Letter to the Editor. Phase III randomized controlled trials are essential to properly evaluate the role of radiotherapy in WHO grade II meningioma

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Phase III randomised controlled trials are essential to properly evaluate the role of radiotherapy in WHO grade II meningioma

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Rogers et al. report the findings from the Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539 study.[7] Intermediate risk meningiomas were defined as those with a higher recurrence rate and includes gross total resection (GTR) WHO grade II meningioma (Simpson 1-3) and any recurrent WHO grade I meningioma regardless of the extent of resection. Despite the relative radioresistance of meningiomas, radiotherapy remains the only available adjuvant therapy for these tumors and in WHO grade II meningioma there is a lack of class I evidence for the role of early adjuvant radiotherapy.[5] Treatment decisions (i.e. adjuvant radiotherapy *vs.* no adjuvant radiotherapy) after surgery currently factor in tumor location, patient's pre-treatment characteristics and the willingness of the surgeon to re-operate if recurrence occurs.[4] Tumor recurrence undoubtedly has an impact on patient quality of life and if adjuvant radiotherapy can deliver prolonged control with low risk it should be considered in the multi-modality management of WHO grade II meningioma. RTOG 0539 was a phase II non-randomised study with a primary endpoint of 3-year progression free survival and included 36 patients with GTR grade II meningioma who received post-operative radiotherapy of which 1 patient progressed and 1 patient died of disease resulting in a 3 year local failure rate of 4.1%. It is reassuring to note that the early adverse events (AE) from radiotherapy were limited to CTCAE grade 1 or 2 (mainly dermatological) with no severe events. Neurosurgeons have been historically sceptical about adjuvant radiotherapy citing concerns about the risk of late cognitive decline and this is also a concern for patients.[8] It is also reassuring that the RTOG 0539 study reported that mild memory decline affected only a small number of patients although detailed cognitive assessment was not performed. Likewise, another phase II trial performed by the European Organisation for the Research and Treatment of Cancer (EORTC 22042-26042) submitted for publication did not show any cognitive impact after high-dose radiotherapy and similar control rates (Damien C. Weber, personal communication; submitted for publication). The

relatively mild adverse events may be attributable to better radiotherapy planning techniques that minimise the radiotherapy dose to normal brain[1] however it is important to emphasis that both phase II studies only had only 3 years follow-up and later meningioma recurrence may occur. The lack of a control arm is the main limitation of the study and neurosurgeons are likely to remain sceptical about adjuvant radiotherapy in GTR WHO grade II meningioma. Nevertheless, the favorable AE profile of radiotherapy supports the continued enrolment into open phase III studies. The ROAM/EORTC 1308 trial [ISRCTN71502099] (Radiation versus Observation following surgical resection of Atypical Meningioma) is a multi-centre, phase III, randomised controlled trial (RCT) that will answer the question 'in patients who have undergone gross total resection of atypical meningioma, does early adjuvant radiotherapy reduce recurrence compared to active monitoring?'[3] The study is open across the UK, Europe, Australia and New Zealand (http://roam-trial.org.uk) with 44 sites open (63 planned) and 36 patients randomised (190 planned). The study is powered to detect an absolute reduction in recurrence rate from 40% (control arm) to 20% (radiotherapy arm) at 5 years and importantly will collect data on quality of life, neurocognitive function and assess whether adjuvant radiotherapy is cost-effective. Studies of intervention versus monitoring can pose a recruitment challenge since clinicians and patients often exhibit bias.[2,6] Preliminary results from the embedded qualitative research study of audio recordings of the recruitment consultation have led to improvements by researchers in balancing the treatment arms and explaining equipoise. In parallel the NRG BN-003 study (http://clinicaltrials.gov/ct2/show/NCT03180268) will also provide class I evidence. It is incumbent on the neurosurgery and oncology community to work collaboratively to ensure both trials are successfully delivered in order to establish the best way to manage patients with complete resection of WHO grade II meningioma.

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