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Atypical Meningioma: An Evolving Landscape and Moving Target

By Michael D. Chan, MD, Nadia N. Laack, MD, Lia M. Halasz, MD, Giuseppe Minniti, MD, PhD, Scott G. Soltys, MD, John P. Kirkpatrick, MD

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While World Health Organization (WHO) grade 2, or atypical, meningiomas comprise approximately 25% of meningiomas, they represent the population with increased propensity for local recurrence and even decreased survival (1). Unfortunately, there are a paucity of prospective data to guide clinical management, as the largely retrospective studies on this disease are fraught with patient selection bias, insufficient follow-up, and small numbers of events. Unanswered clinical questions for grade 2 meningiomas include the role of adjuvant radiation therapy for gross totally resected tumors (2, 3) and the use of stereotactic radiosurgery given the higher local and marginal failure rate after stereotactic radiosurgery (4). Proton radiation therapy is also being explored, allowing for treatment of larger volumes more suitable for conventional fractionation but with decreased integral dose than photon therapy.

The lack of effective systemic agents for the treatment of progressive or recurrent meningiomas represents an unmet clinical need. A population of patients with meningiomas will experience multiple recurrences and suffer from the cumulative toxicities of multiple sequential local therapies (1, 2, 4). For this population, treatment options are ultimately exhausted, and patients succumb to unrelenting meningioma. While past studies have yielded few options with even modest antitumor activity (5), present and future trials will use next-generation sequencing to triage patients to identify suitable clinical trials.

WHO updated the definition of grade 2 meningiomas in both 2000 and 2007. The rationale for these changes was the limited ability of histology to predict biological behavior. In spite of the updates, serious limitations persist. Since the 2007 WHO update, there has been a growing interest in the molecular pathogenesis of meningiomas, particularly in the search for specific mutations that may be associated with more aggressive behavior (6). Mutational analysis has been met with mixed results as none of the recurring mutations in meningiomas have clear prognostic value for a significant proportion of meningiomas, as discussed later.

The past few years have witnessed the publication of several important studies that are likely to shape meningioma management and clinical trial design for the next generation. Three of these studies are highlighted in the current Oncology Scan and illustrate progress in the evolving treatment of atypical meningiomas.

Rogers et al. Intermediate-risk meningioma: Initial outcomes from NRG Oncology RTOG 0539. *J Neurosurg* 2017. (7)

Summary: This first report from the Radiation Therapy Oncology Group (RTOG) 0539 trial describes the outcomes of patients with intermediate-risk meningiomas, defined as those patients with completely resected WHO grade 2 or recurrent grade 1 tumors. RTOG 0539 was a phase 2 prospective trial in which patients were stratified prognostically by risk group and then uniformly treated based on their assigned group. Patients in the intermediate-risk cohort received 54 Gy in 30 fractions with either 3-dimensional conformal radiation therapy or intensity modulated radiation therapy. The 3-year progression-free survival rate for all patients in the intermediate-risk cohort was 94%, with a 3-year overall survival rate of 96%.

Comments: The completion of the RTOG 0539 study represents a landmark achievement for the study team, as prospective trials for meningiomas have been rare, and it was unclear how well such a trial would accrue patients and be completed. The excellent results obtained in this trial

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compared with prior historical cohorts provide a modern control population for powering future prospective studies. In a parallel study, the European Organisation for Research and Treatment of Cancer (EORTC) has recently completed a 78-patient single-arm phase 2 trial of grade 2 or 3 meningiomas using adjuvant radiation therapy in all patients but including a boost to 70 Gy for patients with residual disease. No results have yet been reported for the EORTC 26042 study. In combination, the RTOG 0539 and EORTC 26042 trials represent the first generation of meningioma prospective radiation therapy studies, collectively demonstrating feasibility of accrual and retention in a tumor with a long natural history. It is important to note, however, that the 3-year time mark is early given the indolent natural history of meningiomas, and it will be interesting to see what the true long-term local control rates are.

While the scientific literature has generally shown improved local control with adjuvant radiation therapy after complete resection of a grade 2 meningioma (2, 3), controversy exists as to whether improved local control translates to improved overall survival for this patient population. Given the lack of prospective evidence for improved survival, it is important to weigh the cognitive decline from adjuvant therapy against the risks of neurologic and cognitive morbidity of salvage treatment. However, quality-of-life and cognitive outcomes remain lacking. Clearly, cognitive decline can occur in meningioma patients who receive radiation therapy, as evidenced by their inclusion in published prospective trials of irradiation-induced cognitive decline (8). Unfortunately, RTOG 0539 began accrual prior to the standard collection of cognitive data and patient-reported outcomes. To address these issues, the NRG-BN003 study opened in July 2017 to randomize patients with completely resected grade 2 meningiomas to adjuvant radiation therapy versus observation. The EORTC is currently performing enrollment in the Radiation versus Observation of Atypical Meningioma (ROAM) study with the same randomization scheme. This next generation of meningioma trials includes modern quality-of-life and neurocognitive metrics and will ultimately inform the use of adjuvant radiation therapy in grade 2 tumors.

The inclusion of recurrent grade 1 tumors in the intermediate-risk cohort of RTOG 0539 adds a degree of heterogeneity to the population of interest. Recurrent grade 1 tumors often exhibit more aggressive behavior than those that do not recur, and this aggressiveness appears to bear out in their clinical outcomes (9). However, it is unclear whether recurrent grade 1 tumors are equivalent to grade 2 tumors with regard to recurrence risk and survival. In the present report, there was no statistical difference in outcomes between WHO grade 2 tumors with gross total resection and recurrent WHO grade 1 tumors. As discussed later, improved molecular characterization should improve our ability to identify those patients at greater risk of recurrence.

Ji et al. Double-blind phase III randomized trial of the antiprogestin agent mifepristone in the treatment of unresectable meningioma: SWOG S9005. *J Clin Oncol* 2015. (10)

Summary: The SWOG S9005 study was the first conducted and published randomized phase 3 trial for meningioma. Patients with primary, recurrent, or residual unresectable meningiomas were randomized to mifepristone (n = 80) or placebo (n = 84). While mifepristone was well tolerated, the results showed no evidence of a progression-free survival benefit, with a median freedom-from-failure period of 10 months in the mifepristone arm and 11 months in the placebo arm.

Comments: Prior to the report of SWOG S9005, mifepristone had been a systemic treatment option for progressive meningioma. Thus, these negative results highlight the importance of randomized studies in evaluating therapeutic agents. The SWOG S9005 trial was conceived because of the 70% expression rate of progesterone receptors in meningiomas. While the trial design has been criticized, an argument could be made that the trial was ahead of its time in its search for active systemic agents for meningiomas using agents targeted against meningioma biology. The success rates of systemic agents in clinical trials have been poor as cytotoxic agents, anti-angiogenesis agents, and small-molecule inhibitors have all shown a lack of significant activity (5, 11). While somatostatin analogues showed some promise in early studies, later studies have been unable to confirm their activity (12). An area of current interest is the use of systemic agents that target meningioma-specific mutations. The Alliance for Clinical Trials in Oncology is currently conducting a phase 2 study in which patients with progressive meningiomas are first screened for targetable mutations and then appropriately assigned to SMO, AKT, or NF2 inhibitors.

The SWOG S9005 trial provides a prospective cohort documenting the natural history of untreated meningiomas. As the only completed multi-institutional randomized trial for meningiomas, the control arm represents an important historical control cohort for powering future studies. The median freedom-from-progression period was only 11 months. Approximately one-third of patients who died while enrolled in the study did so during the first 2 years of follow-up. The actuarial survival rate at 2 years was only 80%. These data show that for aggressive meningiomas that either are untreated or receive ineffective therapy, there is a significant death rate within a few years. As many of the patients in SWOG S9005 had already received radiation therapy, the results emphasize the need for effective systemic agents for progressive meningiomas.

There have been several criticisms of the SWOG S9005 study, which also highlight the difficulty of designing trials for meningioma patients. Patient accrual occurred between 1992 and 1998, but the trial was published 18 years later in 2016, after which many aspects of meningioma management

have evolved. Perhaps the greatest concern for this trial is the heterogeneity allowed within the entrance criteria. The study attempted to recruit mainly patients in whom prior radiation therapy had failed, but it allowed enrollment of patients who did not receive radiation therapy, because of either the patient's choice or an inappropriate tumor location. The trial unfortunately did not report the proportion of patients who received no prior radiation therapy or the proportion of patients who experienced tumor recurrence prior to enrollment. Furthermore, it did not report the number of patients with either grade 2 or 3 meningiomas. The failure to provide these data in a heterogeneous population limits the ability to interpret the outcome in the setting of modern meningioma management, as grade and recurrence status often direct the use of adjuvant therapies.

Sahm et al. DNA methylation-based classification and grading system for meningioma: A multicentre, retrospective analysis. *Lancet Oncol* 2017. (13)

Summary: The multicenter analysis published by Sahm et al (13) assessed DNA methylation patterns in meningioma surgical specimens from 490 patients and identified 6 distinct methylation classes. Of the 6 classes, 3 (MC ben-1, MC ben-2, and MC ben-3) were associated with benign behavior. Two of these classes (MC int-A and MC int-B) were consistent with an intermediate probability of recurrence, and a single class (MC mal) was consistent with a high likelihood of recurrence. This classification scheme was subsequently confirmed using a validation data set.

Comments: Several prior studies have attempted to analyze genomic patterns of meningiomas in search of specific mutations that are associated with aggressive behavior or malignant progression, with mixed results. Next-generation sequencing has demonstrated that recurrent somatic mutations in NF2, KLF4, AKT1, SMO, PIK3CA, and TRAF7 are present in approximately 80% of sporadic meningiomas (6). None of these mutations have yet been shown to significantly affect prognosis. The loss of CDKN2A (generally through locus loss on 9p) has been identified as a marker associated with progression from grade 1 to grade 2 tumors (14). The study by Sahm et al (13) represents a major advance in the genomic classification of meningiomas as these 6 classes clearly affect prognosis. In a comparison with the WHO grading system, the methylation classes more accurately identified patients with grade 1 tumors that were at high risk of progression and grade 2 tumors associated with a lower recurrence risk.

The impact of this publication from the standpoint of a radiation oncologist derives from the imperfect nature of the histology-based WHO grading system. In spite of updates to the WHO grading system in both 2000 and 2007, a proportion of histologically benign-appearing meningiomas act aggressively, while a proportion of high-grade tumors show no evidence of recurrence in the absence of adjuvant therapy. The changes to the WHO definition have led to a corresponding increase in the diagnosis of atypical meningiomas over time. The disadvantage of overestimating the number of truly aggressive tumors is the overtreatment of a larger proportion of patients. The cognitive decline seen in meningioma patients treated with radiation therapy is not trivial, and the treatment options are limited once the onset of cognitive decline occurs.

A molecular classification system for meningiomas that provides a clinically relevant tool to perform risk stratification in patients should ultimately help to inform the proper choice of observation versus adjuvant radiation therapy. As modern studies are assessing the role of adjuvant therapy based on WHO grading, the imperfect prognostic value of the current grading system may dilute the effects of radiation therapy by assigning treatment to benign-behaving tumors. Future studies will likely need to be performed in which patients are stratified by biological behavior, such as methylation class.

In conclusion, our field is entering a new era in meningioma management. In RTOG 0539, we have the first prospective data on intermediate-risk meningiomas to help guide clinical management. We encourage enrollment in the ongoing NRG-BN003 and ROAM trials to determine our future standard of care and await the long-term outcomes of RTOG 0539. Last, similar to how molecular classification in gliomas is more prognostic than histologic type, we await further data on nonhistologic means to classify meningiomas.

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