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Accuracy of frozen section in determining meningioma subtype and grade

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ABSTRACT

Frozen section intraoperative consultation is a well-established means of evaluating brain tumors at the time of surgery. Limitations to the procedure are also well recognized resulting in less than perfect specificity of diagnosis. This study retrospectively reviewed 424 consecutive meningioma cases ($N = 310$ females; mean age 57.3 years) to examine concordance between frozen section evaluation of meningioma subtype and grade as compared with the final diagnosis subtype and grade. A discrepancy between frozen section diagnosis and final diagnosis was observed in 114 (26.9%) of cases. Of the WHO grade I subtypes, the most common discrepancy involved transitional meningiomas ($N = 31$) which were most commonly diagnosed at frozen section as either fibrous ($N = 18$) or meningothelial ($N = 13$) meningiomas. None of the grade I tumors were diagnosed as higher grade lesions. Of the higher grade meningiomas (WHO grade II and III) ($N = 145$) reviewed, concordance between tumor type and grade was seen in only 26.2% of cases; most commonly, 73/98 atypical meningiomas were under-graded as some subtype of WHO grade I meningioma (71/73 cases). In conclusion, discrepancies at frozen section with respect to accurately identifying higher grade meningiomas and higher grade meningioma subtypes are common and are generally due to tumor sampling and heterogeneity.

1. Introduction

Utilization of intraoperative consultation in the assessment of potential brain tumors is a well-established practice which provides information to the surgeon at the time of surgery which may guide operative management as well as provide information as to whether or not the tissue being sampled is representative of the lesion as it appears on imaging studies [1-3]. It is also well established that there is an error rate associated with the interpretation of frozen sections that is due to a variety of factors including tumor heterogeneity, surgeon operator error, pathologist interpretation error and technical artifacts i.e. cautery, crush or freeze artifacts [1,3-6].

The purpose of this study was to systematically review a series of meningioma cases to assess concordance/discordance between the diagnosis made based on the frozen section slide alone and the final diagnosis with respect to tumor subtype and grade, using the recently revised World Health Organization (WHO) tumor classification [7].

2. Methods and materials

Institutional Review Board (IRB) approval was obtained prior to commencement of the study. The departmental surgical pathology files were searched for all tumors diagnosed as “meningioma” between 2012 and 2016. A total of 523 cases were identified. Of those cases, a frozen section was performed in 424 cases (81.1%); these cases comprised the first part of the study group. The frozen section slide(s) were reviewed separately without knowledge of the final diagnosis and an attempt was made to classify and grade the tumors based solely on the frozen section slide(s) alone, using the most recent guidelines of the WHO [7]. In 399 cases, a single frozen section slide was available for review in the case. In the remaining cases, two frozen section slides were available for review in 21 cases, three slides in two cases, four slides in one case and six slides in one case. The frozen section diagnoses were then compared with the final diagnosis based on review of all slides in each case, looking for discrepancies. All available microscopic slides were reviewed in each case (range 3–28 slides; mean 7 slides).

In order to obtain a larger number of grade II and III meningioma cases, an additional four years of meningioma cases (2008–2011) were reviewed and the higher grade tumors culled out. In a similar fashion, a diagnosis was made based on the frozen section slide(s) alone, and then these results were compared with the final diagnoses, looking for discrepancies.

Clinical information in terms of patient age, gender and tumor location was tabulated from information contained in the pathology reports.

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3. Results

Of the 424 patients who formed the study group, there were 310 females (73.1%) and 114 males who ranged in age from 6 months to 89 years of age at the time of surgery (mean age 57.3 years). One hundred forty seven tumors (34.7%) were situated on the right side of the brain or spinal cord, 136 (32.1%) on the left side. Four tumors (1%) were bilateral and 2 (0.5%) intraventricular tumors were noted. In 135 cases (31.8%), laterality was not specified. The most common site of origin for the tumors studied were frontal lobes (n = 133, 31.4%), skull base (n = 112, 26.4%), parietal lobes and spinal cord (n = 25 each, 5.9%), temporal lobes (n = 21, 5.0%), convexity not further specified (n = 19, 4.5%), sella/suprasellar region (n = 18, 4.2%), and orbital or spheno-orbital region (n = 16, 3.8%).

When the frozen section slides were separately analyzed with respect to tumor type and grade, a discrepancy with the final diagnosis was observed in 114 (26.9%) cases. Among the grade I tumors (n = 47/114, 42.2%), the most frequent discrepancy arose in cases that were classified, based on the frozen section as transitional meningiomas (n = 31); based on permanent sections, 18 of these cases were diagnosed as fibrous meningiomas and the remaining 13 cases as meningothelial meningiomas. Five tumors which appeared to represent meningothelial meningiomas on frozen section turned out to be a variety of other lesions (one each of transitional, fibrous, microcystic, secretory and meningothelial meningioma and one hyperplasia on permanent sections). Five secretory meningiomas diagnosed at frozen section turned out to be all meningothelial meningiomas (Fig. 1A and B). Four tumors classified as angiomatous meningiomas at frozen section were diagnosed as meningothelial meningiomas based on permanent sections. One psammomatous meningioma on frozen section was diagnosed as a fibrous meningioma on permanent section. One microcystic meningioma at frozen section was diagnosed as a meningothelial meningioma on permanent sections.

A total of 145 cases from 2008 to 2016 were diagnosed as grade II or III meningiomas (98 atypical WHO grade II meningiomas, 26 clear cell WHO grade II meningiomas, 12 chordoid WHO grade II meningiomas, 9

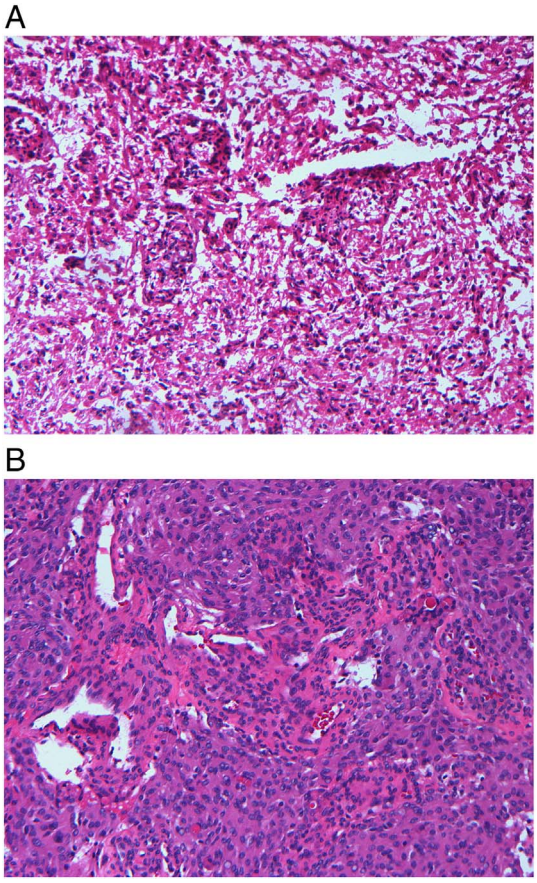

Fig. 1. A: Frozen section of a right frontal convexity mass resembling a meningothelial meningioma, WHO grade I with some freeze artifact (hematoxylin and eosin, original magnification 200×).
B: Permanent section from the case in Fig. 1A showing round eosinophilic protein accumulations consistent with a secretory meningioma, WHO grade I (hematoxylin and eosin, original magnification 200×).

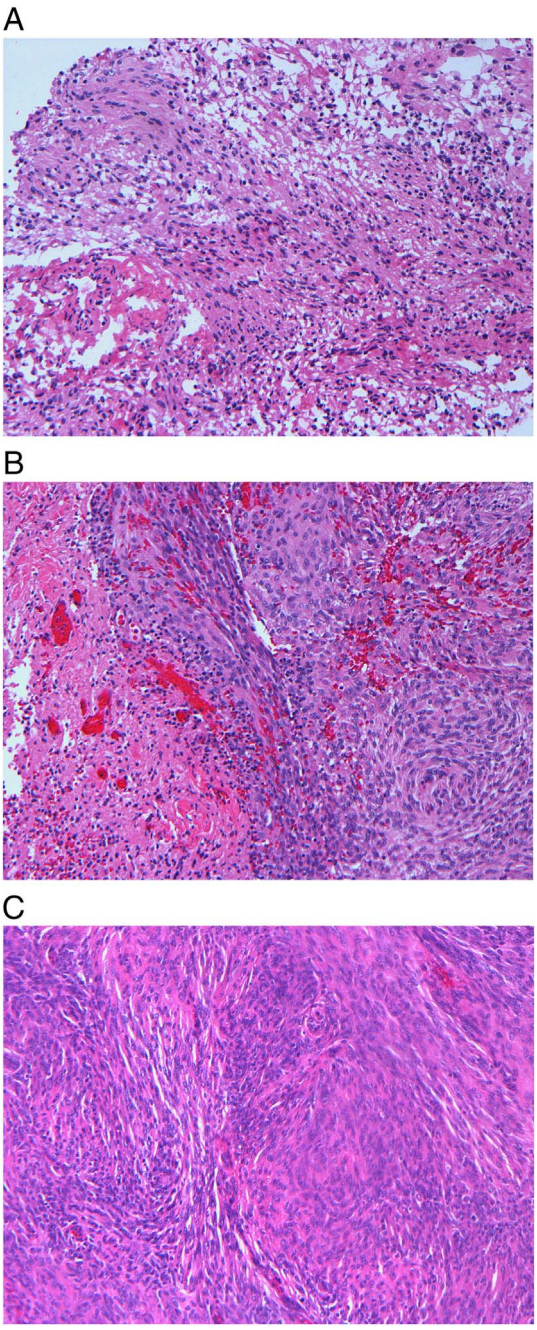

Fig. 2. A: Frozen section of a temporal lobe mass showing a spindled appearing meningioma resembling a fibrous pattern, WHO grade I (hematoxylin and eosin, original magnification 200×).
B: Permanent section from the case in Fig. 2A showing focal necrosis (hematoxylin and eosin, original magnification 200×).
C: Permanent section from the case in Fig. 2A showing hypercellularity and nucleolation. The tumor also had increased numbers of mitotic figures (5 mitotic figures/10 high power fields) and was diagnosed as an atypical meningioma, WHO grade II (hematoxylin and eosin, original magnification 200×).

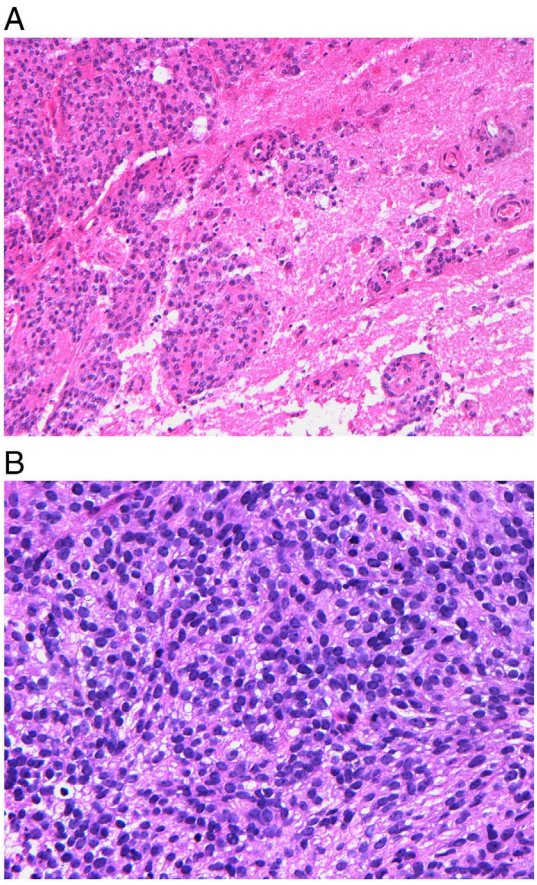

Fig. 3. A: Frozen section of a left frontal convexity meningioma marked by focal brain invasion (seen here), consistent with an atypical meningioma, WHO grade II (hematoxylin and eosin, original magnification 200×).
B: Permanent sections from the case in Fig. 3A showing increased mitotic figures (the tumor had a mitotic count of 22 mitotic figures/10 high power fields), consistent with an anaplastic meningioma, WHO grade III (hematoxylin and eosin, original magnification 400×).

anaplastic WHO grade III meningiomas and 1 papillary WHO grade III meningioma). In 38 of these 145 cases (26.2%), the frozen section diagnosis was concordant with the final diagnosis. In the remaining 107 cases (73.4%), the frozen section diagnosis was discordant with the final diagnosis; in 69 of these cases (64.5%), atypical features were observed on the frozen section slides but findings were insufficient to make a definite diagnosis of a grade II or III tumor. In the 73 discordant atypical meningioma cases, diagnoses made based on the frozen section slides included meningothelial (n = 56), fibrous (n = 14), no tumor (n = 2) or transitional (n = 1) (Fig. 2A and B). Of the 18 discordant clear cell meningioma cases, 13 were diagnosed based on the frozen section slides alone as meningothelial meningiomas, and one each as microcystic, fibrous, angiomatous, and secretory meningiomas and one case in which there was no evidence of tumor. Of the 7 discordant anaplastic meningioma cases, all were diagnosed as atypical meningioma based on the frozen section slides (Fig. 3A and B). The one papillary meningioma was diagnosed based on the frozen section slide as an atypical meningioma.

4. Discussion

There is an error rate known to be associated with the diagnosis of brain tumors. The diagnostic accuracy of intraoperative consultation in the evaluation central nervous system lesions is generally good, in the range of 85–97% [6,8-18]. In a large study of 4172 patients utilizing cytologic smears in the evaluation of brain tumors, an overall complete correlation of the frozen section diagnosis with final diagnosis was reported to range from 83 to 93.7% per year over a 15 year experience (mean 89.8%) [8]. The most accurate intraoperative diagnoses where among meningiomas (97.9%) in this study [8]. In a more recent study examining frozen section discrepancies in the context of intraoperative consultations in 2156 cases, overall discrepancies between frozen section and final diagnoses was observed in 57 cases (2.7%) (6). Of these, 7 involved the misdiagnosis of meningioma with schwannoma (N = 3), sarcoma (N = 2), hemangioblastoma (N = 1), and paraganglioma (N = 1) [6]. The focus of this study was primarily on discrepancies in which tumors were misdiagnosed with respect to tumor type or confused with nonneoplastic entities.

The current study focused on meningiomas and was constructed to assess whether or not, at the time of frozen section, one can accurately subtype and grade them. In real practice, many of the tumors in the series were simply diagnosed as ‘meningioma’ at the time of frozen section or rarely as ‘meningioma’ with some additional descriptor indicating the presence of a worrisome histologic feature, such as “brain invasion” or “necrosis”. If one could accurately predict tumor subtype (particularly higher grade subtypes such as clear cell, chordoid, rhabdoid or papillary types) and grade at the time of surgery, this could potentially impact surgical approach. A more aggressive approach to resection might be undertaken, if the tumor were diagnosed as grade II or III at the time of intraoperative consultation. The frozen section diagnosis may also be important in discussions with patients and families and for starting to plan followup and treatment [5].

Very few studies have focused specifically on meningiomas in the context of intraoperative consultation. In 2008, Ali et al. examined a series of 107 meningiomas using crush preparations to determine whether grade can be accurately evaluated at the time of intraoperative consultation [19]. The study included 72 grade I tumors, 22 grade II tumors and 13 grade III tumors. The authors concluded that it is difficult to reliably distinguish between grade I and II meningiomas on crush preparations but that grade III tumors could be fairly easily diagnosed [19].

The current study, utilizing frozen section as the intraoperative consultation methodology, noted a discrepancy of 26.9% between frozen section diagnosis with respect to tumor type and/or grade versus final diagnosis based on permanent sections. 41.2% of those cases involved discrepancies between grade I meningioma subtypes, most commonly centering on transitional meningiomas. These are clinically insignificant distinctions and are not likely to impact intraoperative or patient management.

In order to more extensively evaluate the higher grade lesions which are the potentially more clinically relevant lesions, the time frame for this study was expanded in order to include more of these tumors. Of 145 grade II and III meningiomas on final diagnosis, a discrepancy with the frozen section diagnosis was noted in the majority of cases (73.4%); in most instances, the frozen section diagnosis underestimated the grade of tumor. The major reason for this is most likely attributable to tissue sampling and tumor heterogeneity. In many of the atypical meningiomas, one or two worrisome histologic features were evident on the frozen section slide, insufficient to meet WHO criteria for the diagnosis of an atypical meningioma. In some cases, brain invasion was observed on the permanent sections and not the frozen section. Mitosis counts in some cases did not reach the threshold of 4 mitotic figures/10 high power fields on the frozen section but did so on permanent sections. If worrisome features are noted at the time of frozen section, even if insufficient to warrant a definitively designation of a grade II or III tumor, they should be conveyed to the neurosurgeon so it can be appropriately considered.

Although the WHO provides guidelines with respect to meningioma subtyping and grading, there are limitations to the classification. Definitions of subtypes are somewhat vague. For example, how much of a secondary pattern should be present to make a diagnosis of transitional meningioma? How many psammoma bodies are needed to make

a diagnosis of psammomatous meningioma? How much of a clear cell or chordoid component is sufficient to designate the tumor as a grade II neoplasm? How much cellularity constitutes hypercellularity? Such vagaries lead to inevitable interobserver and likely some intraobserver variability in diagnosis [20]. Superimpose on this tumor heterogeneity, tumor sampling, and artifacts generated surgically (i.e. crush or cautery artifacts) or related to the frozen section process itself (i.e. freeze artifact), then it is not surprising that there will be some variability in diagnoses. Some of these discrepancies, such as distinguishing between two grade I subtypes, are essentially inconsequential. Others, such as undergrading a tumor as grade I when in fact it is grade II or III, have potential clinical implications.

In conclusion, the current study shows that discrepancy at frozen section with respect to higher grade meningiomas are common, most likely related to a variety of factors. Despite this, when worrisome histologic features are noted at frozen section or criteria are met for a grade II or III tumor, this information should be conveyed in the frozen section diagnosis.

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