Relationship between tumor location, size, and WHO grade in meningioma

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OBJECTIVE Prior studies have investigated preoperative risk factors for meningioma; however, no association has been shown between meningioma tumor size and tumor grade. The objective of this study was to investigate the relationship between tumor size and grade in a large single-center study of patients undergoing meningioma resection.

METHODS A retrospective chart review of patients undergoing meningioma resection at the University of California, San Francisco, between 1985 and 2015 was performed. Patients with incomplete information, spinal meningiomas, multiple meningiomas, or WHO grade III meningiomas were excluded. The largest tumor dimension was used as a surrogate for tumor size. Univariate and multivariate logistic regression models were used to investigate the relationship between tumor grade and tumor size. A recursive partitioning analysis was performed to identify groups at higher risk for atypical (WHO grade II) meningioma.

RESULTS Of the 1113 patients identified, 905 (81%) had a WHO grade I tumor and in 208 (19%) the tumors were WHO grade II. The median largest tumor dimension was 3.6 cm (range 0.2–13 cm). Tumors were distributed as follows: skull base (n = 573, 51%), convexity/falx/parasagittal (n = 431, 39%), and other (n = 109, 10%). On univariate regression, larger tumor size ($p < 0.001$), convexity/falx/parasagittal location ($p < 0.001$), and male sex ($p < 0.001$) were significant predictors of WHO grade II pathology. After controlling for interactions, multivariate regression found male sex (OR 1.74, 95% CI 1.25–2.43), size 3–6 cm (OR 1.69, 95% CI 1.08–2.66), size > 6 cm (OR 3.01, 95% CI 1.53–5.94), and convexity/falx/parasagittal location (OR 1.83, 95% CI 1.19–2.82) to be significantly associated with WHO grade II. Recursive partitioning analysis identified male patients with tumors > 3 cm as a high-risk group (32%) for WHO grade II meningioma.

CONCLUSIONS Larger tumor size is associated with a greater likelihood of a meningioma being WHO grade II, independent of tumor location and male sex, which are known risk factors.

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KEY WORDS meningioma; convexity; parasagittal; skull base; tumor size; atypical; grade; location

MENINGIOMAS are the most common primary intracranial neoplasm. They are more common in women and their incidence rises with increasing age.^{3,5,10} Meningiomas are categorized into 3 histopathological grades by the WHO, with 70%–95% of meningiomas being classified as WHO grade I.^{15,17,18,20} Symptomatic tumors are treated primarily with surgery or radiotherapy. The WHO grade II and III meningiomas are more aggressive, with higher rates of mitosis, and are more likely to recur after surgery and require adjuvant treatment with radiotherapy.²³ Therefore, determining preoperative risk factors for higher tumor grade can provide useful information for both neurosurgeons and patients.

Prior studies have found risk factors for high-grade meningiomas. Male sex and convexity location are known to be associated with increased likelihood of a meningioma being atypical.¹⁹ Although convexity meningiomas are more commonly grade II or III compared to skull base meningiomas, atypical tumors do occur along the skull base. Liang et al. reported that up to 19% of skull base meningiomas were either grade II or III.¹⁹ Radiographic findings, including brain invasion, bone invasion, and peritumoral edema in the surrounding brain, have also been associated with higher-grade meningiomas.²² However, to our knowledge no study has shown that size is independently associated with tumor grade. Interestingly, in our

ABBREVIATIONS RPA = recursive partitioning analysis.

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experience we anecdotally observed that larger tumors tended to be higher grade. Thus, we performed a retrospective study to evaluate whether tumor size was associated with tumor grade.

Methods

Study Design, Setting, Size, and Participants

We performed a retrospective chart review of patients who underwent resection of meningioma at the University of California, San Francisco, between 1985 and 2016. Variables were collected from provider notes, pathology records, operative notes, and radiological reports. Patients were excluded if no size information was available, the tumor was located in the spine, or the tumor was WHO grade III. Grade III tumors were removed due to their rarity in our data set. The manuscript was drafted consistent with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.²⁸ The institutional review board at our institution approved this study.

Demographic and Tumor Variables

Demographic variables included age, sex, and follow-up duration. Tumor grade was obtained from the pathology report at the time of resection, and thus tumors resected prior to 2007 will be biased toward WHO grade I due to the 2007 WHO grading changes. Tumor size was determined from the preoperative MRI scan and radiologist report. The largest diameter in either the anterior-posterior, transverse, or craniocaudal dimension was used as an overall surrogate for tumor size. Tumor locations were obtained from operative and radiology reports, which included convexity, falx, parasagittal, tentorium, cavernous sinus, clinoid, parasellar, tuberculum sellae, planum sphenoidale, olfactory groove, orbital, middle fossa, sphenoid wing, clivus, cerebellopontine angle, posterior fossa, petroclival, petrous, foramen magnum, jugular foramen, skull base, intraventricular, and multifocal. The locations were further categorized into 3 groups: convexity/falx/parasagittal, skull base tumors, and other. Skull base location was defined as cavernous sinus, cerebellopontine angle, clinoid, clivus, foramen magnum, jugular foramen, middle fossa, olfactory groove, orbital, parasellar, petroclival, petrous, planum sphenoidale, posterior fossa, skull base, sphenoid wing, and tuberculum sellae. Other locations included intraventricular and multifocal tumors that could not be easily classified into skull base, convexity, or falx locations.

Study Bias

This is a retrospective study, and thus is limited by selection bias. No patients were excluded if they had information regarding the variables of interest in the chart, thus limiting selection bias.

Statistical Analysis

All statistical analyses were performed using JMP Pro (version 13.0; SAS Institute, Inc.). Demographic data were assembled and analyzed in the standard fashion. For cat-

egorical data, Pearson's chi-square (multiple categories) or Fisher exact (2 categories) tests were reported. Univariate and multivariate logistic regression was performed and used to calculate odds ratios. A recursive partitioning analysis (RPA) was performed to split the continuous size data into clinically relevant groups. The RPA was also used with multiple variables to determine groups at risk for having a WHO grade II tumor. The number of partitions performed was based on maximal R^2 as calculated by k-fold cross-validation ($k = 5$).

Results

Demographics and Tumor Characteristics

A final sample size of 1113 patients (mean age 55.7 years, range 8–90 years, 73.9% female) was obtained from the electronic medical record (Table 1). The majority of patients presented with either a headache or cranial nerve deficit. The WHO grade at the time of resection was used to assign the WHO grade. The majority (81%) of patients had a WHO grade I tumor and 19% were WHO grade II. The mean tumor size was 3.8 cm (SD 1.8 cm), and the median size was 3.6 cm (range 0.2–13 cm). Roughly half of the patients in our study had meningiomas located in the skull base, 40% of tumors were located in the falx/parasagittal or convexity area, and the remaining 10% of tumors were found in other locations (Table 2).

Risk Factors for WHO Grade II

We performed univariate logistic regression to determine if age, sex, tumor location, and tumor size were significantly associated with WHO grade (Table 3). Age was not a significant predictor of grade ($p = 0.61$). Tumor size was significantly associated with a meningioma being WHO grade II (Fig. 1; $p < 0.001$). Tumor convexity/falx/parasagittal location (OR 1.90, 95% CI 1.38–2.63, $p < 0.001$) and other location (OR 1.71, 95% CI 1.02–2.86,

TABLE 1. Characteristics in 1113 patients with meningioma

Characteristic	Value
No. of patients	1113
Median age in yrs (range)	55.7 (8–90)
Female	822 (73.9%)
Initial presenting symptoms	
Headache	408 (36.7%)
Focal cranial nerve deficit	348 (31.3%)
Seizure	188 (16.9%)
Cognitive change	160 (14.4%)
Weakness	123 (11.1%)
Vertigo/dizziness	109 (9.8%)
Incidental	80 (7.2%)
Ataxia/gait change	70 (6.3%)
Pain/sensory change	62 (5.6%)
Proptosis	23 (2.1%)
Syncope	11 (1.0%)
Not recorded	160 (14.4%)

TABLE 2. Tumor characteristics

Tumor Location	No. of Patients	Median Diameter (cm)	WHO Grade II
Skull base	573		
Anterior cranial fossa	152	2.7	9.9%
Middle cranial fossa	191	3.6	18.8%
Posterior cranial fossa	230	3.0	13.0%
Convexity/falx/parasagittal			
Falx/parasagittal	212	4.5	20.3%
Convexity	219	3.7	27.4%
Other	109	3.8	22.0%
Total	1113	3.6	18.7%

$p = 0.03$) were also significantly associated with a meningioma being WHO grade II compared to skull base meningiomas. Finally, male sex was also associated with a meningioma being WHO grade II (OR 1.94, 95% CI 1.41–2.69, $p < 0.001$). Next, we performed multivariate logistic analysis and included all significant variables from the univariate model. Given the relationship between tumor location and WHO grade II seen on univariate analysis, we crossed tumor size with location. Tumor size remained significantly associated with tumor grade, even with the crossed variables in the model: tumor size ($p = 0.02$ for size between 3.0 and 6.0 cm; $p = 0.002$ for size > 6.0 cm compared to tumors < 3.0 cm) and tumor location ($p = 0.006$ for falx/parasagittal/convexity tumors compared to skull base tumors).

To identify meaningful size cutoff points for risk of higher-grade tumors, we performed RPA. We identified 3.2 cm as the optimal split, and divided the tumors into groups of < 3 cm, 3–6 cm, and > 6 cm. We then performed multivariate logistic regression and calculated odds ratios for the groups (Table 4). Last, we used a multivariate RPA to identify subgroups at highest risk for having a WHO grade II tumor. The k-fold cross-validation was used to determine that 3 splits was the optimal number of splits.

TABLE 3. Univariate logistic regression for predictors of WHO grade II

Variable	OR*	95% CI*	p Value
Age			0.61
Tumor size			$<0.001^\dagger$
Tumor location			
Skull base	1		
Falx/parasagittal/convexity	1.90	1.38–2.63	$<0.001^\dagger$
Other	1.71	1.02–2.86	0.03 ‡
Sex			
Female	1		
Male	1.94	1.41–2.69	$<0.001^\dagger$

* Not calculated for continuous variables.

$^\dagger p < 0.01$.

$^\ddagger p < 0.05$.

FIG. 1. Scatter plot and logistic regression of tumor grade by tumor size. Each circle represents an individual case and is plotted by tumor size. Tumors above the blue line are WHO grade I, whereas those below are grade II. The blue line is the logistic fit showing that as size increases, the proportion of WHO grade II tumors increases as well ($p < 0.001$).

The first split was tumor size at 3.2 cm, which increased the likelihood of a WHO grade II tumor (23.9% vs 11.3%). The second split was on sex, with male patients having an increased likelihood of a WHO grade II tumor compared to female patients (32.5% vs 20.0%). Finally, the third split was made for tumors < 3.2 cm based on location, with non-skull base tumors having an increased likelihood of a WHO grade II tumor (16.6% vs 8.8%) (Fig. 2).

Discussion

Key Results

Our results show that larger tumor size is associated with an increased likelihood of a meningioma being WHO grade II, even after controlling for interactions with the known risk factors of sex and meningioma location.

TABLE 4. Multivariate logistic regression for predictors of WHO grade II

Variable	OR	95% CI	p Value
Tumor size			
<3.0 cm	1		
3.0–6.0 cm	1.69	1.08–2.66	0.02*
>6.0 cm	3.01	1.53–5.94	0.002 †
Tumor location			
Skull base	1		
Falx/parasagittal/convexity	1.83	1.19–2.82	0.006 †
Other	2.37	1.21–4.64	0.02*
Sex			
Female	1		
Male	1.74	1.25–2.43	$<0.001^\dagger$

* $p < 0.05$.

$^\dagger p < 0.01$.

FIG. 2. The RPA for WHO Grade II meningiomas. The optimal number of splits (3) was based on R^2 calculated by k-fold cross-validation.

Interpretation of Results

Here, we show that larger meningiomas are more likely to be WHO grade II tumors. Importantly, this relationship was maintained as an independent risk factor even after crossing with tumor location and male sex in a multivariate analysis. Consistent with prior studies, skull base tumors were less likely to be higher grade than convexity and falx/parasagittal meningiomas.^{8,19} Male sex, another known risk factor for atypical meningioma, was also found to be significant in our study.^{6,16,19,24} As with prior studies, age was not related to WHO grade. Interestingly, the RPA found that among size, sex, and location, tumor size was the most important dividing factor between the likelihood of WHO grade I and II tumors. It also identified a subset of male patients with large tumors who are at particularly high risk. Figure 1 shows how this risk continues to increase with increasing tumor size. These findings are useful when discussing management plans with patients and when preparing expectations for care that may be more likely to include adjuvant radiotherapy.⁷

A recent report found that 20% of giant meningiomas (i.e., > 5 cm) were WHO grade II or III.²¹ Furthermore, in that study, tumor location also influenced recurrence-free survival. Another retrospective analysis reported that tumor size was related to disease-free survival for patients with atypical meningiomas who received radiotherapy.¹¹ Our findings add to these prior reports by being the first study to demonstrate that tumor size is directly related to tumor grade.

The findings in this study raise the question of what mechanisms drive the relationship between tumor size and grade. Simplistically thinking, one possibility is that grade II tumors grow more quickly than grade I tumors and are

more likely to reach a larger size. However, if that were the case, one might imagine that a faster-growing tumor would present earlier, because rapidly growing tumors often become symptomatic at a smaller size. Alternatively, it is possible that once a slow-growing tumor reaches a large size, a microenvironment develops (perhaps caused by hypoxia) that facilitates the transformation of the tumor to a more aggressive phenotype. Moving forward, we will need to turn to the laboratory to identify what mechanisms drive meningioma growth and cause them to become higher grade.

Significant progress has been made in the last several years to identify what genes are mutated in meningioma. In addition to *NF2*, mutations have been found in *TRAF7*, *SMO*, *KLF4*, *PI3K*, and *AKT1*.^{1,8} Mutations in *POLR2A* were identified in recurrent meningiomas.⁹ Multiple independent groups have shown that *TERT* promoter mutations are associated with shorter time to recurrence, survival, and overall poor prognosis.^{2,12,13,25} In addition to somatic mutations, specific DNA methylation patterns have recently been discovered that complement known chromosomal rearrangements that are associated with tumor grade and survival.^{4,26} In contrast to mechanisms occurring within the meningioma, another possibility is that the immune environment and tumor-immune system interaction may alter tumor growth and drive the development of large size. Interestingly, we recently found that increased PD-L1 expression in meningioma was associated with shorter survival.¹⁴ We hypothesize that the relationship between meningioma size and grade reflects changes in the molecular landscape of each individual tumor and the way in which individual meningioma interacts with the surrounding microenvironment and immune system. Contin-

ued basic and translational research efforts are needed to further characterize these drivers of meningioma growth and, we hope, to identify additional molecular targets for treatment.

Limitations of the Study

This study is limited by its retrospective design. In addition, the criteria for WHO classification changed during the years of this study, and regrading all the samples in this series is not practical. With the 2007 WHO classification, there are more meningiomas classified as grade II, which means that our study probably underestimates the incidence of grade II tumors.²⁷ However, the rate of atypical meningiomas in our cohort is similar to that in previously published series.²² Another limitation is the use of tumor diameter as a proxy for overall tumor size because meningiomas can take many shapes. Retrospectively performing volumetric analysis was beyond the scope of the current study. Future prospective studies with volumetric analysis and contemporary grading criteria would be an excellent addition to strengthen these results.

Generalizability of the Findings

One of the most significant strengths of this study is its very large sample size, which makes these results widely generalizable and applicable to all providers treating this disease and to patients who are diagnosed with meningioma.

Conclusions

In this study, we identified tumor size as an independent risk factor for a meningioma to be WHO grade II. In addition, we recapitulate other studies showing that male sex and tumor location are also risk factors for a meningioma to be WHO grade II. Predicting tumor grade from radiological factors such as preoperative tumor size and location can impact surgical decision making, operative planning, and treatment strategies.

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Disclosures

The authors report no conflict of interest concerning the materi-

als or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Magill, Aghi, Theodosopoulos, McDermott. Acquisition of data: Magill, Young, Chae, Aghi, Theodosopoulos. Analysis and interpretation of data: Magill, Young, Chae, McDermott. Drafting the article: Magill, Young, Chae. Critically revising the article: Magill, Young, McDermott. Reviewed submitted version of manuscript: Magill, Young, McDermott. Approved the final version of the manuscript on behalf of all authors: Magill. Statistical analysis: Magill, Young. Study supervision: Magill, McDermott.

Supplemental Information

Previous Presentations

A preliminary version of this work was presented at the 2017 North American Skull Base Society Annual Meeting in New Orleans, LA.

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