing acne treatment for 4 weeks and were then treated twice a week for 4 weeks. Four weeks after the treatment phase, there was a 60.2% mean reduction in the number of inflamed lesions compared to a 32.4% increase after the control phase. Erythema was the most common and only side effect reported.

6.2.6 Photopneumatic Therapy

Photopneumatic therapy attempts to increase the photoactivation of endogenous porphyrins by reducing the competition from other chromophores for available photons. In addition, the sebaceous gland is mechanically "cleaned" of sebaceous material, which may assist in improving acne lesions [45]. Photopneumatic therapy works by applying negative pressure to the skin surface under the handpiece, which stretches the skin, thereby reducing the concentration of melanin and hemoglobin. This method also partially ejects the sebaceous gland contents. With one commercially available device, after the application of negative pressure a broadband pulsed light source (400–1,200 nm) is activated, delivering energy to the sebaceous gland with reduced competition from other chromophores. The negative pressure is then released, allowing the skin to return to its normal position [45]. Gold and Biron [13] studied photopneumatic therapy in 11 patients with mild to moderate facial acne. Patients underwent four photopneumatic treatments (Isolaz, Aesthera Inc. Pleasanton, Calif., USA) at 3-week intervals. One month after treatment there was a 78.8% reduction in inflammatory lesion counts and a 57.8% reduction in noninflammatory lesion counts, with 82% of patients being moderately to very satisfied with the treatment. Wanitphakdeedecha et al. [51] also studied a photopneumatic therapy device in 20 patients with mild to severe facial acne. Patients received four treatments (IPL fluences of 3.6–4.2 J/cm^2 and a negative pressure of 3 psi) at 2-week intervals. The majority of patients experienced modest reduction in acne lesion counts and global clinical improvement, with patients with severe acne experiencing the greatest clinical improvement. Adverse effects were generally mild and included acne worsening early in the treatment course, erythema, and rare purpura.

6.2.7 532-nm Laser

The 532-nm potassium titanyl phosphate (KTP) laser targets the chromophores oxyhemoglobin and melanin. As such, it is frequently used to treat superficial vascular lesions such as facial telangectasia and superficial pigmented lesions. Its mechanism of action in acne is presumably via activation of porphyrins. However, the KTP laser may also cause mild collateral thermal injury of sebaceous glands and may modify the sebaceous gland vasculature. Bowes et al. [6] studied the 532-nm KTP laser (Aura, Laserscope, Palo Alto, Calif., USA) in a randomized split-face trial of 11 patients with mild to moderate acne. Two weekly treatments were delivered for 2 weeks (total of four treatments) using fluences of 7–9 J/cm^2, a spot size of 4 mm, and a pulse duration of 20 ms. The mean Michaelsson acne lesion scores on the laser-treated side decreased by 33.9% and 35.9% at the 1-week and 1-month visits, respectively, as compared with no change and a 11.8% increase on the untreated side. Two patients experienced blistering and crusting in the nasal groove, which healed uneventfully. Baugh and Kucaba [4] also studied the 532-nm KTP laser (Aura, Laserscope, Palo Alto, Calif., USA) in a randomized split-face trial involving 26 patients with moderate facial acne. Each patient received two treatments weekly for 2 weeks using a fluence of 12 J/cm^2 with a 30 to 40-ms pulse duration. One week after treatment there was a 34.9% mean reduction in the Michaelsson

acne severity score ($p = 0.011$), and 4 weeks after treatment there was a 20.7% mean reduction in the Michaelsson acne severity score ($p = 0.25$). At the 4-week follow-up visit, all patients expressed at least 50% satisfaction in treatment outcomes, and there were no side effects observed.

6.2.8 Pulsed Dye Laser

The pulsed dye laser (PDL) is also presumed to work through endogenous porphyrin photoactivation. However, it may have additional mechanisms, including altering sebaceous gland microvasculature, that cause mild collateral thermal injury to sebaceous glands, and possibly anti-inflammatory actions. The PDL has been investigated in acne using low-fluence, nonpurpuric settings. Seaton et al. [44] reported on 41 adults with mild to moderate facial acne who were randomized to PDL or control treatments. Patients were treated with a 585-nm PDL (Nlite laser, ICN pharmaceuticals, Costa Mesa, Calif., USA) with a spot diameter of 5 mm and a pulse duration 350 μs, and were randomly allocated to receive 1.5 J/cm^2 on one side of the face and 3.0 J/cm^2 to the other. Twelve weeks after a single treatment there was a significant improvement in the Leeds acne score: from 3.8 to 1.9 compared to 3.6 to 3.5 in the control group ($p = 0.007$). Inflammatory lesion counts were observed to decrease by 49% compared to 10% in the control group, with the most rapid improvements seen during the first 4 weeks of treatment. The treatment was well tolerated, with pain and transient purpura the most common adverse events. In contrast to these promising results, Orringer et al. [35] also reported their experience using the PDL for the treatment of acne. They performed a randomized, controlled split-face trial in 40 patients with active facial acne. Patients were randomized to receive either one laser treatment at baseline or two laser treatments at baseline and 2 weeks later. A nonpurpuric PDL was used (585- nm Nlite laser, ICN Pharmaceuticals, Costa Mesa, Calif., USA) with a fluence of 3 J/cm^2, a spot size of 7 mm, and spulse duration of 350 μs. After 12 weeks there were no significant differences between the laser-treated and control sides in lesion counts or the Leeds acne score. The treatments were well tolerated, with the adverse events being one episode of postinflammatory hyperpigmentation in a patient with type IV skin and two episodes of minimal purpura.

6.3 Light-Based Therapies that May Target Sebaceous Glands

The sebaceous gland plays a critical role in the pathogenesis of acne, making it an attractive target for light-based acne therapy. Sebum serves as a nutrient for *P. acnes*, and acne sufferers produce more sebum than individuals without acne [19]. Furthermore, systemic isotretinoin, which is a highly efficacious acne therapy, acts in part by reducing the size of sebaceous glands and sebum production [39]. Light-based therapies that target the sebaceous gland require deep penetration because the sebaceous glands are located at differing depths within the dermis (approximately 0.2- to 1-mm depth) [37]. This deeper penetration is achieved with longer infrared wavelengths that target water. These infrared wavelengths result in a selective injury zone in the mid-dermis, which causes collateral damage to the sebaceous glands while preserving the epidermis [37]. Treatment-related pain is common with the use of infrared lasers and may be severe enough to limit the use of such therapies [23, 36, 50].

6.3.1 1,450-nm Diode Laser

The 1,450-nm diode laser has been shown to cause damage to the duct epithelium and sebocytes of sebaceous glands and seems to have efficacy in treating acne [37]. Jih et al. [23] performed a split-face trial in 20 patients with facial acne using the 1,450-nm diode laser (Smoothbeam, Candela Corporation, Wayland, Mass., USA), randomizing between a fluence of 14 J/cm^2 (6-mm spot size and dynamic cooling at 40 ms) or 16 J/cm^2 (6-mm spot size and dynamic cooling at 45 ms) [23]. Patients used topical anesthetic (Ela-Max; Ferndale Laboratories, Ferndale, Mich., USA) and received three treatments at 3- to 4- week intervals. After three treatments, there was a 75.1% (14 J/cm^2 treatment side) and 70.6% (16 J/cm^2 treatment side) reduction in inflammatory lesion counts, which persisted for up to 12 months. Patients tolerated the

treatments well, with pain scores of 4.4–5.5 (on a 1- to 10- point scale), and no treatments were stopped due to pain. Adverse effects were restricted to erythema and edema at treatment sites. Wang et al. [50] studied the use of the 1,450-nm diode laser in 20 patients with active inflammatory facial acne. They performed a randomized split-face trial of laser treatment alone compared to laser treatment and microdermabrasion. Topical 5% lidocaine (Ela-Max; Ferndale Laboratories, Ferndale, Mich., USA) was applied to the entire face, which was then treated with the smooth beam 1,450-nm laser (Candela Corporation, Wayland, Mass., USA) using the following parameters: fluence 13.5–14 J/cm^2, spot size 6 mm, DCD spray 30–40 ms. One side was also treated with microdermabrasion. Patients received four treatments 3 weeks apart and were assessed at 6 and 12 weeks after the last treatment. The diode laser alone decreased the mean acne lesion count by 52.8% by 6 weeks and 54.4% by 12 weeks ($p < 0.02$ compared to baseline counts), and microdermabrasion plus diode laser therapy reduced the counts by 53.5% by 6 weeks and 61% by 12 weeks ($p < 0.05$ compared with baseline counts). There was no statistically significant difference between the two treatments. Adverse events were generally transient and mild; however, discomfort during the treatment was common, with a mean pain score of 5.2 on a 1- to 10- point pain scale.

6.3.2 1,320-nm Neodymium:Yttrium Aluminum Garnet Laser

Orringer et al. [36] performed a randomized split-face trial of a 1,320-nm neodymium:yttrium aluminum garnet laser (CoolTouch II, ICN Pharmaceuticals, Inc., Costa Mesa, Calif., USA) in 46 patients with facial acne [36]. Patients received three treatments at 3-week intervals using a 10-mm spot size, with two passes, the first in precooling mode using a 30-ms spray time and the second in postcooling mode using a 30-ms spray time. Fluences were adjusted to maintain peak epidermal temperatures in the 40–45°C range. Patients were assessed 7 and 14 weeks after treatment. A significant reduction in open comedone counts was observed at 7 weeks but not at week 14, and there were no significant changes in counts of other lesion types or in Leeds acne severity score ratings.

6.3.3 1,540-nm erbium:glass laser

The 1,540-nm erbium:glass laser is another infrared laser that produces a wavelength that is rather deeply penetrating; hence, it is able to target sebaceous glands and the surrounding dermis. A potential advantage of the 1,540-nm erbium:glass laser is that it seems to cause comparatively little discomfort in contrast to the other infrared lasers [5, 32]. Bogle et al. [5] reported on the treatment of 15 patients with moderate to severe facial acne treated with a 1,540-nm erbium:glass laser (Aramis, Quantel Medical, Clermont-Ferrand, France). Patients received four treatments at 2-week intervals using a 4-mm spot size, 3.3-ms pulse duration, 500 ms between pulses, and contact cooling at 5°C. Active lesions were treated with six pulses at 10 J/cm^2, and the remaining face was treated with a single pass using four pulses at 10 J/cm^2. No anesthesia was required, and 6 months after treatment there was a 78% improvement in mean scores using the Burton acne scale. Patients tolerated the treatments well, with no significant adverse events.

6.4 Photodynamic Therapy

Photodynamic therapy (PDT) aims at enhancing the moderately beneficial effect observed with some light-based acne therapies. The use of exogenous photosensitisers maximizes singlet oxygen production and results in more effective *P. acnes* photodestruction compared with treatments that solely rely on light absorption by endogenous porphyrins. The exogenous photosensitisers are preferentially absorbed by the pilosebaceous unit, and, consequently, PDT is able to achieve simultaneous sebaceous gland injury and *P. acnes* destruction while minimizing epidermal injury [20, 22].

6.4.1 Photosensitizer

PDT for acne has mainly involved the use of topical 5-aminolaevulinic acid (ALA) and methyl aminolaevulinate (m-ALA). m-ALA is a methylated ester of ALA, which is subsequently hydrolyzed to ALA. ALA is metabolized by the heme synthesis pathways to produce

protoporphyrin IX (PpIX), a potent photosensitizer. When photoactivated by an appropriate light source, PpIX produces singlet oxygen and free radicals that damage the pilosebaceous unit and destroy *P. acnes*.

The photosensitizers, ALA and m-ALA, have absorbance and photoactivation at wavelengths in the 650- to 850-nm range [25]. This allows longer wavelengths with deeper penetration to be used while still achieving adequate singlet oxygen formation. Though wavelengths longer than 850 nm are able to penetrate deeply, they are poor photoactivators [25].

ALA and m-ALA are commercially available at concentrations of 20% and 16%, respectively. Table 6.2 summarizes various properties of ALA and m-ALA that are relevant to PDT for acne. Both are often applied under occlusion to maximize penetration, although this may be unnecessary for m-ALA, which is lipophilic and well absorbed. Both agents are generally used with 3–4 h of contact time before light exposure for some indications; however, in the treatment of acne there has been great interest in shorter contact times of 15–90 min, which may result in milder adverse events such as pain, exfoliation, and erythema [47]. Though ALA penetrates the epidermis at a slower rate than does m-ALA, the final penetration depths appear to be equivalent [26]. m-ALA has more lesion specificity than ALA and may result in less severe adverse events [40]. Wiegel and Wulf [54] compared m-ALA and ALA in a split-face study using a 620-nm red light source in 15 patients. There were no significant differences in acne improvement (83% had a slight to marked improvement on the m-ALA-treated side vs. 75% on the ALA side) or the maximal pain scores during illumination between the two sides. However, there was more pronounced erythema, edema, and pustule formation observed on the ALA-treated side.

Table 6.2 Features of topical 5-aminolaevulinic acid and methyl aminolaevulinate

	5-aminolaevulinic acid	Methyl aminolaevulinate
Penetration rate	Slower penetration	Faster penetration
Penetration depth	Equivalent	Equivalent
Pilosebaceous unit absorption	Less specific	More specific
PpIX production	More	Less

PpIX protoporphyrin IX

6.4.2 Light Source

A variety of light sources are used in acne PDT, including broadband light, IPL, and lasers. Noncoherent light sources have a number of advantages over coherent light, including larger illumination fields, lower cost, and possible photoactivation of photosensitizer degradation products (photoproducts), which may result in additional PDT effects [7].

The optimal wavelengths for acne PDT are unknown. Blue light PDT does not seem to be significantly better than blue light alone, which is probably due to the shallow depth of penetration of light at these wavelengths [1,15]. Yellow/red light sources seem to achieve the best balance of depth of penetration while having sufficient energy for photoactivation. However, at the current time, the optimal light source and treatment parameters for maximal acne improvement are yet to be defined.

6.4.3 Clinical Effects

It is clear that PDT can improve acne for many patients, at least in the short term. Most studies of PDT for acne have reported a 50–90% improvement in inflammatory lesion counts and/or global acne severity scores 8–12 weeks after treatment [18, 20, 21, 41, 43, 56]. To our knowledge only one published study has compared PDT to a traditional acne therapy. Yeung et al. [56] reported on 30 Chinese patients who were enrolled in a split-face study comparing m-ALA with IPL (530–750 nm) to IPL alone or control. Patients used topical 0.1% adapalene gel on both sides of the face at night during the treatment period. Four light treatments were administered at 3-week intervals. Although there was a significant reduction in comedone counts in the group receiving m-ALA/IPL and IPL alone, only the 0.1% adapalene control group experienced a significant reduction in inflammatory lesion counts.

In our experience with PDT for acne, many patients have experienced fairly modest improvements compared with traditional treatments. However, there does seem to be a subset of acne patients who respond well to PDT (Fig. 6.2), particularly with respect to inflammatory lesion counts. We believe that PDT is generally more effective than many other light-based therapies,

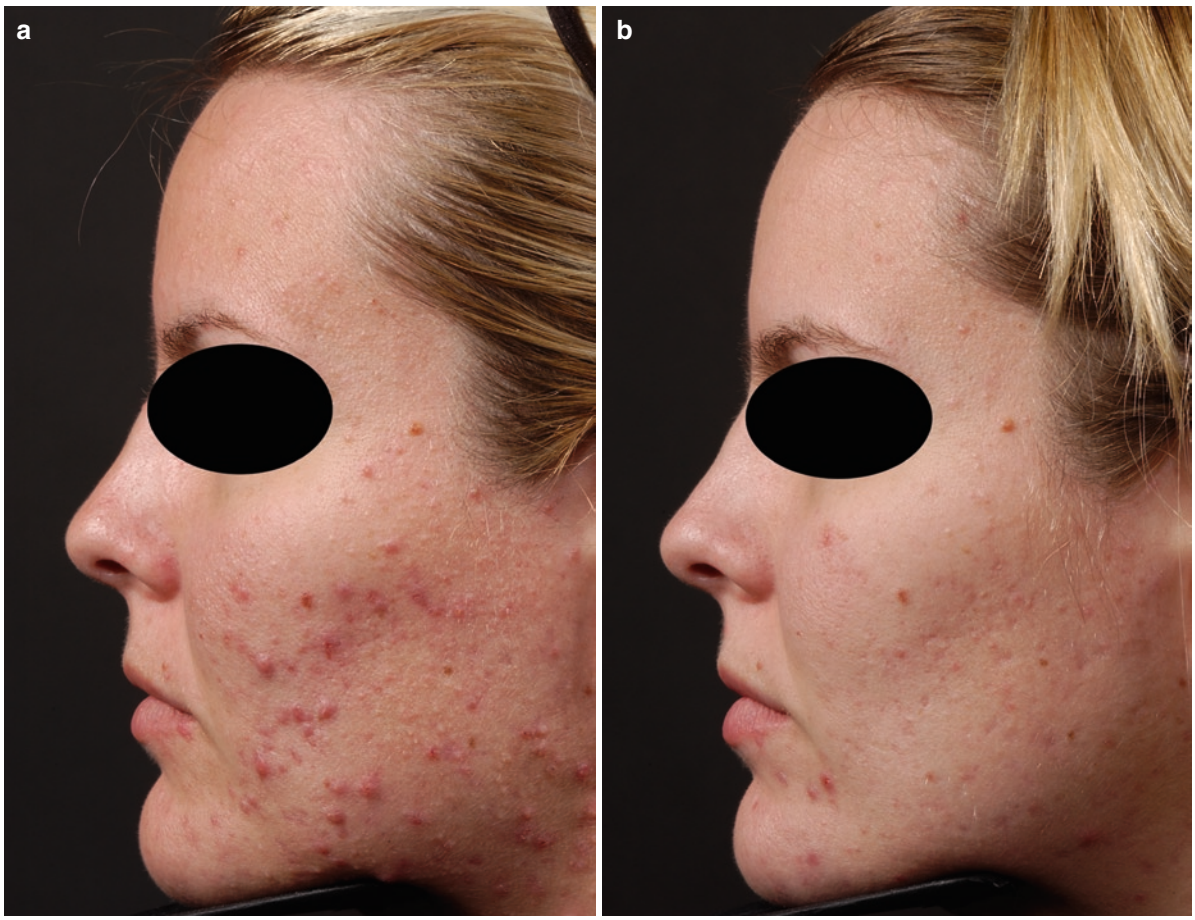

Fig. 6.2 Clinical photographs demonstrating a good response to aminolaevulinic acid (ALA photodynamic therapy (PDT). (**a**) Moderate to severe inflammatory acne before PDT. (**b**) Significant clearing of inflammatory lesions after three treatments with topical 20% ALA and the 595-nm pulsed dye laser

but at this time, we still cannot regard it as a first-line treatment. In our opinion, PDT is best utilized if traditional therapies have failed or are contraindicated, or if patient compliance with medical therapies is a particular issue. In some cases, PDT may be used in conjunction with a traditional antiacne medication regimen with good results.

6.4.4 Adverse Events

Adverse effects are fairly common with PDT and include erythema, edema, blistering, crusting, acneiform eruptions, and postinflammatory hyperpigmentation. Treatment-related pain is also very common and can limit the utility of PDT. PDT-related pain is thought to be due to singlet oxygen species stimulating cutaneous nerves, and causing a characteristic stinging or burning sensation [7]. Treatment-associated pain can be reduced by skin cooling during treatment, using shorter photosensitizer contact times, and possibly with the use of lower fluences and/or lower fluence rates (mW/cm^2) [9, 12, 21, 33, 53]. In addition, ALA seems to be associated with more pain and significant adverse events than m-ALA [33, 52].

6.5 Summary

Though study design-based deficiencies of many clinical trials in this area make it impossible to draw firm conclusions at this time, there is considerable

evidence that light-based therapies that act via photodestruction of *P. acnes* may be capable of clinically improving acne. seem light-based therapies are well tolerated and have a low incidence of adverse events. They seem to result in a generally rapid clinical improvement, which is advantageous when compared to the comparatively slow onset of action of many traditional acne therapies. However, because *P. acnes* regenerates rapidly, regular and ongoing maintenance treatments may be necessary to prolong any clinical improvements achieved. Though all of the modalities presented have merit, in our opinion the combination of blue and red broadband light and photopneumatic therapy may hold the most promise by maximizing porphyrin photoactivation and penetration depth, but additional rigorously designed studies are required to confirm this.

With regard to the use of infrared laser therapy for acne, there is evidence of transient alteration of sebaceous gland structure and function that may underlie clinical improvements. Pain associated with some of these devices may limit their practical utility, but there is some evidence of efficacy in the treatment of acne with several of these lasers. Again, there is a relative paucity of randomized, controlled clinical trials in this area, which currently limits our ability to draw firm conclusions about the safety and efficacy of this approach.

PDT for acne shows significant promise. However, to date no perfect balance has been struck between efficacy and safety with PDT. That is, the treatment regimens reported to promote the most profound clinical improvements have often been those that produce the most pain, epidermal disruption, and potential for significant side effects.

Research on novel light-based acne therapies and on the optimization of current treatment approaches is ongoing. It is our hope that in the future, laser and light-based therapies for acne may take on an increasingly important role in the clinical armamentarium in the fight against this common disorder.

Take Home Pearls

- *P. acnes* produces endogenous porphyrins that are photo-activated, thus producing singlet oxygen species and free radicals that may result in bacterial destruction.
- Blue light results in the most pronounced photo-activation of endogenous porphyrins. However, its clinical efficacy is limited by a shallow depth of penetration.
- Combined blue and red light and photopneumatic therapy are among the potentially promising therapies for acne that are believed to work, at least in part, by targeting *P. acnes*.
- Infrared wavelength lasers are often able to treat acne by causing sebaceous gland alterations while preserving epidermal integrity.
- Variable clinical responses have been observed with the 1,450-nm diode, 1,320-nm neodymium:yttrium alumium garnet, and 1,540-nm erbium:glass lasers that target sebaceous glands.
- Pain is often an issue with the use of infrared lasers for acne.
- PDT is potentially an effective light-based acne therapy and may cause photodestruction of both *P. acnes* and sebaceous glands.
- The optimal photosensitizer, light source, and therapeutic protocol for PDT as a treatment for acne is unknown. However, noncoherent yellow-red light has shown particular promise in some studies.
- Common PDT adverse effects include treatment-related pain, erythema, edema, blistering, crusting, acneiform eruptions, and postinflammatory hyperpigmenation.

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Inflammatory Dermatoses: Other than Acne Vulgaris

7

Pablo Boixeda, Lorea Bagazgoitia, João Borges da Costa, and Maria Calvo

Core Messages

- In cases of resistant lesions of acantholytic genodermatoses (Darier´s and Hailey-Hailey disease), ablative lasers are the best surgical option.
- Pulsed dye lasers have been shown to be a good option for cutaneous lesions of lupus erythematosus (LE) resistant to conventional treatments, with the best results being observed in the erythema and telangiectasia.
- The carbon dioxide, erbium:yttrium aluminum garnet, and fractional lasers have demonstrated good cosmetic results in the treatment of the disfiguring lesions of chronic lupus erythematosus.
- Angiolymphoid hyperplasia with eosinophilia, reticular erythematous mucinosis, and sarcoidosis are inflammatory difficult-to-treat conditions. Laser therapy has been shown to be effective in cases resistant to conventional therapies.

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7.1 Angiolymphoid Hyperplasia with Eosinophilia

Angiolymphoid hyperplasia with eosinophilia (AHLE) was first described by Wells and Whimster in 1969 [121]. It is a benign endothelial proliferative condition that commonly affects the head and neck regions. Women in the third or fourth decade of life are most frequently affected. It presents as single or multiple tender nodules that might bleed, be painful or itchy, and cause cosmetic disfigurement. Occasionally, peripheral eosinophilia can be found. It can resolve spontaneously. Histologically, a vascular proliferation with plump endothelial cells and prominent cytoplasmic vacuoles are seen, associated to a dense interstitial lymphocytic infiltrate with eosinophils and plasma cells.

The treatment of AHLE is known to be difficult. Intralesional corticosteroids, surgical excision, and lasers are the most frequently used therapies, although none of them is uniformly effective in all cases. Other options reviewed in the literature are topical or oral corticosteroids, cryotherapy [63], oral retinoids [20], imiquimod [36], tacrolimus [76], bleomcycine [2], and INFA-2a [87]. Laser therapy can be a useful tool, especially for challenging locations in which surgery cannot be performed.

The most frequently used lasers to treat AHLE are those targeting oxyhemoglobin. The use of the argon laser (484 nm–514 nm) was first reported in 1988 [54, 93]. Its pulse duration (continuous) is too long and the heat generated by the laser has time to spread peripherally, causing additional nonselective damage and scarring.

There are several reports about the use of pulsed dye lasers (PDLs) for AHLE; most of them are single case reports in which complete remission has been observed

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_7, © Springer-Verlag Berlin Heidelberg 2011

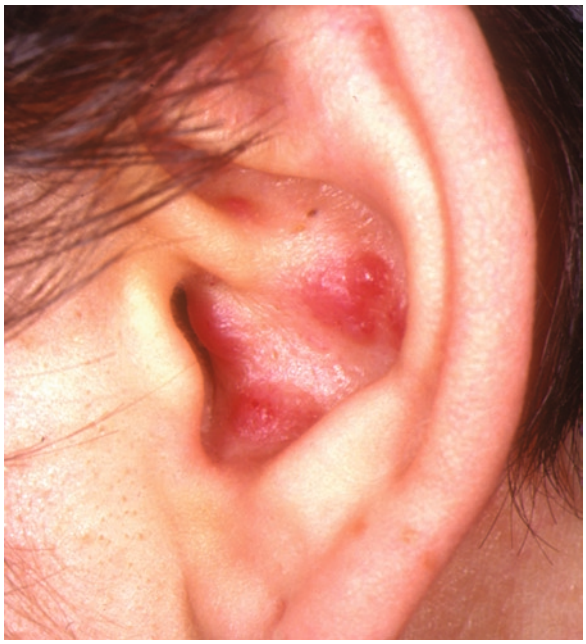

Fig. 7.1 Angiolymphoid hyperplasia with eosinophilia (pre-treatment)

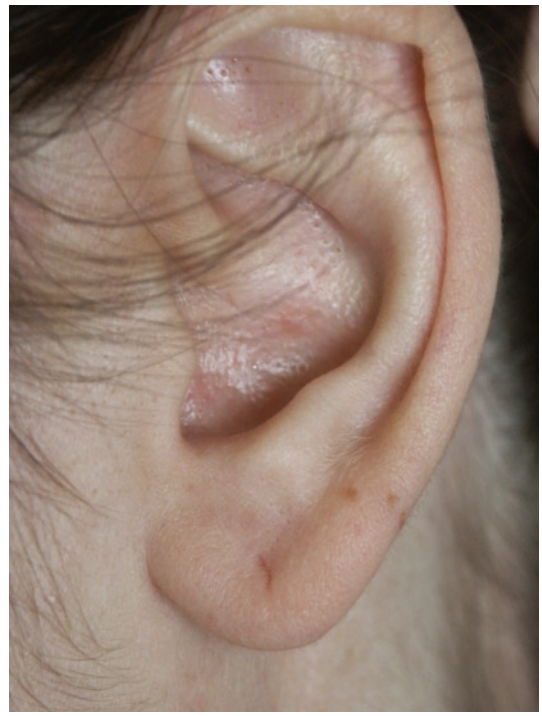

Fig. 7.2 Angiolymphoid hyperplasia with eosinophilia (after treatment with a pulsed dye laser)

(Figs. 7.1 and 7.2). The wavelengths, fluences, spot sizes, and pulse durations are described in Table 7.1. The use of the 585-nm PDL has been most commonly reported [1, 45, 72, 83, 89, 91]. However, longer wavelength PDL (595 nm) seems to be slightly more effective because it enables deeper tissue penetration (around 2.5 mm) [7, 103]. No scarring and only mild side effects such as bruising or postinflammatory hyperpigmentation [91] have been observed after PDL use.

A case of AHLE treated with the 1,064-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser [59]has been reported, using a 6-mm round spot size with two pulses of 7 ms duration with a 20-ms interpulse delay and a fluence of 100–150 J/cm^2. The patient showed complete remission after five treatments and 1-year follow-up.

A copper vapor laser (CVL) was used for the treatment of AHLE in one patient [35]. CVLs emit yellow light (similar to PDLs) of 578 nm. The pulse duration is 20 ns, with a pulse repetition rate of 15,000 cycles

Table 7.1 Pulsed dye laser parameters for angiolymphoid hyperplasia with eosinophilia treatments

Reference	Wavelength (nm)	Spot size (mm)	Fluency (J/cm^2)	Pulse duration (ms)	Number of treatments	Response
Lertzman et al. [72]	585	7–10	5–7.5	0.45	7	Partial
Rohre and Allan [103]	595	7	8.5	1.5	2	Complete
Papadavid et al. [91]	585	5	5–6	0.45	2	Partial (70%)
Gupta and Munro [45]	585	5	9	0.45 (double pulse)	10	Partial (80%)
Abrahamson and Davis [1]	585	5	6.5–7.25	NA	4	Complete
Nomura et al. [83]	585	7	7	0.45	5	Partial
Angel et al. [7]	595	7	15	3	2	Complete
Ozcanli et al. [89]	585	7	8.6	NA	8	Complete

NA not addressed

per second. It is a continuous laser, and thus its effect is similar to that of argon lasers (which has fallen into disuse). The patient showed no recurrence after 6 years of follow-up.

Because the carbon dioxide (CO_2) laser is an ablative laser that targets water, it is less selective than vascular lasers. However, that it excises and thermocoagulates at the same time and causes little surrounding tissue damage makes it a suitable treatment. Moreover, it has been suggested that it might be especially useful in settings where more expensive devices (such as PDL a or Nd:YAG lasers) are not available [63]. Four cases of AHLE treated effectively with carbon dioxide laser have been reported [48, 54, 63].

7.2 Darier Disease

Darier disease is an autosomal dominant genodermatosis characterized by acantholysis due to mutations in an endoplasmic reticulum Ca^{2+} adenosine triphosphatase (ATPase) [34]. The disease has mucocutaneous manifestations and nail involvement without spontaneous remission. The most characteristic lesions are keratotic red to brown papules that coalesce in plaques, mainly on the trunk. The disease worsens in the summer and the lesions frequently macerate, causing malodor due to secondary baterial infection and severe distress to the patient.

The general measures for the treatment of this disease consist of topical retinoids combined with topical corticosteroids to prevent irritation and with antimicrobials to avoid secondary bacterial colonization [56]. Systemic therapy with retinoids demonstrates good results, but relapses occur when they are stopped. Pregnancy prevention in women of childbearing age is mandatory with this drug and its use is also limited by its frequent side effects. Surgical therapy, including with lasers, is an option for localized or refractory lesions, but destruction down to the follicular infundibulum is necessary to avoid recurrences, with re-epithelization occuring from the the remaining adnexal structures within 7-14 days [56]. Nevertheless, the risk of scarring with ablative lasers increases with the depth of treatment and so the therapeutic window can be narrow.

The carbon dioxide laser was successfully used to destroy recalcitrant plaques in two patients with Darier disease by McElroy et al. [77], with significant improvement and recurrence in only one treatment site. The same laser was used by Chen et al. [79] to treat a patient with lesions involving 40% of total body area. The authors used a 3-mm spot and energies ranging from 10 to 40 W in two passes with tumescent local anesthesia, without recurrence at 2 years of follow-up. Nevertheless, the risk of scarring with a carbon dioxide laser increases with the depth of treatment and the thermal damage.

Beier et al. [12] treated 2 patients with an erbium (Er):YAG laser (2,940 nm) under local anesthesia with the painting technique and with an overlap of 30%. The treatment endpoint was the exposure of the papillary dermis including a margin of adjacent normal skin, using up to seven stacked pulses, a spot size of 1.6 mm and fluences of 5–8.5 J/cm^2. No recurrences and/or scarring were observed in the two patients in a follow-up of 20 months. Both patients had remission of the pruritus; posttreatment hypopigmentation was observed in the cubital and popliteal area of one patient and a few spots with the other patient. Posttreatment biopsies showed no signs of Darier´s disease in both patients.

7.3 Dermatomyositis

Dermatomyositis (DM) is an idiopathic myopathy with characteristic cutaneous findings. The characteristic cutaneous features of DM are the heliotrope rash and Gottron papules.

The first-line therapy for cutaneous lesions is the use of topical steroids and avoidance of sun exposure. Hydroxychloroquine, chloroquine, mycophenolate mofetil, immunoglobulins, and methotrexate have been beneficial in some case studies.

There have been some reports of poikilodermatous erythema and telangiectasias of DM treated with pulsed dye lasers and argon lasers, with good response [125, 128].

In 2006 we reported a case of a woman with Gottron papules that were treated with a PDL (Fig. 7.3). After three laser treatments there was a 70% improvement of the lesions [18]. Lasers have also been used successfully to treat other connective tissue diseases [13].

7.4 Eczema

Eczema is a form of dermatitis or inflammation of the epidermis characterized by a range of recurring skin conditions, which include dryness and recurring skin rashes.

Topical corticosteroids are the mainstay of treatment for eczema. Other treatments used are topical

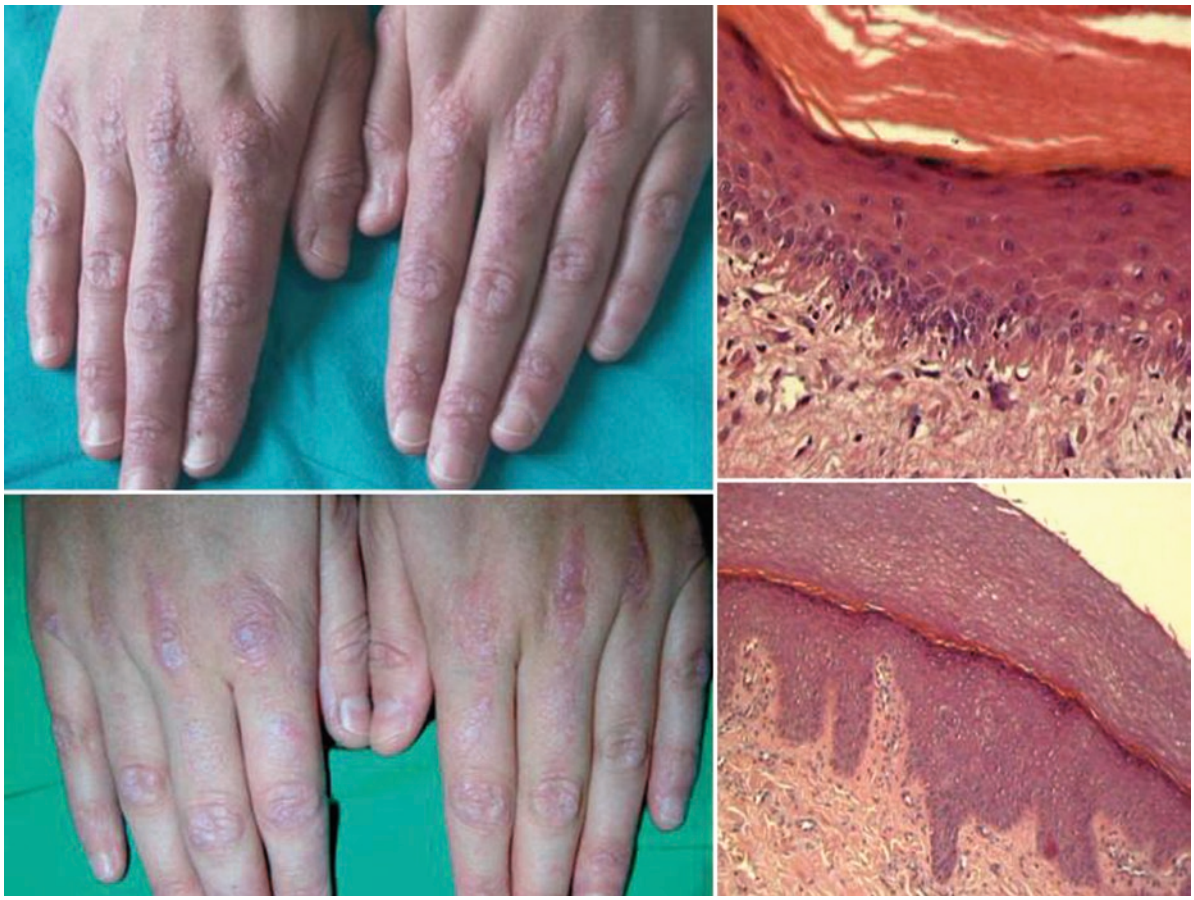

Fig. 7.3 Gottron papules before and after pulsed dye laser treatment (Used with permission from Calvo et al. Eur J Dermatol. 2006)

calcineurin inhibitors (e.g., tacrolimus, pimecrolimus), systemic corticosteroids, systemic cyclosporin A, and oral antihistamines [122].

In 2008, [108] reported a pilot study showing that PDL treatment improves localized areas of chronic eczema. Twelve children with localized chronic eczema were treated with PDL (595 nm). After 2 and 6 weeks, a significant decrease in eczema severity score was seen for the a PDL-treated areas compared with the control areas. Treatment was well tolerated. This may suggest that dermal vasculature plays an important role in chronic eczema or that PDL treatment may have an effect on cutaneous immunological activation [124].

7.5 Elastosis Perforans Serpinginosa

Elastosis perforans serpiginosa (EPS) is a rare skin disease in which abnormal elastic tissue fibers, other connective tissue elements, and cellular debris are expelled from the papillary dermis through the epidermis (transepithelial elimination).

Although many medications have been tried, no uniformly effective one has been reported. A few reports suggest benefit from isotretinoin and imiquimod [123]. Freezing with liquid nitrogen may have helped several patients.

Treatment with pulsed carbon dioxide and Er:YAG laser techniques may have been modestly helpful in patients with idiopathic EPS [118]. The pulsed dye laser has appeared to be beneficial in one reported case of EPS in a patient with Down syndrome [69].

7.6 Granuloma Annulare

Granuloma annulare (GA) is a inflammatory dermatosis characterized clinically by dermal papules and annular plaques. Localized lesions have been treated with potent topical corticosteroids, intralesional corticosteroids, and

cryotherapy. Treatment of the generalized disease unfortunately is fraught with a lack of consistently effective options. Though the treatment of choice remains to be defined, the available literature supports the use of isotretinoin or phototherapy with oral psoralen and ultraviolet A (PUVA) as first-line options for generalized GA [45].

In 1988, a carbon dioxide laser was used with good results to treat GA [115]. There are two single case reports of GA treated with a PDL. The localized GA was treated on three occasions: initially and at months 5 and 13. After the first session of treatment, significant flattening and reduction of erythema were evident. After the second and third treatments, further improvement was observed and long-term remission was achieved [118, 119]. In 2008, Karsai et al. [66] reported a patient with disseminated GA who was treated with fractional photothermolysis using a 1,440-nm Nd:YAG laser. A complete remission was achieved after two treatment sessions.

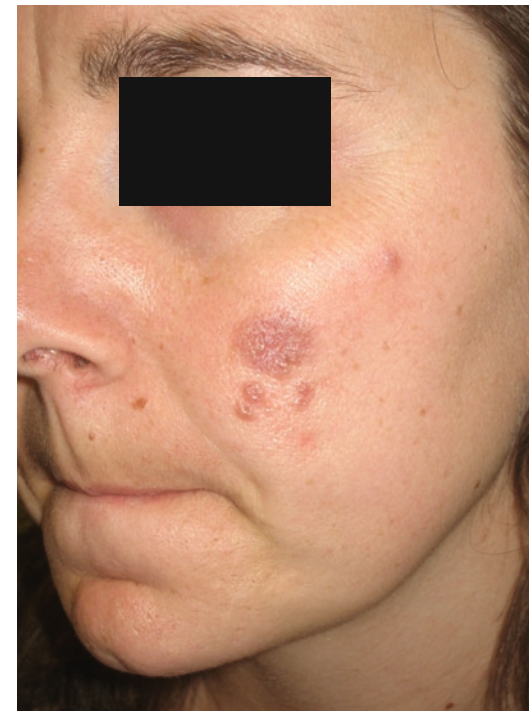

Fig. 7.4 Granuloma faciale before treatment

7.7 Granuloma Faciale

Granuloma faciale (GF) is an uncommon, benign, chronic skin disease of unknown origin characterized by single or multiple cutaneous nodules, usually occurring over the face. GF is notoriously resistant to treatment; therefore, many different medical therapies have been tried. Therapeutic options that have been tried and are reported to be effective include topical corticosteroid therapy, intralesional corticosteroid injections, intralesional gold injections, oral bismuth, antimalarials, isoniazid, oral potassium arsenite, *p*-aminobenzoic acid, calciferol, topical PUVA, and radiation therapy. More recently, topical tacrolimus has been reported to be effective. Dapsone is the oral medication most frequently reported to be of some benefit [73].

A variety of surgical procedures may be used in the management of GF: surgical excision, dermabrasion, electrosurgery, cryotherapy, and different types of lasers. Argon laser use was first reported in 1988, resulting in resolution of the clinical and microscopic abnormalities [9]. The laser most frequently used to treat GF has been the pulsed dye laser (Figs. 7.4 and 7.5). Since the first report of this treatment modality for GF in 1999, several single-patient case reports have demonstrated the successful use of PDL in the treatment of GF. In 2005, Cheung and Lanigan reported a series of four patients with GF treated with PDL. Resolution of

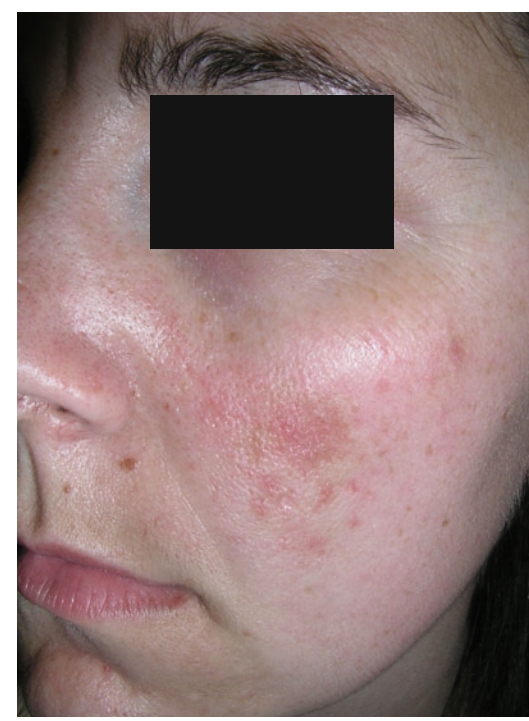

Fig. 7.5 Granuloma faciale after pulsed dye laser treatment

GF was achieved in only two of the four patients (50%). PDL often produces resolution without scarring and should generally be tried before the patient is started on long-term medication.

7.8 Hailey–Hailey Disease

Hailey–Hailey disease is an autosomal dominant genodermatosis characterized by acantholysis due to mutations in a Golgi apparatus Ca^{2+} ATPase and was first described in 1939 [46]. The lesions occur mainly in the intertriginous areas as erythematous plaques that macerate and may evolve into malodorous vegetations [56]. The course of the disease is characterized by flares and worsens in the summer.

The general measures for the treatment of this disease consist of topical corticoids and avoidance of secondary bacterial colonization with the use of antimicrobials [56]. Systemic therapies with retinoids or immunosuppressive drugs do not show consistent results, and surgery is reserved for cases that fail all other treatment options [78]. Dermabrasion is also an option for refractory lesions [47], with clearance rates as high as 83% but with hypertrophic scarring being observed. Similar to the patients with Darier's disease, the use of the carbon dioxide laser to vaporize the lesions has been described by several authors [22, 62, 77], with the treatment endpoint being skin destruction reaching the follicular infundibulum while sparing the adnexal glands to avoid hypertrophic scarring. Kartamaa et al. [62] used a continuous carbon dioxide laser to treat six patients with symmetrical lesions, leaving one side as an untreated controls. The vaporization was performed with a collimated beam in 4-5 layers; and improvement on the treatment side was reported in five patients, with hypertrophic scarring occurring in the axilar area of the other patient. Christian et al. [22] reported one patient with refractory axillary lesions treated with three passes of a short dwell carbon dioxide laser using a fluence of 28 J/cm^2; focal recurrences were managed with a short dwell carbon dioxide laser with a fluence of 15 J/cm^2. Complete resolution was observed in only one side.

Beier et al. [12] treated two patients with an Er:YAG 2,940-nm laser under local anesthesia with the painting technique. These patients had axillary and groin lesions and the treatment parameters were as follows: 0.35 ms pulse duration, up to 7 stacked pulses, 5 mm spot size, and 5–8.5 J/cm^2 fluence. Complete remission was observed in one patient at 1 year of follow-up; in the other patient lesion recurrence occurred at the edges and adjacent areas, which were managed with an additional treatment.

7.9 Lichen Sclerosus

Lichen sclerosus is an inflammatory disorder of the superficial dermis, more frequently observed in women between 50 and 60 years of age and in the anogenital area [97]. The pathogenesis of this disease is still unknown; clinically, it is characterized by ivory white patches with a wrinkled surface, telangiectasia, and purpura [101]. Severe pruritus is a main feature of this disease that can also cause dispaurenia and constrictions, with accentuated morbidity in the genito-urinary tract. The patients with genital lichen sclerosus also have a greater risk of developing squamous cell carcinoma in that area [96].

The first line of therapy are potent topical corticosteroids, such as clotebatosol propionate for at least 3 months, combined with emollients [81]. Recalcitrant lesions can be treated with a carbon dioxide laser, as published by Peterson et al. [94].

The carbon dioxide laser is an ablative option for this pathology; a retrospective study of 50 patients with histologically confirmed penile lesions and phimosis or meatal stenosis demonstrated that 80% of the patients were disease free at a median follow-up of 14 years [122].

Twelve women with vulvar lichen sclerosus were treated with photodynamic therapy using a 20% solution of 5-aminolevulinic acid that was irradiated (30–70 mW/cm^2) by an argon ion-pumped dye laser with a wavelength of 635 nm. Treatment was well tolerated by eight patients and a marked improvement in pruritus was observed in 10 women, which was maintained for a mean of 6 months, without relevant side effects [52].

A case report of one female patient with vulvar lichen sclerosus treated with PDL was published by Greve et al. [43] in 1999, with complete response after four treatments and no recurrences during the follow-up.

Several lasers as summarized in Table 7.2 are a suitable option for lesions of lichen sclerosus that are resistant to high-potency topical steroids or for complications of this disease, such as strictures and stenosis.

Table 7.2 Parameters and results of laser treatment of patients with lichen sclerosus

Reference	Wavelength (nm)	Spot size (mm)	Fluence	Pulse duration (ms)	Number of treatments	Response
Windahl [122]	10,600	Not mentioned	15–20 W (defocused beam)	Continuous	1	80% of the 50 patients were disease free
Kartamaa and Reitamo [61]	10,600	2	5–6 W (defocused beam)	Continuous	1 (3–4 passes)	Good response in 9 of 10 treated patients
Raulin et al. [98]	585	7	5.3–6 J/cm^2	0.3–0.45 ms	4	Complete remission

7.10 Lupus Erythematosus

Lupus erythematosus (LE) is a common autoimmune, multisystemic disorder with significant morbidity and mortality, the pathogenic mechanisms of which are not yet fully understood. This disease was only differentiated from a cutaneous form of tuberculosis, lupus vulgaris, in the mid-1800s by Cazenauve.

Skin disease is the second most frequent manifestation of LE [24], and its subtypes can indicate the pattern of LE activity. The skin lesions of this disorder range from discrete papules, as in lupus tummidus, to atrophic lesions with telangiectasias in discoid lupus erythematosus (DLE).

The gold standard therapy are antimalarials, with other options being systemic steroids, other immunosuppressive agents, and thalidomide [71].

Cutaneous lesions can be refractory to topical therapy with steroids or systemic treatment with immunosuppressive drugs or antimalarials, and patients may also have major contraindications to these drugs.

Since the 1980s, the use of lasers, namely the argon laser, has been reported in the literature as a therapeutic option in the discoid lesions of LE. The argon laser targeted the vessels and showed a good response in the treatment of telangiectactic plaques refractory to conventional therapies [68, 85].

The PDL is used in several vascular disorders, such as rosacea telangiectasias or port wine stains. The wavelengths of 585 or 595 nm are selectively absorbed by oxyhemoglobin and allow a selective destruction of the vessel walls [53]. The rationale for the therapeutic success of PDL in LE is the growing evidence that endothelial cells play a major role in the inflammatory process and systemic manifestations in LE [69, 109]. The targeting of endothelial cells in rheumatic diseases is now an important field in the development of new drugs [109], and even classic drugs used in the treatment of LE, such as chloroquine, have been shown to reduce skin lesions from LE partially through inhibition of angiogenesis [73].

Two published series of patients with LE lesions treated with a PDL [11, 98] showed significant improvement of skin lesions, even in those patients with the systemic form of the disease (Table 7.3). The older series used a PDL with a wavelength of 585 nm, achieving a clearance rate of 70% in nine patients. Hyperpigmentation was observed in two

Table 7.3 Parameters and results of two published series of pulsed dye laser treatment of lupus erythematosus

Reference	Wavelength (nm)	Spot size (mm)	Fluence (J/cm^2)	Pulse duration (ms)	Number of treatments	Response
Raulin et al. [98]	585	5; 7; 10	6–7; 3–7; 3.4–3.5	0.3–0.45	1–10	70% lesion clearance in 9/12 patients
Baniándrés et al. [11]	585; 595	5; 7	5–8.75; 6–13	0.45; 1.5–10	1–9	60% lesion improvement in 14/14 patients

patients; one patient relapsed but there were no scarring and/or laser induced LE lesions. The authors recommended the use of a 7-mm handpiece with a fluence of 5–5.5 J/cm^2.

In the series of 14 patients published by Baniandrés et al. [11] using both a 585- and 595-nm PDL, an average clearance rate of 60% was obtained, with the best results on the erythema and telangiectasia, as previously described by Nuñez et al. [84]. The majority of the patients were treated with the 7-mm handpiece, with fluences ranging between 6 and 12 J/cm^2 for a pulse duration of 1.5 ms and between 7 and 11 J/cm^2 for a pulse duration of 10 ms (Figs. 7.6–7.9). Posttreatment biopsies performed in three patients did not show histological findings of LE (Figs. 7.10 and 7.11). In four patients a transient hyperpigmentation was observed, one patient had slight atrophic scarring, and in three patients a partial relapse of their skin lesions occurred more than a year after the treatment.

Another application for lasers in the treatment of LE are the atrophic scars, especially in DLE because this subtype frequently causes disfiguring and cribriform scars. The carbon dioxide laser in continuous wave mode was used to vaporize a disfiguring plaque [50] and, more recently, the erbium:YAG laser [114], the latter with regional nerve blocks and 6–10 passes

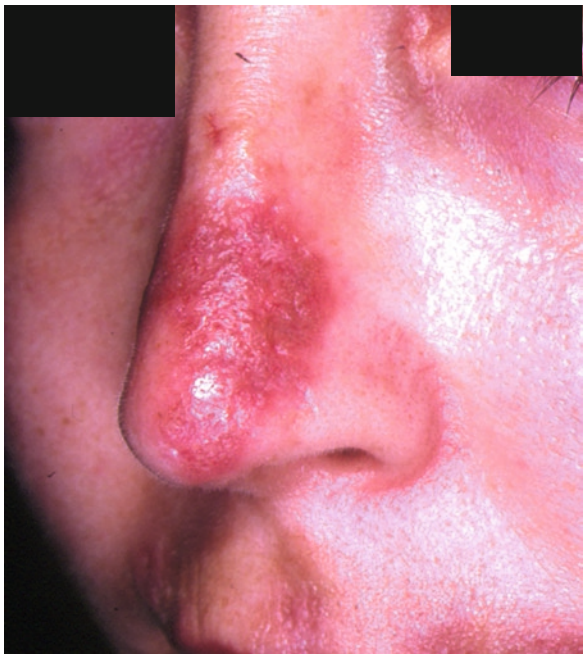

Fig. 7.6 Cutaneous lupus erythematosus before treatment

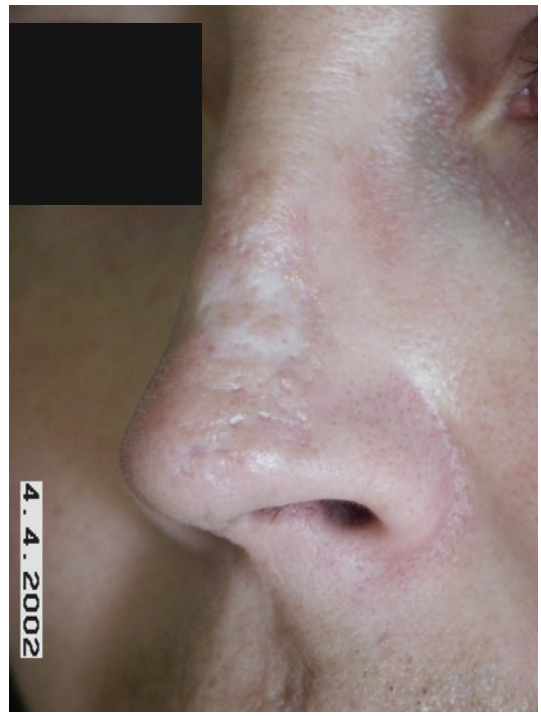

Fig. 7.7 Cutaneous lupus erythematosus after pulsed dye laser treatment

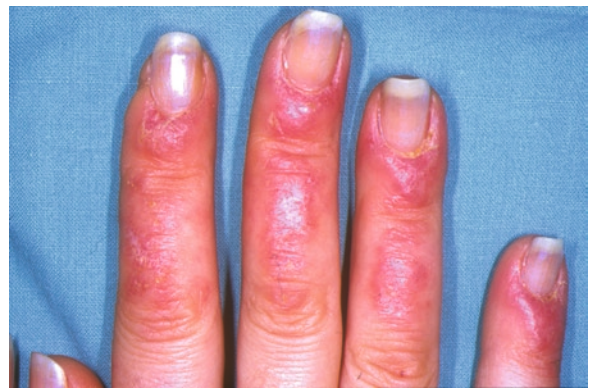

Fig. 7.8 Cutaneous lupus erythematosus before treatment

with fluences ranging from 10.2 to 28.2 J/cm^2 at 5 pulses/s. Good cosmetic results were observed in both patients without disease reactivation in the treated areas during the follow-up.

The safety of lasers in the treatment of LE is a matter of debate because this disease might be precipitated or aggravated by UV light; the argon laser, with a wavelength in the range of visible blue to green light, was already implicated by two articles to induce LE skin lesions [119, 123]. A percentage of 93% of

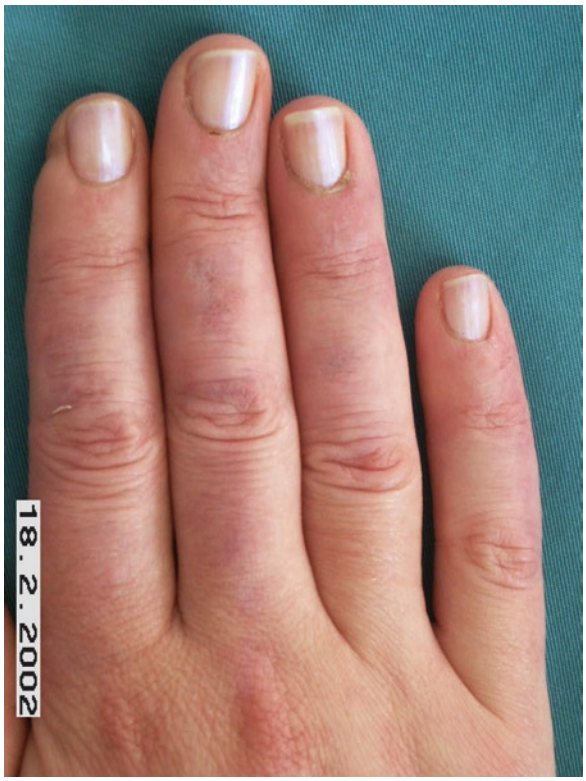

Fig. 7.9 Cutaneous lupus erythematosus after pulsed dye laser treatment

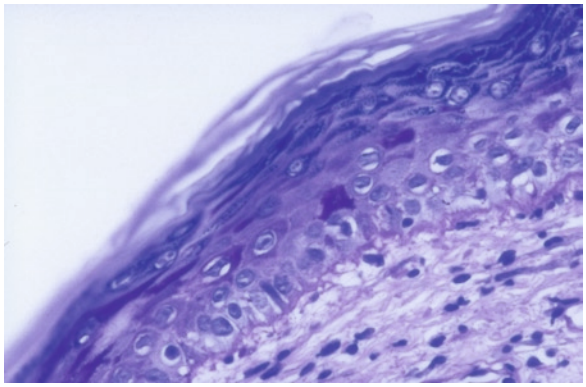

Fig. 7.10 Cutaneous lupus erythematosus before treatment

abnormal reactions to UV and visible light was found in one series of patients with LE, without correlations being observed between the LE subtype or positivity for autoantibodies and the presence of photosensivity [105]. As far as we were able to search the literature, there are no published cases of LE lesions induced by the PDL, CO_2, or erbium:YAG lasers, but different authors recommend that prior to laser treatment spot testing in a concealed area should be done to detect potential laser-induced LE lesions [60, 98].

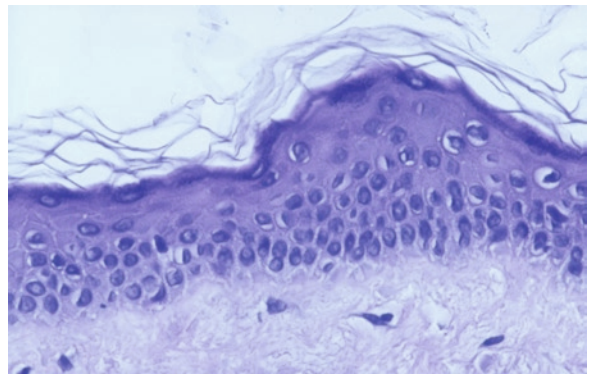

Fig. 7.11 Cutaneous lupus erythematosus after pulsed dye laser treatment

7.11 Necrobiosis Lipoidica

In 1929, Oppenheim first described necrobiosis lipoidica and called it dermatitis atrophicans lipoidica diabetica, but it was later renamed necrobiosis lipoidica diabeticorum by Urbach in 1932. In 1935, Goldsmith reported the first case in a nondiabetic patient. Today, the term necrobiosis lipoidica is used to encompass the same clinical lesions in all patients, regardless of whether or not diabetes is present [66].

Treatment for NL is not very effective. Topical and intralesional steroids can lessen the inflammation of early active lesions. Other treatments reported with successful results are 0.1% topical tacrolimus, cyclosporine, and antiplatelet aggregation therapy with aspirin and dipyridamole. Agents such as etanercept and infliximab, and topical psoralen plus UV-A light therapy have also been used. [66].

In 1999, Currie et al. [25] described a case report of NL treated with a PDL. At low fluences, minimal therapeutic effect was achieved, and at higher fluences skin breakdown occurred, so they concluded that caution is required when attempting to treat NL with a laser [25]. In contrast, Moreno-Arias and Camps-Fresneda reported an overall cosmetic improvement after three treatment sessions with respect to erythema and telangiectasias. In another study the lesions' progression was prevented with PDL treatments [80]. In addition, there are many reports of successful treatment with photodynamic therapy [15, 26].

7.12 Nodular Amyloidosis

Localized cutaneous amyloidosis (LCA) refers to a condition characterized by the deposition of amyloid or amyloid-like proteins in the dermis. Nodular localized cutaneous amyloidosis is the rarest type of LCA [118].

Various methods attempt to improve the appearance of the lesions, including topical and intralesional corticosteroids, cryotherapy, dermabrasion, shaving, curettage, electrodesiccation, carbon dioxide laser, and the PDL [118].

A patient with a large scalp lesion of nodular primary LCA was treated with a CO_2 laser with excellent cosmetic results and minimal morbidity [55, 116]. In 1999, a case report of multiple nodules treated with a PDL was described, with clinical improvement in the color, size, and friability of nodules maintained for 6 months [5]. Histologic examination revealed decreased inflammation and improvement in dermal collagen after laser irradiation. None of these treatment methods totally eradicates lesions, which can recur.

7.13 Prurigo Nodularis

Prurigo nodularis (PN) consists of multiple, intensely pruritic, excoriated nodule erupting on the extensor surfaces of the limbs secondary to itching or rubbing. Many conditions have been reported to induce PN (e.g., neurodermitis, chronic liver or kidney disease).

Current available treatments of PN are topical, oral, and intralesional corticosteroids. Menthol, phenol, pramoxine, capsaicin cream, vitamin D3 ointment, and topical anesthetics are some other topical agents used to reduce pruritus. UV light treatment using UV-B or UV-A plus psoralen may be beneficial for severe pruritus. Antihistamines, anxiolytics, opiate receptor antagonists, and (most recently) thalidomide are oral medications used. A few case reports and small studies have shown efficacy of the topical immunomodulators tacrolimus and pimecrolimus. Cryotherapy with liquid nitrogen helps reduce pruritus and flatten lesions [74]. In 2000, Woo and colleagues reported a case using the pulse dye laser, which may help reduce the vascularity of individual lesions [124].

7.14 Psoriasis

Psoriasis is a chronic inflammatory skin condition that affects 1–2% of the population. It is characterized by scaly, sharply demarcated plaques that are most frequently located on extensor surfaces. It can also affect palms, soles, nails, and scalp, and can present in an erythrodermic or pustular form.

The treatment of psoriasis is complex and it depends mainly on the location and extension of the lesions. Therefore, several therapies have been used to treat this condition: tar preparations, vitamin D analogs, corticosteroids, anthralin, phototherapy (UVB, PUVA), methotrexate, retinoids, cyclosporine, and fumarates.

Laser therapy for psoriasis was first addressed in 1985 by Bekassy et al. [13, 14], who performed CO_2 laser vaporization of plaques of psoriasis that had proved intractable with conventional topical therapy. They treated three patients who did not relapse during 3–5 years of follow-up. Nevertheless, Alora et al. [4] obtained a high rate of relapses after treating 12 recalcitrant psoriatic plaques within 8 weeks, concluding that it did not seem to be an acceptable treatment modality for psoriasis.

Because the dermal papillary vasculature is believed to be involved in the initiation and perpetuation of psoriasis, vascular lasers such as PDL and Nd:YAG have been used for this condition. for this condition.

A PDL emits at a wavelength of 585 nm, which selectively targets superficial blood vessels to a depth of at least 0.5 mm. It has been shown that the PDL reduces the microvessel density and the length of microvessels per unit of psoriasis plaque [51]. Zelickson et al. [130] treated 36 patients by using both long- and short-pulse PDL. They found improvement and clearance for longer than a year in some patients. No difference was found between the long- and short-pulses width. Moreover, they obtained confocal microscopic images of the dermal vasculature of each patient. The finding of more tortuous vessels under the rete ridges corresponded to a poorer clinical response. Lanigan et al. [70] reported that 5 out of 8 patients they treated using a PDL showed a reduction of at least 50% of their plaques.

PDL has shown to be as effective as UVB in the treatment of plaque-type psoriasis; however, no synergistic effect of combining both has been found [28].

Erceg et al. [30] compared PDL to calcipotriol/betamethasone (CB) ointment in eight cases. They observed that the desquamation and induration had significantly declined in the patients treated with PDL after 12 weeks as compared to CB. These authors [17] also addressed that PDL therapy of recalcitrant psoriatic plaques results in sustained reduction of memory and cytotoxic T-cells, as well as normalized proliferation

and keratinization of the epidermis. Also, PDL seems to be useful to treat psoriasis of the palms and soles [27].

Van Lingen et al. [117] suggested that, although the 1064-nm Nd:YAG laser can penetrate to deeper abnormal psoriatic vasculature, targeting the more superficially located microvasculature in psoriasis seems to be of stronger significance for achieving a clinical effect.

Ruiz-Esparza [104] described three anecdotal cases of psoriatic plaques responding to low-energy Nd:YAG (1,320-nm) irradiance. The author suggested a biomodulatory effect of the cell activity; nevertheless, mechanisms involved in the resolution of the lesions in these cases remain unknown.

As Parrish and Jaenicke [92] demonstrated, the action spectrum of phototherapy for psoriasis clearing is 300–313 nm. UVB phototherapy has consistently been shown to be one of the safest and most effective therapies for generalized psoriasis. Because the 308-nm xenon chloride (XeCl) excimer laser is within the above-mentioned spectrum, it was first used for the treatment of recalcitrant plaques of psoriasis in 1997 [16]. Subsequently, several studies have confirmed that it is effective and comparable to narrow band UVB [31, 32, 37, 38, 49, 65, 111].

The 308-nm xenon chloride excimer laser is more selective than conventional UVB therapy because it is directed at lesional skin, sparing surrounding uninvolved skin from UV exposure, therefore reducing the carcinogenic effect of UV radiation on the skin.

Standard UVB therapy typically requires 25–30 treatments; in contrast to this, improvement can be seen with an excimer laser within one-third of the number of treatments required with standard phototherapy regimens [112]. It therefore provides a high level of satisfaction and compliance [102]. It has been suggested that the more rapid effect of the 308-nm excimer laser is due to the higher fluences used, the deeper tissue penetration, and a higher effectiveness in inducing cell death and skin immune system suppression than traditional UVB therapy [129].

Different therapeutic approaches have been proposed for treating plaque type psoriasis with the 308-nm excimer laser (Table 7.4). Both high- [8, 113] and medium-dose [8, 112] protocols have shown to clear the lesions, with remission periods ranging from 3.5 months to 2 years. Low fluences are those 0.5–1 times the minimal erythema dose (MED); medium doses are 2, 3, 4, and 6 MEDs; and high doses are 8 and 16 MEDs. Asawananda et al. [8] reported significantly better results using high fluences than low or medium ones. Moreover, the ability to directly use high-dose therapy allows for a reduction in the number of treatments, whereas a gradual increase of the dose is needed in UVB therapy because both involved and uninvolved skin is being exposed. This allows for a lower cumulative dose when using the excimer laser as compared to traditional phototherapy.

The fluence can also be chosen according to the severity of the lesion's induration, increasing or decreasing it during each treatment to obtain a subblistering dosage that allows for an individualized treatment [110].

Gerber et al. [37] proposed an individually tailored regime using the MED of the involved skin as the starter dose, which correlates with the thickness of the lesion. The fluence was increased during subsequent treatments depending on the erythema observed after each session. Using this protocol, significantly lower cumulative doses and number of treatments can be obtained.

Effectiveness in palmoplantar [42, 82], scalp [45, 111], and inverse psoriasis as well as a case of inverse psoriasis treated in combination with tacrolimus have also been reported [21]. The combination of PUVA and a 308-nm excimer laser makes the lesions heal quicker than using PUVA alone [115].

Use of the 308-nm excimer laser in children seems to be safe; however, only one small study has been carried out in patients older than 6 years of age [90].

The treatment with a 308-nm excimer laser is generally well tolerated. No anesthesia is needed for the treatment and only side effects such as erythema and occasionally bullae can be observed 24 h after treatment. These bullous areas become crusted within 1 week and heal afterwards without scarring.

7.15 Reticular Erythematous Mucinosis

Reticular erythematous mucinosis (REM) was first described by Steigleder in 1974 [107]. It is a rare condition typically presenting as erythematous urticariform plaques on the chests of young women and commonly appear after sun exposure. Histologically, perivascular round cell infiltrates and alcian blue positive mucoid deposits are found in the dermis. It has been associated with with LE and lupus tumidus; however, this remains unproven as fact. Successful treatment with pimecrolimus [75], tacrolimus [19], and chloroquine [88] has been reported.

The PDL has also been shown to be effective for treatment of REM. Greve and Raulin [44] reported

Table 7.4 Summary of the treatment of psoriasis using a 308-nm excimer laser

References	Number of patients	Location of lesions	Starter dose	Treatments per week	Number of treatments	Cumulative dose (J/cm^2)	Results	Follow-up period
Bónis et al. [16, 64]	10	Body	0.5 MED	3	8.6	4.45	Remission	2 years
Asawanonda et al. [8]	13	Body	0.5–18 MED	NA	1–20	NA	Remission in those treated with high doses (8–16 MED)	4 months
Trehan and Taylor [113]	16	Body	8-16 MED	–	1	NA	>75% improvement in 5 of 16 patients	4 months
Feldman et al. [32]	80	Body	2–3 MED	2	10	NA	90% clearance in 50% of the patients	–
Trehan and Taylor [112]	15	Body	MED	3	≤24	NA	95% clearance (mean remission time: 3.5 months)	6 months
Taneja et al. [109]	14	Body	Doses according to thickness	2	10	8.8	Improvement in all patients	NA
Gerber et al. [37]	145	Body	Group 1: 3 MED Group 2: MED of involved skin	2 (first 3 weeks) 1 (afterwards)	Group 1: ≤10.8 Group 2: 7.1	Group 1: 11.25 Group 2: 6.25	85.3% (Group 1) and 83.7% (Group 2) of patients showed a ≥90% improvement in PASI after 13 sessions improvement in PASI after 13 sessions	NA
Taylor and Racette [111]	13	Scalp	MED	2	NA	1.7	3 of 13 remission after 6 months	6 months
Pahlajani et al. [90]	19 (7 children, 12 adults)	Body	3 MED	NA	NA	NA	Children: 91.3% reduction in PSS score Adults: 61.6% reduction in PSS score	NA
Köllner et al. [65]	31	Body	Group 1: MED Group 2: 2 MED	3	24	Group 1: 52.9 Group 2: 29.27	90% clearance	4 months
Nistico et al. [82]	54	Palmoplantar	MED	1–0.5	10	NA	PASI 75 in 44/54 patients	8 weeks

Rivard and Lim [100]	28	Body	NA	NA	12	NA	PASI 75 in 80% of the patients	NA
Goldinger et al. [38]	16	Body	2 MED	3	12	NA	Complete clearance in 5/16 patients	NA
He et al. [49]	40 (26 macular type; 14 chronic plaque type)	Body	1–2 MED	2	15	6.86	90.19% PASI reduction in macular type	NA
		Body					77.34% PASI reduction in chronic plaque type	

NA not addressed; *MED* minimal erythema dose; *PSS* psoriatic severity score; *PASI* psoriasis area and severity index

two cases treated with a 585-nm PDL (7-mm spot, 0.3- to 0.45-ms pulse duration, 5.4- to 6.9-J/cm^2 fluence). In both cases an almost complete response was obtained. Damage of small blood vessels or activation of immunologic processes [6] might be involved in these satisfactory outcomes, similar to what occurs in keloid scars, LE, or lichen sclerosus atrophicus.

7.16 Sarcoidosis

Sarcoidosis is a multisystemic, granulomatous disease of unknown etiology. Skin manifestations occur in approximately 25% of cases. Histologically, widespread noncaseous granulomas can be seen. There are specific (papules, plaques, subcutaneous nodules, and scar sarcoidosis) and nonspecific lesions of cutaneous sarcoidosis. Standard therapeutic interventions for cutaneous sarcoidosis have traditionally included topical, intralesional, and systemic steroids, as well as antimalarial drugs, methotrexate, and combinations of these agents [9]. Newer therapies such as pentoxifylline, tetracyclines, allopurinol, melatonin, isotretinoin, infliximab, or immunossuppressive drugs have also been used [9].

Laser therapy has been used mainly for lupus pernio, which is the most characteristic lesion of cutaneous sarcoidosis. It has a predilection for acral sites, most commonly the nose. The lesions are usually violaceous plaques or nodules that can be disfiguring and can cause significant psychological morbidity. PDL was first used by Goodman et al. [39]. They obtained 75% improvement after two treatments, but recurrence was observed after 6 months. Cliff et al. [23] confirmed the PDL's effectiveness to clear lupus pernio clinically and histologically, with no recurrence after 2 months. However, this follow-up period might not have been long enough to evaluate the long-term effectiveness. Of note, a case of generalized ulcerative sarcoidosis has been reported [40] after PDL therapy of a lupus pernio.

CO_2 laser remodeling and healing by secondary intention have also been performed for lupus pernio. Six cases have been reported [86, 106, 127] with satisfactory a esthetic results and no recurrence in most cases. Some of the authors used intralesional triamcinolone acetonide after laser therapy [86, 106].

In addition, the 532-nm frequency-doubled Nd:YAG laser has been used to treat lupus pernio. A complete remission after a 3-year follow-up has been reported [29].

Scar sarcoidosis is characterized by erythema, infiltration, and progressive induration of a pre-existing scar. It can resemble hypertrophic scars or keloids. Anecdotal use of a Q-switched ruby laser lead to a complete clearance of scar sarcoidosis lesions [41]. Successful treatment of this condition was also reported using a 595-nm PDL. No recurrence was observed after 1 year of follow-up.

Laser treatment seems to be effective for isolated cases of cutaneous sarcoidosis. Nevertheless, only few cases have been reported so far. Paradoxically, a case of sarcoidosis arising in areas where full-face carbon dioxide (CO_2) laser resurfacing had been performed has also been presented [67]. In addition, a case of worsening of the skin lesions after PDL treatment has been addressed [40]. In conclusion, further studies should be performed to assess the role of the lasers in general in the treatment of cutaneous sarcoidosis.

7.17 Zoon's Balanitis

Zoon's balanitis is an uncommon inflammatory disorder that was first reported by Zoon in 1952 [131]. It is more frequently observed on the penile glans of uncircumcised men as smooth or eroded, bright red plaques, which can be associated with pruritus. This disease is also described in women and named Zoon's vulvitis, with a few authors reporting an association with genital neoplasia [58, 95, 120].

The pathogenesis is still unknown, but it has been linked to friction or rubbing [57, 126], irritation by urine or smegma, and local infections. It is not normally reported in circumcised mens and the histology of the lesions is characterized by a thin epidermis and a dermal lichenoid plasma cell infiltrate.

The first goal of therapy is the promotion of good hygiene; circumcision is the most consistently effective treatment [33]. Topical steroids, antimicrobials, and hormonotherapy have all showed inconsistent results.

The carbon dioxide laser is an effective treatment for Zoon's balanitis, especially if circumcision is not a feasible option, and, more recently, good results with an erbium:YAG laser were reported [3, 10, 99] (Table 7.5). The patient was treated with an erbium:YAG by Albertini et al. [3] and showed no clinical or histological evidence of relapsing with complete re-epithelialization occurring one week after treatment, similar to the patient treated with a carbon dioxide laser by Baldwin and Geronimus

Table 7.5 Laser parameters and results for Zoon's balanitis treatment

Reference	Wavelength (nm)	Spot size (mm)	Fluence/ intensity	Pulse duration (ms)	Number of treatments	Response
Baldwin and Geronemus [10]	10,600	Not mentioned	200 W/cm^2 (defocused)	Continuous	1	Complete lesion clearance in one patient
Retamar et al. [99]	10,600	Not mentioned	1–2 W (2–4 passes)	Continuous	1	2 of the 5 treated patients relapsed
Albertini et al. [3]	2,940	3	0.5 J/cm^2 (3–6 overlapping passes)	350 ms	1	The patient had in a 2-year follow-up

[10]. Nevertheless, in a series of 5 patients treated with a CO_2 laser [99], two patients relapsed after 1 or 3 years, with the third patient later developing lichen sclerosus.

Take Home Pearls

- The PDL has demonstrated the best results in the treatment of cutaneous lesions of LE that are resistant to medical therapy.
- The role of the endothelial cell in the pathogenesis of LE increasingly is recognized and it is the rationale for the PDL's use in this dermatosis.
- To avoid potential laser-induced LE lesions, spot testing in a concealed area should be performed before laser treatment.
- The level of tissue ablation in Darier's or Hailey-Hailey disease should spare the adnexal structures in order to avoid hypertrophic scarring.
- PDL might be the most useful laser for treatment of AHLE because it targets the hemoglobin present in the blood vessels, which proliferate in this lesion.
- Well-performed clinical trials are needed to confirm the effectivity of laser therapy for sarcoidosis.
- By targeting the superficial blood vessels and due to a probable immunomodulatory effect, PDL seems to be effective for plaque type psoriasis.
- The 308-nm excimer laser is a well-tolerated therapy that has been shown to be effective for recalcitrant plaques of psoriasis both at high and medium doses. Its main advantages are the selectivity and the lower carcinogenic effect compared to conventional phototherapy.

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Laser-Assisted Liposuction

8

Boris Sommer and Dorothee Bergfeld

Core Messages

- Laser lipolysis means disruption of a number of fat cells by moving a laser probe through the subcutaneous tissue.
- The procedure is performed under sterile condition and involves preparation of the area similar to traditional liposuction.
- At the time of publication, laser lipolysis is almost always done in connection with a traditional liposuction, and therefore a more appropriate term is "laser-assisted liposuction."
- Exact treatment parameters, the most suitable wavelength, and other factors are still to be determined.

8.1 Introduction

Since the first description of a liposuction procedure by Georgio and Arpad Fischer in Rome in 1975, liposurgery has constantly been improved. It is still the most commonly performed procedure in cosmetic surgery worldwide.

Initially, the term "liposuction" meant the surgical procedure of removing fat cells with specially designed suction devices, using stiff hollow cannulas to remove the subcutaneous fat.

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Today liposuction is only part of a wide variety of procedures used in "liposculpturing" that allow the precise forming of body areas ("body contouring").

The suction process is often combined with or sometimes substituted by other techniques to reduce adipocytes, e.g., a variety of procedures that destroy the fat cells by physical (e.g., laser) or chemical (e.g., phosphatidylcholine) means.

To better describe the use of a combination of various techniques, we introduced the term "lipotherapy." Besides the cosmetic indications, lipotherapy also has been established as an effective treatment of noncosmetic disorders of the adipose tissue. Over time it has been possible to establish high-quality standards to achieve predictable operative outcome and minimal surgical risk.

To understand the position of laser-assisted liposuction in this concept, it is important to know the current state of the art of lipoplasty surgery.

8.2 Important Historical Milestones in Liposuction Surgery

The "Dry Technique": In 1975, Georgio and Arpad Fischer in Rome were the first to give a description of removing fat using cannulas inserted through tiny incisions. They invented a machine to suction unprepared fat through hollow needles under general anesthesia. The fat was fragmented by a motorized cutting blade. This procedure suffered from high intraoperative risks such as severe blood loss and poor aesthetic results as well as a high rate of postoperative complications (e.g., dents and seromas) [6].

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_8, © Springer-Verlag Berlin Heidelberg 2011

The "Wet Technique": Yves-Gerard Illouz, a surgeon from Paris, introduced the so-called "wet technique." To facilitate aspiration of the adipose tissue and reduce blood loss, he installed physiologic saline solution mixed with hyaluronidase into the operation site [11].

8.2.1 Tumescent Local Anesthesia

In 1987, Jeffrey Klein [15] first described the tumescent (from *tumescere*, "to swell") technique, a combination of the wet technique and a local anesthetic procedure. He installed large volumes of physiologic saline with added lidocaine anesthetic solution. His idea revolutionized the history of liposuction because tumescent liposuction minimized the operative and anesthetic risks and turned the operation into an outpatient procedure.

The tumescent solution is infiltrated subcutaneously into the surgery field. The solution stabilizes the subcutaneous connective tissue, which is consequently less traumatized. This also makes the procedure less painful for the patient and physically less strenuous for the surgeon. The alert patient is able to cooperate: he or she can shift their position on the operating table when required or even get up during the operation to control the already achieved result in a standing position.

Further advantages of tumescent liposuction include:

- No need for general anesthesia
- Significantly reduced blood loss
- Immediate patient mobilization
- Significantly shorter reconvalescence
- Long-lasting postoperative analgesia

All of these advantages make tumescent liposuction an ideal outpatient procedure and today's method of choice [20, 22, 24].

It should be noted that some misunderstandings concerning technical aspects of the tumescent technique still exist. Some surgeons use minimal amounts of the Klein tumescent solution in conjunction with deeper sedation or general anesthesia. When applying only little amounts of the fluid, one cannot reach a correct "state of tumescence." Consequently, the advantages of the tumescent technique are lost if the application is done incorrectly. Jeffrey Klein introduced the terms "true tumescent anesthesia" or "liposuction in tumescent anesthesia alone" to distinguish the correct technique from the fake forms. We introduced the term "tumescent local anesthesia" to clearly link the aspect of local anesthesia to the tumescent technique [24].

8.3 New Developments in Liposuction Surgery During the Last Decade

Improvement and changes in the tumescent solution helped to establish a safer therapy and made the use of greater volumes of fluid and smaller cannulas possible. New liposuction-assistant techniques have changed the technical side of the procedure.

8.3.1 Ultrasound-Assisted Liposuction (UAL)

In 1987, Scuderi and DeVita [21] first described a method of homogenizing the fat with ultrasound waves. Due to severe disadvantages, such as a raised number of seromas and skin burns and as a result of a destruction of the myelin sheath of peripheral nerves, the method did not succeed.

8.3.2 Vibration-Assisted Liposuction, also Called Power-Assisted Liposuction

Vibrating cannulas facilitate the treatment of fibrous or pretreated areas. Because they pass more easily through the tissue and do not tangle with the fibers, they make the procedure more comfortable for the patient and the surgeon [23]. Severe complications have not been reported.

8.4 History of Lasers in Liposuction Surgery

Laser energy in combination with liposuction was first used by Apfelberg [1] in 1992. The idea was not to destroy the adipocytes but to achieve a coagulation of

the vessels after suctioning. Due to lack of success, this work remained experimental [1].

Cook [5] reported about a combined procedure of liposuction and laser in neck and jowl liposculpturing. This procedure involved a carbon dioxide laser used on the inside of the skin of the neck after liposuction of the neck. The disadvantages of having to produce a larger incision on the skin and a risk of skin necrosis prevented this method from developing into a standard procedure.

Blugerman and Schavelzon started interstitial laser-assisted lipolysis (laser lipolysis) for tissue reduction in Argentina in the late 1990s [3, 8, 9]. The idea was to facilitate the liposculpturing process by melting the adipose tissue with laser energy. The lasers used were 1,064-nm neodymium:yttrium aluminum garnet (Nd:YAG) and diode lasers.

Parallel working groups in Germany (Sattler/Sommer, Rosenparkklinik) and Austria (Sandhofer) were working with the same laser system [18].

Compared to other techniques, especially the vibration-assisted liposuction, the effort was too high and the effect too little, and the laser was not established as a routine device. One reason was the relatively low power of 6 W that resulted in a marked prolongation of the operating time.

In 2002, Badin published his experience with laser lipolysis emphasizing a tissue retraction effect with this technique [2]. Reported effects of externally applied low-level lasers could not be reproduced [4, 16]. The US distributer of the low-level laser device, Erchonia Medical Laser, announced an application at the US Food and Drug Administration in 2004, but since then no communication of this method has reached the scientific community.

8.5 Current Laser Devices for Laser-Assisted Liposuction

In 1999, a new 1,064-nm Nd:YAG pulsed laser system with 300-μm fibers was introduced to the market (SmartLipo Deka Laser, Firenze, Italy). By 2007 the initial energy level of 6 W maximum output was increased up to 10 W and later even 18 W. A skin-penetrating microcannula (1 mm), through which the fiber is passed, permits direct contact with the subcutaneous fat (interstitial lypolysis).

Clinical studies showed good results in small areas, excellent patient tolerance, and quick recovery. There was a good skin retraction overlying the treatment site [14]. In larger areas, it soon became obvious that the laser lipolysis can only be a means to facilitate and assist a consequent liposuction (laser-assisted liposuction).

Looking at the absorption maximums of the wavelength in tissue, it is obvious that the wavelength of 1,064 nm is not ideal for adipose tissue, which has an absorption spectrum comparable to water (Fig. 8.1).

In 2008, the SmartLipo MPX was introduced, an Nd:YAG laser system that combines two wavelengths: 1,064 and 1,320 nm. Both wavelengths can be emitted separately. In the MultiPlex Mode they are released in sequence. Energy levels are up to 20 W for the 1,064-nm wavelength and up to 12 W for the 1,320-nm wavelength. In consideration of the absorption maxima, the 1,064-nm wavelength is used in rather superficial layers to improve the skin tone, whereas the newly introduced 1,320-nm wavelength is supposed to induce the rupture of adipocytes.

With higher energy levels, the risk of heat-induced skin damage is an important issue. A new and very important feature is a safety device that regulates the level of laser energy being delivered in relation to the speed at which the handpiece is moved to ensure constant energy delivery (SmartSense). The SmartSense shuts down the laser automatically when the handpiece is not moved at a certain speed and helps to avoid skin burning. A thermistor that constantly measures the effective temperature of the subcutaneous layer already has been introduced in the USA and awaits CE clearance in Europe.

A 980-nm diode laser (Oyris, Hellemmes, France) was tested by Reynaud et al. [17], who surprisingly found not a single complication despite using high accumulated energy up to 51,000 J.

8.6 Effect of Laser Energy on Fat Tissue

Laser lipolysis works through a combination of photoacoustic ablation and selective photothermolysis of fibrous septae. Acoustic damage occurs with thermal damage and is difficult to capture histologically.

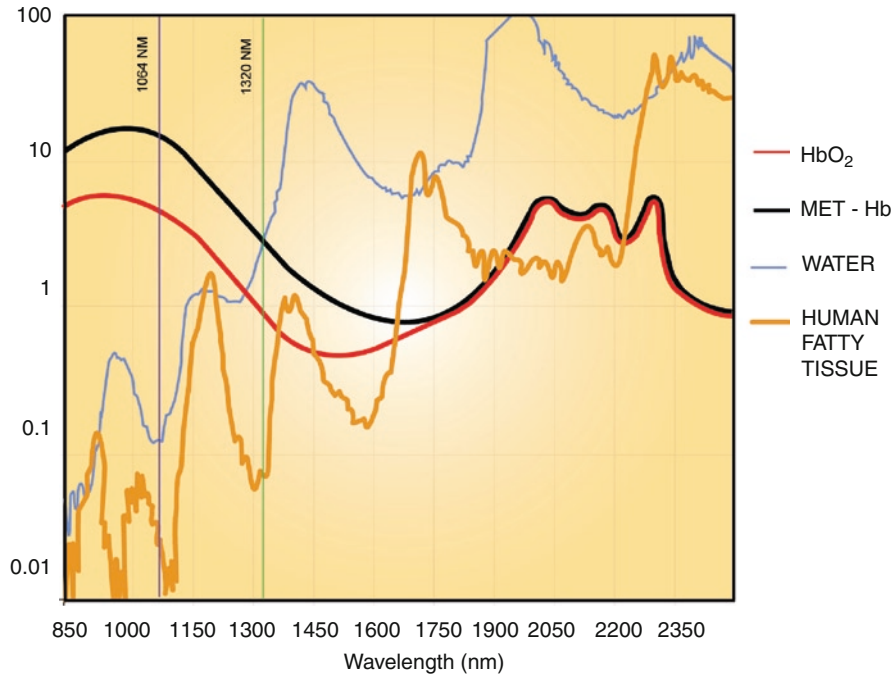


Fig. 8.1 Absorption coefficients of water and human fatty tissue (cm^{-1}). *HbO_2* oxyhemoglobin, *Hb* hemoglobin, *MET* methemoglobin

First, there is an immediate heat-induced cell disrupture close to the laser fiber. The mechanism of action is a selective photohyperthermia when the laser light is converted into heat energy when absorbed from the fat. The adipocytes absorb the energy, expand their volume, and rupture.

The laser shock wave also seems to be effective in removing fat tissue: the high-density energy in short pulses has an explosive effect on atoms, creating a shockwave by microdischarge of energy. The histology, 1 day after laser treatment, showed small tunnels with necrotic areas and collagen coagulation. In addition, small blood vessels were coagulated. There is rupture of adipocyte membrane with consequent release of cellular content into the extracellular space. Collagen degeneration and reorganization of the subdermis were also seen [7, 10].

In a study in which freshly excised human skin and subcutaneous fat were irradiated with a 1,064 Nd:YAG laser, Ichikawa et al. [10] could prove that human adipocytes were effectively destroyed with laser irradiation. Their electron microscopy studies showed degenerated cell membranes, vaporization, liquefication, carbonization, and heat-coagulated collagen fibers.

Histological and clinical findings suggest that the effect of laser energy on adipocytes might be dual. Sandhofer [18] postulated a photodynamic process that leads to a conducted and delayed cell disrupture and can cause a tissue reduction with a delayed effect.

When evaluating the biological impact of three different wavelengths, the greatest amount of thermal damage was seen in the specimens with the highest energy per pulse; however, the patchiness and variability of thermal damage within the cross-sections evaluated made it difficult to draw any strong conclusions. So, Khoury et al. [13] concluded that further studies are warranted to more fully evaluate the histologic effects and mechanisms behind laser lipolysis.

As technical note, Ichikawa and colleagues [10] applied the laser as proposed in the early literature: the energy was delivered only during the slow extraction mode of the probe. Interestingly, we have not seen this technique in any of the live workshops – all surgeons tend to move the probe at a fast speed and apply laser

energy in all directions. When hit directly with a fast, forward-moving, small laser probe, chances are that small vessels are disrupted rather than coagulated because the laser-induced coagulation process would need some contact time between the laser and the vessel.

8.7 Surgical Technique of Interstitial Laser-Assisted Liposuction and Applied Parameters

Preoperative photographic documentation is mandatory. After marking and disinfecting the area to be treated, a tumescent local anesthesia is performed. The amount of tumescent solution used varies among surgeons. The more tumescent solution used the less effective (and necessary) the laser energy seems to be.

Through a 1-mm incision, the stainless steel microcannula is inserted into the subcutaneous fat and the 300-µm-fiber can be conducted to the areas to be treated. The distal portion of the optic fiber is extended approximately 2 mm beyond the end of the cannula. For visualization of the tip of the fiber, a helium-neon laser source is combined into the beam path because this leads to transcutaneous illumination. The cannula is then moved in a criss-cross technique in the fat tissue at various depths.

Parameters vary widely depending on the laser used and the area treated. Up to now there has been no standardization. Recommended total energy levels range from 1,500 to 5,000 J.

The clinical endpoint is skin temperature, which should not exceed 39°C when measured at the surface (Conclusions). Especially when treating the superficial layers, constant temperature control is necessary to avoid skin burns. Currently this is done externally using a nontouch temperature metering device. In the future there will be a temperature regulation system inside the moving cannula (communication from Cynosure Lasers, Inc. Smartlipo Compendium Cynosure; Cynosure GmbH, Langen, Germany).

Treatment with laser lipolysis alone can be tried only in very small areas (e.g., the submental region). One has to keep in mind that the radius of the laser effect is 1 mm in diameter around the tip of the optic fiber (Fig. 8.2). In the majority of cases, the fat debris needs to be aspired after treatment through laser-assisted liposuction.

8.8 Indications of Laser-Assisted Liposuction

- Small areas, e.g., the submental area or small fat deposits (Fig. 8.3).
- Fibrotic areas, e.g., male breast and flanks (Fig. 8.4)
- Tissue tightening (Fig. 8.5)
- LipoRepair
- Touch-up procedures
- Cellulite (??)

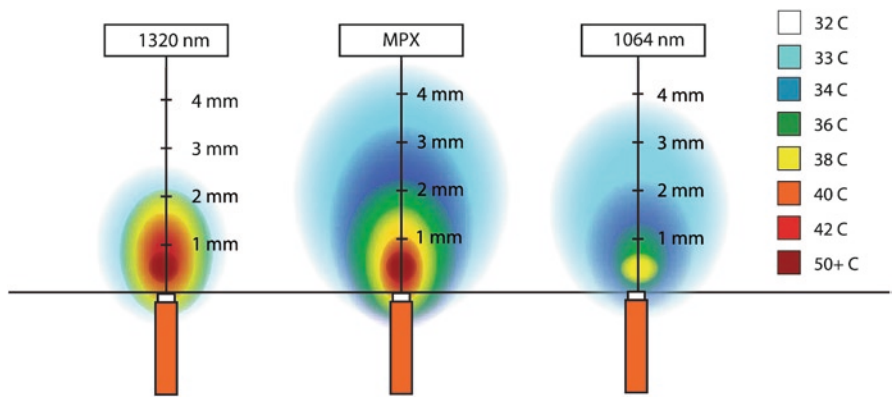


Fig. 8.2 Thermal application of wavelength MPX; this stands for the lasersystem Smartlipo(R) MPX with combined wavelenghts

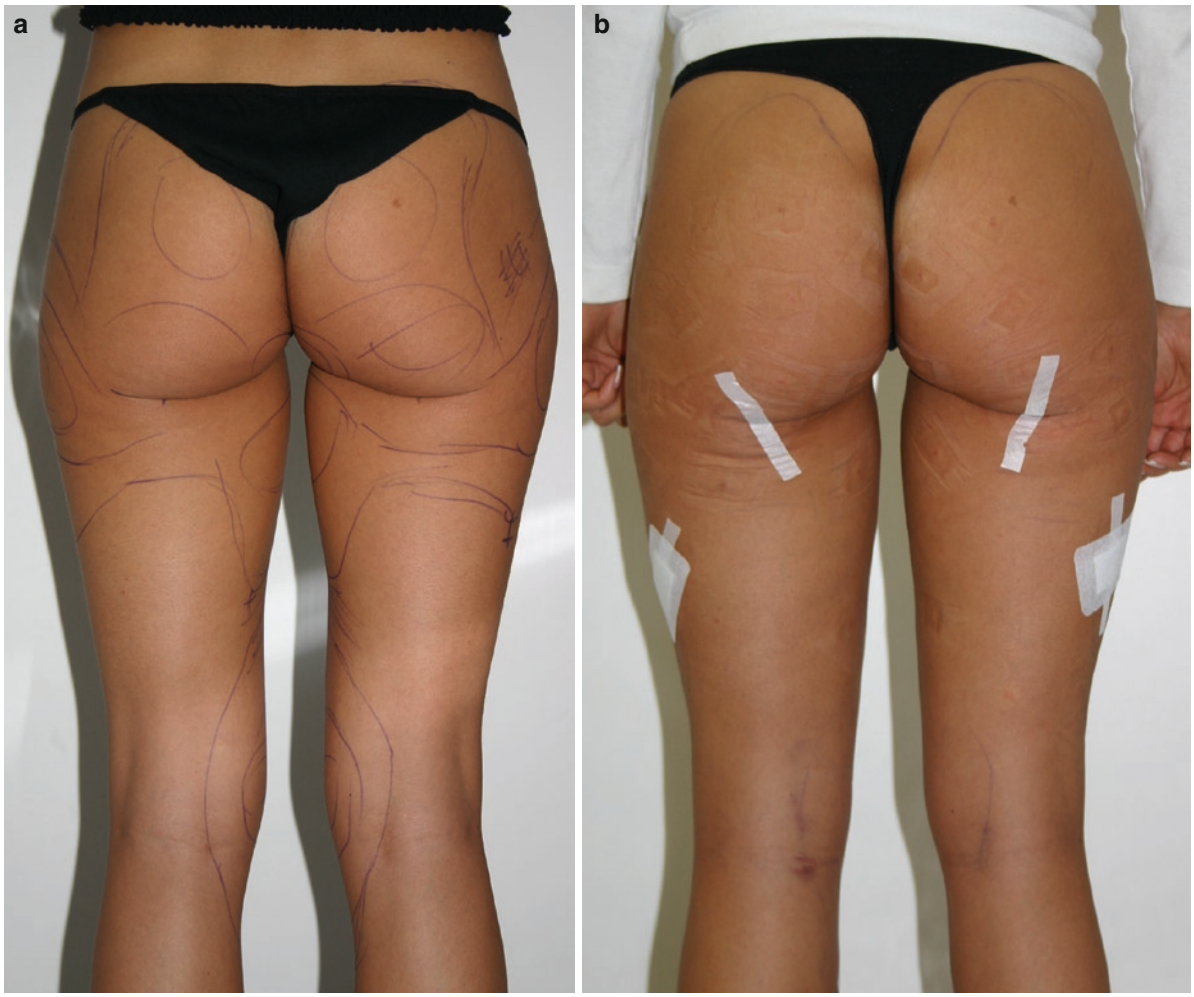


Fig. 8.3 Female patient, aged 26 years, before (**a**) and 2 days after (**b**) treatment of small fat depots at the knees using laser-assisted liposuction

8.9 Advantages

8.9.1 Facilitates Operation in Fibrotic or Difficult Regions

The treatment of areas where fat removal is difficult due to a high amount of fibrous tissue, like the male breast or areas that have undergone previous operations, can be facilitated by the thermal energy of laser-assisted liposuction. Fibrotic areas are very good fields of application for the laser.

8.9.2 Better Skin Retraction

As a delayed effect of laser-assisted liposuction, a better skin retraction is described. Histological findings suggest that, by the use of the 1,064-nm Nd:YAG

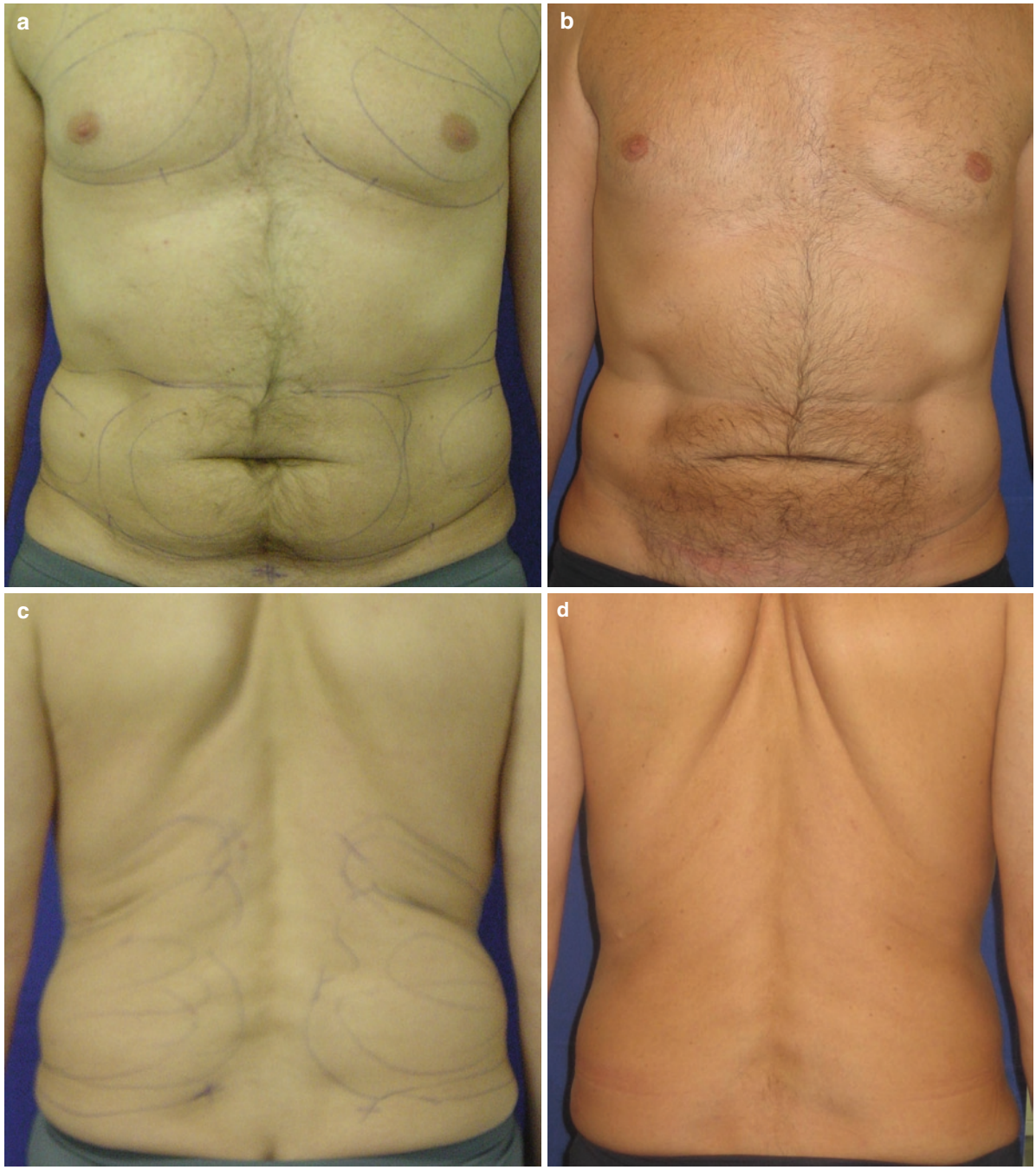


Fig. 8.4 Male patient, aged 51 years, before (**a–c**) and 9 months after (**d–f**) laser-assisted liposuction of the breast, abdomen, and flanks

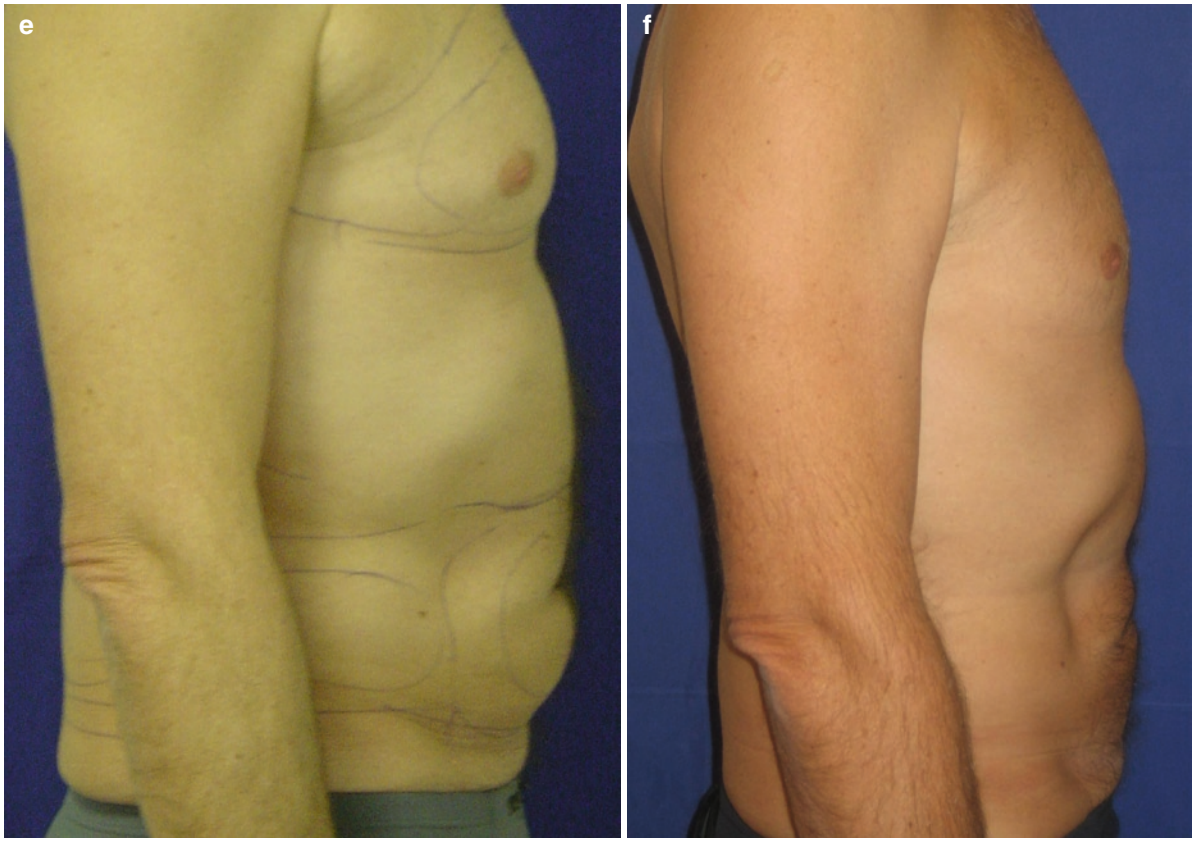


Fig. 8.4 (continued)

laser, collagen neoformation is induced [5]. A strictly controlled, evenly distributed heating of the treated area is necessary (39–40°C maximum).

8.9.3 Less Hemorrhage (???)

Blood loss has not been a matter of concern in liposurgery since the tumescent method was introduced in 1987, if it is used properly. The described coagulation of small blood vessels might only influence the frequency of hematomas. In our patients (using the true tumescent technique), we could see no difference in the degree of bleeding with or without a laser.

8.9.4 Faster Healing, Less Downtime, Faster Recovery (???)

A greater comfort during the postoperative time and an enhanced quality of outcome are claimed.

We found that sometimes healing was rather slow after the use of laser energy due to prolonged swelling (possibly induced by heat). The outcome can be enhanced when fibrotic areas are treated or when skin tightening is needed.

8.10 Disadvantages of Laser-Assisted Liposuction

8.10.1 Potential of Side Effects

Even with constant control of temperature, skin burns can occur, especially when the laser is used in superficial layers to improve skin tone (Fig. 8.6).

8.10.2 Costs/Time

Laser-assisted liposuction is more costly and time-consuming than conventional liposuction (additional time for laser use, between 10 and 30 min per region).

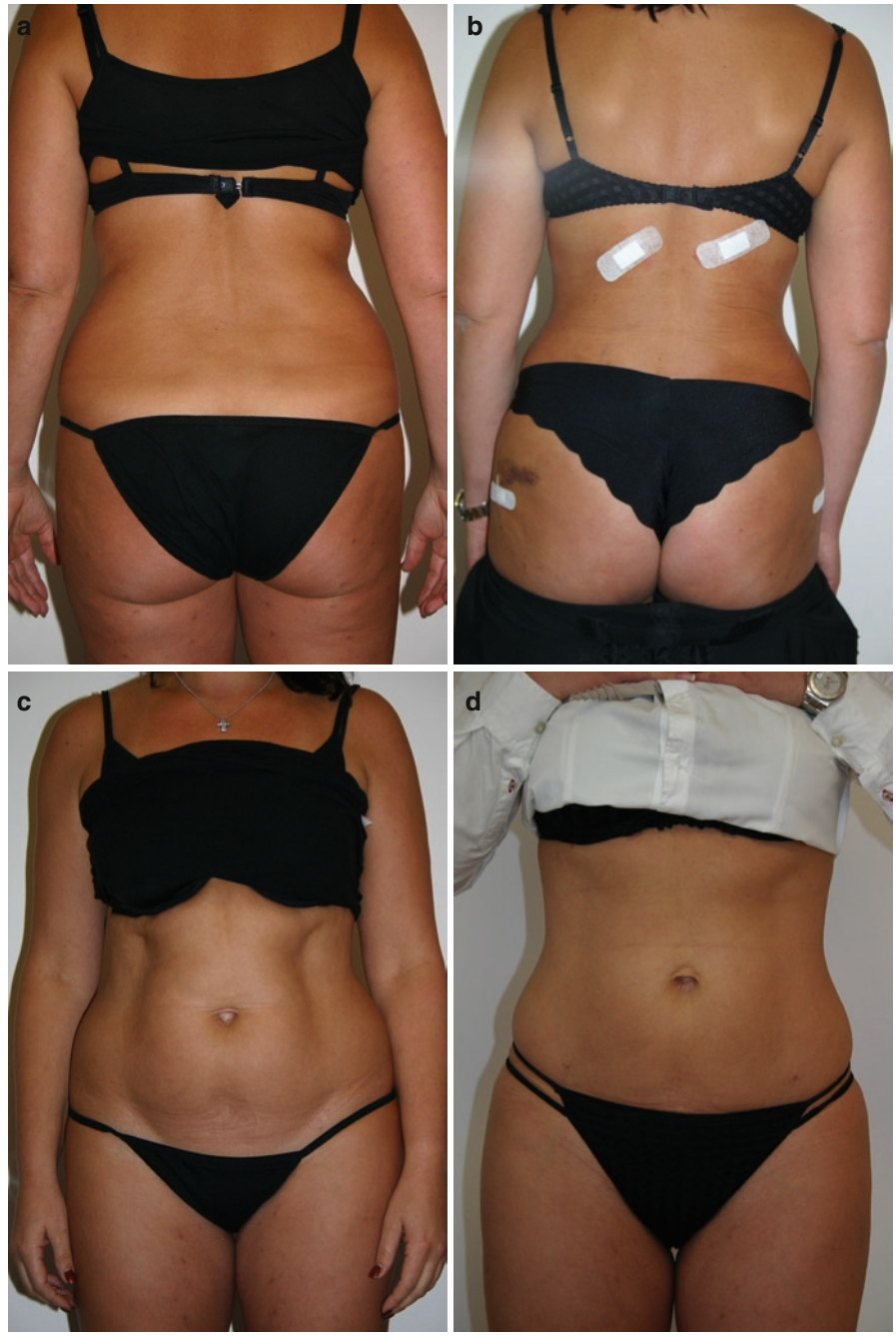
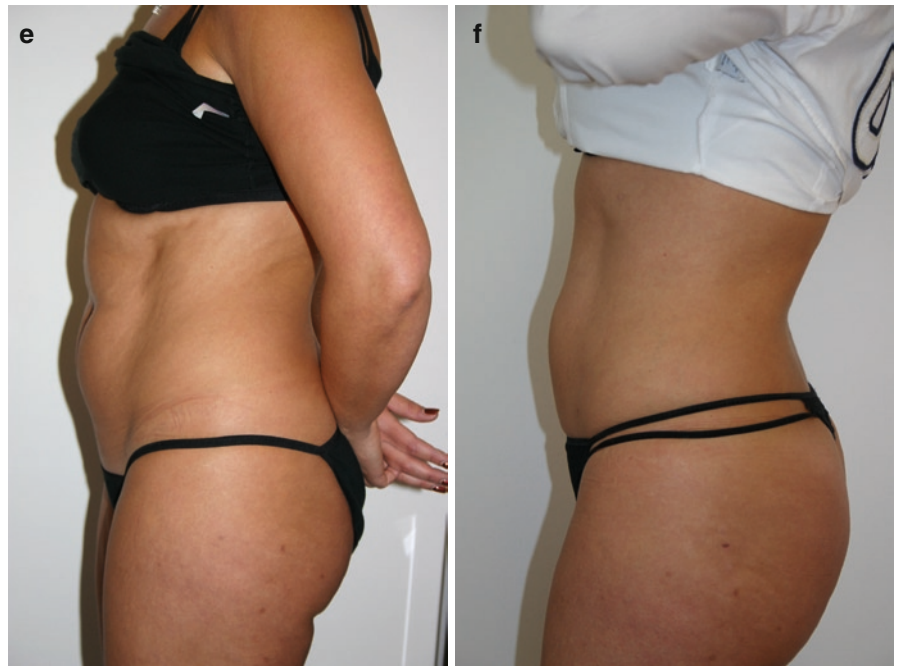


Fig. 8.5 Example of good skin retraction and fast healing after laser-assisted liposuction of the abdomen and hips. The hips were done first, then 1 month later the abdomen (**a**, **c**, **e**) Before and (**b**, **d**, **f**) after

8.10.3 Complications

When all safety measures are taken, this is a procedure with very little side effects. Katz [12] reports one local infection and four skin burns in a series of 527 consecutive sessions of laser-assisted liposuction using the 1,064-nm Nd:YAG laser. In our own patients we observed a skin burn despite a skin temperature of no more than 40°C, which was reported to be a safe margin when measured continuously on the skin's surface. We conclude that the skin should not be heated to more than 39°C when measuring temperature on the skin's

Fig. 8.5 (continued)



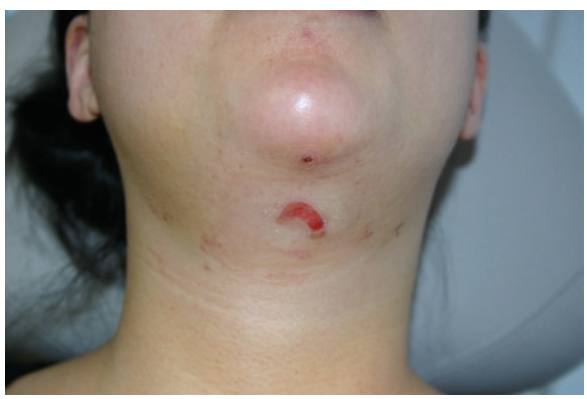


Fig. 8.6 Skin burn 2 days after submental laser-assisted liposuction

surface. Increasing fluence leads to more extensive dermal coagulation with associated risk of epidermal thermal injury [12].

8.11 Conclusion

Some of the advantages claimed for laser-assisted liposuction are routinely achieved when the surgeon uses a correct tumescent liposuction technique:

- Little blood loss, few hematomas, and short recovery time.

Since the introduction of the tumescent technique and its consequent development, bleeding no longer is a problem in liposuction surgery. The treatment has turned into an outpatient procedure; patients are on their feet immediately after surgery and in most cases back to work within the next 2 days.

When combined with vibration-assisted liposuction, the advantages of reduced tissue traumatization and facilitated operation with higher patient comfort can be achieved to at least the standard of laser-assisted liposuction.

The final result obtained with laser lipolysis is equal to traditional liposuction methods [7].

These advantages are not specific for laser-assisted liposuction and can be achieved when using the correct technique with the true tumescent technique (high volumes of tumescent solution).

It is not yet clear how much skin tightening is really induced by the laser; preliminary results are promising but need further exploration.

Limitations that need to be considered include:

Several different protocols using different devices and wavelengths generate variable results. Up to now, there have been no standardized parameters.

The domain of laser lipolysis is the treatment of fibrotic areas.

On the positive side, there is a very high patient acceptance. Patients like the idea of melting the fat with a laser before extracting it from the body; so, patient satisfaction is very high.

Take Home Pearls

- Laser lipolysis is a promising new tool in body contouring surgery.
- There are no standardized treatment protocols, and further developments have to be observed and followed.
- Laser lipolysis is mostly used in conjunction with tumescent liposuction. Because the same risks and side effects apply, the surgeon should be well trained and experienced in liposuction surgery.

Unsolved issues:

- How much of the tumescent fluid should be used? If too little fluid is used, the anesthesia is incomplete. If a proper "supertumescence" is applied, much of the laser energy is absorbed by the infiltrated fluid instead of the tissue.
- Which wavelength gives best results?
- What is the most effective energy delivered with the fewest side effects?
- What is the best way to move the handpiece through the subcutaneous tissue: release of the laser energy only when pulling back or during a back and forth movement; moving slowly and evenly or faster and in a more random way?

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Photoepilation of Unwanted Hair Growth

9

Annesofie Faurschou and Merete Haedersdal

Core Messages

- Laser and intense pulsed light (IPL) treatments for hair removal depend on the presence of melanin in the hair shaft.
- The ideal patient for laser hair removal has light skin with black, coarse hair.
- There is substantial evidence for laser and photoepilation, with a total of 43 identified controlled trials as of the beginning of 2009.
- Laser treatment and photoepilation are superior to conventional treatments such as shaving, waxing, and electrolysis.
- Repetitive treatments improve the efficacy of lasers and photoepilation.
- A short-term hair removal efficacy up to 6 months after treatment has been well-documented for ruby, alexandrite, diode, and neodymium:yttrium aluminum garnet (Nd:YAG) lasers, as well as IPL.
- Evidence exists for efficacy of long-term hair removal beyond 6 months after repetitive treatments with alexandrite, diode, and long-pulsed Nd:YAG lasers.
- White, grey, and red hairs do not respond sufficiently to standard treatments, but eflornithine, topical melanin, and photodynamic therapy may offer new treatment options for these difficult-to-treat hair types, although substantial evidence today is lacking.
- Today, there is no evidence for complete and persistent hair removal.
- Patients should be preoperatively informed of the expected treatment outcome from laser and IPL hair removal procedures to gain realistic expectations.
- Consumer-based home devices are evolving.

9.1 Introduction

Since 1996, lasers and high-intensity pulsed light sources have been successfully used for hair removal. When the procedure was first described by Grossman et al. [35], it created much controversy. However, the devices and their technical specifications have been developed, and today photoepilation with lasers and intense pulsed light (IPL) sources constitutes an established method that is widely accepted for long-term hair reduction. There is a substantial need for efficient hair removal techniques because millions of people all over the world remove unwanted hair at regular

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_9, © Springer-Verlag Berlin Heidelberg 2011

intervals and spend considerable amounts of time and money to achieve hair-free appearances. Traditional treatments include shaving, plucking, waxing, chemical depilatories, and electrolysis [58]. None of these methods are ideal because of limited and short-term efficacies. Electrolysis is a tedious procedure that may be considered for smaller hair-bearing areas. Lasers and IPL devices are, in general, regarded as the most efficient methods for the reduction of unwanted hair [16, 19, 30, 31, 46].

Excess hair growth covers a broad range of severity and may present as hypertrichosis or hirsutism, although most individuals seek hair removal treatments primarily because of cosmetic concerns. Common areas of cosmetic treatments include the axilla, bikini line, legs, and face in women, as well as chest, back, and shoulders in men. Hypertrichosis is defined as an increase in hair growth that is not androgen-dependent and may present at any body site. Hypertrichosis occurs in both sexes and may be acquired or congenital; it may present from genetic predisposition; from medications such as ciclosporin, prednisolone, phenytoin; or it may be part of a variety of diseases like porphyrias, thyroid disorders, internal malignancies, malnutrition, or anorexia nervosa [71]. Hirsutism denotes the growth of terminal hair in women at androgen-dependent sites where normally only men develop coarse hair, primarily on the face and neck around the beard area and sideburns (Fig. 9.1). Excess endogenous androgen may be released either by the ovaries or the adrenal glands, most commonly due to polycystic ovarian syndrome. Genetic predisposition may also play a role [52]. Pseudofolliculitis barbae and hair-bearing flaps, used for reconstruction, are other dermatological conditions that respond well to hair removal with lasers and light sources [10, 14].

This chapter gives an overview of hair removal with lasers and light sources, discusses expected benefits and harms, and estimates the treatment outcomes from an evidence-based point of view. The evidence-based approach is considered to be essential to provide patients with realistic expectations. Thus, the patients' specific expectations have to match the capabilities and facts of laser and IPL hair removal, which is considered a pivotal issue that has to be discussed before commencing treatment sessions with lasers and IPL devices for hair reduction.

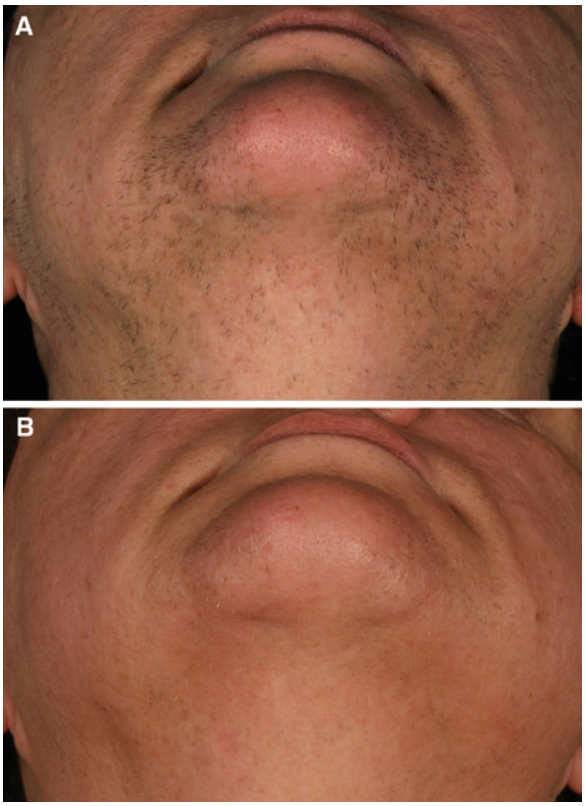

Fig. 9.1 Before (**a**) and after (**b**) photos (3 months) for a patient who was treated with a diode laser and intense pulsed light for hirsutism

9.2 Mechanism of Laser Hair Removal

Light can potentially destroy hair follicles by three different mechanisms: (1) a photothermal reaction due to local heating, (2) a photomechanical reaction due to shock waves, and (3) a photochemical reaction due to toxic mediators induced by the combination of a topical photosensitiser and light exposure (photodynamic therapy). Photothermal destruction of hair follicles today constitutes the fundamental concept for hair removal. However, all three mechanisms of hair removal have been examined [16, 19]. The approach of photodynamic therapy (PDT) has been studied so far in pilot studies and provides a potential for future hair removal with the advantage of treating nonpigmented hairs [19]. Hair reduction due to photomechanical destruction with nanosecond Q-switched lasers was

examined at the early stage of laser hair removal in combination with and without a topical carbon suspension, leading to temporary hair loss. Today this treatment approach is of minor relevance.

Photothermal destruction of hair follicles is based on the concept of selective photothermolysis. Selective photothermolysis states that selective thermal damage to a pigmented target structure will occur when a specific wavelength is delivered at a sufficient fluence level during a time equal to or less than the thermal relaxation time (TRT) of the target [5]. Applying the principle of selective photothermolysis to hair removal means that laser and IPL procedures are dependent on the presence of melanin in the hair shaft since melanin is the target chromophore that absorbs energy from specific wavelengths, resulting in spatially confined thermal damage to melanin-containing structures when pulse durations correspond to the TRT. However, recent evidence suggests that the goal of laser hair removal is to damage stem cells in the bulge area of the outer root sheath, which requires diffusion of heat from melanin in the hair shaft [67]. The concept of thermal damage time (TDT) has, therefore, been introduced for hair removal when suggested pulse durations are longer than the TRT, allowing dissipation of thermal damage to the follicular stem cells [67]. Wavelengths in the red and near-infrared parts of the electromagnetic spectrum are suitable for hair removal, and the 600-nm to 1,100-nm range covers an optical window that is ideal for hair removal due to (1) sufficient energy absorption by melanin, (2) decreased absorption from the competitive skin chromophores, oxyhemoglobin, and water, and (3) light penetration to deeper dermal structures [30]. Deep, selective heating of the hair shaft, the follicular epithelium, and the matrix region therefore is possible with laser and IPL devices when adjusting wavelength and pulse duration. Epidermal melanin provides a competitive chromophore, and it is essential to protect the epidermis from unspecific damage, especially in darker-skinned individuals with skin types IV–VI. Selective cooling of the epidermis has been shown to minimise epidermal injury [55]. Cooling can be obtained before, during, and after laser treatment (pre-, parallel-, and post-cooling) as contact cooling (cooled sapphire, metal or glass plates integrated into the handpiece, cooled gel layer); cold air ventilation; and dynamic cooling devices when pulsed cryogen spray is used as a cooling agent [20].

9.3 Selecting Appropriate Lasers and IPL Parameters

The lasers and IPL devices that are currently available for photoepilation take advantage of photothermal destruction of hair follicles due to the principle of selective photothermolysis. These devices include the normal mode ruby laser (694 nm), normal mode alexandrite laser (755 nm), pulsed diode lasers (800 and 810 nm), long-pulsed neodymium:yttrium-aluminium-garnet (Nd:YAG) lasers (1,064 nm), and IPL sources (590–1,200 nm) (Table 9.1) [3, 8, 36, 50]. The devices operate in the red or near-infrared wavelength regions corresponding to the recommended wavelength range of 600–1,100 nm. Today, the alexandrite laser, diode laser, and IPL devices cover the majority of hair removal treatments, whereas the ruby laser has a minor role due to limited penetration of light and substantial absorption in melanin, which implies a potential risk of adverse events, especially in tanned and darker skin types [20]. Regarding safety, the long-pulsed Nd:YAG laser is attractive for use in individuals with darker skin types IV–VI.

The physical parameters within the specific devices vary considerably in terms of wavelength, pulse duration, spot size, and fluence. When choosing treatment parameters, several factors must be considered, and according to guidelines from the European Society for Laser Dermatology essential parameters have to be individually selected and adjusted to the clinical situation before commencing treatment sessions [20]:

Table 9.1 Lasers and intense pulsed light used for hair removal

Type of Laser	Wavelength (nm)
Ruby	694
Alexandrite	755
Diode	800–810
Nd:YAG	1,064
IPL	590–1,200

Nd:YAG neodymium:yttrium-aluminiumgarnet; *IPL* intense pulsed light

Table 9.2 Increased epidermal protection with longer wavelengths

Skin type	I	II	III	IV	V	VI
Laser – Wavelength (nm)						
Ruby – 694	●	———	●			
Alexandrite – 755	●	———	———	●		
Diode – 800, 810	●	———	———	———	●	
Nd:YAG – 1,064	●	———	———	———	———	●
IPL – 590–1,200[a]	●	———	●			

[a]Recommended skin type depends on filter used and output wavelength spectrum. *Nd*:*YAG* neodymium:yttrium-aluminiumgarnet; *IPL* intense pulsed light

Wavelength: Shorter wavelengths are absorbed more strongly by melanin than longer wavelengths. Longer wavelengths penetrate deeper and are safer to use in individuals with darker skin types. Accordingly, shorter wavelengths can be used for patients with fair skin types and longer wavelengths for patients with darker skin types at the risk of adverse effects. Selecting appropriate wavelengths according to skin types is summarised in Table 9.2.

Pulse duration: TRT of human terminal hair follicles is estimated to vary between 10 and 50 ms, depending on the size of the hairs. The ideal pulse duration should be longer than the TRT for the epidermis (3–10 ms) and adjusted to the TRT/TDT for hair follicles. Devices for hair removal, therefore, operate with pulse durations in the long millisecond range, and it seems that pulse durations between 10 and 50 ms are optimal to target hair follicles as well as super long pulse heating (>100 ms) may allow for long-term hair removal [19].

Spot size: Bigger spot sizes penetrate deeper than smaller spot sizes due to reduced backward scattering [62]. Moreover, bigger spot sizes speed up treatment procedures for the convenience of patients and laser operators. Accordingly, it is preferred that the spot size be at least 10 mm while operating at high-fluence levels.

Fluence: The energy level is different for each laser and IPL system according to the specific output range of the device and the corresponding absorption in melanin. It is recommended that the operator be familiar with the output range for the specific device. In general, the effectiveness for hair removal correlates strongly with the delivered fluence level, which has to be adjusted according to the actual amount of target chromophore in terms of hair colour and hair density. It is, therefore, crucial that the operator be experienced at evaluating the immediate treatment endpoints to adjust the optimal treatment level for the specific patient without any initial signs of adverse events. The immediate response to treatment should be vaporisation of the hair shaft that, in a few seconds, is followed by erythema and possibly perifollicular oedema (Fig. 9.2). In general, these should resolve within approximately a few hours. Widespread erythema and confluent oedema may be initial signs of adverse reactions, and

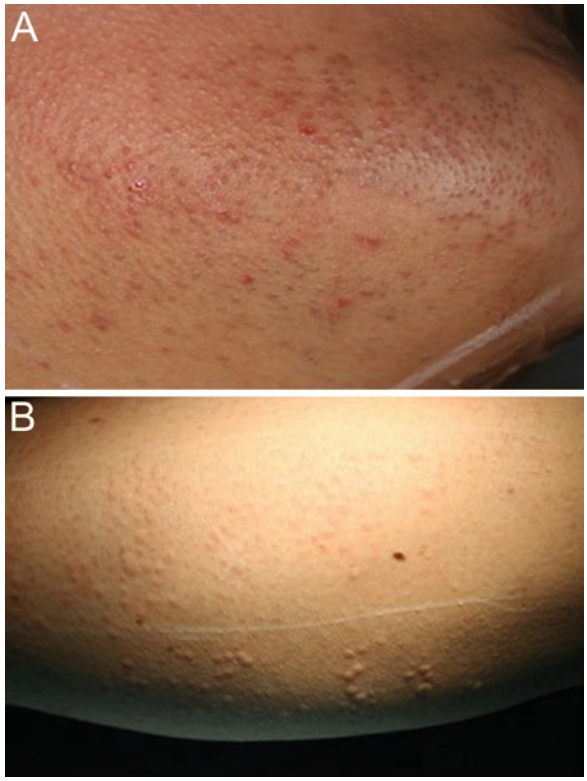

Fig. 9.2 (**a**, **b**) Immediate skin reactions with erythema and perifollicular oedema

reduced fluence levels are recommended. Grey and white discolouration is a definite initial sign of epidermal damage and should be avoided [31].

9.4 Factors Affecting Treatment Outcome

A favourable treatment outcome depends on various factors that may be ascribed to the laser or IPL system used, to the experiences of the operator, and to proper patient selection. Concerning individual patient variables, it is well known that the ideal patient has dark, thick terminal hairs and white skin with a normal hormonal status and no signs of polycystic ovarian syndrome or other hormonal imbalances. On the other hand, currently available techniques are not successful in removing thin vellus hairs, and individuals with white, grey, or red hairs do not respond sufficiently well to photoepilation with lasers and IPL systems. Whether the hair cycle affects the treatment outcome has been examined, and attempts have failed to correlate effective hair removal with targeting anagen hairs. Initial studies were performed in animals where anagen phase follicles were sensitive to ruby laser pulses whereas catagen and telogen phase hair follicles were insensitive due to lack of pigmentation [48]. However, in humans, the hair follicles remain pigmented during the entire hair cycle, explaining why today targeting the human hair follicles during specific growth phases is considered to be of insignificant importance [31]. Dark skin types and sun exposure also influence the treatment outcome with an increased risk of inducing side effects. Therefore, it is recommended that suntanned patients avoid treatment until the skin tan has faded, and patients with darker skin types IV–VI must be treated with carefulness. Patient selection thus remains mandatory for optimal treatment outcomes.

9.5 Expected Benefits

To date, no method of permanent hair eradication is available, and it is important that patients have realistic expectations for long-term results before treatments commence. Concerning *permanent hair reduction,* the US Food and Drug Administration has given the definition that "permanent hair reduction refers to a long-term, stable reduction in the number of hairs regrowing after a treatment regime, which may include several sessions. The number of regrowing hairs must be stable for a period of time longer than the complete growth cycle of hair follicles, which varies from 4 to 12 months according to body location" [69]. Unfortunately, this definition may lead to unrealistic patient expectations because "permanency" from the patients' points of view means that hairs do not regrow and that the hair-free appearance lasts persistently. *Temporary hair loss* is defined as a delay in hair growth, which usually lasts for 1–3 months, consistent with the induction of telogen [19]. However, several factors contribute to the patients' overall subjective impression of hairiness and include the number and rate of regrowing hairs as well as the thickness and colour of regrowing hairs. The most substantial data about the effectiveness of hair removal exist for reduction in the number of regrowing hairs whereas information is sparse and anecdotal on thickness and colour of regrowing hairs.

9.6 Hair Removal from an Evidence-Based Point of View

Various studies have reported on the efficacy of different laser systems to reduce hair growth, and reduction in the number of hair counts is the endpoint most often evaluated. To make meaningful comparisons between treatments, it is important to consider under which circumstances the treatment results are reported, because huge diversities are seen in terms of study design (randomised and nonrandomised controlled studies, uncontrolled studies, retrospective studies, case reports); patient inclusion; treatment settings, including specific devices; number of treatment sessions; and follow-up periods.

To demonstrate the true effectiveness of laser and IPL devices, we approach the treatment-efficacy topic from an evidence-based point of view, implying that controlled trials are evaluated, whether randomised or not, whereas uncontrolled trials, retrospective studies, and case reports are excluded from this review. Only studies with sample sizes of at least 10 individuals are included. Hair reduction estimated up to 6 months after treatment is considered as "short-term efficacy" and beyond 6 months postoperatively as "long-term efficacy."

9.6.1 Identification and Inclusion of Studies

Original publications were identified through searches in MEDLINE (1990 – December 2008) and the Cochrane Library of controlled clinical trials using text words and the Medical Subject Heading [MeSH] database: "laser," "light," "hair," "clinical trial," "lasers/therapeutic use [MeSH]," "light [MeSH]," "hair removal [MeSH]," and "controlled clinical trials [MeSH]." Moreover, we evaluated cited references from reference lists.

A total of 17 randomised clinical trials (RCTs) and 26 nonrandomised controlled clinical trials (CTs) were identified (Tables 9.3 and 9.4). In the RCTs, different randomisation methods were applied (e.g., coin tossing, blinded card draw, list of random allocation, clockwise rotation), and response evaluations were performed blinded in most of the studies (Table 9.3). The efficacy of hair removal was assessed mainly as short-term efficacy up to 6 months postoperatively, although three RCTs evaluated the long-term efficacy up to 8–9 months postoperatively and 1 RCT had a follow-up period of 18 months (Table 9.3). In the CTs, the efficacy of hair removal was evaluated as both short-term and long-term efficacy, and 6 CTs had follow-up evaluations up to 12 months or longer postoperatively (Table 9.4). Only a few of the CTs made blinded response evaluations (Table 9.4).

9.6.2 Ruby Laser: 694 nm

Hair removal with the ruby laser treatment was evaluated in 2 RCTs and 7 CTs (Tables 9.3 and 9.4). Two CTs reported significantly better short-term hair reduction 2–4 months after treatment with a ruby laser (38–49% hair reduction depending on fluence used) than after electrolysis, wax, shave, or untreated control skin (no significant decrease) [35, 59], whereas complete hair regrowth was found 3 months after shaving and 1–3 ruby laser treatments in another study [70]. No long-term hair reduction was obtained 12 months after three ruby laser treatments in one study [59], but Dierickx et al. [17] found obvious hair loss 1 and 2 years after one ruby laser treatment in 4/7 individuals. One RCT has described that 3 repetitive treatments with the ruby laser resulted in 19% hair reduction at 5 months after the last treatment in contrast to only 6% hair reduction after two treatments [2]. In patients with facial hirsutism, the benefit of repetitive treatments has been confirmed; four repetitive treatments resulted in significantly better hair reduction than a single treatment (61% vs. 42%) at 9 months postoperatively [66].

Compared to newer treatment modalities, one study has demonstrated the ruby laser to be less efficient than IPL at 6 months after three repetitive treatments with a hair reduction of 49% in IPL-treated patients and 21% in patients treated with the ruby laser [8]. Adverse events have been reported with low incidences; hypopigmentation is the most frequently reported adverse event in pigmented skin [40] and less epidermal damage was found for 20-ms pulse duration vs. 1-ms pulse duration in darker skin types [21].

9.6.3 Alexandrite Laser: 755 nm

The efficacy of hair removal after alexandrite laser treatment was evaluated in 11 RCTs and 10 CTs (Tables 9.3 and 9.4). Three studies evaluated the laser-assisted efficacy vs. that of conventional therapies up to 6 months postoperatively [36, 45, 54]. In comparison with shaving, the short-term hair removal efficacy was transiently superior after one alexandrite laser treatment 3 months postoperatively (27% hair reduction vs. no significant effect of shaving), whereas complete regrowth was seen 6 months postoperatively [54]. Similar hair regrowth occurred independently of whether pulse durations of 5, 10, or 20 ms were used [54]. Another study showed that three treatments with the alexandrite laser (74% hair reduction) were significantly more efficient than four treatments of electrolysis (35% hair reduction) at 6 months postoperatively, and all patients preferred laser treatment to electrolysis due to higher efficacy and less pain [36]. A comprehensive RCT including 144 Asian patients evaluated the efficacy of hair removal after one, two, and three treatments up to 9 months postoperatively and found a significantly improved long-term clearing after two and three repetitive treatments (44% and 55% hair reduction) vs. a single treatment (32% hair reduction) at 9 months postoperatively [41]. A well-conducted RCT confirmed the improved efficacy of repetitive laser treatments, showing that five alexandrite laser treatments (23.6 J/cm^2) resulted in significant hair

Table 9.3 An overview of randomised clinical trials in laser and photoepilation of unwanted hair growths

Study	Interventions	Study design Randomisation method blinded response evaluation	Subjects No., hair colour, treatment site, skin type	Major results
Davoudi et al. [15]	Long-pulsed Nd:YAG laser 4 tx Long-pulsed Alexandrite laser (12-mm spot) 4 tx Long-pulsed Alexandrite laser (18-mm spot) 4 tx Long-pulsed Nd:YAG laser combined with long-pulsed Alexandrite laser (12-mm spot) 4 tx	Computer-generated randomisation in opaque sealed envelopes Blinded assessment	$n=15$ Black hair Legs Skin type: III–IV	Follow-up 8, 18 months Hair reduction at 18 months: 73.6% (Nd:YAG laser), 75.9% (12-mm spot size alexandrite laser), 84.3% (18-mm spot size alexandrite laser), and 77.8% (combination alexandrite and Nd:YAG laser) ($p=$ns) Pain severity: more severe for alexandrite than Nd:YAG Hyperpigmentation: temporarily present in all treatment groups, most frequently for 12-mm spot size alexandrite laser and the combination treatment. At 18 months, hyperpigmentation was 27% (combination alexandrite and Nd:YAG laser) and 0% (Nd:YAG laser, 12-mm spot size alexandrite, 18-mm spot size alexandrite)
McGill et al. [51]	Alexandrite laser 6 tx vs. IPL 6 tx	Drawing of sealed envelopes Blinding unclear	$n=31$ Brown–black hair PCO patients Face Skin type: I–IV	Follow-up: 1, 3, 6 months Decrease in hair count was better with the alexandrite laser than IPL at 1, 3, and 6 months (52%, 43%, 46% vs. 21%, 21%, 27%) ($p<0.05$) Hair-free interval after 6 treatments: 7 weeks (alexandrite) vs. 2 weeks (IPL) Purpura: 13% (alexandrite laser) Blistering: 10% (IPL) Temporarily hyperpigmentation: 3% (IPL) Leukotrichia: 6% (IPL)

(*continued*)

Table 9.3 (continued)

Study	Interventions	Study design Randomisation method blinded response evaluation	Subjects No., hair colour, treatment site, skin type	Major results
Sand et al. [63]	Diode laser 3 tx + liposomal melanin spray 12 times per day	Randomisation unclear Blinded assessment	$n=16$	Follow-up: 6 months
			White, grey, light hair	Hair reduction at 6 months: 14% (diode+ melanin spray) and 10% (diode+saline spray) ($p<0.05$)
	Diode laser 3 tx + physiological saline spray 12 times per day		Chin, upper lip, legs, backs, shoulders, underarms, graft surface	Mean satisfaction: 4.0 (diode+ melanin spray) and 4.7 (diode+saline spray)
			Skin type: II	Perifollicular urticaria: 12.5% (diode+melanin spray) and 0% (diode+saline spray) Mild erythema: 31% (diode+melanin spray) and 12.5% (diode+saline spray) Folliculitis: 12.5% (diode+melanin spray) and 0% (diode+saline spray)
Hamzavi et al. [37]	Long-pulsed alexandrite laser combined with eflornithine cream 5–6 tx	Coin tossing Blinded assessment	$n=31$	Follow-up: 2 weeks
			Dark hair	Hair reduction at 2 weeks: investigator global scoring: hair removal grade of clear or almost clear for 93% (eflornithine) and 67.9% (placebo) ($p<0.05$)
	Long-pulsed alexandrite laser combined with placebo 5–6 tx		Upper lip Skin type: II–V	Patient self-assessment: 41.9% thought hair reduction was better with eflornithine, and 0% preferred placebo ($p<0.05$) Hair count analysis: hair count was 7.9% lower with eflornithine than placebo ($p<0.05$) Transient pigmentary alteration: 6.5% Eflornithine were associated with a mild tingling sensation in one patient for the first 7 days of use

Smith etal. [65]	Nd:YAG laser or alexandrite laser combined with eflornithine cream 2 tx Nd:YAG laser or alexandrite laser combined with vehicle 2 tx	Computer-generated randomisation Blinded assessment	$n=54$ Grey, white, light brown, brown, black hair Lip, chin Skin type: I–IV	Follow-up: 34 weeks Hair reduction was significantly better at the eflornithine cream site than the vehicle site between weeks 6 and 22 Hair reduction was not significantly different at week 34 Acne: 13% (eflornithine), 11% (vehicle) Herpes simplex: 6% (eflornithine), 3% (vehicle)
Toosi et al. [68]	Alexandrite laser 3–7 tx Diode laser 3–7 tx IPL 3–7 tx	Randomised by their last digit of their file number Blinding unclear	$n=232$ Dark hair Jaw, chin, forehead, lip, neck Skin type: II–IV	Follow-up: 6 months Hair reduction at 6 months: 68.8% (alexandrite laser), 67.0% (IPL), and 71.7% (diode laser) ($p=$ns) Increased number of treatment sessions improved the results Folliculitis: 6% (alexandrite laser), 3.9% (diode laser), 9.7% (IPL) Pigmentary changes: 3% (alexandrite laser), 15.8% (diode laser), 0% (IPL) Blister: 0% (alexandrite laser), 9.2% (diode laser), 2.8% (IPL) Crust: 0% (alexandrite laser), 0% (diode laser), 2.8% (IPL) Adverse events occurred significantly more frequently for the diode laser
Clayton et al. [13]	Alexandrite laser high fluence 5 tx Alexandrite laser low fluence 5 tx	Randomised by a random number table Unblinded to the treating physician but blinded to the research psychologist and the patients	$n=75$ Dark hair PCO patients Face Skin type: I–pale V	Follow-up: 6 months 6 months postop.: self-reported severity of hirsutism fell from 7.3 to 3.6 (high fluence) and 7.1 to 6.1 (low fluence) ($p<0.05$) Self-reported time spent on hair removal declined from 112 to 21 min (high fluence) and 92 to 56 min (low fluence) ($p<0.05$) Depression scores fell from 6.7 to 3.6 (high fluence) and 6.1 to 5.4 (low fluence) ($p<0.05$) Psychological quality of life improved from 49.6 to 61.2 (high fluence) and 50.1 to 51.5 (low fluence) ($p<0.05$)

(*continued*)

Table 9.3 (continued)

Study	Interventions	Study design Randomisation method blinded response evaluation	Subjects No., hair colour, treatment site, skin type	Major results
Nouri et al. [57]	Alexandrite laser 18-mm spot 3 tx Alexandrite laser 12-mm spot 3 tx	Randomisation unclear Blinding unclear	$n=11$ Hair colour unmentioned Axilla Skin type: II–IV	Follow-up: 6 months Hair reduction at 6 months: 52.2% (18-mm spot) and 41.9% (12-mm spot) ($p=$ns)
Allison et al. [2]	Ruby laser 2 tx Ruby laser 3 tx	Coin tossing Blinding unclear	$n=69$ Hair colour unmentioned Lip, axilla, legs Skin type: I–III	Follow-up: 8 months Hair reduction at 5 months: 18.5% (3 tx) and 6.3% (2 tx)
Fiskerstrand et al. [23]	Diode laser (Mediostar 810 nm) 3 tx Diode laser (Lightsheer 800 nm) 3 tx	Randomisation unclear Blinding unclear	$n=29$ Upper lip Brown–black hair Skin type: II–IV	Follow-up: 6 months Hair reduction 6 months after first tx: 49% (Mediostar) and 48% (Lightsheer) ($p=$ns)
Goh [27]	Long-pulsed Nd:YAG laser 1 tx IPL 1 tx	Randomisation unclear Blinding unclear	$n=11$ Black hair Face, axilla, legs Skin type: IV–VI	Follow-up: 2, and 6 weeks Hair reduction at 6 weeks: 64% (IPL) and 73% (Nd:YAG laser) of patients obtained <20% hair reduction ($p=$ns) Postinflammatory pigmentation: 45% (IPL) and 0% (Nd:YAG laser)
Hussain et al. [41]	Alexandrite laser 1 tx Alexandrite laser 2–3 tx	Randomisation unclear Blinded assessment	$n=144$ Asian patients Axilla, extremities, face Skin type: III–V	Follow-up: 1, 2, 3, 6, and 9 months Hair reduction at 9 months: 55% (3 tx), 44% (2 tx), and 32% (1 tx)
Lehrer et al. [45]	Alexandrite laser 1 tx + preop. shave Alexandrite laser (1 tx) + preop. wax	Coin tossing (personal communication) Blinded assessment	$n=13$ Brown–black hair Back Skin type: I–III	Follow-up: 1 month In 12 of 13 subjects, the reduction in hairiness was better in wax + laser-treated areas than shave + laser-treated areas ($p<0.05$)

Baugh et al. [6]	Diode laser, 24, 38, 48 J/cm^2 Shave	Clockwise rotation (personal communication) Blinded assessment	$n=36$ Brown–black hair Back, thigh, bikini area Skin type: I–IV	Follow-up: 1, 3 months Fluence-dependent hair reduction was better than shave ($p<0.05$) A mean hair reduction of 43% at 1 month (mean of 1.6 tx) and 34% at 3 months (mean of 2.0 tx) at the highest fluence level
Handrick and Alster [38]	Alexandrite laser 3 tx Diode laser, 3 tx	Blinded card draw Blinded assessment	$n=20$ Axilla Brown–black hair Skin type: I–IV	Follow-up: 1, 3, and 6 months Hair reduction at 6 months: Similar hair reduction (37–46%) for the two lasers Similar clinical improvement scores on a 0–4 arbitrary scale (3.4–3.5 corresponding to >51% improvement) Pain: mild to moderate (alexandrite) and moderate to severe (diode) Slightly more hyperpigmentation and blistering after diode laser than alexandrite laser
Haedersdal et al. [40]	Ruby laser 1 tx Shave	List of random allocation Blinded assessment	$n=17$ Red, blonde, brown–black hair Pubic region Skin type: I-IV	Follow-up: 3 months Hyperpigmentation: 1/51 (laser), 0/17 (shave) Hypopigmentation: 5/51 (laser), 1/17 (shave)
Nanni and Alster [53]	Q-switched Nd:YAG laser 1 tx ± preop. wax, carbon solution Wax	Blinded card draw (personal communication) Blinded assessment	$n=12$ Brown–black hair Face, truncus, legs Skin type: I–IV	Follow-up: 1, 3, and 6 months Hair reduction at 3 months: overall 2–21% hair reduction Better clearing for Q-switched Nd:YAG laser-treated areas than wax alone ($p<0.05$) Hair reduction at 6 months: full hair regrowth in all test areas Patient subjective evaluations of hair density closely approximated hair count data

Tx treatment; *IPL* intense pulsed light; *Ns* nonsignificant; preop. preoperative; *Nd:YAG* neodymium:yttrium aluminum garnet; *PCO* polycystic ovary syndrom

Table 9.4 An overview of clinically controlled, nonrandomised trials in laser treatment and photoepilation

Study	Intervention Comparative intervention	Subjects No., hair colour, treatment site, skin type	Blinded response evaluation	Major results
Khoury et al. [42]	Alexandrite laser 3 tx Nd:YAG laser Alexandrite laser combined with Nd:YAG laser Diode laser	$n=18$ Dark-brown hair Axilla Skin type: I–III	Unmentioned	Follow-up: 1 and 2 months Hair reduction at 2 months: 70.3% (alexandrite), 67.1% (alexandrite+Nd:YAG), 59.7% (diode) and 47.7% (Nd:YAG). Alexandrite and alexandrite+Nd:YAG were more effective than diode and Nd:YAG ($p<0.05$) The patients found the alexandrite and diode lasers more tolerable than the alexandrite+Nd:YAG and Nd:YAG
Amin and Goldberg [4]	IPL (red filter) 2 tx IPL (yellow filter) 2tx Diode laser 2 tx Alexandrite laser 2 tx	$n=10$ Dark hair Back thigh Skin type: I–III	Yes	Follow-up: 1, 3, and 6 months Hair reduction at 6 months: approximately 50% by all four light devices ($p=$ns)
Lee 2006	IPL (600–950 nm, mean 800 nm) 4 tx IPL (645–950 nm, mean 830 nm) 4tx	$n=48$ Korean women Hair colour unmentioned Axilla Skin type: II–IV	Yes	Follow-up: 8 months Hair reduction at 8 months: 52.8% (600–950 nm) and 83.4% (645–950 nm) ($p<0.05$) Pain level during procedure: 6.5 (600–950 nm) and 3.3 (645–950 nm) ($p<0.05$) The 600- to 950- nm IPL source resulted in 1 case of hyperpigmentation and 1 with hypopigmentation
Goldberg et al. [33]	Optical bipolar radiofrequency and IPL (680–950 nm) 2 tx Optical bipolar radiofrequency and IPL (680–950 nm) combined with topical aminolevulinic acid 2 tx	$n=15$ 10 patients with white terminal hair 5 patients with fine, non-pigmented vellus hair Face Skin type: II–IV	Unmentioned	Follow-up: 6 months Hair reduction at 6 months: 35% of terminal white hairs (light treatment) and 48% (combined treatment) No response for the vellus hairs

Rao and Goldman [60]	Alexandrite laser 3 tx Diode laser 3 tx Long-pulsed Nd-YAG laser 3 tx Rotational treatment with a single session by each three lasers	$n=20$ Dark hair ($n=17$), red or light hair ($n=3$) Axilla Skin type: II	Unmentioned	Follow-up: 3 months Hair reduction at 3 months: 59.3% (alexandrite), 58.7% (diode), 31.9% (Nd:YAG), 39.8% (rotational treatment). The alexandrite and diode lasers were better than Nd:YAG and rotational treatment ($p<0.05$) The lasers were less effective in patients with red or light-coloured hair The patients found the alexandrite and diode lasers to be most and equally tolerable
Bäumler et al. [7]	Diode laser 8-mm spot, 3 tx Diode laser 12-mm spot, 3 tx Diode laser 14-mm spot, 3 tx	$n=20$ Hair colour unmentioned Legs Skin type: I–III	Unmentioned	Follow-up: 1 and 3 months Hair reduction at 3 months: 33% (8-mm spot), 46% (12-mm spot), 45% (14-mm spot) ($p=$ns)
Lorenz et al. [49]	Long-pulsed Nd:YAG laser 1–5 tx Shave	$n=29$ Blond, brown–black hair Legs Skin type: I–IV	Unmentioned	Follow-up: 3, 6, and 12–16 months Hair reduction at 12–16 months: 5 tx: 40% of patients obtain greater than 50% hair reduction 1 tx: 100% of patients have less than 25% of hair reduction Shave: no hair reduction 1 atrophic scar
Goldberg and Silapunt [34]	Long-pulsed Nd:YAG laser 1 tx, 50 J/cm^2 Long-pulsed Nd:YAG laser 1 tx, 80, 100 J/cm^2	$n=15$ Brown–black hair Axilla, bikini regions Skin type: II–IV	Yes	Follow-up: 3 months Hair reduction at 3 months: 29% (50 J/cm^2), 29% (80 J/cm^2), and 27% (100 J/cm^2) ($p=$ns) Blistering at highest fluence level ($n=2$)
Chan et al. [12]	Diode laser 1 tx Long-pulsed Nd:YAG laser 1 tx	$n=15$ Axilla, legs Chinese patients Skin type: IV–V	Yes	Follow-up: 1–6 weeks and 9 months Hair reduction at 9 months: similar and substantial regrowth for both laser systems (mean 9.1, VAS 0–10) Pain: Nd:YAG laser more painful (7.8) than diode laser (5.3) (VAS 0–10)
Eremia et al. [22]	Diode laser 4 tx Alexandrite laser 4 tx	$n=15$ Hair colour: unmentioned Axilla Skin type: I–V	Unmentioned	Follow-up: 12 months Hair reduction at 12 months: 85% (alexandrite) and 84% (diode) ($p=$ns)

(*continued*)

Table 9.4 (continued)

Study	Intervention Comparative intervention	Subjects No., hair colour, treatment site, skin type	Blinded response evaluation	Major results
Lou et al. [50]	Diode laser 1 tx, 20-ms diode laser, 2 tx, 5- to 20- ms shave	$n=50$; 18 at end of study Brown-black hair Back, extremities Skin type: II-IV	Unmentioned	Follow-up: 1, 3, 6, 9, and average 20-month Hair reduction at average 20-month: 13-36% (laser) and 7% (shave) ($P<0.05$) 34-53% (2 tx) and 28-33% (1 tx) ($P<0.05$)
Freedman and Earley [24]	Alexandrite laser, structured tx protocol (4 tx) Alexandrite laser, variable tx protocol (mean tx = 2.5)	$n=200$ Hair colour: unmentioned Face, truncus, extremities Skin type: I–IV	Unmentioned	Follow-up: 3 months Hair reduction at 3 months: 78% (structured tx protocol) and 48% (variable tx protocol) ($p<0.05$) Patient satisfaction closely approximated hair count data
Freedman and Earley [25]	Alexandrite laser, physician treated (mean tx = 3.5) Alexandrite laser, nurse treated (mean tx = 3.3)	$n=100$ Hair colour: unmentioned Face, truncus, extremities Skin type: I–IV	Unmentioned	Follow-up: 3 months Hair reduction at 3 months: 74%(physician treated) and 70% (nurse treated patients) (p = ns) Similar patient satisfaction in physician- and nurse-treated groups Similar self-reported transient adverse events
Görgü et al. [36]	Alexandrite laser 3 tx Electrolysis 4 tx	$n=12$ Hair colour: unmentioned Axilla Skin types: unmentioned	Unmentioned	Follow-up: 6 months after first tx Hair reduction at 6 months: 74% (alexandrite laser) and 35% (electrolysis) ($p<0.05$) Alexandrite laser less painful than electrolysis 12 of 12 patients preferred alexandrite laser to electrolysis
Fournier et al. [26]	Long-pulsed Nd:YAG laser 1 tx Shave	$n=14$ Hair colour: unmentioned Extremities, bikini lines Skin type: I–IV	Unmentioned	Follow-up: 1 and 3 months Hair reduction at 3 months: 24% (Nd:YAG) and 0% (shave) ($p<0.05$)
Bjerring et al. [8]	IPL 3 tx Ruby laser3 tx	$n=31$ Hair colour: unmentioned Chin, neck Skin type: II–IV	Unmentioned	Follow-up: 6 months Hair reduction at 6 months: IPL: 94% of patients obtained hair reduction (mean 49%) Ruby laser: 55% of patients obtained hair reduction (mean 21%) Patients'subjective evaluation closely approximated hair count data

Elman et al. [21]	Ruby laser 1 tx, 20 ms Ruby laser 1 tx, 1 ms	$n=16$ Hair colour: unmentioned Back, leg Skin type: IV	Unmentioned	Follow-up: 3 months Adverse events: less epidermal damage with 20-ms pulse duration (scar, pigmentary changes) than 1-ms pulse duration
Polder-man et al. [59]	Ruby laser 3 tx Wax 3 tx Electrolysis 3 tx Untreated control	$n=30$ Blond, brown–black hair Face, arm, pubic region Skin type: I–III	Unmentioned	Follow-up: to 12 months after first tx Hair reduction 2–4 months after last tx: 38–49% before/after hair reduction in laser-treated areas vs. no significant reduction for electrolysis, wax, or untreated control Hair reduction at 12 months after first tx: no significant hair loss at all
Sommer et al. [66]	Ruby laser 1 tx Ruby laser 4 tx	$n=51$ Hair colour: unmentioned Facial hirsutism Skin type: I-IV	No blinding	Follow-up: 1, 3, 6, 9, and 12 months Hair reduction: 1 tx: 20%, 35%, and 42% hair reduction at 3, 6, and 9 months 4 tx: 55%, 59%, and 61% hair reduction at 3, 6, and 9 months ($p<0.05$) Patient satisfaction closely approximated hair count data
Boss et al. [11]	Alexandrite laser 2 ms, 3 tx Alexandrite laser 20 ms, 3 tx	$n=18$ Hair colour: unmentioned Face, neck, truncus, extremities Skin type: I–IV	Unmentioned	Follow-up: 6 months Hair reduction at 6 months: by global assessment, 13/18 subjects reported no difference between the two pulse durations Similar blistering and hypopigmentation with the two tx modalities
Goldberg and Ahkami [32]	Alexandrite laser 2 ms, 3 tx Alexandrite laser 10 ms, 3 tx	$n=14$ Brown–black hair Face, neck, truncus, extremities Skin type: I–III	Unmentioned	Follow-up: 6 months Hair reduction at 6 months: 33% (2 ms) and 34% (10 ms) ($p=$ns)

(*continued*)

Table 9.4 (continued)

Study	Intervention Comparative intervention	Subjects No., hair colour, treatment site, skin type	Blinded response evaluation	Major results
Nanni and Alster [54]	Alexandrite laser 5 ms, 1 tx 10 ms, 1 tx 20-ms, 1 tx Shave	$n=36$ Grey, blonde, brown–black hair Lip, back, legs Skin type: I–V	Yes	Follow-up:1 week, 1, 3, and 6 months Hair reduction at 3 months: 27% (alexandrite) and -3% (shave) ($p<0.05$) Similar regrowth for 5-, 10-, and 20-ms pulse durations Hair reduction at 6 months: no significant hair reduction in laser or shave areas
Rogers et al. [61]	Alexandrite laser 1 tx Q-switched Nd:YAG laser + carbon-solution, 2 tx	$n=15$ Blond, brown hair Axilla Skin type: I–III	Unmentioned	Follow-up:1, 2, and 3 months after first tx Hair reduction at 3 months: 19% (alexandrite) and 27% (Nd:YAG) ($p<0.05$)
Dierickx et al. [17]	Ruby laser 1 tx + preop. wax or shave Shave Wax	$n=13$ (→ 7 at 2 years) Brown–black hair Back, thigh Skin type: I–III	Unmentioned	Follow-up: 1 and 2 years Hair reduction at 1 and 2 years: 4 of 7 persons still had obvious, significant hair loss after ruby laser tx
Walther et al. [70]	Ruby laser 1, 2, and 3 tx Shave	$n=15$ Brown–black hair Back, thigh Skin type: II–III	Unmentioned	Follow-up: 1, 2, and 3 months Hair reduction at 3 months: Complete regrowth with no difference between laser-treated areas (1, 2, and 3 tx) and shave control
Grossman et al. [35]	Ruby laser 1 tx + preop. wax or shave Shave Wax	$n=13$ Brown–black hair Back, thigh Skin type: I–III	Unmentioned	Follow-up: 1, 3, and 6 months Hair reduction at 3 months: significant less regrowth in laser-treated areas than shave and wax Hair reduction at 6 months: 4 of 13 persons less than 50% regrowth, 5 of 13 complete hair regrowth

Tx treatment; *IPL* intense pulsed light; *VAS* Visual analogue scale; *Ns* nonsignificant; *preop*. preoperative; *Nd*:*YAG* neodymium:yttrium aluminum garnet

reduction and significantly improved psychological profile in hirsuite women with polycystic ovary syndrome at 6 months after the final treatment compared with a low-dose sham treatment (fixed fluence 4.8 J/cm^2) [13]. Self-reported severity of hirsutism fell from 7.3 to 3.6 in the high-fluence group compared with a minor decrease from 7.1 to 6.1 in the low-dose sham-treated group [13]. Variations in pulse durations or spot size did not influence the hair removal efficacy or the occurrence of adverse events [11, 15, 32, 57]. Nurse treatment vs. physician treatment resulted in similar patient satisfaction and treatment outcomes [25]. Short-term reduction in hairiness may be improved when wax epilation is performed before alexandrite laser treatment compared with shaving preoperatively [45].

The alexandrite laser has been compared with other photoepilation equipment in several studies. Two RCTs and three CTs have shown that repetitive treatments (2–7) with the alexandrite laser and the diode laser result in similar patient tolerance and similar hair reductions at 3 months (59%), 6 months (37–72% with increasing efficacy for increased number of treatments), and 12 months (84–85% described in one unblinded CT with limited patient number) postoperatively [4, 22, 38, 60, 68]. One study found the alexandrite laser slightly more efficient than the diode laser at 2 months after three treatments (70% vs. 60% hair reduction) [42]. Adverse events including pigmentary changes occurred significantly less frequently with the alexandrite laser than the diode laser [38, 68]. Compared with the Nd:YAG laser, two CTs have shown the alexandrite laser to be significantly better for hair removal than the long-pulsed Nd:YAG laser at 2–3 months postoperatively (59–70% vs. 32–48%) [42, 60]. Moreover, one RCT has described substantial long-term hair reduction at 18 months after four treatments with both the alexandrite laser and the Nd:YAG laser with no significant difference in efficacy (84% for 18-mm spot size alexandrite laser, 76% for 12-mm spot size alexandrite laser, and 74% for the Nd:YAG laser) [15]. Combining the alexandrite laser with either a diode laser or long-pulsed Nd:YAG laser did not improve treatment outcomes but led to a higher frequency of adverse events [14, 42, 60]. In comparison to IPL, one RCT showed that 6 treatments with the alexandrite laser resulted in a significantly larger decrease in hair counts than six treatments with the IPL (46% vs. 27% hair reduction 6 months postoperatively) [51], whereas two CTs compared 2–7 treatments of alexandrite vs. IPL and demonstrated similar treatment efficacies at 6 months after treatment [4, 68]. Finally, two RCTs have evaluated the efficacy of the alexandrite laser in combination with either topical application of eflornithine or placebo cream [37, 65]. In one of the studies, the follow-up was only 2 weeks. At this time point, the eflornithine-treated skin showed significantly fewer hairs upon examination (93% hair reduction vs. 67.9%) [37]. Similarly, Smith et al. [65] showed a significantly better short-term hair reduction in their group of patients treated with eflornithine before laser treatment, but no difference was found 34 weeks after treatment.

9.6.4 Diode Laser: 800 and 810 nm

The hair removal efficacy after diode laser treatment was evaluated in 5 RCTs and 7 CTs (Tables 9.3 and 9.4). One RCT and one CT showed that the efficacy was significantly better than shaving in both short-term and long-term studies (13–36% hair reduction in laser-treated areas after 12 months vs. no effect in shaved areas) [6, 50]. Two repetitive treatments with the diode laser were superior to a single treatment at an average follow-up time of 20 months [50]. Six studies compared the diode laser with the alexandrite laser, and similar treatment outcomes were seen in all studies [4, 22, 38, 60, 68] except for one CT by Khoury et al., [42], where the alexandrite laser was found superior to the diode laser (see Sect. 9.6.3). Adverse events (pain, blistering, pigmentary changes) were described to occur more frequently using the diode laser than the alexandrite laser [38, 68]. Three studies compared the diode laser with the long-pulsed Nd:YAG laser, and the diode laser conveyed better results 2–3 months after treatment (58.7–59.7% vs. 31.9–47.7%) whereas similar, almost complete hair regrowth was seen for the both lasers at 9 months postoperatively [12, 42, 60]. Patients found the diode laser more tolerable than the long-pulsed Nd:YAG laser [42, 60], and the immediate pain scores (Visual Analogue Scale, range 0–10 cm) were higher for the Nd:YAG laser (7.8) than the diode laser (5.3) [12]. No difference in outcome measures was reported for the diode laser compared to IPL in two studies with follow-up times of 6 months; both resulted in around 50–70% hair reduction after 3–7 treatments [4, 68]. One RCT showed that combining the diode

laser with a liposomal melanin spray increased the hair reduction efficacy of the diode laser marginally at 6 months after three treatments (14% vs. 10% hair reduction) [63]. Different spot sizes of the diode laser (8, 12, and 14 mm) did not influence the short-term hair removal efficacy 3 months postoperatively [7], and two different diode laser systems had similar treatment outcomes 6 months postoperatively [23].

9.6.5 Long-Pulsed Nd:YAG laser: 1,064 nm

The hair removal efficacy after Nd:YAG laser treatment was evaluated in 4 RCTs and 7 CTs (Tables 9.3 and 9.4). One RCT and 2 CTs evaluated the laser-assisted efficacy vs. conventional therapies [26, 49, 53]. One treatment with the long-pulsed Nd:YAG laser was superior to shaving in both short-term (24% hair reduction vs. 0% at 3 months) and long-term studies (>75% hair reduction in 11% of the patients vs. 0% of shaved patients at 10 months) [26, 49]. One atrophic scar occurred in one of the studies [49]. Five repetitive treatments improved the long-term treatment outcome compared to a single treatment (>50% hair reduction in 40% patients vs. <25% 12 months postoperatively) [49]. One RCT found no significant difference between hair removal with the alexandrite and Nd:YAG lasers [15], whereas two studies found the Nd:YAG laser to be less efficient (see Sect. 9.6.3) [43, 59]. Two studies found better efficacy of three treatments with the diode laser than three treatments with the Nd:YAG laser [43, 59]; similar hair growth was found in another study 9 months after one treatment (see Sect. 9.6.4) [12]. The short-term hair removal efficacy after 6 weeks was similar for one treatment with a long-pulsed Nd:YAG laser (73%) and IPL (64%) [27]. Eflornithine increased the efficacy of the Nd:YAG laser on a short-term basis (6–22 weeks) but not on a long-term basis (34 weeks) [65]. Application of increasing fluences did not improve the hair removal efficacy in a short-term CT but resulted in blistering [34].

The short-pulsed, nanosecond, Q-switched Nd:YAG laser today is, as previously mentioned, considered of minor relevance for hair removal. One study reported that the short-pulsed Q-switched Nd:YAG laser was transiently superior to wax epilation 3 months postoperatively whereas full regrowth was seen 6 months postoperatively [53]. Moreover, one study found two treatments with the Q-switched Nd:YAG laser more efficient than one treatment with the alexandrite laser, although the difference in treatment sessions makes the results difficult to compare [61].

9.6.6 IPL: 590–1,200 nm

The hair removal efficacy after IPL treatment was evaluated in three RCTs and three CTs (Tables 9.3 and 9.4). Three treatments with IPL (94% of patients had a mean hair reduction of 49%) were superior to three treatments with the ruby laser (55% of patients had a mean hair reduction of 21%) evaluated 6 months postoperatively by hair counts and patients' subjective evaluations [8]. Two studies of IPL vs. the alexandrite laser found similar treatment outcomes at 6 months after treatment with these devices (50–68.8% hair reduction after 2–7 treatments) [4, 68], whereas one RCT showed better outcome with the alexandrite laser than IPL (43% vs. 27% after 6 months) [51]. One RCT and one CT showed the IPL and the diode laser to be equally effective at 6 months after the final treatment (50%–71.7% hair reduction after 2–7 treatments) [4, 68]. Similarly, one treatment with a long-pulsed Nd:YAG laser and IPL resulted in equal hair removal efficacies 6 weeks postoperatively (73% and 64%), whereas the IPL treatment more often resulted in postinflammatory pigmentation compared with the long-pulsed Nd:YAG laser [27].

Two CTs have evaluated the influence of using IPL sources with different output wavelengths [4, 39]. One of these studies, which included 48 Korean women, showed that the wavelength output spectrum influences the treatment outcome because four treatments with IPL at 600–950 nm (mean 800 nm) were significantly less efficient for hair reduction at 8 months after the final treatment than IPL with an output spectrum of 645–950 nm (mean 830 nm) (52.8% vs. 83.4%) [39]. Another study showed no difference in the efficacy of IPL using a red (650–1,200 nm) vs. a yellow (525–1,200 nm) filter; both resulted in approximately 50% hair reduction at 6 months [4].

9.6.7 Summary and Overall Evaluation of Evidence

Five different lasers and light sources were evaluated, and the best evidence was found for the alexandrite

laser (11 RCTs, 10 CTs); followed by the diode laser (5 RCTs, 7 CTs); the Nd:YAG laser (4 RCTs, 7 CTs); the ruby laser (2 RCT, 7 CTs); and IPL (3 RCT, 3 CT). Most of the studies have limited sample sizes (10–20 individuals) and may therefore introduce a risk of a type-2 error, i.e., a risk of missing a true difference between the different laser systems. Moreover, differences in patient populations may introduce bias and uncertainty duringinterpretation of the results. However, the included material is relevant to the clinical situation, and some of the patient characteristics have been outlined in Tables 9.3 and 9.4.

9.6.7.1 Evidence for Short-Term Efficacy up to 6 Months After Epilation

Substantial evidence exists for a short-term efficacy of hair removal up to 6 months after treatment with the ruby laser, alexandrite laser, diode laser, Nd:YAG laser, and IPL. The efficacy is improved when repetitive treatments are given [2, 27, 49, 50, 66, 68] and there is considerable evidence that the short-term efficacy from photoepilation is superior to conventional treatments with shaving [6, 26, 35, 49, 50, 54], wax epilation [35, 53, 59], and electrolysis [37, 59]. Overall, the short-term efficacy is reported between 30% and 70% hair reductions up to 6 months after the last treatment; the treatment outcomes depend on the treatment settings, and a few studies are reporting higher and lower efficacy outcomes.

9.6.7.2 Evidence for Long-Term Efficacy Beyond 6 Months After Epilation

The long-term efficacy of hair removal beyond 6 months postoperatively and onwards was evaluated in 4 RCTs and 6 CTs (Tables 9.3 and 9.4), and evidence was found for a long-term efficacy of hair removal after repetitive treatments with the alexandrite laser, the diode laser, and the long-pulsed Nd:YAG laser [15, 22, 41, 49, 50]. Moreover, it may be possible that repetitive treatments with the ruby laser (3–4 treatments) and IPL (5 treatments) are capable of inducing long-term hair reduction as well, although the actual evidence is sparse, with unambivalent results from the ruby laser (probably due to different pulse durations) [59, 66]; only one CT evaluates the long-term efficacy from IPL treatment [39]. The overall results from long-term studies with the alexandrite, diode, and Nd:YAG laser vary, a lot, but show on average a 50% hair reduction from repetitive treatments with these devices [15, 22, 41, 49, 50].

9.7 Adverse Events and Complications

Hair removal procedures with lasers and IPL sources have expanded outside dermatology clinics, which means that treatments increasingly are performed without supervision from trained physicians. Unfortunately, adverse events and injuries are seen that might have been avoided by proper training and education. However, complications are rare if the patients' skin types are kept in mind and if treatments are performed by properly educated and trained operators.

Before treatment, the possibility of adverse events must be discussed with patients. Risks and complications include blistering, ulceration (Fig. 9.3), infections, postinflammatory hyperpigmentation (Fig. 9.4), hypopigmentation, scarring, eye injury, paradoxical hair stimulation, and livedo reticularis [28, 29, 47]. Higher incidences of laser-induced pigmentary alterations are associated with darker skin types and the

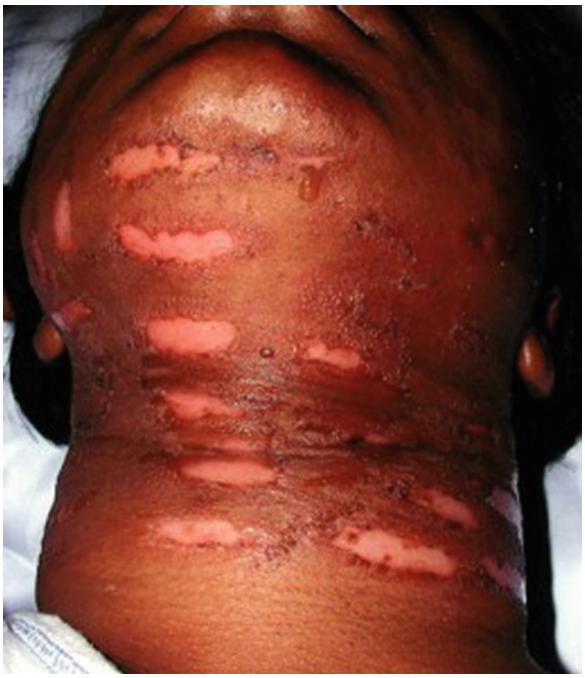

Fig. 9.3 Acute skin reaction and adverse effects in patient with Fitzpatrick skin type VI

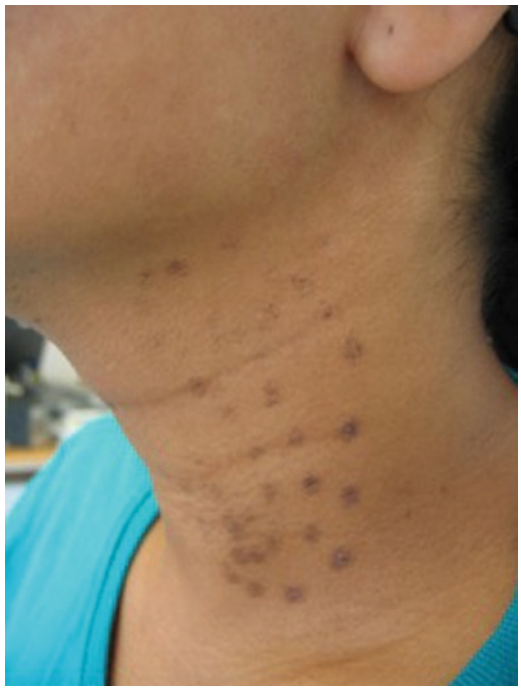

Fig. 9.4 Postinflammatory hyperpigmentation 1.5 months after intense pulsed light treatment

use of shorter wavelength lasers and IPL devices [47]. The pigment changes are usually transient and resolve spontaneously without sequelae, although permanent dyschromia may occur [28, 47]. The risk of eye injury is severe when any hair removal laser or IPL device is used within the bony orbit and therefore, should be avoided. If treating near the eyes, the cornea must be covered with metal eye shields.

Paradoxical hair stimulation has been noted after laser and IPL treatments in approximately 5% of women of Mediterranean and Middle Eastern descent [1, 44, 73]. Reactive hair growth, which is usually long-lasting or permanent, may appear at the borders of previously treated areas, mainly on the face and neck. Patients with ill-defined frontal hairlines seem to be at risk for developing paradoxical hair growth, and it is recommended that treating these patients be avoided. Finally, patients have to be instructed to avoid sun exposure before, during, and after treatment sessions for hair removal to reduce the risk of postoperative complications and adverse events.

9.8 New and Alternative Treatment Strategies

Laser hair removal continues to be a popular treatment, and treatment procedures are evolving. New hair removal approaches involve consumer-based treatments with portable home devices [72], photopneumatic technology [43, 56], and PDT potentially may be a useful future approach for hair removal since photosensitizers tend to accumulate in the follicular epithelium [19]. Moreover, topical application of eflornithine (a medical enzyme that irreversibly inhibits the enzyme ornithine decarboxylase involved in controlling hair growth and proliferation) or meladine (a topical melanin-encased, phosphatidylcholine-based liposome solution) may be useful adjuvants for laser and IPL hair removal [9, 19]. Studies have shown that eflornithine in combination with the alexandrite or Nd:YAG laser may increase the efficacy of laser hair removal and that topical melanin improves the efficacy of the diode laser [37, 63, 65]. Also, optical bipolar radiofrequency has been evaluated in combination with laser and IPL and with or without preceding application of topical aminolevulinic acid [33], showing that new devices and treatment techniques are being developed. However, clinical controlled trials and long-term data are needed to determine efficacy and safety of these new modalities.

Take Home Pearls

- Epilation with lasers and light sources induces a short-term hair reduction up to 6 months postoperatively. Long-term hair reduction beyond 12 months has been described, but the results are varying.
- Today, there is no evidence for a complete and persistent efficacy of hair removal after laser treatment and photoepilation.
- Eflornithine, topical melanin, and PDT may be future treatment options for difficult-to-treat white, grey, and red hairs, but further evidence of efficacy is needed.
- Longer wavelengths are safer for patients with darker skin types.

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Pigmentation and Hypopigmentation: Benign Pigmented Lesions

10

Henry H.L. Chan

Core Messages

- Several factors affect the clinical outcome in the use of laser and light sources for the treatment of benign pigmentary conditions, including the type of lesions, skin type, device selection, and operator's skill.
- Conditions that respond well to laser/light source treatment include freckles/lentigines, nevus of Ota, and Hori's macules.
- Melanocytic nevi can also be very responsive to laser treatment, but such use on whites is controversial.
- Conditions that yield inconsistent response to the use of laser and light source treatment include melasma, café au lait patches, and Becker's nevi.

Despite the widespread use of lasers and light sources for the treatment of benign pigmentary conditions, clinical outcome varies and depends upon several factors, including the type of lesions, skin type, device selection, and operator's skill. Freckles, lentigines, the nevus of Ota, and congenital or acquired melanocytic nevi can respond very well to laser/light source treatment. Other conditions including melasma, café au lait patches, and Becker's nevi are much less predictive. Skin type is an important determining factor; light-skinned patients carry a much lower risk of complications, such as postinflammatory hyperpigmentation (PIH) compared with people who have skin of color.

In this chapter, the role of laser and light sources for the treatment of pigmentary conditions will be discussed under the following categories:

1. Conditions that respond well to laser/light source treatment.
2. Conditions that may respond to the use of laser and light source treatment.

10.1 Conditions that Respond Well to Laser/Light Source Treatment

10.1.1 Freckles and Lentigines

Q-switched (QS) lasers can be most effective for the treatment of freckles and lentigines, especially in light-skinned patients. Complete or near complete degree of clearance can be achieved after even one treatment (Fig. 10.1). The main disadvantage with QS lasers is the downtime associated with redness and swelling, which can last for 1–2 days, and crusting that can persist for about a week. PIH can occur among people with darker skin types, and previous studies have indicated that such risk seems to be higher among patients with lentigo as compared to those with mainly freckles [7, 48]. Many QS lasers can be used, including neodymium: yttrium-aluminum-garnet (Nd:YAG) lasers (532 nm), alexandrite (Alex) lasers (755 nm), and ruby

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_10,

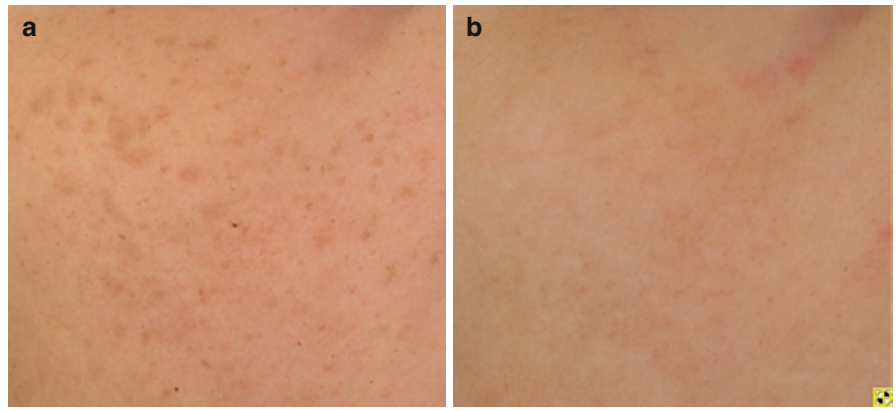

Fig. 10.1 Freckles and lentigines. (**a**) Before treatment and (**b**) after three treatments with a Q-switch 532-nm neodymium:yttrium-aluminum-garnet laser

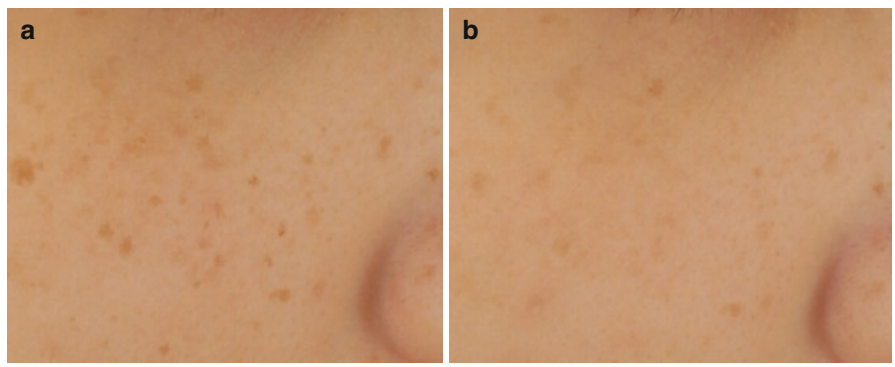

Fig. 10.2 Freckles. (**a**) Before treatment and (**b**) after three treatments with intense pulsed light

lasers (694 nm). A 532-nm Nd:YAG laser tends to induce more purpura than the other two [4, 21, 45]. The appropriate clinical endpoint is immediate whitening and, for dark-skinned patients, the smallest spot size should be used to avoid unnecessary injury to the surrounding normal skin.

To reduce the downtime and potential complications associated with the use of QS lasers, intense pulsed light (IPL) sources have been used and can be most effective, especially when patients want to improve other components of their skin, such as pore size and facial telangiectasia [20]. Unlike lasers, which have a fixed wavelength radiation, IPL consists of a fixed spectrum of wavelengths and m if used appropriately, can target different components of photoaging. IPL is particularly suitable for the treatment of light-skinned patients with extensive dark freckles and lentigines; for this group of patients the greater degree of contrast can ensure a larger safety margin, which is necessary given the relatively lower selectivity of IPL (Fig. 10.2). The large spot size of IPL can also be a particular advantage when it is used to treat a large surface area. Because IPL is less specific, several treatment sessions are necessary for it to remove freckles and lentigines. The downtime associated with IPL is often much less and can be of particular advantage for those who cannot afford to have downtime. There are now many IPL systems on the market, and clinical endpoints can vary. Immediate redness and darkening of the lesions are the appropriate endpoints for IPL with shorter pulse duration (2 ms). However, for IPL with longer pulse width (40 ms), such changes can occur in a delayed manner (the next day), especially among dark-skinned patients. For such systems, the patient's subjective response, such as the degree of pain, is more appropriate.

For patients with dark skin, the lesser contrast between the normal and lesioned skin implies that care should be used to avoid potential complications such as hypo- and hyperpigmentation. If the contrast is low (light-color lentigines in dark-skinned patients), it would be best to choose a small spot size pigment laser over

IPL to avoid unnecessary injury to the surrounding normal skin.

Besides QS lasers, long-pulsed (LP) pigment lasers can also be used for the treatment of freckles and lentigines. They are particularly effective for the treatment of such lesions among people with skin of color; previous studies have indicated a lower risk of PIH as compared to QS lasers when used in this group of patients. It is also associated with less downtime but does require several treatment sessions to achieve a complete or near complete degree of clearance. Many LP lasers can be used to achieve such a task, including LP 532-nm Nd:YAG lasers, pulsed dye 595-nm laser, LP ruby lasers, and LP Alex lasers [7, 34]. The appropriate endpoint is immediate darkening of the lesion. Purpura can occur, especially with vascular lasers, such as an LP 532-nm Nd:YAG or LP dye 595-nm laser. Compression of the skin's surface by the flat glass window on the handpiece leads to emptying of blood vessels and therefore reduces the risk of dermal vascular damage by lasers and subsequent bruising and PIH (Fig. 10.3) [24, 25].

10.1.2 Nevus of Ota

Nevus of Ota is a dermal melanocytic hamartoma characterized clinically by mottled, dusky blue and brown hyperpigmentation. The pigmentation can cause marked disfigurement and mostly affects the skin and mucous membranes innervated by the first and second branches of the trigeminal nerve. Histologically, ectopic melanocytes are present in the dermis. This condition is more common among Asians and affects about 0.6% of the population. QS ruby, QS Alex, and QS 1,064-nm Nd:YAG lasers have all been used to achieve good therapeutic results [8, 14, 49] (Fig. 10.4). Three

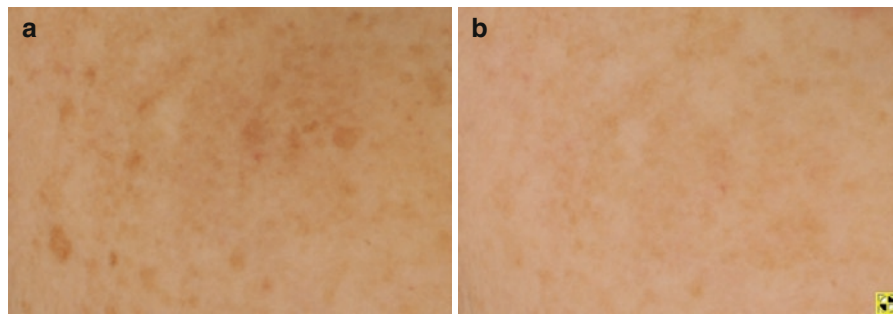

Fig. 10.3 Freckles. (**a**) Before treatment and (**b**) after three treatments with long-pulsed 532-nm neodymium:yttrium-aluminum-garnet laser

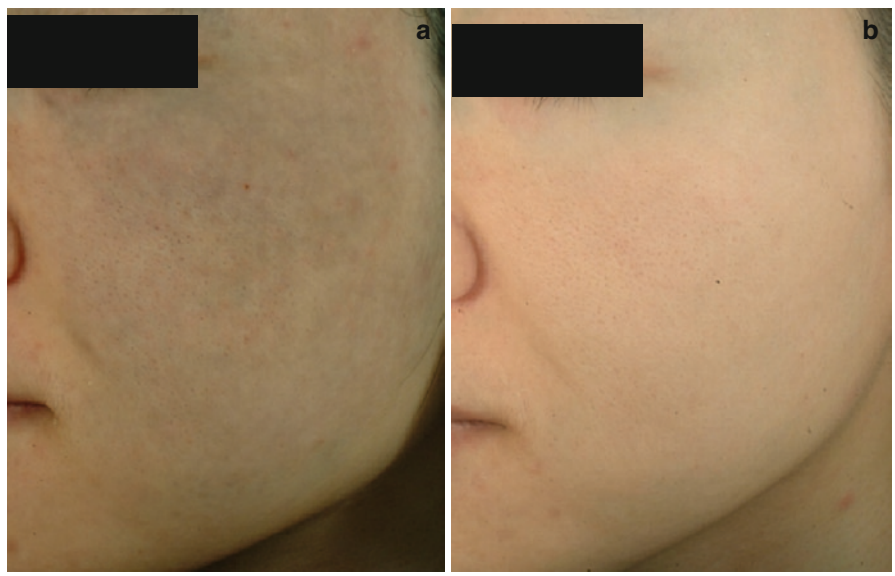

Fig. 10.4 Nevus of Ota. (**a**) Before treatment and (**b**) after seven treatment sessions with a Q-switch 1,064-nm neodymium:yttrium-aluminum-garnet laser

or more treatment sessions are necessary before any clinical improvement can be observed. Clinical endpoint is defined as immediate whitening for QS ruby and Alex lasers, and immediate whitening with punctuate bleeding for QS 1,064-nm Nd:YAG lasers. The treatment interval initially should be 6–8 weeks, and towards the end of the treatment, when the lesion has lightened significantly and requires higher fluence to achieve the clinical endpoint, the treatment interval should be lengthened to several months.

QS ruby lasers are associated with the lowest number of treatment sessions but a greater risk of hypopigmentation. Besides hypopigmentation, other potential complications include erythema after the laser procedure, transient PIH, texture changes, and repigmentation, which can occur among 0.6–1.2% of patients [26].

The number of treatment session has been shown to be related to several factors, including the age when treatment is initiated, with younger patients requiring fewer treatment sessions [23]. Periorbital involvement was also found to be associated with more treatment sessions [9]. Recently, a study of 10 Asian patients with dermal-pigmented lesions (three of which were nevi of Ota) showed that the use of a QS Alex laser delivered with compression was associated with a lower risk of purpura and dyspigmentation when compared with laser treatment without compression [25]. The efficacy was not compromised with compression. Diascopy caused emptying of the cutaneous blood vessels and hence reduced the risk of laser injury to blood vessels.

Fractional resurfacing was recently found to be effective in the removal of nevus of Ota in a patient who failed to respond after treatment with a QS 1,064-nm Nd:YAG laser [29].

10.1.3 Acquired Bilateral Nevus of Ota-like Macules (ABNOM or Hori's macules) (Fig. 10.5)

Hori's macules are dermal hyperpigmentations commonly seen in Asian patients that affect approximately 0.8% of the population. Hori's macules present as bilateral blue-gray macules typically located over the malar region in a symmetrical pattern. The lateral temples, alae nasi, eyelids, and foreheads can also be involved. Histologically, dermal melanocytes are dispersed in the papillary and middle part of the dermis.

In contrast to nevus of Ota, the pigmentation of Hori's macules is acquired, has a late onset in adulthood, and does not affect the mucosa. Melasma and Hori's macules can coexist in some patients. Like nevus of Ota, QS lasers have been shown to be effective for treatment of Hori's macules. QS ruby, QS Alex, and QS 1,064-nm Nd:YAG lasers have all been found to achieve complete clearance of PIH that ranged from 7% to 73%, with QS ruby lasers associated with the greatest degree of improvement and the lowest risk of PIH [30, 31, 39]. Combined laser therapy has also been found to be effective. One study indicated that a QS 532-nm Nd:YAG laser used in conjunction with a QS 1,064-nm Nd:YAG laser can achieve better results than laser on its own [13]. Another study indicated that

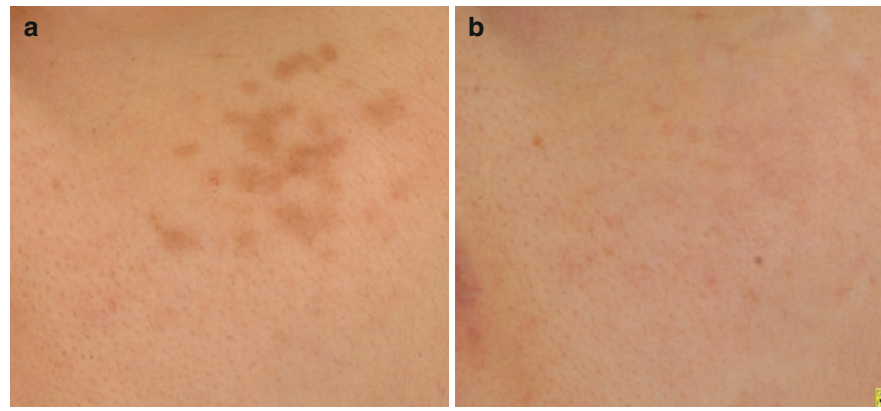

Fig. 10.5 Hori's macules. (**a**) Before treatment and (**b**) after five treatments with a Q-switch ruby laser

an ablative laser used first to remove the epidermis allowed better penetration of the QS ruby laser and obtained superior results as compared with use of a QS ruby laser on its own [36].

10.1.4 Melanocytic Nevi

The use of lasers for the treatment of melanocytic nevi is controversial; the main concern regarding the use of lasers for the treatment of melanocytic nevi is the potential delay in the diagnosis of neoplastic changes. Indeed, there have been reports of histological atypia in patients with melanocytic nevi that were treated by carbon dioxide lasers as well as lasers for hair removal [11, 41]. In the author's opinion, racial differences need to be taken into consideration because the incidence of melanoma differs among different ethnic groups. In Asians, the incidence of melanoma has been reported to be between 0.2 and 2.2 per 100,000, much lower than among whites [6]. Furthermore, the most common sites for the development of melanoma among people with skin of color are areas not directly exposed to the sun, such as palmar, plantar, subungual, and mucosal surfaces. As a result, the use of lasers for the treatment of melanocytic nevi is common in Asian countries.

Different pigment lasers have been used in the removal of melanocytic nevi. Treatment of congenital melanocytic nevi using a QS ruby laser was found to achieve an average clearance of 76% after eight treatment sessions [46]. The use of a QS ruby laser followed immediately, or 2 weeks later, by a normal-mode ruby laser (NMRL) can lead to a 52% visible decrease in pigment without complete histologic clearance [12]. The short- and long-term histologic findings of congenital nevi that have been treated with an NMRL indicate that subtle microscopic scars reaching 1 mm in diameter are frequent. It has been proposed that such scars cover the underlying nevus cells, leading to cosmetic improvement [18]. Better cosmetic result has been reported by first using an NMRL to remove the epidermis, followed immediately by multiple passes with a QS ruby laser [27]. This approach for allows the effective removal of the epidermis and enables a greater degree of penetration by the QS ruby, of which multiple passes further enhance the clinical efficacy.

10.2 Conditions that May Respond to the Use of Laser and Light Source Treatment

10.2.1 Melasma

Melasma is an acquired symmetrical hypermelanosis involving sun-exposed areas and is commonly seen among middle-aged women, especially those with skin of color. Genetics, ultraviolet radiation, pregnancy, hormonal therapies, other phototoxic drugs, and, more recently, vasodilatation are all thought to be contributing etiologic factors [19, 22]. Among all the pigmentary conditions, melasma is the most challenging in terms of successful treatment outcome.

Melasma was formerly classified histopathologically as epidermal, dermal, or mixed type depending on the location of the pigmentation [16]. However, a recent histopathologic study suggested that there is no true dermal type and the dermal melanophages are in fact due to Hori's macules [19].

Because the pathogenesis of epidermal and mixed-type melasma is believed to be due to an increased number of melanocytes and increased activity of melanogenic enzymes, which lead to hyperactive melanocytes [19], suppression of such hyperactive melanocytes is essential before the use of any laser or light source to prevent an increase in pigmentation. As a result, the use of sunblock and topical bleaching agents remains the first-line treatment. To allow the topical agents to affect the follicular melanocytes, at least 6 weeks of topical treatment is necessary.

Given the potential risk of an increase in pigmentation, lasers and light sources should only be considered in resistant cases. There are three types of lasers/light sources for the treatment of melasma, and they are categorized as follows:

1. Resurfacing lasers
2. Pigment lasers/IPL
3. Vascular lasers

10.2.2 Resurfacing Lasers

Ablative resurfacing using carbon dioxide or erbium: yttrium–aluminum-garnet (Er:YAG) lasers have been shown to be effective in the treatment of melasma and are probably the only therapeutic option that can lead

to a long-term cure [5, 35]. The intention of using such lasers is to remove the abnormal clonal expansion of melanocytes in diseased skin and, in doing so, lead to long-term remission. Such procedures can also affect the epidermal barrier function and enhance the absorption of topical bleaching agents postoperatively. The morbidities associated with such procedures, including PIH, infection, and even scarring, have made them unpopular. In recent years, fractional resurfacing has largely replaced laser resurfacing for skin rejuvenation as well as treatment of melasma [40]. One study indicated the effectiveness of fractional resurfacing for the treatment of melasma to be of excellent response in 60%, a mild to moderate degree of improvement in 30%, and worsening in 10% of cases. Furthermore, most cases tend to recur after treatment [32]. It is the opinion of the author that fractional resurfacing has failed to achieve complete removal of the abnormal melanocytes in diseased skin, and its role is therefore mainly adjunctive.

10.2.3 Pigment Lasers/IPL (Fig. 10.6)

Earlier studies using 510-nm pulsed dye and QS ruby lasers were found to be ineffective, with a possibility of increased pigmentation [15, 43]. Though a lack of adequate preoperative preparation with topical bleaching agents may contribute to such findings, it is the experience of the author that pigment lasers yield variable results despite the use of preoperative bleaching agents. LP pigment lasers (532-nm Nd:YAG, LP Alex) can be used, but a test area is necessary to assess the clinical outcome. The appropriate clinical endpoint is an ashen gray appearance and, postoperatively, application of a topical steroid (such as mometasone furoate twice daily for 3 days) to suppress inflammation that can lead to increased pigmentation is warranted.

Previous studies have examined the use of IPL (570-nm and 590- to 615-nm filters at 4-week intervals for a total of four treatments) for the treatment of melasma and indicated that melasma improved by 39.8% compared to only 11.6% in the control group [47]. Two patients in the IPL group experienced transient PIH, and partial repigmentation was noted 24 weeks after the last treatment session. In a more recent study, 89 patients with melasma were treated with an intense pulsed light device with a uniform pulse profile. They were able to achieve excellent results (77.5% of treated subjects had more than 50% improvement 3 months after treatment) with a low risk of increase in pigmentation (3%) [33]. This was despite the lack of use of topical bleaching agents during the study period. This study's findings differ significantly from previous data. Although the uniform profile of this IPL device may be one of the reasons for such an observation, as suggested by the investigators, other factors are more likely to contribute to the differences in clinical outcome, including location on the body of the tested site and recruitment criteria.

Laser toning involves the use of large spot size, and a low-fluence, QS 1,064-nm Nd:YAG laser (6- to 8-mm spot size, 1.6–2.3 J/cm^2) in the treatment of melasma and has gained much popularity in Asian countries in recent years [38]. Mild erythema is used as the clinical endpoint, and treatment is often performed in 1 or 2 weekly intervals. Though melasma

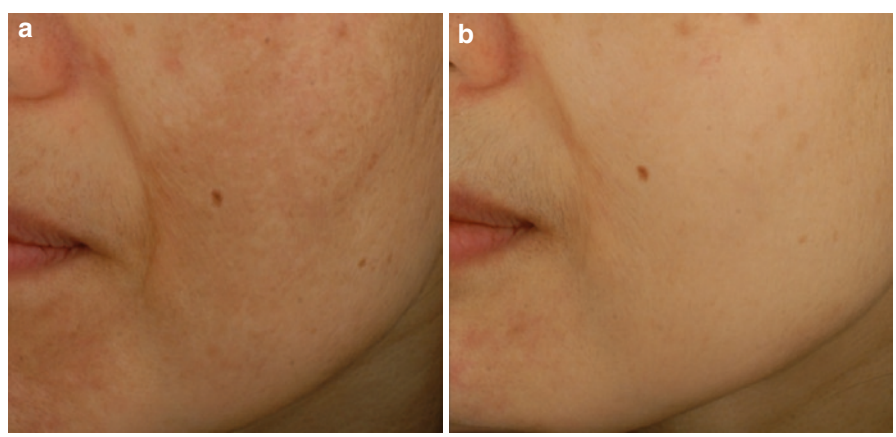

Fig. 10.6 Melasma. (**a**) Before treatment and (**b**) after the use of topical bleaching agents and two treatments with a long-pulsed 532-nm neodymium:yttrium-aluminum-garnet laser

can certainly be lightened with such treatment, prolonged treatment can lead to mottled depigmentation, which is most difficult to manage [10] (Fig. 10.7). Furthermore, relapse of melasma and, in some cases, rebound can occur. Laser toning should therefore be used as an adjunctive therapy.

10.2.4 Vascular Laser

The use of vascular lasers in the treatment of melasma is based upon the recent observation that the number and size of dermal vessels in melasma are significantly greater than in nonlesioned skin. It has been suggested that vascular endothelial growth factor may play an important angiogenic role in melasma [22]. Vascular lasers have since been used, especially when there is a significant component of telangiectasia within the melasma.

10.3 Café au Lait Patch (Fig. 10.8)

The use of lasers for the treatment of café au lait patches has led to inconsistent results. Although an early study looking at the use of a continuous-mode, 511-nm copper vapor laser indicated good to excellent results in 15 of 16 patients after two treatment sessions [42], such findings have not be consistent. Five hundred ten-nm pulsed dye laser and Er:YAG lasers have also been shown to be successful in some cases [1–3].

Among all lasers, QS lasers yielded the most variable results with high recurrence rates, and paradoxical darkening has also been reported. In a study using a QS 694-nm ruby laser and a QS 532-nm Nd:YAG laser, it was found that the degree of clearance varied across the lesions [17]. One possible explanation is that QS lasers failed to remove the follicular melanocytic component of the café au lait macules.

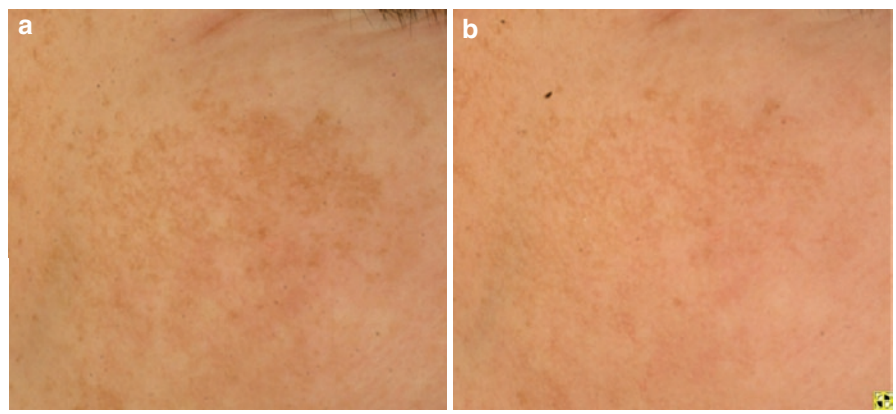

Fig. 10.7 Melasma (**a**) Before treatment and (**b**) after the use of topical agents and a Q-switch 1,064-nm neodymium:yttrium-aluminum-garnet laser

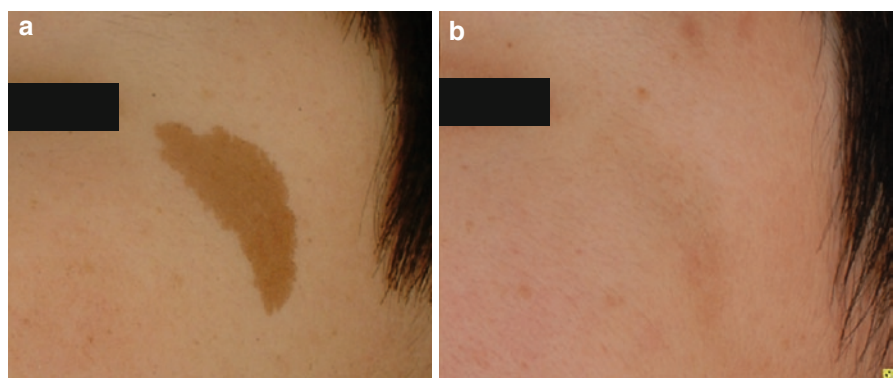

Fig. 10.8 Café au lait. (**a**) Before treatment and (**b**) after four treatments with long-pulsed, 755-nm Alex laser

My current approach is to use an LP pigment laser, such as NMRL or LP Alex laser without cooling, to target not only the epidermal melanocytes but also the follicular melanocytes. In doing so, the recurrence rate can be reduced. In one study of 33 patients with café au lait macules, NMRL was shown to have a lower risk of recurrence (42.4%) compared to QS ruby laser (81.8%) 3 months after a single treatment.

10.4 Becker's Nevus

In the past, argon and carbon dioxide lasers were used, which often resulted in scarring or permanent hypopigmentation. One previous study using a QS ruby laser showed a postoperative increase in pigmentation after 4 weeks [28].

A study comparing the use of Er:YAG lasers to QS 1,064-nm Nd:YAG lasers in 22 patients with a follow-up of 2 years indicated the ER:YAG laser to be significantly better even after one treatment [44].

LP pigment lasers have also been employed to remove hair and pigmentation in Becker's nevi, but textural change is a possible complication [37]. In my practice, a long-pulse 755-nm Alex laser (20–35 J/cm^2, 10-mm spot size, pulse duration of 1.5 ms) is used to target the pigment and surrounding hair follicle. Four to eight treatment sessions are usually given, with a 50% success rate. Possible adverse effects include scarring and hypopigmentation.

Take Home Pearls

- QS lasers are more effective in the treatment of freckles and lentigines in light-skinned patients, whereas LP pigment lasers are associated with lower risk of PIH in the treatment of freckles and lentigines in patients with skin of color.
- QS lasers are the best choice for treatment of nevus of Ota and Hori's macules.
- Combined LP lasers followed immediately by use of QS lasers can produce the most cosmetically acceptable result in the treatment of melanocytic nevi among the appropriate patient group.
- Lasers and light sources can be considered as a second-line treatment as well as an adjunctive therapy to topical medication in the management of melasma.
- LP pigment lasers used to target not only the epidermal but also the follicular melanocytes can be effective in the treatment of café au lait patches and Becker's nevi.

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Pigmentation and Hypopigmentation: Vitiligo and Other Disorders

11

Thierry Passeron and Jean-Paul Ortonne

Core Messages

- Lasers and light-emitting devices have now taken on a key role in the treatment of vitiligo and hypomelanosis.
- Q-switched depigmenting lasers can be used to treat the residual pigmented spots in the generalized forms of vitiligo.
- Ablative lasers bring a rapid and reproductive tool to prepare the grafting bed for the segmental and localized forms of vitiligo or for inherited hypochromic disorders such as piebaldism.
- The 308-nm excimer lasers and lamps are clearly the devices that brought the most progress for taking charge of hypochromic disorders. With higher rates of repigmentation as compared with conventional phototherapy and with a specific targeting of the lesions that spares the surrounded skin, their main limitation remains the surface to treat.
- New wavelengths will certainly be used in the near future to enhance repigmentation. The 632.8-nm helium–neon laser already have brought encouraging results that are worth further study.

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Skin lightening or whitening (leukoderma, hypopigmentation) is most commonly the result of decreased melanin content in the skin (hypomelanosis). Epidermal hypomelanosis may be the result of at least two different pathogenic mechanisms: a partial or total andbsence of epidermal melanocytes (melanocytopenic hypomelanosis) or a normal number of epidermal melanocytes with an alteration in melanin synthesis in melanosome biogenesis, or in the transport and transfer of the melanosomes (melanopenic hypomelanosis). Increase of epidermal turnover can also induce hypomelanosis.

Hypopigmentation disorders can be inherited or acquired [34, 41]. In clinical practice, vitiligo, idiopathic guttate hypomelanosis, postinflammatory hypopigmentation, nevus depigmentosus, and, to a lesser extent, piebaldism are the most common forms of hypomelanosis. Vitiligo and disorders of hypopigmentation are often considered to be benign disorders, but they are cosmetically important and have a strong impact on the quality of life of affected individuals. Thus, they induce a strong therapeutic request. If the treatment of most of the postinflammatory hypopigmentations, such as hypochromic lesions of atopic dermatitis, psoriasis, or mycosis fungoides, consists in the treatment of the underlying disorder, the treatment of vitiligo or primitive disorders of hypopigmentation remain challenging [37]. Medical approaches with topical steroids or topical calcineurin inhibitors and phototherapy with ultraviolet (UV) B or UVA light are considered to be the best actual treatments for localized and generalized vitiligo, respectively [10, 12, 36, 52]. Surgical treatments that bring new melanocytes to the affected lesions are preferred for segmental or stable, localized forms of vitiligo and for genetic hypomelanosis [9, 37, 50].

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_11, © Springer-Verlag Berlin Heidelberg 2011

Although useful, those treatments do not provide fully satisfactory results. During the last decade, laser technology has greatly progressed and lasers and other light-emitting devices have a key role in the actual dermatological practice. Depigmenting lasers were the first to be used for treating hyperpigmentation from endogenous (e.g., lentigos) or exogenous (e.g., tattoos) pigments. Those devices quickly were proposed for depigmenting residual pigmented spots in generalized vitiligos. Then, ablative lasers, such as the carbon dioxide (CO_2) and erbium lasers, have been used for the desepidermization before grafting procedures. More recently, new devices have been developed to enhance repigmentation. These new approaches have allowed marked improvement in the treatment of vitiligo and disorders of hypopigmentation.

11.1 Depigmenting Lasers

Laser devices were first used for depigmenting the residual pigmented areas in generalized vitiligo. Permanent depigmentation is usually proposed for people older than 40 years and after detailed information is given to the patient. Psychological evaluation is also useful. The monobenzylether of hydroquinone (MBEH) causes a permanent depigmentation of the skin that has been used for generalized vitiligo. MBEH is metabolized to reactive free radicals inside the cells, resulting in melanocyte destruction. However, the side effects, including irritant and allergic contact dermatitis, postinflammatory hypermelanosis, leukoderma en confetti at treated sites, and hypomelanosis at sites distant from the application areas, strongly limit the use of this compound and prompt clinicians to seek therapeutic alternatives. To date only depigmenting lasers have been studied in this regard. However, literature about the subject remains poor. A short, retrospective study suggests that a Q-switched ruby laser is as effective as MBEH (depigmentation was observed in 69% of the subjects with both kinds of treatments) [33]. Of interest, a repigmentation of treated areas was observed in 44% and 36% of the patients treated with lasers and MEBH, respectively. Thus, patients should be informed of the risk of repigmentation after both kinds of treatment. An isolated success has been reported in a patient with generalized vitiligo who was treated with a Q-switched ruby laser, with no repigmentation observed 1 year after the treatment [26]. More recently, a Q-switched alexandrite laser has shown its efficacy in the depigmentation of one patient. Again, no repigmentation was observed at follow-up after 1 year [43].

Thus, depigmenting lasers seem to be an attractive alternative to MEBH for depigmenting patients with generalized vitiligo. They should be reserved for limited surfaces and they should not be proposed if depigmentation involves less than 50% of the affected area. In all the cases, patients have to be clearly informed of the potential risk of later repigmentation and photoprotection of the treated areas should be systematically prescribed.

11.2 Lasers and Melanocyte Grafting

Surgical approaches are interesting for segmental vitiligo or for localized vitiligo that has been stable for more than 3 years. It is also a useful method for congenital hypomelanosis, such as piebaldism, or for nevus depigmentosus. The preparation of the recipient bed before grafting requires a homogeneous desepidermization. Several clinicians are now using ablative lasers for the easy and rapid desepidermization that those devices allow. Thus, the CO_2 lasers [23, 35] and more recently, the erbium:yttrium aluminum garnet (YAG) lasers [16, 40] followed by epidermal skin grafts or epidermal suspension grafts have been used (Fig. 11.1a–d). Such a method has also been reported to allow a permanent repigmentation in six patients suffering from piebaldism [17].

Recently, dermabrasion with erbium:YAG laser followed by fluoruoracil applications before narrowband (NB) UVB therapy was compared to NB UVB alone in 50 patients with symmetrical patches of vitiligo [1]. Interestingly, a moderate to marked improvement was observed in 78.1% of the lesions treated with the combination protocol as compared with 23.4% of the lesions that have only received phototherapy. Pain and transient hyperpigmentation was reported in the combination group. Those results clearly need to be confirmed, but they suggest an interesting new approach for treating vitiligo.

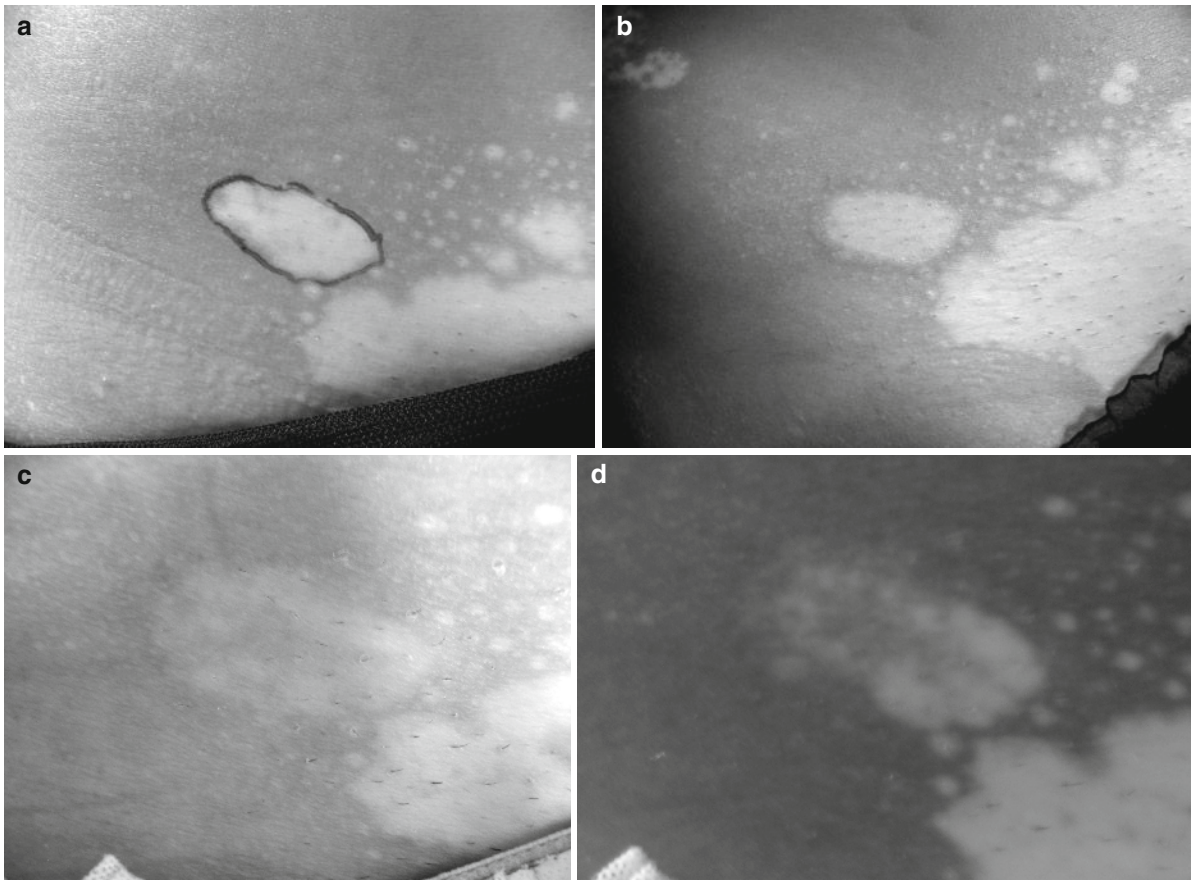

Fig. 11.1 (**a**) Vitiligo lesion of the abdomen before treatment. (**b**) Clinical aspect just after desepidermization with an erbium laser. (**c**) Partial repigmentation 60 days after epidermal suspension grafting. (**d**) Clinical aspect under wood lamp examination at day 60 (Coll. P. Bahadoran)

11.3 Repigmentation of Vitiligo and Disorders of Hypopigmentation with Laser and Light-Emitting Devices

11.3.1 308-nm Excimer Laser and Excimer Lamp

The 308-nm excimer laser and lamp have been used in dermatology since 1997 [3]. These devices emit a wavelength in the UVB spectrum. The monochromatic wavelength at 308 nm provides photobiological effects for those devices that are theoretically superior compared with NB UVB, especially for their immunologic effects. Indeed, 308 nm is the most effective wavelength to induce lesions to the lymphocyte deoxyribonucleic acid and the dose required to induce the apoptosis of lymphocytes is clearly lower with 308 nm compared with NB UVB [5, 7]. However, for vitiligo and more clearly for the other hypopigmentary disorders, the stimulation of the migration and the proliferation of melanocytes seem to have a key role, but no fundamental data are available as yet to compare the respective photobiological propigmenting properties of the 308-nm and NB UVB wavelengths. The use of the 308-nm excimer laser is approved by the US Food and Drug Administration for the treatment of vitiligo.

The clinical efficacy of the 308-nm excimer laser is now well demonstrated [2, 6, 8, 20, 39, 46, 47]. Overall, 20–30% of the treated patches reach a satisfactory aesthetic result, that is, a repigmentation of at least 75%.

Those results appear superior to those usually obtained with NB UVB phototherapy but direct comparison data between NB UVB and 308-nm emitting devices are still very limited. The only available study is methodologically questionable, but it seems to confirm the greater efficacy of 308-nm UVB compared with NB UVB [21]. Sessions can be performed once, twice, or three times a week because the repigmentation rate depends on the total number of sessions and not their frequency [19]. The fluencies used are low and the immediate side effects are limited to erythema and to some rare blisters (especially if sessions are repeated 3 times a week). These devices allow treatment of areas that are usually difficult to reach with UV cabins such as the folds, and they specifically target the affected depigmented patches, preventing hyperpigmentation of the surrounding skin. On the other hand, only relatively small surfaces can be treated and most authors propose the use of those devices for lesions affecting less than 10% of the total surface body area. Localization of the treated lesions seems to be the most important factor that influences the therapeutic response [20, 39, 47]. The results are usually excellent on the face, with more than three-fourths of patients reaching at least 75% repigmentation (see Fig. 11.2a–c). However, the extremities and the bony prominences remain very difficult to treat. The treatment of the other localizations provides interesting results but they are more inconstant than results from treatment of the face and a combination with a topical treatment can bring a useful help (see below). Finally, it is difficult to predict if the repigmentation induced by those treatments will be stable in the long term because most series do not report long-term follow-up. Some authors report no repigmentation after 1 year of follow-up [8]. In our experience, about 15% of the treated patches showed a partial or total repigmentation 2 years after the end of the treatment.

Fig. 11.2 (**a**) Vitiligo of the face before treatment. (**b**) Clinical aspect after 40 sessions of treatment with a 308-nm excimer laser. (**c**) Clinical aspect 18 months after the end of the treatment

The development of the 308-nm excimer lamp is more recent. Unlike lasers, the wavelength is not strictly monochromatic and the beam of light is not coherent and those systems are much less expensive than lasers. The data concerning the treatment of vitiligo with the 308-nm excimer lamps are much more limited compared with excimer lasers, but they seem to provide a comparable rate of repigmentation [4, 30]. We have performed a prospective trial comparing the 308-nm excimer laser and the 308-nm excimer lamp. The results confirm that these two devices are equally effective in repigmenting vitiligo patches [29].

Vitiligo is the only indication for 308-nm excimer lamps and lasers that is supported by controlled studies. However, these devices have shown some potential therapeutic effects in other disorders with hypopigmentation. Two cases of postresurfacing leukoderma have been successfully treated (repigmentation >75%) with 8 and 10 sessions of treatment with a 308-nm excimer laser, respectively [11]. One case of leukoderma after laser tattoo removal with a Q-switched neodymium:YAG laser performed 4 years earlier was successfully repigmented with 40 sessions with a 308-nm excimer laser [18]. In all the cases no side effect was reported. The 308-nm excimer laser was also proposed for the treatment of mature hypopigmented striae [13]. Seventy-five patients were treated. All patients achieved a substantial increase in the darkening of their striae after an average of 8.4 sessions. Clinically evident improvement in the cosmetic appearance of striae due to an increased pigmentation was noted by 80% of patients. The absence of a group of control, the weaknesses in the evaluation of the results, and the need for maintenance sessions should moderate those results. Although a long-term follow-up is necessary, these results are encouraging in a disorder suffering from a dearth of alternative therapies. More recently, the 308-nm excimer laser has been reported to be effective in repigmenting halo nevus [32] and nevus depigmentosus [25]. These data only rely on isolated cases but they suggest interesting new indications in the field of hypopigmentary disorders. The hypomelanotic macules of idiopathic guttate hypomelanosis are associated with chronic sun exposure. Any phototherapy, even focused treatment with the 308-nm excimer laser or lamp, should be avoided. Surprisingly, no laser treatment approach of this very common disorder has been reported so far in the literature. Some isolated successes have been reported with liquid nitrogen or localized superficial dermabrasion treatments. Thus, it could be expected that ablative lasers such as CO_2 or erbium lasers should also be effective, but clinical data are still missing.

11.3.2 Combined Treatment

Topical calcineurin inhibitors such as tacrolimus and pimecrolimus have showed encouraging results in treating vitiligo. However, the best results were achieved in sun-exposed areas, especially on the face [15, 31, 45, 48, 49]. Monotherapy with such drugs for other areas provides disappointing results [38]. Studies have clearly demonstrated that the association of tacrolimus ointment with 308-nm excimer laser treatment increases the rate of repigmentation [24, 42]. In the two published studies, a total of 24 sessions were done and tacrolimus ointment 0.1% was applied twice a day. The results were similar and showed a greater efficiency with the combined treatment compared with the laser alone. Tolerance was good and side effects were limited to constant erythema, sticking, and rare bullous lesions. However, the increased risk of skin cancers promoted by the association of two immunosuppressive treatments cannot be ruled out. Meanwhile, a long term follow-up this association should be reserved to control studies.

The use of topical steroids in combination with phototherapy does not present such a reservation concerning the increased risk of skin cancers. Combining topical steroids with UVA phototherapy has been shown to be more effective than using topical steroids or UVA alone [51]. Recently, the benefit of adding topical steroids to the use of the 308-nm excimer laser was reported in a prospective randomized trial performed with 76 patients with vitiligo on the face and neck [44]. After 12 weeks, 16.6% of patients- in the 308-nm excimer laser monotherapy group achieved at least 75% repigmentation, and patients in the combined therapy group achieved 42.8% repigmentation. ($p = 0.0087$). In our experience, adding highly potent topical steroids daily for the first 3 months of treatment does increase the efficacy of the 308-nm excimer laser in treating vitiligo. However, because the side effects of topical steroids are more pronounced on the face and such localization usually responds well to phototherapy (including therapy with 308-nm excimer devices) or to

topical calcineurin inhibitors in monotherapy, we think that such a combination should be proposed mainly in difficult-to-treat areas such as bony prominences or if the lesions did not respond to a first line of treatment.

Finally, the use of topical vitamin D derivatives now has been demonstrated to be useless monotherapy in the treatment of vitiligo. Its association with UVA or UVB light is still under debate. The association of calcipotriol and the 308-nm excimer laser has been evaluated in a short prospective trial [14]. The results suggest that the adjunction of topical calcipotriol does not increase the efficacy of the 308-nm excimer laser for treating vitiligo.

To the best of our knowledge, combination approaches still have not been reported for disorders with hypopigmentation other than vitiligo.

11.3.3 632.8-nm Helium–Neon Laser

The 632.8-nm helium–neon laser is the first device that does not use the UV spectrum to repigment hypochromic lesions and especially vitiligo. Indeed, this laser emits a wavelength in the red visible-light spectrum has been proven to enhance the proliferation and the differentiation of melanoblasts to mature melanocytes in vitro [28]. It has also been demonstrated that this laser acts on mitochondria to increase the proliferation rate of the cells [22]. These photobiological effects could explain, at least in part, the action of the 632.8-nm helium–neon laser in repigmenting vitiligo. However, clinical data about the efficacy of this device in hypochromic disorders are still very poor. In a prospective study performed on 30 patients with segmental vitiligo, 20% of the lesions achieved a repigmentation of at least 75% [53]. No side effect was reported. However, the total number of sessions to get those results was very high (137 sessions during 2.5 years of treatment). The association of this laser with tacrolimus ointment was recently reported to induce more than 75% of repigmentation after 4–12 weeks of treatment in four patients [27]. Of note, all of the lesions were located on the face, which usually responds very well to tacrolimus alone, and it is difficult to estimate without a control group which was the real effect of the 632.8-nm helium–neon laser. In conclusion, the 632.8-nm helium–neon laser seems to give encouraging results in the treatment of hypochromic disorders (at least vitiligo), but the actual data remain too poor to estimate its true efficacy and further studies are still required.

11.4 Conclusion

Lasers and light-emitting devices have now taken on a key role in the treatment of vitiligo and disorders of hypopigmentation. For vitiligo, they have not replaced topical treatments and conventional phototherapy, but they have clearly improved the rate of repigmentation. Indeed, Q-switched depigmenting lasers allow avoidance of the side effects induced by MEBH for people with residual pigmented spots in the generalized forms of vitiligo. Ablative lasers bring a rapid and reproductive tool to prepare the grafting bed for segmental and localized forms of vitiligo or for inherited hypochromic disorders such as piebaldism. The 308-nm excimer lasers and lamps are clearly the devices that have brought more progress in taking charge of hypochromic disorders. With higher rates of repigmentation compared with conventional phototherapy and with specific targeting of the lesions with sparing of the surrounding skin, their main limitation is the surface being treated. Finally, new wavelengths will certainly be used in the near future to enhance repigmentation. The 632.8-nm helium–neon laser has brought encouraging data that are worthy of further study. It now seems clear that laser technology will bring, in the near future, new and powerful tools to the clinicians to treat hypochromic disorders.

Take Home Pearls

- Note the increasing role of lasers and light-emitting devices in the treatment of vitiligo and other disorders of hypopigmentation.
- 308-nm excimer lamps and lasers have demonstrated their efficacy in the treatment of localized forms of vitiligo. The neck and face are the best localization to treat. Once-daily applications of topical steroids should be added when bony prominences are treated. The results reported on the hands and feet remain too poor to propose such a treatment on those areas.

- Laser -assisted dermabrasion is currently used for preparing the grafting bed of epidermal suspension for the treatment of piebaldism or segmental and stable localized forms of vitiligo.
- Q-switched lasers are very useful for depigmenting the remaining pigmented areas in extended forms of vitiligo and should now be preferred to chemical depigmentation with MEBH.
- Visible light-emitting devices such as the helium–neon laser and the use of ablative lasers combined with topical treatments and phototherapy both seem potentially to be useful, but data are still too limited and further investigations are warranted.

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Precancerous Conditions and Malignant Tumors

12

Christian Raulin, Syrus Karsai, and Laurenz Schmitt

Core Messages

- Lasers can often be used successfully to treat flat precancerous lesions, and photodynamic therapy (PDT) is becoming increasingly important here as well. The role of the laser must be newly and more clearly defined. In certain cases lasers are a good alternative to PDT and to cryotherapy.
- Thicker and/or nodular lesions should be excised by conventional surgical methods in most cases because histological monitoring of the margins is needed and the long-term results are better.
- The decision to use laser systems in the treatment of malignant tumors should be reserved for exceptional cases; it may be indicated when a lesion is inoperable.
- Whenever there is the slightest doubt about the benign or malignant nature of a tumor, a biopsy must be taken and examined to exclude malignancy.
- The occurrence of a precancerous lesion or a malignant tumor demands careful and frequent follow-up observation of the patient in all cases.

There are quite narrow restrictions when laser therapy is planned for precancerous lesions and tumors of the skin. Three factors play a part in the planning:

- The depth of penetration of the lesion.
- The efficacy of the laser procedure.
- The inability to perform a histological examination.

Laser therapy is now being used with good results for precancerous lesions, in situ squamous cell carcinomas, and superficial basal cell carcinomas. By contrast, the laser is not the standard procedure for malignant tumors that have penetrated deep into the skin, and its use should be restricted to exceptional cases. It is indicated, for example, when palliative treatment is needed when cutaneous metastases are present, when a tumor is inoperable, and in multimorbid or elderly patients. In such cases, lesions are coagulated with the carbon dioxide (CO_2) laser or ablated with the neodymium:yttrium aluminum garnet (Nd:YAG) laser. For safety's sake, treatment of this kind must be restricted to experienced specialists because the effectiveness of laser treatment depends heavily on the experience and expertise of the practitioner [4]. In this chapter we discuss a few selected clinical conditions that we believe are now amenable to laser therapy.

12.1 Actinic Cheilitis

Actinic cheilitis is a precancerous condition and is an absolute indication for treatment. Accepted risk factors are genetic predisposition, exposure to ultraviolet (UV) light, tobacco smoking, inadequate hygiene, and mechanical irritation. Circumscribed foci can be treated with several different procedures. In every case a biopsy with a high predictive value must be performed

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_12, © Springer-Verlag Berlin Heidelberg 2011

to confirm the diagnosis so that invasive growth can be ruled out [88]. Both cryotherapy procedures and electrodesiccation are used for superficial lesions. In addition to photodynamic therapy (PDT) [2, 43], vaporization of the lesions with the erbium (Er):YAG laser and ablation with the CO_2 laser are the most effective laser methods currently available [21, 59, 76]. The Er:YAG laser is used less frequently than the CO_2 laser because of the absence of hemostasis and the thermal effect [25, 88]. Smaller actinic cheilitis lesions can be ablated through an outpatient procedure under local anesthetic working in either the continuous or the pulsed mode. Monitored ablation of the outer layers of tissue down to the dermis generally requires several passes [18, 34]. The object of this is complete de-epithelization, which can be recognized by a whitish-yellowish color of the tissue contrasting with the pink of the lips before the treatment [42]. It has also been observed that recurrences are less frequent when the ablation extends beyond the pink area of the lips. Re-epithelization takes between 2 and 4 weeks depending on the intensity of the treatment and the size of the treated area. Overall, the long-term results are very good and cosmetically satisfactory. The recurrence rate is relatively low at 10–12% [18]. When the findings are very pronounced in the case of actinic cheilitis, however, the standard procedure performed is still vermillionectomy followed by a histological examination of the excised tissue with monitoring of surgical margins.

From the cosmetic point of view, the CO_2 laser yields a substantially better result than conventional vermillionectomy or electrodesiccation because it creates fewer scars. In addition, the healing process is often longer after electrodesiccation than after laser treatment [48]. In our experience, cryotherapy is a good alternative, but it entails a higher recurrence rate, especially with deep lesions. Regular and frequent follow-up monitoring is essential after all of the procedures mentioned here (Fig. 12.1).

12.2 Actinic Keratosis

Actinic precancerous lesions are defined as in situ carcinomas, and they occur with greater frequency on the scalp and the facial skin as a field cancerization. The main cause is UV radiation [11]. There are currently two different basic methods of treating the condition: one is a topical treatment and the other is a surgical or physical procedure. In addition to using PDT [1, 23, 79], actinic precancers can be successfully treated particularly with ablative lasers such as CO_2 and Er:YAG lasers [18, 39, 41, 63]. The thermal CO_2 laser is generally preferred to the Er:YAG laser because of its coagulating properties. Alternatives include cryotherapy as well as topical application of diclofenac, 5-fluorouracil, or imiquimod. Especially in the case of smaller, isolated lesions, it is our experience that cryotherapy has the advantage of lower cost while often being more practicable and better tolerated. Results reported by other authors suggest that, to date, superficial ablation of the skin (e.g., laser resurfacing) has not proven worthwhile for patients with field cancerization [77]. In addition, no reliable long-term results obtained in large patient populations are yet available. In cases of extensive lesions and treatment with the CO_2 and Er:YAG lasers, 13–20% of the patients (depending on the author)

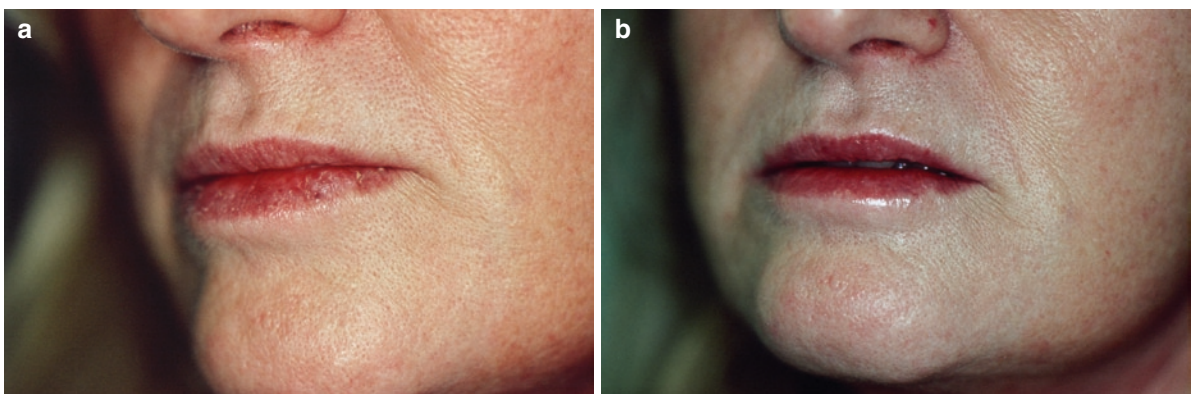

Fig. 12.1 (**a**) Histologically confirmed actinic cheilitis; (**b**) 3 months after a single treatment session with the ultrapulsed carbon dioxide laser [68]

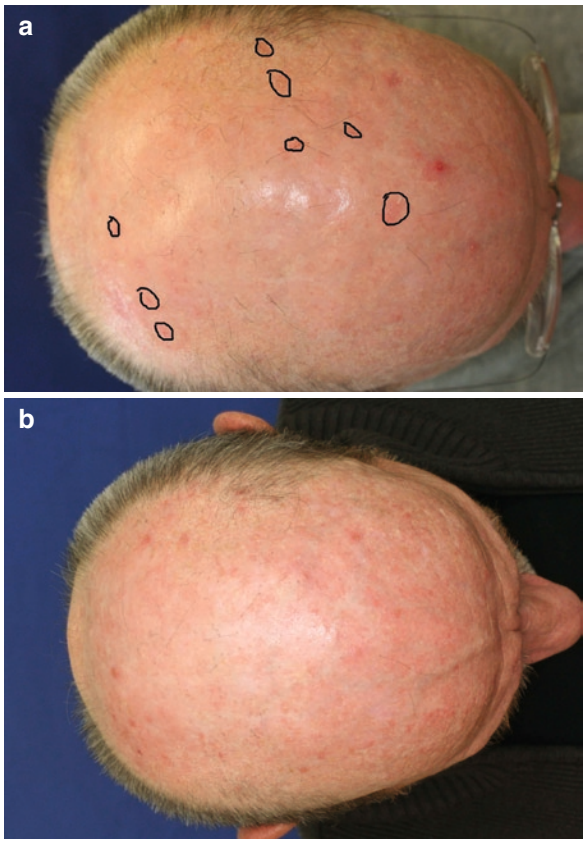

Fig. 12.2 (**a**) Disseminated precancerous actinic lesions (*circled*); (**b**) 2 months after superficial ablation with the ultrapulsed carbon dioxide laser and overall moderate results (the areas are marked). The laser treatment was subsequently followed by cryotherapy, showing that a combined approach might be reasonable and necessary in some cases

experienced a recurrence within an average follow-up period of 1 year [26, 38, 62]. After 2 years this rate rises to 36–42% [38, 62]. This relatively high recurrence rate is perhaps explained by histologically smaller tumor residues, which proved especially problematic [36]. Cosmetically, laser ablation of actinic keratoses has very good results overall. The main source of cosmetic distress is hypopigmentation, which occurs in up to 48% of cases. Scars are seen in a good 8% [62] (Fig. 12.2).

12.3 Basal Cell Carcinoma/ Squamous Cell Carcinoma

Basal cell carcinomas (BCCs) develop from basal cells of the epidermis and grow in a locally infiltrating and destructive manner. Squamous cell carcinomas (SCCs) develop from the acanthocytes of the epidermis. The cause of both of these tumors is often chronic damage to the skin as the result of UV exposure. Before laser therapy, one or more biopsies must always be taken to confirm the diagnoses histologically [8]. The following laser procedures are worth mentioning in these cases:

- Ablative lasers such as CO_2 and Er:YAG
- Thermal lasers such as Nd:YAG
- PDT and similar approaches

12.3.1 Ablative Lasers (CO_2 and Er:YAG)

Ablative techniques such as CO_2 and Er:YAG laser ablation can be used either to vaporize or to excise superficial SCCs and BCCs [46, 47, 71, 90]. Energies of 500 mJ/pulse and 3- to 5-mm spot diameters are applied when the CO_2 laser is used for ablation [36, 38, 58]. In a study conducted by Iyer et al. [38] (23 patients, 61 lesions), the 3-year recurrence rate was 3% after treatment with the pulsed CO_2 laser. Patients with basal cell nevus syndrome can also benefit from treatment with the CO_2 laser if it is intended to prevent further progression of extensive and multiple cancerization [20, 58].

Kroon et al. [45] were also able to achieve good results in treating initial SCC of the penis. From both aesthetic/cosmetic and functional viewpoints, the laser is superior to conventional surgical treatment in early stages.

The limits of laser procedures are inherent in the depth of penetration of the lesion that requires treatment: according to Horlock et al. [35], treatment with the CO_2 laser is advantageous especially for patients with histologically superficial BCC. In addition, the extent of the ablation increases with the practitioner's clinical experience. In a study with 30 lesions (17 BCCs, 13 SCCs in situ), Humphreys et al. [36] also found that superficial lesions responded very well to treatment with the CO_2 laser. In this study an energy density of 500 mJ/cm^2 in two to three passes was used. With increasing thickness of the lesions, there was histologically minimal thermal damage to the underlying tissue, so that after completion of the laser treatment, residual tumor cells were still present.

As of this writing, the laser still has not been accepted as the standard procedure in the therapy of nodular BCC and non in situ SCC. Our experience cannot, therefore,

justify advising the routine use of the laser on larger and nodular lesions, given the myriad alternative treatments and the inability to do histological examinations.

12.3.2 Long-Pulsed Nd:YAG Lasers

Because of its limited penetration of 4–7 mm, the Nd:YAG laser is particularly suitable for the treatment of smaller and flatter tumors [22]. To avoid damaging the surrounding layers of skin, the surface should be adequately cooled during the treatment. Scarring usually forms during healing. Up to now, no large-scale studies designed to determine success rates have been conducted. A study published by Landthaler [47] found a recurrence rate of around 15% and showed good cosmetic results overall for smaller tumors. El-Tonsy et al. [22] used a continuous Nd:YAG laser to treat circumscribed BCC and also achieved a good level of success until the desired effect was attained after a maximum of four treatment sessions. The main effect is ascribed to the laser's thermal properties. During a follow-up period of up to 5 years, recurrences were observed in 2.7% of these cases. Overall, however, the data collected thus far are too insubstantial for us to say that there has been a definitive breakthrough in therapy. There are as yet no studies of large patient populations. On the basis of our own experience, we do not currently advise routine use of this laser.

12.3.2.1 Photodynamic Therapy

PDT is becoming more widely used, especially in the treatment of superficial basaliomas and squamous cell carcinomas of up to 2 mm in depth. This therapeutic approach is only mentioned here in passing; a separate chapter has been dedicated to an extensive discussion because of its growing significance in dermatological treatment (Chap. 28). There have been many reports of treating nodular lesions with a combination therapy of ablative lasers and PDT [75, 90]; recurrence was observed in only 1% of cases during a mean follow-up of 12–18 months. Although this is an interesting and promising therapeutic approach, the lack of long-term data means that it should not yet be regarded as a routine procedure for nodular lesions.

12.3.3 Pulsed Dye Lasers

The results of the pulsed dye laser in treating superficial BCCs have been contradictory so far [3, 12]. According to Campolmi et al. [12, 13] and Shah et al. [73], this laser is certainly a very promising alternative to other techniques. Campolmi reported successful treatment of 16 patients in a study conducted on BCCs of this type in 20 patients with a follow-up period of 1–2 years. In three patients recurrence was observed, and one patient did not respond to treatment. Five treatment sessions were held at 3-week intervals with an energy density of 6.5–7.5 J/cm². The study published by Shah et al. [73] described that, in 91% of cases, smaller BCCs with a diameter less than 1.5 cm showed a complete histologic response to four PDL sessions (595 nm, 15 J/cm², spot diameter 7 mm, no cooling, 10% overlap, pulse duration 3 ms, 1 pass, 2-week intervals). With the same parameters, the pulsed dye laser can also help reduce tumor burden, with a complete response rate of 25% in patients with larger BCCs and a diameter bigger than 1.5 cm. The lack of any published long-term experience and the lack of data available from large patient populations mean that this technique cannot be recommended as standard procedure at the moment. But if these results are confirmed, however, in our eyes the pulsed dye laser can certainly become a very promising alternative to other procedures in the treatment of superficial BCCs, not least because of its favorable side effect profile, the simple and rapid treatment process, and its safety during use (Fig. 12.3).

In all of these cases, the patient must to do careful and frequent follow-up monitoring. Crucial measures here include avoiding further UV exposure and early detection of new lesions.

12.4 Erythroplasia of Queyrat/ Bowen's Disease

Erythroplasia of Queyrat in the genital area and Bowen's disease are counted by definition as forms of carcinoma in situ. Because of their tendency to grow invasively, they should be treated immediately. Known triggers are exposure to UV light and infection with

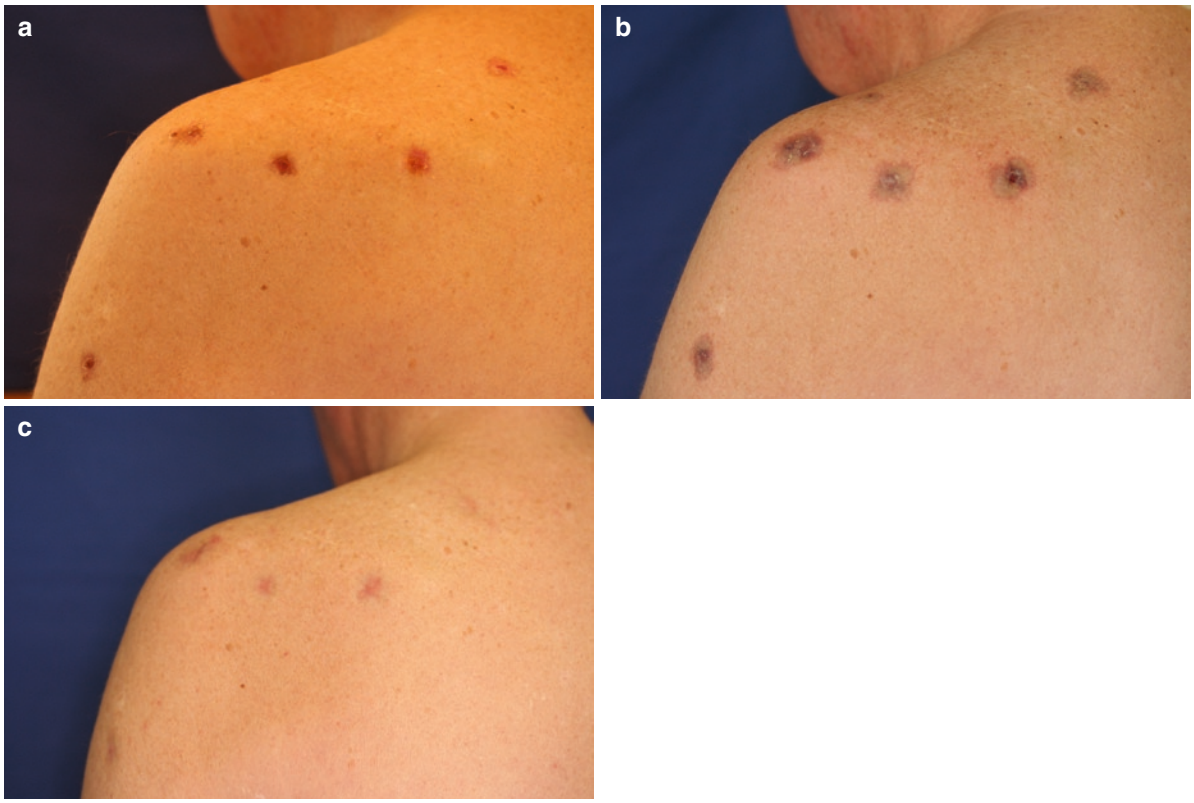

Fig. 12.3 (**a**) A total of five histologically confirmed superficial basal cell carcinomas on the left shoulder and upper arm of a patient on Marcumar; (**b**) immediately after an initial treatment by pulsed dye laser with typical purpura (585 nm, 7–8 J/cm^2, 10 mm, and 0.5 ms without cooling); (**c**) results after four sessions in 3-week intervals

the human papillomavirus types 16 or 18. The standard treatment is micrographically monitored excision, preceded in all cases without exception by a biopsy to confirm the diagnosis and determine the depth of penetration. Alternatives available are curettage, electrodesiccation, cryotherapy, topical application of 5-fluorouracil, imiquimod, PDT, and laser therapy [5, 15–17, 43]. A case report published by Wang et al. [86] also describes a combined treatment with the Er:YAG laser followed by topical application of 5-fluorouracil in one patient. It is not certain whether this procedure will eventually be accepted as standard, because no long-term observations of patient populations are yet available that would allow extrapolation of the results to other patients.

After initial attempts at therapy with the argon laser [10], the pulsed CO_2 laser is now generally used for the treatment of Bowen's syndrome and erythroplasia of Queyrat. Numerous case reports of successful treatment are available [19, 32]. Martinez-Gonzalez et al. [54] describe a lasting success achieved in 85% of their cases after only one treatment session with the CO_2 laser. In 8% of cases there was a later recurrence. A total of 2% of patients did not respond to laser therapy [54]. Vaïsse et al. [82] also report similar results in Bowen's syndrome in one study (eight patients, ten lesions). In a period of almost 3 years there was a single recurrence of one lesion.

To keep the recurrence rate as low as possible, an adequate safety margin must also be created in the healthy tissue when a laser surgical technique is used. Very close follow-up monitoring is necessary, as with all techniques, especially because complete removal of tumor complexes cannot be absolutely guaranteed and there are still no adequate long-term observations on recurrence rates available.

12.5 Lentigo Maligna and Malignant Melanoma

Although the literature has long since reported about laser treatments of lentigo maligna and malignant melanoma [6, 30, 44, 61, 80], laser therapy is ill-advised as a curative treatment according to the current consensus recommendations and guidelines from specialist societies. New advances will emerge, however, because the effect of laser irradiation on molecular mechanisms of melanoma cells remains a subject of research [14].

By contrast, a laser treatment can be useful in palliative treatment [78]. Arndt [6] and Orten et al. [61] each describe the successful treatment of lentigo maligna by means of an argon laser or a Q-switched Nd:YAG laser. Arndt reported a recurrence 4 years after treatment [7]. After treatment with the Nd:YAG laser, Orten et al. had not observed any recurrence during a follow-up period of 42 months. Iyer and Goldman [40] describe a combined approach with the ruby and the alexandrite lasers in an 89-year-old patient, in whom a recurrence was observed after 9 months. That the use of laser technology should be looked at critically when it is considered for lentigo maligna was illustrated by Niiyama [56], who describes lentigo maligna progressing into an invasive lentigo maligna melanoma after therapy with a Q-switched ruby laser.

It must be mentioned in this context that lentigo benigna and the malignant form can pose problems with the differential diagnosis. Lee et al. [49] report two cases in which recurrences developed after laser therapy of seemingly benign lentigines. Histological investigation revealed a lentigo maligna in each of these cases. This example shows that before planning laser treatment the indications must be carefully considered, and in the case of any doubt a histological examination must be performed to exclude malignancy. We are, therefore, of the opinion that laser treatment of lentigines should be carried out only by dermatologists who are experienced working with lasers.

12.6 Oral Leukoplakia

Oral leukoplakia (OL) is one of the most common potentially malignant disorders. The World Health Organization first defined OL as follows: "Leukoplakia is a whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease, and is not associated with any physical or chemical causative agent, except the use of tobacco." This diagnosis is still defined by exclusion of other known white lesions, such as leukoplakias with an infectious origin, candidosis, inflammatory disorders, oral submucous fibrosis, congenital lesions, autoimmune disorders, or carcinomas. The proportion of OL cases that become malignant varies between 0.9% and 17.5% [70]. In most cases leukoplakia can resolve if the etiological factor is avoided [27]. To date, there are still no generally accepted guidelines on the treatment of OL [51]. Although excision of a lesion still seems to be the predominant therapeutic approach performed by the majority of relevant health care professionals, no randomized controlled trials have been undertaken to test the hypothesis that excision (either by scalpel or by laser) greatly influences the potential for later malignant transformation within the oral mucosa [50]. In these circumstances, laser surgery offers the option of precise lesion excision and full histopathological assessment with minimal postoperative morbidity. Before laser therapy is administered, the diagnosis should be confirmed by histological examination to exclude an invasive growth. Complete surgical removal with margins of healthy tissue is recommended for all cases of epithelial dysplasia [52]. If no epithelial dysplasia is present, CO_2 laser surgery, cryosurgery, and PDT [75] are all available options in addition to surgical excision, as is systemic therapy with retinoids and beta carotene. The disadvantages of systemic treatment are the high incidence of side effects and the high recurrence rate after discontinuation of the therapy.

One advantage of treating OL with the CO_2 laser is the minimal small blood loss when the mucous membrane is ablated. Schoelch et al. [72] treated 70 patients with the continuous-mode CO_2 laser or the Nd:YAG laser. The average follow-up period was 32 months (15 of the patients were lost to follow-up). The leukoplakia had been completely ablated in the follow-up group. In 34% of the patients a partial recurrence (less than 5 mm in diameter) was observed, and in 4% a complete recurrence was observed. In 9% of the treated patients SCC developed; the recurrence rate was highest for verrucous leukoplakia, at 83% [72] (Fig. 12.4).

In a study conducted in 78 patients with OL, Hamadah and Thompson [33] were able to show that a procedure using the CO_2 laser led to a disease-free

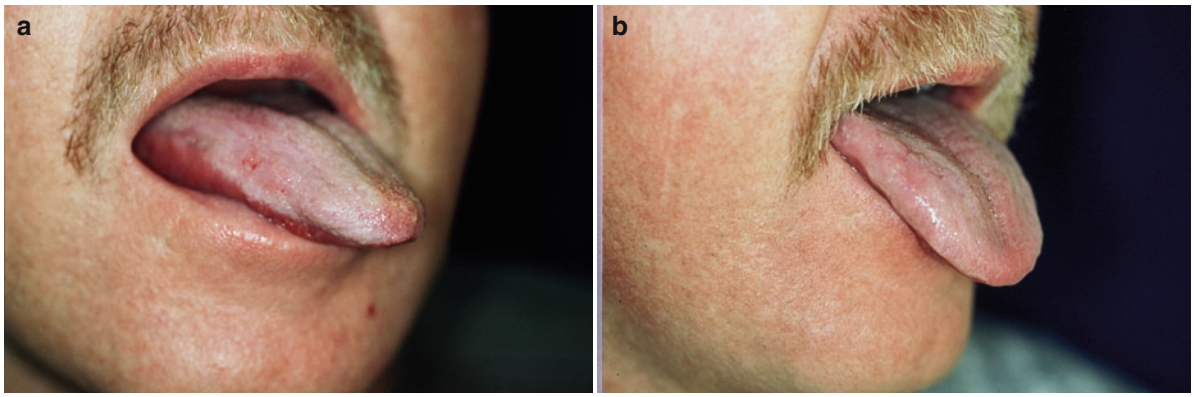

Fig. 12.4 (**a**) Leukoplakia of the tongue; (**b**) 1 month after a single treatment with the carbon dioxide laser [68]

clinical outcome in 64% of these patients during an average follow-up period of around 5 years. After treatment, local recurrent dysplasia or dysplasia at a new site developed in 32% of the patients, and 4% developed an SCC, which, however, also appeared at quite different sites from their initial OL and in untreated sites [33].

Despite successful macroscopic ablation and insistence on a safety margin, laser therapy of OL involves the risk of incomplete ablation of the lesions, and this risk should not be underestimated. Vivek et al. [85] treated 28 patients with histologically confirmed OL with the Nd:YAG laser. During an observation period of 3 years recurrence developed in 7% of the cases. Delayed wound healing was observed in two patients, and in others there was scarring [85]. According to various authors, after a period of several years the recurrence rates for OL after laser therapy are between 8% and 38% [31, 37, 89], whereas an SCC occurred in 1–9% of patients [37, 84]. It must be stated that the frequency of recurrence is usually no lower after a surgical excision. Close monitoring and, if needed, repeated biopsies from the affected sites are therefore essential.

12.7 Paget's Disease

Extramammary Paget's disease is, by definition, an intraepithelial adenocarcinoma that occurs with particularly high frequency in the genitoanal region. There have been several reports of its treatment with the pulsed CO_2 laser [9, 24, 47, 83] and the pulsed Nd:YAG laser [87]. Louis-Sylvestre et al. [53] described recurrence rates of up to 67% after a year after treatment with the pulsed CO_2 laser; these rates can be reduced to 23% (minimum) by combining the laser therapy with extensive surgical excision. In a few cases it proved possible to achieve a disease-free state lasting up to 4.5 years with the combined treatment [24]. For some time, PDT has been used with increasing frequency as an alternative to the laser for treatment of Paget's disease [74].

As of this writing, however, there still have not been any studies about this disease in large patient populations. The application of laser systems to date has been based mostly on case reports. Because there also have been reports of ineffectual treatments with the CO_2 laser, careful consideration must be given to whether laser treatment is indicated, and very close follow-up is an essential part of the therapy [67].

12.8 Parapsoriasis/Mycosis Fungoides

Mycosis fungoides (MF) is a T-cell, non-Hodgkin lymphoma. Goldberg et al. [29] already reported a successful treatment of palmoplantar foci with the pulsed CO_2 laser in 1997. During a follow-up period of 5 years, the patient remained free of recurrence. MF and parapsoriasis are also conditions for which the majority of publications are case reports, most of which record use of the excimer laser in early stages of the disease [28, 29, 55, 57, 65, 66]. This type of laser is used because it is thought that, compared with total-body irradiation with UV light, the selective application of lasers makes it possible to protect healthy skin at the same time. Passeron et al. [65] showed that complete healing of circumscribed plaques

can be attained with a mean of 7–15 sessions and an average of 7 J energy applied per cm^2. These results remained stable for a total of 3 months. Mori et al. [55] were able to confirm this in a study with seven stage 1A lesions. Complete lack of recurrence was reached in 3–28 months. Nicticó et al. [57] achieved this more than a year after treating ten lesions in the same stage; a cumulative energy dose of 6–12 J/cm^2 was applied. In a study with 8 stage 1A or 1B patients, Upjohn et al. [81] showed that after 20 treatment sessions with the excimer laser there was complete clinical and histological remission in 37% of cases, which persisted for at least 30 months. In a further 37% there was an initial clinical and histological remission. However, during the course of follow-up there was a recurrence [81].

PDT has also already been successfully applied in these conditions, although as of now there are no long-term data about recurrence rates [60, 64, 69]. In summary, laser therapy can be a helpful complement to the treatment of MF, especially in its early stages. Long-term results and studies of large patient populations are not yet available (Fig. 12.5).

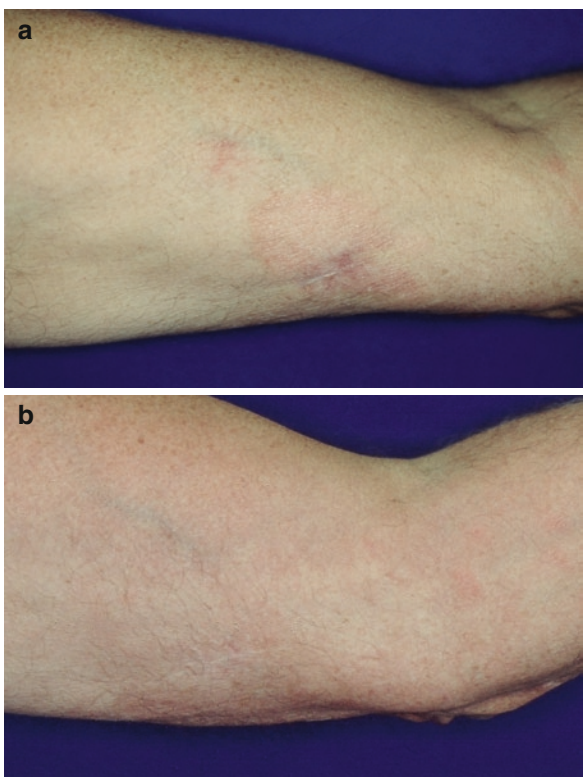

Fig. 12.5 (**a**) Histologically confirmed mycosis fungoides on the upper arm; (**b**) after ten sessions of treatment with the excimer laser

Take Home Pearls

- Reliable diagnoses and the ablation of precancerous lesions with laser systems both demand a great deal of experience from practitioners and should, therefore, be confined, for the moment, exclusively to selected centers.
- Depending on the findings, a combination treatment (e.g., laser plus PDT, laser plus surgical intervention) may be justified.
- In cases of precancerous lesions and malignant tumors, close follow-up monitoring is essential after laser treatment as well as after the alternative methods so that any recurrence or new lesions can be diagnosed early.
- The pulsed dye laser may develop into an outstanding therapeutic option for treating superficial basalioma.
- Malignant tumors or metastases should only be treated with lasers in exceptional cases. The decision to use laser therapy in these circumstances is an individual one and should be made under controlled conditions.
- Prospective multicenter studies are needed to evaluate laser treatment of actinic precancerous lesions relative to other techniques.

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Scars, Keloids, and Stretch Marks

13

Hilda Justiniano, Andrea Willey, and Suzanne L. Kilmer

Core Messages

- Large controlled studies are needed to comprehensively evaluate current laser modalities and treatment protocols.
- Characterization of the scar subtype is essential for selection of appropriate laser modalities and treatment parameters.
- Both ablative and nonablative lasers targeting vessels within scar tissue or water surrounding collagen can improve the appearance of scars.
- Fractional resurfacing modalities that allow for deep penetration of light and sparing of normal tissue show great promise for the treatment of a variety of scar types.
- Although the ideal time of intervention has not been elucidated, early initiation of laser treatments for scars is advantageous in most circumstances.
- Future advances are aimed at the use of lasers to stimulate tissue regeneration and prevent scar formation in addition to treating scars.

13.1 Introduction

Scars are a common concern among a dermatologist's patient population. Although a great number of therapies exist for the treatment of scars, there exists a lack of large controlled studies to examine currently available and newly emerging strategies to standardize scar treatment protocols [32]. Currently available therapies include topical and intralesional corticosteroid injections, intralesional 5-fluorouracil (5-FU) or bleomycin, silicone gel sheets, pressure therapy, cryotherapy, radiation, surgery, and laser treatments. Other strategies, including the use of transforming growth factor-β, COX-2 inhibitors and other nonsteroidal anti-inflammatory agents, collagen synthesis inhibitors, angiotensin-converting enzyme inhibitors, minocycline, and gene therapy, are still under study. The ideal scar treatment would address both the mechanism of abnormal scar formation and the mechanical and physical properties of the resulting scar itself [32]. Future therapies aim to achieve regeneration of normal skin rather than scar formation after tissue injury.

Advances in laser technology have led to progress in the treatment of many skin conditions; scars are not an exception. Most recent advances explore the use of lasers in the prevention of scar formation. Once formed, a number of lasers may be used in the treatment of scars. However, it is important that the scar to be treated be adequately characterized so that the most appropriate laser treatment may be chosen [8].

In this chapter we will address the use of lasers in the scar revision process and potential strategies to minimize scar formation. The chapter will be arranged according to the type of scar being treated, with the emphasis on newer techniques and emerging technologies. Treatment of acne scars is discussed elsewhere in this book.

13.2 Types of Scars

13.2.1 Hypertrophic and Keloid Scars

Hypertrophic scars and keloids are a common problem; the latter are especially prevalent in people of African,

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_13, © Springer-Verlag Berlin Heidelberg 2011

Hispanic, or Asian descent. Although both hypertrophic scars and keloids are clinically indurated and characterized by abundant deposition of collagen and glycoproteins, they differ in several clinical and histologic aspects. Clinically, hypertrophic scars are generally white to pink scars that remain within the borders of the original wound. These generally occur within 1 month of the injury and tend to improve over time. In contrast, keloids are usually deep red to purple in color, extend beyond the original wound, and, once present, do not usually regress spontaneously. In fact, keloids tend to recur after excision. Histologically, both are characterized by increased collagen deposition; however, their differences lie in the organization of collagen fibers and deposition of mucoid matrix. Keloids are composed of disorganized, thick, collagen fibers with a prominent mucoid matrix. Hypertrophic scars contain more organized collagen fibers within a scant mucoid matrix.

13.2.1.1 Laser Treatment of Hypertrophic Scars

Hypertrophic scars and keloids can be difficult to treat. As stated above, hypertrophic scars, if left alone, tend to improve with time. However, to hasten their improvement, numerous treatments have been used. Similar treatments have been used to treat keloids, but with limited results. These include topical and intralesional corticosteroids, 5-FU, imiquimod, cryosurgery, radiation therapy, pressure therapy, retinoic acid, and the application of silicone creams or gels, among others [6, 11, 12, 17, 31, 41]. Many of these provide unreliable results and may be associated with complications such as tissue atrophy and hypopigmentation.

Since the 1980s, lasers have been used to treat hypertrophic scars and keloids. The first lasers used for this purpose were continuous wave carbon dioxide (CO_2) and argon lasers that poorly confined thermal injury within the targeted tissue. These lasers were often not effective in the treatment of keloids and high recurrence rates were observed after treatment of hypertrophic scars. More promising results were obtained when using pulsed dye lasers (PDLs) with variable pulse durations and cryogen spray cooling that allowed for spatial selectivity of thermal effects. The PDL has since become the laser of choice for the treatment of hypertrophic scars and keloids because it has been shown to improve scar texture, size, redness, and pliability [2] (Fig. 13.1). These improvements are thought to be the result of collagen remodeling within the scar, which results from coagulation necrosis induced by hypoperfusion of tissue.

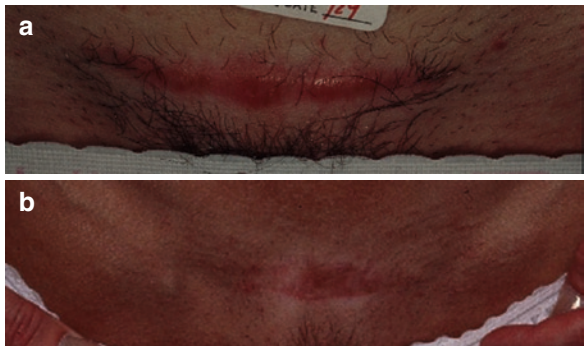

Fig. 13.1 Hypertrophic scar (**a**) 1 month after (**b**) one treatment with pulsed dye laser

Most hypertrophic scars have an average of 50–80% improvement after two laser treatments. Keloids, however, usually require more treatments and/or other ancillary treatments, including surgical excision, to achieve acceptable results. This can be explained by the histologic differences between these lesions, where keloids have a much less vascular base, thus explaining their increased resistance to PDL-induced coagulation necrosis. Intralesional corticosteroids, 5-FU, and hydroquinone can be useful adjunctive therapies to laser treatments. One recent study demonstrated improvement in symptoms only with the addition of intralesional corticosteroids to laser treatment with a 585-nm PDL [4].

When using the PDL to treat scars, energy densities range from 6.0 to 7.5 J/cm^2 (5- to 7-mm spot size) and from 4.5–5.5 J/cm^2 (10-mm spot size). [26]. When treating patients with darker skin these should be reduced by 10% for the initial treatment. If the desired response is not obtained at these fluences, energy may be increased by 10% for subsequent treatments. However, if crusting, blistering, or oozing occurs, the fluence must be decreased for later treatments. Treatment should be delivered over the entire scar with adjacent, nonoverlapping pulses. The patient will experience a sensation similar to a snapping rubber band over the skin along with transient mild burning for 15–30 min, which may be improved by the application of cold packs. Subsequent treatments may be needed and should be done in the same manner, adjusting the fluences as described above.

Nonablative fractional photothermolysis with near infrared 1,540- and 1,550-nm erbium-doped fiber lasers is a promising new modality for the treatment of hypertrophic scars. Studies evaluating efficacy of the treatment of hypertrophic and burn scars using fractional technology are beginning to emerge in the literature. One small series demonstrated significant improvement after two to three treatments, with improvement in pigmentation in all eight hypertrophic scars evaluated [28]. A single randomized, controlled trial evaluating 17 burn scars (five with meshed split-thickness skin grafting) using a 1,540-nm nonablative fractional laser (Starlux, Palomar Medical Technologies, Burlington, Mass., USA) demonstrated significant textural improvement after three treatments. There were some adverse events and no improvement in pigmentation [20].

Even more recently, ablative fractional resurfacing lasers have been used in the treatment of hypertrophic scars and will likely be explored as mechanisms of drug delivery to improve outcomes in future. A single case report recently demonstrated marked improvement in a meshed split grafted burn scar after a single treatment with ablative fractional CO_2 laser. [19].

13.2.2 Atrophic Scars

Atrophic scars are depressions in the skin that commonly occur after an inflammatory process such as acne or varicella, traumatic skin insults, and surgical incisions. Atrophic scars are initially erythematous and with time become increasingly fibrotic and hypopigmented. It is believed that atrophic scars result from inflammatory destruction of collagen with resultant dermal atrophy. Various modalities have been used to treat atrophic scars. Subcision, dermal fillers, and dermabrasion were among the preferred treatments of atrophic scars in the past. Nowadays, lasers have become the mainstay of atrophic scar treatments.

13.2.2.1 Laser Treatment of Atrophic Scars

The treatment of atrophic scars with lasers include ablative lasers, which ablate water-containing tissue, nonablative lasers that target water surrounding collagen beneath the epidermis, ablative and nonablative fractional modalities, and PDLs that target vascular components of atrophic scars (Fig. 13.2). The results obtained with traditional ablative devices have been superior to those with nonablative devices, yet are also accompanied by longer downtimes and a greater risk of complications. In recent years, trends have been shifting towards the use of fractional devices, both ablative and nonablative. These newer devices permit the use of much higher fluences, permit deeper penetration, and diminish the risk of complications.

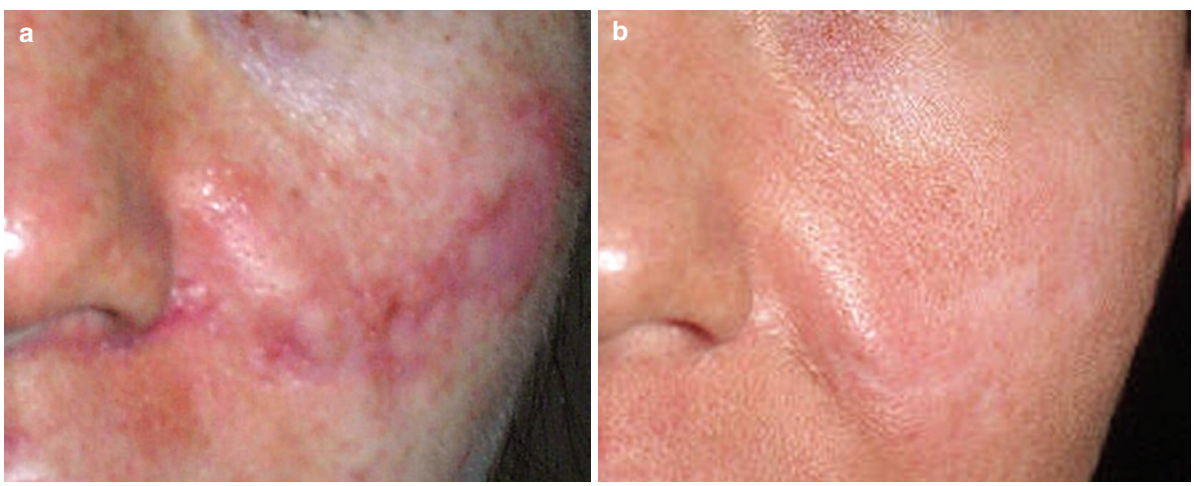

Fig. 13.2 Hypertrophic scar after a motor vehicle accident before (**a**) and after (**b**) treatment with a pulsed dye laser of the hypertrophic scars and ablative erbium and carbon dioxide laser resurfacing to the entire face

13.2.3 Nonablative Treatment of Atrophic Scars

Even though nonablative lasers do not achieve the clinical improvement that can be achieved with ablative treatments, a series of ablative lasers can effectively improve the appearance of scars with minimal side effects. A number of nonablative devices have been used in the treatment of atrophic scars. The most popular nonablative devices include the 1,320-nm neodymium:yttrium aluminum garnet (Nd:YAG) and the 1,450-nm diode lasers; more recently, the 1,064-nm Nd:YAG laser has also been proven effective [24]. These near-infrared systems selectively target water-containing tissue so that, when combined with epidermal surface cooling, they can cause thermal injury in the dermis without causing damage to the epidermis. Although the exact mechanism by which these devices induce collagen formation in the dermis is not understood, when using the Nd:YAG for its traditional uses of hair removal and leg veins, homogenization of superficial collagen has been observed [15]. Some believe that it is possible that the absorption of the 1,064-nm wavelength by the blood vessels in the scar may lead to either conduction to the surrounding dermis to alter the fibrotic collagen within the scar or to significant ischemia within the laser-treated tissue to affect collagen or release collagenase [24].

Although protocols vary, treatments are generally performed at monthly intervals for three consecutive months. Best results are observable 3–4 months after the last treatment. Using this protocol, improvements of 40–50% may be obtained using the 1,320-nm Nd:YAG or the 1,450-nm diode [37]. The results of the nonablative resurfacing depend on the patient's own wound-healing capacities and, as stated before, will not equal those obtainable with ablative treatments. Thus, it is very important to identify patients most suited for nonablative procedures prior to treatment to ensure the best possible patient satisfaction.

In our experience the use of nonablative fractional lasers provides superior results compared to those provided by PDLs. We have treated scars that have improved minimally with a PDL and then had significant improvement with fractional erbium lasers (Fig. 13.3).

13.2.4 Ablative Treatment of Atrophic Scars

CO_2 and erbium (Er):YAG lasers have been the gold standard in the treatment of atrophic scars during the past decade [3, 9]. The CO_2 laser has been studied most often for this purpose. It is highly effective for

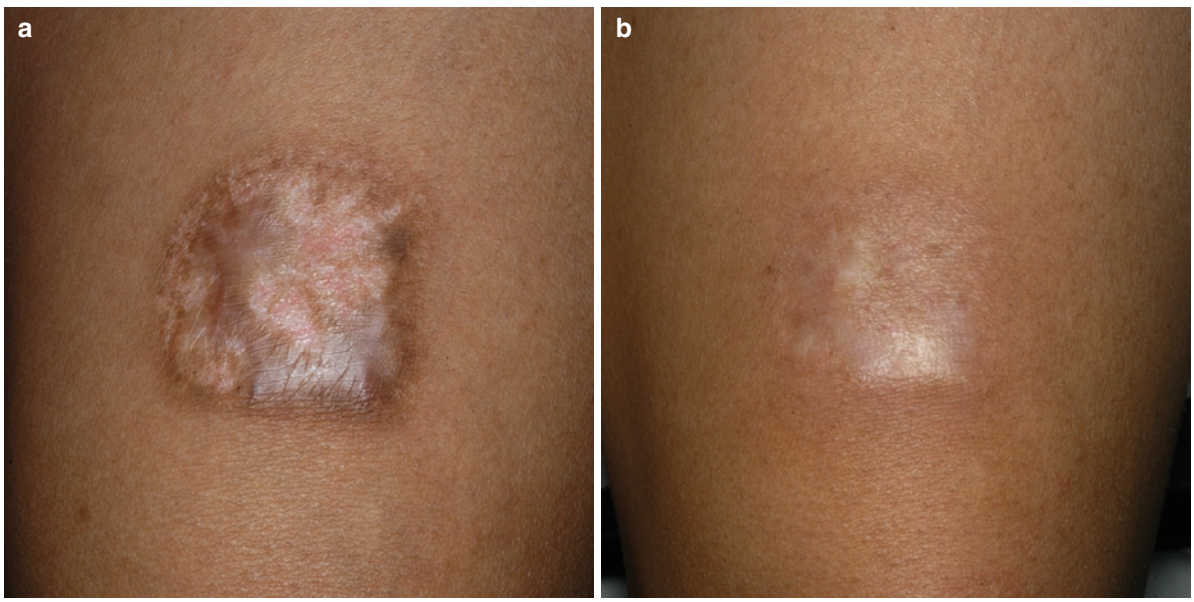

Fig. 13.3 Atrophic, hyperpigmented, and hypopigmented burn scar on the anterior lower leg (**a**) after multiple V-beam treatments and then (**b**) after ten fractional erbium laser treatments

moderate to deep atrophic scars, which often improve 50–80% [5, 13]. Comparison of the healing time and complication profiles between single-pass CO_2 or multiple-pass long-pulsed Er:YAG laser techniques found that, although time to re-epithelialization was similar between the two, postoperative erythema was prolonged in the CO_2-treated group [36].

Both of these modern laser systems emit high energy densities within short pulses that result in tissue vaporization with limited thermal conduction to nontargeted surrounding skin. The depth of tissue ablation and the degree of residual thermal necrosis produced by the CO_2 is directly proportional to the pulse energy and the number of passes used. This allows the operator to individualize lesional treatment by selecting parameters to remove only the amount of tissue needed in a controlled fashion. Pulsed Er:YAG lasers are 10 times more absorptive for water-containing tissue compared to CO_2 lasers; thus, ablative erbium lasers result in greater tissue vaporization and reduced residual thermal damage. The increased residual thermal damage produced by the CO_2 laser in the dermis produces collagen shrinkage that clinically tightens the skin and increases collagen remodeling. Because the Er:YAG produces less residual thermal damage, the effect it has in collagen remodeling is also decreased. Thus, ablative Er:YAG lasers may be the preferred treatment for mildly atrophic scars, whereas ablative CO_2 lasers may be preferable for more extensive scarring. Nonetheless, the results achievable with the Er:YAG may be more comparable to the CO_2 by increasing the aggressiveness of treatment parameters [34].

13.2.5 Fractional Laser Treatment of Atrophic Scars

Fractional photothermolysis has been introduced in recent years for the treatment of photoaging to meet the need for more noticeable clinical results than those achieved with nonablative systems, but with less complication risk and downtime than the ablative devices. These systems, which may be ablative or nonablative, use laser energy to create microscopic, noncontiguous columns of thermal injury in the skin surrounded by zones of viable tissue. Several systems are available, with both ablative and nonablative wavelengths. However, the most commonly employed systems are the 1,550-nm, erbium-doped fiber nonablative fractional laser and the fractional CO_2 for ablative systems.

For the treatment of atrophic scars, the 1,550-nm erbium-doped fiber laser (Fraxel, Reliant Technologies, Mountain View, Calif., USA) has been the most tested in its category. Alster et al. [9] found that, with several treatments, this device improved the appearance of scars by 51–75% in patients with skin types I–V. Laser treatments were well tolerated and side effects were minimal and limited to mild erythema, edema, and skin dryness, all of which resolved within 1 week. In their study, only one patient (skin type V) developed transient postinflammatory hyperpigmentation. Anecdotally, other nonablative fractional erbium devices achieve similar clinical results.

Another study demonstrated greater improvement in overall appearance and redness of surgical scars after treatment with a 1,550-nm nonablative fractional laser (Reliant Technologies) compared to a 595-nm V-Beam PDL (Candela Corporation, Inc., Wayland, Mass, USA) [38]. However, in practice, the combination of both laser technologies is likely superior to either one alone.

We have used both ablative and nonablative fractionated lasers in our practice and are impressed with their greater ability to improve scars. Both textural and pigmentary changes can resolve with these systems (Fig. 13.4). Most remarkable is the dramatic improvement in hypopigmentation and even depigmentation because this has been difficult to treat with any of the earlier devices. In addition, their ability to improve elevated as well as depressed scars is significantly better than that of previous modalities, in our experience.

13.2.6 Striae Distensae

Striae distensae or stretch marks are a common skin abnormality affecting both sexes and all races. These lesions usually evolve through various stages. In the acute stage, striae appear red or violaceous and are referred to as striae rubra. During this stage, they may be raised and often irritated. In the final chronic stage, striae become white, atrophied, and depressed. At this stage they are referred to as striae alba [40].

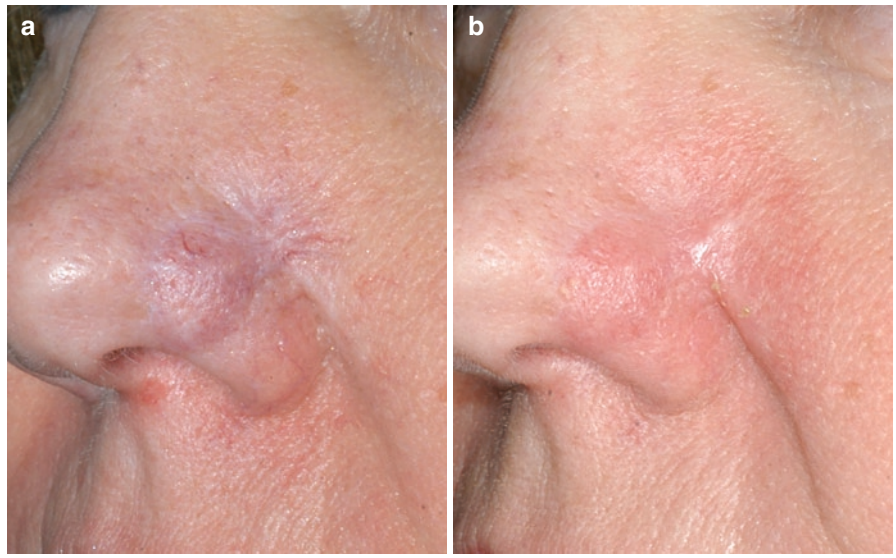

Fig. 13.4 Scar after Mohs reconstruction before (**a**) and after (**b**) single fractional carbon dioxide laser treatment

13.2.6.1 Laser Treatment of Striae Distensae

Although striae are a common cause of concern, highly effective, low-risk treatment modalities are lacking. These lesions are notoriously hard to treat. Many treatments have been tried and tested. Topical treatment with tretinoin cream 0.05%, L-ascorbic acid, and 20% glycolic acid have been shown to improve the clinical appearance of striae alba, and tretinoin 0.1% cream has been proven to improve the redness as well as length/width of striae rubra [10, 23]. However, none of these treatments have been proven to increase collagen or elastin production within the lesions. Ultraviolet (UV) B phototherapy has been used to improve the hypopigmentation observed in striae alba, but it does not correct the lesion's atrophy [1]. Intense pulsed light sources have also been used; however, hyperpigmentation tends to occur frequently with this treatment modality [21].

Laser treatment of striae has gained considerable popularity in recent years. Numerous systems and wavelengths have been used, although, in general, treatment outcomes depend on the characteristics of the striae, with newer lesions responding much better than old ones.

The first lasers that were used in the treatment of striae were continuous wave CO_2 and argon lasers. However, their use was associated with numerous complications. Thus, today 585- and 595-nm PDLs have been the most commonly used for the treatment of striae. PDLs have been used to improve redness in striae rubra. However, striae alba did not show significant change after treatment [22]. Even though the PDL has been shown to increase the numbers of collagen and elastin fibers in sun-damaged skin, no significant increase was observed after treatment in striae [22, 39]. Nonetheless, the PDL remains an important instrument in the treatment of striae that are still pink or red in patients with skin phototypes I–IV. Care must be taken when treating patients with higher skin phototypes, even with lower fluences, because hyperpigmentation is a common occurrence among these patients [29]. When treating striae, lower fluences are preferred, with parameters ranging from 7- to 10-mm spot sizes and fluences ranging from 2 to 4 J/cm^2. One or two treatment sessions are usually necessary to achieve the desired response.

More recently, the fractional devices have gained popularity in the treatment of striae alba and striae rubra. In particular, the 1,550-nm, erbium-doped fiber laser has been shown to improve texture and dyschromia in both striae alba and striae rubra in patients with skin types I–IV [25] and in Asian skin [25, 35]. Fractional photothermolysis creates multiple noncontiguous zones of thermal damage in the epidermis and dermis, sparing the tissue surrounding the wound. This

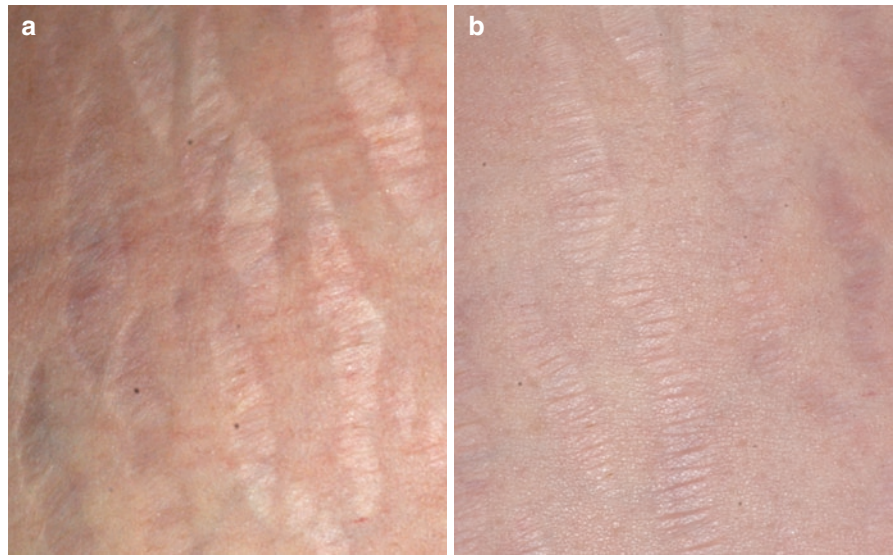

Fig. 13.5 Striae distensae (**a**) 6 months after a single treatment (**b**) with an ablative fractional carbon dioxide laser

in turn stimulates epidermal turnover and dermal collagen remodeling, which results in improvement of a variety of scar types. Although the results observed in these studies were moderate, the 1,550-nm wavelength targets water as a chromophore, and is thus a safe alternative for patients with darker skin types. Further studies are needed to determine the optimal treatment parameters with this device for this application. Even more recently, ablative fractional devices have been used to treat striae distensae with promising results (Fig. 13.5).

13.2.7 Preoperative Patient Evaluation

A patient's suitability for laser scar revision depends on several patient and scar variables. The mechanism by which the scar occurred, its duration, progression, as well as prior treatment will help determine which therapy is more appropriate [26].

13.2.7.1 Timing of Scar Treatment

In general, younger scars respond better to treatment [27]. Younger scars tend to be erythematous, which makes them ideal targets for the 595-nm PDL treatments. In fact, Nouri et al. [30] showed a 54% improvement in surgical scars treated with a PDL at the time of suture removal compared with only a 10% improvement in untreated lesions. Nonetheless, not all scars need to be treated early because many will improve on their own during the first year. This does not apply to scars that are worsening or in patients with a known tendency to form keloids or hypertrophic scars. For these patients, early intervention is highly encouraged.

More recently, the concept of prevention of scar formation using lasers at the time of skin surgery has been explored using the 810-nm diode laser on truncal incisions. Though little difference was observed at early follow-up, remarkable differences at 1 year were observed, suggesting that early thermal injury of skin at the time of surgery may favorably change the basic physiology of wound healing [14]. Additional laser and light sources are likely to be investigated in the future.

13.2.7.2 Prior Treatments

Prior to treatment it is important to know if the scar has been treated before. Previous unsuccessful treatments may have resulted in increased underlying fibrosis. For example, treatment with phenol peels will result in an enlarged papillary dermis, which may decrease the penetration of lasers into the lesion. Also, dermabrasion may increase the bulk of scar tissue, thus making

the scar more resistant to treatment. However, prior treatment with intralesional corticosteroid or 5-FU may actually help achieve the final result faster. This is especially true for thick hypertrophic scars or keloids.

Furthermore, a history of the use of dermal fillers in the area to be treated is important. Studies have been done to determine the effect of different laser devices on skin previously treated with hyaluronic acid fillers [16, 18]. Although the injected material was unaffected by the nonablative laser and intense pulsed light treatments, deeper laser treatments did demonstrate laser-filler interaction. The effect of this interaction is not yet known. Also, newer ablative and nonablative fractional lasers have the ability to penetrate deep into the dermis and, again, the effects this may have on the fillers is not yet known. Further, no studies have evaluated the effects of lasers on other commonly used dermal fillers. Thus, care must be taken when planning to use lasers in combination with soft tissue fillers for the treatment of scars.

13.2.7.3 Skin Phototype and Ethnic Background

Prior to laser treatment it is important to assess the patient's ethnic background. This is important because not only are certain populations at a higher risk for keloid and hypertrophic scar formation, but ethnic background will also help assess the amount of epidermal pigment present, which will in turn affect laser outcomes. Approximately 4.5–16% of African-American and Hispanic populations are prone to keloid formation. Whites are much less susceptible [6, 7]. Patients with darker skin phototypes have more epidermal pigment which would also absorb 595-nm PDL light intended to target skin hemoglobin, thus resulting in increased risk of side effects and complications. Traditionally, laser treatments have been based on the patient's Fitzpatrick skin phototype, which only accounts for the patient's response to UV light. More recently the Roberts Skin Type Classification System has been introduced [33]. This is a four-part serial system that not only identifies a patient's skin type characteristics but also provides data to help predict the skin's likely response to insult, injury, and inflammation. Although a thorough description of this system is beyond the scope of this text, the Roberts Skin Type Classification System may help the laser operator determine the most adequate device and parameters for each individual.

13.2.7.4 Medical History

It is important to obtain a history of any infectious or inflammatory process. History of herpes simplex virus should prompt prophylactic treatment if treating near the affected area. Patients with active infectious processes should wait until the process resolves prior to treatment because it is possible that the procedure may cause the process to koebnerize and result in complications or scarring. It is also important to warn the patient that the lasers may cause or exacerbate inflammatory conditions such as acne, psoriasis, and dermatitis. Of these, acneiform eruptions are the most common but luckily are usually treated effectively with oral antibiotics. If the patient is at high risk for acne breakouts, prophylactic antibiotic treatment prior to laser irradiation is a feasible option. Patients with a history of acne with acne scarring are likely to give a history of previous Accutane (isotretinoin) treatment. It is common practice to wait at least 6 months after termination of treatment with Accutane before laser irradiation due to the increased chance of hypertrophic scarring while taking this drug.

13.2.7.5 Patient Expectations

It is also of outmost importance to discuss the patient's expectations prior to initiating treatment. Laser treatment of scars will not eliminate the scar; it will improve its appearance to a different degree in every patient. The patient should understand that several treatments may be required and that resulting improvements take time to achieve.

13.2.8 Posttreatment Care

Care after laser treatment will vary depending on the laser system used. However, with all systems sun protection is very important. Exposure to sun before or between sessions or after treatments may increase the chance of postinflammatory hyperpigmentation.

Patient compliance is important and a noncompliant patient is not a good candidate for laser treatment.

13.2.8.1 After PDL or Nd:YAG Treatment

Immediately after PDL treatment the patient may feel a burning sensation that should resolve when treatment is finished. Swelling of the treated area may occur but it generally subsides within 48 h. The most commonly experienced side effect with this treatment is postoperative purpura that usually resolves within 10 days. After treatment, the patient is instructed to cleanse the treated area gently with a mild soap. If any crusting or vesiculation occurs after treatment, parameters should be decreased during subsequent visits. In this case, the patient is ordered not to remove the blister roof or scab and to apply a petrolatum-based ointment (Vaseline or Aquaphor) to the affected area until it is healed. If hyperpigmentation occurs, further treatments should be delayed until it resolves. Topical bleaching creams may help hasten this process.

13.2.8.2 After Nonablative Fractional Resurfacing Treatments

After treatment the patient may feel warmth over the treated area that may be diminished with the application of cold compresses or chilled air blown over the area. The area should be cleansed with a mild soap and a moisturizer with sunblock should be applied over the treated area. The nonablative fractional devices will cause marked swelling of underlying tissue. The swelling will be most prominent a few hours after treatment and usually subsides within 48 h. After this, the patient will experience mild erythema that usually lasts 5–7 days. During this phase of erythema, the patient is instructed to wash the area with a mild soap and to apply an ointment-based moisturizer as needed (usually 2–3 times a day). Makeup can be applied over the area beginning on the day after treatment.

13.2.8.3 After Ablative Treatments

Posttreatment care is of the utmost importance when using ablative devices. With these systems the epidermis, the natural skin barrier, is removed, thus making the skin more susceptible to infections and scarring. No matter what device is used, ablative laser treatments can be quite painful during as well as after treatment. The treated skin will be erythematous, edematous, and, in the case of fractional CO_2 treatments, bloody and oozy. After the treatment is completed, topical ointments, semiocclusive dressings, or cooling masks may be applied to help minimize postoperative discomfort. The first week is critical for correct wound healing; thus, patients should be evaluated during this time. During this week, patients are instructed to perform diluted vinegar soaks (one teaspoon of vinegar in two cups of water) every 2–3 h for 2 days, then 2–3 times a day. These soaks are not only antibacterial, but the mild abrasion caused by the gauze in contact with the skin helps remove any debris on the skin without excessively traumatizing the treated area. The soaks should always be followed by application of topical petrolatum-based ointments to maintain skin moisture at all times.

Erythema after treatment is expected. However, with ablative CO_2 and Er:YAG treatments it can be quite persistent, lasting 3–4 months on average with CO_2 treatments and 4–6 weeks after Er:YAG treatments. With fractional CO_2 treatments, this posttreatment erythema duration depends on the intensity of treatment but is, in general, much shorter than with traditional ablative treatments, usually resolving within 3–4 weeks.

Ablative laser treatments have higher risk for complications including hyperpigmentation, delayed hypopigmentation, infectious processes, and scarring. However, with the use of the newer fractional devices, this complication profile has improved considerably. The viable skin, left between the microthermal zones of damage, allows for much faster healing re-epithelialization and an intact skin barrier. Although prophylactic antibiotics and antivirals are still recommended for high-risk patients, the degree of scarring and postinflammatory hyperpigmentation or hypopigmentation has been reduced notably.

13.2.9 Summary

With the advancements in laser technology, the treatment of scars has progressed significantly during the

past decade. The fractional laser devices most recently available will continue to dramatically improve our efficacy for the treatment of scars over nonablative lasers, with less wound care and downtime than with ablative lasers. As our understanding and knowledge of these devices evolves, so should our ability to resolve scars and perhaps further minimize the original scar formation. Adjunctive therapies and appropriate wound care will further facilitate scar resolution.

Take Home Pearls

- Both ablative and nonablative lasers that target vascular structures in scars and water surrounding tissue collagen can be helpful in improving the appearance of scars.
- Newer ablative and nonablative fractional laser treatments are promising modalities for the treatment and prevention of scars.
- Early initiation of laser treatments is advantageous in most circumstances.
- Diligent pre operative and postoperative care is essential for optimal wound healing and avoidance of adverse events, especially for treatments involving lesions on the trunk and extremities.

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Laser Treatment of Tattoos and Other Dyschromia

14

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Core Messages

- Q-switched lasers (alexandrite, neodymium: yttrium aluminum garnet, and ruby lasers) can successfully remove tattoos with few adverse effects.
- Removing professional tattoos usually entails 20–25 treatment sessions at intervals of 4–6 weeks. Residual pigment may remain, especially when multicoloured tattoos are involved.
- Amateur tattoos and traumatic tattoos are usually easier to treat (5–10 sessions).
- Drug-induced hyperpigmentation is fairly common and tends to respond well to treatment with Q-switched lasers (the exception is chrysiasis).
- Frequent adverse effects are changes in pigmentation (particularly hypopigmentation), shifts in tattoo colour, and changes in skin texture; the latter two are usually temporary. Scarring is possible but rare when treatment is performed correctly.

14.1 Introduction

Dyschromia is defined as a discolouration of the skin due to deposits of pigments, which do not contain melanin [20]. The pigments in question may be endogenous or foreign and have made their way into the skin percutaneously or systemically. In dermatologic and aesthetic laser medicine, removing decorative and traumatic tattoos is an issue unto itself. Such tattoos are treated using pigment-specific Q-switched laser systems such as ruby (694 nm), neodymium:yttrium aluminum garnet (Nd:YAG) (532/1,064 nm) and alexandrite lasers (755 nm). These devices are in widespread use across the globe; beyond that, in the Anglo-American world, it is a common practise to work with the 510-nm pigmented lesion dye laser. In the meantime, numerous treatment outcomes have also been published about drug-induced dyschromia, especially cases caused by amalgam, amiodarone, doxorubicin, gold, iron, or minocycline.

14.2 Decorative Tattoos

14.2.1 Historical Background

In October 1991, hikers in the Italian Alps came across a body that turned out to be that of a hunter dating back to the Bronze Age. The remains were the oldest and best preserved ever found and were estimated to be 5,000 years old. It is quite noteworthy that this was not only the oldest human body to be discovered, but also the earliest example of tattoos. The mummy's skin had parallel lines along the lower back, stripes on the right ankle and a cross motif on the inside of the right knee (Fig. 14.1). The meaning of these tattoos is still unknown.

British circumnavigator and explorer James Cook (1728–1779) first presented the art of tattoos to Europeans. Not only did he bring along living specimens from his expeditions, he also wrote extensively about the practice of tattooing. Among the indigenous people he studied, tattoos often served as an insignia (Fig. 14.2) or indicator of tribal affiliation, whereas in

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_14, © Springer -Verlag Berlin Heidelberg 2011

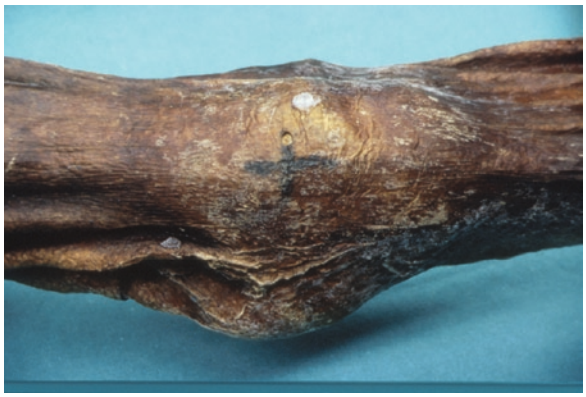

Fig. 14.1 Tattoo found on "Ötzi" the iceman (South Tyrol Museum of Archaeology in Bolzano; photo: Marco Samadelli) [49]

Fig. 14.2 George Pulman photo studio, Auckland, New Zealand: Portrait of tribal chief Anehana around 1870 (print from a touched-up negative), Rautenstrauch-Joest Museum of Ethnography; Cologne, Germany (archives) [49]

other cases they were intended to offer protection from disease. Cook's travelogues introduced the word "tattow," an onomatopoeic transliteration of the Polynesian *tautau*, which Pacific islanders used to describe stabbing, beating and slicing. Over time, the word "tattow" evolved into "tattoo."

Tattoo culture has undergone a remarkable renaissance in the western world since the late 1980s. Prior to that time, tattoos had long been considered the sole domain of sailors, societal misfits, and criminals, but since then the situation has changed dramatically.

Both then and now, tattoo motifs have been a means of expressing membership (Fig. 14.3) and status in certain groups, (supposedly) endless love (Figs. 14.4 and 14.5), or a personal motto ("Born to fight"). Some people intend their tattoos as a provocation (Fig. 14.6), whereas others may simply want to beautify themselves. Seen from a psychological standpoint, every tattoo is a reflection of the search for personal identification and a form of self-actualization, even though tattoos and their motifs have increasingly become a mainstream phenomenon in our society.

Up to 24% of the population of the USA has a tattoo [42]. A survey conducted by the Allensbach Institute for Public Opinion Research revealed that some 9% of all Germans have at least one tattoo, with this figure reaching to 23% among the younger demographic (ages 16–29) [2]. These statistics are more or less comparable to those of other European countries.

Unlike tattoos, which are permanent by nature, people and their attitudes change: what is once worn with pride will often later be stigmatised or become a source of remorse [8]. Even "temporary" or semipermanent tattoo inks, which manufacturers claim will fade completely within 4–7 years, often turn out to be less transitory than anticipated (Fig. 14.7). Research by Varma and Lanigan [67] showed that an average of 14 years passes before a person regrets a tattoo and starts to seek ways to remove it.

Unspecific methods of removal such as surgical excision (Fig. 14.8), dermabrasion, salabrasion, or even infrared coagulation (Fig. 14.9) are invariably linked to scarring and are thus no longer the preferred approach. In the 1960s, Goldman et al. [25] were the first to describe the effect of the ruby laser on the skin. Decorative tattoos were initially listed among the indications for this type of laser [26–28, 70]; however, the method was not pursued in earnest for more than 20 years despite the researchers' reports of their success. In 1983, Reid et al. [51] conducted further clinical studies with a Q-switched ruby laser and were able to demonstrate effective and scar-free removal of black-coloured amateur and professional tattoos. Another 7 years passed before the technique became established in the Anglo-American world, thanks to numerous clinical and experimental studies.

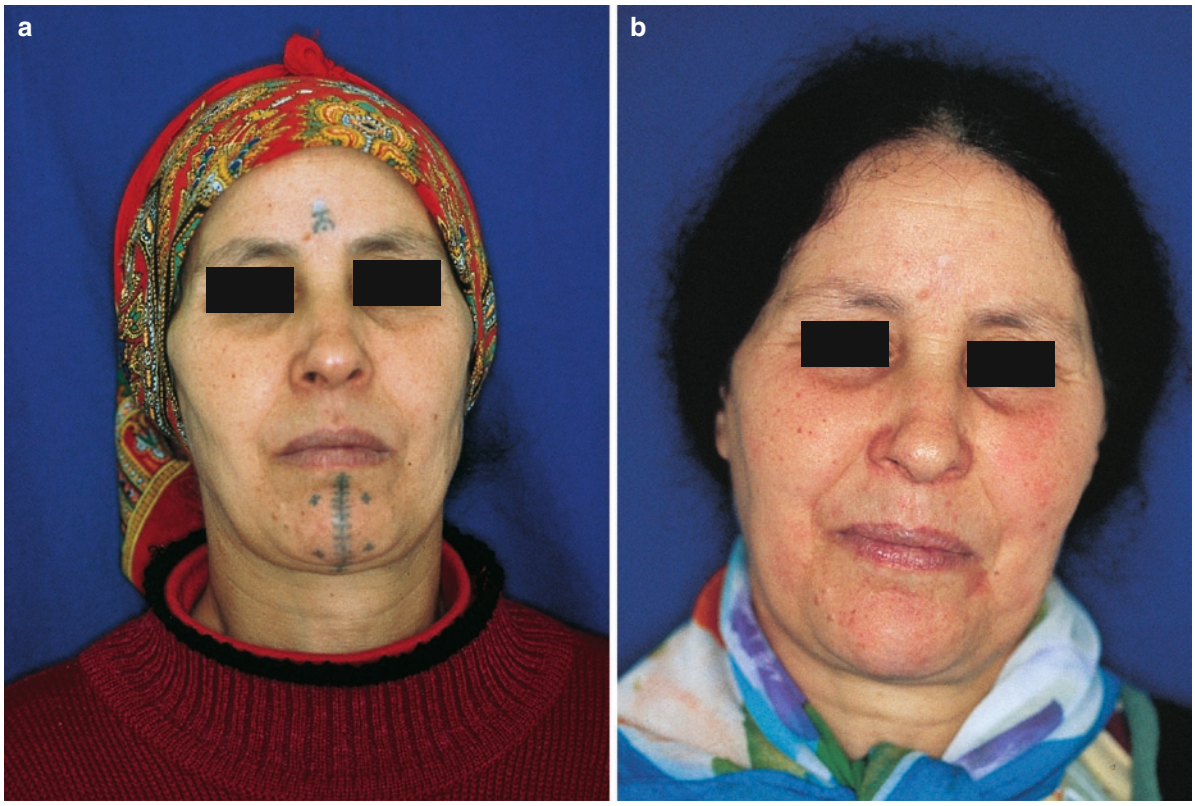

Fig. 14.3 (**a**) Ethnic tattoos. (**b**) After 13 treatments with the Q-switched ruby and neodymium:yttrium aluminum garnet laser [49]

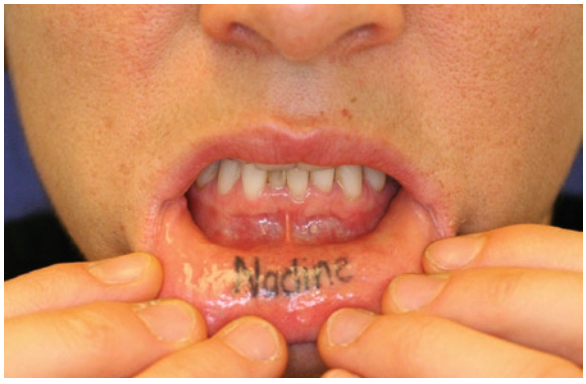

Fig. 14.4 "Endless love"

Fig. 14.5 "Painful love"

In 1987, a Swiss workgroup wrote about removing decorative tattoos with a Q-switched Nd:YAG laser; their publication in the dermatology journal *Der Hautarzt* was both the first German-language manuscript and the first international report about using this particular laser for this indication [15].

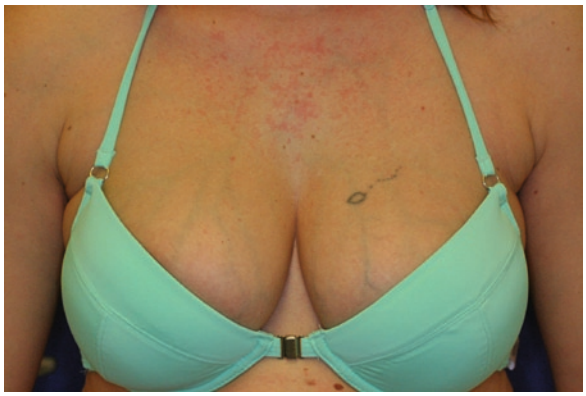

Fig. 14.6 Amateur tattoo (a "youthful indiscretion") in a young woman's decolletage

14.2.2 Histopathology

Tattoo pigments are primarily found in dermal fibroblasts and macrophages, most frequently surrounded by fibrosis and located perivascularly (Fig. 14.10). Minute amounts can also be present in the connective tissue as small extracellular aggregates [45, 72]. Particle size may vary: polymorphic granules of black pigment with a diameter of 0.5–4.0 μm have been found, whereas turquoise and red granules are usually twice that size [63]. The depth at which the pigment is found can vary dramatically; amateur tattoos show the greatest discrepancies in terms of size, shape, and position of the corpuscles. Pigments can often be detected in the lymph nodes, even when the tattoos were recently applied [4]. The lightening process that occurs with most tattoos over the course of years can be histopathologically explained by the pigment granules migrating into deeper layers of the dermis.

14.2.3 The Lightening Mechanism

The mechanism of action by which selective laser treatment successfully lightens tattoos has yet to be fully resolved. A distinction must be made here between lightening that is visible immediately after laser treatment and late-onset effects that are not evident for several weeks.

Laser treatment brings about an immediate change in the physical and optical properties of tattoo pigments; this is apparent by the whitening effect that occurs. The key factors here are photoacoustic destruction of pigment particles as well as dermal and epidermal vacuolisation (Fig. 14.11), but thermal and photochemical reactions are also involved [35].

The subsequent lightening that occurs weeks or even months after treatment can be attributed to immunological mechanisms. In histological and electron-microscopic analyses of biopsies, fragmentation of the previously intracellularly localised pigments was

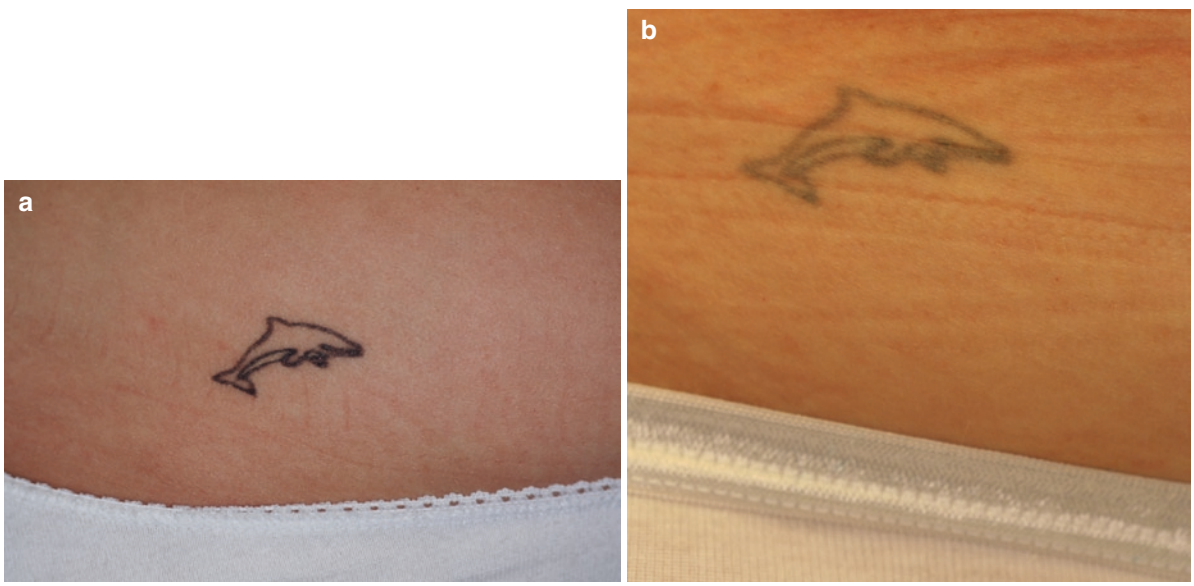

Fig. 14.7 (**a**) Temporary tattoo: a vacation souvenir, which was intended to have faded after 2–3 years. (**b**) Twelve years later, the tattoo has indeed faded but is still clearly visible. Scar-free removal is only possible via laser treatment

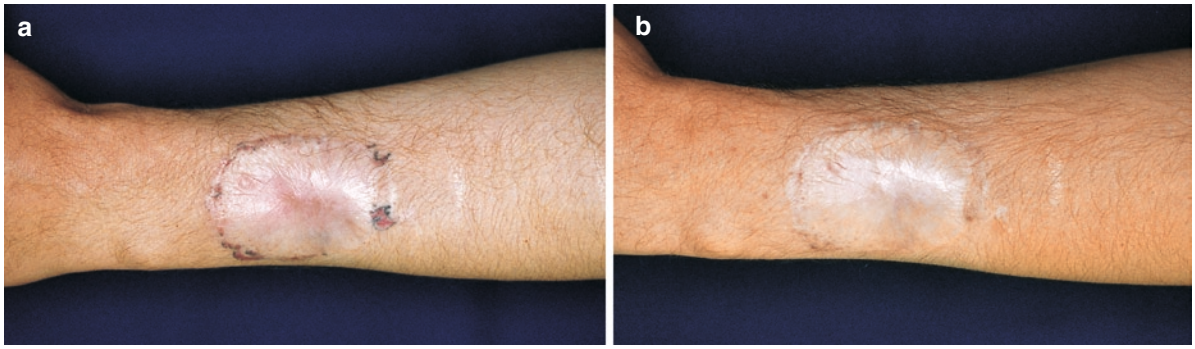

Fig. 14.8 (**a**) Residual pigment of a professional tattoo after surgical excision and a full skin graft. (**b**) Residual pigment removed after six sessions with a Q-switched neodymium:yttrium aluminum garnet laser (532 nm and 1,064 nm). This case study clearly shows the advantages of professionally conducted laser treatment compared to surgical removal [49]

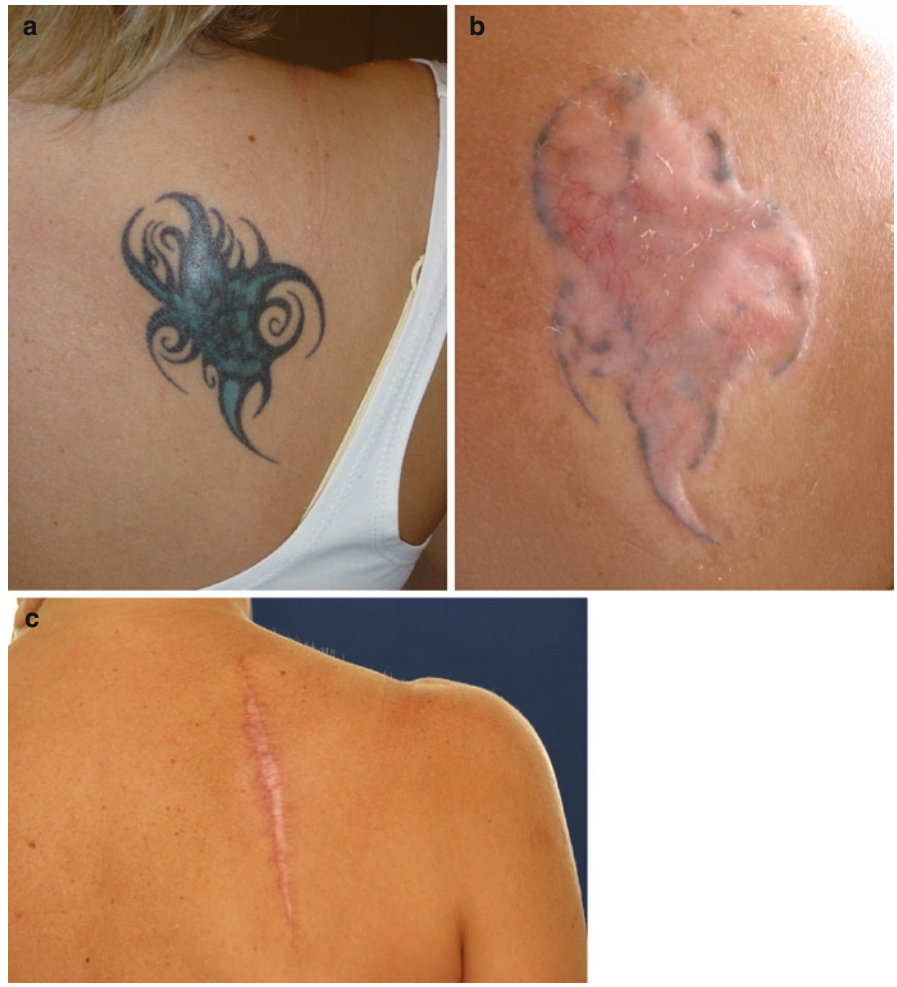

Fig. 14.9 (**a**) Professional tattoo. (**b**) Pronounced formation of keloids after an attempt to remove the tattoo with an infrared coagulator. (**c**) After multiple-staged excisions

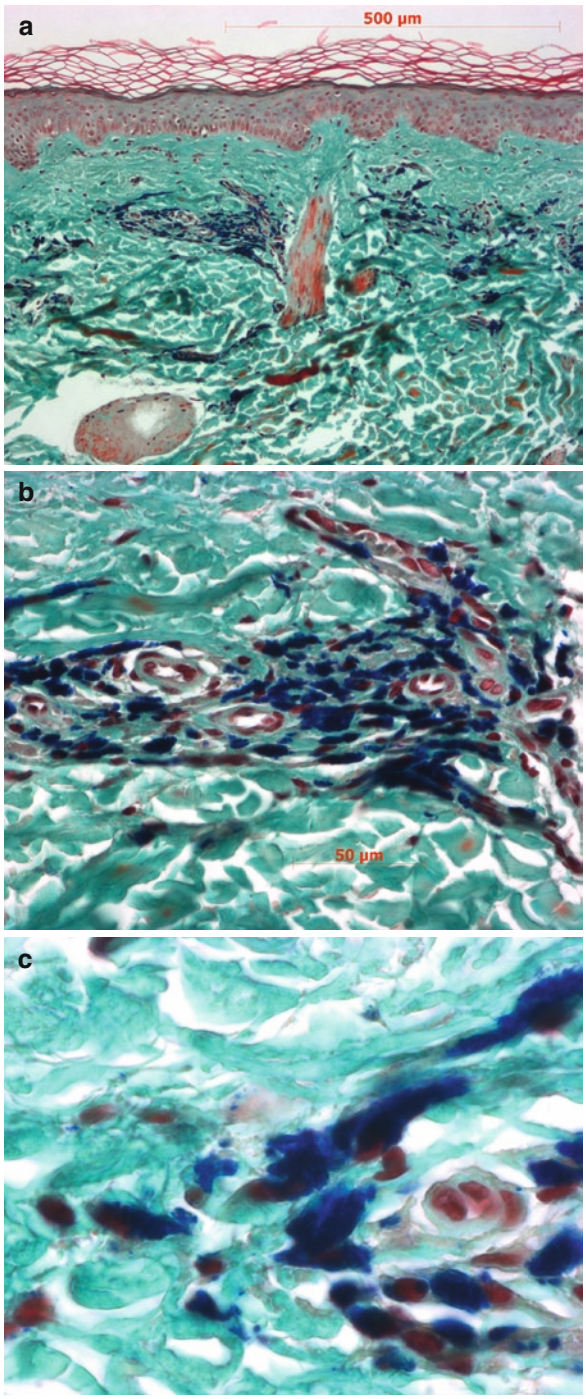

Fig. 14.10 Histological section (Masson–Goldner stain) of a tattoo before laser treatment. Clearly visible perivascular agglomerations of blue tattoo pigment can be detected in the dermis; as a rule, it is intracellular and measures a few micrometres in diameter: (**a**) 10× magnification, (**b**) 40× magnification, (**c**) 100× magnification

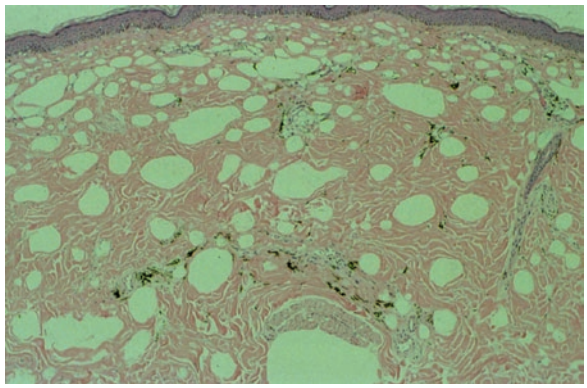

Fig. 14.11 The ultrashort pulse duration of Q-switched lasers and the several joules of energy of the laser pulse combine to generate extremely intense beams of up to 10^8 W/cm^2. This creates a dramatic temperature increase among the ink particles located in the dermis; they reach several hundred°C and are shattered explosively. Some 5 min after laser treatment, vacuoles are clearly formed in the dermis; this can be clinically identified by the whitening of the skin. Since the vacuoles are resorbed within 20–30 min, the whitening dissipates as well. (Reproduced with permission from Baumler and Landthaler [13] © 2006 Springer)

detected; these granules had been extracellularly phagocytised by macrophages or transported lymphatically. Some 4 weeks after treatment, residual pigment has migrated intracellularly again; this rephagocytosis by local macrophages may contribute to lightening but may also cause therapeutic resistance [19, 23, 63].

14.2.4 Practical Aspects of Tattoo Removal

Tattoo removal ranks among one of the most important indications for treatment with Q-switched ruby, Nd:YAG, and alexandrite lasers. The efficacy and rate of adverse effects of these lasers have been studied and compared extensively in numerous studies during the past several years (Table 14.1). The pigmented lesion dye laser (510 nm) is also used, primarily in the USA. The pulse duration here is considerably longer (300 ± 100 ns) than that of Q-switched lasers, but good results are described, especially when red pigments are involved [29, 59]. Unlike Q-switched lasers, however, there has not been widespread clinical experience with these devices in Europe.

Table 14.1 Clearance rates and side effects in select clinical trials using Q-switched lasers to treat professional and/or amateur tattoos (sorted by publication year)

Author(s)	Q-switched Nd:YAG laser	Clearance rates and side effects
Kilmer et al. [39]	λ, 1,064 nm F, 6–12 J/cm^2 t_p, 10 ns SS, 2.5 mm	*N = 25 professional tattoos and 14 amateur tattoos* *Clearance:* ≥95% (28%) and ≥75% (77%) *Side effects:* Textural changes 5.1%, hyperpigmentation 2.6%
Levine and Geronemus[44]	λ, 1,064 and 532 nm F, 10–14 J/cm^2 (1,064 nm); 5–7 J/cm^2 (532 nm) t_p, 5–10 ns SS, 2 mm	*N = 39 professional tattoos* No defined rating of clearance reported *Side effects:* Hypopigmentation 7.6%, hyperpigmentation 10.2%, textural changes 10.2%, scars 2.5%
Ferguson andAugust [22]	λ, 1,064 and 532 nm F, 10 J/cm^2 (1,064 nm); 2.5 J/cm^2 (532 nm) t_p, 10 ns SS, 1.5–2 mm	*N = 27 professional tattoos* *Clearance:* ≥90% (51.8%); ≥75% (22.2%); ≥50% (22.2%); ≥25% (0%); <25% (3.8%) *Side effects:* Hypopigmentation (N/A), hyperpigmentation 18.5%, textural changes (N/A), scars 3.7%
Leuenbergeret al. [43]	λ, 1,064 nm F, 5–10 J/cm^2 t_p, 10–20 ns SS, 3 mm	*N = 42 professional/amateur tattoos (exact numbers not reported)* *>95% clearance* per number of tx: 2% (after 3 tx), 10% (after 4 tx), 23% (after 6 tx) *Side effects:* Hyperpigmentation (transient) 7%, hypopigmentation 0%; no other side effects reported
Werner et al. [69]	λ, 1,064 and 532 nm F, 12 J/cm^2 (1,064 nm); 5 J/cm^2 (532 nm) t_p, 5–7 ns SS, 2–6 mm	*N = 25 professional tattoos* *Clearance:* Black tattoos, 70–99% (20%); coloured tattoos, 70–99% (6.7%) *Side effects:* Pinpoint bleeding (100%), vesicular eruption 7.5%, hypopigmentation 4.3%, hyperpigmentation 2.2%
Antony and Harland [6]	λ, 532 nm F, 1.4–6.4 J/cm^2 t_p, 20 ns SS, 2–3 mm	*N = 7 professional/amateur tattoos (exact numbers not reported), all red* *Clearance:* "substantial flattening and depigmentation" after 6 tx *Side effects:* Initial erythema (1 day) followed by superficial erosion and crust formation (7 days); no other side effects reported
Karsai et al. [38]	λ, 1,064 nm F, 3.2–9.0 J/cm^2 t_p, 8–10 ns SS, 4–8 mm	*N = 36 professional tattoos* *Clearance:* 0–25% (33.3%); 26–50% (16.7%); 51–75% (16.7%); 76–95% (30.5%); 96–100% (2.8%) *Side effects:* Hyperpigmentation 5.6%, hypopigmentation 2.7%
	Q-switched ruby laser	
Taylor et al. [62]	λ, 694 nm F, 1.5–8 J/cm^2 t_p, 40–80 ns SS, N/A	*N = 22 professional tattoos and 35 amateur tattoos* *Clearance:* Substantial lightening or total clearing occurred in 18 (78%) of 23 amateur tattoos and 3 (23%) of 13 professional tattoos after 10 tx. Response was related to exposure dose; optimal fluence was 4–8 J/cm^2 *Side effects:* Hypopigmentation 40% (at 1-year follow-up); scars occurred in one case

(*continued*)

Table 14.1 (continued)

Author(s)	Q-switched ruby laser	Clearance rates and side effects
Scheibner et al. [55]	λ, 694 nm F, 2–4 J/cm^2 t_p, 40 ns SS, 5–8 mm	*N = 62 professional tattoos and 101 amateur tattoos* *Clearance:* In amateur tattoos, 4% (completely clear), 83% (>80% clear), 11% (>60% clear), 2% (>40 clear) after 4 tx In professional tattoos, 3% (completely clear), 8% (>80% clear), 29% (>60% clear), 40% (>40% clear), 19% (<40%) after 4 tx *Side effects:* Pain (more than 50% of the patients required local anaesthesia), hypopigmentation (lasting 2–6 months), textural changes (lasting 6–8 weeks)
Leuenberger et al. [43]	λ, 694 nm F, 4–10 J/cm^2 t_p, 25–40 ns SS, 5 mm	*N = 42 professional/amateur tattoos (exact numbers not reported)* *>95% clearance per number of tx: 2% (after 3 tx), 20% (after 4 tx), 38% (after 6 tx)* *Side effects:* Hypopigmentation 38% (long-lasting), hyperpigmentation 0%; no other side effects reported
	Q-switched alexandrite laser	
Leuenberger et al. [43]	λ, 755 nm F, 6–8 J/cm^2 t_p, 50–100 ns SS, 3 mm	*N = 42 professional/amateur tattoos (exact numbers not reported)* *>95% clearance per number of tx: 2% (after 3 tx), 5% (after 4 tx), 31% (after 6 tx)* *Side effects:* Hypopigmentation 2% (long-lasting), hyperpigmentation 0%; no other side effects reported

λ wavelength; *F* fluence; t_p pulse duration; *SS* spot size; *tx* treatment(s); *Nd:YAG* neodymium:yttrium aluminum garnet

Regardless of the type of laser used, patients can apply a thick layer of an anaesthetic cream (e.g., eutectic mixture of lidocaine and prilocaine) 2–3 h before the procedure to the area that is to be treated. During treatment, the light of the laser is aimed at the skin at a spot size of 3–8 mm. The handpiece has to be held perpendicular to the treatment area to ensure even coverage. Depending on any concomitant reactions, 1–2 passes are performed with minimal overlap of the pulses; whitening and then pinpoint bleeding serve as therapeutic endpoints. After the treatment, topical antibiotics are applied to prevent infection. The treatment intervals are typically set at 4–6 weeks. During the treatment course the treated site(s) should be protected from direct ultraviolet (UV) exposure.

The cosmetic outcome of laser tattoo removal is not always satisfactory and is contingent on several factors. Distinctions must be made here between amateur and professional tattoos, single- and multicoloured tattoos, and pigment density.

One defining characteristic of black pigment is its ability to absorb all laser wavelengths efficiently on a broad scale, but when it comes to treating coloured inks, laser surgeons are often confronted with the difficult challenge of finding the proper wavelength (Fig. 14.12). The first point of clinical orientation is the colour of the tattoo (Table 14.2), but this does not provide clear-cut suggestions as to the chemical composition of the suspected pigment and the corresponding absorption spectrum. Coloured tattoo pigments have widely varying absorption properties, and this is also true for tints that appear at first glance to be identical. Multicoloured tattoos thus respond very differently and, to some extent, very unsatisfactorily to laser treatment. As a result, testing a small, inconspicuous site is recommended before commencing treatment on a larger area. Local whitening immediately after treatment is usually a sign that the laser light the practitioner selected is being well absorbed by the pigment in question. Several laser systems with different wavelengths will be necessary to achieve an ideal therapeutic outcome in removing multicoloured tattoos. In clinical practise, all laser systems (ruby, 1,064-nm Nd:YAG, and alexandrite lasers) have proven effective in treating black, black-blue, blue, and brown inks. Red and orange tattoos only

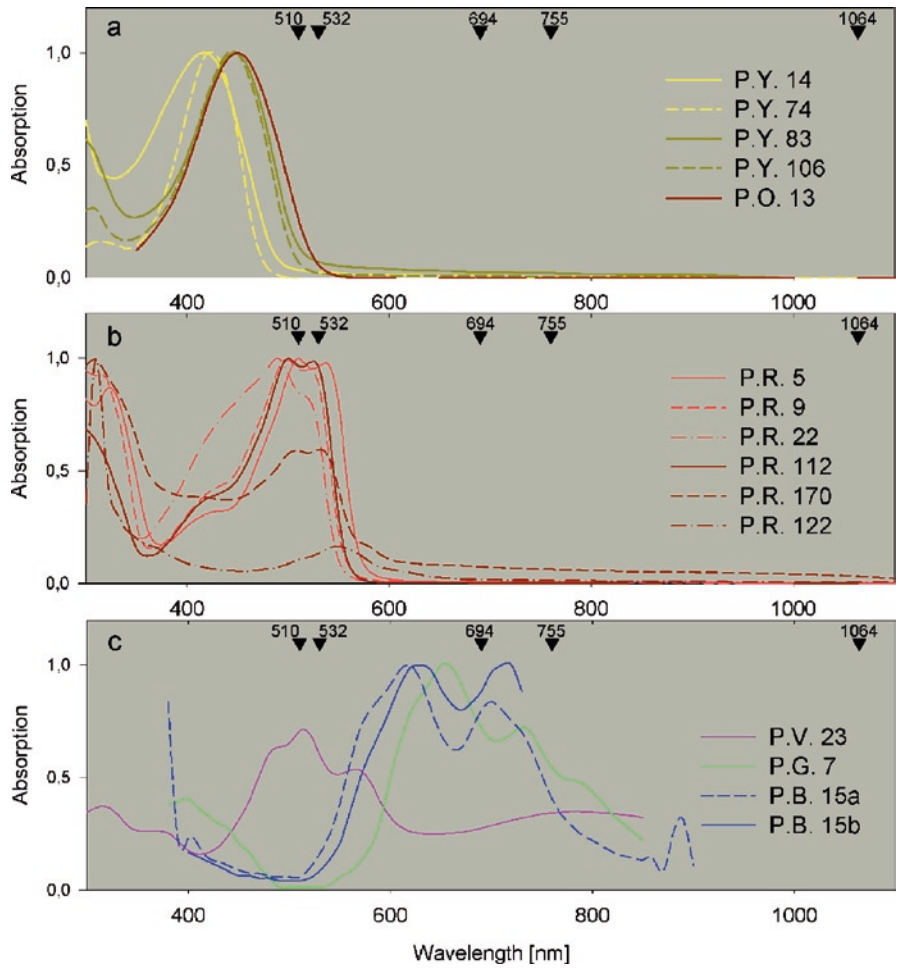

Fig. 14.12 (**a**) The wavelength-dependent absorption of *yellow* and *orange* pigments calculated with regard to the absorption maximum. The symbols inside the graph indicate the wavelength of Q-switched lasers used for tattoo removal. (**b**) The wavelength-dependent absorption of *red* pigments calculated with regard to the absorption maximum. The symbols inside the graph indicate the wavelength of Q-switched lasers used for tattoo removal. (**c**) The wavelength-dependent absorption of *violet, blue* and *green* pigments calculated with regard to the absorption maximum. The symbols inside the graph indicate the wavelength of Q-switched lasers used for tattoo removal. The spectral range is restricted to 850 nm. (Reproduced with permission from Baumler et al. [12] © 2000 John Wiley & Sons, Inc)

Table 14.2 Different tattoo colours and their response to Q-switched laser treatment

	Black	Brown	Blue	Purple	Red	Orange	Yellow	Green
Ruby laser	+++	+	+++	+	–	–	–	+++
Nd:YAG laser (1,064 nm)	+++	+	+++	–	–	–	–	–
Nd:YAG laser (532 nm)	–	+	–	–	+++	++	+	–
Alexandrite laser	+++	+	+++	–	–	–	–	+++
Pigment dye laser	–	–	–	+	+++	+++	+	–

It is nearly impossible to anticipate how pigments will respond in individual cases because their chemical structure and the correlating absorption spectrum are unknown. Trial sessions are strongly recommended
+++ excellent; ++ good; + fair; – poor response; *Nd:YAG* neodymium:yttrium aluminum garnet

absorb light from the Q-switched frequency-doubled Nd:YAG lasers (532 nm) (Fig. 14.8) and pulsed dye lasers (510 nm). Green tattoos respond best to treatment with Q-switched ruby (Fig. 14.13) or alexandrite lasers, whereas purple, yellow, white and flesh-tone dyes do not yield satisfactory results [48, 52].

Professionally applied tattoos (Fig. 14.15) are not only usually multicoloured but also feature a much higher, more even and deeper-reaching pigment density due to the use of tattoo guns; consequently, they often require more laser treatments than amateur tattoos (Figs. 14.3, 14.13 and 14.16). The average number

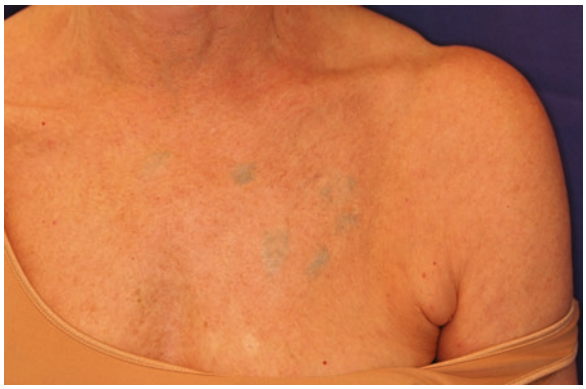

Fig. 14.13 Extensive ink darkening after a ruby laser was used to treat permanent make-up that was initially matched to the skin tone and had been applied to conceal lentigines

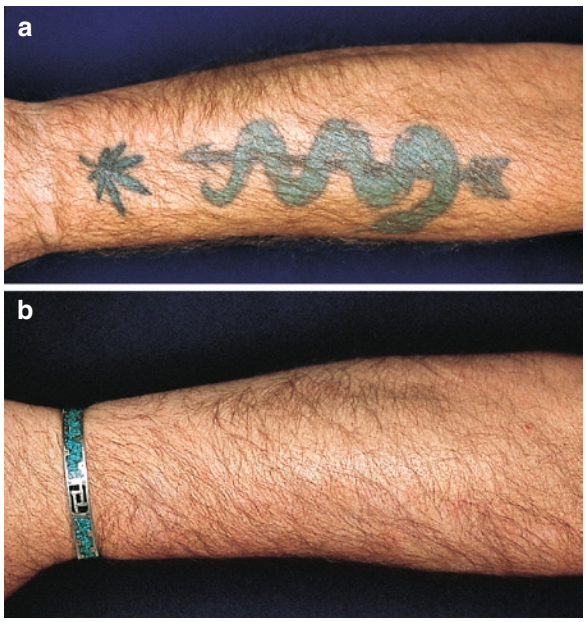

Fig. 14.14 (**a**) Green–black amateur tattoo. (**b**) After six sessions with the Q-switched ruby laser [49]

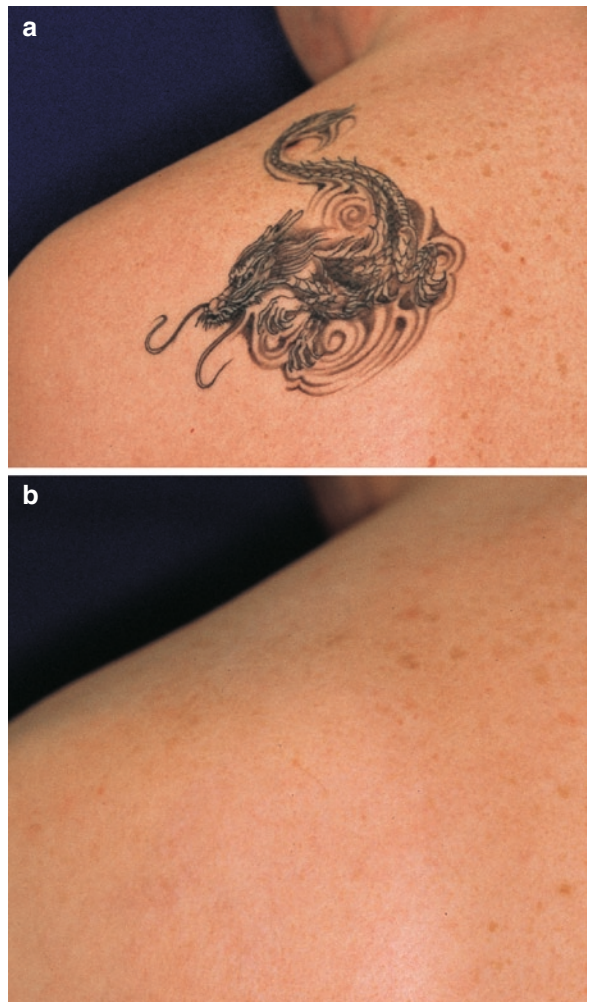

Fig. 14.15 (**a**) Professional tattoo. (**b**) Complete removal after 18 sessions with a Q-switched neodymium:yttrium aluminum garnet laser (1,064 nm) [49]

of sessions depends more on the kind of the tattoo than on the laser used: 5–10 sessions are standard for amateur tattoos (Figs. 14.14 and 14.17) and 15–20 for professional tattoos, even up to 25 sessions in rare cases.

The location of the tattoo has a major effect on therapeutic success as well. Experience shows that it takes longer to lighten tattoos in distal anatomical regions such as forearms and calves. This may be due to slower lymphatic transport, which in turn leads to delayed elimination of the colour pigments.

The ink darkening that can occur after laser treatment is often attributable to iron oxide and titanium dioxide, both of which serve as excipients that shade and brighten other inks [52]. Both substances are chemically reduced by means of high-energy laser pulses, which later make them darken. This can be seen in particular in white tattoos, which almost exclusively consist of titanium dioxide. This is why at least one, if not several, trial sessions should be conducted when removing cosmetic tattoos (such as permanent make-up) (Fig. 14.18). Patients are to be given detailed information about this side effect, especially since it may be irreversible. Anderson et al. [5] reported that in two of five patients, further laser treatments could not influence the colour any further. We have had

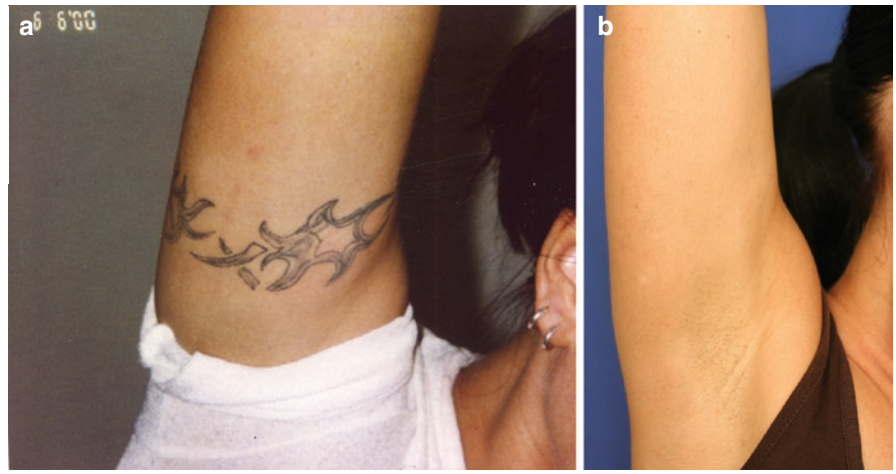

Fig. 14.16 (**a**) Professional tattoo. (**b**) Complete removal after 15 sessions with a Q-switched neodymium:yttrium aluminum garnet laser (1,064 nm)

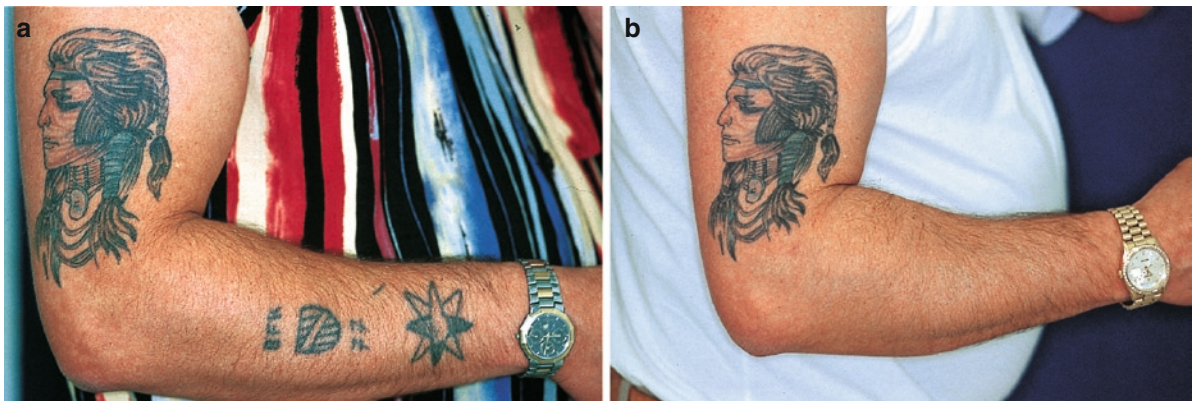

Fig. 14.17 (**a**) Amateur tattoo. (**b**) Complete removal after seven sessions with a Q-switched ruby and neodymium:yttrium aluminum garnet laser (1,064 nm). The patient wanted to keep the tattoo on his right upper arm [49]

Fig. 14.18 (**a**) Permanent make-up of the eyebrow. (**b**) Complete removal without any hair loss after five sessions with a Q-switched ruby laser [49]

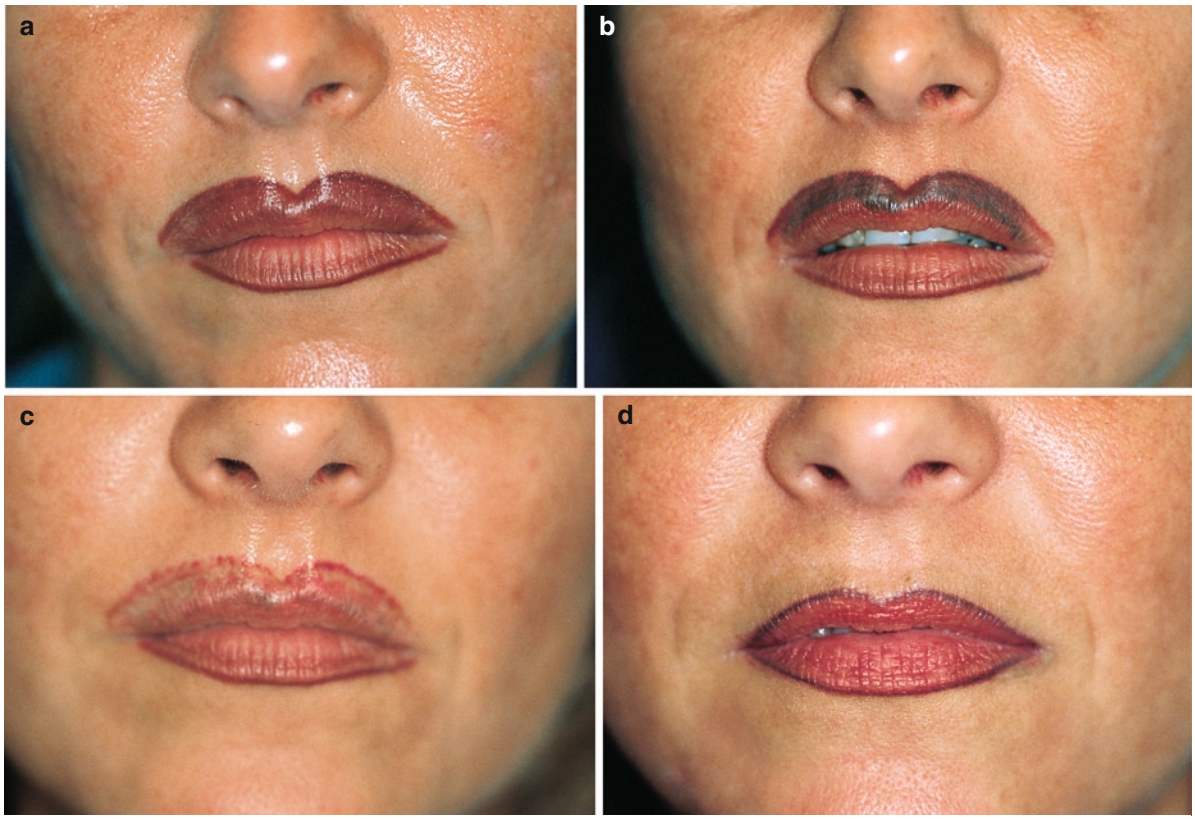

Fig. 14.19 (**a**) Thirty-five-year-old patient whose permanent make-up had been corrected several times. (**b**) One month after the first treatment, the colour shifted from red to black (ink darkening). (**c**) One month after the seventh treatment with the Q-switched ruby laser. (**d**) Six months after five further treatments with the Q-switched 532-nm neodymium:yttrium aluminum garnet laser. Please note the discrete hyperpigmentation and the newly applied permanent make-up [49]

more positive experiences in such cases, but numerous sessions are needed (Fig. 14.19).

14.2.5 Adverse Effects and Concomitant Reactions

Table 14.1 provides an overview of how often adverse effects occur with different kinds of lasers. Depending on the fluence used, wheals, pinpoint bleeding, blistering, and crusting may occur after treatment. Changes in texture usually resolve within 4–6 weeks, which is why this is the suggested interval for treatment sessions.

One common adverse effect is the occurrence of hypopigmentation (Fig. 14.20), which is usually transient and lasts for 2–6 months; it occurs in more than 38% of cases treated with the Q-switched ruby laser [43]. The number of sessions can often be a risk factor

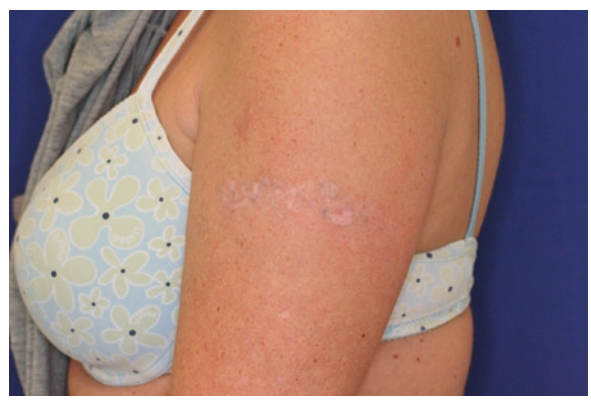

Fig. 14.20 Near-complete removal of professional tattoo on the left upper arm with persistent hypopigmentation

in and of itself: the more that are needed, the greater the risk of hypopigmentation. In our experience, permanent hypopigmentation occurs in approximately 10% of all cases, although unfortunately most studies do not feature a correspondingly long follow-up period [41, 43]. This adverse effect is observed much less frequently with the 1,064-nm Nd:YAG laser because melanin does not absorb the light of its wavelength as fully, making it a very well-suited device for treating darker skin types and tanned skin [36].

In rare cases, local allergic and photoallergic dermal reactions can be caused by the metal salts that were once frequently used in tattoo inks, such as mercury (red), cadmium (yellow), chromium (green), and cobalt (blue); in very rare cases, these salts may even lead to systemic reactions. Interestingly, Ashinoff et al. [11] observed lightening of more than 75% after a mere two sessions in a patient with an allergic reaction. It may well be that the profound inflammatory and immunological reaction, which occurred after laser treatment, may have contributed to the lightening process [11]. Despite this observation, treatment should only be continued or performed with great caution if an allergic reaction occurs because it cannot be ruled out that the laser treatment will disseminate the allergenic pigment particles throughout the body and trigger generalised urticaria, disseminated contact eczema, or even an anaphylactic reaction [73].

Recently, industrially manufactured organic pigments (monoazo and diazo dyes, polycyclic dyes from the group of phthalocyanines, dioxazines, and chinacridones) have become more commonplace than the metal salts listed above. Chemical analyses have shown that two widely used red azo dyes are cleaved by laser treatment, which can lead to potentially toxic and carcinogenic cleavage products such as nitroanilines [21]. It has yet to be determined whether this is also the case in vivo and the extent to which this issue may be clinically relevant. Newer kinds of dyes are also not to be regarded as "tissue-inert"; they can act as a chronic stimulus that triggers reactive lymphoid hyperplasia (pseudolymphoma). One unresolved question is whether inflammatory chronic stimulation of lymphocytes or dendritic cells can generate cutaneous lymphoma [16, 57, 68].

The Koebner phenomenon may manifest in predisposed patients (e.g., those with psoriasis or vitiligo). It results from trauma that occurred during tattooing, but it can also happen when the tattoo is removed via laser.

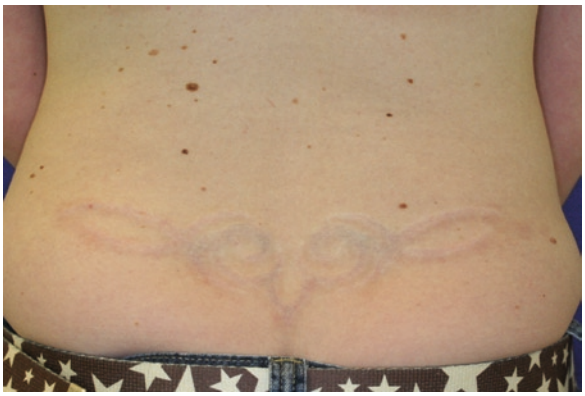

Fig. 14.21 Complete removal of a "lower-back tattoo" using a Q-switched laser. There is clear evidence of scarring that occurred during tattooing. In cases such as these, the initial findings should be meticulously photographed for forensic reasons

The risk of scarring is slight when lasers are used properly (Table 14.1). A much larger concern is the scarring that results during the process of applying the tattoo; the patient often only sees the scars for the first time when the pigments are removed (Fig. 14.21).

14.2.6 Potential Treatment Strategies for Adverse Effects

- Allergic reactions
  Allergic reactions (Fig. 14.22) most frequently manifest as urticarial, lichenoid, or granulomatous changes of the skin. As a matter of principle, laser

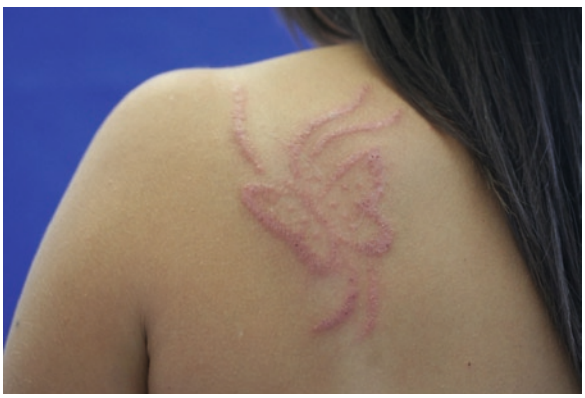

Fig. 14.22 Type IV allergic reaction 1 week after second application of a henna tattoo

treatments should be conducted exclusively by board-certified medical specialists since the extent of allergic reactions cannot be foreseen [11, 73]. Further treatment should initially be discontinued if a local or generalised allergic reaction takes place; otherwise, the allergens may be dispersed and prompt a systemic reaction. In some cases, fractionated photothermolysis can prove to be useful because it eliminates the pigments transepidermally, thus reducing the amount of allergenic ink particles. Prophylactic treatment with oral antihistamines and corticosteroids has been discussed; however, there has not yet been any wide-ranging clinical experience to draw upon.

- Hypopigmentation
  Gündogan et al. [31] used a 308-nm excimer laser to treat a patient with persistent hypopigmentation that had occurred after tattoo removal with an Nd:YAG laser (532 nm). During the 23-week follow-up period, stable repigmentation had occurred after 40 (!) sessions within 14 months.
- Hyperpigmentation
  The occurrence of hyperpigmentation usually depends on the skin type, with the risk being greater for people with darker skin types. For therapeutic purposes, 2–4% hydroquinone creams are to be applied in combination with rigorous sun protection; fractionated photothermolysis may be another possible approach [56].
- Textural changes and scarring
  In cases of change in texture and scarring, aesthetic improvement may be achievable via fractionated photothermolysis in addition to erbium:YAG or carbon dioxide lasers [24].
- Residual ink
  As is the case with every kind of laser treatment, there are constraints in removing tattoos because of both the fundamental physical principles involved and the physiological processes in tattooed skin. Residual tattoo ink may remain visible in the skin, despite numerous time-consuming and expensive treatment sessions.

If the skin has palpably thickened because of tattoo-related permanent infiltrate or scarring (Fig. 14.20), it is more difficult for the laser to penetrate the dermis, and the pigment particles' ability to absorb light will be affected. Furthermore, the particles may reach as far as the subcutis; depending on the location of the tattoo on the body, this can mean a depth of 5 mm or more. The penetration depth of the laser into the tissue is determined by the wavelength (the two factors correlate proportionally) and the spot size, which is usually limited to about 3–4 mm. There is thus always the possibility that the laser light cannot reach the ink particles with sufficient intensity, which means they cannot be destroyed. The penetration depth of the laser can be optimised by using the largest spot size possible (≥4 mm) and a homogenous beam profile [38]. Transepidermally applied glycerol could also help reduce the diffusion of the laser beam, thereby increasing its effect [46].

In the early 1990s, Ross et al. [53]. Herd et al. [34] described an improved lightening rate with pulses in the picosecond range versus the nanosecond range; all other parameters remained constant. It remains to be seen whether this technical approach will become more prevalent.

Perhaps advances can be anticipated when methods emerge that increase pigment migration (transepidermally or lymphatically) or minimise re-uptake via local connective-tissue cells [17]. Transepidermal elimination of the ink pigment could be further increased by disrupting the dermoepidermal junction zone via fractional photothermolysis [33].

Solis et al. [58] used imiquimod to treat freshly applied tattoos on guinea pigs. After 7 days, barely a trace of pigment could be histopathologically detected; however, after 28 days, they observed fibrosis and a loss of dermal appendages. When administered under optimised conditions, imiquimod may be a nonsurgical means of removing fresh tattoos.

Other approaches to finding a simpler and more effective way of tattoo removal include developing new dyes and determining the absorption characteristics of the pigments so that the ideal laser wavelength can be identified before treatment commences [14, 32].

14.3 Traumatic Tattoos

Traumatic tattoos commonly result from injuries involving explosions, impaled objects, or abrasions. The first-line treatment is carefully removing or brushing the

foreign matter (particles of dust, dirt, asphalt, metal, or gunpowder) by rinsing with saline within 48 h. This, however, is not always possible in first-aid treatment of injuries and/or particles may remain in the skin even despite brushing; in such cases, Q-switched systems such as ruby, Nd:YAG (1,064 nm), and alexandrite lasers have proven to be effective alternatives [1, 3, 9, 60, 65] (Figs. 14.23 and 14.24).

Normal debris, soot, carbon particles and similar substances respond well here, whereas harder matter such as iron particles or pebbles do not. As is the case with decorative tattoos, the number of treatment sessions is largely dependent on the depth, size, and colour of the debris. Gunpowder deposits, which strike the skin at high velocity and penetrate deeper levels of the skin, call for a greater number of treatments and higher fluences than superficial traumatic tattoos (such as abrasions). In our experience, one to seven sessions are needed to treat localised and shallow traumatic tattoos, whereas those resulting from explosions can entail up to 25 sessions. Complete lightening, however, cannot be achieved in every case, and caution is required when treating gunpowder wounds: even months after the impact, the gunpowder can still ignite, causing scarring and further spread of the particles.

In one special case, we were able to use the Q-switched ruby laser to correct the discolouration that had taken place on the eyelid of a 9-year-old girl who had accidentally been injured with the lead of a coloured pencil at the age of 18 months (Fig. 14.25). We began with a trial session to rule out the possibility of ink darkening. The sessions occurred at intervals of 6–8 weeks; the patient was put under twilight anaesthesia for some of the treatments to minimise pain.

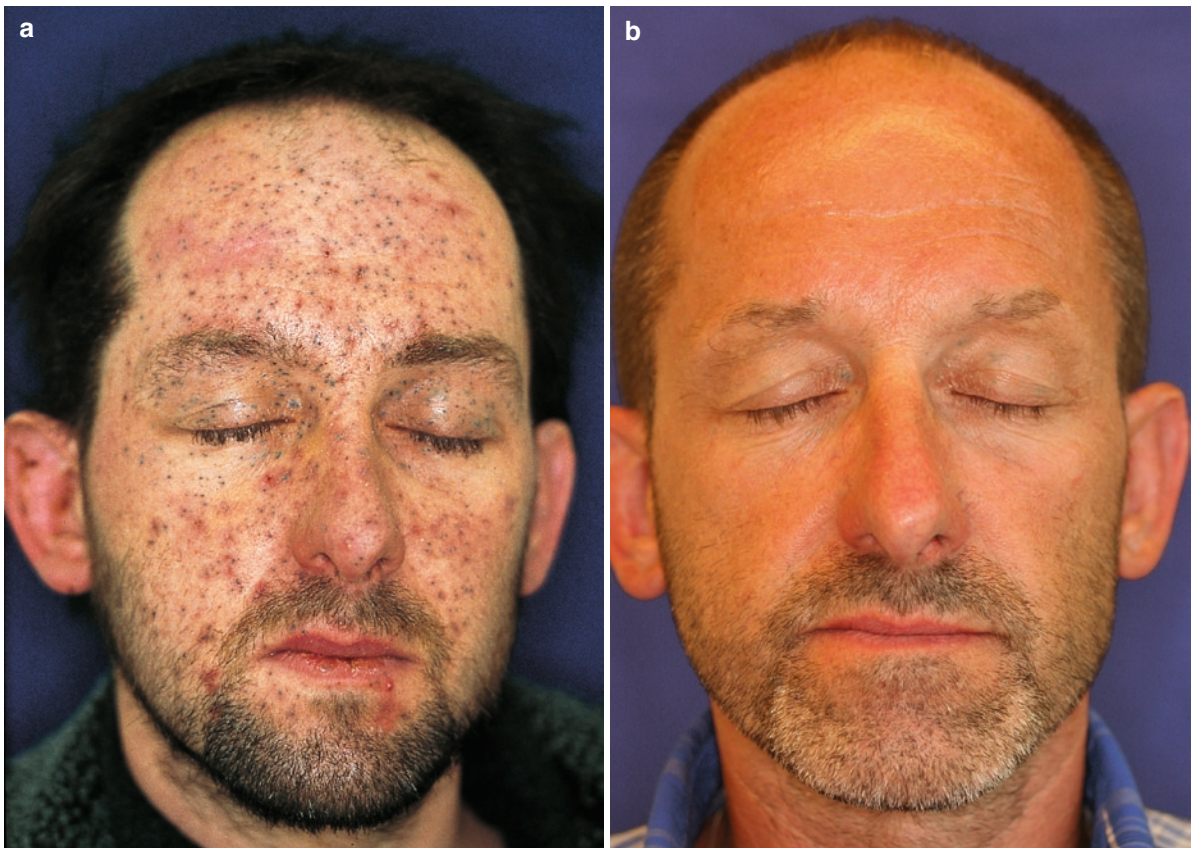

Fig. 14.23 (**a**) Traumatic tattoo 1 month after an injury due to a New Year's Eve firecracker. (**b**) Periorbital residues after a total of 23 sessions with the Q-switched ruby and neodymium:yttrium aluminum garnet laser (1,064 nm) [49]

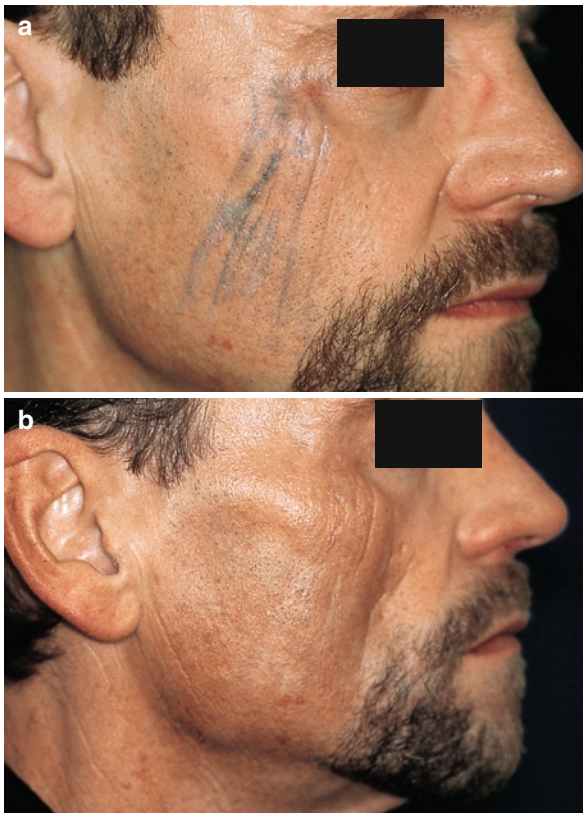

Fig. 14.24 (**a**) Traumatic tattoo after a cycling accident. (**b**) Complete removal of debris after five sessions with the Q-switched ruby laser and resolution of the scarring after one session with an ultrashort pulsed carbon dioxide laser [49]

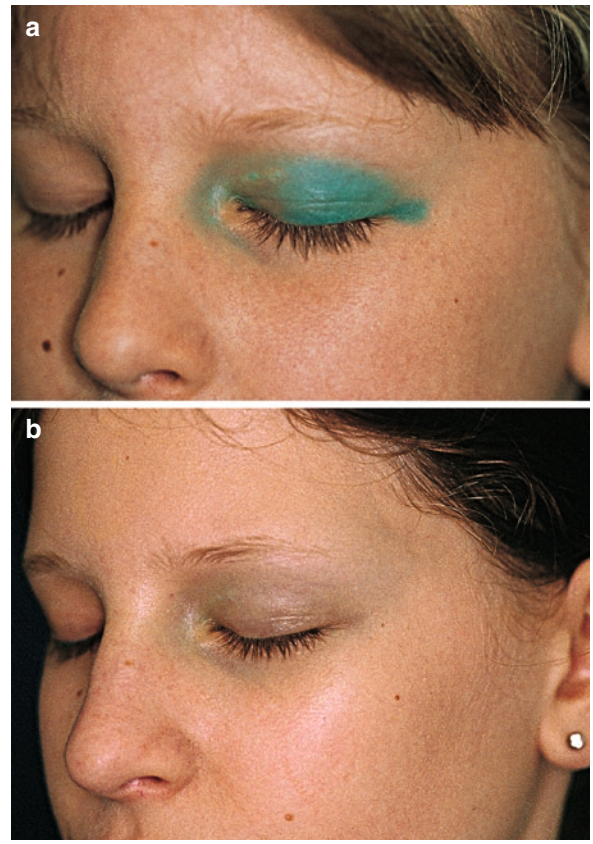

Fig. 14.25 (**a**) Nine-year-old girl with green pigment on her eyelid after injury with the lead of a coloured pencil at the age of 18 months; the colour later spread locally. (**b**) Clearly evident lightening after eight sessions with the Q-switched ruby laser [49]

14.4 Drug-Induced Dyschromia

Ashinoff and Geronemus [9] reported on successful removal of amalgam-induced dyschromia of the gingiva after seven sessions with the Q-switched ruby laser. Their findings were reproduced by other workgroups [10].

Another case of drug-induced hyperpigmentation caused by amiodarone was observed in a patient who had taken the drug for 10 years (cumulative dose >900 g). Karrer et al. [37] successfully corrected the dyschromia in a single session with the Q-switched ruby laser. The results remained stable for 12 months despite the fact that the patient continued to take amiodarone; there were no adverse effects.

A 41-year-old AIDS patient had undergone intravenous treatment for disseminated Kaposi's sarcoma with liposomal doxorubicin, which had led to cosmetically distressing hyperpigmentation on the face, neck, and trunk. After 1–3 sessions with the Q-switched ruby laser, these sites were dramatically lightened [54].

Blue–black dyschromia is a rare and little-known adverse effect of intramuscular iron injections; it develops in a radius of approximately 10 cm around the injection site and is almost never reversible. It is thought that the injection solution flows back into injection site, and subsequently iron (Fe^{3+}) complexes are dispersed into the surrounding tissue. For quite some time, there were no treatment options other than the wait-and-see approach. In five patients in our surgery, Raulin et al. [50] attained significant lightening with the Q-switched ruby and/or 1,064-nm Nd:YAG laser (Fig. 14.26). Between 3 and 16 treatments were needed. Remarkably, some 80% of the therapeutic success took place within the first 2–4 sessions. All

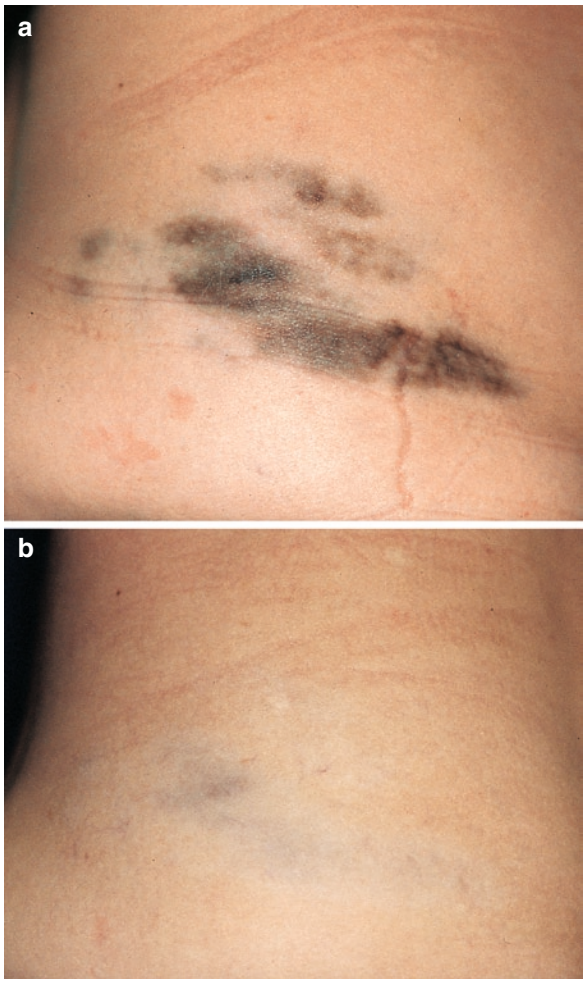

Fig. 14.26 (**a**) Iron deposits at a patient's right hip after intramuscular injection. (**b**) Lightening after seven sessions with the Q-switched ruby laser and nine sessions with the Q-switched neodymium:yttrium aluminum garnet laser (1,064 nm) [49]

patients experienced postoperative swelling and temporary crusting regardless of the type of laser used. Transient hyperpigmentation was observed in one patient; no cases of hypopigmentation or scarring were reported. Four in five patients were satisfied with the outcome. A preoperative biopsy was taken in two cases: histological findings confirmed numerous iron-laden macrophages, which were detectable at a depth of up to 7 mm in the subcutis. The deep subcutaneous deposits of pigments explain the incomplete clearance. Despite the fact that the Q-switched Nd:YAG (1,064 nm) laser theoretically has a greater penetration depth, the present data do not allow any statements to be made about the relative efficacy of different laser systems.

Cutaneous hyperpigmentation subsequent to high-dose or long-term treatment with minocycline is a well-documented adverse effect, albeit a rare one. This dyspigmentation can persist for years even after medication is discontinued. Indeed, no effective treatment option was available until laser treatment was introduced. In 1996, three separate workgroups simultaneously reported the successful treatment of minocycline-induced hyperpigmentation with the Q-switched ruby laser [18, 40, 66]. Greve et al. [30] first used the Q-switched Nd:YAG laser at a wavelength of 1,064 nm in 1998, and after eight sessions they achieved complete clearance in a 61-year-old patient with grey–black periorbital dyschromia (Fig. 14.27). Laser treatment did not cause permanent hypo- or hyperpigmentation or scarring.

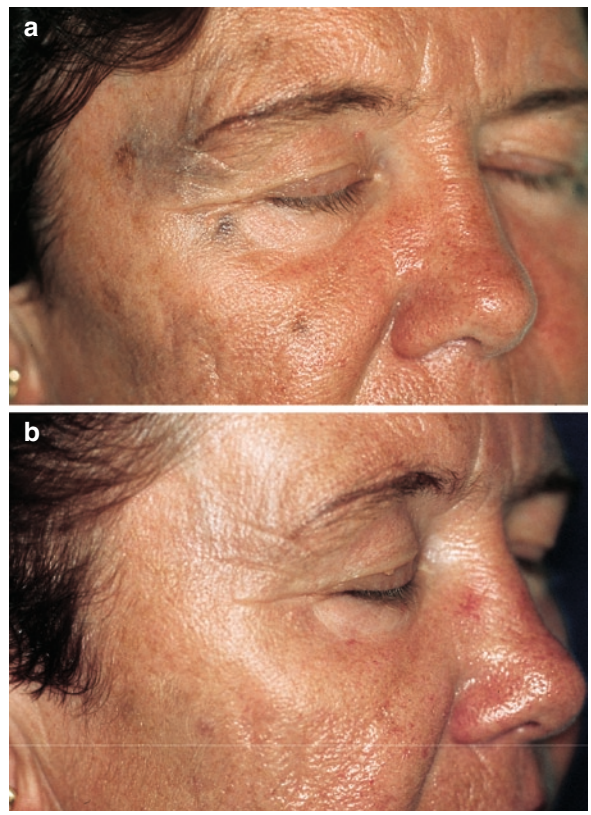

Fig. 14.27 (**a**) Sixty-one-year-old patient with hyperpigmentation after 3 years of minocycline treatment. (**b**) Complete and scar-free removal after eight sessions with a Q-switched neodymium:yttrium aluminum garnet laser (1,064 nm) [49]

The pathogenesis of hyperpigmentation caused by minocycline has yet to be conclusively resolved. There has been discussion of the fact that minocycline or its cleavage products may form complexes with iron and other substances in the skin especially bivalent metal ions. Furthermore, minocycline, which is a yellow crystalline powder, can take on a black colour when exposed to oxidation. In our experience, type I minocycline-induced hyperpigmentation is an ideal candidate for treatment with a Q-switched Nd:YAG laser at a wavelength of 1,064 nm if immunohistological analyses have demonstrated the presence of pigment-laden macrophages in the dermis and show positive reactions to iron and melanin [7]. In cases of type II minocycline-induced hyperpigmentation (i.e., generalised hyperpigmentation along the basal membrane zone), we regard the Q-switched ruby laser as the more effective device [7] because the shorter wavelength (694 nm) is better absorbed by the pigment particle in the epidermis. The skin type and extent of tanning pose constraints on the efficacy of the ruby laser, however.

Caution is advised when treating drug-induced dyschromia with Q-switched lasers, even despite the therapeutic successes discussed in this chapter. Patients who take or have taken gold medication (e.g., to treat rheumatic arthritis) may experience mottled hyperpigmentation (laser-induced chrysiasis) after treatment with a Q-switched laser, regardless of the indication for laser therapy (Fig. 14.28). One such patient who had developed chrysiasis after being treated for lentigines responded well to treatment with a long-pulsed ruby laser (3 ms) [71].

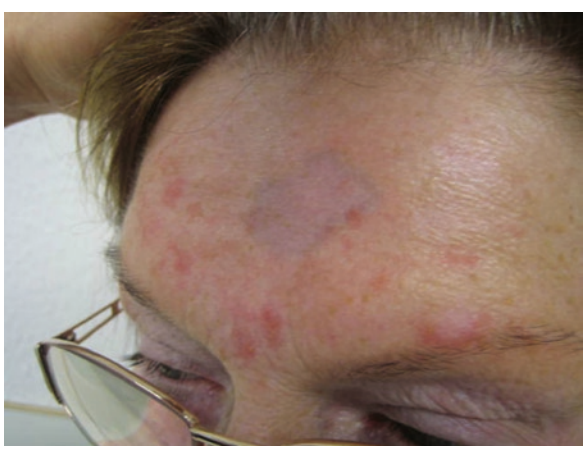

Fig. 14.28 Chrysiasis following laser treatment of a benign lentigo with a Q-switched ruby laser; the patient had taken gold medication to treat rheumatoid arthritis 16 years (!) earlier

14.5 A Discourse on Tattoo Pigments

14.5.1 Chemical Classification

Inorganic pigments were used very frequently in the past. In 2001, Timko et al. [64] performed quantitative x-ray microanalysis to study 30 tattoo inks made by a US manufacturer. The researchers analysed the following basic colours and their compositions: black (carbon and iron); blue (titanium, carbon, copper); brown (titanium, iron); green (titanium, carbon, copper, chromium); red (titanium, carbon, iron, magnesium); and white (titanium). This study also showed that inks often do not have an identical chemical structure even though they may look identical.

Most inorganic dyes are characterised by colourfastness, lasting properties, and good coverage. A disadvantage here is that the colours are far less intense than those of organic pigments. Furthermore, inorganic pigments create dull colours in tattoo inks, and the low number of suitable substances automatically limits the shades that can be created by blending.

For the most part, coloured tattoos consist largely of inks based on organic compounds. Chemical analyses show that they are primarily industrially manufactured azo compounds or polycyclic compounds [12], which were originally designed as coatings or paints for consumer goods (e.g., car paints). Tattooists like to use these inks because they last well and are nearly dissoluble – properties that create a brilliant and long-lasting design in the skin. Engel et al. [21] recently showed that significant quantities (approximately 2.5 g/cm^2) of these ink pigments are placed in the skin during tattooing. Black tattoos often consist of industrial soot in the form of pulverised elemental carbon.

14.5.2 Specific Problems and Risks in Treating Standard Tattoo Pigments

The suspensions used to manufacture tattoo inks almost always contain certain kinds of impurities (Table 14.3).

Table 14.3 Typical impurities in pigments

Type of pigment	Impurity
Azo compounds	Aromatic amines, traces of heavy metals, polycyclic aromatic hydrocarbons, PCBs, dioxins
Inorganic substances (including titanium dioxide, chromium oxide, iron oxide)	Traces of heavy metals
Polycyclic compounds	Traces of heavy metals, PCBs, dioxins
Soot	Traces of heavy metals, polycyclic aromatic hydrocarbons

PCBs polychlorinated biphenyls

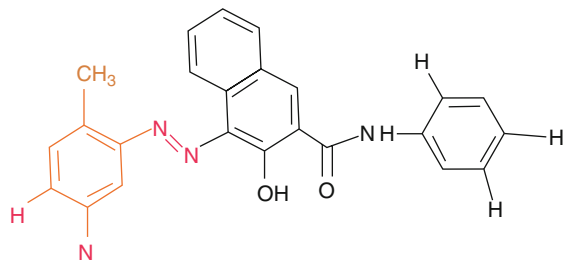

Fig. 14.29 Azo compounds such as the "Pigment Red 22" shown here contain at least one azo group (–N=N–) with a chromophore nitrogen double bond (highlighted in *red*). If this bond is broken – no matter whether by prolonged exposure to ultraviolet light or by laser treatment – a toxic substance is released: 2-methyl-5-nitroanilin (*left* of the azo bond)

Nearly 47% of all tattoo inks on the market feature azo compounds (Fig. 14.29); therefore, this particular group of pigments can serve as an example with which to discuss the problems and risks related to the issue as a whole. For the most part, azo compounds are primarily composed of aromatic amines, aromatic diamines, and nucleophile aromatic or methylene-active aliphatic components. The aromatic amines used have carcinogenic, mutagenic, and teratogenic properties. As a matter of principle they should not be present in any pigment or be able to be cleaved by any azo compound. It is not yet clear whether these substances can develop in vivo during laser treatment. In theory, cleavage products can also form after UV exposure; their clinical relevance is unknown and is probably slight given the low amounts that are released, but a risk cannot be completely ruled out. Research describes a few cases of neoplasias such as malignant melanoma in a tattooed area [47]. Causality is currently difficult to ascertain due to the lack of pharmacological and toxicological studies on the pigments, and at the time of this writing there have not been any epidemiological studies that could confirm the health threat posed by these inks. Surprisingly, the Cosmetics Directive of the EU (Annex IV) forbids the topical use of many pigments, but there are no restrictions about what is injected into the skin. Given the millions of people with tattoos, there is an urgent need for legislation to establish appropriate parameters around the world.

14.5.3 Legal Regulations

The official website of the US Food and Drug Administration (FDA) made the following statement about the situation:

> FDA considers the inks used in intradermal tattoos, including permanent make-up, to be cosmetics and considers the pigments used in the inks to be colour additives requiring premarket approval under the Federal Food, Drug, and Cosmetic Act. However, because of other public health priorities and a previous lack of evidence of safety concerns, FDA traditionally has not exercised its regulatory authority over tattoo inks or the pigments used in them. The actual practice of tattooing is regulated by local jurisdictions. FDA is aware of more than 150 reports of adverse reactions in consumers to certain permanent make-up ink shades, and it is possible that the actual number of women affected was greater. In addition, concerns raised by the scientific community regarding the pigments used in these inks have prompted FDA to investigate the safe use of tattoo inks. FDA continues to evaluate the extent and severity of adverse events associated with tattooing and is conducting research on inks. As new information is assessed, the agency will consider whether additional actions are necessary to protect public health. (http://www.fda.gov/Cosmetics/ProductandIngredientSafety/ProductInformation/ucm108530.htm, accessed on 1 September 2009)

In Germany, the tattoo colourant agents regulation went into effect in May 2009; it regulates the use of tattoo inks and bans azo compounds, which can generate particular aromatic amines via reductive

cleavage [61]. This regulation does not define any purity criteria, however, which means that – as was the case before the regulation was passed – pigments that have not been listed in the EU Cosmetics Directive may be used as long as they do not contain any of the forbidden substances. The regulation is an important first step and serves as a role model for other legislation, even though initially only a minimal improvement can be anticipated in terms of protecting consumers from misleading or incomplete information provided by manufacturers.

The shortcomings of this regulation could be eradicated by mandating that manufacturers provide safety data about tattoo inks, including information about the purity of the ingredients as well as general and specific toxicologic properties. Table 14.4 shows some of the key data that should be included in a safety assessment.

14.5.4 The Ideal Tattoo Ink

From the perspective of the physician and laser operator, the pigment has to have a chemical composition that can be broken down with minimal effort and without the formation of any toxic by-products. To prevent such carcinogenic substances as much as possible, tattoo inks should be completely free of azo compounds; it is unlikely that an aromatic amine will occur as an impurity or be cleaved by a laser if no amines were used as starting substances in manufacturing the pigments.

Table 14.4 Data to be included in a safety analysis of tattoo pigments

Purity criteria
Excipients
Stability (vis-à-vis bacteria, enzymes, ultraviolet light exposure, possibly laser light)
Toxicity categories
Potential for local irritation of skin and mucous membranes
Phototoxicity
Immunotoxicity
Genotoxicity (both of individual substances and cleavage products)

Our research confirms that this is indeed possible: to name one example, H-A-N – *Haus der Angewandten Naturwissenschaften* (Esslingen, Germany) produces organic tattoo inks that contain exclusively polycyclic pigments and deliberately do not have azo compounds. These polycyclic pigments have the aforementioned advantage of not creating any aromatic amines.

Take Home Pearls

- Tattoos are not decals, and lasers are not erasers!
- Despite the latest advances in laser treatment, it is still not always possible to remove each tattoo completely and without complications.
- Restraint should be exercised in laser treatment, especially when multicoloured tattoos are involved, and the patient should be thoroughly informed about residual ink. In every instance, the practitioner should begin by testing the efficacy of the laser system and wavelength in question by performing a trial treatment.
- Thorough informed consent is essential; it must clearly emphasise that the same area of the skin will need multiple treatment sessions and that complete removal is not always possible. Different colours often show different responses to laser treatment, even when they look similar. When there are multicoloured tattoos with several blended colours, it may be advisable for a practitioner to refuse treatment. In some cases, it makes more sense not to treat a tattoo than to do an incomplete job.

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Varicose Veins: Endovenous Laser Treatment

15

Serge R. Mordon and Marc E. Vuylsteke

Core Messages

- Endovenous laser ablation (EVLA) has been developed as an alternative to surgery of the great saphenous vein and short saphenous vein in an attempt to reduce morbidity and improve recovery time.
- EVLA can be performed in an outpatient special procedure room in a hospital.
- EVLA works by means of thermal destruction of venous tissues. Several wavelengths can be used: 810, 940, 980, 1,064, 1,320, 1,470, and 1,500 nm.
- Heating decreases with tissue depth as absorption and scattering attenuate the incident beam. Consequently, the laser beam must heat the vein wall and not the blood.
- Before EVLA is performed, the vein lumen must be emptied of its blood by using leg elevation (Trendelenburg positioning), manual compression, and infiltration with perisaphenous subcutaneous tumescent saline solution.
- The appropriate linear endovenous energy density (LEED) must be selected as a function of the diameter of treated segment. Veins larger than 9–12 mm in diameter are difficult to treat, even when using higher energy.
- In a general manner, side effects are energy dependent. LEED more than 100 J/cm is very often associated to superficial burns and palpable indurations.

15.1 Introduction

Varicose veins are dilated, tortuous veins of the subcutaneous/superficial venous system. Varicose veins represent a significant clinical problem because they actually represent underlying chronic venous insufficiency with ensuing venous hypertension. This venous hypertension leads to a broad range of clinical manifestations, ranging from symptoms to cutaneous findings like varicose veins, reticular veins, telangiectasias, swelling, skin discoloration, and ulcerations. Once venous hypertension is present, the venous dysfunction continues to worsen through a vicious cycle. Over time, with more local dilatation, other adjacent valves sequentially fail, and after a series of valves has failed, the entire superficial venous system is incompetent. This lower-extremity venous insufficiency is a common medical condition afflicting 25% of women and 15% of men in the United States and Europe. The drainage of the superficial system takes several pathways. The most important is the great saphenous vein (GSV). In patients with varicose disease, the GSV is

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_15, © Springer-Verlag Berlin Heidelberg 2011

incompetent in 70–80%. The GSV reflux is due to saphenofemoral junction (SFJ) incompetence. The small saphenous vein (SSV) is affected in about 10% of patients with varicose disease. Sapheno-popliteal junction (SPJ) incompetence and SSV reflux, although less common than GSV reflux, may result in symptoms of equal severity. Isolated anterior saphenous vein reflux occurs in approximately 10% of patients [2, 20, 51]. Another cause of reflux is incompetent perforating veins. All four major causes of reflux can be treated with endovenous laser ablation (EVLA). In about 10% of the patients, varicose veins appear without affecting one of those four pathways.

Treatment of GSV reflux has traditionally been surgical. However, recurrence in 30–60% of cases has been reported [2]. It is also associated with significant perioperative morbidity. Less invasive surgical treatments, including high ligation of the GSV at the SFJ, have been attempted in the hope that gravitational reflux would be controlled while the vein is preserved for possible use as a bypass graft. Unfortunately, ligation of the GSV alone usually results in recurrent varicose veins. Even when high ligation has been combined with phlebectomy of varicose tributaries or retrograde sclerotherapy, recurrence has been the rule. Therefore, when it is determined that GSV reflux is the principal underlying problem, treatment should involve eliminating this source of reflux with ablation of any associated incompetent venous segments [20]. Though inadequate surgery of the SFJ and progression of the disease are mechanisms that explain some cases of recurrence, another important mechanism is neovascularization around the junction after venous surgery. Neovascularization has been reported to be the principal cause of recurrence with clear histologic evidence [51]. Surgery for the incompetent SSV is even more challenging, with more complications and higher recurrence rates, than for the GSV. The potential for damage to the sural nerve with resulting neurological deficit has deterred many vascular surgeons from stripping the SSV routinely [28, 41]. Most commonly, the SSV is ligated only at the SPJ. Recurrence rates of SSV after surgery are about 30–50% at 5 years [2, 26, 47].

Within the last few years, minimally invasive techniques such as radiofrequency ablation and chemical ablation have been developed as alternatives to surgery in an attempt to reduce morbidity and improve recovery time. EVLA is one of the most promising of these new techniques. EVLA is becoming an established treatment option for GSV and SSV incompetence, with success rates comparable to those of conventional surgery [7, 20, 25].

15.2 EVLA Mechanism of Action

EVLA works by means of thermal destruction of venous tissues. Laser energy is delivered to the desired incompetent segment inside the vein through a bare laser fiber that has been passed through a sheath to the desired location.

Several wavelengths have been proposed: 810, 940, 980, 1,064, and 1,320 nm [4, 14, 19, 29, 34] with 810, 940, and 980 being the most commonly used. More recently, use of a 1,470- to 1,500-nm diode laser has been proposed. Wavelengths of 1,470–1,500 nm are preferentially absorbed by water [43, 48].

When using laser light, heat is generated within the zone of optical penetration by direct absorption of laser energy. Absorption is the primary event that allows a laser or other light source to cause a potentially therapeutic (or damaging) effect on a tissue. Without absorption, there is no energy transfer to the tissue and the tissue is left unaffected by the light. Scattering of light occurs in all biological tissues: blood, vessel walls, and perivenous tissue. Due to fluctuations in the refractive index of these media, the propagation of light into the tissue is modified and the scattering affects "where" the absorption will occur, usually reducing the penetration of light into the tissue.

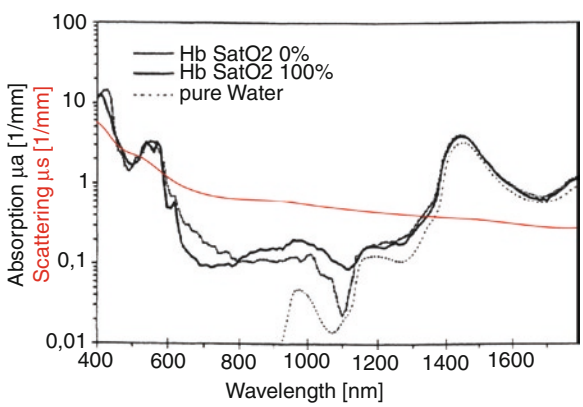

Fig. 15.1 Absorption and scattering (*red*) coefficients of blood relative to wavelength (from Vuylsteke et al. [48])

Table 15.1 Absorption, reduced scattering and extinction coefficients of blood, vessel wall, and perivenous tissue relative to wavelength [48]

	(mm^{-1})	Wavelength				
		810	940	980	1,320	1,500
Blood	μ_a	0.16	0.25	0.28	0.38	3.0
	μ'_s	0.73	0.64	0.6	0.54	0.52
	μ_{eff}	0.65	0.82	0.86	1.02	5.63
Vessel wall	μ_a	0.2	0.12	0.1	0.3	2.4
	μ'_s	2.4	2.13	2.0	1.8	1.7
	μ_{eff}	1.25	0.9	0.79	1.37	5.43
Perivenous tissue	μ_a	0.017	0.027	0.030	0.045	0.35
	μ'_s	1.2	1.1	1.0	0.9	0.84
	μ_{eff}	0.25	0.3	0.3	0.36	1.12

This table clearly shows that the optical extinction is much higher at 1,470–1,500 nm (5–9 times higher) compared to 810, 940, 980, and 1,320 nm. Interestingly, for these wavelengths, the optical extinction is similar for blood and vessel wall

Heating decreases with tissue depth as absorption and scattering attenuate the incident beam. Based on the absorption and effective scattering coefficients of the biological tissue, the optical extinction (μ_{eff}) can be determined [21] (Fig. 15.1, Table 15.1).

15.3 Role of Blood

The exact mechanism of EVLA remains the subject of controversy. Many studies are based on the assumption that during EVLA the vein is filled with blood. Based on our clinical experience with more than 1,000 patients, the presence of blood inside the vein has several consequences [6, 7, 23]:

- Blood around the fiber tip reduces the transmission of light to the biological target of EVLA: the venous wall [49]. Because thermal damage of the inner vein wall (tunica intima) is required to achieve the tissue alterations necessary for permanent vein occlusion, the presence of blood greatly hinders the effect of the laser to the vessel wall.
- If the laser light energy is entirely absorbed by blood, the initial success rate will be mainly due to a thrombotic effect; however, thrombus dissolution will lead to recanalization, as clearly demonstrated by Proebstle et al. [36]
- The presence of blood can generate steam bubbles. The formation of these steam bubbles has been confirmed by Proebstle et al. [33], who have observed that they were generated in hemolytic blood by 810-, 940-, and 980-nm diode lasers, whereas no bubbles were produced in normal saline or plasma. However, this mechanism is now considered of secondary importance for EVLA efficacy [46].
- Last, but not least, the presence of blood induces carbonization at the fiber tip and often melting of the glass fiber tip. This phenomenon implies fiber tip temperatures in excess of 1,200°C. This melting point of the glass fiber tip has been observed by Fan and Anderson [12]. Figure 15.2 gives a good example of the fiber tip destruction obtained when laser irradiation is performed inside a vein filled with blood. The partial destruction of the tip compromises beam homogeneity, which leads to unpredictable energy distribution inside the vein. Furthermore, the carbon layer rapidly forming at the tip absorbs most of the light energy and converts it into heat, radically altering the laser/tissue interaction process.

The variability in the amount of blood within the vein leads to inconstant results. In our experience, before performing EVLA the vein lumen is emptied out of its blood by using leg elevation (Trendelenburg positioning), manual compression, and infiltration with a perisaphenous subcutaneous tumescent saline solution. This solution of local anesthesia serves three purposes. First, the vein itself and the surrounding tissues are anesthetized. Secondly, the fluid around the vein helps to protect the surrounding tissues from any collateral injury from the heat of the laser. This

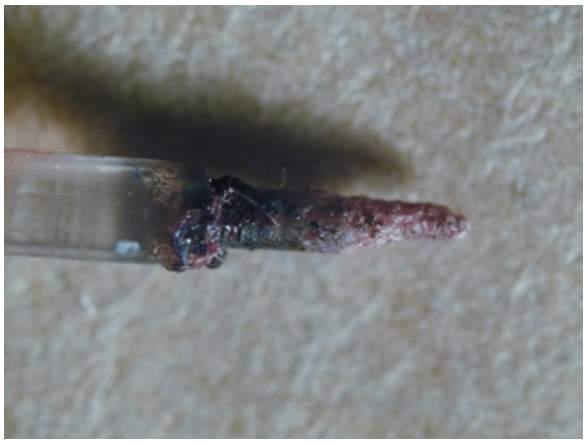

Fig. 15.2 Tip of the fiber inserted in a vein filled with blood; there was no Trendelenburg positioning and no manual compression, only tumescent saline solution infiltration (vein length 45 cm, 980 nm, 15 W, CW)

surrounding fluid acts as a "heat sink" to protect these tissues. Thirdly, the fluid exerts compression around the vein and induces spasm of the vein (Figs. 15.3 and 15.4).

Thanks to these three maneuvers, no or little blood remains in the vein. Figure 15.2 shows the example on a fiber tip after the treatment of a GSV (vein length: 45 cm, 980 nm, 15 W, continuous wave (CW)). This tip is intact with no carbonization (Fig. 15.5).

15.4 Procedure

A clinical history is taken, and physical examination, including duplex ultrasound (US) imaging evaluation of the superficial venous system, is performed in the limbs of patients with varices suspected of arising from the GSV or the SSV. Patients with impalpable pedal pulses; cardiovascular disease; inability to ambulate; deep vein thrombosis; general poor health; and patients who are pregnant, nursing, or planning to become pregnant are usually not treated. Patients with extremely tortuous GSVs or SSVs that would not allow endovenous catheterization and passage of the laser fiber as identified on pretreatment venous duplex US mapping are excluded.

Duplex US is performed in the upright position to map incompetent sources of venous reflux and then to mark the skin overlying the incompetent portion of the GSV starting at the SFJ (Fig. 15.6). GSV diameter is measured, with the patient in an upright position, in different locations (1.5 cm below the SFJ, crural segment, condylar segment, and sural segment) to enable selection of the appropriate linear endovenous energy density (LEED) for each segment. For the SSV, the incompetent portion is marked starting at the SPJ, following the same procedure.

Usually, in an outpatient special procedure room in a hospital, the target extremity is sterilized, prepped,

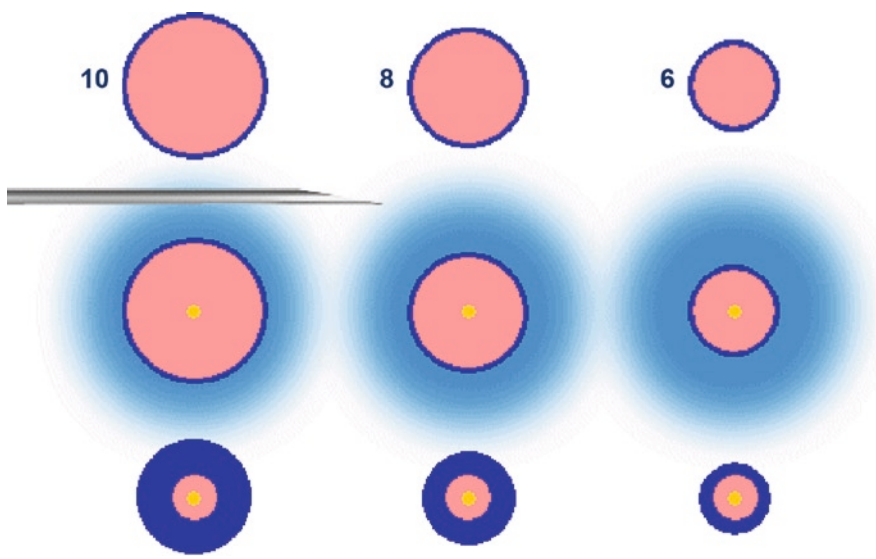

Fig. 15.3 Principle of tumescent anesthesia. This solution of local anesthesia serves three purposes. First, the vein itself and the surrounding tissues are anesthetized. Secondly, the fluid around the vein helps to protect the surrounding tissues from any collateral injury from the heat of the laser. Thirdly, the fluid exerts compression around the vein. Consequently, the diameter is considerably reduced and no or little blood remains in the vein

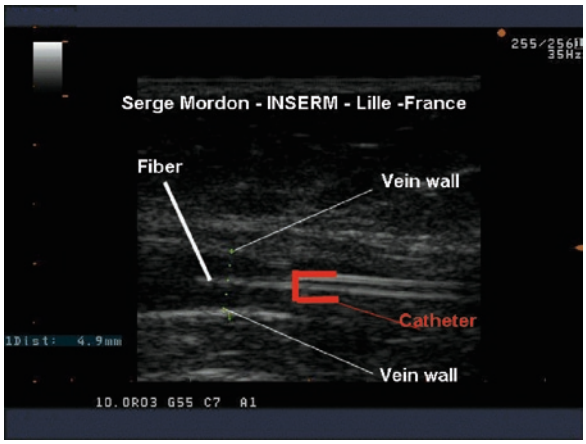

Fig. 15.4 Ultrasound image showing the catheter and the laser fiber inserted in the Saphenous vein

Fig. 15.5 Tip of the fiber inserted in to a vein with almost no blood. In this case, the patient was maintained in Trendelenburg positioning and manual compression was performed (vein length 45 cm, 980 nm, 15 W, CW-tumescent saline solution infiltration)

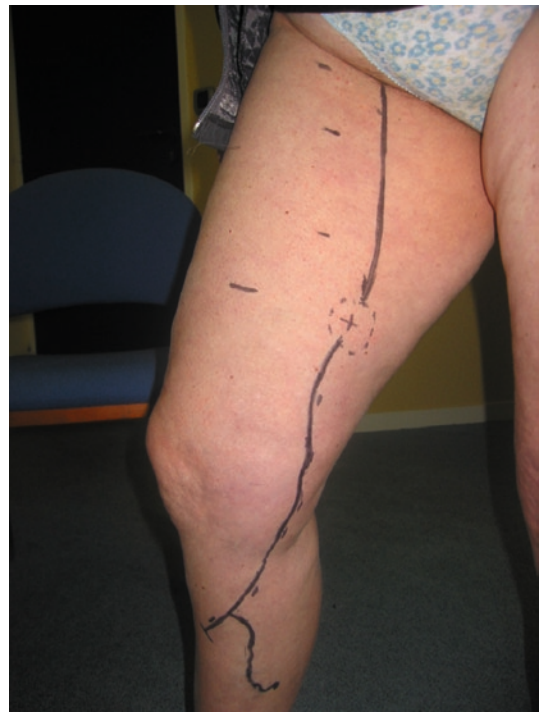

Fig. 15.6 Duplex ultrasound is performed in the upright position to map incompetent sources of venous reflux and then to mark the skin overlying the incompetent portion of the great saphenous vein starting at the saphenofemoral junction

and draped. Under US guidance through a sterile US probe cover, the GSV is visualized at the level of the knee. The vein is percutaneously punctured with a 21-gauge needle under US guidance. A 5-F microintroducer guidewire is threaded through the needle followed by the introducer. A 0.035-in. guidewire is passed under ultrasound guidance up to the SFJ; a 5-F introducer is placed over the guidewire. A 600-μm optical fiber is passed through the introducer to the SFJ. Its position is verified by US and by visualization of the aiming beam through the skin. Duplex control is used to guide injection of 7–8 mL aliquots of the tumescent solution (Fig. 15.7). Several solutions can be used: (a) 10 mL lidocaine 1% withepinephrine and 10 mL lidocaine 1% without epinephrine and an additional 60 mL physiologic serum, (b) 10 mL 1% xylocaine with epinephrine diluted in 200 mL of saline, mainly to not exceed the safe limits of local anesthesia, and (c) a cocktail of 500 mL bicarbonate 1.4% with 1 ampule (20 mL) of xylocaine at 1%. HCO_3 diminishes the burning sensation from the injection of the local anesthesia. It reduces the amount of xylocaine necessary to obtain good anesthesia and accelerates the anesthetic effect [28, 41].

The injections are performed into the fascial space surrounding the vein at intervals down its length. For the SSV, the procedure is similar except that the SSV is cannulated in the mid to lower calf using a 21-gauge needle and that the fiber is passed through the introducer to the SPJ.

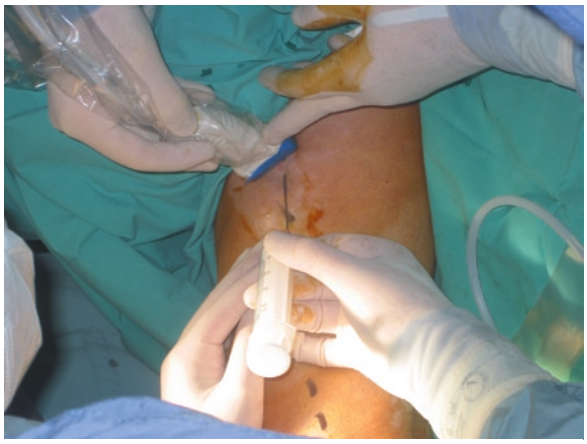

Fig. 15.7 Duplex control is used to guide injection of 7- to 8-mL aliquots of the following solution: 10 mL lidocaine 1% with epinephrine and 10 mL lidocaine 1% without epinephrine and additional 60 mL physiologic serum

To reduce the amount of blood inside the vein, patients are in a 15–20° head-down position (Trendelenburg position) (Fig. 15.8) [6].

Whatever the wavelength is (810, 940, 980, 1,320 nm), power is usually set between 10 and 15 W. The energy is administered endovenously, either in a pulsed fashion (pulse duration of 1–3 s with fiber pullback in 3- to 5-mm increments every 2 s) or continuously with a constant pullback of the laser fiber (pullback velocity ranging from 1 to 3 mm/s) (Figs. 15.9 and 15.10). With these parameters, the average LEED, which is commonly used to report the dose administered to the vein, ranges from 20 to 140 J/cm [24, 36]. Interestingly, even when using 1,450–1,500 nm, the power is set at 15 W and LEED applied is around 100 J/cm [30]. For GSV diameters between 2 and 4.5 mm, the LEED applied is 50 J/cm. The LEED is 70 J/cm for 4.5–7 mm, 90 J/cm for 7–10 mm, and up to 120 J/cm for larger diameters. Consequently, the pulse duration is adjusted for each individual GSV segment from 1.2 s (2 mm) up to 6 s (>10 mm). The last shot is systematically controlled by duplex US to avoid any skin burn and delayed healing. Because tumescent anesthesia is always used, patients feel no pain during EVLA. At the end of the surgical procedure, venous compression is applied for 24 h by irremovable compression bandage (Fig. 15.11). In addition, the patients are asked to wear full-thigh class 2 or 3 compression stockings only during the day for 3 weeks. Patients are instructed to walk immediately after the procedure and to continue their normal daily activities with vigorous workouts. Patients generally report discomfort 5–8 days after EVLA, which is related to the inflammation resulting from successful endovenous ablation (i.e., wall thickening) [42]. It is not related to the presence or degree of ecchymosis, nor is it the result of laser damage to perivenous tissue. If the pain is too intense, nonsteroidal anti-inflammatory drugs can be prescribed.

Fig. 15.8 To reduce the amount of blood inside the vein, patients are placed in a 15–20° head-down position (Trendelenburg position)

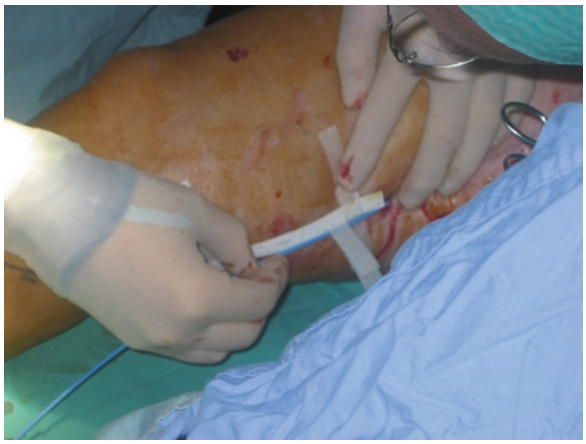

Fig. 15.9 During laser irradiation, the withdrawal of the laser fiber is controlled to apply a constant linear endovenous energy density (in this case, a metric ruler)

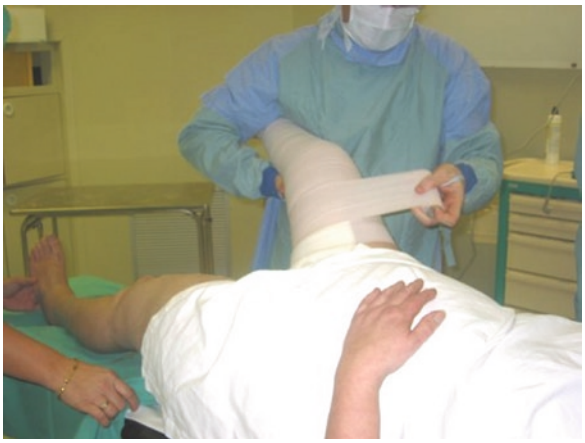

Fig. 15.11 At the end of the surgical procedure, venous compression was applied for 24 h by irremovable compression bandage

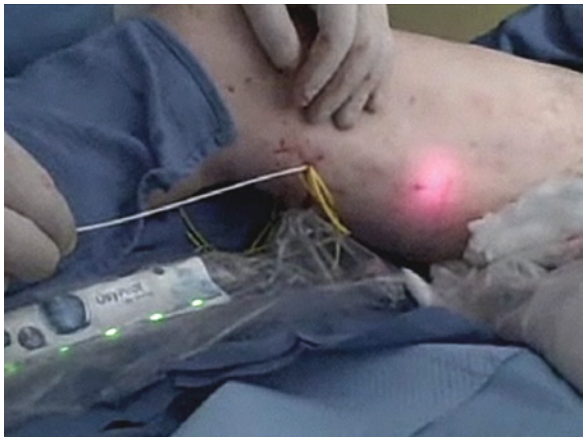

Fig. 15.10 During laser irradiation, pullback of the laser fiber is controlled to apply a constant linear endovenous energy density (LEED) (in this case, the LEED running lights of the Osypilot guide the physician when retracting the fiber from the vein). This controlled fiber withdrawal ensures a precise and consistent delivery of energy throughout the procedure, resulting in maximized safety and results

15.5 Great Saphenous Vein

Valvular incompetence of the GSV is the most common contributor to primary varicose veins. EVLA of the GSV has been widely accepted, and numerous studies already have been published. The largest studies now report data on more than 2,500 patients with a 7-year follow-up. In 2003, [20] have published results of 499 GSVs in 423 subjects with varicose veins treated during a 3-year period with an 810-nm diode laser. Successful occlusion of the GSV, defined as absence of flow on color Doppler imaging, was noted in 490 of 499 GSVs (98.2%) after initial treatment. One hundred thirteen of 121 limbs (93.4%) followed for 2 years have remained closed, with the treated portions of the GSVs not visible on duplex imaging. Forty subjects have been followed for 3 years and no new recurrences were seen at 2 or 3 years that were not present at 1-year follow-up [20]. In 2005, Duran [10] presented a study including 517 GSV in 426 patients with a 24-month follow-up. Among 112 GSVs followed at least 24 months, 98% remained closed or reabsorbed. In 2006, the Italian Endovenous-laser Working Group reported a cooperative multicenter clinical study of 1,050 patients (1,076 limbs) during a 6-year period but with only a 3-year follow-up for all the centers using duplex scanning. The total occlusion rate has been 97% [1]. At 3-year follow-up, Desmyttere et al. [7] obtained an occlusion rate of GSVs of 99.3%. Desmyttere et al. [7] also noted a complete disappearance of the GSV or minimal residual fibrous cord. Finally, in 2009 Ravi et al. [39] reported a 98% occlusion rate in 2,460 GSVs during a 7-year period.

Recanalizations are usually always observed when the SFJ diameter is greater than 1.1 cm in diameter or if the GSV truncular diameter is greater than 0.8 cm [7]. This observation is in agreement with mathematical modeling demonstrating that higher energy should be necessary to treat larger GSV diameters [21, 22]. Several authors have proposed the use of higher LEED to

improve the closure rate. Proebstle et al. [36] have observed that nonocclusion and early reopening of the GSV is energy dependent. Timperman et al. [45] compared two groups of patients: one treated with an average energy delivered of 63.4 J/cm (range 20.5–137.8 J/cm) and a second group treated with 46.6 J/cm (range 25.7–78 J/cm). They showed that failures were mostly associated with the lower LEED. However, treatment failures were also identified in patients who received doses of 80 J/cm or more. Energy delivery for the failures was 120, 80, 110, 98, and 80 J/cm (mean 98 J/cm; SD 18 J/cm), respectively [45]. That failures were always observed when SFJ diameter was greater than 1.1 cm or the GSV truncular diameter was greater than 0.8 cm, where the content of blood is very important even in the Trendelenburg position, confirms that laser irradiation was not sufficient to heat the vessel wall. One can hypothesize that blood remaining inside the lumen could absorb the laser light energy, consequently limiting the light transmitted to the vessel wall.

When performed properly, no dyschromia, superficial burns, thrombophlebitis, or palpable indurations are reported after EVLA. The main side effect is ecchymosis with a rate usually around 50–60%. For example, Sadick and Wasser [40] reported an ecchymosis rate of 61.7%, comparable to the rate obtained by Desmyttere et al. [7]. Proebstle et al. [37] obtained ecchymosis rates of 73.2% (940 nm, 15 W, 1 s, pulsed); 78.2% (940 nm, 15 W, CW); and 81.2% (940 nm, 20 W, CW) [37](Fig. 15.13).

In a general manner, side effects are energy dependent. LEED more than 100 J/cm is very often associated with superficial burns and palpable indurations. For example, vascular perforation with subsequent perivascular bleeding was occasionally (<10%) seen in cases treated with 40–80 J/cm and in all cases treated with 110–200 J/cm [5]. Unintentional vein wall contact and perforation cannot be avoided with any certainty when using a bare-tip fiber [17].

Pain could also be an issue. However, the difficulty with studies that evaluate pain is the significant variation in pain tolerance between patients. What may seem like soreness to one patient might be considered severe pain to another. Even objective measures such as carefully recording usage of pain medication can vary because patients have different pain tolerances. For example, Gibson et al. [13] reported pain in 97% of treated patients. In the series reported by Proebstle [37], the percentage of patients complaining of pain was 72%. In this case, pain was treated with analgesics

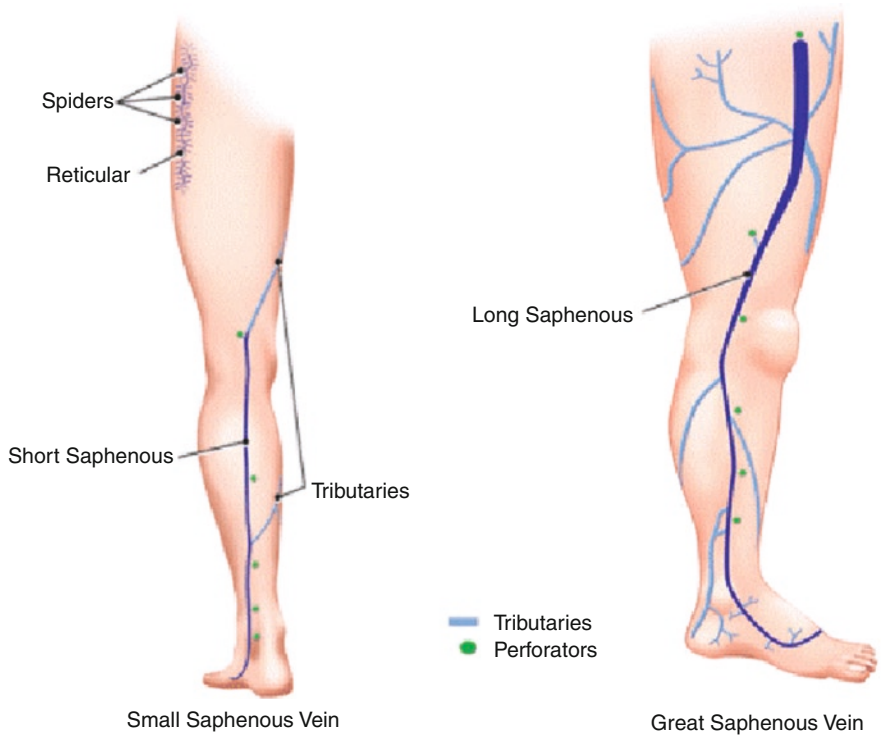

Fig. 15.12 Small saphenous vein and great saphenous vein

Fig. 15.13 Visual grading used to quantify ecchymosis (from Vuylsteke et al. [48])

twice daily. The median duration of pain and the demand for analgesics lasted usually 1 week, with a maximum duration of 2 weeks [37]. Transitory paresthesia was observed in 7% of treated legs with a median duration of 2 weeks. Huang et al. [16] noted paresthesia in 7.2% of patients. In another study, Proebstle et al. [35] reported an 11% incidence of paresthesia for 3–8 weeks after treatment despite postoperative graduated compression for 8 days.

15.6 Small Saphenous Vein

Surgery for short saphenous varicose veins is more challenging, with more complications and higher recurrence rates than for GSVs. If EVLA of the GSV has been now widely accepted as a treatment for primary varicose veins, EVLA is less often used in the treatment of SSV reflux. The reluctance of practitioners to use EVLT for the treatment of SSV incompetence may be related to concerns about the proximity of the sural nerve to the vein as well as concerns about popliteal thrombosis. However, as demonstrated by previous studies, adequate tumescence of the SSV, which theoretically separates the nerve from the vein, can avoid sural nerve injury [13].

As already proposed by [32] EVLA was started from 1 to 1.5 cm distal to the SPJ to avoid leaving a long residual SSV stump. Therefore, for almost all patients, EVLA was conducted proximal to the site where the Giacomini vein is drained. Similar to GSV, the role of blood during the EVLA should be considered because this may reduce the amount of light transmitted to the vein wall. It is usually recommended that the presence of blood be reduced by emptying the vein lumen using leg elevation (Trendelenburg positioning), infiltration with perisaphenous subcutaneous tumescent saline solution, and manual compression. However, larger veins are often only partially compressed by

these measures, and leg elevation may not be enough to empty the vein. Using higher energy has been proposed to avoid the creation of a thrombus, which can recanalize and cause treatment failure [36, 45]. However, larger veins fold usually, and the fiber-tip is found eccentric intraluminal. In such a situation it is difficult to heat the vein wall sufficiently at the opposite side. Consequently, using higher energy can result in perforation and possible perivenous tissue destruction.

The correct tumescent anesthetic technique is essential to ensure that this procedure is safe and painless. A surrounding fascial envelope containing the tumescent solution provides a margin of safety so heat damage to surrounding structures does not occur [3].

LEED applied during treatment was the main determinant of success because thermal damage of the inner vein wall (tunica intima) is required to achieve the tissue destruction necessary to lead the vein to permanent occlusion. Most clinical studies have been performed with equivalent LEED. When using 980 nm, LEED reported by Park et al. [32] varied between 62 and 77 J/cm. Similarly in a study performed by another team (Park and Hwang [31]), LEED was adjusted to between 50 and 60 J/cm. Theivacumar et al. [44] delivered a LEED of 66.3 J/cm (range 54.2–71.6 J/cm). In a recent study, Desmyttere et al. [8] have adjusted the LEED to the SSV diameter: for SSV diameters between 2 and 4.5 mm, the LEED applied was 50 J/cm. The LEED was 70 J/cm for 4.5–7 mm and 90 J/cm for 7–10 mm [8].

The length of vein treated in this last study (18.2 SD 8.3 cm) was similar to that treated by Nwaejike et al. [27] (18 cm; range 5–33 cm) and Theivacumar et al. [44] (17 cm; range 12–20 cm). The mean total energy (1,200 J) was comparable to mean energy reported by Nwaejike: 955 J (range 135–2,800 J). The mean SSV diameter (5.2, SD 1.5 mm) was also comparable to the average diameter of the SSV in the Elias and Khilnani's [11] series of 50 limbs, which was 5.8 mm.

The clinical outcome of EVLA in the SSV has been reported in few articles. In Park et al.'s [31] series, 4 of 95 SSVs recanalized with the recurrence of reflux at 1-month follow-up. Continued closure of the SSV was seen in 89 of 93 limbs (96%) at the 1-month follow-up, in 87 limbs at the 3-month follow-up, in 82 limbs at the 6-month follow-up, in 77 limbs at the 1-year follow-up, in 71 limbs at the 2-year follow-up, and in 55 limbs (100%) at the 3-year follow-up [31]. In [8] study only three recurrences occurred in veins with a diameter greater than 9 mm. Park et al. [32] also observed recanalization of large diameter SSVs, in most cases greater than 9 mm. Because, the energy applied during treatment is the main determinant of success; it seems that LEED was too low in those three cases. This observation is in agreement with Timperman et al.'s [45] clinical study: greater energy delivery improves treatment success of endovenous laser treatment.

Similarly, the incidence of ecchymoses, pain, and paraesthesia was similar to previous studies, and major complications were not reported. In Desmyttere et al.'s [8] study, all paraesthesia was temporary. In Park et al.'s [31] study, only one patient complained of paraesthesia at 6-month follow-up, with complete resolution at 1-year follow up. The ecchymosis rate is also similar to that observed in GSV, usually around 60%.

15.7 New Developments

As explained in above, most complications (ecchymosis, postoperative pain, paresthesias) are mostly due to vein perforations. Two main factors contribute to these complications: (1) an inadequate LEED, which plays a major role, and (2) an unintentional vein wall contact and perforation, which cannot be avoided with any certainty when using a bare-tip fiber [17].

15.7.1 LEED Standardization

A standardized withdrawal of the fiber is required to deliver a reproducible LEED along the vein. For example, Osyris Medical (Villeneuve d'Ascq, France) has developed a system that helps the operator to achieve a consistent energy delivery during EVLA procedures. The running lights of the Osypilot guide the physician when retracting the fiber from the vein. This controlled fiber withdrawal ensures a precise and consistent delivery of energy throughout the procedure (Figs. 15.14 and 15.15).

Similarly, the motorized pullback of the fiber can secure the exact emission of laser energy during the procedure that could contribute to decrease the rates of perforation, posttreatment bruising, and pain [15].

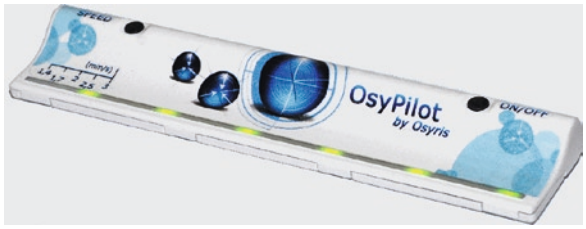

Fig. 15.14 Manual withdrawal can be assisted predetermined speed of the running light-emitting diodes of the Osypilot

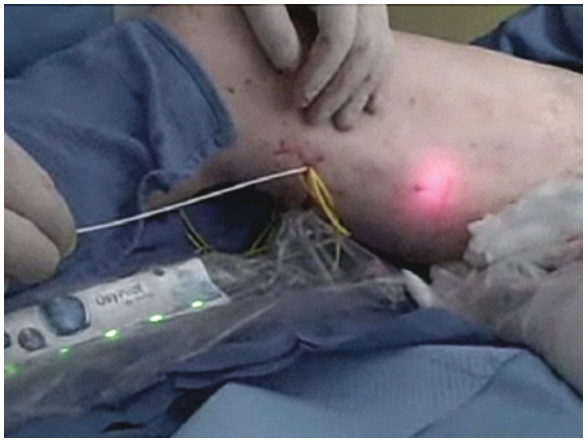

Fig. 15.15 Manual withdrawal can be assisted predetermined speed of the running light-emitting diodes of the Osypilot

Figure 15.16 shows the CoolTouch Corp.'s CTEVTM (Auburn, Calif., USA).

15.7.2 Centering the Bare Fiber

As illustrated in Figs. 15.17 and 15.18, the rigid bare fiber can hit the vein wall during withdrawal and causes ulcerations and perforations of the vein wall.

Recently, two devices have been developed to avoid direct contact of the bare fiber with the vein wall. A possible solution to eliminate vein perforations from laser-tip wall contact is the jacket-tip fiber (NeverTouch, AngioDynamics, Inc., Queensbury, New York, USA) (Fig. 15.19). This type of fiber features a "jacket" at the distal tip of the fiber that covers the energy-emanating portion of the fiber. The jacket prevents the flat emitting face of the fiber from coming into contact with the vessel wall (Fig. 15.19).

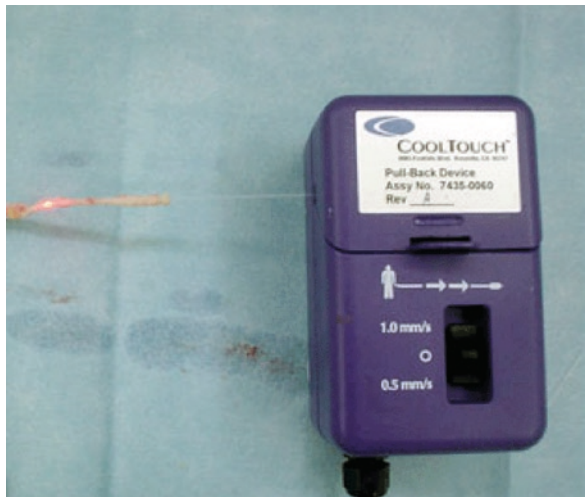

Fig. 15.16 An automated fiber pullback device can withdraw the laser fiber at a rate of 1 or 0.5 mm/s (from Hirokawa et al. [15])

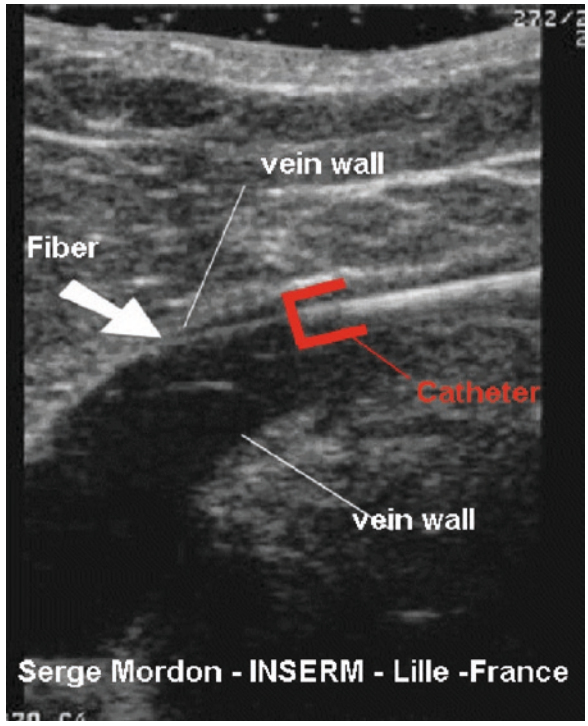

Fig. 15.17 Ultrasound image showing the fiber in contact with the vein wall

A second solution was developed by Vuylsteke et al. [48]. It consists of a tulip-shaped catheter fixed to the fiber to avoid direct contact between the fiber

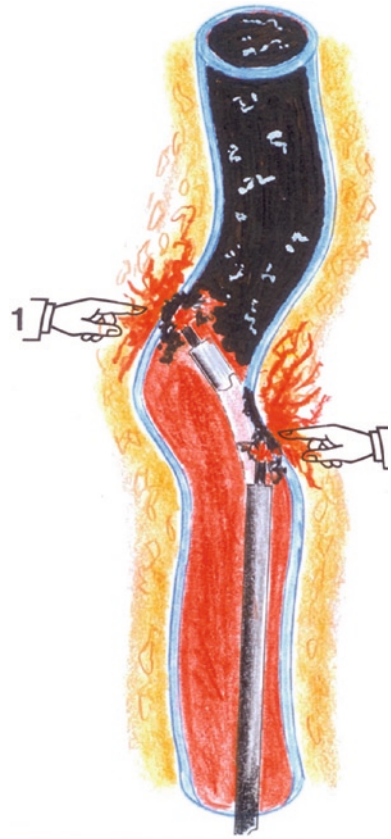

Fig. 15.18 In tortuous veins, the rigid bare fiber hits the vein wall during withdrawal and causes ulcerations and perforations of the vein wall

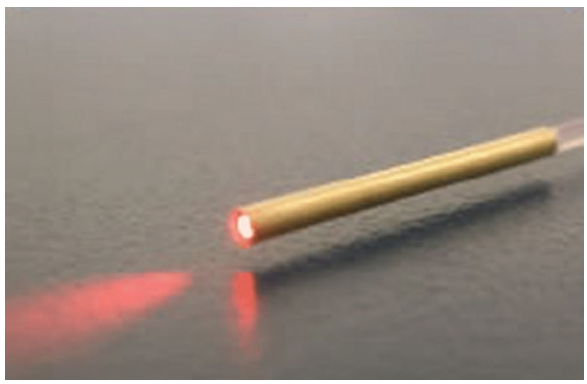

Fig. 15.19 Jacket-tip laser fiber (NeverTouch) developed by AngioDynamics, Inc. from Kabnick and Caruso [17]

tip and the vein wall. This catheter is made of Stainless Steel, a shape-memory and super-elastic material [48].

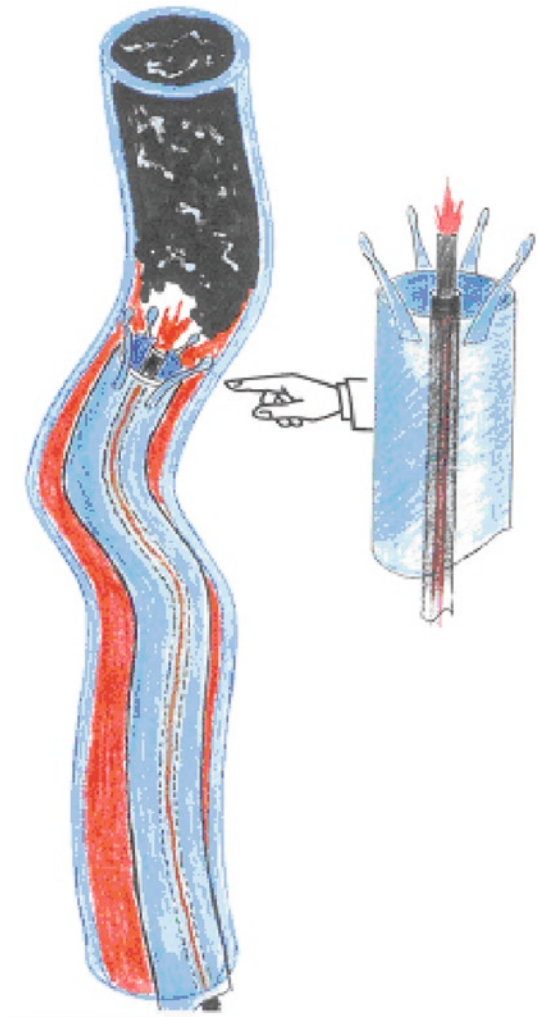

Fig. 15.20 A "Tulip" catheter can be used to center the fiber inside the vein [47]

In an experimental study in goats, Vuylsteke et al. [50] demonstrated that the use of this device avoided the usual ulcerations and perforations of the vein wall. They also observed a more even vein wall destruction with necrosis of a higher percentage of the circumferential vein wall (Figs. 15.20 and 15.21).

15.7.3 Radial Emission

A homogenous, circumferential (360°) energy emission has been proposed recently to avoid the direct

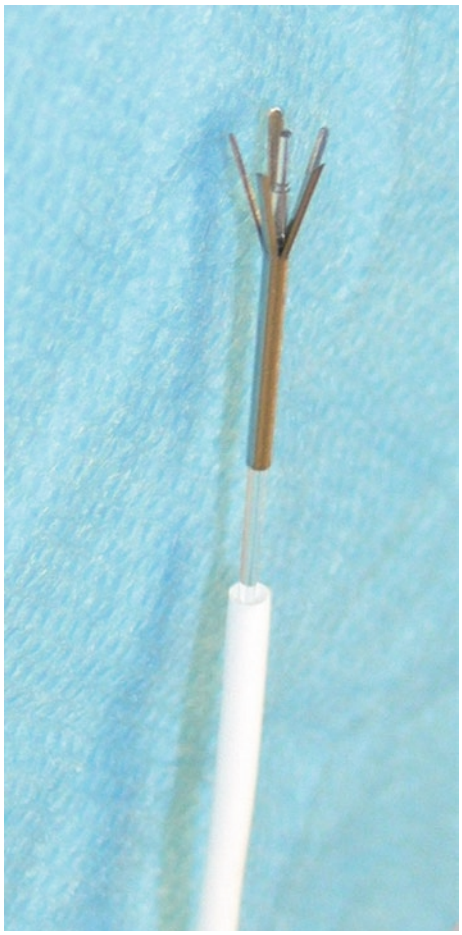

Fig. 15.21 "Tulip" catheter developed by Vuylsteke et al. [47]

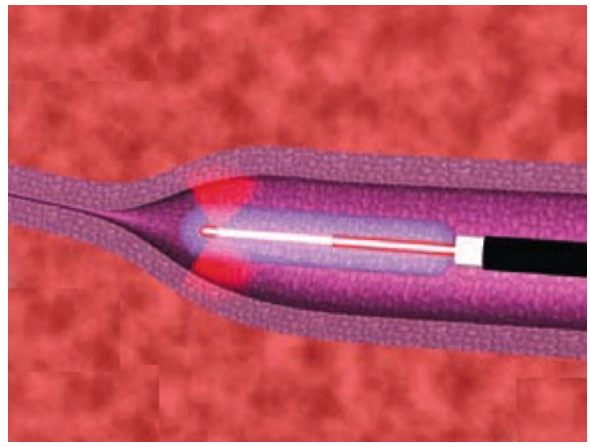

Fig. 15.22 The Elves radial fiber developed by Biolitec

contact of the bare fiber tip (Elves Radial, Biolitec AG, Germany). With this system, the light is directed toward the vessel wall that is the biological target during the EVLA [43]. Long-term follow-up is required to evaluate if the advantages are able to compensate for the higher price of this system compared to the conventional bare fiber (Fig. 15.22).

In conclusion, these new systems could potentially reduce the risk of vein perforations. However, they need to be carefully evaluated.

15.7.4 New Wavelengths

Recently, the 1,470- to 1,500-nm diode laser has been proposed because it is preferentially absorbed by water [43, 48]. However, these wavelengths need to be evaluated carefully. In 2009, there was still a controversy about the power required for treatment. For Maurins and coworkers [18], a power of 15 was required with 1,470 nm, and LEED varying from 90 to 120 J/cm was necessary to achieve occlusion of the vein. However, with such a high LEED, the rate of paresthesia is very high: 9.5% after 6 months and 7.6% after 1 year [18, 30]. For Vuylstke et al. [48] the LEED was reduced to 60 J/cm. For Soracco et al. [43] the average power was in the range of 2–6 W corresponding to a LEED of 10–30 J/cm.

15.8 Costs

Although EVLA is replacing surgical stripping, proper economic evaluation is important to consider the cost of this technique. In a recent study, Disselhoff et al. [9] calculated that the costs of cryostripping and endovenous laser per patient were 2,651 and 2,783€, respectively. When comparing EVLA to high ligation and stripping (HL/S), Rasmussen et al. [38] reported that the HL/S and EVLA groups did not differ in mean time to resumption of normal physical activity (7.7 vs. 6.9 calendar days) and work (7.6 vs. 7.0 calendar days). Postoperative pain and bruising were higher in the HL/S group, but no difference in the use of analgetics was recorded. The total cost of the procedures, including lost wages, was 3,084€ ($3,948 US) in the HL/S group and 3,396€ ($4,347 US) in the EVLA group [38].

Take Home Pearls

- EVLA, when performed under tumescent local anesthesia, is clinically feasible and well tolerated for both GSVs and SSVs.
- Because the vein is accessed via a 21-gauge needle, this is a minimal invasive procedure, leaving virtually no scar on the patient's skin.
- Local cutaneous side effects, such as skin burns, which have been reported in less than 1% of EVLA procedures, can be easily avoided by injection of enough tumescent fluid.
- EVLA offers many potential advantages over conventional surgery for GSV or SSV reflux; the procedure is performed with on-table ultrasound imaging, providing safe and reliable identification of the variable anatomy.
- It is likely that the role of surgery will diminish as endovenous methods such as EVLA become more widely used.

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Common Vascular Lesions

16

Emil A. Tanghetti, Mirko Mirkov, and Rafael A. Sierra

Core Messages

- Wavelength is an important factor for both hemoglobin absorption and depth of effective treatment. Longer wavelengths are better for deeper vascular lesions.
- Spot size is important for both degree of coverage and depth of effective treatment. Bigger spots go deeper.
- Remember that melanin and hemoglobin absorption peaks are very similar. Attention to the degree of pigmentation and tan are important.
- Though oxyhemoglobin is the primary target, met-hemoglobin and clot area are also important, especially when considering multiple pass and multiple wavelength strategies.
- Attempt to match the appropriate pulse duration with the size of the intended target. Shorter pulse durations are better for smaller vessels, whereas longer pulse durations are better for larger vessels.
- Be cautious with high doses (1,064 nm) when treating vascular lesions. Runaway thermal damage is always a risk.

The treatment of vascular lesions is both challenging and rewarding. Optimal results are obtained when the laser surgeon has a complete understanding of the intended target and of the device being employed for the procedure. The location of a vascular lesion in the skin can range from very superficial, as with senile hemangiomas, to deep in the lower dermis and subcutaneous fat, millimeters from the epidermis as with some abnormal leg veins. When choosing the ideal device to treat a specific lesion, the depth of the intended target matters greatly. Figure 16.1 illustrates the depth that each specific wavelength might ideally be used at during a treatment. At the penetration depth, the fluence has dropped to l/e or 37% of its peak value. Dermal targets located deeper than the penetration depth would be exposed to less than 37% of the peak dermal fluence and the treatment efficacy would be significantly diminished. It becomes clear when examining this graph that not all wavelengths are equivalent for the treatment of all vascular lesions. Deeper

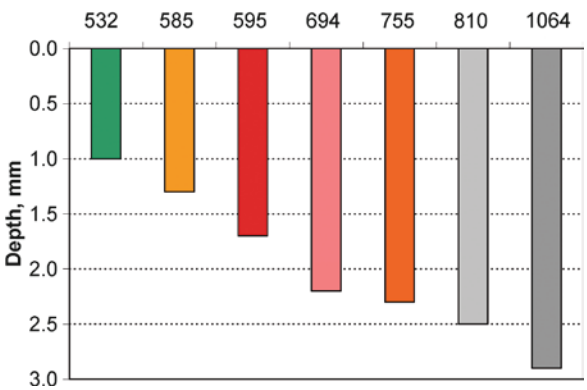

Fig. 16.1 Dermal penetration depth for various laser wavelengths. Penetration depth defined as the depth for 1/e fluence reduction on-axis from its peak value in dermis. Depths calculated from the Monte Carlo model, 7-mm spot size, lightly pigmented adult skin type

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_16,

dermal vessels, 1.2–2.0 mm in depth, often can be out of range for most 532- and 595-nm lasers and intense pulsed light (IPL) devices. By contrast, 755-, 800-, and 1,064-nm lasers can treat superficial as well as deep vessels.

Another important consideration is the spot size of the hand piece used to deliver the light. Many novice laser surgeons often intuitively pick a hand piece that matches the diameter of the intended target. However, because light has to traverse the epidermis and travel at least some dermal distance, there will be loss of photons due to scattering. This results in a less effective transmission at the periphery of the propagated pulse (see Fig. 16.2). With an equivalent fluence delivered to the skin surface using larger spots, there is an increase in the effective depth of delivery of light at both the center and at the periphery of the spot. The plots in Fig. 16.2 also illustrate the different fluence distribution in the skin when using a pulse dye laser (PDL) at 595 nm versus a neodymium:yttrium aluminum garnet (Nd:YAG) laser at 1,064 nm. The PDL radiation encounters larger epidermal absorption due to melanin and larger distributed absorption due to the blood content in the skin. With an equivalent fluence delivered to the skin's surface, the Nd:YAG laser delivers a higher effective fluence at any skin depth. However, due to the much lower blood absorption at 1,064 nm, a much higher fluence is required to achieve equivalent vessel heating. When pain is not a consideration, it is best to use the largest spot available with a device for optimal delivery of light to the intended target. Another approach is to use a smaller spot at a high fluence with the idea that scatter will decrease the fluence of the light as it approaches a deeper target. Ross et al. [25] showed convincingly in a series of studies that this approach works for the long-pulse Nd:YAG laser

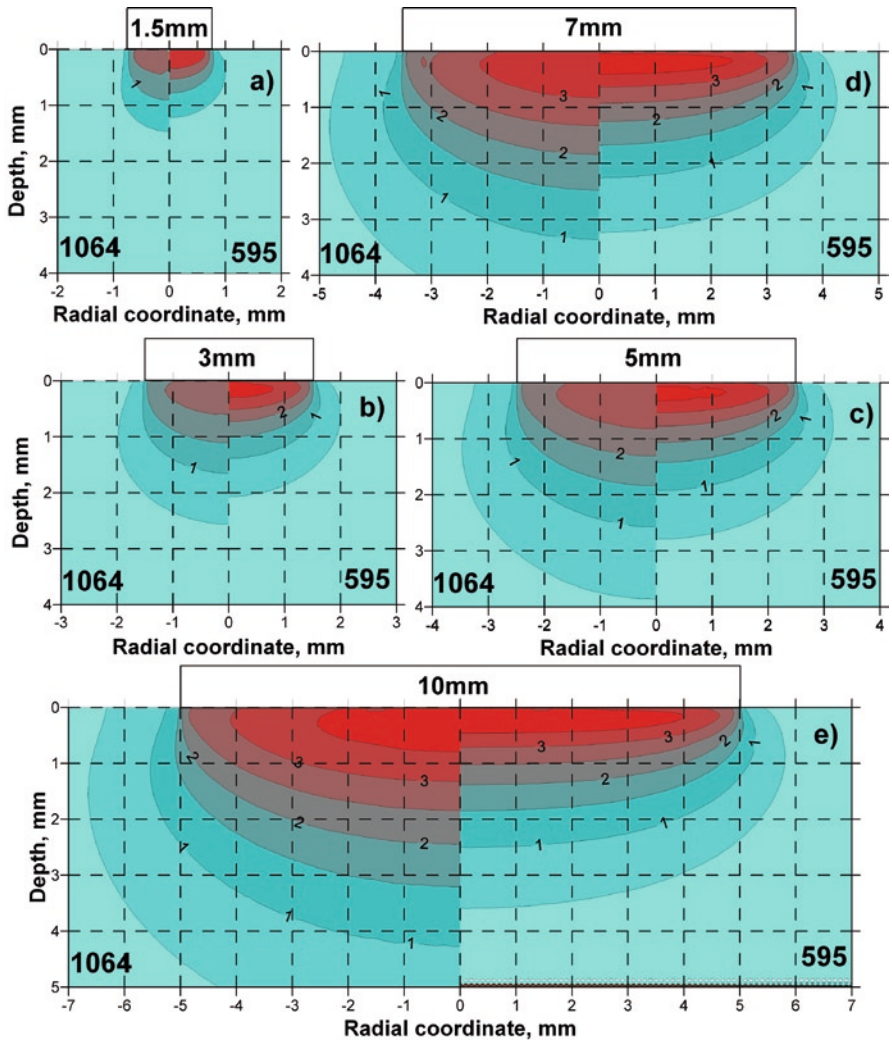

Fig. 16.2 Radiant exposure on skin is a nominal 1 J/cm² in spot sizes of 1.5, 3, 5, 7, and 10 mm (**a**–**e**) 1,064-nm neodymium:yttrium aluminum garnet laser on the left, 595-nm dye laser on the right, lightly pigmented adult skin type

where there is little in the way of epidermal pigmentation. However, with devices such as the high-powered 532-nm devices, 585- and 595-nm PDLs, or a long-pulse Alexandrite laser at 755 nm, this approach can cause significant epidermal damage due to the high fluence required to deliver an effective amount of energy deeper into the dermis [25].

When delivering any type of light to the skin it is important to understand that there are competing chromophores. The most obvious is melanin, which is seen both in the epidermis and within hair follicles, as well as in appendageal structures. The absorption characteristics of melanin and hemoglobin (Hgb) are both important and must be taken into account during treatment (see Fig. 16.3). If the amount of melanin in the skin is limited, as can be seen in untanned individuals with skin types I–IV, cooling can remove the heat that is generated by irradiation before significant epidermal or dermal damage occurs. The cooling can be effectively accomplished by cryogen, contact, or air devices.

The amount of epidermal melanin is significant in individuals who have skin types V and VI or tanned skin. Tanning greatly alters the epidermal pigment load. It is often difficult to discern a recent tan in some individuals. When multiple treatments are required, it is important to remember to question the patient about tanning because repeating a previously well-tolerated fluence after a new tan can dramatically change the range of safe treatment parameters. Treatment of darker skin types or tanned skin can generate a great deal of heat. This thermal load can overwhelm the cooling device employed, leading to blistering and dermal burns. If there is any question of a tan or an issue about the individual's skin type, it would be best to do a small test spot to be evaluated 24–48 h later or wait 4 weeks for the tan to fade. The laser surgeon can also consider using a device such as an Nd:YAG laser that is less susceptible to epidermal pigment absorption and that can be held in check by cooling.

Blood is the primary vascular target. Heating associated with light absorption by Hgb results in damage to the endothelial cells and adjacent structures, thereby destroying vascular channels. Hgb, oxy-Hgb, met-Hgb, and clot are probably the most important targets to consider. Figures. 16.3 and 16.4 show some interesting features of the absorption characteristics of these components of blood. The majority of the Hgb in most healthy individuals' arterial and venous blood is primarily oxygenated Hgb. Met-Hgb and clot are generated

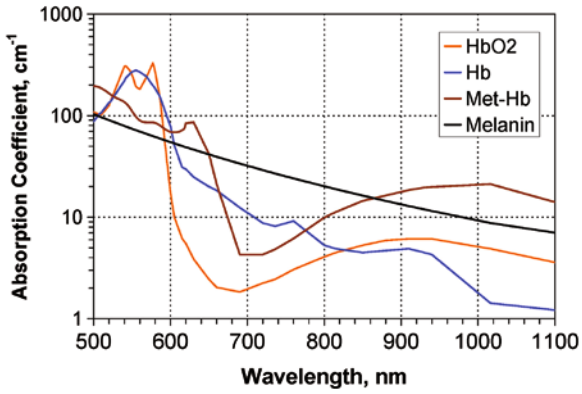

Fig. 16.3 Absorption coefficients for chromophores in the blood and epidermis

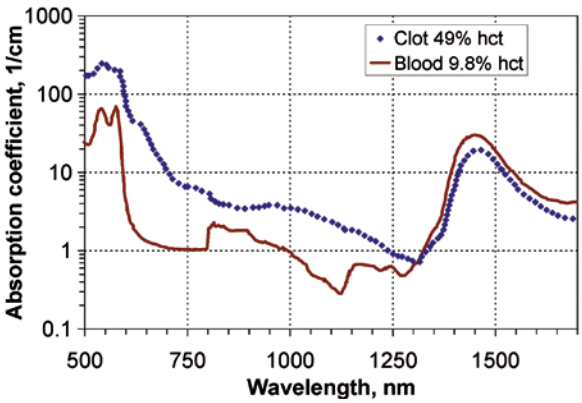

Fig. 16.4 Absorption coefficients for blood and blood clot. From Barton et al. [6]

from a light injury to blood during a typical treatment with a laser or IPL [4–7]. When vessels are treated with multiple pulses or passes, there is an opportunity to further damage a vessel by targeting these chromophores, which often have a greater light absorption coefficient than oxy-Hgb. We performed a series of investigations studying the effects of a single pass, as well as two passes of a 0.5-ms PDL on normal buttock skin, with 1, 10, 30, and 60 s between the passes. We identified a threshold response as the dose of light that resulted in a slight purpuric response, and then biopsied these areas 24 h after the treatment to determine the depth of vascular injury (see Fig. 16.5). Much to our surprise, we found that the depth of injury increased as the delay of the second pulse was varied from 10–60 s after the first pulse. Intuitively, one would have anticipated that the two pulses given at 1-s intervals would have resulted in

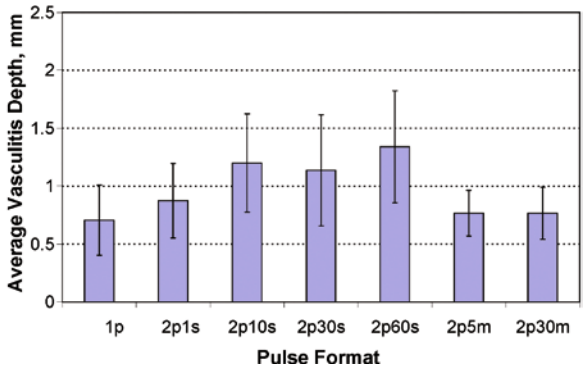

Fig. 16.5 Average depth of vascular injury measured at the purpuric threshold with a 595-nm pulse dye laser with 0.5-ms pulse duration. In the two-pulse series, the pulse separations are 1 s, 10 s, 30 s, 60 s, 5 min, and 30 min

more and deeper damage to targeted blood vessels due to heating. This data suggest that another chromophore, such as met-Hgb or clot, had been generated and resulted in more damage by the second pulse. We also performed a similar series of treatments with time delays in between 1, 30, and 60 s, 5 min, and 30 min at purpuric doses of 7 J/cm^2 with the same 595-nm/0.5-ms PDL (see Fig. 16.6). We found that the depth of injury increased exponentially with more time between the two pulses. These data also strongly suggest that the effects of the second pulse were probably mediated by a different chromophore that had been generated. If the damage were mediated by oxy-Hgb, the damage would have been greatest 1 s after the first pulse. These findings, taken with direct measurement of met-Hgb formation during laser treatment, paint a compelling picture that met-Hgb or clot are generated, and provide another compelling reason to treat vascular lesions with multiple delayed passes [23].

This background can be applied to the very practical issue of the treatment strategy for vascular lesions where the optimally determined dose for treating a particular vascular lesion fails. Some have advocated high dose settings [11, 14, 30]. Unfortunately, this can be accompanied by a risk of unwanted thermal injury from a high heat load. Conversely, we have demonstrated the safety and efficacy of performing multiple passes with seconds to minutes between passes. The heat generated by each individual pass can be effectively eliminated by cooling, with the added benefit of an enhanced result due to the possibility of generating met-Hgb, clot, or a partially damaged vascular target.

The utility of multiple passes with a single wavelength or IPL also suggests the possibility of combining another wavelength to take advantage of this generation of met-Hgb and clot resulting from the first shot. A device was developed that sequentially delivered 595-nm radiation followed by long-pulse 1,064-nm radiation. We have termed this "multiplex" delivery because there are two laser heads in one device that sequentially fires them through a single fiber and hand piece. The utility of this device has been demonstrated in a number of cutaneous lesions, from facial and leg telangiectases to bleb port wine stains [33].

Another way to view the utility of single and multiple wavelengths is to construct a model that describes heating of vessels of different diameters and calculates peak heating (see Fig. 16.7). From a graph of peak temperature, which reflects vascular damage, we can see

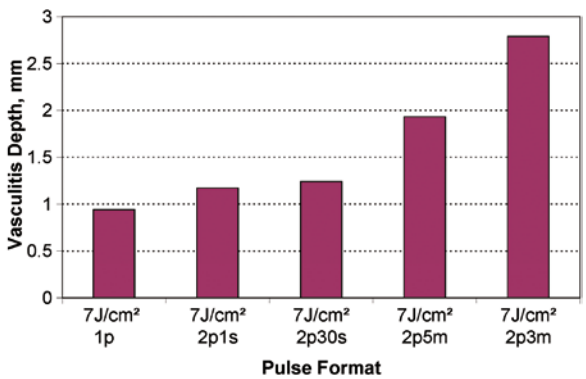

Fig. 16.6 Average depth of vascular injury measured at purpuric 7 J/cm² setting with a 595-nm pulse dye laser with 0.5-ms pulse duration. In the two-pulse series, the pulse separations are 1 s, 30 s, 5 min, and 30 min

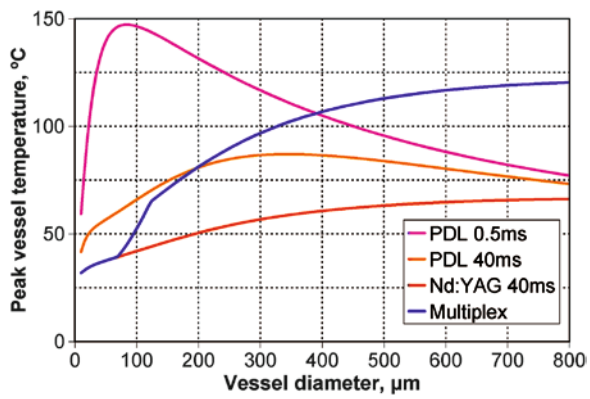

Fig. 16.7 Peak vessel temperature rise calculation based on analytical model published in Mirkov et al. [16]. Pulse dye laser (PDL) fluence is 12 J/cm² in 0.5 or 40 ms; neodymium:yttrium aluminum garnet (Nd:YAG) fluence is 50 J/cm² in 40 ms. In the Multiplex PDL/Nd:YAG combination, the 40-ms PDL is delivered first

that high temperatures are generated by using a 0.5-ms PDL to heat small blood vessels less than 100 μm. This suggestion is confirmed by very real clinical experiences that have demonstrated the efficacy of this pulse duration for the treatment of some infant port wine stains and areas of diffuse facial erythema. However, for larger vessels, the same graph shows much more effective temperature increases with a combination of 595-nm and 1,064-nm radiation.

The major cosmetic problem using the older PDLs with 0.5-ms pulse durations is purpura. This is in large part due to the rupture of small blood vessels from rapid heating at that short pulse duration. To address this issue, a new generation of long PDLs was developed. This was accomplished by combining a train of low-energy pulses lasting 2–40 ms, which is meant to reduce the energy of the individual spikes and allow partial cooling of the small vessels during the time interval between the spikes and avoid purpura. The treatment efficacy for large vessels is not affected by partial cooling between the spikes because of the much slower cooling of the larger vessels. We have demonstrated purpuric thresholds on buttock skin and showed a nearly linear relationship between the number of subpulses and purpura for 40-ms pulse duration (see Fig. 16.8) [16]. For instance, if one were to deliver 12 J/cm^2 for 40 ms with a three-spike device, each spike would consist of 4 J/cm^2 and would surely result in purpura. However, if one were to deliver 12 J/cm^2 during 6 spikes, each subpulse would consist of 2 J/cm^2, and purpura would be avoided (see Fig. 16.9). The benefit of multiple spikes is more pronounced for longer pulse durations that allow sufficient time for cooling of the small blood vessels between the spikes. For short pulse durations like 6 ms, adding more spikes does not leave enough time for cooling between the spikes, and the purpura threshold increase is greatly decreased. A new generation of 6- and 8-spike lasers has been developed by two companies to address the issue of purpura during routine treatment. The same issues of subpulses and pulse energy are applicable to many IPL devices. Each individual unit has its own power and pulse configuration. However, there are now high-energy IPL devices that allow treatments at pulse durations as short as 5 ms that effectively treat smaller vessels and some port wine stains.

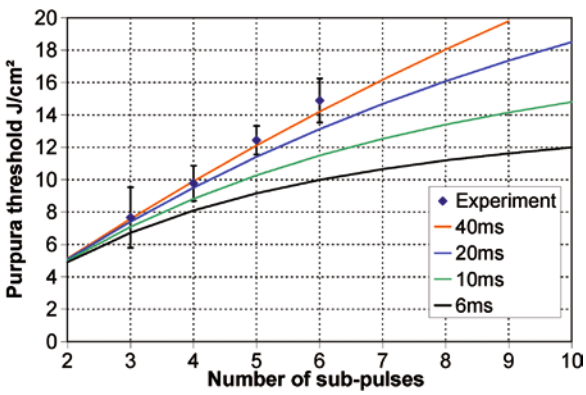

Fig. 16.8 Purpura threshold vs. number of subpulses. Experimental data are for a 595-nm dye laser, 40-ms pulse duration published in [34]. Modeling calculations (*solid lines*) for 40, 20, 10, and 6 ms based on Mirkov et al. [16]. An increased number of subpulses has a larger effect, increasing the purpura threshold for the longer pulses

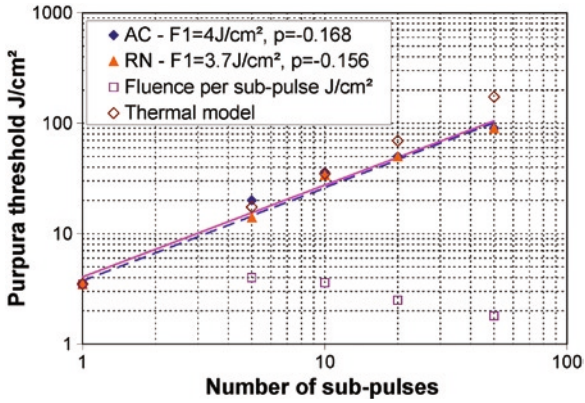

Fig. 16.9 Multiple subpulse clinical data for purpura threshold for two patients (AC, RN). *Straight lines* indicate model based on the Center for Devices and Radiological Health's formula for ocular damage from multiple pulses $F_n = nF_1n^p$ *Open diamonds* indicate thermal model based on Mirkov et al. [16]

Dierickx et al. [10] have cleverly demonstrated that multiple low-energy pulses delivered over many seconds to minutes can achieve an additive effect in gradually wounding the blood vessels of a port wine stain [10]. In an effort to duplicate their experience with a device that could be used in a commercial manner, a laser was developed that could produce a single 150-μs pulse or be combined with a group of five pulses, each 150 μs with 70 ms between the five pulslets and 210 ms between groups of five. This device could produce pulslet configurations of 1, 5, 10, 20, 50, and 100 groupings. The purpura threshold went from 3.5 J/cm^2 at one spike to 180 J/cm^2 at 100 spikes (see Fig. 16.9). The observed purpura thresholds were fitted to a model based on the Center for Devices and Radiological Health's ocular damage guidelines for multiple pulses. Purpura thresholds calculated from a purely thermal model published by Mirkov et al. [16] were in agreement with the experimental data for a small number of

subpulses (less than 20) and progressively diverged for 20 and 50 subpulses. There could be a number of underlying mechanisms producing purpura thresholds that cannot be accounted for in a purely thermal model. It is possible that the 20–50 subpulses delivered in pulse durations of 2–5 s allow for chromophore changes in the blood that lead to more effective heating (and a lower purpura threshold). Or, it is possible that the additive effect of gradual wounding accumulated in less than 2 s, and any pulse 2 s or longer leads to purpura at lower fluences than those expected for a purely thermal process. The longer pulse formats of 50 and 100 pulslets were associated with a significant amount of pain. Unfortunately, single or multiple passes with these pulse configurations did not show an enhanced result in clearing recalcitrant pink/salmon-colored port wine stains. During the longer pulse trains there seemed to be thermal changes in the subcutaneous skin that occurred as a result of heat transmission exchange to the dermis without destroying the targeted vessels. At this juncture, we feel that it is difficult to construct a device that will allow effective practical treatment with seconds to minutes between individual pulses.

Work done many years ago on the use of broadband ultraviolet B and petrolatum by Anderson and Parrish [21] and Parrish et al. [22] demonstrated that there was enhanced transmission of light through psoriatic plaques by the use of this topical agent. There appeared to be a better optical matching of the interfaces with the petrolatum. For years we have been using a clear water-based gel to facilitate cooling with air delivery systems and contact devices. Clinically, this seemed to facilitate the transmission of light with our lasers and IPL devices. Recently, a group at the Beckman Laboratory has demonstrated the ability of topically applied sugar alcohols and dimethyl sulfoxide (DMSO) to facilitate the transmission of light through the skin by mitigating the effects of scattering [8]. Some believe that refractive index matching and skin hydration facilitate this process. There is also a suggestion that some of these agents work by stabilizing the structure of collagen with both sugar alcohols and DMSO. We are hopeful that there will be new products that will help facilitate transmission through both the epidermis and dermis.

To enhance the efficacy of lasers and other light sources in the treatment of vascular lesions, some practitioners have used intravascular-administered photoactivated agents, such as porphyrins. This enhances the destruction of blood vessels. This work has been done experimentally in the USA and has been used clinically in China [12, 18]. This procedure certainly results in the destruction of vessels by appropriate light sources, which excite porphyrins. At this point, this work has to be viewed as experimental and not for routine clinical use, but it does offer an opportunity for future investigations.

One frustrating and little studied area of vascular lesion treatment has been repair and re-emergence of blood vessels after destruction by light. Often, thermal damage heals with the rapid re-emergence of vascular channels that replace those destroyed or damaged by treatment. Cytokines are generated by the inflammatory cells, which are part of the repair process. These factors are potent upregulators of angiogenic factors and are an important part of this problem. Neovascularization that appears after sclerotherapy and laser treatments of leg vessels is probably a common example of this problem. There has been some recent work performed by Dr. Martin Mihm and Dr. Stuart Nelson [17], who have used Rapamune (Pfizer, Inc., New York, New York, USA), an inhibitor of cytokine production, with some success in preventing the reoccurrence of vessels after light treatment. Recently, these investigators and others have reported the use of imiquimod, which upregulates a number of proinflammatory factors after PDL treatments of port wine stains to prevent re-emergence of vascular channels, with limited success [9, 29]. The future of this approach seems to be promising, and we are hopeful that there will be a number of new agents that specifically target the re-emergence of abnormal vascular channels after light treatment.

16.1 Common Vascular Lesions

Facial telangiectases are one of the most common conditions presented to a laser surgeon for treatment. This condition can occur as an isolated problem or be associated with acne rosacea and photodamage. There are many lasers and IPLs that have proven useful in treating this problem. Because most of the targeted vessels are relatively superficial on the face, deeper penetration with longer wavelengths is not essential. High-powered 532-nm lasers with large spot treatments and cooling are clinically useful and very effective without producing purpura [1] (see Fig. 16.10). There are also continuous wave low-powered devices in the 532- and 980-nm ranges, which are useful in tracing superficial vessels. The main limitation of these devices is that high energy delivery through a small spot makes it difficult to treat diffuse erythema with the tracing technique. Multiple

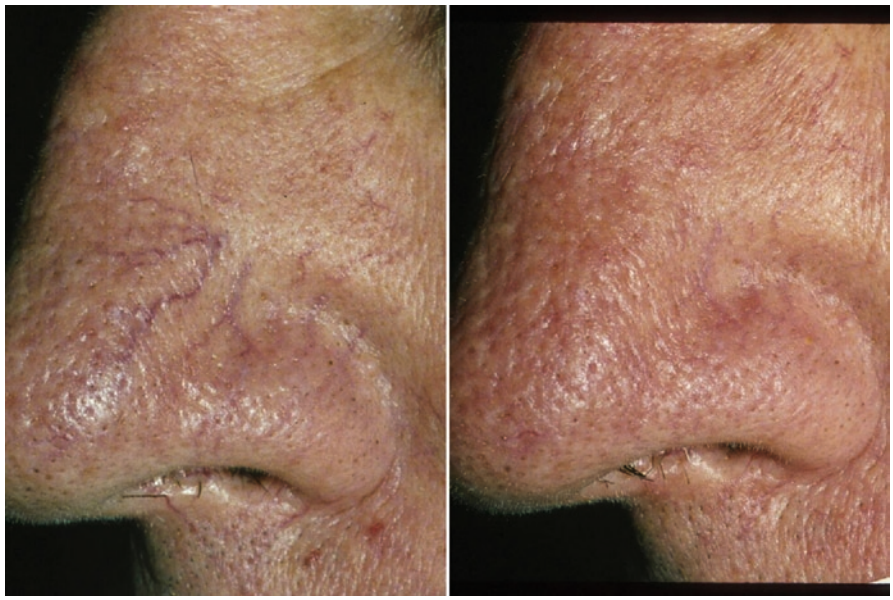

Fig. 16.10 Facial telangiectasia on the nose, treated with a 532-nm potassium titanyl phosphate laser (Versapulse) before (*left*) and after (*right*) one treatment

pass techniques with seconds to minutes between the passes ensure good results with a better safety margin. Pulse stacking with seconds between pulses can result in unwanted dermal thermal damage and scars.

PDLs at 585 and 595 nm have been reliable tools in the treatment of facial telangiectasia and diffuse erythema. The 0.5-ms pulse duration has a high peak power, which results in efficient heating and damage to blood vessels, ranging from 60 to 200 μm. Unfortunately, however, this also results in purpura due to the rupture of some of the smaller blood vessels during the treatment. This intradermal hemorrhage often takes 1–2 weeks to clear. This purpura is a major problem for facial treatments in active working people. Based on the work of Dierickx et al. [10], a generation of PDLs was developed to address this problem.

Vessel rupture is largely dependent on the energy delivered during a 100- to 500- μs pulse. The new long PDLs were developed with multiple individual pulslets of durations of 150–200 μs. They are grouped to be delivered over an interval of 2–40 ms. Initially, the subpulses in these longer pulse durations numbered 3 and 4. Unfortunately, at therapeutic fluences with 10 ms, purpura was seen at the typically used 8–10 J/cm². There were 2.5–3.3 J/cm² per subpulse. This energy resulted in purpura. When the subpulses were increased to 6 and 8, it became possible to give largely purpuric-free treatments. Nevertheless, due to the low peak power of these subpulses, multiple stack pulses and multiple passes are necessary for vascular treatments. The vessels ideally treated at 10 ms are generally between 150 and 300 μm. Diffuse erythema is also seen in many of these patients due to abnormal vessels in the 60- to100-μm range. For these lesions, the 0.5-ms pulse duration or some of the new higher-powered IPLs would be most appropriate.

The combination of 595-nm and 1,064-nm wavelengths is very effective in treating telangiectatic vessels from 150 to 1,000 μm (see Fig. 16.11). The smaller vessels ranging from 150 to 400 μm are best treated in the 10-ms pulse range for the dye and the Nd:YAG laser. The larger vessels, measuring 400–1,000 μm, are ideally treated with the 40-ms pulse duration. In a study that we performed using multiple wavelength devices, we demonstrated approximately a 75% clearance rate in most patients with one to two treatments.

Long-pulse devices with a 1,064-nm wavelength are useful in treating patients with facial telangiectasia [26]. In some instances, small spots have been used to trace vessels, and others have used larger spots with higher energies to eradicate telangiectatic vessels. The only concern is the narrow margin of safety noted between the therapeutic and toxic doses.

There are many IPL devices that have been used for the treatment of facial telangiectasia (see Fig. 16.12). It is important to understand that these devices are unique and from different manufacturers. Cutoff filters and the optic spectrum are often very different. The power of some of these devices makes it difficult to treat smaller vessels at pulse durations as short as 5 ms. Like lasers, IPLs are often best used with multiple passes to treat

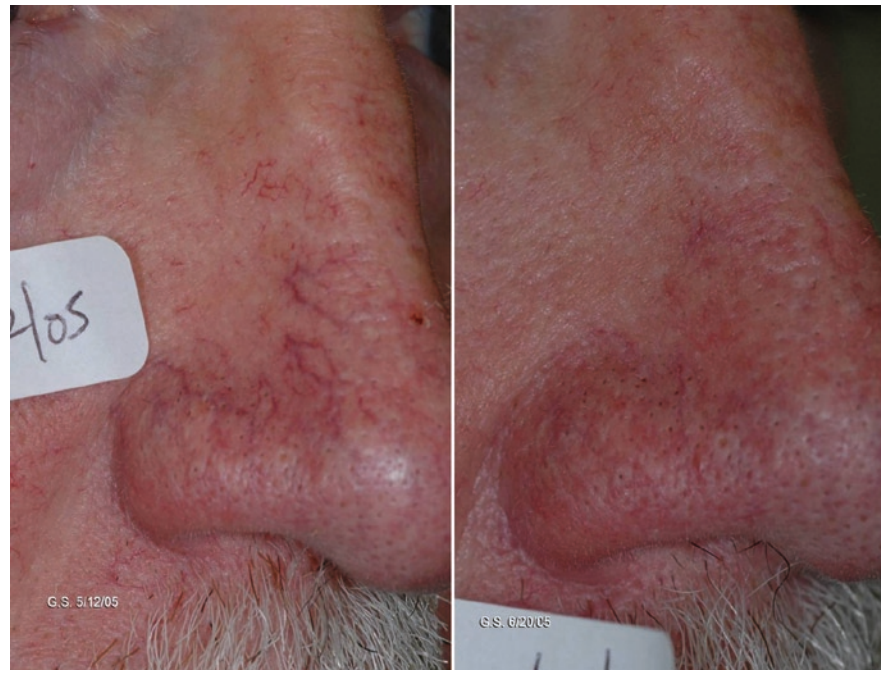

Fig. 16.11 Facial telangiectasia on the nose treated with a combination of 595- and 1,064-nm Cynergy Multiplex before (*left*) and after (*right*) one treatment

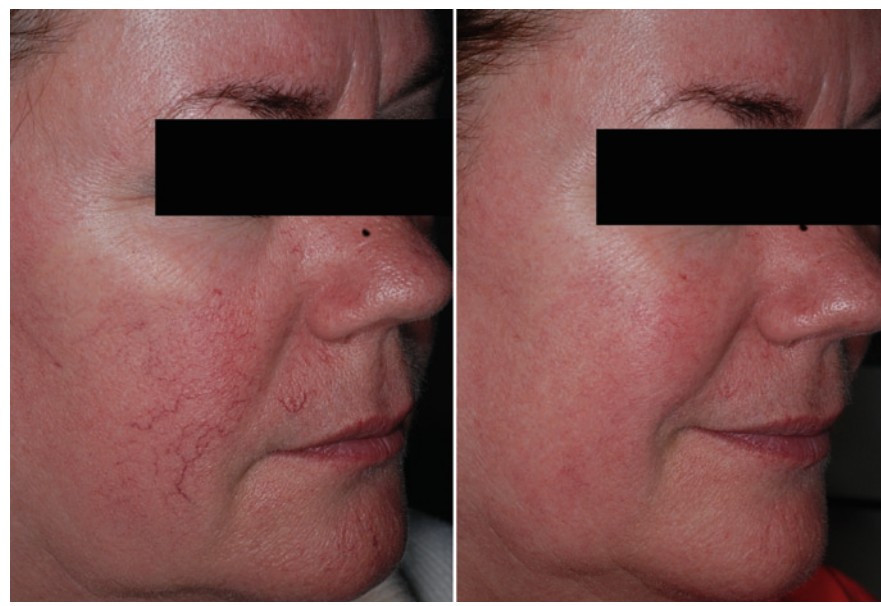

Fig. 16.12 Facial telangiectasia treated with intense pulsed light before (*left*) and after (*right*) one treatment

lesions when one moderately powered pulse is ineffective. Attention to tanned skin is also very important.

16.2 Leg Veins

These lesions are often deeper in the dermis than are facial telangiectasia. They exist in a complicated milieu with feeder vessels and are often in communication with larger vessels with incompetent valves. Sclerotherapy is the "gold standard," but not all patients desire or are tolerant of this type of therapy. Most of the mentioned vascular lasers and light devices have been used to treat this problem. The smaller red vessels measuring 300 μm or less and areas of neovascularization from previous treatments can be treated with only fair results. These vessels often reappear hours to months after treatment. The high-powered large spot,

532-nm lasers, and 595-nm PDLs are useful for this problem [2]. However, these devices are often largely ineffective for the treatment of the larger vascular lesions that are commonly located deeper in the dermis due to the depth limitations of the wavelengths used.

Larger and deeper vessels (0.3 mm and larger) can be treated effectively with 755-nm Alexandrite lasers, long-pulse 1,064-nm lasers, and the combination 595-nm/1,064-nm devices. Kauvar [13] showed good efficacy using a 3-ms Alexandrite laser with cryogen cooling at 80–90 J/cm². Unfortunately, there was some degree of posttraumatic hyperpigmentation that persisted for many months. We performed a similar study using a 40-ms Alexandrite laser with air cooling at 40–50 J/cm² with similar results and less dyspigmentation [27] (see Fig. 16.13). Ross et al. [25] recently demonstrated in a dose-ranging study that the optimal treating pulse duration for these devices is somewhere between 40 and 60 ms. Adrian [32] also demonstrated the utility of an 800-nm, diode laser with contact cooling to effectively treat these lesions [32]. He used a device with a contact cooling tip, which, with gentle compression, brought the light source closer to the intended target.

The 1,064-nm long-pulsed laser has been used with good success to treat leg veins. The optimal pulse duration for treating smaller vessels between 0.2 and 0.5 mm is between 5 and 20 ms [19, 20]. For larger vessels 0.6–1 mm in diameter, 30–60 ms was found to be optimal. Some practitioners use a large spot (6–7-mm) device with appropriate fluences, whereas others use a smaller 3-mm spot with higher fluences. A constant concern is unwanted thermal damage that sometimes can occur as a result of the narrower therapeutic window of a 1,064-nm device.

The use of 595-nm/1,064-nm together is very effective for the treatment of leg veins [3] (see Fig. 16.14). The 10-ms pulse duration for dye and Nd:YAG lasers,

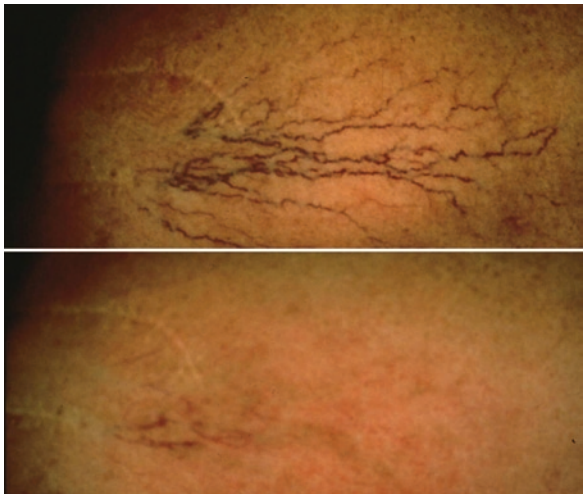

Fig. 16.13 Leg telangiectasia treated with a 755-nm long-pulse Alexandrite laser before (*top*) and after (*bottom*) one treatment

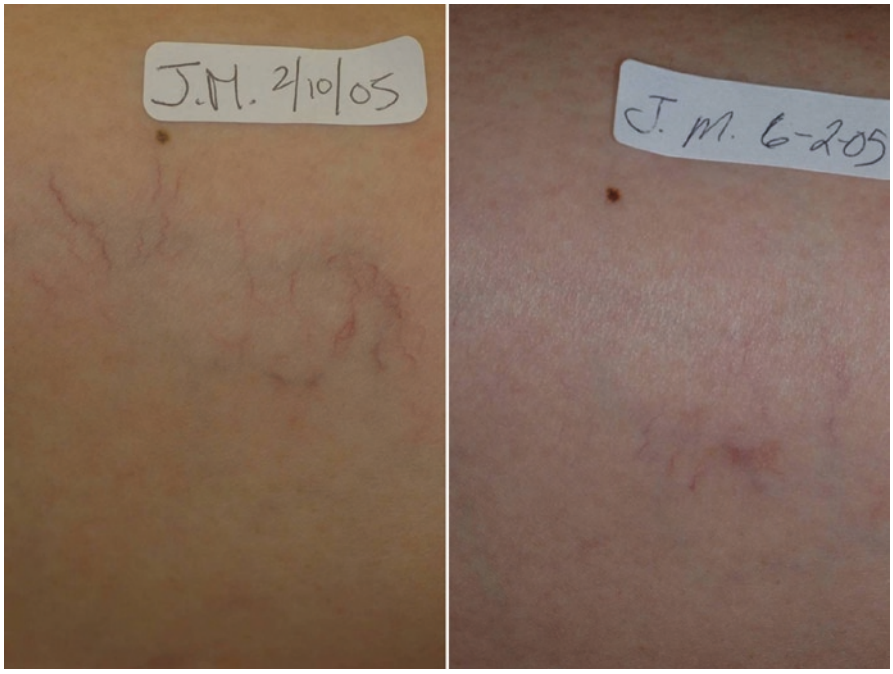

Fig. 16.14 Leg telangiectasia treated with a combination of 595-nm/1,064-nm Cynergy Multiplex before (*left*) and after (*right*) one treatment

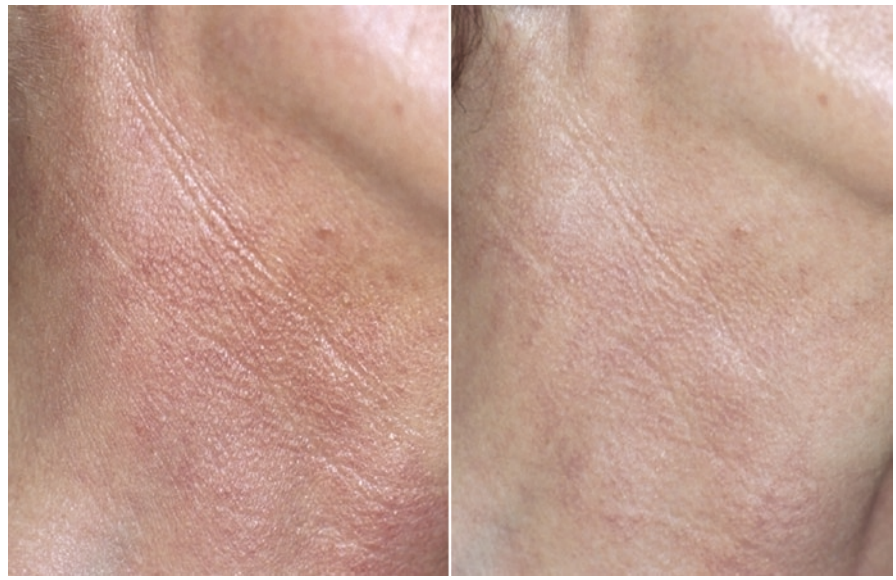

Fig. 16.15 Poikiloderma of Civatte treated with intense pulsed light before (*left*) and after (*right*) three treatments (courtesy of Dr. Syrus Karsai, Laserklinik, Karlsruhe, Germany)

when used sequentially, is clinically useful for vessels between 0.2 and 4 mm, with a 75% clearance rate with one to two treatments. The longer pulse duration of a 40-ms dye and Nd:YAG laser combination is ideally suited to treating the larger vessels between 0.4 and 1 mm, with 75% success rates after one or two treatments. Unfortunately, some degree of hyperpigmentation can occur with this device. However, one author notes that this is much less common with the combined wavelengths than with the Nd:YAG laser alone.

16.3 Poikiloderma of Civatte

This problem is a manifestation of chronic solar damage resulting in hyperpigmentation and redness, particularly of the chest and neck. There are often striking differences in the degree of hyperpigmentation and erythema in individual patients. Because epidermal pigment is the first chromophore in the path of any light device, it is essential to remember that the fluence should be appropriate and not overwhelm the ability of a particular device to cool both the epidermis and dermis. If the pigment load is too great, overheating can occur. This is problematic in areas such as the neck where the dermal thickness is only 100–150 μm. Overheating this thin area can significantly damage the dermis and appendages, resulting in a scar. Many do not treat the neck and chest during the summer months when sun stimulates melanin deposition in the epidermis. Even with sunscreen use, a significant tan can and does occur. During the fall and winter months, treatments are often successful, especially when combined with a hydroquinone-based system. The high-powered 532-nm and 585- to 595-nm PDLs have been used with success [15]. In one of the authors' opinion, the IPL devices are probably best suited to treat this problem due to the spectrum of action against melanin as well as Hgb (see Fig. 16.15). If there is any doubt about the ability of a patient to tolerate a specific treatment of a test spot is highly recommended. Treating small areas with an evaluation after 24–48 h will often demonstrate the ability of a patient to tolerate a treatment plan. It is important to remember when using IPL devices that the pulsing, filters, and cooling are different from one device to another [24, 31]. It is also important to check the manufacturer's recommendations and correlate them with the laser surgeon's personal experience.

16.4 Spider Hemangiomas

These lesions are common in children and sometimes reverse spontaneously during puberty. They are also a common occurrence among pregnant women and can

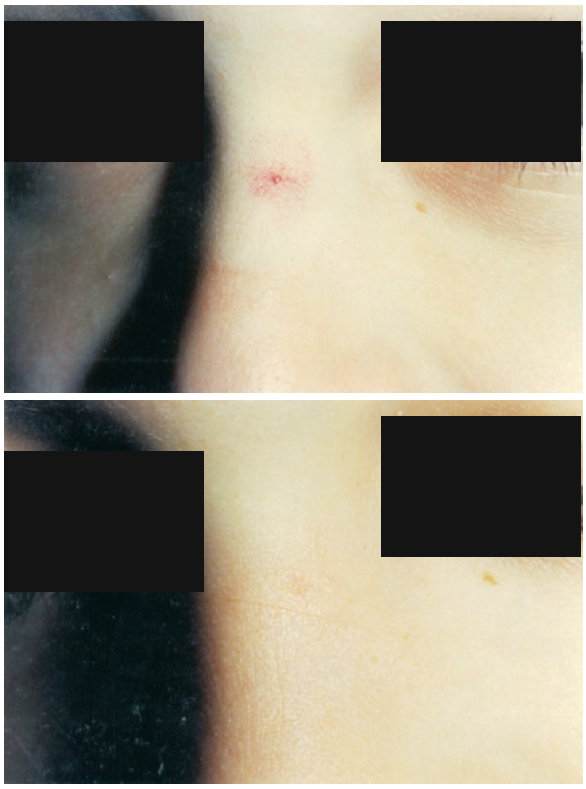

Fig. 16.16 Spider hemangioma treated with 595-nm pulsed dye laser, before (*top*) and after (*bottom*) one treatment

be seen with some hereditary conditions, such as hereditary hemorrhagic telangiectasia. These lesions often have a central dilated vessel. They can be treated with most vascular lasers. We agree that they are often best treated with a PDL or a high-powered 532-nm device. Because there is often a larger dilated feeder vessel, these lesions seem to respond best to a 40-ms pulse duration with energies of 13–15 J/cm² with both of these devices (see Fig. 16.16). Most IPLs, low-energy 532-nm lasers, and 980-nm diode devices can also be used.

16.5 Senile Hemangiomas

These lesions can be treated with a wide variety of devices but are best treated with a PDL at 40 ms with 14–15 J/cm² and a 7-mm spot. The high-powered 532-nm devices at 40 ms between 13 and 15 J/cm² can also be used effectively. This longer pulse duration is ideal because these lesions are composed of densely packed vessels, which absorb light much like a larger mass of blood or vessels. Sometimes multiple passes with cooling between pulses are necessary to achieve adequate vascular damage.

16.6 Venous Lake

Venous lakes are very common about the lips and other mucous areas. They are large vascular channels, which are often deeply situated and respond nicely to most high-powered, long-pulse devices with pulse durations of 20–60 ms (see Fig. 16.17). It makes good sense to consider using PDLs, 755-nm Alexandrite lasers, long-

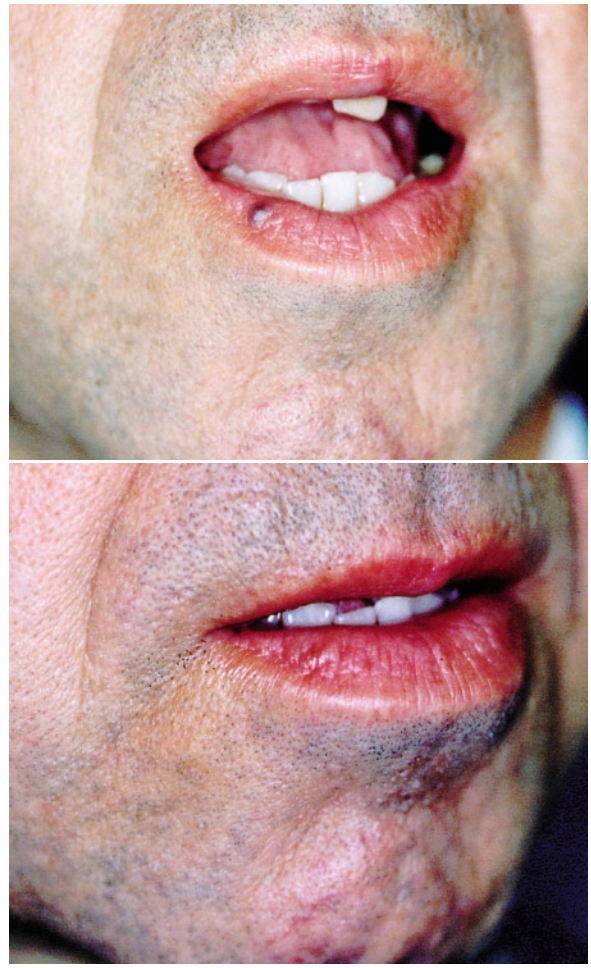

Fig. 16.17 Venous lake treated with a 532-nm potassium titanyl phosphate laser (Versapulse) before (*top*) and after (*bottom*) one treatment (courtesy of Dr. Syrus Karsai, Laserklinik, Karlsruhe, Germany)

pulse Nd:YAG lasers, and the combined 595-nm/1,064-nm multiplex device. This combination wavelength device can also be used effectively to treat bleb port wine stains as well as venous lakes with a 40-ms pulse duration of dye at 11–12 J/cm², followed 1–2 s later by 30–60 J/cm² of the Nd:YAG laser at 1,064-nm. Some authors have also used IPL devices effectively for these lesions.

16.7 Conclusions

This brief review has focused on the ability of many devices to treat a wide array of common vascular lesions. It is important to remember that devices from different companies can have substantially different pulse structures, hand piece specifications, and cooling abilities. IPLs can also have many different spot sizes, cooling mechanisms, and filters. All of these characteristics make each of these devices unique. It is often difficult to transfer parameters and settings from one company's device, such as with an IPL or PDL, to another company's machine. Finally, it is important to recognize and remember that the visible tissue responses experienced during a typical laser treatment are a much more important guide than a predetermined dialed-in setting.

Take Home Pearls

- Larger spots enhance the depth of penetration.
- Multiple passes are useful in the treatment of vascular lesions when a single pass is not effective.
- Consider multiple wavelength treatments when dealing with larger bleb lesions or other resistant vascular lesions to take advantage of generation of met-hemoglobin and clot.
- Longer pulse durations are best for larger vessels, and shorter pulse durations are ideal for smaller blood vessels.
- When there is a question of epidermal pigment or tan, consider performing test spots with a delayed reading before treating the entire lesion.

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Vascular Lesions: Port Wine Stains

17

Sean Lanigan

Core Messages

- The pulsed dye laser is the treatment of choice for most port wine stains.
- Only a minority of patients have their port wine stains cleared completely after treatment.
- Vascular-specific lasers, particularly the pulsed dye, can treat a variety of cutaneous vascular disorders.

17.1 Port Wine Stain Treatment with the Flash Lamp Pulsed Dye Laser

Port wine stains (PWSs) are benign vascular birthmarks that comprise abnormal, ectatic capillaries in the superficial dermis. They affect 0.3% of the population. Unlike strawberry hemangiomas, PWSs do not involute and persist throughout life. PWSs are thought to be caused by a deficiency of perivascular nerve endings leading to a passive dilation of dermal capillaries.

PWSs are usually flat and pink in infancy, becoming darker, more purple, and nodular with advancing age. They can lead to significant morbidity, especially when they are located over the face (Fig. 17.1).

The flash lamp pulsed dye laser (PDL) was the first laser specifically designed for the selective photothermolysis of cutaneous blood vessels and is considered the best laser for the overall treatment of a mixed population of patients with PWS, although individuals may benefit from other lasers.

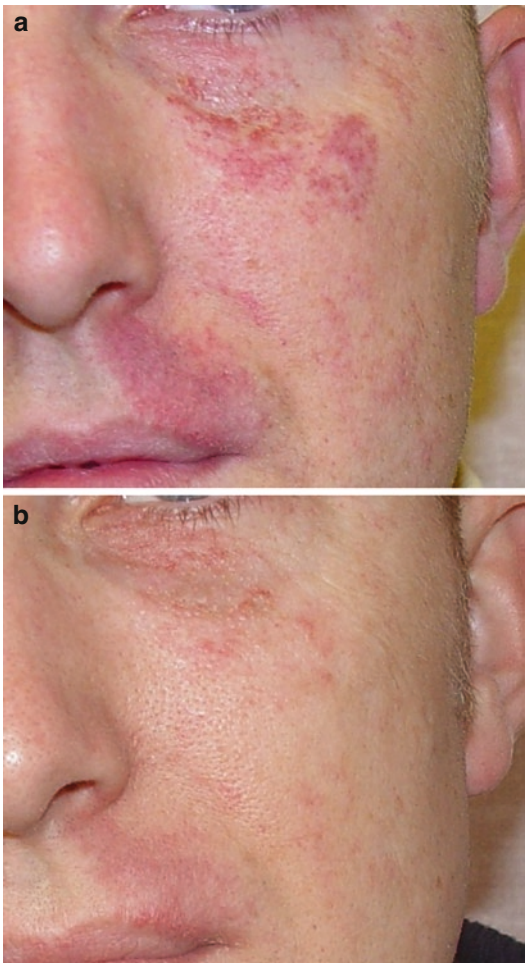

Fig. 17.1 (**a**) Port wine stain on face before treatment. (**b**) Port wine stain on face after pulsed dye laser treatment

The majority of researchers use subjective criteria for improvement compared with baseline photography.

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_17, © Springer-Verlag Berlin Heidelberg 2011

Approximately 40% of patients with PWS achieved 75% lightening or more after laser treatment and more than 80% of PWS lightened by at least 50% [9]. Laser treatment failed to eradicate PWS in a significant number of patients despite a prolonged course of treatment. Several prognostic criteria had been put forward to assist in predicting the outcome of treatment. Some authors reported best results in pink lesions [6]; others report better results in red lesions [20]. In a study of 261 patients treated over a 5-year period [9], the color of PWS was not found to be a prognostic value. Although it is generally considered that younger children will require fewer treatments than adults, Alster and Wilson [1] reported that younger children may require more treatments because of the rapid growth of residual blood vessels between treatments. Van der Horst et al. [21] found no evidence that treatment of PWS in early childhood was more effective than treatment at a later stage.

Two features that may affect outcome are site of the PWS and size of the nevus. PWS on the face and neck respond better than those on the leg and hand [11]. On the face, PWS on the forehead and lateral face respond better than those over the middle of the face, particularly those involving the second branch of the trigeminal nerve [18]. The chest, upper arm, and shoulder generally respond well. PWSs less than 20 cm^2 at the initial examination cleared more than those greater than 20 cm^2 irrespective of age [14].

The majority of patients who experienced satisfactory lightening of their PWSs do so in their first four to ten treatments. Although improvements can occur beyond 20 treatments, the small benefits should be balanced with the morbidity from treatment [10].

Efforts to improve results with laser treatment of PWS have led to modification of the original PDL design and have given rise to a number of second-generation lasers. The most important modifications include longer pulse widths, longer wavelengths, higher fluences, and the use of dynamic cooling devices. Many of these lasers have proved to be useful in the treatment of PWS [2, 4, 7, 19].

For example, Geronemus et al. [7] used the Sclerolaser®, which has a 595-nm wavelength, 1.5-ms pulse width, and fluences up to 11–12 J cm^{-2} with a dynamic cooling spray, and obtained more than 75% clearing of PWS in 10 out of 16 patients (63%) after four treatments. All patients were children younger than 12 months of age.

Recent work using high-fluence long-pulsed dye lasers with cryogen cooling (V beam®) in the treatment of resistant PWS has demonstrated that further lightening can be obtained, though this may be at the expense of an increased incidence of side effects [12].

17.2 Other Lasers and Light Sources for Port Wine Stain Treatment

17.2.1 The KTP Laser

The potassium titanyl phosphate (KTP) laser emits green light at 532 nm. High fluences are available with this laser and the pulse durations may be more appropriate for some PWSs. The KTP laser has been shown to produce further lightening in PDL-resistant lesions [3]. In this study, 30 patients with PWS that had failed to lighten after at least five treatments with the PDL at 0.5-ms pulse widths were treated with the KTP laser. Fluences ranged from 18 to 24 J cm^{-2} with pulse widths of 9–14 ms. Five patients (17%) showed more than 50% response. In general, patients preferred the KTP laser because there was less discomfort and purpura. However, two patients (7%) developed scarring.

A study comparing the PDL with a frequency-doubled Nd:YAG laser showed similar response rates among 43 patients; however, a substantially higher scarring rate with the 532-nm Nd:YAG laser was noted [13].

It would seem that the KTP laser has a role to play in the treatment of PWS, but the long pulses and the shorter wavelength of light employed by this laser can cause significant epidermal injury and may increase the incidence of adverse effects when compared with modern PDLs.

17.2.2 Infrared Lasers

Longer-wavelength lasers such as the alexandrite (755 nm) and Nd:YAG (1,064 nm) may have a role in PWS treatment. In the millisecond modes these lasers have been widely used for hair removal and leg vein telangiectasia. These lasers may be particularly useful in the treatment of bulky malformations and mature PWSs, lesions that are typically more resistant to PDL because of the predominance of larger and deeper vessels and higher content of deoxygenated hemoglobin. No et al. [16] used a 3-ms alexandrite laser with dynamic cooling to treat three

patients with hypertrophic PWSs, using fluences ranging from 30 to 85 J cm^{-2}. All lesions significantly lightened without side effects. There is much deeper penetration of the near-infrared light and it is difficult to visualize laser-induced changes within the deeper dermis. Mild to moderate lightening of PWSs was associated with the immediate endpoint of a transient gray color that gradually evolved into persistent deep purpura [8].

Yang et al. [22] treated 18 patients with PWSs, comparing a 595-nm PDL to a long-pulsed Nd:YAG laser with contact cooling. Similar clearance rates were achieved, and scarring was only noted in one patient, in whom fluences exceeded the minimum purpura dose. Patients preferred the Nd:YAG laser because of the shorter recovery period between treatments.

17.2.3 Noncoherent Light Sources

Intense pulsed light (IPL) has also been used to treat PWSs. Unlike laser systems, these flash lamps produce noncoherent broadband light with wavelengths in the range of 515–1,200 nm and permit various pulse widths. Filters are used to remove unwanted wavelengths. The first report of thermocoagulation of PWSs by polychromatic infrared light was in 1976 [15].

A study of 37 patients treated with IPL showed a clearance of pink and red PWSs, and lightening of purple PWS [17]. In another study, 20 patients with PWSs [5] received one side-by-side treatment with PDL and IPL. Both PDL and IPL lightened PWSs. Median clinical improvements were significantly better for PDL, and a higher proportion of patients obtained good or excellent clearance rates. Skin reflectance also documented better results after PDL than after IPL. Eighteen of 20 patients preferred to receive continued treatments with PDL. Both the PDL and IPL used in this study lightened PWSs with no adverse events. However, the PDL conveyed the advantages of better efficacy and higher patient preference.

There are multiple choices of treatment parameters with noncoherent light sources, and further work is necessary to determine optimum settings. There are conflicting results from published research as to whether IPL as a treatment modality is superior to PDL, but it seems that some patients will benefit from treatment with these devices.

Take Home Pearls

- Although PWSs will lighten after treatment in most cases, only a minority clear completely and patients need to be aware of this at the outset.
- When treating a limb, test at both proximal and distal sites because the latter may fail to lighten adequately.
- Although infrared lasers may lighten PWSs there is a significant risk of scarring, particularly in flat, pink PWSs.

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Vascular Lesions: Hemangiomas

18

Margitta Poetke, Peter Urban, and Hans-Peter Berlien

Core Messages

- Congenital vascular tumors have a wide variety of origins. The most common congenital vascular tumor is the glucose transporter 1 positive infantile hemangioma (IH). This has to be differentiated from the congenital hemangioendothelioma.
- Though the majority of IHs have a high rate of spontaneous regression, severe complications are possible and it is important to identify the dangerous forms as early as possible and start early treatment to prevent secondary complications.

18.1 Introduction

The general term "strawberry hemangioma" covers a series of diverse hereditary vascular abnormalities. To determine the type of therapeutic procedure to employ – active or restrained – early differentiation is essential [8]. Infantile hemangiomas (IHs) are proliferating embryonal tumors that possibly stem from placental tissue or resemble it (they are glucose transporter 1 [GLUT-1] positive). Congenital hemangioendotheliomas (HEs) are not part of the IH and are GLUT-1 negative. Both have to be differentiated from arterial, venous, lymphatic, and combined vascular malformations (VMs), including glomangiomas and systemic congenital glomangiomatosis such as hamartomatous abnormalities. They show no spontaneous regression but rather steady growth, with the exception of the abortive forms of port wine stains (PWSs) such as Unna's nevi, certain forms of cutis marmorata telangiectatica, and isolated monocytic lymphangiomas of the neck, such as hygroma colli.

18.2 Classification of Congenital Vascular Tumors

IHs have to be classified according to stage, growth pattern, appearance, and organ specificity. Congenital HEs are classified according to their progression, growth pattern, appearance, and organ specificity, whereas VMs have to be classified according to their growth pattern, appearance, and organ specificity but also according to the embryological disorder and their predominant vascular origin [15]. This means that a common feature of all congenital vascular abnormalities is that they can appear in all organs and regions of the body. Another joint feature is that they can appear in singular, multiple, or disseminated forms and may vary in their growth pattern, with well-demarcated to diffuse infiltrating shapes. Any classification, therefore, has to answer the three central questions: what, where, and how (Table 18.1). The "Hamburg classification" has become the standard procedure for classification of VMs [8]. Because of the sometimes difficult

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_18, © Springer-Verlag Berlin Heidelberg 2011

Table 18.1 Classification of congenital vascular anomalies

	Vascular tumor		Vascular malformation				
What	Infantile hemangioma	Hemangioendothelioma	*Origin*			Embryological defect	Compartment
	Stage	*Type*	Capillary			Aplasia	Truncular
	I Prodromal	Rapid involuting	Venous			Hypoplasia	Extratruncular
	II Initial	Non involuting	Lymphatic			Dysplasia	
	III Proliferation	"Tufted" angioma	Arterial			Hyperplasia	
	IV Maturation	Kaposiform	Arteriovenous			Hamartoma	
	V Regression		Mixed				
Where			*Organ*				
	Intra/ subcutaneous	Intra/submucous	Intramuscular			Intraosseous/intraarticular	
	Intracranial	Parenchymatous	Intracavitar			Mesenterial	
			Number				
	Singular		Multiple			Disseminated	
			Localization				
	Peri-/intraorbital		Peri-/intra-auricular Peri-/enoral	Laryngo/ tracheal	Face (other)	Head/neck	
	Perimammary		Anogenital/intra-anal/ intestinal	Trunk (other)	Acral/hand/ feet	Extremities (other)	
How			*Growth*				
	Limited		Moderate infiltrative			High infiltrative	
			Complication				
	Exulceration	Infection	Bleeding	Cardiac failure		Intravascular coagulopathy	Associated defects
	Excessive growth	Visual obstruction	Feeding problems			Intestinal obstruction	Visual obstruction

The three major questions of what, where, and how are valid both for vascular malformations and for congenital vascular tumors. Therefore, this classification follows the Hamburg classification of vascular malformations

differential diagnosis, a classification of congenital vascular tumors should be modeled accordingly. IHs (Fig. 18.1a–d) appear only days or weeks after birth, but about half of them show precursor lesions such as circumscribed telangiectasias; anemic, reddish-bluem or blue maculae; and PWS lesions [31]. They sometimes cannot be detected, particularly in newborns with high hematocrit or hyperbilirubinemia levels. Color-coded duplex sonography (CCDS) does not yet provide a typical result, but in cases of intracutaneous manifestation there is sometimes already a broadening of the dermal double lamina structure (Table 18.2).

18.3 Differential Diagnoses

Pronounced lesions at birth should include the differential diagnosis "congenital HE" or "VM." A PWS is already evident at birth as a macular reddening of differing extents and on ultrasound reflects no disintegration of the normal double laminar structure. This is a decisive differential diagnostic criterion for the prodromal phase of IH. In addition, PWSs in newborns almost never progress, so that an increase in color intensity, size, or a change in the typical skin texture is almost the proof of the presence of the most aggressive form of IH.

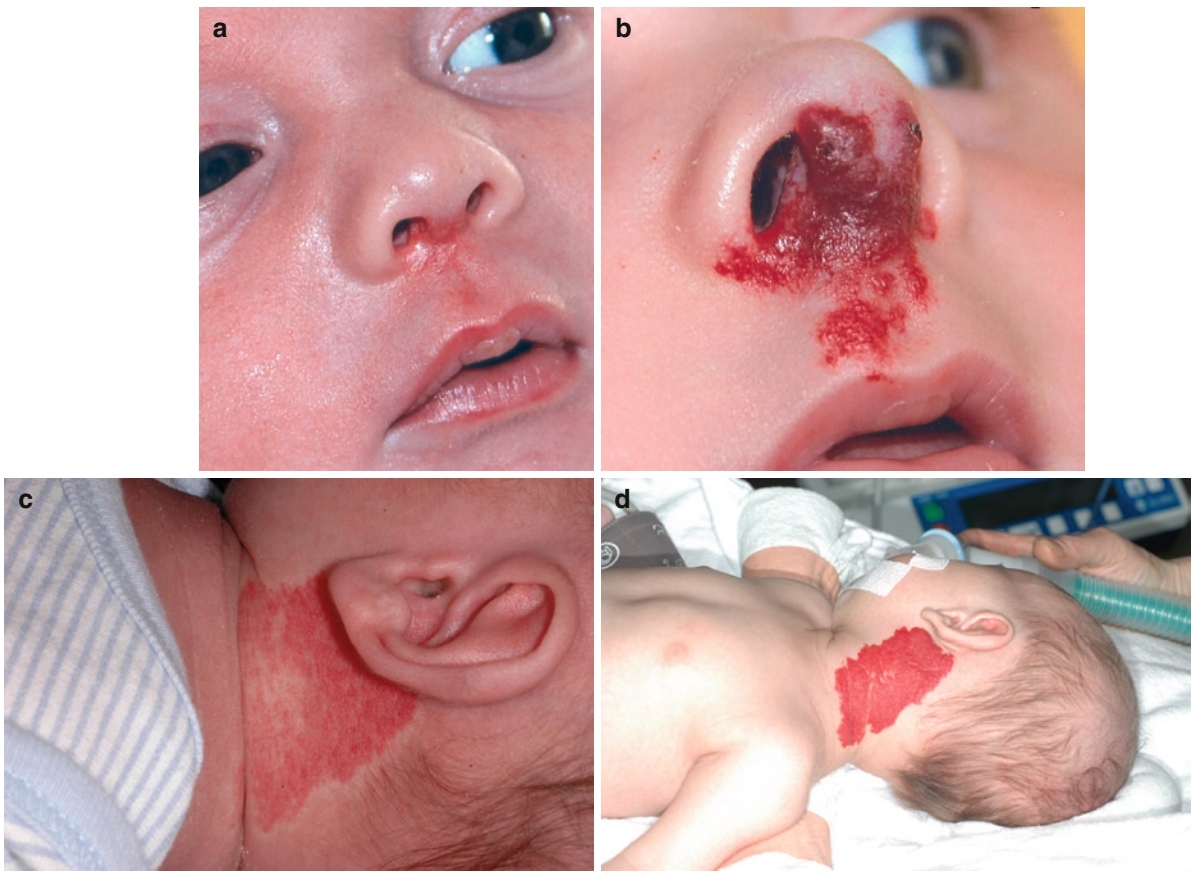

Fig. 18.1 Rapid progression of infantile hemangioma. (**a**) Prodromal phase with faint telangiectasia 3 weeks after birth. (**b**) Deeply infiltrating hemangioma 3 months later. (**c**) Typical hemodynamic steal effect in the edge of an early hemangioma. (**d**) Rapid thickening only 4 weeks later

Table 18.2 Classification of IH

Stage	Clinic	CCDS
I. Prodromal phase	Red/white spot; tellngiectasia; blurred swelling	Structureless; low echo space; no signs of pathological vessels
II. Initial phase	Loss of typical skin structure; increasing thickness and induration	Hyposonoric center; hypervascularization beginning at edges
III. Proliferation phase	Bright red cutaneous infiltration; flat spreading subcutaneous growth of thickness; infiltration of surroundings possibly even at organ borders	Increasing intratumoral hyperperfusion; center vessel density; nutrition tumor vessels; drainage veins with arterial flow profile
IV. Maturation phase	Pale and livid color; possible central exulceration; decreasing growth	Declining central vessel density; increasing ectatic drainage veins; declining arterialization of drainage veins; central increasing hypersonic aspect
V. Regression phase	Hypopigmentation; wrinkled skin/telangiectasis; surrounding subcutaneous drainage veins; subcutaneous palpable induration	Circumscribed hypersonoric area; loss of typical tissue structure; nearly no central tumor vessels; residuals supplying tumor arteries; residuals of ectatic drainage veins

Correlation of clinic and color-coded duplex sonography (CCDS)

18.3.1 Initial Phase

18.3.1.1 Clinical Symptoms

During the early or initial phase, IHs may partially appear within a few days. Depending on the type of growth, limited or infiltrative (see below), they are diffuse, infiltrating the surrounding tissue, or, in the case of limited growth, are sharply demarcated. The latter frequently clearly protrude from the skin, are light reddish in color, and shine brightly, causing parents to show these to a physician more readily than the infiltrative hemangiomas. In CCDS often only a diffuse hyposonic structure will be seen, similar to the image of a fresh hematoma without visible vessels or capillarization. In intracutaneous hemangiomas, the typical double lamina structure of the skin vanishes (Fig. 18.2a–d).

18.3.1.2 Differential Diagnoses

The venous malformation is also rarely very pronounced at birth with little tissue proliferation, so that in newborns, a venous malformation is easily "squeezable," in contrast to an IH. Early forms of angiokeratomas and a lymphangioma circumscriptum can be easily differentiated from the initial phases of IH simply by their rather livid color.

18.3.2 Proliferation Phase

18.3.2.1 Clinical Symptoms

During the proliferation phase, a cutaneously located hemangioma proliferates at a different pace while spreading in size, by either exophytic or endophytic subcutaneous growth but sometimes both. Hemangiomas of limited growth usually only expand minimally. Primary subcutaneous hemangiomas appear at a later stage and grow for a longer period of time. The coexistence of two forms is common, whereby a dissociated growth of the two parts is possible. With CCDS, hypercapillarizations can now be seen: the stronger they are, the more active the proliferation of the hemangioma (Fig. 18.3a, b). Thus, CCDS is the only method with which the activity and aggressiveness of an IH can be checked dependably. In addition to hypersonic parts that are already regressing, hyposonic, early proliferative parts may exist in the very same hemangioma (Fig. 18.4a–c). In cases of very excessive growth, secondary capillarization cannot keep up, so there may be trophic disturbances with exulcerations.

18.3.2.2 Differential Diagnosis

The hereditary glomangioma is already dark-bluish at birth; IHs only appear during their late phases.

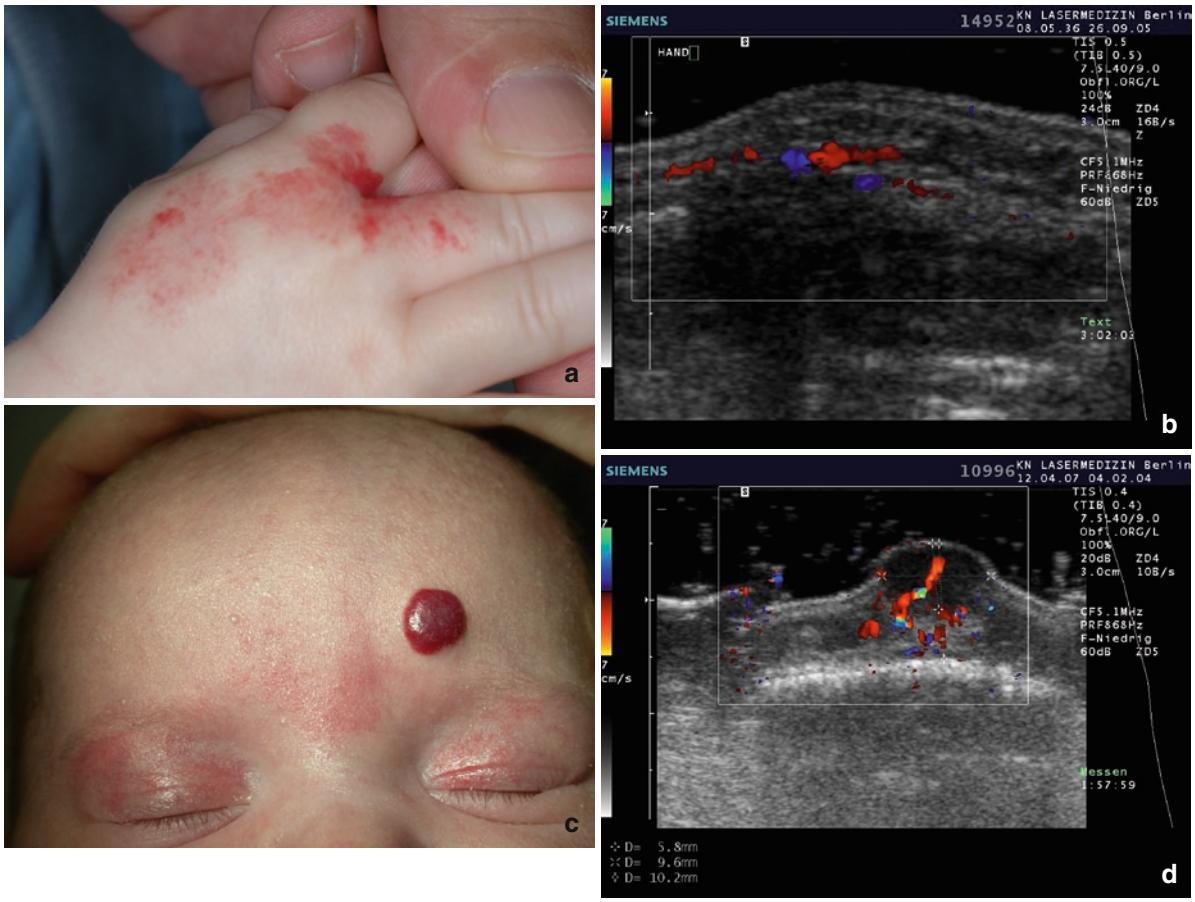

Fig. 18.2 (**a**) Prodromal phase with spotted swelling. (**b**) Increasing hyposonic thickness of the skin; no pathologic vessels to be seen. (**c**) Initial phase with ballooning skin surface and glossy redness. (**d**) Hyposonic nearly echoless structure and beginning of hypervascularization

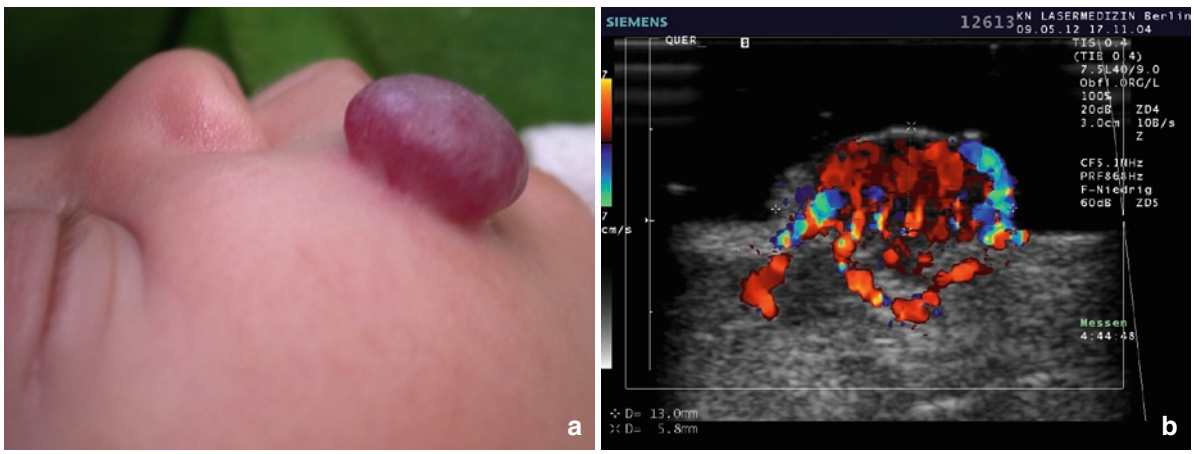

Fig. 18.3 (**a**) Proliferation phase with rapidly increasing volume and pale redness. (**b**) Hyposonic tissue now filled completely with highly perfused vessels

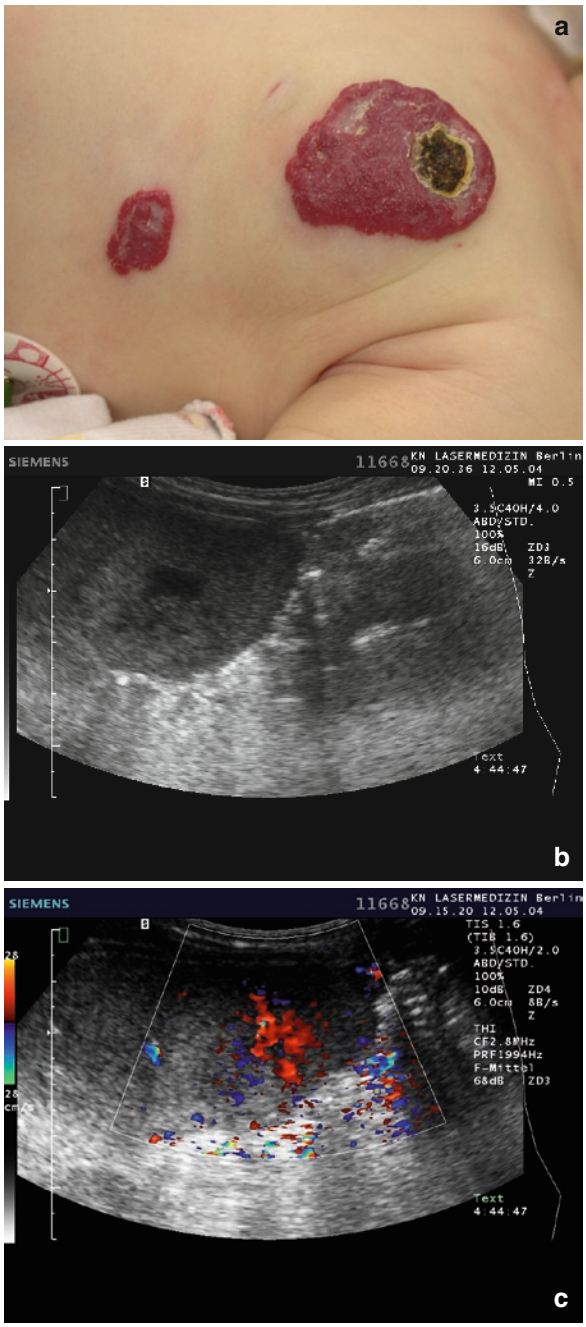

Fig. 18.4 (**a**) Spontaneous ulceration caused by superficial hemodynamic steal effect. (**b**) Multiple infantile hemangiomas are associated with liver hemangioma. (**c**) Color-coded duplex sonography can detect the hypervascularization in the mostly hyposonic lesions

Congenital glomangiomas are actin antibody positive and thus clearly differ from the late phases of IH, which always, even after regression, remain GLUT-1 positive.

18.3.3 Maturation Phase

18.3.3.1 Clinical Symptoms

A maturation phase follows during which proliferation comes to a halt. In intracutaneous hemangiomas, this can be seen by a reduction of the bulk and accompanying wrinkles of the epidermis. In addition, gray regression areas form in the dark red hemangioma. The tissue is rather plastic; sonography reveals hypersonic areas as signs of maturation. Duplex sonography, on the one hand, shows that microcirculation decreases; on the other hand, drainage veins are formed, which usually run vertical to the surface (Fig. 18.5a, b). If a biopsy is performed at this point, the pathologist will find large veins with only a single-layered endothelium, which

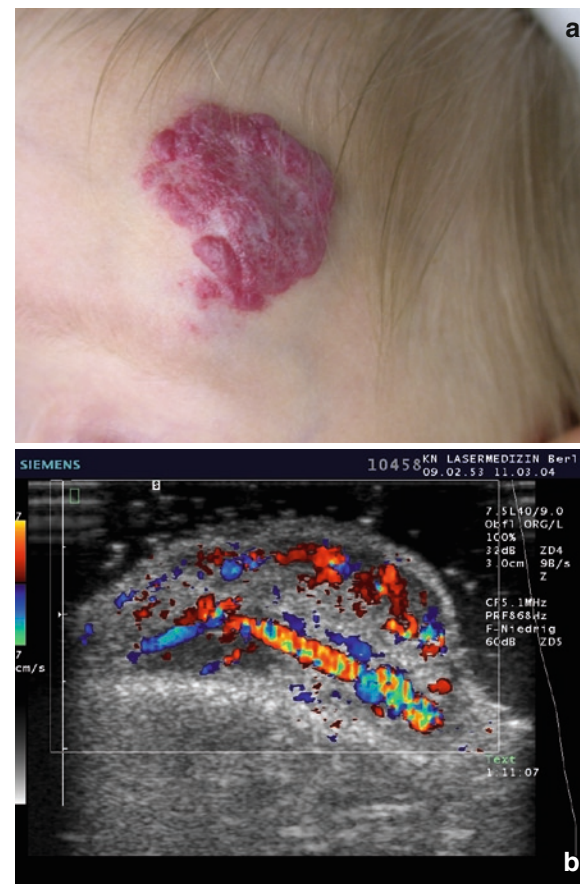

Fig. 18.5 (**a**) Maturation phase with reducing volume, shrinking surface, and pale spots. (**b**) Increasing ectatic drainage veins in hypersonic tissue

are responsible for the term "cavernous hemangioma." They can trigger ulceration by the steal effect. The smaller the distance from these drainage veins to the epidermis, the greater the risk.

18.3.3.2 Differential Diagnosis

The bluish color of pure subcutaneous IHs also may occur in venous VMs, but this is not expressible and with CCDS shows ectatic caverns with little or no spontaneous flow.

18.3.4 Regression Phase

18.3.4.1 Clinical Symptoms

The regression phase is usually finished by the sixth birthday – as a rule, this occurs faster in cutaneous localized hemangiomas than in diffuse infiltrating cutaneous or subcutaneous hemangiomas. CCDS is now hypersonic as an expression of a fibrolipomatous transformation. Large, reticular veins remain in the vicinity for a number of years; these appear as a secondary change and show normal vessel walls (Fig. 18.6a, b). Small hemangiomas, at the end of the proliferation phase and in the beginning of regression that have not yet caused secondary destruction of the surrounding tissue, can completely heal without residues. Larger hemangiomas often leave telangiectasias; areas of atrophic, multiple foldable skin; cutis laxa; hyper- or hypopigmentations; or prune belly-like lumps of fibrolipomatous tissue. The larger hemangioma before the entry into the quiescent and regressive phase, the more pronounced the residues.

18.3.4.2 Differential Diagnosis

An IH will not become active again after regression. There is no recurrence. A hemangioma, which begins or develops during infancy is not an IH. The most probable differential diagnoses are VMs, but also vasculitis, and cutaneous metastases of malignant tumors may have to be excluded by a biopsy. Plexiform neurofibromas may appear as part of a venous or lymphatic malformation (Fig. 18.7).

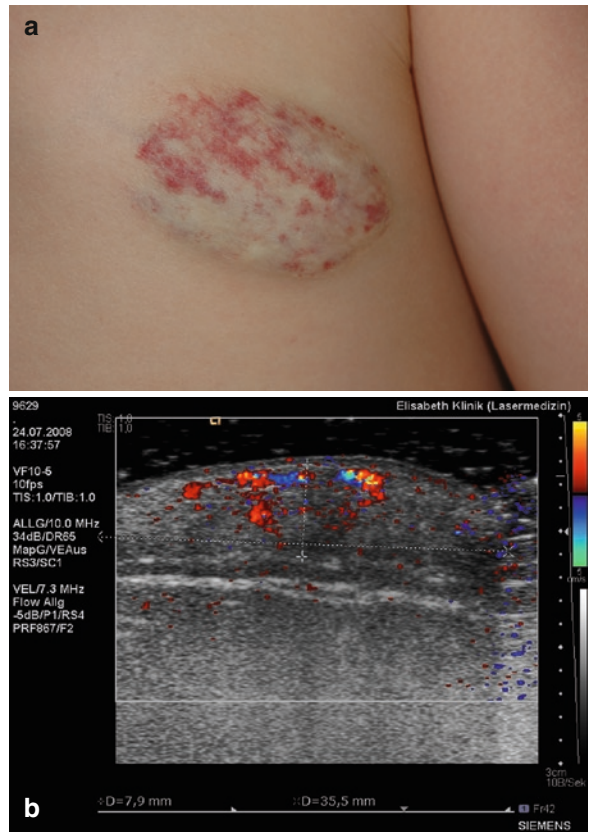

Fig. 18.6 (**a**) Regression phase with hypopigmentation in wrinkled skin. (**b**) Homogenous hypersonic area with residuals of pathologic vessels

18.4 Congenital Hemangioendothelioma

The congenital HE is a real vascular tumor [30] but has to be differentiated from the HE of adults because the acquired ("adult") HE belongs to the "borderline" tumors with uncertain biological behavior, whereas a congenital HE has never been reported to have turned malignant [27]. Unlike in the case of the IH, the primary intracutaneous form is less common, but if there is aggressive growth, a secondary involvement of the dermis is possible. The clinical appearance of the cutis marmorata may be similar to the dermal findings of a congenital HE, but the cutis marmorata lacks subcutaneous proliferation. Depending on their proliferation pattern, entirely different forms must be differentiated before establishing the indication for any therapy. During healing, spontaneously or after therapy, they

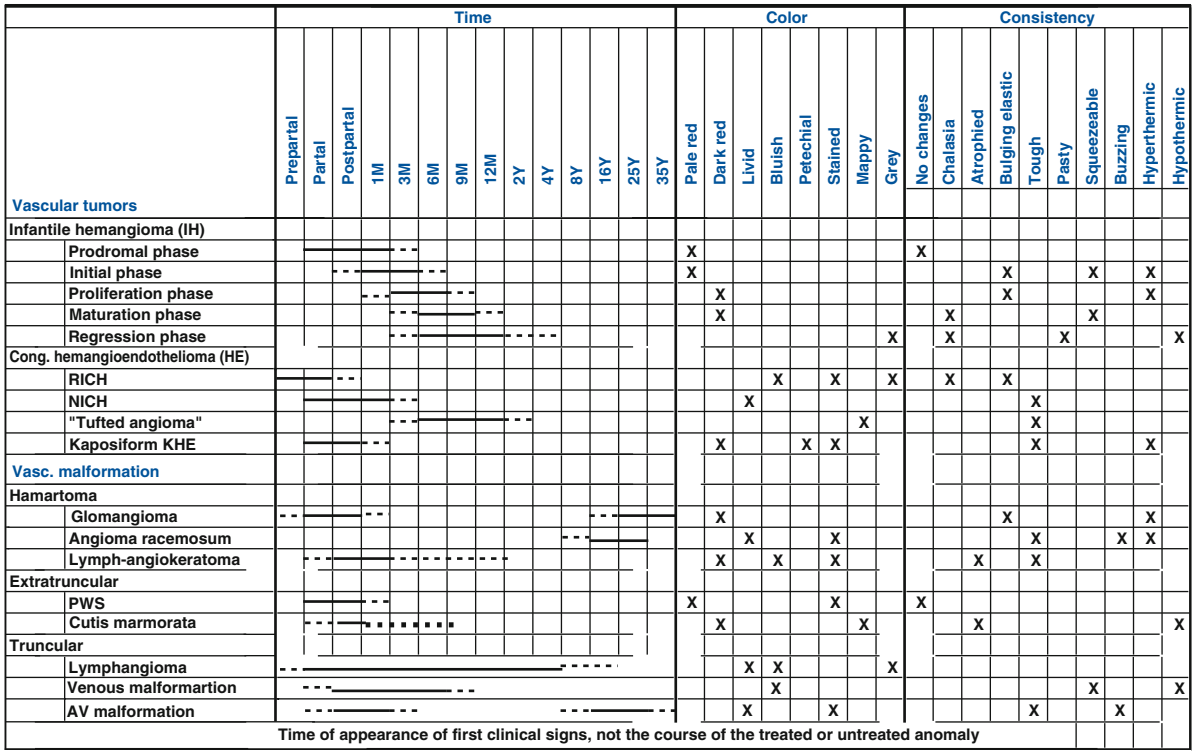

Fig. 18.7 Differential diagnostic algorithm of the appearance of first symptoms, color, and consistency, but not the course of the treated or untreated disease. The algorithm gives a probability of a diagnosis

all show the same picture: atrophy of the subcutis to the fascia and cutis laxa.

18.4.1 The Rapidly Involuting Congenital Hemangioendothelioma

This tumor totally matures prenatally ("prenatal mature hemangioma") and should be clearly differentiated from an IH because it is negative for GLUT-1. Because of its bluish hue, which often shines through the skin, it is often mistaken for a venous VM. However, unlike this malformation, which at birth is always soft and "squeezable," the congenital HE is tough. Ultrasound reveals the initial fibrosis as a hypersonic area. Intratumoral vessels are rare, and frequently there are bowl-like veins. Unlike the pure venous VM, which is usually hypothermic due to blood pooling, thermography shows a normothermic image. The skin above may be shimmering and bulging, but there are never any inflammatory symptoms. Within a few days of birth the spontaneous regression begins, noticeable by a decrease in turgor. Regression as a rule is completed within 3 months, but as a primary destructive tumor of the subcutis it leaves a lesion in the subcutaneous tissue with chalasis of the dermis on top and occasionally muscle atrophy and an atrophy of the fascia below due to the pressure (Fig. 18.8a, b). A teratoma must be excluded by differential diagnosis, especially in the case of presacral localization.

18.4.2 The Noninvoluting Congenital Hemangioendothelioma (NICH)

Contrary to a rapidly involuting congenital hemangioendothelioma (RICH), a noninvoluting congenital hemangioendothelioma (NICH) may be only sparsely developed at birth. The skin above is not directly infiltrated but often shows a light bluish

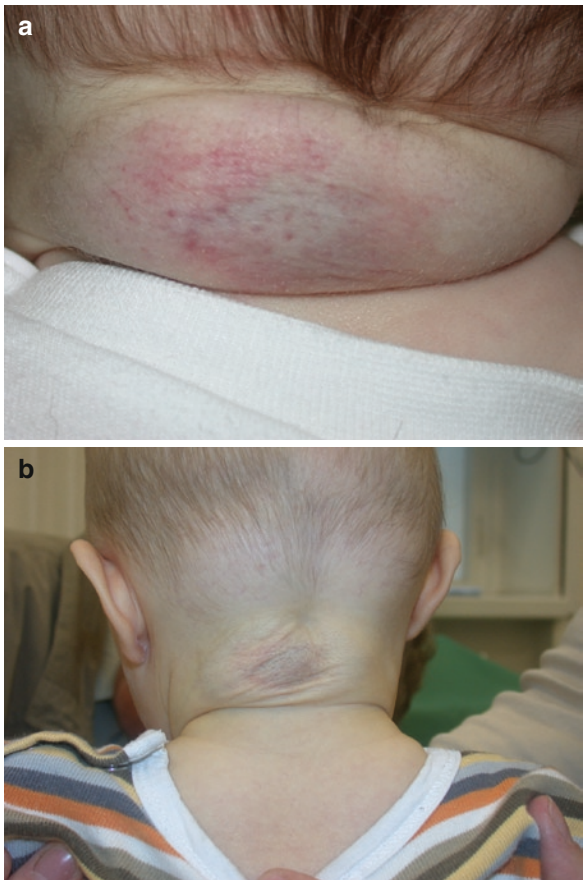

Fig. 18.8 (**a**) Rapidly involuting congenital hemangioendothelioma 2 weeks after birth; large volume and atrophic skin. (**b**) After only 3 months wrinkled skin due to rapidly reducing volume

change in coloring with a more pronounced telangiectasia. This sometimes makes it difficult to differentiate it from a hamartomatous extratruncular arteriovenous malformation known as angioma racemosum. Unlike the arteriovenous malformation, which always shows a massive hyperperfusion on a sonogram even without direct evidence of an arteriovenous shunt and in thermography shows a pronounced hyperthermia, sonography of an NICH reveals – besides lobular hypersonic areas – arteries and veins running vertically to the surface, and thermography shows a clear but rather weak hyperthermia. During the first few years of the child's life there is progressive growth, which is increased by infections. In some cases there is spontaneous regression, recognizable on a sonogram by an increasing fibrosis and a decrease in vascularization, and, similar to a RICH, a remainder of a chalasia of the cutis and an atrophy of the subcutaneous fat. On the other hand, as long as a NICH is still active, transition to a Kaposi-like HE is possible at any time with the formation of a Kasabach-Merritt syndrome (KMS). Therefore, in all patients with an NICH, regular control of thrombocytes and, if necessary, clotting parameters is mandatory.

18.4.3 The "Tufted Angioma"

It is not yet clear if the "tufted angioma" is a separate entity to the congenital HE or only a delayed occurrence of a NICH variation. Ultrasound reveals separate lobular structures with vessels along the edges. Multiple lesions are reported in the "tufted angioma" (Fig. 18.9a, b).

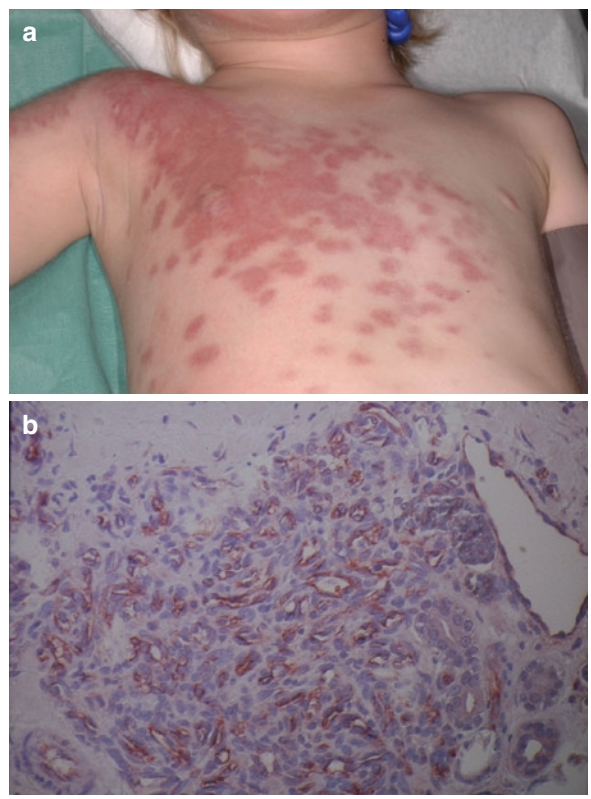

Fig. 18.9 (**a**) Congenital hemangioendothelioma disseminated late onset. (**b**) Typical histological findings with "cannonball pattern" and lymphatic clefts

18.4.4 The Kaposi-Like Congenital Hemangioendothelioma

At birth, a result similar to a NICH may be seen. In most cases, however, the skin covering the tumor does not show any signs of infection, but a tough infiltration, which, besides erysipelas, is differential diagnostically reminiscent of a mixed intracutaneous-subcutaneous lymphangioma ("wasp sting symptom") (Fig. 18.10). Thermography shows significant hyperthermia, whereas ultrasound reveals almost structureless interstitial gaps sited between lobular hypersonic areas. CCDS clearly shows an increased microcirculation, which is not located in the center, as in active IHs, but at the lobuli divided by septa. There are no symptoms at this point. Clinical and sonographic signs are present before the beginning of a disseminated intravascular coagulopathy in KMSs, so that at this point thrombocytes and fibrinogen, or rather fibrin, degradation products may still be quite normal (Fig. 18.11a–d).

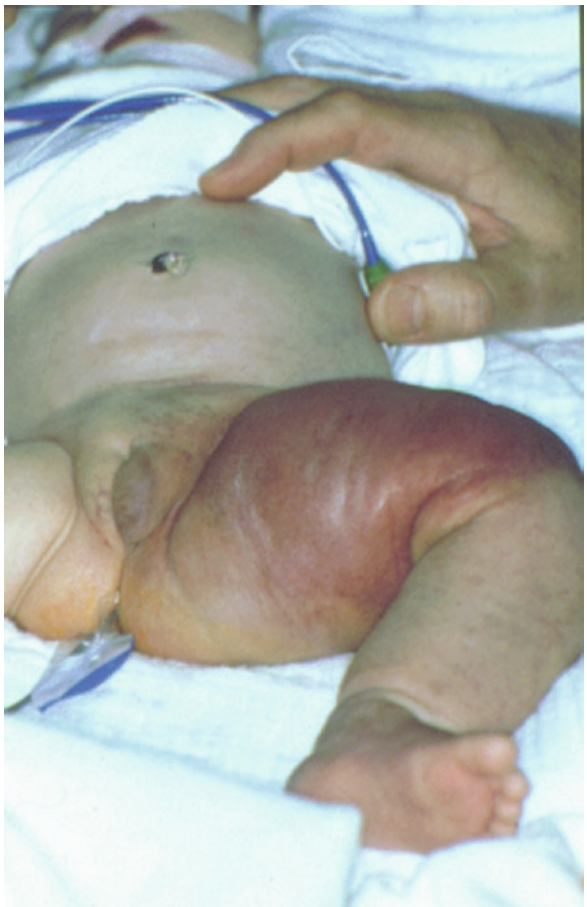

Fig. 18.10 Kaposi-like congenital hemangioendothelioma of the thigh with contiguous residuals of hemorrhage due to Kasabach-Merritt syndrome

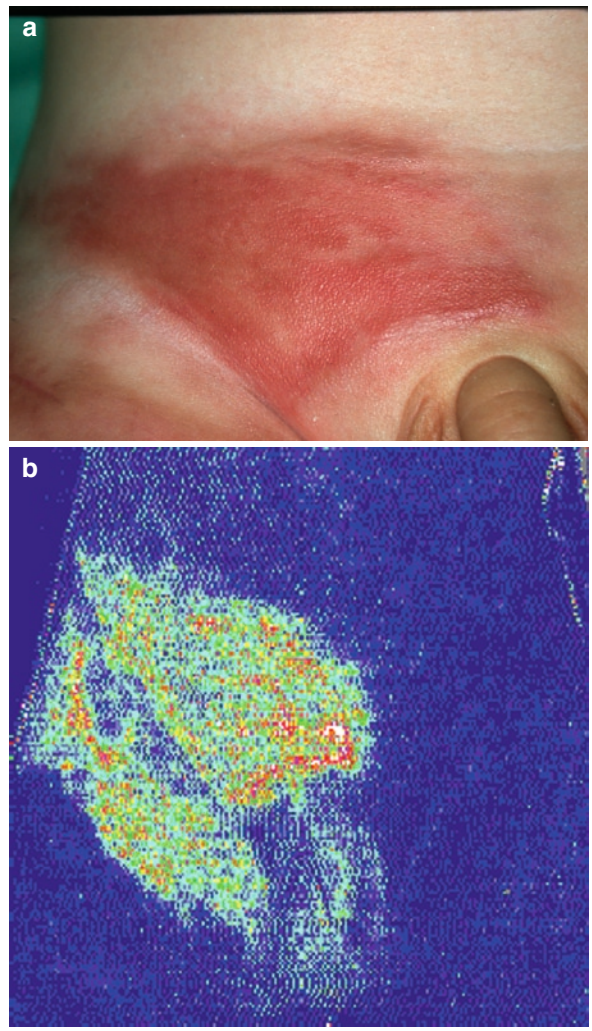

Fig. 18.11 (**a**) Kaposi-like congenital hemangioendothelioma with "wasp sting symptom" reminiscent of a bacterial infection. (**b**) Detection of superficial hyperperfusion in the laser doppler imaging. (**c**) Magnetic resonance imagnig showing the depth of subcutaneous infiltration. (**d**) Only color-coded duplex sonography can demonstrate the pathognomonic pattern: interstitial hypersonic areas separated by hyposonic septa with palisade-like vessels

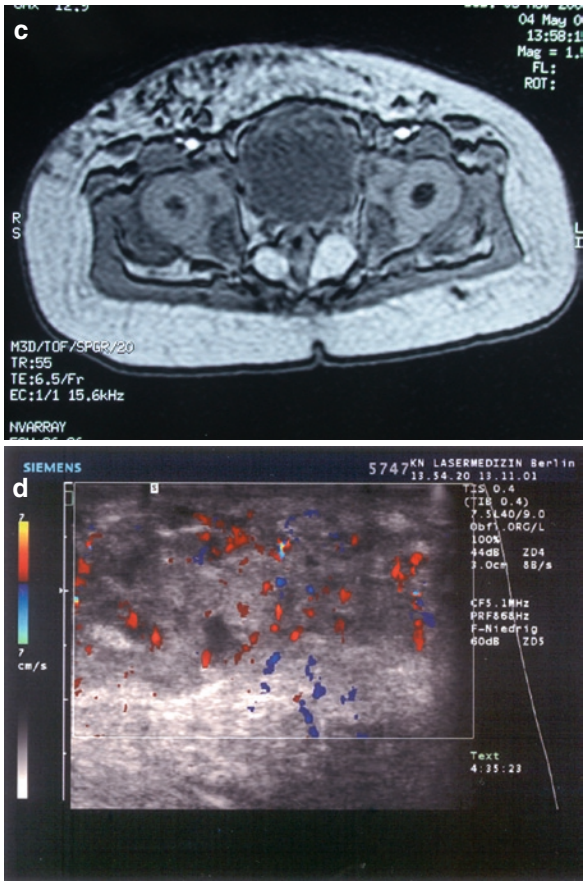

Fig. 18.11 (continued)

18.5 Organ/Number/Localization ("Where")

18.5.1 Organs

An intraosseous or intra-articular manifestation of hemangioma described in the literature is probably a faulty classification and has been ascribed to VMs. Otherwise, all soft tissue, solid organs, or hollow viscera can be affected (Table 18.3). Most commonly affected are certainly the cutis and subcutis, but the mucous membranes and submucosa of the aerodigestive tract and the urogenital and anogenital region can be affected as well. Of the parenchymal organs, the liver is mainly affected, particularly when there are multiple hemangiomas [16]. The parotid gland and the mammary glands are seldom affected primarily by the IH, but an excessively proliferating IH can lead to secondary displacement or infiltration. HEs affect soft tissue rather than the cutis. If body cavities (pleura and peritoneum) or lungs are affected, or if there is an intracranial effect in the meninx, an IH is unlikely, and a malignant neoplasm should be ruled out by biopsy. The most important differential diagnosis besides (a benign) congenital systemic glomangiomatosis (glomuvenous malformation) is a congenital neuroblastoma (stage IV).

18.5.2 Number

Even though a single site is the rule among most children, several IHs may also develop, possibly at different times. For this reason, if there are more than three IHs, a thorough check-up should be performed, clinically and with the aid of ultrasound, to identify occult hemangiomas, particularly in the liver, as early as possible. The systemic hemangiomatosis has a special status here. Two completely biologically different clinical courses should be noted [23]. The most common is the so-called "benign" neonatal hemangiomatosis, in which multiple tiny, pinhead-sized intracutaneous hemangiomas pop up within a few days and quickly stop growing. Except for tight monitoring, therapy is not required. It should be considered, however, that there also may be a few fast-growing, vast subcutaneous hemangiomas, which then are an indication for treatment. Rather rare is the aggressive diffuse hemangiomatosis ("disseminated neonatal hemangiomatosis"), which may involve the organs, particularly the gastrointestinal tract and the liver (Fig. 18.12a–d). This type more often forms primarily enlarged solitary lesions. HEs, especially RICHs and NICHs, tend to be solitary. Tufted HEs may appear at multiple sites; the Kaposi-like HE may be – besides its monstrous size – lobular and thus seem to be multiple.

18.5.3 Localization

Though the criteria listed so far are decisive for the diagnosis, the following determine the indication for

Table 18.3 Evaluation of vascular tumors

What				Where						How			
IH		HE											
Phase		Type		Organ		Number		Localization		Growth		Complications	
Prodromal	2	RICH	1	Intracutaneous	1	Singular	1	*Life-threatening*		Limited	1	Exulceration	5
Initial	3	NICH	3	Intramucous	2	Multiple	2	Tracheal	7	Moderate infiltrative	2	Infection	5
Proliferation	5	"Tufted angioma"	5	Subcutaneous	3	Disseminated	5	Pharyngeal	6	High infiltrative	5	Bleeding	10
Maturation	2	KHE	10	Submucous	4			Intestinal	5			Cardiac failure	10
				Intraosseous	3			*High risk*				LIC	5
				Intra-articular	5			Parabulbar	4			Associated defects	3
				Intracranial	5			Enoral	4			Excessive growth	5
				Parenchymatous	5			Intra-anal	4			Vent. obstruction	10
				(mixed lesions add up)				Finger/toe	4			Intestinal obstruction	10
								Medium risk				Ear obstruction	5
								Periorbital,/oral	3			Coagulopathy	10
								Periauricular	3			(Combinations add up)	
								Preauricular	3				
								Paranasal	3				
								Perineal	3				
								Breast	3				
								Vulva/urethra	3				
								Hand/foot	3				
								Low risk					
								Hairy head	2				
								Neck	2				
								Axilla	2				
								Perianal	2				
								Remaining face	2				
								No risk					
								Trunk	1				
								Arm/leg	1				

These different criteria are not equally important, but as indications for therapy they are counted for their risk of complication. *IH* infantile hemangioma, *RICH* rapidly involuting congenital hemangioendothelioma, *NICH* noninvoluting congenital hemangioendothelioma, *KHE* Kaposi-like congenital hemangioendothelioma, *LIC* localised intravascular coagulopathy, Vent ventricular

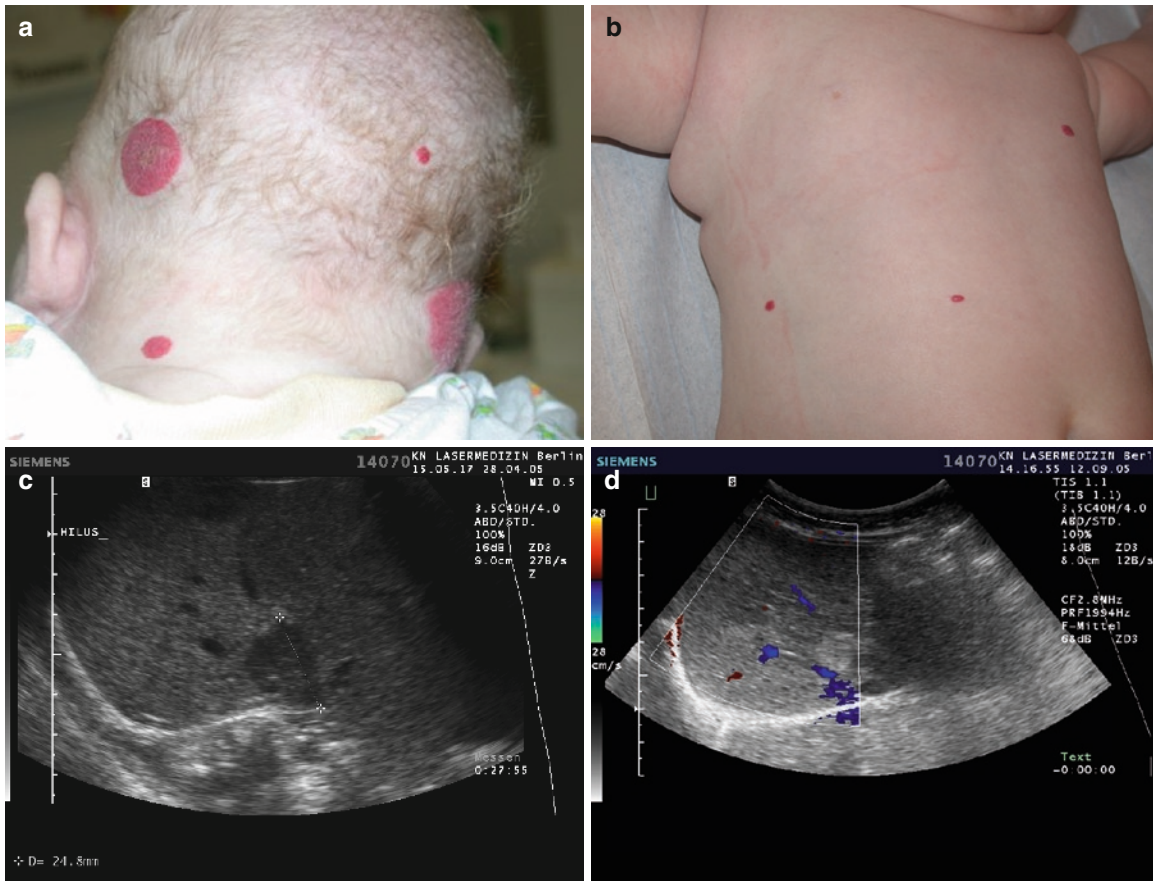

Fig. 18.12 (**a**, **b**) Disseminated neonatal hemangiomatosis; the cutaneous infiltrations do not reveal the severity of the disease. (**c**) Infiltrations of the liver in an early stage hemangioma demarcate as hyposonic regions. (**d**) Five months later hemangioma have turned into hypersonic patterns

therapy. Besides the proliferation pattern, localization is the most important criterion for the occurrence of complications that require therapy. This is why it is of utmost importance in the score. Eyelid, periorbital, or intraorbital IHs may hamper the orbit and thus lead to irreversible amblyopy, and by compression of the eyeball lead to anisometropy and astigmatism and may be accompanied by primary cataract. Strongly vascularized hemangiomas of the ears often cause hypertrophy of ear growth and cartilage destruction. A relocation of the ear canal may trigger infections due to fluid retention and secondary deafness. This is why all hemangiomas of the ear, periauricular and preauricular, require otoscopy. Similar precautions have to be taken for the nose, with the consequence of skeletal malformations or obstruction of nasal breathing. Perioral localization can hamper food intake and lead to permanent deformation of lips and, in extreme cases, to abnormalities of the lower jaw and irregular dentition. With perioral localization and involvement of the mucous membranes of the oropharynx or the pretracheal skin, tracheal involvement must be excluded. In hemangiomas in the face, residues (ptosis, facial asymmetry) can be very irritating and lead to functional impairment depending on their size and extension. Here it is important to initiate – by active treatment – the quiescent or regression phase as early as possible. Hemangiomas localized in the anogenital area also have a high risk of ulceration and often cause complications such as bleeding, infections, pain, and dermatitis.

18.6 Proliferation Pattern/ Complications ("How")

18.6.1 Growth Pattern

In cases of nonprogressive IHs that are not very extensive, complications as a rule do not interfere, especially when the IHs are localized on the trunk or upper and lower extremities. Hemangiomas that grow rapidly and infiltrate, on the other hand, can cause intertriginous ulcerations at all sites with the risk of secondary infections, bleeding, and pain. In diffuse growing, infiltrating hemangiomas, proliferation can be very quick, and there is a greater danger of remaining residues after regression. Diffuse growing, infiltrating IHs of the face are described as "segmental" by some authors, although they follow neither dermatome nor nerve supply patterns. As a result, nearly a third of the diffuse, infiltrating growing IHs of the face are classified as "not determinable" [33]. This view fails completely for the extremities, the body, and the anogenital area, although proliferation in these regions does not differ from the face.

18.6.2 Complications

Hemangiomas of the face and head may be associated with malformations of the central nervous system [10], the intra- and extracranial arteries, the heart, the eyes, and sternal clefting (PHACES syndrome) [24]. The association with urogenital and anal malformations as well as spina bifida occulta has been described as PELVIS syndrome. The expression "syndromal hemangiomas" for these IHs is erroneous and suggests that they form a separate entity of hemangiomas. In reality, these IHs do not differ in their phases or proliferation from other sites or in their relation to organs, only in their biological activity. It is important that for these typical findings a careful, more extensive diagnosis is performed to identify and avoid later complications. KMS does not appear in IHs, even in extended complicated IHs, but only in Kaposi-like HEs and rarely in tufted HEs [35]. Very large and widely spread hemangiomas with or without ulcerations may lead to cardiac problems, complications of the systemic circulation, infections, and hemorrhage.

18.7 Principles of Therapy of Infantile Hemangiomas and Other Congenital Vascular Tumors of Newborns and Infants

In contrast to VMs, of which a spontaneous regression never occurs, in congenital vascular tumors such as IHs there is a great potential for spontaneous regression. However, the indication for active therapy is wider and earlier in endangered regions than in other regions. Due to their mesenchymal origin, vascular tumors do not primarily involve the epithelial layer either in the epidermis or in the mucous membrane. This means that any treatment has to avoid secondary effects from growth and additional damage caused to the epithelium by therapy (Tables 18.4 and 18.5).

18.7.1 Spontaneous Course

Because hemangiomas may involute spontaneously, waiting for spontaneous regression remains a viable therapeutic option. But the wait-and-see principle is always wrong. If it means that treatment arrives too late, then "see-and-wait" as a control is correct because at the first sign of progression of complication an action can be taken. Therefore, in small, uncomplicated IHs in nonproblematic areas (extremities, body) without any tendency to proliferate, especially in cutaneous hemangiomas, one can "see-and-wait." If delayed growth cannot be excluded, frequent controls are required. Clinical check-ups alone may not be sufficient; subcutaneous IHs may remain unnoticed because they grow deeply and then are recognized only after complications result. This is why a periodic duplex scan control is mandatory. For hemangiomas in the quiescent or regression phase, a "see-and-wait" attitude should normally be recommended. However, if complications are expected from ulcerations, treatment is also required for these forms. Because therapy may cause adverse systemic or cutaneous side effects, particularly scarring, sometimes intervention has been reserved for patients with significant complications. Therefore, it is difficult to choose a therapy that eliminates hemangiomas before the development of complications and without systemic side effects [20]. For this reason, the following IHs must be considered to be

Table 18.4 Exemplary grading of typical localizations of IH

		Phase/type/form	Organ	Number	Localization	Growth pattern	Complication	Score	No treatment, no control necessary	No treatment, but control necessary	Close control, laser therapy in case of progress	Definite laser indication	Additional adjuvant systemic therapy
	Grade								1	2a	2b	3a	3b
Number	Localization	1–10	1–5	1–5	1–5	1–5	5–10	Sum	>6	7–9	10–12	<13	<16
1	Trachea	5	3	1	7	5		21					X
2	Pharynx	3	4	1	6	2		16					X
3	Cheek	1	3	1	3	2		10			X		
4	Cheek	5	4	1	3	3	5	21					X
5	Back	2	1	1	1	1		6	X				
6	Breast	5	3	1	3	2	5	19					X
7	Oral	2	4	1	4	1		12			X		
8	Leg	2	3	1	1	1		8		X			
9	Finger	3	4	1	4	2		14				X	
10	Neck	2	1	1	2	1		7		X			
11	Neck	5	4	1	2	1		13				X	
12	Eye	5	4	1	4	3	10	27					X

Table 18.5 Classification of the different grades

Grade	Definition	Procedure
G1	Uncritical region/organ	No treatment
No action	Signs of/or final regression	No control
G2a	Uncritical region/organ	Control, if no progress or sign of regression follow G1
Control	No expectation of progress	If slight progress follow G2b
G2b	Although no progress expected but critical region/organ and/or	If slight progress and no complication close control
Close control	Uncritical region/organ but progress expected	If major progress or slightly progress but complication follow G3a
G3a	Progress, in case of further progress complication expected	If progress or no progress but remaining hemangioma causes functional impairment, start laser therapy to prevent complication
Laser treatment	No further progress, but critical region/organ complication expected	If regression starts follow G2b If complication occurs, follow G3b
G3b	Critical region/organ complication has occurred early regression/reduction necessary	If primary complication due to critical localization and/or biological aggressivity additional to laser therapy systemic therapy
Additional systemic treatment	Monotherapy not successful	If stabilization achieved follow G3a

Grade 1 means uncomplicated hemangioma with no risks; Grade 2a hemangiomas with low-risk factors need controls; G2b with risk factors need close controls and laser therapy if any progress is observed; Grade 3 has a laser indication due to risks of complication; and Grade 4 requires additional systemic therapy

"problematic hemangiomas" for which active treatment is mandatory: (1) hemangiomas of the face, particularly periorbitally and periorally, in the areas of the ear, lips, and nose. (2) Hemangiomas at the mammary gland and in the anogenital area, particularly the vulva, the urethralorifice, and the anal derma. (3) Rapidly growing, diffuse, infiltrating hemangiomas at any anatomic site. (4) Hemangiomatosis, either aggressive, diffuse, or involving an organ. Hemangiomas in problem zones (face, anogenital region) should be treated during their early stages to prevent complications. This is the rule for hemangiomas near the eyes (threat to vision), lips (little regression tendency) and nose area (malformations of the nose, e.g., Cyrano nose). Treatment is also indicated when hemangiomas are located on the fingers (tactile problems), toes (shoe problems expected later on), and breast and cleavage areas in women. Extended, highly proliferating hemangiomas or those already causing complications, as well as diffuse infiltrating hemangiomas, should be treated actively. Early treatment initiation can be decisive for the further course. In particular, as a rule, diffusely growing, infiltrating hemangiomas also require a systemic approach. Of the HEs, RICHs need only frequent ultrasound controls. For NICHs, provided there is tight CCDS and thrombocyte monitoring, one may wait for a possible spontaneous regression, as in RICHs. If transition to a Kaposi-like HE is suspected, however, due to an increase in inflammatory infiltrates and a thickening of interstitial septae in the sonogram, therapy should be started prior to manifestation of a KMS. In addition to a local neodymium:yttrium aluminum garnet (Nd:YAG) laser therapy, high-dose prednisone treatment is required. This, a treatment with cytostatics often can be avoided (Fig. 18.13).

18.7.2 Induction of Regression

Treatments have included laser therapy, radiation therapy, electrosurgery, cryosurgery, surgical excision, sclerotherapy, embolization, and drug therapy. The aim of therapy in cases of IH as a rule is not to remove it immediately but to stop proliferation of the hemangioma, speed up regression of large hemangiomas, and avoid or remove functional problems (e.g., of the eye) (Table 18.6).

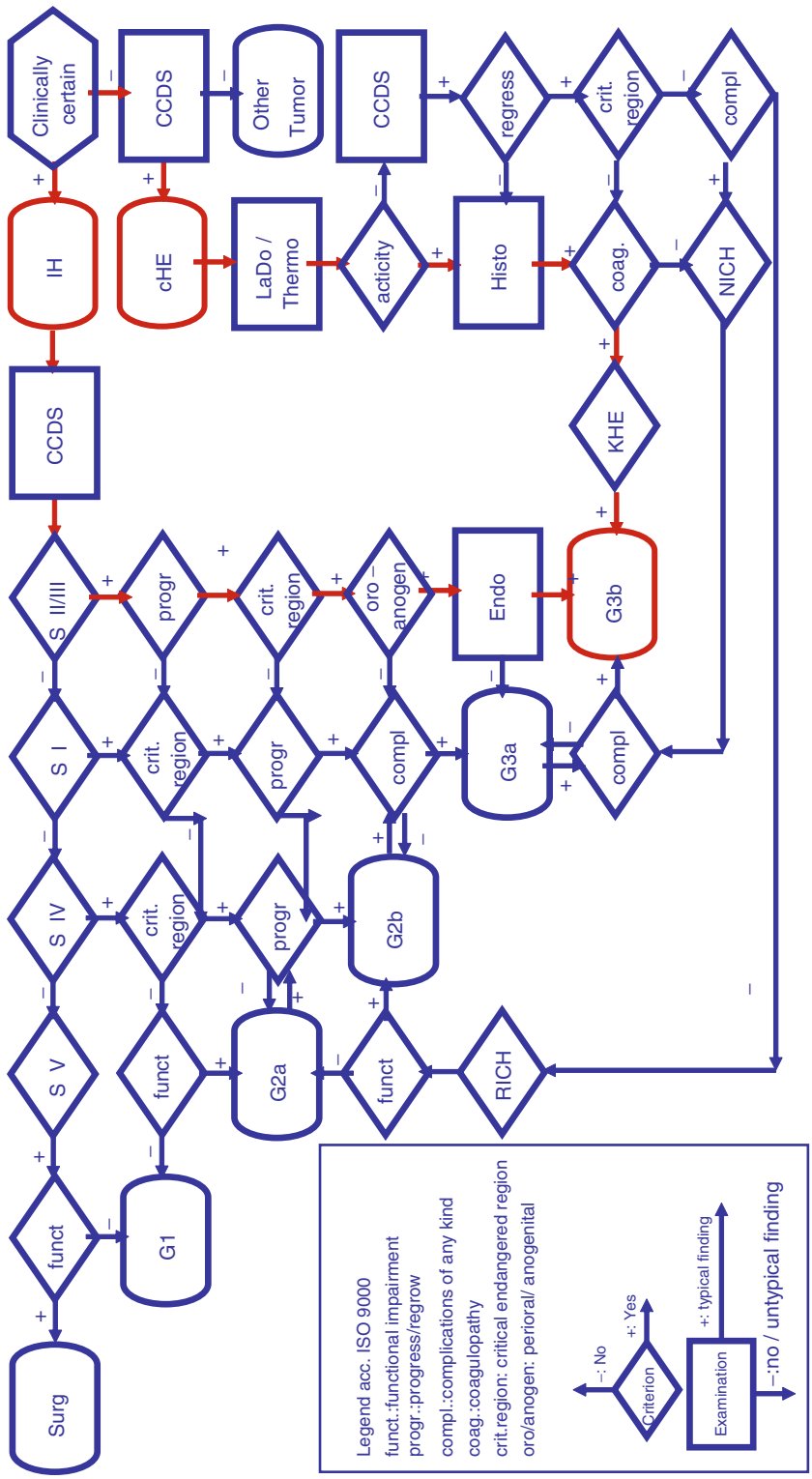

Fig. 18.13 Therapeutic algorithm for infantile hemangiomas (IHs) and congenital hemangioendotheliomas. The symbols are according to ISO 9000. The grading for IH is given in the figure. The therapeutic principle is a down-grading to an uncomplicated form either of IH or congenital hemangioendothelioma to allow the spontaneous regression. *DIC* disseminated intravasal coagulopathy; *CCDS* color-coded duplex sonography; *cHE* congenital hemangioendothelioma; *H* infantile hemangioma; *RICH* rapid involuting congenital hemangioendothelioma; *NICH* noninvoluting congenital hemangioendothelioma; *KHE* kaposiform congenital hemangioendothelioma; *Thermogr* infrared thermography

Table 18.6 Aim of laser treatment

Aim of laser treatment
Infantile hemangiomas and other benign vessel tumors
Induction of regression through inflammatory processes after intravascular absorption and vessel occlusion
Vascular malformation (VM)
Destruction of pathologic capillarization (extratruncular VM) and occlusion of cavernous vessel spaces and small arteriovenous fistulas (truncular malformations)

In contrast to vascular malformations in congenital vascular tumors, the aim of laser therapy is not to remove or completely destroy the hemangioma, but only to induce a stop of progression and initiation of regression

18.8 Local Procedures

18.8.1 Physical Procedures

The application of physical energy can be divided into direct tissue removal or destruction and secondary apoptosis by primary inflammation.

18.8.1.1 Cryotherapy

Cryotherapy at −30° (electrical) or at −176° (liquid nitrogen) is used in the contact procedure for the therapy of small plane hemangiomas with a maximal diameter of 1 cm. Cryotherapy has no specific absorption in the tissue and causes a severe frostbite with a congelatio escharotica III [26]. Because of the physical principle of thermal conductivity, treatment is only possible by destroying the overlying epithelial layer. Complications include hypopigmentations (10–15%) and scars or atrophies. After application, blisters and crusts occur. For infiltrated or disseminated and subcutaneous hemangiomas, this method is not suitable (Fig. 18.14a, b). Furthermore, there is no place for cryotherapy in treating any type of HE.

18.8.1.2 Scarification Techniques

Due to the observation that hemangiomas can start involution after trauma or infection, one principle used in the past for treatment was the scarification technique with needle radiofrequency. However, this procedure, like cryotherapy, causes scars on the skin, so the reason for reporting it here is purely historical. Furthermore,

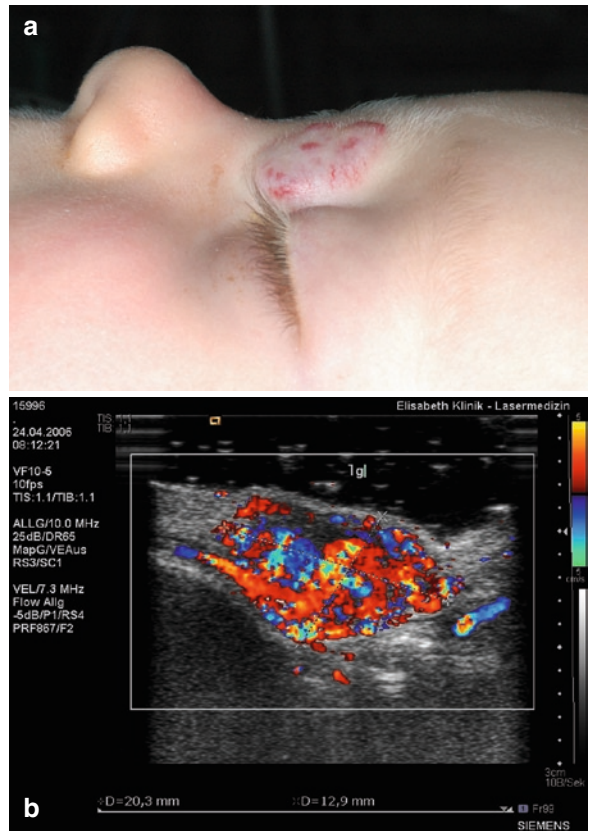

Fig. 18.14 (**a**) Status after three sessions of cryotherapy; brightening of the superficial infiltration but increasing subcutaneous volume. (**b**) Color-coded duplex sonography shows the unaffected deeper pathological vessels down to 13 mm

there is a high risk of massive bleeding, especially in proliferation hemangiomas. At the beginning of the laser era, some surgeons started using carbon dioxide (CO_2) laser scarification, but the results were similar to radiofrequency. Though the previous techniques treat hemangiomas only by destruction, the following induce inflammation.

18.8.1.3 Laser Therapy

Due to high specific absorption of the correct selected wavelength in the dermal or subcutaneous layers, laser therapy has been demonstrated to be effective and safe for the treatment of congenital vascular tumors in children while significantly minimizing any cutaneous adverse effects. Several positive clinical trials have been reported. Through laser treatment, an early and careful therapy of hemangiomas has also become possible so

that hemangiomas can be treated during early or prodromal phases to avoid enlargement [18]. However, laser treatment is required in rapidly growing hemangiomas of the head when these lesions interfere with important functions (e.g., hands and feet) or when they endanger delicate structures because of their location (e.g., the eye [Fig. 18.15a–g], anogential region). Treatment of large hemangiomas may also be desirable.

18.8.1.4 X-Ray Therapy

Comparable to the procedure in x-ray therapy of keloids or other inflammatory diseases, radiotherapy has also been used. The principle of tissue interaction is comparable to laser therapy: induction of inflammation followed by regression. Both techniques will not affect the unintended epithelial layer. However, in laser therapy the specific reaction causes selective absorption; in radiotherapy the specific reaction of this radiation is more effective in highly proliferative tissue. It seems to be an ideal tool for hemangioma treatment except that, in contrast to laser therapy, radiotherapy is an ionizing radiation that carries a high risk of mutagenity and carcinogenity. Furthermore, a secondary cataract is a major complication of treatment near the eyes. Therefore, for IHs and kaposiform HEs, x-ray therapy is discussed here only as a historical treatment and is no longer applicable today.

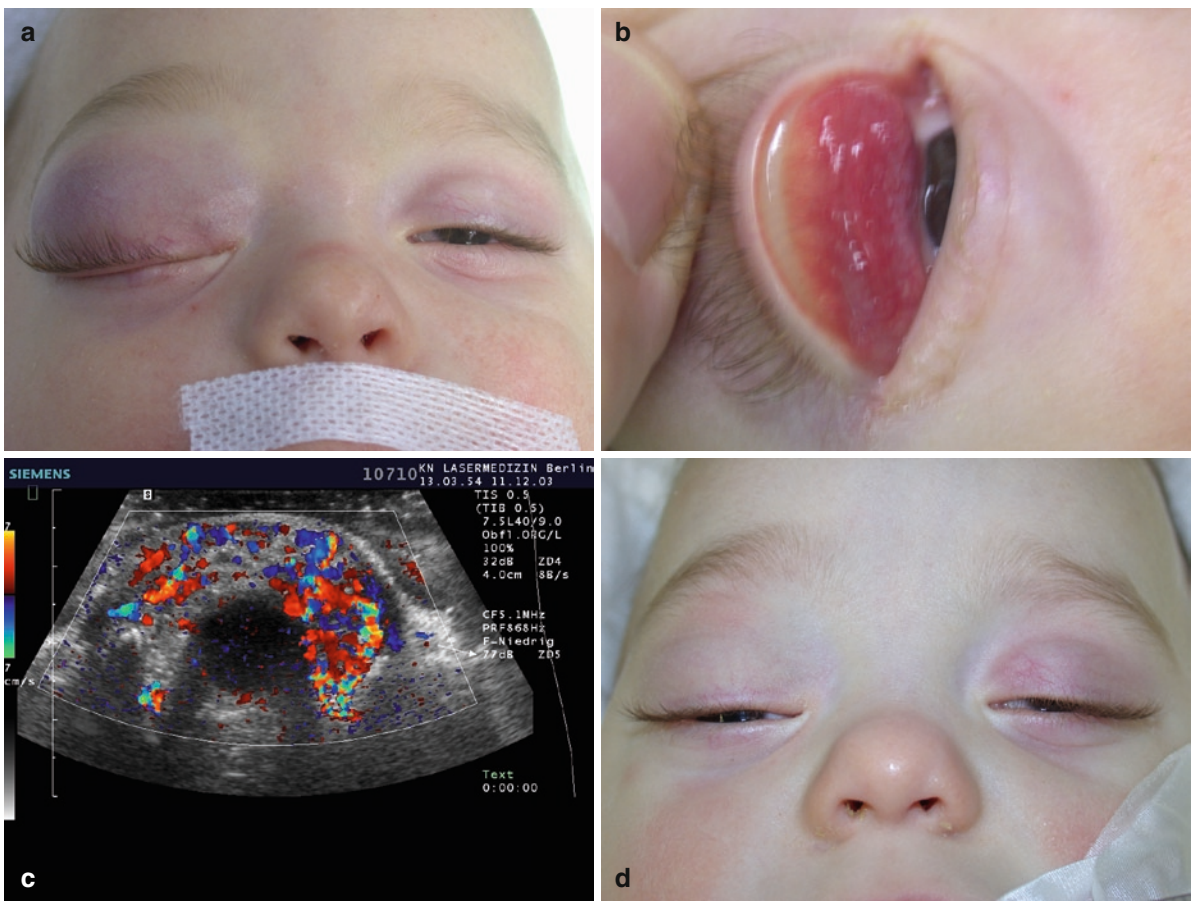

Fig. 18.15 (**a**) Prior to laser treatment: voluminous hemangioma of the right upper lid with increasing line-of-sight obstruction. (**b**) Massive infiltration and thickening of the conjunctiva. (**c**) Color-coded duplex sonography (CCDS) demonstrates the encapsulation of the eyeball. (**d**) After three laser applications significant reduction of volume. (**e**) The optical axis is no longer affected. (**f**) Reduction of the conjunctival infiltration. (**g**) CCDS demonstrates only minor vascular residuals

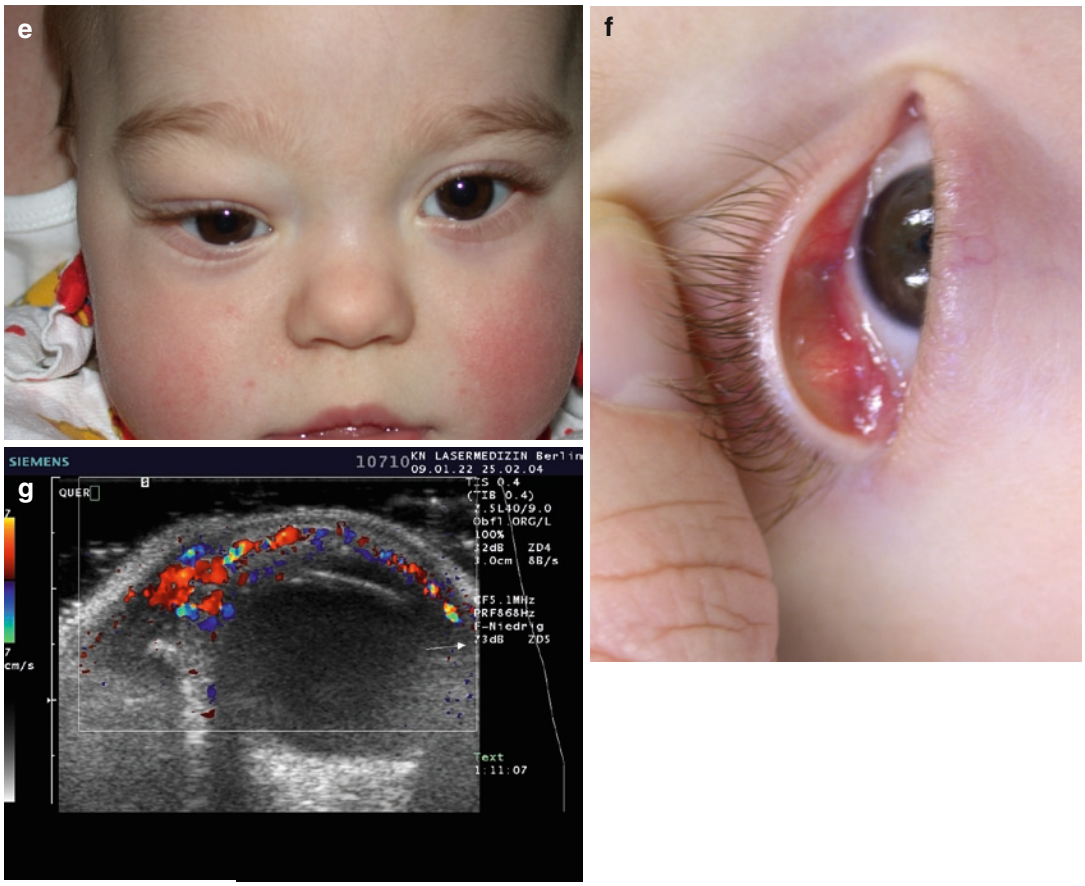

Fig. 18.15 (continued)

18.8.2 Mechanical Procedures

18.8.2.1 Compression

The idea of the compression technique for IH comes from burn scar therapy to prevent keloids. Due to the biological behavior of the proliferating tumor, this causes only ulcerations by pressure to the primarily unaffected epithelial layer. Therefore, this report is purely historical.

18.8.2.2 Ligation

Ligation and embolization [9] follow the experiences of acquired malignant tumors: occlusion of feeding arteries induces a necrosis of the tumors. However, this is a misunderstanding of the biology of congenital vascular tumors such as IHs. The origin is a highly proliferative tissue, which has secondary vessels. So, any occlusion either by ligature or embolization will be compensated immediately by the formation of new nutritional arteries.

18.8.2.3 Embolization

Comparable to ligation because of the collaterals of congenital vascular tumors, embolization is nonsensical [29]. One exceptional indication for embolization is in IHs of the liver with massive cardiac failure or massive bleeding from ulcerated hemangiomas [13]. In special cases of kaposiform HEs such as KMSs, which cannot be treated successful by cytostatics or lasers, an embolization may be considered, but only as the last option.

18.8.3 Chemical Procedures

The basis of chemical agents for the therapy of congenital vascular tumors is comparable to the indication of physical energy: induction of inflammation.

18.8.3.1 Sclerotherapy

Polidocanol is the main drug for sclerotherapy of varices, where it is a safe and successful procedure. However, in IHs or in congenital HEs there is a diffuse microcirculation, which does not allow a complete compression to avoid a systemic outflow. In newborns, even low concentrations of this drug can cause myocarditis. So, the indication for sclerosing drugs is replaced by laser therapy [34].

18.8.3.2 Interstitial Magnesium Seeds

Therapy with oxidizing metals such as copper and magnesium is outdated. The biological reaction is the production of free radicals in contact with the tissue. The application is not controllable; the technique is the seed technique known from radiotherapy, which carries a high risk of puncture failure and complete necrosis. As with sclerotherapy, this procedure has been completely replaced by the different laser techniques.

18.8.3.3 Interstitial Corticoid Crystals

An interstitial direct corticoid crystal injection has been reported for localized IHs. In the eye there is a high risk of crystal embolization of the artery, resulting in permanent blindness. Topical corticoid creams can cause skin atrophy and systemic side effects due to uncontrolled resorption [17].

18.8.3.4 Imiqiumod

Imiquimod was introduced for the therapy of intraepithelial neoplasias induced by human papilloma viruses. The basis is a local production of cytokines, and it has replaced the topical application of interferon. However, due to the mesenchymal origin of congenital vascular tumors, this principle works only by destruction and ulceration of the epithelial layer followed by a secondary inflammation in the hemangioma itself. Therefore, this treatment is comparable to the scarification techniques and has no effect on deep dermal or subcutaneous hemangiomas, which are the main indication for any therapy. In congenital HEs, because of the epidermal barrier, this procedure has no effect.

18.8.4 Systemic Procedures

There is no specific systemic treatment for IHs or congenital HEs. Two main principles are used: antiproliferating drugs [14] and antiangiogenesis.

18.8.4.1 Antiproliferative Drugs

The higher the proliferation rate, the more effective is the therapy with antiproliferative drugs. However, several complications of IHs are caused even at a low proliferation rate due to the complicated localization. Furthermore, not all antiproliferative drugs are able to induce regression, which explains the risk of the rebound effect after systemic therapy. Therefore, systemic therapy is an adjuvant for complicated IHs or congenital HEs and requires additional induction of regression, especially by differentiated laser therapy. In endotracheal or periorbital IHs, the laser-induced regression sometimes comes too late, necessitating an adjuvant systemic therapy to stop further growth. Furthermore, in kaposiform HEs with KMS, an immediate halt to progression is important to stop the coagulopathy [19].

18.8.4.2 Antiangiogenesis

Inhibitors of vascular growth factors have been well investigated for the therapy of malignancies. The problem with an IH is that this tumor forms vessels as a sign of maturation and not as a sign of aggression. In several investigations a strong relationship between vascular endothelial growth factor and the activity of the IH was not found. On the other hand, the long-term side effects during early childhood have not been completely investigated, so at this time antiangiogenic factors are only experimental in congenital vascular tumors [12].

18.8.5 Removal

18.8.5.1 Early Complications

In complete obstruction of the visual axis or in ulcerated hemangiomas with massive bleeding, an immediate resection of the IH may be necessary if the combined local laser therapy and systemic drug therapy cannot solve the problems rapidly enough. However, here one has to take into account that, because of the biological activity of the IH, an early local recurrence may be possible, requiring subsequent laser therapy. Besides in situ coagulation, in subglottic or endotracheal hemangiomas an complete endoscopic removal of the hemangiomatous tissue may be necessary to prevent tracheotomy.

18.8.5.2 Residuals

The longer the IH grows, the more commonly one can find huge residuals of fibrolipomatous tissue or cutis laxa after spontaneous or induced regression. Furthermore, after regression of IHs on a hairy head there may be hair loss. In these cases, a plastic correction after the end of the regression phase is an important option. With early therapy to prevent such uncontrolled growth, the number of indications is reduced. Even in late involuting congenital HEs, either RICHs, laser-induced NICHs, or Kaposi-like congenital hemangioendotheliomas (KHEs), a surgical resection of the remaining tissue sometimes is necessary. However, in most cases the growth stops so early due to the early therapy that a nearly complete resorption of the tumor tissue occurs.

18.9 Laser Therapy

The indication for any therapy in congenital vascular tumors is growing or other complications. Due to specific and calculable reactions, lasers offer the best modality for localized therapy because only with lasers it is possible to preserve the unaffected epithelial layer. Besides the different wavelengths with their specific absorption patterns, a great variety of tissue interactions can be achieved by variation of the interaction time and surface protection by cooling and/or compression.

Because IHs especially have a high capability of spontaneous regression the indication for active therapy is only in cases where this spontaneous regression occurs too late or there is an excessive growth before regression. The aim of laser therapy is to induce this regression – except in cases where an immediate surgical intervention is needed – not a removal of the hemangiomatous tissue. This means that any additional damage of surrounding tissue caused by the laser therapy must and can be avoided. The principle of laser treatment is an inflammatory process as a result of intravascular absorption of light and vessel obstructions and generally not definitive coagulation. This means that for different forms, depths, organs, and localizations, different lasers and different laser procedures are obligatory.

18.9.1 Superselective Laser Systems

The specific absorption is not only a question of the wavelength and the tissue properties; it also reciprocally depends on the exposure time [2]. This means that, for superselective absorption, the lower the specific absorption the shorter the exposure time and the longer the exposure time, the higher the specific absorption. This results in an overlap of indications between the different laser systems. Generally, the term "superselective laser systems" is used for lasers with an exposure time of less than 100 ms (short pulsed lasers) [28].

18.9.2 Flash Lamp-Pumped Pulsed Dye Laser

Today the flash lamp-pumped pulsed dye laser (FLPDL) is generally accepted as the treatment of choice for macular PWSs. Also, patients with diffuse telangiectases as a component of Rothman-Thompson syndrome or Louis-Bar syndrome demonstrate dramatic clearing after treatment with the pulsed dye laser.

However, the use of the FLPDL with wavelengths of 585 or 595 nm and a pulse duration of 300 μs to 2 ms is only indicated in the very early stages of IHs not thicker than 2 mm, provided there is no subcutaneous part [22]. Treatment is simple and quick. When the faces of newborns and small children have to be treated, anesthesia is required, whereas only local anesthesia (e.g., a eutectic mixture of local anesthetic [lidocaine

and prilocaine]) is sufficient for treatment of areas other than the face. Side effects are extremely rare. Occasionally, blisters and scabs are observed, which require cooling and stabilization of the epidermis by a fluid cooling cuvette. The obligatory bluish-black coloring disappears within 14 days (Fig. 18.16a, c). Scars appear in <1% of all cases. Particularly in the anogenital area there is a danger of ulceration with secondary infection. Early FLPDL therapy of all IHs and their precursor lesions brought no essential advantages compared to an untreated control group [1], but the authors of this study differentiated the hemangiomas according to neither their depth nor their various stages of development (Fig. 18.17a–d). Tuberous hemangiomas are no indication for the use of an FLPDL, [4]. Telangiectatic changes, either primary or as residues of mature IHs, also are not suited for the use of an FLPDL (Fig. 18.18). This is an indication for the potassium titanyl phoasphate (KTP) laser.

18.9.3 Frequency-Doubled Nd:YAG Laser ("KTP")

This type of laser must not be confused with the pulsed Nd:YAG laser or even with the continuous wave (cw) ND:YAG laser [25]. Here, the infrared (IR) light of the Nd:YAG laser is channeled through a potassium-titanyl-phosphate crystal, which produces from the

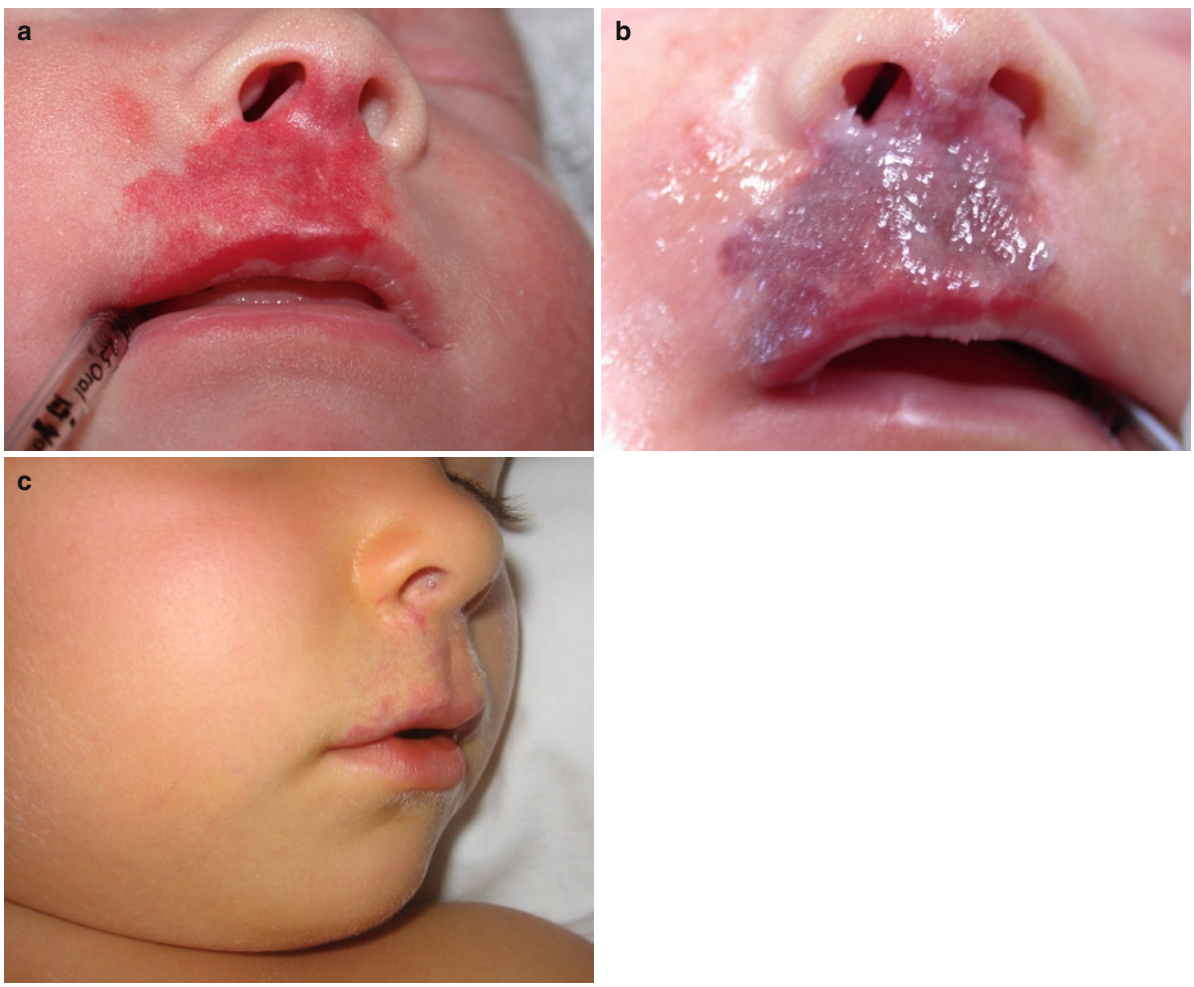

Fig. 18.16 (**a**) Hemangioma with sole cutaneous infiltration. (**b**) Typical postinterventional mauve purpura (ointment applied). (**c**) After one treatment only faint residuals left for further spontaneous regression

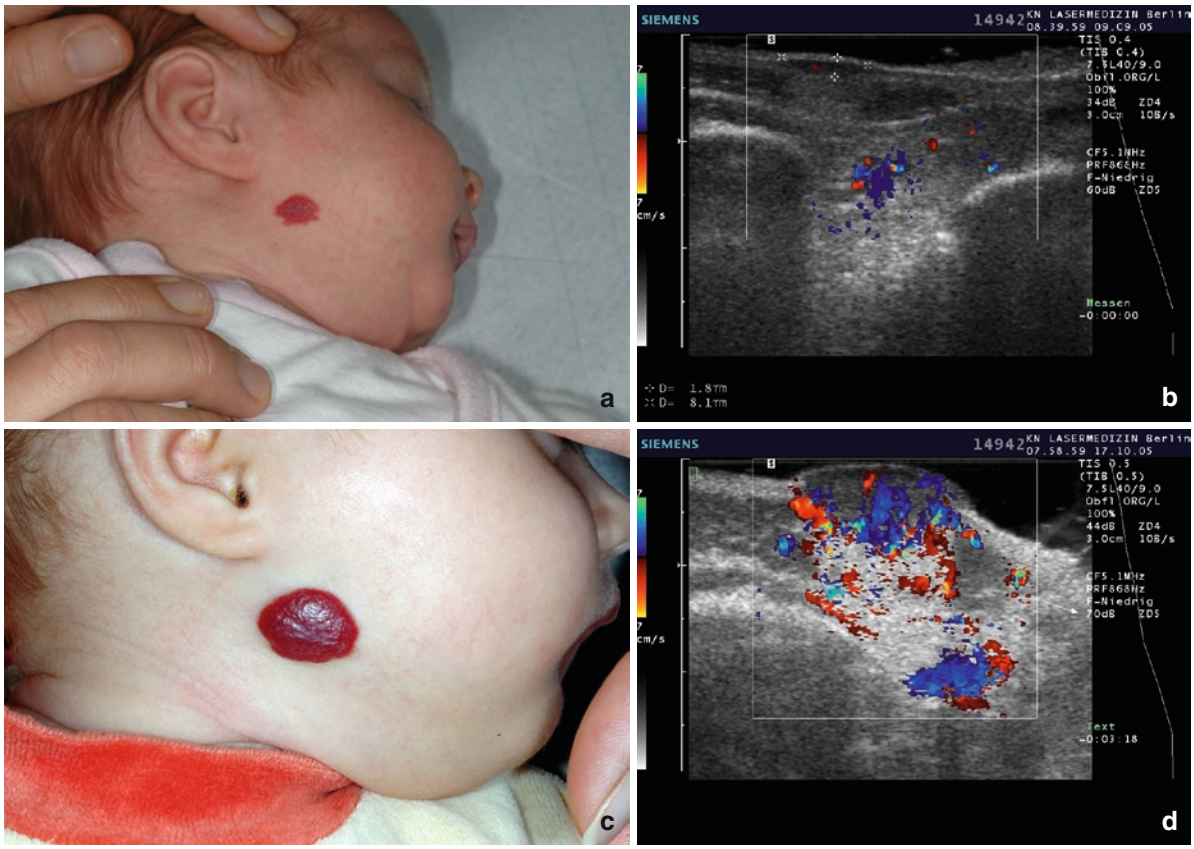

Fig. 18.17 (**a**) Hemangioma assumed to be only superficial. (**b**) In color-coded duplex sonography (CCDS) hyposonic swelling of the skin; notice the faint hypersonic modification of the subcutaneous region with some small color coded vessels: indication of deeper infiltration. (**c**) Rapid growth despite flash lamp- pumped pulsed dye laser therapy. (**d**) Now CCDS shows the pre-existing subcutaneous infiltration more clearly

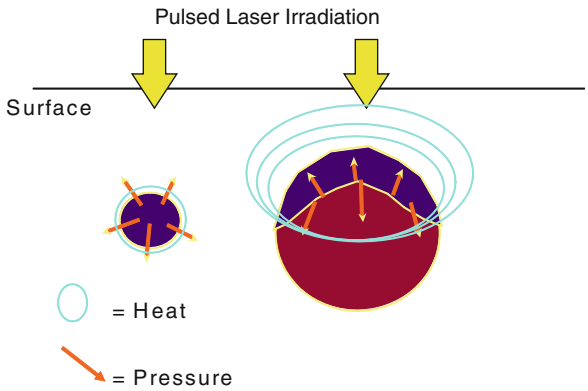

Fig. 18.18 Vessel size limits the effect of the flashlamp-pumped pulsed dye laser. The shorter the pulse length the smaller the affected volume. This explains why the pulsed dye laser is not suitable for larger telangiectatic vessels

near IR (NIR) wavelength of 1,064 nm by frequency doubling half the wavelength of 532 nm. Thus, the biological effect is comparable to that of an argon laser [1]. The advantage of this type of laser is that the KTP, because of its better efficacy, especially when pumped with diodes, does not need water cooling, unlike the argon laser. This makes it easier to handle.

Due to the experience of use for treatment of other telangiectases such as the angioma serpiginosum, small tuberous hemangiomas and residual telangiectasias after regression are being directly treated under glass spatula compression dot to dot (Fig. 18.19a, b). With short pulse durations of a maximum of 100 ms and avoidance of double exposure or overlapping, absorption only takes place in the hemoglobin of the vessels and no thermal side effects are to be expected in the surrounding tissue.

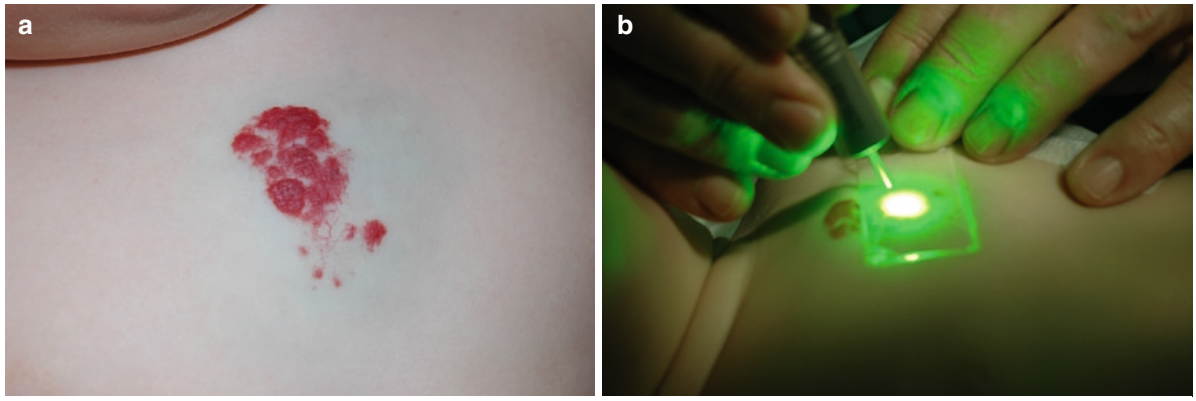

Fig. 18.19 (**a**) The cutaneous part of this combined hemangioma shows vascular ectasias and tuberous infiltrations. (**b**) Treatment with a potassium titanyl phosphate laser under quartz glass compression

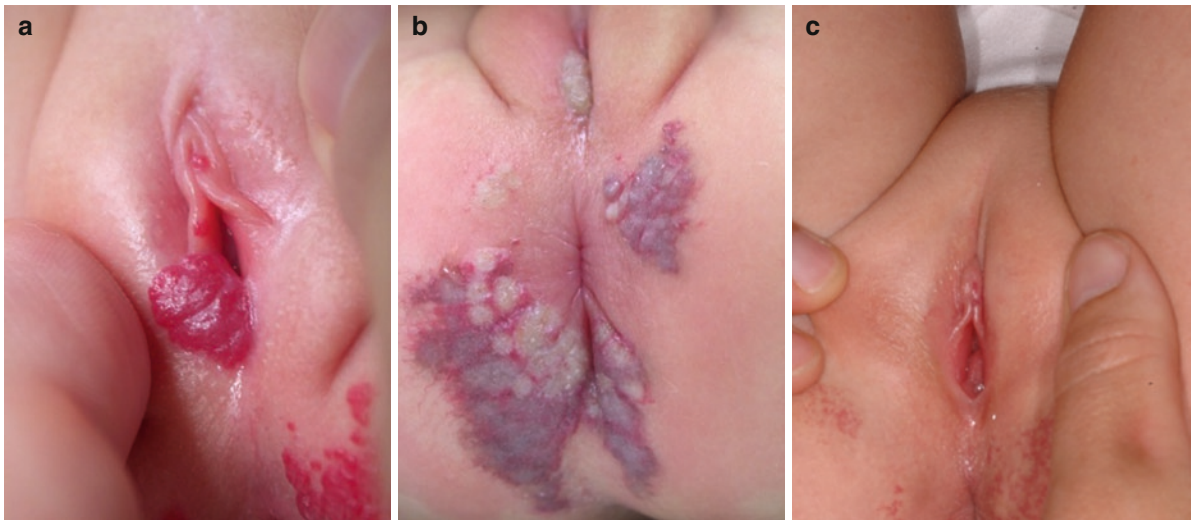

Fig. 18.20 (**a**) Markedly elevated cutaneous infiltration in the sensitive anogenital region. (**b**) Circumscribed spotted superficial coagulations after pulsed neodymium:yttrium aluminum garnet laser exposition. (**c**) Only minor hemangioma residuals after healing without any scar

18.9.4 Pulsed Nd:YAG Laser

Unlike the KTP laser, NIR radiation is applied directly. The difference of the standard cw Nd:YAG laser is its short pulse rate of 2–10 ms, albeit with high pulse peaks. Though the biophysical penetration is the same as that of the cw Nd:YAG laser, the actual penetration depth is limited because of the short pulse duration (Fig. 18.20a–c). For this reason, this laser is suited for use in anatomically endangered regions or larger vein ectasias and tuberous lesions [5]. To avoid secondary damage by scattered radiation or heat conduction, at least one intermittent cooling system by cold air or ice cubes is required, unless the beam is led through the fluid cooling cuvette or the ice cube as with the cw Nd:YAG laser.

18.9.5 Continuous Wave Lasers

With exposure times longer than 100 ms, thermal conductivity by the laser-heated tissue is a main effect. This means that, for the primary reaction, a specific absorption is important but the whole tissue interaction is also triggered by the exposure time

(Fig. 18.21). Lasers with a high water absorption like erbium or CO_2 lasers have the same primary effect in all tissue, the real tissue interaction depends only on the exposure time. Besides the argon laser, the cw Nd:YAG laser is the laser type that has been used for the longest time in the treatment of congenital vascular anomalies. It is the same laser that is used for endoscopic surgery. In addition to the possibility of directing the laser beam via thin glass fibers, the immense biophysical variability has made this laser the "workhorse" in the treatment of congenital vascular anomalies. The biophysically determined penetration (drop in photon density to 1/e2) is 8 mm for most tissues. Using cw made during high performance, an effective photon density can still be attained at depths of 20 and 30 mm. On the other hand, the photon density and thus the effective depth can be limited to less than 14 mm by short pulse durations. Suitable cooling procedures protect the penetrated surface enough despite surface absorption to allow no tissue reactions there, only deeper down. Moreover, different absorption coefficients are responsible for the selective effect. Blood and organs rich in blood absorb this NIR radiation considerably better than connective or fatty tissue. The tissue reaction to the NIR radiation also differs from tissue to tissue. Collagen shows considerable shrinkage; the endothelium already reacts with a serious vasculitis to power densities, which do not yet trigger a reaction in other tissue. High power densities quickly lead to carbonization, which then fully absorbs the laser radiation. Thus, vaporization sets in with two consequences: if one wants to ablate or cut, this process must occur very quickly to avoid unwanted thermal effects in the vicinity. If coagulation is intended, especially in the deep regions, this process must be avoided because no radiation gets deep down enough. The direction of these processes determines the wide usage of the cw Nd:YAG laser [7].

18.9.5.1 Transcutaneous Direct Application

As in patients with Osler syndrome, small tuberous lesions and telangiectasias may also be treated with the cw Nd:YAG laser analogous to the pulsed Nd:YAG laser and the KTP laser. To avoid thermal damage, short pulse rates of 100 ms maximum, an output of 25 W, and small spot diameters of up to 0.5 mm are required by using a focusing handpiece. Intermittent and cooling with ice cubes after treatment has to take place to avoid thermal damage by heat blockage.

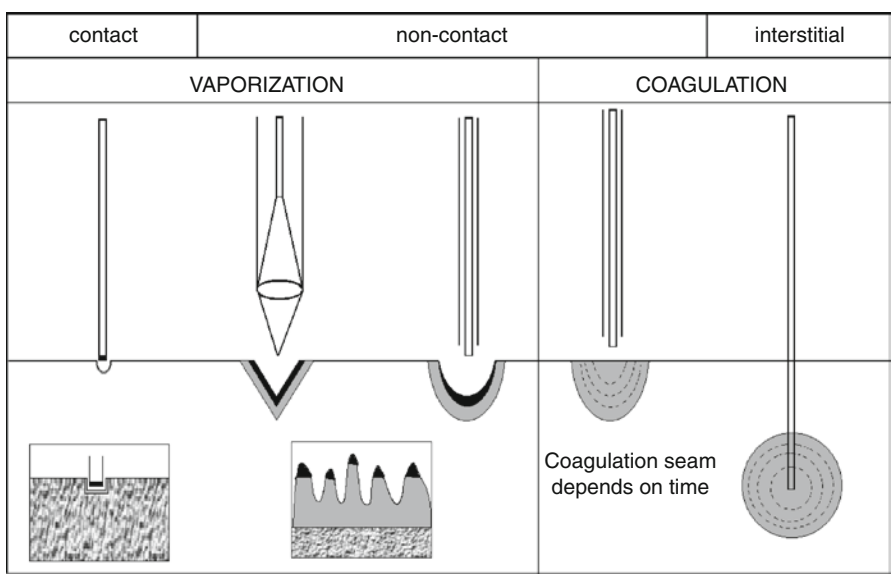

Fig. 18.21 Principle application modes of the continuous wave neodymium:yttrium aluminum garnet laser. With the different procedure of surface cooling the variety of tissue interactions increases

18.9.5.2 Transcutaneous Application with Fluid Cooling Cuvette

If intermittent cooling is not sufficient, continuous cooling is required. The heat capacity of spray or cold air cooling is not sufficient for the heat blockage caused by the cw Nd:YAG laser. Various contact cooling systems are available. Cooled sapphire plates are easy to handle but have a series of disadvantages. The metal frame of the cooling Peltier element may lead to frostbite if there is direct contact with skin. The biggest disadvantage, however, is that the plane surface cannot adapt to the anatomic situation, especially when used on children's faces, so that they either don't have full contact with the surface or are too heavily compressed at the edges, causing not only frostbite but also a change in microcirculation. Thus, they can actually be used only for large plane areas. The fluid cooling cuvette with a 40% refrigerated glycol solution has a highly flexible, highly transparent latex membrane, through which changes in the outlet valve can adapt even when used on difficult anatomic silhouettes (Fig. 18.22). An additional advantage is that this prestressing makes it possible to adjust the compression pressure and the blood flow to vary the tissue absorption [21]. With maximum compression, the overlying tissue can be made transparent for Nd:YAG laser radiation. With negative pressure (suction), the tiniest capillary vessels can be expanded, boosting the specific absorption. The cooling capacity has been calculated to have a reaction in the center of the laser beam given the necessary absorption and adverse events by scattering and thermal conduction are avoided in the surrounding areas. In cases of vein ectasias, this procedure is better suited than use of the KTP laser.

18.9.5.3 Transcutaneous Application with Continuous Ice Cube Cooling

If subcutaneous lesions have to be treated transcutaneously, a continuous Nd:YAG laser application would create so much heat that none of the above mentioned cooling systems would be able to completely protect the transient tissue from unwanted coagulation. Deep freezing systems such as liquid nitrogen or deep-temperature Peltier elements cannot be directed sufficiently and frostbite would result. Here, radiation through a transparent ice cube without air bubbles seems to be the solution. The melting of ice to water is one of the most energy-consuming processes. This high heat capacity is capable of completely rerouting the heat that builds up in the transient tissue by basic absorption, so there are no reactions on the surface. On the other hand, natural law prevents the temperature from dropping below 0°C, avoiding frostbite. Because meltwater always guarantees good tissue contact, contact gels, etc., are superfluous. This cooling effect is limited to 2 mm due to the thermal conductivity properties of the tissue, and laser radiation can treat subcutaneous lesions without causing any defects on the surface thanks to its greater penetration. Prerequisites are the use of a focusing hand piece with a focus diameter of 0.5–1 mm. This focus has to be positioned on the tissue surface through an ice cube; otherwise, no sufficient penetration will be attained because of diffraction scattering. Because the ice cube has its own absorption for this laser radiation, a prolonged exposition would drill a hole into the ice cube ("chimney effect"), letting radiation get directly to the tissue surface. Therefore, the ice cube has to be moved above the hemangioma under laser exposition, the ray itself moving in small spiral motions with a

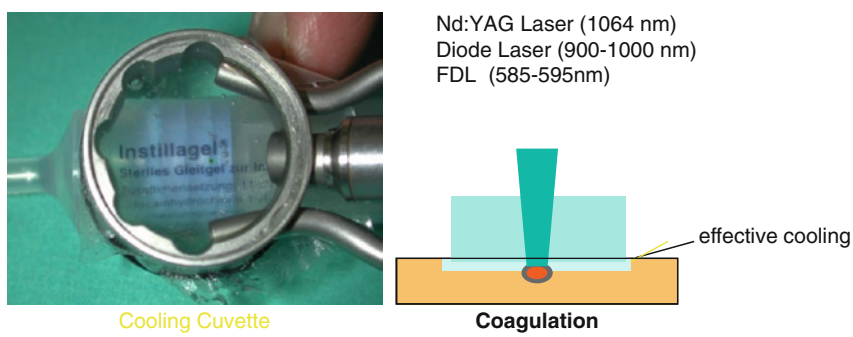

Fig. 18.22 Cooling chamber, principle of the fluid cooling cuvette. The high transparent flexible latex membrane allows a continuous control of the laser process and follows any anatomical structure without uncontrolled compression. However, the heat capacity is limited for pulsed applications

radius of about 5 mm to avoid too high a load for a single spot. If the laser beam is moved above the ice cube and the ice cube itself not be moved, the chimney effect could be avoided; however, but the developing heat on the surface of the hemangioma would melt the ice cube so much that there would be no more direct tissue contact between the ice cube and the hemangioma ("igloo effect"). Through compression, especially in the treatment of large hemangiomas with an ice cube, the depth of penetration can be increased and by pressure on the surface the absorption decreased, boosting the protection (Fig. 18.23). This procedure is only recommended under anesthesia because of the associated pain. This is also necessary because of laser safety; most hemangiomas are located in the face near the eyes. For the exact positioning of the laser parameters an intraoperative CCDS is required; this alone enables determination of activity and exact stage, dimension, and location of applicable involvement of various layers (Fig. 18.24a–d). To choose the laser output, the following rules apply: The more active and aggressive the growth and the earlier the stage, the smaller the output to avoid an overreaction. The more vessels are visible already, the higher the output to attain involution. Moreover, the stronger the intracutaneous lesion, the smaller the output. However, in exclusive subcutaneous lesions, the output is higher. Treatment next to the eyes necessitates protection from forward scattered radiation. For this purpose, metal spatulas ("eye spatulas") that float on a kanamycin ointment bed in such a way that the back side never touches the cornea are suited. For this reason, the laser beam should always be turned away from the eyeball. At the columella, attention should be paid to the cartilage structure of the nose. In hemangiomas on the lips, the laser also has to be turned away from the gingiva to avoid destruction of dental germs. A hemangioma of the gingiva itself can be treated with and FLPDL. The aim is not a definite coagulation of the IH but the induction of a vasculitis. A visible blanching or even an involution during laser treatment should be avoided because this would be equivalent to overdosing. The optimal total dose has been reached when the hemangioma during laser treatment starts to show a swelling and is bulging and the surrounding area turns red, which lasts up to 12 h. Occasionally, 6–24 h postoperatively, subcutaneous blue indurations develop as an expression of the vasculitis with a vessel breakdown. This reaction is common in very active IHs during the early proliferation phase. Because the overlying epidermis is easily damaged postoperatively, enough ointment should be applied and the area should be protected against scratches with suitable measures such as the wearing of gloves. A bandage is rarely necessary, except in cases of heavy mechanical abrasions. Although this treatment does not cause injuries on the surface of the skin, about 2% of children develop erysipelas with a beginning lymphangitis 12–48 h after the operation (Fig. 18.25a, b). This is seen frequently in the face. Erysipelas doesn't develop in the hemangioma itself or around it, but occurs occasionally a few centimeters away from draining into the lymph. This inflammation can be differentiated from the direct, postoperative, laser-induced inflammation because this region is sensitive to touch and hardened. In already exulcerated or even secondarily infected hemangiomas, this reaction has never been noted, nor has it been noted during interstitial treatment when puncturing. Thus it is not a nosocomial infection. An immediate treatment with oral antibiotics with broad-spectrum cephalosporin will cause the clinical symptoms to subside within a few hours. Fever and symptoms do not exist at any time then, but the infiltrate may persist for a few days.

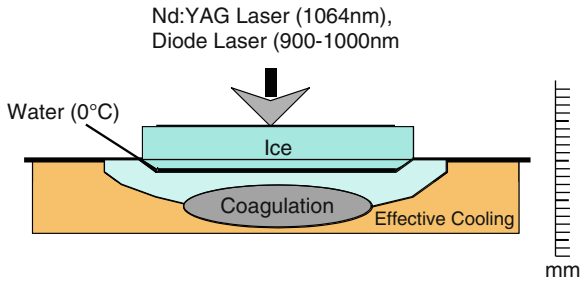

Fig. 18.23 Transcutaneous neodymium:yttrium aluminum garnet laser treatment with ice cube cooling. Fort continuous laser application, a greater heat capacity is required to save the overlying skin. Irradiation through a clear ice cube allows a deep laser reaction without any damage to the overlying skin. The protection is so perfect that in eyelid treatment it is possible to carry out a transpalpebral coagulation without any noticing. Therefore, the cornea in this case must be protected with a metal spatula

Because a regression in HEs cannot be attained as easily as in IHs, clearly more output– up to 60 W– is required, although normally it is used only for the treatment of VMs. As with the treatment of VMs, the incidence of side effects from Nd:YAG laser treatment of hemangiomas is quite small.

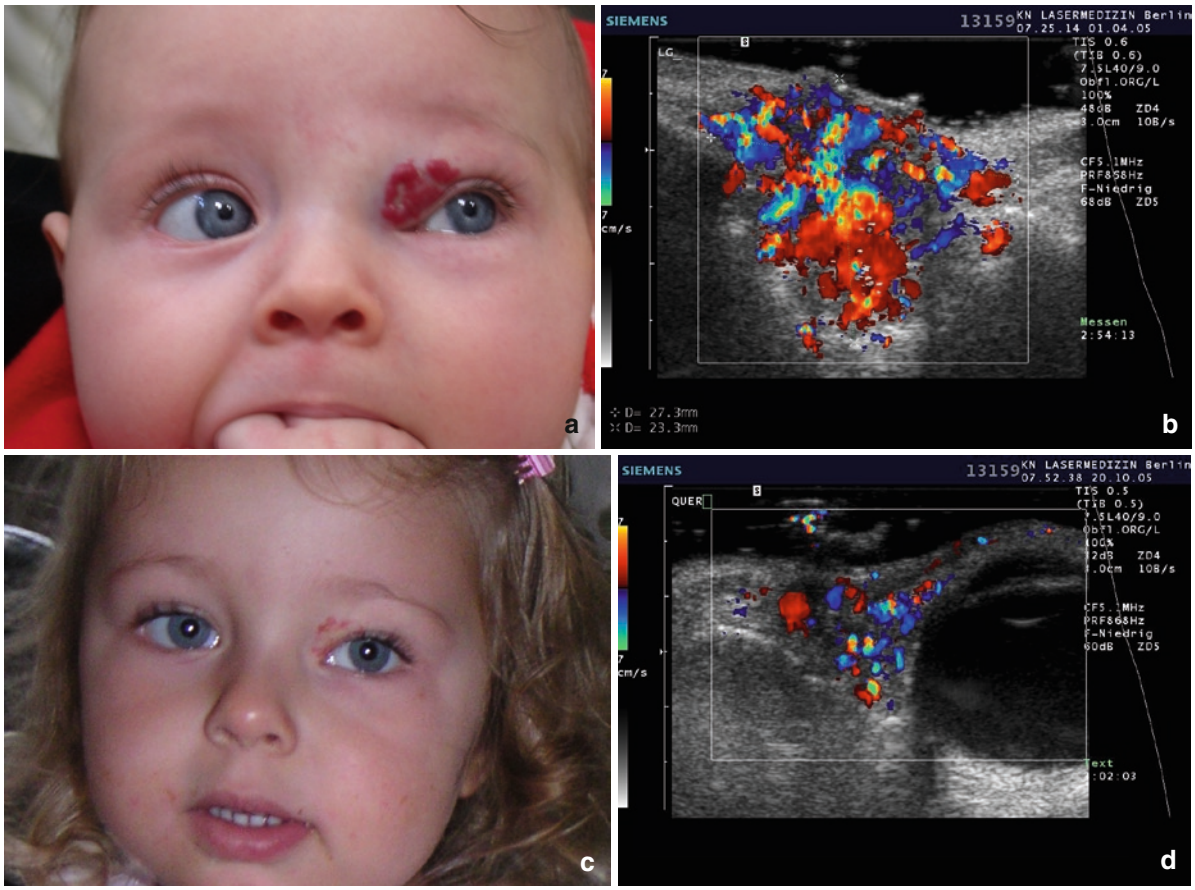

Fig. 18.24 (**a**) Besides a cutaneous infiltration the subcutaneous volume hinders the eyelid motility. (**b**) Color-coded duplex sonography detects the deep infiltration medial of the bulb. (**c**) After four transcutaneous treatments advanced regression in both components. (**d**) Even close to the bulb only marginal residuals

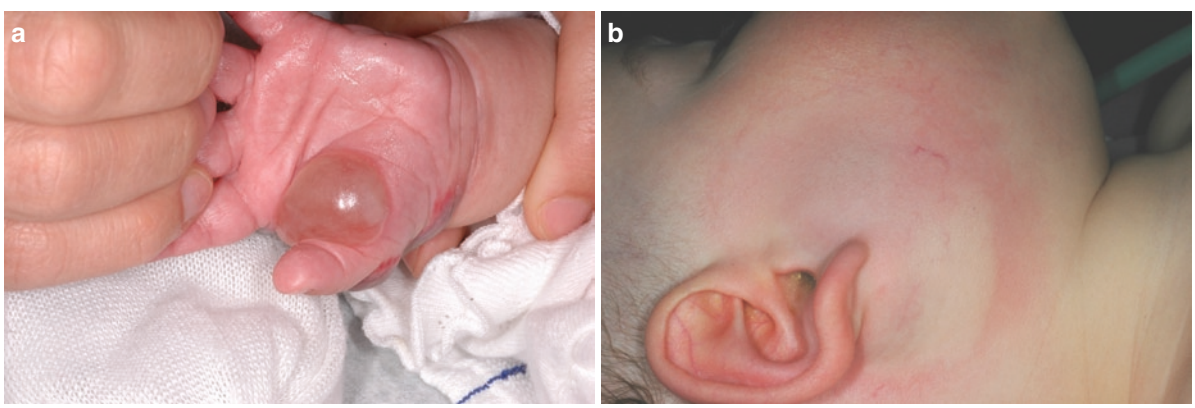

Fig. 18.25 (**a**) Blebs after laser therapy develop after a latency of seven hours, not as a sign of burning but a result of swelling expansion. (**b**) Pale swelling in the center of the treatment region with surrounding reddish rim; suspect for beginning infection

In contrast to the interstitial puncture technique, uniform coagulation can be achieved and fibrosis will not be as pronounced after healing is completed.

Impression Technique

Unlike interstitial puncturing, during the impression technique the fiber is put on the surface and pressed into the hemangioma. This way, a shift of the laser effect below the surface is attained without triggering coagulation on the surface of the hemangioma (except for the fiber contact area). Therefore, this technique should be used for the skin only in limited cases because it may cause small scars. However, it is an ideal technique for hemangiomas reachable from the mucosa, including the conjunctiva (Fig. 18.26a, b), because it leads to a "restitutio ad integrum" even in the contact area. With a laser output of 5 W maximum, the in-depth effect can be adjusted by the length of exposition. This way, laser application becomes possible even near critical structures. In hemangiomas on the upper as well as the lower eyelids, a curved fiber holder is used for laser application from conjunctiva to the outside (Fig. 18.27a–e). The skin temperature above the hemangioma is constantly being controlled with a finger; the position of the fiber point can be controlled with CCDS. In lip hemangiomas, the laser can be likewise applied enorally. The impression technique closes the gap between direct application, even with the pulsed Nd:YAG laser, which operates only on the surface, and the transcutaneous ice cube application, which reaches large volumes.

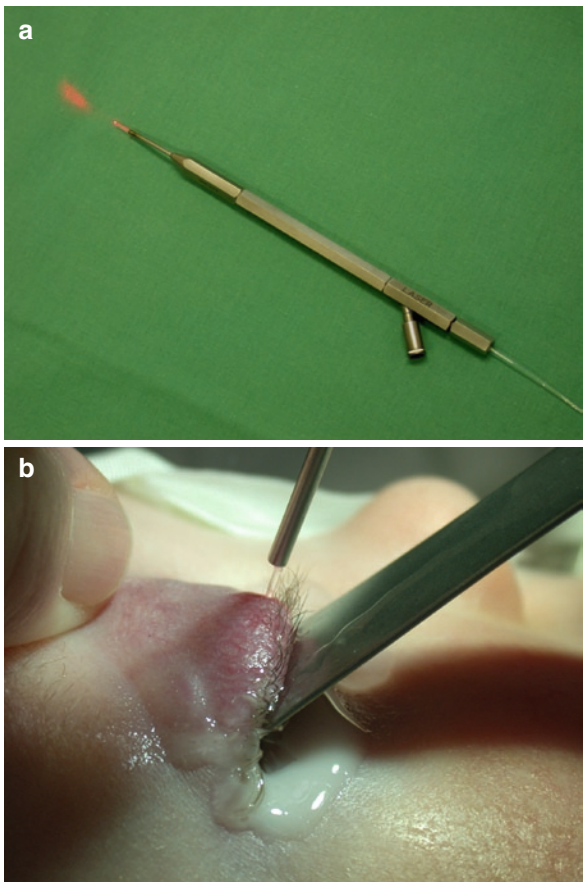

Fig. 18.26 (**a**) Fastener for bare fiber application. (**b**) Bare fiber impression technique in the sensitive region of the upper-lid ridge; even without scattering protection of the eye is mandatory

Interstitial Puncture Technique

In very large, deep, and particularly purely subcutaneous hemangiomas, neither the impression technique nor the transcutaneous ice cube method can totally avoid thermal damage to the surface. In these cases, the hemangioma is being punctured with a teflon vein catheter and the fiber is being inserted (Fig. 18.28a–c). Output should be between 4 and 5 W; with higher outputs there are immediate carbonizations at the fiber tip, which would burn the tissue and would prevent a uniform distribution of the laser radiation. Intraoperative CCDS control is obligatory [32] to avoid erroneous puncturing and to monitor the adequate laser reaction via the color bruit. Skin temperature above the laser area must be monitored continually with a finger, just as in the impression technique, when the distance from the fiber tip to the surface is less than 10 mm. Thermal damage of the surface thus can be safely avoided, but when nerves are being directly aiming for, with the fiber tip, they may be damaged. This can be excluded by the transcutaneous ice cube technique. By optimizing the laser parameters and the ice cube quality, the indication for the interstitial technique for IHs has clearly dropped. Even vast parotid hemangiomas only rarely are treated this way. For large HEs, be it the KHE or the NICH, this technique represents an expansion of

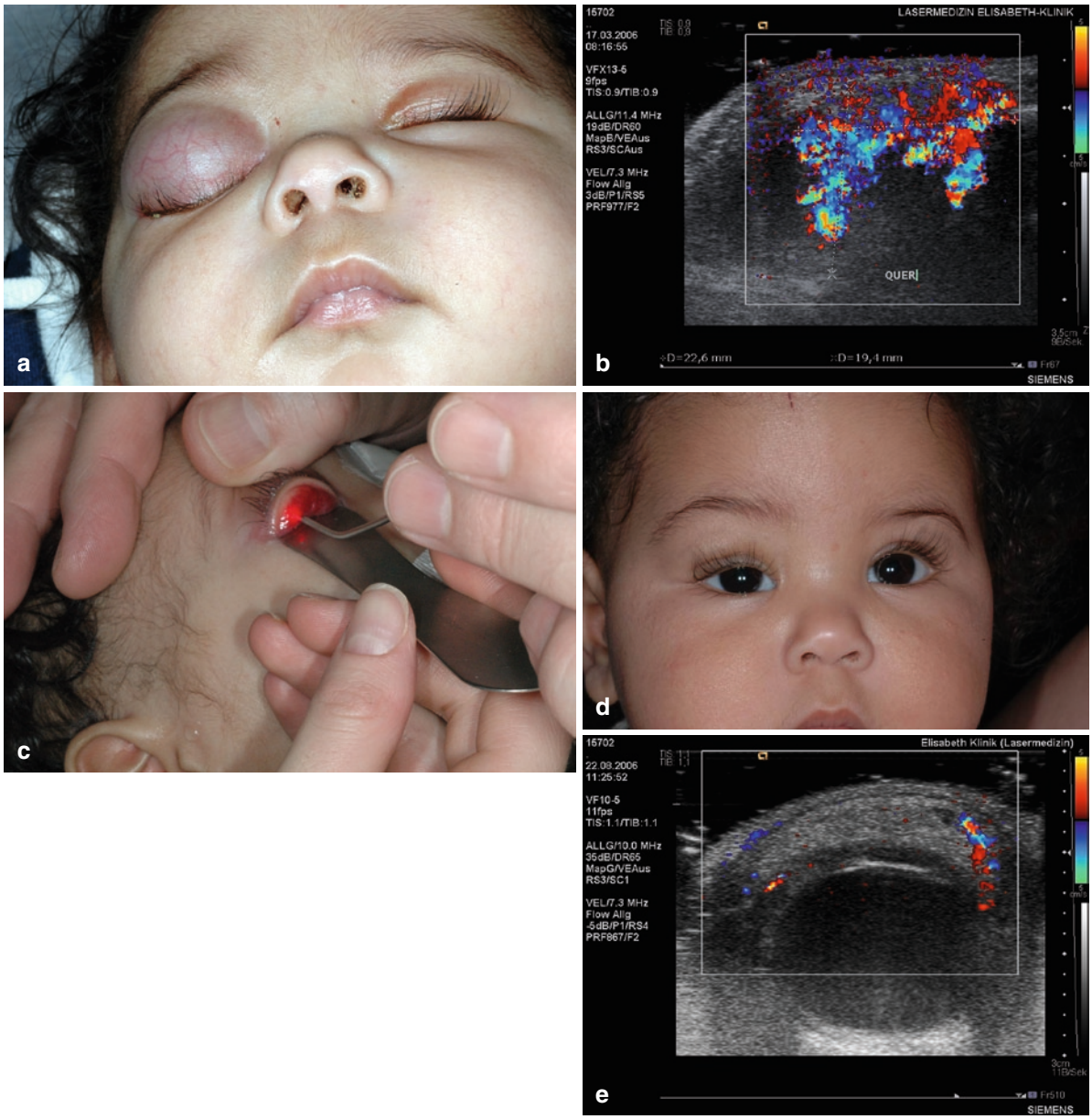

Fig. 18.27 (**a**) Purely subcutaneous hemangioma. (**b**) Infiltration depth >20 mm above the bulb. (**c**) Directional impression technique trans conjunctival allows high energy input without risk of scars. (**d**) Perfect reduction of the volume. (**e**) Five months later barely smallest residuals are left

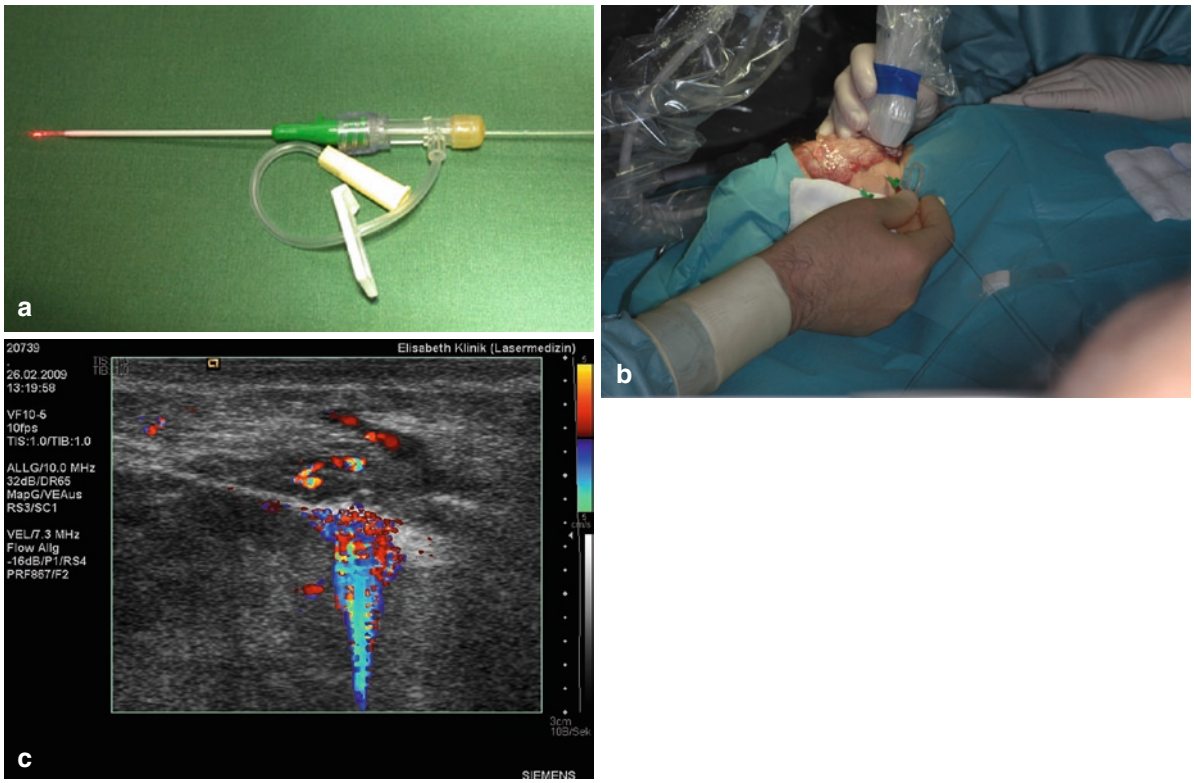

Fig. 18.28 (**a**) Equipment for interstitial application: bare fiber within a standard Teflon intravenous cannula. (**b**) Puncture, positioning of the bare fiber and online laser monitoring under color-coded duplex sonography control. (**c**) The typical intralesional color bruit during laser exposition

the transcutaneous ice cube technique (Fig. 18.29a–d). Through direct subcutaneous application an immediate coagulation of the HEs can be achieved. In patients with a KMS along with a coagulopathy, however, the bleeding risk through puncturing has to be avoided. In such cases, small coagulations of the dermis should be accepted and the ice cube technique with a high output of 60 W should be applied.

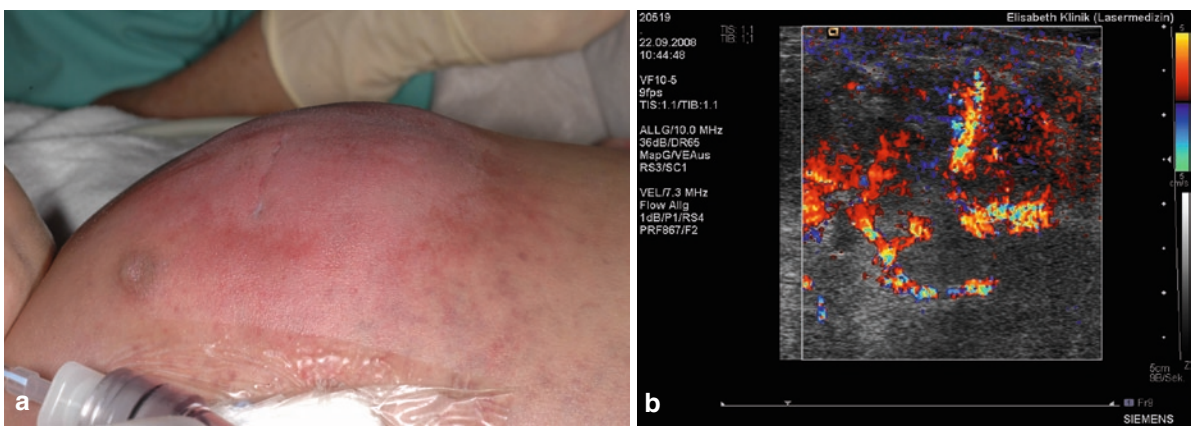

Fig. 18.29 (**a**) Widespread Kaposi-like congenital hemangioendothelioma in the right thorax. (**b**) Large infiltrating vessels in the chest wall. (**c**) Magnetic resonance imaging shows the infiltration of the pleural space and mediastinum. (**d**) Status after multimodal treatment sessions, including interstitial laser therapy

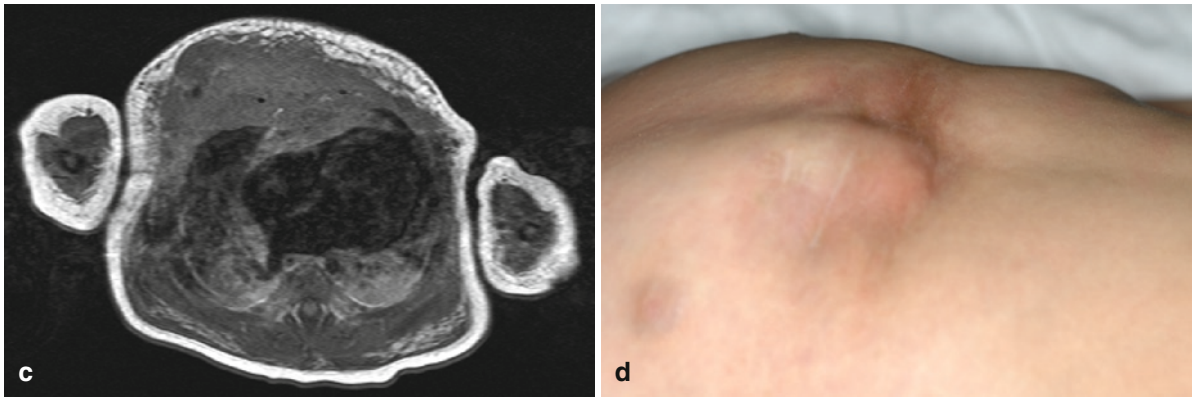

Fig. 18.29 (continued)

Endoscopy

In IHs, there is an indication for endoscopic treatment, primarily in subglottal and tracheal IHs [11] as well as IHs in the urethra and the anal canal. Though an involvement of the male urethra is rare, and by differential diagnosis a VM should be considered, in girls, especially vulvar and perineal IHs are clearly more common. To exclude further lesions at the bladder neck, which is usually affected by a VM, a cystourethroscopy always should be performed. The endoscope is entered through the working canal with the fiber and in flat, disseminated hemangiomas a punctual coagulation is achieved by noncontact of the fiber tip with the tissue with an output of 10 W, pulsed, and exposures lasting a maximum of 100 ms. Confluent coagulation definitely has to be avoided. In pad-like hemangiomas, the impression technique is performed over the endoscope, as described earlier, with a maximum output of only 5 W. Especially in subglottal and tracheal hemangiomas, the hemangioma must not be coagulated completely because scarred strictures may remain [3]. Circular applications should be avoided as well (Fig. 18.30a–d). When treating IHs one has to be particularly careful of the vocal cords. Only short, single, punctual applications are permissible to avoid fibrosis and thus limited function of the vocal cords. In no case should an attempt be made to remove the hemangioma during one session. For this procedure, a postoperative intubation usually is not necessary for safety reasons. In IHs of the larynx and the trachea, simultaneous, short-interval, high-dose prednisone therapy is essential. With this regimen we were able to avoid primary tracheotomy for more than 20 years in patients with IHs [6].

In children who have undergone tracheotomy in emergency situations elsewhere and then came to us, the tracheostoma could be closed after a maximum of two sessions.

Take Home Pearls

Infantile hemangioma

- Tumor with primary endothelial proliferation and secondary neoangiogenesis.
- High potential of a spontaneous regression (not healing!) but high risk of tissue damage with scars and other complications during the proliferative phase.
- Never recurs after regression.

Vascular malformation

- Dysregulation of the vessel architecture with primary uncontrolled, pathological vasculogenesis and/or persistence or aplasia of embryonal vessels.
- Not always fully developed at birth; they can never “heal” and do have a high risk of recurrence.
- The clinical appearance can change during the course, which means that only symptomatic treatment is possible.

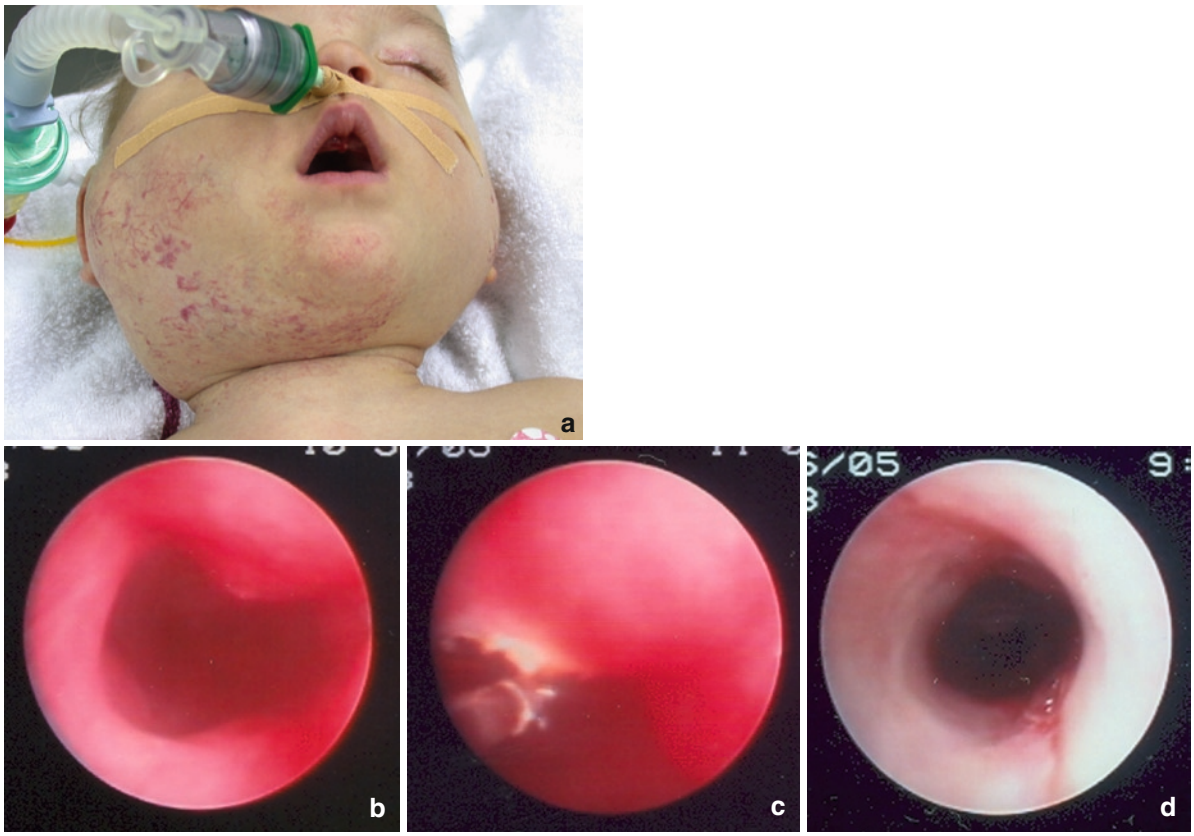

Fig. 18.30 (**a**) Extensive hemangioma in the face and neck frequently involve the subglottic trachea as well. (**b**) Hemangioma of the right-anterior tracheal wall. (**c**) During Nd:YAG laser bare fiber contact coagulation. (**d**) Almost no residuals in control after only one treatment

› Infantile hemangiomas have a stadium, vascular malformationen do have an orign.

Treatment principles: Infantile hemangiomas and other benign vessel tumors

› Induction of regression through inflammatory processes after intravascular absorption and vessel occlusion ("downgrading").

Vascular malformation

› Destruction of pathologic capillarization (extratruncular malformations) and occlusion of cavernous vessel spaces and small atrioventricular fistulas (truncular malformations).

› Due to the mesenchymal orign of any congenital vascular anomalies in which primarily only the dermis and not the epidermis is affected, any therapeutic technique has to preserve and not destroy the epithelial layer.

› Systemic therapies change the metabolism and inhibit the production of future cells ("preventive"). Laser therapy works on existing cells and induces by photoinflammation the regression by photoinflammation ("destructive").

› Congenital vascular anomalies are not only a skin disease, they can involve every structure of the body and they need all forms of therapy; a laser really is not enough.

› Laser therapy is not only a therapy of the surface, it can reach every region of the body.

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Rare Vascular Lesions

19

Sean Lanigan

Core Messages

- A number of rare vascular disorders can be treated by lasers. Lasers target hemoglobin in lesional vessels.
- The evidence for laser effectiveness is based mainly on case reports.

19.1 Pyogenic Granuloma

Pyogenic granuloma is a common, acquired, vascular tumor of the skin in children; it often ulcerates or bleeds, and is commonly localized to the face. The treatment of choice has been surgical removal, but this may lead to permanent scarring. Because of the pulsed dye laser's ability to cause selective destruction of superficial capillary-sized cutaneous blood vessels, it has been used in the treatment of pyogenic granuloma in children [12]. The Nd:YAG laser has also been reported as a successful treatment option [3].

19.2 Treatment of Rare Cutaneous Vascular Lesions

A number of rarer cutaneous vascular disorders can be treated by lasers. Because of the rarity of these disorders most knowledge of their treatment is based on case reports and small, uncontrolled case series.

Angioblastoma usually develops in infancy or early childhood on the neck or upper trunk. It is known to be slowly progressive and benign in nature. Spontaneous regression has been documented occasionally, and treatment with the pulsed dye laser and carbon dioxide (CO_2) laser has been successful in individual patients. In one case report, however, after long-pulsed Nd:YAG laser (1,064 nm) treatment the tumor was rapidly aggravated [8]. Caution should be exercised when using lasers in this potential aggressive tumor.

Angiokeratomas of Fordyce are typically asymptomatic vascular lesions characterized by blue-to-red papules with a scaly surface, most often located on the scrotum. Although considered benign, the lesions may bleed, either spontaneously or secondary to rupture. These lesions are easily treated with both the pulsed dye laser and long-pulsed Nd:YAG lasers [5, 9]. Prompt cessation of bleeding is the norm.

Angioma serpiginosum is a rare, benign, vascular disorder that presents as nonblanchable, punctate, red-to-purple lesions in a gyrate or serpiginous configuration. Pulsed dye laser therapy has been successfully used in the treatment of this disorder, with excellent cosmetic outcomes [6, 7] (Fig. 19.1).

Hereditary multiple glomus tumors constitute an autosomal dominant skin disease that is known to demonstrate cutaneous mosaicism typified by type 1 and 2 segmental arrangements. These lesions characteristically can be spontaneously painful. Pulsed dye laser treatment can be used to relieve pain but may not be curative [1, 11].

Lymphangioma circumscriptum is an uncommon skin condition characterized by large muscule-coated lymphatic cisterns that lie deep within the subcutaneous tissue and that communicate with dilated dermal

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_19, © Springer-Verlag Berlin Heidelberg 2011

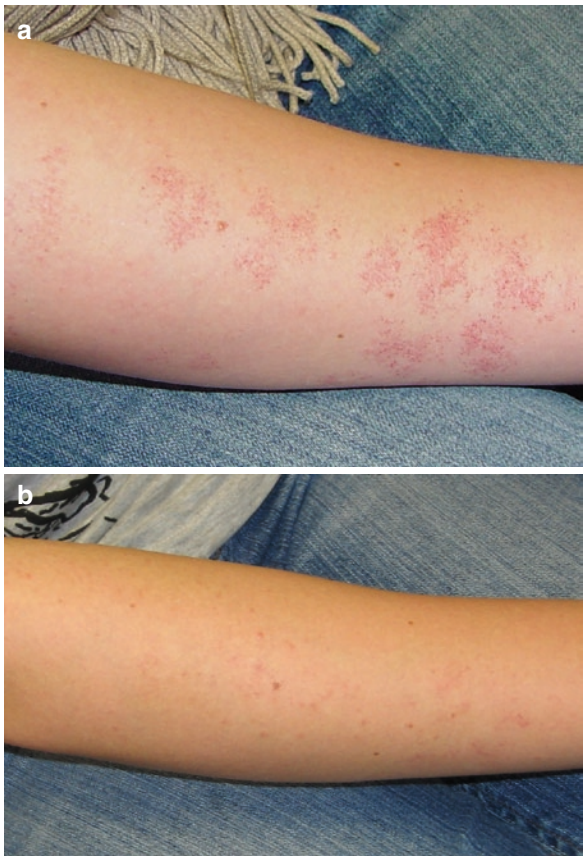

Fig. 19.1 (**a**) Angioma serpiginosum on arm before treatment. (**b**) Angioma serpiginosum on arm after a course of pulsed dye laser treatment

lymphatics. Patients suffer from edema and lymphatic leakage. For superficial lymphatic malformations containing blood, the pulsed dye laser might be considered as a treatment option [4]. Surgical excision and reconstruction is the gold standard for widespread disease. This can be a mutilating procedure if the disease is extensive. Excellent symptomatic relief of the disease can be achieved by treatment with the CO_2 laser [13].

Hereditary hemorrhagic telangiectasia is a familial, autosomal, dominant, multisystem, vascular dysplasia. Epistaxis, gastrointestinal bleeding, and cutaneous eruptive macules and nodules occur. These cutaneous lesions lead to recurring bleeding and cosmetic problems and can be treated with both the long-pulsed Nd:YAG and pulsed dye lasers [14].

Venous malformations of the skin and subcutaneous tissue are compressible, blue-purple tumors that are present at birth. According to the location and symptoms caused, venous malformations can be treated with surgery, sclerotherapy, or a combination of both. Laser therapy can also be used, especially when surgery is contraindicated [2, 10]. The Nd:YAG is generally preferred because it penetrates deeper than the pulsed dye laser and seems to be an effective and safe therapy in experienced hands. Initial Nd:YAG laser therapy is also important in the treatment of venous malformations regarding shrinkage of the tissue, discoloration, and induction of the desired dermal fibrosis that facilitates the surgical handling of the skin and reduces the risk of skin loss during surgery and sclerotherapy.

Take Home Pearl

› A variety of lasers can be used for rare vascular lesions. In general, the pulsed dye laser has been used most widely with an excellent safety record.

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Viral Infections

20

Daisy Kopera

Core Messages

- Viral infections of the skin are self-limited.
- Nevertheless, the duration of disease may be unpredictable. Among various options there is no state-of-the-art management for viral infections.
- The ease of application and comparatively good results make flashlamp-pumped pulsed dye laser application a preferred method for treatment of viral infections.

Viral infections can cause a variety of skin lesions; their treatment may be a challenge for physicians. For some viral infections, lasers may be used experimentally, but for three virally induced indications laser treatment seems to be most effective: *Molluscum contagiosum,* common viral warts, and genital warts or *Condylomata acuminata*. The virus' activity depends on the actual immune situation and the immune response of the individual [18].

20.1 Molluscum Contagiosum

M. contagiosum is a viral infection of the skin that affects children as well as atopic and immunodeficient persons [3]. It is represented by papules that may be mistaken for warts. Though warts are caused by human papilloma viruses (HPV), *M. contagiosum* is caused by a pox virus. Most adults have come in contact with this virus and have developed immunity to it; therefore, the rash is most often seen in children. The rash caused by *M. contagiosum* is characterized by discrete, 2- to 5- mm papules that are flesh colored and dome shaped with a central, sharply depressed center, or umbilication. In children it is most often found on the face, trunk, armpits, and extremities. In adults the rash may be typically located in the pubic and genital regions. The lesions are frequently grouped together and several groups can be found on various areas of the body. One way in which *M. contagiosum* can be distinguished from warts is that the rash caused by *M. contagiosum* is usually not found on the palms of the hands or soles of the feet. Usually it is a self-limited disease, meaning it will eventually disappear on its own. Each lesion generally lasts for about 6–9 months, but lesions may also last for several years. While a lesion is present, there is a chance of spreading the rash to another area of the body by transmitting the soft, whitish content of the papules over other body areas. This soft, whitish content may also be contagious for other persons [2] (Figs. 20.1 and 20.2).

Treatment for *M. contagiosum* must be individualized. Some treatments may be painful and would not be the first choice for children. Other treatments are not painful but require diligence over a long period of time. Sometimes the best treatment is reassurance that the lesions are self-limited. Among the variety of treatments encountered in the management of *M. contagiosum*, such as curettage, cryosurgery, toxic or irritating topical agents (e.g., cantharidin, fluoruoracil (5-FU), tretinoin, salicylic acid), and immunomodulating topical imiquimod [1], the use of laser systems may be a choice. Although the carbon dioxide (CO_2) laser may be too invasive, flashlamp-pumped pulsed dye laser (FPDL) represents the tool of choice [7, 8, 13].

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_20, © Springer-Verlag Berlin Heidelberg 2011

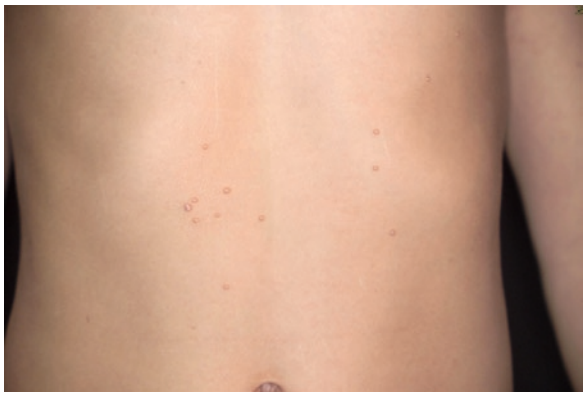

Fig. 20.1 *Molluscum contagiosum* on the trunk [2]

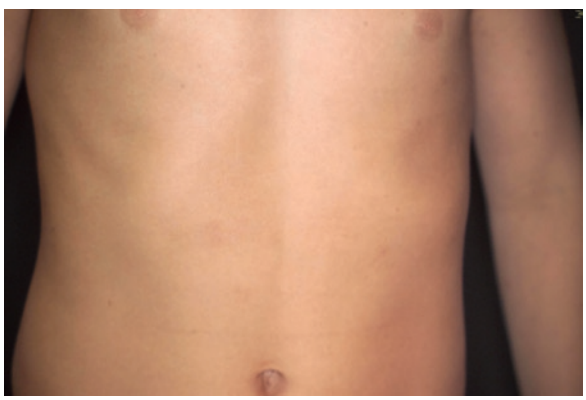

Fig. 20.2 Bland skin on the trunk after two sessions of flashlamp-pumped pulsed dye laser for *Molluscum contagiosum* [2]

20.2 Common Viral Warts

Common viral warts are noncancerous skin growths caused by more than 100 different papillomavirus types [5]. Warts are more common among children than adults, although they can develop at any age. Warts can spread to other parts of the body and to other persons. There are many different types of warts: common warts (periungual, dorsum of hands, palmar); plantar warts (sometimes painful, clusters of these are called mosaic warts); flat warts (small, smooth growths that grow in groups up to 100 at a time; most often appear on children's faces); filiform warts (small, long, narrow growths that usually appear on the eyelids, face, or neck) and genital warts (see next section). Warts may disappear, without any treatment, over an extended period of time.

Specific treatment for warts is determined by the age of the patient and their compliance with treatment [4]. Among the many different treatments available for the management of viral warts are surgical excision, electrodesiccation and curettage, cryosurgery, topical application of toxic or irritating topical agents (e.g., cantharidin, 5-FU, tretinoin, salicylic acid), and immunomodulating topicals (imiquimod). The use of aCO_2 laser may be too invasive; FPDL represents the tool of choice [2, 11].

20.3 Genital Warts (*Condylomata Acuminata*, Squamous Cell Papilloma)

Among viral warts, genital warts present with special features [12]. Most commonly they are sexually transmitted, but they also may be spread by oral sex, vertically (from mother to baby), or by autoinoculation (from one site to another). Whether they can be transmitted from objects like bath towels remains controversial. Genital warts are located in genital areas (vulva, vagina, cervix, urethra, penis, scrotum, anus) and appear as soft papillomas, without a rough surface like other common warts. At least 75% of sexually active adults have been infected with at least one type of genital HPV at some time in their life. Most do not develop visible warts and the infection may only show up on a cervical smear. This is known as *subclinical infection*. Visible genital warts are often easy to diagnose by their appearance. They are usually caused by HPV types 6 and 11.

C. acuminata may be confused with normal anatomical structures like pearly penile papules (around the glans of the penis), Fordyce spots (sebaceous glands on the labia), and vestibular papillae (fronds found around the vaginal entrance). These do not require any treatment.

However, as a caveat, genital warts raise the possibility of sexual abuse, but in many cases it is due to vertical transmission.

Treatment options for genital warts consist of topical applications of various solutions containing podophyllotoxin, immunomodulating imiquimod cream, cryotherapy with liquid nitrogen, podophyllin resin

Table 20.1 Specifications using a flashlamp-pumped pulse dye laser (585-7-nm spot) in viral infections

Lesion	Number of Tx	Pulse length (ms)	Energy (J/cm²)	Anesthetic
Molluscum contagiosum	1–2	0.45	6–7	EMLA
Common Warts	Hands: 4 Feet: 8 Others: 1–2	0.45–1.5	8–12	EMLA
Genital Warts	1–5	0.45	6–7	None

EMLA, eutectic mixture of local anesthetics = 2.5% lidocaine and 2.5% prilocaine emulsion in an oil-in-water base

suspension, 5-FU, trichloroacetic acid, electrocautery, curettage, surgical excision, and lasers [10, 17]. The risk of HPV transmission is extremely low if no warts recur a year after successful treatment. Visible warts are probably more infectious than a subclinical HPV infection.

20.4 Laser Treatment of Viral Infections

Several treatment options used for the management of viral infections bear the risk recurrence of infection. Moreover, several studies have shown a certain number of nonresponders to all these treatments. Also, metaphysical methods like homeopathy and hypnotherapy have been used [6].

Laser treatment is based on the principle of photothermic or photomechanic destruction of target tissue. Monochromatic coherent light of a certain wavelength and fluence is absorbed by specific target structures. Light energy is converted to thermal energy, thus affecting the target structure. According to pulse duration and energy density, this effect may result in coagulation (photothermic effect) or blasting (photomechanic effect) of these structures.

CO_2 laser light (wavelength of 10,600 nm) is mainly absorbed by water. It is able to vaporize tissue of any kind [19]. Because a CO_2 laser creates temperatures of 200–300°C the treatment is painful and requires some type of anesthesia stronger than an eutectic mixture of local anesthetics (2.5% lidocaine and 2.5% prilocaine emulsion in an oil-in-water base). Therefore, for the treatment of viral infections, this type of laser may be considered too invasive.

The most commonly used laser for the treatment of viral infections is the FPDL, which emits light in the yellow-orange part of the visible light spectrum at 585 or 595 nm [14] (Table 20.1). When turned against skin, this light is best absorbed by hemoglobin and oxyhemoglobin and is therefore used for the treatment of vascular lesions. Short, powerful laser pulses are eagerly absorbed by red structures like small blood vessels. The content of capillaries and teleangiectasias is heated up quickly and the vessels burst because they are unable to withstand this rapid rise of temperature. With very short pulses (0.45 ms) purpura develops within minutes in the treated areas and needs 10–14 days to resolve as macrophages digest damaged material and blood residua. The yellow-orange light of this particular laser is designed to destroy superficial blood vessels. Vascular lesions can be expected to appear lighter after every treatment session. This is employed when treating viral warts to destroy the warts' energy supply and supposedly induce their regress, although a number of studies using the FPDL and the same treatment parameters offer controversial results [9, 11, 15, 16, 20].

Other than transient purpura, side effects from FPDL treatment of viral infections of the skin, when 0.45-ms pulses are used, are rare. They include postlesional hyperpigmentation, blistering, and sometimes scarring.

Take Home Pearl

› Whereas CO_2-laser treatment may be considered too invasive and painful, FPDL treatment of viral infections of the skin is easy to perform and does not require any wound dressing or other concomitant treatment or special compliance by the patient.

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Wrinkles and Acne Scars: Ablative and Nonablative Facial Resurfacing

21

Melissa A. Bogle, Geeta Yadav, Kenneth A. Arndt, and Jeffrey S. Dover

Core Messages

- Fully ablative carbon dioxide (CO_2) laser resurfacing is the traditional gold standard for the treatment of moderate to severe rhytides and acne scars. It offers the most dramatic results but can have extensive downtime of 2 or more weeks.
- The erbium:YAG laser, erbium:YSGG laser, and plasma skin regeneration were developed to improve photoaging and textural abnormalities without the prolonged recovery time of traditional CO_2 resurfacing. Clinical efficacy is generally not as impressive; however, there is less recovery time and an improved side-effect profile.
- The term "nonablative resurfacing" encompasses a wide range of treatments aimed at tissue remodeling and skin rejuvenation. The results vary depending on the laser or light source that is used.
- The goal of nonablative resurfacing is to induce selective injury of the dermis while keeping the overlying epidermis intact.
- Nonablative resurfacing devices include infrared lasers, visible light lasers, intense pulsed light, and light-emitting diode technology.

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21.1 Ablative Resurfacing

Ablative skin resurfacing involves using energy to remove the entire epidermis and a portion of the upper dermis. The primary laser modalities for ablative resurfacing are the carbon dioxide (CO_2) laser, the erbium:yttrium-aluminum-garnet (Er:YAG) laser, and the yttrium-scandium-gallium-garnet (YSGG) laser. A fourth modality for ablative tissue regeneration is plasma resurfacing. Depending on the device used, ablative resurfacing can produce dramatic improvement in acne scars, deep facial rhytides, and dyspigmentation by replacing the damaged epidermis and upper papillary dermis with new tissue. The drawback to ablative procedures is that they can have more severe potential complications, especially when performed by untrained individuals, and can have longer healing periods than their nonablative counterparts.

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_21, © Springer-Verlag Berlin Heidelberg 2011

21.1.1 Carbon Dioxide Laser Resurfacing

CO_2 lasers were first introduced in the 1960s as continuous wave lasers for cutting tissue [35]. Their early use in dermatology focused mainly on tattoo removal and the treatment of various cutaneous lesions [8, 33]. In the late 1980s, it was discovered that using continuous wave CO_2 technology for skin resurfacing yielded more predictable depths of injury when compared to either chemical peels or dermabrasion. Though results were promising, excessive thermal injury in the dermis produced an unacceptable risk of scarring [15]. It was not until the 1990s, with the development of high-energy, short-pulsed CO_2 lasers, that the device became a truly viable tool for facial resurfacing [26].

CO_2 lasers emit light at a wavelength of 10,600 nm (Fig. 21.1). Energy at this wavelength is absorbed by both intracellular and extracellular water, causing rapid heating and vaporization of tissue [26]. With traditional continuous wave lasers, nearly 90% of the laser energy is absorbed in the initial 25–50 μm of ablated skin; however, there is a thick zone of coagulative necrosis in the dermis measuring 20–100 μm [36].

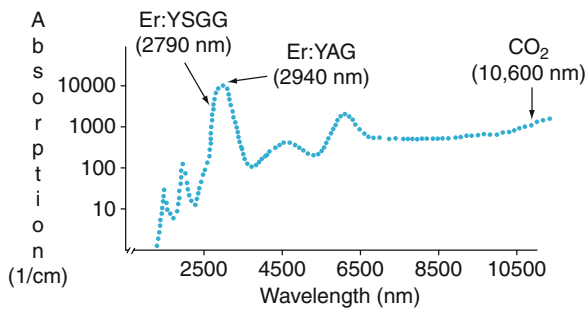

Fig. 21.1 Absorption coefficient of water by wavelength

Ultrashort-pulsed CO_2 lasers with a pulse duration of less than 1 ms typically ablate 20–50 μm of tissue with 1 pass with a thin zone of thermal necrosis measuring 40–120 μm [26, 38]. Dermal heating below the zone of ablation induces a wound-healing response, which causes collagen remodeling and heat-mediated tissue contraction [21].

CO_2 laser resurfacing is commonly used for the treatment of photodamaged skin, acne scars, and the destruction of skin lesions. An early study to assess the efficacy of an ultrashort-pulsed (<1.4 ms) CO_2 laser revealed a 90% overall improvement in photoaging in 259 subjects, with the periorbital area demonstrating the most impressive results [3]. Areas of dynamic rhytides, such as the glabella and forehead, had the least improvement in wrinkle reduction [3]. CO_2 resurfacing for mild, superficial, or atrophic acne scars tends to have the best results, with an approximate 50–89% improvement [5, 32, 45]. Pitted or angular (boxcar) scars respond to a lesser degree, with studies documenting 25–50% improvement [6, 10, 37].

The optimal candidate for CO_2 laser resurfacing has moderate to severe photodamage or acne scars and skin rated as Fitzpatrick types I–III (Fig. 21.2). Excellent postoperative care is essential to achieve good results. Generally, bland ointments or semiocclusive dressings are applied for the first 2–3 days to help avoid crusting from serous exudate and to shorten the overall healing time [25, 31]. Re-epithelialization generally takes 5–10 days, and erythema may persist for months. Side effects may include dyschromia (hyper- or hypopigmentation), infection, lines of demarcation between treated and untreated areas, and scarring [9]. Hyperpigmentation is more likely among people with darker skin types and typically resolves within weeks to months with topical bleaching preparations. Infection risk can be greatly

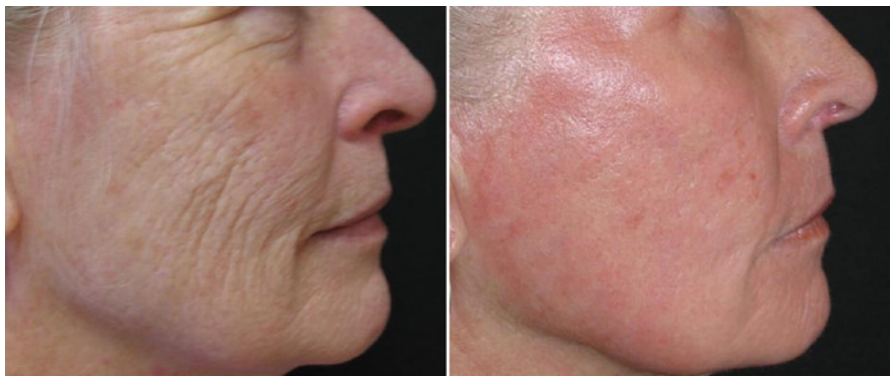

Fig. 21.2 Patient before (*left*) and 1 month after (*right*) full face resurfacing with an ultrashort-pulsed carbon dioxide laser. (Photos courtesy of Melissa A. Bogle, MD, Houston, TX)

reduced with appropriate postoperative care and antiviral and antibacterial prophylaxis starting the day before treatment. Delayed hypopigmentation can occur in 8–19% of patients and may be more common with deeper ablation and, thought to be related to resultant thermal injury to melanocytes [10]. Fractional versions of the CO_2 laser have an improved side-effect profile and less extensive downtime.

21.1.2 Erbium:YAG Laser Resurfacing

The short-pulsed (250 μs) Er:YAG laser was approved by the United States Food and Drug Administration (FDA) for cutaneous resurfacing in 1996 and was introduced as an alternative to the pulsed CO_2 laser. It emits light at a wavelength of 2,940 nm, which targets intra cellular and extracellular water, similar to the CO_2 laser (Fig. 21.1). The main difference is that energy from the Er:YAG laser more closely approximates the absorption peak of water (3,000 nm), so virtually all the energy is absorbed in the epidermis and superficial papillary dermis.

When cutaneous tissue absorbs energy from the Er:YAG laser there is an immediate removal of the desiccated tissue, resulting in a characteristic "popping" sound. This conversion of light energy to mechanical energy is important because there is very little thermal collateral damage or char formation. Thus, it has a more superficial ablation profile and a smaller zone of thermal damage beneath the ablated layer, leading to shorter healing times and a lower rate of side effects [4]. The drawbacks to the decreased thermal damage are reduced intraoperative hemostasis and less dramatic clinical improvement when compared to traditional CO_2 resurfacing. A typical short-pulsed Er:YAG laser with a pulse duration of 250 μsec and a fluence of 5 J/cm^2 ablates 15–20 μm of tissue per pass with minimal residual thermal damage, compared to 25–50 μm of ablated skin and 20–100 μm of residual thermal damage with the millisecond-pulsed CO_2 laser [36]. Even with multiple passes of the Er:YAG laser, the depth of underlying thermal damage appears to be limited to approximately 50 μm, with no visible contraction of dermal collagen fibers during resurfacing [4, 26].

Variable and long-pulsed (10 ms) Er:YAG devices were developed in the late 1990s in an attempt to achieve a greater depth of tissue ablation and increased collagen remodeling via thermal injury [4]. Variable-pulse Er:YAG lasers can be used in a short-pulse mode for tissue ablation and a long-pulse mode for thermal damage and collagen contraction. They have better tissue penetration, improved hemostasis, and deeper zones of thermal necrosis than traditional short-pulsed devices. Long-pulsed (10 ms) Er:YAG lasers increase the zone of thermal damage to approximately 60 μm [1].

For most resurfacing techniques, the potential for improvement seems to be related to the depth and degree of injury, regardless of the method used. Clinical results from Er:YAG resurfacing are generally not as impressive as those of CO_2 resurfacing [45]. The ideal patient is one with fine wrinkles and mild to moderate photodamage or mild acne scarring (Fig. 21.3). Patients with mild to moderate rhytides have been shown to have at least a 50% improvement in surface texture

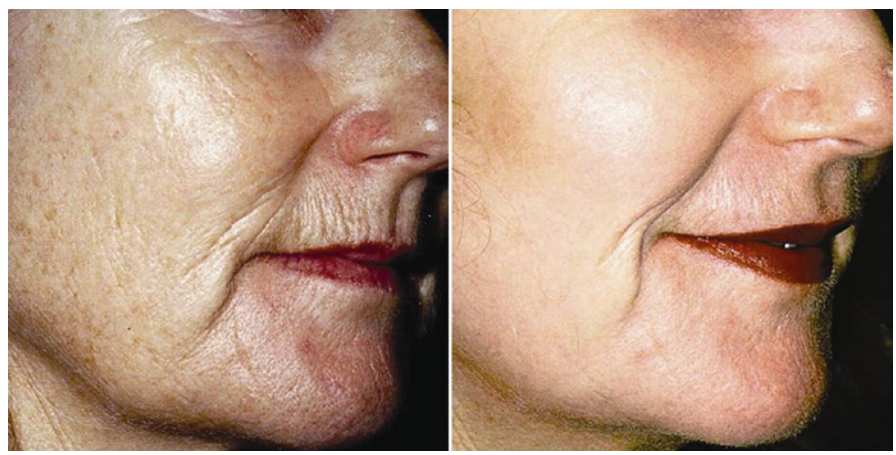

Fig. 21.3 Patient before (*left*) and after (*right*) resurfacing with an ablative erbium:yttrium-aluminum-garnet laser. (Photos courtesy of Iridex Corporation, Mountain View, CA)

after Er:YAG resurfacing [2, 32]. Another study found that patients who underwent one full face pass of Er:YAG resurfacing with an additional 2–3 passes over the periorbital and perioral regions to have a 58% improvement in pigmentation and a 54% improvement in texture [7]. Similarly, acne scars demonstrate about a 50% improvement [29].

The Er:YAG laser has been used in combination with CO_2 laser resurfacing. One pass with the Er:YAG laser immediately after the CO_2 procedure speeds healing and reduces the duration of postoperative crusting, swelling, and itching, but it has not been found to add to the clinical result [34].

The mean healing time with the Er:YAG laser is 4–10 days, depending on the number of passes, with erythema resolving in 2–4 weeks [43]. Short (microsecond)-pulsed lasers tend to have recovery times at the lower end of the spectrum, whereas long (millisecond)-pulsed lasers can be on the longer end with the same number of passes given the deeper zone of thermal necrosis. Adverse events may include infection, scarring, and dyschromia; however, in general, the procedure has an improved side-effect profile compared with fully ablative CO_2 resurfacing [27].

21.1.3 Erbium:YSGG Laser Resurfacing

The Er:YSGG laser was approved by the United States FDA in 2008. It generates a wavelength of 2,790 nm and has a water absorption coefficient that lies between that of the Er:YAG (2,940 nm) and CO_2 (10,600 nm) lasers (Fig. 21.1). It was developed in an attempt to provide deeper dermal heating than the traditional Er:YAG laser while still minimizing healing time. Like the Er:YAG laser, the Er:YSGG laser removes a portion of the epidermis with a controlled thermal effect. What makes it unique is that there is only minimal epidermal tissue removal, thus creating a natural protective dressing that diminishes the extent of the recovery process, similar to plasma skin regeneration technology. A fractional version of the Er:YSGG laser is also available (this device is discussed in Chap. 8).

The first published study on the Er:YSGG laser for facial resurfacing involved nine patients receiving two treatments spaced 1 month apart [40]. Histologic examination of treated skin revealed thermal damage 80 μm below the stratum corneum. Patients demonstrated significant improvement in pigment, rhytides, and tone with an average 4-day healing time [40]. No comparison studies with the Er:YAG laser or for the indication of acne scarring have been published when this chapter was written

21.1.4 Plasma Skin Regeneration

Plasma skin regeneration technology uses pulses of ionized nitrogen gas to deliver heat energy directly to the skin. Like other ablative resurfacing lasers, its development came from the desire to approach the results of traditional CO_2 resurfacing without the lengthy recovery time. Unlike lasers, there is no dependence on a specific target such as water, hemoglobin, or melanin.

The first such device on the market was the Portrait PSR system (Rhytec, Inc., Waltham, Mass). The system uses energy from an ultrahigh-frequency radiofrequency generator to convert nitrogen gas into plasma within the handpiece. The plasma emerges from a nozzle on the handpiece directly onto the skin's surface, thus transferring energy in a process that is not chromophore-dependent [13]. The energy per pulse can be adjusted to create a spectrum of effects from low-energy heating with very little recovery time to high-energy resurfacing treatments with a greater depth of thermal modification [13].

At high-energy settings, thermal injury reaches the papillary dermis and extends up to 11.8 μm in depth below the dermal-epidermal junction [28]. The thermally altered dermis has some degree of denaturation, but the cells remain viable and do not slough during the recovery phase. The overlying epidermis remains intact for the first 24–48 h, with subsequent sloughing. At roughly day 10 after treatment, fibroblasts depositing new collagen and elastin fibers can be seen [28].

In clinical trials, a single-pass, high-energy plasma regeneration treatment has been shown to give a mean overall improvement of 50% to patients with mild to moderate photodamage during 30-day follow-up [28]. These results are roughly comparable to a single-pass CO_2 resurfacing treatment with a less-intense recovery period, complete re-epithelialization by 7 days, and significant erythema resolving by 2 weeks [28]. Side effects are rare and can include temporary hyperpig-

mentation, erythema, edema, epidermal de-epithelialization, infection, and scarring [28].

In late 2008, the company that produced the only plasma device on the market closed its doors. At the time of writing this chapter, the handpiece nozzles necessary for the plasma treatments are unavailable. The treatment modality, however, certainly has a place in the cosmetic armamentarium, and hopefully, treatments will once again be made available with production of the tips by a new manufacturer.

21.2 Nonablative Resurfacing

Nonablative resurfacing that can improve a variety of skin conditions including texture, scars, and dyschromia is an alternative to ablative laser resurfacing. The term "nonablative resurfacing" encompasses a wide range of treatments aimed at tissue remodeling and skin rejuvenation, and the results vary depending on the laser or light source that is used. The common goal is to induce selective injury within the dermis while keeping the overlying epidermis intact.

21.2.1 Infrared Lasers

Infrared lasers use the principles of selective photothermolysis to heat water in dermal tissue. The epidermis is spared with the use of concomitant cooling. By heating water in the dermis, the main effect is stimulation of collagen production, helping to improve skin texture, fine lines, and acne scars. Because infrared wavelengths are not absorbed by melanin or hemoglobin, there is no improvement in lentigines or telangiectasias, but the devices are safe for use on all skin types. There are four primary infrared lasers used for skin rejuvenation, including the 1,320-nm pulsed YAG laser, the 1,450-nm diode laser, the 1,540-nm erbium:glass laser, and the 1,064-nm neodynium (Nd):YAG laser. With all devices, treatments are generally administered in a series of 4 or more treatments, with continued improvement for 6–9 months after completion of the treatment series.

The 1,320-nm infrared laser was the first system specifically designed for nonablative resurfacing. Clinical studies have shown modest improvement in rhytides and acne scars. After a series of five treatments on ten subjects with mild to moderate photodamage, two subjects showed substantial improvement, four subjects showed some modest improvement, and four subjects showed no apparent improvement [23]. The first study to show improvement in rhytides with the 1,450-nm laser revealed a mild to moderate improvement in 12 of 16 patients [39]. A split-face study comparing the 1,320-nm laser to the 1,450-nm laser in a series of three treatments for mild to moderate acne scars found that both lasers gave clinical improvement, with the 1,450-nm laser giving a greater clinical response [42]. The study is insufficient to draw conclusive results, however, because treatment settings with the 1,320-nm laser were lower than optimal [19]. The 1,540-nm laser has been found to be more comfortable than the 1,320- and 1,450-nm lasers, presumably due to the use of contact cooling rather than cryogen spray cooling, a smaller spot size, and the use of relatively lower energies [14]. In one large study, all 60 participants reported subjective improvement in the quality and visual aspect of their skin after four treatments with the 1,540-nm Er:glass laser [22]. In the same study, objective ultrasound imaging documented a 17% increase in skin thickness [22]. The millisecond-pulsed 1,064-nm Nd:YAG laser has been shown to lend a 12% improvement in coarse wrinkling, a 17% improvement in skin laxity, and a 20% improvement in overall skin rejuvenation during a series of at least seven treatments in patients with Fitzpatrick skin types I through V [16].

The Q-switched Nd:YAG laser has also been used for skin rejuvenation. A study evaluating histological changes after two passes with a nanosecond-pulsed Nd:YAG laser revealed slight fibrosis in the papillary dermis with unremarkable epidermal changes 3 months after treatment [18]. These changes are similar to those seen with ablative resurfacing but to a lesser degree [18]. Clinical studies have shown significant clinical improvement in rhytides in six of eight patients treated at 3 monthly intervals [17].

In general, nonablative laser resurfacing has less dramatic effects than ablative resurfacing, but significantly less downtime. It remains a viable option for the treatment of facial rhytides and acne scarring in patients who cannot tolerate downtime and who are realistic about treatment expectations.

21.2.2 Visible Light Lasers

Visible light lasers are an excellent choice for the treatment of erythematous or hypertrophic scars and for nonablative photorejuvenation in patients with facial redness and telangiectasias. The pulsed dye laser (585–595 nm) has been documented to induce fibroblast proliferation and neocollagenesis in the papillary dermis. Light at this wavelength is selectively absorbed by hemoglobin within cutaneous blood vessels. Heat from the vessels is thought to radiate out to the surrounding dermis, stimulating tissue remodeling. Although visible light lasers improve texture to a lesser degree than infrared lasers, they are very effective at improving facial erythema and telangiectasias and have a modest effect on collagen regeneration via the release of growth factors and procollagen I [30]. The pulsed dye laser also targets melanin, and skilled operators can decrease the fluence and epidermal cooling of the pulsed dye laser to target lentigines for enhanced overall rejuvenation.

A study of 20 patients with mild-to-severe wrinkles demonstrated improvement in rhytides with purpuric treatment settings with the pulsed dye laser [49]. Patients with mild to moderate rhytides (90%) were more likely to have improvement than patients with moderate to severe rhytides (40%). Histologic examination of treated skin showed a band of newly organized collagen and elastic fibers in the superficial dermis after one treatment [48]. In another study, investigators found 50% of treated subjects to have a mild improvement in facial rhytides after two treatments with the pulsed dye laser [24].

A split-face study comparing a 585-nm pulsed dye laser to a 1,064-nm millisecond-pulsed Nd:YAG laser for acne scarring in patients with darker skin types revealed significant improvement in all types of acne scars after four treatment sessions. The two lasers performed comparatively, with both inducing notable improvement in superficial scars (25–35%); however, the pulsed dye laser was found to be slightly more effective on ice-pick scars (12% vs. 9%), and the 1,064-nm laser was found to be slightly more effective on boxcar scars (15% vs. 9% improvement) [30]. In the same study, investigators noted procollagen I and transforming growth factor-β protein expression to be significantly increased in treated skin 8 weeks after completing both laser treatments, which likely plays a fundamental role in stimulating dermal remodeling [30].

The millisecond-pulsed (532-nm) frequency-doubled Nd:YAG laser has also shown success in skin rejuvenation. Light at 532 nm is absorbed by both melanin and hemoglobin, so the laser is able to improve both pigment irregularities and telangiectasias with a slight improvement in fine rhytides and texture. Visible light lasers have been successfully combined with infrared lasers to enhance textural improvement in nonablative resurfacing treatments [41].

21.2.3 Intense Pulsed Light

Intense pulsed light sources use high-intensity flashlamps, which emit noncoherent light in a broad wavelength spectrum from approximately 515–1,200 nm. There are a number of devices available with varying wavelengths, spot sizes, pulse durations, pulse delays, and maximal fluences, allowing for great variability in the selection of treatment parameters to suit different skin types and indications. The mechanism of action of intense pulsed light systems follows the principles of selective photothermolysis. With a broad wavelength spectrum, they are able to target telangiectasias, pigmentary abnormalities, and, to a lesser extent, fine wrinkling.

In a large study of 49 patients, more than 90% were found to have visible improvement in all aspects of photoaging, including fine wrinkling, smoothness, skin laxity, irregular pigmentation, erythema, and flushing [11]. Almost half of the patients noted a 50% or greater improvement in fine wrinkles [11]. Another study demonstrated an 18% increase in type I collagen transcripts with intense pulsed light treatments (compared to 23% for the pulsed dye laser), with more than 85% of patients getting an increase in types I and III collagen, elastin, and collagenase [48].

Photodynamic therapy using intense pulsed light to activate 5–aminolevulinic acid has been shown to give a greater percent improvement in overall photodamage (fine lines and mottled pigmentation) vs. intense pulsed light alone [20]. Intense pulsed light has also been combined

with radiofrequency energy to further enhance skin rejuvenation, with a purported lower risk of side effects than either treatment alone. A series of 3–5 treatments to photoaged skin demonstrated a 70% improvement in facial erythema and telangiectasia, a 78% improvement in lentigines, and a 60% improvement in skin texture as determined by subject satisfaction levels [12].

Adverse effects of intense pulsed light treatments can include transient purpura, blisters, or crusting, particularly with the use of high fluences or short pulse widths. Patients who are tan or who have darker skin are prone to blisters, crusting, and hypo- or hyperpigmentation. Blisters or crusts may also develop over curved surface areas if epidermal cooling is insufficient. Scarring, necrosis, and permanent changes in pigmentation are rare.

21.2.4 Light-Emitting Diode Technology

The theory behind light-emitting diode (LED) technology is that low-intensity light photons of the proper parameters are able to interact with subcellular chromophores to activate cells to induce or inhibit activity in a nonthermal, nonablative fashion. Most devices have either a panel or handpiece containing an array of focused diodes, which can emit light in a pulsed or continuous fashion. Some LEDs emit light of a single color whereas others emit multiple colors of light to maximize the therapeutic approach.

Red light at 633 nm and yellow light at 588 nm both have been shown to have antiaging benefits through the preferential degranulation of mast cells, the decrease in collagenase and matrix metalloproteinases, the stimulation of fibroblast growth factors, and the ultimate promotion of epidermal remodeling and collagen synthesis [44, 47].

Results of a 12-month, multisite clinical trial of pulsed yellow light for facial photodamage revealed 85% of subjects improved by at least one grade in the Fitzpatrick scale of periorbital wrinkles [47]. Histologic studies have also documented new collagen formation [46]. Low-intensity LED devices have shown no significant side effects; however, patient expectations should be managed to avoid disappointment due to the subtle clinical improvements in comparison to other nonablative laser and light modalities.

Take Home Pearls

- The CO_2, Er:YAG, and Er:YSGG lasers target intra- and extracellular water based on the principles of selective photothermolysis.
- The Er:YAG and Er:YSGG lasers have faster re-epithelialization and an improved side-effect profile compared with traditional CO_2 resurfacing, but have less dramatic results.
- Plasma skin regeneration transfers energy to the surface of the skin in a process that is not chromophore dependent. The technology can be used at varying energies for different depths of effect, from superficial epidermal sloughing to deeper dermal heating.
- Nonablative resurfacing technologies should be tailored to individual patients. Infrared technologies are ideal for patients who desire primarily textural improvement and cannot tolerate the healing time of ablative procedures. Visible light lasers (pulsed dye laser, frequency-doubled Nd:YAG laser) and intense pulsed light devices are particularly good at improving superficial skin pigmentation and telangiectasias, and, to a lesser extent, skin texture.
- LED treatments can be used alone or in conjunction with more aggressive procedures. They target subcellular chromophores to improve skin tone, minimize fine lines and wrinkles, and reduce erythema and dyschromia. Patients should be counseled about expectations to avoid dissatisfaction.

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Wrinkles and Acne Scars: Technology-Based Treatment of Periorbital Wrinkles

22

Laurel Naversen Geraghty and Brian S. Biesman

Core Messages

- Although many energy-based devices offer well-documented benefits in treating facial rhytids, less comprehensive study exists to support the safety and efficacy of their use within the orbital rim.
- Choose ocular safety devices appropriate to the therapy. These include plastic eye shields for radiofrequency treatments and metal eye shields for laser resurfacing.
- To determine the optimal treatment, consider the anatomic basis for the patient's periorbital rhytids: photodamage, volume loss, frequent use of the underlying musculature, or a combination of the three.
- Understand the primary indications and limitations of each of the major treatment options that are safe and efficacious for use in the periorbital region.
- Multiple treatment approaches are often required to optimize cosmetic results in the periocular area. These may include dermal fillers, chemical peels, neurotoxins, or blepharoplasty in addition to lasers or other energy-based devices.
- Surgery is indicated for individuals with excessive periorbital laxity or skin redundancy, which cannot be treated effectively with laser and energy treatments alone.

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22.1 Introduction

As the demand for minimally invasive cosmetic treatments increases, consumers demonstrate particular interest in the periorbital region because it is often the site of the first and most dramatic manifestations of aging. The optimal approach for treating signs of age and skin laxity around the eyes requires careful consideration of the anatomic basis for the patient's rhytids. Generally, rhytids and other cosmetic concerns in the eye area may be attributed to (1) photodamage, which may result in sagging, dyschromia, and textural changes in addition to rhytids; (2) soft tissue volume loss; (3) frequent use of the underlying musculature; or (4) a combination of these three factors. Energy-based treatments, including laser, light, and radiofrequency modalities, most effectively target signs of photodamage in the periocular region. Wrinkles resulting from volume loss may be effectively treated with dermal fillers or surgical redistribution of fat, whereas rhytids caused by muscular overuse may be improved with botulinum toxin injections or surgery. The optimal treatment for many individuals involves a combination of energy-based treatments, dermal fillers, neurotoxins, blepharoplasty, and chemical peels.

An increasingly wide array of safe and effective energy-based treatments now exists to treat signs of photodamage and laxity around the eyes. Currently available therapies include ablative laser skin resurfacing for skin

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_22, © Springer-Verlag Berlin Heidelberg 2011

rejuvenation; nonablative remodeling, which may modify collagen and upregulate neocollagenesis to improve the appearance of wrinkles and sagging skin; and fractional laser treatments, which create microscopic columns of thermal injury to generate improvements in wrinkling and surface texture. Though many energy-based devices have been well-established as safe and efficacious for use on the face, relatively little data exist to support their use on the eyelids and within the periocular rim. The use of resurfacing or skin-tightening devices in the periorbital area is not recommended in the absence of well-designed clinical safety and efficacy trials. This chapter will review the safety and efficacy of energy-based treatments that target rhytids, skin laxity, and other cosmetic concerns in the periorbital region.

22.2 Ablative Laser Skin Resurfacing in the Periorbital Region

Ablative laser skin resurfacing, which is accomplished with devices such as carbon dioxide (CO_2; 10,600 nm) and Erbium: Yttrium Aluminum Garnet (Er:YAG; 2,940 nm) lasers, is considered the gold-standard treatment for patients with advanced periorbital wrinkling, skin laxity, and acne scars. Traditional ablative technologies remove the entire epidermis, ablate to the level of the middermis, and produce significant residual thermal effect. These treatments are therefore associated with prolonged recovery periods and incur a higher risk of complications than nonablative or newer fractional ablative approaches. Possible side effects include infection, scarring, prolonged erythema, hypo- or hyperpigmentation, and the development of an unnatural sheen to the skin [1].

The efficacy and safety of ablative treatments in the periorbital region are well established. Blinded assessments have noted improvements of 63–82% in periorbital rhytids after CO_2 laser resurfacing in the periorbital area [2]. In a retrospective study of 67 patients (Fitzpatrick skin types I–IV), high-energy, pulsed CO_2 laser treatments produced significant improvements in dermatochalasis and periorbital rhytids, according to photographic assessment and caliper measurements of the upper eyelids. Patients who exhibited the most severe signs of skin redundancy and wrinkling showed the greatest improvement. Erythema and transient hyperpigmentation were reported, with no instances of scarring, hypopigmentation, or ectropion [3]. A split-face study of single-pass CO_2 laser skin resurfacing of the periorbital area suggested that cold-air cooling is associated with reduced pain, a more rapid recovery, and quicker resolution of erythema [4].

Er:YAG lasers, which are ideally suited for milder cases of photodamage than those requiring CO_2 lasers, have been shown to be safe and effective in the treatment of periorbital photodamage, rhytids, scarring, and dyschromia [5, 6]. Er:YAG lasers are associated with a lower risk of side effects and are safer for use among dark-skinned patients compared with CO_2 lasers [1, 5]. In a study of 50 patients (Fitzpatrick skin types I–III; age range 35–62 years), researchers assessed the use of high-energy Er:YAG for resurfacing in the periorbital area. Mean re-epithelialization occurred within 3 days, the average duration of erythema was 15.4 days, side effects were minimal, and most patients achieved approximately 75% improvement in periorbital rhytids 6 months to 1 year after treatment [6].

Yttrium-scandium-gallium-garnet (YSGG) (Pearl, Cutera, Inc., Brisbane, Calif.), the most recently introduced ablative technology for treating photoaging and rhytids, targets water within the epidermis and produces soft tissue ablation and adjacent coagulation. This therapy involves less lateral thermal injury than CO_2 lasers, more coagulation than traditional Er:YAG devices, and reduced downtime relative to both lasers. YSGG may be used for fractional ablative resurfacing or more superficially to treat epidermal changes. The full clinical implications of YSGG treatment remain to be seen, but it is expected to play a significant role in laser skin resurfacing.

Special care and safety precautions are required for ablative skin resurfacing in the periorbital area, particularly on the eyelids. This includes the use of metal, laser-safe corneoscleral protective lenses, inserted after a topical anesthetic has been applied and removed. Metal, laser-safe external eye shields are only acceptable for use if the eyelids are not treated. Ablative skin resurfacing in the periorbital area requires adjustments to enhance the cosmetic outcome. A lower fluence and decreased energy density are typically used on the delicate tissues of the periorbital region [5]. A reduced number of passes near the periphery of the treatment area helps to avoid a visible demarcation between irradiated and untreated areas [5].

22.3 Nonablative Laser Skin Resurfacing in the Periorbital Region

In contrast to ablative skin resurfacing, nonablative technologies leave the stratum corneum intact and are therefore associated with much lower risk and posttreatment downtime. Nonablative technologies for treating periorbital rhytids include visible light lasers, such as pulsed dye and pulsed 532-nm lasers; broadband light sources, such as intense pulsed light (IPL) and photodynamic therapy; and infrared (IR) lasers, such as the 1,450-nm Nd:YAG laser, 1,320-nm Nd:YAG pulsed laser, and 1,540-nm erbium glass (Er:glass) laser. The IR devices consistently demonstrate mild moderate improvement in rhytids in clinical trials and can also be used for periorbital skin tightening or to improve the quality of the skin (see Fig. 22.1a, b). Multiple treatment sessions are typically required to optimize outcomes. IR is safe for use in the crow's feet area with the proper precautions. Ocular protection is essential because IR wavelengths can pose a grave risk to the pigmented tissues within the eye.

IR nonablative laser therapies are most effective for individuals with rhytids resulting from photodamage or acne scarring [1]. In a study of a 1,540-nm Er:glass laser with contact cooling (Aramis, Quantel Derma, Inc., Erlangen, Germany), 60 patients (Fitzpatrick skin types I–IV) were treated four times for periorbital and perioral rhytids at 6-week intervals. Six weeks after treatment, the subjects demonstrated a 17% increase in dermal thickness on ultrasound, new collagen formation on histologic evaluation, and clinical improvement in rhytids according to subjective assessment, digital photography, and profilometry with silicone imprinting. No adverse events were reported [7]. Additional studies demonstrated similar results and side-effect profiles for the 1,450-nm diode laser (Smoothbeam, Candela, Wayland, Mass.) and 1,320-nm pulsed Nd:YAG laser (CoolTouch, ICN Photonics, Costa Mesa, Calif.) [8–10].

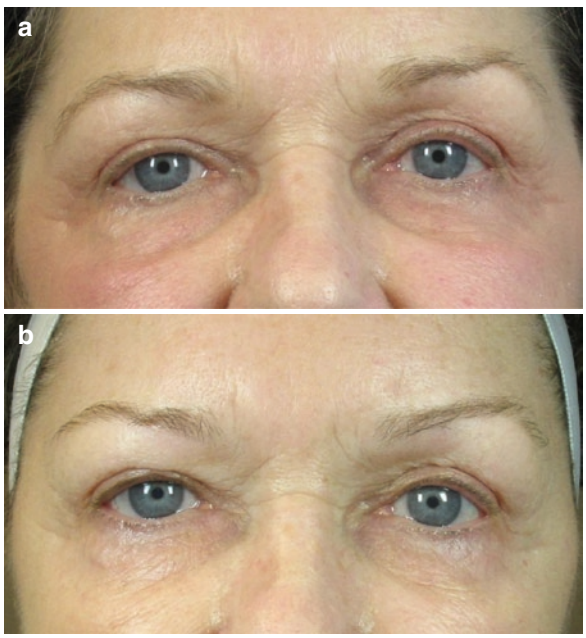

Fig. 22.1 (**a**) Eyelids prior to treatment with a coagulative resurfacing laser. (**b**) One month after a series of four treatments with a coagulative resurfacing laser. Note the modest improvement in skin quality, most evident in the lower eyelids

22.4 Fractional and Plasma Skin Resurfacing in the Periorbital Region

Fractional skin resurfacing generates improvements in surface texture, wrinkling, and global skin appearance. The treatment is ideally suited to patients with mild to moderate textural changes or rhytids who desire more dramatic results than traditional nonablative lasers may provide but less downtime than traditional ablative therapy. Fractional resurfacing delivers ablative or nonablative laser energy in a pixilated pattern, creating microscopic columns of thermal injury in the epidermis and dermis. These coagulated areas are surrounded by areas of untouched skin, which allow for rapid healing and re-epithelialization. As a result, fractional resurfacing more effectively treats rhytids and surface texture compared with nonablative or skin-tightening techniques and offers decreased downtime and a reduced risk of adverse events relative to ablative laser skin treatments [1].

A range of devices are now used for fractional skin resurfacing. They include fractional coagulative lasers, such as the 1,540-, 1,550-, and 1,440-nm lasers, and fractional ablative lasers, such as CO_2, Er:YAG, and YSGG lasers. Few fractional devices have been

studied as a treatment for eyelid wrinkling and surface texture. The Fraxel laser (Solta Medical, Inc., Hayward, Calif.) has been proven safe for use on the eyelids and has been approved by the United States Food and Drug Administration (FDA) for skin resurfacing and the treatment of periorbital wrinkles, melasma, and scars. This 1,550-nm, diode-pumped, erbium fiber laser creates microthermal zones of coagulated tissue [11]. Re-epithelialization of the treated skin generally occurs within 24 hours of treatment.

With the proper precautions, fractional resurfacing of the eyelids is a low-risk, well-tolerated procedure that can produce clinically significant improvement. In a trial of 20 patients (Fitzpatrick skin types I–III), four treatment sessions at 2-week intervals were performed under topical anesthesia using a fractional treatment tip specifically created for use on the eyelid. The average downtime was 2–3 days. Follow-up after 1 and 3 months revealed significant wrinkle reduction and improvement in surface texture and overall eyelid appearance, as rated by subjects and the treating physician [11]. Preliminary evaluation of another fractional device, the Affirm Anti-Aging Workstation (Cynosure, Inc., Westford, Mass.), suggests that it is also safe and effective for use on the eyelids [11]. A recently developed 2,790-nm fractional YSGG laser (Pearl Fractional, Cutera, Inc.) effectively targets deep rhytids in the periorbital area and also is indicated for eyelid skin laxity and acne scarring (see Fig. 22.2a, b).

As with other resurfacing lasers, eyelid treatment with fractional devices requires metal, laser-safe corneoscleral protective lenses. To enhance patient comfort, topical anesthetic may be applied to the skin for approximately 1 hour prior to treatment, taking care to avoid getting it in the eyes. Systemic sedation or analgesics are often used when performing fractional ablative treatments but are generally not required for fractional coagulative laser treatments.

Plasma skin regeneration, an FDA-approved resurfacing modality, has been proven safe and efficacious in the treatment of facial photoaging, skin laxity, and acne scars. An unpublished study of 24 patients demonstrated its safety and efficacy for use on the eyelids (Biesman 2008). However, discussion will remain limited in this chapter because the sole producer of a plasma device (Portrait Plasma, Rhytec, Inc., Waltham, Mass.) ceased operations in 2008.

22.5 Radiofrequency and Optical Devices for Periorbital Skin Tightening

Certain noninvasive, nonablative treatments generate eyelid skin tightening by heating the deeper dermis while preserving the epidermis. Ideal candidates for these therapies include patients with mild to moderate skin sagging, but not so much dermatochalasis that blepharoplasty or surgical brow lifting is required. Available skin-tightening treatments include radiofrequency (RF) energy, RF energy combined with IR laser or light energy, and pulsed light in the near- or mid-IR range.

The most thoroughly studied skin-tightening device, ThermaCool (Thermage, Solta Medical, Hayward, Calif.) is a monopolar RF technology that is FDA-approved for the treatment of periorbital rhytids and skin tightening of the face, neck, and body. Though the original ThermaCool treatment tip penetrated too deeply to be used safely within the orbital rim, a newer, shallower,

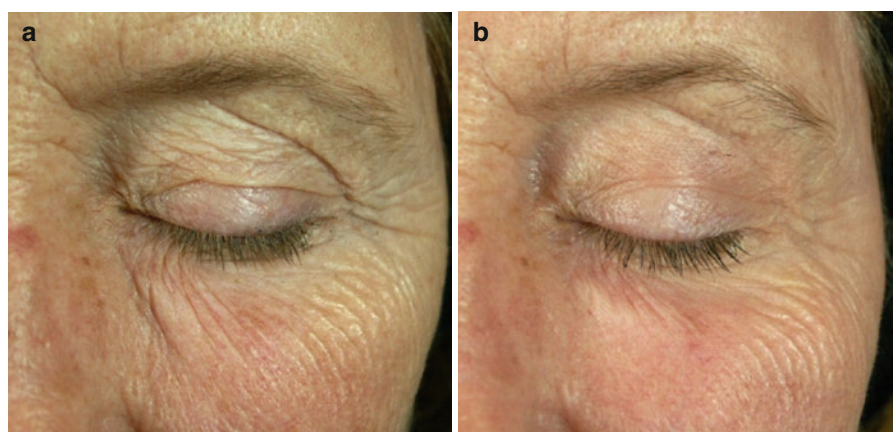

Fig. 22.2 (**a**) Eyelids prior to ablative fractional resurfacing. (**b**) Three weeks after one treatment with the 2,790-nm ablative fractional resurfacing laser

0.25-cm^2 treatment tip, known as ThermaTip, was approved by the FDA in 2007 for use on the eyelids.

Monopolar RF energy generates an electric field that causes molecular rotation in the dermis and subcutaneous fat, resulting in deep and controlled volumetric heating (approximately 65–75°C) [12]. These temperatures denature collagen's triple helix structure, causing immediate tissue contraction. The resulting inflammatory cascade also promotes neocollagenesis in the weeks after treatment, contributing to additional skin tightening [13] (see Fig. 22.3a, b).

For reasons that remain unclear, monopolar RF energy creates dramatic eyelid tightening and lifting in some patients and yields minimal results in others. In a multicenter trial, in which the 0.25-cm^2 treatment tip was used on the upper and lower eyelids and in the crow's feet region, upper eyelid tightening was observed in 88% of subjects, reduced hooding was seen in 86% of subjects, and lower eyelid tightening occurred in up to 74% of subjects six months after treatment, as evaluated by patients, the treating physician, and independent photographic review [14]. Most subjects achieved an improvement of 25% or greater, whereas a smaller number demonstrated more dramatic results. No serious adverse events were observed. Histological study confirmed the presence of thickened, shortened collagen fibrils after treatment, and northern blot analysis demonstrated upregulated collagen type I messenger ribonucleic acid expression, suggesting that the therapy induces a wound-healing response [13, 15]. In another prospective, 6-month trial of 86 patients with periorbital rhytids (Fitzpatrick skin types I–IV), 83% of patients improved by at least one point on the Fitzpatrick wrinkle scale after a single monopolar RF treatment (average energy setting 16, or 58–140 J/cm^2 area of skin). More than 60% of eyebrows were elevated by at least 0.5 mm, according to objective analysis [16].

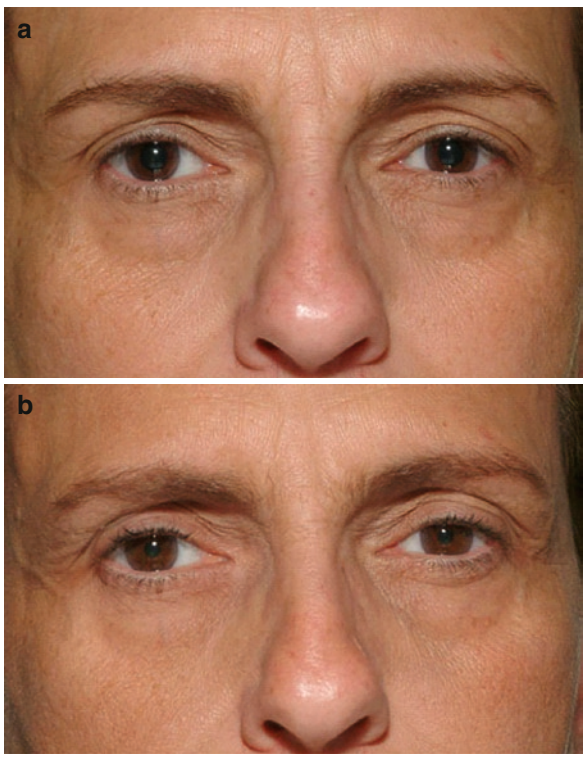

Fig. 22.3 (**a**) Prior to treatment with the monopolar RF device. (**b**) Four months a one treatment with the monopolar RF device

With the proper safety precautions, monopolar RF treatments using the 0.25-cm^2 treatment tip are well-tolerated without supplemental anesthesia and do not cause injury to the eyelids or delicate structures within or surrounding the eyes [17]. Plastic corneoscleral protective lenses should be coated with an ophthalmic lubricant and inserted after a drop of anesthetic is added to each eye. Metal shields must never be used with RF therapy. Liberal use of coupling fluid on the treatment zone helps to maximize patient comfort and minimize the risk of eyelid skin burns. Reduced energy levels are advised when treating the thin skin overlying the lateral orbital rim. The treatment is considered safe for use on all skin types and for patients who have undergone laser or plastic surgery or who have had injections of botulinum toxin or dermal fillers (silicone is a possible exception) [13]. Common side effects of monopolar RF energy include transient erythema and edema. Less frequent events include burns, crusting, and scarring [13, 16, 18].

IR technologies produce skin tightening via a mechanism similar to that of monopolar RF energy. A device that emits IR energy in the 1,100- to 1,800-nm range (Titan, Cutera, Inc.) produces dermal heating to produce collagen remodeling and skin tightening [19]. More than one treatment is usually required, at 1- to 3-month intervals. Clinical study showed that skin laxity improved approximately 30% in the cheeks [19]. Mild to moderate improvement has been observed in more than 85% of patients. Subjects exhibiting relatively little skin laxity improved the most [20]. Though the device may safely be used in the periorbital region, insufficient safety evidence exists to recommend its use on the eyelids.

A variety of devices combine RF energy with laser or light energy to target rhytids and skin laxity. In theory, such combinations may minimize the amount of

energy required from each modality to achieve the desired results and may reduce the incidence of adverse events [21, 22]. Optical energy is absorbed by specific chromophores in the skin and converted to heat, increasing the resistance of the target tissue. This increased resistance directs RF energy to the target and increases the selective heating for greater dermal modification [22]. Devices that combine optical energy and RF may be safely used in the crow's feet area, but they have not yet been studied on the eyelids and are not recommended for use within the periorbital rim.

An RF and IPL combination device (Aurora SR, Syneron, Irvine, Calif.) used in a trial of 100 patients was shown to generate a 60% average improvement in facial wrinkling, including rhytids in the periocular area, after 2 to 5 treatments. The investigators concluded that wrinkle reduction with RF and IPL was superior to IPL alone [23]. A 20-person trial of a 900-nm diode laser with bipolar RF (Polaris WR, Syneron) resulted in significant improvements in rhytids of the face and neck, as rated by subjects and investigators. Modest improvements in skin laxity were also observed, with transient erythema and edema noted as the most common side effects [24]. A combination IR and bipolar RF device (ReFirme ST, Syneron) demonstrated improvement in skin laxity on the neck and face, including in the crow's feet area, with no serious adverse events [25].

Another device uses vacuum suction to draw the skin between parallel electrodes so that RF energy may be directed through it (Aluma, Lumenis Aesthetic, Yokneam, Israel). In a trial of 46 adults who underwent eight facial treatments with this device, standard evaluation tools revealed significantly decreased wrinkling, improved skin appearance, and enhanced skin texture 6 months after treatment. Adverse events included transient erythema, burning or blistering, edema, purpura, crusting, and hyperpigmentation [26]. Though some clinicians use this device on the eyelids, ocular safety studies have yet to be conducted.

Fractional technology has also been applied to bipolar RF energy (Renesis, Primaeva Medical, Inc., Pleasanton, Calif.) with the goal of treating facial rhytids while sparing the dermis. Histological study demonstrated neocollagenesis, neoelastogenesis, and complete replacement of the thermal treatment zone by 10 weeks [27]. Additional research is necessary to determine whether this technology is safe for use on the eyelids.

22.6 Conclusion

A number of energy-based devices demonstrate safety, efficacy, and future promise for the treatment of skin laxity and rhytids in the periorbital area. Resurfacing treatments may improve skin texture, color, and laxity, while IR, RF, and other devices generate skin tightening and mild to moderate wrinkle reduction. Traditional ablative resurfacing requires fewer treatments but longer recovery times compared with nonablative laser treatments, and fractional resurfacing offers intermediate results and downtime. With all energy-based therapies used in the periorbital area, care must be taken to ensure the safety of the delicate structures and tissues of the eye and the surrounding region. Careful evaluation of the patient's concerns and the etiology of the periocular rhytids is necessary to achieve the best possible outcome, and a combination of energy-based modalities with dermal fillers, neurotoxins, chemical peels, or blepharoplasty may be required. For individuals who require a marked reduction in dermatochalasis, the management of orbital fat, an elevation of the brows or midface, or the repair of malpositioned eyelids, blepharoplasty is indicated rather than energy-based treatments.

Take Home Pearls

- Ocular safety is of paramount importance. Resurfacing addresses surface texture, color, and laxity, whereas nonablative IR, RF, and other similar devices primarily produce skin tightening and modest wrinkle reduction.
- There is typically no "downtime" associated with IR, RF, and other similar devices.
- Coagulative resurfacing typically requires 4–6 sessions to achieve ideal outcomes but offers the advantage of minimal downtime.
- Ablative fractional resurfacing requires 1–2 treatments with longer recovery times (3–7 days) but offers more dramatic outcomes than even a full series of coagulative fractional resurfacing.
- Fractional resurfacing of the eyelids can be a safe and effective method of improving skin texture, wrinkling, and laxity.

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Wrinkles and Acne Scars: Fractional Ablative Lasers

23

Arielle N. B. Kauvar and Melanie A. Warycha

Core Messages

- Fractional ablative lasers create columns of ablated tissue separated by zones of intact tissue, resulting in rapid re-epithelialization and induction of new collagen production.
- Fractional ablation provides a greater margin of safety compared to conventional laser ablation by avoiding the production of open wounds.
- Fractional ablative lasers improve photodamage and scars in one to two treatment sessions.

23.1 Introduction

Ablative laser resurfacing with pulsed carbon dioxide (CO_2) or "hot" erbium:yttrium aluminum garnet (Er:YAG) lasers is highly effective for severe photodamage and skin laxity. Vaporization of skin combined with immediate collagen shrinkage and long-term collagen production and remodeling produces predictable and long-lasting results [1, 5, 17, 18, 34, 38]. Despite the dramatic clinical outcomes achieved with these procedures, the use of ablative laser resurfacing was severely limited by the risk of prolonged periods of wound healing and redness and the risk of infection, scarring, and persistent hypopigmentation.

The concept of fractional photothermolysis (FP) was developed by Manstein et al. [23] in 2004, based on the premise that deep, dermal, nonablative heating of the skin could produce sufficient collagen production and remodeling to improve wrinkles, photodamage, and scars with minimal adverse effects. Mid-infrared, nonablative fractional lasers heat small-diameter (100–300 μm), deep (up to 2 mm) columns of tissue, termed microthermal zones (MTZs), separated by varying intervals of intact bridges of tissue. The coagulated column of tissue is eliminated through the epidermis as necrotic debris, thereby eliminating a fraction of the damaged tissue with each laser treatment. Histologic studies show that the MTZs of treated tissue are then replaced by new, healthy collagen. Treatment results in rapid healing without significant epidermal disruption or downtime and improved neocollagenesis compared to traditional nonablative lasers. Because healing occurs three dimensionally, from the adjacent untreated bridges of tissue as well as from the hair follicles, adnexal-poor tissue can also be treated. Fractional nonablative lasers permitted safe deep dermal treatment of the skin of the neck, trunk, and extremities for the first time. After an average of 4–6 treatment sessions, the fractional nonablative lasers produce excellent improvement of superficial photodamage and pigment disorders, scars from acne, surgery, trauma, and striae [2, 13, 14, 16, 19, 21, 27, 28, 31, 33, 36]. The results for resurfacing moderate to severe photodamage and wrinkles, however, have been largely disappointing compared to those observed with traditional ablative resurfacing lasers.

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_23, © Springer-Verlag Berlin Heidelberg 2011

23.2 Fractional Ablative Lasers

The concept of FP was therefore applied to ablative laser wavelengths based on the hypothesis that deep dermal fractional ablation would achieve the efficacy of traditional ablative resurfacing while minimizing the side effects of these procedures, such as protracted periods of healing and erythema and the risk of infection, scarring, and long-term hypopigmentation [15]. The first lasers designed to achieve ablative fractional photothermolysis (AFP) were CO_2 (10,600-nm) lasers, followed by the Er:YAG (2,940-nm) and Er:yttrium scandium gallium garnet (YSSG) (2,790-nm) lasers, and a wide array of technology presently is available for clinical use (Table 23.1). These lasers vaporize microscopic columns of tissue with varying degrees of coagulation. Like the fractional nonablative devices, the diameter, depth, and density of the ablated columns of tissue (or percentage of surface area coverage) can be varied with most systems (Fig. 23.1).

The type of injury created by fractional ablative lasers will also vary depending on the amount of coagulation produced beyond the ablated tissue. Based on the water absorption coefficients of their respective wavelengths, the Er:YAG laser (~10^4/cm at 2,940 nm) produces the least amount of coagulation or residual thermal damage (~10 μm), the CO_2 laser (~10^3/cm at 10, 600 nm) produces the greatest amount of coagulation (~100 μm), and the Er:YSSG laser (10^2/cm at 2,790 nm) lies

Table 23.1 Fractional Laser Technology

Manufacturer	Pulse duration	Beam diameter (μm)	Ablative depth (μm)	Fluence or power	Scanner area	Delivery method
Fractional carbon dioxide lasers						
Deka Smartxide Dot	200 μs–2.0 ms	350	500–800	30 W	15×15 mm	Scanned conventional
Ellipse Juvia	2.0–7.0 ms	500	400	0.1–15 W	7×7 MTZ/cm	Scanned
Lasering USA Mixto SX	2.5–16 ms	180 300	200	0.5–30 W	20×20 mm	Scanned (four quadrants)
Lumenis	<1 ms			60 W		Scanned
Active FX		1,300	10–300		9×9 mm	
Deep FX		120	150–1,600		10×10 mm	
Lutronic eCO_2	Variable	120 300 1,000	2,500	30 W	14×14 mm	Stamping dynamic
Solta repair	0.15–3 ms 0.8–1.8 ms	<140	1,600	40 W	10×10 mm	IOTS (paintbrush) continuous motion
Fractional erbium lasers						
Alma Pixel XL Harmony	1, 1.5, or 2 ms	250	300	2,500 mJ/p	11×11 mm	Scanned
Palomar Lux 2940	0.2–5.0 ms	100	200	Up to 5 mJ/microbeam	10×10 mm 6×6 mm	Stamping
Sciton Profractional	Variable	250 430	1,500	45 W	20×20 mm	Scanned
Fractional YSGG laser						
Cutera Pearl	Variable	300	1,500	60–320 mJ/microspot	12×14 mm	Scanned

YSSG yttrium scandium gallium garnet, *MTZ* microthermal zone, *IOTS* intelligent optical tracking system

somewhere in between (~40 μm) when supra-ablative fluences are used with pulse durations shorter than the thermal relaxation time of the tissue (Fig. 23.2). The purely ablative wounds created by the short-pulsed fractional Er:YAG lasers produce increased bleeding intraoperatively, but may have an advantage in reducing the risk of postinflammatory hyperpigmentation in patients with darker skin types. By lengthening the pulse duration, the wounds produced by the Er:YAG laser can be made to approximate those of the CO_2 laser (Fig. 23.3). The longer pulse duration results in a larger zone of coagulation [1, 9]. In addition to providing hemostasis, it seems that the large volume of collateral tissue coagulation is beneficial for inducing increased skin tightening.

The first clinical and histologic results of in vivo treatment using a novel microprocessor-controlled, scanned, fractional ablative CO_2 laser were described by Hantash et al. [15] in 2007. The device produced an array of pixilated damage to the skin, with columnar zones of ablated tissue extending from the stratum corneum through the epidermis and various levels of the dermis. A zone of coagulation surrounded each column of ablated tissue and the device enabled customization of the depth and density of these microscopic treatment zones (Fig. 23.4). Increasing the pulse energy increased the depth of ablation. Forty-eight hours after treatment,

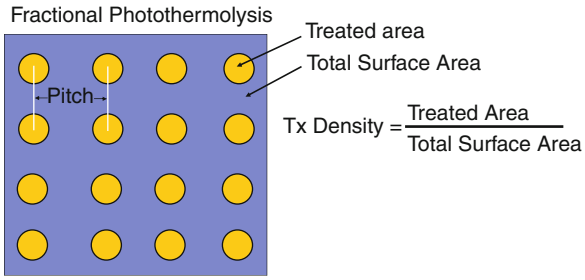

Fig. 23.1 Microbeams of laser light produce columns of ablated tissue with varying degrees of lateral coagulation. The density of coverage is changed by varying the pitch of the microbeams or increasing the number of laser passes

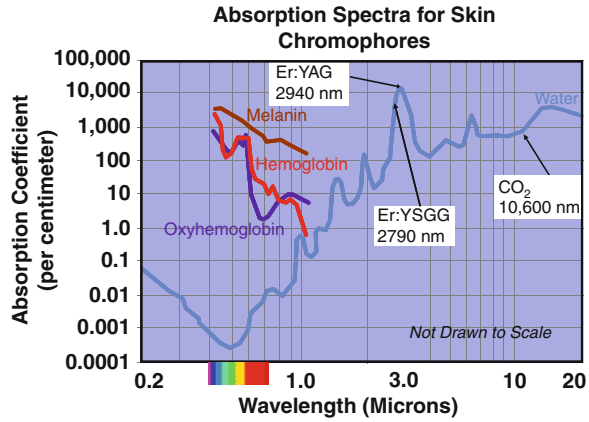

Fig. 23.2 Of the ablative laser wavelengths, the erbium:yttrium aluminum garnet (Er:YAG) laser has the greatest absorbtion coefficient for water and consequently the least amount of lateral thermal damage. The carbon dioxide (CO_2) laser has the lowest absorption coefficient for water and consequently the greatest amount of lateral thermal damage. The effects of the erbium:yttrium scandium gallium garnet (Er:YSSG) laser falls between these two wavelengths

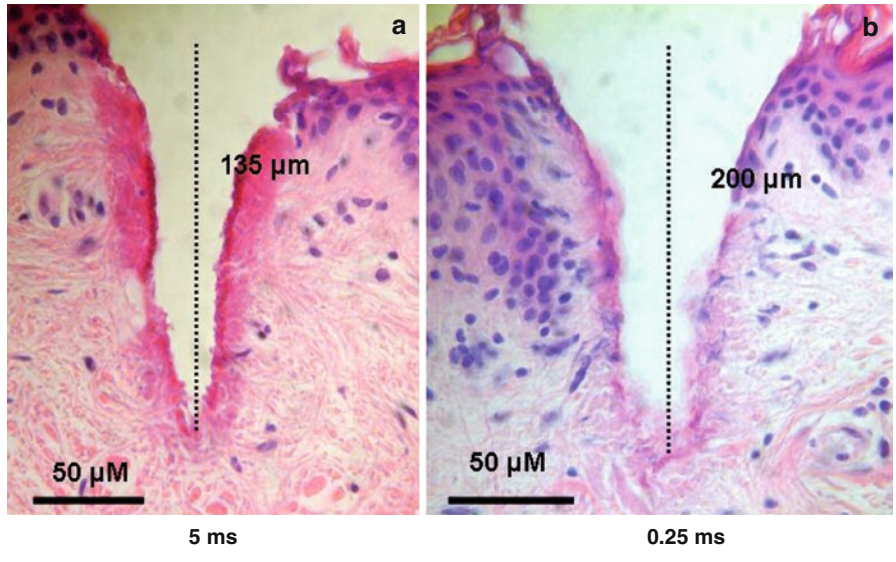

Fig. 23.3 The erbium:yttrium aluminum garnet laser can produce lateral coagulation by lengthening the pulsewidth. At 5 ms there is substantial coagulation, whereas a pulse duration of 0.25 ms produces nearly pure ablation. Reprinted with permission from Dierickx et al. [9]

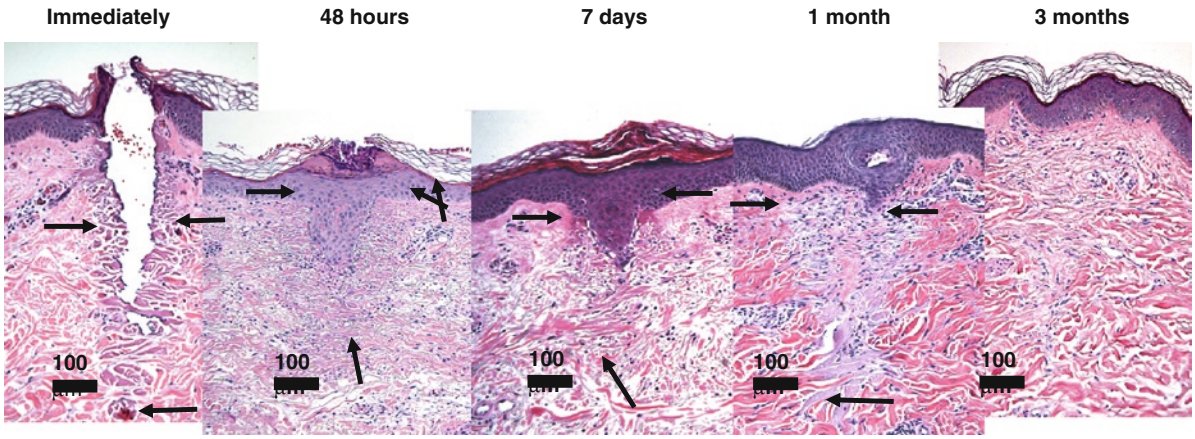

Fig. 23.4 Progression of healing after treatment with a fractional carbon dioxide laser (Fraxel Re:Pair, Solta Medical, Inc.). Photographs courtesy of Solta Medical, Inc

the ablated zones were replaced by new epidermal tissue, and new collagen production was evident by 7 days. Immunohistochemistry confirmed that persistent collagen production and remodeling occurred for at least 3 months after treatment. The authors hypothesized that greater clinical improvement in skin texture and wrinkling could be achieved with the prolonged wound-healing response induced by AFP as compared to nonablative FP. Multiple clinical studies have since confirmed that the degrees of correction of wrinkling and photodamage with AFP devices far exceeds those of the nonablative technologies in fewer treatment sessions.

23.3 Mechanism of Action

Fractional ablative lasers improve the appearance of skin by removing portions of the epidermis and dermis as well as heating MTZs extending from the epidermis to the mid- or deep dermis. Portions of the epidermis and dermis are replaced by wound-healing responses after the injury, replacing the damaged tissue with healthy, new foci of epidermis and dermis. These procedures also produce skin tightening. Immediate tissue shrinkage is visible during laser pulse application and results from the collapse of the small vaporized channels created by the laser and from heat-induced collagen shrinkage. Heating tissue to 50–60°C produces immediate alterations in the triple helix structure of collagen molecules and causes the collagen molecules to shrink by about one-third their length [12, 29]. These areas of thermally altered dermis are thought to provide a structural lattice for the growth and reorganization of the new collagen produced by wounding the skin. Ultimately, replacement of superficial to deep zones of the dermis with new, well-organized collagen molecules and extracellular matrix is required for the long-term clinical improvement of hypertrophic and atrophic scars as well as wrinkles and solar elastotic skin. These histologic changes correlate with the increased clinical improvement observed 3–6 months after laser treatment.

23.4 Fractional Carbon Dioxide Lasers

The first two "microfractional" systems to reach the market in 2007 were the Re:Pair (Solta Medical, Inc., Hayward, Calif., USA) and the Lumenis DeepFx (Santa Clara, Calif., USA) The Solta device uses a continuous paint-brush motion to apply the laser microbeams to the tissue, whereas the Lumenis device employs a "stamped" scanning technology. The Solta Re:Pair uses a microprocessor-controlled handpiece to deliver a laser beam with a penetration depth of 300–1,600 μm, which is determined by the pulse energy, up to a maximum of 70 mJ. Treatment densities (or coverage) may be adjusted from 5% to 50% by performing multiple passes and choosing higher treatment densities, which are chosen based on the severity of photodamage or scarring present.

Lumenis introduced a "macrofractional" handpiece (ActiveFX, Lumenis as an attachment to their CO_2 resurfacing laser in 2006. The macrofractional handpiece scans patterns with a 1.3-mm spot size, at

treatment densities providing 50–90% of surface area coverage. Ablation is limited to the epidermis with some coagulation of the papillary dermis, producing a superficial laser peel that heals in 3–4 days. In 2007, a microfractional attachment (DeepFX) was introduced. This microfractional handpiece fractionates the laser beam to a diameter of 0.12 mm and uses a stamping-style microscanning method. The handpiece produces multiple different geometric scan shapes, and treatment densities can be varied from 5% to 50%. The pulse energy determines the depth of tissue injury, with a maximum of 70 mJ providing tissue penetration up to 1 mm.

The DEKA system (SmartXide DOT, Calenzano, Italy) is a low-power (30 W) CO_2 laser used with a scanning handpiece. The scanned microbeam measures up to 350 μm and the pulse duration varies from 200 to 2,000 μs. The longer pulse durations used with this system produce larger zones of coagulation around the ablated channels of tissue.

During the past 2 years multiple different fractional CO_2 lasers have been developed. The same basic principles apply to all these systems: CO_2 laser microbeams are applied to tissue, producing columnar wounds with a prescribed diameter, density, and depth. However, the power and delivery systems of the individual units vary considerably. Lower power lasers have pulsewidths longer than the thermal relaxation time of skin and produce larger zones of coagulation beyond the ablated wound, which affects the safe, allowable treatment depth and surface area coverage. Practitioners should, therefore, be familiar with the histologic and clinical correlates of varying parameters with the fractional ablative device they are using.

23.5 Fractional Erbium:YAG Lasers

Palomar's fractional Er:YAG has an active rod pumped by a Xenon flashlamp. There are multiple interchangeable optical tips that provide various densities (170–1,000 microbeams/cm^2) of focused miocrobeam arrays (each ~75–150 μm in diameter) with up to 12 mJ/microbeam of energy. The density of microbeams is fixed for each optical tip, but the total density of microbeams delivered will vary depending on the number of laser passes. This laser ablates tissue to depths of 1,000 μm without coagulation when used with a pulsewidth of 0.25 ms, and produces zones of coagulation up to ~70 μm with 5-ms pulse durations (Fig. 23.3). Another optic produces a 6-mm spot size with a directional or "groove" pattern of injury, with each groove measuring 100–200 μm in width and 350 μm in depth spaced at 350-μm intervals. The treatment density is increased by performing additional laser passes with varied orientations of the linear pattern (Fig. 23.5). Another interchangeable optic produces a traditional macrobeam pattern of ablation.

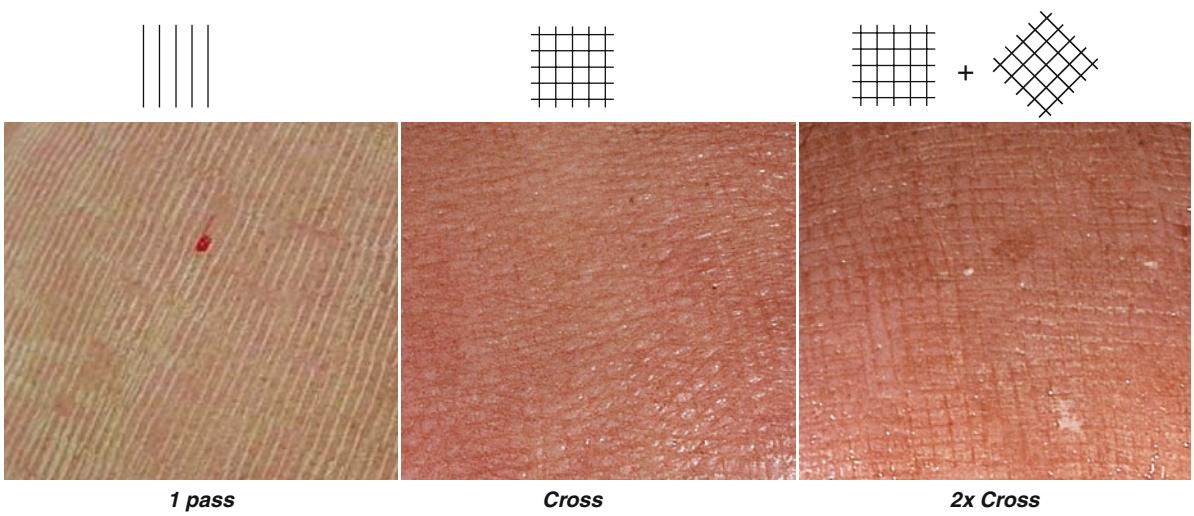

Fig. 23.5 Crossed patterns of linear grooves are used with an erbium:yttrium aluminum garnet laser (Lux 2,940 nm, Palomar Medical) to increase treatment densities. Photographs courtesy of Palomar Medical

Sciton, Inc. (ProFractional Palo Alto, Calif., USA) developed two microfractional handpieces for their Er:YAG laser base unit. One handpiece uses a 250-μm spot to vaporize tissue from 25 to 1,500 μm per pass with treatment densities (coverage) from 1.5% to 60%. The other uses a 430-μm spot with predetermined densities of either 5.5% or 11%. The latter offers the ability to add depth-selectable tissue coagulation for enhanced collagen remodeling by delivering a train of subablative laser pulses that heat the tissue to three selectable depths: level 1, up to 50 μm; level 2, up to 100 μm; and level 3, up to 150 μm. Both handpieces produce scan sizes ranging from 6×6 to 20×20 mm.

Alma's fractional Er:YAG laser produces superficial epidermal ablation. It uses a microlens arranged in a matrix of either 9×9 microbeams with energies up to 17 mJ or 7×7 microbeams with energies up to 28 mJ. The channels produced by this laser measure 120–140 μm in depth and 150 μm in diameter, limiting treatment to the epidermis and superficial papillary dermis. The treatment density is increased by performing multiple passes.

23.6 Fractional Erbium:YSGG Laser

Cutera (Brisbane, Calif., USA) was the first company to develop an Er:YSGG laser for superficial skin resurfacing. With a water absorption coefficient roughly one-third that of the Er:YAG laser and five times that of the CO_2 laser, it vaporizes tissue with a zone of coagulation approximately midway between that of the CO_2 and short-pulsed, or "cold," Er:YAG laser. In 2008 they developed a fractional Er:YSGG laser (Pearl) with a pulse duration of 600 μs and a spot size of 300 μm. It produces scans of variable densities and patterns up to 12×14 mm, ablating up to 100 μm in depth with a coagulation zone of ~40 μm.

23.7 Published Results

23.7.1 Photodamage

In a pivotal clinical trial, Rahman et al. [26] evaluated a microprocessor-controlled scanned CO_2 laser in 30 patients for the treatment of photodamage of the neck and chest. Anesthesia included a 1-h application of topical lidocaine cream, oral diazepam, and hydrocodone/acetaminophen. A fixed spot size of 120 μm was used with energies up to 20 mJ/pulse and total treatment densities up to 1,200 MTZ/cm^2 on the face and 800 MTZ/cm^2 on the neck. Subjects experienced erythema, edema, petechial bleeding, and crusting up to 48 h, with mild erythema and edema still present at 1 week and still present in 33% at 1 month. Twenty percent of subjects experienced postinflammatory hyperpigmentation ($n=6$, skin types II and III). The erythema and postinflammatory hyperpigmentation were completely resolved by 3 months. There was continued clinical improvement in the rhytides and laxity throughout the 3-month follow-up period. Based on blinded scoring of photographs taken before and after treatment, at least moderate (50–100%) improvement was observed in 83% of subjects. Using a high-power, microfractional CO_2 laser with a scanning handpiece, Pardo et al. [25] showed that higher-density coverage (10.1% ablated tissue) produces a greater inflammatory response and improved results compared to a lower density of ablation (3.5%) at the same pulse energy of 15 mJ without a higher incidence of side effects.

In a split-face study comparing nonablative, fractional 1,550-nm and fractional CO_2 laser treatment, Weiss et al. [37] reported a 75% improvement compared to a 25% improvement in periocular rhytides, respectively. A split-face comparison of a 30-W, 300-μm spot fractional CO_2 and Er:YAG laser in 10 patients by Lomeo et al. [22] demonstrated improved skin texture and color on the CO_2 laser-treated side as compared to the Er:YAG laser-treated side. The healing time for the Er:YAG laser treatment was 3.4 days compared to 4.5 days for the CO_2 laser-treated side. Munvalli [24] found that a fractional CO_2 laser produced significant wrinkle reduction in severe lower eyelid rhytides in 10 women. Another study [6] showed 50–100% improvement in all 20 patients who underwent periorbital resurfacing with a fractional CO_2 laser using a 15-mm spot and fluencies of 25–40 J/cm^2 with 200 MTZ/cm^2. Lapidoth et al. [20] treated mild to moderate photodamage in 28 subjects with a fractional Er:YAG laser producing superficial (120–140 μm in depth) ablation. They reported excellent improvement in 75% ($n=21$) and good improvement in 25% ($n=7$) of patients 2 months after up to four treatments, with persistence of improvement in 19 of 21 subjects evaluated at 6 to 9-month follow-up. Ross et al. [30] studied the histologic and clinical effects of a fractional 2,790-nm Er:YSGG laser. Thirty-six patients were treated in a

multicenter trial. A 300-μm microbeam was used with pulse energies of 40–360 mJ. Biposies showed ablation depths of 600–1,000 μm and coagulation zones of 40–60 μm. The mean re-epithelialization time was 6 days and all patients showed improvement in wrinkles and fine lines.

A fractional Er:YAG laser producing a groove pattern of injury for facial resurfacing was studied by Doherty et al. [10]. The optic generated a pattern of 5 lines 6 mm in length and separated by an interval of 1.35 mm. Contiguous laser pulses were used to generate a unidirectional pattern of injury during the first pass, and the groove pattern was rotated in subsequent passes to generate an "x" pattern or start patterns, depending on the pass number. Grooves of 100–330 μm with depths of 150–500 μm were produced. A single procedure produced a 50% or greater reduction in perioral and periorbital wrinkles in 76% of patients ($n=17$) and a more than 25% reduction in dyschromia in all patients.

Bass et al. [4] examined the tissue-tightening effects of combining nonablative, fractional 1,540- or 1,440-nm laser treatment with fractional Er:YAG laser treatment for a total of 60% surface area coverage in 14 subjects. The average Fitzpatrick wrinkle score improvement was 2.2 and dyspigmentation score improvement was 2.4. Treatment of ex vivo skin samples yielded up to 47% shrinkage of the specimens. Fractional CO_2 (Figs. 23.6 and 23.7), Er:YAG (Fig. 23.8), and Er:YSGG (Fig. 23.9) lasers produced improvement in dyschromia, textural changes, and rhytides associated with photodamage in 1 to 2 treatment sessions. Aggressive treament can result in skin tightening (Fig 23.10).

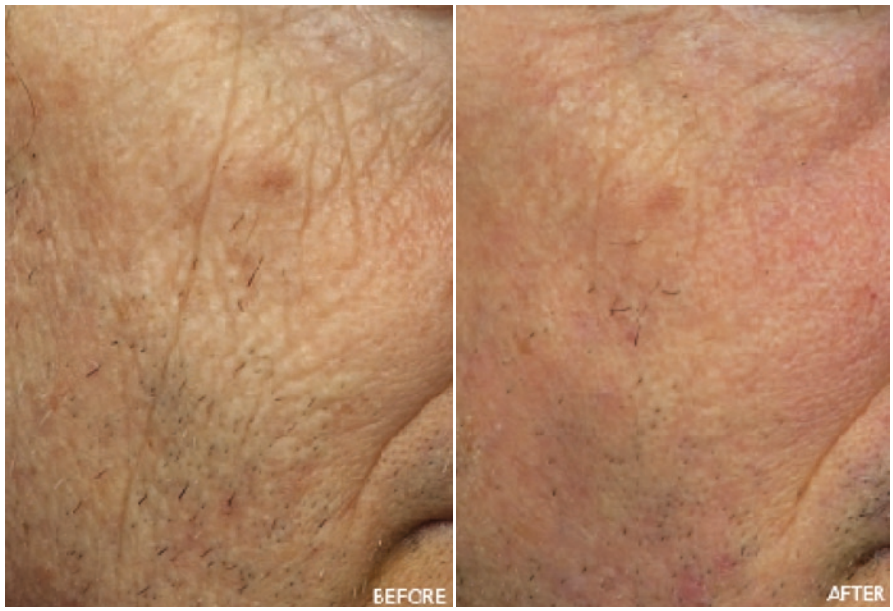

Fig. 23.6 Treatment of photodamage with a fractional carbon dioxide laser (Fraxel Re:Pair, Solta Medical, Inc.)

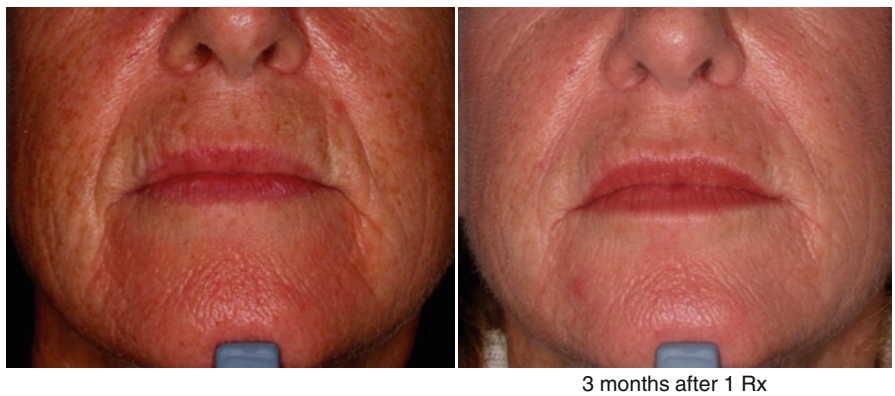

Fig. 23.7 Treatment of photodamage with a fractional carbon dioxide laser (DeepFX and ActiveFX, Lumenis)

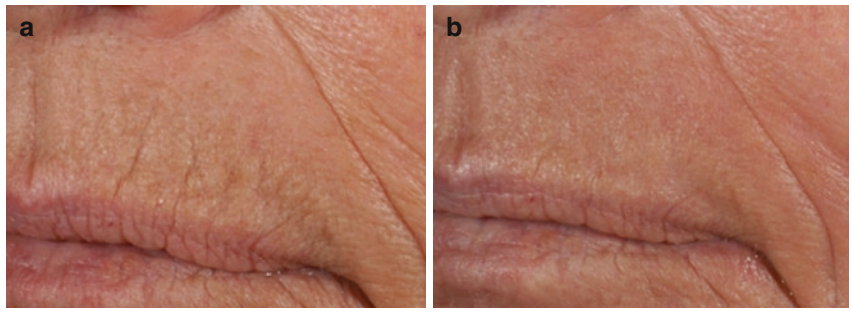

Fig. 23.8 Before (*left*) and 3 months after (*right*) one treatment with a fractional erbium:yttrium aluminum garnet laser (Lux 2940, Palomar Medical). Photographs courtesy of Brooke Seckel, MD

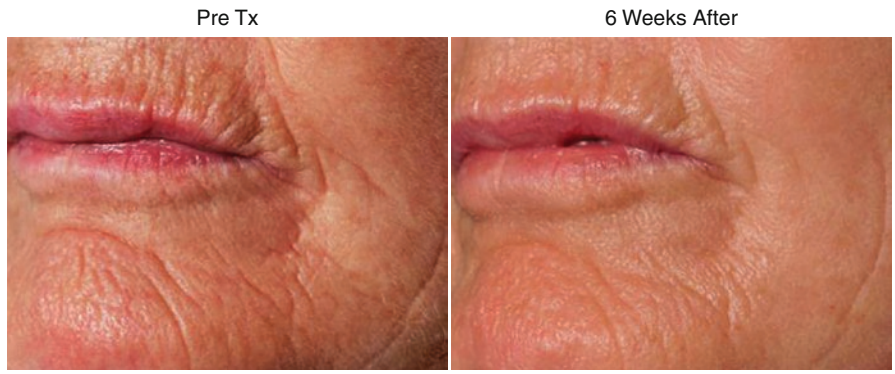

Fig. 23.9 Treatment of rhytides with a fractional erbium:yttrium scandium gallium garnet laser. Courtesy of Cutera.

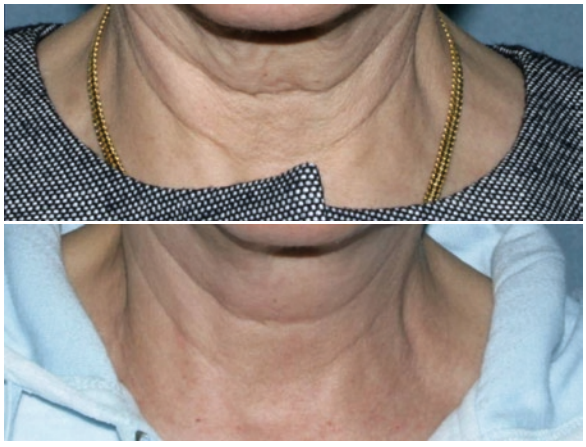

Fig. 23.10 Neck skin tightening with a fractional carbon dioxide laser (Fraxel Re:Pair, Solta Medical, Inc.)

23.7.2 Scars

Chapas et al. [8] used an ablative fractional CO_2 laser to treat 13 subjects with moderate to severe acne scars. Two to three treatments were performed at 1- to 2-month intervals. In this study, pulse energies ranged from 20 to 100 mJ per pulse, energy densities per pass were 100–400 MTZ/cm^2, and total treatment densities ranged from 200 to 1,200 MTZ/cm^2, depending on the location. Three passes were delivered to the cheeks, forehead, neck, and chin, and fewer to the uninvolved skin. Erythema, edema, petechiae, crusting, and oozing were nearly resolved among all subjects within 1 week. Three months after the last treatment, at least 26–50% improvement in texture and atrophy was noted in all subjects. Quantitative topographic analysis of acne scars showed an improvement of 43–79.9% in the depth of the acne scars. There was no incidence of scarring or hypopigmentation. The results of a similar study of 30 subjects with moderate to severe acne scars, following up to three treatments with a fractional ablative CO_2 laser, was reported by Walgrave et al. [35]. Twenty-three of 25 subjects had sustained clinical improvement of their scars 3 months after treatment. Several studies have recently demonstrated improvement of thermal burn scars as well as surgical scars after fractional ablative resurfacing. A study of Asian patients with scarring and wrinkles using a

fractional CO_2 laser [7] demonstrated significant improvements in skin laxity, wrinkles, and atrophic scars, with mild postinflammatory hyperpigmentation developing in approximately half the subjects. Successful treatment of a 50-year-old third-degree burn scar using a high-power fractional CO_2 laser was reported by Waibel and Beer [32]. Fractional ablative lasers improve atrophic acne scars in 1 to 2 treatment sessions (Figs. 23.11 and 23.12).

23.8 Treatment Guidelines

23.8.1 Preoperative Considerations

When large surface areas are to be treated, such as the full face or neck, prophylactic oral antibiotics and antiviral therapy should begin 1 day prior to the procedure and be continued for 5–7 days. Ablative fractional

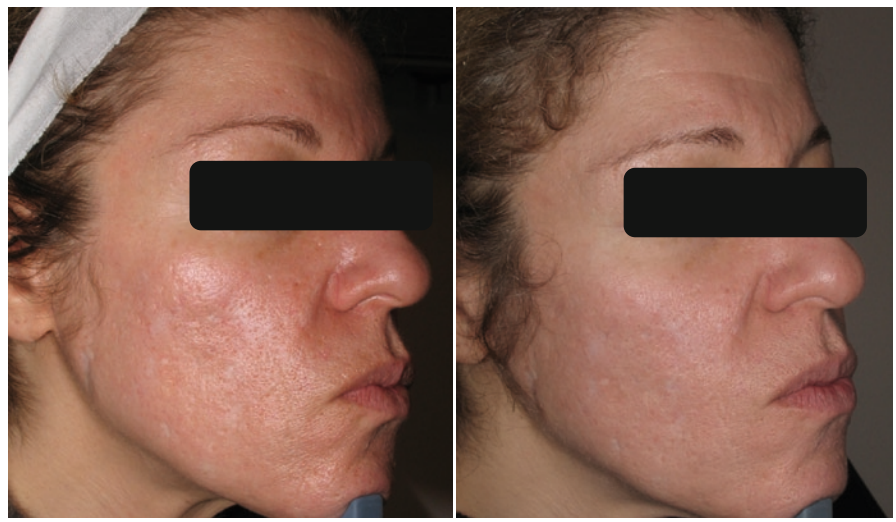

Fig. 23.11 Treatment of acne scars with a fractional carbon dioxide laser (DeepFX and ActiveFX, Lumenis)

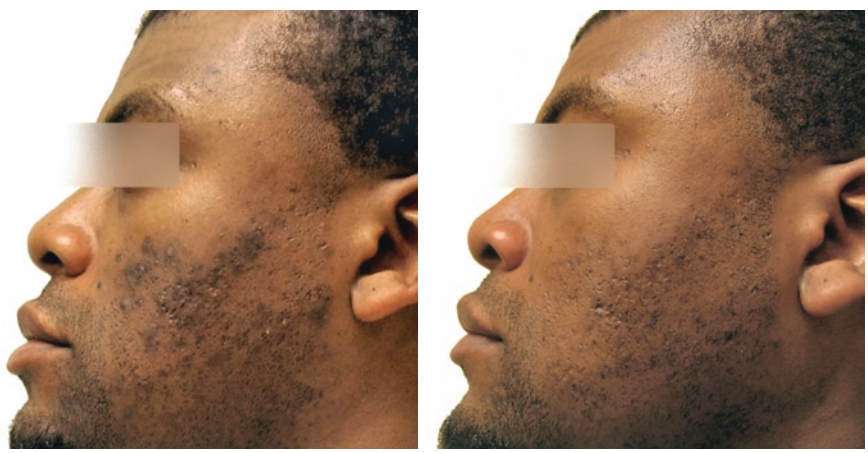

Fig. 23.12 Before (*left*) and 2 weeks after (*right*) two treatments with a scanned fractional erbium:yttrium aluminum garnet laser (Profractional, Sciton) for acne scarring. Photographs courtesy of Sciton

resurfacing can be painful, and clinicians are using a variety of anesthesia options, ranging from a combination of a high-potency topical anesthetic cream with oral or intramuscular sedatives and pain medication to intravenous sedation or general anesthesia. The degree of anesthesia required will depend on the density and depth of treatment and individual patient tolerance. Prior to the procedure, the skin is cleansed and then wiped with isopropyl alcohol to remove any remnants of the topical anesthetic. The patient's eyes must be protected with internal stainless steel eye shields if the eyelid skin is being treated. External eye shields are otherwise appropriate. A smoke evacuator should be used during laser irradiation because all ablative lasers produce a plume.

23.8.2 Intraoperative Care

The treatment parameters and number of passes are often varied on different areas of the face and neck, depending on the degree of damage and treatment indication. When treating moderate to severe photodamage or scars, higher pulse energies and treatment densities are required. Less aggressive treatment parameters are required for eyelid, preauricular, jawline, and neck skin. It is helpful to outline the overall treatment plan with a diagram prior to initiating treatment. Because the fractional lasers do not treat the entire skin surface, treatment with a nonablative laser for the vascular and pigmented lesions, or with a superficial ablative laser peel, is often performed during the same treatment session. Generally speaking, nonablative laser treatment should precede the fractional ablative treatment, and superficial macroablation should follow the deep fractional treatment. Treatment parameters for individual devices cannot be generalized, and the physician must be familiar with the treatment guidelines for the lasers he or she is operating.

23.8.3 Postoperative Care

Frequent application of ice compresses during the first 4–6 h after treatment help to reduce the swelling and burning sensation. Cold-water compresses are applied for 10–15 min 4–6 times per day during the first 2–3 days, followed by the application of a bland emollient such as hydrophilic petrolatum.

23.9 Adverse Side Effects

The open, exudative wounds that develop after traditional ablative laser resurfacing are not seen after fractional ablative treatment (Fig. 23.13). Posttreatment edema and erythema are most severe during the first 48 h and then begin to subside, typically lasting 3–5 days on the face and up to 10 days on the neck and upper chest. Pinpoint bleeding and petichiae may occur with deeper dermal penetration or with devices that are primarily ablative and produce insufficient coagulation to achieve hemostasis. When high-density coverage is used, a grainy crust may cover the treated skin and take several days to resolve. The incidence of postinflammatory hyperpigmentation is very low after fractional ablative laser treatment, even among susceptible populations. To date there have been no reports of delayed hypopigmentation. There are several reports of scarring [3, 11] after ablative fractional resurfacing that occurred with overly aggressive treatment densities and pulse energies, most of them having occurred on the skin of the neck. Re-epithelialization is slower in skin areas with a

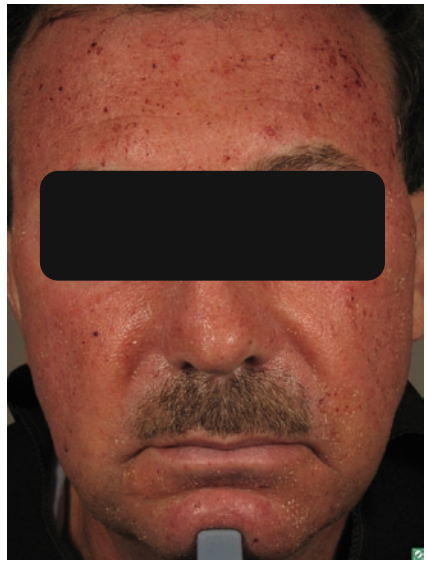

Fig. 23.13 Erythema, edema, pinpoint bleeding, and microcrusts are evident immediately after fractional ablative laser resurfacing. Complete healing usually requires 3–5 days

lower density of adnexal structures, such as the neck and chest, and healing in these areas will take approximately twice as long as it does on the face. Treatment of these areas should only be undertaken by a physician experienced in laser resurfacing, and it is essential to understand the clinical and histologic effects on tissue of the individual laser system being used.

23.10 Conclusions

Fractional ablative lasers can achieve much greater improvement in deeper wrinkles, solar elastosis, acne scars, and skin laxity in fewer treatment sessions compared to nonablative fractional lasers. There are likely several mechanisms responsible for these effects, including the removal of a fraction of the epidermis and dermis with ablation, the immediate collagen contraction due to tissue coagulation, and the induction of vigorous neocollagenesis and dermal remodeling.

It remains unclear what constitutes the ideal combination of ablation and coagulation or treatment depth and density. It is also unclear whether varying the pattern of ablative or coagulative injury or delivering them sequentially or simultaneously will be most beneficial. These devices permit us to treat photodamage and scarring in a reliable, safe, and efficacious manner. With further investigation, treatment outcomes will likely improve as will our ability to treat new indications.

Take Home Pearls

- Laser parameters vary with each device. The treating physician must be familiar with the particular parameters and laser-tissue interactions for the specific laser being used.
- Anesthesia requirements (high-potency topical anesthetics versus regional blocks or oral analgesics and sedatives) will depend on the aggressiveness of the treatment.
- Prophylactic antiviral and antibiotic therapy should be used for large surface area treatments (e.g., the full face).
- Ice water compresses followed by application of petrolatum speed recovery and re-epithelialization.
- Treatment of the neck, trunk, and extremities must be performed using lower treatment densities (or surface area coverage) to avoid bulk heating and adverse effects.

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Wrinkles and Acne Scars: Fractional Nonablative Lasers

24

Uwe Paasch

Core Messages

- Minimally invasive laser therapies using fractionated laser beams have become increasingly more prevalent, especially for treating wrinkled, sun-damaged skin and acne scars. Moreover, indications for their use also have increased significantly.
- Fractional lasers apply energy using microscopic dimensions and leave the surrounding tissue unaffected, intact, and therefore vital. This permits a much shorter period of recovery than if a larger area was treated at once.
- Treating the skin with nonablative fractional laser results in a unique wound-healing process that is assisted by persistence of vital epidermis even in treatment areas.
- Each laser spot also creates a deep dermal column of coagulated tissue, known as a microthermal treatment zone.
- One of the advantages of this process is that keratinocytes, stem cells, melanocytes, inflammatory cells, and their respective molecular signaling capacities remain intact, leading to fast dermal remodeling at depths up to 1 mm.
- Currently, this technology is widely used to treat fine wrinkles and acne scars. The overall efficacy of these devices seems to be comparable in both cases, and similar results have been demonstrated with both photodamaged skin and acne scars.
- Finally, there is production and depositing of newly formed collagen over time.
- Despite these advantages and the availability of a wide range of systems, the clinical effectiveness is most often rated as only moderate in magnitude.

24.1 Introduction

The demand for minimally invasive treatments that hold or improve skin smoothness and tonicity continues to increase. In the past, a variety of laser systems have been developed to address this issue. Depending on the device's wavelength, energy, and density settings, the application of laser light on human skin induces remodeling of connective tissue in aged and scarred skin and results in tightened skin with a smoother texture.

Early in its development, the application of heat to deep cutaneous layers was thought to trigger dermal remodeling; this notion resulted in an increased usage of ablative (e.g., carbon dioxide [CO_2]) and nonablative (e.g., neodymium:yttrium aluminum garnet [Nd:YAG]) lasers, also referred to as dermal subsurface remodeling, photorejuvenation, or skin toning [2, 65]. In terms of efficacy, ablative skin resurfacing is the best established treatment for the repair of photoaged skin. However, its high frequency of side effects and very long recovery time prevent its frequent usage. Therefore, nonablative resurfacing (subsurfacing) has come to be a widely used technology that is especially appealing to patients who are either unwilling or unable to submit to prolonged recovery times or increased side effects and risks related to ablative

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_24, © Springer-Verlag Berlin Heidelberg 2011

approaches. However, the efficacy of subsurfacing has never reached that of the ablative techniques.

Nonablative fractional photothermolysis is a novel approach to treat photodamaged skin by subdividing the laser beam into many microscopic laser beams or scanning a single microbeam, creating microscopic columns of thermal injury (microscopic treatment zones [MTZs]; Fig. 24.1) within the dermal tissue. This technique reduces side effects such as infection, erythema, scarring, and hypopigmentation of the treated area [52]. Because the MTZs are surrounded by vital tissue, epidermal and dermal remodeling is stimulated over time. This has the advantage of allowing keratinocytes, stem cells, melanocytes, inflammatory cells, and their respective molecular signaling capacities to remain intact. Moreover, this results in both rapid re-epithelialization of the epidermis and dermal remodeling at depths of up to 1 mm [41]. Later, the concept of fractional laser intervention was also implemented with ablative CO_2 and erbium:YAG lasers [12, 32].

Though the nonablative laser systems apply heat in deeper tissue layers without influencing the integrity of the epidermal barrier (subsurfacing, i.e., treatment of the superficial dermal parts or papillary dermis), ablative systems induce a classic wound-healing process by removing epidermal and dermal tissue parts. This removal is accompanied by local inflammation reactions and therefore creates a more distinct clinical effect [23, 61]. All fractional approaches have in common a reduction of 5–20% in treated surface area compared to traditional methods (Fig. 24.2).

From a historical point of view, fractional photothermolysis was first used to treat vascular malformations uniformly with argon laser energy. At this time, single spots 2 mm in diameter were arranged in a linear fashion, leaving alternately 2- or 3-mm-wide untreated bands, from which the skin healed by controlled scar formation. The technique was executed using either a manual technique or a scanner [56].

Very often, spot sizes of less than 1 mm are also used and are known as microfractional photothermolysis. It

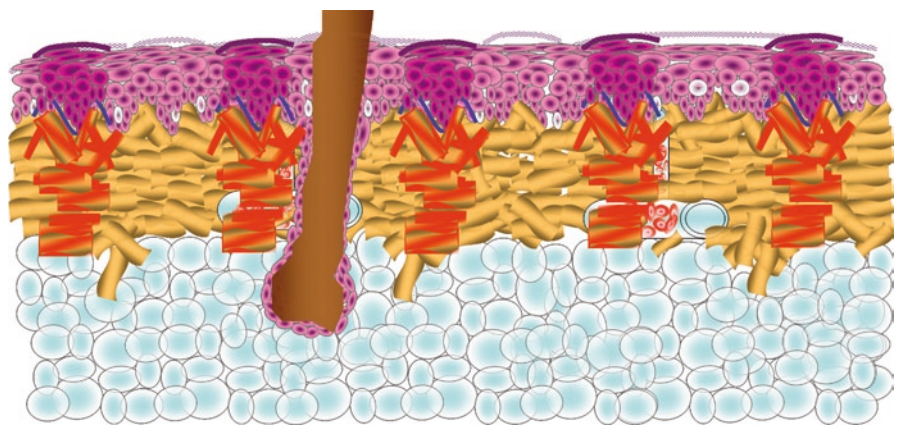

Fig. 24.1 Scheme of fractional nonablative effects on skin. Microscopic treatment zones are applied, leaving intact healthy skin in between as a source of rapid healing, minimal downtime, and high efficacy in dermal remodeling

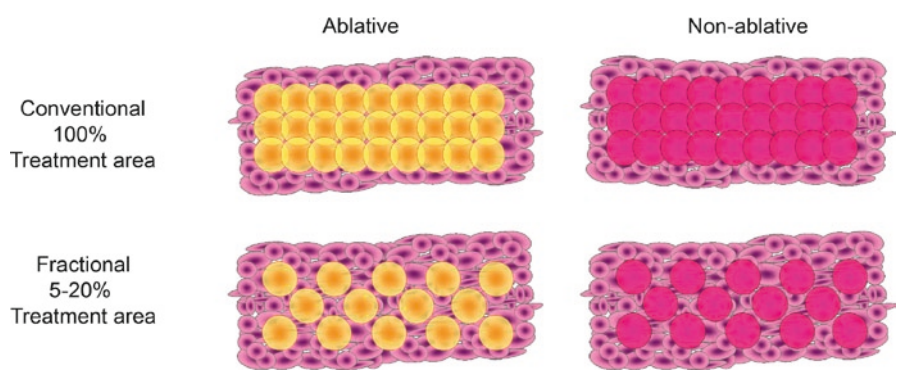

Fig. 24.2 Comparison of traditional and fractional approaches with nonablative (*right*) and ablative (*left*) lasers. With fractional lasers only 5–20% of the surface area is treated. The nonablative approach leaves the epidermal layer almost unaffected, and it serves as a natural dressing

has proven to be efficient for the treatment of wrinkles, melanocytic pigmentation, melasma [63], and acne scars, as well as for wrinkled and otherwise photodamaged skin [35, 58, 76].

The first microfractional skin rejuvenation system was based on a 1550-nm glass fiber laser that was introduced in 2003 (Fraxel, Reliant Technologies, Mountain View, Calif. USA). This laser system uses computerized scanned arrays of microscopic spots, which induce fixed patterns of microthermal zones in the skin tissue. The density of these microspots can be selected to be either 125 or 250 MTZ/cm^2. Due to an overlapping and multiple pass technique, the treated areas can receive 1,500–2,500 MTZ/cm^2 in total. The energy used typically varies between 6 and 12 mJ per microspot. The spot sizes of 50–70 mm result in MTZs of about 70–100 mm in diameter due to lateral heat conduction in the tissue. The damage extends to a depth of about 250–750 μm, depending on the amount of energy per pulse. Time, these systems have been further developed over time and now provide different settings to allow the physician to treat between 5% and 45% of the skin surface area [6, 41, 58, 76].

The so-called stamping technique is used in other systems, in which hundreds of MTZ/cm^2 are delivered in a single shot. The treatment area of skin reaches square areas of 10–15 mm^2, whereas the maximum energy delivered per MTZ is 70 mJ. The pulse duration ranges between 5 and 10 ms, and the procedure results in a damage depth of up to 1 mm. Due to the relatively low absorption of the 1,540- and 1,550-nm wavelengths, damage to the stratum corneum is reduced; however, cooling is still advised.

24.1.1 Basic Biological Concepts in Nonablative Fractional Laser Effects on Skin

Skin is composed of a variety of biological compartments and functions that inherit typical changes in structure, function, and appearance with age. Though the superficial epidermal layers keep their functional competence [69], collagen fibers appear thickened, fragmented, and bluish colored in standard histology workups if photo or ultraviolet (UV) damage is present (Fig. 24.3). Proteins in the photoaged skin are more compact and demonstrate limited interaction with water relative to younger skin [27]. There is a shift from collagen type III to collagen I when levels are compared in UV-protected and young skin. This shift leads to a loose woven network of fibers and precludes effective stretching [48]. Elastic fibers also show structural and functional abnormalities and tend to accumulate as solar elastotic material in the upper dermis (Fig. 24.4), contributing to wrinkle formation [48]. Along with these changes, nonfibrous parts of the dermis show tremendous alterations. First, hyaluronic acid and other proteoglycans are degraded [4], leading to impaired water-binding capacity and therefore an

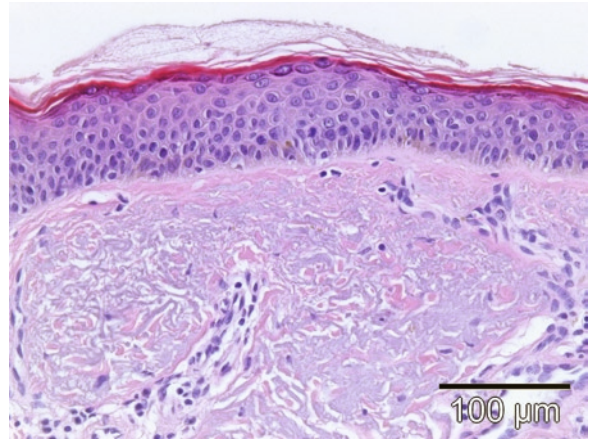

Fig. 24.3 Photoaged skin is characterized by a flattening of rete ridges, dyspigmentation, wide vessels, and collagen fibers that appear thickened, fragmented, and *bluish colored*

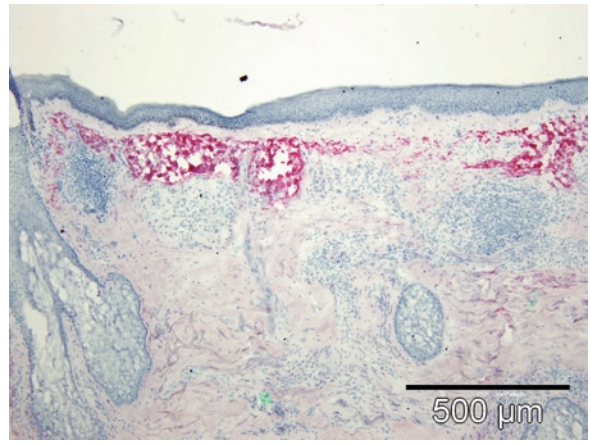

Fig. 24.4 Clumped aggregates of elastic fibers (*red*) typically found in chronically sun-damaged skin (antielastin 1:100)

increased presence of nonprotein-bound water [10, 27]. Clinically, all of these changes manifest as dry, wrinkly, and fragile skin. The extent of wrinkle formation correlates with damage as well as age and, therefore, judging age as an expression of photodamage by the unarmed eye is very subjective. Recently, systems have become available to quantify those conditions. This so-called profilometry is now increasingly used to evaluate the degree of wrinkle formation [1]. Other clinical features of aging skin that are relevant for photorejuvenation are mottled pigmentation, telangiectasia, irregular and coarse texture, and increased pore size. The ideal laser system would provide help with all of these changes.

Fractional, nonablative, mid-infrared lasers are capable of producing light in wavelengths that are absorbed by water. Precise focusing of the laser beam ensures that thermal damage is spatially confined, with surrounding tissues unaffected [41]. With increasing absorption by water, however, the penetration depth sinks. Typically, penetration rates of 300–450 μm are achieved with 1,320–1,450 nm [34]. Furthermore, a significant scattering of light occurs, resulting in energy being deposited outside of the actual laser beam. This scattering leads to the spread of heating within the untreated tissue areas and may therefore contribute to unwanted bulk heating. Nevertheless, an increase in pulse energy leads to increases in the depth and width of MTZs without compromising the viability of interlesional tissue in vivo and in explant models, provided that the density of the MTZ is low enough [7]. Using this approach, researchers found no destruction of sebaceous glands or secondary functional impairment of other skin function when using a 1,450-nm diode laser [45].

The typical clinical effects comprise urticaria, erythema, and slight edema, all of which resolve within 1 day. Histological immediate changes include thermal damage to the deeper epidermal layers, a subepidermal clefting, and a column-like coagulation of the dermal compartment. Vessels of the superior plexus appear to coagulate as well (Fig. 24.5).

It is believed that the keratinocytes are the first product of heat shock proteins, marking the beginning of remodeling; a new epidermal compartment begins to emerge within 24 h at the basal cell layer. This occurs in line with strong upregulation of heat shock protein 70 within the epidermal compartment and is continuous until an entirely new epidermal compartment is built within 7 days [46]. The remodeling of the dermal compartment is accompanied by the active expulsion of microscopic epidermal necrotic debris, known as MEND,

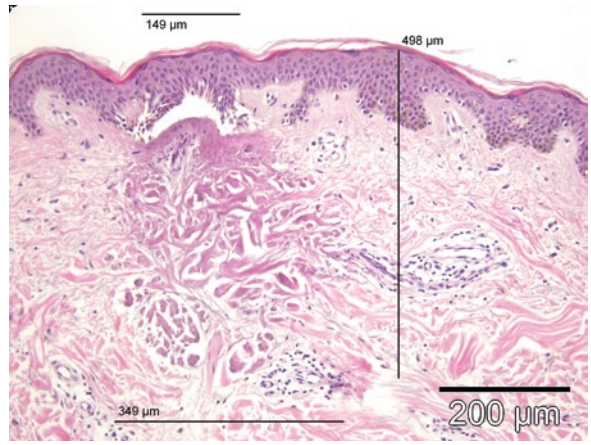

Fig. 24.5 Histology of human skin after nonablative fractional laser intervention (Lutronic Mosaic, 100 mJ, 100 MAZ, Modus Static & Thermal, H & E, ×20) displaying an intact epidermal layer, subepidermal clefting, and a triangular-shaped column of coagulated dermal tissue and vessels

to the skin's surface [46]. MEND appears in suprabasal layers as early as 24 h after treatment. This process of skin repair is clinically accompanied by flaking and bronzing [16]. The extent to which MEND truly simulates reactive perforating dermatoses is not fully understood [77]. In perivascular fashion, a predominant lymphocytic infiltration marks a slight inflammatory reaction. Up to day five, MENDs move upward and are found in subcorneal positions. The clefts at the epidermal-dermal interface can be tracked for several days in vivo by confocal microscopy. The consequences of this process are believed to be twofold: (1) dermal conditions are approached by epidermal wounding, and (2) the remaining intact tissue allows rapid healing without the presence of multiple adnexal structures [72].

Therefore, it was proposed that even areas that are poor in adnexae could be treated safely. It has been shown that the system is safe in the resurfacing textural aspects of the photoaging, e.g., at the hand [39]. However, an increased rate of side effects is a commonly observed problem in sites other than the face. This can be attributed to several factors, such as reduced hair follicle density, reduced vascularization, and, consequently, bulk heating [33]. On top of this, it is known that facial pore size, the epidermal architecture around facial pores, and the interfollicular epidermis differ between ethnic groups; therefore, adjusted treatment protocols are needed [68].

If heating is sufficient, dermal collagen denaturation (or coagulation) results (Fig. 24.6). During this process,

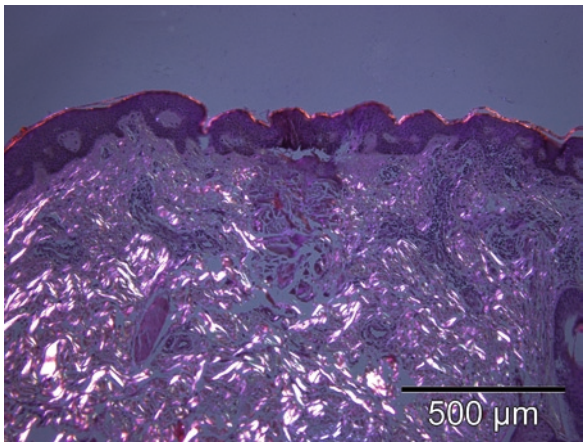

Fig. 24.6 Histology of human skin after nonablative fractional laser intervention (Lutronic Mosaic, 100 mJ, 100 MAZ, Modus Static & Thermal, polarization of H & E, ×20) displaying an intact epidermal layer, subepidermal clefting, and a triangular-shaped column of coagulated dermal tissue surrounded by vital fibers marked in *white*

the right-handed helical structure of the collagen triple helix assumes a random-coil configuration due to the rupture of hydrogen bonds, leading to a shortening and thickening of collagen fibers [49]. Denaturation of collagen triggers a typical wound-healing process. To what extent lymphocytes and macrophages are attracted depends on the energy level applied. This is accompanied by the release of matrix-metallo-proteinases and collagenases, which precede the proliferation of fibroblasts and collagen formation [61]. The increased presence of myofibroblast and collagen III has been demonstrated within 1 week [46]. It seems to be subject to a threshold effect, where increased collagen production is found only beyond laser fluences of 12 J using a 1,450-nm diode laser [60].

With increasing wavelengths, the absorption of laser energy within the melanin decreases. Although throughout the spectrum of the mid-infrared laser absorption is low, appropriate system settings and most importantly effective skin cooling techniques need to be applied in patients with darker skin types.

24.1.2 Patient Selection and Pretreatment Care

The goal of photorejuvenation is an overall improvement of the effects of skin changes related to aging. To begin, proper patient selection is critical. The patient to be selected is ideally aged between the mid thirties and the fifties. Mild to moderate photodamage or rhytids constitute reliable conditions for treatment.

A history of excessive or keloidal scarring, intake of retinoic acids during the past 6 months, active skin disease in the treatment area, or any photosensitivity should lead to exclusion from treatment.

A special treatment regimen is advised if a higher risk of postinflammatory hyperpigmentation cannot be excluded, especially in individuals with darker skin types [58]. Ideally, hydroquinone 4% and tretinoin should be administered 4–6 weeks before a planned laser intervention [16]. Any retinoic acid needs to be discontinued 2 weeks before intervention and can be resumed after treatment has been completed.

In the case of a history of herpes or "cold sores," aciclovir, valaciclovir, or famciclovir should be begun 24–48 h before laser treatment and continued for 1 week after laser treatment. Some authors advise routine prophylaxis [58].

On the contrary, botulinum toxin (BTX) is not deactivated by the laser energy and may even be injected prior to laser therapy [67]. Ideally, BTX is administered 10–14 days before laser intervention to enable its full effectiveness. A flattened skin surface may help to treat the dermal compartment more uniformly and to provide access to deeper photodamage. Finally, the muscle relaxation properties of the toxin may contribute to uniform dermal remodeling.

High-resolution photographs should be obtained before and after each treatment session to document any improvement. This is important because, with nonablative technologies, subtle improvements may not be discovered by the patient over time but can be evaluated with documentation before and after treatment.

Immediately prior to the laser intervention, all makeup, creams, and other substances need to be removed from the skin surface because they may absorb, scatter, or reflect the photons, causing overheating at the epidermis.

Overall, the procedure is well tolerated by most individuals. Men tolerate it less well than women do, and a lower energy level may need to be used. However, the intervention is not entirely pain free; therefore, based on patients' preferences, topical anesthesia should be offered, such as topical lidocaine cream 4% or an eutectic mixture of local anesthetic (lidocaine and prilocaine) [76]. Others use topical lidocaine 23%/tetracaine 7% first for 45 min to 1 h followed by 30% lidocaine gel

[16]. Pain decreases further with the addition of handheld cooling devices [20]. Epidermal cooling is especially critical for Asian skin [58]. To prevent any adverse effects due to failure of the cooling system, the equipment should be tested regularly and before usage. Eye protection is important to guarantee the safety of the patient and all staff members in proximity to the laser.

Once all the precautions have been taken, the nonablative fractional laser can be used to treat the photoaged skin. To address the specific condition safely, both the anatomic site and the intensity of changes desired should be taken into account.

24.1.2.1 Rhytides

To achieve satisfactory results with deep or dynamic rhytides, ablative lasers are usually necessary. Frequently, a combination of fillers and neurotoxins are used. The use of nonablative lasers for these conditions has provided only modest results [18, 21, 28, 34, 54, 66].

Clinical studies suggest that 4–6 treatments spaced approximately 1–4 weeks apart produce a gradual remodeling of dermal matrix components, firming collagen and elastin [6]. Mean improvement seems to be higher in facial than in nonfacial skin [74]. Perioral wrinkles are the most difficult to treat. They are slow to respond to treatment and may still require skin fillers. Higher energy is usually needed (12–15 mJ/cm^2), and 3–4 passes should be applied. Nevertheless, improvement is less evident than that obtained with deep laser resurfacing [6]. However, researchers' experience, recovery time, side effects, and adverse events are dramatically reduced when compared with the use of a thermoablative nonfractional resurfacing technique.

24.1.2.2 Melasma and Dyschromia

In line with the finding that melanin is present within the MEND [46], the successful treatment of melasma has been reported [63, 71]. Furthermore, the optical clearance is believed to take place via melanophage rupture with consecutive dispersion of melanin within the dermal tissue [32, 70, 71]. In addition, a relative decrease in melanocytes and a reduction in melanin within keratinocytes have been reported [29]. According to physicians, 60% of patients achieved 75–100% clearing, although 30% had less than 25% improvement [63]. Low density and cautious energy settings may be warranted, especially in darker skin types, to avoid postinflammatory hyperpigmentation [72]. Recently, the efficacy of nonablative fractional photothermolysis has been shown for the treatment of postinflammatory hyperpigmentation after CO_2 laser resurfacing [62].

24.1.2.3 Scars

In a special subgroup of patients with photoaged skin, acne scars play an important role in addition to the other changes already discussed. This is especially true in men and lesions on the back [14, 57]. Positive responses have been reported in four out of five patients, with improvements of 50% or more [8, 71, 75, 76]. Similar results have been obtained in Asian skin with enlarged pores [13, 35, 36], although the effect has been attributed mainly to better blending with surrounding skin [17]. Also, laser- or light-induced scars and demarcation lines are possible indications [58], as are hypopigmented scars [26], hypertophic scars [59], burn scars [31], and atrophic scars [3]. For acne scarring, one must be patient and allow time for collagen remodeling in concert with a more aggressive regimen [17, 47, 61]. Because dual treatment with subcision and 1,320-nm Nd:YAG nonablative laser resurfacing has been shown to be superior to subcision alone, this regimen has been integrated into daily routines using fractional nonablative lasers [22]. This should be considered for rolling acne scars in particular [38]. Devices vary in their penetration capacities, and optimal parameters still need to be defined [72].

24.1.2.4 Other Indications

Vascular treatment may be considered as a treatment option since coagulation within vessels takes place even in dermal areas located in between MTZs (Fig. 24.7). Successful fractional photothermolysis of telangiectatic matting has been described in a single case [24]. Its benefit has also been reported in postinflammatory erythema [25]. However, this could not be confirmed by other researchers [75]. Recently, a combined treatment of a 1,540-nm erbium:Glass laser and intense pulsed light at 570–1,200 nm showed superior results in vessel

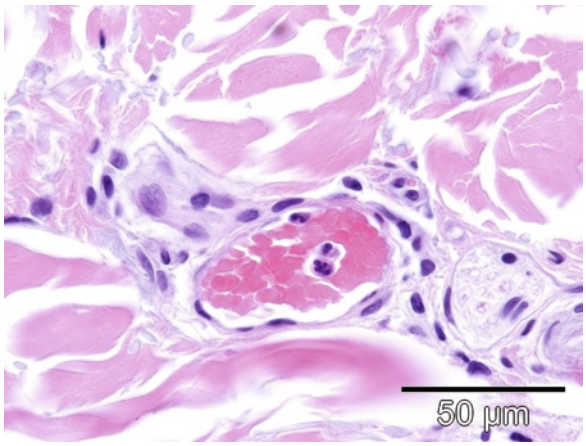

Fig. 24.7 Histology of human skin after Fraxel restore treatment using 70 mJ at treatment level 8 with 6 passes (H&E ×20). Note the coagulation within the vessel, which was located next to the microscopic treatment zone

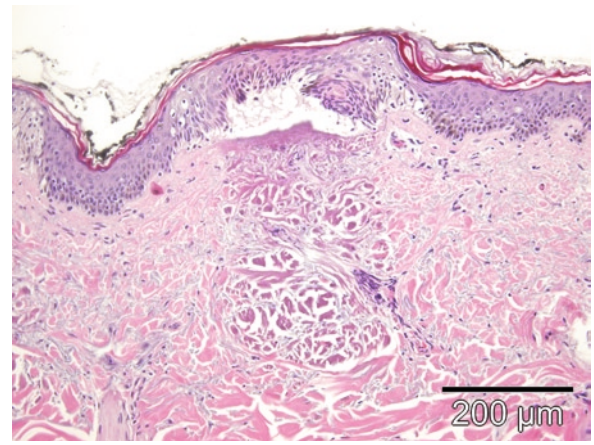

Fig. 24.8 Histology of human skin after Fraxel restore treatment using 70 mJ at treatment level 8 with 6 passes (H&E, ×20). Note the exact penetration of the laser to the depth of sun damage, which is clearly marked by the thicker eosinophil unaffected collagen fibers underneath

treatment [55]. Fractional photothermolysis of residual hemangioma has been successful with minimal patient morbidity [11]. Also, poikiloderma of Civatte that refers to a change in the skin represented by atrophy, dyspigmentation, and telangiectasia has been successfully treated with these methods [9]. Using the 1,450-nm diode laser treatment with 4–12 J/cm^2 of striae distensae was not successful [73]. It might constitute an effective approach if repetitive treatments are considered [42]. However, later case reports showed some effectiveness [72]. Pearly penile papules, a type of angiofibroma, have also been treated with fractional resurfacing [64]. There is one new report of a rapid response of nevus of a Ota in the infraorbital cheek area to two treatments with a 1,440-nm fractionated Nd:YAG laser [44]. Finally, the resolution of blue minocycline pigmentation of the face and of grannuloma anulare has been reported [37, 40].

24.1.3 Systems and Devices

Fractionated mid-infrared lasers are typically used for photorejuvenation, including the 1,320-, 1,410, and 1,440-nm Nd:YAG laser, the 1,450-nm diode laser, and the 1,535-, 1,540-, and 1,550-nm ytterbium:erbium-phosphate glass (also known as erbium:glass or Er:Glass) laser [63]. By choosing the right laser parameters, the laser penetrates to the exact depth of the sun-damaged area (Fig. 24.8). In principle there are systems with stamping modes and those equipped with scanners. Though gaps or Moire artifacts are often seen when the stamping mode is applied, the scanning device produces a randomized treatment pattern with a blended appearance after treatment [33]. The application of multiple passes results in clustering of the lesions (microscopic treatment cluster, [MTC]). The size of MTCs increases linearly as a function of the number of passes. Confluent thermal damage may result in prolonged recovery time and a higher frequency of side effects [53].

The 1,320-nm Nd:YAG laser typically leads to an epidermal heating of 40–50°C accompanied by a temperature elevation within the dermis up to 70°C with a fluence of 12–18 J/cm^2 (17–19 J/cm^2 CoolTouch3, CoolTouch Corp., Roseville, Calif., USA) [76]. Out of a spot size fixed to 10 mm, six stacked pulses performed at a duration of 50 ms. Using three passes has shown greater posttreatment changes on a histologic level than the use of a single pass [19].

A 1,410-nm system (Fraxel re:fine) with variable spot size and a continuous motion scanner enables MTZs of 500 µm in depth [72].

The 1,440-nm Nd:YAG laser (Affirm, Cynosure, Westford, Mass., USA) uses a microarray of lenses and delivers a 10-mm fractional beam [75]. Another system uses a spot size of 15 mm (470 microbeams), with a microbeam density of 320 spots per cm^2.

Though 2.5 pulses per second can be applied, 10 mJ/microbeam can be delivered (Lux1440, Palomar Medical Technologies, Inc., Burlington, Mass., USA).

The 1,450-nm diode laser provides four stacked pulses totaling 210 ms, interspersed with five cryogen applications to ensure cooling. It is equipped with a 4 or 6-mm spot size providing typical fluences ranging from 9 to 14 J/cm^2. The usage of energies above 12 mJ/cm^2 has been reported to lead to an increased production of collagen type III but not collagen type I or elastic fibers (Smoothbeam, Candela, Wayland, Mass, USA) [76]. This lower penetration wavelength is especially suitable for patients with thinner skin (400 μm with 1,320 nm vs. 200 μm with 1,450 nm).

The 1,540-nm Er:Glass laser (Lux1540, Palomar Medical Technologies, Inc.) can be used in a normal or single pulse mode. The pulses are delivered with a frequency of up to 3 Hz. The system is equipped with a 4-mm spot size to apply typical fluences of 8–10 J/cm^2 up to 70 mJ throughout a chilled sapphire window [72].

The 1,550-nm erbium laser (Fraxel, Reliant Technology) was the first device to adopt the concept of fractional photothermolysis [72]. The 1,550-nm Er:Glass laser (Mosaic, Lutronic Corporation, Gyeonggi, Korea) enables a large energy range up to 120 mJ. In addition, the system allows for the application of the laser energy in different modes. The so-called static mode, also known as stamp mode, delivers, with the appropriate tips, light to treatment areas of varying sizes (6×6, 8×8, 5×10, and 10×10 mm). The system has the advantage of using nonlinear, nonsequential microbeam delivery technology (Controlled Chaos Technology). In combination with variable microbeam delivery and a skin sensing feature within the tips, a decrease of the likelihood of postinflammatory hyperpigmentation in darker skin types is advertised [13].

All laser systems require multiple treatment sessions: usually 4–6 sessions administered monthly to achieve long-term improvement in mild to moderate rhytids, skin laxity, thinned epidermis, and other clinical features of photoaged skin of the face [52, 74] or nonfacial areas [65]. It has been reported that there is less impressive efficacy for the treatment of advanced photodamaged skin conditions [23].

The overall efficacy of these devices seems to be comparable if applied to photodamaged skin. The production and deposition of newly formed collagen have been found up to 6 months after treatment [28, 50]. However, this does not necessarily lead to clearly visible clinical effects (Figs. 24.9–24.15).

More recently, a CO_2 Laser equipped with a scanner has been used for nonablative fractional treatments. In this study, a spot density of 8×8 spots/cm^2 (64 MTZ/cm^2) was used. The spot size was set to 500 μm, laser power adjusted to 12 W, and pulse duration set to 3–5 ms (36–60 mJ). On histology slides, the microthermal treatment zone was characterized mainly by absence of ablation and display of very superficial epidermal coagulation immediately after exposure, leading to average increases in skin density of 40.2% without any signs of postinflammatory hyperpigmentation [15].

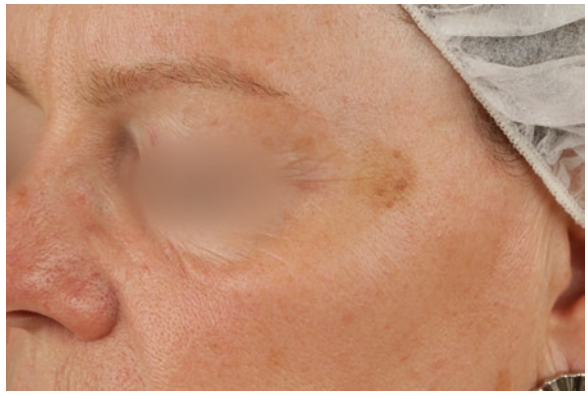

Fig. 24.9 Before the operation; a female patient aged 53 years to be treated on the infraorbital, left side, after application of local anesthetic (an eutectic mixture of local anesthetic [lidocaine and prilocaine]) for 60 min and removal

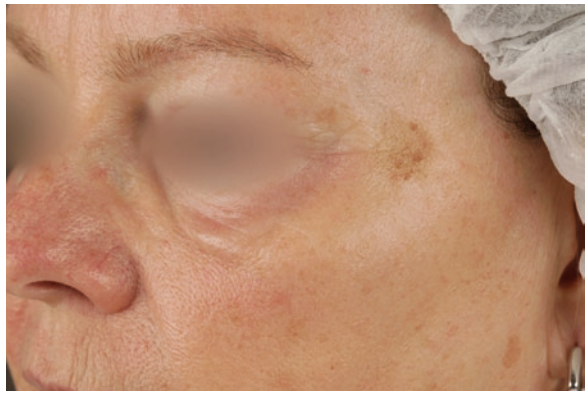

Fig. 24.10 One day after the operation; a female patient aged 53 years, to be treated on the infraorbital, left side using the Mosaic system at dynamic application mode, spot size 10, frequency 150 Hz, energy 15 mJ, until 150 microscopic treatment zone/cm²

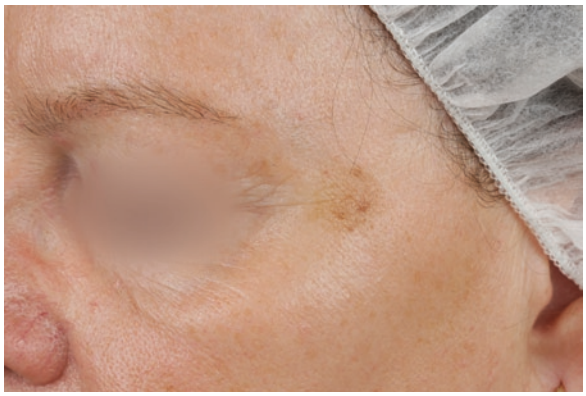

Fig. 24.11 Twelve days after an operation on a female patient aged 53 years who was treated on the infraorbital, left side using the Mosaic system (Lutronic Corporation, Gyeonggi, Korea) at dynamic application mode, spot size 10, frequency 150 Hz, energy 15 mJ , until 150 microscopic treatment zone/cm²

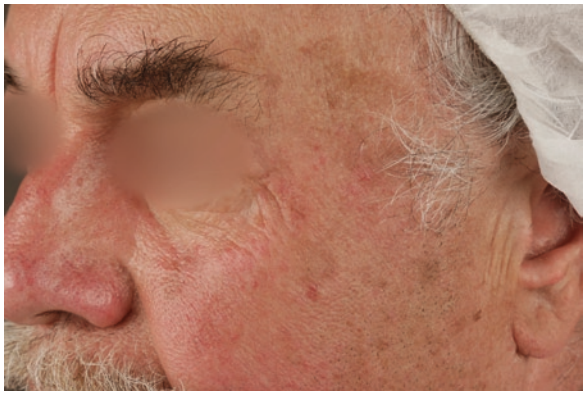

Fig. 24.12 Before the operation on a male patient aged 69 years who is to be treated on the infraorbital, left side, after application of local anesthetic (an eutectic mixture of local anesthetic [lidocaine and prilocaine]) for 60 min and removal

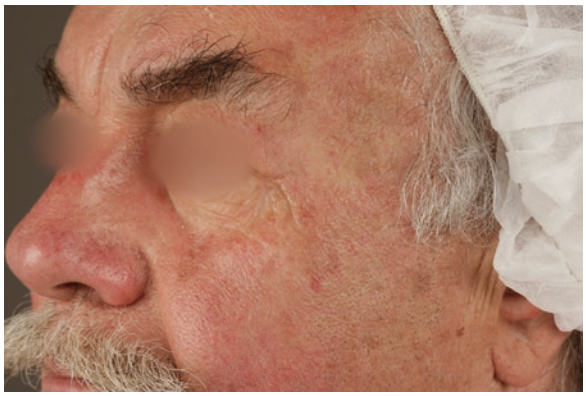

Fig. 24.13 Five minutes after the operation on a male patient aged 69 years who was treated on the infraorbital, left side using the Mosaic system (Lutronic Corporation, Gyeonggi, Korea) at dynamic application mode, spot size 12, frequency 100 Hz, energy 20 mJ, until 300 microscopic treatment zone/cm²

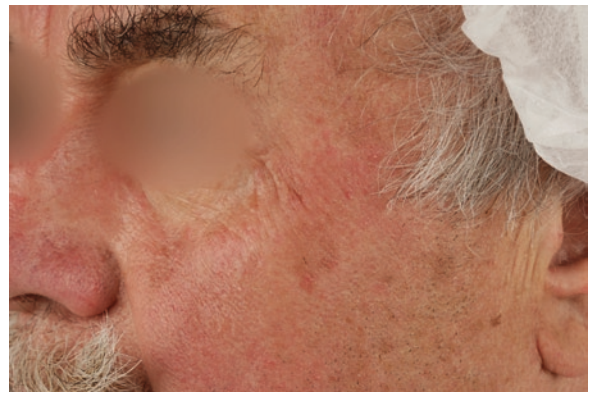

Fig. 24.14 One day after the operation on a male patient aged 69 years who was treated on the infraorbital, left side using the Mosaic system (Lutronic Corporation, Gyeonggi, Korea) at dynamic application mode, spot size 12, frequency 100 Hz, energy 20 mJ, until 300 microscopic treatment zone/cm²

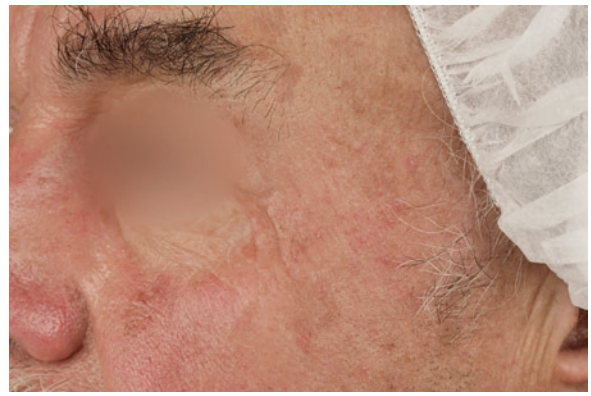

Fig. 24.15 Twenty-three days after the operation on a male patient aged 69 years who was treated on the infraorbital, left side using the Mosaic system (Lutronic Corporation, Gyeonggi, Korea) at dynamic application mode, spot size 12, frequency 100 Hz, energy 20 mJ, until 300 microscopic treatment zone/cm²

24.1.3.1 Postoperative Care, Management of Adverse Effects

The usage of mid-infrared lasers requires the same attention as all other laser interventions. The application of a soothing agar immediately after intervention is highly appreciated by patients. To avoid any dyspigmentation, the use of sunscreen throughout the process as well as 4 weeks before and after is absolutely necessary.

A mild sunburn sensation occurs approximately 1 h after the treatment [16, 70]. Posttreatment care begins with application of a substance such as Cicaplast cream (La Roche-Posay, France) immediately after intervention. This is followed by a standard moisturizer

application on a daily basis up to 1 month thereafter. Bronzing and flaking are usually noted on the third postoperative day. However, the detailed protocol may be modified [15]. In men, 590-nm light-emitting diode treatments may help to reduce erythema and edema, especially when higher settings were used [57].

The most often reported adverse effects include mild transient pain, especially in thinner epidermal regions and over bony prominences, as well as mild erythema and edema or swelling [75]. Superficial scratches (laser nicks), blistering, and crusting can occur, although these are not common [70]. All of these side effects should resolve within 2–5 days. Pain, erythema, and swelling are reported to be significantly more evident or persist longer in Asians when higher densities and fluences have been used [58].

Complications are reported in 7.6% of patients who undergo a large series of treatments; however, they are reported without persistent sequelae [30]. Most frequently acneiform lesions (1.87%) and herpes simplex virus outbreaks (1.77%) occurred. Recently, eruptive keratoacanthomas have been reported after treatment of the legs [51]. Postinflammatory hyperpigmentations are related to darker skin types, whereas all other side effects and complications were equally distributed across patients and laser settings. If postinflammatory hyperpigmentation occurs, the usage of hydroquinone, tretinoin, vitamin C, and sunscreen have been shown to be useful [16].

Petechiae can occur if aggressive treatment has been applied to thin skin, particularly in the periorbital area [5, 58]. Severe but less common side effects include blistering, dyschromia, and scarring. They are most often related to prolonged cooling or excessive fluences. Taken together there is a significantly decreased risk for complications compared to traditional ablative techniques.

Take Home Pearls

- Nonablative fractional laser therapy for photoaged skin using induction of dermal or subsurface remodeling produces mild improvement in skin quality on a variety of skin regions with a relatively short recovery time. This technology is based on a circumscribed dermal heating technique with associated epidermal cooling. In response, MTZs of coagulated dermal tissue are applied without substantial epidermal insults. Remodeling of the dermal compartment is accompanied by active expulsion of MEND to the skin surface [46]. The duration of remodeling mainly depends on the amount of energy applied.
- Therefore, this type of mild dermal remodeling may be employed for improvement of fine wrinkles, skin tone, age spots, blotches, dyschromia, and other features of aging or photodamaged skin on the face, neck, shoulders, hands, and arms. In some patients, coarse, deeper wrinkles may demonstrate considerable improvement. The tightening is particularly evident in the nasolabial folds and glabella. It has found its place in the treatment of acne scars and is often used in combination with subcision, especially in Asians.
- Achieving superior outcomes requires appropriate matching of the patient's expectations with his or her skin type, indication wavelengths, and parameter settings. The highest efficacy levels were found in patients who were treated with high fluences and low density, even in darker skin types [43, 58]. Optimal improvement may take 3–6 months. As a general rule, it is best to set patients' expectations to the minimal results for any given device [76].

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Part III

Special Aspects

Complications in Laser Surgery and IPL Treatment

25

Christian Raulin, Syrus Karsai, and Laurenz Schmitt

Core Messages

- A personal, open, and honest discussion with the patient is essential prior to laser treatment.
- During this consultation, realistic treatment objectives, possible complications, and secondary effects should all be discussed in detail with the patient.
- A careful and comprehensive discussion of the procedure with (photographic) documentation is indispensable for the protection of both patient and physician.
- Selection of the optimal laser or intense pulsed light (IPL) equipment is impossible without accurate diagnosis and patient selection, with due consideration given to the indications.
- Typical sources of error in laser or IPL treatment are selection of the wrong type of equipment and/or settings and inadequate care or lack of practical experience.

Recent years have seen rapid progress in laser technology. It is used with great success in almost all branches of medicine and for myriad indications and will continue to gain in importance in the future for both diagnosis and treatment. With their selectivity and precision, therapeutic lasers are unique tools that allow completely new approaches to treatment [2]. There are currently a number of different laser systems available from various suppliers and in various configurations. However, we must not allow the very promising treatment results to blind us to the knowledge that interventions also involve the risk of complications [11, 12, 16, 29, 34, 38, 47]. Errors can often be avoided when sufficient importance is attached to careful planning and patient information at the beginning of a laser treatment. Typical secondary reactions to laser or intense pulsed light (IPL) therapy must nonetheless be reckoned with; these should not be confused with unwanted complications. One example is the occurrence of a temporary purpura after treatment with the pulsed dye laser.

This chapter gives an overview of the strategies needed to avoid complications in laser surgery and IPL treatment. Only if these are strictly adhered to can the safety of doctor and patient be ensured. Unfortunately, IPL equipment and even lasers increasingly are being used with no supervision by persons with no medical qualifications, especially for photoepilation and tattooing but also in other cosmetic or even medical applications, which emphasizes the problems discussed in this chapter and illustrates how disturbingly necessary it is to discuss this subject. In this context it is no longer possible to refer to patients, only to customers. In this way certain ethical boundaries fall when those concerned are knowingly given false information, e.g., by franchise holders, and they have treatments thrust upon them, in some cases without their knowledge. Tempting advertising suggests false ideas of the objectives and suppresses any mention of side effects. Given this situation, there is no way that treatment errors could fail to be increasing dramatically in frequency.

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_25, © Springer-Verlag Berlin Heidelberg 2011

25.1 Training

Inadequate training and lack of experience are two of the most frequent factors in any treatment error. At present most European countries have no uniform directives for the application of laser or IPL systems. In the guidelines of the specialist dermatology societies (Deutsche Dermatologische Lasergesellschaft; www.ddl.de) or the international university postgraduate course of study at the University of Greifswald (Diploma in Aesthetic Laser Medicine [DALM]), the basic principle is that only fully qualified doctors with appropriate specialist training are allowed to use a therapeutic laser system. This is now especially important because in recent years there have been more and more reports of laser treatments administered by personnel with no medical qualifications at all [7, 17]. Safe treatments depend on a detailed preoperative consultation, thorough examination, and stringent patient selection. In our opinion, non-physicians do not normally possess the skills required to achieve all these (Fig. 25.1). Specialist medical knowledge in combination with knowledge of laser surgery can limit the complication rate. Once it has been decided that the treatment is indicated for a particular patient, it should be administered either by the specialist doctor personally or at least under his or her supervision, and any intervention that is immediately necessary must be possible at any time.

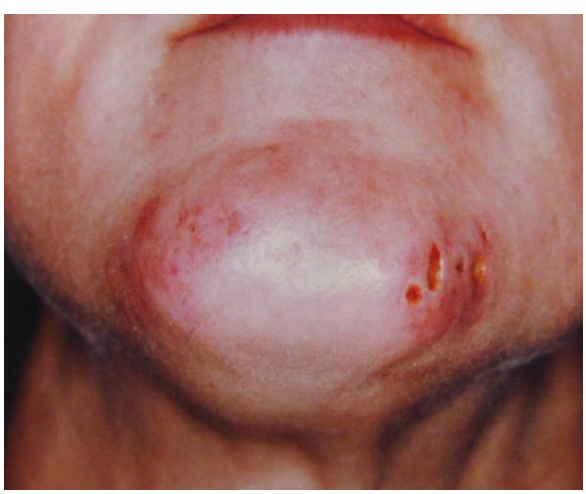

Fig. 25.1 Burns and scars after photoepilation with intense pulsed light technology in a cosmetic salon. Possible sources of error include too-high energy density, or wrong cut-off filter, wrong wound treatment (courtesy of Dr. W. Kimmig, Hamburg)

In addition, the specialists responsible must have appropriate documentation of their qualification. A certificate of training on equipment supplied directly from the manufacturer is also acceptable. Ideally, practitioners should supplement their medical training with a preset training syllabus that is worked through in approved and qualified centres and follows a standardised logbook. The content should be presented and worked through in a comprehensible form complying with the guidelines, and the possibilities, hazards and limitations of particular laser methods must be discussed in detail during the training. An oral or written test at the end of each course module could check what has been learned and then also be used as documentation of a specialist qualification. Knowledge of postoperative treatments should also be a firm component of such a course to ensure that the graduates will be able to give the optimal care for any impaired wound healing after a laser treatment and ultimately to achieve the best possible outcome for the patient [1, 8, 12, 14–16, 44, 45]. The new DALM course at the University of Greifswald is an excellent example of such a course. The way it is designed means that both theoretical and practical, quality-assured, and documented continuing education in aesthetic laser medicine is required. The basis is a dynamic catalogue of objectives that trainees are obliged to achieve in turn. Lectures, shadowing of established practitioners in approved laser centres and, finally, preparation of a thesis followed by an oral examination round off this demanding training course. At the end a university diploma is awarded. As yet, it is unique in its aims and scope, which are being extended for international use by upgrading to a Master's degree course.

25.2 Detailed Discussion of the Planned Treatment with the Patient

No planned laser or IPL treatment should go ahead until the doctor in charge of the case has given the patient comprehensive and honest information about the treatment, uninfluenced by any financial considerations. This must include a comprehensible description of the illness, the intended therapeutic procedures, the benefits and the risks involved in each, and possible alternative methods of treatment. If the intervention is not urgently needed or indicated from a medical point

of view, the physician must make a particular point of drawing attention even to very rare hazards the therapy involves. This puts the patient in the position of being able to decide if specific risks involved in the intervention really need to be accepted. This means that it is the consultation between doctor and patient that is at the heart of the patient information – a written consent is nothing more than confirmation of what has been said and what the patient has understood. A consent form signed without a previous consultation may be regarded as invalid in the case of a legal dispute.

The ideal is a sympathetic and detailed discussion of the planned intervention, the diagnosis, extent and course, possible damage that will pass and damage that will persist, the type of anaesthetic procedure, what costs have to be expected, and alternatives to the treatment under scrutiny. Side effects and risks and any undesirable secondary effects that are typical of the intervention are also a part of the information that must be supplied to the patient. One example of this is the occurrence of temporary purpura after treatment with the pulsed dye laser. In this connection the necessity of adequate sun protection until the purpura clears up should be explained to the patient at the same time to lower the risk that hyperpigmentation will result [27]. At the end of this detailed and personalised discussion a consent form is issued, and any additions or changes can be inserted by hand. Ideally, the planned intervention should not take place on the same day as the consultation to give the patient all the information needed in this way it is possible to relieve the patient from the stress of making the decision under time pressure. This will not be possible in every case, for a number of widely varying reasons, so realistic compromises will have to be made in all cases to achieve the best possible result for the patient.

25.3 Documentation

Comprehensive and individual documentation is an essential component of the patient information session. It is designed for the clinical and legal protection of both patient and physician. The documentation includes notes of the patient's name and date of birth; dates of visits to the physician, the patient information consultation, the preoperative diagnosis; the condition for which the intervention is indicated; any test treatments carried out; the type of anaesthetic procedure; laser type; application parameters; the observed treatment outcome at follow-up, including secondary reactions, side effects, and complications, and, if available, histological findings. Especially in the case of cosmetic procedures, photographic documentation urgently is advised to record the initial findings and the treatment outcome. In our experience, this procedure is not only very important for forensic medicine reasons, but it also proves its worth when a patient later questions the success of the treatment.

25.4 Diagnosis

It goes without saying that a correct diagnosis is needed before a planned intervention, and it ensures the use of the laser/IPL best suited to the dermatological alterations. When there is the slightest doubt about the malignancy of a tumour it is essential to perform at least one histological check. This procedure is necessary particularly in the case of precancers and of malignant and pigmented cutaneous lesions [26]. We strongly recommend leaving the treatment of cutaneous pathologies and skin tumours to dermatologists who are experienced in laser therapy to keep the patient's risk of complications as low as possible.

25.5 Indications

If the indications have been determined wrongly or not at all, the best that can be expected is that the therapy just will not be successful. Depending on the severity and course, however, a laser or IPL treatment can also have lasting and irreparable sequelae (Figs. 25.2–25.5). It is, therefore, of decisive importance that two questions be answered before the start of a therapy:

1. In the case of the existing cutaneous alterations, is use of the laser or IPL actually indicated? If so,
2. What equipment is indicated for the condition diagnosed?

Influential factors in the decision are skin type and localisation of the lesion to be treated. In the case of tanned patients with skin types III to VI (Fitzpatrick), for example, treatment with pigment-specific lasers,

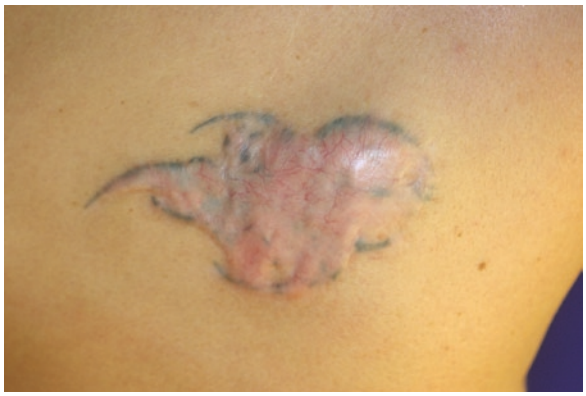

Fig. 25.2 Keloid formation after treatment with an "infrared coagulator." Sources of error include too-high energy density and/or too many passes and the inappropriate type of equipment

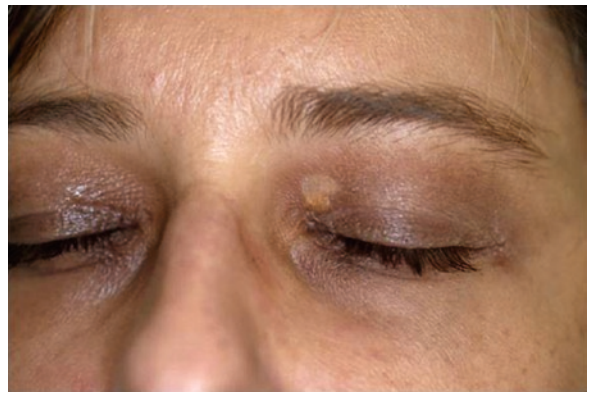

Fig. 25.5 Hypopigmentation after removal of xanthelasma with the carbon dioxide laser. Sources of error include ablation too deep, skin type too dark as a result of the concurrent rings under the patient's eyes

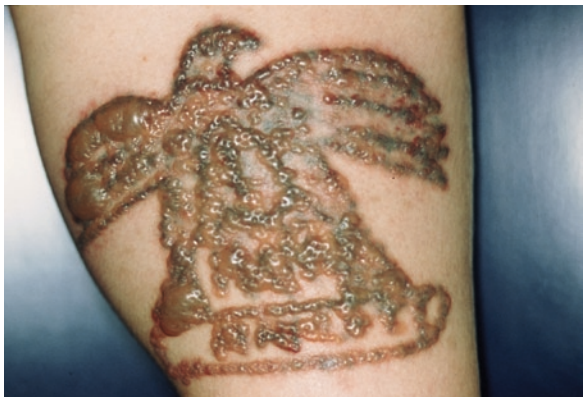

Fig. 25.3 Development of small blisters after treatment of a tattoo with a ruby laser. These healed without scarring in a later course. Source of error was a too-high energy density [37]

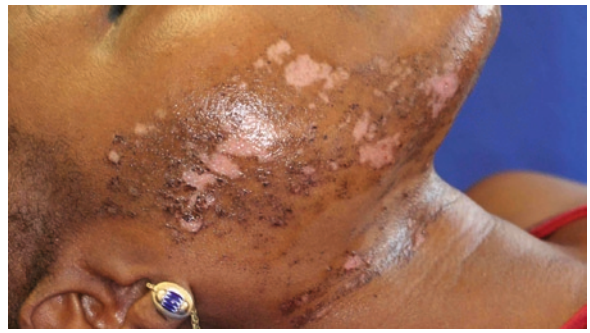

Fig. 25.6 Burns after photoepilation with intense pulsed light technology administered by non-medically qualified personnel. Sources of error include skin type too dark and wrong equipment

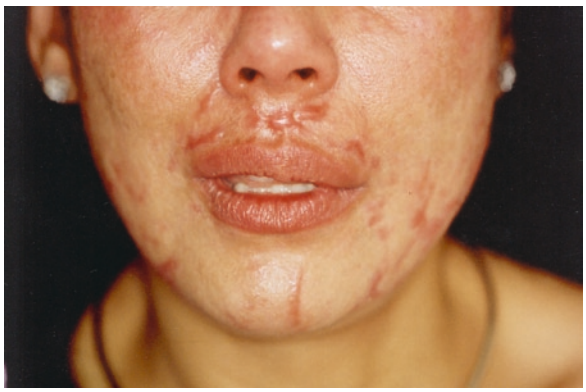

Fig. 25.4 Keloids 7 months after melasma treatment with the carbon dioxide laser. Sources of error include: wrong laser type, too-high energy density, and/or too many laser passes

such as the alexandrite and ruby lasers, and IPL systems can only be applied for the treatment with extreme caution or not at all [7, 24, 27, 28, 32, 45, 46] (Figs. 25.6–25.8). Before the use of a pigment- or vessel-specific laser nothing but a white marker must be used to avoid absorption of the laser irradiation and resultant burning and scarring (on this subject, the reader is also referred to the section about cooling systems). For sensitive areas of skin, e.g., the neck or the skin surrounding the eyes, thermal lasers such as the CO_2 laser should be used only with appropriate caution or in fractionated mode [20, 23] (Fig. 25.9). Of late, however, and particularly in the case of fractionated CO_2 lasers, there have been increasingly frequent reports of complications; this treatment should also be administered exclusively by qualified doctors of medicine who are also experienced in the

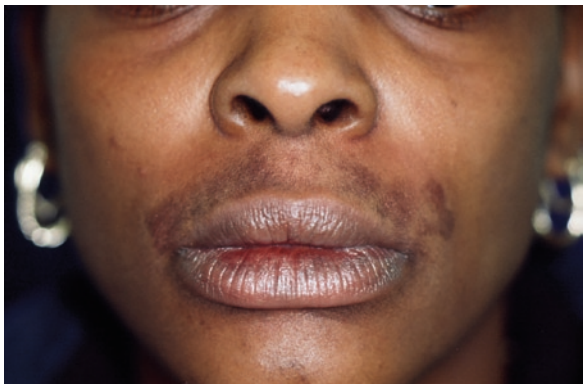

Fig. 25.7 Hyperpigmented areas after photoepilation with the long-pulse alexandrite laser. Sources of error include too-high energy density with a too-dark skin type and wrong laser [37]

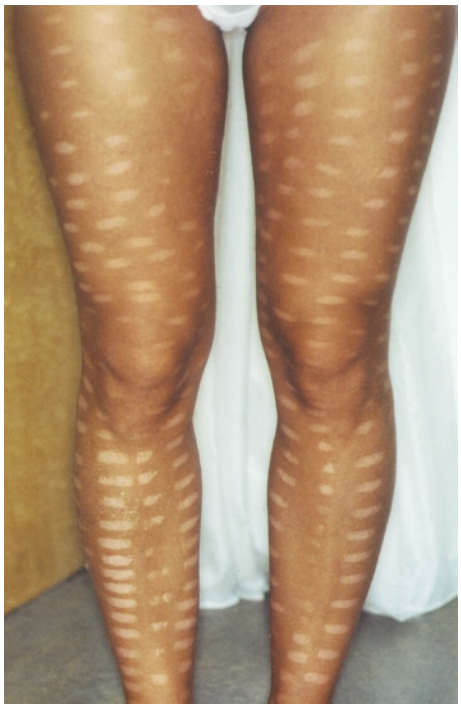

Fig. 25.8 Areas of lasting hypopigmentation after photoepilation of the legs by non-medically qualified personnel using intense pulsed light technology. Sources of error include skin type too dark, too-high energy density, and wrong cut-off filter (courtesy of Dr. W. Kimmig, Hamburg)

therapeutic application of lasers [5, 9]. Because of the impossibility of performing histological investigations and the still unknown long-term effects with the danger of the formation of a pseudomelanoma, dysplastic naevi are an absolute contraindication for laser treatment (Figs. 25.10–25.12).

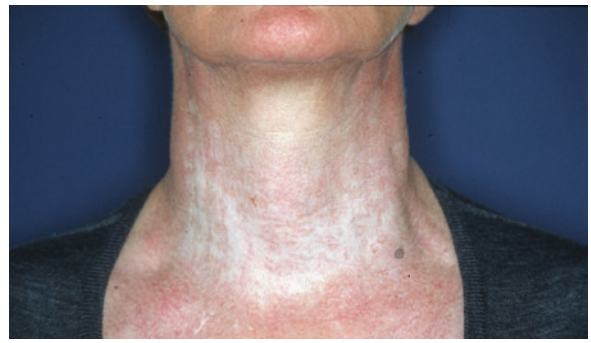

Fig. 25.9 Scars after skin resurfacing on the neck with the pulsed carbon dioxide laser. Sources of error include incorrect localisation, too-high energy density, and/or too many passes (courtesy of Dr. W. Kimmig, Hamburg)

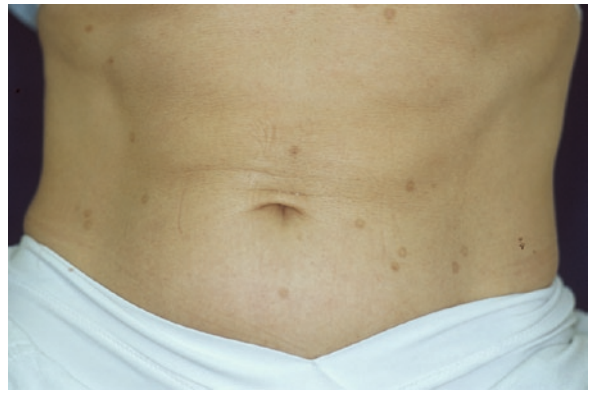

Fig. 25.10 Areas of long-lasting hyperpigmentation after treatment of multiple lentigines with the ruby laser. Sources of error include no test treatment performed and inadequate information supplied to patient

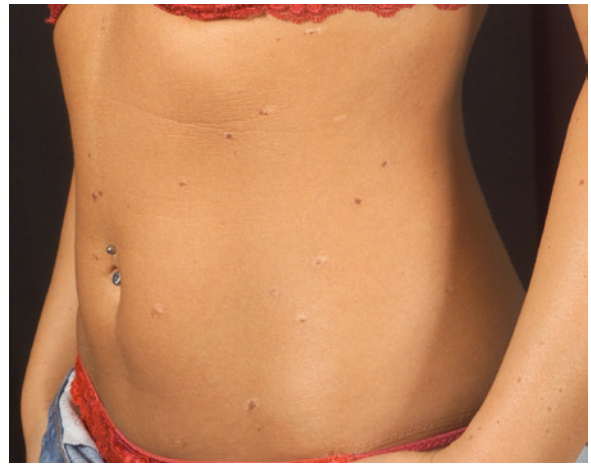

Fig. 25.11 Areas of hypopigmentation and recurrences after attempted removal of multiple naevus cell naevi with the ruby laser. Naevus cell naevi are not an indication for this treatment (courtesy of Dr. W. Kimmig, Hamburg)

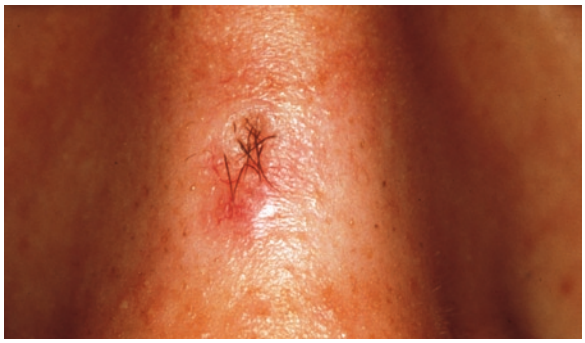

Fig. 25.12 Atrophic scar and recurrence of a hairy, papillomatous dermal naevus after treatment with the carbon dioxide laser. Sources of error include wrong information supplied to patient and a too-high energy density. No photoepilation was carried out when the naevus was treated (courtesy of Dr. W. Kimmig, Hamburg)

25.6 Test Treatments

Test treatments are carried out as a matter of policy, especially in the case of extensive lesions, exposed skin areas, or doubts about whether the treatment will be successful. They make it possible to evaluate the result, secondary reactions, and side effects, thus enhancing the protection of doctor and patient. Errors in treatment and resulting claims of recourse thus can be kept within bounds. An example of this is the so-called "ink darkening" when permanent make-up is removed [3], which is attributable mainly to the ingredients of the tattoo ink, such as ferrous oxide (Fig. 25.13). There has also been a report of chrysiasis occurring after a patient had taken gold preparations and subsequently been treated with the ruby laser (Fig. 25.14). In a case of this kind Q-switched laser therapy should be avoided and treatment in a long-pulsed mode used in preference. It is assumed that the lower irradiance (power delivered per unit area, W/cm²) in this mode makes it possible both to prevent the occurrence of chrysiasis and to treat chrysiasis successfully. If chrysiasis does occur, Q-switched versions of alexandrite, ruby, neodymium:yttrium aluminum garnet (Nd:YAG), frequency-doubled Nd:YAG, and short-pulsed 510-nm dye lasers, as well as the quasi-continuous potassium titanyl phosphate laser and xenon chloride excimer lasers should be avoided during the further course of the treatment [48].

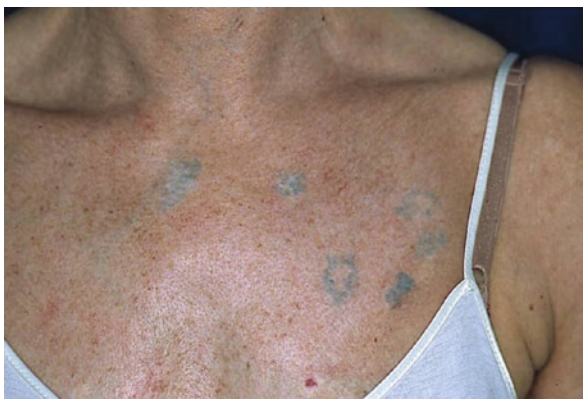

Fig. 25.13 Lentigines on chest and neck, originally overtattooed with light-coloured ink by a cosmetic therapist. Change of colour after treatment with the ruby laser. It proved possible to remove these changes completely during further treatment sessions. No information was supplied to the patient about the occurrence of so-called "ink darkening" [37]

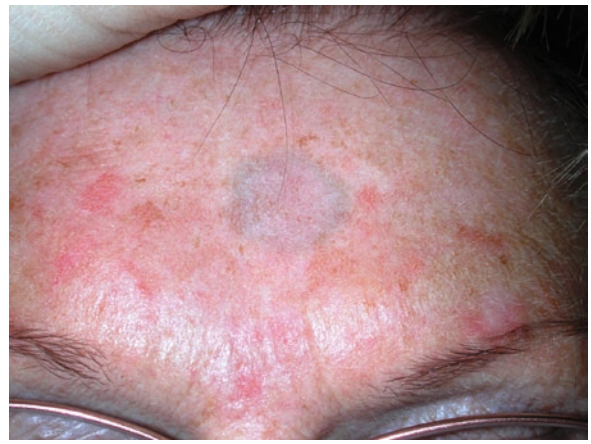

Fig. 25.14 Chrysiasis after laser treatment of a benign lentigo with a ruby laser in Q-switched mode; the patient had taken gold preparations to treat rheumatoid arthritis 16 years earlier. Q-switched mode should not have been used for this treatment (courtesy of Dr. Grimme and Dr. Tesmann, Stuttgart)

25.7 Practical Considerations

Technical sources of error in laser treatment are bound up with:

- Selection of the type of equipment
- Setting of the variable technical parameters
- Practical application of the equipment

Avoidable complications can arise because too many laser passes have been made one after the other or the impulse density is set too high. This leads to uncontrolled accumulation of the heat absorption. Use of ablative lasers such as CO_2 and erbium:yttrium aluminum garnet (Er:YAG) lasers can lead to irreparable

scarring and keloid formation or to permanent dyspigmentation [32–35, 39] (Figs. 25.15–25.21). Even when the nonablative pulsed dye laser is used, lasting pigment shifts can be caused if the energy density selected is too high [42]. Impulses selected too close together can have undesired reactions such as scarring, whereas when the impulses are too wide

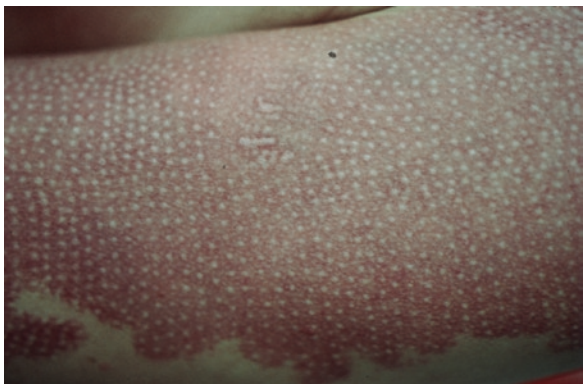

Fig. 25.15 Multiple scars after treatment of a port wine stain with an argon laser. Sources of error include too-high energy density and incorrect laser type; this condition is a contraindication

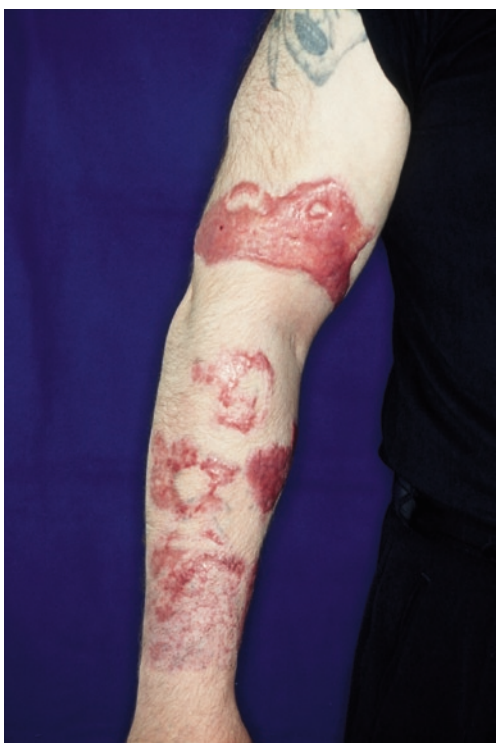

Fig. 25.16 Keloids after treatment of tattoos with ablative lasers (erbium:yttrium aluminum garnet and carbon dioxide). Source of error was the use of the incorrect type of laser [37]

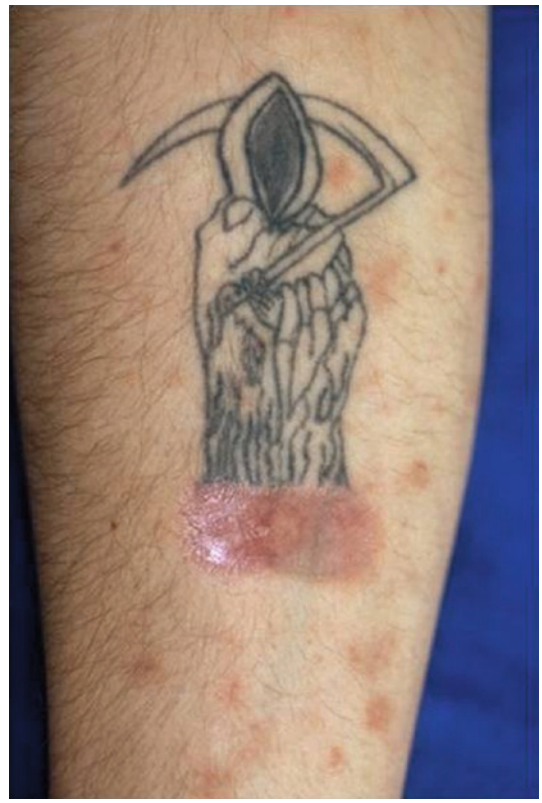

Fig. 25.17 Keloids after treatment of tattoos with an ablative laser (carbon dioxide). Source of error was use of the wrong laser type [37]

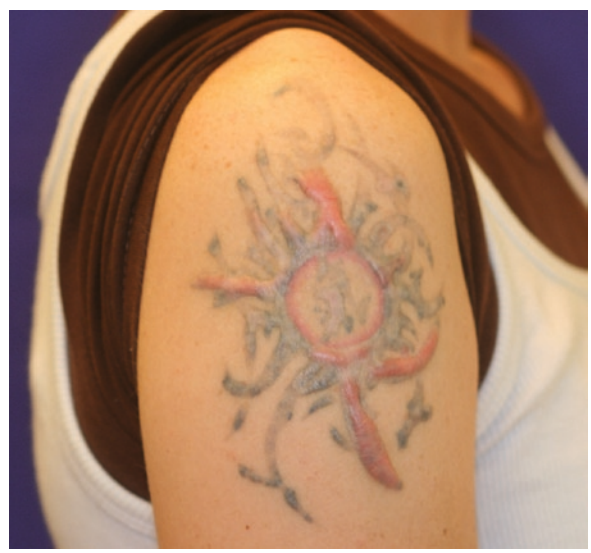

Fig. 25.18 Scarring after treatment of a tattoo on the upper arm with ablative lasers (erbium:yttrium aluminum garnet and carbon dioxide). Source of error was use of the incorrect laser type [37]

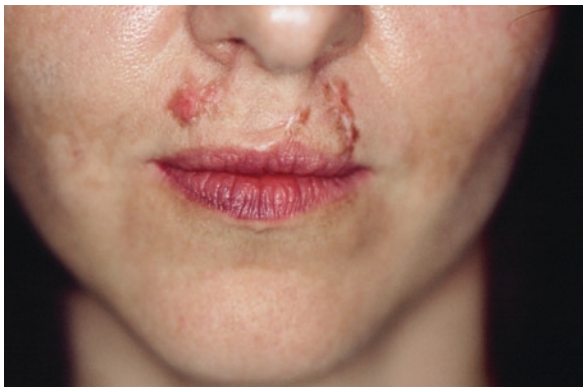

Fig. 25.19 Keloid on the upper lip after photoepilation with a diode laser without surface cooling. Sources of error include too-high energy density and lack of cutaneous cooling [37]

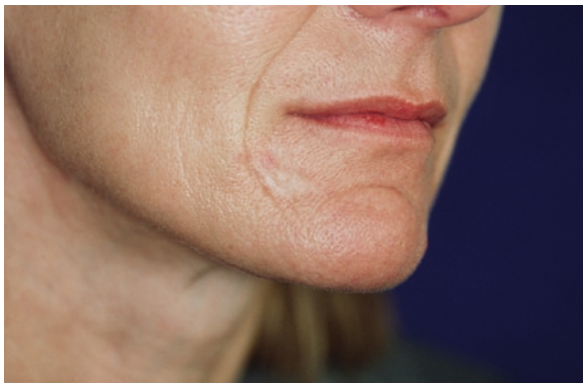

Fig. 25.20 Scarring after attempted reduction of facial wrinkles with the erbium:yttrium aluminum garnet laser. Sources of error was that this treatment is not indicated for facial wrinkles and incorrect localisation [37]

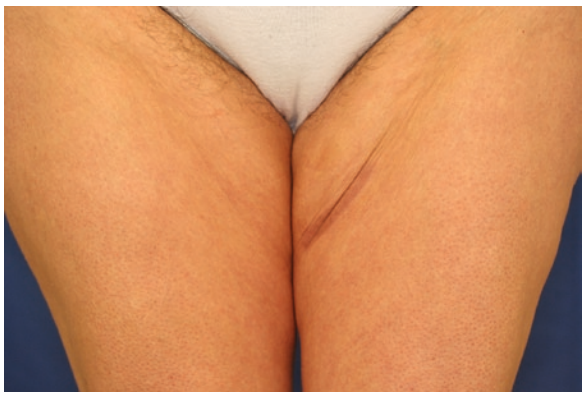

Fig. 25.21 Hyperpigmentation on the inner aspect of the left thigh after carbon dioxide laser treatment of lax skin (4 months after treatment). Source of error was an incorrect indication

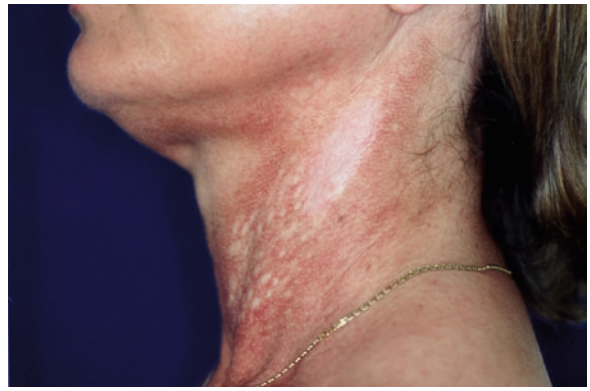

Fig. 25.22 Areas of hypopigmentation persisting 3 years after treatment of a poikiloderma of Civatte with a pulsed dye laser. Source of error was a too-high energy density with unsuitable (too dark/tanned) skin type. Subsequent attempt to match colour with the pulsed carbon dioxide laser. Source of error here was use of the incorrect laser type [37]

apart this leads to some zones remaining untreated. During the treatment, then, it is necessary to take care that the interval and overlap of the laser or IPL system is optimal (Figs. 25.22 and 25.23).

In the removal of tattoos, too-high impulse densities or an inadequate number of passes involves the risk of blistering and incrustation, which in turn cause a predisposition to wound infection or the development of hypopigmented scars [19, 22, 31]. There is a hidden risk in tattoo removal: there have been repeated reports of allergic reactions specifically after laser treatment for this purpose [4, 21, 49]. It is suspected

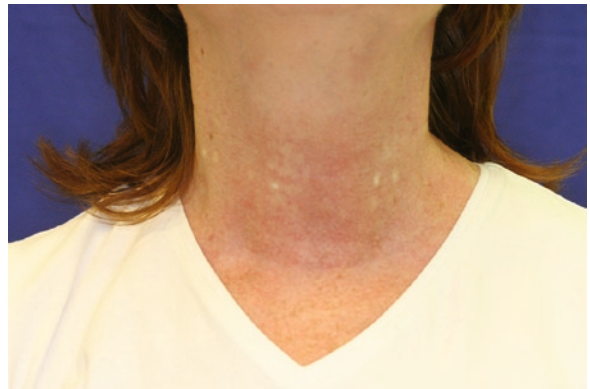

Fig. 25.23 Areas of persisting hypopigmentation after treatment of a poikiloderma of Civatte with a pulsed dye laser. Sources of error were too-high energy density and the patient was too tanned

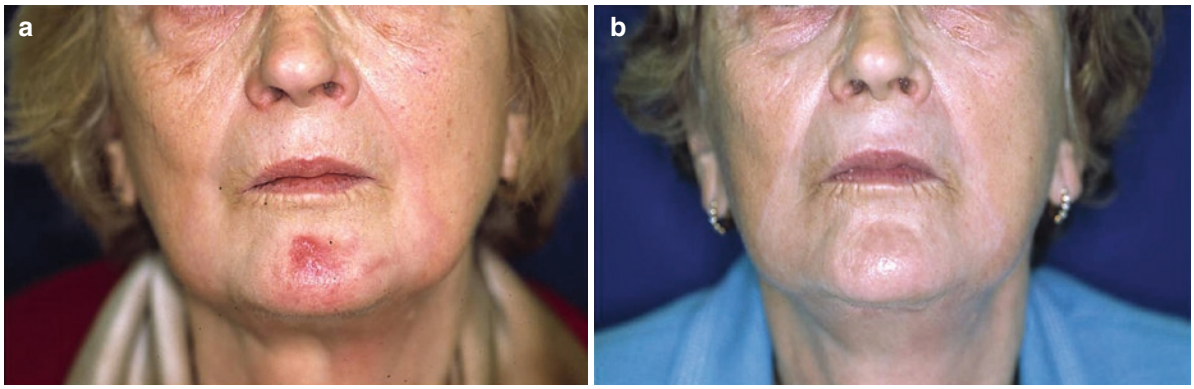

Fig. 25.24 (**a**) Hypertrophic scarring on chin and areas of hypopigmentation after skin resurfacing with a carbondioxide laser (alabaster skin, milk-white mouth). Sources of error were a too-high energy density and/or too many passes. (**b**) Condition after three treatments with the pulsed dye laser. Overall, a definite improvement of the hypertrophied scarring on the chin [37]

that this is because the antigenicity of the tattoo pigment is changed after the treatment. Local reactions in these circumstances can be treated with topical corticoid preparations. The use of topical antibiotics and local anaesthetics should be avoided as much as possible, however, because they themselves have some allergenic potential [10, 30]. The treatment of systemic reactions is very difficult.

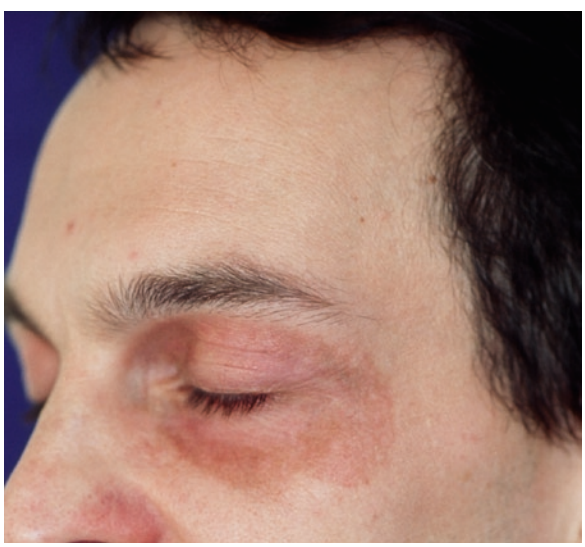

Fig. 25.25 Postinflammatory hyperpigmentation 6 weeks after skin resurfacing of periocular wrinkles with the ultrapulsed carbon dioxide laser. Sources of error include failure to match skin resurfacing to the surrounding skin and possible a too-high energy density and/or too many passes [37]

In the practical application of the treatment for skin resurfacing it is necessary to approximate the treated areas to the untreated surrounding skin with a lower energy density. This procedure is intended to avoid demarcation lines. The number of passes and the laser system used also has a decisive influence on result, side effects, and infection rate [6, 25, 36, 40, 43] (Figs. 25.24 and 25.25). It must be emphasised that all treatments with laser systems require extreme care. Proposed laser treatments to be administered by practitioners who are not qualified doctors of medicine, or even by doctors of medicine who are not experienced in the use of laser systems, should be strictly declined.

25.8 Cooling Procedures

During every laser treatment particular attention needs to be paid to cooling procedures. We differentiate between air, spray, gel, and contact cooling. If no cooling is implemented or if the cooling is inadequate, there is a threat of irreparable skin damage as a result of overheating and burning of the epidermis and/or deeper layers of the skin. An example of this is integrated contact cooling, which has to be in position on the surface of the skin during each impulse (Fig. 25.26). Possible sequelae of faulty cooling are hyperpigmentation, blistering or incrustation, ulceration, and, worst of all, permanent scars and keloids formed on the areas of skin concerned (Fig. 25.27).

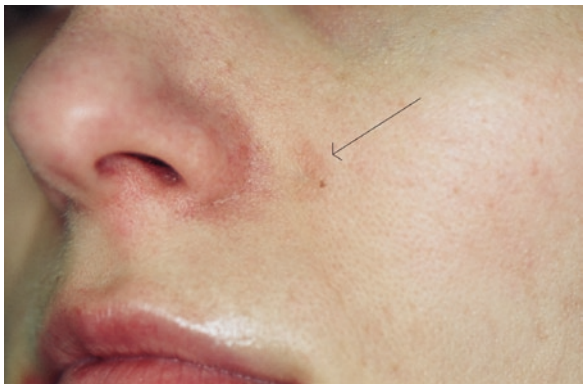

Fig. 25.26 Atrophic scar (*arrow*) after treatment of teleangiectasiae with the long-pulsed potassium titanyl phosphate–neodymium:yttrium aluminum garnet laser. Source of error was no contact of cutaneous cooling handpiece with skin [37]

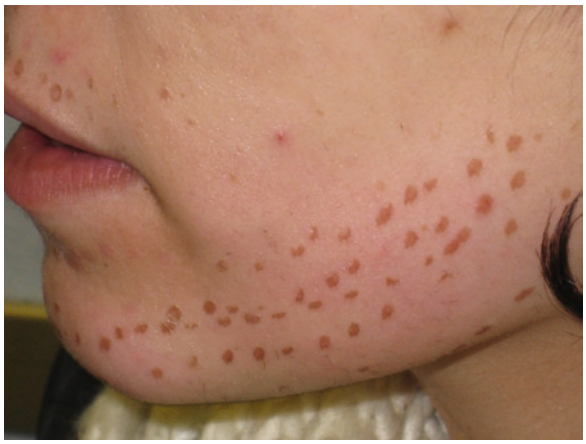

Fig. 25.27 Dots of incrustation after photoepilation with the alexandrite laser. Source of error here was heating of the spacer during treatment

25.9 Other Complications

25.9.1 Damage to the Eyes

Damage to the eyes can occur if the eye is exposed to direct or indirect laser irradiation. Various typical patterns arise depending on laser type, wavelength, and energy used. For example, there is nothing to stop the pulsed dye laser (wavelength 585 nm or 595 nm; chromophore haemoglobin) and lasers in the infrared spectrum, such as the alexandrite (wavelength 755 nm), ruby (wavelength 694 nm), and Nd:YAG (wavelength 1,064 nm) lasers, from penetrating the cornea and lens.

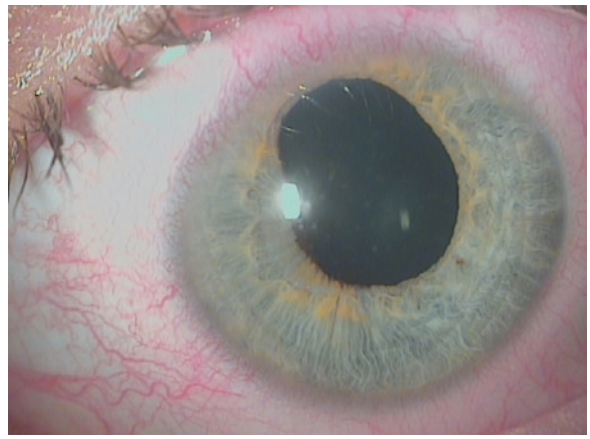

Fig. 25.28 Damage to the pupil after treatment of a port wine stain on the eyelid with the alexandrite laser. Source of error was that no account was taken of the alexandrite laser's depth of penetration. Protective goggles should have been worn during treatment in this region

Irreversible damage to the blood vessels and pigment in the retina and to the pupil can result [13, 18] (Fig. 25.28). Ablative lasers such as CO_2 and Er:YAG lasers (wavelengths 10.600 nm and 2.940 nm, respectively) are more likely to lead to corneal damage by way of the target chromophore water. To avoid lesions to the eyes, both doctor and patient must always use wavelength-specific eye protection and/or special protective eye shields when treatment is administered to this region.

25.9.2 Risk of Infection for Staff

Depending on the indications for treatment and the type of equipment, when the laser is used gases and vapours develop, consisting of, among other things, cell detritus, viruses, and bacteria. Even though there have been hardly any case reports of infections in medical staff so far, the demonstration of vaporised and potentially infectious material is nonetheless cause for concern [41]. Therefore, it is necessary to ensure that adequate protection is provided for ancillary staff, the patient, and the therapist during any laser treatment. This should include extracting all vapours that develop with a suction device and neutralising them with the aid of a special microfilter (<0.3 μm). In addition, masks and gloves should be worn as an additional safety measure during use of lasers to keep down the risk of infection.

Take Home Pearls

- The success of the information and consent procedure and preparation of documentation before a laser treatment depends on great care and comprehensive attention to detail. Description of realistic objectives of the treatment is part of this.
- The degree of success of a laser treatment rises with the level of qualification and experience in the centre where it is administered.
- "If you don't need the laser, don't use it" (Leon Goldman).
- "Nil nocere" (Hippocrates, 460–377 BC).
- Laser treatment belongs in the domain of a doctor experienced in laser surgery to keep the risks to a minimum and avoid irreparable sequelae. Laser treatments offered by practitioners with no medical qualifications should be stringently refused.

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Cooling Techniques

26

Stefan Hammes

Core Messages

- Cooling methods in dermatological laser therapy facilitate analgesia and protection of the epidermis.
- These can be divided into contact cooling methods and contactless cooling methods.
- Liquids, solids, and gases are used as cooling agents.
- The effects of additive cooling methods on clearance have been the subject of recent research.

26.1 Cooling Methods

In ancient times, snow and ice were well-known therapeutic agents. Hippokrates of Kos (460–377 BC) recommends in his scriptures cold drinks to fight fever and the application of cold compresses and pieces of ice to relieve gout pain and burns. Today, cooling is an indispensable part of daily treatment in rheumatology, orthopedics, sports medicine, and neurology [21]. Cooling is targeted at deep-lying tissue structures. For some time now, attention has also been paid to the application of cold as an additive in dermatological laser therapy [8, 25, 31]. The underlying intentions are:

- Analgesia, which makes the treatment less uncomfortable for the patients
- Thermal protection of the epidermis, which allows the use of higher therapeutic energy density

Contrary to the classic fields of application, this is intended, in the ideal case, to cool the epidermis while leaving deep-lying structures and the laser beam uninfluenced [1, 3, 4].

26.1.1 Overview

With *contact cooling* the mostly liquid or solid cooling agent is applied directly to the skin. For example:

- Moisturization of the skin (cold caused by evaporation)
- Application of cooling elements (direct cooling)
- Application of ice (gel; direct cooling and cold caused by evaporation)
- Application of cold conductors, such as the "Chilled Tip™ handpiece for the long-pulsed KTP-Nd:YAG-laser, metal "cooling finger" for the ruby laser, and sapphire lens at the diode laser (direct cooling)

With *contactless cooling*, the cold is transferred to the skin by means of an appropriate gaseous agent. For example:

- Cooling with cold air
- Cooling with other cold gases, especially liquid nitrogen

The application of cooling sprays or dynamic cooling devices (DCDs) mostly halogenized hydrocarbon are in the middle because they have both a contact phase and a contactless phase.

26.1.2 Contact Cooling

Frozen ultrasonic gel is easy to use and effective. The solid gel is spread on the skin and left for some seconds; then the treatment is carried out. A disadvantage is that

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_26, © Springer-Verlag Berlin Heidelberg 2011

the cooling effect decreases quickly and thus the therapy must be interrupted frequently. Furthermore, effect losses are possible due to the reflecting gel surface.

Chess and Chess [7] used an ice water unit. The authors state that refraction losses are not to be expected when the laser handpiece is held in an upright position. This is, however, questionable because several junctions must be penetrated. Other authors used a cooled glass unit [2, 26]. Here, too, optical losses (steaminess, reflection, scattering) must be expected with the use of ice cubes, through which the laser beam is applied. A loss of intensity due to enclosed air bubbles is also possible.

The cooling effect with contact cooling methods can, according to Kauvar et al. [13], be improved by the additional application of a coupling gel. In all cases, the target area is not directly visible. Its assessability is deteriorated because of the mechanical compression of the skin. How much these theoretical disadvantages lead to a lower effectiveness of the laser treatment in the field cannot yet be assessed.

26.1.3 Contactless Cooling

An advantage of the contactless cooling methods is that there is no medium that impedes the course of the laser beam, and, especially, there is no junction, which, in most cases, would lead to losses through scattering, transmission, and reflection. Furthermore, they facilitate and accelerate the work for the person treating and the person being treated because no substances must be applied to the skin.

A special advantage of contactless cooling methods is their independence of topography. Areas without an even surface (such as finger joints and deep wrinkles), mucous membranes, or orifices like the oral cavity, ears, or nose, cannot or can only with difficulty be treated with contact cooling methods.

There is no compression of the skin. This might be important with superficial vascular lesions. But, if structures are supposed to be compressed for therapeutic purposes, as is the case with voluminous hemangioma, the use of contact cooling can be advantageous [29, 30].

26.1.3.1 Liquid Nitrogen

Cooling with liquid nitrogen has been well known for some time. The advantage of deeper temperatures can, however, be reversed because there is the main inherent danger of skin lesions through freezes.

26.1.3.2 Halogenized Hydrocarbons

The use of halogenized hydrocarbons in the form of cooling sprays (dichlordifluromethane and 1,1,1,2-tetrafluorethane) has been described several times in the literature [6, 14, 15, 18, 20, 22, 28]. They have position between contactless and contact cooling; first, the liquid medium is applied to the skin, then it transforms with a temporal delay into the gaseous phase.

Torres et al. [27] describe that the cryogen spray film persists on the skin for several hundred milliseconds, which suggests interactions with the laser beam. By using an additional air stream the time of evaporation could be restricted to the duration of the cryogen spray impulse. Hirsch et al. [12] report freeze-induced hypopigmentations after application of cryogen spray due to the long exposure time on the skin. The occurrence of rime from ambient humidity after evaporation of the cryogen film may reduce the cooling effect, according to Majaron et al. [18, 19].

An in vitro comparison between cooling sprays and contact cooling methods showed an identical cooling profile in the skin. It remains unknown how far this can be transferred to in vivo processes. The cooling sprays were well tolerated and reduced the pain, but halogenized hydrocarbons should be assessed reservedly for ecological reasons.

26.1.3.3 Cold Air

An innovative form of therapy among the contactless cooling methods is cold air, used in certain doses, between −20 and −30°C [25]. Thanks to the higher minimal temperature, the danger of cold-induced lesions is lower than with the use of liquid nitrogen. What is important is an effective adaptation of the air transport tube to the laser handpiece. For some laser types, there are ready-to-use adapters; others are being developed.

Knollmann and Berliner [16] proved that the lowering of the skin temperature through cold air (45% of the initial value) can be compared to that through ice gel (49%) and through liquid nitrogen (41%). The laser Doppler signal showed that the blood circulation was

reduced by about 40% with each of the compared methods. Thus, cold air therapy resembles the comparison methods, at least regarding these objective parameters. Kröling and Mühlbauer [17] proved through electromyographic examinations of epicondylus radialis humeri that the pain barrier rises considerably quicker and stronger after the application of cold air than after the application of liquid nitrogen and ice gel. According to Biesman et al. [5], the use of cold air in animal experiments allowed considerably higher energy densities with an 810-nm diode laser than with cooling with a sapphire unit (150 J/cm² vs. 75 J/cm²).

The acceptance of cold air is very high among patients, as became obvious in a number of studies [9, 25]. The good compatibility of this method was confirmed in other examinations, too. Thanks to analgesia with cold air, it was possible to use energy densities that were on average 15–30% higher. Still, the rate of side effects was lower. Regarding the result of the therapy, no significant changes were observed. For the provider, the therapy with cold air is easier, more secure, and more comfortable. The work can be done quicker; the target area is visible at all times and the laser handpieces and protective devices are not soiled [25].

26.1.4 Problems, Developments, Prospects

So far, no long-term study has been conducted on the impact of cooling therapy with regard to the results of dermatological laser treatments. With our patients, there was no significant decrease of the effect even with unchanged energy fluences (Fig. 26.1). However, the cooling caused skin brightening, among other results. This might theoretically have a negative impact on the results of dye laser therapy of, for example, telangiectasia.

Greve et al. [9] showed that in 84% of cases the use of cold air did not lead to a decrease, but in 15% of cases it led to an increase of the clearance rate with the therapy of port-wine stains with the dye laser. Also, according to an examination of Hammes et al. [11], on average, better clearance and higher comfort during treatment is possible thanks to the possibility of the use of higher energy densities under cold air cooling in the treatment of port-wine stains. Hammes and Raulin [10] observed similar results with the treatment of facial telangiectasia.

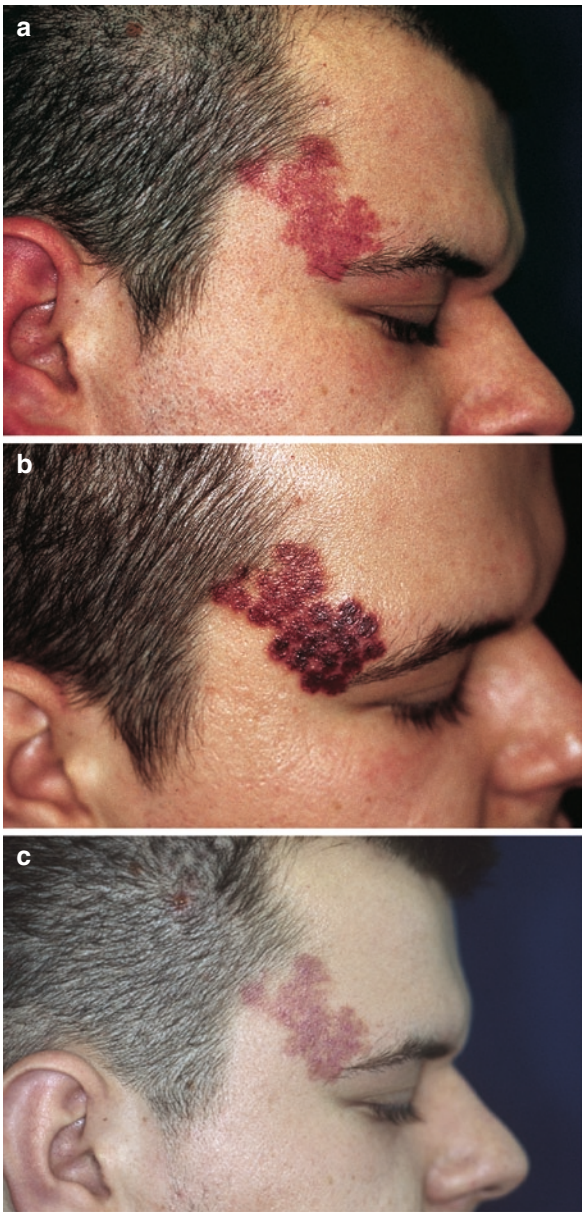

Fig. 26.1 (**a**) Nevus flammeus directly after therapy with a pulsed dye laser (1/00). The upper area was treated with cooling, the lower without cooling. (**b**) Patient after 3 days. Clearly less purpura in the area with cooling. (**c**) After 4 weeks (2/00). No difference in the treatment result. Reproduced with permission of the publisher from Raulin and Greve [24]

A prospective side-by-side study on cold air cooling in the field of skin resurfacing with the carbon dioxide laser also showed a considerable increase in patient satisfaction with unchanged clearance [23].

Chang et al. [6] achieved a reduction of the number of treatment sessions and an improvement of the clearance rate in the treatment of hemangiomas with a high-energy dye laser (585 nm, 9–10 J/cm²) and cryogen cooling. Majaron et al. [18] reported only minimal deterioration of the therapy results with the use of cryogen spray in the course of an Er:YAG skin resurfacing.

The effect of cooling methods on the therapeutic success seems to depend on the necessary temperature gradient (ΔT) of the target structure. The bigger ΔT in relation to the lowering of the temperature T_k, the lower the potentially negative impact of additive cooling. In the treatment of tattoos, for example, ΔT amounts to approximately 1,000°C. A T_k of about 20°C is, in relation to ΔT, very low and can thus be negated. In the therapy of vascular lesions (ΔT of ~40°C), the quotient $\Delta T/T_k$ is very small and thus might eventually have a negative impact on the result.

Another impact factor in the context of clearance assessment is the position of the target structure in the skin. The more superficial its position, the more sensitive it is to changes in temperature. Thus, superficial vessels in the form of essential telangiectasia clearly react more sensitively to temperature than do deep-lying hair follicles.

The thermal protection of the epidermis is reflected in the stable or even lower rate of side effects in spite of higher energy densities [9]. Faulty or missing application of cooling procedures may, however, lead to errors in treatment (Fig. 26.2).

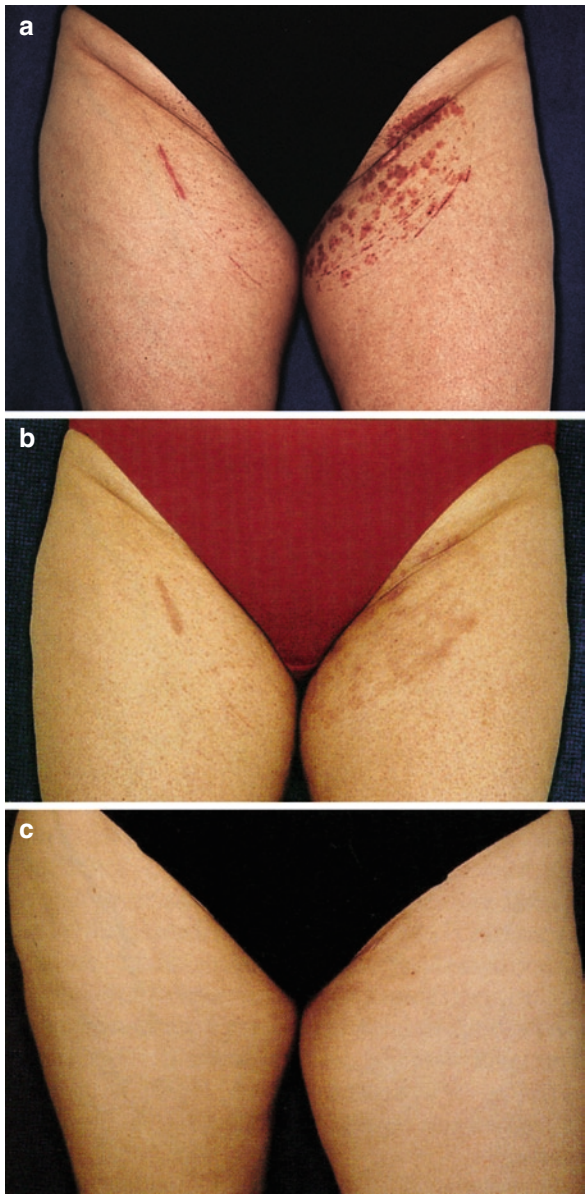

Fig. 26.2 (**a**) Crusting on left thigh after photoepilation with the long-pulsed alexandrite laser (3/00). Therapy on the left side without cooling, on the right side with cold air cooling. (**b**) Partial recovery of the skin lesions 2 weeks after treatment (3/00). (**c**) Eight weeks after treatment. Complete recovery of the skin lesions (5/00). Reproduced with permission of the publisher from Raulin and Greve [24]

Take Home Pearls

- The application of cold for analgesic purposes in dermatological laser therapy now can be classified as an indispensable and – among patients and treating staff – accepted method.
- More prospective studies are necessary to find out whether the possibility of using higher energy densities does, aside from better compatibility, lead to better results.

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Ethical Considerations in Aesthetic Medicine

27

Giovanni Maio

Core Messages

- This chapter discusses the arguments as to why the field of medicine should not unreflectively link and ingratiate itself to the beauty industry.
- If aesthetic medicine is oriented purely towards economic concerns, it runs the risk of creating a demand that would not exist without its own advertising.
- There is also the danger that a fiscal approach to aesthetic medicine will embrace the ideologies of our consumption- and performance-oriented society, with the primary goal of profiting from it.
- Over time, this could lead to a situation in which aesthetic medicine will be completely eradicated as a discipline that is the domain of physicians.

A winning smile, a more successful career, greater opportunities in one's personal life – when aesthetic medicine advertises its services, it more or less explicitly promises all of these things and then some. At first glance, these promises make it seem as if it would be all but ridiculous not to take advantage of such options. After all, what objection could there be? Why should medicine only be used to help heal or prevent diseases when it can also assist people in becoming more "successful" in their personal and professional lives? This question is all the more important in light of the fact that we have learned in recent years that medicine should respect patient autonomy and that physicians should do their best not to decide themselves what is good for patients. In many aspects of today's medicine, patients are often presented to us as customers; what's more, they usually show the sense of entitlement that customers have. Consequently, it seems quite obvious that we should treat them like customers. Ethically speaking, however, it remains unclear whether this sort of reorientation in medical thinking can truly be reconciled with medicine's basic identity as the science of treating diseases.

27.1 Aesthetic Surgery as a Market-Driven Discipline

What motivates aesthetic surgeons to remould the human body in keeping with a patient's requests? There are some naturally occurring body shapes and facial features that can seem so malformed in some people's eyes that it causes the patients great psychological distress. The correlating emotional strain could be enough of a justification to perform a surgical intervention on a healthy body. The objective of such a procedure would be to relieve suffering. An issue of vital importance here, however, is that the suffering does not actually result from the person's figure itself, but from how our aesthetically oriented media and society interpret the body. Nevertheless, the positive effects of surgery can be so great in terms of their impact on the patients' self-esteem and social integration that it may seem ethically justified.

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_27,

What is to be done, though, when people approach aesthetic physicians with the request to have their figures resculpted to resemble a particular pop idol, or when they want to be "made over" because they believe it will give them competitive advantages in finding a partner and/or professional success? Why should a physician respond to requests like these? There is no emotional or physical suffering, which means that the goal is not to relieve or physical suffering. This scenario highlights the fact that, in many cases, aesthetic surgery is not anchored in addressing a medical need, but fulfilling a longing: here, the aesthetic surgeon is not a healer, but merely someone who makes wishes come true. To be more specific, the issue of granting wishes comes down to the fact that only two parameters matter in finding the right clients: the clients' aesthetic wish in and of itself, and the clients' purchasing power. Or, in other words, the only constraints on some aesthetic measures are people's wants and wallets. The ultimate goal of such an approach would be to optimise profits and exploit aesthetic medicine as a business. If, however, profit were indeed the central objective, this form of "medicine" would be completely removed from its inherent purpose of being a source of aid and healing.

Performing aesthetic surgery on demand is not a problem in and of itself, and modern people have the freedom to avail themselves of these services. But this sort of wish-oriented aesthetic measure does not have anything to do with true medicine. It is one thing for such services to be offered by "technicians" or salespeople in beauty salons, but if they are offered by physicians in surgeries, this poses major damage to the entire profession. The more aesthetic medicine performed on demand – and performed for money – gains ground in the world of everyday medicine; the more disastrous it is for all of us because we lose credibility, respectability, and, above all, patient confidence. It is no coincidence that in many countries the physicians' code of conduct explicitly states that medicine is not to be treated as a trade, especially because patients will only have faith in physicians and their counsel if they can assume that they are interacting with a physician and not a salesperson in a lab coat. There is a great deal of evidence that modern medicine and its excessive focus on aesthetics are well en route to becoming (nothing but) a business enterprise, since it directly or indirectly advertises its services. This advertising is usually subtle, but it exists nonetheless. People who want to sell goods and services are welcome to do so, and a salesperson is not fundamentally unethical for making sales. The problem arises when salespeople present themselves as physicians; behaving like a doctor cannot be reconciled with behaving like a salesman. The physicians' greatest responsibility is to be an advocate for the well-being of the ill, and for this they deserve to be remunerated appropriately, but financial reward cannot be what motivates medical recommendations. By contrast, salespeople may quite legitimately place their own personal interests first; no one will reproach them for earning money by selling products that are not really needed. But if physicians blur the lines between their work and sales work, they will lose more than they win. Above all, they lose their standing as members of a profession that serves the sick. And herein lies the delicate issue: patients have to be able to have confidence that at least their physicians can be relied upon to make beneficial recommendations. We all know that it would be more of an exception to the rule to give this vote of confidence and the benefit of the doubt to a salesperson.

At this point, one could counter with the argument that physicians do not sell patients things that are not wanted. It must be taken into consideration, however, that patients usually do not come up with the idea to have a given aesthetic procedure entirely on their own. As a rule, they consult with their doctor, which means that physicians have a critical moral role here: patients are usually lay people, so physicians have far more medical knowledge, which in turn entails greater responsibility. Their expert recommendation, has a fundamental impact on the patients' decision. If physicians recommend something only because it earns them money, there is the danger that they may abuse the patient's faith in the integrity of the profession. Physicians who proactively advertise by informing patients about new options in aesthetic medicine even though their patients have not requested this information cause double the damage to the patients' goodwill. There are rising numbers of alarming reports about patients who avoid seeking medical care because they are confronted with more and more with marketing pitches.

Aesthetic medicine that focuses squarely on market interests will rate the patients' well-being as a secondary concern at best, not as its primary objective. Consequently, aesthetic medicine that targets market concerns would be flawed, which is to say it would no longer be medicine.

27.2 Aesthetic Procedures as "Pure Cosmetics"

The ethic defensibility of aesthetic procedures rises and falls with the question as to whether it can be legitimately claimed that the priority is to help the patient. This argument is trotted out regularly by doctors when the discussion turns to the limits of aesthetic measures. There can be no doubt that it is safe to speak of helping patients in cases where aesthetic measures can alleviate an emotional strain that results solely from a patient's appearance. Examples could include malformed or unpleasantly conspicuous physical features, especially on the face; these can erode the patient's self-esteem from childhood onward. There may be a valid and convincing argument in favor of enlisting a physician's help in such cases. But what about patients who want aesthetic procedures that will make them look younger or increase their resemblance to certain celebrities? Let us assume here that we are dealing with people whose appearance causes them distress and assume that they are not disfigured or otherwise particularly unattractive. How can physicians help those who look more or less "normal" but still struggle because of their looks? Is cosmetic surgery really the answer?

If physicians truly want to help people who suffer from their physical appearance, they must be interested in correcting the underlying condition that causes the "suffering." Physicians must ask themselves what is the true source of the anguish and why are fashion trends wielding such a strong influence. As helpers who take their obligation to help seriously, physicians must ask themselves why people have sought out an aesthetic surgeon and what is the underlying source of the prevailing beauty trend. It soon becomes obvious that the real reason people want to look younger or more attractive is not actually a desire for beauty or youth per se; in many cases, the real motivation is fear. Their actions are governed by the fear of not being appreciated, the fear of not being loved, the fear of being inadequate, the fear of being marginalised, or the fear of being unable to compete [6]. It seems more than spurious to claim that lasers are a tool that can help such fear-driven people because an aesthetic procedure will often not correct the cause of the emotional distress; instead, the treatment is seen as a "purely cosmetic" approach. This patient cohort does not need service providers who will respond to their every whim; they need help – help that will allow them to handle their fears and find methods of coping with society's pressure to perform and succeed *without* resorting to the use of lasers.

People who suffer from their appearance are not really afflicted by their looks per se, but rather by their lack of self-confidence. Physicians who only treat the external problem are failing to address the actual core of the problem, which can lead to the conclusion that they are relatively indifferent to the patient's true wellbeing. They would be truly indifferent to patients' well-being if they understood that they were not only leaving the fundamental problem uncorrected, their services also were leaving the patient in poorer financial straits and that their "treatments" were probably bringing about only a short-term success. After all, if someone's self-esteem remains poor, it will not be long until the next justification arises to make other physical changes. This leads to the third point, which is closely linked to this idea.

27.3 Exploiting the Pressure of Conformity that Vulnerable People Feel

These points are intended to make clear that it would be short-sighted to respond unquestioningly to people's wishes for body modifications. It would be short-sighted not only because such measures rarely provide genuine help, but also because, strictly speaking, the mandate of honouring autonomy has not been fulfilled in many such cases, even when it is cited as the ethical justification. This begs the question, How autonomous are people if they are swayed by fashion trends and turn to aesthetic surgeons because of their anxieties about competing in society? Studies have shown that many who seek out the services of aesthetic surgeons are not only acting on their free will but also are "subjugated to the dictates of internalised beauty standards" [2]. Many people "want" an aesthetic procedure, not because they enjoy them, but because they can no longer withstand the pressure of sociocultural norms. Seen from this perspective, these patients are not the deeply autonomous individuals many aesthetic surgeons like to cite; instead, they are weak individuals who are giving in to the pressure to conform [3, 8]. Whether or not one can even speak of autonomy in this context is quite dubious, at least from an ethical perspective. In each case, medicine that defines itself as a source of assistance must be more concerned with promoting individual autonomy instead

of affirming the pressure to fit in. The enormity of this issue becomes that much greater when aesthetic procedures are performed on minors, a situation that is becoming increasingly common. There certainly can be no question about whether a decision is autonomous in such cases [2]: parents who consent to cosmetic procedures are neither acting on their child's best interest nor developing their child's future sense of autonomy, since aesthetic surgery serves to confirm that people "compete for sought-after attention by means of their appearance" [7]. Minors are inherently vulnerable persons and are thus especially susceptible to peer pressure, and aesthetic interventions do not alleviate the situation but exacerbate it. This leads us to the fourth point.

27.4 The Body as a Project and Beauty as an Unattainable Achievement

This critique of aesthetic medicine should be seen against a broader canvas, because physicians are not the sole culprits here; ultimately, aesthetic medicine is flourishing as the result of a certain attitude in our competitive society, not as the result of medical practice itself. That more and more aesthetic procedures are being performed has to be correctly interpreted as evidence that the body is being increasingly regarded as a project, as a tool for people to express themselves in their social environment. Many studies have confirmed that our physical appearance can play a key part in our professional lives, and this has become all the more true during the past 15 years. More than ever before, physical traits are seen as indicators of certain character traits, and there are growing numbers of attributes that can help make or break someone's ability to advance in the world. Having a dynamic and youthful appearance often is seen as a critical advantage in one's career. The state of the body is not accepted as a given; it is seen as an achievement, which one can attain and which requires constant maintenance to make sure one is not left behind. Put bluntly, this means that our job qualifications are not only professional in nature, but appearance-based as well. Invariably, modern competitive people are increasingly turning themselves into victims of an obsession that dictates that they must be attractive. This imperative becomes a burden because most people cannot liberate themselves from such thinking and eventually become entrapped by it. This phenomenon can be compared to doping in the world of sport; the tighter the spiral of competition grows, the more some people encounter disadvantages when they try to abstain from it, and at some point they are swept up in the process even though initially they wanted nothing to do with it. This simply means that as aesthetic medicine spreads it becomes all but essential. The thought is that those who are not "attractive" have no one but themselves to blame because they certainly could have done something about it. Gernot Böhme once stated that more and more, beauty is expected of others in much the same way that etiquette is [1].

Aesthetic medicine cannot, however, be held accountable for all of this; it might even be argued that this context clearly demonstrates that society is the problem, which means medicine is not at fault. Though this statement may be true, it is not the whole truth. The point of contention is not aesthetic medicine per se, but the way in which it is dealing with this trend. The problem that aesthetic medicine faces is that its own advertising is only contributing to this trend. In lieu of ads, the field would be wise to remain modest and reflect again on what it truly can and cannot promise. The services of aesthetic medicine may have a positive impact on helping someone advance in his/her career – and that is certainly no small matter – but boosts like this can only occur if other things fall into place as well. Aesthetic medicine has completely failed to see that attractiveness may correlate with one's physical appearance but is not defined by it. Being attractive is just as much an issue of having charisma and being natural, and someone is not considered attractive unless their outward appearance, a certain aura, and a relaxed and unstudied manner come together. At the end of the day, attractiveness can be seen as harmony between someone's external appearance and his/her inner allure. The absolute reverse can be observed if there is any discord between these two aspects, which can easily be seen in the "doll-faced" look of some overly made-up young girls. Aesthetic medicine that vows that lasers can create attractiveness is too grandiose; it deals in propaganda. This misleads many people, and it is thus irresponsible to make such promises.

It is just as difficult to deal with the promise aesthetic medicine often makes, i.e., that it will create "beauty." Those who attribute beauty to certain external constructs are working from a reductionist perspective of the concept [4]. Beauty is not something

that can be produced in a particular form; beauty is something that is expressed, not merely a visual quality. Beyond that, though, the more aesthetic medicine attempts to help people attain "beauty," the greater the risk that it will generate uniformity instead. Contributing to this sort of standardisation will mean that aesthetic medicine moves its patients further and further away from true beauty because being beautiful is always a matter of being exceptional in some way. The promise of offering beauty by creating standardised looks is as foolhardy as the promise of creating a competitive advantage and "making" people more attractive simply by altering their physique. In today's world, beauty and appearances have become a commodity, and medicine exploits this trend without keeping in mind the fact that it can only lose in the long run if it is not careful enough with its promises and the wishes it aspires to fulfil.

27.5 Is Patient Autonomy the Only Ethical Justification?

During the past few decades, people have repeatedly criticised that the field of medicine needs to respect patients' autonomy more. The patients themselves should be the ones who decide what is best for them, and physicians should not interfere with an individual's values. If patients' autonomy has been made the ultimate principle, which guides ethical decisions in medicine, it would seem only logical for physicians to have no scruples about honoring someone's request to perform an aesthetic procedure. There cannot be any viable reason to prohibit aesthetic procedures in general as long as the patient has provided informed consent, the surgery is of the patient's free will, and the risk-benefit ratio permits it. In a free democracy, there would be no cause to outlaw such a thing; however, simply because something is not forbidden, legally speaking, does not mean that it is justifiable, ethically speaking. The criticisms conveyed in this article are intended to shed light on the potential ethical pitfalls of aesthetic procedures.

The concerns expressed here do not give rise to the fundamental conclusion that all aesthetic procedures are ethically problematic. There are plenty of physicians who are governed by noble ideals, even in their aesthetic work, and they do offer valuable help for their patients. Furthermore, there are many physical manifestations and states that can cause patients anguish, and aesthetic surgeons can truly help by correcting these situations. The line between serving humankind and immoral marketing of medical services is very fine indeed [5]. This makes it all the more important to be certain that aesthetic medicine always bears in mind the greater context in which it is embedded, and each physician must take decisions within the framework of this context, acting with greater awareness and perhaps greater deliberation. Many things hinge on taking a thoughtful approach because aesthetic medicine – like all of medicine – will only be able to protect its future credibility and identity as a discipline of healing if it deals responsibly with clinical indications; it must be able to persuade people that its central mission is the patients' well-being alone, not maximising profit. If it is unable to represent this stance with conviction, modern medicine runs the risk of responding to the current boom in beauty treatments not only by selling aesthetic services on demand, but also by selling out its most fundamental identity.

27.6 Conclusions

The key challenge is to cement people's faith in the moral integrity of physicians' work. If loss of trust in the profession is the greatest jeopardy we face, this means that the central task is to regain or to retain this trust. Trust can only be given to those who not only have technical expertise but also personal integrity. One path to this integrity would be to hearken back to an old tradition of ethics: the ethics of virtue. There were four cardinal virtues in ancient times, and they very elegantly illustrate this message: in aesthetic medicine, there cannot simply be categorical bans; there must be a sensible basic attitude and, when necessary, a long-term perspective. The first cardinal virtue is prudence, and for us this specifically means that a physician's recommendation must remain rooted in realistic outcomes and not unwarranted promises. This is a particularly important condition in this marketing-heavy day and age. The second cardinal virtue, restraint, decrees that impracticable standards and wishes have to be turned down, and physicians should not be swayed by the opportunity they have to profit – only in the short term – from aesthetic medicine.

The third virtue, justice, can be seen as a call to make certain we do not exploit weak patients. The last of the cardinal virtues is courage. In aesthetic medicine, this means not being afraid of stating the truth, acknowledging the limits of feasibility and thus refusing some requests even if it is clear that they will be simply met at the surgery next door.

When aesthetic medicine promises that it can "make" a beautiful smile or uses glossy brochures to suggest that it (alone) is all that is needed to make someone "happy," then this kind of "medicine" is neither prudent, nor restrained, nor just, nor courageous. This is why I call for aesthetic medicine to heed its true identity as a discipline of healing; it must reflect on how it can train its disciples to be not merely technicians and salespeople, but real physicians with moral integrity. Perhaps it would be wise to channel money that would otherwise be invested in offering more marketing seminars and reroute it towards creating platforms so practitioners in the field can discuss the extent to which they wish to remain physicians or become servants of the beauty industry.

Take Home Pearl

› The logical conclusion put forth by this chapter is a call for our field to invest much more in its own moral authority and credibility; this can only be ensured when all of the representatives of aesthetic medicine see themselves as helpers, not as salespeople.

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Photodynamic Therapy

28

Philipp Babilas and Rolf-Markus Szeimies

Core Messages

- Photodynamic therapy (PDT) is an approved treatment option for actinic keratoses, Bowen's disease, in situ squamous cell carcinoma, and both superficial and nodular basal cell carcinomas.
- PDT is especially indicated in cases of field cancerization.
- Therapeutic benefit has been proven for nononcologic indications like localized scleroderma, acne vulgaris, granuloma annulare, and leishmaniasis.
- PDT has been shown to have impact on aesthetic indications like photoaging or sebaceous gland hyperplasia.
- Key benefits of PDT are low level of invasiveness and excellent cosmetic results.

28.1 Introduction

Hermann von Tappeiner, director of the Institute of Pharmacology at the University of Munich, coined the term "photodynamic reaction" 100 years ago. According to the observations of one of his doctoral students, Oscar Raab, the reaction was characterized as an oxygen-dependent tissue reaction after photosensitization and irradiation with light [80, 105]. Oscar Raab showed in his experiments that the organic dye acridine orange, acting as sensitizer, was lethal for paramecia in the presence of daylight [80]. The toxicity of acridine orange on protozoae was dependent not only on the dye concentration but also on the intensity of the ambient light. Von Tappeiner sucessfully treated patients who were suffering from lupus vulgaris, secondary syphilis, and superficial skin cancer with topical cosin red solution (1–5%), in cooperation with the dermatologist Jesionek [105]. In 1911, Hausmann reported photodynamic effects on mice injected with hematoporphyrin, which showed extensive edema and erythema after light exposure. The German researchers Auler and Banzer in 1942 observed the specific uptake and retention of hematoporphyrin in tumors with subsequent higher fluorescence in the cancerous tissue compared to the surrounding tissue. After irradiation with a powerful quartz lamp, they could also demonstrate histologically the induction of necrosis [105]. Thereafter, photodynamic therapy (PDT) was forgotten until Thomas Dougherty initiated a renaissance in the mid-1970s by treating patients with cutaneous and subcutaneous tumors after injection of the photosensitizer dihematoporphyrin followed by red light irradiation using a laser. The majority of the treated tumors showed either complete or partial remission [24, 25, 105]. Today, it is precisely known that PDT requires the simultaneous presence of a photosensitizer, light, and oxygen inside the diseased tissue. The photosensitizer is accumulated in the target cells and absorbs light of a certain wavelength. The energy is transferred to oxygen, and highly reactive oxygen species (ROS) – mainly singlet oxygen – are generated. When treated with appropriate light doses, the ROS directly lead to cell and tissue

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_28, © Springer-Verlag Berlin Heidelberg 2011

damage by inducing necrosis and apoptosis; they and indirectly stimulate inflammatory cell mediators. After lower light doses when treating inflammatory dermatoses, immunomodulatory effects are induced. In the past decades PDT has gained worldwide popularity, first as an experimental therapy for a variety of human cancers. Mainly porphyrins, chlorine derivatives, or phthalocyanines have been studied so far for primary or adjuvant cancer therapy [117]. However, for dermatological purposes, only hematoporphyrin derivatives (HPDs) like porfimer sodium (Photofrin, Axcan Pharma, Birmingham, Al., USA) or protoporphyrin IX (PpIX)-inducing precursors like 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) are of practical concern. Because systemic photosensitizing drugs induce a prolonged phototoxicity [64], topical photosensitizers are preferred for the use in dermatology. Several formulations containing drugs like ALA or MAL have reached approval status for epithelial cancers or their precursors throughout the world, and there is growing interest in the use of PDT not only for nonmelanoma skin cancer but also for other skin tumors like lymphoma, or for tumor surveillance in transplant patients as well as for nononcological indications [16, 27, 28, 69].

28.2 Photosensitizers

Eosin red or erythrosine were the first dyes Georges Dreyer in Copenhagen and Albert Jesionek in Munich used at the beginning of the last century as topical "photosensitizers" to treat conditions like syphilis, lupus vulgaris, pityriasis versicolor, psoriasis, molluscum contagiosum, or skin cancer [105]. However, due to recurrence and severe side effects (pain, unspecific deep tissue necrosis) these experiments were abandoned. Since 1908, the tumor localizing effects of porphyrins have studied. In the late 1970s, HPD-based PDT for the treatment of skin cancer came up again [24, 25, 105]. The main problem in the use of HPDs is the prolonged skin photosensitization, which lasts for several weeks [91]. A topical application is not possible because the rather big molecules (tetrapyrrol rings) do not penetrate the skin sufficiently. Therefore, the introduction of the porphyrin precursor ALA by Kennedy and coworkers [58] in 1990 was a significant milestone in the development of PDT in dermatology because the small molecules easily penetrate into the epidermis due to their low molecular weight [105]. In the USA, 5-ALA hydrochloride (Levulan Kerastick, Dusa Pharmaceuticals, Wilmington, Mass., USA) is approved for photodynamic treatment of actinic keratosis (AK) in combination with blue light [117]. The 5-ALA-based photosensitizers are not photoactive by themselves but show a preferential intracellular accumulation inside the altered cells constituting the diseased tissue and are metabolized in the heme biosynthesis to photosensitizing porphyrins rather selectively inside these cells [104, 105]. If no surface illumination is given, the porphyrins are metabolized to the photodynamically inactive heme within 24–48 h. The requirement of good tissue penetration and a selective accumulation in tumor tissue is fulfilled perfectly with the hydrophilic molecule ALA. However, tumor thickness using ALA as photosensitizer should not reach more than 2–3 mm to induce sufficient necrosis upon illumination. An alternative is the methyl ester of ALA, the methyl-5-amino-4-oxopentanoate (MAL). This molecule accumulates more selectively in neoplastic tissue and obviously penetrates faster and deeper. The maximum intracellular concentration of PpIX is reached earlier, which allows a shorter incubation time (MAL at 3 h vs. ALA at 4–6 h) [52]. Christiansen et al. [21] reported on the fluorescence profile of ALA in a cream formulation (20%) compared to liposomal-encapsulated ALA (0.5 and 1.0%). Maximal fluorescence was achieved after 2 h using the liposomal form; 8 h after application, no further fluorescence was detectable. The duration of fluorescence represents the duration of the iatrogenic photosensitivity after PDT. ALA in a cream formulation showed an increase of fluorescence up to 8 h. The mean fluorescence was equivalent in both groups. Therefore, the use of a liposomal form allows a reduction of the ALA concentration because the penetration is significantly better using this vehicle. Further studies regarding liposomal or nanocolloidal ALA compositions are ongoing.

Cumbersome in clinical practice is the requirement of a mechanical curettage prior to application of the photosensitizing drug, which should be performed when using MAL. New modalities were introduced very recently [43]. In three clinical studies, the liberation of ALA from a patch matrix (PD P 506 A, Photonamic GmbH, Wedel, Germany) was investigated. No side effects or phototoxic reactions were reported. In a multicenter trial (phase II), 149 patients with 520 AK (grade I/II) were treated with the ALA patch and subsequent PDT. Curettage was omitted.

The patches were applied for 0.5, 1, 2, or 4 h. The highest remission rate (86%) 8 weeks after therapy was achieved in the group with a 4-h incubation time. Side effects were comparable to those after standard PDT. In a further series of studies, PDT with an ALA patch was compared to cryotherapy in a multicenter trial of 346 patients with 4–8 AK each. After a 4-h inclusion period, illumination was performed with a light-emitting diode (LED) light source (630 nm). Comparative treatment was cryotherapy with liquid nitrogen. Although designed as a noninferiority study, both lesion- and patient-based outcomes after 3 months of PDT were superior to cryotherapy (89% vs. 77% complete clearance [lesion based]; 67% vs. 52% [patient based]), despite the fact that – as is necessary when MAL is used for PDT – no lesion preparation, i.e., slight curettage prior to patch application, was performed [43].

Meso-tetrahydroxyphenylchlorin or benzoporphyrin derivative monoacid A ring (verteporfin) is another photosensitizer that has been applied systemically for the treatment of basal cell carcinoma (BCC) and Bowen's disease [6, 63]. In contrast to HPD, those second generation photosensitizers show only limited cutaneous phototoxicity. Both drugs are already registered for head and neck cancers or age-related macular degeneration, but so far it is not clear whether a registration for dermatological purposes will follow.

28.3 Light Sources

After formation the photosensitizing porphyrins can be activated by light of the appropriate wavelength. The porphyrins or related photosensitizers with a tetrapyrrolic structure exhibit a very typical absorption spectrum with the highest peak at approximately 405 nm, the so-called "Soret band. Besides," Several Q-bands exist, the last having an absorption peak at 635 nm. Although the peak is much smaller than that at 405 nm, this wavelength is preferentially used for irradiation because light in the red spectrum shows the best tissue penetration [20, 103]. However, blue light is approved in the USA in the combination with 5-ALA hydrochloride (Levulan Kerastick, Dusa Pharmaceuticals) for photodynamic treatment of nonhyperkeratotic AK [78, 117]. In addition, white light sources or green light sources exist for PDT. However, it has been demonstrated in a comparative trial that light at shorter wavelengths is less effective in the treatment of Bowen's disease at a theoretically equivalent dose; therefore, only the use of red light is recommended for PDT of skin tumors [70, 72]. Nonmelanoma skin cancer up to a thickness of 2–3 mm can be treated with red light; thicker lesions require multiple treatments or tissue preparation (debulking) prior to PDT [42, 94, 109].

For irradiation in PDT, lasers and incoherent light sources have been used [18, 53, 54, 102]; pulsed laser light sources matching one of the Q-bands at 585 nm have been evaluated with equal results compared to an incoherent light source in the treatment of AK [54]. An advantage of lasers is the shorter exposition time compared to incoherent light sources. Although not an ideal match for the porphyrin absorption spectrum, the use of a long pulsed dye laser at 595 nm also seems to be effective for the same indication [1]. However, incoherent light sources exhibit fundamentally different irradiation characteristics compared to lasers. Because coherence is lost within less than a millimeter of penetration into skin, this property is not mandatory for PDT [102]. The high versatility of intense pulsed light (IPL) has promoted these incoherent light sources to become a favored device for PDT. The emission spectrum of IPL devices ranges from 500 to 1,300 nm. With the aid of convertible cutoff filters, the IPL device can easily be adapted to the desired wavelengths, which underlines its high versatility. Recently, several authors have reported successful treatments of acne vulgaris [37, 65, 89], AK [5, 59], photoaging [2, 26, 40], and sebaceous gland hyperplasia [38] with IPL devices for PDT.

Babilas et al. [8] compared the effectiveness of a gas discharge lamp with a LED system in vitro and in vivo. Human epidermal keratinocytes were incubated for 24 h with ALA (100, 200, 300, 400, or 500 μmol/L) and irradiated consecutively using either an incoherent halogen lamp (λ_{em}=580–700 nm, 24 J cm^{-2}, 40 mW/cm^{-2}) or a LED system (λ_{em}=633±3 nm; 3, 6, 12, or 24 J cm^{-2}, 40 mW/cm^{-2}). For the in vivo experiments, the authors performed topical ALA and PDT on 40 patients with AK (n=584) in a symmetrical dissemination suitable for two-side comparison. After incubation with ALA (20% in cream base), irradiation was performed with the incoherent lamp (160 mW cm^{-2}; 100 J cm^{-2}) on one side and the LED system (80 mW cm^{-2}; 40 J cm^{-2}) on the opposite side, followed by re-evaluation up to 6 months later. The authors reported no significant differences between the LED system (3, 6, 12,

or 24 J cm^{-2}) and the incoherent light source (24 J cm^{-2}) regarding cytotoxicity in vitro. The complete remission rate yielded in the in vivo investigation was also not significantly different 6 weeks ($p=0.95$), 3 months ($p=0.75$), and 6 months ($p=0.61$) after therapy. Six weeks after the completion of therapy, remission rates of 84.3% (LED system) and 82.8% (incoherent lamp) were achieved. There was also no significant difference between both sources regarding pain during treatment ($p=0.68$) or between patient satisfaction ($p=1.0$), as well as cosmesis ($p=1.0$) after therapy. Therefore, the authors were able to demonstrate the efficacy of a LED system for ALA-PDT both in vitro and in vivo. When using the LED system, lower light doses were sufficient because these devices emit only a narrow band of wavelengths that perfectly match the absorption spectrum of porphyrins; wavelengths that are unnecessary for the phototoxic reaction and that only contribute to heat effects are omitted. In another work, the same group evaluated the painfulness and effectiveness of an IPL device in a prospective, randomized, controlled, split-face study [9]. They conducted topical MAL-PDT in 25 patients with AK ($n=238$) who were suitable for two-side comparison. After incubation with MAL, they performed irradiation with an LED (50 mW cm^{-2}; 37 J cm^{-2}) vs. IPL (80 J cm^{-2}; 610- to 950- nm filtered hand piece), followed by re-evaluation up to 3 months later. They reported significantly less pain during and after therapy using the IPL [$t(df=24)=4.42$; $p<0.001$]. The overall infiltration and keratoses score 3 months after treatment was not statistically significant (0.86 ± 0.71 [LED system] vs. 1.05 ± 0.74 [IPL device]). The patient satisfaction after both treatment modalities did not significantly vary during the 3-month follow-up, according to their data. The authors concluded that IPL use for MAL-PDT is an efficient alternative for the treatment of AK that results in complete remission and cosmesis equivalent to LED irradiation but causes significantly less pain. In a further work by the same group, the authors evaluated the efficacy, painfulness, patient satisfaction, and cosmesis of LED-based PDT in a prospective, randomized, controlled, split-face study [10]. They conducted topical ALA-PDT in 17 patients with AK ($n=131$) in a symmetrical dissemination suitable for a two-side comparison. After incubation with MAL (16%), irradiation was performed with the incoherent lamp (160 mW cm^{-2}; 100 J cm^{-2}; PDT 1200L, Waldmann Medizintechnik, Villingen-Schwenningen, Germany) on one side and an LED system (120 mW cm^{-2}; 40 J cm^{-2}; LEDA, WaveLight AG, Erlangen, Germany) on the opposite side followed by re-evaluation up to 6 months later. They reported no significant difference between the infiltration and keratoses scores in both treatment regimes ($p=0.812$) 6 months after treatment. The remission rate was 78.5% (LED system) vs. 80.3% (incoherent lamp). The authors reported no significant difference between the light sources regarding the painfulness ($p=0.988$) and patient satisfaction ($p=1$) during therapy (Fig. 28.1).

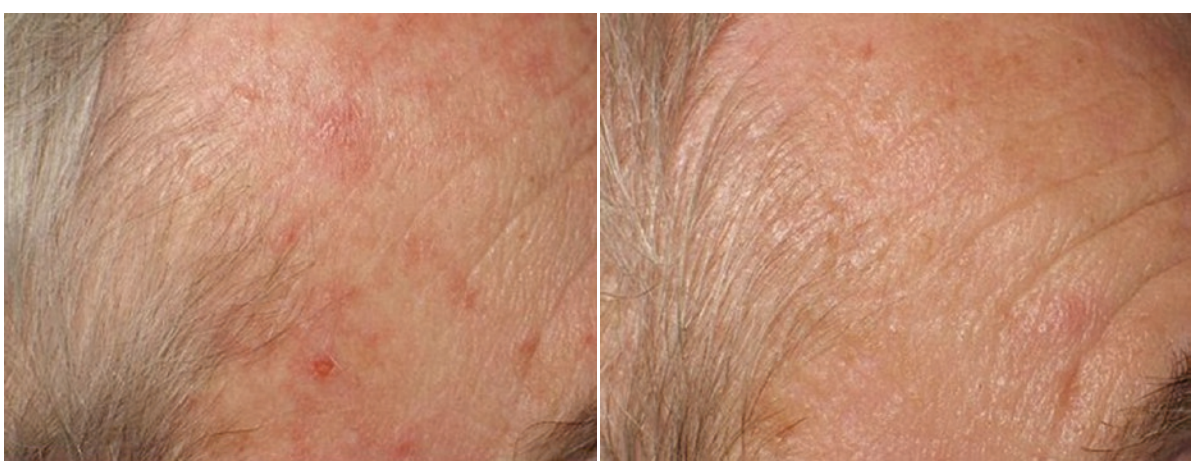

Fig. 28.1 *Left*: 74-year-old patient with field cancerized area on his left temple. Treatment of area with methylaminolevulinate (3 h) followed by an illumination with red light (light-emitting diode light source, 37 J/cm²). *Right*: complete clearance of lesions and improved cosmesis 6 months after a single photodynamic therapy session

Currently, the gold standard in topical PDT is an incoherent light source, either lamps (e.g., PDT 1200L, Waldmann Medizintechnik) or LEDs (e.g., Aktilite, Galderma, France; Omnilux PDT, Phototherapeutics, UK), which match the absorption maxima of the ALA- or MAL-induced porphyrins and accomplish the simultaneous irradiation of larger areas [20, 22, 70, 112, 116]. For tissue destruction during the treatment of malignant tumors, a light dose – using broad spectrum red light (580–700 nm) – of 100–150 J cm^{-2} (100–200 mW cm^{-2}) is chosen. For the more narrow emission spectra of the LED systems (bandwidth approx. 30 nm), the values are significantly lower (37–50 J cm^{-2}). The light intensity should not exceed 200 mW cm^{-2} to avoid hyperthermic effects [20, 22]. For inflammatory dermatoses, a light dose of 10–40 J cm^{-2} and a light intensity of 50–70 mW cm^{-2} are sufficient (broad-spectrum red light, usually multiple treatments). During irradiation, both the patient and clinic staff should be wearing protective goggles to avoid the risk of eye damage [68].

28.4 Mechanism of Action

In the presence of oxygen, the activation of a photosensitizer by light of the appropriate wavelength leads to the generation of ROS, in particular singlet oxygen. Depending on the amount and localization in the target tissue, these ROS modify either cellular functions or induce cell death by necrosis or apoptosis [69, 104, 117]. There is a need for heme and related molecules in fast proliferating, relatively iron-deficient tumor cells of epithelial origin. Therefore, intracellular uptake of heme-precursors like ALA or MAL is eased, resulting in a preferential sensitization of those cells. The same applies to target cells constituting inflammatory dermatoses. Therefore, tissue damage is mostly restricted to the sensitized cells, especially cells of mesenchymal origin like fibroblasts, almost omitting the surrounding tissue and resulting in an excellent cosmesis [72]. Aside from two case reports with possible coincidence, no further report of the carcinogenic potential of ALA/MAL-PDT has been published [72]. Moreover, in a recent study, even long-term topical application of ALA and subsequent irradiation with blue light in a hairless mouse model did not induce skin tumors [13]. Stender et al. [97] showed a delay in photoinduced carcinogenesis in mice after repetitive treatments with ALA-PDT.

28.5 Practical Aspects of Topical PDT

Because it could be shown that hyperkeratosis is the reason for a poor response by AK localized on the hands to PDT [104], keratolysis should be performed in hyperkeratotic lesions prior to incubation with the aid of a gentle abrasion or a nonbleeding curettage [67, 68, 109, 116]. Overnight incubation with an ointment for easy mechanical removal might also work. Extemporaneous ALA preparations are mostly applied to the lesions with little overlap to the surrounding tissue for 4–6 h prior to irradiation under occlusion and with a light protective dressing or clothing [104]. For the licensed MAL formulation (Metvix, Galderma, France; Metvixia, Galderma, USA), a shorter incubation time of 3 h is sufficient due to preferential uptake and higher selectivity [32, 106]. The entire area is here also covered with an occlusive foil to allow for better penetration. Lesion preparation is mandatory when using MAL as a photosensitizer.

The most important side effects of PDT are stinging pain and a burning sensation. Even if they are usually restricted to the time span of irradiation and a couple of hours thereafter [72], they often limit the patients' compliance. Especially if an extended irradiation field is selected, administration of analgesics is often necessary [110]. Pain perception can also be alleviated by concurrent cold air analgesia, which improves the tolerability of ALA/MAL-PDT [76]. Application of topical analgesics like eutectic mixtures of lidocaine/prilocaine (EMLA) prior to irradiation is not recommended because their high pH might chemically inactivate the photosensitizer. In addition, it could be shown that the topical application of EMLA induces a local vasoconstriction, which might reduce the pO_2-dependent effect of PDT [46].

Recently, it was shown that MAL-PDT is less painful than ALA-PDT. In the respective study, 69 patients with AK in field cancerization were treated and asked about their sense of pain on a visual analog scale (VAS; 1–10). If a score of ten was reachedn (worst imaginable pain), the study was discontinued. Fifty-four percent of the patients treated with ALA-PDT compared to 14% of patients who were treated with MAL-PDT reached this critical value. These results are confirmed by another work about AK distributed in field cancerization [66]. It is discussed whether ALA instead of MAL is transported in the endings of the peripheral nerves via gamma-

aminobutryic acid receptors. Independent of the photosensitizer used, pain medication is mandatory for the treatment of field cancerization, especially on the face and scalp. The complementary application of cold air (e.g., Cryo 6 derma, Zimmer Medizinsysteme, Neu-Ulm, Germany) can further reduce the sense of pain. Green light is less painful than red light, which can be explained by the lower penetration depth (1–2 mm) [88]. Babilas et al. [9] showed that the use of an IPL induces significantly less pain compared to an LED but reaches comparable remission rates. Another study pointed out that pain is the most frequent (92%) side effect of PDT; however, in only 2% of treatments the therapy must be discontinued due to pain [61]. A central prognostic factor is the dimension of the affected skin area. Cooling was reported as the most effective regime against pain. Other frequent side effects are edema and erythema (89%) that persist for 4–7 days and are reported not very bothersome to the patients. The development of pustules is reported by 6% of patients and is often the source of great uncertainty. In nearly all cases, the pustules are sterile. Days after tumor treatment, a dry necrosis sharply restricted to the tumor-bearing areas frequently develops. After 10–21 days, formed crusts come off, and usually complete re-epithelialization is observed. During this phase, most patients report only slight discomfort. Due to significant lower doses of both light and photosensitizer in the context of "low-dose PDT" for treatment of inflammatory dermatoses, few or no side effects are observed, although multiple treatments are necessary.

Due to photosensitization, which is restricted to cells of epithelial origin and does not sensitize fibroblasts or dermal fibers, usually no scarring or ulceration is observed clinically [72, 94, 104]. Pigmentary changes are also rare and only of temporary duration. Irreversible alopecia has not yet been observed in treated patients; however, due to the concomitant sensitization of the pilosebaceous units, this effect should be taken into account when treating hairy areas [72, 104].

Except in patients with known history of porphyrias or allergic reactions to active ingredients of the applied sensitizers, no severe limitations to performing ALA/MAL-PDT are known [115]. PDT can be repeated several times, and PDT is possible even in areas with prior exposure to ionizing irradiation [41].

28.6 Therapeutic Applications – Oncologic Indications

Regarding oncologic indications, AK and nodular or superficial BCCs and – since 2006 – Bowen's disease are approved indications for MAL. Approval was given by the US Food and Drug Administration for the use of ALA in combination with blue light for the treatment of AK and, more recently (2009), the ALA patch was approved for use in combination with red light for the treatment of AK in Europe.

28.6.1 Actinic Keratosis

AK become apparent in areas exposed to ultraviolet (UV) light and are the most frequent precancerous lesion of the skin. They often impose in a widespread pattern, which leads to the term *field cancerization*. The treatment of AK is mandatory because they have the potential to develop into invasive squamous carcinomas. In addition to PDT, there exist a number of registered chemical and/or immunological treatment options for the treatment of AK: 5-fluorouracil (5-FU), podophyllin, imiquimod, and diclofenac (PDT) [7]. The choice of the suitable treatment depends on numerous factors, one of which is the number and localization of the lesions that have to be treated. For therapy of single lesions, surgical or physical treatment options like, for example, cryotherapy, laser ablation, or surgery might be favorable, whereas for therapy of multiple lesions, PDT may be the first choice, in particular for AK of the scalp and face or in cases of basal cell nevus syndrome [117]. A great advantage of PDT compared to chemical and/or immunological treatment options is that the patient himself does not have to account for weeks of the treatment, which is a great problem if compliance is lacking.

The efficacy of ALA-PDT has been observed in multiple studies and is recommended in numerous consensus works and therapy guidelines of different national and international dermatologic societies [17, 75]. In a European multicenter, randomized, prospective study, MAL-PDT was compared to cryosurgery for the treatment of AK. A total of 193 patients (95%) with 699 lesions completed the trial. Patients received either a single treatment with MAL-PDT (repeated after 1 week in 8% of cases) or a double freeze-thaw course of liquid

nitrogen cryosurgery. MAL was applied for 3 h after slight lesion preparation, followed by illumination with broad-spectrum red light (75 J cm^{-2}). A follow-up visit was performed 3 months after treatment. The efficacy for MAL-PDT (single application) was 69% vs. 75% for cryosurgery, which was of no statistical significance. Thin lesions on the scalp had the highest response rates (80% and 82% for PDT and cryosurgery, respectively). Cosmetic outcome, as judged by the investigator, was superior for MAL-PDT (96% vs. 81%) [106].

Another comparable trial was conducted in Australia. In this study, MAL-PDT was used as a dual cycle, with two treatment sessions 1 week apart. PDT was compared to a single course of cryosurgery or placebo in 204 patients. Lesion response was also assessed after 3 months. A significantly higher complete remission rate with MAL-PDT was observed (91%) vs. 68% with cryosurgery and 30% with placebo. The cosmetic result was rated excellent in 81% of MAL-PDT patients vs. 51% of patients who were treated with cryosurgery [34].

A multicenter, randomized, double-blind, placebo-controlled study with two MAL-PDT cycles was performed in 80 patients with AK in the USA. PDT treatment parameters were similar to the above-mentioned trials. Assessment after 3 months revealed a complete lesion response rate of 89% for MAL-PDT vs. 38% for placebo. An excellent or good cosmetic outcome was reported in more than 90% of MAL-treated patients [77].

Dragieva et al. [28] focused on their recent prospective, randomized, double-blind, placebo-controlled study of MAL-PDT in the treatment of AK ($n=129$) in 17 transplant recipients. Because transplant recipients have an increased propensity to develop multiple AKs, which demonstrate an increased transformation rate into invasive squamous cell carcinoma, an effective treatment is imperative. Sixteen weeks after illumination with red light (incoherent light source, 75 J cm^{-2}, 80 mW cm^{-2}), they observed complete remission in 13 of 17 patients. They concluded that MAL-PDT is a safe and effective treatment for AKs in transplant recipients that may reduce the risk of transformation of AK to squamous cell carcinoma [28].

Also for ALA-PDT in the treatment of AK, a randomized, placebo-controlled, uneven parallel group study was published recently. In 243 patients, clinical response (CR), based on lesion clearing, was assessed at weeks 8 and 12. Patients were randomized to receive either vehicle or ALA (Levulan Kerastick, DUSA Pharmaceuticals), followed within 14–18 h by illumination with visible blue light (BLU-U, DUSA Pharmaceuticals; low-pressure fluorescent lamps). Complete response rates for patients treated with ALA-PDT with ≥75% of the treated lesions clearing at weeks 8 and 12 were 77% and 89%, respectively. In the placebo group, clearing rates were 18% and 13%. The 12-week clearing rates included 30% of patients who received a second ALA-PDT course. Moderate to severe discomfort during illumination was reported by at least 90% of patients; however, only 3% of patients required discontinuation of therapy [78].

For the purpose of lowering the amount of side effects of ALA-PDT, shorter incubation periods (1, 2, 3 h), in conjunction with pretreatment with 40% urea to enhance ALA penetration and the use of topical 3% lidocaine hydrochloride to decrease discomfort, were also evaluated. One and 5 months after therapy in 18 patients with at least four nonhypertrophic AKs, a reduction of lesions in the target of up to 90% was observed. No difference was seen between the three incubation periods nor did pretreatment with urea or lidocaine have an influence on the therapeutical outcome [110].

Morton et al. [73] compared the effectiveness of MAL-PDT with cryotherapy in a randomized, multicenter trial in a side-by-side design. They treated 119 patients with 1,501 lesions. Twenty-four weeks after treatment both groups showed no significant difference in terms of remission rate (MAL-PDT 89.1%, cryotherapy 86.1%). Patients as well as investigators favored PDT because of a significantly better cosmesis. In a recently published randomized, double-blinded, prospective study, Moloney et al. [42] compared MAL- and ALA-PDT in a split-face modus in 16 patients. Effectiveness of both treatments was not significantly different. However, MAL-PDT turned out to be less painful.

In the USA, ALA is approved only in combination with blue light for the treatment of AK. In a multicenter phase IV trial, 110 patients with 748 lesions were treated with a 20% ALA formulation (Levulan Kerastick, DUSA Pharmaceuticals). One month after therapy, 76% of lesions showed complete remission; 2 months after therapy 72% showed complete remission. The recurrence rate 1 year after therapy was 19% [95].

In patients who have received an organ transplant ($n=27$), the potential of PDT to prevent the appearance of epithelial tumors was investigated. The patients showed AKs, BCCs, and viral warts. A randomized area was treated with MAL-PDT ($\lambda_{em}=570–670$ nm; light dose of 75 J cm^{-2}) and compared to an untreated area. All

patients were immune-suppressed for 3 years. The median time until appearance of a new lesion was significantly longer in the treatment group compared to the control group (9.6 vs. 6.8 months). Twelve months after treatment, 62% of the treated areas did not show any lesion compared to 35% of the control areas. Thus, PDT seems to have a preventive character in terms of epithelial neoplasias [71]. Dragieva et al. [27, 28] investigated in a prospective, randomized, double-blinded, placebo-controlled study of the effectiveness of MAL-PDT in the treatment of AK ($n=129$) in patients who had received an organ transplant. In 13 of 17 patients, a complete remission was reported 16 weeks after treatment.

28.6.2 Basal Cell Carcinoma

Various studies concerning ALA/MAL-PDT for BCC have been performed during the past years [49, 64, 71, 82, 94, 104, 109, 113]. The weighted average complete clearance rates, after follow-up periods varying between 3 and 36 months, were 87% in 12 studies treating 826 superficial BCCs and 53% in 208 nodular BCCs [64, 72]. Available data compiled from other trials have shown an average of 87% for superficial BCCs, and 71% for nodular BCCs [117]. To ameliorate poor outcome after PDT of thicker BCC lesions, Thissen et al. [109] treated 23 patients with 24 nodular BCCs once with ALA-PDT (incoherent red light; 100 mW cm^{-2}, 120 J cm^{-2}) 3 weeks after debulking of the BCCs. The former tumor areas were excised 3 months later and histopathologically evaluated for residual tumor. Twenty-two (92%) of the 24 nodular BCCs showed a complete response both clinically and histologically.

In a prospective phase III trial comparing ALA-PDT with cryosurgery, Wang et al. [113] included 88 superficial and nodular BCCs. Recruited individuals could only allowed to have one lesion to be included in the trial. A 20% ALA/water-in-oil cream was applied for 6 h under an occlusive dressing, followed by irradiation with a laser at 635 nm (80 mW cm^{-2}, 60 J cm^{-2}). In the cryosurgery arm, lesions were treated with liquid nitrogen with the open spray technique using two freeze-thaw cycles for 25–30 s each time. After 3 months, punch biopsies were performed and revealed a recurrence rate of 25% in the PDT group and 15% in the cryosurgery group. However, the clinical recurrence rates were only 5% for ALA-PDT and 13% for cryosurgery. The discrepancy between the clinical appearance of the treated lesion and the actual status in histology is problematic because tumor recurrence can be masked. In the PDT-treated group, a better cosmetic outcome and a shorter healing time were documented. Another work reported the recurrence rates after a 48-month follow-up period after treatment of superficial BCC (sBCC) with PDT (22%) vs. cryotherapy (19%) [11]. In a review of Lehmann, the recurrence rates in a 60-month follow-up were quoted as comparable for PDT (74%) and cryotherapy (74%) [62].

Soler et al. [94] studied the long-term effects of MAL-PDT in 59 patients with 350 BCCs. Curettage of nodular tumors occured before MAL-PDT (160 mg/g) was applied to all tumors for 24 or 3 h prior to irradiation with a broadband halogen light source (50–200 J cm^{-2}). Patients were followed for 2–4 years (mean 35 months). The overall cure rate was 79%; cosmetic outcome was excellent or good in 98% of the completely responding lesions.

In a recent, open, uncontrolled, prospective, multicenter trial, patients with superficial and/or nodular BCCs who were at risk of complications, poor cosmetic outcome, disfigurement, and/or recurrence using conventional therapy were studied. Ninety-four patients were treated with a single cycle of MAL-PDT involving two treatment sessions 1 week apart, and followed up at 3 months, at which time nonresponders were retreated. The clinical lesion remission rate after 3 months was 92% for superficial BCCs, and 87% for nodular BCCs. Histological cure rate at this time point was 85% for superficial BCCs and 75% for nodular BCCs. Twenty-four months after treatment the overall lesion recurrence rate was 18% [49].

In a comparative trial in Australia, MAL-PDT for the treatment of nodular BCCs was compared to placebo. Lesions from 66 patients were treated with two sessions of either placebo or MAL-PDT in a randomized, double-blind, controlled study. If there was no complete response 3 months after initial treatment, lesions were excised. After 6 months, the complete remission rate was 73% for MAL-PDT compared to 21% for placebo [32].

In another European multicenter, open, randomized trial, MAL-PDT for treatment of nodular BCCs was compared with surgery. A total of 101 patients were included and received either PDT twice 7 days apart (75 J cm^{-2} red light) or surgical excision. The primary endpoint of this trial was the clinically assessed lesion clearance 3 months after treatment in addition to

cosmesis. The 3-month cure rate was similar for MAL-PDT and surgery (91% vs. 98%); the 24-month recurrence rate was 10% with MAL and 2% with surgery. The cosmetic result was rated good/excellent in 85% of the patients who received PDT vs. 33% of those who received surgery [82].

ALA-PDT also can be used for adjuvant therapy in combination with Moh's micrographic surgery, as reported by Kuijpers et al. [60]. In four patients who underwent Moh's micrographic surgery for extensive BCC, the central infiltrating tumor part was excised first. After re-epithelialization, ALA-PDT was performed on the surrounding tumor rims (2–5 cm) that bore remaining superficial tumor parts. This led to a complete remission of the tumors with excellent clinical and cosmetic results (follow-up period up to 27 months) [60].

Szeimies et al. [107] compared in a multicenter, randomized, controlled, open study of MAL-PDT (two sessions 7 days apart and repeated 3 months later if there was incomplete CR) with simple excision surgery (at baseline) in 196 patients with an average of 1.4 BCCs lesions per patient. Primary endpoints were efficacy and cosmetic outcome over a 1-year period. Mean lesion count reduction at 3 months was 92.2% with MAL-PDT vs. 99.2% with surgery, which confirmed the noninferiority hypothesis (95% confidence interval [CI] −12.1, to −1.9). A total of 92.2% lesions showed CR at 3 months with MAL-PDT vs. 99.2% with surgery. At 12 months, 9.3% lesions recurred with MAL-PDT and none recurred with surgery. Cosmetic outcome was statistically superior for MAL-PDT at all time points. At 12 months, 94.1% of lesions that were treated with MAL-PDT had an excellent or good cosmetic outcome according to the investigator, compared with 59.8% treated with surgery. This difference was confirmed by the patients' assessment. The proportion of excellent cosmetic outcome markedly improved over time with MAL-PDT, unlike surgery. However, the surgical standard treatment of BCCs is curettage, and this procedure likely would lead to significant better cosmetic results compared to simple excision surgery [107].

However, even if all clinical studies qualify PDT as an effective treatment of BCC, Moh's micrographic surgery shows generally higher cure rates compared to PDT. Besides, the relatively short follow-up of most of the performed studies has to be considered. Mandatory indications for surgical treatment are different histological subtypes like pigmented or morpheic BCCs or BCCs located in the area of the facial embryonic fusion clefts, as well as all BCCs thicker than 3 mm if no debulking procedure is performed prior to PDT.

28.6.3 Bowen's Disease and Initial Squamous Cell Carcinoma

MAL-PDT has been approved for the treatment of Bowen's disease since 2006 and is – as a planar epithelial precancerous lesion – highly suitable for PDT.

In a recent study by Salim et al., [87], ALA-PDT was compared to topical 5-FU for the treatment of Bowen's disease. In this bicenter, randomized, phase III trial, 40 patients with one to three lesions of previously untreated, histologically proven Bowen's disease received either PDT or 5-FU. ALA 20% in an oil/water emulsion was applied 4 h prior to illumination with an incoherent light source (Paterson lamp, Photo Yherapeutics, UK; $\lambda_{em} = 630 \pm 15$ nm, 50–90 mW cm^{-2}, 100 J cm^{-2}). Treatment with 5-FU was once daily during week one and then twice daily during weeks 2–4. At the first follow-up (week 6), both ALA-PDT and 5-FU applications were repeated, if required. Twenty-nine of 33 lesions (88%) treated with PDT showed complete response vs. 67% after 5-FU (22 of 33). After 1 year of follow-up, further recurrences reduced the complete clinical clearance rates to 82% and 42%, respectively [87]. In another recently published, placebo-controlled, randomized, multicenter study, Morton et al. [74] compared the effectiveness of MAL-PDT with cryotherapy and 5-FU in the treatment of histologically confirmed squamous cell carcinoma in situ (iSCC) (lesion size 6–40 mm) in 225 patients with 295 lesions, with follow-up at 3 and 12 months after the last treatment. MAL-PDT or matching placebo-cream PDT ($n = 17$), cryotherapy ($n = 82$), or topical fluorouracil (5% cream; $n = 30$) was performed. MAL or placebo cream was applied for 3 h before illumination with broadband red light (75 J/cm^2, 570–670 nm). Treatment was repeated 1 week later. Cryotherapy was performed with liquid nitrogen spray. Fluorouracil was applied for 4 weeks. Lesions with a partial response at 3 months were retreated. The primary endpoint was a clinically verified complete response by the lesions and the cosmetic outcome on a 4-point rating scale. The authors reported that at 12 months the estimated sustained lesion complete response rate with MAL-PDT was superior to that of the response rate with cryotherapy (80% vs. 67%; odds ratio, 1.77; 95% CI,

1.01–3.12; $p=0.047$) and better than that with fluorouracil (80% vs. 69%; odds ratio, 1.64; 95% CI, 0.78–3.45; $p=0.19$). Cosmetic outcome at 3 months was good or excellent in 94% of patients who were treated with MAL-PDT vs. 66% of patients who were treated with cryotherapy and 76% of those who were treated with fluorouracil, and this cosmetic outcome was maintained at 12 months. The authors concluded that MAL-PDT is an effective treatment option for iSCC, with excellent cosmesis.

28.7 Therapeutic Applications – Nononcologic Indications

In contrast to PDT treatment of tumors, where cellular destruction is the main goal of the therapy, the modulation of functions on the cellular and subcellular levels probably plays the main role in PDT treatment of inflammatory skin conditions. We know that Langerhans cells are temporarily suppressed in their activity, which leads to a minor immune suppression [44]. Activating protein 1 and nuclear factor kappa B, and thus different cytokines–are induced and influence inflammatory cells in the epidermis and dermis and fibroblasts [56, 57]. The therapeutic protocols differ significantly to those used for the treatment of tumors. Significantly lower doses of both light and photosensitizers are used in the context of a "low-dose PDT" for the treatment of inflammatory skin conditions. However, multiple treatments are necessary to achieve the desired therapeutic effects with little or no side effects. So far, the best results for PDT in inflammatory skin conditions have been achieved with ALA. Even though numerous publications report a remarkable therapeutical benefit after PDT of, for example, acne vulgaris, localized scleroderma, psoriasis, or genital warts, there is a need for controlled clinical trials to study the different indications [50, 51, 55, 99]. However, it is very likely that PDT will be of great value for a choice of nononcologic indications.

28.7.1 Psoriasis Vulgaris

The data provided in the literature for the treatment of psoriasis vulgaris is very controversial. It could be shown that ALA is able to penetrate the parakeratotic stratum corneum in the area of a psoriatic plaque and to accumulate selectively in the diseased tissue [14, 101]. Boehncke et al. [15] compared in three patients the efficacy of ALA-PDT with a conventional topical treatment using dithranol in a half-side trial. The lesions were incubated with a 10% ALA ointment for 5 h followed by irradiation with an incoherent light source (600–700 nm, 70 mW cm^{-2}, 25 J cm^{-2}). This treatment was performed once weekly for 3 weeks; the plaques on the other side received anthralin on a daily basis. The time to reach complete remission of psoriatic plaques was similar in both treatment settings. In a recent study performed by Collins and coworkers [23], 22 patients with psoriasis were treated with ALA-PDT. After application of a 20% ALA preparation for 4 h, the plaques were illuminated using an incoherent light projector (400–650 nm, 300 mW cm^{-2}, 2–16 J cm^{-2}). In 7 of the 22 patients, some of the treated plaques healed. In another study, the same working group studied the effect of multiple treatments with ALA-PDT [83]. Ten patients with chronic plaque-stage psoriasis were treated up to 3 times a week for a maximum of 12 treatments. A 20% ALA emulsion was applied for 4 h; afterwards the plaques were irradiated with a broadband light source at 15 mW cm^{-2} and 8 J cm^{-2}. In eight patients a clinical success was achieved. However, all patients complained of pain during the irradiation process. Beatti et al. [12] reported a lack of efficacy and tolerability of topical PDT for psoriasis compared with narrowband UVB phototherapy. Furthermore, Radakovic-Fijan et al. [81] performed a randomized, intrapatient comparison study of topical ALA-PDT in psoriatic patients and documented not only an unsatisfactory clinical response but also frequent occurrence of pain during and after irradiation. They concluded that topical ALA-PDT is an inadequate treatment option for psoriasis. The pain seems to be dose-dependent for both the photosensitizer and light, and it sustains for a period of 2 days after therapy. It is, therefore, important to study whether both light dose and drug concentration can be lowered following the concept of a "low-dose PDT," with the goal being reduction of pain without hampering the efficacy of the therapy.

In another work this group performed a prospective, randomized, double-blind, phase I/II intrapatient comparison study of the use of topical ALA-PDT in 12 patients with chronic plaque-type psoriasis. In each patient, three psoriatic plaques were randomly treated with a light dose of 20 Jcm^2 and 0.1%, 1%, and 5% ALA, respectively. Treatment was conducted twice a week

until complete clearance or for a maximum of 12 irradiations. Therapeutic efficacy was assessed by weekly determination of the psoriasis severity index. The authors reported that the mean percentage improvement was 37.5%, 45.6%, and 51.2% in the 0.1%, 1%, and 5% ALA-treated groups, respectively. However, due to severe burning sensations and pain, irradiation had to be interrupted several times. The authors concluded that topical ALA-PDT was not an appropriate treatment option for plaque-type psoriasis due to disappointing clinical efficacy, the time-consuming treatment procedure, and its unfavorable adverse event profile [90].

Another side effect reported in the literature is Koebnerization [96]. One patient receiving PDT with ALA for the treatment of AK and initial squamous cell carcinoma developed psoriatic lesions on her lower leg 2 days after PDT.

The impact of PDT on psoriatic lesions is not yet fully clear because the therapeutic protocols used differ significantly and, so far, no controlled clinical trials with high numbers of patients are available. However, potential advantages do exist for PDT in contrast to UV irradiation because there is no evidence of an increased risk of cutaneous cancer developing after PDT. Some investigations also show that the number of treatments needed to gain therapeutic success seems to be lower in comparison to psoralen plus UVA (PUVA) therapy.

28.7.2 Human Papilloma Virus-Induced Skin Diseases

Vulgar warts on the hands and feet, plain warts, or genital warts (*Condylomata acuminata*) are common skin diseases induced by human papilloma viruses [19]. Even after surgical removal or application of cytotoxic drugs, a high rate of recurrenc can be observed. Because the fast proliferating cells in viral acanthomas accumulate ALA-induced PpIX selectively [31, 85] and because ALA-PDT has virucidal properties [93], PDT has been introduced as a possible alternative treatment modality.

28.7.2.1 Vulgar Warts

Kennedy et al. [58] did not achieve success in the treatment of vulgar warts with ALA-PDT in their study that was published in 1990. Correspondingly, Amman et al. [3] could not report successful topical ALA-PDT in the treatment of recalcitrant vulgar warts. Only in one out of six patients was a complete remission achieved within 2 months after PDT. The reason for the treatment failures was probably the less effective cutaneous penetration of ALA due to the prominent hyperkeratosis in vulgar warts. Smetana et al. [93] tried to increase the effectivity of ALA-PDT by adding the penetration enhancers Ethylenediaminetetraacetic acid (2%) and Dimethyl sulfoxide (2%). With this formulation they were able to treat successfully widespread vulgar warts in a patient who received a kidney transplant. Within a follow-up period of 2 years, no recurrence was observed [93].

Stender et al. [98] conducted a comparative trial in 30 patients with recalcitrant warts. After incubation with a 20% ALA-cream for 5 h, irradiation was performed using a slide protector with different wavelengths and a total light dose of 40 J cm^{-2}. Before ALA-PDT, keratolysis of the warts was performed [98]. After PDT with white light, which was performed three times, complete remission was significantly higher (CR 73%) than after PDT performed three times with blue light (CR 28%) or red light (CR 42%) or with the use of cryotherapy as a comparative treatment modality (CR 20%). Within the follow-up period of 12 months, no further recurrences were observed. This study was then followed by a double-blinded, randomized trial of 45 patients by the same working group, which consolidated the results of the first pilot trial [99]. In this trial it also was shown that ALA-PDT is successful in the treatment of recalcitrant warts of the hand and the soles of the feet. Irradiation was performed with an incoherent light source (Waldmann PDT 1200L, 590–700 nm) at a light intensity of 50 mW cm^{-2} and a total light source of 70 J cm^{-2}. The procedure was repeated after 1 and after 2 weeks. If the warts were still present after 7 weeks, another therapeutic cycle (three treatments in weekly increments) was performed. The patients were advised to debride their warts prior to PDT. The trial resulted in a complete remission of warts in 56% of patients in the ALA-PDT-treated group compared to 42% in the placebo group. A major side effect of this treatment is pain [99].

Fabbrocini et al. [30] performed another placebo-controlled trial where 64 plantar warts were treated with 20% ALA after keratolysis. Fifty-seven warts served as controls (treated only with the emollient without drug). Irradiation was performed with an incoherent light source (400–700 nm, 50 J cm^{-2}); it was repeated,

depending on the results, up to 3 times per week within a period of 3 weeks. Two months after therapy, 75% of the warts treated with ALA-PDT showed complete remission, whereas only 22.8% of the warts treated with placebo showed complete remission.

These results show that ALA-PDT in combination with a sufficient keratolysis is a successful alternative for the treatment of recalcitrant warts. Again, the main drawback is pain during irradiation, which probably will hinder a broad use of PDT, especially among children.

28.7.2.2 Genital Warts

Most of the destructive therapeutic modalities of anogenital condylomata, like electrodessication or vaporization using a carbon dioxide (CO_2) laser only lead to a destruction of the visible part of the warts, whereas subclinical lesions will not be treated effectively and cause the high rate of recurrence. ALA-PDT could be of great interest for this indication, especially because of the selective destruction of subclinical virus-shedding areas, which help to reduce the high rate of recurrence.

Because a selective enrichment of PpIX in warts is the main prerequisite for the therapeutic efficacy, Fehr et al. [31] studied the fluorescence of PpIX after topical application of ALA in vulvar condylomata in 22 patients. Three to 6 h after application of ALA, a homogeneous distribution of PpIX was seen in the epidermis. After 24 h, fluorescence was seen only in the region of the granular layer. Similar results were reported by Ross et al. [85]. They were able to show a selective accumulation of PpXI in condyloma after topical application of ALA. Two hours after the start of incubation, highest selectivity compared to the surrounding normal skin was achieved. In a pilot study, seven patients with anogenital warts were treated with a cream containing 20% ALA in combination with lidocaine hydrochloride. The incubation time was 14 h. After this time period, a local anesthetic was applied again for another 2 h. Afterwards, the area was irradiated with an argon-ion pumped dye laser (630 nm, 75–150 mW cm^{-2}, 100 J cm^{-2}). Four of seven patients treated with ALA-PDT showed a complete remission [33]. The most important goal in the treatment of anogenital warts is the reduction of the high rate of recurrences after conventional treatment modalities. Perhaps the combination of classic ablative treatments with PDT, which contributes to a selective destruction of subclinical virus-shedding areas, might be of help. However, a recent trial studied whether vaporization of condyloma acuminata (CA) using a CO_2 laser before PDT may enhance efficacy. CO_2 laser ablation was followed by ALA-PDT in a phase III prospective, randomized, bicenter, double-blind study to prevent recurrence of CA. One-hundred seventy-five patients with CA received CO_2 laser vaporization plus adjuvant ALA-PDT ($n=84$) or adjuvant placebo-PDT ($n=91$). A 20% ALA or placebo ointment was applied to the CA area 4–6 h before CO_2 laser vaporization, followed by illumination with red light (600–740 nm, 100 mW cm^{-2}, 100 J cm^{-2}). The cumulative recurrence rate 12 weeks after treatment was 50.0% in the ALA-PDT group vs. 52.7% in the placebo-PDT group ($p=0.72$). No statistically significant difference between groups was detected with regard to recurrence rates up to 12 months after treatment. No major complications were observed. Although adjuvant ALA-PDT of CA after CO_2 laser ablation was well tolerated, no significant difference with regard to recurrence rate was observed with CO_2 laser vaporization alone [108].

28.7.3 Acne Vulgaris

PDT in the treatment of acne is based on the fact that *Propionibacterium acnes* contains endogenous porphyrins, in particular coproporphyrin III [50]. Therefore, visible as well as blue light phototherapy is effective. Hongcharu et al. [47] treated 22 patients with acne vulgaris on the back with ALA-PDT in an open, prospective trial. Eleven patients received a single treatment; the other 11 patients were treated 4 times. ALA (20%) was applied occlusively for 3 h; afterwards, the area was irradiated with red light (550–700 nm, 150 J cm^{-2}). The phototoxic reaction after ALA-PDT was restricted selectively to areas containing sebaceous glands. The function of the sebaceous glands was altered, and the number of bacteria in the follicles was reduced. Histopathology showed acute cytotoxic damage to the sebaceous glands. Clinically, a significant improvement of the inflammatory acne lesions was observed after ALA-PDT, which was sustained after multiple PDT sessions for more than 20 weeks. Although ALA-PDT was very effective in the treatment of acne, severe side effects were observed:

pain, erythema, edema, transient hyperpigmentation, sometimes even blistering, purpura, or an acute acneiform rash. These results were in accordance with Itoh et al. [51]. Twenty-three patients with acne vulgaris on the face that was resistant to standard therapy were treated with ALA-PDT. An emulsion containing 20% ALA was applied for 4 h and irradiated with polychromatic light from a halogen lamp (600–700 nm, 17 mW cm^{-2}, 13 J cm^{-2}). In all patients acne improved, and the development of new acne spots was reduced up to 6 months after PDT. Considerable side effects were pain, edema, crust formation, erythema, and hyperpigmentation [51]. Pollock et al. [79] showed a statistically significant reduction in inflammatory acne lesions after three courses of ALA-PDT performed within 3 weeks. However, because they documented no statistically significant reduction in *P. acnes,* they suggested an alternative mode of action for ALA-PDT for acne.

Wiegell and Wulf [114] evaluated the efficacy and tolerability of MAL-PDT in patients with moderate to severe facial acne vulgaris in a randomized, controlled, investigator-blinded trial. The treatment group ($n=21$) received two MAL-PDT treatments 2 weeks apart; 15 patients were assigned to the control group. Both groups were evaluated 4, 8, and 12 weeks after treatment. Efficacy evaluation included changes from baseline in numbers of noninflammatory and inflammatory lesions, changes from baseline in global acne severity grade, and clinical assessments of clinical improvement by patient and the evaluating dermatologist. Pain scores during treatment and local adverse effects were also evaluated. The authors reported that, 12 weeks after treatment, the treatment group showed a 68% reduction from baseline in inflammatory lesions vs. no change in the control group ($p=0.0023$). There was no reduction in the number of noninflammatory lesions after treatment. All patients experienced moderate to severe pain during treatment and developed severe erythema, pustular eruptions, and epithelial exfoliation. Seven patients did not receive the second treatment due to adverse effects. The authors concluded that MAL-PDT is an efficient treatment for inflammatory acne but that the use of this treatment option is limited because of severe pain and severe adverse effects [114].

Horfelt et al. [48] investigated the efficacy and tolerability of MAL-PDT in patients ($n=30$) with moderate to severe acne in a blinded, prospective, randomized, placebo-controlled, multicenter study. Each side of each patient's face was randomly assigned to treatment with MAL or placebo cream. A second treatment was given 2 weeks later. Patients assessed the intensity of pain on a VAS. Inflammatory and noninflammatory acne lesions were counted at baseline and 4 and 10 weeks after the last PDT treatment. The authors reported a statistically significant greater reduction in the total inflammatory lesion count with MAL-PDT compared with placebo-PDT at week 12 (median reduction 54% [95% CI 35–64%] vs. 20% [95% CI 8–50%]). However, MAL-PDT was associated with more pain than placebo-PDT. The authors concluded that MAL-PDT is effective in the treatment of moderate to severe inflammatory facial acne.

These investigations indicate that ALA-PDT is very potent in the treatment of acne vulgaris. However, with most of the present protocols, the massive side effects do not qualify it for routine use. Perhaps significantly lower doses of both light and photosensitizer combined with a higher number of treatments may improve the efficacy and lower the rate of side effects.

28.7.4 Morphea and Lichen Sclerosus

Morphea is a chronic inflammatory reaction of the skin, which results after an inflammatory phase in a circumscribed sclerosis of the skin. Although the prognosis of morphea is mostly favorable, widespread lesions could lead to contractions of joints and immobilization. Although PUVA or bath-PUVA therapy and high-dose UVA_1 are effective in the treatment of morphea, the limited penetration depth of UV light as well as the long-term side effects of UV therapy (carcinogenic potential, skin aging) should be considered. In a clinical observation, ten patients with morphea who did not respond to bath-PUVA, penicillin infusions, or local therapies were treated with topical ALA-PDT. After application of the ALA gel (3%) for 6 h, irradiation was performed with an incoherent light source (PDT 1200L, 40 mW cm^{-2}, 10 J cm^{-2}). This treatment was repeated once or twice weekly for 3–6 months [55]. The mean number of therapies was 26 ± 8. Morphea was judged before, during, and after therapy using a durometer [92] or a clinical score [84]. In every patient, both scores were reduced significantly at the end of therapy. A slight burning sensation or mild pruritus and transient hyperpigmentation in the treated area were reported as side effects during the irradiation sessions. Even after 2 years, no further progression or recurrence were observed. However, in some patients,

new morphea lesions developed on sides not treated with PDT previously.

The effectivity of ALA-PDT was also reported for lichen sclerosus [45]. Twelve women with lichen sclerosus and severe pruritus were treated with a 20% ALA formulation followed by irradiation with light from an argon-ion pumped dye laser (635 nm, 70 mW cm^{-2}, 80 J cm^{-2}). If the pruritus did not resolve after the first treatment, the patients were retreated within 1–3 weeks after the first therapy. PDT was tolerated well, and 6–8 weeks after the last session pruritus improved in 10 of 12 patients.

28.7.5 Cosmetic Indications

A general advantage of PDT that is consistent through all clinical studies is the excellent cosmetic result. Numerous studies attest to an improvement in cosmesis. The use of PDT with the sole aim of improving different cosmetic aspects of the skin is obvious, especially of sun-damaged or prematurely aged skin. For this cosmetic-aimed PDT, IPLs, blue light, incoherent red light, and pulsed diode lasers are light sources in the focus of interest [111].

Touma et al. [110] investigated the effects of ALA-PDT in patients ($n=18$) with AK and moderate sun-damaged skin on the face. ALA was incubated for 1, 2, or 3 h followed by an irradiation with blue light (10 J cm^{-2}). The different incubation times induced no different effect. At 1 and 5 months after therapy there was not only a significant reduction of AK but also a significant improvement of several photodamage parameters. The authors concluded that ALA-PDT is safe and effective for AK treatment as well as for improving photodamage.

Babilas et al. [8] investigated the cosmetic outcome in a prospective, randomized, controlled, split-face study of 25 patients with AK ($n=238$) and sun-damaged skin using two different light devices. After incubation with MAL, irradiation was performed with an LED device (50 mW cm^{-2}; 37 J cm^{-2}) vs. and IPL device (80 J cm^{-2}, 610–950 nm filtered hand piece), followed by re-evaluation up to 3 months later. Cosmesis of the treated but perilesional area was evaluated before and up to 3 months after treatment using a four-level rating for wrinkling, hyperpigmentation, hypopigmentation, hair coat, redness, and desquamation. The sum of the score value was calculated. In addition, the overall cosmeses were evaluated by both the patient and the physicians (two independent and blinded investigators) on a scale of 1 (very bad) to 10 (excellent). According to their results, the patients (5.52 ± 2.06 [both treatment sites prior to PDT] vs. 7.76 ± 1.39 [IPL site 3 months after PDT] and 7.92 ± 1.29 [LED site 3 months after PDT] as well as the investigators (6.64 ± 1.79 [both treatment sites prior to PDT] vs. 8.20 ± 1.06 [IPL site 3 months after PDT] and 8.16 ± 0.97 [LED site 3 months after PDT] assessed a significant improvement of cosmesis due to treatment, which was irrespective of the light device used [8]. In another study the combination of ALA-PDT with an IPL device induced an excellent cosmetic result in 17 patients with diffuse sun-damaged skin. Side effects like hypopigmentation and scars were not visible [86]. Gold et al. [39] evaluated short-contact (30–60 min) ALA-PDT using IPL vs. the use of IPL alone in 16 patients with a side-by-side study design. Three treatments were given at 1-month intervals, and follow-up visits occurred 1 and 3 months after the final treatment. The authors reported a greater improvement in the ALA-PDT/IPL side than in the side treated with IPL alone side for all facets of photodamage – crow's feet appearance (55% vs. 29.5%), tactile skin roughness (55% vs. 29.5%), mottled hyperpigmentation (60.3% vs. 37.2%), and telangiectasias (84.6% vs. 53.8%). The clearance rate of AK lesions was also higher (78% vs. 53.6%). They concluded that short-contact ALA-PDT/IPL induces a greater improvement of photodamaged skin and greater clearance of AK lesions than IPL alone, and they confirmed the usefulness of ALA-PDT in photorejuvenation.

Corresponding results were published by Dover et al. [26], who performed a prospective, randomized, controlled, split-face study. The patients ($n=20$) received series of three split-face treatments 3 weeks apart, during which half of the face was pretreated with 5-ALA followed by IPL treatment and the other half was treated with IPL alone. Two additional full-face treatments (with IPL alone) were then delivered 3 weeks apart. Assessment of global photodamage, fine lines, mottled pigmentation, tactile roughness, and sallowness (on a scale of 0–4) was performed by a blinded investigator before each treatment and 4 weeks after the final treatment. Patients also completed an assessment at the conclusion of the study comparing their results with pretreatment photographs. The authors reported that pretreatment with 5-ALA resulted in more improvement in the global score for photoaging

(16 subjects [80%] vs. 9 subjects [45%]) and mottled pigmentation (19 subjects [95%] vs. 12 subjects [60%]) than IPL treatment alone. More successful results were achieved on the side pretreated with 5-ALA compared with the side treated with IPL alone for fine lines (12 subjects [60%] vs. 5 subjects [25%]) and mottled pigmentation (17 subjects [85%] vs. 4 subjects [20%]). Though there was noticeable improvement over baseline scores with respect to tactile roughness and sallowness, pretreatment with 5-ALA did not seem to enhance the results of the IPL treatment. The final investigator cosmetic evaluations and subject satisfaction scores were significantly better for the 5-ALA-pretreated side. The authors concluded that the adjunctive use of 5-ALA for the treatment of facial photoaging with IPL provides significantly greater improvement in global photodamage, mottled pigmentation, and fine lines than treatment with IPL alone, without a significant increase in adverse effects [26].

28.7.6 Leishmaniasis

A recently published placebo-controlled, randomized study compared the effectiveness of PDT to topically applied paromomycin in patients ($n=60$) with cutaneous leishmaniasis. The patients were randomly divided into three treatment groups of 20 subjects each. Group 1 was treated weekly with topical PDT, and groups 2 and 3 received twice-daily topical paromomycin and placebo, respectively. The duration of treatment was 4 weeks for all groups. These groups were followed for 2 months after the end of treatment. The authors reported that 57 patients with 95 lesions completed the study. At the end of the study, complete improvement was seen in 29 of 31 (93.5%), 14 of 34 (41.2%), and 4 of 30 lesions (13.3%) in groups 1, 2, and 3, respectively. At the same time point, 100%, 64.7%, and 20% of the lesions had parasitological cure in groups 1, 2, and 3, respectively. The authors concluded that topical PDT can be used safely as a rapid and highly effective alternative treatment choice for cutaneous leishmaniasis [4]. Enk et al. [29] performed ALA-PDT twice on 11 patients with 32 cutaneous leishmaniasis lesions and reported a lack of any parasites in 31 out of 32 lesions; the average reduction in size was 67%. Cosmetic results were excellent, and there was no recurrence within 6 months. Further case reports document the successful use of PDT in cutaneous leishmaniasis [35, 36]. Regarding the mechanism of action, it is proposed that PpIX leads to the generation of singlet oxygen that induces the destruction of the parasite's coat and oxidates bacterial lipids and proteins [100]. All in all, PDT seems to be a valuable treatment strategy with exceptional cosmetical results.

28.8 Conclusion

PDT in dermatology is approved for the treatment of sBCC, AK, and Bowen's disease in many countries all over the world. Numerous publications also demonstrate the effectiveness of PDT for the treatment of other cutaneous malignancies and nononcologic indications [69]. However, controlled clinical trials are required to clarify whether PDT for nononcologic indications can demonstrate superiority over existing, approved therapeutic modalities. The proven advantages of PDT include the simultaneous treatment of multiple tumors and incipient lesions, relatively short healing times, good patient tolerance, and excellent cosmesis. Very promising is the potential tumor control in immunocompromised patients (i.e., transplant recipients). Cost-effectiveness analysis indicates that, with relatively low costs for permanent equipment, topical PDT probably is no more expensive than conventional therapy when its lower side-effect profile is considered [72].

Take Home Pearls

- A key indication for PDT is field cancerization of AKs.
- PDT enables the simultaneous treatment of both multiple tumors and (invisible) incipient lesions.
- A relatively short healing time, good patient tolerance, and excellent cosmesis are advantages of PDT compared to other treatment options in many cases.
- PDT allows potential tumor control even in immunocompromised patients (i.e., organ transplant recipients).
- Due to a lower side-effect profile, PDT is a cost-effective treatment.

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Quality Standards in Aesthetic Medicine

29

Hans-Robert Metelmann, Peter D. Waite, and Stefan Hammes

Core Messages

- Aesthetic laser medicine requires the standardization of the training of doctors practicing in this branch of medicine. This will provide the most effective approach to consistently good quality management in this specialty.
- Good educational standards require a program that is certified by a university at an academic-degree level with an integrated, multi discipline approach and with learning objectives based on innovation and high-quality research.
- Since 1999, the Diploma of Aesthetic Laser Medicine (DALM) has been the only university degree in this field. The teaching program is based at Greifswald University in cooperation with the ScanBalt Academy. A Master of Science degree course in Health and Aesthetics is under development. This new course is a complementary, research-oriented program on top of DALM and initiated by the same institutions.

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Evidence-based medical judgment is rare in aesthetic medical procedures, including laser medicine, because it is difficult to define clear objectives for the aesthetic outcome of the treatment. So much depends on the patients' expectations and their visual appreciation of themselves.

Consistently good quality management may be achieved by standards of education rather than setting standards in therapy results. To date, the lack of proper training has been the main risk factor in terms of skill, experience, and interdisciplinary knowledge in a highly demanding specialty [1].

Therefore, a postgraduate study program, which intends to follow tried and tested principles of good educational practices, should be university based and must aim for education at the level of an academic degree. It should have an integrated multidiscipline approach and be based on relevant and innovative topics, techniques, and specialties such as dermatology, facial surgery, or plastic surgery, following the recent recommendations by Hammes [2] in Aesthetic Medicine (Fig. 29.1).

Standards should be both professionally and scientifically oriented, independent from industry, and driven by an international community of experts as the core of the teaching staff. The objective should be a high-standard academic degree recognized by both patients and public authorities.

At present there is only one program known to us that sets standards of this kind in teaching aesthetic medicine: the Diploma in Aesthetic Laser Medicine (DALM). One program is in statu nascendi.: the Master of Science in Health and Aesthetics. Both programs are based at Greifswald University under the umbrella of ScanBalt Academy [4] jointly with ScanBalt Campus and the Summer School system [5].

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_29, © Springer-Verlag Berlin Heidelberg 2011

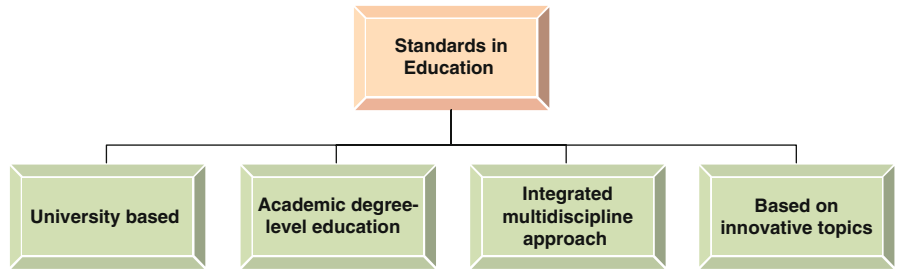

Fig. 29.1 Standards in postgraduate education

29.1 Diploma in Aesthetic Laser Medicine

This study program, which was initiated in 1999, is focused on professional aesthetic laser medicine; that is, the special aspects of a laser technology-assisted medicine in dermatology, maxillofacial surgery, otorhinolaryngology, ophthalmology, gynecology, plastic and reconstructive surgery, or dentistry. It teaches the basic principles of laser technology, laser physics, laser-tissue interactions, and laser safety under practical, clinical, and research aspects. Essential subjects studied are legal and business aspects, practice management, and marketing as well as a comprehensive view of aesthetic medicine in the light of the humanities and social and cultural sciences. All study subjects and training requirements are assembled in a scientific and practice-oriented study program that is the basis of the lectures, training units, and the final exam.

At the outset there is individual, personal study counseling, which covers the terms and individual aspects of admission to the study, the individual study focus, a personal curriculum, and examination specifics. The counseling serves to assess the prior experience of the individual and prior knowledge in aesthetic laser medicine, to design a flexible study program, and to exempt experienced candidates from appropriate parts of the study program, thus lowering the number of required certificates.

The definitive start of study is the enrollment as a guest student at the Greifswald of University. Students thus enrolled then individually and by their own initiative set up a study program by registering for lectures and practical training with lecturers of their own choice.

Enrollment is restricted to medical doctors only. Applications should be sent to the Master of the program via the DALM office (metelman@uni-greifswald.de).

Hammes has recently performed a scientific investigation of the educational effectiveness of the DALM program [3]. Based on his results, the program is a combination of lectures, training sessions, self-study, and in-depth scientific foundation, which lasts 18–24 months and is organized in three pillars of study (Fig. 29.2).

29.1.1 *Dies Academicus (Lecture Units)*

The basic lectures are offered at the monthly *Dies academicus*, held regularly on the last Saturday of every month throughout the year. The *Dies* has the form of an all-day seminar with alternating input by all lecturers and in the facility of the responsible lecturer; that is, in alternating locations. Successful participation is certified by a lecture certificate that the teacher issues after the student passes a brief exam. A complete *Dies* program consists of eight certificates of this kind that cover all areas of laser medicine in theory.

29.1.2 *Hospitationes (Training Units)*

The basic training units are the *Hospitationes* in the institutes of the lecturers, scheduled individually between student and lecturer. The main thrust of the training program is the observation, assistance, independent treatment with assistance, and independent laser-medical treatment under supervision. The successful participation during every practical training session is certified by a training certificate that is issued by the lecturer after a practical examination. The full *Hospitationes* program consists of eight certificates of attendance that cover all areas of laser medicine clinical practice.

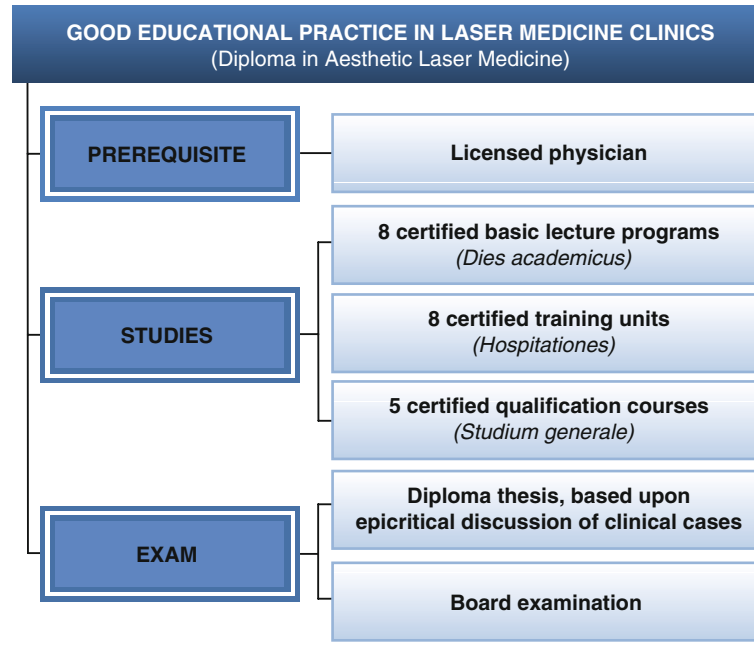

Fig. 29.2 Diploma program

29.1.3 Studium Generale (Self-Study)

Self-study through participation in additional lectures, scientific and technical meetings, and continuing education courses outside the regular study program is mandatory. Initially, visiting highly esteemed conferences also serves to orient the student within the subject area. Informal certificates of attendance at such conferences, one of which should be certified as an orientation module, must be presented at the time of enrollment for exams because they are regarded as orientation certificates. At least five certificates of attendance at meetings and international conferences document the self-study in laser medicine.

The Examination Board at Greifswald University finalizes this three-pillar study program. It is performed as a panel discussion according to the regulations for the conduct of examinations agreed upon by the federal university and put into force by the Ministry of Education. Examination dates are regularly the last Saturdays in March (winter semester) and in September (summer semester), making visible the connection to the university. The examinations take place at Greifswald University. To be admitted to the exam, the candidate needs eight *Dies* certificates and eight *Hospitationes* certificates that cover all the requirements of interdisciplinary laser medicine as well as an orientation certificate and a minimum of four additional certificates that prove self-study. The exam comprises the presentation of a Diploma thesis, an epicritical discussion of at least five cases treated as the responsibility of the candidate, and demonstration of expertise in the whole range of aesthetic laser medicine.

29.2 Master of Science in Health and Aesthetics

In 2009, a masters program in aesthetic medicine was initiated based upon the network of DALM and additionally under the auspices of the University of Birmingham, Alabama (USA) and the American Academy of Cosmetic Surgery. The Master of Science in Health and Aesthetics will be a significant academic achievement for advanced professional fellowship and for the purposes of education and research.

The program generally consists of two routes: (1) following the completion of the DALM after medical school (i.e., must be a licensed physician) and at least one postgraduate year of experience, or (2) based upon board certification by the American Board of Cosmetic Surgery.

The masters program is intended to deepen the scientific understanding of and to promote quality training

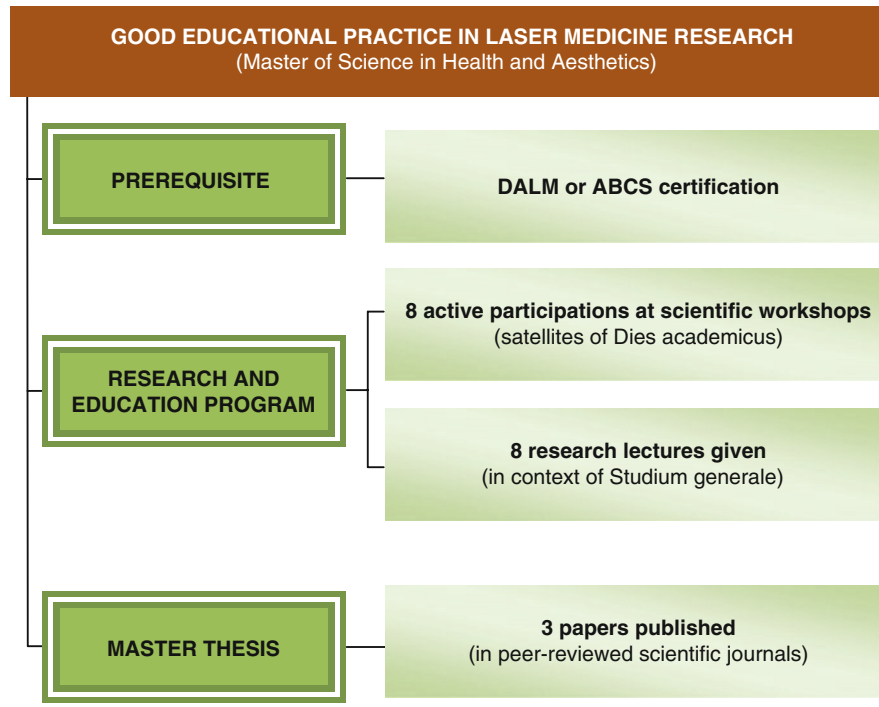

Fig. 29.3 Masters program (underway). *DALM* Diploma in Aesthetic Laser Medicine, *ABCS* American Board of Cosmetic Surgery

in the areas of aesthetic medicine, such as laser medicine, facial rejuvenation, liposurgery, or body sculpture enhancement.

The DALM provides an avenue into the masters program. Those completing the DALM would be encouraged to apply for this advanced masters program and to improve their own professional teaching skills.

The study program (Fig. 29.3) consists of an independent curriculum leading to a masters thesis with special scientific topics in aesthetic medicine. The participants are expected to develop their own unique research thesis that is suitable for publication in international, peer-reviewed scientific journals. The minimum work load will be 1,800 h of work, corresponding to 60 points at the European Credit Point transfer system or the US equivalent.

The masters program curriculum requires participation in eight master workshops (organized, for example, with the program of the DALM *Dies Academicus* and/or legitimate American Academy of Cosmetic Surgery program courses), eight presentations given at scientific conferences (four could be in the context of the *Dies Academicus* of the DALM program), and three papers published in scientific journals (one of which should be in the *American Journal of Cosmetic Surgery*), creating *in cumulo* the masters thesis.

Faculty will consist of academicians with special interest in aesthetic medicine and who have demonstrated mentoring skills in the guidance of scholarly activity.

Applicants eligible for this master program should have attained successfully either DALM or ABCS certification. Applicants will be reviewed objectively on the basis of merit. The masters program is committed to excellence in the scientific community and is globally oriented, setting new standards of education in aesthetic laser medicine.

Take Home Pearls

- The Diploma in Aesthetic Laser Medicine (Greifswald University) is setting educational standards in this highly demanding specialty.
- This clinically oriented, strictly postgraduate study concept is structured by attendance at eight certified basic lecture programs, eight certified training units, and five certified qualification courses, followed by writing a diploma thesis and concluded by a board examination.
- On top of the diploma, a master study program will add to the standards of education from a research point of view.
- This mainly scientifically oriented program will be concluded with the Master of Science in Health and Aesthetics.
- Applications for joining the education programs in aesthetic laser medicine should be sent to the master of the study program's address, which is the authors address.

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Safety/Eye Protection

30

Wolfgang Bäumler

Core Messages

- The chapter presents a short overview of basic radiation parameters of laser and intense pulsed light sources (ILSs)
- Information is provided about the safety issues and regulations for lasers and ILSs that are used in medical practice
- The manufacturers of such devices must conform to various requirements to provide a safe laser or ILS for their customers
- The most important issues for physicians are highlighted to enable the safe use of medical devices such as lasers and ILSs in patients

30.1 Introduction

Based on the equations of James Maxwell, electromagnetic radiation can be described as a plane wave that propagates in space with a constant velocity, c, of 299,790 km/s. The major properties of radiation are wavelength, λ, and frequency, ν, which are correlated as:

$$c = \lambda \cdot \nu$$

Likewise, radiation can be considered as particles, which are called photons of the energy

$$E = h \cdot \nu = \frac{h \cdot c}{\lambda}$$

with h being Planck's constant (6.6×10^{-34} J/s). It is obvious that the energy of radiation increases with decreasing wavelength. The spectrum of electromagnetic radiation exhibits a broad range, which is classified by the respective wavelength of the radiation ranging from a few nanometers to thousands of meters. Only a small part of the spectral range is visible to human eyes (400–700 nm), which is solely called light. In this chapter, "radiation" is considered to be a generic term, and the term "light" is also used for wavelengths outside the visible range. This is a concession to the frequent interchange of the terms light and radiation in the medical literature.

It was recognized early that radiation of any wavelength can pose a risk for humans, in particular on unshielded eyes [7, 10]. This risk is caused by the absorption of photons in human tissue, leading to photochemical or photothermal alterations of tissue, [1, 8]. These alterations may affect tissue integrity for a short period of time or may damage tissue permanently. When lasers or ILSs are used for treatments of skin lesions, people have to take a variety of measures into account that prevent humans from radiation-induced hazards (Table 30.1).

30.2 Lasers and Intense Pulsed Light Sources

For many years, physicians have used various types of lasers to treat different skin disorders. Due to the high optical power and the monochromatic nature of laser radiation, it was regarded as the optimal radiation source to achieve effective and selective destruction of targets inside skin [2]. However, a new light source appeared some years ago that is frequently used in medical

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_30, © Springer-Verlag Berlin Heidelberg 2011

Table 30.1 Spectral ranges of electromagnetic radiation

Radiation	Wavelength	Frequency
Radio waves	1 m–100 km	300 MHz–3 kHz
Micro waves	0.1–3 cm	300–10 GHz
Infrared radiation	0.7–100 μm	4.2×10^{14}–3×10^{12} Hz
Visible light	400–700 nm	7.5×10^{14}–4.3×10^{14} Hz
Ultraviolet radiation	1–400 nm	3×10^{16}–4.3×10^{14} Hz
X-ray	0.1–1 nm	3×10^{18}–3×10^{17} Hz

treatment now: the ILSs [5, 11]. It mainly consists of a flash lamp that emits white light of wavelengths ranging from about 250 to 1,400 nm. The short wavelengths, in particular the ultraviolet radiation, are blocked by optical edge filters that cut the white spectrum at different wavelengths in the range of 500 to 650 nm. The infrared part of the ILS (λ>~900 nm) is usually blocked by the absorption in a water layer (coolant) in front of the flash lamp.

The major difference between a laser and an ILS is the spectrum of the emitted radiation. Laser radiation is monochromatic with a spectral width of usually a few tenths of a nanometer, whereas ILS emission covers a broad range of up to 500 nm. Both emission spectra can be used for the treatment of many skin lesions because the absorption of chromophores such as oxyhemoglobin or melanin exhibits a broad absorption spectrum.

The use of lasers in medical fields is part of the rules and standards, which are established in the Safety of Laser Products of the International Electrotechnical Commission (IEC) or American National Standards Institute (ANSI). This chapter describes the safety based on IEC 60825-1 or ANSI Z136.1 for all laser systems, including medical lasers. The rules are applicable to the safety of laser products emitting laser radiation in the wavelength range of 180 nm to 1 mm. All details of these regulations are outside the scope of this chapter, but the important items are highlighted here.

Unfortunately, these regulations do not cover the use of ILSs so far; for example, there is no existing Food and Drug Administration (FDA) performance standard for intense pulsed light products [6]. This chapter provides advice regarding safety of ILSs, which are based on comparisons with laser systems. ILS systems emit high radiant exposures (J/cm²) that are comparable to lasers and have, therefore, the potential to cause substantial damage to eyes and skin. In addition, due to the broad spectrum of an ILS emission, such radiation interacts with all chromophores in skin to a higher extent than that of monochromatic lasers. Thus, there is the urgent necessity that the worldwide use of ILSs should be regulated in a way that is comparable to the regulation of lasers.

30.3 Parameters of Laser and ILS Radiation

To appraise the safety of radiation that is used in the treatment of skin disorders, it is important to know the main parameters of radiation. These main parameters are wavelength, optical power, intensity, the exposure time, and radiant exposure, which is often phrased as "fluence" "fluence" instead of radiant exposure in the medical literature. The connection of these parameters is shown in Table 30.2; the unit for energy is Joule (J), optical power is Watt (W), intensity is W/cm², radiant exposure is J/cm², the exposure time in seconds, and the area of irradiation on skin surface is cm².

Table 30.2 Definitions of some radiation parameters

Parameter	Formula	Units
Energy	$\text{Energy} = \text{power}\times\text{time}$	$\text{J} = \text{W}\times\text{s}$
Intensity	$\text{Intensity} = \frac{\text{power}}{\text{area}}$	$\frac{\text{W}}{\text{cm}^2}$
Radiant exposure	$\text{Radiant exposure} = \frac{\text{power}\times\text{time}}{\text{area}}$	$\frac{\text{J}}{\text{cm}^2} = \frac{\text{W}\times\text{s}}{\text{cm}^2} = \frac{\text{W}}{\text{cm}^2}\times\text{s}$

30.3.1 Energy and Intensity of Radiation

As already mentioned in the introduction, the photon is the smallest portion of radiation with the energy:

$$E = h \cdot \nu = \frac{h \cdot c}{\lambda}$$

The energy of a single photon at 532 nm (fd neodymium:yttrium aluminum garnet laser and potassium titanyl phosphate laser) is about 4×10^{-19} J, which requires a high number of such in the order of 10^{17} to generate a single laser or ILSs pulse. Table 30.3 shows typical intensities that are emitted by ILSs or lasers. These intensities are substantially higher as compared to typical radiation sources encountered during daily life, for example, light bulbs or solar radiation.

On one hand, the high intensities enable therapeutic effects such as coagulation or vaporization. On the other hand, the high intensities imply the risk of damaging the eyes and skin of the physician, patient, and other personnel involved in the treatment procedure. Thus, the use of lasers and ntense pulsed light requires a profound understanding of such radiation sources and their interaction with tissue. Although the intensity of an ILS is in the range of ms-lasers (at the front of the glass applicator), the use of ILSs is not included in the regulations of laser safety (IEC 60825-1) [4, 6]. Regarding safety concerns, the user of an ILS should decidedly consider an ILS as being much closer to lasers than to light bulbs [3].

Table 30.3 Intensities of different radiation sources

Radiation	Intensity (W/cm²)	Comments
Light bulb, 100 W	0.001	About 1-m distance from bulb
Solar radiation	0.1	Estimated terrestrial value, summer, northern hemisphere
UV radiation sources in dermatology	0.1	
PDT light sources in dermatology	0.2	
ILS	1,500	15 J/cm², 10 ms, broadband
fd Nd:YAG laser (KTP)	500	25 J/cm², 50 ms
Pulsed dye laser	12,000	6 J/cm², 500 μs
Q-switched ruby laser	2.5×10^8	5 J/cm², 20 ns

UV ultraviolet, *PDT* photodynamic therapy, *ILS* intense pulsed light source, *Nd:YAG* neodymium:yttrium aluminum garnet, *KTP* potassium titanyl phosphate

30.3.2 Exposure Time of Radiation

Because of therapeutic requirements, physicians use different exposure times for radiation, which range from a few nanoseconds to seconds. In the case of continuous wave (cw) lasers, the exposure time is in the range of seconds, which is usually managed by pressing the foot switch of the laser. In most medical treatments, physicians use the exposure time that is predefined by the pulse duration of a single laser or ILS pulse. For pulsed radiation sources, the exposure time is equivalent to either a single pulse or to a train of single pulses.

The broad range of pulse durations imply a broad range of intensities that must be considered for safety issues. Therefore, the lasers are classified as cw lasers (>0.2 s), pulsed lasers (0.2 s–1 μs), and giant pulsed lasers (1 μs–1 ns) in safety regulations. In medical laser applications, the latter systems are usually the Q-switched lasers that are used for the treatment of pigmented lesions.

30.3.3 Radiant Exposure of Radiation

The most frequent parameter used in laser treatments is the radiant exposure that is frequently called "fluence." It comprises intensity and exposure time (Table 30.2). When taking the whole spectrum of medical treatments into account, the radiant exposure varies from about 1

Table 30.4 Radiant exposures for different intensities and pulse durations

Radiation	Intensity (W/cm²)	Exposure time (ms)	Radiant exposure (J/cm²)
ILS	1,500	10	15, broadband
fd Nd:YAG laser (KTP)	500	50	25
Pulsed dye laser	12,000	0.5	6
Q-switched ruby laser	2.5×10^8	0.00002	5

ILS intense pulsed light source, Nd:YAG neodymium:yttrium aluminum garnet, KTP potassium titanyl phosphate

to 400 J/cm² for pulsed radiation. For cw applications, this range can be exceeded. Table 30.4 shows a few examples for different intensities and exposure times that are applied in the treatment of different skin lesions. It is striking that the values of radiant exposures are within a rather narrow range, whereas the respective intensities and pulse durations become inversely proportional in the order of magnitudes.

30.4 Classification of Lasers

The treatment of skin lesions with lasers or ILSs requires a broad range of exposure times, intensities, and radiant exposures (Table 30.4). Lasers have been classified into four groups based on accessible emission limits (AELs) (Table 30.5). These limits indicate the class of the laser and are listed in IEC 60825-1 and the American National Standards ANSI Z136.1 for Safe Use of Lasers. The AEL values for the laser classes are derived from the medical maximum permissible exposure (MPE) values. The MPE values specify the danger levels for the eyes or the skin with respect to laser radiation.

30.5 Radiation-Induced Damages in Humans

Physicians use laser and ILSs that can emit radiation of very high intensities and radiant exposure, respectively. The absorption of radiation in the chromophores hemoglobin, melanin, and water damage the treatment target in skin; the more radiation energy the higher is the damage (Fig. 30.1). The radiation is applied to the treatment site. However, it is inevitable that part of the treatment radiation reaches other anatomical locations (e.g., the eyes) due to reflection and scattering at the treatment site. Other reasons are accidental and careless handling of lasers and ILSs during treatment.

One of the most important safety issues is the protection of the eyes from radiation that exceeds the MPE values for the eyes. Essential parts of the eye such as the cornea, the lens, the choroid, and the retina can be subjected to radiation-induced damage. The part of the eye that sustains damage depends on the wavelength of radiation. The unwanted effects of radiation in the eye are more or less comparable to those effects at the treatment site. Depending on the intensity at the site of interaction, the well-known effects of coagulation (low intensity), vaporization (high intensity), and ablation (very high intensity) may occur.

In the spectral range of light of about 370–1,000 nm, radiation readily penetrates the cornea and the lens to reach the choroid and retina. The radiation of this spectral range is, for example, well absorbed in hemoglobin in choroid vessels (Fig. 30.1). The induced heat simultaneously damages the retina. Additionally, when visible radiation passes the lens and cornea, the refraction increases the intensity of the incoming radiation by several orders of magnitude. A rather low intensity of 2.5 mW/cm² at the cornea can thereby reach a value of 1,250 W/cm² at the retina. Consequently, all laser-induced mechanisms, ranging from coagulation to explosion, may occur at the same time in the retina.

Table 30.5 Laser classifications

1	The radiation emitted by this laser is not dangerous	No need for protection equipment
1M	Eyes are safe when used without optical instruments, may not be safe when optical instruments are used	No need for protection equipment, if used without optical instruments
2	Eyes are safe by aversion responses, including the blink reflex	No need for protection equipment
2M	The light that can hit the eye has the values of a class 2 laser, depending on a divergent or widened beam; it may not be safe when optical instruments are used	No need for protection equipment, if used without optical instruments
3R	The radiation from this laser exceeds the MPE values. The radiation is max. 5 × AELs of class 1 (invisible) or 5 × AELs of class 2 (visible). The risk is slightly lower than that of class 3B	Dangerous to the eyes; safety glasses are recommended
3B	Old class 3B without 3R. The view into the laser is dangerous. Diffuse reflections are not considered to be dangerous	Dangerous to the eyes; safety glasses are obligatory
4	Old class 4. Even scattered radiation can be dangerous for the eyes, also danger of fire and danger to the skin	Personal safety equipment is necessary (glasses, screens)

MPE maxiumum permissible exposure, AEL accessible emission limit

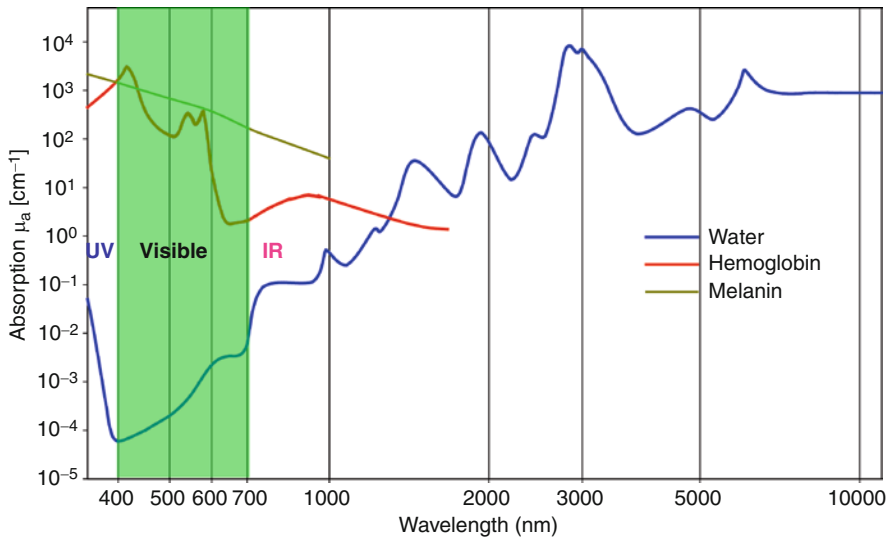

Fig. 30.1 Absorption of radiation in water. Ultraviolet (UV) (<350 nm) and Infrared (IR) radiation are strongly absorbed in water, whereas visible laser light (400–700 nm) shows absorption in the chromophores melanin and hemoglobin

The wavelengths from about 750–1,000 nm are particularly dangerous to the retina. Radiation in this spectral range is invisible and will not be detected by the eye and, therefore, the eye will not blink.

In the spectral range of light of less than 370 nm and more than 1,000 nm, radiation is predominantly absorbed in water (Fig. 30.1) and does not pass the lens and cornea (Fig. 30.2). Wavelengths shorter than 370 nm can lead to injury of the cornea (cornea ablation) or to cataract formation in the lens. With increased wavelengths above 1,000 nm, the penetration of radiation decreases, leading again to cataract formation (Fig. 30.3).

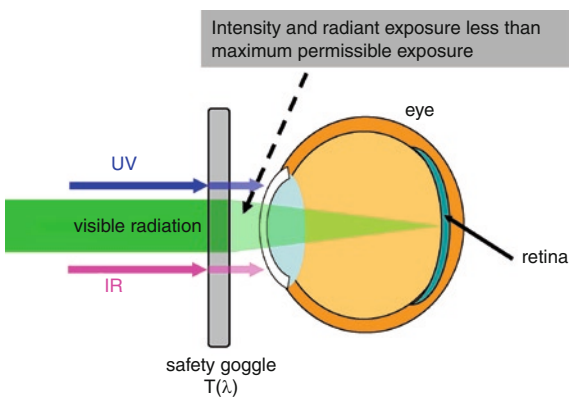

Fig. 30.2 Scheme of the eye and the penetration of radiation. Visible laser light and part of near infrared (IR) radiation penetrate the cornea and the lens, reaching the choroid and the retina at least. The cornea and the lens hamper ultraviolet (UV) or IR radiation to penetrate the eye. The extent of damage depends on the radiation parameters

For wavelengths around 3 μm, the water absorption is maximal and may cause cornea ablation. For even longer wavelengths, vaporization of the cornea may occur.

Usually, the eyes protect themselves from damage that could be induced by excess radiation energy. If the retina detects high radiation intensity, the eyelid is closed in an automatic reaction. However, the time span that is necessary to close the eyelid is about 250 ms, which is definitely longer than most of the pulse durations used for lasers and ILSs. In addition, this safety feature reliably works for an optical power of less than 1 mW, which is quite small compared to lasers or ILSs. Thus, the eye blink is not sufficient protection except against some nonmedical lasers classified in group 1 (see Table 30.5). Radiation that is invisible for the eyes (ultraviolet, infrared) will not trigger an eye blink to protect the cornea, lens, or retina from damage.

Users of lasers or ILSs should always keep in mind that even small intensities reaching the open pupil can cause severe damage of the retina, which in most cases is irreversible and may entail a complete loss of eyesight. Besides the eyes, radiation from lasers or ILSs can also damage skin outside the treatment area.

30.6 Measures for Human Safety – Eye Safety

Nearly all medical laser systems used in dermatology are classified as class 4. Even scattered radiation can be dangerous to the eyes and skin and can set on fire

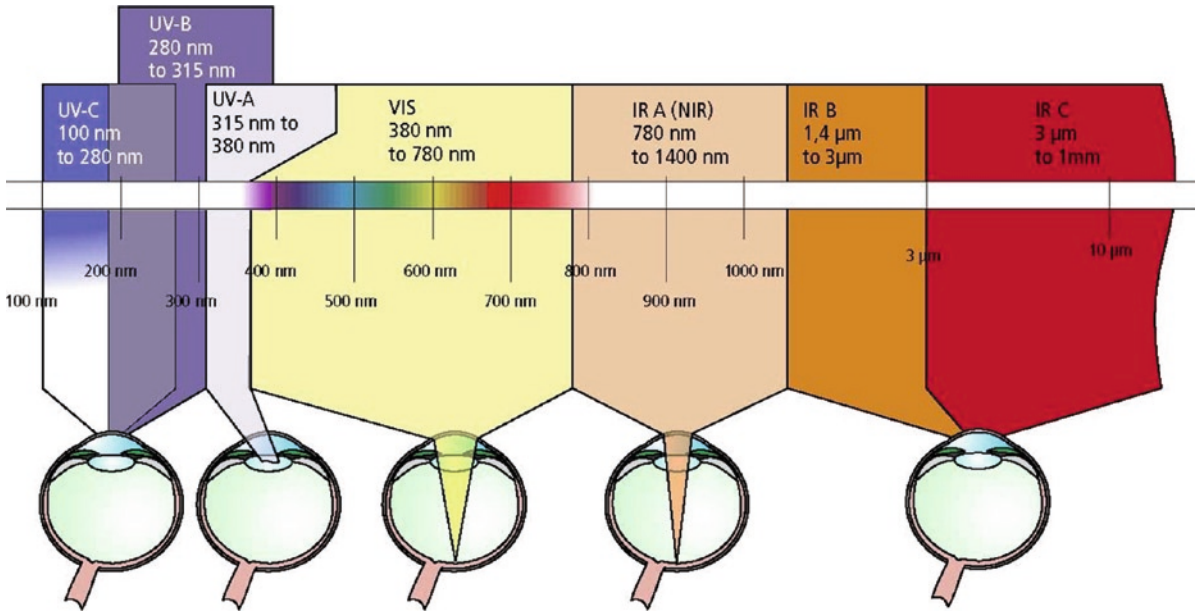

Fig. 30.3 Wavelength dependency of damage. The location of damage in the eye depends clearly on the wavelength of radiation and the absorption of the chromophores water, hemoglobin, and melanin. *UV* ultraviolet, *VIS* visible light, *IR* infrared (source: Laservision)

material that is exposed to laser radiation. The most important safety measure is the protection of the eyes from excess laser radiation. To shield the eyes, it is mandatory to wear safety goggles during treatment with lasers or ILSs. In medical practice, the treatment of various skin lesions with lasers or ILSs necessitates the use of a variety of devices that emit radiation in a wavelength range of about 300–11,600 nm.

To protect the eyes from such radiation, full protection is needed, according to EN 207 in Europe or to ANSI Z136 in the United States. There are different options to shield the eyes. Safety goggles may consist of glasses, which are optical filters, and the appropriate frame (Fig. 30.4a). It is often necessary to cover the entire eye area using special goggles without a transparent optical filter (Fig. 30.4b). If a physician performs laser treatment in the vicinity of the eyes, the use of patches that are positioned directly on the eyeball is recommended (Fig. 30.4c).

The optical filters of goggles either absorb or reflect the incoming radiation to a sufficient extent. When using safety goggles with optical filters and frames (Fig. 30.4a), both are selected to match the maximum power and beam size of the laser to make sure that the amount of radiation that penetrates to the eye behind the glasses is below the MPE values (Fig. 30.5). For the safety goggles shown in Fig. 30.4b and c, the material will completely block radiation, whereas the material of the goggles should not heat up by radiation exposure and should resist thermal damage. Heating up of such goggles would entail thermal damage of the adjacent tissue by heat conduction.

Because physicians have to view the patient and the treatment area, the optical filters must fulfill both criteria at the same time: protection against laser or ILS radiation and sufficient transmission of daylight to enable viewing. To achieve maximal safety for the eyes, it is important to adjust the optical filters of the safety goggles to the radiation source used (laser or ILS). The important parameters of the radiation sources are wavelength, pulse duration, intensity, and radiant exposure. These parameters of a laser or ILS system determine the characteristics of the safety goggles (Table 30.6). Each laser or ILS requires special safety goggles that are labeled for their use (wavelength range of protection, laser mode, and scale number of protection) (Fig. 30.6). If a physician uses several lasers or ILSs, confusion of safety goggles of the different systems is possible and must absolutely be avoided.

The ANSI Z136 standard requires specifications according to optical densities (ODs) only. The OD (or $D[\lambda]$) is the attenuation of light that passes through an optical filter. The higher the OD value, the

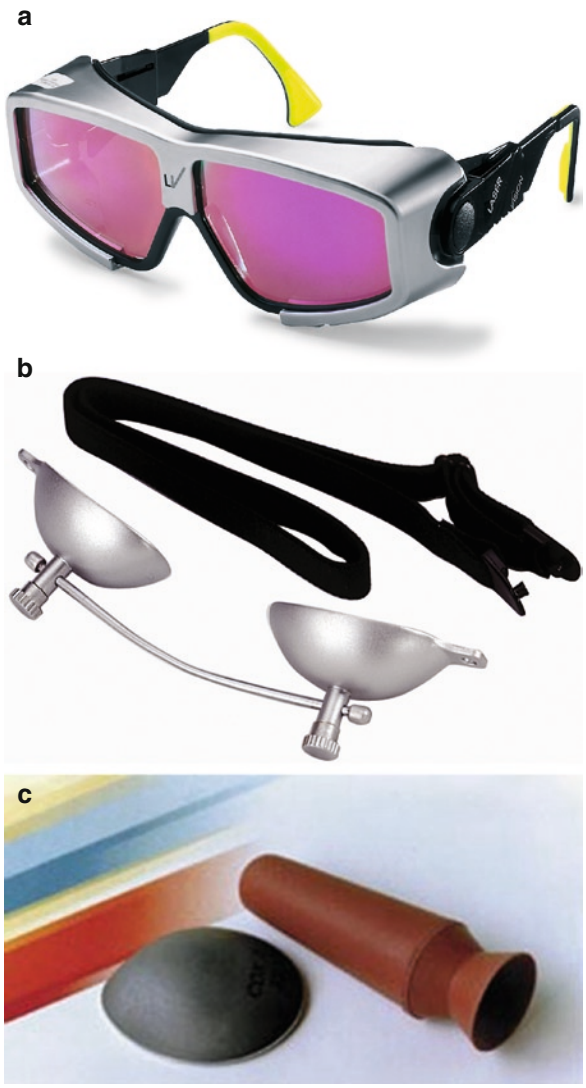

Fig. 30.4 Safety goggles. All individuals who are present in the room for laser therapy must wear appropriate safety goggles. A typical pair of safety goggles with optical filters (**a**). The patient can wear special safety goggles that block any radiation (**b**), in particular to protect the eyeball when treating in the vicinity of the eye (**c**) (source: Laservision)

higher the attenuation. The mathematical expression of OD is the logarithm to the base ten of the reciprocal of the transmittance and is given by an equation (where $T[\lambda]$ is the transmittance of radiation through the filter). In Europe the intensity (W/cm²) or radiant exposure (J/cm²) also must be taken into consideration. Intensity is frequently named "power density." Radiant exposure is frequently named "energy density" or "fluence."

According to the EN 207 standard for laser safety, eyewear needs to be tested for direct laser exposure of 10 s or 100 pulses. During these 10 s, the MPE values cannot be exceeded under defined conditions. It is, however, advisable to avoid direct exposure of the eye to a laser. The safety eyewear (filter and frame) must be able to withstand standardized conditions. After a successful test, laser glasses receive the CE certification and are labeled with protection levels. A copy of the certificate can be requested by any user of the laser safety eyewear.

Laser safety glasses are high-value optical products, which need cleaning and care. Do not use goggles, windows, filters, or glasses with a damaged or scratched ocular lens or glasses with filters that have undergone a color change. In some cases, goggles may be repaired by the manufacturer. If repair is impossible, the goggles must be replaced. Goggles may be expensive but they sustain the eyesight of the patient and the physician!

Manufacturers of safety goggles provide the following recommendations: do not expose the eyewear permanently to daylight or ultraviolet lamps; protect the glasses from scratches and mechanical stress; avoid contact with chemicals, acids, alkali, and toxic (i.e., reactive) fumes; never place the glasses with the filters facing down; do not put the glasses on heaters or equipment that may heat up; store the glasses in dry and robust boxes.

30.7 Measures for Equipment Safety and Laser Safety Officer

All laser systems, including the medical lasers, sold in Europe must be certified to EN 60825-1, which is a part of the CE marking process. EN 60825-1 is the basic laser safety document to which all other laser safety documents refer. It defines the MPE, AELs, laser classes and measurement conditions, the labeling, and the engineering controls. In Europe, product conformity is achieved by requiring manufacturers to certify the applicable standards for their product. The manufacturer identifies the relevant standards, designs the product accordingly, and makes a declaration of conformity in the user instructions. It is then the responsibility of the various national enforcement bodies to detect nonconformances and intervene if

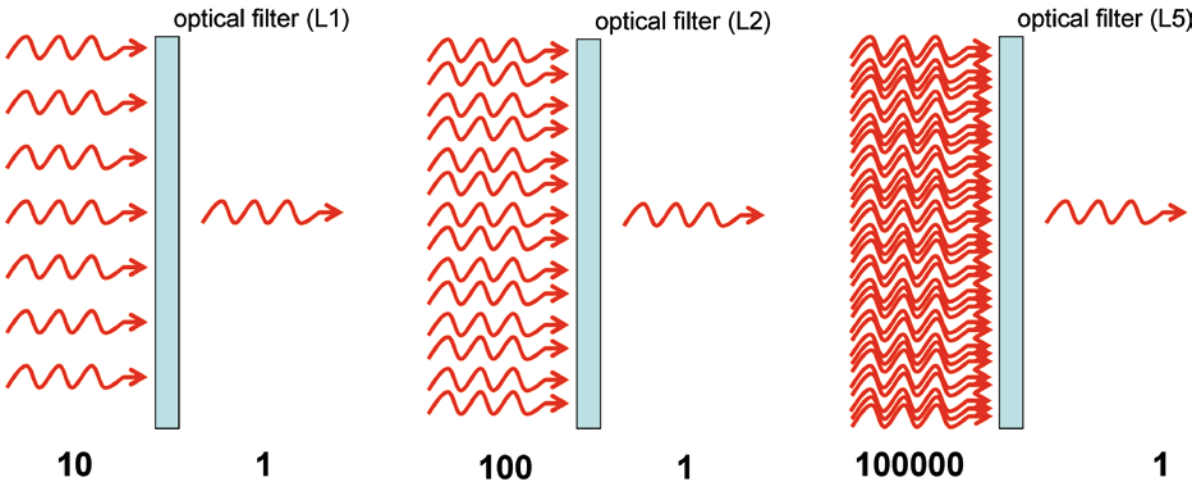

Fig. 30.5 Attenuation of radiation. The figure is an exemplary illustration of the attenuation of radiation for three different scale numbers L1, L2, and L5. In this example, the number of incoming photons (*bottom*) is lowered by the optical filter to 1

Table 30.6 Maximal values of intensity and radiant exposure pulse duration in seconds

Scale number	$T(\lambda)$	180–315 nm		>315–1,400 nm		>1,400–1,000 μm	
		Cw $>3\times10^{4}$	Pulsed 3×10^{4}–10^{-9}	Cw $>5\times10^{-4}$	Pulsed 5×10^{-4}–10^{-9}	Cw >0.1	Pulsed 0.1–10^{-9}
		Intensity (W/cm²)	Radiant exposure (J/cm²)	Intensity (W/cm²)	Radiant exposure (J/cm²)	Intensity (W/cm²)	Radiant exposure (J/cm²)
L1	10^{-1}	10^{-2}	3×10^{2}	10^{2}	5×10^{-2}	10^{4}	10^{3}
L2	10^{-2}	10^{-1}	3×10^{3}	10^{3}	5×10^{-1}	10^{5}	10^{4}
L3	10^{-3}	1	3×10^{4}	10^{4}	5×10^{0}	10^{6}	10^{5}
L4	10^{-4}	10^{1}	3×10^{5}	10^{5}	5×10^{1}	10^{7}	10^{6}
L5	10^{-5}	10^{2}	3×10^{6}	10^{6}	5×10^{2}	10^{8}	10^{7}
L6	10^{-6}	10^{3}	3×10^{7}	10^{7}	5×10^{3}	10^{9}	10^{8}
L7	10^{-7}	10^{4}	3×10^{8}	10^{8}	5×10^{4}	10^{10}	10^{9}
L8	10^{-8}	10^{5}	3×10^{9}	10^{9}	5×10^{5}	10^{11}	10^{10}
L9	10^{-9}	10^{6}	3×10^{10}	10^{10}	5×10^{6}	10^{12}	10^{11}
L10	10^{-10}	10^{7}	3×10^{11}	10^{11}	5×10^{7}	10^{13}	10^{12}

Cw continuous wave

necessary. The standards are set by committees of experts and are under continual review and enhancement. This system places considerable responsibility and trust in the hands of the manufacturers.

In the United States, several organizations concern themselves with laser safety. These organizations include the ANSI; the Center for Devices and Radiological Health (CDRH) of the FDA; the Department of Labor's Occupational Safety and Health Administration; and the Council of Radiation Control Program Directors. The regulations are controlled by the CDRH. Manufacturers of electronic radiation-emitting products (e.g., lasers) sold in the United States are responsible for compliance with the Federal Food, Drug, and Cosmetic Act, Chap. V, Subchapter C – Electronic Product Radiation Control. In addition, surgical lasers must comply with radiation safety performance standards in Title 21, Code of Federal Regulations (Subchapter J, Radiological Health), Parts 1010, 1040.10, and 104.11. Because they are medical devices,

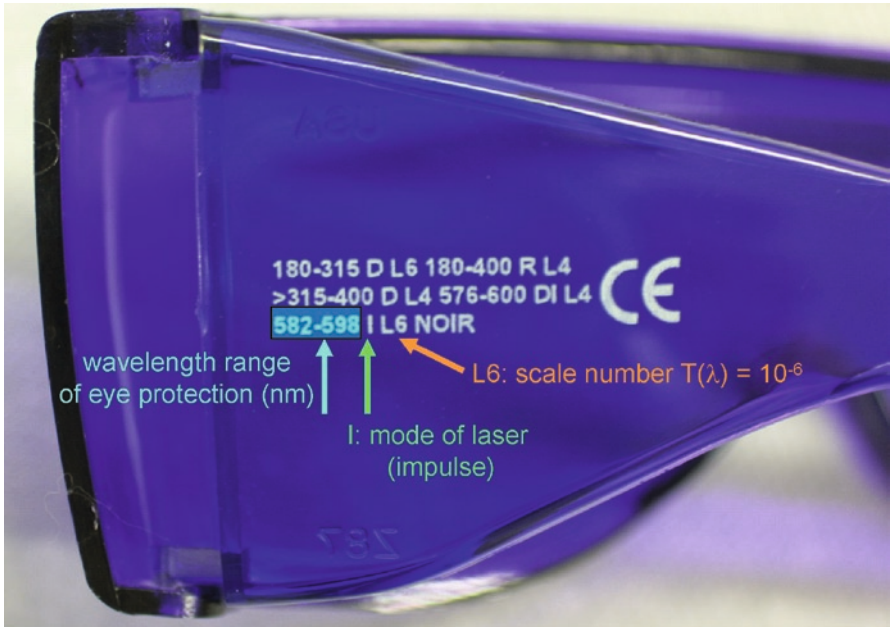

Fig. 30.6 Scale numbers for eye protection. All safety goggles must be labeled according to their protection features (see Table 30.6). The example here shows a pair of safety goggles for a pulsed dye laser that emits 585-nm light. Therefore, the filter protects the eye from radiation in the range of 582–595 nm with a scale number of L6. It also filters radiation of other spectral ranges, for example, from 576 to 600 nm with L4 for pulsed and continuous mode (I, D)

surgical laser products must also comply with the medical device regulations. Manufacturers of surgical laser products are responsible for compliance with all applicable requirements of Title 21, Code of Federal Regulations (Subchapter J, Radiological Health), Parts 1000 through 1005.

To reduce inequality of safety regulation in both areas, in 2001 the CDRH launched a document called Laser Products – Conformance with IEC 60825-1, Am. 2 and IEC 60601-2-22; Final Guidance for Industry and FDA (Laser Notice No. 50). This guidance describes the conditions under which laser product manufacturers may introduce into United States commerce laser products that comply with the IEC standards 60825-1, as amended, and 60601-2-22. This guidance also describes additional requirements of the CDRH standard and alternate certification statements to be used with such products.

There are some basic categories of controls useful in laser environments. These are engineering controls, personal protective equipment, administrative and procedural controls, special controls, and correct labeling of the laser products. Important in all controls is the distinction between the functions of operation, maintenance, and service. First, laser systems are classified on the basis of the level of the laser radiation accessible during operation. Maintenance is defined as those tasks specified in the user instructions for assuring the performance of the product and may include items such as routine cleaning or replenishment of expendables. Service functions are usually performed with far less frequency than maintenance functions (e.g., replacing the laser resonator mirrors or repair of faulty components) and often require access to the laser beam. The safety procedures required for such beam access during service functions should be clearly delineated in the laser product's service manual [9].

It is required and mandatory to appoint a laser safety officer (LSO). This person has the authority to monitor and enforce the control of laser hazards and effect the knowledgeable evaluation and control of laser hazards. The LSO administers the overall laser safety program; those duties include items such as:

- Confirming the classification of lasers
- Assuring that the proper control measures are in place and approving substitute controls
- Recommending and/or approving eye wear and other protective equipment
- Specifying appropriate signs and labels
- Approving overall facility controls
- Providing the proper laser safety training as needed
- Conducting medical surveillance
- Designating the laser and incidental personnel categories

The LSO should receive detailed training, including laser fundamentals, laser bioeffects, exposure limits,

classifications, control measures (including area controls, eye wear, barriers, etc.), and medical surveillance requirements.

30.8 Recommendations and Remarks for the Safe Use of Laser and ILS

When using medical lasers it is unavoidable that part of the beam path from a class IIIB or IV laser is not sufficiently enclosed and/or baffled and radiation exposures may then exceed the MPE. Then a "laser-controlled area" is required. Because most of the medical lasers in use are class IV lasers, the following items are recommended. Although recommendations for the safe use of ILSs in medical practice are currently not available, many of the recommendations listed below can be applied for ILSs as well, in particular those regarding eye protection.

- Supervision directly by an individual knowledgeable in laser safety.
- Training is required for all personnel who may frequently require entry into the area.
- Entry of any noninvolved personnel requires approval.
- Rapid egress by the laser personnel at all times and admittance to the laser-controlled area in an emergency condition must be allowed.
- A blinking entryway warning should be installed when laser or ILS is in operation.
- The appropriate laser warning sign shall be posted both inside and outside the laser-controlled area (Fig. 30.7).
- All windows, doorways, and open portals of an enclosed facility should be covered or restricted to reduce any escaping laser radiation below the appropriate ocular MPE level.
- Use diffusely reflecting materials near the beam, where appropriate.
- Avoid the use of dry materials adjacent to laser exposure; if possible dry material should be wetted using water.
- Avoid exposure of flammable objects to laser radiation.
- Appropriate laser-protective eye wear must be provided to all personnel, including patients, within the laser-controlled area.
- All lasers are equipped with an emergency switch to shut down the laser in any case of emergency.

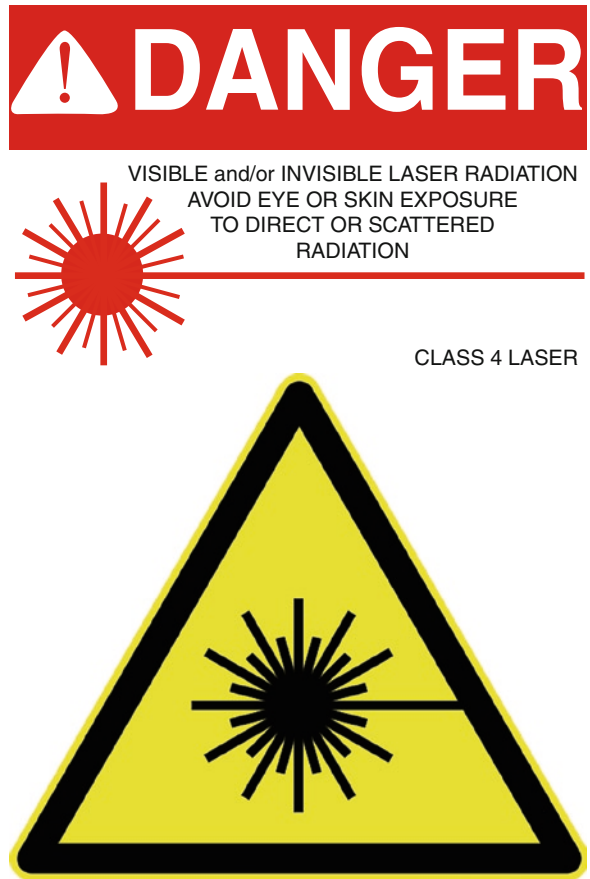

Fig. 30.7 Warning signs. All lasers (classes IIIb and IV) and their controlled areas in the USA (*top*) or Europe (*bottom*) must have the corresponding warning sign

- Continuous, pulsed, or repetitive laser radiation for medical treatments is triggered only by the use of a foot/hand switch.
- Require storage or disabling of lasers when not in use.
- Avoid kinking of the optical fiber.
- Staring into the end of any broken, severed, or unterminated optical fiber or cable should be avoided.
- A broken optical fiber is a source of uncontrolled radiation emission; shut down the laser immediately and replace the fiber.
- Training of individuals in aspects of laser safety is required for laser installations.
- Training of physicians in aspects of medical laser or ILS treatments is required.

Take Home Pearls

- Lasers and ILSs can emit optical radiation with high intensities that is either visible or invisible.
- Laser and ILS radiation has the potential to harm skin and eyes.
- The duration of radiation pulses are usually shorter than an eye blink.
- Appropriate eye protection must be provided to all personnel, including patients, within the laser-controlled area.
- Training of physicians in aspects of medical laser or ILS treatments is required.
- The use of lasers, ILSs, and safety accessories is regulated by different authorities and is restricted to approved devices.

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Part IV

Afterword

The Business of Laser Surgery

31

How Our Lives are Challenged by Healthcare Regulations, the FDA, and Quackery

Christopher B. Zachary

Core Messages

- Regulations are making it more difficult to provide innovative treatments for our patients.
- Deregulation of the healthcare industry and the US Food and Drug Administration (FDA) would likely save lives and cost much less.
- The public needs to take some responsibility for their own healthcare.
- The FDA has the responsibility to release all relevant supporting information after approval of a device.
- Quackery is rampant within the aesthetic world.

Originally presented as the Leon Goldman, M.D. Memorial Lectureship Award lecture at the 29th Annual Conference, April 1–5, 2009, National Harbor, MD

The issues I wish to address herein relate to the pressures that drive the practice of laser surgery and medicine at large. With regard to this chapter, I have no financial disclosures to make. I do, however, like most of us, have my biases. That said, I want to share some major concerns I have with the inherent problems of offering services for financial gain, whether it be big pharma, laser companies, physicians, or indeed the government and healthcare insurers. There is a natural business element here that none of us can ignore. The cognoscente will recognize this; the rest of us could choose to ignore it. I'm not for it, nor against it; I just want people to be honestly aware of it because it impacts our decisions on a daily or hourly basis. What's healthcare all about? For some, it's about the money; for others, it's about the patients. In truth, it's a sensible mixture of both, for as they say, "No money, no mission!"

Before venturing any further, the one question that will decide any dilemma about treatment choice is, What is in the best interests of my patient?

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31.1 Healthcare Is Taking It in the Shorts Right Now...

Wall Street, housing, and the auto industry have all had their upheavals during the past 12 months, and healthcare is no exception. We all need to understand the problems, get involved, and be part of the solution.

In the United States, approximately 50% of all healthcare regulations add to the cost of delivering healthcare and in no way add to the quality or efficiency of providing care. The role of the Food and Drug Administration (FDA) should also be questioned because there are real doubts about its overarching role. In both these areas, I shall examine the cost/benefit ratio and attempt to relate this to the working physician's life. I do not wish to be alarmist or reactionary. We just need some common sense.

Healthcare regulation is a necessity. However, as Lawrence Brown put it, "Paradoxically, healthcare has become steadily more regulated at all levels of government and in the private sector, too, at the same time as other economic sectors – such as transportation, telecommunications, and banking – have moved the opposite way" [13]. Given the chaos in the banking

C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_31,

industry, one might conclude that more regulation is better than less.

When examining the regulation of business in the United States, one can find a significant amount of literature about the benefits and costs of regulation on the national economy. Such regulations have been found to impose a real burden on US businesses and consumers. The consequence of regulation on the overall economy is said to have approached $1 trillion in 2004 [5] (http://www.epa.gov/fedrgstr/EPA-GENERAL/2000/February/Day-11/g3175.htm).

So who's paying for all these healthcare regulations? In practice, business is paying, and so too are we physicians. For every patient one sees, how much time is spent on clinical care? How much time is spent on administrative paperwork? The answer is depressing given the extraordinary time and effort that physicians put into getting the paperwork straight, in comparison to listening to the patient. This has to change!

Physicians have been roundly criticized in the United States for trying to block healthcare reform. However, physicians are only a part of the problem, and many will indeed acknowledge that changes are necessary and that the provision of healthcare needs to be more appropriate, timely, and cost-effective. Physicians can no longer practice defensive medicine, a phenomenon wherein unnecessary confirmatory tests and procedures are performed, which are generally associated with high technical and professional fees.

At a recent conference, I asked the audience (700 strong) if they would be prepared to accept a nationalized healthcare system if the regulations were curtailed just to those with evidence of benefit, if meaningful tort reform were passed, and if they were paid 10% more than they currently earn. Eighty percent of the audience voted in favor! So, it's not that the medical profession is determined to prevent healthcare reform, it's just that they want the irrelevant and onerous administrative aspects, which make the practice of medicine so hard these days, to be curtailed.

Great healthcare could be provided at much lower costs. Among the world's 30 most industrialized countries, only Mexico, Turkey, and the United States do not have universal health coverage. This fact alone should make us strive to provide affordable care for all. According to recent data, some 47 million Americans are without health insurance. These without insurance avoid medical care because it is too costly or, if they do seek care, they are saddled with the highest costs.

So what does the cost of healthcare regulation include? It takes into account the *regulation* of healthcare facilities, healthcare professionals, health insurance, drugs and medical devices, the medical tort system, and the costs of defensive medicine [2].

There is no unifying agreement on how to measure the costs of regulation vs. the benefits of regulation; this is as much an art as a science because of imperfect methodology and insufficient data. But the main question here is, Do the benefits of regulations exceed their costs? If yes, then let's consider keeping them; if not, then let's consider scrapping them.

To look at this from another perspective: what are the opportunity costs of regulation in terms of alternative uses to which these same resources might be put? What is the number of lives that could be saved each year by repealing "excess" regulations that fail a cost-benefit test?

A conservative estimate of the total cost of healthcare regulation exceeds $339.2 billion, and the benefits of health services regulation exceeds $170.1 billion. Thus, the net burden of health services regulation amounts to about $169 billion annually. This exceeds the annual consumer expenditures on gasoline and oil in the United States!

Of the 45–50 million Americans who lack health insurance, 6.8 million might be attributed to excess regulatory costs. The people aren't dying from lack of insurance coverage or reduced societal income (those things can't cause a death); more likely they are dying because they can't afford medication or services to treat disease *because of* their lack of insurance or reduced societal income. [4].

Healthcare mandates (generally unfunded) represent the worst form of healthcare management. An unfortunate but solitary event that occurs in the life of one senior administrator (for instance, a US Senator) might have a national consequence when that same senator proposes a mandated remedy for this isolated occurrence. No matter how tragic this event might have been, such knee-jerk reactions are no way to run national health policy. This is not evidence-based government! A greater benefit might be to look at real hard data based on facts and assess outcomes on the scientific evidence at hand.

Other aspects of healthcare mandates may be seen in the current White House. The Obama administration is working with Congress to mandate that all Medicare payments be tied to "quality metrics." But an analysis of this drive for better healthcare revealed an elemental flaw in how quality is defined and metrics

applied. In too many cases, the quality measures had been hastily adopted, only to be proven wrong and potentially dangerous at a later time [6].

A growing number of rigid protocols, which are meant to guide physicians, have perverse consequences, as reported by Jerome Groopman and Pamela Hartzband. Health-policy planners define quality as "clinical practice that conforms to consensus guidelines written by experts." The guidelines present specific metrics for physicians to meet, so-called "quality metrics." Since 2003, the federal government has piloted Medicare projects at more than 260 hospitals to reward physicians and institutions that meet quality metrics.

This has had an impact on private insurers, many of which are following suit with similar "pay-for-performance" incentive programs. In Massachusetts, there are not only rewards but penalties too. Physicians who do not act in accordance with these quality guidelines can be excluded from prime contracts, and their patients are required to pay premium rates to see them.

One might ask, How did we get here? In practice, medical providers and hospitals largely brought this upon themselves. The quality improvement initiatives were originally oriented toward patient safety and public health issues. Hospitals had widely disparate records with regard to rates of infection, pressure sores, postoperative complications, and utilization issues. A remarkable degree of carelessness existed with regard to hand washing, for example, though this has largely been remedied by standardized protocols. These successes have encouraged governmental and private insurance regulators to vastly overreach. They've manipulated clinical guidelines for complex diseases into iron-clad rules, to deleterious effect. One key quality measure in the intensive care unit (ICU) became the blood glucose levels among critically ill patients. Expert consensus endorsed tight control. The Joint Commission on Accreditation of Healthcare Organizations, which generates report cards for hospitals, adopted this and other guidelines as gospel.

Physicians who might disagree with this universal approach for tight control of blood glucose don't have an option to practice what they believe is an appropriate standard. Instead, they are criticized and some are forced to attend "re-education sessions" where they are lectured on the need to adhere to the rule. Further noncompliance will result in their hospital being downgraded in its quality rating and the risk of financial loss. Their Medical Executive Boards will take a dim view of this substandard behavior.

So, it was all the more alarming when the *New England Journal of Medicine* published a randomized study by the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Canadian Critical Care Trials Group of more than 6,000 critically ill patients in an ICU. Half of the patients received insulin to tightly maintain their blood glucose in the normal range, and the other half were on a more flexible protocol, allowing higher blood glucose levels. More patients died in the tightly regulated group than those who were cared for with the flexible protocol [11].

Indeed, medicine is an imperfect science. Information evolves and changes. Regulatory bodies need to be aware of this and apply more flexibility instead of rigidity.

Good doctors exercise insightful judgment before deciding what is in the best interests of their patients. And what is best sometimes deviates from the norms. So much of what we learn is just plain wrong. Anecdotal evidence is hogwash, but if it is said by those who are held in eminence it will sadly take on the mantle of truth. Before we have any more mandates on healthcare, let's be a little more reflective of reality.

31.2 Why Do We Need the FDA?

In 1937, a sulfa drug by the name of Elixir Sulfanilamide was released in the United States and killed more than 100 Americans, including many children. Thalidomide became available in Europe in 1957. Taken for pregnancy-associated nausea, it caused serious birth defects in more than 10,000 children. In November 2006, *The Journal of the American Medical Association* reported four cases of botulism in cosmetic patients who had all received facial injections of botulinum toxin. This was an illegal use of a highly concentrated unlicensed toxin product. A subsequent analysis of the patients' blood revealed blood serum levels up to 40 times the estimated lethal human dose. Fortunately, all four patients survived [10]. These famous episodes remind us that terrible things can happen and need to be prevented.

Conversely, by 1988 it was recognized that aspirin could significantly reduce the risk of myocardial occlusion. But for many years the FDA would not allow aspirin makers to advertise this fact. It has been suggested that, through this action, the FDA had surely killed tens and possibly hundreds of thousands of Americans.

Further, it is claimed that current FDA policy tends to delay, stifle, and suppress life-saving drugs and devices. And there are many other examples cited by concerned individuals.

It's reasonable to question whether drug and device safety is a "yes-or-no" issue. For instance, is chemotherapy safe? Indeed, many medicines might be regarded as poisons. Though few FDA-approved drugs are manifestly unsafe, there are countless problems associated with their use each year. In 1994, adverse reactions to FDA-approved drugs are said to have killed more than 100,000 hospital patients. But in 1998, about 130 people died while on Viagra! I am not sure what conclusion to draw from this latter point, but there might be some merit in it.

The Center for Devices and Radiological Health is one arm of the FDA, which specializes in the analysis and assessment of devices such as lasers and other energy-based systems. It offers (a) *premarket notification* 510(k), wherein a device has substantial equivalence to existing technology; (b) *premarket approval* for high-risk class III devices or those not meeting 510(k) equivalence; and (c) *investigational device exemption* for those devices under clinical trials using unapproved medical devices on human subjects. These must be approved by the FDA and by an institutional review board [9].

Many aspects of device safety could be certified, assured, and adjudicated by an independent, private-sector, voluntary institution and the tort system. There is nothing inherently different about the safety of a medical device in comparison to the safety of a non-medical device. That is, one can be killed as easily by a car as a faulty mechanical heart valve. So why the special treatment for drugs? Indeed, how is safety assured in other industries? In electronics, manufacturers submit products to Underwriters' Laboratories (UL), which is a private organization. The process is voluntary, and upon completion of the assessment UL grants its "safety mark" to products that pass its inspection. It's important to understand that manufacturers may sell without the UL mark, but retailers and distributors usually prefer the products with it. So do we really need the FDA? In the USA, we are so entrenched in our traditional thought processes that it is difficult for us to even contemplate adopting a new more open-minded strategy. There are many reasons for considering this approach and, similarly, there are cogent reasons why we might keep a trimmed-down version of the current safety and validation process, or maybe a hybrid of the two systems.

It is important to realize that these concerns are not limited to physicians and laser surgeons. They are a major concern of many economists in the USA. Most economists find the FDA to be overly restrictive and favor freer markets. Some propose specific decontrol; others favor creating a free market by abolishing the agency. Though I do not support this personally, it is difficult to find a single economist who defends or supports the contemporary FDA or advocates tighter regulation.

> Gary Becker, the 2003 Nobel laureate said, "...experience indicates that the FDA frequently has delayed approval to avoid embarrassing political and medical mistakes.... Eliminating all requirements except a reasonable safety standard would vastly reduce drug prices in the US, as companies would be encouraged to develop additional compounds to compete for customers."

> John E. Calfee, Resident Scholarin Economics at University of California, Berkeley, has said, "… the evidence is very strong that the FDA suppresses a great deal of useful information ... experience from related markets in this nation and abroad also strongly indicates that informational competition involving drugs and devices is likely to be beneficial, and that the pharmaceutical market does not pose unique problems that make it unsuitable for traditional competitive dynamics."

This concept is a recurring theme amongst economists and has the ring of correctness about it. Some might consider it a conspiracy of silence. All too often, new and brilliant concepts are quietly snuffed out in their embryonic state (by acquisition and shelving) to avoid a negative impact on profits of less ingenious devices.

> Milton Friedman, who was awarded the Nobel Memorial Prize in Economic Sciences, said, "The FDA has already done enormous harm to the health of the American public by greatly increasing the costs of pharmaceutical research, thereby reducing the supply of new and effective drugs, and by delaying the approval of such drugs as survive the tortuous FDA process." When asked, "If you could do anything to improve health in America, what would you do?" Friedman replied, "No more licensing of doctors. No more regulation of drugs. Not of any kind, period."

Though this might seem more than a little extreme to those of us who know the importance of moderation, one might also understand that there is some benefit in the concept of less federal and state control of healthcare.

> Robert Higgs said in 1995, "Americans would be better off with drastic curtailment – ideally the complete abolition – of the current regulatory regime, which imposes major costs while providing little if any genuine protection of the public health."

How is it that these brilliant and competent economists seem pretty united and militant in their views, while we physicians have been happy to respond with meek niceties [3]?

> Henry G. Grabowski and John M. Vernon jointly said in 1983, "... A more fundamental kind of regulatory reform could be accomplished through congressional change in the FDA's regulatory mandate. It is possible to envision an FDA regulatory structure that would operate more as a certifier and disseminator of information for the vast majority of new products introduced. ... Manufacturers would have the option to market a new drug even if it failed to be certified by the FDA."

My colleague at University of California, Irvine, Randall Holcombe, always a very reasonable and sane individual, said in 1995:

> ... government regulation of medical drugs has several negative consequences, raises the cost of all drugs, delays the introduction and use of beneficial drugs, reduces the amount of innovation in the drug industry, and prevents certain types of drugs from ever being introduced. In exchange for these costs, the government certifies that medical drugs are safe and effective. The policy experts who have evaluated the costs and benefits of drug regulation have almost uniformly concluded that the costs of the regulations are not worth their benefits.

Tough words from a reasonable man.

> Daniel B. Klein said in 2000, "Even without the government approval systems, voluntary institutions and the tort system would utilize testing and professional certification to screen out unsafe drugs. The government approval process here and abroad is a set of bureaucratic hoops and hurdles often inappropriate or unnecessary for the drug in question. The harms of the FDA are unredeemed."

> Paul Rubin said in 1995, "When we think of the FDA and overregulation, we tend to think of the inexcusable delays in approval of new drugs. Scholars have long been aware that the agency causes unnecessary deaths and suffering by this policy. But there's more ... The FDA's policies greatly retard the spread of [drug] information. ... The FDA should allow manufacturers to advertise any claim for which reliable scientific evidence exists, whether or not this claim has been approved for the label, and this advertising should be allowed for both consumers and physicians. The results will be greatly improved health of consumers and reduced prices of pharmaceuticals."

Personally, I think that this is pushing the envelope of what makes sense. But is it important to understand what influential economists are thinking?

> Russell S. Sobel said in 2002, "… a free market in over-the-counter medicines, with laws regarding only the factual content of statements, would result in an improvement in public health."

Very reasonable ...

> Murray Weidenbaum in 1993 raised the question of great drugs that are not necessarily profitable for the manufacturers. "... while some drugs are very profitable, many more are not. Price controls would be a mistake. What is needed is more competition, warts, and all; the competitive marketplace is the best protector of consumers."

In other words, if we restrict the ability of the pharma companies to have some reasonable return on their investment, why would they bother?

What is so depressing in all this discussion is summarized in the casual words, said in 1992 by the then-FDA Commissioner, David Kessler, who concluded that

> It is too great a burden for average Americans to make decisions concerning their own healthcare. If members of our society were empowered to make their own decisions ... then the whole rationale for the agency (FDA) would cease to exist. ... To argue that people ought to be able to choose their own risks, that government should not intervene ... is to impose an unrealistic burden on the people.

To my mind, these are troubling words, which imply that the public is not to be trusted. For my own part, I believe that the public needs to exercise a degree of personal responsibility with regard to healthcare. We can't be handholding the public from cradle to grave. But we can give them the same opportunity to benefit from an expanded number of services, drugs, and devices as we would if they were at a Best Buy store looking for a new DVD player.

Basically, banning a risky product does not improve any consumer's welfare. The fundamental idea of risk in healthcare is an inescapable condition of opportunity. A fundamental idea in finance is the relationship between *risk* and *return*. The greater the amount of risk that an investor is willing to take on, the greater the potential return. A similar approach can be used in healthcare. If your patient has an incurable and fatal disease, they might absolutely want you to think outside the box. One could offer nothing, because evidence-based medicine has never proven success, or one might offer something, even if it only has anecdotal benefit. The treatment might not work but will give hope to the patient. The FDA makes it very difficult to adopt the latter approach.

People may prefer to live in a world of complete certainty, but that is simply not possible. Just banishing risk by regulation or otherwise is not a feasible act. Treatment is not good or bad; there are always risks, lack of efficacy, and adverse side effects, which are the yin and yang of medicine.

Some have suggested replacing FDA regulation of medical devices with third-party certification, and I believe this has some merit. As it stands in the USA, no manufacturer can market a medical device, alter manufacturing processes for a device, or propose a new use for an existing device without the approval of the FDA. The FDA monopoly over market access creates a bottleneck, delaying the introduction of new medical devices for up to 3 years and restricting the flow of information from the manufacturer to users about approved devices. These actions not only violate the basic rights of the device manufacturers and consumers who wish to trade with one another, but they have resulted in thousands of deaths.

I want to state that the FDA is staffed with decent and hardworking scientists and administrators who generally have tried to do the right thing. However, as was discussed very publically recently, there are tensions and disagreements at the very highest levels within the FDA about the many serious recommendations concerning drugs and devices. In many instances, the FDA has achieved success in the proactive prevention of serious injury and death by its actions. But this government entity is poorly funded and understaffed, and at the same time is under pressure from companies, government, lobbyists, and physician groups to approve or curtail certain drugs and devices. Under such circumstances, it is easier for the FDA to postpone, shelve, or deny approval rather than to spend the time necessary to establish a safety and efficacy basis for a responsible determination [1].

To paraphrase Noel Campbell, though it might seem a little over-the-top, some are suggesting that we should replace the FDA regulation of medical devices with third-party certification and turn over the certification of medical devices to *certification agencies* competing in a free market, such as UL, Inc. This is a privately funded institution that certifies safety and performance, provides valuable information to consumers, leaves manufacturers and consumers free to trade with one another, frees businesses from the crippling costs of undue regulation, and gives consumers the freedom to choose the amount of risk that best suits them (http://www.ncpa.org/media/replace-fda-with-underwriters-laboratories-method-study-suggests).

I understand that this is difficult for many of my colleagues, but consider the following. If the Obama White House suggested a proposal to create a new government agency that forbade manufacturers from making any electronic products until approved by the agency, it would be considered authoritarian and extreme. But these are the rules for drugs and devices. Free enterprise is OK for your stereo system, but for medical devices, we shroud new information in secrecy and restrict development, manufacturing, testing, and sales of every new medical device idea that comes along. The pendulum of government restrictions has swung too far in the wrong direction. It's time for change.

31.3 Reality Check: What Our Colleagues Believe Would Fix the System

I recently chose a panel of colleagues whose opinions are renowned. The issue was simple, namely, "how to fix our healthcare problems." These panelists included Brian Biesman, Brian Zelickson, Whitney Tope, Kristen Kelly, Jay Burns, Tina Alster, Richard Felton, Jeff Dover, and Bruce Tromberg. I thank them for their assistance.

31.3.1 Panel's Suggestions

1. *US healthcare is in crisis.* A major overhaul of the healthcare system is needed. Set up a universal health insurance as a requirement of all US inhabitants. Enhance both the Medicare and Veterans Affairs (VA) healthcare systems and consider amalgamation of these. Require state and federal legislators to use and appreciate the standard Medicare/VA system. Create a single-payer system for nongovernmental health insurance. Provide emphasis on prevention rather than treatment. Deregulate most healthcare regulations except a significant and proven core group. Develop real medical tort reform. Serve the underserved; champion volunteerism. A requirement for newly qualified physicians would be to work in underserved communities before specialty training. In return, the government should pay these physicians well, provide forgiveness of their student loans, and simplify medical malpractice and compliance regulations.
2. *Fix the FDA.* It's broken. It's "opaque" to industry and medicine alike and is hamstrung with isolation, hesitation, and fear of bad results. It takes too long to make decisions; its focus is wrong, and full of irrelevancies. For instance, the FDA required

"extensive biomechanical review of hand motion and mobility" in the study of patients undergoing Scuptra hand injections for esthetic enhancement. (This made little sense at the time, and in retrospect, even less now.) Provide a system of transparent peer review in the decision-making process to help both patients and businesses. The panels reviewing the devices need to be made up of people who really know devices. Data submitted to FDA for approvals by drug and device companies should be made immediately available upon clearance of any product. Serious, concise, and truthful postmarket reporting should be required of companies. Make sure devices do what they are said to do.

3. *Protect intellectual property.* Too many companies disregard others' intellectual property. There needs to be a better, faster way to solve patent infringement issues, with meaningful consequences. Hold physicians and companies to a higher standard. Be tougher on those doing poor science or those spouting the benefits of devices lacking science. False claims should disqualify from continued approval. Demand critical safety studies. Empower physicians to do what they do best. Take care of people with real problems and train each other. As for certification, people who wield lasers should have, at least, some medical degree after their name, be directly supervised by a real physician, and both should be required to go to laser college, take refresher courses, and actually pass a test.
4. *It's about healthcare.* The US healthcare system is suffering because it's about money, not people. Educate the public as to what constitutes a well-trained or qualified laser specialist. Patients having no problems are going to the neighborhood Medspa to be treated by someone with no experience and zero training. The fact that the public is not well informed is our problem, and we have no one else to blame.
5. *The public needs to own the problem*. Make the public more responsible for its own health by rewarding good habits and penalizing bad ones.

31.4 Who Are the Quacks, and Why Do We Tolerate Them?

Most of us would do almost anything to extend our lives or to alleviate the misery of some serious illness. Conversely, others might do anything to take advantage of these innate wishes by selling what they claim to be life-prolongation remedies and cures. In the early twentieth century, those offering "the cure" saw a huge interest in "patent" medicine, though this specialty began a steady decline in 1907, shortly after the passage of the Food and Drugs Act of 1906. As a matter of historical interest, this argues strongly that the passage of appropriate legislation and with appropriate enforcement can be an important inhibitor of any industry, no matter how well entrenched or how popular it might be with the public [12].

Oddly enough, it was the existence of quacks that helped to legitimize the medical profession. Acting as an impetus for "demands of greater transparency, therapeutic rationality, and ultimately, controls" in medicine (http://www.winterhouse.com/editions/books/quack.html), William Helfand correctly noted that "the promotion of bogus health-related products has never ceased, and in our own time, it has found perhaps the most potent vehicle ever invented – the internet."

The question of scope of practice or "turf" is as prominent now as it was centuries ago. The conundrum of "who should be allowed to do what to whom" has a long history. Prejudice or bias was clearly present in the mid-eighteenth century in the town of Preci, a municipality in the Province of Perugia in the Italian region of Umbria. Within its walls was a school famous for its sophisticated practice of urology, providing unparalleled and superior care. The school came to an abrupt end after 1751, when a Papal edict declared that *only surgeons with a degree* could remove stones. This is despite the fact that the Preci School surgeons performed lithotomy and many other sophisticated urological procedures, designing and making their own instruments, which were well ahead of their time and used by other surgeons even centuries later [7]. So, we need to be mindful of the fact that we can bring about profound changes for both good and bad by knee-jerk and autocratic reactions. Great ideas are still shelved on a regular basis for financial and other reasons.

By my own reckoning, today's quack doctor provides, with hyped lectures and convoluted science, exaggerated promises of therapeutic cure. Quacks have a need to define themselves; some quacks inflate their university credentials, others dress elaborately or use gimmicks, and yet others embrace a nuanced and extravagant vocabulary, a process called "marketing," to promote their latest antioxidants. Quacks used to be of an itinerant nature, which was necessary to enable them to avoid the inevitable consequences of dissatisfied customers. Later, succeeded by the makers of proprietary

medicines, these vendors advertised widely, often with celebrity testimonials. Currently, they can stay right at home and use the internet as their favorite device for ensnaring their prey. Until the mid-nineteenth century, both physicians and quacks relied upon certain standard agents, including opium, quinine, and antimony (which worked), and a great many others (which did not).

Quackery is a serious business. People die from medical complications related to twenty-first-century quackery, which the district attorney's office is more prone to regard as manslaughter, reckless endangerment, or reckless homicide. One of the major goals of the medicolegal death investigation system is to safeguard the public health [8]. Although one might think that we are far from this type of behavior, it was only 2 years ago that several young ladies died from illegal prescription of topical anesthetic in preparation for laser hair removal procedures by unqualified individuals. Are we not, in some regards, still living in the mid-nineteenth century?

Complementary and alternative medicine (CAM) is flourishing. Yet it is not appropriate as primary treatment for serious diseases, particularly neoplastic ones. However, each year there are many examples of cases treated (or not treated) by CAM. It is important for the public to realize that this could, on occasions, be viewed as a form of physical abuse. Patients should be given the facts concerning homeopathic medicine with the requirement for some evidence-based assessment of such treatment, allowing them to make informed decisions. What's good for allopathic medicine is good for CAM.

So I would ask the question, Is mesotherapy quackery? A technique that involves microinjections of conventional homeopathic medications and/or vitamins to promote healing, this has not been able to withstand standard objective analysis. It is a debatable addition to the therapeutic armamentarium in the management of anything. Dermatologists should use this with caution because at present there is much controversy regarding its efficacy and safety despite the fact that mesotherapy is gaining popularity in the West.

The uncritical acceptance of many new treatment modalities (including light, laser, and energy-based systems) is related to slick marketing and media enthusiasm, even when many are without much evidence of real benefit. It's not good enough for us to accept some bland approval by the FDA that these devices are "safe." Efficacy is critical. If they don't work, then someone has the responsibility to say so.

At the end of the day, we all have the responsibility to challenge traditional remedies, some of which are worse than the disease. Remember the priest physicians of the fifteenth century who would use bleeding and tripe as primary treatment protocols. In the twenty-first century, it seems audacious to suggest that the FDA can promote bad medicine. But to some degree it's inevitable. We all need to keep an open mind. None of us likes to hear that we use quackery. However, in collective decision making, quackery often prevails over sense (http://lsb.scu.edu/~dklein/papers/FDA_piece_June_2000.htm).

Take Home Pearls

Rules for success and happiness in medicine:

- Treat all patients as if they were members of your own family.
- Always tell the truth.
- Don't be afraid to ask questions. or ask for help.
- Learn to say "I don't know" and "I'm sorry."
- Thank every patient who comes to see you, so that they understand that you feel it's a privilege to take care of them.
- Take care of yourself:
- Exercise. Take vacations. Learn to say "no."
- Appropriate eye protection must be provided to all personnel, including patients within the laser-controlled area.
- Training of physicians in aspects of medical laser or ILS treatments is required.
- Never sacrifice your dignity to make money, but charge what you are worth.

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The Hall of Shame

32

Christopher B. Zachary

Dedicated to my father, Robert B. Zachary, FRCS: Poet, Author, and Surgeon.

The association of physicians and business technology
Is good, established, and needs no apology
But developing good science
And the right alliance
Might require a doctor of theology

It's important for us, I think you'll agree
To examine our deals with the laser companies
A hearty discussion
Might have repercussion
And affect critical thinking of us meeting attendees

With our little clique here at Mont Tremblant
And our Chateau Briande with DomPerignon
I might burst a few bubbles
Cause a little trouble
Especially for some, so let us bring it on!

Without the cooperation of investors and the like
New laser development would go on hunger strike
Turning off the spigot
Would make one look a bigot
Spinning and going nowhere, like a stationary bike

The launch of a laser appliance
Is often a grand alliance
But where there's charade,
You might feel betrayed
Or confused by the pseudoscience

The types of things that upset one
Is research done by a hired gun
Everyone's losing
With too much schmoozing
While investors walk away with a home run

One problem here is that to succeed
Laser companies must at full speed
Satisfy their investor
Or their product might fester
Instead of a claim "results guaranteed"

One of the things that we should insist
Are measurable outcomes, for they do exist
And good photography
Should show topography
And define any changes, should they persist

Defining improvement in texture and tone
Can result in wild statements, way overblown
When minimal changes
In plus minus ranges
Are published in journals and sensationally prone

In reality, my friends, as we have seen
Some macho physicians and some queens
Can see temptation
Where there's desperation
To make it look good on the big screen

Some laser studies are open to scorn
"Getting it right" is a special art form
You get so piqued
When results have been tweaked
That you never do trust those that misinform

And when they are caught in flagrante delicto
Avoid them like a malarial mosquito
Keep the higher standard

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1_32, © Springer-Verlag Berlin Heidelberg 2011

Be not gerrymandered
Dismiss, disregard, use editorial veto!

Each week in the throwaway journals
We're encouraged by adverts infernal
To succumb to excitement
(Could lead to indictment)
And invest in a lease eternal

But many of the studies do indeed show
What we were told by the CEO
Specific changes, measurable indeed
Allowing us to proceed
With trust in the purchase, and a quid pro quo

Good news, dear patient, after critical review
We can endeavor to make you new
With this device
For quite a price
I promise to change you a micron or two!

Today's most exciting laser production
Will result next week in a NASDAQ eruption
No need to take Paxil
Just invest in Fraxel
And take an incredible business deduction

Microscopic epidermal necrotic debris
No wonder they call it MEND
It sounds like a hatch
There must be a catch
But no, it's totally guaranteed

They say this latest box of tricks
Makes lots of 40-μm nicks
Quoth one who knew:
"Beat's the CO_2
And all those wrinkles it will fix"

I ask you, Is this a modern nonablative creation
Or simply an old ablative mutation?
Why God all mighty! it's AC DC
Yes a pseudohermaphrodite
Designed to create dermal reincarnation

The boast of this image is plain
Look carefully and you'll ascertain
That the pigment is braun
And now it is gone!
As quick as a subway train

But hold, I'll tell you before you spasm
Don't just fall for that mighty chasm
An IPL or chemical peel
Can definitely look that surreal
And better and cheaper than this orgasm

These anchoring points were discussed last year
Top-notch design of a biomedical engineer
But, number of passes, power, and location
And how do you stop that painful sensation
Oh give us a hint, a little souvenir

When it first came out, the IPL
Was a hell of a system, so they did tell
Could treat any thing
From here to Beijing
It's the first of its kind, it's celestial

But soon we saw that it had limitations
A few burned patients caused many frustrations
So it took a while
To correctly compile
The parameters and correct permutations

Is it 2.4 or 4.0?
Which pulse duration will be our hero?
And what's the delay
For a café au lait
To avoid a burn a la Nero?

Extra extra!, Good news for white hair
Or even if gray, you need not despair
For now with Aurora
You'll lose your plethora
No more humiliation and visible stares!

This here image by Galaxy from Syneron
Shows dramatic changes this patient has undergone
Now, I know it's taboo
To misconstrue
But for me I'd say it's a sine qua non!

Here in this image the muscle is plain
And now it is gone like a spasm of strain
I might be deluded
But I have concluded
That she passed some gas and got rid of the pain

Am I wrong? Is this an error?
Or are you too frightened and sulking with terror
In this does she purse
Her lips and then reverse
To relax and be calmer than ever?

There is a slimier seamier side
Of medical business we can't abide
Seems such a shame
No-one to blame
When they close the gates and hide

The heavenly road of good intention
Is paved with lasers without redemption
The littered streets
Are totally replete
With N-lites donated by ICN

Combining six diodes and suction
You should add magnetic induction
It's not too complex
You're just selling sex
In a big theatrical production

Tri-Active will, for a small surcharge
Improve those butts, both small and large
But the Cynosure models
Displaying their caudals
Though impressive, are only here for a massage

Tri-Active is officially recommended
"A course of 12 weeks would be splendid"
But the sponge in the buns
"Is back in one month"
Contrary to what is contended

Cynosure I hate to diss you
Suction for adipose tissue?
It's mental confusion
A foregone conclusion
Most of us here would take issue

Take a look at this image, Oh confusion!
Am I wrong to reach this conclusion?
The pre and the post
Despite what they boast
Is just photographic illusion

"With lypolysis you can improve
All those nasty cellulite grooves"
Where's the proof?
It may be a spoof
No matter, "it's the next generation," it's the Vela-Smooth

When I was a boy I had the ambition
To grow and be something, maybe a physician
But, I'm a trendsetter
Now, I can do better
I'm coming out! I'm a cosmetician!

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C. Raulin and S. Karsai (eds.), *Laser and IPL Technology in Dermatology and Aesthetic Medicine*,
DOI: 10.1007/978-3-642-03438-1, © Springer-Verlag Berlin Heidelberg 2011