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Benign versus atypical meningiomas: Risk factors predicting recurrence

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ABSTRACT

Objective: The aim of the study is to determine which clinic, radiologic, and surgical characteristics of benign and atypical meningioma are associated with tumor progression.
Methods: 335 patients who underwent gross-total resection of intracranial benign and atypical meningiomas between 2000 and 2009 were followed during the period of at least 3 years. Clinical, radiological and surgical features possibly associated with progression-free survival and influencing tumor recurrence were assessed.
Results: 291 lesions were benign (WHO Grade I) and 44 were atypical (WHO Grade II). In the median follow-up period of 82 months 34 meningiomas recurred. The 3-, 5- and 10-year progression-free survival (PFS) rates for benign and atypical tumors were 99.7 and 81.4%, 97.5 and 69.7%, 87.5 and 69.7%, respectively. In a Kaplan–Meier analysis subpial plane of surgical dissection (pial invasion) was associated with increased tumor progression both in benign ($p = 0.0084$) and atypical cohort ($p = 0.0104$), and bone involvement ($p = 0.0033$) and peritumoral brain edema ($p = 0.0073$) were associated with increased tumor progression only in atypical meningiomas. In a multivariate analysis pial invasion and WHO Grade II type were significantly associated with tumor recurrence. All recurrences in atypical meningioma group occurred within 4 years of the surgical resection.
Conclusion: Pial invasion is an important predictor of tumor recurrence in benign and atypical meningiomas. In atypical meningiomas bone involvement and large peritumoral brain edema are associated with increased tumor progression.

1. Introduction

Meningiomas are usually slow-growing, well-circumscribed, extra-axial tumors, and account for about 20% of all central nervous system neoplasms. Despite gross-total resection many patients experienced tumor recurrence. Each recurrence carries further risk of repeated surgery and much greater risk of morbidity and mortality for the patient [1]. It has been well established that the completeness of resection and histological

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type of meningioma are prognostic factors for tumor recurrence. The World Health Organization (WHO) grading system is helpful for predicting aggressive meningioma subtypes. Although most meningiomas are benign, approximately 10–40% demonstrate a more aggressive clinical behavior and correspond to atypical (Grade II) and anaplastic (Grade III) subtypes [2–4]. Among non-benign lesion types, atypical meningiomas are most common, however, there is limited information about them. According to the 2000 and 2007 WHO tumor classification [5], brain invasion does not imply WHO Grade III meningioma. This revision of diagnostic criteria was associated with increased incidence of atypical meningiomas over the last decade [4]. Atypical meningiomas show a heterogeneous treatment response in contrast to anaplastic subtype which carry uniformly poor prognosis. Some atypical meningiomas behave most like benign subtype, others show slow progression from atypical to anaplastic lesions or exhibit a precipitous decline [3]. Progression-free survival at 5 years after definitive treatment of atypical meningiomas has been reported to be 38–62% [6–8]. However, even benign meningiomas sometimes show relatively rapid growth and may recur after total removal. Recurrence has been estimated to occur in 9–15% of benign meningiomas after total removal [9–11]. Preoperative identification of high risk groups for recurrence among benign and atypical subtypes would help guide management and reduce treatment related toxicity. Postoperative radiotherapy (RT) is used to reduce the probability of recurrence, however, it remains unclear which benign and atypical meningiomas will recur. Thus, we should try to identify those patients who are at risk of recurrence and consider adjuvant postoperative RT for these individuals.

The aim of the study is to determine which clinic, radiologic, and surgical characteristics of benign and atypical meningioma are associated with tumor progression and analyze which prognostic factors are common and which are divergent in the populations of benign and atypical meningiomas.

2. Material and methods

2.1. Patient population

From 2000 to 2009, we operated on 463 patients with primary intracranial meningiomas. We have retrospectively reviewed the clinical records, neuroimaging studies, and follow-up data of the treated patients. We included in the study patients with the diagnosis of benign or atypical meningioma and no multiple meningiomas or neurofibromatosis who had undergone gross-total resection (GTR) and were observed for at least 3 years. The GTR designation included Simpson Grade I and Grade II excisions [12], based on the surgeon's impression in the operative report with postoperative confirmation of absence of residual tumor checked via MR imaging at the 3rd postoperative month. 46 of the 463 patients were excluded because extent of resection was documented as subtotal resection (STR) which included Simpson Grade III and IV excisions. Twelve tumors represent malignant histological type (WHO Grade III). Fifty four patients were excluded because their follow-up period was less than 3 years. Sixteen of these died perioperatively and 38 patients died of various diseases within 3 years or were lost to follow-up. Sixteen patients had neurofibromatosis and/or were operated on for multiple meningiomas. A total of 335 patients met the inclusion criteria and were suitable for analysis.

2.2. Parameters assessed

Patient age at the initial surgery and patient gender were recorded. According to their ages patients were classified into two groups: patients younger than 60 years and patients of 60 years or older. All patients underwent Magnetic Resonance Imaging (MRI) before surgery. Tumor locations were placed into skull base and non-skull base. Tumor size was defined by the largest tumor diameter and categorized as large (≥4 cm) or small (<4 cm). Tumor margins were described as smooth or irregular. Calcification of the tumor was categorized as present or absent and edema around the tumor was classified as small and large according to Trittmacher criteria [13]. Surgical finding included cleavage plane with pial-cortical invasion present or absent. Bone changes were coded as present if they were reported in operative or imaging reports. Among atypical meningioma the use of postoperative adjuvant radiotherapy (RT) was registered.

2.3. Patient's follow-up

Patients were examined in the outpatient clinic. The patient's condition was assessed at follow-up based on neurological examination and brain MRI in all of the patients. First radiological examination performed 3 months after discharge was mandatory. Then, each patient with atypical meningioma underwent MRI every year. Postoperative MRI in cases of benign tumor was obtained every 1 to 3 years.

Time to recurrence was calculated from the date of GTR to the date of radiological evidence of tumor recurrence which was determined with MRI. Patients underwent follow-up until an endpoint of recurrence for progression-free survival (PFS) analysis. In patients who did not experience progression follow-up was censored at the last MRI study.

2.4. Statistical analysis

Tumor recurrence was analyzed against clinical and radiological factors. Association between these variables was tested by using Chi square and Fisher's exact tests. Risk for recurrence with a confidence interval of 95% (95% CI) was calculated for each variable, and statistical significance was determined for $p < 0.05$. PFS rates were estimated using the Kaplan–Meier method. Differences between survival curves were assessed by the long-rank test. The prognostic influence of different factors was determined by a multivariate analysis using the Cox's proportional hazards model.

3. Results

3.1. Patient and tumor characteristics

Of the 335 patients in the study, 44 (13%) had atypical and 291 (87%) had benign meningiomas. There were 246 women

(73.4%) and 89 men (26.6%) with a mean age at diagnosis of 57.9 ± 11.3 years (range 18–85 years). There was no significant association between the WHO grade and sex or age at diagnosis.

Patient and tumor characteristics are summarized in Table 1.

In 39 (11.6%) cases cleavage plane of dissection was predominantly subpial because of pia mater invasion. Intraoperative evidence of bone involvement included hyperostosis and bone destruction and was documented in 57 (17%) patients. However, bone samples were not sent for histopathological evaluation and hyperostosis or bone destruction were usually drilled down to normal bone. WHO Grade II meningiomas were significantly more often to exhibit pial invasion ($p = 0.0001$), present large edema around the tumor ($p = 0.001$) and surprisingly show higher tumor calcification rate ($p = 0.0047$). Of the 44 atypical meningiomas in the series, 11 (25%) received adjuvant postoperative radiotherapy in the form of 3D conformal radiotherapy.

3.2. *Recurrence rates*

The median radiographic follow-up period for the entire cohort was 82 months (mean 85 ± 24.5 months, range 36–158 months). Thirty four recurrences were detected during this time period. There were no significant differences in follow-up time between the WHO Grade I and the WHO Grade II tumors (Table 2a). WHO Grade II type was associated with a higher recurrence rate than WHO Grade I type ($p = 0.0001$) (Table 2b). Moreover, the mean time to progression was significantly shorter among patients in the WHO Grade II subgroup ($p = 0.0001$). The 3-, 5- and 10-year progression-free survival (PFS) rates for WHO Grade I meningiomas were significantly higher compared to atypical meningiomas (log-rank = 4.75, $p = 0.0001$) (Table 3, Fig. 1).

Table 1 – Patient and tumor characteristics.

Factor	Atypical meningioma (44 cases)	Benign meningioma (291 cases)	Total (335 cases)	*p*-Value
Age (years)				
Mean ± SD[a]	57.4 ± 10.5	58.0 ± 11.4	57.9 ± 11.3	0.5936
Range	28–78	18–85	18–85	
Median	58.5	58.0	58.0	
95% CI[b]	[54.2; 60.6]	[56.7; 59.3]	[56.7; 59.1]	
Age (years)				
<60	25 (56.8%)	155 (53.3%)	180 (53.7%)	0.6595
≥60	19 (43.2%)	136 (46.7%)	155 (46.3%)	
Sex				
Female	28 (63.6%)	218 (74.9%)	246 (73.4%)	0.1144
Male	16 (36.4%)	73 (25.1%)	89 (26.6%)	
Tumor size (cm)				
<4 cm	19 (43.2%)	130 (44.7%)	149 (44.5%)	0.8528
≥4 cm	25 (56.8%)	161 (55.3%)	186 (55.5%)	
Tumor location				
Skull base	26 (59.1%)	169 (58.1%)	195 (58.2%)	0.8987
Non-skull base	18 (40.9%)	122 (41.9%)	140 (41.8%)	
Pial invasion				
Present	17 (38.6%)	22 (7.6%)	39 (11.6%)	0.0001
Absent	27 (61.4%)	269 (92.4%)	296 (88.4%)	
Bone involvement				
Present	12 (27.3%)	45 (15.5%)	57 (17.0%)	0.0520
Absent	32 (72.7%)	246 (84.5%)	278 (83.0%)	
Tumor margins				
Regular	39 (88.6%)	272 (93.5%)	311 (92.8%)	0.2465
Irregular	5 (11.4%)	19 (6.5%)	24 (7.2%)	
Edema				
Absent/mild	30 (68.2%)	254 (87.3%)	284 (84.8%)	0.0010
Moderate/severe	14 (31.8%)	37 (12.7%)	51 (15.2%)	
Tumor calcification				
Present	7 (15.9%)	14 (4.8%)	21 (6.3%)	0.0047
Absent	37 (84.1%)	277 (95.2%)	314 (93.7%)	
Resection				
Simpson Grade I	26 (59.1%)	178 (61.2%)	204 (60.9%)	0.7924
Simpson Grade II	18 (40.9%)	113 (38.8%)	131 (39.1%)	
Adjuvant radiotherapy				
Yes	11 (25%)	–	11 (3.3%)	–
No	33 (75%)	–	324 (96.7%)	

[a] Standard deviation.
[b] Confidence interval.

Table 2a – Clinical follow-up.

	Atypical meningioma (44 cases)	Benign meningioma (291 cases)	Total (335 cases)	p-Value
Follow-up (months)				
Mean ± SD	81.9 ± 24.9	85.5 ± 24.4	85.0 ± 24.5	0.4621
Range	36–135	42–158	36–158	
Median	84.0	82.0	82.0	
95% CI	[74.3; 89.6]	[82.6; 88.3]	[82.4; 87.7]	

3.3. *Analysis of factors potentially related to progression-free survival (Kaplan–Meier analysis using log-rank testing)*

3.3.1. *Benign meningiomas*

Table 4 shows the correlation between clinical, radiographic and intraoperative findings and progression-free survival in benign and atypical meningiomas. Subpial surgical cleavage plane (pial invasion) was associated with an increased rate of progression compared to extrapial cleavage plane of dissection ($p = 0.0084$) (Fig. 2). Tumor recurred in 5 of 22 (23%) patients with subpial surgical plane. In contrast tumor progression was noted in 16 of 269 (6%) cases of extrapial surgical plane. There was no significant association between tumor relapse and other variables assessed.

3.3.2. *Atypical meningiomas*

Similarly to benign meningiomas in atypical tumors pial invasion (tumor progression in 53% of cases) was also associated with an increased rate of recurrence compared to no evidence of pial invasion ($p = 0.0104$) (Fig. 3 and Table 4). Furthermore, evidence of bone involvement ($p = 0.0033$) and large peritumoral brain edema ($p = 0.0073$) were also associated with tumor relapse (Figs. 4 and 5). Tumor progression was found in 7 of 12 (58%) cases with bone involvement and in 6 of 14 (43%) cases of large edema. On the other hand there was evidence of meningioma recurrence in 6 of 32 (19%) cases without evidence of bone involvement and 7 of 30 (23%) cases with small edema.

One of the 14 (7%) patients who received immediate postoperative radiotherapy experienced recurrence over the follow-up period, compared to 12 of the 30 (40%) patients who had not received radiotherapy. Using Kaplan–Meier analysis with log-rank testing, these differences were not statistically significant ($p = 0.079$).

3.4. *Multivariate analysis of factors predicting tumor recurrence*

In a multivariate analysis pial invasion and WHO Grade II type were significantly associated with tumor recurrence (Table 5). However, the Cox's regression model reached statistical significance only for the entire combined group of both WHO Grade I and Grade II tumors, while separate statistical models for benign and atypical meningiomas were not statistically significant. When a subpial plane of dissection changes to an extrapial plane the hazard ratio (HR) is 0.26 ($p = 0.0021$). This means that change in plane of dissection from subpial to extrapial causes a decrease in the risk of recurrence. Similarly a change from atypical to benign tumor decreases the risk of relapse (HR = 0.37; $p = 0.0158$).

4. Discussion

This retrospective analysis of prognostic indicators for recurrence from a single-institution case series of benign and atypical meningioma revealed that subpial plane of surgical dissection is associated with increased tumor progression both in benign and atypical cohort. Furthermore bone involvement and peritumoral brain edema were associated with increased tumor progression in atypical meningiomas. All recurrences in atypical meningioma group occurred within 4 years of the surgical resection.

The advantages of this series are the large number of cases, relatively high length of radiographic and clinical follow-up and direct comparison of the groups of benign and atypical meningiomas.

There is a general agreement that completeness of surgical resection and histological features (WHO classification) are the most important predictors of meningioma recurrence

Table 2b – Tumor recurrence.

	Atypical meningioma (44 cases)	Benign meningioma (291 cases)	Total (335 cases)	p-Value
Tumor recurrence	13 (29.6%)	21 (7.2%)	34 (10.2%)	0.0001
Tumor recurrence (months)				
Mean ± SD	31.0 ± 9.4	72.7 ± 25.2	56.8 ± 29.0	0.0001
Range	16–47	32–122	16–122	
Median	30.0	75.0	47.0	
95% CI	[25.3; 36.7]	[61.3; 84.2]	[46.7; 66.9]	

Table 3 – Progression-free survival rates in atypical and benign meningiomas.

	Atypical meningiomas (44 cases)	Benign meningiomas (291 cases)	Total (335 cases)
3-year progression-free survival rate	81.4%	99.7%	97.3%
5-year progression-free survival rate	69.7%	97.5%	93.9%
10-year progression-free survival rate	69.7%	87.5%	85.2%

[7,12,14]. Dziuk et al. [6] reported that in patients with atypical meningioma GTR was associated with lower recurrence rates (17%) than STR (87%). Palma et al. [3] revealed that radical resection (Simpson Grade I vs. Grades II–III) and histological type (WHO Grade II vs. WHO Grade III) were significantly related to progression and survival. In the Mayo Clinic series [15], estimated 5-year mortality rates in atypical and anaplastic meningiomas were 25 and 83%, respectively. Adeberg et al. [16] reported significant impact of histological grade on overall (81% for atypical and 53% for malignant meningioma at 5 years) and progression-free survival (50% for atypical and 13% for malignant meningioma at 5 years).

Because of well-known beneficial impact of GTRs on tumor control and survival we sought to define other clinical and radiologic features predicting recurrence of meningioma. There is limited knowledge on clinical features associated with progression especially in atypical meningiomas, which represents an intermediated prognostic group between the benign and malignant types. Furthermore, it was interesting to find out common factors that could affect tumor recurrence in benign and atypical cases.

Many case series postulated other prognostic factors associated with the meningioma recurrence rate but most of them were not uniformly accepted. Several studies reported significant influence of male sex on recurrence [17–19] although this has been not confirmed by other studies [10,20,21]. The explanation of this conflicting results is probably the fact that in many series males more frequently have atypical or anaplastic meningiomas [18,19] which are associated with poorer prognosis. Mahmood et al. [18] analyzed benign and malignant meningiomas separately and then found that gender did not influence the recurrence rate.

Perry et al. [19] reported increased rate of meningioma recurrence in patients at a young age (<40 years) but most studies found no significant difference among patients who have benign, atypical or anaplastic tumors [10,17,20]. However, some new studies found that older age (>60 years) is associated with unfavorable outcome [22–25] in series of atypical and malignant meningioma.

Among radiologic findings associated with less favorable outcome in patients operated on for meningioma are the presence of marked surrounding edema, absence of calcifications and the presence of irregular tumor borders or ''mushrooming''. The presence of irregular tumor margins is considered significant prognostic factor for tumor recurrence in that it could reflect high proliferative potential of meningioma [20]. Our study does not confirm this suspicion, both in

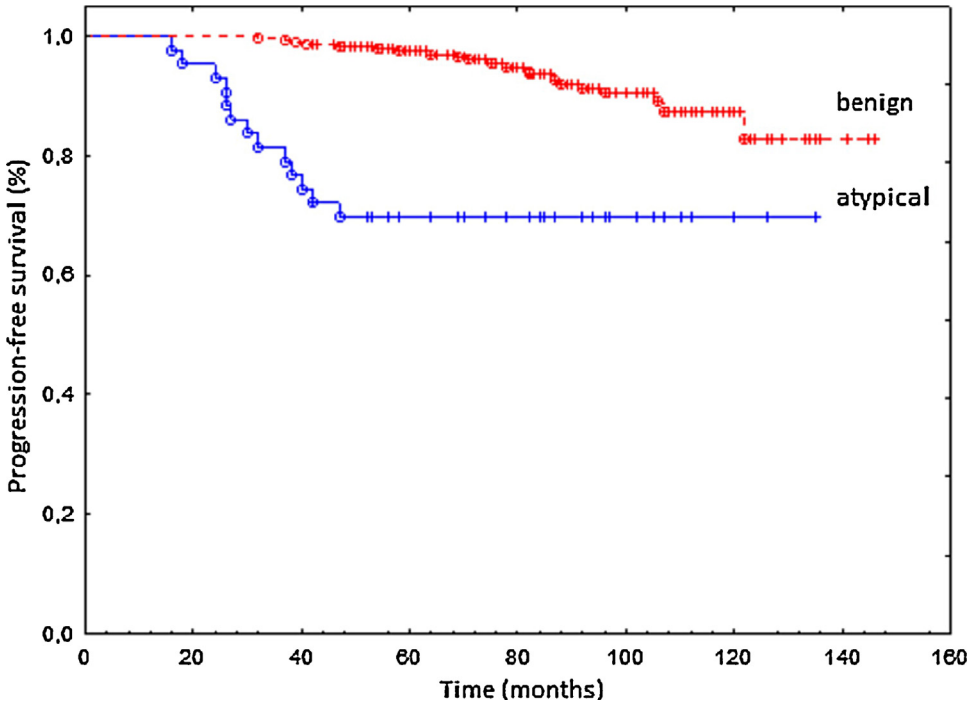

Fig. 1 – Kaplan–Meier progression-free survival curve of atypical versus benign meningioma. Log rank testing demonstrated a significant difference between the groups favoring benign subtype ($p = 0.0001$).

Table 4 – Patient and tumor factors influencing progression-free survival.

Factor	Variable	Atypical meningiomas		Benign meningiomas		Total	
		Log-rank test	*p*-Value	Log-rank test	*p*-Value	Log-rank test	*p*-Value
Sex	Female vs. male	−0.09	0.9247	−1.26	0.2091	−1.5	0.1344
Age (years)	<60 vs. ≥60	0.48	0.6301	0.32	0.7456	0.57	0.5708
Tumor size	<4 cm vs. ≥4 cm	0.12	0.9066	0.23	0.8155	0.29	0.7693
Tumor location	Skull base vs. non-skull base	0.75	0.4554	0.72	0.4721	1.01	0.3125
Pial invasion	**Present vs. absent**	**2.56**	**0.0104**	**2.64**	**0.0084**	**5.57**	**0.0001**
Bone invasion	**Present vs. absent**	**2.94**	**0.0033**	1.06	0.2888	**3.11**	**0.0019**
Tumor margins	Regular vs. irregular	−0.55	0.5835	−1.24	0.2138	−1.60	0.1088
Edema	**Absent/mild vs. moderate/severe**	**2.68**	**0.0073**	1.25	0.2127	1.31	0.1904
Calcification	Present vs. absent	−0.10	0.9233	−0.06	0.9560	0.69	0.4871
Resection	Simpson Grade I vs. Simpson Grade II	−0.49	0.6208	−1.31	0.1900	−1.39	0.1659
Radiotherapy	Yes vs. no	1.76	0.0790	–	–	–	–

Values in bold indicate statistical significance.

benign and atypical meningioma. Similarly, we did not find association between lack of tumor calcification and tumoral recurrence presence. Mantle et al. [26] demonstrated that the peritumoral edema grade correlated with tumor recurrence after complete resection. They found that brain invasion was demonstrated in all cases in which tumor recurred. It implies that tumor cortical invasion was the cause of peritumoral edema thus causing greater incidence of the tumor recurrence. In the current series, it was demonstrated that pial invasion assessed as lack of clear extrapial cleavage plane has a significant influence on increased recurrence rate, both in benign and atypical meningiomas. In our study a similar correlation was found between progression-free survival and higher amount of peritumoral edema only in atypical meningiomas. It suggests that larger amount of peritumoral edema is also associated with other postulated factors such as: tumoral compression to the adjacent parenchyma causing cerebral ischemia [27], compression of large veins or sinus vein producing venous engorgement [27], possible role of a secretory-excretory phenomenon (VEGF) [28,29] or tumor drainage vein hypoplasia [30]. Alwernia et al. [31] demonstrated that independent of histological finding subpial cleavage plane is associated with a higher recurrence rate than an extrapial cleavage plane, probably because meningioma tendency to invade the pia mater layer results in leaving small piece of tumor tissue during surgery. Our study

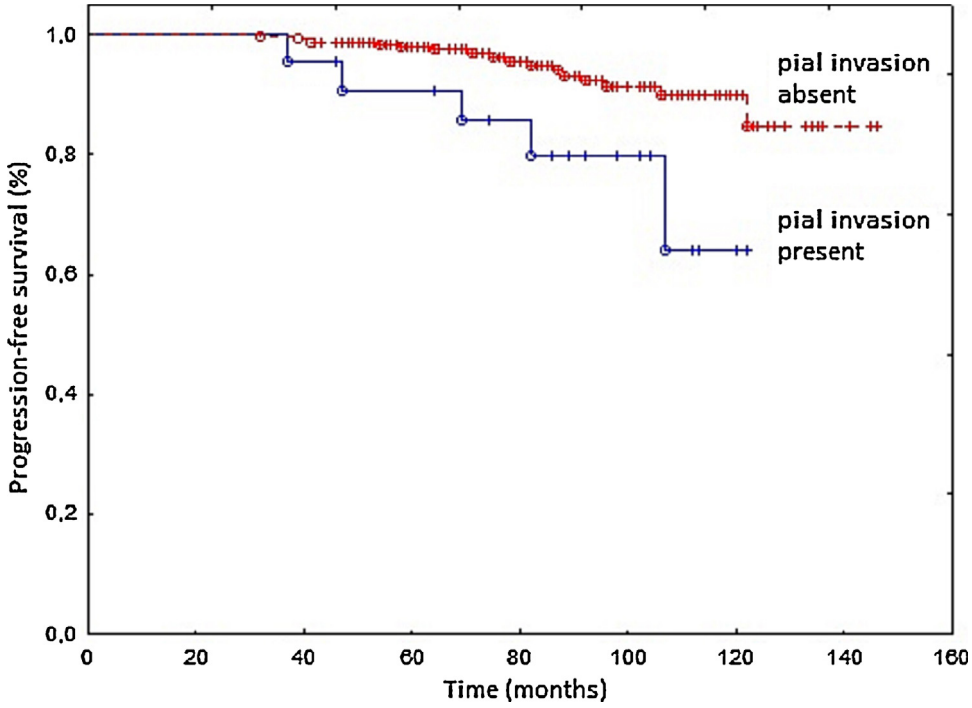

Fig. 2 – Kaplan–Meier progression-free survival curve of subpial versus extrapial surgical cleavage plane in patients with benign meningioma. Log rank testing demonstrated a significant difference between the groups favoring extrapial cleavage plane of dissection ($p = 0.0084$).

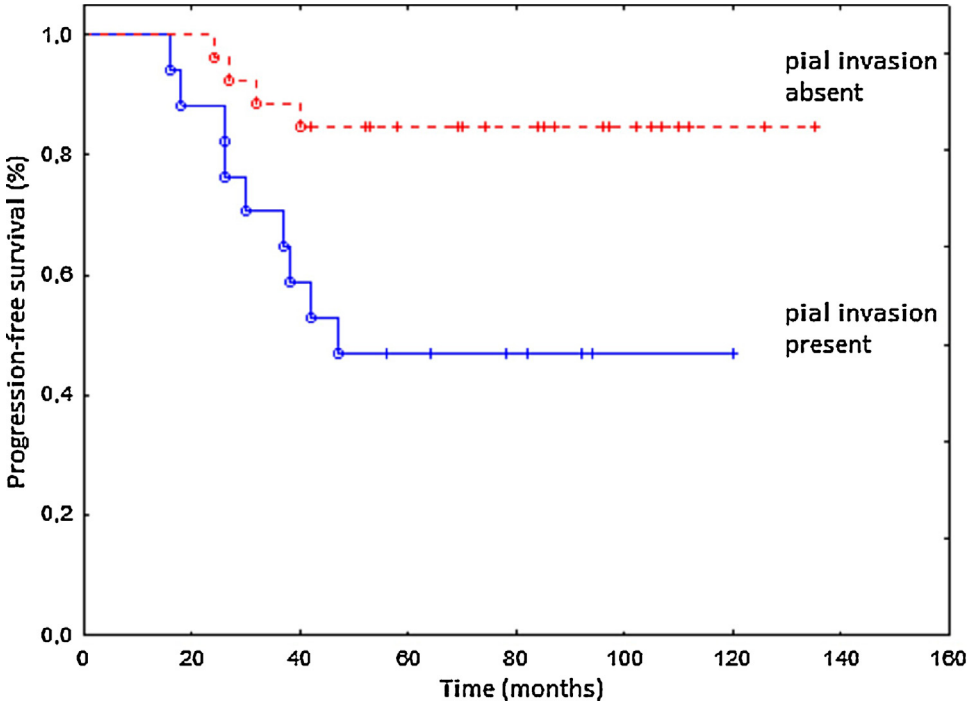

Fig. 3 – Kaplan–Meier progression-free survival curve of evidence of pial invasion compared with no evidence of pial invasion in patients with atypical meningioma. Log rank testing demonstrated a significant difference between the groups favoring no evidence of pial invasion ($p = 0.0104$).

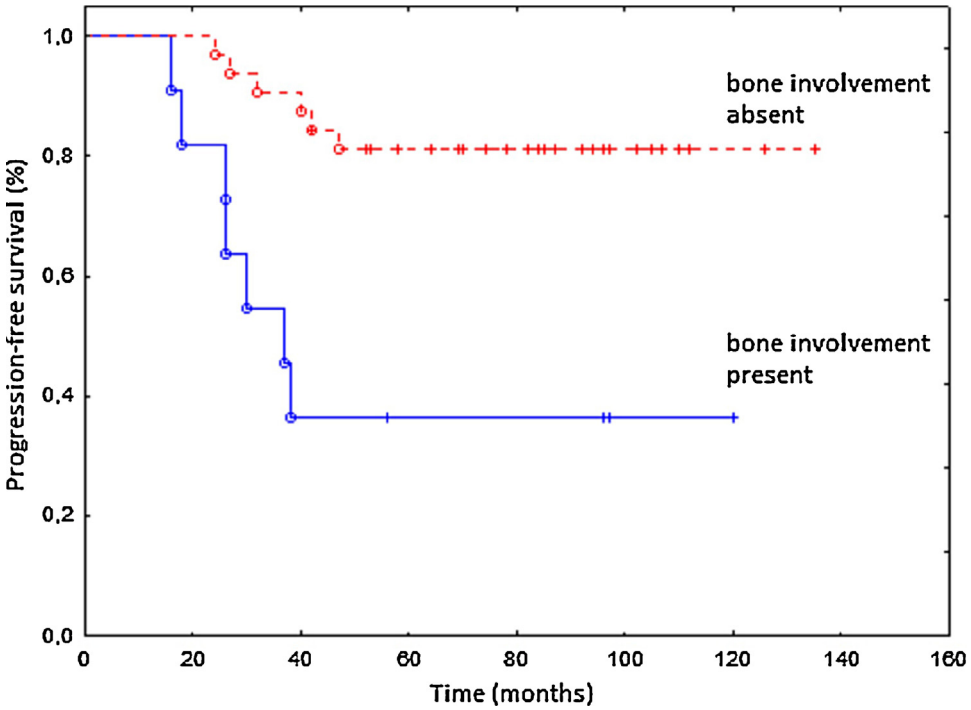

Fig. 4 – Kaplan–Meier progression-free survival curve of evidence of bone involvement compared with no evidence of bone involvement in patients with atypical meningioma. Log rank testing demonstrated a significant difference between the groups favoring no evidence of bone involvement ($p = 0.0033$).

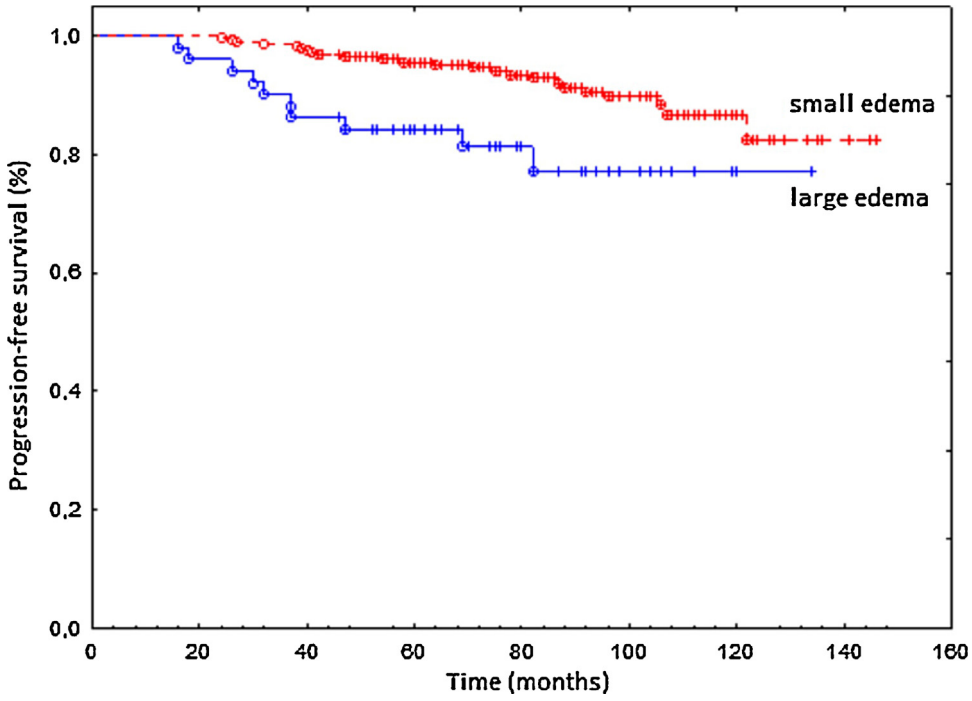

Fig. 5 – Kaplan–Meier progression-free survival curve of evidence of large versus small peritumoral brain edema in patients with atypical meningioma. Log rank testing demonstrated a significant difference between the groups favoring evidence of small edema ($p = 0.0073$).

confirm that pial invasion affects the recurrence rate in meningioma and probably these patients may benefit from postoperative adjuvant irradiation regardless of meningioma histology.

In this study we reported that bone involvement is associated with increased recurrence rate of atypical meningioma but does not influence cases of benign tumor. Bone involvement was considered poor prognostic factor of atypical meningioma in few studies [32,33]. Meningioma causes changes in adjacent bone usually in the form of hyperostosis, which results from direct tumor invasion into bone [34] and the new bone growth probably results from periosteal stimulation by tumor invasion [35]. Kallio et al. [36] reported patients with hyperostotic tumors had a 2.1-fold relative excess risk of death compared to patients without hyperostosis. In a study of Jaaskelainen [9] on histologically benign meningioma tumor attachment to bone was determined an independent risk factor for recurrence. Gabeau-Lacet et al. [32] found bone involvement in strong association with progression and death in atypical meningiomas. These authors postulated that worse outcomes in patients with bone involvement in the course of atypical meningioma reflect more

Table 5 – Multivariate analysis (Cox's model). Patient and tumor factors associated with recurrence in a patient operated on for intracranial meningioma.

Variable	Regression coefficient (*b*)	Standard error	*p*-Value	Hazard ratio	95% CI for hazard ratio	
					Lower	Upper
WHO Grade	**−0.98**	**0.41**	**0.0158**	**0.37**	**0.17**	**0.83**
Sex	0.47	0.40	0.2317	1.61	0.74	3.50
Age	−0.05	0.04	0.1883	0.95	0.89	1.02
Tumor size	−0.33	0.37	0.3723	0.72	0.35	1.49
Tumor location	−0.51	0.38	0.1813	0.60	0.29	1.27
Pial invasion	**−1.36**	**0.44**	**0.0021**	**0.26**	**0.11**	**0.61**
Bone invasion	−0.79	0.42	0.0578	0.45	0.20	1.03
Tumor margins	0.39	0.52	0.4524	1.48	0.54	4.07
Edema	−0.53	0.46	0.2462	0.59	0.24	1.44
Tumor calcification	−0.41	0.64	0.5197	0.66	0.19	2.33
Resection	0.25	0.38	0.5093	1.29	0.61	2.73

Values in bold indicate statistical significance.

aggressive biological characteristics of these meningiomas compared to those that do not invade bone and poor outcomes may result from inadequate treatment of affected bone. Positive correlation between bone involvement and increased rate of tumor progression confirms the importance of GTR in the outcome of patients with atypical meningioma since tumor invasion into bone may result in leaving a small amount of tumor and subsequent STR.

We examined the effect of postoperative radiotherapy on recurrence in patients with atypical meningioma and although there was a trend toward postoperative radiotherapy having a benefit on tumor recurrence, a log-rank test failed to demonstrate a statistically significant difference. In the published literature the use of postoperative radiotherapy in WHO Grade II meningiomas is a matter of debate. Some authors recommended postoperative radiation therapy for all cases of atypical meningiomas to improve outcome [2,23,37]. On the other hand Mair et al. [38], Goyal et al. [39] and Jo et al. [40] concluded that postoperative radiotherapy should be considered only in case of STR. Modha and Gutin [33] proposed administration of postoperative radiotherapy after STR and in cases of demonstrated brain invasion or higher proliferative index. In contrast, Hardesty et al. [41] did not demonstrate a significant benefit on overall survival or progression-free survival from adjuvant radiotherapy, even among patients whose tumors have been subtotally resected. As the authors implied, additional molecular studies would help to predict both radiosensitivity and propensity for tumor recurrence.

5. Conclusions

(1) WHO Grade II type is associated with a higher recurrence rate than WHO Grade I type.
(2) Pial invasion is associated with an increased rate of recurrence both in benign and atypical meningiomas. In atypical meningiomas evidence of bone involvement and large peritumoral brain edema are associated with tumor progression.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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