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Histopathological prognostic factors of recurrence following definitive therapy for atypical and malignant meningiomas

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OBJECTIVE Patients with atypical and malignant (WHO Grade II and III) meningiomas have a worse prognosis than patients with benign (WHO Grade I) meningiomas. However, there is limited understanding of the pathological risk factors that affect long-term tumor control following combined treatment with surgery and radiation therapy. Here, the authors identify clinical and histopathological risk factors for the progression and/or recurrence (P/R) of high-grade meningiomas based on the largest series of patients with atypical and malignant meningiomas, as defined by the 2007 WHO classification.

METHODS Patients diagnosed with WHO Grade II and III meningiomas between 2007 and 2014 per the WHO 2007 criteria and treated with both surgery and external beam radiation therapy were retrospectively reviewed for clinical and histopathological factors at the time of diagnosis and assessed for P/R outcomes at the last available follow-up.

RESULTS A total of 76 patients met the inclusion criteria (66 Grade II meningiomas, 10 Grade III meningiomas). Median follow-up from the time of pathological diagnosis was 52.6 months. Three factors were found to predict P/R: Grade III histology, brain and/or bone invasion, and a Ki-67 proliferation rate at or above 3%. The crude P/R rate was 80% for patients with Grade III histology, 40% for those with brain and/or bone involvement (regardless of WHO tumor grade), and 20% for those with a proliferative index ≥ 3% (regardless of WHO tumor grade). The median proliferation index was significantly different between patients in whom treatment failed and those in whom it did not fail (11% and 1%, respectively).

CONCLUSIONS In patients with atypical or malignant meningiomas, the presence of Grade III histology, brain and/or bone involvement, and a high mitotic index significantly predicted an increased risk of treatment failure despite combination therapy. These patients can be stratified into risk groups predicting P/R. Patients with high-risk features may benefit from more treatment and counseling than is typically offered currently.

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KEY WORDS atypical; malignant; meningioma; histopathological; oncology

Meningiomas represent the most common primary brain tumor in adults, accounting for approximately 36% of all cases.[30] They have many histological subtypes but, based on biological behavior, are classified into low- (WHO Grade I) and high-grade (WHO Grade II and III) tumors. The 2007 WHO classification recognizes 3 histopathological grades: benign WHO Grade I meningiomas with an indolent course and high-grade WHO Grade II (atypical) and III (malignant or anaplastic) meningiomas that are more aggressive and have an overall significantly worse prognosis.[3] In 2016, the WHO classification system was updated. With respect to meningiomas, the only change has been the introduction of brain invasion as a criterion for the diagnosis of atypical meningioma.[27]

Given the high rate of progression and recurrence for atypical and malignant meningiomas, patients with these lesions often receive radiation therapy following resection. Numerous techniques, including stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, and standard

ABBREVIATIONS CTCAE = Common Terminology Criteria for Adverse Events; EQD2 = equivalent dose in 2 Gy/fraction; P/R = progression and/or recurrence.

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fractionated radiation therapy, can be applied. Retrospective analyses of patients treated with these modalities suggest variable local control in the short term but a high risk of recurrence with longer follow-up.[5,8,15,24] However, adjuvant radiotherapy has been shown to improve disease-free survival and overall survival among patients with atypical and malignant meningiomas.[11,17,20,29] Regardless of the treatment used, the risk of long-term recurrence is still high with WHO Grade II and III tumors.[5,8,15,24]

Current literature on this topic suffers from a lack of prospective randomized data. Furthermore, because the 2007 revised WHO criteria led to the reclassification of a significant number of tumors, studies prior to this date are difficult to interpret and apply to current patient cohorts.[9,38,45] There remain limited data on the characteristics of local and regional recurrence of atypical and malignant meningiomas since the revision of WHO diagnostic criteria. A number of studies have established risk stratification for benign meningiomas (WHO Grade I), which has led to the clinical stratification of Grade I meningiomas with brain invasion into a high-risk category, as reflected in the new 2016 WHO criteria in which brain invasion is included as a histological feature for the diagnosis of WHO Grade II meningioma. However, the significance of brain invasion in otherwise high-grade meningiomas is unknown, and there is clinical value in determining features associated with a higher risk of recurrence to improve patient care.

Together, atypical and malignant meningiomas comprise approximately a quarter of all meningiomas.[3,9] These tumors are pathologically characterized as having high proliferative activity and/or anaplastic features including dense cellularity, patternless sheet-like growth, necrosis, prominent nucleoli, or a high nuclear/cytoplasmic ratio.[3] Clinically, these tumors are important since patients are at a far increased risk for recurrence compared with patients harboring benign meningiomas, even after treatment with combined modalities.[2,18,22,25,31]

While a number of studies have looked at prognostic factors following treatment with surgery alone, only a few studies have specifically examined clinical and histopathological risk factors predicting the progression and/or recurrence (P/R) of high-grade meningiomas following surgery and radiation therapy combined. Progression-free survival at 60 months following combined treatment ranges widely from 20% to 62% for Grade II and III meningiomas[11,18,20] with a limited number of studies detailing higher-grade meningiomas post-2007 WHO classification.[20,22,25] In the present study, we sought to identify clinical and histopathological factors predicting P/R following the combined treatment of higher-risk meningiomas that may allow us to select and counsel patients most likely to benefit from more aggressive upfront surgery and/or adjuvant radiation therapy.

Methods

Patient Selection

This study was conducted with institutional review board approval. We retrospectively reviewed all patients consecutively treated at our institution from 2007 to 2014 for the pathological diagnosis of intracranial WHO Grade II or III meningioma according to the 2007 WHO classification. Patients who had surgery but no radiation therapy were excluded from this analysis.

Parameters Assessed

Age at diagnosis was defined as age at the time of initial biopsy, surgery, or, for those undergoing initial observation, the appearance of radiographically suspected meningioma. The clinical risk factors of prior radiation exposure, hormonal exposure, chemical exposure, and gravidity and parity status were recorded. Comorbidities of breast cancer or any gynecological cancer and obesity were also recorded. Tumor volume was determined by the largest diameter in the anteroposterior (x), superoinferior (y), and transverse (z) dimensions by using the formula for nonspherical tumor volume $[(\pi/6)(x)(y)(z)]$. Tumor location was divided into 2 categories: skull base (anterior, middle, and posterior fossa) and non–skull base (convexity, tentorium, and parasagittal/falx).

Brain invasion and Ki-67 index were determined by reviewing the pathology slides of the initial biopsy or surgery. Bone involvement was coded as positive if it was affirmatively described in imaging, operative, and/or pathology reports. Extent of resection according to Simpson classification was determined by reviewing the operative notes and imaging studies.[40] Radiation treatment information was gathered and recorded. To compare total doses between fractionated radiation therapy and single-fraction therapy, the linear quadratic formula with $a/b = 10$ Gy was used to calculate equivalent doses in 2 Gy/fraction (EQD2).

Follow-up was calculated from the date of initial radiological diagnosis until the last known follow-up. Side effects after surgery and radiation treatment were recorded as early (< 6 months from radiation treatment) versus late (≥ 6 months from radiation treatment). Grading of side effects was standardized via the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The primary end point was P/R as defined by radiological evidence and correlated with clinical review. No P/R meant progression-free survival at the time of the last follow-up. The secondary end point was overall survival.

Statistical Analysis

Fisher's exact test was used to compare categorical variables. Time to P/R was analyzed using univariate Cox proportional-hazards methodology. The actuarial data were represented with Kaplan-Meier plots. Cumulative incidence curves were compared using the log-rank test. All p values were 2-tailed. A p value of 0.05 was considered significant.

Results

Baseline Characteristics

The characteristics of 76 high-grade meningioma patients who underwent treatment at our institution between 2007 and 2014 are summarized in Table 1. Total resection was favored (68%), and a minority of patients (32%) underwent subtotal resection. Following surgery, most pa-

TABLE 1. Summary of characteristics in 76 patients with high-grade meningioma

Factor	Value
Total no. of patients	76
Sex	
F	40 (53%)
M	36 (47%)
Median age at diagnosis in yrs (IQR)	56.44 (47.02, 64.30)
Tumor location	
Non–skull base	47 (62%)
Skull base	29 (38%)
Simpson resection grade	
I	15 (20%)
II	16 (21%)
III	21 (28%)
IV	24 (32%)
Radiation modality	
Proton therapy	59 (78%)
Photon therapy	14 (18%)
Proton & photon therapy	3 (4%)
Radiation technique	
Fractionated radiation therapy	58 (76%)
Single-fraction SRS	18 (24%)
WHO tumor grade	
II	66 (87%)
III	10 (13%)
Subtype of pathology	
Grade II, atypical	62 (82%)
Grade II, chordoid	1 (1%)
Grade II, clear cell	2 (3%)
Grade III, rhabdoid	4 (5%)
Grade III, anaplastic	7 (9%)
Median Ki-67 proliferation index in % (IQR)	2.00 (0.10, 8.50)
Dichotomized Ki-67 index	
Ki-67 <3%	41 (54%)
Ki-67 ≥3%	35 (46%)
Brain &/or bone invasion	
No invasion	41 (54%)
Brain invasion	11 (14%)
Bone invasion	13 (17%)
Both	11 (14%)
Median time to last FU in mos (IQR)	52.57 (43.29, 68.01)

FU = follow-up; IQR = interquartile range; SRS = stereotactic radiosurgery.

tients underwent proton therapy (78%) with a smaller percentage (18%) receiving photon therapy. A small number of patients (4%) underwent both proton and photon therapy. A majority of patients had a WHO Grade II tumor subtype (86%) without evidence of brain or bone invasion (54%). The median time to the last known follow-up was approximately 52 months. Table 2 details dosimetric data by fractionated and single-fraction radiation therapy. Most

TABLE 2. Dosimetric data

Factor	No. of Patients	Median	Min	Max
Fractionated radiation therapy				
Dose/fraction (Gy)	58	1.8	1.8	3.0
No. of fractions	58	33	14	36
Dose prescription (Gy)	58	59.4	42.0	68.0
Target vol (cm^3)	58	36.3	3.2	174.9
Single-fraction SRS				
Dose prescription (Gy)	18	15.0	12.0	20.0
Target vol (cm^3)	18	5.2	1.9	30.5

TABLE 3. Progression and/or recurrence of tumor

Factor	HR	95% CI 1	95% CI 2	p Value
Sex	0.73	0.27	1.97	0.53
Age at diagnosis	1.00	0.96	1.03	0.92
Tumor location (non–skull base vs skull base)	1.14	0.41	3.13	0.81
Target vol	1.00	0.99	1.01	0.96
Simpson resection grade (any)	1.03	0.66	1.60	0.89
Dose prescription	1.02	0.99	1.06	0.19
Fractionated therapy (vs unfractionated)	1.58	0.45	5.57	0.47
EQD2	1.04	0.99	1.10	0.12
Tumor grade	7.36	2.72	19.95	0.00
Tumor pathological subtype (any)	10.01	3.62	27.69	0.00
Ki-67 (continuous)	1.14	1.08	1.21	0.00
Ki-67 (dichotomized)	5.86	1.67	20.59	0.01
Brain invasion	8.61	2.77	26.72	0.00
Bone invasion	4.16	1.51	11.49	0.01
Brain &/or bone invasion	9.39	2.13	41.35	0.00
Any risk factor	2.07	0.47	9.18	0.34

patients received some form of fractionated radiation therapy, and the most common radiation prescription was 59.4 Gy in 33 fractions.

Univariate Cox Regression Analysis

Univariate analysis for tumor P/R and overall survival was performed, and the results are presented in Tables 3 and 4, respectively. The factors significantly associated with P/R were tumor grade, tumor pathological subtype, Ki-67 index, and brain and/or bone invasion. None of the factors studied were significantly associated with overall survival.

Toxicity

Table 5 denotes acute and late complications following surgery and radiation for all patients. Most patients experienced some form of acute side effect, usually fatigue (33%) or headache (18%). A minority of patients had late complications in the form of seizures or new motor and/

TABLE 4. Overall survival

Factor	HR	95% CI 1	95% CI 2	p Value
Sex	1.05	0.15	7.49	0.96
Age at diagnosis	0.99	0.93	1.06	0.83
Tumor location (non–skull base vs skull base)	0.64	0.07	6.17	0.70
Target vol	1.01	0.99	1.03	0.56
Simpson resection grade (any)	1.13	0.47	2.75	0.78
Dose prescription	1.14	0.90	1.45	0.26
Fractionated therapy (vs unfractionated)*	0	0	0	1
EQD2	1.16	0.93	1.45	0.17
Tumor grade	2.22	0.23	21.47	0.49
Tumor pathological subtype (any)	1.48	0.15	14.23	0.73
Ki-67 (continuous)	1.05	0.91	1.21	0.51
Ki-67 (dichotomized)	1.16	0.16	8.21	0.89
Brain invasion	7.53	0.78	72.42	0.08
Bone invasion	6.31	0.66	60.77	0.11
Brain &/or bone invasion†	0	0	0	1
Any risk factor	0	0	0	1

* There were no deaths among single-fraction cases; thus, the hazard ratio, confidence intervals, and p values could not be estimated.
† There were no deaths in the no-invasion group; thus, the hazard ratio, confidence intervals, and p values could not be estimated.

TABLE 5. Toxicity

Factor	No. of Patients (%)
Acute complications (<6 mos)	
None	30 (39%)
Fatigue (CTCAE Grade 1, 2)	25 (33%)
Headache (CTCAE Grade 1, 2)	14 (18%)
Seizures	
CTCAE Grade 1, 2	1 (1%)
CTCAE Grade ≥3	1 (1%)
New neurological changes	
CTCAE Grade 1, 2	6 (8%)
CTCAE Grade ≥3	1 (1%)
Late complications (≥6 mos)	
None	58 (76%)
Seizures	
CTCAE Grade 1, 2	4 (5%)
CTCAE Grade ≥3	2 (3%)
New neurological changes	
CTCAE Grade 1, 2	7 (9%)
CTCAE Grade ≥3	6 (8%)
Radiation necrosis	3 (4%)
Cause of death	
Alive	71 (93%)
Death by meningioma	4 (5%)
Death by other cause (myocardial infarct)	1 (1%)

or sensory dysfunction. By the last known follow-up at a median of approximately 52 months, most patients were alive (93%).

Comparison of Patients With and Without Treatment Failure

At 12 months, the actuarial rate of P/R for all patients was 5% (95% CI 0.02–0.14). At 60 months, 21% of all patients (95% CI 0.14–0.34) had P/R. Patients with higher-grade meningiomas and any of the following 3 features—Grade III meningioma ($p < 0.001$), brain invasion or bone involvement ($p < 0.001$), Ki-67 index at or above 3% ($p < 0.001$)—were significantly more likely to have P/R after treatment than those without any of these features. Analysis by individual tumor pathology was not feasible given the limited incidence of tumor subtypes. Of the 17 patients in whom treatment failed, all cases of P/R happened within 72 months. Between 72 and 120 months of follow-up, we did not observe any additional cases of P/R. Of the 17 patients who experienced P/R, 5 died. Median time from initial diagnosis to death was 48 months.

Some patients with P/R had symptoms that were believed to be secondary to the disease progression. These ranged from headaches, visual changes (diplopia, visual field deficits), and vertigo to seizures, motor impairment, and sensory deficits. Among the 17 patients with P/R, 6 underwent another resection, 6 had radiation therapy, and 5 did not receive any salvage treatment.

Tumor Grade

On univariate analysis, having a Grade III (vs Grade II) tumor was highly predictive of P/R (Fig. 1). At 12 months, 5% of patients with Grade II tumors (95% CI 0.02–0.14) and 10% of patients with Grade III tumors (95% CI 0.15–0.53) experienced P/R. At 60 months, 16% of patients with Grade II tumors (95% CI 0.08–0.29) and 60% of patients with Grade III tumors (95% CI 0.33–0.88) suffered P/R.

Brain Invasion or Bone Involvement

Brain invasion and/or bone involvement were noted in 46% of all patients. All patients without evidence of brain invasion or bone involvement remained free of progression at 12 months (Fig. 2). At 60 months, 5% of patients without brain invasion and/or bone involvement (95% CI 0.01–0.19) demonstrated P/R. In contrast, in patients with either brain invasion or bone involvement, at 12 months, 9% (95% CI 0.02–0.31) had P/R. At 60 months, 23% (95% CI 0.10–0.46) of these patients had evidence of P/R. In patients demonstrating both brain invasion and bone involvement, the risk of P/R increased to 18% (95% CI 0.05–0.55) and 73% (95% CI 0.46–0.93) at 12 and 60 months, respectively.

Ki-67 Proliferative Index

The Ki-67 index (either continuous or dichotomized at 3%) was strongly predictive of P/R (Fig. 3). For patients with a Ki-67 index below 3%, no P/R was evident at 12 months. At 60 months, 8% of patients (95% CI 0.03–0.22) had P/R. For patients with a Ki-67 index at or above 3%,

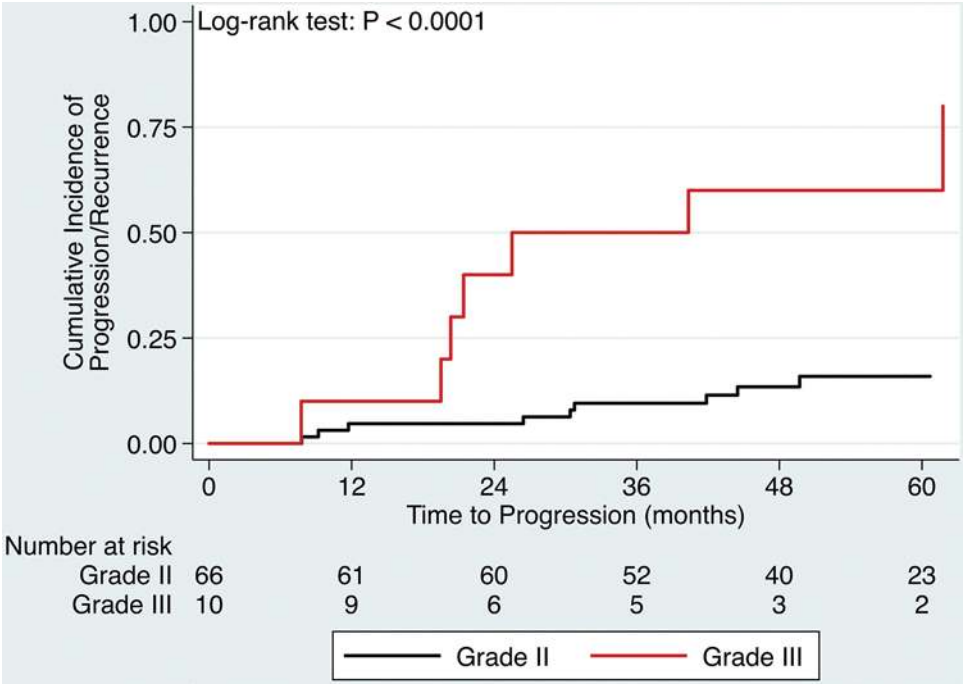

FIG. 1. Cumulative incidence of P/R versus time to progression stratified by tumor grade. Figure is available in color online only.

the P/R rate at 12 months was 12% (95% CI 0.05–0.28). At 60 months, the P/R rate was 38% (95% CI 0.23–0.57).

Risk Stratification Model

We developed a P/R risk model based on tumor grade with or without the presence of risk factors that were deemed significant on univariate analysis (Fig. 4). The multivariate Cox proportional-hazards model enabled the creation of a clear risk stratification model. The model consisted of 3 risk groups based on a combination of

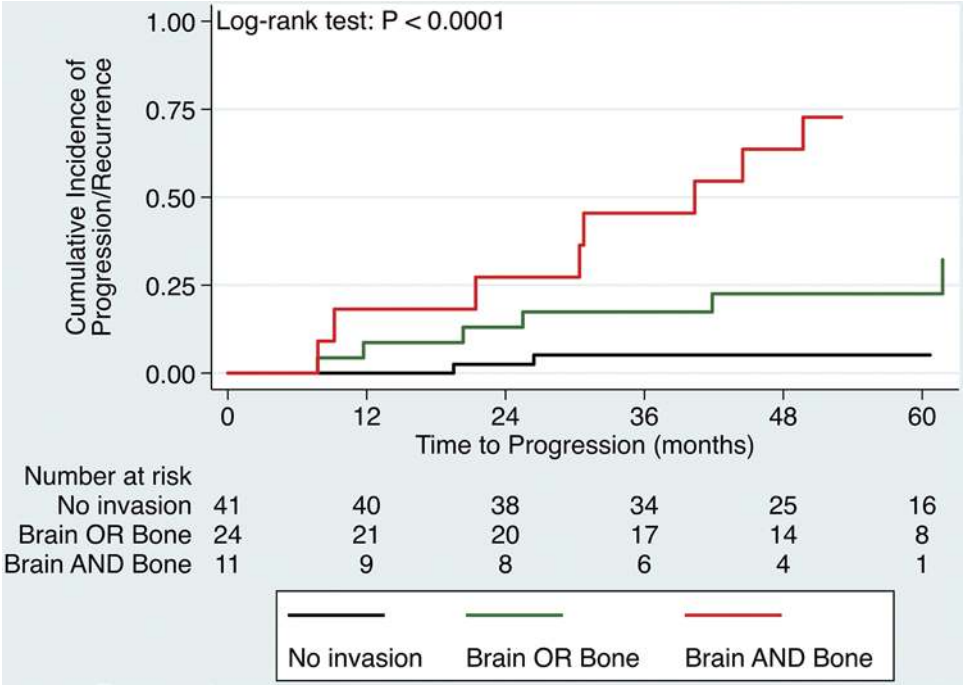

FIG. 2. Cumulative incidence of P/R versus time to progression stratified by brain invasion and/or bone involvement. Figure is available in color online only.

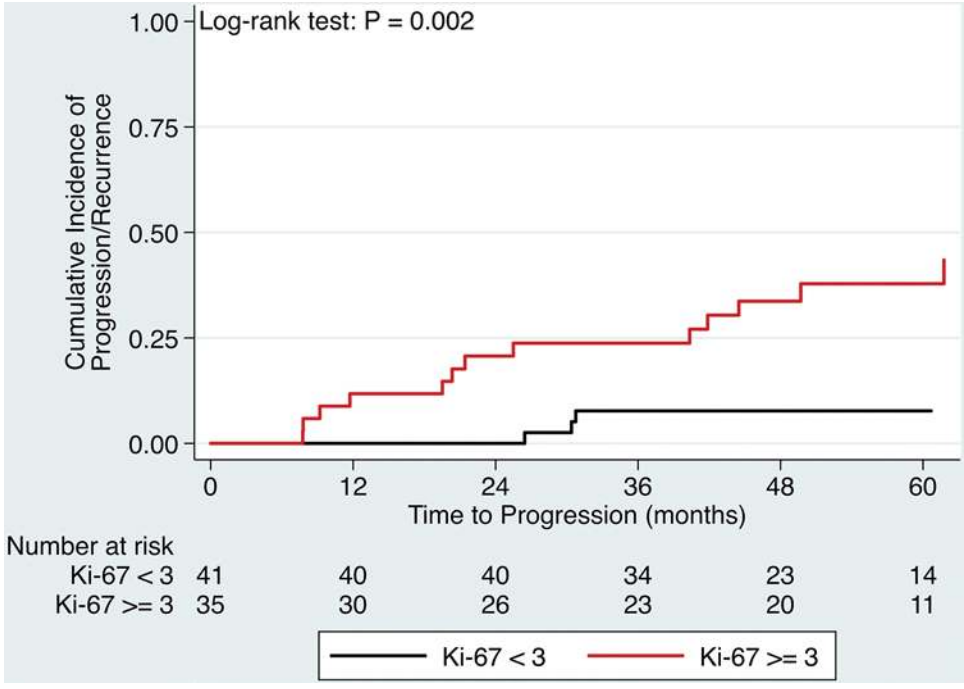

FIG. 3. Cumulative incidence of P/R versus time to progression stratified by Ki-67 proliferative index. Figure is available in color online only.

the significant risk factors identified in our cohort: tumor grade, brain invasion and/or bone involvement, and Ki-67 index. The 3 groups were low risk, intermediate risk, and high risk. Low-risk patients had Grade II tumors and no additional risk factors. Intermediate-risk patients had Grade II tumors along with any risk factor (brain invasion and/or bone involvement and/or Ki-67 index). The high-risk group consisted of patients with Grade III tumors with or without the other risk factors. The actuarial P/R rate for the 3 risk groups at 12 months was 0%, 8% (95% CI 0.03–0.22), and 10% (95% CI 0.01–0.53), respectively. At 60 months, the P/R rate for the risk groups was 4% (95% CI 0.01–0.26), 23% (95% CI 0.12–0.41), and 60% (95% CI 0.33–0.88), respectively.

The log-rank tests for equality of survivor functions ($p < 0.0001$) and for trend ($p < 0.0001$) were both statistically significant, indicating that the risk of P/R increases progressively from the lowest risk group to the highest risk group (Fig. 4).

Discussion

In this study we demonstrated that clinical and histopathological features of high-grade meningiomas are associated with a higher risk of recurrence. With the exception of histopathological grade, evidence supporting established prognostic risk factors for progression in benign meningiomas is inconclusive among higher-grade meningiomas. There are a number of reasons for this discrepancy, including the wide range of study periods and significant differences in the criteria for tumor definition and study inclusion. The WHO criteria have been established and/or updated in 1993, 2000, 2007, and, most recently, in May 2016. Each revision has changed the classification of meningiomas, making data comparisons across these time periods difficult. Moreover, while our cohort includes only patients who underwent combined treatment (surgery and radiation therapy), previous studies often included patients treated with resection alone, adding heterogeneity to patient management and thus limiting the ability to compare clinical outcomes across studies.

In the present study, we evaluated a wide range of clinical and pathological features of high-grade meningiomas (Grade II and III) and looked for prognostic factors for P/R after initial, definitive treatment. We found that tumor grade, brain invasion and/or bone involvement, and Ki-67 index were highly associated with the risk of P/R after definitive treatment (Figs. 1–3). Interestingly, when stratified by risk groups, the patients with Grade II meningiomas and statistically significant risk factors on univariate analysis, namely brain invasion, bone involvement, and/or high Ki-67 index, had progression at significantly higher rates than patients with Grade II tumors and none of these risk factors. These findings raise the possibility that atypical meningiomas (Grade II) with certain characteristics represent an intermediate risk and that there is a continuous spectrum between "standard" Grade II tumors and the most aggressive Grade III tumor type. Moreover, these findings raise the question of whether Grade II tumors accompanied by certain risk factors should be treated as clinical Grade III tumors.

The WHO grading system for meningioma correlates strongly with tumor natural history and thus has a significant impact on treatment planning and patient counseling. Our study is partly validated by the WHO grading system as histopathological grade is one of the strongest predic-

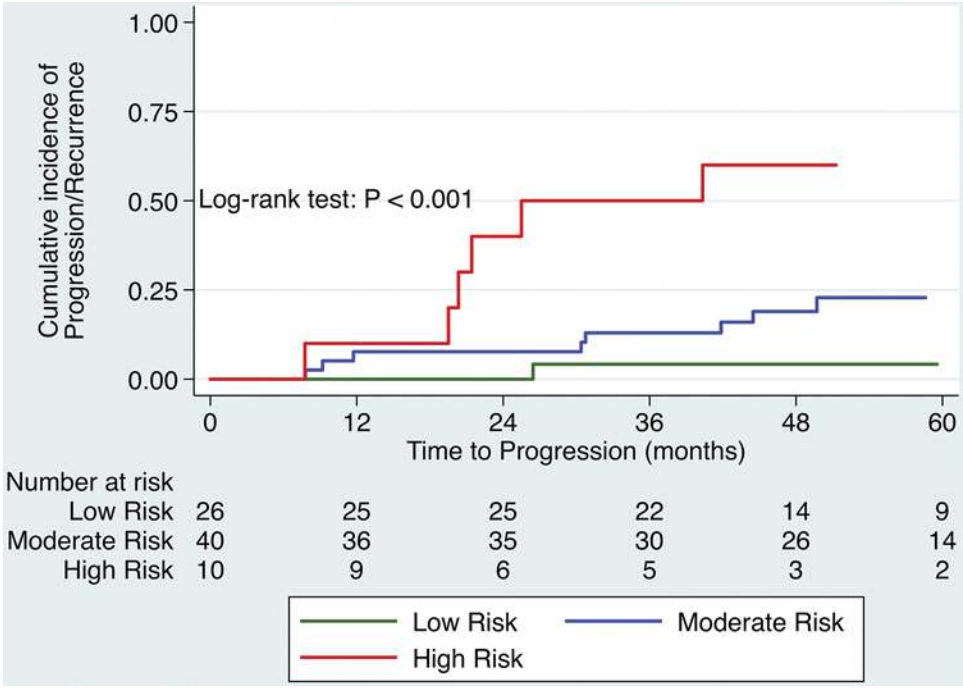

FIG. 4. Cumulative incidence of P/R versus time to progression—risk groups. Figure is available in color online only.

tors for P/R in our cohort and forms the basis of our risk stratification groups. The inferior prognosis with higher-grade disease following definitive treatment is seen in our cohort in which at 60 months, 16% of patients with Grade II tumors showed evidence of P/R and 60% of patients with Grade III tumors had P/R. It should be noted, however, that some high-grade meningiomas can behave more like low-grade tumors and vice versa. As a consequence, histopathological grading by itself is insufficient for optimal risk stratification, and further examination of key variables is warranted for these tumors at higher risk of P/R.[21,33]

Brain invasion is a recognized ominous feature in benign meningiomas, but there is a paucity of data regarding the prognostic significance of brain invasion for high-grade meningiomas. In one report examining brain invasion in 74 atypical and malignant meningiomas based on the 2000 WHO classification, brain invasion was associated with decreased survival in both tumor groups.[46] Our study demonstrates a clear role for brain invasion as a risk factor for P/R in high-grade meningiomas. This observation raises a few biological possibilities. For example, the worse outcomes with brain-invasive versus non–brain-invasive Grade II meningiomas may reflect more aggressive tumor biology and/or underlying genetic differences. Past genomic investigations have reported specific allelic deletions associated with high-grade meningiomas and certain morphological changes suggestive of malignant disease, including brain invasion.[36,37,39] Additional studies are needed to definitively link certain chromosomal aberrations to higher-grade brain-invasive meningiomas that have an increased P/R risk.

In high-grade meningiomas, the prognostic value of bone involvement has only been reported once for atypical meningiomas.[14] Authors showed that bone involvement, including hyperostosis, was significantly associated with an increased P/R risk and decreased survival in patients with Grade II meningiomas. Bone involvement, however, is not universally accepted as a prognostic factor for high-grade meningioma recurrence.[3,28] Meningiomas are known to induce changes in bone adjacent to tumor, but it is unclear whether the phenomenon represents direct tumor invasion or secondary manifestation (hyperostosis), although increasing evidence points to direct tumor invasion into bone.[4,10,34] As with brain invasion, bone involvement's effect on P/R risk in high-grade meningiomas raises certain biological possibilities. Bone invasion (with or without brain infiltration) could represent a more aggressive tumor or could result from failure to resect or irradiate diseased bone. Regardless of the cause, the role of bone involvement with or without brain invasion could contribute to the mixed outcomes observed in high-grade meningiomas that histopathological grade alone often fails to predict.

The Ki-67 or MIB-1 index is an established determinant of proliferative activity. It has been shown in a number of studies that the Ki-67 index is an important prognostic factor and should be used in combination with histopathological grade to identify meningiomas with an increased risk of recurrence.[1–3,6,19,43] Our analyses demonstrate that the Ki-67 proliferative index is a strong predictor for P/R, but this finding should be interpreted cautiously in any individual tumor as there is often a considerable overlap of index values within and among meningioma grades.

A number of other factors we examined were not significantly associated with P/R risk, most notably Simpson

resection grade. In 1957, Simpson first asserted the importance of the extent of resection for meningiomas.[40] Subsequent studies showed that complete resection, when possible, was associated with longer survival and decreased rates of recurrence.[23,40,41] However, most of these studies were observational in nature and generally predated the widespread use of adjuvant radiation following surgery. More recent examinations of Simpson grading in prognosticating higher-grade meningioma P/R risk are mixed, with clear benefit of extent of resection on P/R risk when no adjuvant radiation was delivered.[18,31,44] Experiences with combined surgery and radiation therapy for high-grade meningiomas generally do not show any association between the extent of resection and progression-free survival, perhaps suggesting that adjuvant radiation therapy can compensate for less comprehensive resection.[2,12,13,16,17,32,35,42] Aghi and colleagues reported on 108 patients with Grade II meningiomas who had undergone gross-total resection in the period from 1993 to 2004.[2] The 60-month actuarial rate of recurrence in patients who did not receive adjuvant radiation therapy was 41% compared with 0% for patients treated with radiation therapy following surgery. Given the literature, it is not surprising that extent of resection was not significantly associated with P/R risk in our study as the entire patient cohort received adjuvant radiation therapy. We hope that in the near future, the Radiation Therapy Oncology Group (RTOG 0539) and European Organisation for Research and Treatment of Cancer (EORTC 22042–26042) trials will provide prospective data on the role of adjuvant radiation therapy for patients with atypical and malignant meningiomas.

We developed a multivariate model for stratifying high-grade meningioma patients into risk groups based on clinical and histological factors that were deemed significant on univariate analysis (Fig. 4). In this model, the low-risk group included patients with Grade II tumors and no additional risk factors. The intermediate-risk group consisted of patients with Grade II tumors and any combination of the risk factors of brain invasion, bone involvement, and/or a Ki-67 index at or above 3%. The high-risk group represented patients with Grade III tumors with any combination of the previously mentioned risk factors. The P/R rate in the low-risk and high-risk group was 2% and 56%, respectively, with the overall risk stratification highly significant ($p < 0.0001$). This model shows a stepwise progression between the 3 risk groups with discrete delineation and little overlap between the groups. Intuitively, stepwise progression of P/R observed in this model is consistent with our hypothesis that these risk factors are surrogates for underlying aggressive tumor biology as discussed above. However, we note that our ability to conclusively establish this relationship is limited by a relatively small sample size, leading to low statistical power and wide confidence intervals.

Higher-risk patients, including Grade II patients with any risk factor and Grade III patients, would most likely benefit from a more aggressive treatment approach, perhaps with additional surgery to maximally approach a Simpson Grade I resection and/or adjuvant radiation therapy. Low-risk patients such as those with Grade II tumors and no risk factors and perhaps those with Grade II tumors and a single risk factor may not benefit from such aggressive therapies, since these treatments also harbor risks, and may instead be best served by periodic clinical and imaging surveillance. In moderate-risk patients, other factors such as patient preference and patient performance status may be of particular importance in determining the relative risk/benefit ratio of additional treatment. As the WHO criteria have continued to evolve over time, they have become more prognostically accurate. Compared with the 1993 criteria, the 2007 version demonstrates statistically significant differences in progression-free survival between histological groups.[9] With the 2016 criteria now released, one would expect this trend to continue. As mentioned, the 2016 revision focuses primarily on identifying Grade I tumors that behave more like Grade II tumors. In a similar fashion, our study identifies the most aggressive Grade II tumors that may behave essentially as Grade III malignancies.

Our study has a number of limitations. It is a single-institution retrospective analysis with a modest sample size given the relative rarity of these high-grade tumors. Of the 26,000 new meningioma cases occurring annually in the United States, only approximately 10%–15% are Grade II and 1%–3% are Grade III.[7,26] Though we considered including patients diagnosed before 2007, we chose to limit our study to tumors that could be graded with certainty based on a relatively current WHO classification. One advantage of our single-institution study is that it allows for a more consistent diagnosis of these higher-grade meningiomas, avoiding the interinstitutional discrepancies that have been described elsewhere.[45] Going forward, the evaluation of genetic mutations will play an important role in stratifying patients into risk groups, and future studies should evaluate tumor specimens for meningioma-specific oncogenic alterations.

Conclusions

In summary, we present the largest study on atypical and malignant meningiomas in the modern post-2007 WHO classification era. We identified histopathological grade, brain invasion and/or bone involvement, and Ki-67 index as key prognostic factors in predicting P/R risk for WHO Grade II and III meningiomas. Using these factors, we developed a risk stratification model for P/R. Our findings should enhance future clinical treatment decisions and counseling of patients. Additionally, this study lays the foundation for future work aimed at better defining the clinical, pathological, and genomic features of Grade II tumors that are associated with aggressive behavior reminiscent of clinical Grade III tumors.

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Disclosures

Dr. Shih is a writer for UpToDate and served on the advisory board of Genentech until October 2016. Dr. Curry is a consultant for Stryker CMF. Dr. Oh has received research funding from from Merck & Co., Inc., and Elekta for non–study-related clinical or research effort and is a writer for UpToDate.

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