

## Editorial

### Stereotactic radiosurgery and atypical meningiomas

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Resection continues to be the cornerstone of management of patients with meningiomas, regardless of WHO grade. The continued emphasis on surgery's primary role is strengthened by the absence of effective chemotherapeutic options in the recurrent or residual setting,<sup>11</sup> which may be due to an insufficient understanding of the biological basis of these tumors. There also exists an overall lack of consensus on the role of radiation in treatment. Most experts generally accept that postoperative radiation is a necessary adjuvant in WHO Grade III tumors regardless of the extent of resection, given their malignant course and reported recurrence rates of up to 90%.<sup>14</sup> However, the management of Grade II tumors that are completely resected, subtotally resected, or recurrent is the subject of significant debate. This inconsistency is highlighted by substantial reported variation amongst treating physicians related to the utilization of adjuvant radiation in either gross-totally or subtotally resected atypical meningiomas.<sup>9,16</sup>

The need to clarify a role for adjuvant radiation in atypical meningiomas is underscored by recurrence rates of 28%–50%.<sup>14</sup> Moreover, the revisions of the WHO histological grading criteria in 2000 have led to a significant increase in the proportion of meningiomas diagnosed as Grade II, with estimates placing the current incidence at more than 20% as compared with a historical incidence of approximately 5%.<sup>15</sup> To date, the data are unclear regarding the utility of adjuvant radiation of any form in the postoperative setting, regardless of Simpson resection grade. Aghi et al.<sup>1</sup> noted that an overall recurrence rate of 28% in 3 years after gross-total resection (GTR) was dramatically reduced in cases in which postoperative fractionated radiotherapy was added, although conclusions are confounded by the small number of patients treated with radiation (8 of 108). Other series have reported improved progression-free survival (PFS) with adjuvant radiotherapy after GTR.<sup>12</sup> However, recent data from Mair et al.<sup>8</sup> do not support the use of adjuvant fractionated radiotherapy in patients with GTR, but do validate its use in limiting recurrence rates in cases of subtotal resection.

The risks of radiation, which vary among studies using different techniques and doses with relatively short follow-up durations, must also be considered along with the clinician's desire to maintain sufficient radiation options in cases in which recurrence is a significant concern. Newer approaches with purportedly lower risk profiles center on the use of particle radiation: in the treatment of benign meningioma, proton radiation therapy decreases the risk of radiation-associated tumors by half and can deliver significantly lower doses to neurocognitive and critical structures of vision and hearing.<sup>2</sup> Carbon ion radiotherapy has been used to supplement more conventional radiation in treating higher-grade meningiomas.<sup>5</sup> However, these particle radiation modalities have greatly limited applicability to most neurosurgical centers without access to a cyclotron.

The increasing use of stereotactic radiosurgery (SRS) has led to a growing literature describing its use in the adjuvant treatment of atypical meningiomas. Potential advantages to this approach include reduced radiation exposure to surrounding neural tissue and possible fewer neurocognitive sequelae when compared with larger-field radiation, limited (if any) alopecia,<sup>4</sup> and fewer treatment sessions. Residual tumor treated with SRS early (within 6 months) of craniotomy and before radiographic progression confers higher rates of tumor control in some series,<sup>5-7</sup> with no survival difference noted between patients treated with conventional external beam radiation therapy and those treated using SRS.<sup>4</sup> Other recent series report 3-year PFS in recurrent Grade II tumors treated with SRS with varying marginal dosing, with the suggestion in 1 series that a marginal dose of < 20 Gy is associated with shorter time to progression<sup>7,10</sup> and more modest control rates in other series.<sup>3</sup>

Hardesty et al.<sup>6</sup> add to this growing literature in reviewing a large series of patients treated with SRS after microsurgical resection of 257 atypical meningiomas in 228 patients. In their patient series, postoperative SRS showed no significant benefit in PFS for gross-totally or subtotally resected tumors. These investigators report a median time to recurrence of 20.2 months in 51 patients. Seventy-one patients received postoperative radiation, of whom 32 underwent SRS and 39 received intensity modulated radiation therapy (IMRT). Twenty-five percent of patients receiving SRS suffered a recurrence, compared with 18% receiving IMRT, neither of which were significantly different from the overall recurrence rate. Thirty-one patients represented transformation from Grade I to Grade II tumors, and 25 patients had previously undergone radiotherapy. Of those patients who had received

SRS, 69% had undergone a Simpson Grade I or II resection. Median radiation dose was 14–16 Gy in a single fraction to as high as 27 Gy in 3–5 fractions. Overall, there was no association between adjuvant SRS and PFS. Moreover, the subgroup analysis of patients with subtotal resection receiving postoperative SRS also showed no benefit, although the extent of residual tumor treated is not highlighted. There was no significant benefit to PFS to adding SRS to patients who had undergone Simpson Grade I/II resections. Similar findings were noted when adjuvant IMRT was given. Longer follow-up durations in these cohorts would help ascertain whether radiotherapeutic intervention by SRS or IMRT alters the natural history of completely or subtotally resected tumors.

The retrospective nature of the study and relatively short follow-up time are inherent limitations, and separate analyses by Simpson Grade I and II tumor resections, and location (skull base vs non-skull base), MIB-1 profiles, as well as further classifying “subtotal resection” would be preferable, although likely complicated by sample size. That 31 patients representing transformation of previously resected Grade I tumors to Grade II tumors may also reflect an underlying biological heterogeneity within grade that may also confound results. Indeed, evidence from other common brain tumor types suggests that tumor grade alone may be an inadequate method of classifying meningioma, and distinct molecular subclasses may exist with differential clinical outcome and/or responses to radiation. Clear examples of this concept exist in glioblastoma and medulloblastoma, in which genomic profiling has identified additional subtypes differing in, among other factors, survival length and treatment response.<sup>17,18</sup> That meningiomas may represent a more complicated group of tumors than suggested by grade may confound our current attempts to decipher the response of atypical variants to postoperative radiation.

While variability in patient selection may also be considered a weakness of the study, one may consider it a strength as well, because it likely simulates how radiation is incorporated into the management strategy of atypical meningiomas across many large-volume centers.<sup>13</sup> This factor certainly mirrors treatment selection at our center, where the decision to administer postoperative radiation is made on a case-by-case basis after discussions with a multidisciplinary tumor board and radiation oncology colleagues.

Questions for study further stimulated by Hardesty et al. include timing of radiation administration (planned postoperative radiation vs close observation and subsequent treatment of local recurrence); whether or not patients with GTR should undergo radiation of any form; and the mode of radiation delivery (external beam radiation therapy vs SRS vs proton radiation therapy) and attendant dosing, among other issues.<sup>6</sup> To date, there continues to be no formal consensus on the use of adjuvant radiation of any mode of delivery, dose, or timing in the management of atypical meningiomas that have been gross-totally or subtotally resected. The thoughtful contribution of Hardesty et al. underscores this point and adds to the increasingly equivocal body of literature. We hope that further guidance will emerge from con-

tinuing efforts to understand the biological heterogeneity of higher-grade meningiomas in combination with two Phase II clinical trials currently underway (RTOG-0539 and EORTC 22042-26042) exploring the effect of radiation on both gross-totally and subtotally resected Grade II meningiomas, as well as the impact of radiosurgery on postoperative residual tumor.

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#### Disclosure

The authors report no conflict of interest.

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## Response

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We would like to thank Drs. Chiocca and Dunn for

their thoughtful editorial and critical review of management paradigms for WHO Grade II meningiomas. We agree that these patients require individualized, multidisciplinary treatment strategies and believe that large-scale, single-institution retrospective studies remain an important source of data in the modern neurosurgical literature, given that randomized studies for such a population remain uncommon.

The current study defines, for the first time, the clinical value of adjuvant radiosurgical techniques in the context of the extent of resection in atypical meningiomas. This 228-patient analysis is the largest such study to date, yet despite a median follow-up of 4.3 years, it does not associate a survival benefit with postoperative radiosurgery or radiotherapy. Given the scarcity of genetic and epigenetic studies to predict atypical meningioma radiosensitivity, such data could not be incorporated into our analysis, but should be an area of further investigation. Nevertheless, we believe this study represents the most rigorous effort to date quantifying the survival benefit associated with atypical meningioma surgery and adjuvant radiosurgery.

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