4 ■ MENINGIOMA

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QUICK HIT ■ Meningiomas are the most common primary brain tumors in adults, representing approximately 40% of all primary brain tumors with ~30,500 cases per year in the United States, 80% of which are WHO grade I.¹⁻³ Asymptomatic grade I meningiomas can be observed, whereas maximal safe surgical resection is otherwise the standard of care for lesions that are surgically accessible. The extent of surgical resection and grade of meningioma determine initial postsurgical approach (see Table 4.1). Recurrent meningiomas are generally managed with re-resection followed by RT when no previous RT has been administered. Unresectable meningiomas are managed with fractionated RT or SRS, depending on grade, size, and location. Similar strategies are employed in the setting of spinal meningiomas (approximately 10% of cases). While the vast majority of meningiomas are benign, they may ultimately cause significant morbidity and mortality. Particularly in young patients, the likelihood and morbidity of recurrence must be weighed against the potential long-term sequelae of RT to the brain. Grade II meningiomas have an intermediate prognosis, while grade III meningiomas are aggressive with high recurrence and mortality rates. Recurrent meningiomas have higher subsequent recurrence rates than newly diagnosed meningiomas, adding further complexity to management decisions.

TABLE 4.1: RT Dose Guidelines for Meningioma

Extent of Resection	WHO Grade I	WHO Grade II	WHO Grade III
GTR	Observe	EBRT 54–59.4 Gy/30–33 fx	60–66 Gy/30–33 fx
STR	Observe OR EBRT 54 Gy/30 fx OR SRS 12–14 Gy	59.4–60 Gy/30–33 fx	60–66 Gy/30–33 fx
Recurrent disease	Consider further resection + EBRT 54 Gy/30 fx OR SRS 12–14 Gy	Consider further resection + 59.4–60 Gy/30–33 fx OR SRS 16 Gy	Consider further resection 60–66 Gy/30–33 fx OR SRS 18–24 Gy (based on size)
Unresectable disease	EBRT 54 Gy/30 fx OR SRS 12–14 Gy	59.4–60 Gy/30–33 fx OR SRS 16 Gy	60–66 Gy/30–33 fx OR SRS 18–24 Gy (based on size)

EPIDEMIOLOGY: 30,551 cases per year in the United States; approximate 1-, 5-, and 10-year survival rates are 80%, 65%, and 58%, respectively (decreased survival rate with increasing age). Incidence increases with age (especially >65).¹ There is approximately a 2:1 female predominance though males are slightly more likely to have atypical or malignant meningiomas.^{1,2}

RISK FACTORS: Older age, ionizing radiation, NF2, MEN1, exogenous/endogenous hormones, elevated BMI, decreased physical activity, increased height (women), uterine fibroids, and breast cancer.^{2,4-10} The degree to which estrogen exposure is an independent risk factor from BMI, decreased physical activity, increased height, uterine fibroids, and breast cancer is unclear.

ANATOMY: Arises from the arachnoid layer of the meninges between the dura mater and pia mater, commonly at sites of high density of arachnoid villi and associated arachnoid cap cells. Most frequently noted at supratentorial sites of dural reflection, such as at the cerebral convexity (~20%) and parasagittal/parasagittal (~25%), along the sphenoid wing (~20%) and skull base (resulting in decreased surgical accessibility), intraventricular and suprasellar region, and olfactory groove (~10%) and in the posterior fossa most commonly along the petrous bone (~10%).

PATHOLOGY: Classified by the WHO into three grades: WHO grade I (benign), WHO grade II (atypical, yet still benign), and WHO grade III (malignant).

TABLE 4.2: Summary of WHO Grading for Meningiomas				
WHO Grade	Frequency	Subtypes	Characteristics	Recurrence After GTR
Grade I	80%	Meningothelial Fibroblastic Transitional Psammomatous Angiomatous Microcystic Secretory Metaplastic Lymphoplasmacyte-rich	Psammoma bodies Cellular whorls Calcifications	7%–25%
Grade II	18%	Chordoid Clear cell Atypical	≥4 mitoses/10 HPF, brain invasion OR ≥3 features below: <ul style="list-style-type: none">• Hypercellularity• Small cells w/ high nuclear:cytoplasm ratio• Prominent nucleoli• Patternless/sheet-like growth• Foci of spontaneous necrosis	29%–52%
Grade III	2%	Anaplastic Papillary Rhabdoid	≥20 mitoses/10 HPF and/or <ul style="list-style-type: none">• Carcinomatous features• Sarcomatous features• Melanomatous features• Loss of usual growth pattern• Brain invasion• Abundant mitoses with atypia• Multifocal necrotic foci	50%–94%

GENETICS: Genetic mutations are common, but the clinical impact of mutations is evolving. DNA methylation profiling and other molecular signatures are promising to better risk-stratify meningiomas.¹¹ Relevant molecular alterations include TERT, PIK3CA, POLR2A, SMO, KLF4, AKT1, TRAF7, NF2, and SUFU.¹²

CLINICAL PRESENTATION: May be asymptomatic. If symptomatic: headaches, seizure, altered cognition, focal neurologic deficit—these are further detailed in Table 4.3 (data modified from Raizer).¹³

TABLE 4.3: Common Presenting Symptoms of Meningioma Based on Location
Parasagittal: motor and/or sensory changes
Frontal: personality change, avolition, executive dysfunction, disinhibition, urinary incontinence, Broca’s aphasia
Temporal: memory changes, Wernicke aphasia (left), aprosody (right), olfactory symptoms including seizures
Cavernous sinus: CN symptoms (nerves III, IV, V1–V2, VI pass through the cavernous sinus), decreased visual acuity, impaired extraocular motion with resultant diplopia, numbness
Occipital lobe: visual field deficit
Cerebellopontine angle: unilateral deafness/decreased hearing, facial numbness, facial weakness
Optic nerve sheath: ipsilateral decreased visual acuity/blindness, exophthalmos, ipsilateral pupillary dilation nonreactive to direct light but with retained consensual contraction
Sphenoid wing: cranial neuropathy, seizures
Tentorium: extra-axial compression with associated occipital/parietal/cerebellar symptoms
Foramen magnum: paraparesis, urinary/anal sphincter dysfunction, tongue atrophy ± fasciculation
Spinal canal: back pain, Brown-Séquard (hemispinal cord) syndrome

WORKUP: H&P with attention to the neurologic exam, head CT, MRI brain to evaluate for a well-circumscribed, classically homogeneously enhancing extra-axial mass with a dural tail (present in more than half of meningiomas—may also be present in patients with chloroma, lymphoma, and sarcoidosis). Meningiomas are T1 isointense and CT isodense with normal brain parenchyma unless contrast is administered, underscoring the importance of IV contrast when possible. Evaluate for bone invasion and/or reactive hyperostosis. Modest perilesional edema may be present; this is more frequently encountered with rapidly enlarging atypical and/or malignant meningiomas as well as convexity or parasagittal meningiomas. Extensive perilesional edema is a relative contraindication to SRS as patients may have considerable posttreatment edema following treatment of convexity meningiomas.

PROGNOSTIC FACTORS: Poorer prognosis with increasing grade, decreasing extent of resection, proliferative index (Ki-67) >1%, brain invasion, age <45, chromosomal abnormalities involving 14 and 22, aggressive clinical behavior, p53 overexpression.^{14–20}

NATURAL HISTORY: Approximately 1 to 2 mm of growth annually for grade I meningiomas. Most failures occur locally, and local progression can further aggravate associated neurologic symptoms. Marginal failure around the meninges is possible, particularly with high-grade meningioma.

TREATMENT PARADIGM

Observation: Observation may be appropriate for incidentally discovered small, asymptomatic meningiomas. Observation is also appropriate for WHO grade I tumors following GTR and may be considered following STR as well. Surveillance with MRI is recommended annually for patients with WHO grade I meningiomas undergoing observation to assess need for treatment.

Surgery: Standard is maximal safe surgical resection. Often requires craniotomy, but for sphenoid wing/skull base lesions, endoscopic surgery may be indicated. Simpson grade correlates with local failure (Table 4.4). Postoperative brain MRI should be obtained within 48 hours of surgery.

TABLE 4.4: Simpson Grading System for Meningioma Resection

Grade	Extent of Resection	Recurrence Rate at 5 Years (%)
0	GTR, including dural attachment and bone plus stripping of 2–4-cm dura	0
1	GTR, including dural attachment and any abnormal bone	9
2	GTR, with coagulation instead of resection of dural attachment	19
3	GTR of meningioma without resection or coagulation of dural attachment	29
4	Subtotal resection	44
5	Tumor debulking or decompression only	N/A

Chemotherapy: No primary role for CHT. Although medical therapy is nonstandard, 2020 NCCN guidelines suggest patients with radiographic progression may benefit from bevacizumab to prevent rapid neurologic deterioration.²¹

Radiation

Dose: WHO grade I meningiomas generally are treated to 50.4 Gy/28 fx or 54 Gy/30 fx. WHO grade II meningiomas are treated to 59.4 Gy/33 fx or 60 Gy/30 fx. WHO grade III meningiomas are treated to 60–66 Gy/30–33 fx. See RTOG 0539 for common dosing strategy. SRS dose, when feasible, is 12 to 14 Gy for grade I tumors. When surrounding tissues allow, 16 Gy for grade II tumors may be considered as well as RTOG 9005 dosing for grade III tumors (18–24 Gy). Brachytherapy is utilized at select institutions for multiply recurrent meningiomas.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 3.²²

■ EVIDENCE-BASED Q&A

■ Do incidentally discovered meningiomas require aggressive intervention?

Incidentally appreciated meningiomas may not require additional intervention. In at least one study, more than half of patients' meningiomas demonstrated no growth at 5 years. These patients may be followed with imaging at 3 to 6 months and then annually thereafter if no growth is appreciated.²³

■ What is the optimal first-line management in the treatment of meningiomas?

Maximal safe surgical resection provides the greatest opportunity for minimizing recurrence rates. The extent of resection is graded according to the Simpson grading system, which was the foundational study in meningioma.²⁴

Mayo Clinic (Mayo Clin Proc 1998, PMID 9787740): RR of 581 patients treated with initial resection. GTR in 80%. The 5- and 10-year PFS was 88% and 75% for GTR but only 61% and 39% for less than GTR. Perioperative mortality was 1.6%. A matched cohort analysis suggested nontrivial increase in morbidity and mortality from meningioma and/or treatment. Many of the risk factors for recurrence we use today were noted in this study. *Comment: Used an older data set. Surgical techniques, radiographic evaluation, and perioperative care may have improved since that time.¹⁶*

■ What is the role of RT in the management of WHO grade I meningiomas?

GTR (Simpson 1–3) is generally considered definitive, and patients may be followed with surveillance imaging. However, with longer follow-up, recurrence rates as high as 20%, 40%, and 60% have been reported at 5, 10, and 15 years, likely reflecting modern imaging capabilities.^{16,25–27} RT is typically reserved for salvage for these patients. For those with STR (Simpson 4–5), recurrence rates of 40% at 5 years and 60% at 10 years can be reduced to those of GTR (approximately halved) with adjuvant RT doses >50.4 Gy.^{28,29}

■ What is the role of RT in the management of WHO grade II meningiomas?

Adjuvant RT is generally recommended after GTR and strongly recommended after STR. Adjuvant RT after GTR of a WHO grade II meningioma is 54 Gy per RTOG 0539. After STR of a WHO grade II, adjuvant RT to 59.4 Gy/33 fx or 60 Gy/30 fx is recommended to minimize risk of LR based on multiple retrospective series.^{30–34} Without RT, LR rates of up to 60% at 5 years and CSS of only 70% at 10 years have been observed.^{25,35} Following GTR (Simpson 1–2), 5-year PFS is roughly doubled, from approximately 40% to 80% with adjuvant RT.^{31,36} Following STR, adjuvant RT is strongly recommended due to high recurrence rates.

■ Can RT margins be reduced in patients with WHO grade II meningioma treated with IMRT?

Although RTOG 0539 used at least a 1-cm CTV expansion for WHO grade II meningiomas, retrospective data suggest a 5-mm CTV and a 3-mm PTV may be used without undue risk of LR.²⁶

■ What is the role of RT in the management of WHO grade III meningiomas?

Adjuvant RT is necessary regardless of resection extent. WHO grade III meningiomas are relatively rare, with less than 300 cases per year in the United States.¹ As such, decisive data are lacking, although it is clear that OS is relatively poor with a generally accepted mean of >3 years.²⁷ A minimum dose of 60 Gy is recommended.^{30–32,37,38}

■ Are there prospective data to guide the treatment of meningiomas in the modern era?

Rogers, RTOG 0539 (Low Risk, ASTRO 2016, LBA 7; Intermediate Risk, J Neurosurg 2018, PMID 28984517; High Risk, IJROBP 2020, PMID 31786276): RTOG 0539 was the first prospective trial guiding the use of RT for meningiomas. Three risk groups were defined: low, intermediate, and high (see Table 4.5). **Conclusion: This trial supports observation for low-risk patients and 54 Gy for intermediate-risk patients. WHO grade I patients s/p STR may warrant adjuvant RT (crude failure rate 40%).**

TABLE 4.5: RTOG 0539 Summary

Risk Group	Definition	EBRT Dose	Target Volume	Outcomes
Low (<i>n</i> = 63)	WHO grade I meningioma s/p GTR or STR	Observation	N/A	5-yr PFS: 86.1% 5-yr LF: 12.5% (preliminary)
Intermediate (<i>n</i> = 48)	WHO grade II meningioma s/p GTR Recurrent WHO grade I meningioma	54 Gy/30 fx	Tumor bed + 1 cm CTV, reduced to 5 mm around barriers	3-yr PFS: 93.8% 3-yr LF: 4.1%
High (<i>n</i> = 51)	WHO grade III meningioma (any resection) WHO grade II meningioma s/p STR Recurrent WHO grade II meningioma	60 Gy/30 fx (HD PTV) with simultaneous low-dose PTV 54 Gy	HD PTV: gross tumor + resection bed + 1 cm	3-yr PFS: 59.2% 3-yr LF: 31.1% 3-yr OS: 78.6%
			LD PTV: gross tumor + resection bed + 2 cm	

Weber, EORTC 22042-26042 (Radiother Oncol 2018, PMID 29960684): Single-arm phase II study of 56 patients with grade II meningioma s/p GTR and RT 60 Gy/30 fx designed to show 3-year PFS >70%. With MFU 5.1 years, 3-year PFS was 88.7% and OS was 98.2%. Late grade ≥ 3 toxicity was 14.3%. **Conclusion: Grade II meningioma s/p GTR and 60 Gy/30 fx results in PFS of 88.7%.** Note: Observational cohorts of grade II meningiomas s/p STR and grade III meningiomas s/p any extent of resection have not yet been reported.

■ How frequently should patients be surveyed following treatment for meningioma?

For WHO grades I and II or unresected meningiomas, the 2020 NCCN guidelines recommend surveillance imaging with contrast-enhanced MRI at 3, 6, and 12 months, then every 6 to 12 months for 5 years, then every 1 to 3 years thereafter as clinically indicated. More frequent imaging may be required for WHO grade III and for any grade treated for recurrence or with CHT.

■ Should patients previously treated with RT be screened for meningioma?

No. The incidence of clinically relevant meningioma in patients with a history of cranial RT is approximately 3% at 30 years from the time of RT.³³ The incidence of any meningioma in patients with no history of cranial RT may be as high as approximately 13% at 10 years.³⁴ The incidence may reach 20% in patients with previous cranial RT who undergo screening with MRI at 20 years following RT.³⁶ The estimated risk of neoplastic transformation from modern, highly conformal or SRS techniques is low at approximately 1 in 1,000.³⁹ Therefore, a multidisciplinary working group in the United Kingdom has advised against screening as the risks of anxiety from serial MRI examinations and potential knowledge of an asymptomatic (and sometimes unresectable) tumors outweigh the benefits.⁴⁰

■ What dose of SRS should be used to treat meningioma and what are the outcomes?

Similar to brain metastases, SRS dose depends on the volume being treated and the dose to adjacent critical structures. Mean doses generally have ranged from 16 to 24 Gy, depending on location, with >20 Gy associated with higher rates of LC.^{16,41,42} Maximal dose for cavernous sinus meningiomas is 12 to 14 Gy, with doses >18 Gy associated with unacceptable CN toxicity.^{43–45} Fractionated SRT with BED >50 Gy may decrease toxicity rates for patients in whom critical structures limit SRS dose.⁴⁶ Most SRS series report excellent LC, with 10-year rates ranging from >90% for WHO grade I to >60% for WHO grades II and III.^{41,47–49}

■ What is meningiomatosis and how should it be managed?

Meningiomatosis is commonly associated with NF or MEN syndromes. Treatment should be coordinated in a multidisciplinary fashion, with surgery given primary consideration due to concerns of secondary malignancy induction. RT is indicated for surgically unresectable or recurrent lesions.⁵⁰

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