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Original Article

The histopathological spectrum of human meningiomas

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Abstract: Histopathological examination and grading of meningiomas gives valuable prognostic information, although the method is subject for interobserver variability. The aim of this study was to review a large series of human meningiomas in order to examine the frequency of benign (grade I), atypical (grade II), and anaplastic (grade III) forms depending on various WHO classification schemes. In addition, we wanted to describe the frequency of various histopathological features and their mutual correlations. Sections from 196 consecutively treated primary human meningioma patients were revised retrospectively. The established criteria to grade meningiomas, which are also known to be associated with tumorigenesis, were shown to correlate significantly. The number of grade II meningiomas increased when using the WHO 2007 classification (30%) compared with previous editions, mainly due to the definition of brain infiltrating meningiomas as atypical (grade II). A bimodal frequency distribution among age groups of females was observed. Continuous revision of histopathological classification systems is required to improve the diagnostic accuracy.

Keywords: Brain tumors, diagnosis, grading, classification, Clemmesen's hook

Introduction

Meningiomas are neoplasms thought to derive from arachnoidal cap cells in the meningeal coverings of the spinal cord and brain [1]. They are the most common benign intracranial tumours and account for up to 34% of these neoplasms [2]. The peak incidence is in middle-aged patients, and the female:male ratio is approximately 2:1 [3, 4]. Meningiomas are generally benign, slow growing tumours that may produce neurological symptoms and signs due to their compression of adjacent structures. They are, however, a tumour entity with fickle clinical presentations, a heterogeneous histological picture, and an inherent trend to recur [5, 6]. Known risk factors for recurrence include histological malignancy grade, subtotal resection, young age, specific subtypes, brain infiltration, and high proliferative rate [7-11].

Much progress has been made in understanding the molecular and genetic basis for meningioma tumorigenesis [12-14]. In clinical practice, however, the diagnosis is based on light microscopy of routinely stained haematoxylin-eosin sections with criteria given by World Health Organization (WHO) [1]. This classification scheme provides guidelines for tumour grading and subtypes. Reported recurrence rates of grade I, II, and III meningiomas are 7-25%, 29-52%, 50-94%, respectively [1].

In the current WHO edition (2007) grade I meningiomas (benign) are recognised by their histologic subtype and lack of anaplastic features. Grade II meningiomas (atypical) are defined by one or more of the following four criteria: 1) chordoid or clear cell histologic subtype, 2) four to 19 mitoses per ten high-power field (HPFs), 3) brain infiltration, and 4) three or more of the following five histologic features: small cell change, increased cellularity, prominent nucleoli, sheet-like growth, or necrosis. Grade III meningiomas (anaplastic/malignant) are defined by rhabdoid or papillary subtypes, a histological picture of frank malignancy resembling that of carcinomas, melanomas, or high grade sarcomas, or 20 or more mitosis per ten HPFs [1]. The only change between the WHO 2007 and 2000 edition is that brain-infiltrative and otherwise benign meningiomas are classified as

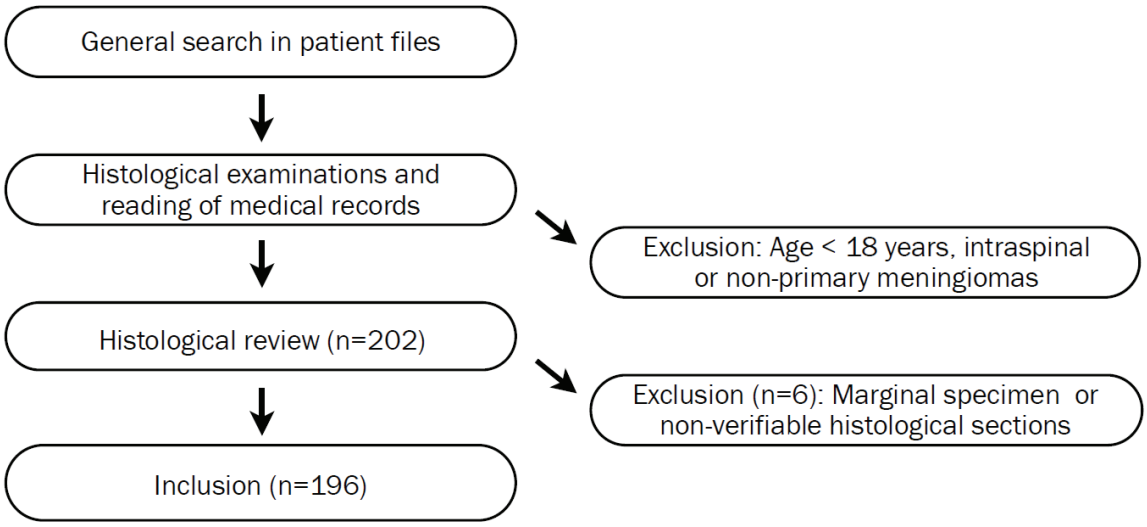

Figure 1. Flow-diagram of patient inclusion.

grade II.

The current grading system is based on histological features found in several clinicopathological studies to be of prognostic importance [1, 8]. However, the criteria given are hampered by subjective assessments and lack of precise definitions that can make the practical application difficult [15, 16]. For instance, features such as small cell changes, hypercellularity, sheeting, necrosis, and mitotic count are in need of more definite definitions and standardized evaluation [6]. Thus, a continuous revision of the histopathology of meningiomas is necessary to improve the accuracy and reproducibility of the histopathological diagnosis and grading of these tumours [17].

The aim of the study was to investigate a large number of human meningiomas, consecutively operated during a ten-year period, in order to record the frequency of various subtypes and malignancy grades according to the latest WHO classification (2007). In addition, we wanted to investigate the frequency of and correlations between various histopathological features.

Material and methods

Selection of specimens

Neurosurgical care in Mid-Norway, which includes three counties, is centralised at St. Olavs Hospital, University Hospital Trondheim (680,110 habitants in 2011 [18]). All patients treated for a primary meningioma over a ten year period, from 1.01.1991 to 31.12.2000, were retrospectively included after search in electronic patient files at the Department of Pathology and Medical Genetics. The selection process is shown in (**Figure 1**). Prognostic and clinical information was collected both from medical records at St. Olavs Hospital and at local hospitals.

Histopathological evaluation and clinical information

Routine HES (Haematoxylin-Eosin-Saffron) stained paraffin sections were reviewed without knowledge of prior grading or patient outcome. New sections were cut if lost or when staining had faded. A Nikon 80i light microscope was used, and a HPF was defined using the 40x objective.

Eighteen histological parameters were evaluated (**Table 1**). The tumours were classified into subtypes according to the dominate growth pattern (roughly 50% of a specimen on microscopic evaluation) [19]. The meningiomas' initial grade was recorded, and WHO classifications of 2000 and 2007 were applied on the material [1].

Mitotic count was assessed in areas with high mitotic activity, both by summing the highest number of mitotic figures in ten consecutive non-overlapping HPFs and by calculating the

Table 1. The histological characteristics in relation to WHO grade (2007) and associations between grade I and II (Chi-square or Fischer exact test). Only the subjective evaluation of hypercellularity is shown.

Histological characteristics	Recorded as	Total material (n=196)		WHO 2007 classification criteria						P-value, WHO I vs II
				Grade I (n=135)		Grade II (n=59)		WHO III (n=2)		
		Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Apopotosis	Absent/present	89	45.4	44	32.6	43	72.9	2	100	<0.000
Sheeting	Absent/present	17	8.7	3	2.2	12	20.3	2	100	<0.000
Macronucleoli	Absent/present	13	6.6	3	2.2	9	15.3	1	50.0	0.001
Nuclear plemorphia	Absent/present	52	26.5	31	23.0	19	32.2	2	100	0.176
Vesicubus nuclei	Absent/present	70	35.7	33	24.4	35	59.3	2	100	<0.000
Necrosis	Absent/present	45	23.0	16	11.9	27	45.8	2	100	<0.000
Hypercellularity	Absent/present	51	26.0	26	19.3	23	39.0	2	100	0.004
Small cells	Absent/present	22	11.2	6	4.4	14	23.7	2	100	<0.000
Lymphocyte s	Absent/present	18	9.2	14	19.4	4	6.8			0.428
Lipidization	Absent/present	18	9.2	9	6.7	8	13.6	1	50.0	0.118
Psammoma bodies	Absent/present	131	66.8	95	70.4	35	59.3	1	50.0	0.132
Fibrosis	Absent/present	145	74.0	103	76.3	41	69.5	1	50.0	0.319
Hemosiderin	Absent/present	33	16.8	21	15.6	12	20.3			0.415
Hypervascularization	Absent/present	144	73.5	98	72.6	44	74.6	2	100	0.774
Mitotic index	Below 0.5	165	84.2	129	78.2	36	21.8			
	Between 0.5 and1	27	13.8	6	22.2	20	74.1	1	3.7	
	Above 1	4	2.0			3	75.0	1	25.0	
Mitosis in 10 PHF	<4	151	76.5	135	89.4	16	10.6			
	4 to 19	43	22.4			43	97.7			
	>19	2	1.0					2	100	
Brain infiltration	Brain-infiltrative	16	8.2			16	100			
	Non- brain-infiltrative	54	27.6	37	68.5	17	31.5			
	Brain tissue not observed	126	64.3	98	77.6	26	20.6	2	1.6	
Soft tissue infiltration	Dura only	159	81.1	109	68.6	48	30.2	2	1.3	
	Bone, dura, othersoft tissue	12	6.1	11	91.7	1	8.3			
	Dura observed	2	1.0	1	50.0	1	50.0			
	Infiltration not seen	23	11.7	14	60.9	9	39.1			

mitotic index (MI) determined by the number of mitosis amid other cells in an ocular grid reticule and expressed as a percentage [20].

Brain infiltration, defined as irregular, tongue-like protrusions of tumour cells infiltrating underlying brain parenchyma without an intervening layer of leptomeninges, was registered as either present, absent, or inaccessible when no brain parenchyma was observed [1, 6].

Increased cellularity was measured by three methods. First, using the 40x objective magnification, an ocular grid reticule was placed in the area of the specimen with the highest density of cells. All tumour cell nuclei crossing an ocular grid reticule-line were counted at three different places, and the mean was recorded. Secondly, the ocular grid reticule, at the same magnification, was placed outside the specimen at random, and moved approximately 2 mm into the specimen, where all meningioma derived cells inside the ocular grid reticule's outer square were counted. The ocular grid reticule covered 0,058 mm^2. If the reticule was placed at random in a non-representative area for cell counting, it was moved an additional 2 mm in a horizontal or vertical direction. This was done in three separate areas and their mean were recorded. Thirdly, hypercellularity was evaluated semi-quantitatively as present or not. Vascular components, lymphocyte-like, or haematogenous cells were not included in these calculations.

Sheeting, defined as lack of typical meningioma growth pattern, was noted as present when this covered more than half of the field of vision at the 10x magnification [1, 21-23]. Macronucleoli were recognized as present when easily observed with the 10x objective [4]. Only cells with chromatin condensation, formation of cytoplasmic blebs, and apoptotic bodies were defined as apoptotic. Cells with an increased nuclear cytoplasmic ratio were characterized as small-cell formations. Hypervascularity was recorded as present when distinct vessels were seen with a 10x objective in two or more HPFs. Vesiculous nuclei were noted as present when they were blast-like.

Recorded clinical data included sex, age at surgery, and original tumour grade. Tumour location was registered based on surgical accessibility determined by CT or MR analyses.

The study was approved by the Regional Ethics Committee (project number 4.2006.947).

Statistical methods

SPSS, edition 18, was used for statistical analysis. Two sided Chi-square or Fischer exact test was used to calculate the relation between histological factors. P-values less than 0.05 were regarded as statistically significant.

Results

Patient data are shown in **Table 2**. A total of 196 meningioma patients were included in the study, 147 females and 49 males giving a female:male-ratio of 3:1. In males younger than the median age at surgery of 59 years, the ratio between benign and atypical meningiomas was 1:1, whereas the ratio was 3:1 for the same age group of females. The ratio between benign and atypical tumours located at the scull base was almost 9:1 in contrast to that of falcine meningiomas of 1:1. **Figure 2** indicates a bimodal distribution of new cases among females.

Table 3 shows the distribution of the different meningioma subtypes. Among grade I meningiomas the most common variants were transitional (40%, n=78), meningothelial (17%, n=34), and fibroblastic (7%, n=14). The frequency of grade I, II, and III meningiomas was 69% (n=135), 30% (n=59), and 1% (n=2), respectively. The percentage of meningiomas classified as grade II, increased from the original 18% to 26% and 30% when the WHO 2000 and the 2007 classification criteria were applied, respectively (**Table 4**). Two cases were down-graded from the original grade III to grade II according to the 2000 and 2007 criteria. Mitotic count was the most common cause of grading meningiomas as grade II (atypical) (73%) (**Table 5**).

Figure 3 illustrates some typical histopathological features found in human meningiomas, and **Table 1** shows the frequency of such features in the various tumour grades as well as the statistical associations between the frequency of these features in grade I and II. The following features occurred more frequent in grade II: apoptosis, sheeting, macronucleoli, necrosis, hypercellularity, small cells, and vesiculous nuclei (p-value $\leq$ 0.004). **Table 6** shows the histological factors' mutual correlations. Mitotic ac-

Table 2. Patient characteristics. Age at surgery, gender, and tumour location is shown in relation to WHO grade (n=196).

Clincal data	WHO 2007 classification criteria					
	Benign (n=135)		Atypical (n=59)		Anaplastic (n=2)	
Age at surgery (years) Median and range)	58 (27-84)		59 (25-86)		61 (53-69)	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Sex						
Female	107	79.3	39	66.1	1	50.0
Male	28	20.7	20	33.9	1	50.0
Localisation						
Falcine	14	10.4	12	20.3	2	100
Convexity	53	393	35	59.3		
Basal	43	31.9	5	8.5		
Tentoriell and posterior fossa	25	18.5	6	10.2		
Interventricular			1	1.7		

Table 3. Histological subtypes of meningiomas and the mean number of mitoses.

WHO grade	Subtype	Frequency	Percent	Mean number of mitoses in 10 PHF
I	Meningothelial	34	17.3	1.4
I	Fibrous (fibroblastic)	14	7.1	0.7
I	Transitional(mixed)	78	39.8	1.2
I	Psammomatous	1	0.5	2.0
I	Angiomatous	3	1.5	0.7
I	Microcystic	2	1.0	0
I	Secretory	1	0.5	1.0
I	Lympholas-	1	0.5	2.0
I	macyterich	1	0.5	1.0
II	Atypical	57	29.1	4.4
II	Clear Cell	2	1.0	2.0
III	Anaplastic	2	1.0	28.5
Total		196	100	2.4

Table 4. Frequencies of WHO tumour grade according to the original, 2000, and 2007 criteria for classification of meningiomas.

	Original grade		WHO 2000		WHO 2007	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Benign (WHO grad I)	157	80.1	144	73.5	135	68.9
Atypical (WHO grade II)	35	17.9	50	25.5	59	30.1
Anaplastic (WHO grade III)	4	2.0	2	1.0	2	1.0
Total (number of cases and %)	196	100	196	100	196	100

Table 5. Number of meningiomas that fulfil the criteria for grade II after the WHO 2007 classification criteria. Some cases may fulfil more than one of the four criteria.

Grading criteria for WHO grade II (n=59)	Frequency	Percent among grade II
Four to 19 mitoses	43	72.9
Three or more of the five features*	14	23.7
Brain infiltration	16	27.1
Histologic subtype	2	3.4

*The five features include sheeting, prominent nucleoli, small cells, necroses, and hypercellularity.

tivity was correlated to the established histopathological features of malignancy. Lymphocytes and plasma cells were observed infrequently and without statistical relation to other histological features or tumour grade. Although present in 59% (35/59) of grade II meningiomas, psammoma bodies were associated with increased fibrosis and soft tissue infiltration rather than

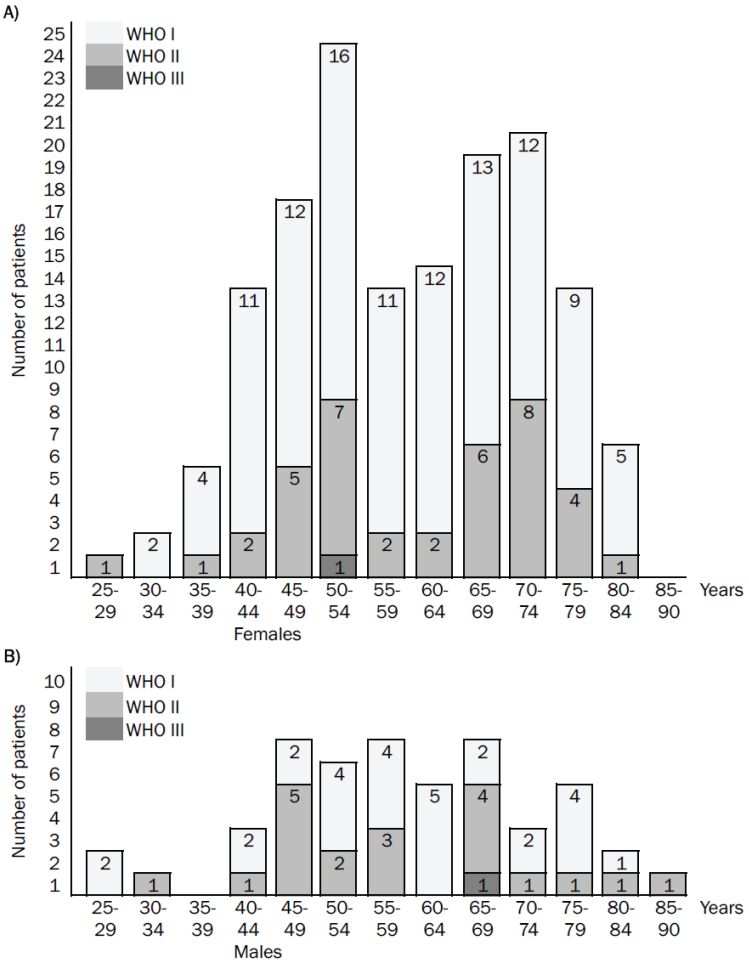

Figure 2. Number of treated patients divided in age groups of five years, WHO grade, and gender. The age-grouped bars for females in Figure 2 A) indicate a bimodal curve.

features indicative of malignancy. Psammoma bodies occurred also more commonly in transitional meningiomas (data not shown). The subjective evaluation of hypercellularity was positively correlated with tumour grade (p=0.004) and features associated with malignancy, such as apoptosis, sheeting, and prominent nucleoli (**Table 1** and **6**). The three methods of evaluation of hypercellularity were significantly mutually correlated (data not shown).

Discussion

Human meningiomas unveil a heterogenous histopathology, which may explain the repeated revisions of classification schemes. This study presents a review of 196 consecutively operated primary meningiomas classified according to the latest WHO classification of 2007, with the aim to investigate the frequency of various histopathological features and their mutual correlations.

Median age at surgery did not diverge between different WHO

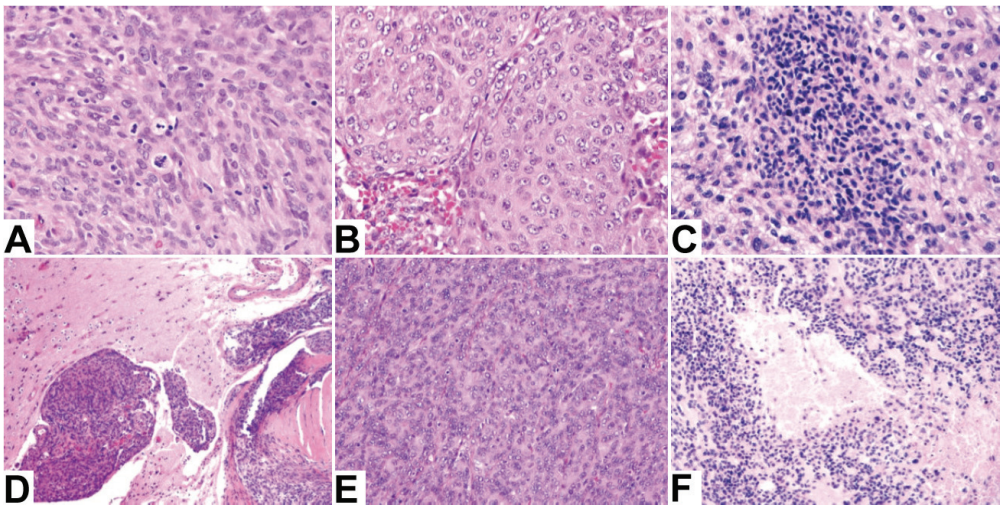

Figure 3. Typical histological features encountered in human meningiomas: Mitoses (A), vesiculous nuclei with prominent nucleoli (B), small cell formation (C), brain infiltration (D), sheeting (E), and necroses (F).

Table 6. Correlations between the different histological features (Chi-square or Fischer exact test). Dura, bone, or other soft tissue infiltration are all regarded as soft tissue infiltration. Hypercellularity refers to the subjective evaluation.

	Apoptosis	Sheeting	Macro-nucleoi	Nuclear pleomorphia	Vesiculous nuclei	Necrosis	Hyper cellularity	Small cells	Immune cells	Lipidi-zation	Fibrosis	Hemo-siderin	Hypervascularization	Soft tissue infiltration	Psammoma bodies
Sheeting	<0.000														
Macronucleoli	0.018	<0.000													
Nuclear pleomorphia	0.038	<0.000	0.001												
Vesiculous nuclei	<0.000	<0.000	<0.000	0.004											
Necrosis	<0.000	0.005	0.079	0.428	0.036										
Hypercellularity	<0.000	<0.000	0.006	0.588	0.021	0.097									
Small cells	<0.000	<0.000	0.043	0.105	<0.000	<0.000	<0.000								
Immune cells	0.56	0.659	0.34	0.262	0.825	0.256	0.257	0.699							
Lipidization	0.16	0.194	1	0.262	0.018	0.376	0.573	0.433	0.382						
Collagen/fibrosis	0.547	0.774	0.52	0.588	0.544	0.508	0.4	0.887	1	0.088					
Haemosiderin	0.697	0.743	0.462	0.59	0.2	0.105	0.26	0.134	0.513	0.513	0.857				
Hypervascularization	0.396	0.46	0.022	0.034	0.596	0.022	0.193	0.146	0.41	1	0.201	0.04			
Soft tissue infiltration	0.478	1	0.38	0.859	0.191	0.521	0.805	1	0.257	0.06	0.002	0.263	0.034		
Psammoma bodies	0.644	0.463	1	0.02	0.438	0.292	0.508	0.27	0.611	0.588	0.002	0.215	0.071	0.002	
>3 mitoses	<0.000	0.001	0.079	0.057	<0.000	<0.000	0.020	0.001	0.256	0.036	0.015	0.518	0.456	0.151	0.001

tumour grades in accordance with the literature [16, 24]. We also confirmed the higher frequency of benign meningiomas in females compared to males, which may be explained by a progesterone-dependent tumour growth [8, 25-28]. In addition, we recognized two peaks in the age-grouped distribution among female patients resembling a phenomenon named Clemmesen's hook. It describes a bimodal age adjusted incidence curve for breast tumours, where cancers with early onset reflect a stronger hereditary pathogenesis versus the later-onset ones that more often display acquired phenotypes [29, 30].

Meningiomas may occur anywhere in the central nervous system, however some predilections do exist, and our data support these sites [1]. Interestingly, atypical meningiomas were observed more often at non-skull base locations, a tendency that has been described by others as well [26, 31, 32]. Etiologic connections between a particular tumour grade and specific locations is not obvious, but may be related to the meninges' complex embryological origin [33, 34].

The frequencies of different meningioma subtypes in this study parallel others [16, 24, 32, 35]. Occurrence of several variants may be related to the progenitor cell's various functions [21]. For instance, meningothelial cap cells exhibit diverse morphological appearances and carry out a unique set of functions that overlap with both mesenchymal and epithelial cells, possible due to the complex ontogenesis of meninges that originate both from mesodermal cells and the neural crest [21, 34, 36]. Distinguishing between benign subtypes of meningiomas is generally of minor importance, however, it is relevant as far as differential diagnoses and specific variants with a more aggressive behaviour are concerned. Although the prognostic significance of smaller areas with such subtypes remains unclear, classification of subtypes according to the growth pattern that dominates more than 50% of specimen appears to be a feasible guideline [6, 19, 21].

Frequencies of meningioma subtypes and histological malignancy grades have changed because of different classification systems. Since up to 25% of tumours with a benign histology recur, the current scheme is not optimal, thus constant improvements of the classification criteria are required [1, 8, 37]. The WHO 2000 classification was an improvement over the 1993 classification in that it brought about more objective and reproducible criteria. Further, it led to recognition of a higher proportion of meningiomas as atypical ranging from 15 to 35% [8, 16, 38]. In the 2007 edition, all brain infiltrative specimens are classified as grade II. In our material, these criteria regarded 30% of the meningiomas as atypical, due to the inclusion of 9 cases with brain invasion and with otherwise benign histology. In contrast, applying the 2000 edition would have resulted in 26% of our specimens being grade II. This illustrates that revision of definitions in classification systems may alter the resultant spectrum of tumour variants and malignancy grades [17]. Consequences of more tumours being recognized as grade II are that increased numbers of patients will need closer radiological follow up and possible radiation therapy [38].

We found that high mitotic count was the most important criterion for determining a meningioma as grade II (73%), thus emphasising its importance in meningioma grading [39-41]. Mitotic figures were often hard to detect, and several factors may bias the assessment, including pycnotic cells and instability of mitotic figures during the fixation process, giving poor interobserver reproducibility [6, 42]. Therefore new techniques have been introduced that are intended to easily and reliably detect proliferative cells or identify mitotic figures, such as Ki-67/MIB-1 and PHH3 immunostaining [7, 43-45]. As mitoses were more commonly seen in areas with increased cellularity, one should search for mitotic figures in such areas.

Meningioma grading can also be based on a combination of five histopathological features that are related to more aggressive behaviour and referred to as "soft criteria" [1]. In our study, these features occurred naturally more frequently in grade II meningiomas, and they were mutually correlated. Concerning sheeting, we found this challenging to evaluate despite the definition used. Confounding factors were areas with immune cell infiltrates or blood vessels, cells in the fibrous subtype that curled in a perpendicular direction to the microscopic slide, and the natural syncytial character of many meningothelial subtypes that resemble sheet-like growth [15]. Regarding hypercellularity, we evaluated this parameter by two quantitative

methods. As they were in accordance with the subjective assessment, the latter is adequate in the daily routine. The definition of prominent nucleoli is ambiguous and not specified in the WHO classification making this parameter encumbered with interobserver variability [15, 22, 46]. In our hands, the description given by Perry et al is useful, where only nucleoli easily observed at 10x are included [4]. Concerning necrosis, this can be seen as either small or large foci [8, 41]. Only spontaneously occurring necrosis should be searched for, not those originated by neither preoperative embolization nor radiation [47]. It is hypothesized that micronecrosis has its origin in insufficient cell nourishment and hypoxia due to high metabolic demands, whereas the larger infarct-like necroses are caused mainly by vascular thrombosis [8, 48, 49]. Small cell formations, interpreted as tumour cells with increased nuclear/cytoplasmic ratio, were also sometimes difficult to assess or define, especially in whirled and hypercellular areas, amid apoptosis and infiltrates of immune cells, or in proximity to necrosis. In fact, Perry describes small cell formation as lymphocyte-like [4]. As long as these "soft criteria" are associated with a more aggressive phenotype, the presence of one of these features warrants the designation "benign meningiomas with atypical features" and should prompt a search for other such features that indicate higher tumour grade [49].

Apoptosis is not a part of the present WHO criteria. We found, however, a strong correlation between other atypical features, such as necrosis, sheeting, and high mitotic count, the latter found by others as well [50, 51]. Hence, one should look for the above mentioned "soft criteria" when apoptotic figures are observed. Further, this context is intriguing as long as apoptosis in meningiomas is associated with poorer survival [52]. It might therefore be of interest to establish methods to detect apoptotic figures, due to the difficulty of distinguishing apoptosis from pycnotic cells, in order to fully explore the clinical value of this change. In this context, the use of the apoptotic marker caspase-3 appears promising [52].

Nuclear pleomorphism in meningiomas is generally regarded as a so-called "benign degenerative atypia" rather than a sign of anaplasia [4, 49]. We found, however, that there was a statistical association between nuclear pleomorphism and features indicative of atypia in concert with others that have demonstrated correlation to decreased survival [24]. Additionally, we also recognised so-called vesiculous tumour cell nuclei to be both significantly more common in grade II tumours and to be correlated to the above-mentioned "soft criteria."

Increased fibrosis or widespread collagen formation are commonly seen in meningiomas regardless of tumour grade, and this is probably linked to the meningothelial cells' proposed functions [21]. The collagen production may be driven by various growth factors and their receptors, such as EGFR (epidermal growth factor receptor) and VEGF [53-57]. Our review also revealed that meningiomas are highly vascularized tumours (74%) even without using immunohistochemistry. This is in accordance with others, and it is proposed that VEGF (vascular endothelial growth factor) plays an important role in the neovascularization of human meningiomas [5, 58, 59]. The frequently encountered intratumoural haemorrhages, which can be seen as haemosiderin depositions, have been associated with more aggressive and recurrent meningiomas [22]. We could, however, not correlate high vascularization or hemosiderin depositions in meningiomas to any atypical features. Psammoma bodies have been found as a protective factor for recurrence [60]. Similarly, we found a trend for psammoma bodies to occur more frequently in benign tumours and without relation to other atypical features. The presence of lymphocytes, plasma cells, and macrophages in the meningioma tissue may reflect various immune responses against the tumour [61, 62]. In addition, the meningothelial cap cells may also exhibit monocyte-like functions [21].

In conclusion, it is important to regularly conduct quality assurance studies to improve the histopathological diagnosis and, hence, the classification systems. For instance, using the latest WHO criteria, we found atypical meningiomas to constitute approximately 30% of all cases, resulting in an obvious increase of this tumour variant compared with previous classification systems. Although the WHO classifications of 2000 and 2007 are more robust than previous ones with regard to interobserver variability, some criteria are hampered with subjective interpretation in such a way that a continuous validation of robust prognostic histological markers is required.

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