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Clinicopathological characteristics and prognostic factors of atypical meningiomas with bone invasion: a retrospective analysis of nine cases and literature review

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Abstract

Background: Meningiomas are the most common primary neoplasms of the central nervous system in adults, arising from the arachnoid cap cells. Thus, grade 2 meningiomas are situated on the border between benignity and malignancy. Among the many prognostic factors that have been investigated in these tumors, bone invasion is one of them. *Objective:* The aim of our study was to identify whether bone invasion influences tumor recurrence and progression-free survival (PFS) in patients with atypical meningiomas (AMs). *Patients, Materials and Methods:* Out of 81 patients with AMs followed over a period of five years, we identified nine patients with bone invasion. We analyzed their demographic, clinical, imaging, and pathological characteristics, such as age, gender, radiological aspects, morphological features, extent of resection, recurrence rate, and PFS over a follow-up period of 60 months. Bone invasion was determined based on preoperative, surgical, and pathological reports. *Results:* Out of the nine patients with bone invasion, four had convexity meningiomas, four had parasagittal meningiomas and one had a falcine meningioma. Regarding tumor recurrence/progression, most patients (n=6) recurred within the first 24 months after surgery. Our study showed that the early recurrence/progression of tumor (at 12 months) correlated with extensive presence of malignancy criteria, especially with the presence of 15–18 mitoses/10 high-power fields, as well as with large foci of spontaneous necrosis, but also with tumor bone infiltration, extensive bone lamellae destruction, and tumor infiltration of adjacent muscle with its atrophy due to tumor compression. Patients with bone invasion had a PFS of 29.3 months, compared to patients without invasion who had a higher PFS (49.3 months). Significant statistical associations were observed between bone invasion and tumor recurrence (p=0.002) and PFS (p=0.004). *Conclusions:* Our study emphasizes the importance of a thorough histopathological examination of the surgical specimen, which can provide significant data for the assessment of the progression of an AM [*World Health Organization* (WHO) grade 2] with bone invasion. AM infiltration in adjacent bone and muscle increases the rate of tumor recurrence and decreases PFS over a follow-up period of 60 months.

***Keywords*:** atypical meningioma, bone invasion, pathology, recurrence, progression-free survival.

Introduction

Meningiomas are neoplasms that have their origin in the meningothelial cells of the arachnoid mater and are classified into 15 subtypes and three grades of malignancy, from grade 1 to grade 3, depending on their biological behavior [1, 2]. Among these, grade 2 meningiomas are at the border between benignity (grade 1) and malignancy (grade 3) and have certain pathological characteristics, such as higher mitosis, increased cellularity, atypia, and

brain invasiveness [1]. However, there are some other clinically prognostic factors that have been investigated in these tumors [3], bone invasion being one of them [4].

The bone involvement of intracranial meningiomas can take the form of bone infiltration by the tumor, hyperostosis, or primary intraosseous development [5], and these features are observed in all *World Health Organization* (WHO) grades of meningioma [6]. Studies have shown that in 25–50% of intracranial meningiomas, the adjacent bone at the tumor epicenter may be influenced by tumor growth [7, 8]. Regarding the interaction between meningiomas and bone, this has been known since Ancient Egypt [9, 10], and the earliest case of hyperostotic lesion of the skull belonged to the First Dynasty of Ancient Egypt (a parasagittal meningioma) [10]. Later, Harvey Cushing was the one who in 1922 furthered the study of intracranial meningiomas with hyperostosis, reporting a series of 20 cases [10–12].

It is known that tumoral cells invade the Haversian canals, stimulating osteoblastic activity, and thereby leading to the appearance of hyperostosis, synonymous in the literature with bone invasion [8]. Currently, the mechanism by which these tumors influence osteosynthesis or osteolysis of the adjacent bone, and the metabolic pathways by which they do so, remain unclear [6]. The presence of bone invasion can predict tumor recurrence, progression-free survival (PFS), and overall survival in all intracranial meningiomas, regardless of the *WHO* pathological grade [13–15]. Moreover, in *WHO* grade 2 meningiomas, bone involvement has been associated with an increase of tumor recurrence and mortality [13].

Aim

The aim of this study was to investigate the impact of bone invasion in intracranial atypical meningiomas (AMs) (*WHO* grade 2) on tumor recurrence and over a follow-up period of 60 months.

Patients, Materials and Methods

We realized a retrospective study on 81 patients with AMs who were admitted, surgically treated, and pathologically diagnosed in the Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iaşi, Romania, between 2010–2020. Among them, we identified nine (11.1%) patients with evidence of bone invasion.

Bone invasion was determined based on preoperative imaging, surgical findings, and pathological reports. Thus, our study included analysis of the following: (*i*) patient's characteristics – age at diagnosis and gender, and (*ii*) tumor characteristics – extent of resection, pathological features, tumor recurrence on follow-up imaging, time until recurrence, and PFS over a 60-month follow-up period. All patients underwent computed tomography (CT) and/or magnetic resonance (MRI) assessment with the addition of contrast agent. We included the following imaging characteristics: tumor location, invasion of bone and dural sinuses, irregularity of margins, and peritumoral edema.

Also, the histological slides, which were previously stained with Hematoxylin–Eosin (HE), were reviewed by two pathologists (G.F.D. and A.S.), who followed the morphological parameters that define AM grade 2 in the latest *WHO Classification of Tumours of the Central Nervous System* [1, 2] [presence of 4–19 mitotic figures/10 high-power fields (HPFs), or brain invasion] and three of the following minor criteria: (*i*) increased cellularity, (*ii*) small cells with high nuclear/cytoplasmic ratio, (*iii*) large and prominent nucleoli, (*iv*) sheetlike growth (without a lobular pattern), and (*v*) foci of "spontaneous" necrosis. We also searched for the invasion of adjacent bone (the presence of patternless "islands" of atypical meningothelial cells into bone trabecula). All these morphological criteria were assessed by their presence in the analyzed samples, *i.e.*, 1+ if the criteria were identified in less than 25% of the sample, 2+ if it were recognized in 25–50% of the sample, and 3+ if the criteria were related with more than 50% of all histological section of a patient.

Statistical data processing was made using Statistical Package for the Social Sciences (SPSS) 24.0 software (SPSS, Inc., Chicago, IL, USA) for Windows.

This study was approved by the Ethics Committee of Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania (Approval No. 25938), and by the Ethics Committee of Prof. Dr. Nicolae Oblu Emergency Clinical Hospital (Approval No. 19092).

Results

Demographic aspects

Our study included 81 patients with AMs (*WHO* grade 2), and out of these, nine (11.1%) had bone invasion (seven males, two females). Among the nine patients with bone invasion, seven were over 60 years old (Table 1). The mean age was 67 years for patients with bone invasion and 60.3 years for patients without bone invasion.

Table 1 – ***Demographic, radiological and prognosis characteristics of atypical meningiomas with bone invasion from our study***

Case No.	Gender/age [years]	Symptoms	Tumor location	Simpson grade	Recurrence (5-year follow-up)
1.	F/87	L hemiparesis, confusion, headache	Convexity (R)	II	No recurrence
2.	M/62	R hemiparesis	Convexity (L)	IV	12 months
3.	F/59	R hemiparesis, headache, aphasia	Falcine	IV	12 months
4.	M/63	R hemiplegia, headache	SSS (posterior third)	IV	12 months
5.	M/62	Paraparesis	SSS (middle third)	III	24 months
6.	M/58	R hemiparesis, headache	SSS (middle third)	IV	12 months
7.	M/71	L hemiparesis	Convexity (R)	III	48 months
8.	M/64	Headache	Convexity (R)	II	No recurrence
9.	M/77	R hemiparesis, seizures, confusion	SSS (middle third)	IV	24 months

F: Female; L: Left; M: Male; R: Right; SSS: Superior sagittal sinus.

Imaging characteristics

Regarding the tumor location, radiological findings (CT and MRI) revealed that, out of the nine patients with bone invasion, four were convexity meningiomas (Figure 1, A–D), four were parasagittal meningiomas and one patient had falcine meningioma.

Out of the nine meningiomas with bone invasion (Figure 1, C and D), six had irregular margins and six tumors presented significant peritumoral edema (Figure 1, C and D). Additionally, five patients with bone invasion also had invasion of dural sinuses.

Clinicopathological features and tumor progression

Common symptoms included hemiparesis (7/9 cases), headaches (5/7 cases), confusion (2/9 cases), seizures (1/9 cases), aphasia (1/9 cases), and paraparesis (1/9 cases), being related to the location of the tumor (Table 1).

Of the nine patients, Simpson grade IV resection was achieved in five patients, while Simpson grade III was achieved in two patients (Table 1).

Pathologically, AM with bone invasion and no recurrence at 60 months presented: focal patternless growth, focal increased cellularity, 5 mitotic figures/10 HPFs, brain invasion, no small cells with high nuclear/cytoplasmic ratio, no large and prominent nucleoli, rare foci of spontaneous necrosis (Figure 2, A and B), as well as patternless "islands" of atypical meningothelial cells into adjacent bone trabecula.

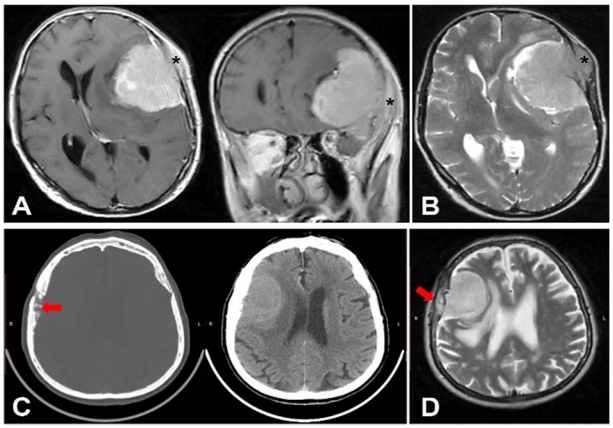

Figure 1 – *Radiological findings illustrate the characteristics of meningioma with bone invasion: (A) Contrast-enhanced T1-weighted and (B) T2-weighted MRI showing a left convexity meningioma with bone invasion (black asterisk); (C) Head-CT and (D) T2-weighted MRI showing a right convexity meningioma with bone invasion (red arrow). CT: Computed tomography; MRI: Magnetic resonance imaging.*

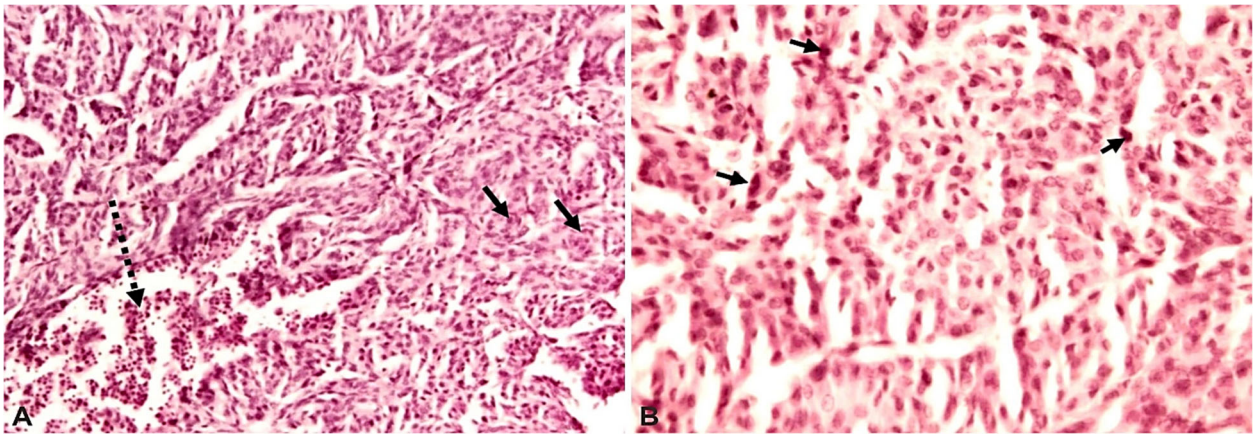

Figure 2 – *Microphotographs showing a meningothelial tumor with increased cellularity: (A) Persistence of small area of "whorls" disposition (black arrows) – however, there was an area of "spontaneous" necrosis (dotted black arrow); (B) Nuclear atypia and numerous mitoses (3 mitoses/10 high-power fields) (black arrows). Hematoxylin–Eosin (HE) staining: (A) ×200; (B) ×400.*

At the same time, the histopathological analysis of the AMs infiltrating adjacent bone revealed the fact that there are bone lamellae showing osteolytic changes as they are replaced by the tumor mass (Table 2; Figure 3A). Also, the adjacent striated muscle did not reveal any tumor invasion (Table 2).

Table 2 – *Pathological features of atypical meningiomas with bone invasion from our study (n=9)*

Case No.	Gender/age [years]	PG	IC	MF	BI	N/C	LNc	SN	Bone invasion		MI	Recurrence (5-year follow-up)
									bL	*bF*		
1.	F/87	+	+	5	+	-	-	+	+	+	-	No recurrence
2.	M/62	++	+++	15	++	++	+	++	+++	+	+	12 months
3.	F/59	++	+++	18	++	++	-	++	+++	+	++	12 months
4.	M/63	++	+++	16	++	++	+	++	+++	+	++	12 months
5.	M/62	+	++	8	+	+	+	+	+	+	+	24 months
6.	M/58	++	+++	16	++	++	+	++	+++	+	++	12 months
7.	M/71	+	+	6	+	+	-	+	+	+	-	48 months
8.	M/64	+	+	5	+	-	-	+	+	+	-	No recurrence
9.	M/77	+	++	9	+	+	+	+	+	+	-	24 months

bF: Bone lamellae formation; BI: Brain invasion; bL: Bone lamellae destruction; F: Female; IC: Increased cellularity; LNc: Large and prominent nucleoli; M: Male; MF: Mitotic figures/10 high-power fields; MI: Adjacent muscle infiltration; N/C: Small cells with high nuclear/cytoplasmic ratio; PG: Patternless growth; SN: Foci of spontaneous necrosis.

On the other hand, AM with bone invasion and rapid recurrence at 12 months showed: patternless growth of the entire tumor, increased cellularity in all areas, 15–18 mitotic figures/10 HPFs, large brain invasion, large areas of small cells with high nuclear/cytoplasmic ratio, more than 25% of tumor cells with large and prominent nucleoli, more than 25% of tumor with foci of spontaneous necrosis, large patternless "sheet-like" atypical meningothelial cells into adjacent bone trabecula, with prominent osteolytic aspects (Table 2; Figure 3, A and B), and large patternless areas of atypical meningothelial cells replacing the muscle fibers of the striated muscle adjacent to the tumor (Table 2; Figure 3B).

AMs with bone invasion and recurrence after 12 months also showed invasion of adjacent striated muscle after full-thickness invasion of adjacent bone (Table 2; Figure 4, A and B).

Out of the patients with bone involvement, four had recurrence/progression after 12 months, two after 24 months, and one patient after 48 months. Two patients did not have tumor recurrence/progression during the 60-month follow-up period (Table 1).

In our study, bone invasion influenced tumor recurrence after 12 months (p=0.002), 24 months (p=0.002), 36 months (p=0.002) and 48 months (p=0.052) since surgery. Regarding PFS, patients with bone invasion had a shorter PFS (29.3 months), compared to patients with no bone invasion who had PFS of 49.3 months (p=0.004) (Figure 5).

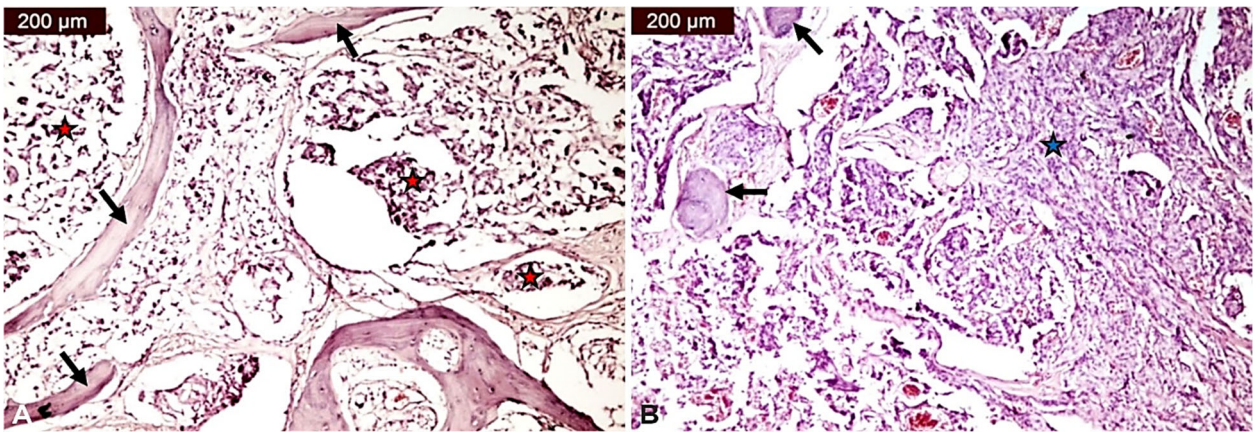

Figure 3 – ***Microphotographs showing areas of tumor bone invasion with osteolysis: (A) Thin and irregular bone lamellae (black arrows) are separated by patternless meningothelial tumor with increased cellularity (red asterisks) – some sheets of tumor cells were located inside the capillaries of this area; (B) Two small bone lamellae (black arrows) are separated by a patternless meningothelial tumor with increased cellularity (blue asterisks). HE staining: (A) ×200; (B) ×100.***

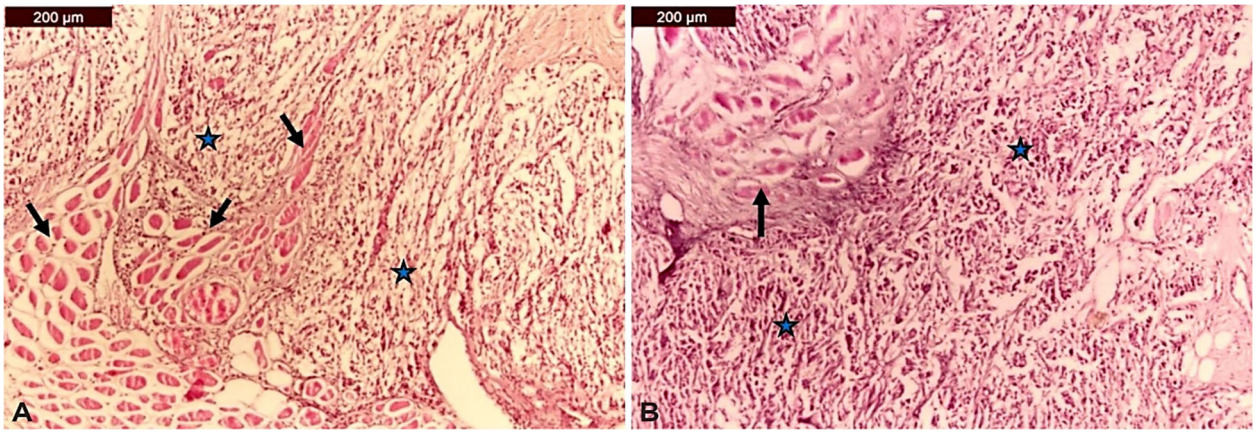

Figure 4 – ***Microphotographs showing areas of striated muscle invasion by AMs, after tumor surpassing of the adjacent bone: (A) Patternless AM (blue stars) infiltrates the adjacent muscle and replaced or compressed the striated muscle fibers (black arrows); (B) Atrophied striated muscle fibers (black arrow) due to compression realized by large areas of AM invasion. HE staining: (A and B) ×100. AM: Atypical meningioma.***

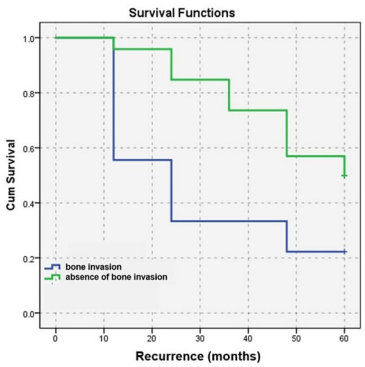

Figure 5 – ***Kaplan–Meier plots demonstrating a significant association between bone invasion and recurrence/progression regarding progression-free survival of patients (p=0.004).***

Discussions

AMs represent less than one fifth of all meningiomas [16], and this is the reason why in the literature there are many case presentations, or the analyzed series are not very large [17, 18].

Hyperostosis and osteolysis in the adjacent area of an AM are frequently encountered, specifically showing the pattern of bone involvement [19]. If hyperostosis of underlying bones is identified especially in meningioma grade 1, osteolysis is seen more often in meningioma grade 2 and grade 3 [19, 20].

These bone changes occur due to invasion and irritation of the adjacent bone by the tumor, and the imaging modality that best highlights these aspects is CT with bony window. Additionally, T2-weighted MRI images demonstrate a hyperintense signal that sometimes extends beyond the hyperostotic nidus [21].

In AMs (*WHO* grade 2), surgical series in the literature have reported a significant association between bone invasion and tumor recurrence/progression or poor prognosis, even in patients who underwent gross total resection [13, 22–24]. In our series, recurrence/progression of tumor was associated with early recurrence at 12 and 24 months, with a statistically significant association. These results were consistent with other studies in the literature that have reported early recurrence in AMs located in this area (parasagittal/falcine location) [25–28]. Additionally, Budohoski *et al*. (2018) consider that this increased recurrence rate is also correlated with the subtotal resection that is achieved at this level [25].

The extent of surgical resection is known to be one of the strongest predictors of the risk for recurrence in meningiomas [29–34]. In our series, out of the nine patients with bone invasion, five underwent Simpson grade IV resection. This is explained by the fact that most parasagittal/falcine meningiomas also invaded the dural sinuses, which did not allow for a larger resection to be achieved. Additionally, in a prospective and retrospective study that included 1469 meningiomas of all *WHO* grades and analyzed prognostic factors, Lemée *et al.* (2019) observed that bone invasion was present in 18.7% of cases and was significantly associated with a lower rate of a low Simpson's grade [15]. While Simpson grade I resection is desirable, in real life, it is not possible in cases of meningiomas with dural sinus invasion due to the high postoperative risks represented by increased morbidity and mortality [35, 36].

Although maximal resection of the adjacent bone is preferred [37], this can be challenging due to anatomical circumstances, such as extensive involvement of the skull base, infiltration of dural sinuses, or envelopment of arteries, cranial nerves, or muscle [38–43].

In these cases, some authors propose the use of stereotactic radiosurgery following incomplete resections, to reduce the rate of recurrence to the same level as that of Simpson grade I resection [43]. In such cases, the extent of resection of the meningioma, including the infiltrated bone area, is a prognostic factor that reduces recurrence and increases survival [5, 44, 45].

In the case of resection of large areas of infiltrated bone, many authors consider a circumferential margin of 1 cm to be sufficient [46], while others recommend a resection of up to 2 cm to ensure radical excision [21].

In cases of convexity meningiomas, removal of bone invasion of the vault is less complicated than in skull base meningiomas, where the tumor spreads to extradural structures, such as the orbital apex, cavernous sinus, or infratemporal fossa, and where the rate of tumor recurrence is higher [8, 47–49].

In their study on 14 patients with convexity meningiomas and hyperostosis, Fathalla *et al.* biopsied bone from four corners of the craniotomy flap at a 2 cm distance from the margin of the hyperostotic nidus. They observed that in cases of grade 1 and grade 2 meningiomas, they were free of tumor cells, while in two cases of malignant grade 3 meningiomas, tumor cells were identified [21]. Additionally, Zwirner *et al.* consider aggressive excision of bone beyond the nidus, including areas with abnormal signal on preoperative MRI, to be justified in cases of grade 3 meningiomas [50].

Our study showed that the early recurrence/progression of tumor (at 12 months) correlated with extensive presence of malignancy criteria, especially with the presence of 15–18 mitoses/10 HPFs, as well as with large foci of spontaneous necrosis, but also with tumor bone infiltration, extensive bone lamellae destruction, and tumor infiltration of adjacent muscle with its atrophy due to tumor compression. Our results are in line with other authors, showing that AMs with bone involvement are associated with increased tumor progression and decreased overall survival [13]. As Di Cristofori *et al.* found out [6], we can also affirm that, unlike meningioma grade 1, which produces hyperostosis, AM grade 2 infiltrates the adjacent bone and produces osteolysis and bone replacement.

Conclusions

In line with most studies in the literature, our report demonstrated with strong statistical significance that bone invasion is a poor predictive factor in atypical intracranial meningiomas. Bone invasion increases the risk of tumor recurrence, negatively influencing local disease control. Additionally, the presence of bone invasion decreases PFS for these patients. Thus, our study emphasizes the importance of a thorough histopathological examination of the surgical specimen, which can provide significant data for the assessment of the progression of an AM with bone invasion.

Conflict of interests

The authors declare that they have no conflict of interests.

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