Annals of Diagnostic Pathology 35 (2018) 80–84

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Extraprostatic extension (pT3a) in prostate biopsy is an under-recognized feature indicating high risk disease

Teemu T. Tolonen[a,*], Jarno Riikonen[b], Teuvo L.J. Tammela[b], Laura Koivusalo[a,c,d], Hannu Haapasalo[a], Paula Kujala[a], Antti Kaipia[d]

[a] Department of Pathology, Fimlab Laboratories, Tampere University Hospital, Tampere, Finland
[b] Department of Urology, Tampere University Hospital, Tampere, Finland
[c] Department of Materials Science, Tampere University of Technology, Tampere, Finland
[d] Department of Urology, Satakunta Central Hospital, Pori, Finland

ARTICLE INFO

Keywords:
Prostate cancer
Prostate biopsy
Prostatic needle biopsy
Extraprostatic extension
pT3a
Fat infiltration
Prognosis

1. Introduction

Extraprostatic extension (EPE+) is a strong prognostic factor of prostate cancer [1], which is commonly detected in the histological examination of radical prostatectomy specimens. The three recognized histological criteria for EPE+ include: deformation of the contour of the prostate by cancer, growth along the posterolateral neurovascular bundles, and infiltration to the periprostatic fat. In the case of prostate biopsies, only the last criterion is applicable.

In previous few reports the incidence of EPE+ in prostate biopsies has been low [2-4]. The pitfalls causing diagnostic uncertainty relate to striated muscle and intraprostatic fat [5]. Cancer infiltrating to the striated muscle may be suggestive for EPE+ in biopsies, but because striated muscle is also found inside the apical prostate (near urethra), it is considered as an unreliable criterion for extraprostatic growth [6]. This is supported by the finding that cancer growing to the striated muscle at apical region in the radical prostatectomy specimen is not associated to adverse prognosis [7]. Some studies have suggested that small amounts of fat may exist in prostate (0–4% cases) [8-10]. Therefore, a reliable histological diagnosis of EPE+ in needle biopsies requires that the cancer infiltrates to the extraprostatic fat through the pseudocapsule at the tip of biopsy core [9]. In the present study, we used criteria suggested by Sung et al. [9] histological examples of prostate biopsies containing EPE+ are presented in Fig. 1.

Due to variable clinical course and different treatment options for prostate cancer, a large number of predictive and prognostic histopathological parameters have been established [11]. These include WHO/ISUP Grade Group, Gleason score (GS), the worst GS consisting of the predominant and the most aggressive pattern in a single biopsy, percentage of Gleason pattern 4/5, the length of the biopsy and the length of cancer, percentage of cancer, number or percentage of positive cores, and perineural invasion [12-19]. Besides grade and volume parameters, EPE+ in needle biopsies is recognized in e.g. in the guideline by the European Association of Urology with a recommendation to include it to the pathology report [11]. However, no specific treatment recommendations are included for patients with EPE+ in needle biopsies.

In summary, the histological criteria for diagnosing EPE+ in the needle biopsies are well established, but the data on the incidence and predictive value of EPE+ in needle biopsies is limited. This study was conducted to find out the incidence and clinicopathological features of EPE+ in prostate biopsies in an unselected, consecutive patient material.

* Corresponding author at: Fimlab Laboratories, Arvo Ylpönkatu 4, FI-33520 Tampere, Finland.
E-mail address: teemu.tolonen@fimlab.fi (T.T. Tolonen).

https://doi.org/10.1016/j.anndiagpath.2018.06.001

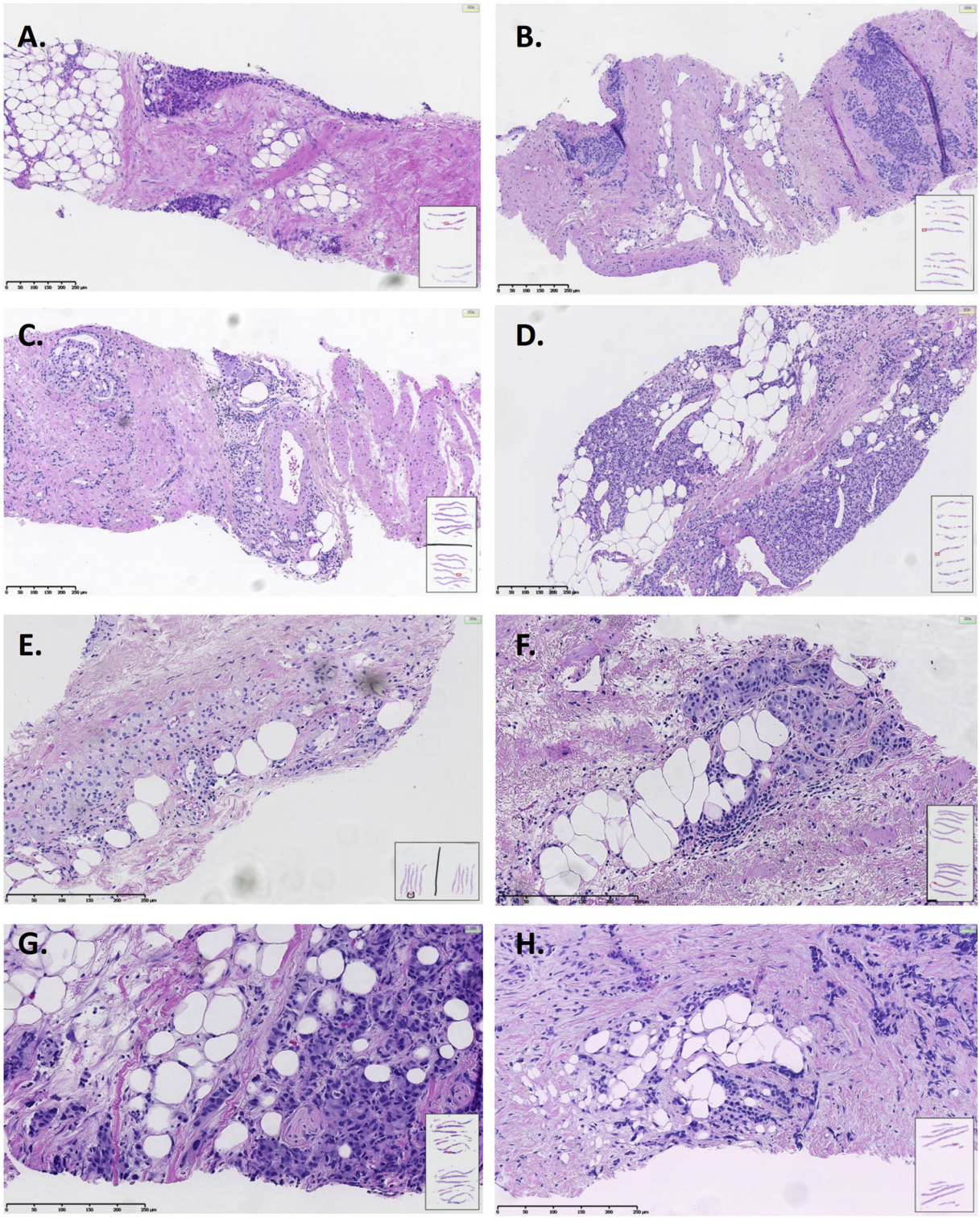

Fig. 1. Histological examples of extraprostatic growth by cancer showing infiltration to the fat in prostate biopsy tip regions. Images were acquired with Hamamatsu Nanozoomer XR slide scanner at 0.23 μm/pixel, captured fields corresponding to 10× (A–D) and 20× (E–H) magnification of NDPView software. A 250 μm scale bar is presented at the lower left corner of each image.

2. Materials and methods

2.1. Case selection

The study was approved by the Ethical Committee of Tampere University Hospital (TAUH) and the National Authority for Medicolegal Affairs. We reviewed1242 consecutive pathology reports of prostate biopsies submitted to Fimlab Laboratories Inc. between 1st March 2013 and 10th September 2014. The biopsies were taken by 26 urologists and one radiologist practicing in TAUH district where Fimlab Laboratories Inc. is the central laboratory receiving all histology specimens in the public healthcare. All except one biopsy set were taken transrectally under ultrasonography guidance using an 18-gauge needle biopsy gun with an 18-mm sample notch (Bard peripheral vascular, Temple, AZ,

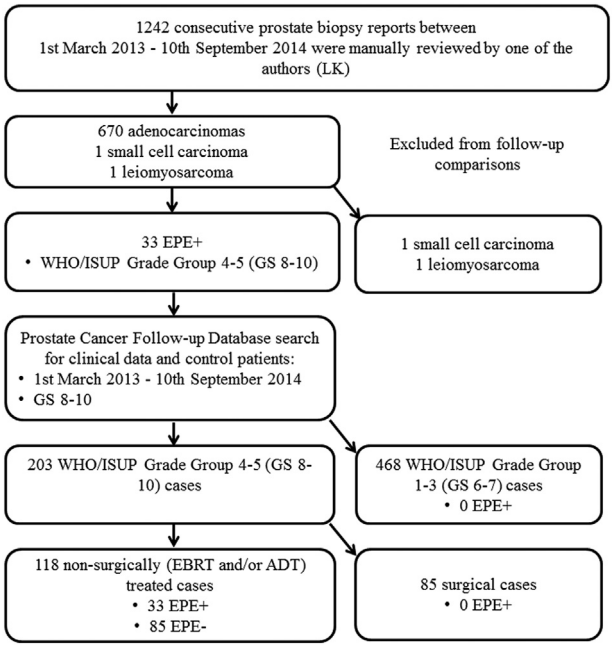

Fig. 2. Study flow chart. EPE+ = positive for extraprostatic extension, WHO/ISUP = the World Health Organization/International Society of Urological Pathologists, GS = Gleason score, EBRT = external beam radiotherapy, ADT = androgen deprivation therapy, EPE− = negative for extraprostatic extension.

U.S.A., ref. no. MC 1825) and a side-fire probe. In one case the biopsies were taken transperineally by a radiologist. The biopsies were processed and analyzed by uropathologists in Fimlab Laboratories, TAUH, in Tampere, Finland.

Pathology reports containing cancer infiltration to the periprostatic fat were considered positive (EPE+) whereas reports indicating infiltration to the striated muscle were considered negative (EPE−). Two cases containing one small cell carcinoma and one leiomyosarcoma were eliminated from further evaluation because their behavior is biologically very different from adenocarcinoma of the prostate. The clinical information of the EPE+ patients (n = 33) was retrieved from the prostate cancer follow-up database maintained by the Prostate Cancer Research Center and the Department of Urology, TAUH. For comparison, the clinical information of all similar (non-surgically treated, EPE-negative, WHO/ISUP Grade Group 4–5) prostate cancer patients (n = 85) of the same time period was retrieved. The study flow chart is presented in Fig. 2.

2.2. Statistics

The differences between EPE+ and EPE− groups were analyzed with one-way ANOVA and Fischers exact test. Statistics were performed with IBM SPSS Statistics version 22 and GraphPad QuickCalcs Web site: https://www.graphpad.com/quickcalcs/ (accessed May 2018).

3. Results

3.1. The incidence of EPE+ in needle biopsies

In this study, prostate biopsies were taken from 1242 men. A malignant finding was reported in 672 (54.1%) patients. All cancers were adenocarcinoma, with the exception of one small cell carcinoma and one leiomyosarcoma. Extraprostatic extension was found in 33 adenocarcinoma cases, leading to the incidence of 4.9% (33/670) in cancerous biopsies and 16.3% (33/203) in WHO/ISUP Grade Group 4–5 cancers.

3.2. Clinicopathological characteristics of patients with extraprostatic extension (n = 33)

The mean (median, range) age was 72.6 (73, 43–94) years and PSA 801.8 (83.0, 3.3–12,810) ng/ml. All patients with EPE+ adenocarcinoma had WHO/ISUP Grade Group 4–5. Three of the cases had Gleason score (GS) 8, 26 had GS 9, and 4 had GS 10. The percentage occupied by cancer was high, 78.2% on average (85.1, 37.0–100.0). Clinical tumor stage was T1–T2 in 4 cases, T3 in 15 cases, T4 in 10 cases, and not

Table 1
Distribution of the clinicopathological variables in EPE-positive and EPE-negative patients.

		EPE+, n = 33	EPE−, n = 85	p-Value
Age, mean (SD)		72.6 (± 10.8)	73.6 (± 8.8)	0.61
Gleason score, mean (SD)		9.0 (± 0.5)	8.8 (± 0.5)	0.01
	GS 8	3/33 (9.1%)	22/85 (25.9%)	
	GS 9	26/33 (78.8%)	60/85 (70.1%)	
	GS 10	4/33 (12.1%)	3/85 (3.5%)	
PSA-value ng/ml, median (range)		83.0 (3.3–12,810)	25.7 (2.6–7366)	0.03
	PSA < 20 ng/ml	11/33 (33.3%)	40/85 (47.1%)	
	PSA > 20 ng/ml	22/33 (66.7%)	45/85 (52.9%)	
Percentage of cancer, mean (SD)[a]		78.2 (± 20.3)	51.1 (± 31.8)	< 0.0001
clinical (c)T-stage				
	cTx-T2	8/33 (24.2%)	36/85 (42.4%)	
	cT3-T4	25/33 (75.8%)	49/85 (57.6%)	0.09
cN-stage				
	cNx-N0	31/33 (93.9%)	82/85 (96.5%)	
	cN1	2/33 (6.1%)	3/85 (3.5%)	0.62
cM-stage				
	cMx-M0	18/33 (54.5%)	57/85 (67.1%)	
	cM1	15/33 (45.5%)	28/85 (32.9%)	0.21
Therapy[b,c]				
	ADT	25/33 (75.8%)	54/85 (63.5%)	
	EBRT + ADT	7/33 (21.2%)	31/85 (36.5%)	0.18
Overall mortality		14/33 (42.4%)	17/85 (20.0%)	0.02
Cancer-specific mortality		7/33 (21.2%)	9/85 (10.6%)	0.14

[a] Percentage of cancer could not be retrieved for five EPE− cases.
[b] One patient died before therapy was started.
[c] ADT; androgen deprivation therapy. EBRT; external beam radiotherapy.

Table 2
Summary of the current literature on extraprostatic extension in prostatic needle biopsies.

Study	EPE + (%)	Criteria for EPE +	Slides reviewed	Age (range/SD)	Follow-up time, years	Median PSA value (ng/ml)	Median Gleason score	% cancer in biopsy cores	Treatment	n:o of cases in RP (%)	Metastatic disease (%)	Overall mortality (%)
Yilmaz et al. 2004 [2]	23/1017 (2.2)	Fat involvement	EPE + cases	70 (57–83)	NA	15.5	8	NA	NA (1 RP)	1 (4)	NA	NA
Miller et al. 2010 [3]	99/51891 (0.19)	Presence of malignant glands within periprostatic adipose tissue	No review; initial dg by one uropathologist	64 (48–87)	Mean 2.9 (median 2, range 0.1–9)	7.8	8	70 (mean)	ADT, EBRT, RP, cryo	11 (15)	29 (40)	NA
Fleshner et al. 2016 [4]	112/19950 (0.6)	DB search for "extracapsular" or "extraprostatic" or "adipose"; exclusion terms	NA	68 (61–75)	Median 1.3 (IQR 0.3–4.2)	15.9	9	86 (median)	ADT, EBRT, RP	24 (21)	36 (32)	41 (37)
Current study	33/670 (4.9)	fat invasion at the tip of biopsy core (Sung 2006)	EPE + cases	73 (43–94)	Median 1.6 (range 0.8–2.8)	83.0	9	85 (median)	ADT, EBRT + ADT	0 (0)	15 (46)	14 (42)

Abbreviations: EPE +, extraprostatic extension; RP, radical prostatectomy; NA, data not available; dg, diagnosis; ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; cryo, cryotherapy; DB, database; RT, radiotherapy

assessed in 4 cases. Bone metastasis was present in 45.5% (15/33) cases and lymph node metastasis in 6.1% (2/33) patients. The treatment choice was ADT in 25 cases and combination of EBRT and ADT in 7 cases. The overall mortality of the EPE + patients was 42.4% (14/33).

3.3. Comparison of EPE + (n = 33) and EPE − (n = 85) patients

The mean age and the number of patients that received EBRT were similar in both groups. The cancer percentages, PSA-values and Gleason scores were significantly higher in EPE + patients. Tumors of the EPE + cases tended to be locally more advanced, but the difference did not reach statistical significance. The rate of distant metastasis was high in both groups. Despite short follow-up time (median 19 months, range 1–33), the overall mortality of EPE + patients was significantly higher compared to EPE-negative patients (42.4% vs. 20.0%, $p = 0.02$). There was no statistically significant difference in cancer specific mortality (21.2% vs. 10.6%, $p = 0.14$). The distribution of the clinicopathological variables of EPE + and EPE − patients are presented in Table 1.

4. Discussion

Extraprostatic extension in radical prostatectomy specimen is a strong prognostic factor that alters tumor staging category from pT2 to pT3a and above, but there is little data on the incidence and prognostic value of EPE + in needle biopsies. Literature search revealed only three previous publications on the incidence of EPE + on prostatic needle biopsies. In the study by Yilmaz et al., the incidence of EPE + was 2.2%, and in the study by Miller et al., the reported incidence of EPE + was 0.19% in a very large needle biopsy series [2, 3]. In the latter study, many of the cases were consultation cases typically harboring small atypical foci and the material was likely to underestimate the incidence of EPE + . Recently, Fleshner et al. reported 0.6% incidence for EPE + in a large series in which EPE-positive cases were retrieved from pathology reports by a text search [4]. Considering the variety of terms used to denote EPE + , the authors conclude that they may have missed some EPE + cases. In our material, the incidence of EPE + was 4.9% in biopsies harboring adenocarcinoma, which was higher than expected based on the existing literature. Instead of non-structural database search, one person (LK) screened personally 1242 consecutive pathology reports to detect all EPE + cases. Taken that there were almost ten-fold difference on the incidence, it is likely that different methodology does not account for all observed variance. Other explaining factors include higher age and stage of our patients, and possibly more laterally targeted biopsies. The main findings from the four aforementioned studies representing current knowledge about EPE + in prostatic needle biopsies are summarized in Table 2.

It is important for clinicians as well as for pathologists to recognize that EPE + in a needle biopsy is a sign of highly aggressive disease. Almost half of our EPE + patients had distant metastasis at the time of diagnosis, 3 of 4 patients in the EPE + group belonged to cT3–4 staging categories, and all cases harbored high grade adenocarcinoma (WHO/ISUP Grade Group 4–5, GS 8–10). Our early finding that EPE + in a biopsy could be associated with higher mortality led us to search for EPE- control patients with GS 8–10 who had received similar treatment (ADT or EBRT in combination with ADT) for statistical comparison. In addition to the high overall mortality in the EPE + patients, their cancer-specific mortality was 21.2% (7/34) within a median follow-up time of 19 months from the diagnosis, which is a short clinical course for prostate cancer. In comparison, the cancer-specific mortality of the EPE − patients was 10.6% (9/85). External beam radiation was applied to 32% (38/118) of the patients and only one death was noted during follow-up time. EPE + patients were treated with chemical castration alone ($n = 25$) or with both EBRT and adjuvant ADT ($n = 7$), either chemical castration ($n = 6$) or total androgen blockade ($n = 1$). None of EBRT treated EPE + patients succumbed. In both EPE + and EPE − groups, radiation therapy was applied exclusively to patients with a

local or locally advanced disease. The results are concordant with the previous studies showing that external beam radiation improves short term survival of patients with aggressive prostate cancer [20].

Approximately half of biopsies during the study period were diagnosed with adenocarcinoma, which is a high incidence. Possible explanations include previous widespread PSA testing which has led to strict indications for biopsy at the TAUH region, and high median age of the patients. In addition, diagnoses such as atypical small acinar proliferation (ASAP)/suspicious for cancer are rare due to low threshold for immunohistochemical stainings and an experienced uropathology team.

There are some limitations in the current study. First, it is a non-randomized retrospective study that suffers from a selection bias: Treatment by external beam radiotherapy was offered to the patients with a localized or locally advanced disease in a non-randomized fashion. Second, control patients were selected on the basis of WHO/ISUP Grade Group and treatment because of the observation that all EPE+ patients belonged to Grade Groups 4–5 and were treated non-surgically. Database search revealed 203 WHO/ISUP Grade Group 4–5 cancers of which 118 were included to comparisons using the aforementioned treatment criteria. The survival data of the remaining 85 surgically treated patients were not retrieved. Third, follow-up time was short, although comparable to the previous studies. On the other hand, the main observation of the study, the high the incidence of EPE + among patients with WHO/ISUP Grade Group 4–5 (16%; 33/203), is an undisputed finding in a consecutive series of biopsies.

5. Conclusions

In conclusion, one in twenty cancerous biopsies and one in six WHO/ISUP grade group 4–5 cancers harbored EPE+ in prostate biopsies, suggesting that EPE+ in prostate biopsies is not rare; it seems to be far more common than previously thought (4.9% vs. 0.19–2.2%). Considering that EPE+ was associated with highly adverse clinicopathological features, our results agree the importance of recognizing histological criteria of EPE+ in needle biopsies and reporting its presence to the clinicians.

Conflict of interest

The authors declare no conflicts of interest.

Funding

Competitive funding of Pirkanmaa and Satakunta Hospital Districts.

References

[1] Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 2003;169:517–23.
[2] Yilmaz A, Trpkov K. Rockyview. Fat invasion in ten-core prostate needle biopsies: incidence, biopsy and clinical findings. Mod Pathol 2004;17(suppl. 1):186A.
[3] Miller JS, Chen Y, Ye H, Robinson BD, Brimo F, Epstein JI. Extraprostatic extension of prostatic adenocarcinoma on needle core biopsy: report of 72 cases with clinical follow-up. BJU Int 2010;106:330–3.
[4] Fleshner K, Assel M, Benfante N, Lee J, Vickers A, Fine S, et al. Clinical findings and treatment outcomes in patients with extraprostatic extension identified on prostate biopsy. J Urol 2016;196:703–8.
[5] Amin A. Pitfalls of diagnosis of extraprostatic extension in prostate adenocarcinoma. Ann Clin Pathol 2016;4:1086.
[6] Hasui Y, Shinkawa T, Osada Y, Sumiyoshi A. Striated muscle in the biopsy specimen of the prostate. Prostate 1989;14:65–9.
[7] Ye H, Walsh PC, Epstein JI. Skeletal muscle involvement by limited Gleason score 6 adenocarcinoma of the prostate on needle biopsy is not associated with adverse findings at radical prostatectomy. J Urol 2010;184:2308–12.
[8] Billis A. Intraprostatic fat: does it exist? Hum Pathol 2004;35:525.
[9] Sung MT, Eble JN, Cheng L. Invasion of fat justifies assignment of stage pT3a in prostatic adenocarcinoma. Pathology 2006;38:309–11.
[10] Nazeer T, Kee KH, Ro JY, Jennings TA, Ross J, Mian BM, et al. Intraprostatic adipose tissue: a study of 427 whole mount radical prostatectomy specimens. Hum Pathol 2009;40:538–41.
[11] Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. European Association of Urology. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011;59:61–71.
[12] Bismar TA, Lewis Jr. JS, Vollmer RT, Humphrey PA. Multiple measures of carcinoma extent versus perineural invasion in prostate needle biopsy tissue in prediction of pathologic stage in a screening population. Am J Surg Pathol 2003;27:432–40.
[13] Cozzi G, Rocco BM, Grasso A, Rosso M, Abed El Rahman D, Oliva I, et al. Perineural invasion as a predictor of extraprostatic extension of prostate cancer: a systematic review and meta-analysis. Scand J Urol Nephrol 2013;47:443–8.
[14] Elharram M, Margel D, Finelli A, Trachtenberg J, Evans A, van der Kwast TH, et al. Perineural invasion on prostate biopsy does not predict adverse pathological outcome. Can J Urol 2012;19:6567–72.
[15] Sebo TJ, Bock BJ, Cheville JC, Lohse C, Wollan P, Zincke H. The percent of cores positive for cancer in prostate needle biopsy specimens is strongly predictive of tumor stage and volume at radical prostatectomy. J Urol 2000;163:174–8.
[16] López JI, Etxezarraga C. The combination of millimetres of cancer and Gleason index in core biopsy is a predictor of extraprostatic disease. Histopathology 2006;48:663–7.
[17] Zam NA, Tan PH, Sim HG, Lau WK, Yip SK, Cheng CW. Correlation between prostate needle biopsies and radical prostatectomy specimens: can we predict pathological outcome? Pathology 2008;40:586–91.
[18] de la Taille A, Katz A, Bagiella E, Olsson CA, O'Toole KM, Rubin MA. Perineural invasion on prostate needle biopsy: an independent predictor of final pathologic stage. Urology 1999;54:1039–43.
[19] Epstein JI, Amin MB, Reuter VE, Humphrey PA. Contemporary Gleason grading of prostatic carcinoma: an update with discussion on practical issues to implement the 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2017;41:e1–7. doi: 10.1097/PAS.0000000000000820.
[20] Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066–73.