



A management dilemma: adjuvant radiotherapy after gross total resection of atypical meningioma

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Weber *et al.* recently published initial results of a prospective phase II trial of patients with grade II and III meningiomas treated with adjuvant radiotherapy (RT) after subtotal or gross total resection (GTR) (1). This initial publication of EORTC 22042 reports outcomes of the 56 enrolled patients with grade II meningiomas who underwent GTR followed by adjuvant RT, and shows favorable 3-year progression free survival (PFS) with moderate toxicity. Together with RTOG 0539 intermediate risk cohort (2), these two trials provide the only prospective data on outcomes of adjuvant RT for atypical meningiomas. Despite meeting the primary endpoints for both of the aforementioned trials, adjuvant RT remains controversial in the management of gross totally resected grade II meningiomas.

The short-term efficacy of radiotherapy has now been demonstrated prospectively in each of these two recent trials. Both EORTC and RTOG studies show favorable results of their primary endpoint, with 3-year PFS rates of 88.7% and 93.8%, respectively. These results are in concordance with multiple retrospective reports showing 3-year local control rates after GTR and adjuvant RT of 96% to 100% (2). The importance of locoregional control should not be underestimated, as each trial had a small number of patients with fatal local progression, 2 in EORTC and 1 in RTOG. Subsequent long term outcomes will be important to determine if control remains durable in this cohort of patients.

Although adjuvant RT has shown promising efficacy, its toxicity is not negligible based on this study, which reports a

19.6% rate of acute grade 3+ side effects, 14.3% late grade 3+ side effects, and 32.1% incidence of late grade 2 side effects. Since these results were not further characterized by the relationship to RT, the reported side effects likely overestimate the true toxicity profile. The authors estimate that 50% of serious events were likely related to RT. In contrast, RTOG 0539 did categorize toxicity based on relation to RT. 15.4% of patients experienced grade 3+ adverse effects; however, none were felt to be possibly related to RT. There were, however, a sizeable number of grade 2 toxicities, with a 25.5% rate of events considered at least possibly related to RT. Potential explanations for higher toxicity in the EORTC trial include the increased dose of 60 *vs.* 54 Gy and the decreased use of IMRT (53.6% compared to 84.6%). Previous studies using modern radiotherapy techniques have shown rates of grade 3 toxicity of 2–4% (3-5).

Acknowledging that adjuvant radiotherapy carries a risk of adverse effects, the side effects of additional therapy must be weighed against the risk of recurrence with observation alone. Multiple retrospective reports of observation after gross total resection have shown 3-year PFS rates of 57% to 90%, with the majority near 70%; most, but not all, have shown significant improvement with the addition of adjuvant radiotherapy, and it appears this benefit is sustained over longer periods of follow up (2,5-9). These outcomes will be prospectively confirmed by EORTC 1308 and NRG BN003, both phase III trials randomizing patients with gross totally resected grade II meningiomas to adjuvant radiotherapy versus observation (10,11).

Though recurrence rates seem convincingly lower with adjuvant RT, effective salvage therapy could obviate the need for upfront treatment. However, even for perfectly compliant patients, this approach is not without risk. Allowing for recurrence may predispose patients to future relapse, as recurrence itself has been associated with increased risk of local failure (5). The increased tumor volume of even small macroscopic recurrences may potentially decrease the efficacy of salvage RT. Long-term results of the EORTC and NRG trials will be required to adequately compare close observation and adjuvant RT. In addition to PFS, outcomes evaluating toxicity, neurocognitive function, and quality of life will help guide future decision making.

To better select patients for observation versus adjuvant radiotherapy, additional histopathologic and genetic factors may be useful in risk stratifying patients. Bone and brain invasion, Ki-67 proliferation rate, and TERT promoter mutations have all been independently associated with increased risk of disease recurrence (12-14). In addition to risk stratification, specific mutations may prove to be actionable targets for systemic therapies; targeted therapies against AKT, SMO, NF2, BAP1, mTOR, and PD-1 are currently under investigation (15-17). Targeted systemic therapies will be particularly important for grade II and III meningiomas, which are more likely to recur despite aggressive treatment and exhaust all focal therapeutic options.

Management of gross totally resected atypical meningioma remains a controversial and important area of research. Two recent prospective trials have shown favorable short term control with moderate toxicity after adjuvant radiotherapy. We await long term outcomes of these studies as well as the results of the randomized trials NRG BN003 and EORTC 0138 to fully ascertain the benefit of adjuvant radiotherapy versus observation. Additional histopathologic and genetic factors are likely to further influence patient selection in the foreseeable future. Targeted therapies may eventually prove to be another therapeutic option for refractory disease.

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