

Challenges and opportunities in meningiomas: recommendations from the International Consortium on Meningiomas

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Meningiomas are the most common primary intracranial brain tumor¹. However, in comparison to the more typical aggressive intracranial tumors, such as gliomas, meningiomas are considerably understudied. Data-driven benchmarks are almost entirely lacking for meningiomas, and when put into the context of the age-related incidence of the tumor and overall aging population¹, the unmet clinical need is concerning. Although the majority of these tumors are indolent, there is a substantial and highly relevant subset (20–30%) of tumors that result in early recurrences with some tumors harboring a dismal prognosis similar to other well recognized fatal brain malignancies².

Although meningiomas were first described nearly 100 years ago³, advancements in the understanding and management of these tumors have largely been limited to the last decade. Recently, large scale genomic profiling of meningiomas has uncovered possible driver mutations for a subset of tumors^{4–6}. Now, as a result of these efforts and for the first time in meningiomas, cooperative clinical trials aiming to investigate the efficacy of targeted therapies are underway. A national Alliance-sponsored phase-II trial is currently evaluating the efficacy of SMO, AKT1 and FAK inhibitors in patients with residual, recurrent or progressive meningiomas with targetable alterations in *SMO*, *AKT1* and *NF2*. The use of dual mTOR inhibitor is also currently under evaluation in two phase-II trials for patients with recurrent WHO grade II and III meningiomas and in neurofibromatosis type 2 patients with progressive or symptomatic meningiomas. In addition to this, two large cooperative group clinical trials evaluating the role of adjuvant radiotherapy following resection of high grade meningiomas have recently been closed to accrual, with promising preliminary results⁷. Lastly, traditional chemotherapies such as trabectedin are also now being investigated in Phase II trials

for use in recurrent higher grade meningiomas. The increased attention and momentum driving advances in clinical trials in meningiomas is promising and should continue to be a focus of future efforts.

Despite these advancements, several areas of key critical challenges limit the management of patients with meningiomas. For example, standard of care diagnostic tests cannot reliably differentiate worrisome from indolent meningiomas prior to surgery, and therefore surgical approaches and extent of resection cannot be individualized to the biology of the tumor. Moreover, histopathological classification and grading of meningioma, while prognostic in population settings, are insufficiently precise and informative to fully account for the biological aggressiveness of these tumors in order to guide clinical management decisions regarding adjuvant treatment in meningioma. Additionally, the lack of medical or chemotherapy treatment options leaves clinicians ill-equipped to offer any durable or effective treatments to patients with complex, multiply recurring and aggressive meningiomas. Consequently, it is not uncommon for patients with aggressive meningiomas to have repeat surgical procedures for the same tumor and to have multiple rounds of radiation therapy as an attempt to control disease. Lastly, it is clear that patients with meningiomas can be affected by both the disease and their treatments, and some have long-lasting effects, resulting in chronic quality of life impairments that compound the challenges mentioned above.

Given the magnitude of the problem and the relative rarity of highly aggressive meningiomas (including lethal anaplastic meningiomas) collaboration from multiple international centers combining multidisciplinary expertise, resources and tumor tissue is necessary. The International Consortium

on Meningiomas (ICOM) is a multidisciplinary and multi-institutional collaborative group founded in 2016 with the vision to advance the entire spectrum of care for patients with meningiomas. Expertise within the consortium ranges from neurosurgery, neuropathology, neuro-oncology, radiation oncology, biostatistics, epidemiology and clinical trials, computational biology, and molecular and translational biology to allow for a vertical exchange of knowledge and comprehensive approach to disease from across the globe. In order to highlight recent advances and emphasize critical areas of unmet needs, the ICOM has generated a compilation of four manuscripts discussing advances in diagnosis and treatment of meningiomas as well as our understanding of the biology and long-term sequelae of these tumors. Our goal is that this series of articles will serve to raise awareness, promote engagement and enhance research, ultimately allowing to advocate for more funding support focused on this important area of the field.

In this supplement, the Consortium provides several fundamental recommendations. First, although the last decade has witnessed advancements in our understanding of the biology and genomic landscape of meningioma, further developments are necessary and critical for improving care for patients. Identification of molecular alterations driving the aggressive meningioma phenotype will be critical to advance care for patients and should be done in parallel with the development of reliable preclinical models that allow for rapid translation of discovery to clinical trials. Collaboration with the World Health Organization is needed to advocate for the integration of key molecular alterations that refine standard-of-care classifications to allow for more individualized diagnosis and prognostication such that management and decision-making can be tailored to the patient. In addition to this, standardized core outcomes and definitions that evaluate intervention complication rates, tumor recurrence, seizures, cognitive function, and health-related quality of life are needed to unify language and facilitate assessment of key metrics in meningiomas. Although most meningiomas requiring treatment will be managed primarily with surgery, particularly challenging cases will likely benefit from review by a multidisciplinary team that can offer the spectrum of various treatment options in meningiomas, including ongoing investigational clinical trials. Lastly, since a subset of patients with meningiomas can have continued impairments that extend beyond the treatment of their tumors, centers of excellence that are able to address the complex

needs of these patients in a longitudinal fashion will be key to addressing the unmet needs of this growing population of patients.

ICOM is committed to improving patient outcomes by focusing efforts and harnessing the expertise of various international groups and by providing platforms for knowledge transfer and collaboration amongst an international group of scientists and clinicians in order to further improve our understanding of the most common primary intracranial tumor. The principal goal of the consortium is to pool resources, promote collaboration, and collectively focus efforts to complete and integrate a comprehensive multi-omics profiling effort on the largest cohort of clinically annotated meningioma samples. With this approach, we will aim to uncover novel mechanisms of aggressive behavior in meningiomas that can be rapidly translated into clinical trial settings to overcome the therapeutic limitations faced today. ICOM promotes collaborative partnerships to ensure all existing members and groups throughout the globe with an interest in meningiomas are brought together and welcomes new institutions who share our vision.

References

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