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Proliferation potential of spinal meningiomas

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Abstract *Objectives*: The goal of the present study was to quantitatively assess the proliferation index and progesterone receptor status of spinal versus intracranial meningiomas and to determine if these biological indicators can describe the clinical behavior of these tumors. This information could provide the spinal surgeon with important additional information concerning surgical management and follow-up recommendations for the individual patient. *Methods*: The study group consisted of 26 patients with spinal and 241 patients with intracranial meningiomas. Patients with atypical or anaplastic tumors as well as with neurofibromatosis type II were excluded from the study. Furthermore both groups were matched according to age, sex and resection grade (total resection according the Simpson classification). Proliferation index (Ki-67 Labelling index [LI]) and progesterone-receptor (PR) status of spinal and intracranial meningiomas were compared. Clinical charts including surgical and histological records and imaging studies were reviewed. Correlations with histological subtype, intratumoral calcifications, tumor vascularity and recurrence-free survival were analyzed. *Results*: Compared to the spinal group with a mean Ki-67 LI of 2.48% and a positive PR-status of 46%, proliferation rates of intracranial meningiomas were significant higher (Ki-67 LI 3.6%; *P*-value 0.041). No significant difference in PR status was seen (spinal PR-status 46%, *P*-value 0.261). Furthermore spinal meningiomas were less vascularized and showed less intratumoral calcifications. Time to recurrence was similar in spinal and intracranial tumors. *Conclusion*: Spinal and intracranial meningiomas differ in their proliferation activity but not in their PR status. However, despite lower proliferation rates, time to recurrence in spinal and cranial meningiomas is comparable in totally excised tumors. Further studies are needed to determine the role of other biological indicators in spinal meningioma growth and response to therapy.

Keywords Meningioma · Recurrence · Proliferation · Ki-67 · Progesterone receptor · Spinal neoplasm

Introduction

The clinical behavior of benign meningiomas varies considerably [14]. Between 7 and 32% of benign meningiomas recur after total resection and even more after subtotal removal [5, 12]. Recurrence of spinal meningiomas has been the subject of numerous reports [7, 11, 20]. Meningiomas tend to recur, and their unfavorable

outcome after repeated surgeries suggest that, despite their pathological classification, they are not completely benign from a clinical perspective.

Several biological variables have been studied in an attempt to identify which factors can help predicting the natural history of meningiomas and their response to therapy [30]. It has been suggested that the tumor proliferative potential can be used to describe the clinical course of meningiomas, together with other parameters [1, 2, 5, 9, 12, 13, 17, 18, 21, 23–25]. The Ki-67 antigen has been shown in several studies to be a reliable indicator of biological activity of the tumor as its expression represents proliferating cells only. Meningioma location as a factor-influencing prognosis has also been the subject of previous studies [7, 11, 20]. Our data indicate that intraspinal and intracranial meningiomas have similar recurrence rates. We evaluated the Ki-67 LI and PR-status in benign totally resected tumors at cranial and spinal location and observed a higher expression of Ki-67 LI but not PR-status in the latter. Based on these observations we performed and analysis of the clinical behavior of the tumors at these two locations to determine if Ki-67 LI and PR-status could help predicting the natural history in this entity.

Materials and methods

Between 1990 and 2000, 98 spinal and 1191 intracranial meningiomas have been operated on at the Neurosurgical Department. Patients with neurofibromatosis type II, patients with atypical or anaplastic meningiomas or with preoperatively embolized tumors, as well as with subtotally removed meningiomas according to the Simpson classification (III and IV) were excluded from statistical analysis [32]. Groups were matched for age, sex ratio and length of follow-up. Twenty-seven paraffin blocks of 26 patients with spinal and 241 patients with intracranial meningiomas were selected (Table 1).

Clinical information about each patient was obtained through review of medical records, follow-up examinations, clinical and neuroradiological evaluation or through detailed questionnaires with radiological reports of the latest MRI findings. A semi-quantitative score to assess the vascularity of the meningioma was obtained at time of surgery, ranging from 0 (i.e. "dry meningioma" or very low vascularity) to 4 (highly vascularized).

Paraffin sections were stained with hematoxylin-eosin, and neoplastic areas were delineated. They were grouped according to the current WHO classification [14]. Immunohistochemistry was performed with paraffin sections staining Mib-1 resp. Anti-Human progesterone receptor 1A6, purchased from DAKO (Copenhagen, Denmark), according to standard protocols. Sections were counterstained with Hemalaun. Positive control specimens were run in every staining session using glioblastoma tissue for Mib-1 immunohistochemistry, and breast cancer tissue for progesterone immunohistochemistry. Using an optical grid on high power fields (400 times, ZEISS microscope) the entire section was systematically examined for the presence of immunoreactivity. Only unquestionably stained nuclei were accepted as positively stained. For Ki-67 the area of densest staining ('hot spot') was identified, and counting was then performed in ten contiguous fields. The average of the counts in the fields was defined as the proliferative index (labeling index). The progesterone receptor status was determined by a semi-quantitative scoring scale with respect to staining intensity and percentage of positive tumor cells according to the immunoreactive score (IRS) introduced by Remmele and Stegner [28] (Table 2). Randomly chosen stains were also counted by independent researchers to test for inter-individual difference in interpretation of the mean Ki-67 LI or the PR-status.

Statistical analysis was performed using the SPSS 11.0 (SPSS Inc.) software program for MS Windows (Microsoft). Differences were considered significant at a value of $P < 0.05$.

Results

Clinical data of both groups is summarized in Table 1. The female to male ratio was 8.6:1 in spinal and 4.2:1 in intracranial meningiomas (Table 3). Two hundred forty-eight from 267 patients were newly diagnosed patients, whereas four patients with a spinal meningioma and 14

Table 1 Patient data of matched groups

	Spinal Group	Intracranial Group
No of patients	26	241
Sex ratio F:M	8.6:1	8.6:1
Mean age (range)	59.3 (25–93)	55.9 (23–83)
Mean Follow-up (range)	45 (4–122)	45.3 (12–154)
NF-II	None	
Grade of Resection	Simpson I + II	

Table 2 Evaluation of PR—receptor status (according to Remmele and Stegner [28])

Progesterone receptor status IRS = Staining intensity × percentage of positive cells	
0 = absent	1 = <10%
1 = weak	2 = 10–50%
2 = moderate	3 = 51–80%
3 = strong	4 = >80%
IRS >2 is considered PR—positive	

Table 3 Histology and Follow-up in totally resected benign meningiomas

	Spinal group	Matched intracranial group	Significance
Histology	Meningotheliomatous (73%) Fibrous (7.7%) Psammomatous (7.7%) Transitional, angiomatous, chordoid (each 3.8%)	Meningotheliomatous (67.2%) Fibrous (17.4%) Transitional (10.3%) Psammomatous (2.5%) Microcystic (2.4%) Angiomatous (0.8%) Chordoid (0.4%)	
High vascularity*	18.7%	60%	< 0.01
Intratumoural calcification	28%	68%	< 0.01
Mean Ki-67 (range)	2.48% (0–11%, SD 2.68)	3.6% (0–58%, SD 4.61)	0.041
PR-Status (pos.)	46%	52.7%	0.261
Recurrences	2 (7.4%)	18 (7.4%)	
Mean time to recurrence	73 months (26–120)	33.4 months (9–76)	0.071
Mean Ki-67 at recurrence	1.0% (0–2%)	7.0% (1–12%)	0.007

* Intra-operative derived semi-quantitative score from 0 to 4 (*0* dry to *4* highly vascularized)

patients with an intracranial meningioma presented with local recurrence. Spinal meningiomas with high vascularity and calcifications occurred less than in intracranial meningiomas (18.7 vs. 60%, *P*-value < 0.01; 18 vs. 68%, *P*-value < 0.01).

Histopathology

Histological tumor classification was performed according to the World Health Organization (WHO) [14]. All patients in this study harbored benign meningiomas, predominantly of meningotheliomatous and fibrous type. The mean proliferation index in spinal meningiomas was significantly lower than in cranial tumors (2.48 vs. 3.6%, *P*-value 0.041). There was no statistically significant difference in progesterone receptor status between the two groups in (46% of spinal cases versus 52.7% in intracranial meningiomas).

Follow-up

Patients were followed for an average of more than 45 months (range 4–152 months). During the clinical and radiological follow-up two spinal and 18 intracranial meningiomas recurred. This measured for a recurrence rate of 7.4% for both groups. However, the Ki-67 LI at time of recurrence was significantly lower in spinal than in intracranial meningiomas (1.0 vs. 7.0%, *P*-value 0.007) and the Ki-67 LI in spinal cases did not increase with recurrent disease, as observed in intracranial meningiomas (Table 2). Mean recurrence free survival time in spinal meningiomas was longer than in intracranial tumors (73 vs. 33.4 months)—although not statistically significant (*P*-value 0.07).

Discussion

Spinal meningiomas account for about 25% of all spinal cord tumors [33]. They carry a favorable prognosis if completely resected, however radical surgery may result in higher morbidity. This is particularly true for anteriorly located and en plaque meningiomas, for tumors located in the thoracic spine due to their peculiar configuration of feeding vessels and in the presence of intratumoral calcifications [7, 15, 31, 34]. Recurrence of spinal meningiomas often result in higher morbidity compared to intracranial cases [16, 33].

The Mib-1 monoclonal antibody, staining for the Ki-67 antigen, has been used to estimate meningioma growth and recurrence potential [2, 19, 22, 23, 26]. Furthermore the expression of progesterone receptors in meningiomas seems to indicate a more benign clinical behavior of these tumors [4, 6].

In this study we analyzed the Ki-67 LI and PR-status in spinal versus intracranial meningiomas and we found the former to be higher in spinal disease (the latter being almost identical). We therefore compared these findings with recurrence free survival at follow up to determine if a relationship between these two biological indicators and clinical behavior of the tumors could be seen. However, recurrence free survival after total tumor resection was found to be very similar in both patients groups. An analysis of our data was performed to find explanations for this apparent discrepancy.

Literature provides only little information about the histological subtype distribution of spinal meningiomas. In numerous case reports it has been suggested that distinct subtypes of meningiomas have a predilection for spinal locations, and that clear-cell meningiomas tend to have a more aggressive clinical behavior despite their

benign pathological nature [8, 11]. Our patient group displays a similar distribution of meningioma subtypes in spinal and intracranial tumors. Philippon et al. [27] suggested the higher percentage of calcified psammomatous meningiomas as a reason for lower recurrence rates in spinal meningiomas. We indeed found a high percentage of spinal psammomatous meningiomas with a low rate of intratumoral calcifications. Additionally psammomatous meningiomas did not show different proliferation rates than other benign subtypes. The higher degree of calcification in intracranial compared to spinal meningiomas might be due to the longer tumor growth-tumor detection interval in intracranial tumors, as spinal meningiomas can lead to neurological deficits while still relatively small.

Neo-angeogenetic activity of meningiomas might account for higher proliferation in these tumors as reflected by higher Ki-67 expression [3, 10, 30]. The semiquantitative subjective evaluation of the vascularity in our series seems to agree with these data. Spinal meningiomas however inherit a different vascular supply than intracranial meningiomas. As the tumor size is significant smaller, only few pathological tumor feeders are necessary for the tumor to reach a substantial size producing neurological deficits.

Interestingly the PR-status in spinal meningiomas did not allow any prediction of recurrence. Furthermore more comparable expression rates between the genders were found. These results differ significantly from those in intracranial meningiomas, where PR-status was found to be reliable in predicting tumor recurrence [29].

Spinal meningiomas are rare tumors and our series should be considered large compared to existing publications regarding spinal meningioma histology. However, one should caution that our statistical analysis, although formally correct, is still based on small samples and confounding statistics can occur. Only prospective multi-center histopathological studies might gain more insight in the different pathology of spinal versus intracranial meningiomas.

The present data, however, suggest that the treating spine surgeon should not plan his strategy just based on tumor location. However, the distinct proliferation activity of meningiomas should influence the surgical approach (i.e. radicality) and individual follow-up recommendations for each patient.

Conclusion

Our data suggest that spinal meningiomas differ from their intracranial counterpart in terms of proliferation as measured by the Ki-67 LI, however they display similar clinical behaviour and PR-status.

The discrepancy between the Ki-67 LI and recurrence rates cannot be fully explained on the basis of the present data. We suggest that further studies are needed to verify how other biological markers can better describe the clinical behavior of fully resected benign spinal meningiomas.

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