Chapter 5
Meningioma

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Meningiomas are the most frequent primary intracranial neoplasm, for which the treatment strategies range from observation to surgical resection and/or radiotherapy, depending on tumor size, location, histology, and growth pattern over time. Notably, stereotactic radiosurgery and conventionally fractionated radiotherapy are well-established techniques for the treatment of meningiomas with high local control rates and robust long-term follow-up data. Recent studies have applied the principles of SRS to fractionated stereotactic radiotherapy techniques, typically for patients with large tumors or those abutting critical OARs. Fractionation schemes are variable, though early data are promising. This chapter summarizes hypofractionated radiotherapy techniques, including SRS and FSRT, for meningiomas.

5.1 Pearls

- Arise from arachnoid cap cells of the arachnoid villi and are the most frequent primary intracranial neoplasm, accounting for one-third of all primary brain tumors.
- The average annual age-adjusted incidence is 7.86 per 100,000 people, with a median age at diagnosis of 65 years.
- More frequently diagnosed in women; female:male ratio of 2–3:1.

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- Risk factors include exposure to ionizing radiation (therapeutic or incidental) and genetic conditions such as type 2 neurofibromatosis (NF2) and schwannomatosis.
- The link between ionizing radiation exposure and risk for meningioma is well established from studies of therapeutic radiation, atomic bomb fallout, and historic use of cranial and scalp irradiation for tinea capitis.
- The role of sex hormones is less clear, although more than 70% of meningiomas express PR and nearly 40% express ER and androgen receptor.
- Meningiomas can arise from any location of the dura (see local anatomy below) and presenting symptoms depend largely on anatomic location, time course over which it developed, and presence of edema.
- While generally slow growing and clinically asymptomatic, there is a higher association with seizure in convexity and parasagittal/falcine locations and those with peritumoral edema.
- The WHO describes 3 grades (I–III) and 13 histologic subtypes (see Sect. 2).
- Local anatomy:
  - Meninges: Comprised of three membranes that envelop the brain and spinal cord, including the outer dura mater (including an outer endosteal and an inner meningeal layer), the middle arachnoid mater, and the inner pia mater. The arachnoid and pia mater form the leptomeninges and CSF flows between the two.

    The dura has four areas of infolding to form the falx cerebri (separating the cerebral hemispheres), the tentorium cerebelli (separating the occipital lobes from the cerebellum), the falx cerebelli (separating the cerebellar hemispheres), and the diaphragma sellae (covering the pituitary gland and sella turcica).
  - Meningiomas develop in various regions: parasagittal/falcine (25%), convexity (19%), sphenoid ridge (17%), suprasellar (9%), posterior fossa (8%), olfactory groove (8%), middle fossa/Meckel's cave (4%), tentorial (3%), peritorcular (3%), lateral ventricle (1–2%), foramen magnum (1–2%), and orbit/optic nerve sheath (1–2%) [1]. Of those in the parasagittal region, 49% occur in the anterior one-third of the falx cerebri.
- Medical workup:
  - History: Assessment of performance status, potential risk factors (prior therapeutic radiation exposure, hormonal status), genetic predisposition syndromes (NF2, schwannomatosis), conditions that can also cause a dural-based lesion (sarcoidosis, hematologic and non-hematologic malignancy, infection/fungal/tuberculosis), and associated neurological symptoms (e.g., seizures, headaches, vision changes).
  - Physical examination: Thorough neurologic examination.
- Imaging workup:
  - CT: Meningiomas are well-circumscribed, extra-axial masses that display strong, homogenous contrast enhancement, and are iso- or hyper-dense to

normal brain parenchyma—which is often displaced adjacently. Approximately 20–30% of meningiomas harbor calcifications, while approximately 50% are associated with hyperostosis or osteolysis in the adjacent bone.
  - MRI: Meningiomas are typically iso- or hypo-intense to gray matter on T1-weighted images, and hyperintense to gray matter on FLAIR sequences, and may display associated peritumoral edema. More than 90% of meningiomas display strong, homogenous contrast enhancement and approximately two-thirds demonstrate an adjacent dural thickening or "dural tail."
- Management strategies include observation, surgical resection, and/or radiotherapy, depending on tumor size, location, histology, and growth pattern over time.

5.2 Staging, Grading, and Other Classifications

The WHO describes 3 grades (I–III) and 13 histologic subtypes of meningioma. The WHO grade is prognostic, with strong associations between grade, RFS, and OS (Table 5.1, [2]). Surgery is often an appropriate therapy for benign (WHO Grade I) meningiomas, with extent of resection based on the Simpson grade and correlating to the rate of tumor recurrence (Table 5.2, [3, 4]).

5.3 Patient Selection for SRS or FSRT

- Factors influencing treatment recommendations include patient age, medical comorbidities, cranial nerve deficits, tumor size and/or growth rate, presenting symptoms, competing symptoms (i.e., contralateral hearing or vision loss), and proximity to critical organs at risk (OAR, such as brainstem, cochlea, optic apparatus, eloquent brain).
- For single-fraction SRS, targets should generally be:
  - <3 cm.
  - Not directly abutting critical OARs.
  - >3–5 mm from the optic apparatus (optic chiasm, optic nerves) to achieve adequate dose falloff between the prescription dose and OAR tolerance (<8–10 Gy for single-fraction SRS).
- For FSRT, tumors may be larger (>3–4 cm), in closer proximity to or involving OARs.
- Case-by-case consideration of SRS for parasellar meningiomas (including cavernous sinus and medial sphenoid wing) given proximity to optic apparatus.
- Optic nerve sheath and tuberculum sellae meningiomas are generally a contraindication for SRS in patients with preserved vision given that the lowest therapeutic dose (12–13 Gy) exceeds optic apparatus tolerance (8–10 Gy).

Table 5.1 The 2016 WHO meningioma grading criteria[a]

Grade	Tumor histology/features
I (benign)	1. Any major histologic subtype, ***except*** clear cell, choroid, papillary, or rhabdoid 2. Does not otherwise meet the criteria for grade II or III
II (atypical)	1. Choroid or clear cell subtype, ***or*** 2. Presence of brain invasion, ***or*** 3. Increased mitotic index (4–19 per 10 hpf), ***or*** 4. Three or more of the following histologic features: Sheetlike or patternless architecture, increased cellularity (focal or diffuse), prominent nucleoli, small cells with high nuclear:cytoplasmic ratio, foci of spontaneous or geographic necrosis
III (anaplastic or malignant)	1. Papillary or rhabdoid subtypes, ***or*** 2. High mitotic index (≥20 per 10 hpf), ***or*** 3. Anaplastic by the following criteria: Focal or diffuse loss of meningothelial differentiation, resembling sarcomata, carcinomata, or melanoma

[a]Modified from Louis et al. [2]. Hpf, high-power field

Table 5.2 Simpson grade of resection and recurrence risk[a]

Grade	Extent of tumor resection	Recurrence rate (%)
I	Macroscopic complete resection of tumor, dural attachments, and abnormal bone	9
II	Macroscopic complete resection of tumor, coagulation of dural attachments	19
III	Macroscopic complete resection of tumor, without resection, or coagulation of dural attachments or extradural disease	29
IV	Subtotal resection of tumor	44
V	Decompression or biopsy only	N/A

[a]Modified from Simpson et al. [3]

5.4 Treatment Planning Considerations (Table 5.3)

Table 5.3 Treatment planning considerations

Simulation instructions	**Position**: Supine, arms at sides, head and neck neutral. **Immobilization**: A rigid (frame or frameless) stereotactic immobilization system[a]. – GaK: Head frame in conjunction with a metal collimator helmet. – Linac based: Various, including rigid frame with external skull fixation, noninvasive modified GTC frame (noninvasive fixation by use of a dental plate), or a three-point thermoplastic mask with a modified stereotactic frame (see Fig. 3.1). **CT**: Thin-cut CT images (1.0–3.0 mm slice thickness) ideally with IV contrast spanning from vertex to mid-cervical spine. **Diagnostic imaging**: Co-registration of planning CT with the appropriate diagnostic imaging (contrast-enhanced MRI or CT) for target and OAR delineation. MRI sequences should include pre- and post-contrast T1-weighted, pre-contrast T2-weighted and FLAIR, and multi-planar (axial, sagittal, and coronal) post-contrast T1-weighted images. Post-contrast T1-weighted images with thin (1 mm) sectioning should be obtained. High-resolution series, such as MP-RAGE, should be obtained for contrast-enhancing targets. Cranial nerves may be more readily visualized on a CISS or 3D FIESTA series as needed [5].
Image guidance	Imaging options include CBCT, orthogonal KV X-rays; misalignment corrections via positional systems with four or six rotational axes of the patient couch/platform.
Target delineation	For benign meningiomas, the tumor bed/GTV is defined as the enhancing lesion on the post-gadolinium T1-weighted MRI ([5], and see Fig. 5.1a). The GTV does not include any surrounding edema on T2-weighted images. The linearly enhancing dura adjacent to the primary meningioma is defined as the dural tail, which can be included in the GTV electively (the proximal component only) or if there is any enhancing nodularity [5]. Dural tail: Defined as presence of ≥2 consecutive slices and >1 imaging plane, tapering adjacently from the mass with increased contrast enhancement [6, 7]. This is most often an inflammatory effect of the tumor that does not require inclusion in grade I tumor target definition. For postoperative cases, the GTV is defined as the resection bed plus any residual nodular enhancement.
Margins	For benign meningiomas, GTV = CTV. May consider 0.5–1.0 cm margin for dural tail or uncertainty in contrast enhancement on T1-weighted images. PTV = CTV plus 0–5 mm uniform expansion (depending on institutional setup error, including accuracy and reproducibility of immobilization). Generally CTV plus 3–5 mm uniform expansion for standard thermoplastic mask or CTV plus 0–2 mm uniform expansion for a stereotactic frame.
Tumor/target coverage considerations	≥98% of the GTV/CTV should receive the prescription dose. ≥95% of the PTV should receive the prescription dose.

Table 5.3 (continued)

Treatment modality	Linac, GaK, CyK, proton beam
Planning strategies/ assessment	Steep PTV to OAR dose gradients are generated using multiple beam arrangements or non-coplanar arcs together with dose prescription to the steepest portion of the beam profile (often the 50% IDL for GaK or the 80–90% IDL for linac based). For linac-based SRS, the standard beam profile is shaped by collimation with cones or MLCs. An example treatment plan is depicted in Fig. 5.1a. Notably, as target size increases, the dosimetric advantages of SRS tend to decline—as the sharp dose falloff becomes shallower and the higher doses to adjacent normal tissue become prohibitive, thereby generally precluding safe and effective SRS delivery to targets >3 cm in diameter. The following indices should be generated [8]: **Conformality index**: Prescription isodose volume/target volume (ideally ≤2). **Heterogeneity index**: Maximum dose to target volume/prescription dose (ideally ≤2). **Gradient index**: Volume receiving half the prescription isodose/volume receiving the full prescription isodose (ideally ≥3).

[a]Based on delivery system and institutional protocol. *GTC* Gill-Thomas-Cosman, *FLAIR* fluid-attenuated inversion recovery, *MP-RAGE* magnetization-prepared rapid gradient echo, *CISS* constructive interference in steady state, *FIESTA* 3D fast imaging employing steady-state acquisition

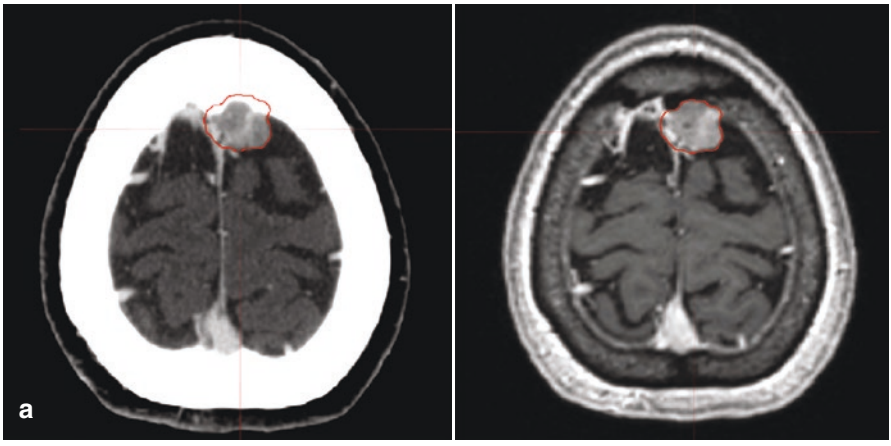

Fig. 5.1 A 2.6 cc left frontal meningioma; GTV target delineation in red. (**a**) Simulation CT (left), post-contrast T1-weighted MRI (right). (**b**) Treatment plans with prescription IDL in green, effective normalization 90%. FSRT, 3 GyRBE protons × 13 fx (39 GyRBE total). Simulation CT axial (left) and coronal (right). IDL, isodose line

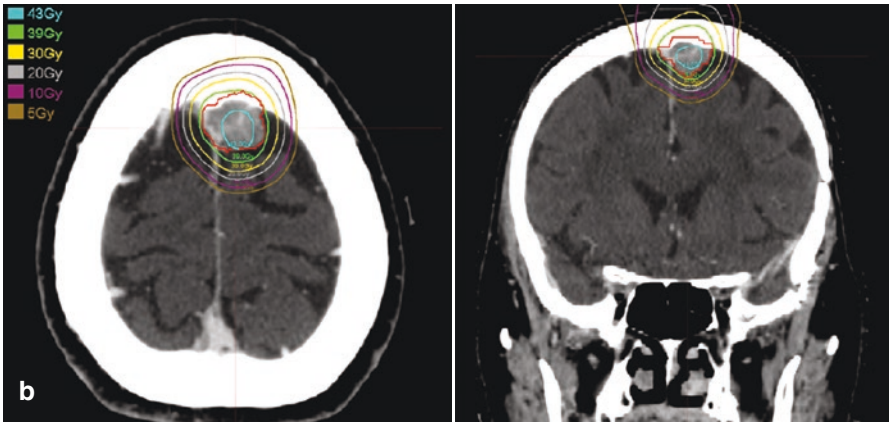

Fig. 5.1 (continued)

5.5 Commonly Used Dose/Fractionation Schemes (Table 5.4)

Table 5.4 Commonly used dose/fractionation schemes

Commonly used dose/fractionation schemes			
	Patient selection considerations	Dose/fractionation	Criteria for SRS
SRS	– More than 3–5 mm from optic apparatus – Optic nerve sheath and tuberculum sellae meningiomas are generally a contraindication to SRS (therapeutic doses exceed OAR tolerance)	WHO grade I: 12–15 Gy × 1 fx WHO grade II–III: 16–20 Gy × 1 fx	• Lesion <3 cm • Not directly abutting critical OARs • >3–5 mm from the optic apparatus
FSRT	Larger tumor and/or <2–3 mm from optic apparatus or other critical OAR	WHO grade I: 5–6 Gy × 5 fx [9], 2.5 Gy × 15 fx [10]	

Table 5.5 Relevant literature

Dmax[a] (Gy) in critical structures for SRS and FSRT							
Organ	Authors' recommendations			TG101 [14]			QUANTEC [15]
Fractions	One	Three	Five	One	Three	Five	One
Brainstem	≤12 Gy	≤21 Gy	≤30 Gy	15 Gy	23.1 Gy	31 Gy	<12.5 Gy
Cochlea	<4.2 Gy	–	–	9 Gy	17.1 Gy	25 (5 Gy/fx)	≤14 Gy
Optic apparatus	≤8 Gy	≤16.5 Gy	≤ 25 Gy	10 Gy	17.4 Gy	25 (5 Gy/fx)	–
Optic chiasm	≤8 Gy	–	–	–	–	–	<12 Gy
Optic nerve	≤8 Gy	–	–	–	–	–	–

5.6 Normal Tissue Tolerances

Rates of radiation-induced optic neuropathy are very rare <8–10 Gy but reach >10% at single-SRS doses between 12 and 15 Gy [11, 12] (Table 5.5). In a study by Kano et al., patients with vestibular schwannomas treated with GammaKnife SRS had improved serviceable hearing preservation if they received a central cochlea dose <4.2 Gy [13].

5.7 Patient Management Considerations

- Premedication/prophylactic medication:
  - There is no standard premedication regimen.
  - Consideration of steroids, benzodiazepines, and/or anticonvulsants is dependent on severity and progression of symptoms or neurologic deficit(s), treatment volume/location and number of fractions, if known prior seizures, as well as patient age and/or medical comorbidities.
- Acute toxicity: Side effects are tumor location dependent and include, but are not limited to, rare transient nausea, headache, alopecia, skin erythema, conjunctivitis, and fatigue.
- Late toxicity: Transient complications (3%), permanent neurologic deficits (5–9%), radionecrosis, or delayed CN deficits (<6%) [16, 17].

5.8 Follow-Up

- H&P every 6–12 months.
- Yearly imaging (ideally MRI, CT with contrast if non-tolerant, or MRI contraindicated) for 4–5 years, then every 2 years.
- For cavernous sinus or base of skull locations, monitor for hypopituitarism with regular serum analyses annually or as needed.
  - Recommend endocrinologist for long-term management and monitoring of endocrine dysfunction.

5.9 Relevant Literature

- Stereotactic radiosurgery and conventionally fractionated radiotherapy are well-established techniques for meningiomas with high local control rates and extensive long-term follow-up data.
- While FSRT is a promising treatment modality in patients with large tumors or those abutting critical OARs, more mature data are needed for robust evaluation of the long-term efficacy and toxicity profile for FSRT compared to SRS or conventionally fractionated radiotherapy (Table 5.6).

Table 5.6 Relevant literature

Study	Patients (*n*)	Median follow-up (months)	Median tumor vol (cm^3)	Modality, dose, fractionation	LC (%)
Torres, 2003 [18]	77	40.6	12.7	Linac, 15.6 Gy × 1 fx	– 92% 5 years
DiBiase, 2004 [19]	162	54	4.5	GaK, 14 Gy × 1 fx	– 86% 5 years
Kreil, 2005 [20]	200	95	6.5	GaK, 12 Gy × 1 fx	– 98.5% 5 years – 97% 10 years
Kollova, 2007 [21]	368	60	4.4	GaK, 12.5 Gy × 1 fx	– 98% 5 years
Feigl, 2007 [22]	214	24 (mean)	6.5 (mean)	GaK, mean 13.6 Gy × 1 fx	– 86% 4 years
Kondziolka, 2008 [17]	972	48 (mean)	7.4	GaK, mean 14 Gy × 1 fx	– 87% 10 years
Gorman, 2008 [10]	38	47	8.3	Linac, 2.5 Gy × 15 fx	100%
Mahadevan, 2011 [23]	16	22	10.5	CyK, mean 5.62 Gy × 5 fx	100%
Han, 2014 [9]	– SRS, 55 – FSRT, 22 – Conventional fx, 143	32	2.8 4.8 11.1	Linac, 12.5 Gy × 1 fx (SRS), 5 Gy × 5 fx (FSRT), 1.8 Gy × 28 fx (conventional fx)	– SRS 91% – FSRT 94% – Conventional fx 95%
Smith, 2014 [24]	28	32.6	14.7	CK, 4.5–6 Gy × 5 fx	100%
Navarria, 2015 [25]	26	24.5	13	Linac, 5 Gy × 5 fx	100%
Conti, 2015 [26]	25	17 (mean)	4.95	CyK, median 4.6 Gy × 5 fx	100%

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