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ORIGINAL ARTICLE - TUMOR - MENINGIOMA

Risk factors associated with postoperative recurrence in atypical intracranial meningioma: analysis of 263 cases at a single neurosurgical centre

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Abstract

Objective Atypical meningioma (AM) has a high rate of local recurrence after surgery, and the role of adjuvant radiotherapy in AM remains controversial. We analysed progression-free survival (PFS) and identified the factors associated with postoperative recurrence in AM patients.

Methods Data were obtained from 263 AM patients who underwent surgery at our institution between October 2009 and September 2018. Analyses included factors such as the extent of surgical resection, MIB-1 labelling index, brain invasion and therapy modality. Univariate and multivariate analyses were used to assess recurrence-related prognostic factors.

Result The median follow-up duration was 41 months, and the median PFS was 28 months. Gross total resection (GTR) was achieved in 213 (81.0%) patients, and 86 (32.7%) patients received postoperative radiation therapy (RT). During follow-up, there were 61 (23.2%) tumour recurrences. In a Cox multivariate analysis, MIB-1 labelling index (hazard ratio = 2.637; $p < 0.001$), secondary tumour (hazard ratio = 3.541; $p < 0.001$), tumour size (hazard ratio = 1.818; $p = 0.032$) and extent of resection (hazard ratio = 2.861; $p < 0.001$) were independent significant predictors of tumour recurrence. RT was associated with reduced tumour recurrence in subtotal resection (STR) ($p = 0.023$) but not GTR ($p = 0.923$). An analysis of 6 meningioma patients who underwent more than 3 operations suggested that the recurrence time became shorter and the MIB-1 labelling index increased as the number of recurrences increased.

Conclusions MIB-1 labelling index, secondary tumour, tumour size and extent of resection were powerful predictors of recurrence in AM patients. Postoperative RT did not decrease the risk of recurrence in GTR patients.

Keywords Atypical meningioma · Progression-free survival · Recurrence · Adjuvant radiotherapy · Prognostic factors

Introduction

Meningiomas, which are the most common intracranial brain tumours, account for more than 35% of primary brain tumours [7]. According to the grading system of central nervous system (CNS) tumours proposed by the 2016 World Health Organization (WHO) classification, meningiomas are classified into three grades (meningioma, atypical meningioma (AM) and anaplastic meningioma) with 16 histological subtypes [21]. Previously, AM (WHO grade II) was diagnosed when at least 3 of the following 5 histological features were present: spontaneous necrosis, architectural sheeting, prominent nucleoli, high cellularity and small cells (tumour clusters with a high nuclear: cytoplasmic ratio) [20]. According to the 2016 classification, brain invasion joins a mitotic count of 4 or more as a histological criterion that can alone suffice for the diagnosis of AM [21].

AM (WHO grade II) accounts for approximately 4.7–7.2% of all meningiomas, and its postoperative recurrence rate is approximately 29–52% [20]. Many factors, such as surgical resection, tumour size, and proliferation index, have been shown to potentially affect tumour recurrence [3, 13, 22, 26,

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27]. Many studies have recommended complete resection as the first choice for patients with AM [3, 9, 12, 22, 32]. Until recently, whether adjuvant RT reduces recurrence after the surgical resection of AM has remained controversial; the role of adjuvant RT has continued to be particularly controversial after GTR [3, 4, 13, 22, 26, 27, 29]. Conflicting results in previous studies may have been caused by small case series or potential selection bias from different studies. Therefore, studies involving a relatively large number of patients from a single centre are needed.

Over the past decade, more than 300 patients were diagnosed with AM at our centre. In this retrospective study, we analysed the medical records of 263 eligible patients to identify the prognostic factors affecting the tumour recurrence rate and PFS in AM patients. Another objective of this study was to investigate the impact of postoperative RT on local recurrence in patients who underwent GTR and STR.

Materials and methods

Patient selection

In total, 4647 consecutive patients were diagnosed with meningiomas at our institution between October 2009 and September 2018, 302 (6.5%) of whom were diagnosed with AM (WHO grade II). In this cohort, the pathology of 52 patients (19.8%) was determined according to the criteria of the 2016 CNS WHO, while the pathology of the other patients ($n = 250$) was determined according to the criteria of the 2007 CNS WHO. The pathologies of these 250 patients were re-reviewed by a neuropathologist independent of the outcomes based on the 2016 criteria. Thirty-nine patients were excluded from participation in the present study due to the following reasons: inadequate follow-up time (defined as a minimum of 6 months), multiple intracranial tumours, and incomplete information or refusal to join the study. The flow diagram of patient selection is shown in Fig. 1. Overall, 263 eligible patients with complete information were included in this retrospective study. Informed consent was obtained from all patients or their families. The follow-up time of all enrolled patients was longer than 6 months.

Data acquisition and parameters assessed

The baseline characteristics of the patients (e.g., pathology reports, imaging scan, surgical records) were obtained from our institutional records. The follow-up information was obtained by reviewing magnetic resonance images (MRI) and telephone communications. The following parameters were collected and analysed: sex, age at surgery, tumour location (cerebral convexity, skull base, parasagittal/falx cerebri, or intraventricular), preoperative tumour size (maximum diameter), primary or secondary tumour, peritumoural oedema (degree 0 of Trittmacher criteria) [28], brain or bone involvement, preoperative Karnofsky Performance Status (KPS), extent of resection, tumour necrosis, MIB-1 labelling index, treatment and recurrence.

The patients were divided into two groups according to age (≤ 50 and > 50 years), two groups according to the tumour location (convexity and non-convexity, i.e., skull base, parasagittal/falx cerebri, or intraventricular), and two groups according to the tumour size (threshold: 41.5 cm, as calculated from the maximum Youden's index by statistical software).

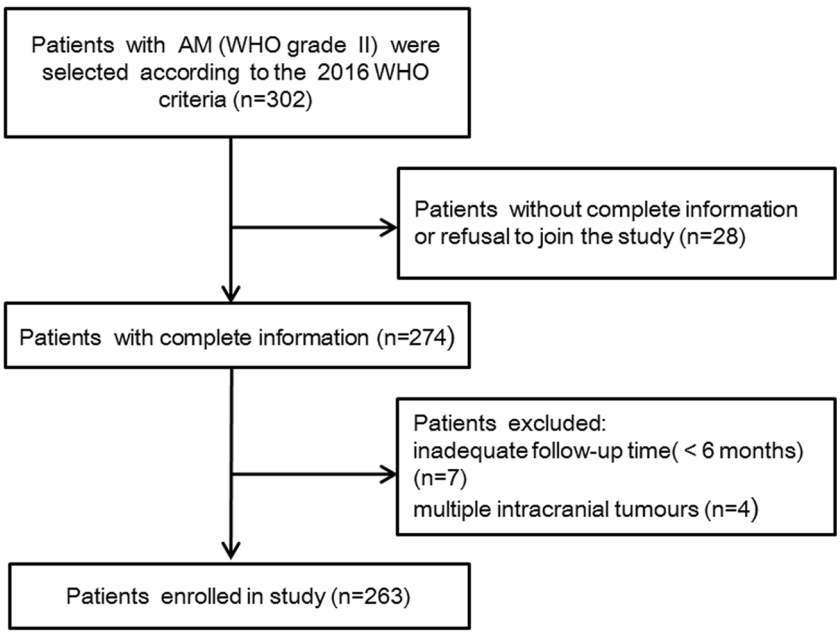

Fig. 1 Patient selection in this study

Bone and brain invasion were explored if they were described in the operative recordings and/or postoperative pathology reports. The preoperative KPS was used to classify the tumours into the following two categories according to symptoms: basically normal (KPS 70–100) and severe (KPS ≤ 70). The extent of resection was documented as GTR (Simpson grade I–III excisions) or STR (Simpson grade IV excision). The MIB-1 labelling index was used to divide the subjects into two groups (≤ 10% and > 10%) [14]. Tumour recurrence was defined as new lesions or a significant growth of (more than 25%) residual tumour on an MRI scan [30].

Treatment

In this study, all patients underwent surgery. The extent of resection was determined based on the operative recordings and postoperative imaging. The surgeons recommended the patients with AM to accept RT when they underwent STR or received a second surgery. The radiation regimen was determined by radiation oncologists according to the tumour location and size 3 to 4 weeks after surgery. Adjuvant RT was usually delivered at a median dose of 56 Gy (range, 54–60 Gy) at 2 Gy per fraction.

Statistical analysis

We defined the PFS as the time between surgery and tumour recurrence and chose this variable as the endpoint. A univariate analysis was performed to determine the prognostic factors that influenced recurrence. A Cox regression was used for the multivariate analysis. Then, Kaplan-Meier survival analyses were used to assess PFS. A log-rank test was used to test the equality of the Kaplan-Meier curves. The relative risk of tumour recurrence was calculated with a 95% confidence interval for each variable, and $p < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using IBM SPSS Statistics 21.

Results

Patient characteristics

The detailed characteristics of all 263 patients are presented in Table 1. There were 164 females and 99 males (F:M = 1:0.6). The median age of the patients was 52 years (range, 20–85 years). The median follow-up period was 41 months (range, 6–118 months). The lesions were located at a convexity in 89 patients (33.8%) and non-convexity in 174 patients (66.2%). The median tumour size was 43 mm (range, 12–98 mm). The median MIB-1 labelling index of the patients was 10% (range, 2–40%). There were 232 patients (88.2%) with primary tumours and 31 patients with secondary AM

Table 1 Baseline characteristics of patients with atypical meningioma

Variable	No. of patients (%)
Overall	263 (100)
Sex	
Female	164 (62.4)
Male	99 (37.6)
Age (years)	
≤ 50	125 (47.5)
> 50	138 (52.5)
Tumour location	
Convexity	89 (33.8)
Skull base	86 (32.7)
Parasagittal/falx cerebri	76 (28.9)
Intraventricular	12 (4.6)
Tumour size (mm)	
< 41.5	123 (46.8)
≥ 41.5	140 (53.2)
Primary or secondary tumour	
Primary tumour	232 (88.2)
Secondary tumour	31 (11.8)
Peritumoural oedema	
Yes	146 (55.5)
No	117 (44.5)
Brain involvement	
Yes	59 (22.4)
No	204 (77.6)
Bone involvement	
Yes	60 (22.8)
No	203 (77.2)
Preoperative KPS	
> 70	149 (56.7)
≤ 70	114 (43.3)
Extent of resection, Simpson	
I	69 (26.2)
II	99 (37.7)
III	45 (17.1)
IV	50 (19.0)
Tumour necrosis	
Yes	42 (16.0)
No	221 (84.0)
MIB-1 labelling index	
≤ 10	173 (65.8)
> 10	90 (34.2)
Postoperative radiotherapy	
Yes	86 (32.7)
No	177 (67.3)
Recurrence	
Yes	61 (23.2)
No	202 (76.8)

(11.8%) after previously treated grade I meningioma. In total, 146 patients (55.5%) exhibited significant brain tissue oedema surrounding the tumour. Brain and bone involvement were found in 59 (22.4%) and 60 (22.8%) cases, respectively. Overall, 213 patients (81.0%) underwent GTR, and 26.2, 37.7 and 17.1% of these patients had Simpson grades I, II, and III, respectively. The other patients (19.0%) underwent STR. Tumour necrosis was observed in 42 patients (16.0%). According to the pathology reports of these 263 patients, the MIB-1 labelling index was over 10% in 90 patients. Among the entire cohort, 86 patients (32.7%) accepted RT after surgery, the median dose of which was 56 Gy (range, 48–62 Gy), and 61 patients (23.2%) experienced tumour recurrence.

Prognostic factors

The median PFS was 41 months (range, 3–106 months). Table 2 shows the results of the univariate and multivariate analyses of the prognostic factors for tumour recurrence. Tumour size, secondary tumours, extent of resection and MIB-1 labelling index were significantly associated with tumour recurrence in both the univariate and multivariate analyses (Fig. 2a–d). Brain involvement was associated with increased tumour recurrence in the univariate analysis (HR 1.924; $p = 0.011$) but not the multivariate analysis (HR 1.148; $p = 0.624$). Sex, age at surgery, tumour location, peritumoural oedema, bone involvement, preoperative KPS, tumour necrosis and postoperative RT were not associated with tumour recurrence in either the univariate or multivariate analysis.

Postoperative RT did not decrease the risk of tumour recurrence according to the univariate and multivariate analyses of all patients. Then, we divided the 263 patients into a GTR group ($n = 213$) and an STR group ($n = 50$) and performed a univariate analysis. Overall, 71 patients who received RT were included in the GTR group and 10 patients were included in the STR group. There was a significant difference between the results obtained in the GTR (HR 0.966; 95% CI 0.476–1.958; $p = 0.923$) and STR (HR 0.246; 95% CI 0.074–0.825; $p = 0.023$) groups (Fig. 2e, f).

The results obtained in 6 meningioma patients who underwent more than 3 operations

Detailed information on the patients who underwent more than 3 operations is displayed in Table 3. Of these six patients, one patient underwent 5 operations, one patient underwent 4 operations, and the remaining 4 patients underwent 3 operations. Four patients received postoperative RT, one patient refused RT, and one patient received four gamma knife treatments in addition to surgery. At the end of follow-up, all six patients were alive; one patient had significant tumour growth even after five surgeries and four gamma knife treatments, and the other 5 patients had no tumour recurrence. Regarding tumour recurrence, the interval between relapses became considerably short, while the WHO grades and MIB-1 labelling indexes of the tumours became increasingly higher. To the best of our knowledge, this phenomenon has not been previously described.

Table 2 Univariate analysis and multivariate analysis prognostic factors in atypical meningioma

Variable	Progression-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Sex (female vs. male)	0.883	0.524–1.488	0.641			
Age, years (> 50 vs. ≤ 50)	1.352	0.802–2.276	0.257			
Tumour location (convexity vs. non-convexity)	0.712	0.401–1.265	0.247			
Tumour size, mm (< 41.5 vs. ≥ 41.5)	2.533	1.491–4.302	< 0.001*	1.818	1.052–3.141	0.032*
Primary or secondary (secondary vs. primary)	5.529	3.258–9.381	< 0.001*	3.541	2.018–6.213	< 0.001*
Peritumoural oedema (yes vs. no)	1.683	0.924–2.841	0.063			
Brain involvement (yes vs. no)	1.924	1.159–3.196	0.011*	1.148	0.662–1.991	0.624
Bone involvement (yes vs. no)	0.994	0.536–1.843	0.985			
Preoperative KPS (> 70 vs. ≤ 70)	1.018	0.610–1.699	0.945			
Extent of resection (STR vs. GTR)	4.243	2.540–7.089	< 0.001*	2.861	1.649–4.963	< 0.001*
Tumour necrosis (yes vs. no)	1.270	0.658–2.452	0.476			
MIB-1 labelling index (> 10 vs. ≤ 10)	3.432	2.028–5.806	< 0.001*	2.637	1.532–4.538	< 0.001*
Postoperative radiotherapy (yes vs. no)	0.629	0.351–1.128	0.120			

*Statistical significance. *HR*, hazard ratio; *CI*, confidence interval; *p*, *p* value; *KPS*, Karnofsky Performance Status; *STR*, subtotal resection; *GTR*, gross-total resection

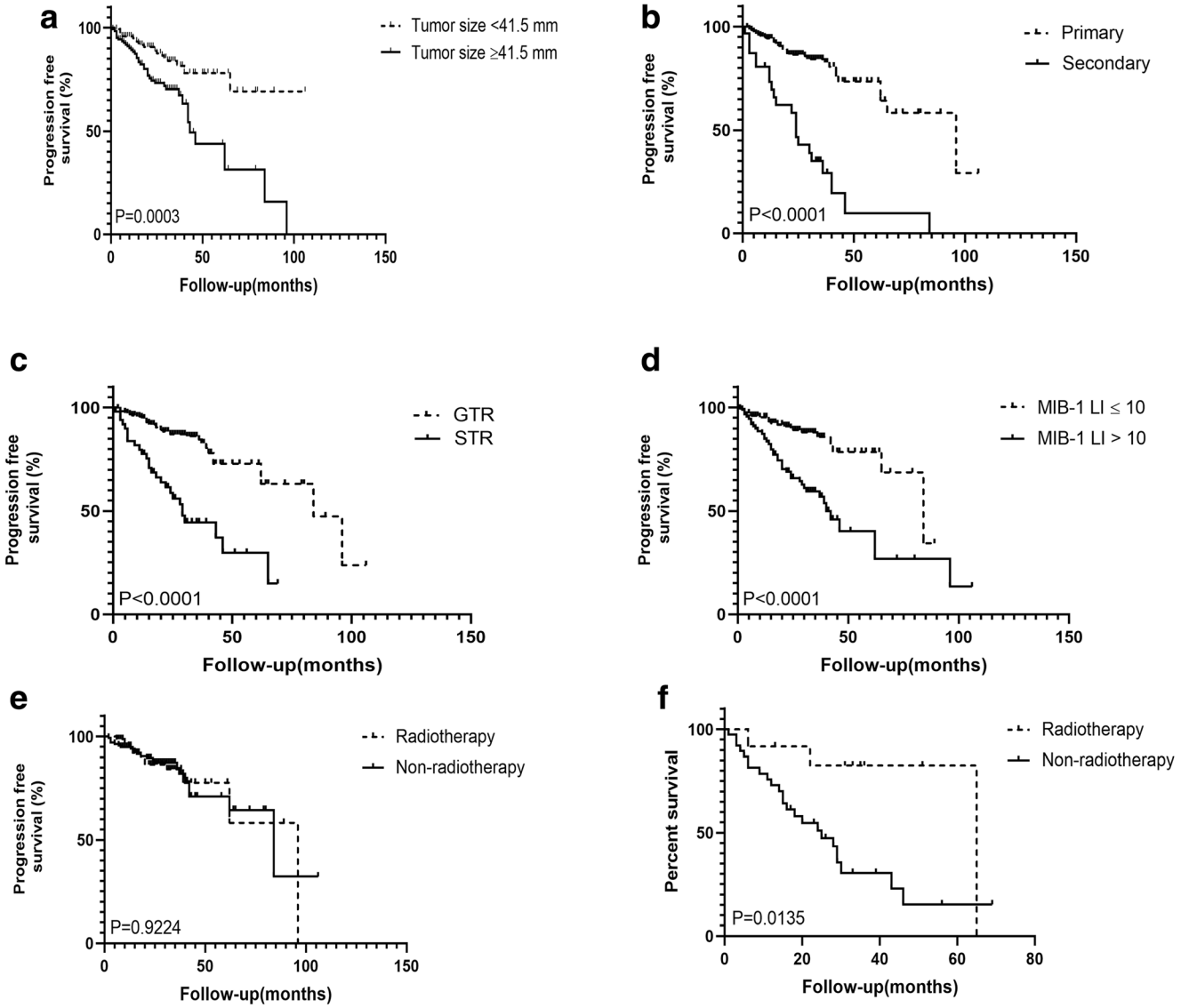

Fig. 2 Kaplan-Meier curves revealing that tumour size (**a**), secondary tumour (**b**), extent of resection (**c**) and MIB-1 labelling index (**d**) are associated with progression. Kaplan-Meier curves revealing that PFS rates for patients who underwent GTR (**e**) or STR (**f**) with or without adjuvant postoperative RT

Discussion

We identified several factors, such as the tumour size, secondary tumours, extent of resection and MIB-1 labelling index, correlated with progression-free survival. Furthermore, sex, age at surgery, tumour location, peritumoural oedema, bone involvement, preoperative KPS and tumour necrosis were not associated with tumour recurrence in either the univariate or multivariate analysis. Notably, our study showed that additional adjuvant RT could significantly increase PFS after incomplete resection but does not decrease the risk of recurrence in patients who undergo GTR.

In this study, based on Youden's index, a tumour size ≥ 41.5 mm is correlated with a worse PFS (Fig. 2a). Shakir also concluded that patients with residual tumour volumes larger than 8.76 cm^3 had an increased risk of disease progression according to Youden's index [27]. We found that the tumour size was significantly associated with tumour recurrence in patients with AM, which is consistent with the views presented in previous studies [3, 10]. However, other retrospective studies have reached different conclusions [9, 19, 26].

Regarding surgical resection, many retrospective studies have demonstrated that a greater extent of surgical resection is significantly associated with a lower probability of tumour recurrence in AM [3, 9, 12, 22, 24, 32]. Ayal et al. retrospectively analysed 963 patients who were diagnosed with AM and showed that the extent of resection was a powerful predictor of outcome [3]. Our findings support the notion that the complete surgical resection of lesions plays an important role in reducing tumour recurrence (Fig. 2c). In our opinion,

Table 3 Treatments and pathological information for patients with more than 3 operations

Basic information			Date of surgery, the WHO grade and MIB-1 labelling index of tumour					
Case	Sex	Date of birth	The 1st operation	The 2nd operation	The 3rd operation	The 4th operation	The 5th operation	Other treatments
1	F	1932	2009; WHO-I MIB-1 (−)	2012; WHO-I; MIB-1 (2%)	2018; WHO-II MIB-1 (5%)	–	–	2018; Radiotherapy (56Gy)
2	F	1970	2011; WHO-I MIB-1 (5%)	2015; WHOI–II; MIB-1 (15%)	2017; WHO-II MIB-1 (40%)	–	–	2015; Radiotherapy (52Gy)
3	F	1960	2010; WHO-I MIB-1 (−)	2015; WHO-II MIB-1 (5%)	2017; WHO-II MIB-1 (40%)	2018; WHO-II MIB-1 (40%)	–	2015; gamma knife radiosurgery
4	F	1952	2003; WHO-I MIB-1 (−)	2011; WHO-I MIB-1 (5%)	2016; WHO-II MIB-1 (10%)	–	–	No (refused radiotherapy)
5	F	1947	2000; WHO-I MIB-1 (5%)	2010; WHOI–II; MIB-1 (10%)	2015; WHO-II MIB-1 (20%)	–	–	2010; Radiotherapy (54Gy)
6	M	1945	1996; WHO-I MIB-1 (−)	2004; WHO-I MIB-1 (−)	2011; WHO-I MIB-1 (−)	2014; WHOI–II; MIB-1 (1%)	2017; WHO-II MIB-1 (15%)	Since2008, 4 gamma knife radiosurgery

complete surgical resection is viewed as the first-line treatment for patients with preoperatively suspected AM. During the surgery, the surgeon should maximize the extent of tumour resection, as this approach was highly significant in improving the prognosis of the patients and reducing tumour recurrence.

In our cohort, secondary AM carried a distinctly higher risk of recurrence as compared with primary AM (Fig. 2b). Li et al. collected clinical data from 302 patients with atypical meningioma, including 52 patients with secondary tumours. These authors found that secondary tumours tended to be associated with high recurrence and mortality rates [19]. A study involving a series of 194 patients demonstrated that secondary tumours were associated with worse local control and overall survival (OS) than primary tumours [18]. The findings of some previous reports are also consistent with these conclusions [6, 31]. Among the six patients who underwent more than 3 operations, we found that regarding tumour recurrence, the interval between relapses became considerably shorter, and the WHO grades and MIB-1 labelling indexes of the tumours were significantly elevated (Table 3). We propose that the risk of recurrence is significantly higher among patients in the secondary group than among patients in the primary group, and this information may be helpful when deciding to perform RT for secondary AM given its highly malignant nature.

MIB-1 labelling index is a powerful prognostic tool in AM. Abry et al. performed a literature search and identified 53 articles that reported a positive correlation between MIB-1 labelling index and the histological malignancy grade [2]. These authors also found that the mean labelling index in AM was 8% and that in meningiomas with a labelling index higher than 4%, the relapse rate increased. In our study, we show that an MIB-1 labelling index higher than 10% is significantly correlated with a higher recurrence rate in patients (HR 2.637; 95% CI 1.532–4.538; $p < 0.001$). Bruna et al. found that an MIB-1 labelling index $\geq 9.9\%$ was associated with a higher probability of tumour recurrence in patients with either AM or anaplastic meningioma [5]. Several studies have also suggested that an MIB-1 labelling index of 10% is a powerful prognostic marker that predicts the outcome of AM [9, 14, 22].

In this study, the results of the statistical analyses showed that additional postoperative RT improved tumour control only in the patients who underwent STR (HR 0.246; 95% CI 0.074–0.825; $p = 0.023$). This finding is consistent with the results reported by Zhi et al. and Li et al. [19, 32]. For incompletely resected tumours, the European Association of Neuro-Oncology (EANO) guidelines recommend that adjuvant RT (54–60 Gy given in 1.8–2.0 Gy per fraction) should be considered [11]. Observation and fractionated RT are both therapeutic options for GTR patients because the role of postoperative RT in GTR patients remains controversial, and prospective data on adjuvant RT after gross total resection are missing [11, 15, 17, 23, 25]. Most studies advocate for the use of adjuvant RT in patients with AM after incomplete resection [1, 3, 4, 16, 19, 32]. However, in a recent meta-analysis, Hasan evaluated the benefit of RT and suggested that adjuvant RT had an important effect on tumour control in patients with AM after GTR [13]. Shakir also implied that the use of postoperative RT was associated with improved PFS, even among

patients who underwent GTR [27]. In contrast, other studies have reported that postoperative RT was not beneficial in this group of patients [8, 22]. When considering potential long-term toxicity, which can occur in up to 53% of cases after RT, after a mean follow-up of 12 years [11], we do not recommend that GTR patients receive additional postoperative RT.

Limitations of the study

One of the limitations of this study is that this study is retrospective. Additionally, a small portion of the clinical data, such as the extent of resection, may have been affected by the subjective opinions of the surgeon. Another limitation is that the number of GTR patients who also received postoperative RT was small. However, despite these limitations, we hope that the detailed information of these 263 patients with AM could be useful for future studies.

Conclusion

According to the statistical results of this study, the patients with AM who had a tumour size greater than 41.5 mm and an MIB-1 labelling index higher than 10% had a significantly higher rate of recurrence. Secondary tumours and the extent of resection are powerful predictors of outcomes, and GTR could significantly decrease the recurrence of AM. With recurrence of these tumours, the interval between relapses becomes considerably shorter, while the WHO grade and MIB-1 labelling index of recurrent tumours are significantly higher. Additional adjuvant RT could significantly increase PFS after incomplete resection but does not decrease the risk of recurrence in patients who undergo GTR. For AM patients after surgery, individualized treatment should be provided by doctors after a comprehensive consideration related to various patient and tumour factors.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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