Recurrent Atypical Meningiomas: Combining Surgery and Radiosurgery in One Effective Multimodal Treatment

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■ OBJECTIVE: **Owing to their rarity and proteiform pathologic features, the clinical behavior of atypical meningiomas is not yet well characterized. Though the extent of resection is believed to be a key determinant of prognosis, limited data exist regarding optimal management of patients with recurrent disease.**

■ METHODS: **In this 20-year retrospective case series, we reviewed the medical records of 46 patients with recurrent atypical meningomas (185 lesions, 89 of which were local, 78 marginal, and 18 distant recurrences); treatment was radiosurgery ($n = 60$), surgery ($n = 56$), or both ($n = 8$). The median follow-up period was 53 months. Outcome measures were length of overall survival and disease-free intervals and prognostic factors for survival.**

■ RESULTS: **Overall, the median progression-free survival was 26 months at the first recurrence and 100 months thereafter (the sum of the later intervals). Multivariate analysis showed that no treatment-related factors influenced prognosis, whereas recurrence at the skull base was a significant tumor-related factor limiting further treatment. Irrespective of treatment type, the recurrence-free interval was increasingly shorter during the clinical course, with a higher occurrence of marginal and distant lesions migrating to the midline and to the skull base. In sporadic cases, disease-free intervals were longer after wide craniotomy, tumor and dural resection with tumor-free margin.**

■ CONCLUSIONS: **The disease-free interval was substantially similar after surgery and radiosurgery for treating recurrent disease in patients with atypical meningiomas. Surgery is the mainstay for prolonging survival, while radiosurgery can be an adjuvant strategy to gain time for clinical observation and planning aggressive surgical treatment.**

INTRODUCTION

Atypical meningiomas, because of their rarity and proteiform pathologic features, pose diagnostic and treatment challenges in neuro-oncology. Their incidence is increasing (>5%–10% reported for all meningiomas) and accounts for 20%–25% of recurrent meningiomas.[1,2] Definitive cure after surgical resection is achieved in 16%–18% of patients; however, disease will recur within a few months in many cases (62%–69%).[3,4] The main determinants of survival time are tumor histology and extent of surgical resection.[5-11] Unlike radiosurgery, which has been shown to improve recurrence-free survival after subtotal resection,[9,10,12-15] studies on combined treatment have reported inconsistent and controversial results, hindering comparative effectiveness research. Furthermore, because the bulk of published studies deals only with the first treatment or the first recurrence,[5,9,10,13,16] disease recurrence remains a centrally important concern in the management of patients with atypical meningiomas. Treatment, whatever the type, will not halt tumor progression though it may prolong survival.

Aggressive tumor behavior is characterized by local and distant progression. Because the modality of progression is difficult to predict, a better understanding of the natural history of this type of tumor can contribute to improving treatment outcomes.[5]

Key words
- Meningiomas
- Recurrence
- Treatment
- Tumor progression

Abbreviations and Acronyms
SRS: Stereotactic radiosurgery
WHO: World Health Organization
MRI: Magnetic resonance imaging

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There are no studies investigating the changes in prognosis in patients with tumor recurrence after combined treatment, namely, why and how one or more partial responses can be achieved while creating the conditions for effective treatment. The aim of the present study was to assess the limitations and possibilities of each single treatment by exploring the potential benefits of their combination under specific conditions. To address this issue, we describe the intermediate steps of tumor progression and growth patterns.

MATERIAL AND METHODS

Between January 1990 and December 2010, 46 patients with histologically confirmed recurrent atypical meningiomas were treated at the University Hospital of Verona. This patient subset accounts for nearly 2.7% of all intracranial meningiomas ($n = 1677$) treated at our hospital. Histology was reclassified for the present study according to the 2007 World Health Organization (WHO) classification criteria; the Ki-67 index was noted when available. First treatment, time-to-disease recurrence, and relative treatments received until the last follow-up visit were recorded, in addition to clinical presentation at recurrence, pattern of recurrence, and tumor site. Treatments included surgical resection and stereotactic radiosurgery (SRS) with Leksell instrumentation. Surgical treatment was classified as total (Simpson grade I–II) or subtotal resection (Simpson grade III–IV) according to postoperative radiologic findings; SRS was characterized by the peripheral dose intensity and target volume delivered.

The indications for type of treatment were based on radiologic and clinical findings. Intracranial hypertension, clinical signs, and epilepsy were more likely to require open surgery, whereas small lesions (<2.5 cm) received SRS. Adjuvant treatment was considered when long-term benefit was anticipated and entailed surgery followed by SRS to the same lesion(s). With this exception, each treatment was given at disease progression and based on close clinical and radiologic monitoring. Treatment for >1 lesion could be performed simultaneously or not. In the latter case, the second intervention completed the first one within an interval of a few weeks apart. Overall, salvage treatment, often provided without any precise synergy or specific goal, was based essentially on physician or patient preference. Aggressive surgical treatment, large craniotomy, and extensive dural resection around the tumor was seldom performed. As a rule, it was not determined by disease progression per se but rather by pretreatment planning.

Disease-free interval was defined as the period between treatment and disease progression event, as documented by magnetic resonance imaging (MRI), and served as the end point for measuring the treatment effect. Recurrence was defined as a disease progression event as documented by follow-up MRI findings (3–6 months). During tumor progression, salient characteristics of recurrent lesions were recorded, including histology, laterality, pattern of failure, number of lesions, number, and site of recurrences.

Based on tumor characteristics and the goal of treatment, which is ideally to control the disease rather than the single lesion, the pattern of failure was classified as local, marginal, or distant. Local failure was defined as tumor regrowth within the field of previous treatment, taking as reference the craniotomy and effective marginal radiation dose; marginal failure was defined as tumor regrowth at the resection margin and within 2 cm of the aforementioned limits; and distant failure was defined as the occurrence of a new lesion distant (>2 cm) from any other lesion. This means that during the clinical course, marginal recurrences might lead to lesions that are distant from the original field. Furthermore, tumor behavior may potentially involve multiple foci in the perimeter of any lesion, resulting in devastating spread of disease.

Disease and treatment-related variables were entered into the prognostic analysis to identify the determinants of survival in 2 different Cox regression models: 1 included tumor side, histology, site, and type of recurrence; the other included tumor side, histology, first treatment, and type of subsequent treatments.

RESULTS

The study sample was 46 patients operated on for recurrent meningiomas (23 men and 23 women; age range 28–73 years). The mean clinical history was 6.3 months (range 1–60 months, median 3 months); diagnosis was based on symptoms and clinical signs. All cases presented a single mass (mean tumor size 5.1 cm, range 2.8–7.6 cm) on radiology. The mass was on the right side in 25 cases and on the left side in 21; the prevalent site was located along the midline (falx cerebri and parasagittal in 17% and 26% of cases, respectively). Sixteen (35%) were WHO grade I meningiomas at the first treatment. Total surgical resection was performed in 72% of cases and subtotal resection in 28% (Table 1).

First Recurrence of Disease

First recurrence occurred at 26 months (median), 66 months after total resection and 22 months after subtotal resection, demonstrating a significant efficacy of the extent of removal ($P < 0.01$) (Figure 1). Recurrence was local in 31 cases (62%), marginal in 17 (34%), and distant in 2 (4%). Multiple lesions were detected in 9 cases (19%).

Tumor Growth Pattern Following Treatment and Survival

Following the first recurrence, 3.6 subsequent recurrences per patient on average were noted (range 1–7), with a mean time to overall survival of 100 months (interquartile range 72–144). Symptomatic presentation was rare (18%) as compared with radiologic evidence of tumor regrowth. At the time of the last follow-up examination (median 52 months, range 33–146), 89 of the 185 lesions were local recurrences, 78 marginal, and 18 distant and had been treated with SRS in 60 cases, surgery in 56, and both treatments in 8. Five (11%) patients presented with 1 lesion, and 41 (89%) with multiple lesions, 22 of which were bilateral (48%). The tumor harbored atypical features at the second recurrence in only 1 patient and showed malignant transformation at the end of the clinical course in 10 patients (21%). Thirty-three patients were alive (72%), and 13 (28%) had died at the time of the last follow-up.

Determining which future strategy to choose case-by-case ultimately relies on knowledge of the disease growth pattern. Given this multifaceted picture, we describe the factors associated with time-to-disease intervals between recurrences and discuss the treatment modalities and strategies in relation to tumor behavior.

Table 1. Characteristics of Patients, Tumors, and Treatment

Characteristic	Number of patients	%
Age (years)		
≤65	34	74.0
>65	12	26.0
Sex		
Male	23	50.0
Female	23	50.0
Tumor side at onset		
Left	21	45.6
Right	25	54.4
Tumor location at onset		
Convexity	16	34.7
Parasagittal	12	26.1
Skull base	10	21.7
Falx	8	17.4
Presenting symptom at onset		
Seizures	12	26.0
Intracranial hypertension	10	21.7
Unilateral hyposthenia	6	13.0
Cognitive deterioration	3	6.5
Others	15	
Neurologic signs at onset		
Hemiparesis	9	19.5
Cognitive deterioration	6	13.0
Ataxia	5	10.8
Others	8	17.4
Multicentricity		
Initial	0	0
Final	41	89.1
Resection at first surgery		
Total	33	71.7
Subtotal	13	28.3
Atypical meningioma		
Initial	20	65.3
Recurrence	16	34.7
Ki-67 index (recurrence only)		
<5%	8/19	42.1
≥5%	11/19	57.9
Surgery		
<3 Recurrences	38/56	67.8
≥3 Recurrences	18/56	32.2
Extent of resection		
Total	17/56	30.3
Subtotal	39/56	69.7
Stereotactic radiosurgery		
<3 Recurrences	35/60	58.4
≥3 Recurrences	25/60	41.6
Radiation dose delivered		
≤12 Gy	28/60	46.7
>12 Gy	32/60	53.3

Continues

Growth Pattern. The tumor growth pattern changed during the clinical course. The prevalent pattern at the first recurrence was local, becoming marginal at the second and third recurrence and distant at the fourth and fifth recurrence (Figure 2A). This pattern of progression suggests that early aggressive treatment may be more effective than repeated salvage treatments. The tumor location changed during the clinical course. Most lesions migrated to the midline, with fewer in the convexity or the skull base (Figure 2B). This latter result is probably biased by the fact that large, recurrent skull-base tumors are not amenable to treatment. Evaluation of the direction of tumor progression can prevent unmanageable situations and help in planning radical surgery. In tumor invasion of the superior sagittal sinus, for example, the right time for sinus resection is problematic: if the tumor is resected before it occludes the superior sagittal sinus, venous engorgement may occur; if it is removed after the superior sagittal sinus has been invaded, the tumor may have already spread. The effect of tumor behavior on survival was demonstrated by the adjusted Cox regression model. Among the disease-related factors examined, skull base location was the only one significantly associated with shorter survival times ($P = 0.01$) (Table 2).

Treatment. The overall survival in recurrent cases was 100 months, and the progression-free survival rate at 5 years was 30% after total resection and 11% after subtotal resection. Differently from the initial treatment, when progression-free survival depended on the extent of resection, the subsequent disease-free intervals were increasingly shorter independent of treatment type (SRS vs. surgery) and modality (extent of resection and radiation dose) (Figure 2C; see Table 1). The general rule is that the higher the number of recurrences, the shorter the disease-free interval regardless of treatment. This was confirmed on prognostic analysis, which showed that treatment-related factors were not associated with survival nor that adjuvant treatment ($n = 16$

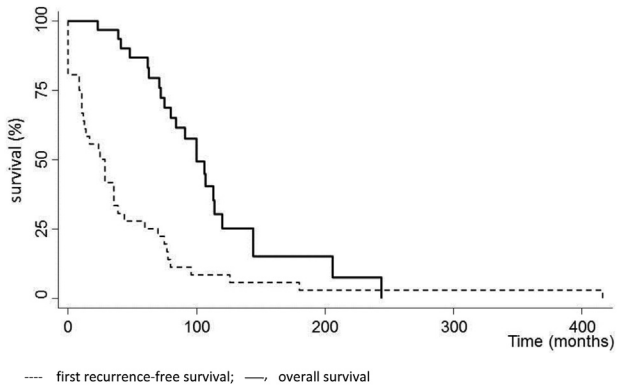

Figure 1. First recurrence-free survival (*dashed line*) and overall survival (*solid line*) curves estimated by the Kaplan-Meier method.

procedures) performed in 8 patients (17%) prolonged disease-free survival (16 months) (see Table 2). But this is an apparent finding because the efficacy improved by changing the treatment approach, being more aggressive and aiming at Simpson grade 0, as was seen in sporadic cases (see Case 2).

Exemplificative Cases

Case 1. A 58-year-old woman had a history of generalized epileptic seizures. MRI showed a right parasagittal meningioma infiltrating the anterior and middle third of the superior sagittal sinus. Simpson grade III resection was performed in March 2007. The patient was followed up with periodic MRI. The first recurrence (1 local and 1 posterior marginal lesion) occurred 18 months later. In March 2009, SRS was performed on the posterior marginal lesion (14 Gy); 8 months later, in November 2009, surgical resection was performed because of local recurrence with progression. In January 2011, another operation was performed to remove the lesion, which had previously been treated with SRS, again limiting the target to the growing lesion. Eight months later, there was evidence of dural and falcine infiltration without tumor mass. In March 2012, a new recurrence occurred and palliative SRS was performed (11 Gy). No further treatment was administered 8 months later when MRI showed a large contralateral parasagittal meningioma. Tumor histology remained unchanged since the first procedure (Figure 3).

Comment: 6 years of survival; disease-free intervals: first recurrence at 18 months postoperative; 4 further treatments (2 operations and 2 SRS), 1 for each new lesion, with disease-free periods shorter or similar in duration to that after the first treatment.

Case 2. A 64-year-old woman had a 3-month history of recurrent motor epileptic seizures affecting the left side of her body. MRI showed a right parasagittal meningioma infiltrating the middle third of the superior sagittal sinus. The sinus was not occluded by the tumor; some remnants were left inside at the first operation (April 2004). Local regrowth was treated with SRS (12 Gy) in January 2006. MRI studies were obtained every 6 months thereafter. In May 2008, 13 months after the initial finding of

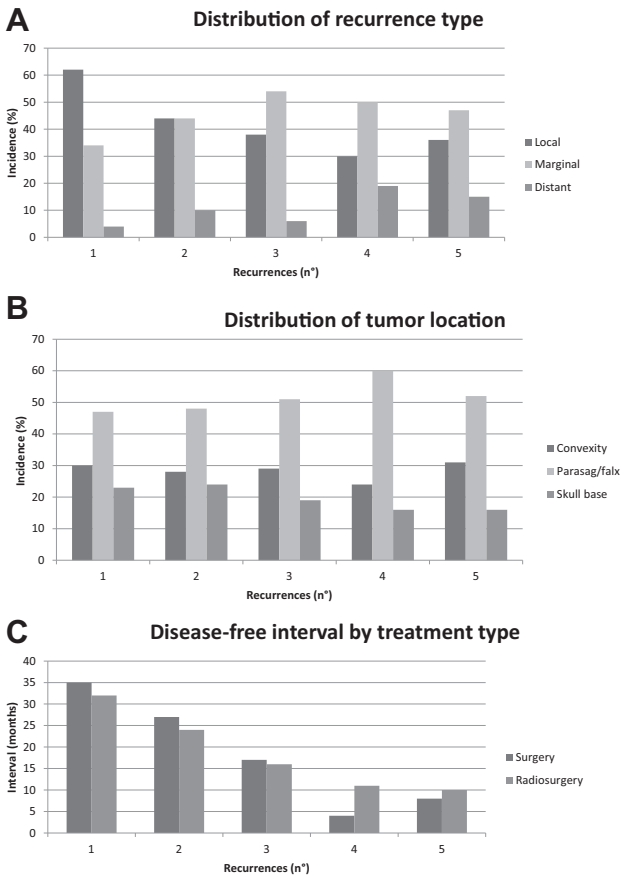

Figure 2. (**A**) Changes in recurrence type during the clinical course; (**B**) changes in tumor location during the clinical course; and (**C**) changes in the length of disease-free intervals during the clinical course.

recurrence, surgery was performed to remove a local lesion occluding the superior sagittal sinus and a marginal lesion of the falx. In January 2010 and March 2011, three lesions (1 local, 2 marginal) close to the superior sagittal sinus were treated with SRS (10 Gy and 12 Gy, respectively). The patient was carefully monitored for evidence of new tumor growth. In April 2012 she was reoperated with the intention to remove the tumor completely with free dural margins. At the last follow-up examination the patient is still tumor free. Histology remained unchanged since the first procedure (see Figure 3).

Comment: 10 years of survival and still alive; disease-free interval: first recurrence at 21 months postoperative; 4 further treatments (2 operations and 2 SRS) for 8 lesions, with disease-free periods shorter or similar in duration to that after the first treatment, except for 1 Simpson grade 0 resection followed by a 32-month disease-free period, and still disease free.

Case 3. A 71-year-old woman had a 1-month history of progressive headache. MRI showed a left frontal hyperostotic meningioma. In October 2009 surgery was performed to remove the tumor, bone,

Table 2. Hazard Ratio (HR with 95% Confidence Intervals [CI] and *P* Value) of Death from Recurrent Meningioma in the 46 Patients Controlling for Tumor and Treatment Variables

	Tumor				Treatment		
	HR	**95% CI**	***P* value**		**HR**	**95% CI**	***P* value**
Side	0.44	0.17-1.15	0.10	Side	2.25	0.49-10.25	0.29
Histology	1.26	0.38-4.22	0.71	1-treatm	0.55	0.18-1.64	0.28
Recurr base	0.24	0.08-0.75	0.01	Histology	0.98	0.29-3.32	0.97
Recurr sss	0.33	0.10-1.10	0.07	Surgery	0.19	0.02-1.93	0.16
				SRS	1.68	1.65-17.13	0.66

Side, left, right; histology, atypical on new tumor, atypical on recurrence; 1-treatm, total removal, subtotal removal; recurr base, skull base as final site of recurrence; recurr sss, superior sagittal sinus as final site of recurrence; surgery, cases with surgery as prevalent treatment on recurrences; SRS, cases with SRS as prevalent treatment on recurrences.

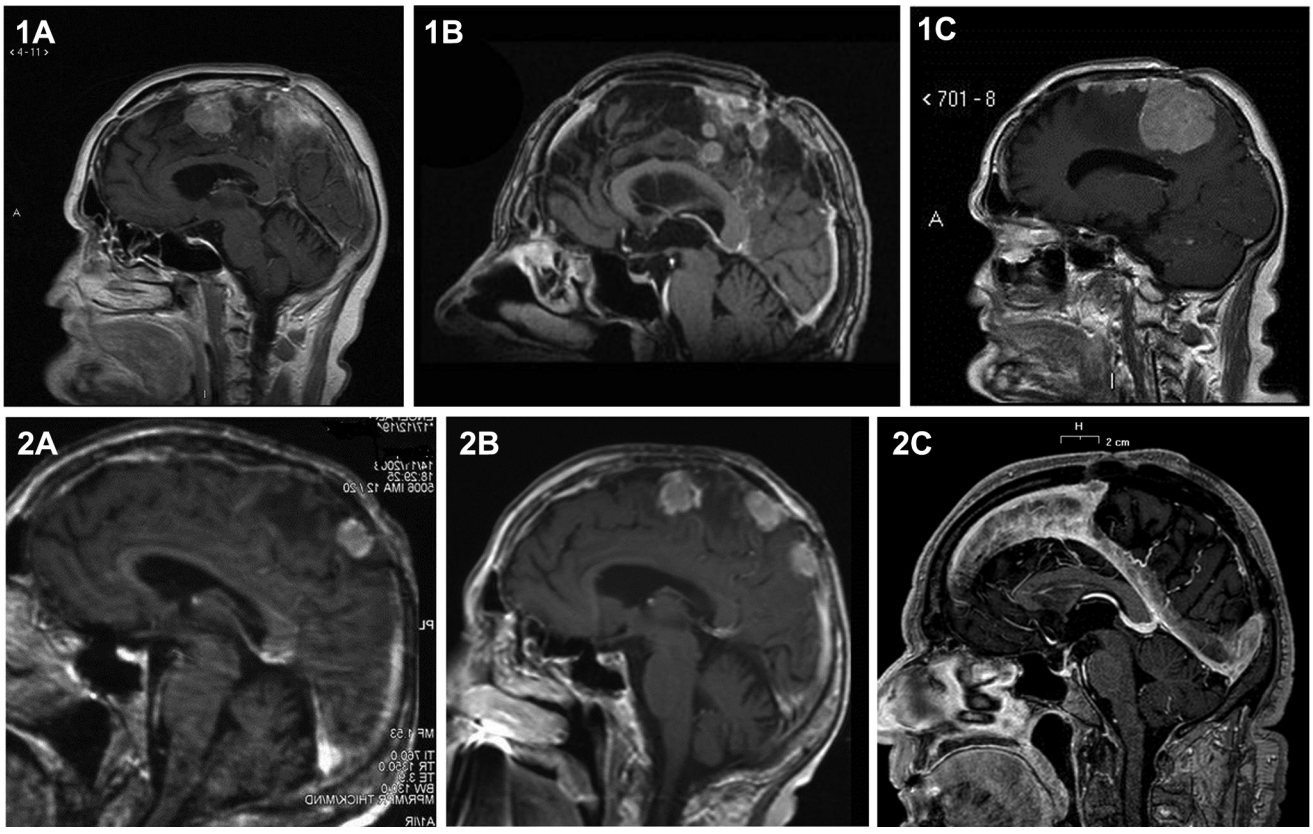

Figure 3. Exemplifying different strategies in similar tumors. Case 1: a strategy leading to failure (sagittal magnetic resonance [MR] images). (**A**) First recurrence with 2 marginal lesions; the anterior lesion underwent surgery, the posterior lesion stereotactic radiosurgery (SRS) and then surgery. (**B**) A new recurrence developed from the infiltrated dura 8 months after Simpson grade II resection and received SRS. (**C**) New and last recurrence 8 months later (patient refused operation). Case 2: a successful strategy (sagittal MR images). (**A**) First local recurrence received SRS. (**B**) New recurrences grew slowly despite repeated SRS; aggressive surgery was planned. (**C**) Postoperative image.

and dura, followed by cranioplasty and duraplasty during the same operation. MRI scans obtained in April 2010 were negative. A local lesion appeared in September. Progression was noted in December, at which time the patient was reoperated. MRI scans obtained in February 2011 were negative. Two lesions appeared at the margins of the craniotomy in June; SRS to the growing lesions was performed (14 Gy each) in September. At that time, 1 of the 2 lesions had reached the skull base and was judged inoperable at progression (Figure 4). The patient died in February 2012 due to intracranial hypertension. Histology remained unchanged since the first procedure (Ki-67 index 9%).

Comment: 28 months of survival; disease-free interval: first recurrence at 11 months postoperative; 2 further treatments (1 operation and 1 SRS) for 3 new lesions, with disease-free periods shorter or similar in duration to that after the first treatment. Rapid progression was probably due to higher tumor malignancy.

DISCUSSION

Atypical meningiomas pose diagnostic and treatment challenges because of the many potential determinants for prognosis. We investigated the clinical course from the first recurrence onward and report findings that could aid in decision making. In this retrospective series, midline meningiomas were the prevalent location at presentation and increased in occurrence with subsequent recurrences. This prevalence is different from other authors who reported a tumor distribution comparable with benign counterparts but similar with the recurrence sites Cao et al. reported.[3,9,12,17] Prevalence on the midline may be due to either dysembryogenetic defects during closing of the neural crest or an acquired mutation, but it does not seem to be linked to a higher rate of subtotal resection.[6] Kane et al. proposed an embryologic origin of the skull base dura different from the convexity dura to explain why non–skull base locations are a prognostic factor for the development of atypical meningiomas.[18]

Whatever the cause, the tumor originates as an isolated mass and regrows as multiple lesions stemming from the margin of the previous lesions (with or without residual mass), often distant from one another and sometimes unconnected with the previous lesions in the final stages. A variable but high number of cases (14%–57%) become atypical on the second operation after inadequate extent of resection of the first tumor.[12,19]

Multicentricity varies from 19% at the first recurrence to 89% at the last follow-up, and marginal recurrence is progressively higher than the local type at the second and third recurrence, rendering management increasingly difficult.[10] Therefore local control is an erroneous outcome measure because it provides no effective indications about the state of the disease. As the disease may be local, marginal, or distant with respect to the previous localization, a preferable indicator of treatment efficacy is disease-free interval.[20-23]

Multiple lesions are clinically difficult to manage because of refractoriness to treatment (total and subtotal surgical resection, high- or low-dose intensity SRS) and disease progression, with ever shorter disease-free intervals during the clinical course regardless of treatment type.[12] The findings from this retrospective analysis challenge assumptions about treatment. As regards surgery, the definition of Simpson grade I–II (total resection) should be revised in light of mounting criticism that even Simpson grade I might not be a reliable gold standard for this particular type of tumor.[19,24,25] As regards radiotherapy, SRS seems to be as efficacious as fractionated radiotherapy and it is associated with fewer side effects: depending on peripheral dose intensity, tumor volume, and timing, it can delay tumor regrowth.[13,21,26,27]

We also found a considerable length of overall survival (100 months) after first recurrence at the cost of multiple interventions (3–4 per patient on average), each covering 1 or more lesions.[11,28,29] The time to first relapse in our series compares favorably with the published data (20–43 months).[30] There is some evidence that later performance is worse; unfortunately, however, studies do not report further details about survival

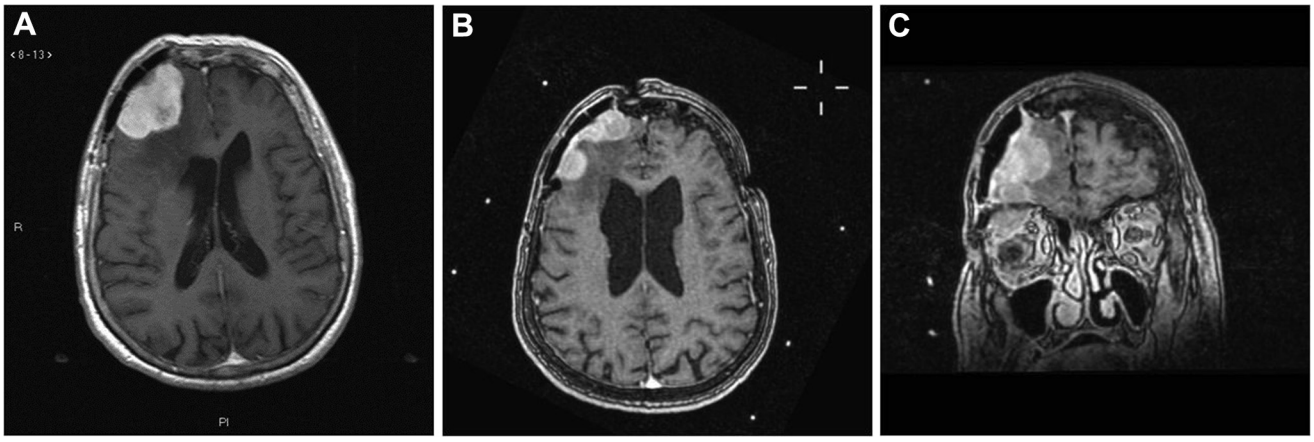

Figure 4. Exemplifying an aggressive case. Case 3: (**A**) First recurrence 11 months after Simpson I removal; second and last recurrence 9 months after repeated Simpson I removal, on axial (**B**) and coronal (**C**) planes. The tumor has reached the skull base and infiltrated the orbit.

time.[12,13,16,19,21,29,31] In our series, the mean disease-free survival time for each subsequent recurrence was 24 months (similar to the first recurrence), but it decreased with each recurrence, ranging from 32–35 months after treatment for the first recurrence to 6–10 months after the fourth or fifth recurrence. This can be explained by evidence showing that molecular and behavior progression toward an aggressive clinical course is more rapid in atypical than benign meningiomas.[6,19,29,32] In a minority of our cases, however, the clinical course was shorter after the first recurrence because of high tumor cell proliferation, without a significant correlation with Ki-67, which remains a controversial marker of tumor aggressiveness.[3,33]

The dysembryogenetic mechanism does not contrast with the notion of a treatment-driven mechanism such as stepwise tumor progression, according to which subtotal resection and selection of radioresistant cells may stimulate tumor progression.[4,22] Simpson grade III–IV, as well as stable disease after SRS, is a provisory result because viable tumor cells capable of migration and replication make the disease even worse at each new recurrence. Nonetheless, SRS may slow regrowth while new lesions may develop, for which a larger craniotomy can be planned to treat old and new lesions during the same session. Sharing Borovich et al.'s observation of tumor nests within the dura some centimeters around the mass, we suggest giving priority to tumor resection where a dural-free margin is resectable and to tumors with mass effect or being symptomatic, at the second or third recurrence, but possibly not later.[24,25] In the absence of any preferential treatment, this strategy holds promise to achieve better results and prolong disease-free intervals.

Moreover, arguments claiming that large craniotomy and parallel dural resection are trivial technical issues in brain tumor surgery or meningioma treatment are akin to the questionable belief that minimal invasive surgery is synonymous with safety. On the contrary, the choice of surgical technique is vitally important in treating benign tumors, should be adapted to the disease, and should obtain a definitive cure for the disease. This holds true particularly in light of evidence that many atypical meningiomas (30%–35%)[3] originate from recurrent grade I meningiomas, which, we might add, often start from the margin of dural resection.[4] In addition, second or further surgery for tumor recurrence is no more burdened by complications than primary surgery.[34]

Importantly, the skull base and midline are inevitable sites of tumor migration, and skull base represents the only single negative prognostic factors for survival. Because this is a potential limiting factor for treatment, every effort should be undertaken before the tumor reaches the skull base or the tentorium.[7,28] At every recurrence, choice and timing of treatment remain crucial and can only be addressed by careful consultation between the radiation therapist and the neurosurgeon. Although standard treatment (SRS and Simpson I removal) have failed per se to prolong progression-free survival, repeat treatment prolonged overall survival in our series, in which single cases provided further insights and hope for a designing a successful strategy.

This study is subject to the normal biases of a retrospective review, especially the potential selection bias of the cohorts. Because of the relatively rare incidence of atypical meningiomas and their variety, a broad inclusion criterion was necessary, with the drawback that data analysis was limited by the small number of patients.

CONCLUSIONS

Multicentricity is an essential aspect of tumor progression. Marginal regrowth is the most frequent pattern of recurrence and of unpredictable direction in early recurrences. Skull base recurrence after initial treatment is a significant negative prognostic factor for survival. These features are key to tailoring treatment on a case-by-case basis. Total surgical resection in recurrences is not as effective as it is the first time, and progression-free intervals are shorter with each later recurrence and treatment, regardless of the treatment type (surgery or SRS). Stereotactic radiosurgery, as part of palliative care in recurrences, should be delivered to delay and optimize surgical treatment. Timing is critical for appropriate aggressive surgery to obtain tumor resection and extended dural detachment with wide craniotomy.

For the majority of patients, overall survival after recurrence may be less hopeless than previously reported if care is pursued with perseveration by neurosurgeons and radiotherapists working together to decide how and when to perform aggressive surgery.

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