Current and emerging principles in surgery for meningioma

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Abstract: Surgery continues to be the preferred method to treat meningioma. Recent advancements in the understanding of meningioma biology, including a new appreciation for remarkable molecular heterogeneity in these tumors, has sharpened the drive for disease control, especially on initial diagnosis. Microsurgical and skull base techniques and principles dominate the surgical approaches for meningiomas. At the same time, biologic tools may improve the extent of surgical resection as well as provide novel adjuvant therapy options for challenging meningiomas.

Keywords: Meningioma; skull base surgery; endoscopic surgery; tumor heterogeneity; genomics; precision medicine

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Surgical treatment for meningioma is nearly as old as contemporary neurosurgery itself and rests upon a keen understanding of the goals of surgery, meningioma growth patterns and biological behavior, and the advantages and limitations of available surgical techniques. As an extra-axial tumor, or one that arises from outside of the brain, meningiomas typically cause symptoms through mass effect and compression, associated peritumoral edema, and involvement of neurovascular structures. Surgical treatment of meningioma is geared towards cure when possible and long-term disease control, with preservation of neurologic function.

Goals of meningioma surgery

Upon radiographic diagnosis of an intradural lesion consistent with meningioma, a clinical decision is made to observe or treat. Treatment is indicated for symptomatic lesions, growing tumors, tumors that are large at diagnosis, tumors whose radiographic features raise the suspicion of an aggressive variant, or based on patient preference. Surgery is the most common treatment of choice for meningiomas, although focused radiation is adopted in some scenarios (1). In slow-growing meningiomas, surgical resection may offer cure or long-term durable control. Complete resection for meningioma is defined by removal of the tumor as well as tumor-infiltrated dura, bone, and vascular sinuses. Residual in any of the adjacent compartments risks tumor recurrence with long follow-up, even for benign meningiomas (2). Radiation therapy may offer an alternative for patients with poor clinical condition which precludes surgery and whose tumor merits treatment (1).

Surgery for recurrent tumors may confer incremental risk for morbidity, especially in regions of the skull base and around critical neurovascular structures, highlighting the need for novel medical therapeutic options, none of which exist with proven efficacy. For benign meningiomas, observation may be warranted for residual tumor. Increased extent of resection is associated with improved overall survival for aggressive high-grade meningiomas (3), and increased recurrence-free survival for all meningiomas (4). Administration of adjuvant radiation is indicated for high-grade meningiomas, but also enhances risk to involved neurovascular structures if further surgery becomes warranted.

Surgical philosophy and strategy varies widely for meningiomas, both in the primary and recurrent settings. The growth pattern of meningiomas dictates their propensity for recurrence. We highlight recent discoveries in meningioma biology that supports the importance of

upfront aggressive surgical removal, when feasible.

Meningioma biology

Meningiomas are postulated to arise from arachnoidal cap cells, which are distributed throughout the cranial vault (5,6). As such, the arachnoid membrane partitions meningioma from the brain parenchyma. Although this arachnoid plane may be violated by invasive meningiomas, the natural barrier typically provided by the arachnoid underlies the principles for surgical resection of meningioma, even in challenging locations.

The World Health Organization (WHO) classifies meningiomas into three grades (I–III), with increasing invasiveness and propensity to recur in higher grades. In particular, brain invasion is observed in grade II and III meningiomas and confounds the ability to respect an arachnoid plane during surgical resection for complete removal of the tumor and its attachments. As such, residual disease is more frequently observed following surgery for higher grade meningiomas and may prompt adjuvant radiation therapy depending on the tumor grade, location, and patient status. Surgical strategies, if not geared towards total removal, should provide appropriate sampling of brain invasion (7). The need for alternative therapeutic strategies for these aggressive subtypes, as well as recurrent and progressive grade I meningiomas, has motivated investigations into the biology and genomics of meningioma.

Approximately 40% of grade I meningiomas are associated with mutation or loss of the *NF2* gene. Recurrent oncogenic mutations in v-akt murine thymoma viral oncogene homolog 1/3 (AKT1/3), phosphoinositide-3-kinase catalytic alpha polypeptide (PIK3CA), smoothened (SMO), TNF receptor-associated factor 7 (TRAF7), Krüppel-like factor 4 (KLF4), or RNA polymerase II subunit A (POLR2A), among others, contribute to another 40% of grade I meningiomas, opening new venues for potential targeted pharmacotherapy (8-14). The identification of these mutations has unlocked the potential for targeted therapies in meningiomas for the first time, with clinical trials of inhibitors against several oncogenic mutations underway for recurrent and progressive tumors.

However, the availability of targeted treatment for meningiomas is tempered by an increasing appreciation for immense heterogeneity within meningiomas. This applies to both their physical consistency, which translates to ease or difficulty of handling during surgical resection, as well as their genomic composition within a tumor and across recurrences (15,16). Molecular heterogeneity in tumors is associated with a propensity for treatment resistance and meningiomas are observed to be more heterogeneous than most other brain tumors (15), which is a recent insight into a tumor once considered uniform. In the setting of incipient targeted therapies for meningioma, awareness for such heterogeneity may prompt investigation into combinatorial treatments and strategies to overcome the anticipated acquired resistance. Furthermore, significant changes in the genomic signature of meningiomas from the primary tumor to subsequent recurrences suggests that even microscopic residual disease following surgical resection may lead to regrowth of a molecularly distinct tumor with different sensitivity to treatment than the prior tumor.

In comparison to grade I meningiomas, grade II–III meningiomas are characterized by frequent chromosomal alterations and structural variants (15). The burden of chromosomal alterations in meningiomas predicts the risk for tumor recurrence, independent of extent of resection, and serves as a prognostic marker to guide post-resection follow-up intervals as well as patient counseling (17). Interestingly, adjuvant radiation increases the genomic complexity of meningiomas in the rate of both mutations and copy number alterations, but distant radiation, such as that associated with radiation-induced tumors, does not (15).

Taken together, the biology of meningiomas offers potential for novel pharmacotherapies in their management. However, the low incidence of specific targetable oncogenic mutations in meningiomas, their heterogeneity within and across tumors, and the possible acquisition of a more complex genomic profile following adjuvant radiation continues to support a role for maximal safe surgery first.

Strategies for meningioma surgery

The goals for meningioma surgery and the pattern of recurrence of these tumors continues to underscore the benefit of aggressive resection, without compromise of neurologic function, at first encounter. Surgical approaches to meningiomas are largely based on removal of bone to expose the base of the tumor given their origin outside of the brain parenchyma. Meningiomas along the convexity of the calvarial vault are generally considered more accessible, although the presence of major venous sinuses such as the superior sagittal sinus and the torcula pose risk for midline convexity tumors. In comparison, meningiomas that grow along the base of the skull may be intimately associated with

or deflect cranial nerves and vital vessels that also enter and exit the skull at its base. Strategies to overcome and safely handle these critical neurovascular structures in the surgery for challenging meningiomas motivated the development of skull base surgery (18).

Principles of skull base surgery include: remove bone to minimize injury to the brain; respect the arachnoid plane; preserve, repair, or reconstruct vessels with meticulous care; plan for reconstruction and closure with the opening; be vigilant to displaced anatomical structures; and seek total removal during the first operation (18). These guidelines provide a framework for meningioma surgery, independent of evolving surgical techniques and technologies.

Over the past 20 years, intraoperative navigation, improved optical systems, and endoscopes that allow visualization around corners have become increasingly available to surgeons. These technologies have helped to reshape classic "open" transcranial approaches for tumor resection. In particular, endoscopic approaches allow for maneuverability through narrow corridors, such as the nasal cavity, with subsequent exposure of skull base bone for removal of select meningiomas. These include meningiomas located at midline anatomic locations, such as olfactory groove, planum sphenoidale, and tuberculum (19). Meningiomas located at other anatomic locations are more challenging to remove using the endoscope, including tumor extension lateral to the carotid artery or cranial nerves. Increased experience, appreciation for the importance of case selection, and fluency with reconstructive techniques and vascularized grafts in the repair of skull base defects have encouraged a wider application of endoscopic techniques for skull base meningiomas on the whole (20). However, the drive for functional preservation in surgery for a benign tumor, such as the ability to maintain olfaction in transcranial approaches as compared to endonasal endoscopic approaches, halts the choice of a purely endoscopic approach for some clinicians. Despite the limitations and reservations for widespread endoscopic approaches for meningioma, combined microscopic and endoscopic approaches are increasingly used due to the periscopic visualization of the endoscope to investigate corners of a surgical field difficult to view with conventional microscopy.

Minimally invasive keyhole approaches, which create a smaller craniotomy than traditional transcranial approaches, are also increasingly described for meningioma surgery. With any of these evolving techniques, a goal for maximal safe resection should be maintained. This becomes more imperative with higher grade meningiomas, given their proclivity for recurrence. Adjuncts such as 5-aminolevulinic acid fluorescence have been investigated for their role in improving detection of tumor satellite cells in adjacent brain, dura, and bone for invasive meningiomas, with initial promise (21,22).

Ultimately, the choice of a surgical strategy should be tailored based on the patient's existing condition; the location, origin, and extension of the meningioma; its suspected grade and consistency; the neurological symptoms inflicted; previous treatment history; a desire for disease control or palliation; and the surgeon's experience and repertoire. All things considered, the primary goal in meningioma surgery continues to be complete resection, regardless of the size of the incision or specific approach employed.

Conclusions

While meningiomas have been considered a fundamentally extra-axial tumor of mostly benign behavior, an increasing appreciation for its biology, invasiveness, heterogeneity, and recurrence pattern should shape the surgical philosophy and strategy for these tumors. Fluency with a combination of surgical techniques and technologies allows for tailoring of the approach to the patient condition and tumor location. The goal for surgical cure on initial encounter, while preserving neurologic function and minimizing potential morbidity, continues to drive innovation in meningioma surgery. It is inevitable that biology and surgery will become further intertwined. A particularly alluring prospect is the pre-surgical identification of targetable mutations with neoadjuvant drug therapy to reduce tumor size, rendering subsequent surgery safer.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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