Intermediate-risk meningioma and NRG Oncology RTOG 0539

TO THE EDITOR: We read with great interest the initial results from NRG Oncology RTOG 0539 published by Rogers et al.3 on the treatment of intermediate-risk meningioma (Rogers L, Zhang P, Vogelbaum MA, et al: Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539. J Neurosurg 129:35–47, July 2018). The authors provide a brief description of the trial and the division of meningioma patients into 3 risk groups according to the chance of recurrence and their treatment (low, observation; intermediate, 54 Gy in 30 fractions; and high, 60 Gy in 30 fractions). They focus on the intermediate-risk-meningioma group and their results support the use of postoperative radiotherapy in this patient cohort, stating that they achieved a progression-free survival (PFS) of 93.8% (historical cohorts: PFS 57%–90%6 at 3 years following gross-total resection [GTR] alone) and overall survival (OS) of 96% at 3 years.

Nevertheless, we would like to clarify the inclusion criteria in the intermediate-risk group. In Fig. 1, it appears that patients with newly diagnosed WHO grade II meningiomas who had a subtotal resection (STR) are in both the intermediate- and high-risk groups, although our understanding from the remaining paper is that these patients were considered to be in the high-risk group.

This is particularly relevant, as immediate postoperative adjuvant radiotherapy is a matter of debate in the treatment of patients with WHO grade II meningiomas who have had STR. The studies by Masalha et al.7 and Champeaux et al.3 support extent of resection continuing to be the most important factor and indicate that adjuvant radiotherapy has no effect on PFS when adjusted for confounding factors.

We have reviewed the current literature describing the risk of tumor recurrence with lesion characteristics; pial invasion and peri-tumor edema (even though only Simpson grade I and II resections were compared);8 necrosis (both WHO grade I and II);9 and proliferation index.7 Chen and coauthors have pointed toward previous STR and radiotherapy as potential risk factors for local failure after salvage treatment for recurrent grade II meningioma.4 Therefore, the timing for radiotherapy administration (as the surgical resection might be defined/limited by the tumor itself) may be crucial not only for PFS assessment but also for the success of further treatment and OS.

The authors have highlighted that the proportion of meningiomas that are classified as WHO grade II has also significantly increased (range 25%–35%)—before the 2016 WHO classification revision, with the introduction of brain invasion as a criterion for the diagnosis of grade II meningioma alone). Therefore, this distinction will become even more important in the coming years, given the expected increase in the diagnosis of grade II meningioma.

We assume that STR in grade II meningioma is related to technical issues (previously planned or intraoperative events) that preclude GTR, and we therefore support the use of radiotherapy, which is proven to reduce the recurrence rate. Nevertheless, if the surgical team considers residual disease following initial debulking to be resectable, complete resection should be the goal for treatment.

Rogers and coauthors have successfully demonstrated the role of postoperative radiotherapy in a newly classified intermediate-risk meningioma group. We look forward to clarification of the inclusion criteria for this group as it will greatly help in treatment decisions and patient counseling.

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Response
We very much appreciate the careful review of our NRG/RTOG-0539 intermediate-risk meningioma article by Dr. Lavrador and colleagues and their identification of an error in Fig. 1 that requires correction. We regret this oversight. The intermediate-risk cohort (Group 2) of the NRG/RTOG-0539 trial was composed of patients with a newly diagnosed gross-totally resected (GTR; Simpson grades I–III) World Health Organization (WHO) grade II meningioma, a recurrent WHO grade I meningioma after resection of any extent, or a patient with progression of a WHO grade I meningioma identified on imaging alone. Patients with a subtotally resected (STR; Simpson grades IV and V) WHO grade II meningioma were not included in Group 2 but were instead assigned to the high-risk cohort (Group 3), which also included patients with recurrent WHO grade II with any extent of resection as well as patients with newly diagnosed or recurrent WHO grade III meningioma with any extent of resection.

Dr. Lavrador and colleagues also correctly point out that early adjuvant radiotherapy (RT) for patients with WHO grade II meningioma, irrespective of the extent of resection, remains open to debate. Many previous reports suggest that progression-free survival (PFS) is superior after GTR plus RT compared with GTR alone. Please see the applicable figure (Fig. 7) in the intermediate-risk article for graphical comparisons. However, a minority of treatment centers (7% to 30%) recommend RT after GTR alone. 1,2,5,7,9,10 Thus, the appropriate approach to patients who have undergone GTR of a WHO grade II meningioma remains an important, clinically relevant, and as-yet-unanswered question.

Regarding STR, recent reports have also suggested improvements in PFS with early RT following STR for WHO grade II meningioma.3,5,9 Shakir et al.9 from McGill University reported a 5-year PFS of 0% in 26 patients treated with STR versus 75% in 4 patients treated with STR plus early RT. Similarly, Dohm and colleagues3 from Wake Forest University reported a 5-year PFS after STR alone (n = 15) of 18% compared with 73% after STR plus early RT (n = 4). Bagshaw et al.3 from the University of Utah noted that at a median follow-up of 42 months no patient with STR alone (n = 2) remained progression-free, whereas 56% were progression-free after STR plus early RT (n = 9). Although these relatively small cohorts suggest an advantage to early postoperative RT after STR, they also confirm that RT is not uniformly recommended in this setting, as its use has ranged from 13% to 74%,5,7,9,10

Lavrador and colleagues’ letter mentions 2 articles that question the value of RT after surgery for atypical meningioma.3,8 These articles are valuable additions to the medical literature and deserve comment. Champeaux et al.4 from Queen Elizabeth University in Glasgow, Scotland, reviewed outcomes from 215 patients with WHO grade II meningiomas treated surgically and reported that RT neither reduced the risk of recurrence nor improved overall survival. This report was not specifically an analysis of early RT, with a median interval of 1.1 years from surgery to RT. Moreover, the use of RT followed recurrence of the tumor in approximately 30% of cases; this situation is dramatically different from the up-front use of RT after STR. Champeaux et al.4 commented, “Radiotherapy indications were incomplete resection of grade II meningioma displaying a high mitotic index, tumor recurrence or tumor residual regrowth.” In their series, the patients who received RT experienced poorer PFS and were more likely to need reoperation for recurrence, which the authors believed was “likely secondary to selection bias.” It is indeed to be expected that patients receiving RT for considerably poorer prognostic features may have poorer outcomes.

Similar comments pertain to the publication by Masalah and colleagues8 from the University of Freiburg. A minority of their 161 patients received RT (n = 33, 20%), and those so treated had either recurrent disease or other poor prognostic features. For instance, 14.1% (18/128) of patients treated with surgery alone had a MIB-1 proliferation index > 10% compared with 45.5% (15/33) of those treated with surgery and RT. Masalah et al.8 identified 5-year and 10-year PFS rates as being numerically inferior for patients treated with RT. At 5 years, PFS was 73% (93/128) after surgery alone and 64% (21/33) with postoperative RT, whereas at 10 years, the rates were 70% (90/128) and 57% (53/93), respectively. Again, the selective use of RT only for high-risk patients is not a reasonable design for comparing outcomes with those of observed lower-risk patients.

It has become clear that meningiomas are more aggressive at recurrence, even when they retain the same WHO grade, as they often do. In a recent Revised Assessment in Neuro-Oncology publication, Kaley et al.6 analyzed the reported results of medical therapies for patients with multiply recurrent meningiomas. With over 500 patients from 37 reports, the weighted average PFS at 6 months was 29% for the surgery- and radiation-refractory WHO grade I meningioma group and 26% for the WHO grade II and III group, which suggests that recurrent meningiomas