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.