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Beating a benchmark: Boron neutron capture therapy for recurrent and refractory meningiomas

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The majority of meningiomas are World Health Organization (WHO) grade 1 and have favorable outcomes when managed with surgery or radiotherapy. However, approximately 18% of meningiomas are grade 2 and 2% are grade 3.[1] Even with aggressive multi-modal management for high-grade meningiomas, outcomes remain modest. The high-risk arm of RTOG 0539 included WHO grade 2 meningiomas which were subtotally resected or recurrent after surgery alone, and any WHO grade 3 meningiomas, regardless of the extent of resection.[2] After fractionated external beam photon radiotherapy to a dose of 60 Gy in 30 fractions, the progression-free survival (PFS) at 3 years was just 59%. Post hoc analysis demonstrated that recurrent grade 2 meningiomas had worse PFS than newly diagnosed grade 3 meningiomas (5-year PFS 30% vs 58.2%), suggesting that recurrent high-grade meningiomas represent a particularly aggressive entity. Furthermore, grade 2 and 3 meningiomas which recur following multimodality therapy with surgery and radiotherapy are even more difficult to manage with an estimated 6-month PFS of just 26%.[3] Multiple systemic agents, such as cytotoxic chemotherapies, targeted therapies,[4] and more recently immune checkpoint inhibitor therapies,[5] have failed to improve outcomes over these historical estimates, leading to a critical and unmet need to evaluate innovative treatment approaches for this patient population.

Local therapy is the mainstay of meningioma treatment. However, treatment-refractory patients have often exhausted their ability to receive repeat surgery, and have either received multiple prior radiotherapy courses which preclude the safe delivery of re-irradiation and/or have large volumes of tumor recurrence which are not amenable to stereotactic re-irradiation techniques. As such, particle therapy has been used as a re-irradiation strategy owing to its physical advantages over photon therapy which limits the volume of normal tissue receiving radiation.[6]

Miyatake and colleagues recently updated their outcomes of 44 patients with recurrent, treatment-refractory, grade 2 and 3 meningiomas treated with reactor-based boron neutron capture therapy (BNCT).[7] Briefly, BNCT is delivered by infusing a ^{10}B compound which is selectively taken up by tumor cells. Subsequently, the target is irradiated with low-energy thermal neutrons, which react with the localized ^{10}B, producing high linear energy transfer particles which travel only the diameter of a cell, and thus selectively destroy tumor cells while sparing adjacent normal tissue cells. While BNCT has been the subject of research for several decades, widespread adoption has been limited by the high cost of developing BNCT centers and the lack of prospective data.

The patient cohort was composed of high-grade (45% with grade 2 and 55% with grade 3 meningiomas) multiply recurrent (mean 3 prior surgeries and 2 prior courses of radiotherapy) and treatment-refractory patients. At the time of BNCT, recurrences were large with mean and median BNCT treatment volumes of 42.7 cm^3 and 24.5 cm^3, respectively. Despite the aggressive characteristics of this cohort, the median PFS after BNCT was 13.7 months among the 36 patients available for analysis. Furthermore, the median overall survival after BNCT was favorable at 29.6 months, and grade 3 radiation necrosis occurred in 13.6% of patients. In addition to this study, several other series using particle re-irradiation have reported their outcomes and are summarized in Table 1. Although direct comparisons between series are challenging given the heterogeneous patient cohorts, particle re-irradiation with BNCT appears to be an efficacious treatment strategy for well-selected patients with refractory meningiomas treated at experienced centers. To put these outcomes into perspective, in 2014, the response assessment in neuro-oncology (RANO) group performed a pooled analysis of refractory meningiomas treated with medical therapy and recommended that studies of experimental therapies demonstrating a 6-month PFS greater than 35% may be worthy of further study.[3] In the current study with its heavily pre-treated cohort, it is likely that most of these patients would have been considered for inclusion on systemic therapy trials, and the median PFS of

Table 1 Selected Series Using Particle Re-Irradiation for Treatment-Refractory Grade 2 and 3 Meningiomas

Series	Technique	WHO Grade (n, %)	Median PFS
Miyatake et al[7]	BNCT	Grade 2 and 3 (44, 100%)	Grade 2 and 3[a]: 13.7 mo
		Grade 2 (20, 45%)	Grade 2: 24.3 mo
		Grade 3 (24, 55%)	Grade 3: 9.4 mo
El Shafie et al[8]	Proton or carbon	Grade 2 and 3 (31, 100%)	Grade 2 and 3: 25.7 mo
		Grade 2 (25, 81%)	Grade 2: 34.3 mo
		Grade 3 (6, 19%)	Grade 3: 10.2 mo
Imber et al[9]	Proton	Grade 2 and 3 (12, 100%)	Grade 2 and 3: ~13 mo
		Grade 2 (8, 66%)	Grade 2: NR
		Grade 3 (4, 33%)	Grade 3: NR

Abbreviations: BNCT, boron neutron capture therapy; NR, not reported; PFS, progression-free survival.
[a]Only 36 of the 44 patients were available for PFS analysis.

13.7 months with BNCT should be viewed favorably relative to the RANO-proposed benchmark.

As newer accelerator-based BNCT systems are developed for clinical use around the world, prospective data from innovative clinical trials will be crucial to advance our understanding of the clinical utility of BNCT, both in treatment-refractory and treatment-naïve patients. To this end, the Japanese group should be commended for supporting this effort and launching a randomized trial of BNCT compared to best supportive care for recurrent high-grade meningiomas with a primary endpoint of PFS (jRCT2051190044; https://jrct.niph.go.jp/). Furthermore, the development of novel compounds which more selectively accumulate in target tissues represents an exciting means of further improving the therapeutic ratio of radiotherapy by biologically targeting specific tumors with particle therapy.

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