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Histopathological and Clinical Features as Prognostic Factors of Atypical Meningiomas

Pinar KARABAGLI[1], Hakan KARABAGLI[2], Zekiye MAVI[1], Fatih DEMIR[1], Eylem Yagmur OZKELES[2]

[1]Selcuk University, School of Medicine, Department of Pathology, Konya, Turkey
[2]Selcuk University, School of Medicine, Department of Neurosurgery, Konya, Turkey

Corresponding author: Pinar KARABAGLI ✉ pinarkarabagli@yahoo.com

ABSTRACT

AIM: To analyze the correlation of clinicopathologic prognostic parameters with atypical meningiomas (AMs) and recurrence development as well as progression-free survival (PFS).

MATERIAL and METHODS: The neuropathology archive and hospital records of 75 patients with AM who underwent surgery in our institution between 2010 and 2019 were retrospectively reviewed. The pathological revision was performed according to the 2016 World Health Organization (WHO) criteria. Other clinicopathological parameters, such as age, gender, tumor location, preoperative tumor size, degree of resection, Psammoma body, nuclear atypia, main histological pattern, Ki67 labeling index (LI), radiotherapy, and dura and bone invasion, were also analyzed. Statistically, univariate and multivariate analyses were assessed to determine their potential impact on recurrence-related prognostic factors.

RESULTS: Recurrence occurred in 20 patients. The mean PFS and follow-up time were 38.9 and 44.8 months, respectively. In univariate analysis, clinical and pathological features such as age of ≤55 years, female sex, skull base tumor location, larger preoperative tumor size, increased mitotic count, small cells, hypercellularity, sheeting, necrosis, and dura and bone invasion were remarkable in patients with recurrence, but were not statistically significant. In multivariate analysis, increased mitotic activity and brain invasion either considered alone or combined were significantly associated with PFS. Nuclear atypia was also not associated with both tumor recurrence and PFS. However, clinical features did not significantly influence the PFS.

CONCLUSION: This study found that recurrence could not be predicted by the presence of any of the clinicopathological features of AMs. We believe that molecular variables determined through routine neuropathological analysis will be needed in the future.

KEYWORDS: Atypical meningioma, Recurrence, Progression-free survival, Prognostic factors

ABBREVIATIONS: AM: Atypical meningioma, **PFS:** Progression-free survival, **WHO:** World Health Organization, **LI:** Labeling index, **GTR:** Gross total resection, **STR:** Subtotal resection, **HPF:** High-power field, **OS:** Overall survival, **SPSS:** Statistical Package for Social Sciences, **P:** Probability

INTRODUCTION

Meningioma is the most frequently reported primary intracranial tumor. Majority of these are benign, slow-growing neoplasms, whereas some can manifest more agressive behaviors. Although meningioma is comprised of many histological subtypes, the World Health Organization (WHO) classifies meningiomas into three main groups according to their biological behavior and grades: benign (grade I), atypical (grade II), and anaplastic (grade III) meningiomas (8,20,31,34). Compared with benign meningioma, atypical meningiomas (AMs) are more aggressive and have been associated with more rapid disease progression and morbidity (11,22).

Pinar KARABAGLI : 0000-0002-5558-0175
Hakan KARABAGLI : 0000-0002-1184-3965
Zekiye MAVI : 0000-0001-9966-7814
Fatih DEMIR : 0000-0002-8181-0739
Eylem Yagmur OZKELES : 0000-0002-8418-5588

Meningiomas consisted of heterogenous histopathology, which may explain the repeated revisions of their classification schemes (3). The WHO criteria have been updated in 1993, 2000, 2007, and most recently, in 2016. AM criteria increased the mitotic activity, histological brain invasion, or at least three of the following features: increased cellularity, small cells with high nuclear-to-cytoplasmic ratio, prominent nucleoli, sheeting, and foci of spontaneous necrosis (31). Several studies revealed that increased mitotic activity is accepted as 4–19 mitoses per 10 high-power field (HPF) (5,8,11,22,34). In the 2016 WHO classification, brain invasion was included as an independent histological criterion to diagnose AM (5,8). Grade II meningiomas are classified as atypical, chordoid, and clear cell meningiomas (5,31). Clear cell and chordoid variants of meningioma are associated with high recurrence rates even without the above criteria (31,34).

The clinicopathological prognostic factors of AMs with unpredictable behavior and uncertain prognosis widely varied (32,35,41). Therefore, we retrospectively analyzed our center's experience with AMs in this study in order to determine the correlation of clinicopathologic prognostic parameters with the recurrence development as well as progression-free survival (PFS).

MATERIAL and METHODS

We reviewed our neuropathology archive to identify all patients who underwent surgery due to the newly diagnosed meningioma at our institution between 2010 and 2019. Histopathologic features were re-evaluated by three of the authors (P.K., Z.M., and F.D.) in accordance with the 2016 WHO diagnostic criteria. In this cohort, patients with AM were retrospectively determined.

Tumors were classified as AM with brain invasion on histology, increased mitotic activity (≥4/10 HPF), or at least three of the five minor criteria (Figure 1A, C-F) (31). An Olympus BX43 microscope was used, and HPF was defined using the 40× objective. Hypercellularity was defined as ≥53 nuclei/1 HPF diameter (32). Small cell formation was determined using light microscopy as tumor cells with high nuclear-to-cytoplasmic ratio (31). When microscopically determining small cell formation in these patients, immunohistochemical staining (CD45) should be performed in some patients to separate them from lymphocytes. The presence of easily observed nucleoli at 10× the objective ratio was considered macronucleoli (30). Sheeting was recorded when the tumor has uninterrupted pattern-less or sheet-like growth (31). Necrosis can be classified as small or large foci (32). Spontaneous necrosis can be distinguished from preoperative embolization and radiation-induced necrosis through detailed clinical information on embolization and radiation obtained before the histopathological examination (3,6).

Some other parameters such as the Psammoma body, nuclear atypia (pleomorphism), main histologic pattern (meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic), Ki67 labeling index (LI), and dura and bone invasion (Figure 1B) were determined. The Ki67 LI was analyzed both as continuous and dichotomous variable, using a 10% cut-point based on previous literatures (6,41).

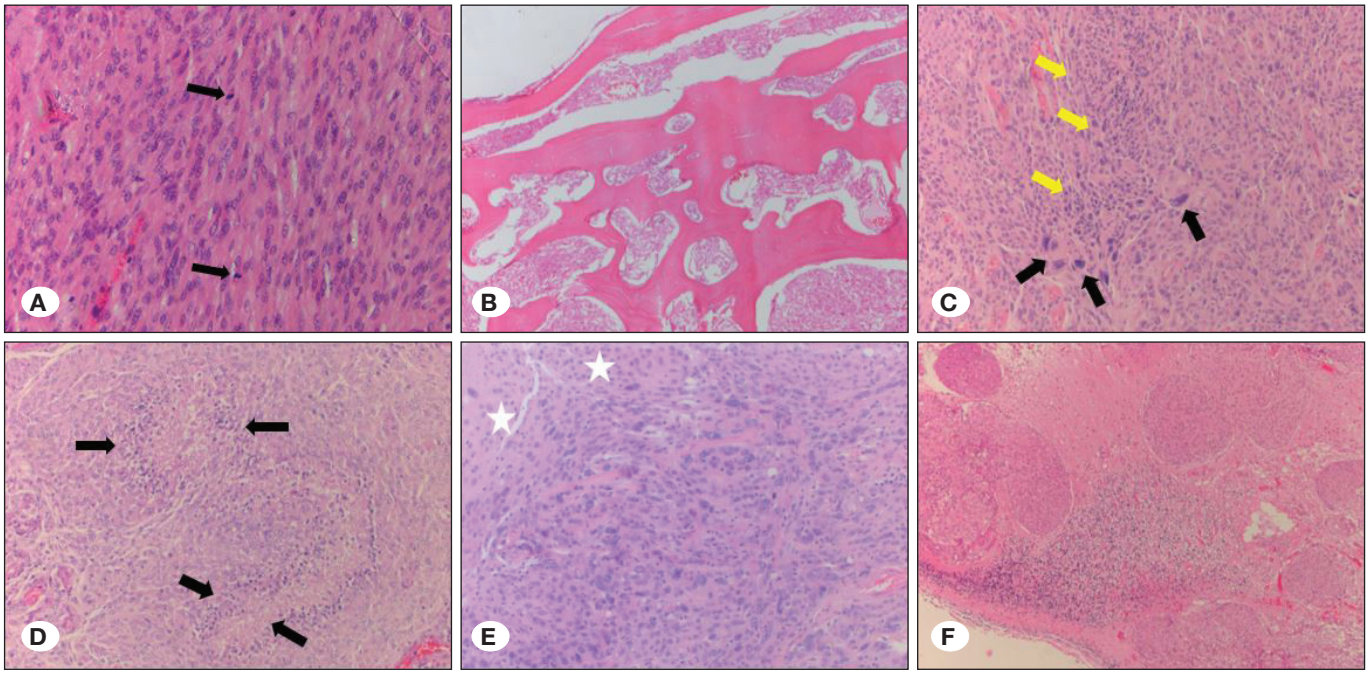

Figure 1: Histologic features of atypical meningioma (hematoxylin and eosin stain). Mitoses (arrows) **(A)**, bone invasion **(B)**, small cell formation (yellow arrows) and nuclear atypia (black arrows) **(C)**, spontaneous necrosis (between arrows) **(D)**, sheeting (stars) and macronucleoi **(E)**, and brain invasion **(F)**.

Histologic evaluation and classification were performed using paraffin-embedded tumor sections stained for hematoxylin-eosin (HE) and using immunohistochemical stainings for epithelial membrane antigen (EMA) (clone E29, Dako) and Kİ-67 (clone MIB-1, Dako). The expression of progesterone receptor (PR) (clone PgR 1294, Dako) was determined only in 21 of 75 patients. Immunohistochemical staining was performed using Dako Omnis autostainer.

Demographic data were retrieved from the hospital's medical record system. Age, sex, and time of diagnosis were recorded. Patients were divided into two groups according to age (≤55 and >55 years) and nine groups according to tumor location (convexity, skull base, posterior fossa, intraventricular, cerebellopontine angle, parasagittal, cerebellum, sphenoid wing, and spinal).

All patients underwent pre- and postoperative MRI and during the subsequent follow-up with intervals of 3–6 months in the first year, and then every 12–18 months thereafter (Figure 2A-F). Contrast-enhanced T1-weighted MR images were used to determine the preoperative tumor size (maximum diameter), location, extent of resection, residual tumor, and recurrence (Figure 3A-H). The extent of resection was documented as gross total resection (GTR) (Simpson grade I-III) or subtotal resection (STR) (Simpson grade IV) (38). Tumor recurrence was defined as new lesions or significant growth of >25% residual tumor (41).

Overall survival (OS) was defined as the time in months from diagnosis to the last revision or death. PFS was determined from the diagnosis to evidence of recurrence or progression.

The total follow-up time, tumor recurrence, time to recurrence/progression, and adjuvant treatment with radiotherapy (RT) were all recorded.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 23.0 (IBM Corporation, Armonk, NY, USA). The descriptive statistics of evaluation results were expressed as numbers and percentages for ordinal data, and as mean, standard deviation, minimum, and maximum values for the interval data. Fisher's exact test and univariate unpaired t- test were used to investigate the statistical correlations between clinicopathological parameters and recurrence. PFS was assessed using the Kaplan–Meier method, with the date of primary surgery as the entry data and length of survival from the detection of a recurrent tumor as the end-point. Multivariate analyses (Cox regression model) was utilized to determine the independent effect of each variable on PFS. A probability (P)-value of <0.05 was considered significant.

Data collection and scientific use were approved by the Ethical Committee of Selcuk University, Faculty of Medicine (2020/171). Informed consent was obtained from all individual participants included in this study.

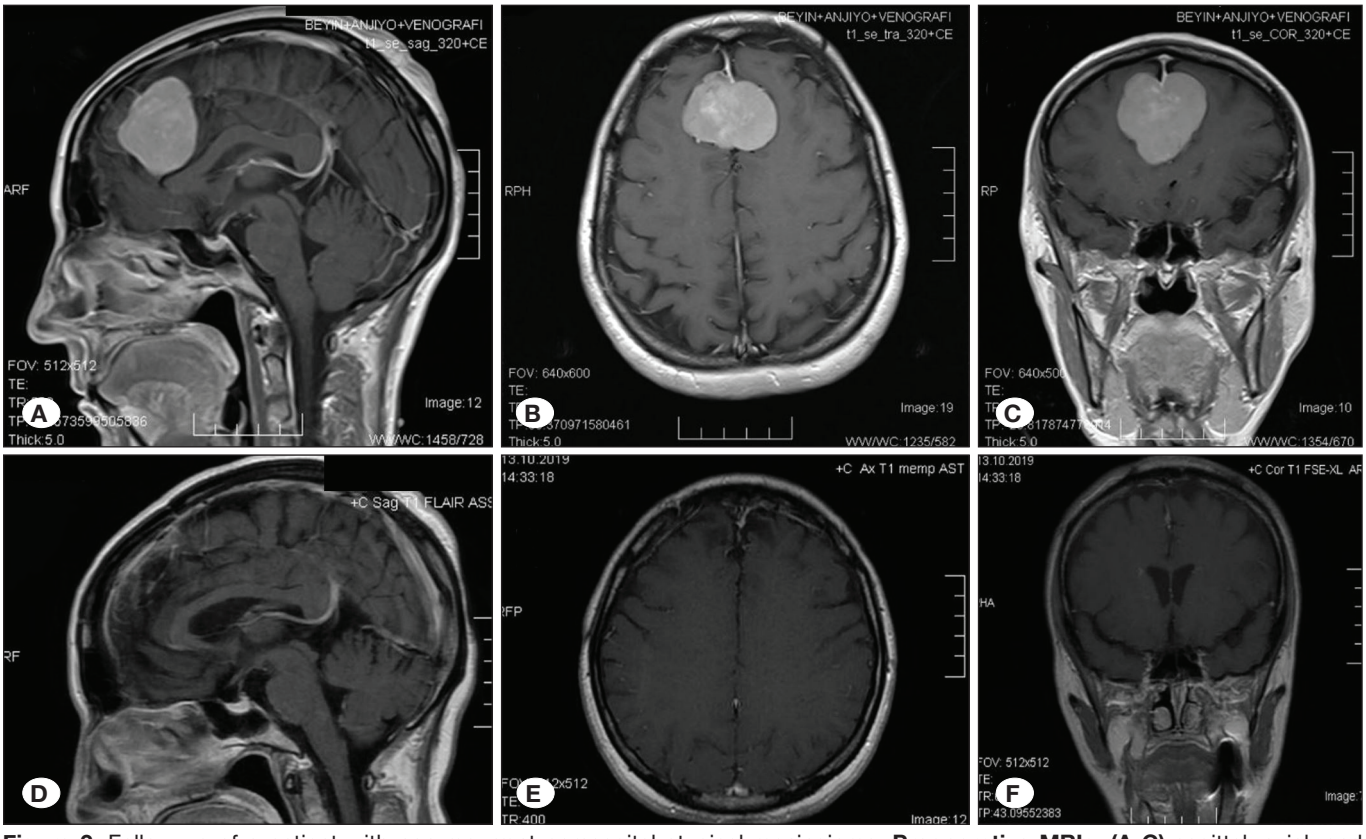

Figure 2: Follow-up of a patient with non-recurrent parasagittal atypical meningioma. **Preoperative MRIs: (A-C)** sagittal, axial, and coronal contrast-encanhed T1W. **Postoperative (51 months) MRIs: (D-F)** sagittal, axial, and coronal contrast-encanhed T1W.

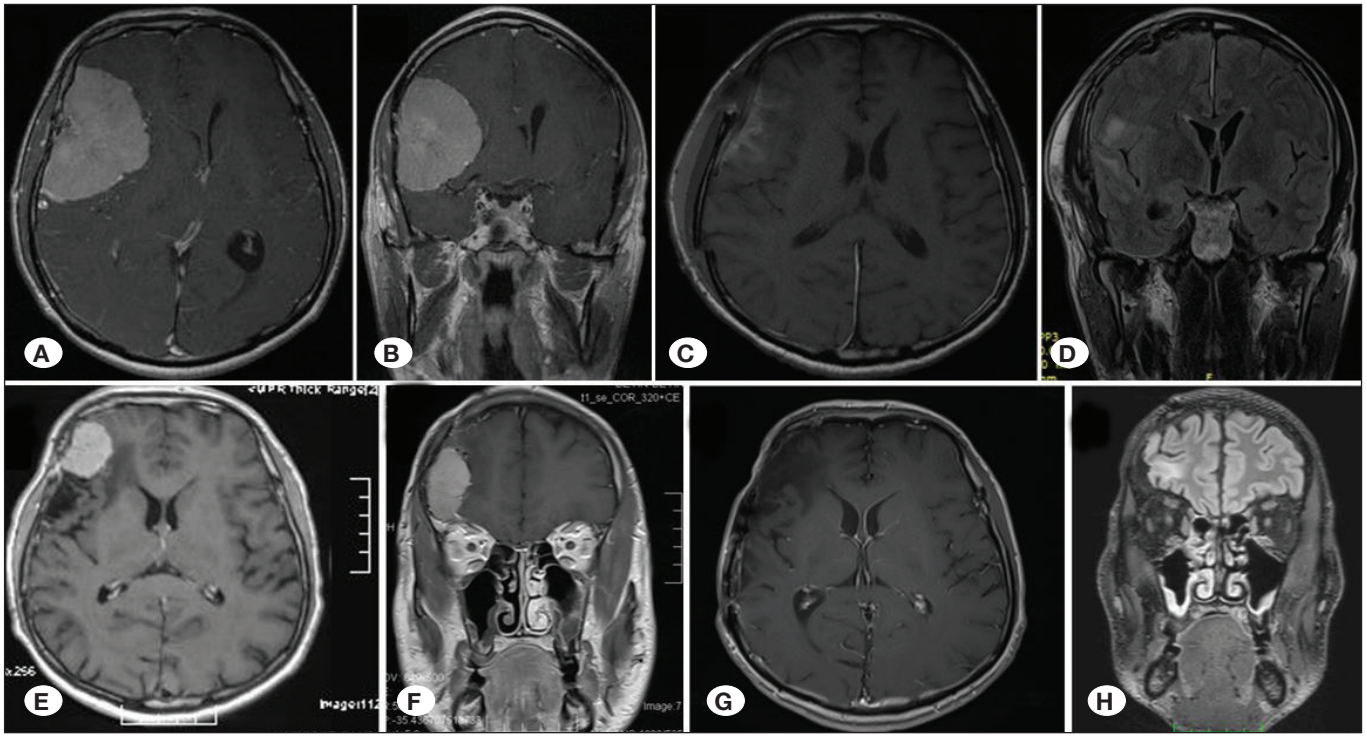

Figure 3: Follow-up of a patient with recurrent convexity atypical meningioma. Axial and coronal contrast-encanhed T1W preoperative **(A, B)** and early postoperative MRIs **(C, D)**. At 51 months after the recurrence, axial and coronal contrast-enhanced preoperative T1W MRIs **(E, F)** and early postoperative MRIs **(G, H)**.

RESULTS

Among 314 patients with meningioma, 95 were detected with grade II histology (30.2%) according to the 2016 WHO criteria. Then, 75 (23.8%) of them were diagnosed with AM. One (1.3%) was secondary AM pathologically evaluated as WHO Grade I histologically following the initial surgery. Interestingly, another patient was diagnosed with small cell lung carcinoma metastasis in AM.

The median age of 75 patients was 53.38 (range, 5–80) years. The tumor was located at a convexity in 30 (40%) and non-convexity in 45 patients (60%). The median tumor size was 45.24 (range, 12–100) mm. Adjuvant irradiation was administered in only 10 patients including both conventional fractionated RT (7 patients) and stereotactic radiosurgery (gamma knife, 3 patients). No adjuvant chemotherapy was initiated. The median PFS was 38.9 (range, 0–109) months. Within a median follow-up period of 44.8 months (range, 0–109) months, 14 (18.7%) patients died. The clinicopathological characteristics of 75 patients with AM are summarized Table I.

Although 87% of patients had histopathologically patternless areas, the most common main pattern distributions in the remaining areas were meningothelial (40%, n = 30), transitional (34.7%, n = 26), and fibroblastic (18.7%, n = 14). Bone invasion was identified in 3 (4%) and dura invasion in 38 (50.7%) patients. Psammoma bodies observed in 35 (45.7%) of the patients were a few in 27 (36%) of them. The median Ki67 LI was 8.3% (range, 0.5–30%). PR expression was evaluated only in 21 patients with AM. Only nine of these patients had >50% PR expression. Focal and weak expressions were obtained in nine and immunonegative results in three patients.

In univariate analysis, clinical features such as aged ≤55 years, female gender, skull base tumor location, and larger preoperative tumor size were noticeable in patients with recurrence, but were not statistically significant. Interestingly, OS was found to be longer in patients with relapse. Table II shows the statistical correlation between different clinical parameters and meningioma recurrence.

Histopathological parameters such as increased mitotic activity, small cells, hypercellularity, sheeting, necrosis, and dura and bone invasion in patients with relapse were remarkable, but were not statistically significant. Recurrence was detected in 6 of 15 patients with AM diagnosed only with minor atypia criteria (p=0.192). No recurrence was detected in any of patients diagnosed with AM only due to brain invasion. Although atypia was not one of the histopathological diagnostic criteria for AM, it was significantly associated with recurrence (p=0.029). Table III shows the statistical correlation between different histopathological parameters and meningioma recurrence.

PR expression was investigated in only three patients with recurrence. Two of them were immunonegative, and the expression was focal and weak in one.

The median Ki67 LI was 8.9% in patients with recurrence. In the cerebellopontine angle meningiomas, the Ki67 LI value (mean, 15.5 %) was significantly higher than that in

other localizations. Statistically, Ki67 LI was found to be significantly influenced by localization (p=0.005). In patients with meningiomas diagnosed only with minor atypia criteria, Ki67 LI values were significantly lower than those of other AMs (mean, 5.28% and 9.05%, respectively) (p=0.028). However, in patients with small cell formation and macronucleoli existence, which are minor criteria, mean Ki67 LIs (9.4% and 9.58%, respectively) were found to be significantly higher (p=0.0025, p=0.030). Conversely, the mean Ki67 LI (15.58%) was significantly higher in six patients with both high mitosis and brain invasion (p=0.001).

In patients with mitosis value of ≥4/10 HPF, tumor size (mean, 47.58 mm), and Ki67 LI (mean, 9.31%) were higher than mitosis of <4/10 HPF (38.8 mm and 5.5%, respectively). This situation was statistically significant (p=0.05, p=0.013, respectively).

Table I: Clinicopathological Characteristics of 75 Patients with Atypical Meningioma

Variable	No. of patients (%)
Age (years)	
≤55	38 (50.7)
>55	37 (49.3)
Sex	
Female	43 (57.3)
Male	32 (42.7)
Simpson Grade	
I	10 (13.3)
II	51 (68)
III	2 (2.7)
IV	12 (16)
Gross total	63 (84)
Subtotal	12 (16)
Tumor location	
Convexity	30 (40)
Skull base	14 (18.7)
Posterior fossa	4 (5.3)
Intraventricular	2 (2.7)
Cerebellopontine angle	2 (2.7)
Parasagittal	16 (21.3)
Cerebellum	2 (2.7)
Sphenoid wing	4 (5.3)
Spinal	1 (1.3)
Grading criteria	
Mitosis ≥4/10 HPF	55 (73)
Brain invasion	11 (14.7)
Increased cellularity	71 (94.7)
Small cells	47 (62.7)
Macronucleoli	43 (57.3)
Sheeting	62 (82.7)
Necrosis	32 (42.7)
Mitosis only	12 (16)
Brain invasion only	3 (4)
Mitosis+ Brain invasion	6 (8)
Minor criteria only	15 (20)
Post-op radiotherapy	
Yes	10 (13.3)
No	65 (86.7)
Recurrence	
Yes	20 (26.7)
No	55 (73.3)
Mortality	
Death	14 (18.7)
Alive	61 (81.3)

Table II: Statistical Correlation Between Clinical Parameters and Recurrence

Parameters	Recurrence		p
	Absent	Present	
n (%)	55 (73)	20 (27)	
Age			
≤55	25	13	0.192
>55	30	7	
Sex			
Female	31	12	0.495
Male	24	8	
Simpson grade			
I	7	3	
II	37	14	0.845
III	2	0	
IV	9	3	
Degree of resection			
Gross total	46	17	0.887
Subtotal	9	3	
Tumor location			
Convexity	20	10	
Skull base	9	5	
Posterior fossa	2	2	
Intraventricular	2	0	
Cerebellopontine angle	2	0	0.548
Parasagittal	13	3	
Cerebellum	2	0	
Sphenoid wing	4	0	
Spinal	1	0	
Tumor size (mm, mean)	43.36 ± 16.26	50.40 ± 20.5	0.720
Mortality			
Death	9	5	
No death	46	15	0.396
PFS (months, mean)	42.12 ± 31.5	30.30 ± 27.46	0.142
OS (months, mean)	42.13 ± 31.5	52.35 ± 28.6	0.207

Data were analyzed using Fisher's exact test and univariate t-test.

Table III: Statistical Correlation Between Pathological Parameters and Recurrence Analyzed Through the Fisher's Exact Test

Parameters	Recurrence		p
	Absent	Present	
n (%)	55 (73)	20 (27)	
Mitosis			
<4/10 HPF	13	7	0.325
≥4/10 HPF	42	13	
Brain invasion			
Absent	47	17	0.961
Present	8	3	
Hypercellularity			
Absent	4	0	0.215
Present	51	20	
Small cells			
Absent	21	7	0.801
Present	34	13	
Macronucleoli			
Absent	21	11	0.193
Present	34	9	
Sheeting			
Absent	10	3	0.748
Present	45	17	
Necrosis			
Absent	35	8	0.067
Present	20	12	
Mitosis only (≥4/10 HPF)			
Absent	47	16	0.569
Present	8	4	
Brain invasion only			
Absent	52	20	0.286
Present	3	0	
Atypia			
Absent	48	13	**0.029**
Present	7	7	
Dura invasion			
Absent	28	9	0.424
Present	17	11	
Bone invasion			
Absent	54	18	0.110
Present	1	2	
Psammoma bodies			
Absent	28	12	0.774
Present	27	8	
Dominant histologic pattern			
Meningothelial	20	10	0.846
Fibrous	11	3	
Transitional	20	6	
Angiomatous	1	0	
Secretory	1	1	
Lymphoplasmacyte-rich	1	0	
Metaplastic	1	0	
MIB-1 LI			
≤10/10 HPF	40	13	0.516
>10/10 HPF	15	7	

The mean tumor size (54.21 mm) was larger in patients who died than those living (43.2 mm) and was found statistically significant (p=0.034). The average age of patients who died was 60.7 years, but 51.7 in living patients (p=0.036).

Table IV shows multivariate analyses for PFS in AMs. Some of the atypical histopathologic features such as increased mitotic activity (≥4/10 HPF), brain invasion, and sheeting were significantly associated with PFS. Both increased mitotic activity and brain invasion, as well as atypia, were also significantly associated with PFS. However, these clinical features did not significantly influence PFS.

DISCUSSION

AMs have unpredictable behavior and uncertain prognosis and are very likely to recur compared to benign meningiomas (6,8,19,22,26,35,40). Recurrences cause reoperation and shortened survival (2,6,40). Therefore, its prognostic factors should be determined to identify patients highly at risk for recurrence postoperatively.

In the literature, the recurrence ratio in grade II meningiomas varies between 4.3% and 69% (5,27,32,35,39). In this study, recurrence was detected in 20 (27%) patients and 14 (18.7%) died. The mean PFS and follow-up time were 38.9 (range, 0–109) and 44.8 (range, 0–109) months.

Unlike previous classifications, brain invasion has been determined as a criterion for AM diagnosis according to the 2016 WHO classification (20,31,39). Brain invasion is characterized by irregular, tongue-like tumor cell protrusions infiltrating the underlying parenchyma, without an intervening layer of leptomeninges in meningiomas (31). The incidence of brain invasion in AMs is reported in 26–48% of patients (3,5,39). Studies have also shown that brain invasion is associated with recurrence probability, even if meningioma shows benign features (5,20,32,39). In this study, brain invasion was observed in 14.7% of all patients and in 7.6% of those with recurrence (p=0.961). No recurrence was detected in three patients diagnosed as AM due to "brain invasion" (p = 0.286). However, in multivariate analysis, brain invasion was significantly associated with PFS (p=0.004).

In this study, increased mitotic activity was the most important criterion to diagnose AM (73%), which has been reported similarly in other studies (3,34). Detecting mitotic figures may be difficult due to several reasons, such as pyknotic

Table IV: Multivariate Analyses for PFS in 75 Patients with AM

Parameter	n	Recurrences (%)	Multivariate HR (95% CI)	p
Mitosis				
<4/10 HPF	20	7 (35)	0.3 (0.1-0.8)	**0.021**
≥4/10 HPF	55	13 (23.6)		
Brain invasion				
Absent	64	17 (26.5)	0.2 (0.01-0.3)	**0.004**
Present	11	3 (27.3)		
Hypercellularity				
Absent	4	0 (0)	1.1 (0.01-17.5)	0.942
Present	71	20 (28.2)		
Small cells				
Absent	28	7 (25)	1.1 (0.2-6.9)	0.903
Present	47	13 (27.6)		
Macronucleoli				
Absent	32	11 (34.4)	0.5 (0.2-1.3)	0.144
Present	43	9 (20.9)		
Sheeting				
Absent	13	3 (23)	0.2 (0.03-0.9)	**0.049**
Present	62	17 (27.4)		
Necrosis				
Absent	43	8 (18.6)	0.8 (0.1-4.8)	0.830
Present	32	12 (37.5)		
Mitosis only (≥4/10HPF)				
Absent	63	16 (25.4)	4.0 (0.9-17.8)	0.068
Present	12	4 (33.3)		
Brain invasion only				
Absent	72	20 (27.7)	13.0 (0.4-454.5)	0.157
Present	3	0 (0)		
Mitosis+ Brain invasion				
Absent	69	18 (26.1)	21.9 (1.3-365.4)	**0.032**
Present	6	2 (33.3)		
Atypia				
Absent	61	13 (21.3)	0.4 (0.1-0.9)	**0.044**
Present	14	7 (50)		
Dura invasion				
Absent	37	9 (24.3)	1.4 (0.7-2.9)	0.316
Present	28	11 (39.3)		
Bone invasion				
Absent	72	18 (25)	0.5 (0.04-6.6)	0.601
Present	3	2 (66.6)		
Psammoma bodies				
Absent	40	12 (30)	0.9 (0.6-1.6)	0.919
Present	35	8 (22.8)		

Table IV: Cont.

Parameter	n	Recurrences (%)	Multivariate HR (95% CI)	p
Dominant hist. pattern				
Meningothelial	30	10 (33.3)	1.1 (0.9-1.3)	0.174
Fibrous	14	3 (21.4)		
Transitional	26	6 (23.1)		
Angiomatous	1	0 (0)		
Secretory	1	1 (100)		
Lymphoplasmacyte-rich	1	0 (0)		
Metaplastic	1	0 (0)		
MIB-1 LI				
≤10/10 HPF	53	13 (24.5)	1.4 (0.6-3.6)	0.420
>10/10 HPF	22	7 (31.8)		
Age				
≤55	38	13 (34.2)	0.9 (0.5-1.6)	0.639
>55	37	7 (18.9)		
Sex				
Female	43	12 (27.9)	1.6 (0.7-3.5)	0.244
Male	32	8 (25)		
Simpson Grade				
I	10	3 (30)	0.9 (0.3-2.7)	0.954
II	51	14 (27.4)		
III	2	0 (0)		
IV	12	3 (25)		
Degree of resection				
Gross total	63	17 (37)	2.2 (0.2-27.3)	0.528
Subtotal	12	3 (25)		
Tumor Location				
Convexity	30	10 (3.3)	0.9 (0.8-1.1)	0.340
Skull base	14	5 (35.7)		
Posterior fossa	4	2 (50)		
Intraventricular	2	0 (0)		
Cerebellopontine angle	2	0 (0)		
Parasagittal	16	3 (18.7)		
Cerebellum	2	0 (0)		
Sphenoid wing	4	0 (0)		
Spinal	1	0 (0)		

cells and mitotic figure instability during fixation, giving poor interobserver reproducibility (3,9). Although methods such as PHH3 immunostaining are widely used, this method was not preferred due to the false-positive possibility. Some studies showed that mitotic index is associated with recurrence probability and/or PFS in AMs (6,22,29,32,34). Increased mitotic activity (≥4/10 HPF) was observed in 23.6% of patients with recurrence in our series (p=0.325). Recurrence was detected in 4 of 12 patients diagnosed with due to "high mitotic rate only" (p=0.569). In multivariate analysis, increased mitotic activity was significantly associated with shorter PFS (p=0.021).

Barresi et al. reported that increased mitotic count and brain invasion either considered alone or combined were significantly associated with PFS and recurrence (5). In this study, alone or combined increased mitotic count and brain invasion were also significantly associated with PFS (p=0.032), but not for recurrence (p=0.700).

The Ki-67/MIB-1 antibody is widely used to determine the proliferative activity and identify aggressive meningiomas. In a literature review including 53 related articles, a positive correlation was found between Ki-67/MIB-1 LI and histological grade of meningiomas. The average Ki-67 labeling index was 8% in grade II meningiomas, whereas the recurrence rate was increased in meningiomas with a LI of >4% (1). Other studies also reported that high KI-67 LI was a significant risk factor in patients with grade II meningioma (6,12,20,27,34,41). Two separate studies found that MIB-1 LI of >10% was associated with higher probability of increased recurrence in AMs (7,41).

In our study, Ki67 LI was not significantly correlated with recurrence and PFS (p=0.516 and p=0.420, respectively). The median Ki67 LI was 8.3% (range, 0.5–30%), but 8.9% in patients with recurrence. As low Ki67 LI value can also be observed in grade II meningiomas, this value should be evaluated together with other histological criteria (10,20).

In this study, minor atypia criteria such as small cells, hypercellularity, sheeting, necrosis, and macronucleoli in patients with relapse were remarkable, but were not statistically significant. Recurrence was detected in 6 of 15 patients with AM diagnosed only with minor atypia criteria (p=0.192). Although Ki67 LI values were significantly lower (mean, 5.28%, p=0.028) in meningiomas diagnosed with minor atypia criteria only, they were higher in patients with small cell formation and macronucleoli existence (mean, 9.4% and 9.58%, p=0.0025 and p=0.030, respectively).

We frequently detected the presence of small cells (65%) in patients with recurrence, but was not statistically significant as in Barresi et al.'s study (p=0.801). In two separate studies, they reported that macronucleoli was associated with the risk of recurrence (2,5). Loewenstern et al. also reported results similar to ours (22).

Previous studies have shown that the presence of necrosis is related to the possibility of recurrence (6,21). In our study, necrosis was observed in 37.5% of patients with recurrence, and necrosis was not statistically significantly related to both recurrence and PFS (p=0.067, p=0.830, respectively). Barresi et al. also reported similar results (5).

Ruiz et al. reported that high cellularity of AMs was an indicator of increased recurrence risk (36). In our study, hypercellularity was observed all patients with recurrence, but was not statistically significantly related between hypercellularity and both recurrence and PFS (p=0.215, p=0.942, respectively), which is consistent with the results of a recent study (5).

Previous studies also expressed that sheeting is one of the minor atypia criteria that can predict recurrence (2,5). In our study, sheeting was not statistically significantly related with recurrence, but significantly with PFS (p=0.049).

Approximately 87% of patients had histopathologically patternless areas, with meningothelial (40%, n=30) as the most common main pattern distributions in the remaining areas, followed by transitional (34.7%, n=26) and fibroblastic (18.7%, n=14) meningiomas. The main pattern was not statistically significantly related to both recurrence and PFS (p=0.846 and p=0.174, respectively). To the best of our knowledge, no further studies analyzed the main morphological pattern observed in AMs histopathologically.

Although the name of the tumor is "atypical" according to the 2016 WHO classification, the presence of nuclear atypia (nuclear pleomorphism) is caused by degenerative changes and therefore is not accepted as a criterion for the AM definition (31,34). However, a significant relationship between nuclear atypia and both tumor recurrence and PFS was found in this study (p=0.029 and p=0.044, respectively).

Meningioma has been known to induce changes in the adjacent bone as hyperostosis and direct invasion. Whether the effects of hyperostosis on survival differed between AM and benign meningioma remains unclear. However, the only study showing that bone involvement was associated with increased recurrence/progression, and decreased survival in AM was also referred in the 2016 WHO classification (13,20,31). In this study, bone invasion was detected in three patients (4%), 2 of them (66.6%) recurred. Both patients were totally resected during their first operations (Simpson grade 1 and 2). However, bone invasion was not significantly related with recurrence and PFS (p=0.110 and p=0.60, respectively).

The presence of Psammoma bodies has been reported as a protective prognostic factor for tumor recurrence (3,36). In this study, no Psammoma body was detected in 12 of 20 patients with recurrence but rare in 6 of 8 patients, but without statistically significant relationship (p=0.774).

PR expression is known as a prognostic factor for better biological behavior and less risk of recurrence in meningiomas (23,24). In this study, PR expression was evaluated in 21 patients with AM only, and three of them had recurrence. Immunohistochemically, two of them are immuno-negative, whereas in the other cases, focal and weak expressions were observed. Although the number of patients is insufficient, this suggests that loss of PR expression may be a poor prognostic factor.

Similar to other studies, AMs are slightly more common in women than men (F: M ratio, 1.34: 1) (10,22). Several previous studies have reported that male gender is considered as one of the clinical risk factors for AM (3,10,15,17,28,31,32,39). Other studies also showed that gender is not related to recurrence (27,29). In this study, the F: M ratio in patients with recurrence was 1.5: 1, but no statistical correlation was found (p=0.495). The mean KI-67LI value was also higher in women (8.44%) than men (8.10%). In contrast to previous studies, brain invasion was found to be more common in women (7 patients) than men (4 patients) (39). Although our results are not statistically significant, unlike many studies, females are more at risk in AM.

Previous studies suggested that the risk of recurrence increases at a young age in AMs (36,42). However, few studies suggest that older age is a recurrence predictor factor (2,11,22). In our study, age was not significantly related with both recurrence and PFS (p=0.191 and p=0.639, respectively); however, the mean age at the time of surgery was correlated with mortality (p=0.036).

Jenkinson et al. reported that the distribution of AMs according to specific anatomical regions is similar to Grade I meningiomas (16). Some studies report that AMs are more common in convexity (14,22,33). Besides, Ruiz et al. reported that convexity location of AMs is a protective prognostic factor of increased risk of recurrence (36). The most common tumor locations in our series were convexity (40%), followed by parasagittal area (21.3%), skull base (18.7%), and posterior fossa (5.3%), and recurrence rates were 33.33%, 18.75%, 35.71%, and 50%, respectively. No recurrence was observed

in tumors located in other sites. Statistically, the location was not associated with recurrence (p=0.548). However, Ki67 LI was significantly higher (mean 15.5%) in cerebellopontine angle meningiomas than in other localizations and Ki67 LI was found to be significantly affected by localization (p=0.005). Similarly, in a recent study, lateral skull base meningiomas showed significantly higher Ki67 LI (p=0.0031) (24).

The tumor size is associated with an increased likelihood of meningioma with WHO grade II and with increased risk of recurrence (14,24,28,33,41). However, studies also suggested otherwise (18,22). We found that the tumor size (mean ± SD) was 50.40 ± 20.5 mm in patients with recurrence and 43.36 ± 16.26 mm in those without recurrence. Larger tumor size was not significantly related with recurrence (p=0.720). However, in 14 cases who died, the mean tumor size was larger than that of patients who survived and was found statistically significant (p=0.034).

The maximum safe tumor resection and dural attachment remain the target for the treatment of meningioma. However, various studies have reported that AMs can often recur, even if they are completely removed (2,12,22,25). In the literature, some studies reported a significant relationship between the greater extent of resection and lower recurrence rate (15,27,28,35,41,42). Conversely, existing studies also revealed no significant relationship (20,29). In this study, the extent of resection both as GTR and STR was evaluated based on the Simpson classification. The Simpson grade There was not significantly related with recurrence and PFS (p=0.845 and p=0.954, respectively). Similarly, GTR/STR was not significantly related with both relapse and PFS (p=0.887 and p=0.528, respectively).

Although some experiences with combined surgery and radiation therapy for high-grade meningiomas do not show any relationship between the extent of resection and PFS (4,20,27,29,35,40), others report that adjuvant RT is effective for high-grade (WHO grades II and III) meningiomas (15,19,37,42). In this study, seven patients were administered with conventional fractional RT postoperatively and three with stereotactic radiosurgery (gamma knife). PFS was 38.56 months in patients treated with RT and 39.03 months in others. Only one patient who received RT died, the one with small cell lung carcinoma metastasis in AM. However, the number of patients in this study was limited to draw a conclusion (n=10).

This study has several limitations. In a series of 314 patients, only 75 had AM with appropriate criteria in this study. In addition, the study is limited as it is conducted in a single institution and retrospectively. The mean follow-up time of 44.8 (0–109) months may not be long enough for the recurrence tendency. Brain and bone invasion, RT history, and PR immunohistochemistry limit the statistical analysis due to their small incidence the series. Determining the causes of death was limited. The distribution of patients according to locations was not homogeneous. The entire tumor tissue was histopathologically analyzed in 52% of patients, but only partially analyzed in 48% of patients (mean number of blocks, 7.3 [range, 3–23]).

CONCLUSION

Our study clearly demonstrates the role for high mitotic rate, brain invasion, and sheeting as risk factors for PFS in AMs. However, according to the 2016 WHO criteria, none of the diagnostic histopathological criteria were determined as a predictive factor for recurrence; however, these factors keep their prognostic value because they determine the WHO grade. Despite being described as a degenerative change, nuclear atypia was statistically significantly related with both tumor recurrence and PFS. Therefore, this morphological feature should be carefully considered.

Clinical factors such as advanced age, female sex, posterior fossa location, and larger preoperative tumor size in patients with recurrence were remarkable but not statistically significant. The extent of resection also did not show any prognostic feature.

In this study, we found that predicting the recurrence is difficult with the presence of any clinicopathological features in AMs. The findings should be evaluated together, and patients diagnosed with AM should be closely monitored. We think that molecular variables that can be determined by routine neuropathological analysis will be needed in the future.

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