Radiosurgery and atypical meningiomas

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The mainstay of therapy for patients harboring meningiomas, including atypical (WHO Grade II) meningiomas, is resection. The optimal initial treatment for all grades of meningioma is gross-total resection (GTR), although factors such as anatomical location and patient comorbidities may preclude aggressive surgical management, and the specific role and importance of resection for meningiomas continue to be evaluated. Higher-grade meningiomas (Grades II and III) are known to have a higher recurrence rate and poorer overall prognosis. Thus, optimization of adjuvant therapy is needed to minimize the risks of recurrence or progression after surgery.

Recent literature has suggested that postoperative adjuvant radiation therapy immediately after GTR of atypical meningioma prolongs progression-free survival (PFS) and overall survival (OS) compared with resection without radiation therapy. In their article, Komotar and colleagues reinforce this treatment strategy with results from a focused retrospective review of 45 patients with atypical meningiomas, all of whom underwent GTR of their tumor. With a median follow-up of 44.1 months, only 1 (8%) of 13 patients who received postoperative radiation therapy demonstrated tumor recurrence, whereas 13 (41%) of 32 patients who did not receive postoperative radiotherapy experienced tumor recurrence. Thus, a trend toward increased PFS was observed in patients who received postoperative radiation therapy, although the results were not statistically significant (p = 0.085). Although the focus of this paper was patients with no residual tumor after surgery, not all meningiomas are amenable to GTR, and there are limits to the efficacy of surgery with recurrent or aggressive tumors. Furthermore, systemic chemotherapy and hormonal therapy have demonstrated minimal efficacy thus far. Thus, radiotherapy will continue to be the primary adjuvant therapeutic modality, and data from studies such as this will have an important role in guiding therapy not only in high-grade tumors after GTR, as discussed in this manuscript, but also in subtotally resected tumors or those amenable only to biopsy procedures.

Postoperative radiation therapy for atypical meningiomas is an important topic given the recent evolution of the WHO classification criteria. Currently, histological grade is the most powerful prognostic factor for patients with meningioma. Recognition of the subclassification of atypical meningioma was first made to distinguish these tumors from benign, WHO Grade I tumors and malignant/anaplastic, WHO Grade III tumors. Based on these initial WHO guidelines, the WHO Grade II tumor incidence rate was reported to be around 5% of meningiomas overall. The WHO classification criteria for meningiomas changed significantly in 2000 based in part on retrospective reviews associating outcomes with histological grading criteria. These criteria broadened the definition of atypical meningioma, leading to a shift in observed incidence of atypical meningioma from roughly 5% to 20%–35% of all meningiomas. A recent study retrospectively reviewed 314 tumors over a 10-year period at a single institution and found that 38% of tumors classified as Grade II using 2000 criteria had originally been classified as Grade I by 1993 WHO criteria. This effective increase in incidence in Grade II meningiomas underscores the importance of determining optimal therapy for these tumors, which have a distinctly worse clinical trajectory than Grade I tumors. The new grading criteria must also be taken into account when reviewing studies that rely on pre-2000 WHO grading criteria.

Despite refinements in the WHO grading criteria, there remains subjectivity in histological diagnosis as well as multiple histological subtypes of atypical meningiomas (for example, chordoid and clear cell). The end result is that atypical meningioma remains a mixed bag of meningioma subtypes that have an intermediate histological appearance and clinical behavior. Progress in meningioma therapy will likely build upon WHO grading criteria by incorporating genetic, molecular, and immunohistochemical subclassifications in further categorizing these tumors. A number of recent studies illustrate potential in this regard. Bruna et al. evaluated 28 patients with atypical (16) or malignant (12) meningiomas in terms of the Ki 67 labeling index. Multivariate analysis found that the Ki 67 labeling index was the only independent predictor of PFS and overall survival. A Ki 67 less than 9.9% indicated longer OS, whereas histological grade failed
to show predictive value. Komotar and colleagues discussed the observation that most meningiomas have intact p53, which may render these tumors sensitive to radiation. Chromosomal abnormalities commonly involve chromosome 22. Monosomy 22 is the most common genetic malformation found in meningiomas. Upregulation of progesterone and estrogen receptors has implied an association between these hormones and meningioma pathogenesis, and progesterone receptor status is related to gene expression near the NF2 gene on chromosome 22. TEMPT-1, also a chromosome 22 gene, is implicated in high-grade meningiomas. Atypical meningiomas are known to have other chromosomal abnormalities such as losses of 1p, 6q, 10, and 18q. Specific clinical scenarios may represent unique opportunities for genetic and molecular research. Examples include malignant transformation of a Grade I tumor in which specimens from both grades are available, as well as tumors that do not respond to radiation therapy. Integration of these and other genetic and molecular findings may help further classify meningiomas and direct targets for therapy.

Further delineation of the role of radiation therapy in atypical meningiomas may evaluate multiple factors, ideally in a prospective fashion. Use of fractionated radiotherapy is described by Komotar and colleagues, but stereotactic radiosurgery has played an increasing role in treating meningioma with or without surgery and its role in meningioma therapy, including high-grade tumors, is likely to expand. Photon radiation techniques are most common, but other techniques such as proton radiotherapy and carbon ion radiotherapy are also described, largely in combination with photon radiotherapy or as salvage treatment following photon radiation therapy. As radiotherapy is likely to remain the mainstay of adjuvant therapy, further refinement of radiation techniques is essential in optimizing clinical results.

The treatment strategy of GTR followed by immediate postoperative radiotherapy for atypical meningioma has gained traction, although support for this treatment algorithm is largely in the form of small- to moderate-sized retrospective case series. A comparison of these studies is difficult due to differences in variables, such as radiation techniques and study design, as well as difficulty comparing data that potentially relied on different WHO classification criteria. Ultimately, further optimization of treatment strategies for atypical meningiomas will depend on prospective studies that make use of improvements in adjuvant radiation techniques. Integration of molecular and genetic knowledge into current diagnostic algorithms may improve classification schemes and prognostic abilities and allow tailoring of adjuvant therapies.

Disclosure

The authors report no conflict of interest.

References


Response

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The standard of care for patients with atypical or anaplastic meningioma is neurosurgical resection. With this approach, local control ranges between 50% and 70%, depending on resection status. Even after GTR, however, subsequent prognosis and optimal management remain unclear. After GTR without postoperative radiation therapy, atypical meningiomas have a high recurrence rate, mostly within 5 years of resection, leading to reoperation and shortened survival. Immediate postoperative radiation therapy appears to lower this recurrence rate, yet surgeons and radiation oncologists may be reluctant to administer this therapy for fear that the potential detrimental effects of cranial irradiation outweigh the benefits of reduced tumor recurrence.

The use of adjuvant therapy in this patient population has become even more important given the evolution of WHO grading criteria. In 2000, the new WHO criteria began to be cited by neuropathologists as the basis by which atypical meningiomas were reported.2 Prior to this change, the percentage of atypical meningiomas reported had been stable at approximately 5.0% for many years. Prior to the acceptance of the WHO 2000 criteria, the diagnosis of atypical meningioma was made most frequently in the presence of increased mitotic activity. No universally accepted quantified criteria to diagnose atypical meningiomas existed at the time. After 2000, however, there was an increase in atypical meningiomas with lower mitotic rates, due to the inclusion of other WHO-quantified pathological features. In 2007, the WHO grading criteria for atypical meningiomas was updated again.3 The new grading system recognized a considerably higher rate of Grade II histology than previously appreciated and strongly supported the reevaluation of patient management paradigms.

This topic has been studied in the past, most recently by Aghi et al.,1 who published a long-term analysis of 108 patients with Simpson Grade I resection of an atypical meningioma. One hundred patients (93%) underwent surgery alone, and 8 (7%) underwent surgery plus radiation therapy, with a mean total dose of 60.2 Gy. After Simpson Grade I surgery alone, the 5-year recurrence rate was 45%, but there was no recurrence after surgery and external-beam radiation therapy (p = 0.1). The authors also documented the consequences of recurrence. Many recurrences (53%) were symptomatic. Salvage treatment included repeat surgery in 73% of patients, with an average of 2.7 craniotomies per recurrence. All patients with recurrence ultimately received either external-beam radiation therapy or stereotactic radiosurgery, and yet 33% died as a result of their intracranial tumor, at an average of 7 years after recurrence.

Our series is in line with previous investigations showing that postoperative radiotherapy in this patient population can increase PFS, which translates into increased overall survival. This work highlights the important questions that surround optimal management for our patients with atypical meningioma and confirms the value of developing large, multicenter, prospective clinical trials for patients with these tumors.

References


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