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Atypical and Anaplastic Meningiomas: Diagnosis and Treatment

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Abstract

The aim of this chapter is to describe the usefulness of surgical technologies such as neuronavigation, intraoperative MRI, fluorescence-guided surgery and intraoperative monitoring as a tool do make neurosurgical procedures to brain tumors more safe and effective. The main topics to be explored are: history of the specific technique, indications and contra indications, description of the technique, real case examples, pros and cons. The focus on the discussion besides practical aspects is going to be relevant literature regarding impact of their use in avoidance of complications, improve in survival rates, cost-effectiveness, some tips and tricks acquired in the experience of our department.

Keywords: neurosurgical procedures, brain neoplasms, neuronavigation, fluorescence-guided surgery, magnetic resonance imaging

1. Introduction

Meningiomas originate from specialized meningotheelial cells called arachnoid cap cells and correspond about up to 26% of all intracranial lesions. According to the World Health Organization (WHO), meningiomas are grouped in grade I (benign), grade II (atypical), and grade III (anaplastic) [1, 2]. This classification reflects the risk of recurrence and aggressive growth. Although uncommon, atypical corresponds to 4.7 to 20% of all meningiomas, while anaplastic for 1–2.8% [3, 4]. Symptomatology varies according to intracranial location and may be related to seizures and/or intracranial hypertension.

The standard treatment of grade II and grade III meningiomas involve total/radical resection, respecting Simpson score, followed by adjuvant therapy with irradiation and, eventually, chemotherapy [5, 6]. Despite the treatment efforts, the evolution of aggressive meningiomas remains unsatisfactory due to the high rates of local recurrence and/or tumor progression [7]. These patients frequently underwent multiple surgical approaches during the course of the disease, increasing the rates of postoperative complications as infection or CSF leakage.

With the continuous improvement of molecular and immunochemistry analysis, the paradigm for treatment of these tumors has been changing. In this chapter, the current management of aggressive/malignant meningiomas focusing on the new discovers in genetic/molecular and radiotherapy field is discussed.

2. Materials and methods

In our database, we reviewed all meningiomas operated between 2012 and 2017 in our institution to describe the epidemiologic characteristics of atypical and anaplastic subtypes, as well as an illustrative case focusing on the treatment and long-term follow-up. Also, literature was reviewed based on the WHO (2016) classification guided through genetic/molecular findings.

3. Results

A total of 170 new diagnosed patients with intracranial meningiomas underwent microsurgical resection at the Neurological Institute of Curitiba (INC) between January 2012 and June 2017. A total of 94 (55%) tumors were classified as skull base tumors, 58 (34%) convexity, 10 (5.8%) parasagittal, and 8 (4.7%) falcine lesions.

In our series, 76.4% (130) of patients were female. Only six (3.5%) patients had atypical/anaplastic tumors with mean age of 53 years (**Table 1**). Simpson grade I resection (total tumor removal including resection of the underlying bone and associated dura mater) was achieved in all patients with malignant histology, and radiotherapy was reserved for progression. Only one patient with atypical meningioma received upfront radiotherapy because of high Ki-67 index. Any case of skull base meningioma exhibited progression to malignant subtypes in this series.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	F	M	M	F	F	F
Age	57	58	36	62	65	44
Topography	Parasagittal	Parasagittal	Convexity	Convexity	Convexity	Parasagittal
Histology at 1 st resection (WHO)	Grade I	Grade I	Grade I	Grade I	Grade I	Grade I
1 st resection (Simpson)	Grade I	Grade I	Grade I	Grade I	Grade I	Grade I
Time to evolution	7m	26m	9m	-	-	16 yrs
	(anaplastic)	(anaplastic)	(anaplastic)			(atypical)
Radiotherapy modality after anaplastic diagnosis	EBRT	EBRT	EBRT	-	EBRT	EBRT

Table 1.
Malignant meningioma at INC (2012–2017).

4. Illustrative case

58-year-old male has sporadic new onset headache, and magnetic resonance imaging (MRI) evidences enhanced parasagittal homogenous mass tumor with surrounding edema (**Figure 1**). Simpson grade I resection (**Figure 2**) was achieved at surgery, and histopathology confirmed atypical meningioma.

Immunohistochemistry of the first sample proved the trend toward malignant progression, with Ki-67 index of 70% in hot spots. Only focal positiveness for progesterone receptor was seen. Because of high Ki-67 index, adjuvant external beam radiotherapy (EBRT) was added to the treatment.

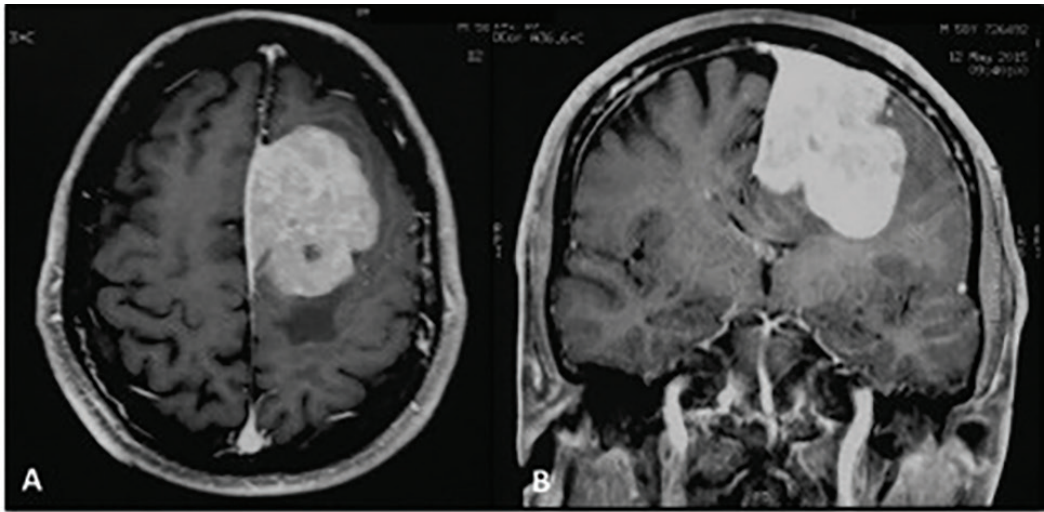


Figure 1.
(A) Post-gadolinium-DTPA axial and coronal. (B) T1-weighted gradient echo (FSPGR) sequence with large parasagittal meningioma with partial occlusion of superior sagittal sinus.

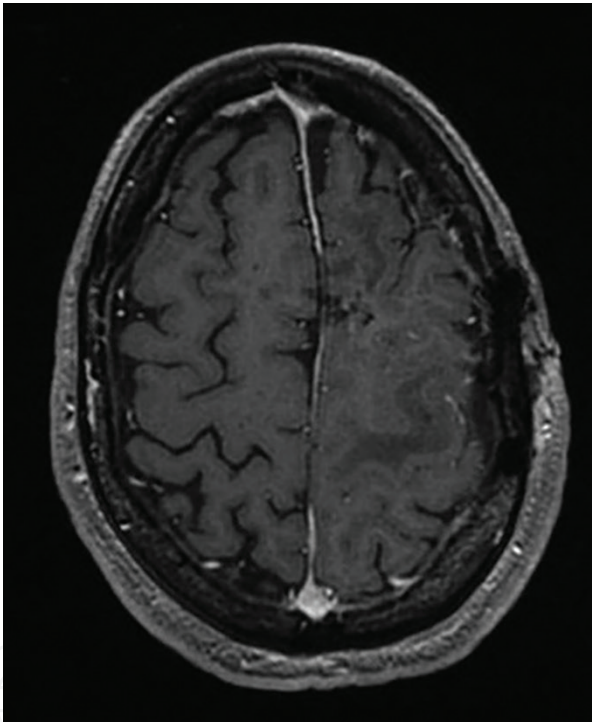


Figure 2.
Postoperative MRI with post-gadolinium-DTPA axial T1-weighted gradient echo (FSPGR) sequence exhibiting complete resection of parasagittal meningioma.

After 1 year follow-up, recurrence at posterior border of previous surgical field was seen, and another gross total resection was necessary (**Figure 3**). The tumor expressed the same imaging characteristics of first analysis, with homogeneous contrast enhancement and peritumoral edema. Histopathological analyses confirmed again an atypical histology. At this time, chemotherapy with octreotide was introduced without response.

After 2 years from the first surgery, another recurrence was seen. At MRI, changes in previous pattern were seen with heterogeneous contrast enhancement and central necrosis (**Figure 4**). After another Simpson grade I tumor removal, progression to anaplastic meningioma was confirmed.

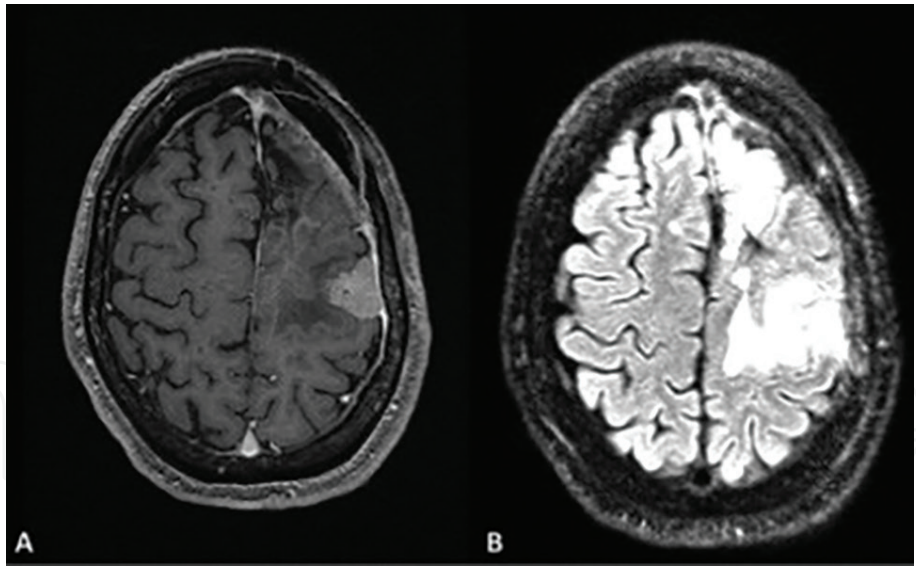


Figure 3.
One-year-follow-up. (A) MRI. Axial post-gadolinium-DTPA T1-weighted gradient echo (FSPGR). (B) Flair sequences evidencing tumor recurrence adjacent to previous resection with the same features of original tumor.

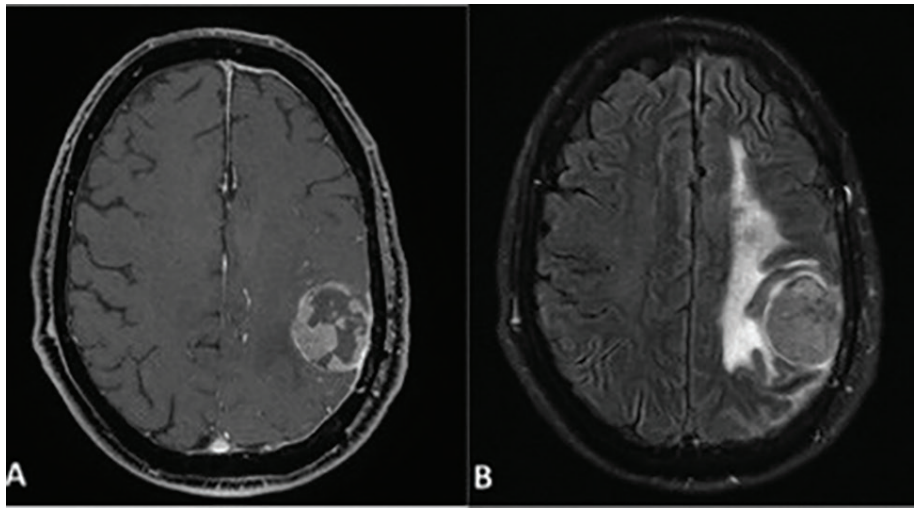


Figure 4.
Axial post-gadolinium-DTPA. (A) T1-weighted gradient echo (FSPGR) showing irregular contrast enhancement and tumoral necrosis. (B) Axial FLAIR magnetic resonance evidencing extensive peritumoral edema with changes in radiological aspect from original tumor.

In comparative analyses, immunohistochemistry evidenced an increase in Ki-67 index from 70 to 90% of the cells. The epithelial membrane antigen (EMA), focal positive at first analysis, now expressed diffuse negativity. Reduction in progesterone receptor expression was also documented.

Later, there was tumor progression again in two more occasions in an interval of 8 months. Progressive neurological impairment and seizures due to motor cortex/eloquent area involvement/gliosis were seemed, and tumor resection with extensive dural removal was performed both times (**Figures 5 and 6**). The patient underwent salvage irradiation, as the last recurrence was far from the original lesion. Two months after adjuvant treatment, the patient evolved with neurological worsening, dying due to clinical complications.

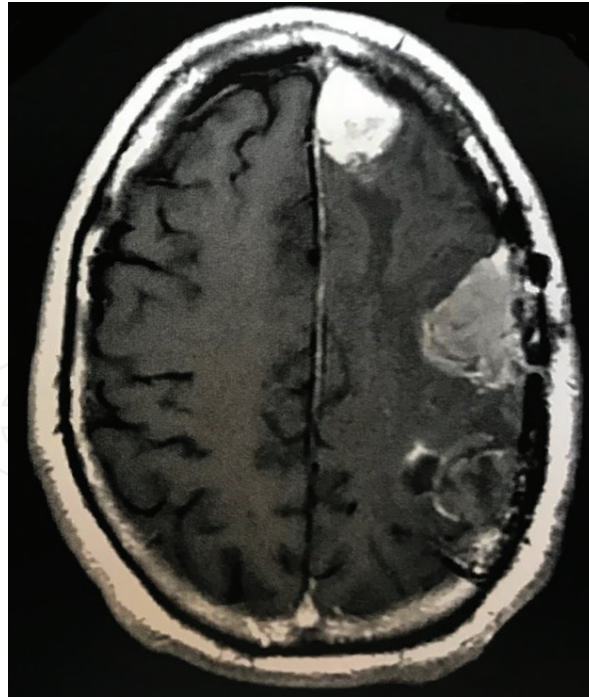


Figure 5.
Axial post-gadolinium-DTPA. (A) T1-weighted gradient echo (FSPGR) showing tumor progression in multiple sites.

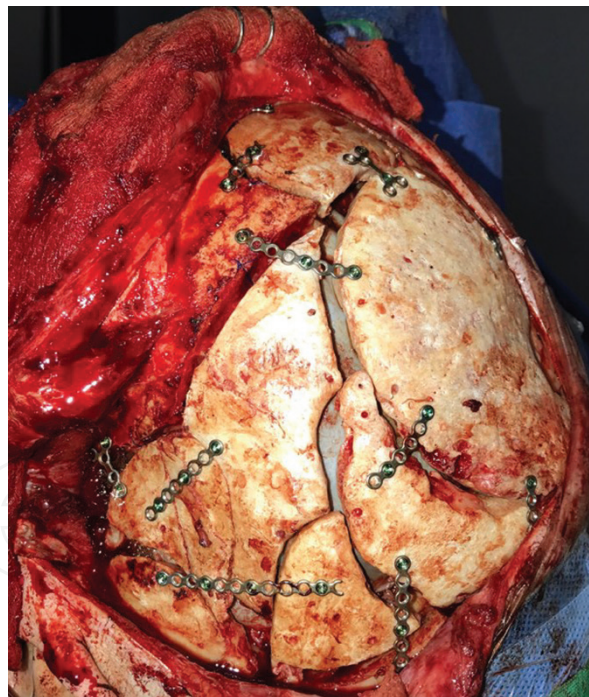


Figure 6.
Intraoperative image showing the skull after multiple craniotomies.

5. Discussion

About 90% of meningiomas are benign grade I tumors. Atypical meningiomas are uncommon (4.7–20% of all meningiomas), while anaplastic meningiomas account for only 1–2.8% of all meningiomas [1–4].

The WHO (2016) classification included brain invasion to the previous histological characteristic (4–19 mitotic figures and 3 of 5 histologic features): increased cellularity, small cells (tumor clusters with high nuclear/cytoplasmic ratio), prominent nucleoli, and sheeting (loss of whorling or fascicular architecture and spontaneous necrosis) in the diagnosis of atypical meningiomas.

Anaplastic meningiomas are diagnosed with 20 or more mitotic figures and presence of frank sarcomatous or carcinomatous histology [3].

Despite of diagnostics criteria, the exact mechanism through how benign meningiomas progress to malignant subtypes remains unclear. Several molecular and genetic hypotheses have been postulated, but the real significance of these alterations is still speculative [8].

Evidence-based literature suggests that the extent of surgical resection, accordingly to Simpson grade system, is the most important prognostic factor for good outcome among those patients harboring malignant meningioma [9].

In our series those cases, with atypical or anaplastic subtypes at primary surgery, demonstrated better response to Simpson grade I resection and adjuvant radiotherapy than those cases that progressed from grade I subtype. Some genetic alteration related to progression, as previously reported in literature, can probably explain different evolution among tumors expressing the same histology like in these series [8, 10, 11].

Among those with atypical and anaplastic histology, tumor size and female gender have been related to poor outcome and presence of radiological features such as heterogeneous enhancement, peritumoral edema, and cyst formation, and absence of calcification have been implicated with lower median recurrence-free survival [9, 12].

In the illustrative case, the tumor progression was followed by changes in radiological characteristics and immunohistochemical pattern. Possibly, in this case, the first immunohistochemistry analysis evidenced some characteristics of aggressiveness. In this scenario, Czonka et al. have previously published the utility of p53 gene expression and Ki-67 index in predicting meningioma progression [13].

Maximal safe resection with dural margins and bone hyperostosis removal stills the main point in the treatment of meningiomas, possibly reducing rates of progression and/or improving progression-free survival [14].

Radiotherapy is a special topic in the treatment of malignant meningiomas. Increase from 15 to 80% in 5 year progression-free survival was reported when EBRT was added to surgical resection for anaplastic meningioma. No consensus exists for atypical meningiomas, and EBRT has mostly been reserved for recurrence and progression [15, 16].

Due to the possibility of margin inclusion in irradiation field with EBRT, radiosurgery is no longer indicated for malignant meningiomas. However, Lubgan et al. have reported excellent results with stereotactic radiotherapy when used as an adjuvant after gross total resection or as definitive treatment regime [17].

In the illustrative case, the lower progesterone receptor expression and higher Ki-67 index could probably predict the chance of progression and help in earlier adjuvant decision.

Several chemotherapy agents have been used for atypical and anaplastic meningiomas refractory to surgery and radiotherapy. In the largest revision, Kaley et al. found 47 publications using different chemotherapy agents (hydroxyurea, temozolomide, irinotecan, interferon-alpha, mifepristone, octreotide analogues, megestrol acetate, bevacizumab, imatinib, erlotinib, and gefitinib) with an average 6 month progression-free survival of 26%, concluding that the available chemotherapy agents provide poor outcomes for refractory malignant meningiomas [18].

6. Conclusion

Atypical and anaplastic meningiomas remain challenging diseases, and no effective treatment is currently available. Against literature evidence, we presume that the biological signature of this specific tumor is more important for evolution than previously reported prognostic factor. In this scenario, new studies aiming objective analyses of immunohistochemistry patterns and genetic profile of meningiomas are probably the next step for the comprehension of such complex neurosurgical pathology.

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