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RESEARCH

Histopathologic risk factors for progression of atypical meningioma: a retrospective cohort study evaluating the impact and clinical value of mitotic count and Ki-67

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Abstract

Purpose Given the heterogeneity of atypical meningioma (AM) and potential interobserver variability in WHO grade assignment among pathologists, there is a need for more objective criteria to improve risk stratification. This study examined conventional and novel risk factors for AM progression, focusing on mitotic count (MC) and Ki-67, and explored their clinical relevance.

Methods This retrospective cohort study included 240 consecutive patients with AM surgically treated at a single tertiary institution between 2001 and 2020. The cut-off values for MC and Ki-67 were determined using the Youden index. Risk factors for progression were analyzed using cause-specific Cox proportional hazards models. Progression-free survival (PFS) was estimated using cumulative incidence function (CIF) and compared using the Gray's test.

Results AM progression occurred in 32.5% of patients with a median time to progression of 25.2 months. The median follow-up was 42.3 months. While a clinically meaningful Ki-67 cut-off was not identified, MC ≥ 6 was significantly associated with AM progression. On multivariate analysis, age, gross total resection (GTR), MC ≥ 6, brain invasion, sheeting, and adjuvant radiotherapy (RTx) were associated with progression. RTx improved PFS in the subtotal resection (STR) group but not in the GTR group. Among GTR patients, those with MC ≥ 6 had worse outcomes.

Conclusion GTR and RTx may reduce the progression of AM. MC ≥ 6 significantly increases the risk of progression, even in GTR patients. RTx should be considered for all STR patients A more vigilant follow-up or consideration of RTx is warranted in GTR patients when a high MC is identified.

Keywords Atypical meningioma · Recurrence · Progression-free survival · Ki-67 · Mitotic count · Radiotherapy

Abbreviations

AIC	Akaike Information Criterion
AM	Atypical meningioma
AUC	Area under the curve
C-Index	C oncordance index
EOR	Extent of resection
GKS	Gamma knife surgery
GTR	Gross total resection
HPF	High power field
HR	Hazard ratio
MC	Mitotic count
MRI	Magnetic resonance imaging
N/C	Nucleus-to-cytoplasm
PFS	Progression-free survival
PHH3	Phosphohistone-H3
RECIST	Response Evaluation Criteria in Solid Tumors
RTx	Adjuvant radiotherapy
SD	Standard deviation
STR	Subtotal resection
WHO	World Health Organization

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Introduction

Meningiomas are the most common primary central nervous system tumors accounting for 41.7%–42.9% of cases [9, 44]. Atypical meningiomas (AM) are WHO grade 2 tumors representing 15%–20% of all meningiomas [58] with the incidence of AM reported to have increased in recent years [45]. The diagnostic criteria for AM have evolved over time [8] with a significant change in 2016 when brain invasion was introduced as one of the diagnostic histopathologic features [33]. The latest 2021 WHO classification defines AM by one or more of the following criteria: a mitotic count (MC) of 4–19/10 in 10 consecutive high-power field (HPF) of each 0.16 mm^2, brain invasion, chordoid or clear cell histology, or at least three of five histologic features—spontaneous or geographic necrosis, prominent nucleoli, high cellularity, small cells with a high nucleus-to-cytoplasm (N/C) ratio, and sheeting [59].

AM is primarily treated with maximal safe resection, while the role of adjuvant RTx remains under investigation, particularly in cases of GTR [43]. Despite a high GTR rate, AM has a relatively high local recurrence rate of 30%–40% [1, 37] with a median time to progression of two years [7]. Recurrence of AM has been shown to be associated with morbidity, reduced survival, and additional treatment burden [27, 48]. Therefore, identifying prognostic factors for AM progression is crucial for risk stratification and treatment optimization.

Several risk factors for AM progression have been reported, with extent of resection (EOR) being one of the most important factors [10, 47]. However, previous studies exploring risk factors of AM progression have been limited by small sample sizes, short follow-up periods and mixed results [23]. Additionally, notable heterogeneity within AM and interobserver variability in WHO grading of meningiomas among pathologists [46] highlight the need for additional objective criteria, such as refined MC thresholds and the Ki-67 index, to improve risk stratification. This study aims to evaluate risk factors for AM progression, with a particular focus on MC and Ki-67, and to explore the potential clinical implications of these findings for improving patient outcomes.

Materials and methods

Study design

This was a retrospective cohort study of AM patients who underwent primary surgical resection between 2001 and 2022 at a single tertiary institution in the Republic of Korea (Seoul National University Hospital). A total of 323 consecutive AM cases were identified, of which 83 were excluded due to missing follow-up brain imaging. Consequently, 240 AM patients were included in the final cohort. No formal sample size calculation was performed and all eligible patients were included to maximize statistical power. All pathological reports were reviewed to confirm that the included cases met the latest 2021 WHO diagnostic criteria for AM. Clinical and histopathological variables were collected from electronic medical records, pathology reports and radiology archives. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB: 2505–039–1638).

Clinical and histopathological variables

Clinical variables assessed included age, sex, tumor size (maximum diameter on preoperative MRI), and tumor location (convexity, falx/parasagittal, skull base, or other). The EOR was categorized as either gross total resection (GTR) or subtotal resection (STR). GTR was defined as complete macroscopic tumor removal with or without resection/coagulation of dural attachment or abnormal extradural extensions, consistent with Simpson grades 1–3 [54]. STR was defined by residual enhancing tumor on immediate postoperative MRI taken within 48 h of surgery. Postoperative MRI and operative records were collectively reviewed to ensure accurate categorization.

As the cohort spanned 21 years, temporal variation was considered. Surgery period was categorized into two groups (2001–2011 and 2012–2022), and baseline characteristics and AM progression rate were compared between the two groups. Surgery period was also included as a covariate in the cause-specific Cox regression model to account for potential temporal effects.

Histopathologic features defining AM, including brain invasion, spontaneous necrosis, prominent nucleoli, high cellularity, small cells with a high N/C ratio, and sheeting were assessed by neuro-pathologists. Brain invasion was defined as irregular, tongue-like protrusions of tumor cells into underlying parenchyma without intervening leptomeninges. Spontaneous necrosis was identified when necrotic foci were clearly separated from viable tumor tissue. Prominent nucleoli were those visible under a 10 × objective lens in ≥ 50% of the sample. High cellularity was defined as more than 53 nuclei per HPF (0.16 mm^2). Small cells were identified as tumor cells with lymphocyte-like morphology. Sheeting was defined as the absence of whorls, lobules, syncytia, or small aggregates in at least 50% of the sample. MC was defined as the number of mitotic figures per 10 consecutive HPF of each 0.16 mm^2 in the most mitotically active area. Phosphohistone-H3 (PHH3) immunostaining (1:100, Cell Marque, Rocklin, CA, USA) was used to distinguish mitotic

figures in some problematic situations to ensure accurate measurement of MC. The Ki-67 proliferation index (1:100, mAb MIB-1; Dako, Glostrup, Denmark) was quantified using an automated cell counting algorithm on a Sectra IDS7 viewer (Sectra AB, Linköping, Sweden) from virtually scanned slides (Aperio AT2; Leica Biosystems, Wetzlar, Germany).

Follow up and RTx

All patients underwent postoperative MRI within 48 h of surgery. Those without immediate postoperative imaging were excluded from the cohort, as the EOR could not be accurately assessed. Active surveillance was performed with serial MRI at approximately 6–12-month intervals, with shorter intervals implemented as needed, particularly in cases of STR. Tumor progression was defined as local recurrence of any size in the GTR group. In the STR group, it was defined using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria [17] as an interval increase of more than 20% in the residual tumor size. Progression-free survival (PFS) was measured from the date of surgery to radiographic recurrence or was censored at the last follow-up imaging if no recurrence was observed.

RTx was defined as treatment within one year of surgery in the absence of tumor progression. The decision to use RTx, including gamma knife radiosurgery (GKS) or conventional fractionated radiotherapy, was based on the EOR and histopathologic findings determined by the surgeon and radiation oncologist.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. Comparisons between categorical variables were conducted using the Chi-squared test or Fisher's exact test as appropriate. The Shapiro–Wilk test was applied to assess the normality of continuous data. Comparisons between continuous variables were performed using either the independent t-test or the Wilcoxon rank-sum test, depending on data distribution. Univariable and multivariable cause-specific Cox proportional hazards models were fitted to evaluate risk factors for progression of AM after surgical resection. Death was treated as a competing event. Covariates associated with progression in univariable analyses were considered for the multivariable model. Backward elimination was applied to obtain the most parsimonious model, while clinically relevant variables were retained regardless of statistical significance. Model performance was evaluated using the concordance index (C-index) for discrimination and the Akaike Information Criterion (AIC) for relative fit. All Cox models included RTx as a time-dependent covariate to account for the influence of RTx timing on AM progression.

The proportional hazards assumption was verified using Schoenfeld residuals. Cumulative incidence functions (CIFs) for progression and death without progression were estimated, and group comparisons were performed with Gray's test. Analyses were performed using SAS version 9.4 (SAS Institute) and R version 4.3.1 (R Project for Statistical Computing). A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics and clinical outcome

The demographic and clinical characteristics of the patients are summarized in Table 1. A total of 240 AM cases were included in the final cohort comprised of 143 females and 97 males with a mean age of 53.8 years (*SD*: 14 years). The median follow-up duration was 42.3 months (range: 0.8–218.8 months). The mean tumor size was 46.7 mm (*SD*: 15.6 mm), with convexity being the most common tumor location ($N = 88$, 36.7%). GTR was achieved in 175 patients.

Tumor progression occurred in 78 patients (32.5%), with a median time to progression of 25.2 months (range: 3.2–118.5 months). Compared to the non-progression group, the progression group had significantly larger tumors (50.6 mm vs 44.8 mm, $p = 0.007$), lower GTR rate (56.4% vs 80.9%, $p = 0.0001$) higher MC (7.5 vs 5.9, $p < 0.0001$), and a greater proportion of sheeting (29.5% vs 16%, $p = 0.016$). However, Ki-67 levels did not differ significantly between the two groups ($p = 0.126$). Of note, Ki-67 data were missing in five patients with two in the progression group and three in the non-progression group. They were subsequently excluded during the relevant analyses regarding Ki-67.

Characteristics according to surgery period, 2001–2011 ($N = 73$) and 2012–2022 (N = 167), are summarized in Supplementary Table 1. Patients in the 2012–2022 group had a significantly higher mitotic count (6.7 ± 3.5 vs. 5.8 ± 2.8, $p = 0.049$) and a higher Ki-67 level (10.2 ± 7.8 vs. 4.7 ± 3.4, $p < 0.0001$). However, progression rates did not differ significantly between the groups (66.5% for 2012–2022 vs. 69.9% for 2001–2011, $p = 0.605$).

Mitotic count and Ki-67 cut off level

The mean MC of the cohort was 6.4 (*SD*: 3.3), with a calculated cutoff for AM progression of 6.5 (AUC: 0.66, Youden index: 0.27). When subcategorized by EOR, the MC cutoff remained 6.5 (AUC: 0.65, Youden index: 0.31) in GTR group, while in the STR group, it was lower at 5.5 (AUC: 0.7, Youden index: 0.35). To evaluate for a clinically significant MC cutoff and adopt a more conservative approach, we conducted further risk analyses using a MC cutoff of 6,

Table 1 Demographic characteristics of 240 atypical meningioma patients

Variables		Total (N = 240)		No Progression (N = 162)		Progression (*N* = 78)		***p***	
Age (year)	Mean ± SD	53.8	± 14.0	52.6	± 13.5	56.3	± 14.8	0.057	3)
Sex	Female	143	59.6%	97	59.9%	46	59.0%	0.894	1)
	Male	97	40.4%	65	40.1%	32	41.0%		
Tumor size (mm)	Mean ± SD	46.7	± 15.6	44.8	± 16.2	50.6	± 13.5	**0.007**	3)
Tumor location	Convexity	88	36.7%	67	41.4%	21	26.9%	0.123	1)
	Falx/Parasagittal	73	30.4%	47	29.0%	26	33.3%		
	Skull base	68	28.3%	40	24.7%	28	35.9%		
	Others	11	4.6%	8	4.9%	3	3.8%		
Extent of resection	GTR	175	72.9%	131	80.9%	44	56.4%	**0.0001**	1)
	STR	65	27.1%	31	19.1%	34	43.6%		
Mitotic count	Mean ± SD	6.4	± 3.3	5.9	± 3.1	7.5	± 3.6	**< 0.0001**	4)
Brain invasion	Absent	185	77.1%	129	79.6%	56	71.8%	0.176	1)
	Present	55	22.9%	33	20.4%	22	28.2%		
Increased cellularity	Absent	9	38.0%	7	4.3%	2	2.6%	0.722	2)
	Present	231	96.3%	155	95.7%	76	97.4%		
Small cells with high N/C ratio	Absent	142	59.2%	98	60.5%	44	56.4%	0.547	1)
	Present	98	40.8%	64	39.5%	34	43.6%		
Prominent nucleoli	Absent	111	46.3%	76	46.9%	35	44.9%	0.766	1)
	Present	129	53.8%	86	53.1%	43	55.1%		
Sheeting	Absent	191	79.6%	136	84.0%	55	70.5%	**0.016**	1)
	Present	49	20.4%	26	16.0%	23	29.5%		
Necrosis	Absent	192	80.0%	135	83.3%	57	73.1%	0.063	1)
	Present	48	20.0%	27	16.7%	21	26.9%		
Adjuvant radiotherapy	No	158	65.8%	104	64.2%	54	69.2%	0.441	1)
	Yes	82	34.2%	58	35.8%	24	30.8%		
Ki-67 (%)	Mean ± SD	8.6	± 7.3	8.5	± 7.9	8.7	± 5.7	0.126	4)

Boldface type indicates statistical significance

GTR Gross total resection, *N/C* Nucleus-to-cytoplasm, *SD* Standard deviation, *STR* Subtotal resection

[1)] Chi-square test, [2)] Fisher's exact test, [3)] T-test, [4)] Wilcoxon rank sum test

based on the overall cutoff level of 6.5. A clinically relevant Ki-67 cutoff for AM progression could not be determined, as the optimal Ki-67 cutoff in our cohort was calculated to be 2, with a low Youden index of 0.17, and an insignificant AUC of 0.56. Given that the mean Ki-67 level in the cohort was 8.6 (*SD*: 7.3), this cutoff was not considered clinically significant. (Fig. 1).

Risk factors for AM progression

Univariate cause-specific Cox regression analysis found age ($p = 0.006$), tumor size ($p = 0.006$), surgery period ($p = 0.034$), EOR ($p = 0.001$), brain invasion ($p = 0.017$), sheeting ($p = 0.039$), MC ($p = 0.005$) and Ki-67 ($p = 0.032$) as a risk factor for AM progression. On multivariate analysis, age (HR 1.03, $p = 0.014$), GTR (HR 0.18, $p < 0.001$), brain invasion (HR 2.31, $p = 0.002$), sheeting (HR 1.69, $p = 0.027$), MC ≥ 6 (HR 2.32, $p = 0.002$) and RTx (HR 0.25, $p < 0.001$) were significantly associated with progression of AM. Ki-67 was not statistically significant on multivariate analysis (Table 2).

Progression free survival

The GTR group had better overall PFS than the STR group ($p = 0.001$). In subgroup analyses based on a MC cutoff of 6, GTR patients with a MC ≥ 6 ($N = 99$) had a worse prognosis than those with a MC < 6 ($N = 76$) ($p = 0.02$). In the STR group, PFS did not differ significantly between patients with MC ≥ 6 and < 6 ($p = 0.061$) (Fig. 2). There was a total of three acknowledged deaths: two in the progression group and one in the non-progression group. The two deaths in the progression group were due to worsening medical conditions during hospice care following treatment for AM. The single death in the non-progression group was unrelated to

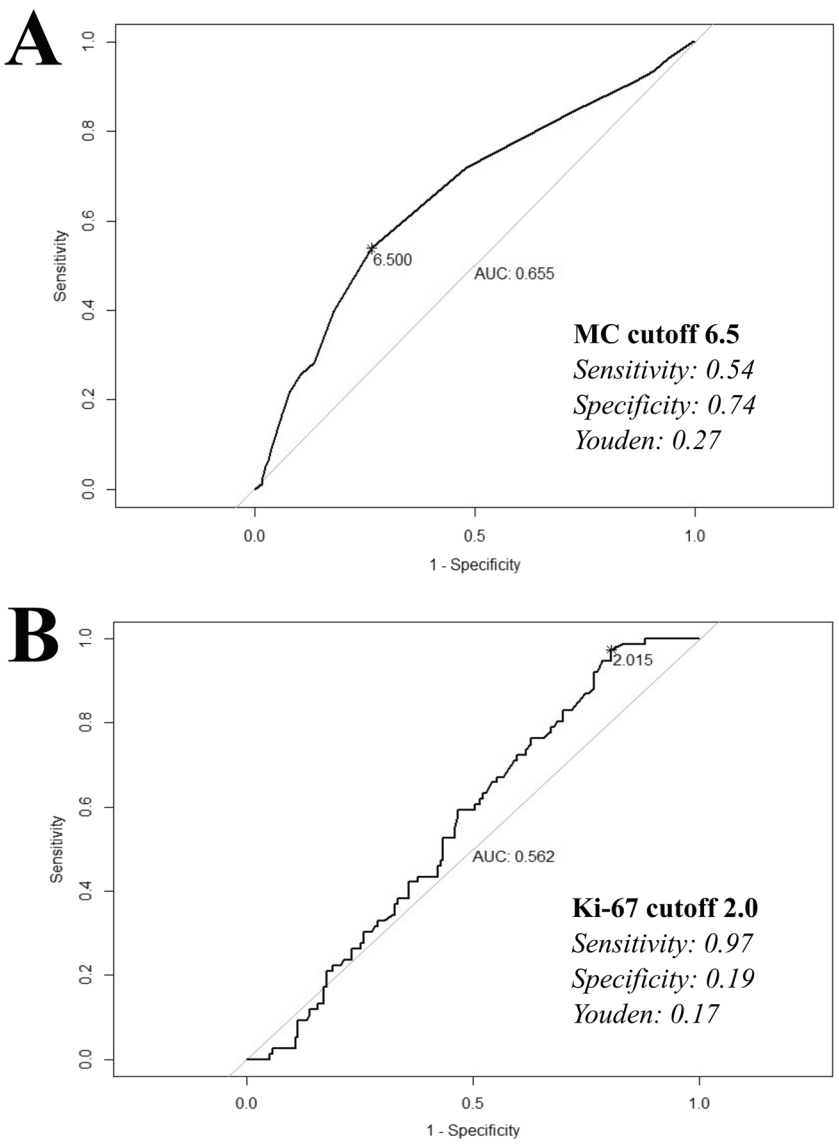


Fig. 1 Cutoff levels for mitotic count and Ki-67. **A** Appropriate cutoff level for mitotic count (MC) associated with atypical meningioma progression was 6.5 (**B**) Ki-67 cutoff level was 2.0 which was not considered clinically significant. AUC: area under the curve; MC: mitotic count

AM and resulted from aspiration pneumonia secondary to progression of prostate cancer.

Adjuvant radiotherapy (RTx)

A total of 82 patients underwent RTx, with 25 patients receiving GKS and 57 patients receiving conventional radiotherapy. The median prescription dose for GKS was 17 Gy (range: 13–25.5 Gy) delivered in one to three fractions. Conventional fractionated radiotherapy was administered at a median dose of 60 Gy (range: 45–61.2 Gy) in 10 to 33 fractions. Among 175 GTR patients, 32 (18.3%) underwent RTx, compared to 50 of 65 STR patients (76.9%) ($p < 0.0001$).

The overall PFS did not differ between AM patients who received RTx and those who did not ($p = 0.615$) (Fig. 3A). The impact of RTx was further analyzed based on a MC cutoff of 6, EOR, and when each EOR group was further sub-stratified by the MC cutoff. RTx had no statistically significant impact on PFS in either the MC ≥ 6 group ($p = 0.541$) or the MC < 6 group ($p = 0.252$). Similarly, RTx had no significant effect on PFS in the GTR group ($p = 0.382$) (Fig. 3B) and remained statistically insignificant when the GTR group was sub-stratified by the MC cutoff (Fig. 3C, 3D). However, RTx was associated with significantly better PFS in the STR group ($p < 0.001$) (Fig. 3E), and this finding remained consistent after sub-stratification by the MC cutoff (Fig. 3F, 3G).

Discussion

The overall AM progression rate in our study was 32.5% with a median time to recurrence of 25.2 months, which were compatible with results from previous studies [7].

Table 2 Time-dependent univariate and multivariate cox analyses of risk factors for atypical meningioma progression

Variables		Univariate				Multivariate			
		HR	95% CI		*p*	HR	95% CI		*p*
Sex (ref: Female)	Male	1.12	(0.71,	1.75)	0.66	1.05	(0.65,	1.69)	0.846
Age (continuous)		1.02	(1.01,	1.04)	**0.006**	1.03	(1.01,	1.05)	**0.014**
Tumor size (continuous)		1.02	(1.01,	1.03)	**0.006**				
Tumor location (ref: convexity)	Falx/parasagittal	1.32	(0.74,	2.35)	0.345				
	Skull base	1.59	(0.91,	2.81)	0.106				
	other	1.34	(0.40,	4.51)	0.633				
Surgery period (ref: 2001–2011)	2012–2022	1.74	(1.04,	2.89)	**0.034**				
Extent of resection (ref: STR)	GTR	0.47	(0.30,	0.74)	**0.001**	0.18	(0.10,	0.31)	**< 0.001**
Mitotic count (ref: < 6)	≥ 6	2.04	(1.24,	3.33)	**0.005**	2.32	(1.37,	3.94)	**0.002**
Brain invasion (ref: absent)	present	1.83	(1.12,	3.02)	**0.017**	2.31	(1.35,	3.96)	**0.002**
Increased cellularity (ref: absent)	present	2.14	(0.53,	8.76)	0.288				
Small cells with high N/C ratio (ref: absent)	present	1.22	(0.78,	1.92)	0.378				
Prominent nucleoli (ref: absent)	present	1.17	(0.75,	1.82)	0.500				
Sheeting (ref: absent)	present	1.67	(1.03,	2.72)	**0.039**	1.69	(1.06,	2.69)	**0.027**
Necrosis (ref: absent)	present	1.40	(0.85,	2.31)	0.190				
Ki-67 (continuous)		1.03	(1.00,	1.07)	**0.032**				
Adjuvant radiotherapy	Yes	0.90	(0.56,	1.44)	0.662	0.25	(0.13,	0.46)	**< 0.001**

Boldface type indicates statistical signficance

CI Confidence interval, *GTR* Gross total resection, *HR* Hazard ratio, *N/C* Nucleus-to-Cytoplasm, *Ref* Reference, *STR* Subtotal resection

Age, brain invasion, sheeting, and MC were positively associated with AM progression, while GTR and RTx were identified as risk-reducing factors.

Age and EOR

Age has been reported as one of the possible risk factors for AM progression [16, 40] with older aged AM showing worse overall survival [61]. EOR has been recognized as an important risk factor for AM progression [19, 49, 51], which aligns with the findings of our study. This supports the fundamental principle that maximal safe resection should be performed in AM whenever possible.

Our study categorized EOR into either GTR or STR, and did not stratify further according to Simpson grades [54]. Although, Simpson grades are still widely used by neurosurgeons, their role in risk stratification especially within the GTR group has been called into question [53]. Further investigation into risk stratification based on Simpson grades is warranted. However, it remains reasonable to support our institution's practice of resecting or coagulating the involved dura and hyperostotic bone during surgical treatment of AM to achieve "maximal" resection whenever it does not significantly increase the risk of neurological deficits or wound complications.

Minor histopathologic features

Among the five minor histopathologic features defining AM, sheeting was the only feature significantly associated with progression. The current diagnostic approach of using histopathologic features is based largely on a single-institution study [42] and its prognostic validity has since been questioned. Concerns include possible lack of prognostic relevance [3], risk of over-grading [2], and low interobserver concordance [46] raising doubts about the reliability of using these histopathologic features for AM diagnosis and risk stratification. Although literature on this issue remains limited, Lee et al. [29] reported sheeting as a potential risk factor. Chiba et al. [12] found sheeting to be associated with malignant transformation in benign meningioma, whereas other studies have reported conflicting results [34, 36]. Overall, which histopathologic features are most predictive of recurrence remains open for question.

Brain invasion

Brain invasion has long been suggested as a possible risk factor for meningioma recurrence, but it was not until 2016 that it was incorporated as a stand-alone WHO diagnostic criterion for AM [33]. Inclusion of brain invasion into the WHO grading criteria has contributed to an increased incidence of AM [35], further adding to the heterogeneity

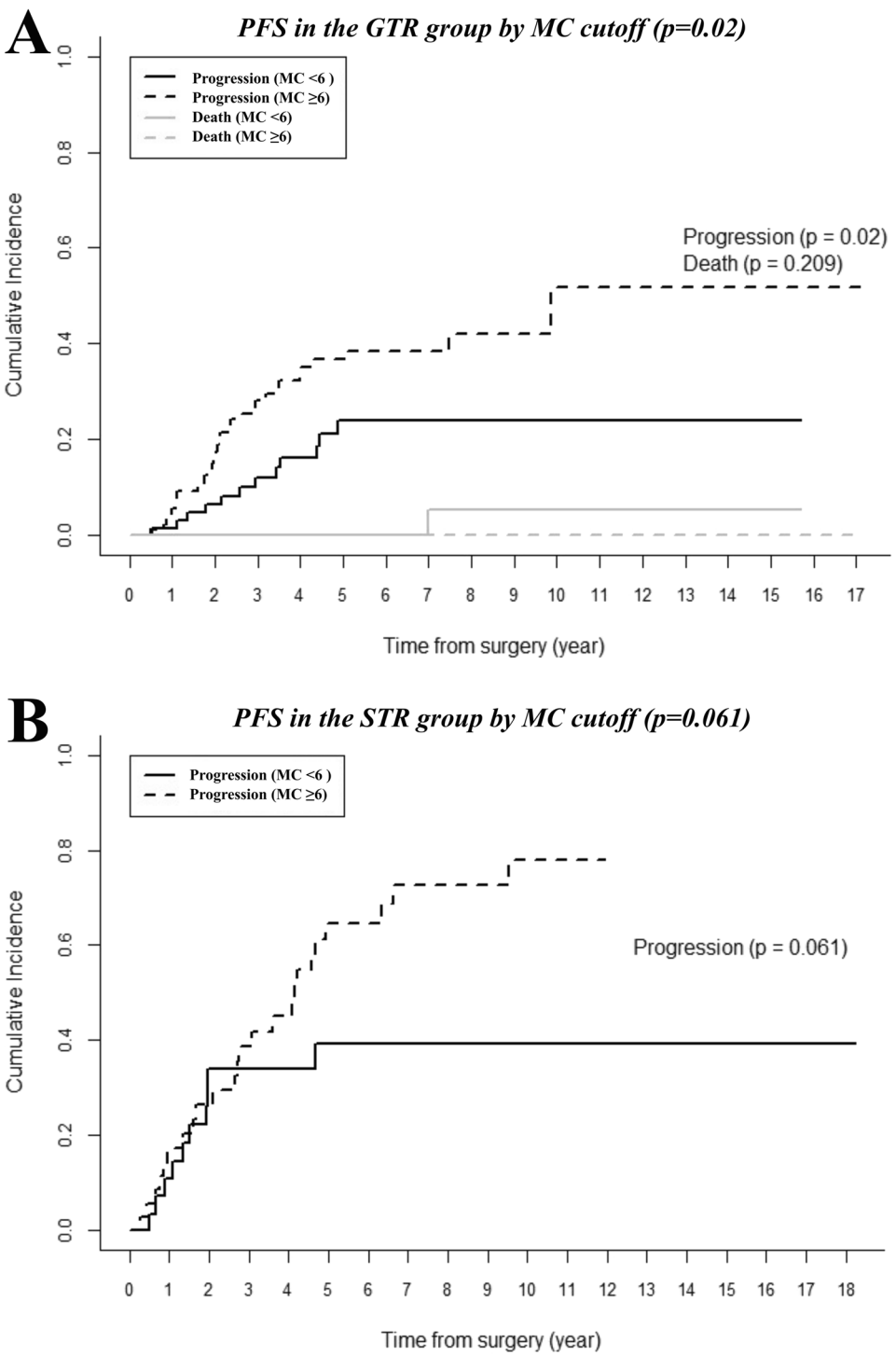
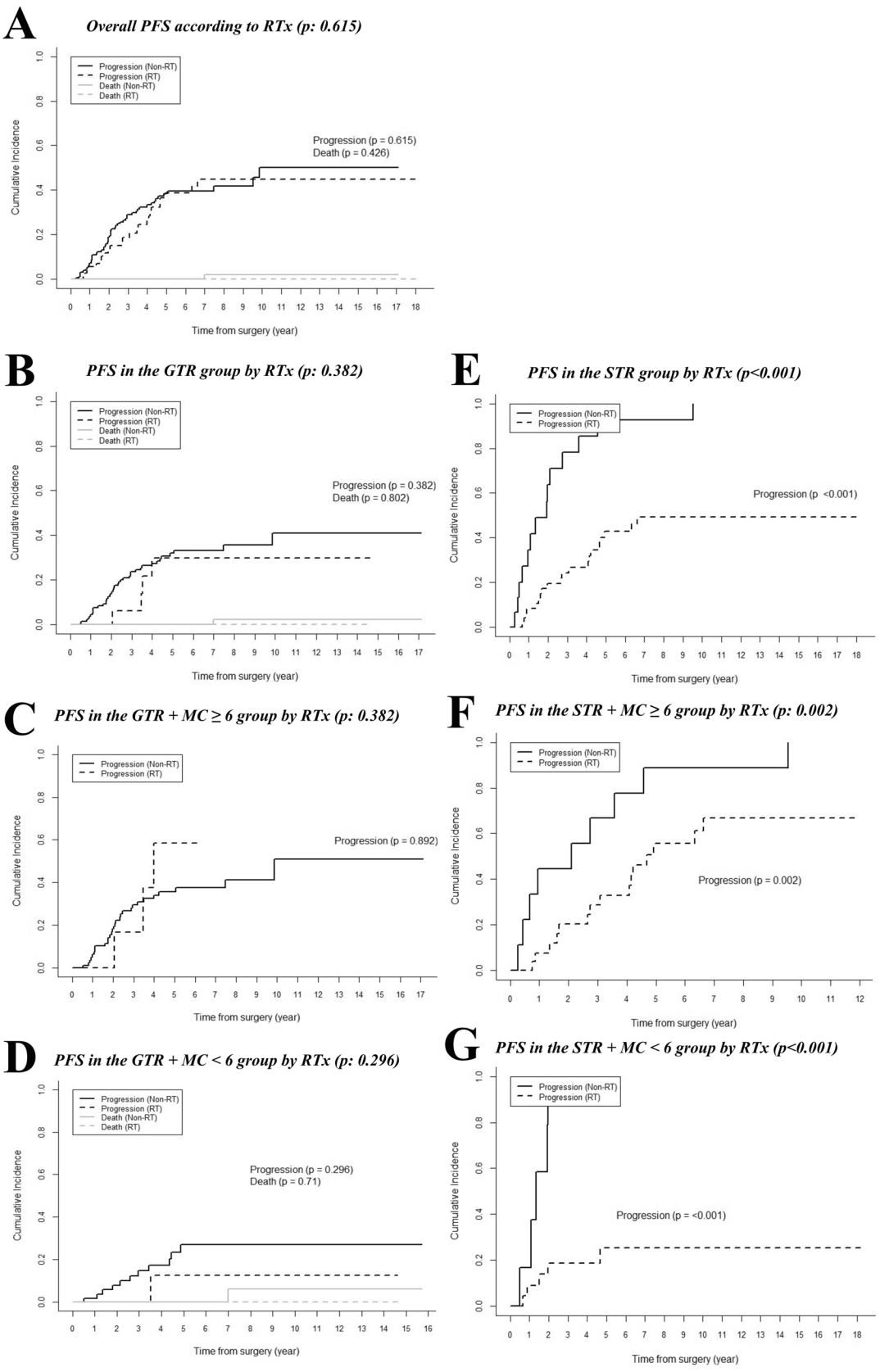


Fig. 2 Progression-free survival (PFS) of GTR and STR groups stratified by a mitotic count (MC) cutoff of 6. **A** PFS of the GTR group. Patients with MC ≥ 6 showed significantly worse prognosis than those with MC < 6 ($p = 0.02$) (**B**) PFS of the STR group. No significant difference in PFS was observed between patients with MC ≥ 6 and MC < 6 ($p = 0.061$). PFS: progression free survival; GTR: gross total resection; MC: mitotic count; STR: subtotal resection

of the group. The validity of brain invasion as an isolated diagnostic marker has been questioned [31], and there are concerns over poor interobserver reproducibility and mixed findings regarding its association with AM progression [5, 6]. However, multiple studies have demonstrated brain invasion to be in fact associated with AM progression [22, 57], particularly when accompanied with other atypical features such as a high MC. Our findings are consistent with these observations.

Brain invasion remains an intuitive and clinically relevant marker of aggressive behavior in AM. One might argue that its presence could indirectly contribute to progression by limiting the EOR. However, in our study, brain invasion remained a significant independent risk factor even after


A
Overall PFS according to RTx (p: 0.615)
Progression (Non-RT)
Progression (RT)
Death (Non-RT)
Death (RT)
Progression (p = 0.615)
Death (p = 0.426)
Cumulative Incidence
Time from surgery (year)
B
PFS in the GTR group by RTx (p: 0.382)
Progression (p = 0.382)
Death (p = 0.802)
C
PFS in the GTR + MC ≥ 6 group by RTx (p: 0.382)
Progression (p = 0.892)
D
PFS in the GTR + MC < 6 group by RTx (p: 0.296)
Progression (p = 0.296)
Death (p = 0.71)
E
PFS in the STR group by RTx (p<0.001)
Progression (p <0.001)
F
PFS in the STR + MC ≥ 6 group by RTx (p: 0.002)
Progression (p = 0.002)
G
PFS in the STR + MC < 6 group by RTx (p<0.001)
Progression (p = <0.001)

◂**Fig. 3** Progression-free survival (PFS) of atypical meningioma patients according to adjuvant radiotherapy (RTx), stratified by extent of resection (EOR) and mitotic count (MC) cutoff of 6. **A** Overall PFS by RTx (**B**) PFS in the GTR group (**C**) PFS in GTR with MC ≥ 6 (**D**) PFS in GTR with MC < 6 (**E**) PFS in the STR group (**F**) PFS in STR with MC ≥ 6 (**G**) PFS in STR with MC < 6. PFS did not differ between patients who received RTx and those who did not (A, $p = 0.615$). RTx had no significant impact on PFS in the GTR group (B, $p = 0.382$). In the GTR group, RTx remained statistically insignificant after sub-stratification by the MC cutoff (C, $p = 0.892$; D, $p = 0.296$).RTx was associated with improved PFS in the STR group (E, $p < 0.001$). Those who underwent RTx continued to show improved PFS in the STR group even after sub-stratification by the MC cutoff (F, $p = 0.002$; G, $p < 0.001$). EOR: extent of resection; GTR: gross total resection; MC: mitotic count; PFS: progression-free survival; RTx: adjuvant radiotherapy STR: subtotal resection

adjusting for EOR in multivariate analysis, stressing its prognostic importance. Barresi et al. [3] investigated which histopathologic features defining AM most strongly predict prognosis and found that the copresence of brain invasion, high MC, and sheeting was most predictive of early recurrence, findings that are in line with our results. While brain invasion alone may not be the most optimal predictor of recurrence, its presence alongside a high MC may help identify patients with higher risk of AM recurrence.

Optimal mitotic count cutoff & Ki-67

The optimal MC cutoff was identified as 6.5 in our cohort. However, since MC is clinically reported as an integer, representing the number of mitotic figures in 10 consecutive HPFs, we proceeded the analyses with a cutoff of 6. This conservative threshold was chosen to explore the possible MC cutoff that had real-clinical clinical applicability and prior evidence linking increased MC to AM progression.

In multivariate Cox analysis, MC ≥ 6 was independently associated with AM progression, while Ki-67 was not. Although elevated Ki-67 has been reported as a potential risk factor in some studies [32, 55], our findings did not support these results. Both increased MC [38] and higher Ki-67 [41] are associated with higher-grade meningiomas, and Ki-67 index was significantly higher in cases with MC ≥ 6 compared to MC < 6 (mean 9.4 vs 7.5, $p = 0.001$) in our study, suggesting collinearity between the two indices. However, the reason only MC remained significant while Ki-67 did not is unclear and whether MC is a better predictor of AM progression than Ki-67 remains debatable.

Nevertheless, increased MC have been reported to be associated with AM recurrence [4, 15, 25, 28] and various mitotic cutoffs [7, 18, 24, 26, 30] have been proposed (Table 3). These thresholds may serve as practical, objective criteria for risk stratification, especially given the wide range of MC observed in the heterogeneous AM population [11]. However, relying solely on MC cutoff levels for risk stratification warrants caution due to potential misclassification and should be considered in conjunction with other reported risk factors.

Adjuvant radiotherapy for AM patients

As AM patients with STR are more likely to receive RTx or undergo closer follow-up, current debate focuses on the management of those with GTR. Although RTx has been reported to reduce the risk of AM progression [14, 20, 50, 52, 56], its role in GTR remains controversial [13, 60]. Collinearity between EOR and RTx is evident, as most STR patients (76.9%) receive RTx. Nonetheless, RTx remained a significant risk-reducing factor even after adjusting for EOR. While overall PFS did not differ significantly between patients who received RTx and those who did not, subgroup analysis by EOR showed significantly better prognosis in the STR group receiving RTx.

Taken together, while it seems reasonable to recommend RTx for AM patients with STR, we propose using an MC cutoff of 6 to help identify GTR patients who may benefit from closer surveillance or consideration of RTx. There was no significant difference in PFS was observed among GTR patients with MC ≥ 6 based on RTx status; however, this may have been due to relatively small percentage of GTR patients receiving RTx and potential over-stratification. Nonetheless, since MC was a significant risk factor for AM progression, and GTR patients with MC ≥ 6 had worse prognosis than those with MC < 6, a MC cutoff of 6 may serve as a useful tool for postoperative risk stratification and treatment planning. Ongoing clinical trials [21, 39] are expected to provide more definitive evidence on the role of RTx in GTR, which may help refine future treatment strategies.

Strengths and Limitations

The current study is limited by its retrospective design, which may have introduced selection bias, as patients without postoperative imaging were excluded. Generalizability of the results may also be restricted because the cohort was drawn from a single tertiary institution. Another limitation is the potential for interobserver variability in the diagnosis of AM. Although all pathology reports were reviewed to confirm that cases met the 2021 WHO diagnostic criteria for AM, variability may still have influenced the original diagnoses since the review was based on the initial pathology reports. Finally, five cases lacked Ki-67 data, but this represented a small proportion of the cohort and is unlikely to have significantly affected the overall results.

Despite these limitations, our study included a relatively large sample size with a mean follow-up duration of over 3 years. We investigated the potential risk factors for AM progression, focusing on identifying appropriate

Table 3 Suggested mitotic count cutoff levels in previous studies

No	Year	Study	*N*	Recurrence rate	Average time to recurrence (months)	Suggested MC cutoff	OR/HR (95% CI)	Other suggested risk factors	Note	Reference
1	2014	Kim et al	67	38.8%	61.8	MC > 8	HR 2.44 (1.27–3.60)	EOR, p16, CDK6, pRB protein, MIB(Ki-67), p53		[49]
2	2015	Klinger et al	57	44%	33	MC ≥ 4	HR 2.51 (0.94–6.69)	MIB(Ki-67)		[50]
3	2018	Budohoski et al	220	32%	24	MC > 7	OR 4.27 (1.4–12.19)	STR, parafalcine/parasagittal location, peritumoral edema, adjuvant radiotherapy		[11]
4	2020	Fioravanzo et al	200	49.5%	24	MC ≥ 6	OR 2.2 (1.1—4.1)	Male, parasagittal location, Simpson grade 3, sheeting	Only GTR patients with no adjuvant radiotherapy	[51]
5	2022	Lee et al	105	36.4%	49.4	MC > 8.5	HR 3.44 (1.30—5.59)	Tumor size, EOR, MIB(Ki-67)		[52]

EOR Extent of resection, *HR* Hazard ratio, *MC* Mitotic count cutoff, MIB, *OR* odd ratio, *STR* subtotal resection

MC and Ki-67 cutoffs that may serve as objective criteria for stratifying risk within this heterogeneous pool of AM. These findings may help guide clinical decision-making, particularly in patients with GTR. While the proposed cutoffs should be interpreted with caution and considered alongside other risk factors, we suggest using an MC cutoff of 6 to identify GTR patients who may benefit from closer surveillance or consideration of RTx, and support recommending RTx for patients with STR.

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Data availability The data supporting the findings of this investigation are available upon reasonable request from the corresponding author.

Declarations

Ethics approval The current study was approved by the Institutional Review Board of Seoul National University Hospital (IRB: 2505–039-1638). This study was conducted in accordance with the ethical standards set forth in the 1964 Helsinki declaration and its later amendments.

Informed consent was obtained from all patients or their family before any surgical procedures were done.

Human ethics and consent to participate Not applicable. As this was a retrospective study, the requirement for informed consent to participate and/or publish was waived by the IRB.

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