Preoperative and Histological Predictors of Recurrence and Survival in Atypical Meningioma After Initial Gross Total Resection

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■ OBJECTIVE: **Atypical (World Health Organization grade II) meningiomas (AMs) have been associated with a substantial risk of recurrence even after complete, gross total resection (GTR). The present study evaluated the clinical and AM tumor histopathological features that might predict for the risk of recurrence and survival within this patient population.**

■ METHODS: **The data from 72 consecutive patients who had undergone primary GTR for AM from 2007 to 2016 and corresponding tumor specimens at a single institution were reviewed. The preoperative patient and tumor characteristics were correlated with the post-resection outcomes, including recurrence and 1-year survival. Cox regression models on recurrence-free survival (RFS) and Kaplan-Meier survival estimates were performed.**

■ RESULTS: **The overall 1-, 3-, and 5-year RFS estimates for the AM cohort were 100.0%, 82.4%, and 78.1% after resection, respectively. A high mitotic index was an independent predictor of RFS on Cox regression analysis (hazard ratio, 1.26; $P = 0.008$), and the tumor volume showed a trend toward a significant association (hazard ratio, 0.93; $P = 0.079$). Patient age and the mitotic index were significantly associated with 1-year mortality (odds ratio, 1.11 and 1.36, respectively; $P = 0.028$ and $P = 0.045$, respectively).**

■ CONCLUSIONS: **AM tumors with a high proliferative index showed an increased likelihood of recurrence and short-term survival even after complete GTR. A smaller tumor volume might also have contributed to an increased risk of recurrence for patients with AM. Although other histopathological features were not linked to recurrence or mortality for patients with AM, the biopsy findings can indicate key predictive information, and further molecular analysis might reveal additional prognostic markers.**

INTRODUCTION

Meningiomas are one of the most common primary intracranial tumor in adults, accounting for one third of resected primary brain tumors.[1,2] The World Health Organization (WHO) has classified meningiomas into 3 grades: grade I, benign; grade II, atypical; and grade III, anaplastic. Compared with the most commonly encountered benign meningioma, atypical meningiomas (AMs) are more aggressive and have been associated with more rapid disease progression and morbidity, leading to poorer outcomes and decreased survival.[3-9]

After the WHO changed the classification system in 2007 such that otherwise benign meningiomas with the presence of brain invasion should be considered atypical, WHO grade II constituted one fifth or greater of meningiomas.[4-6,10] Therefore, the present study restricted the cohort to patients with AM resected after 2007

Key words
- Atypical meningioma
- Meningioma
- Recurrence
- Survival
- Tumor pathology

Abbreviations and Acronyms
AM: Atypical meningioma
GTR: Gross total resection
HPF: High-power field
HR: Hazard ratio
KPS: Karnofsky performance scale
OR: Odds ratio
RFS: Recurrence-free survival
RT: Radiotherapy
WHO: World Health Organization

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to align with the contemporary clinical standards. More recently, the WHO released its 2016 recommendations, which included brain invasion as a definite criterion for grade II classification.[11,12]

The primary management of AM involves surgical resection with or without adjuvant radiotherapy (RT). However, the utility of adjuvant RT remains controversial. Although many clinicians have advocated for adjuvant RT to enhance local control,[8,13-17] others have argued that the techniques for adjuvant RT did not improve the recurrence rates for AM after gross total resection (GTR).[7,18-21]

The rates of the AM tumor recurrence have approached 25%–45%, with recurrence typically with 2–4 years after the initial resection.[4-8,22-26] Tumor recurrence can be symptomatic and necessitate repeat surgery. One important predictor of recurrence is the extent of resection; residual portions after partial resection are much more likely to progress than after GTR.[3,5,6,9,10,19,24-29] Although cases in which tumor is adherent to critical structures or technically inaccessible will preclude complete resection, especially within the skull base, to minimize patient risks,[9,24,25] the present study was limited to GTR only (Simpson resection grade ≤3)[30] to identify other important prognostic factors of AM recurrence.

In the present study, we retrospectively analyzed our center's experience with AM resection and treatment during a 10-year period to evaluate the prognostic factors of long-term clinical outcomes after complete initial resection. The analysis focused on the presenting characteristics, radiological and pathological tumor features, and treatment paradigm as important determinants of postoperative recurrence risk, functionality, and clinical course. Although recent studies have focused on the prognostic aspects of the AM treatment modality, the present study analyzed data from one of the largest cohorts of patients with AM to date, with a focus on the tumor histopathological features.

METHODS

Patient and Tumor Characteristics

The medical center's institutional review board approved the present single-center retrospective analysis. A total of 910 patients had undergone primary intracranial meningioma resection from 2007 to 2016. Of these 910 patients, 89 had a meningioma deemed to be WHO grade II on histopathological examination. Of these tumors, 75 (84%) had undergone GTR (Simpson grade ≤3) and 14 (16%) subtotal resection (Simpson grade ≥4). The latter 14 were, therefore, excluded.[30] Resection was performed by craniotomy using standard surgical approaches to achieve GTR (e.g., frontal craniotomy for an anterior parasagittal lesion, pterional craniotomy for a sphenoid skull base lesion). However, the exact surgical approaches were dependent on the various tumor- and patient-specific factors. Complete GTR was confirmed from the postoperative imaging studies. Three patients who had undergone GTR were excluded because of incomplete records. The resulting final cohort consisted of 72 patients who had undergone GTR of a primary intracranial AM (**Table 1**).

Table 1. Patient- and Tumor-Specific Characteristics ($n = 72$)

Characteristic	Atypical (WHO Grade II)
Patient specific	
Gender	
Female	45 (62.5)
Male	27 (37.5)
Age (years)	61.8 ± 13.9
Preoperative functional status (KPS score)	77.9 ± 8.5
Preoperative KPS score	
≤70	26 (36.1)
≥80	46 (63.9)
Presenting symptom	
Headache	25 (34.7)
Seizure	19 (26.4)
Gait instability	18 (25.0)
Weakness	11 (15.3)
Vision changes	10 (13.9)
Language dysfunction	9 (12.5)
Mental status change	8 (11.1)
Loss of consciousness	6 (8.3)
None	5 (6.9)
Tumor specific	
Tumor location	
Skull base	19 (26.4)
CPF	51 (70.8)
Intraventricular	2 (2.8)
Tumor volume (cm^3)	29.5 ± 33.1
Vasogenic edema	46 (63.9)
Previous radiotherapy	1 (1.4)
Simpson resection grade	
1	5 (6.9)
2	61 (84.7)
3	6 (8.3)
4–5	0 (0.0)

Data presented as *n* (%) or mean ± standard deviation.
WHO, World Health Organization; KPS, Karnofsky performance scale; CPF, convexity, parasagittal, or falcine.

Pathological Review

In accordance with the WHO guidelines, the histological features necessary for AM classification included 4–19 mitotic figures per 10 high-power field (HPF), a chordoid or clear cell subtype, invasion into adjacent brain parenchyma, or ≥3 of 1) increased cellularity, 2) small cell change, 3) sheet-like growth, 4) prominent nucleoli, and 5) a necrotic focus.[11,12] Mitoses were counted in 10 consecutive HPF in the area with the most prominent mitotic activity. Spontaneous necrosis was assessed as present or absent. Brain invasion was defined as irregular projections of tumor into the surrounding brain parenchyma and without an intervening

layer of leptomeninges. Displaying 3 of the 5 features of small cell change, prominent nucleoli, hypercellularity, spontaneous necrosis, or a sheet-like growth pattern, were also classified as atypical.[11] In addition, clear cell and chordoid histologic subtypes were considered WHO grade II (atypical). Furthermore, for some cases, the Ki-67 proliferation index was determined at the time of the original diagnosis. Progesterone receptor immunostaining was also performed for some cases at the examination.

Clinical Outcomes

The postoperative clinical outcomes collected included functional status at the first and most recent follow-up evaluation, measured by the Karnofsky performance scale (KPS) score,[31] 1-year mortality, and tumor recurrence. The interval from primary resection to tumor recurrence, death, or last known follow-up evaluation was recorded.

Statistical Analysis

Analysis of each measured preoperative and histological factor was performed by univariate analysis using χ^2 or independent samples t tests, as appropriate. Factors suggestive of at least a trend-level association with tumor recurrence ($P \leq 0.25$) on univariate analysis were included as covariates in a further multivariate logistic regression analysis of tumor recurrence or 1-year survival.[32] Univariate and multivariate Cox regression analyses on recurrence-free survival (RFS) were similarly performed for the patient and tumor characteristics. The survival estimates were analyzed using the Kaplan-Meier method and were evaluated with log-rank tests to compare RFS stratified by the patient and tumor factors. The results of univariate and multivariate analyses were summarized using odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals. A P value < 0.05 was considered statistically significant. Analyses were completed using the statistical package SPSS, version 22.0 (IBM Corp., Armonk, New York, USA).

RESULTS

Patient and Tumor Characteristics

Patient demographics, imaging features, and tumor characteristics stratified by the relative distribution are depicted in Table 1. The sample included mostly women (62.5%), with a mean age of 61.8 ± 13.9 years. The average preoperative KPS functional score was 77.9 ± 8.5, and the most common presenting symptom was headaches (34.7%), followed by seizure (26.4%), and gait instability (25.0%). Most meningiomas were located in the convexity, parasagittal, or falcine areas (70.8%), with 26.4% in skull base regions and 2.8% intraventricular. The mean tumor volume was 29.5 ± 33.1 cm^3 (range, 1.0–196.2). Most cases of AM presented with vasogenic edema (63.9%). One patient (1.4%) had undergone preoperative RT.

Histopathological Features

The histological patterns for original AM specimens after primary resection are shown in Table 2. Six of the WHO grade II tumors (8.3%) were classified as clear cell, 1 (1.4%) as chordoid, and 65 (90.3%) as atypical because of the presence of atypical histologic features, mitotic count, or brain invasion. The mean mitotic count per 10 HPF was 3.3 ± 3.5 mitoses, with 44.4% having ≥4 mitotic figures. The mean Ki-67 immunostaining, for those with data available (46%), was 14.6% ± 9.8%. For AM tumors for which progesterone receptor testing was performed (29%), 100% were positive. Almost one half (47.2%) of AM tumors had brain invasion, 9.7% had dura infiltration, and 5.6% had bone infiltration. For specific pathologic features, 22.2% of the AM cases had pleomorphic nuclei, 16.7% had small cell changes, 37.5% had increased cellularity, 27.8% had prominent macronucleoli, about one quarter (26.4%) had sheet-like growth patterns, and almost one half (44.4%) had focal necrosis on examination (Figure 1).

Table 2. Histopathological Features of Atypical Meningiomas After Initial Resection ($n = 72$)

Histopathological Feature	Atypical (WHO Grade II)
Histological subtype	
Atypical	65 (90.3)
Clear cell	6 (8.3)
Chordoid	1 (1.4)
Mitotic count (per 10 HPF)	3.3 ± 3.5
Patients with mitotic count ≥4	32 (44.4)
Ki-67/MIB-1 (%)*	14.6 ± 9.8
Progesterone receptor	
Positive	21 (100.0)
Untested	51 (70.8)
Pathological finding	
Brain invasion	34 (47.2)
Dura infiltration	7 (9.7)
Bone infiltration	4 (5.6)
Nuclear pleomorphism	16 (22.2)
Small cell change	12 (16.7)
Hypercellularity	27 (37.5)
Prominent nucleoli	20 (27.8)
Sheet-like growth	19 (26.4)
Necrosis	32 (44.4)

Data presented as *n* (%) or mean ± standard deviation.
WHO, World Health Organization; HPF, high-power field.
*Ki-67 staining results available for 33 patients.

Clinical Outcomes

The postoperative clinical outcomes after primary AM resection are reported in Table 3. At the initial follow-up evaluation after surgical resection, the mean KPS functional status was 77.4 ± 25.6, which was sustained to a mean of 78.5 ± 28.7 at the last follow-up examination. Specifically, 19.4% showed a decrease in functional status at the immediate postoperative follow-up examination and 25.0% had done so at the last known follow-up evaluation. At the postoperative follow-up examination, only a presentation with gait instability or cardiovascular disease comorbidity were associated with a decrease in the KPS score on

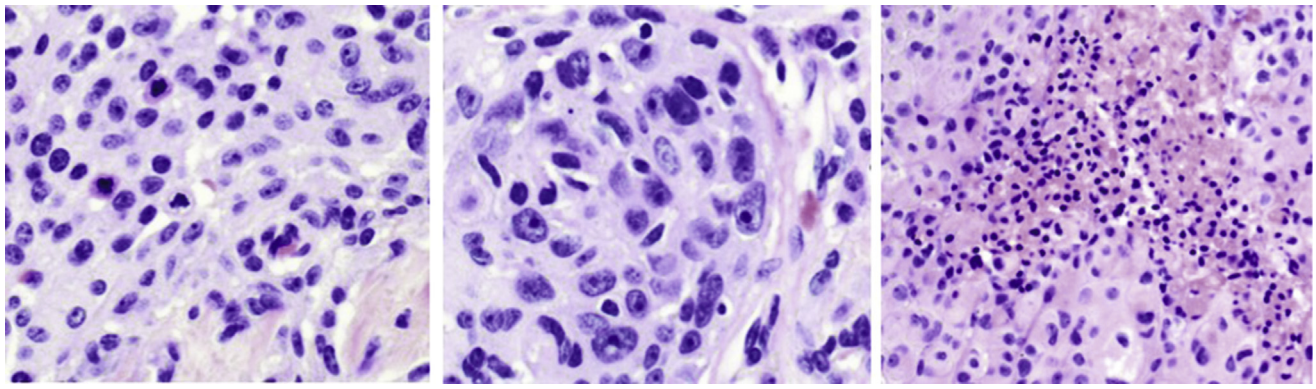

Figure 1. Representative sections from resected atypical meningiomas stained with hematoxylin and eosin showing (**Left**) a high mitotic index (9 per 10 high-powered fields) with a corresponding Ki-67 of 26% (data not shown) on immunohistochemistry stain (×40), (**Middle**) numerous prominent nucleoli (×40), and (**Right**) an area of spontaneous necrosis (×20).

Table 3. Clinical Outcomes After Initial Atypical Meningioma Resection ($n = 72$)

Clinical Outcome	Atypical (WHO Grade II)
Postoperative functional status (KPS score)	77.4 ± 25.3
Postoperative KPS score	
≤70	16 (22.2)
≥80	56 (77.8)
Decreased KPS score relative to preoperatively	14 (19.4)
Functional status at last follow-up (KPS score)	78.5 (28.7)
Last KPS score	
≤70	18 (25.0)
≥80	54 (75.0)
Decreased KPS score relative to preoperatively	18 (25.0)
Adjuvant radiotherapy	
SRS	7 (9.7)
EBRT	3 (4.2)
Recurrence	9 (12.5)
Interval to recurrence (years)	
Mean ± SD	2.9 ± 1.8
Range	1.5–7.5
1-Year mortality	7 (9.7)
Status at last follow-up	
Alive	49 (68.1)
Dead	15 (20.8)
Unknown/lost to follow-up	8 (11.1)

Data presented as *n* (%) or mean ± SD.
WHO, World Health Organization; KPS, Karnofsky performance scale; SRS, stereotactic radiosurgery; EBRT, external beam radiation therapy; SD, standard deviation.

univariate analysis, and gait instability was the only independent predictor of a decreased KPS score at postoperative follow-up on multivariate analysis (OR, 6.13; $P = 0.005$). At the last known follow-up evaluation, both a presentation with gait instability and a presentation with weakness were associated with a decrease in the KPS score on univariate analysis. However, the only weakness was found to be an independent predictor of decreased functional status at the most recent follow-up examination on multivariate analysis (OR, 4.69; $P = 0.024$).

Ten patients (13.9%) had undergone adjuvant RT after initial resection, either stereotactic radiosurgery (9.7%) or external beam RT (4.2%) at a median of 4.5 months (interquartile range [IQR], 2.8–9.8) after resection. At the completion of the present study, 9 patients (12.5%) had developed tumor recurrence, and 8 had undergone a second surgery. The mean interval from primary resection to the discovery of recurrence was 2.9 ± 1.8 years (range, 1.5–7.5). The median length of follow-up for the cohort was 2.5 years (IQR, 1.4–4.5) and was 6.1 years (IQR, 1.4–7.6) for patients with recurrence.

Seven patients (9.7%) had died within 12 months after complete AM resection of any cause, 2 of neurovascular complications in the weeks after resection, and 5 of nonrelated medical causes. At the last follow-up point, 68.1% of the patients were known to be alive, 20.8% had died, and 11.1% had an unknown status or had been lost to follow-up. Of the ~20% of patients in the cohort known to have died, most had died of medical causes unrelated to tumor burden or progression, including other metastatic cancer or cardiovascular disease. Postoperative complications were noted in 6 patients (8.3%) and included postoperative cardiac arrhythmias, urinary retention, thrombocytopenia, and wound infection.

Factors Associated with Tumor Recurrence

On univariate analysis for factors associated with tumor recurrence after primary AM resection, no patient or tumor characteristic was found to correlate with recurrence. Only tumor volume showed a trend toward significance ($P = 0.072$; Table 4) with the tumor volume inversely related to recurrence. No tumors >30.5 cm^3

Table 4. Univariate and Multivariate Regression Analyses of Tumor Recurrence ($n = 72$)

	Univariate			Multivariate		
Characteristic	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Tumor size	0.95	0.89–1.01	0.072	0.94	0.87–1.00	0.064
Preoperative functional status (KPS score ≥80)	0.40	0.10–1.65	0.20	0.43	0.10–1.93	0.35
Histopathology (mitotic index)	1.12	0.94–1.33	0.21	1.16	0.96–1.40	0.13

OR, odds ratio; CI, confidence interval; KPS, Karnofsky performance scale.

recurred. Multivariate analysis demonstrated that although the tumor volume had approached significance as an independent predictor of recurrence for patients with AM (OR, 0.94; P = 0.064), the difference was not statistically significant.

On Cox regression analysis for RFS (Table 5), a higher mitotic index (HR, 1.21; P = 0.002) was associated with shorter RFS on univariate analysis. Tumor volume and lower preoperative functional status were included in the multivariate Cox regression. The multivariate Cox model demonstrated that only the mitotic index was an independent predictor of decreased RFS (HR, 1.26; P = 0.008). When the Cox regression analysis for RFS was repeated after excluding those who had undergone postoperative adjuvant RT (10 patients), a higher mitotic index remained an independent predictor of decreased RFS (HR, 1.62; P = 0.002).

The overall RFS for the AM patient cohort is shown in Figure 2. The overall 1-, 2-, 3-, 5-, and 7-year estimates for RFS were 100.0%, 92.0%, 82.4%, 78.1%, and 65.1% respectively. For each factor found to be associated with RFS on at least a trend level, the comparative Kaplan-Meier plots are shown in Figure 2.

Factors Associated with 1-Year Mortality

Age at presentation and the mitotic index correlated with 1-year survival on univariate analysis after primary AM resection (OR, 1.11 and 1.38; P = 0.006 and P = 0.003, respectively; Table 6). Prominent nucleoli and necrosis found on pathological examination were included in the multivariate analysis. Age at presentation and mitotic index were independent predictors of 1-year mortality for patients with AM (OR, 1.11 and 1.36; P = 0.028 and P = 0.045, respectively). Excluding those who had undergone adjuvant RT, only age at presentation remained a significant independent predictor of 1-year mortality, although the mitotic index was at the trend level (OR, 1.19 and 1.44; P = 0.012 and P = 0.091, respectively).

DISCUSSION

In a single-center review of 72 patients with AM who had undergone complete primary resection during a 10-year period, we adjusted for preoperative characteristics, treatment patterns, and tumor pathology in determining the significant predictors of tumor recurrence or 1-year survival. Patients with a higher mitotic index on pathological examination experienced shorter intervals to recurrence. AMs with a smaller volume showed a trend toward being significantly more likely to recur. Furthermore, although patient age predicted the 1-year mortality, the mitotic index also predicted for short-term survival. These findings strengthen previous evidence of the prognostic factors for WHO grade II meningiomas and emphasize the role of histopathological risk factors in the timing and presentation of recurrent tumors.

Overall, the vast majority of our patients with AM remained recurrence free for up to a few years after initial resection, with an almost two-thirds chance of being recurrence free >7 years after initial GTR (Figure 2). Previous studies of AM clinical outcomes have similarly estimated RFS to range from 84% to 93% at 1 year, 65% to 80% at 3 years, and 30% to 86% at 5 years.[4,5,7,9,13,19,24-26,33] Furthermore, the present sample was comparable in demographic distribution to previous studies of AM, which also reported a slight majority female representation, with average age of 54–60 years.[6,8,9,19,23,25,26] A large epidemiological study from 2010 to 2014 of population-level brain tumors similarly reported a greater incidence of women with a median age

Table 5. Univariate and Multivariate Cox Regression Analyses of Recurrence-Free Survival ($n = 72$)

	Univariate			Multivariate		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Tumor size	0.96	0.91–1.01	0.13	0.93	0.86–1.01	0.079
Preoperative functional status (KPS score ≥80)	0.35	0.08–1.49	0.16	0.47	0.10–2.13	0.33
Histopathology (mitotic index)	1.21	1.03–1.42	0.002	1.26	1.06–1.50	0.008

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance scale.

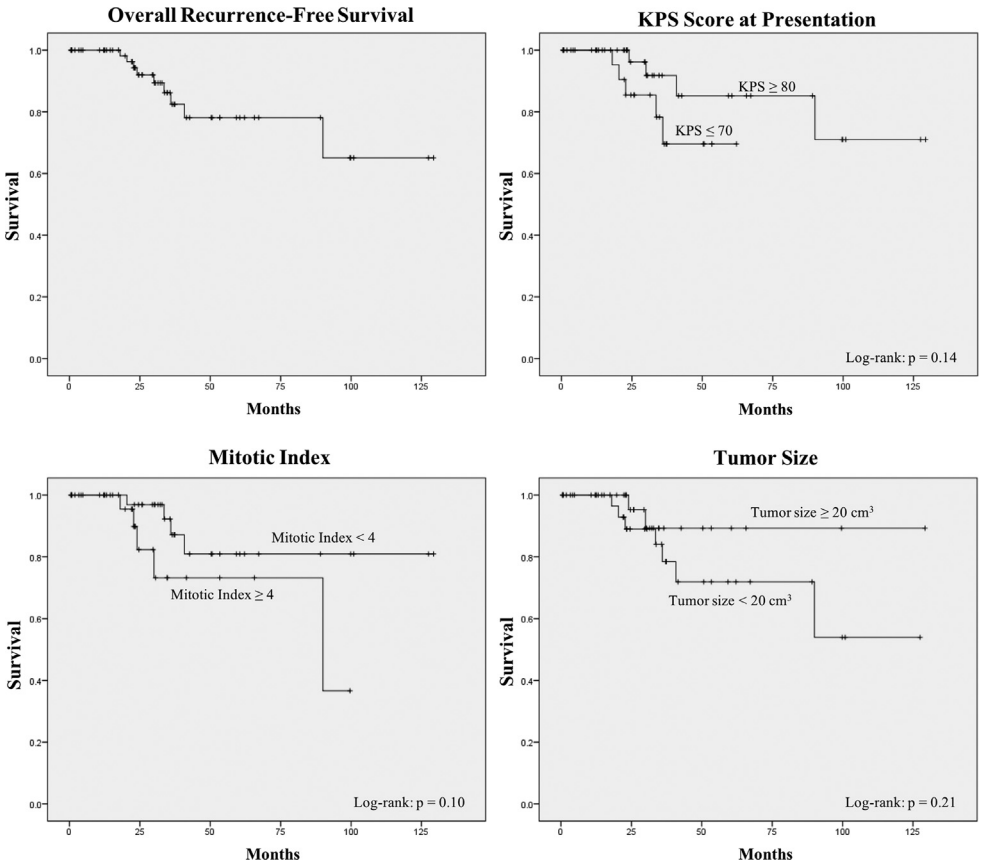

Figure 2. Kaplan-Meier recurrence-free survival curves for (**Top Left**) overall cohort and comparisons stratified by (**Top Right**) Karnofsky performance scale (KPS) score at presentation, (**Bottom Left**) mitotic index, and (**Bottom Right**) tumor volume. Comparisons were made using log-rank tests.

of incidence at 65 years for high-grade meningiomas.[1] Of those that evaluated functional status, a comparable level of functionality at presentation was noted,[3,4,9,13,24] and the most common symptoms were headaches, seizures, and motor deficits.[4-6,23-26]

Tumor Characteristics

Most AMs were located in the convexity, parasagittal, or falcine regions relative to the skull base, which has similarly been reported in previous studies.[4,6-10,13,19,23-26,29,33] Location was not associated with recurrence or 1-year survival in the present cohort

Table 6. Univariate and Multivariate Regression Analyses of 1-Year Mortality ($n = 64$)*

	Univariate			Multivariate		
Characteristic	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Age at presentation	1.11	1.03—1.20	0.006	1.11	1.01—1.21	0.028
Histopathological finding						
Mitotic index	1.38	1.11—1.71	0.003	1.36	1.01—1.84	0.045
Prominent nucleoli	2.50	0.56—11.2	0.23	2.06	0.30—14.2	0.46
Necrosis	4.00	0.74—21.6	0.11	1.76	0.22—13.9	0.59

OR, odds ratio; CI, confidence interval.
*Eight patients had an unknown vital status or had been lost to follow-up.

($P = 0.70$ and $P = 0.68$, respectively). Additionally, although the frequency of a presentation with vasogenic edema in our AM cohort was consistent with that in previous studies, it was not found to be associated with recurrence.[5,23,25,29]

In our study, a smaller AM tumor volume showed a trend toward significantly increasing the risk of recurrence after initial complete resection. A larger sample size might have revealed the true relationship. Kano et al.[34] similarly reported an increased incidence of recurrence for smaller size tumors. However, this finding is in contrast to that of other previous studies, which reported that a smaller AM tumor size was protective against recurrence,[35-37] although the overall tumor volumes in the present study were comparable.[26] Of note, 39% of the smaller volume tumors were located in skull base regions compared with only 14% of the larger volume tumors ($P = 0.030$). Thus, it is likely the increased recurrence resulted from the nature of the skull base lesions. However, tumor volume has infrequently been included in analyses of recurrence factors in previous studies, and the inclusion of this important preoperative factor in future studies might uncover a definitive relationship with recurrence risk.[38]

Histopathological Features

In 2007, the WHO criteria for grade II meningiomas included the presence of brain invasion, a high mitotic rate, or 3 of 5 key histological features consisting of increased cellularity, small cell change, sheet-like growth, macronucleoli, and focal necrosis.[11] Although these features have been shown to be associated with the risk of tumor recurrence relative to the more benign WHO grade I tumor category, the present study only identified mitotic index as a predictor of recurrence or RFS within completely resected WHO grade II tumors. The mitotic index is a direct indicator of cell proliferation, which is a strong predictor of tumor behavior.[12] Each additional mitotic figure per 10 HPF was associated with a 26% increase in recurrence risk (**Table 5**). In addition to Ki-67, an immunohistochemical marker of cell proliferation, mitotic markers have been associated with tumor recurrence and the timing of recurrence in previous studies of AM.[4,6,9,19,23,29,33,39] Klinger et al.[6] recently reported that AM with $\geq$4 mitotic figures per 10 HPF was associated with decreased RFS compared with AM with a low mitotic index.

However, multiple previous studies have reported prominent nucleoli, sheet-like growth, cellular atypia, necrosis, and/or nuclear pleomorphism as increasing the risk of recurrence for patient with AM, which were not found in the present study.[13,19,23,29] For example, Aghi et al.[13] reported prominent nucleoli on pathological examination to be associated with twice the risk of recurrence relative to the presence of typical nucleoli. Lee et al.[19] found focal necrosis to be associated with a sixfold risk of recurrence. Moreover, tumor invasion into the brain parenchyma has been linked to recurrence in previous studies of AM; however, this finding was not replicated in the present cohort.[3,23,26,33] This might have resulted from other treatment and histological features, within an adjusted analysis of patients with AM, being more significant determinants of recurrence than brain invasion.

Role of RT

The present analysis did not find any effect of adjuvant RT after GTR on recurrence or 1-year mortality. Although some previous studies have reported similar findings,[20,21,33] numerous others have demonstrated a beneficial role for adjuvant RT after GTR in decreasing the recurrence risk and providing improved tumor control.[8,13,27,29,38,40-43] In the present study, only 14% of patients had undergone adjuvant RT, because patients will usually be observed conservatively at our institution before implementing adjuvant RT. The decision to administer adjuvant RT is left to the discretion of the operating surgeon if they suspect the tumor to be aggressive by presentation or pathological examination. Of the 10 patients who received adjuvant RT, 8 had received postoperative RT and 2 had undergone RT at tumor recurrence. However, the choice to administer adjuvant RT was not related to the mitotic index or Ki-67 of the primary tumor ($P = 0.25$ and $P = 0.82$, respectively). A larger sample or longer follow-up period might have provided more informative findings. Additionally, because only a few patients had undergone RT, analyses of the RT modality (external beam RT or stereotactic radiosurgery) and dose were not assessed but should be incorporated into further studies examining the role of RT in managing AM. At present, open randomized clinical trials (e.g., NCT03180268 and ROAM/EORTC-1308) are investigating the utility of RT after AM resection.[44]

One-Year Mortality

Age at presentation and the mitotic index were strongly associated with 1-year mortality (**Table 6**). Although older patients can be expected to have increased mortality compared with younger patients, the mitotic index also predicted for short-term mortality after resection. Multiple previous studies have linked a high proliferative index on histological examination with the risk of early death.[4,6,23,26] Champeaux et al.[26] reported twice the risk to overall survival for AM tumors with >4 mitotic figures per 10 HPF relative to those with fewer. Thus, mitotic behavior might serve as a significant prognostic factor of survival that should be considered in patients with AM.

Other histological features, such as prominent nucleoli and necrosis, found to contribute to survival in previous studies,[4,23] were included in the multivariate analysis. However, they were not associated with 1-year survival. Vranic et al.[23] reported a 2.6 greater risk to overall survival for patients with prominent nucleoli in a study of WHO grade II and III meningiomas. However, larger studies are needed to determine whether these characteristics contribute to risk of mortality for patients with AM.

Postoperative Functional Status

At the immediate postoperative follow-up and last follow-up examinations, 19% and 25% of patients demonstrated a decrease in functional status, respectively (**Table 3**). However, on multivariate analysis, only gait instability and weakness on presentation were independent factors of functional status at the immediate postoperative and last follow-up examination, respectively. The mitotic index and tumor volume were not associated with a decrease in functional status ($P > 0.25$ for both). It is likely that patients with meningiomas that resulted in a presentation with gait instability and weakness will have a more difficult postoperative rehabilitation course, leading to overall decreased functionality, regardless of tumor aggressiveness or size.[45] Furthermore, although a recent study of patients with AM found

a significant difference in postoperative functional status between patients with and without a subsequent recurrence, the present cohort did not find any differences either immediately postoperatively or at the last known follow-up evaluation ($P > 0.6$ for both).

Future Directions

Although radiological and histopathological tumor features have been consistently associated with recurrence risk in patients AM, a molecular genomic analysis of tumor specimens might reveal distinct genetic markers of recurrence and survival risk. Previous molecular genomic studies have demonstrated that chromosomal losses of tumor suppressor genes such as 1p, 9p, 10q, and 14q deletions are more common in AM and might relate to the clinical outcomes.[46-48] For example, genetic variations on chromosome 1p have been associated with short progression-free survival for patients with AM.[49] In addition, TERT (telomerase reverse transcriptase) promoter mutations on chromosome 5 have been associated with more frequent recurrences in WHO grade II and III tumors and might represent a significant prognostic genetic marker.[50-52] Therefore, it is crucial that genomic profiling for additional prognostic and potential therapeutic markers in future studies be conducted to help delineate patients with AM who are the greatest risk of recurrence or poor clinical outcomes.

Study Limitations

The present study had several limitations, including its retrospective nature and associated biases in design. Although one of the largest single-center cohorts of AMs that have undergone GTR to date, the study was still limited by small numbers, especially when classified into subgroups for analysis, and was subjected to a wide range of follow-up lengths, which can diminish the optimal characterization of tumor recurrence. Moreover, although 14% of the patients had undergone adjuvant RT, no consistent protocol was in place for RT type or dose in the present study. Further studies and clinical trials are exploring the specific effects of adjuvant RT on recurrence and survival. One limitation of histopathological assessment is the subjectivity in tumor classification. Although official standards are available to classify tumors, it has been shown that interobserver reproducibility can remain suboptimal.[53] Overall, the present study was bounded by clinical limitations, and the interpretations were formed from the best available information.

CONCLUSION

Total resection of WHO grade II meningiomas should be attempted for the best chance of the patient remaining recurrence free. Although most histopathological features were not found to be determinants of recurrence within our AM cohort, a high mitotic index was associated with reduced RFS and contributed to short-term mortality in our center's experience, remaining an important prognostic marker of disease progression and postoperative outcomes. The findings from the present study upheld that tumor volume could have a role in recurrence risk within AM tumors. Thus, patients with AM and evidence of extensive mitotic activity on pathological examination should be closely monitored for signs of recurrence after initial GTR whether or not subsequent RT is performed.

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