Treatment of Meningioma

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Introduction

Clinical Scenario

A 24-year-old man presented with a generalized tonic-clonic seizure. Workup revealed a left parietal dural based lesion with significant edema. He underwent a gross total resection and pathology was

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consistent with a meningioma World Health Organization (WHO) grade 2. In discussion with his clinical team, he elected to defer therapy and follow with surveillance imaging with MRI's every 3–4 months. Two years after surgery, he was found to have recurrence of the meningioma in the same location. A repeat resection was performed and revealed again meningioma WHO grade 2. He underwent fractionated radiotherapy and has been followed with surveillance imaging with no evidence of recurrence.

Meningiomas are the most common primary central nervous system (CNS) tumors. The management of these tumors spans the disciplines of neurosurgery, radiation oncology, neuro-oncology, medical oncology, and neurology, *and* receives input from neuroradiology and neuropathology. An overview of the clinical aspects of the care of these patients will be provided [1–3].

Meningiomas comprise >1/3 of all primary CNS tumors with the majority of these being WHO grade 1. Incidence increases with age and is more than twice as high in women compared to men (2.27:1) [4]. It is higher within the context of some cancer predisposition syndromes such as neurofibromatosis type 2, a neurocutaneous syndrome which follows an autosomal dominant inheritance pattern. A history of prior radiation is also associated with an increased risk of meningioma development within the radiation field, with radiation-induced tumors developing years to decades after radiation exposure. Specific gene rearrangements involving NF2 have been described in approximately half of radiation-induced meningiomas [5, 6] (Table 5.1).

Meningiomas may be incidentally noted or may be radiographically diagnosed after imaging performed due to neurologic symptomatology. Symptoms often correlate with the neuroana-

Table 5.1 Mutations and fusions in meningiomas

Mutation or fusion	Neuroanatomic location	Clinical features
NF2 mutation	NA	• Detected in ~1/2 of sporadic meningiomas • Predominantly fibroblastic and/or transitional subtypes • Germline mutation in patients with NF2. These patients have an increased incidence of meningiomas

Table 5.1 (continued)

Mutation or fusion	Neuroanatomic location	Clinical features
NF2 fusion	NA	• Present in ~1/2 of radiation induced meningiomas
SMO mutation	Olfactory groove	• Predominantly meningothelial subtype
AKT mutation	Base of skull	• Predominantly meningothelial subtype
mTOR mutation	Base of skull	• Predominantly meningothelial subtype
TERT promoter mutation	NA	• Confers a more aggressive natural history
PTCH1 mutation	NA	• Germline mutation in Gorlin syndrome (basal cell nevus syndrome) which is associated with increased incidence of meningiomas • PTCH1 is located upstream of SMO in the hedgehog pathway
SUFU mutation	NA	• Germline mutation is also seen in Gorlin syndrome (basal cell nevus syndrome) which is associated with increased incidence of meningioma • SUFU is located downstream from PTCH1 and SMO in the hedgehog pathway
SMARCB1 mutation	NA	• Germline mutation in Schwannomatosis and Coffin-Siris syndrome which is associated with increased risk of meningiomas
SMARCE1 mutation	NA	• Germline mutation is also seen in Coffin-Siris syndrome and is associated with increased incidence of meningioma

NF2 neurofibromatosis type 2, *NA* not applicable, *SMO* smoothened, *AKT* gene for protein kinase B, *mTOR* mammalian target of rapamycin, *TERT* telomerase reverse transcriptase, *PTCH1* patched-1, *SUFU* suppressor of fused homolog gene, *SMARCB1* SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 gene, *SMARCE1* SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1

tomic location of the tumor. Thus, a careful neurological history and examination often form part of the initial evaluation. Subsequent management can range from clinical and radiographic surveillance to aggressive multi-modality approaches [1–3]. A number of factors which influence these clinical decisions will be discussed below.

Diagnostic Evaluation

Neurological symptoms related to meningiomas are usually subacute in onset due to the relatively slow growth of most of these tumors when compared to other CNS neoplasms. These symptoms typically localize to the associated neuroanatomic structures which are being compressed by the tumor. Patients may also exhibit non-localizable symptoms such as positional headaches which may be associated with other symptoms of increased intracranial pressure such as nausea, vomiting, horizontal diplopia, and somnolence.

The majority of meningiomas are intracranial, arising from the dura covering the brain. A smaller number arises from the spinal dura. Occasionally, meningiomas can be found in unexpected locations such as within the ventricles. Rarely, extra-CNS metastases of meningiomas (including grade 1 meningiomas) are seen. Common locations for extra-CNS metastases include the lungs. Extra-CNS staging is *not* performed as standard of care and is only a component of symptomatic evaluation or if lesions are detected incidentally when imaging is performed for other reasons.

Imaging

The diagnostic evaluation of patients with suspected meningioma involves CNS imaging. Computed tomography (CT) may be the first modality obtained if the patient undergoes initial evaluation in an acute care setting such as the emergency department (ED). It is, however, often possible to move directly to obtaining mag-

netic resonance imaging (MRI) without accompanying CT. If CT is obtained, a hyperdense extra-axial lesion compressing the underlying brain raises suspicion for a meningioma. At times these tumors exhibit calcification, indicative of their slow growth.

MRI similarly reveals an extra-axial mass. These tumors are usually homogeneously enhancing and may exhibit a dural tail, a feature suggestive of but not pathognomonic for meningioma. A delineation between the extra-axial tumor and the underlying brain (termed a CSF cleft) is sometimes noted. This, however, can be seen with any extra-axial tumor and is not specific for meningiomas. Radiographic findings highly suggestive of meningioma, when within the appropriate clinical context, are often adequate to allow for moving forward with next steps in clinical management without a histologic diagnosis. This is one of the few exceptions to the rule in neuro-oncology of the need for confirmation of pathology prior to embarking on therapeutic intervention. There are a number of potential radiographic mimics of meningioma which should be considered when developing a differential diagnosis for these radiographic abnormalities (Table 5.2).

Finally, a number of advanced imaging studies are undergoing investigation for meningiomas. These include MR spectroscopy and advanced positron emission tomography (PET) modalities [1]. None of these are standard clinical practice at this time.

Pathology

Pathologic evaluation of tissue is necessary to establish a definitive diagnosis of meningioma. Unlike some tumors, a needle biopsy is rarely used to do so. Often, a surgical resection with an attempt at a gross total resection (GTR) or at least an extensive subtotal resection (STR) is performed as this has both diagnostic and therapeutic value. These tumors are currently classified into three grades which correlate with their natural histories and guide clinical management. Most meningiomas (~80%) are grade 1. Approximately 18% are grade 2 (also termed atypical meningioma) and only ~2% are grade 3 (also termed anaplastic *or* malignant meningioma) [4].

Table 5.2 Radiographic mimics of meningioma

Diagnostic entity	Clinical features
Dural metastases	• Most frequently seen with breast cancer and prostate cancer • In about 1/2 of patients with dural metastases skull metastases are also present
Solitary fibrous tumor	• Previously termed hemangiopericytoma • Has a high potential for local recurrence, recurrence elsewhere in the CNS, and dissemination outside of the CNS
Langerhans histiocytosis	• A histiocytic infiltrate • Extra-axial CNS involvement is not a common manifestation of CNS Langerhans histiocytosis • More common CNS involvement involves the hypothalamic-pituitary axis
Rosai-Dorfman disease	• A non-Langerhans cell histiocytosis • Often extra-CNS involvement includes lymph nodes, skin, sinuses, renal, orbit, and salivary glands • It is often self-limited • Treatment may include surgery, radiation, steroids
Erdheim-Chester disease	• A non-Langerhans cell histiocytic neoplasm • Often extra-CNS involvement includes skeletal, cutaneous, renal, and pulmonary • Approximately half of Erdheim-Chester cases have somatic V600E *BRAF* mutations • Treatment may include steroids, interferons, and BRAF targeted therapies
IgG4 related disease	• Both serum and lesional tissue can be evaluated for IgG4 • Often responds readily to steroids
Orbital pseudotumor	• Frequently limited to the orbit but in some cases can extend to the cranial dura • This is an inflammatory process treated with steroids and immunosuppressants
Sarcoidosis	• This is usually accompanied by extra-CNS involvement (particularly pulmonary) of sarcoidosis, but in some instances can be limited to the dura
Rheumatoid meningitis	• A rare manifestation of rheumatoid arthritis

Table 5.2 (continued)

Diagnostic entity	Clinical features
Dural lymphoma	• Often follows a much more indolent course than primary central nervous system lymphoma
Schwannoma	• At the base of skull schwannomas arising from cranial nerves can mimic meningiomas • CNVIII is the cranial nerve most frequently affected by schwannoma
Infectious	• A range of acute and chronic infections can involve the pachymeninges and may mimic meningioma • These infections include but are not limited to viral, bacterial, fungal, and mycobacterial infections

CNS central nervous system

Histologically meningiomas can be classified into 15 subtypes [7]. In turn, the pathologist requires familiarity with a range of histopathologic presentations of meningioma to confidently make the diagnosis. While most histologic subtypes do not influence the clinical management, there are a few which when present confer a more aggressive natural history and in turn increase the grade of the tumor (Table 5.3). Other features which increase grade include brain invasion, a higher number of mitoses, high cellularity, a high nuclear to cytoplasm ratio, prominent nucleoli, necrosis, and sheet-like growth pattern [8] (Table 5.4). It is likely that in the near future, methylation profiling may lead to a more robust prognostication for these tumors [9, 10]. At this point in time methylation profiling is not yet standard of care for meningiomas.

Next generation sequencing (NGS), will likely have a growing role in the evaluation of meningioma. Some specific findings such as *TERT* promoter mutation and *CDKN2A/B* homozygous deletion confer a WHO grade of 3. In addition, it is known that a substantial percentage of meningiomas harbor neuroanatomically exclusive mutations [11] (Table 5.1). Targeting of these mutations is undergoing investigation in various studies including a phase II cooperative group study (NCT02523014, Alliance clinical trial A071401).

Table 5.3 Histologic subtypes of meningiomas

Histologic subtype	Grade
Chordoid meningioma	2
Clear cell meningioma	2

Table 5.4 Histologic and molecular features associated with grade

	Grade 1	Grade 2	Grade 3
Histologic subtypes		Chordoid or clear cell subtypes	
Brain invasion	No brain invasion	*Or* Brain invasion	*Or* Brain invasion
Mitoses	0–3 mitoses per 10 HPF	*Or* 4–19 mitoses per 10 HPF	*Or* 20 or more mitoses per 10 HPF
Aggressive features	2 or less	*Or* 3 of the following: • Increased cellularity • Small cells with high nuclear to cytoplasmic ratio • Prominent nucleoli • Sheeting • Foci of spontaneous necrosis	Usually present

NA not applicable, *HPF* high-powered fields

Therapeutic Management

The therapeutic management of meningioma most oftentimes utilizes surgery and/or radiation. Systemic therapy at this time does not have a clearly established role and is primarily used within the context of clinical trials or for disease which has progressed after surgery and radiation. It should be emphasized that many (if not

most) meningiomas do *not* require therapeutic intervention. If upfront treatment is not recommended, clinical and radiographic surveillance is usually warranted as these tumors have the potential to grow over time and can be associated with morbidity and mortality. Of note only a third of presumed meningiomas that are discovered incidentally exhibit growth over time. Often, for small asymptomatic meningiomas the recommendation is to hold off on treatment until there is clear evidence of growth.

Surgery

Surgery serves both diagnostic and therapeutic purposes. With respect to the first, it provides diagnostic certainty to a previously clinical-radiographic diagnosis. The degree of certainty required depends on the specific clinical scenario. It also allows establishment of grade which informs the natural history and prognosis associated with the tumor. Finally, it provides tissue for advanced molecular testing including NGS and methylation profiling. With regards to therapeutic benefit, it is the one modality which decreases tumor burden and mass effect. This has the potential to alleviate at least some of the symptoms associated with the tumor.

The goal of surgery is GTR where feasible and STR when it is not. GTR may be curative in grade 1 and some grade 2 meningiomas [12]. The extent of resection is associated with risk of recurrence and progression-free survival. The most frequently utilized system for assessing extent of resection is the Simpson grading [13](Table 5.5). A number of factors, predominantly the anatomic location of tumor, limit the feasibility of a complete resection. Specific locations in which STR is planned and expected include the base of skull and the posterior portion of the patent sagittal sinus. With meningiomas involving the base of the skull there are critical vessels and cranial nerves which it is often not practical to

Table 5.5 Simpson grade of resection

Simpson grade	Extent of resection
1	GTR with removal of involved dura and bone
2	GTR with dural coagulation
3	GTR without dural coagulation
4	STR
5	Biopsy/decompression

GTR gross total resection, *STR* subtotal resection

sacrifice or to put at undue risk. In regards to the posterior portion of the sagittal sinus, if it remains patent and robust collaterals do not exist, resection which sacrifices the posterior component of the sinus leads to the substantial risk of impeding the venous outflow from the brain and the associate development of a venous infarction. If GTR is felt unlikely to be feasible (and mass effect is not problematic) definitive radiation should be entertained. In cases of STR, postoperative radiation should be considered.

If a tumor recurs, re-resection is often considered as a potential treatment option. As the number of resections increases the enthusiasm for additional resections diminishes, particularly as wound healing is impaired in the context of multiple previous surgeries and radiation. However, it is still often contemplated at every recurrence as it is one of the most effective means of addressing these tumors.

Radiation

As noted earlier, meningiomas are one of the few CNS tumors in which treatment may be initiated based upon the radiographic diagnosis within the appropriate clinical context. This is employed when the suspicion is that the tumor is a grade 1 meningioma. When the imaging or rapid onset of symptoms raises concern for grade 2 and 3 meningiomas, surgery to establish the diagnosis and grade as well as resect or debulk the tumor is the standard of care.

Radiation for meningiomas can be broadly divided into two categories, stereotactic radiosurgery (SRS) and focal fractionated radiotherapy. SRS is a means of delivering a moderate to high dose of radiation to a relatively limited area often in a single fraction. This can be delivered via a linear accelerator (LiNac) via the same device used to deliver standard fractionated radiation or one designed specifically for SRS (such as the Cyberknife device). It can also be delivered via a device utilizing a fixed cobalt source of radiation (ie Gammaknife). Each apparatus for delivery has its advantages and drawbacks. Recommendations regarding individual radiation treatment regimens (Table 5.6) are determined by tumor size, location, histology, and proximity to radiosensitive structures.

Broadly speaking, SRS is the preferred radiation method utilized for relatively small (<3 cm) grade 1 meningiomas. It differs from standard radiotherapy in that the rigidity of setup is heightened, allowing for larger doses per fraction to be delivered in a more conformal fashion than what can be delivered with standard radiotherapy. SRS may be used in place of surgery, to treat residual tumor post-operatively, or to treat progressive/recurrent disease. It has the ability to provide long-term control in the majority of patients [14]. If the meningioma is small or moderately sized it is often reasonable to treat with SRS once radiographic growth is demonstrated. This approach is felt to delay the potential SRS related toxicity while not increasing the risk to the patient. If the tumor is larger in size or located adjacent to critical cranial structures with lower radiation tolerability (Table 5.7) then fractionated SRS (defined as 2–5 fractions) is often employed as a means of limiting the toxicity, versus a fully fractionated course of standard radiotherapy. The primary short term toxicity of SRS is cerebral edema which may worsen neurologic symptoms tran-

Table 5.6 Frequently utilized radiation treatment regimens for meningiomas

RT technique	Grade I	Grade II	Grade III
Single fraction SRS	12–16 Gy	16–20 Gy for recurrent disease	Not generally appropriate
Fractionated RT	45–54 Gy	54–59.4 Gy for adjuvant or salvage indications	60 Gy postoperatively

Table 5.7 Radiation tolerability of critical structures

Structure	Single fraction limit	Fractionated RT limit
Optic nerves, chiasm	8–9 Gy max point dose	55 Gy[a]
Brainstem	<1 cc receiving 12+ Gy	55 Gy[a]

[a] Up to 60 Gy may be allowable for high-grade lesions abutting these structures

siently. In the long term, the primary concern is radiation necrosis which can develop months after the treatment and may first manifest even years after SRS. The risk of radiation necrosis is increased by prior radiation therapy in the same treatment field as well as by some medications such as targeted therapies and immunotherapies.

Fractionated radiation is when a substantial number of small fractions of radiation are administered (typically Monday through Friday) for a number of weeks to reach a high cumulative dose [15]. This modality is often used when the radiation field for the meningioma is large as well as with grade 2 and 3 meningiomas. While there is a lack of comparative studies, when evaluating results *across* studies fractionated radiation appears superior to SRS in grade 2/3 meningiomas. Another indication for fractionated radiation is meningiomas that lie in close proximity to optic structures, such as optic nerve sheath meningioma. In this setting the fractionation allows for adequate tumor dosing, while the small daily fraction allows for optic structure tolerances to not be exceeded. Outcomes in such cases show high rates of tumor control, with high rates of visual preservation [16]. However, these advantages to fractionation must be weighed against the logistical difficulties of daily transport to radiation oncology. This is of particular consideration when patients have neurological deficits or the distance to travel is far. Fractionated radiation is standard of care for the treatment of all grade 3 meningiomas regardless of extent of resection as well as for grade 2 meningiomas post-STR. Post-operative radiation in grade 2 meningiomas post-GTR is associated with high rates of local control in prospective studies, and as is currently being investigated in a randomized cooperative group trial, NRG BN003 (NCT03180268) [17].

Systemic Therapies

Systemic therapies have a limited role in the management of meningiomas at this time. It is possible, however, that this may change in the future. Much of this may be driven by our enhanced understanding of the molecular characteristics of these tumor subtypes. A number of systemic therapies have been investigating in these tumors, and unfortunately thus far none have been overly successful (Table 5.8). Studies have been predominantly single

Table 5.8 Systemic therapies investigated for the treatment of meningiomas

Hydroxyurea
Imatinib
Hydroxyurea + imatinib
Temozolomide
Irinotecan
Cyclophosphamide + adriamycin + vincristine
Interferon alpha
Mifepristone
Megestrol
Tamoxifen
Octreotide
Sandostatin LAR
Pasireotide LAR
Erlotinib
Gefitinib
Vatalanib
Sunitinib
Lapatinib
PTK787
Bevacizumab
Bevacizumab + paclitaxel
Bevacizumab + everolimus
(90)Y-DOTATOC
(90)Y-DOTATOC+(177)Lu-DOTATOC
Abemeciclib
Lutetium Lu177 dotatate

arm utilizing no control or historical controls; a single randomized clinical trial has been performed examining the anti-progestin agent mifepristone (given 70% of tumor express progesterone receptors) which revealed no impact on tumor outcomes [18]. Disappointingly, there have been no systemic regimens which have demonstrated definitive radiographic responses. In contemporary clinical practice, systemic therapies are most often utilized within the context of clinical trials or as salvage regimens for progressive disease (particularly when additional surgery or radiation are not optimal). Specific regimens which are considered include antiangiogenics, targeted therapies, traditional cytotoxic chemotherapies, and immunotherapies.

Ongoing studies which take advantage of mutually exclusive targetable mutations in subsets of meningiomas hold notable promise. In its greatest scope this is undergoing evaluation in the non-randomized multi-arm phase 2 cooperative group trial A071401 (NCT02523014). This study has separate arms for tumors with mutations in *SMO*, *AKT*, and *NF2*. Each arm is treated with a therapeutic targeting the specific aberrant pathway.

Conclusions

Meningiomas are common tumors which arise from the pachymeningeal coverings of the CNS. The natural history of most of these tumors reflects a pattern of slow growth, allowing many to be observed clinically and radiographically without therapeutic intervention. In those which require treatment, surgery can be curative and radiation, often delivered as SRS, can provide excellent long-term control. Some meningiomas, however, prove resistant to therapy and can incur both substantial morbidity and mortality. These oftentimes require repeated interventions with surgery and radiation serving as the cornerstones of their management. Systemic therapies, often within the context of clinical trials, are also added to the armamentarium when meningiomas are not amenable to further localized therapy. As these tumors are genomically less complex than other CNS tumors and are not pro-

tected by a blood brain barrier, the likelihood of therapeutic advances is high as our understanding of the molecular characterization and sub-classification improves.

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