Practical Guides in Radiation Oncology
Series Editors: Nancy Y. Lee · Jiade J. Lu

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Intracranial and Spinal Radiotherapy

A Practical Guide on Treatment Techniques

Springer

Practical Guides in Radiation Oncology

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The series Practical Guides in Radiation Oncology is designed to assist radiation oncology residents and practicing radiation oncologists in the application of current techniques in radiation oncology and day-to-day management in clinical practice, i.e., treatment planning. Individual volumes offer clear guidance on contouring in different cancers and present treatment recommendations, including with regard to advanced options such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). Each volume addresses one particular area of practice and is edited by experts with an outstanding international reputation. Readers will find the series to be an ideal source of up-to-date information on when to apply the various available technologies and how to perform safe treatment planning.

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We dedicate this practical guide to our parents, family, and mentors who have provided unwavering support to our careers as well as numerous patients who have taught us about the power of hope and have inspired us with their collective courage in dealing with their diseases.

Foreword

Radiotherapy for benign and malignant pathologies affecting the central nervous system can both achieve wondrous results and inflict grievous harm. Continuous improvements in neurosurgical technique, refinements in diagnostic imaging, and ever-better understanding of the molecular drivers and differences between pathological entities require commensurate advances in the radiotherapeutic management of pathologies affecting the central nervous system. Fortunately, advances in image guidance and in overall radiotherapy technology have enabled radiation oncologists and collaborative physicians to make large, evidence-based strides to improve care for patients in curative and palliative settings.

I congratulate the editors for their assemblage of a range of experts in central nervous system radiotherapy to write about our contemporary understanding of a broad spectrum of these conditions and how radiotherapy may be judiciously employed in the treatment thereof. I further commend the authors for their careful exposition of relevant materials that inform and guide the reader. And finally, I heartily congratulate the readers for their perspicacity in purchasing this very useful textbook.

New York, USA — Jonathan Knisely

Preface

Intracranial and Spinal Radiotherapy is a concise handbook focusing on the practical aspects of radiotherapy for brain and spinal tumors or diseases presented in a highly accessible format. For each of the disease site-specific chapters, simulation technique, target delineation, treatment planning, normal tissue constraints, and side effects are included. There are four chapters dedicated to side effects and complications from brain and spinal radiotherapy. The editors hope that this practical guide will provide busy radiation oncologists, clinical oncologists, radiation oncology trainees, medical physicists, medical physicist trainees, and dosimetrists a user-friendly reference to aid in their daily practice.

Seattle, WA — Lia M. Halasz
Seattle, WA — Simon S. Lo
Los Angeles, CA — Eric L. Chang
Toronto, ON, Canada — Arjun Sahgal

Contents

Arteriovenous Malformation

1

Bruce E. Pollock

Contents

1.1 General Principles of Simulation and Target Definition

- The goal of cerebral arteriovenous malformation (AVM) stereotactic radiosurgery (SRS) is nidus obliteration to eliminate the risk of intracranial hemorrhage.
- AVM SRS is typically performed in a single fraction using a stereotactic head frame for patient immobilization.
- The target volume for arteriovenous malformation (AVM) stereotactic radiosurgery (SRS) is the nidus, excluding the feeding arteries and draining veins (Fig. 1.1).
- Two factors must be remembered when considering the dosimetric parameters of AVM SRS. First, AVM are congenital lesions and do not invade the surrounding brain parenchyma. Thus, increasing the target volume by several millimeters to encompass disease spread that cannot be imaged is not needed or desirable (GTV=CTV). Second, there is often wide variability in defining the nidus volume between different observers. Therefore, conformality indices do not apply well to the radiosurgical treatment of cerebral AVM.

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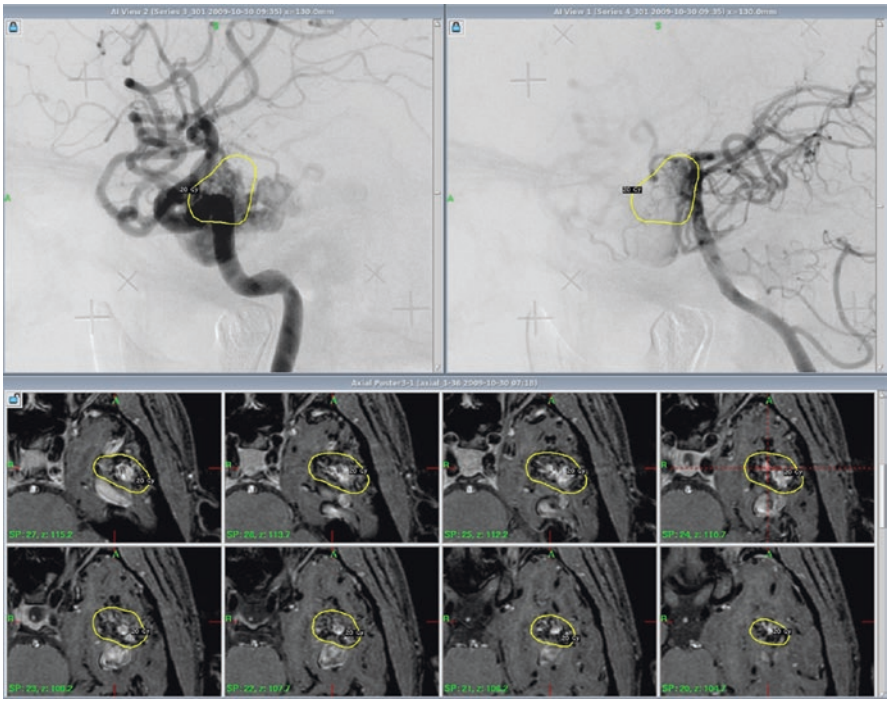

Fig. 1.1 Dose planning for a 29-year-old man with a left temporal AVM who presented with headaches. The volume treated was 3.8 cm^3; the AVM margin dose was 20 Gy. Note the treatment volume excludes the adjacent draining veins

- Catheter-based cerebral angiography remains the gold standard for accurate definition of the AVM by showing not only the nidus shape but also the temporal filling of nidus relative to angiomatous feeding arteries and draining veins. In addition, angiography also shows coexisting abnormalities such as feeding artery and intra-nidal aneurysms.
- The addition of axial imaging, typically gadolinium-enhanced SPGR or T2-weighted MRI allows a better understanding of the three-dimensional shape of the AVM increasing the conformality of dose planning.

1.2 Dose Prescriptions

- Increasing radiation dose directly correlates with the chance of AVM obliteration [1, 2]. The rate of obliteration ranges from 60 to 70% for AVM margin doses of 15–16 Gy, from 70 to 80% for AVM margin doses of 18–20 Gy, and 90% or more for AVM margin doses over 20 Gy.

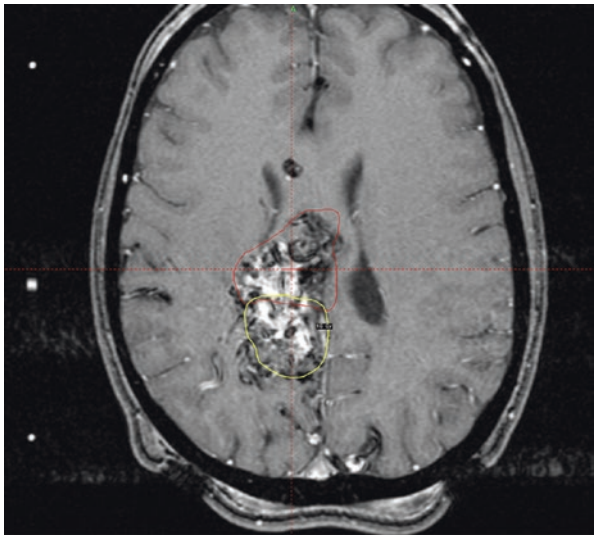

Fig. 1.2 Dose planning for a 43-year-old woman who had an intraventricular hemorrhage and was found to have a large right-sided AVM involving the corpus callosum and frontal and parietal lobes. The AVM was treated with volume-staged SRS using two stages to cover a total volume 19.9 cm^3. The anterior portion was covered during the first SRS, and the posterior portion was covered during the second SRS. The AVM margin dose was 16 Gy

- While higher radiation doses increase the chance of obliteration, the likelihood of adverse radiation effects (ARE) also rises at higher radiation doses and larger AVM volume [3–5]. Patients with deeply located AVM are at greater risk for neurologic deficits secondary to imaging changes noted on MRI after SRS.
- To account for the conflicting goals of increased obliteration while minimizing the chance of ARE, small-volume AVM (≤4.0 cm^3) are generally prescribed margin doses of 20–25 Gy, medium-volume AVM (4–10 cm^3) are prescribed 18–20 Gy, and larger volume AVM (>10 cm^3) are prescribed 15–18 Gy. AVM >14 cm^3 are considered for volume-staged SRS (VS-SRS) [6–9] (Fig. 1.2).
- Patients with AVM located in deep locations are generally treated with 15–18 Gy.
- If initial SRS does not result in obliteration after 3–5 years, then repeat SRS is often performed. Dose prescription for repeat AVM SRS usually ranges between 15 and 18 Gy.

1.3 Treatment Planning Techniques

- Dose planning should cover the entire nidus with prescribed radiation dose. The majority of Gamma Knife cases are prescribed at the 50% isodose line, whereas linear accelerator-based procedures typically are prescribed to higher isodose lines.
- VS-SRS of large AVM allows a higher radiation dose to be delivered to the nidus while reducing the radiation exposure to the adjacent brain. The time between the different stages usually is 2–6 months.

1.4 Side Effects

- Neurologic decline after AVM SRS can occur secondary to intracranial hemorrhage (ICH) or ARE.
- Patients remain at risk for ICH until the nidus is obliterated, which generally requires 1–5 years. Numerous reports have shown that the risk of AVM bleeding during this latency interval is either unchanged or reduced [10–12].
- Radiation-induced changes (RIC) noted in the first 1–2 years after AVM SRS (areas of increased signal on T2-weighted MRI) are noted after 30–50% of patients and are distinct from radiation necrosis [13] (Fig. 1.3). Most are asymptomatic and resolve without treatment.
- Patients with symptomatic RIC (headaches, seizures, focal deficits) can usually be managed with corticosteroid therapy.
- Late ARE develop 5 or more years after SRS and are characterized by perilesional edema or cyst formation [14–15] (Fig. 1.4). Symptomatic late ARE may require surgical removal to improve the patient's neurologic condition.

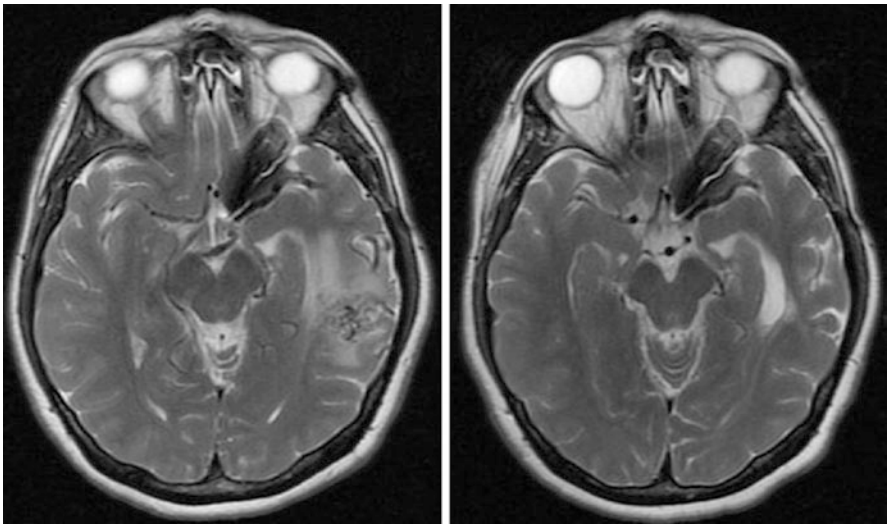

Fig. 1.3 Axial T2-weighted MRI after SRS of a left temporal AVM (AVM volume, 13.8 cm^3; AVM margin dose, 15 Gy). (Left) MRI performed 1 year after SRS shows edema surrounding the AVM. The patient was asymptomatic. (Right) MRI performed 3 years after SRS shows the nidus to be no longer visible and the edema has resolved

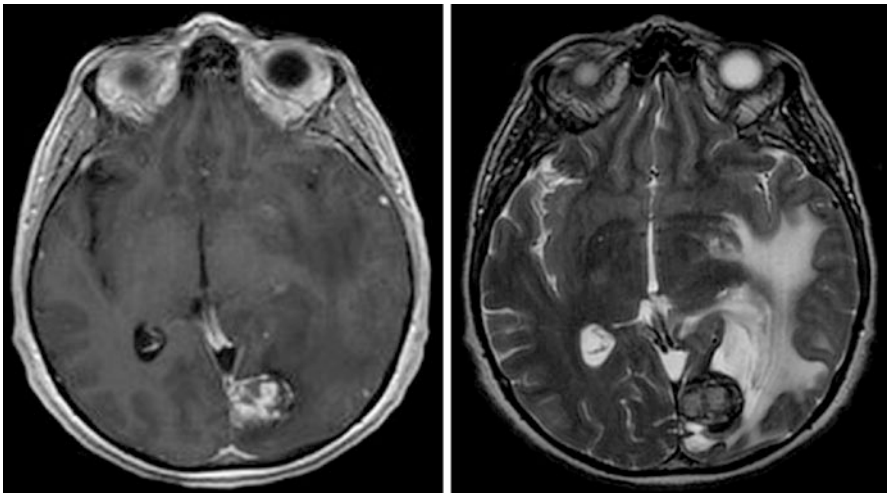

Fig. 1.4 Axial gadolinium-enhanced (left) and T2-weighted (right) MRI 15 years after initial SRS and 11 years after repeat SRS of a left occipital AVM showing late ARE. The patient had progressive visual loss and headaches and underwent resection of the obliterated AVM with improvement in her symptoms

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Benign Meningioma

2

Stephanie E. Weiss

Dedicated to mentor and friend Dr. Moody D. Wharam, the embodiment of Aequanimitas

Stephanie E. Weiss, MD

Contents

2.1 General Principles of Simulation and Target Delineation (Tables 2.1 and 2.2, Fig. 2.2)

- CT simulation in a thermoplast mask at zero angulation.
- Diagnostic CT to evaluate bone invasion requiring inclusion in GTV.
- Volumetric 3D reconstructed thin slice (1.5 mm optimal) MRI with T1 pre-gadolinium and fat-suppressed post-gadolinium, with 3D reconstruction for target delineation. T2 and FLAIR may assist evaluation of dural/calvarial involvement.
- Enhancing lesion on T1 with contrast, bone invasion, and tumor-adjacent dura at risk are targets.

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Table 2.1 Suggested target volumes for conventional fractionation

Target volumes	Definition and description
GTV	T1-enhancing tumor all planes on MRI, bone invasion (use MR + bone windowing on CT). Do not include brain parenchymal edema, which may be present with some low-grade lesions. True brain invasion upgrades lesion to atypical (see chapter on atypical meningioma)
CTV	3–5 mm along proximal dura at risk. May or may not include dural tail (see Fig. 2.1, general principles.) May modify based on clinical/anatomical factors. Exclude brain parenchyma
PTV	3–5 mm per machine/setup specifications

Table 2.2 Suggested target volumes for SRS

Target volumes	Definition and description
GTV	Enhancing lesion on T1 + C all planes
CTV	N/A
PTV	N/A

Note: CTV = GTV for stereotactic radiosurgery (SRS)

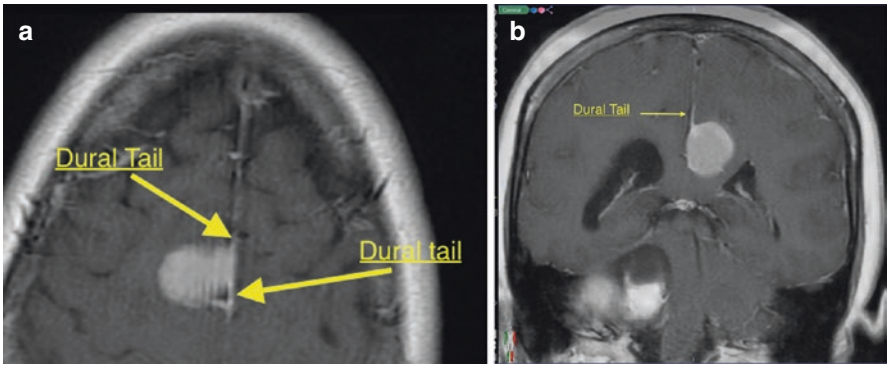

Fig. 2.1 Axial and coronal slices of benign parasagittal meningiomas of the right frontal lobe (Image **a**) and left parietal lobe (Image **b**). A dural tail extends anteriorly and posteriorly and superiorly and inferiorly along dura, respectively. The dural tail is a radiographic finding reflecting hypervascular dura that may or may not harbor tumor cells. All tumor-adjacent dura is at risk of harboring microscopic tumor cells [8], and the "dural tail" is at no higher or lower risk of relapse than other tumor-adjacent dura

- Fuse MR with CT. If postoperative case, fuse preoperative and postoperative imaging.
- Incorporate reconstructed thin-sliced coronal and sagittal MR cuts to help identify and assure three-dimensional coverage of region at risk.
- Distinguish *dural attachment* (tumor) from *dural tail*, which is predominantly hypervascular tissue that may or may not harbor tumor cells along with all tumor-adjacent dura [1].

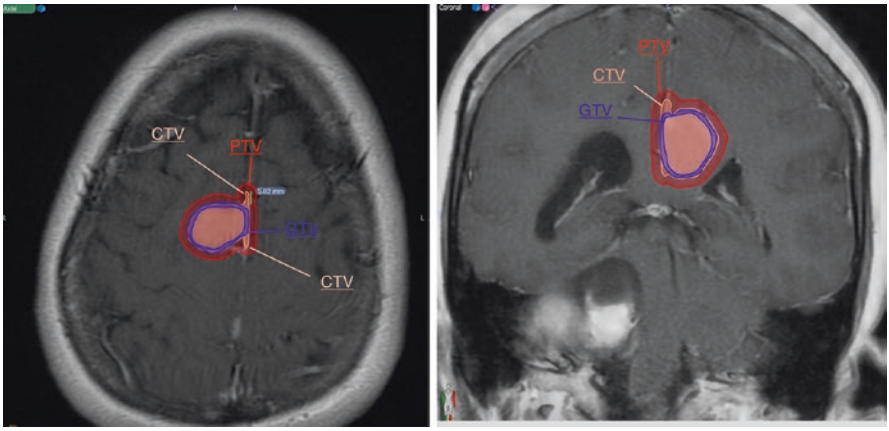

Fig. 2.2 Sample contouring for right frontal and left parasagittal meningioma. The gross tumor is designated as GTV outlined by blue. CTV indicated by peach extends along adjacent dura but not into normal brain parenchyma, which is not at risk of invasion in benign meningioma. Note that the 5 mm CTV margin acknowledges that all tumor-adjacent dura is at risk, regardless of the presence of hypervascular dural tail. Thus, the entirety of dural tail may or may not be included in the CTV, and the CTV should not be reduced along tumor-adjacent dura because of radiographic absence of a dural tail. Care should be taken to distinguish frank meningioma from dural tail with neuroradiologic consultation. CTV should be modified based on all relevant clinical information to incorporate volumes likely to harbor subclinical/microscopic disease. PTV indicated by red is determined by the immobilization and machine setup and localization parameters. Note, for stereotactic radiosurgery, no margin is added to GTV (i.e., CTV = GTV). This targeting paradox is an area of controversy in the management of meningioma [1, 10]. The parasagittal location of both these lesions favors conventional fractionation [2–4]

- If MRI is contraindicated, use thin slice CT (1.0 mm slices) with and without contrast.
- 3D conformal RT, IMRT/VMAT, SRS, and proton therapy may be considered.
- If optic structures or the pituitary abut tumor and/or likely to be in meaningful dose gradient, recommend pretreatment neuro-ophthalmology and endocrine consult, respectively, to assess baseline function. Patient may be at risk for life-threatening adrenal insuffiency over time, along with other endocrinopathies.
- Keep in mind dose-gradient and setup uncertainty when considering SRS in proximity to critical structures.

2.2 Clinical Pearls

- Parasagittal/parasinus lesions are high risk (~25–45%) for post-radiosurgical symptomatic edema requiring medical intervention. Consider conventional fractionation rather than SRS for these lesions [2–4].
- If patients require steroids >3–4 weeks, consider *Pneumocystis jiroveci* pneumonia prophylaxis.
- Consider trial of celecoxib in lieu of/in aid of tapering steroid for patients not tolerating/requiring long-term dexamethasone if not otherwise contraindicated.

- Consider the association of long-term local control with extent of surgical resection/dural stripping [5] when determining region "at risk" (CTV) in radiation treatment planning.
- Low-grade meningioma has a propensity for late relapse. ~50% of patients with "low-risk" lesions die a cause-specific death with extended follow-up of 25 years [6].
- Relapse is associated with subsequent aggressive behavior regardless of up-front treatment [6, 7].
- Data with long-term (≥10 years) median follow-up for SRS is limited. Actuarial data for disease with a propensity for late relapse tends to underestimate recurrence rates.

1. Dose Prescriptions
   - For conventional fractionation: 54 Gy in 30 fractions (1.8 Gy/day), may dose paint to limit normal critical tissue (such as chiasm) to 50.4 Gy.
   - For stereotactic radiosurgery (SRS): 12–14 Gy in a single fraction, respecting normal tissue tolerances.

2.3 Treatment Planning Techniques (Tables 2.3 and 2.4)

- *Conventional fractionation*: 3D CRT, IMRT, VMAT, and protons may all be used with the goal of minimizing dose to brain/critical structures. Dose painting may be necessary (i.e., 54 Gy to most of CTV, limiting critical structure such as optic nerve to 50.4). Mindful of dose to the pituitary, brain stem, cord, cochlea, and cranial nerves, considering long-term survival of most patients. Tolerance of critical structures compromised from baseline if they have been previously injured by tumor encroachment and/or surgical manipulation.
- *SRS*: Data is retrospective and/or median follow-up of <10 years. Actuarial data tends to under-estimate risk of relapse for disease entities with a propensity for late failure. Be wary of outcome curves past median follow-up. Risk for symp-

Table 2.3 Recommended normal tissue constraints for 1.8 Gy/day fractionation schemes

Organs at risk	Suggested dose constraints
Optic nerves and chiasm	<54 Gy [11]
Retinae	<45 Gy [12]
Lenses	<10 Gy [13]
Lacrimal glands	<30 Gy, mean <25 Gy [14, 15]
Pituitary gland	Beam angles/planning techniques to minimize dose to the pituitary
Cochlea	≤35 more conservatively (may escalate to ≤45 so as to not sacrifice coverage of target) but keep as low as possible as no lower threshold for sensory-neural hearing loss determined [16]
Brain stem	≤54 Gy in 1.8 Gy fractions [17]

Table 2.4 Recommended normal tissue constraints for radiosurgery

Object at risk	Suggested dose constraints
Optic nerves and chiasm	<8–12 Gy [18]
Pituitary gland	Beam angles and planning techniques to minimize dose to the pituitary
Cochlea	Keep ≤12 Gy [16]
Brain stem	Keep ≤12 Gy [17]

Table 2.5 Side effects

Acute	Common: Hair loss, fatigue. Less common: headaches, nausea, and inflammation/cerebral edema causing neurological symptoms, often exacerbation of presenting symptoms
Long-term	Cranial nerve deficit, neurocognitive decline and hypopituitarism, subacute symptomatic edema requiring steroids, related to anatomical region treated and dose-fractionation scheme used
Uncommon or rare risks	New onset seizure, vision loss, hearing loss, cranial nerve injury, hemorrhage, necrosis, stroke secondary malignancies

tomatic edema after radiosurgery may be as high as 25–45% for parasinus/parasagittal lesions [2–4, 9].

Side effects. Please see Table 2.5.

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Atypical and Malignant Meningioma

3

Christian Okoye and Leland Rogers

Contents

3.1 General Principles of Simulation and Target Delineation

- CT simulation:
  - The patient should be positioned supine, with arms at sides or across the chest.
  - Immobilization should be provided by a noninvasive, stereotactic, relocatable device (e.g., aquaplast mask with standard or custom headrest).
  - CT should be performed without contrast, with ≤3 mm slices, from the top of the scalp through the bottom of the skull and upper cervical spine. If beneficial for target identification or for improved CT-MRI fusion, a CT with contrast may also be acquired.
- Imaging:
  - Along with treatment planning imaging, preoperative and early postoperative MRIs may be beneficial to assess the extent of resection and aid in delineation of the full extent of tumor involvement, the operative site, and/or the residual nodular enhancement.

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Table 3.1 Suggested target volumes for atypical meningioma after gross total resection (GTR)

Target volumes	Definition and description
Gross tumor volume (GTV)	The entire postoperative tumor bed
Clinical target volume (CTV)	GTV + 0.5 cm expansion, may be reduced within non-invaded brain or along natural barriers to tumor growth
Planning target volume (PTV)	CTV + 3–5 mm expansion

Table 3.2 Suggested target volumes for malignant meningioma or atypical meningioma after subtotal resection (STR)

Target volumes	Definition and description
Gross tumor volume (GTV)	Any residual gross tumor, nodular enhancement, hyperostotic and/or directly invaded bone, and the operative tumor bed
Clinical target volume (CTV)	GTV + 1.0 cm; margins may be reduced within non-invaded brain or along natural barriers to tumor growth
Planning target volume (PTV)	CTV + 0.5 cm

  - Treatment planning MRI sequences should include thin slice pre- and post-contrast T1-weighted images.
- Target delineation (Tables 3.1 and 3.2):
  - In the postoperative setting, a 2- or 3-month delay in treatment planning imaging may improve the assessment of resection extent and delineation of the tumor bed and provide a smaller, more stable target.
  - Treatment planning MRI images should be fused with the simulation CTs to aid in target delineation. If needed, preoperative images may be fused as well.
  - Residual gross tumor is typically demonstrated as nodular enhancement on post-contrast T1 MRI, though areas of necrosis or calcification may not enhance; correlation with preoperative imaging is advantageous.
  - It is not necessary to incorporate dural tail (defined as *linear* enhancement trailing off from the primary meningioma) within the primary GTV. Any *nodular* enhancement, however, should be included.

3.2 Dose Prescriptions

- Atypical meningioma after GTR: 54–60 Gy at 1.8–2 Gy per fraction.
- Malignant meningioma after GTR: 60 Gy at 1.8–2 Gy per fraction.
- Malignant meningioma or atypical meningioma after STR: 60–66 Gy at 1.8–2 Gy per fraction.
- In the latter settings, it is feasible to plan a simultaneous integrated boost, e.g., treating the tumor bed to 54 Gy and gross residuum to 60–66 Gy in 30 fractions.

3.3 Treatment Planning Techniques (Tables 3.3 and 3.4)

- Standard radiotherapy techniques for all patients with atypical or malignant meningiomas include 3DCRT and IMRT/VMAT; for target doses above 54 Gy, intensity-modulated, inverse planning techniques are recommended to allow sparing of uninvolved adjacent brain and other critical structures.
- At present, data regarding SRS among patients with atypical or malignant meningiomas remains sparse, is largely limited to the salvage setting, and has met with higher regional recurrence risk. When employed, it has typically been reserved for smaller (diameter <2.5–3 cm or volume <7.5–10 cm^3) lesions with distinct margins and at sufficient distance from organs at risk to permit acceptable dose constraints.
- Although experience with proton therapy remains limited, for selected patients, it yields theoretical dosimetric advantages and should be considered on a case-by-case basis.
- Image guidance should be used to verify the accuracy of treatment delivery and periodically (daily to at least weekly) throughout treatment. Commonly used methods include orthogonal KV X-rays, cone beam CT, and/or surface-guided techniques.
- Planning risk volumes (PRVs) may also be generated surrounding organs at risk (OARs) to aid in achieving treatment planning objectives. PRVs are commonly defined as their respective OAR plus a 3 mm uniform expansion.

Table 3.3 Suggested organs at risk (OAR) constraints

Organs at risk	Suggested dose constraints[a]
Lenses	Max <7 Gy (acceptable variation 7–10 Gy)
Retinae	Max <45 Gy (acceptable variation 45–50 Gy)
Optic nerves	Max <54 Gy (acceptable variation 54–58 Gy)
Optic chiasm	Max <54 Gy (acceptable variation 54–58 Gy)
Brain stem	Max ≤54 Gy (acceptable variation 54–58 Gy)
Cochlea	Mean dose ≤45 Gy

[a]Per NRG Oncology BN-003 [1], excepting cochlea constraint per QUANTEC [2]

Table 3.4 Suggested target coverage guidelines and constraints

Targets	Suggested dosimetric constraints[a]
PTV	D95 ≥100% prescription D100 >95% prescription
Overall plan, maximum dose	Max <110% prescription

[a]Per NRG Oncology BN-003. In some settings, increased conformality, often with decreased dose homogeneity, is preferable

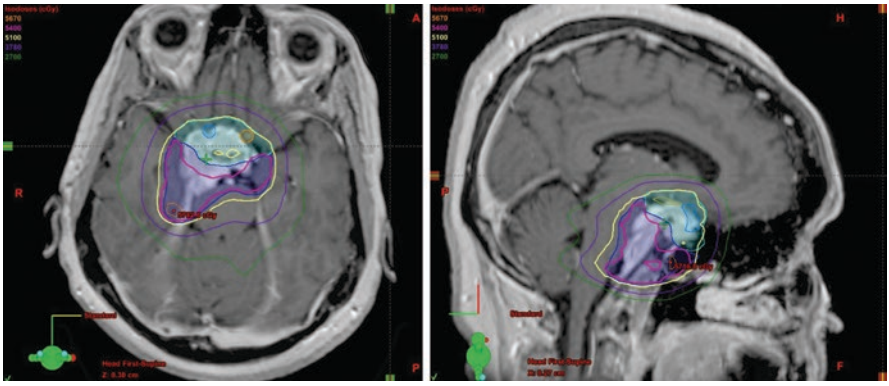

Fig. 3.1 A portion of the PTV (PTV cyan) near a critical OAR such as the optic nerves or chiasm may be defined separately from another portion of a PTV (PTV blue) and prescribed a lower dose in order to meet important constraints while still achieving full-target coverage

Table 3.5 Side effects

Acute	Fatigue, lethargy, scalp irritation/skin desquamation, hair loss (temporary or permanent), middle ear effusion, possible serous otitis with hearing loss, transient worsening of symptoms, headache, nausea/vomiting, peritumoral edema leading to new or worsening neurological symptoms (e.g., headache, nausea, vomiting, seizures, focal weakness)
Long-term	Neurocognitive decline (including mental slowing, cognitive deficits, reduced memory), cataracts, decreased vision and/or blindness, hypopituitarism, hearing loss
Uncommon or rare risks	Motor or sensory deficits, brain edema or necrosis possibly requiring prolonged steroid use or additional surgery, secondary primary malignancies

- Where applicable, doses to structures within the optic apparatus, to the pituitary gland, hippocampus, brain stem, and cochlea, should also be taken into careful account and minimized (Fig. 3.1).
- Depending on the total dose and tumor location, more conservative dose constraints may be considered.

3.4 Side Effects

Please see Table 3.5. Note that side effects are determined primarily by the location of the meningioma and radiotherapy beam arrangement/dose distribution, in addition to any additive morbidity from pre-treatment deficits and previous cranial surgeries. As such, side effects should be expected to vary broadly from case to case.

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Craniopharyngioma

4

Emily S. Lebow, Kylie H. Kang, Marc Bussière, and Helen A. Shih

Contents

4.1 General Principles of Simulation and Target Delineation

- Immobilization via individually molded thermoplastic mask or stereotactic frame.
- Define gross target volume (GTV) with thin-slice T1 pre- and post-gadolinium MRI and T2-weighted MRI, supplemented by treatment planning CT. The target volume should include tumor cyst. Solid portions are T1 hypointense or isointense, T2 hyperintense, and heterogeneously contrasting enhancing. Cysts are T1 and T2 hyperintense with a contrast-enhancing cyst wall [1]. Summary target description is in Table 4.1 and example in Fig. 4.1.

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Table 4.1 Suggested target volumes

Target volumes	Definition and description [3]
Gross target volume (GTV)	Postsurgical tumor bed and/or residual tumor, both solid and cystic components (including cyst wall) on postoperative T2/FLAIR MRI and T1 post-contrast images, **and any surfaces to which the tumor was previously attached to preoperatively**
Clinical target volume (CTV)	GTV + 2–5 mm. Cover additional at-risk regions that may harbor microscopic tumor extension
Planning target volume (PTV)	CTV + 1–5 mm. Account for setup error and/or patient movement during treatment. Depends upon immobilization device and image guidance used

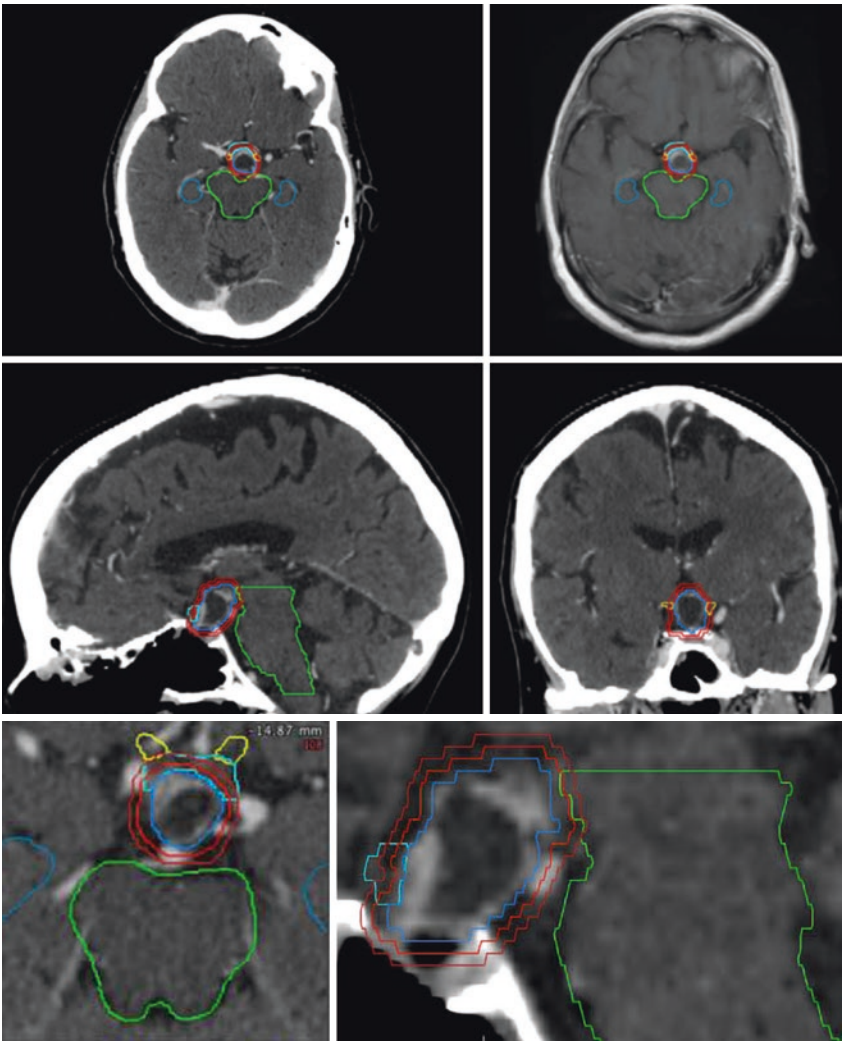

Fig. 4.1 Contours for an adult patient with an adamantinomatous-type suprasellar craniopharyngioma following subtotal transsphenoidal resection. GTV is blue, CTV is red, PTV is maroon, the brain stem is green, optic nerves and tracts are yellow, and optic chiasm is cyan

- In tumors with prominent cystic components, consider reimaging during treatment to assess for changes in cyst dimensions and need for cyst drainage or replanning [2].
- Stereotactic radiosurgery (SRS), fractionated stereotactic radiosurgery (FSRT), 3D conformal radiation therapy (3D-CRT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or proton beam therapy (PBT) can be considered.

4.2 Dose Prescriptions

- Fractionated radiation therapy: 50.4–55.8 Gy in 1.8–2.0 Gy fractions [2, 3]
- Stereotactic radiosurgery (SRS): 12–20 Gy for single fraction [4]
- Hypofractionated stereotactic radiotherapy: 13–25 Gy over 2–5 fractions [5]

4.3 Treatment Planning Techniques

- Consider 3D-CRT, IMRT, VMAT, PBT, or FSRT to limit dose to the optic chiasm. Example of a photon plan using VMAT is seen in Fig. 4.2a, b. PBT offers improved sparing of normal brain parenchyma and should be considered for all children and for many adults (Fig. 4.3a, b) [3]. Comparative DVHs of photon vs proton plans are shown in Fig. 4.2b.
- For external beam radiation therapy, treatment planning should cover at least 95% of the PTV volume by the prescribed dose while not exceeding OAR constraints [3]. Respecting normal tissue tolerances and delivering as low as reasonably possible radiation dose to indicated organs at risk will further decrease risk of tissue impairment (Table 4.2).
- Consider SRS for very small areas of residual or recurrent tumor located at least 3–5 mm from critical structures [6].

4.4 Clinical Considerations

- Craniopharyngiomas are highly curative. Attention to detail should be made to correctly identify regions at risk of harboring residual and often microscopic tumor to encompass in treatment.
- In addition, every effort to minimize collateral irradiation of radiation-sensitive normal tissues is essential to reducing long-term adverse effects of radiation therapy. Patients should be counseled on both potential acute and late side effects (Table 4.3).

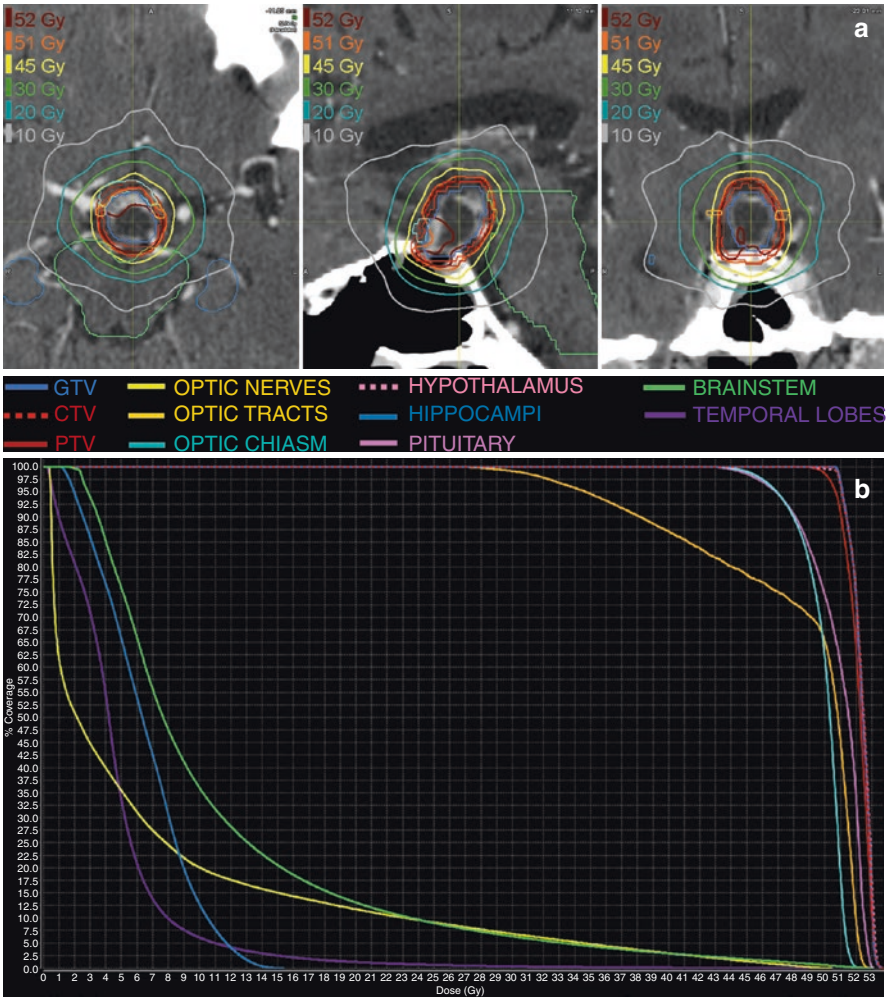

Fig. 4.2 (**a**) Sample photon plan using six VMAT arcs for the above patient with adamantinomatous-type suprasellar craniopharyngioma. GTV is blue, CTV is red, and PTV is maroon. Prescription dose of 51 Gy in 30 fractions. (**b**) Sample photon dose-volume histogram for above patient with adamantinomatous-type suprasellar craniopharyngioma

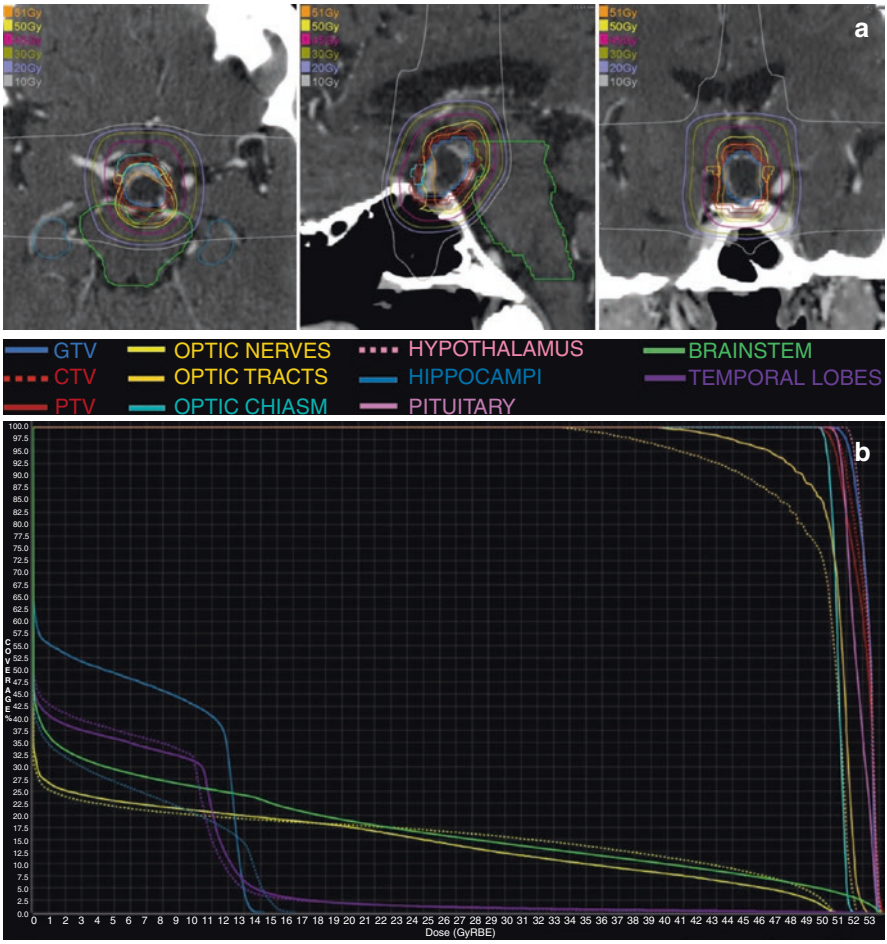

Fig. 4.3 (**a**) Sample proton plan for the above patient with adamantinomatous-type suprasellar craniopharyngioma. GTV is blue, CTV is red, and PTV is maroon. (**b**) Sample proton dose-volume histogram for above patient with adamantinomatous-type suprasellar craniopharyngioma

Table 4.2 Recommended normal tissue dose constraints for 50.4–55.8 Gy with 1.8–2.0 Gy/day fractionation schemes

Organs at risk	Suggested dose constraints [7]
Retina	45 Gy
Lens	10 Gy
Optic nerve/ chiasm	54 Gy
Cochlea	45 Gy, 35 Gy (pediatric)
Brain stem	54 Gy
Pituitary	50–55 Gy, 25 Gy (pediatric).[a] Optimize planning to minimize dose to the pituitary
Hippocampus	Optimize planning to minimize dose to hippocampi

[a]Beyond 20 Gy to the pituitary, screening for hypopituitarism with hormone replacement therapy as needed is strongly recommended

Table 4.3 Side effects

Acute	Dermatitis, alopecia, fatigue, headache, nausea
Long-term	Endocrine derangement secondary to hypothalamic-pituitary dysfunction, vasculopathy, visual decline, neurocognitive dysfunction [2, 8]
Uncommon or rare risks	Secondary malignancy [9]

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Paraganglioma

5

Daniel Mark and Jonathan Knisely

Contents

5.1 General Principles of Simulation and Target Delineation (Table 5.1 and Fig. 5.1)

Table 5.1 Suggested target volumes

Target volumes	Definition and description
GTV (EBRT and SRS)	Tumor extent on CT, MRI, or PET scan images
CTV (EBRT and SRS)	CTV = GTV + 0.0–0.7 cm GTV can be expanded further along adjacent vessels (i.e., internal jugular vein)
PTV	EBRT: CTV + 0.3–0.8 cm depending on the comfort of patient positioning, mask fit, and image guidance technique SRS: CTV + 0.1–0.2 cm

The original version of this chapter was revised. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-64508-3_28

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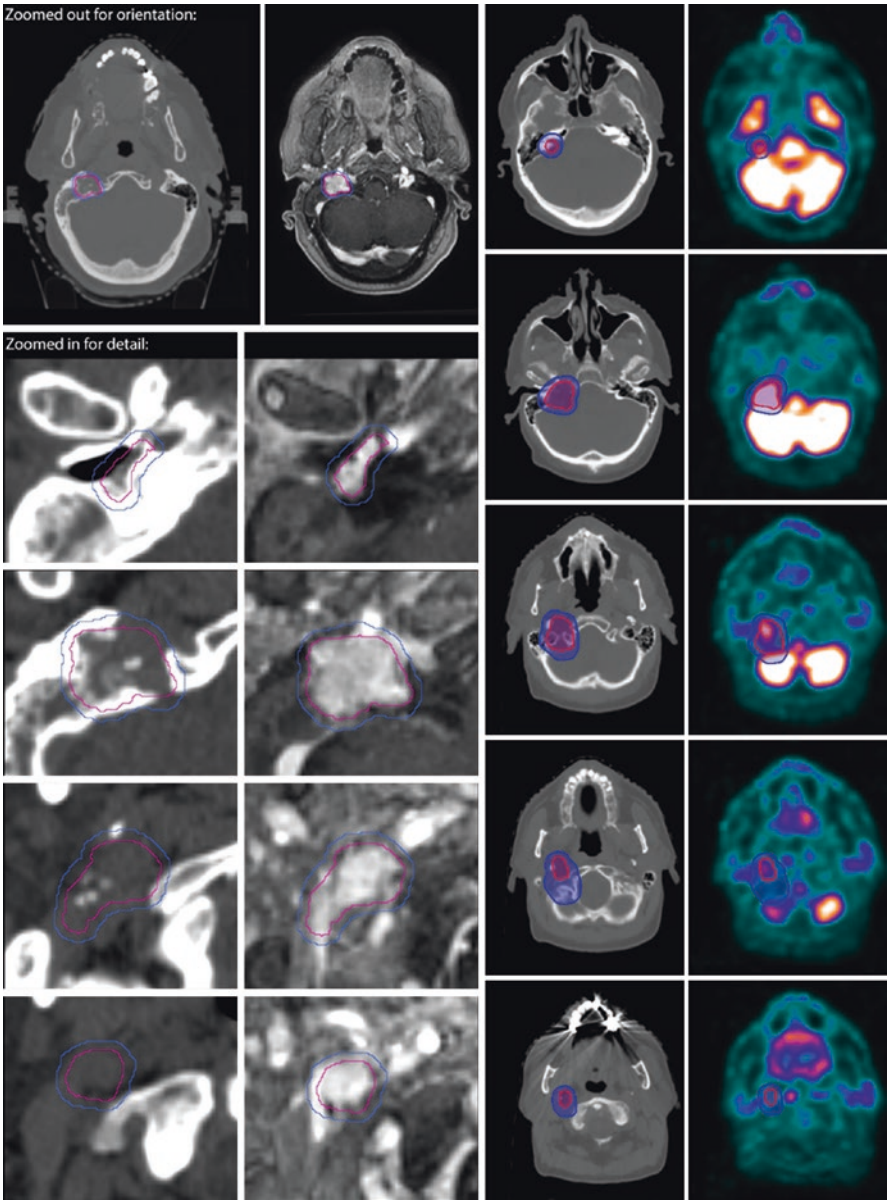

Fig. 5.1 Image fusion techniques used for developing right-sided paraganglioma contours for two patients. GTV and CTV, red; PTV, blue. Left: MRI T2W sequence (multi-fraction SRS with a 0.2 cm margin). Right: PET for guidance (IMRT with a 0.7 cm margin)

- Multifield complex, 3D conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic radiosurgery (SRS) are the standard techniques for definitive radiation therapy for paragangliomas.
- Considerations for type of radiotherapy may best include tumor size and location in relation to critical structures.
- Electrons should only be considered for tumors close to the skin surface that are modest in size.
- If external beam radiation therapy (EBRT) or frameless SRS is to be utilized, CT simulation should be performed with a thermoplast mask for immobilization; otherwise, SRS with a frame is suitable.
- There is long-term follow-up data for photon radiotherapy techniques, but this data is still relatively lacking for SRS. Only a few case reports of proton therapy have been published as yet.
- High-resolution CT with contrast, MRI, or PET with an appropriate tracer (those that bind somatostatin receptor subtypes 2 and 5) such as Gallium-68 DOTATOC or Gluc-Lys-TOCA are useful for fusion to properly identify gross tumor volume [1, 2].

5.2 Dose Prescriptions

- IMRT: 45–55 Gy in 1.8–2.0 Gy fractions, using 6–10 MV photons
- Fractionated SRS: 21 Gy in 3 fractions or 25 Gy in 5 fractions, using 6–10 MV photons
- Single-fraction SRS: 13–20 Gy, using MV photons

5.3 Treatment Planning Techniques (Figs. 5.2, 5.3, and 5.4, Tables 5.2, 5.3, and 5.4)

- Given the generally nonmalignant nature of the tumor, emphasis is placed on avoiding excess dose to adjacent critical structures such as the brain stem, cranial nerves, cochlea, lens, parotid, retina, and temporal lobe, but the tolerance of many of these structures can be respected while delivering adequate dose to achieve a high probability of tumor control. The presence of cranial nerves within the target volumes merits consideration of dose inhomogeneity possibly contributing to permanent loss of function when selecting treatment approaches.
- While 3DCRT is well-documented to be able to achieve tumor control, IMRT, SRS, or proton therapy may be used with the goal of sparing normal tissue morbidity if dose constraints cannot be met with simpler techniques.

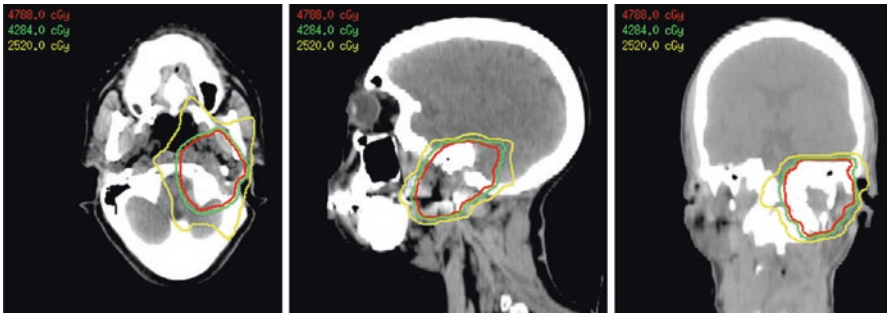

Fig. 5.2 Sample plan for IMRT using a coplanar four-field approach and 6 MV photons (prescription dose of 5040 cGy) for a left-sided paraganglioma. Red line is 95% isodose line, green is 85% isodose line, and yellow is 50% isodose line

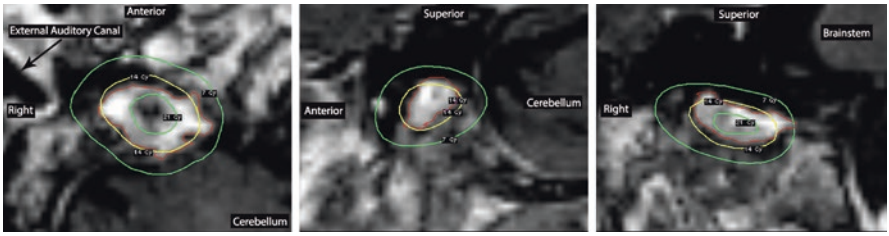

Fig. 5.3 Sample plan for Gamma Knife SRS (prescription dose of 14 Gy to the 50% isodose line) for a right-sided paraganglioma. Yellow line is 50% isodose line. 21 Gy isodose line is shown most central, and 7 Gy isodose line is shown peripherally

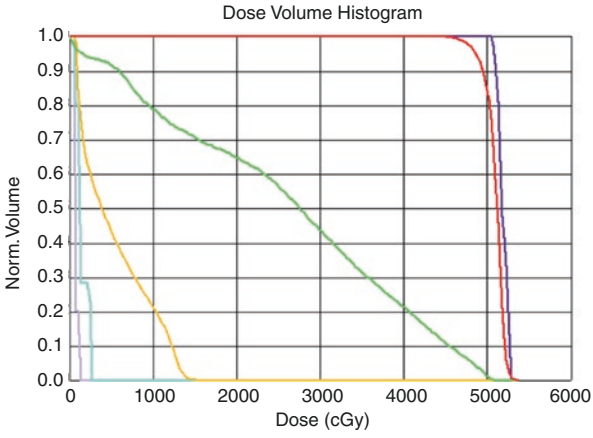

Fig. 5.4 Sample dose-volume histogram for an IMRT plan for a left-sided jugulotympanic paraganglioma (same patient as in Fig. 5.2 with prescription dose of 5040 cGy). PTV, red; ipsilateral cochlea, purple; brain stem, green; contralateral parotid, yellow; contralateral lens, blue; ipsilateral lens, lavender

Table 5.2 Recommended normal tissue constraints for IMRT 1.8–2 Gy fractionation schemes

Organs at risk	Suggested dose constraints
Brain stem	Dmax <54 Gy[a], D1–10cc ≤59 Gy[a], Dmax 55 Gy[b]
Cochlea, ipsilateral	Mean ≤45[a], D5% ≤55 Gy[c]
Lens	Dmax <5 Gy[b]
Optic nerve/chiasm	Dmax <55 Gy[a]
Parotid [sparing contralateral]	Mean dose <20 Gy[a]
Retina/eyes	Dmax <45 Gy[b]
Spinal cord	Dmax <50 Gy[a]
Temporal lobe/brain	Dmax <60 Gy[a]

[a]QUANTEC [3]
[b]RTOG 0539
[c]RTOG 0615

Table 5.3 Recommended normal tissue constraints for single-fraction SRS

Object at risk	Suggested dose constraints
Brain stem	Max <12.5 Gy[a]
Cochlea, ipsilateral	Max ≤14 Gy[a]
Cranial nerves (including optic nerve)	Max <12 Gy[b]
Optic nerve/chiasm	Dmax <12 Gy[a]
Spinal cord	Dmax <13 Gy[a]
Temporal lobe/brain	V12cc <5–10 cc[a]

[a]QUANTEC [3]
[b][4]

Table 5.4 Side effects for OTV and follow-up with suggested management

Acute	Focal alopecia, dermatitis, dizziness, fatigue, mucositis, xerostomia
Long-term	Eustachian tube dysfunction, facial numbness, hearing loss, skin fibrosis, xerostomia
Mitigating treatments	Skin moisturizers (i.e., Aquaphor®, aloe vera, Eucerin®) for dermatitis, lidocaine-based mouthwash (i.e., "magic mouthwash") for mucositis, calcium phosphate rinse for xerostomia (i.e., NeutraSal®)

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Pituitary Adenoma

6

Cheng-chia Lee and Jason P. Sheehan

Contents

6.1 General Principles of Simulation and Target Delineation (Table 6.1, Fig. 6.1)

- Gamma Knife (GK) radiosurgery, Cyberknife, LINAC-based radiosurgery, 3D conformal radiotherapy (CRT), stereotactic radiotherapy (SRT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or proton beam therapy can be used for the treatment of pituitary adenoma. A stereotactic, precise approach is preferred because of the benign nature and clear tumor margin of most pituitary adenomas.
- The Leksell frame is used for head immobilization in a traditional, single-fraction Gamma Knife radiosurgery. However, the other radiosurgery and radiation therapy usually utilize CT simulation with a thermoplast mask for immobilization. In the latest model of the Gamma Knife (Icon®), CT simulation and a thermoplast mask can be used for immobilization, too.
- Obtain volumetric thin slice MRI with T2 and T1 pre- and post-gadolinium (sometimes thin section dynamic contrast-enhanced imaging or fat suppres-

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Table 6.1 Suggested target volumes

Target volumes	Definition and description
GTV	Tumor extent on postoperative T1 pre- and post-gadolinium images. 3-month postoperative MRIs are helpful for determining residual/recurrent tumors. Sometimes, thin section dynamic contrast-enhanced imaging for microadenoma
CTV (clinical target volume)	Generally equal to GTV for most pituitary adenoma cases but to account for dural and/or cavernous sinus invasion, a margin may be added
PTV (planned target volume)	Generally equal to CTV for single-fraction SRS. For hypofractionated SRS or fully fractionated RT, depending on the treatment and immobilization device used, a 1–2 mm margin may be added to account for system uncertainties. For conventionally fractionated RT, a 3–5 mm margin is expanded from CTV to generate a PTV

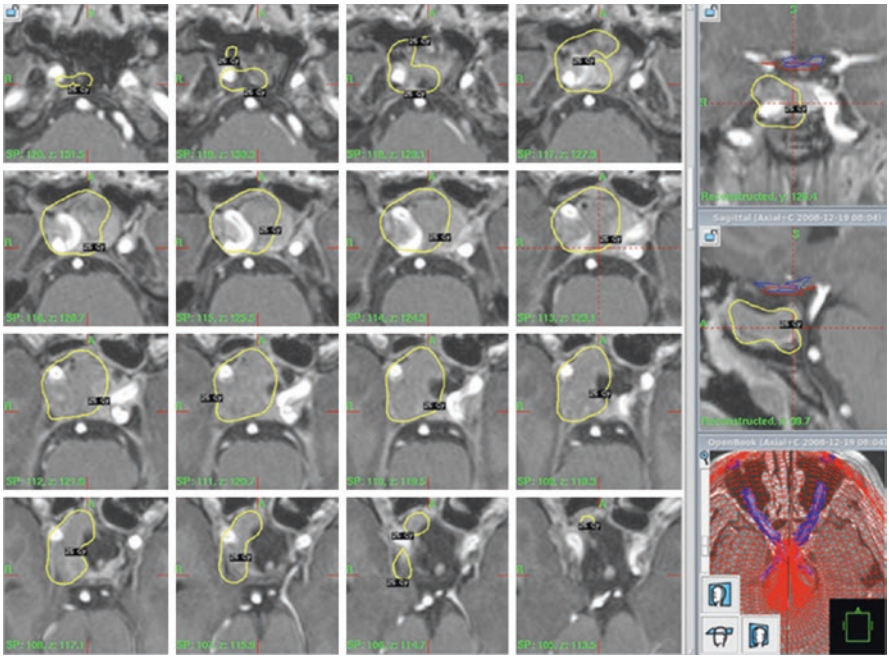

Fig. 6.1 Contours for a patient with a nonfunctioning adenoma (yellow). Usually, we simultaneously delineate the optic nerve, chiasm, and tracts (red and blue)

sion imaging for postoperative adenomas) for target delineation. Pre-contrast sequences included coronal and sagittal T1-weighted (1 mm sections), fast spin echo (FSE) axial and coronal T2-weighted (1 mm sections) images. The post-contrast sequences included coronal T1-weighted (1 mm sections), sagittal FSE T1-weighted (1 mm sections), and coronal spoiled gradient echo (SPGR) T1-weighted images. The use of CT with and without contrast for

target delineation is of value for dose correction calculations and CT simulation of some systems. CT can also be valuable for patients for whom MRI is contraindicated.

- In cases of partial removed or recurrent adenomas, the remaining tumor border and the normal pituitary tissue should be clearly identified. Dura edge along the cavernous sinus may need to be included in the gross target volume (GTV) if the surgeon found dural invasion intraoperatively. The radiation delivery to the dura edge is typically necessary for functioning adenomas such as acromegaly and Cushing's disease due to the frequent nature of dural invasion.
- When possible, care should be taken to avoid high doses or "hot spots" to critical neurovascular structures such as the optic apparatus around the tumor, cranial nerves, or carotid artery within the cavernous sinus region. Ideally, the optic apparatus needs to be delineated clearly, in order to calculate the radiation exposure precisely and mitigate against radiation-induced optic neuropathy. The cavernous portion of the internal carotid artery (ICA) can be included in the GTV if the adenoma encases the ICA and/or invades the dura of the cavernous sinus.

6.2 Dose Prescriptions

- In general, single-session radiosurgical margin doses vary from 12 to 18 Gy for nonfunctioning adenomas and from 15 to 30 Gy for functioning adenomas. Because the systemic effects of functioning adenomas can be so devastating, it seems intuitive to deliver a reasonably high dose ($\geq$20 Gy to the margin) to allow for more rapid hormonal normalization and effective control of tumor growth.
- However, it is not known with precise certainty to what degree a higher margin dose (e.g., 20 Gy versus 30 Gy) will result in delayed hypopituitarism. In cases of functioning adenomas with radiologically identifiable targets in the cavernous sinus, radiosurgical plans can be devised with higher-range margin doses while shielding much of the normal stalk, gland, and optic apparatus. Nonfunctioning pituitary adenomas appear to require a lower radiosurgery margin dose than functioning adenomas. The lowest effective dose for a nonfunctioning tumor is not unknown, but many centers deliver 12–15 Gy to the margin of nonfunctioning adenomas when delivered in a single fraction.
- Hypofractionated and fractionated dose regimens vary based upon the target volume, location, tumor type (functioning versus nonfunctioning), prior radiation delivered, and proximity to critical structures. Commonly used regimens include 21 Gy in 3 fractions, 20 Gy in 4 fractions, and 25 Gy in 5 fractions. For conventionally fractionated 3D conformal radiotherapy, IMRT/VMAT, proton, and carbon ion therapy, the typical prescribed dose is 45–50.4 Gy in 1.8 Gy fractions for nonfunctioning and 50.4–54 Gy in 1.8 Gy fractions for functioning pituitary adenomas.

6.3 Treatment Planning Techniques

- Gamma Knife radiosurgery (Fig. 6.2), Cyberknife, LINAC-based radiosurgery, 3D CRT, IMRT, VMAT, proton (Fig. 6.3), or carbon ion therapy have all been used for treatment of pituitary adenomas over the past few decades. The techniques and devices have evolved tremendously over the past few decades.
- Contemporarily, radiosurgery has had increasing popularity for pituitary adenomas as they are discrete, small volume, late responding tissue, and close to critical structures.
- Radiosurgery (e.g., Gamma Knife Icon or Extend, Cyberknife, LINAC-based radiosurgery) can be hypofractionated in two to five sessions to deliver a more optimal dose plan tailored to the constraints of some particular cases.
- The current treatment planning for a pituitary adenoma is performed with computer-based dose planning software (e.g., Gamma Plan, Elekta Instruments, Inc.). First, the target lesion and the surrounding structures are often contoured. Second, a dose plan can be rendered to deliver an ideal dose to the target and a safe dose to adjacent critical structures. Third, conformality, dose uniformity, and gradient index should be assessed and adjustments made so as to optimize the dose plan.

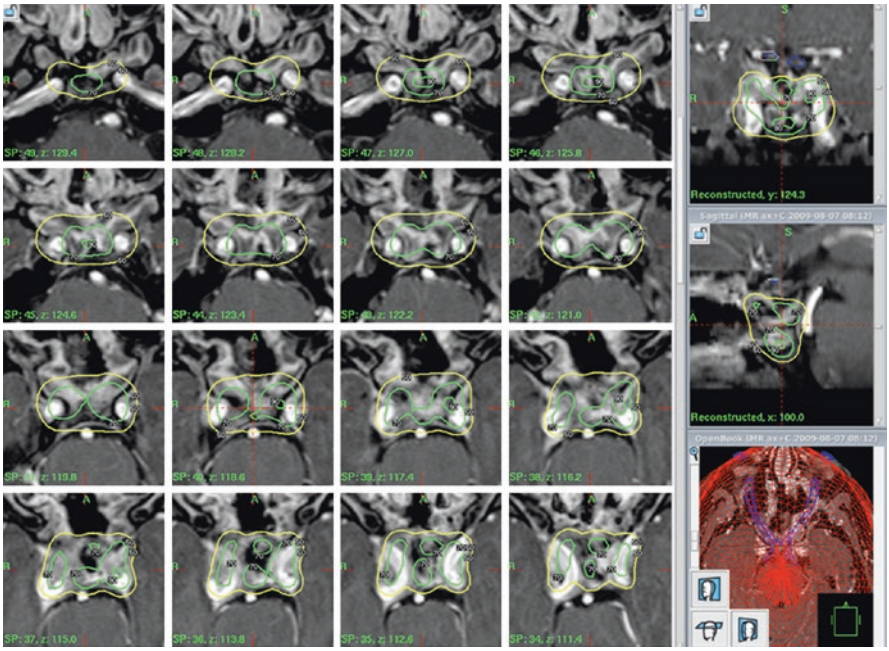

Fig. 6.2 Demonstrate an example of a Gamma Knife plan for a patient with nonfunctioning adenoma. The upper snapshots are showed by percentage of isodose line (%): green line is 95% and 70% isodose line, and yellow is 50% isodose line

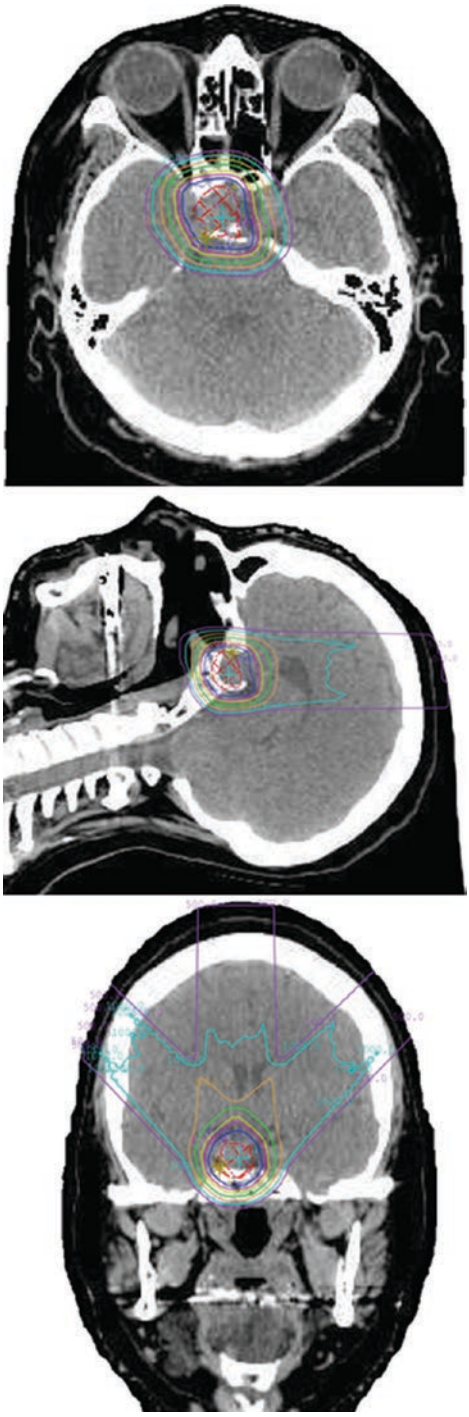

Fig. 6.3 A case example of a proton plan for a patient with a nonfunctioning pituitary adenoma. The prescribed dose is 45 Gy in 25 fractions (isodose line). A three-beam arrangement with uniform scanning is used

- Visual deterioration following SRS is rare and usually can be avoided if the dose to the optic apparatus is restricted to ≦8 Gy in a single fraction, although some groups reported that the optic apparatus was exposed to 10–12 Gy in a single fraction without complications.
- Traditionally, a distance of 3 mm or more between the rostral extent of the adenoma and the optic apparatus is desirable. Although the absolute distance between the optic apparatus is not the limiting factor, it defines how steeply the radiation gradient must be constructed so that a tolerable dose is delivered to the optic apparatus while still delivering an effective dose to the adenoma. If an acceptable gradient cannot be constructed, then alternative treatment should be considered. Modern radiosurgical devices may allow a distance of as little as 1–2 mm.
- Ultimately, the tolerable absolute dose permitted to critical structures likely varies from patient to patient, and it is affected by factors such as previous damage to the optic apparatus by pituitary adenoma compression, ischemic changes, type and timing of previous interventions (e.g., fractionated radiation therapy and surgery), the patient's age, and the presence or absence of other comorbidities (e.g., diabetes or hypertension). See Table 6.2.
- Compared to the optic nerve, the majority of cranial nerves in the cavernous sinus appear to be more resistant to radiation effects, but reports of cranial neuropathy, particularly after repeat radiosurgery, are well documented. Although the tolerable limit to the cavernous sinus nerve is not precisely known, reports have detailed effective single session radiosurgical doses between 19 and 30 Gy

Table 6.2 Recommended normal tissue constraints

Organ at risk	Suggested dose constraints
Optic nerves and chiasm	<8 Gy–12 Gy to Dmax (maximal dose) for single-fraction SRS 23.3 Gy (range 18.3–25.1 Gy) to Dmax for 5-fraction HSRT 50 Gy for optic nerves and 54 Gy for optic chiasm for conventionally fractionated RT (based on RTOG 0539 for intermediate risk meningiomas)
Hippocampi and hypothalamus	Utilize beam angles and planning techniques (e.g., GK, Cyberknife, LINAC-based radiosurgery, IMRT, carbon or proton therapy) to minimize dose to the hippocampi and hypothalamus For conventionally fractionated RT, based on RTOG 0933, <100% receives 9 Gy and Dmax ≤16 Gy for hippocampi
Normal pituitary tissue	Utilize beam angles and planning techniques (e.g., GK, Cyberknife, LINAC-based radiosurgery, IMRT, carbon or proton therapy) to minimize dose to the normal pituitary gland and stalk
Brain stem	As per QUANTEC, Dmax is 12.5 Gy for SRS 25 Gy in 5 fractions for HSRT 55 Gy for conventionally fractionated RT (based on RTOG 0539 for intermediate risk meningiomas)
Eyes	45 Gy to Dmax for retinae for conventionally fractionated RT (based on RTOG 0539 for intermediate risk meningiomas)
Lenses	5 Gy Dmax (0.03 cc) for conventional radiotherapy (based on constraints used in RTOG 0539 for intermediate risk meningiomas)

to this region with a low risk of appreciable side effects. Injury to the cavernous segment of the carotid artery is rare after SRS.

- Using standard fractionation schemes (>5 fractions), 3D CRT, IMRT, VMAT, and carbon or proton therapy may be used for some cases particularly those with larger tumor volumes, less distinct tumor margins, or critical structures that are too close for single or hypofractionated approaches.
- For 3DCRT, multiple non-opposing and noncoplanar beams are typically used. Efforts are made to avoid aiming any beam through the eyes.
- For IMRT or VMAT, inverse planning is used as well as treatment planning objectives listing goals of PTV coverage and constraints of organs at risk (OARs) including the eyes, lenses, brain stem, hippocampi, optic nerves, and optic apparatus.
- For proton therapy, generally three beams are utilized with angles chosen to avoid hippocampi if possible.

6.4 Side Effects

Complications resulting from stereotactic radiosurgery vary depending on tumor size, the extension of tumor, and radiation doses.

Acute (within days)	Some acute radiation injuries such as skin changes and hair loss were rarely present in current SRS era
Early delayed (within weeks to a few years)	Hypopituitarism and hypothalamic dysfunction, radiation necrosis, new onset visual deterioration, or other cranial nerve dysfunctions
Late delayed toxicity (within months to many years out)	Hypopituitarism. Secondary tumor and ICA stenosis or occlusions are rare

Complications associated with conventionally fractionated radiotherapy.

Acute toxicities	Alopecia, skin erythema, fatigue, and headaches
Late toxicities	Hypopituitarism (thyroid and cortisol most common), hypothalamic dysfunction, optic neuropathy, and other cranial neuropathies of the cavernous sinus, radiation necrosis, neurocognitive effects, vascular complications, and secondary malignancies

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Vestibular Schwannoma

7

Colin E. Champ, Haisong Liu, and Wenyin Shi

Contents

7.1 Information on Simulation

- Treatment decisions for vestibular schwannomas (VS) vary based on institutional preferences in regard to stereotactic radiosurgery (SRS) and fractionated stereotactic radiation therapy (FSRT). A thorough discussion evaluating tumor growth, hearing loss, symptoms, cranial nerve function, tumor size, performance status, and patient preference should guide treatment decisions.
- Depending on the method of treatment delivery, immobilization should be achieved with either a thermoplastic facemask or a headframe, such as an MRI compatible Leksell stereotactic frame when using Gamma Knife. For CyberKnife, a thermoplastic mask is used.
- In addition to thorough physical examination, adequate imaging studies should be obtained for diagnosis, staging, and planning. CT simulation without contrast

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should be performed to help guide GTV (gross tumor volume) and normal structure delineation. Unless contraindicated, all patients should undergo volumetric MRI of the base of the skull with gadolinium with 1–1.5 mm slice thickness. VS are best visualized on T1-weighted post-contrast MRI sequence, which should be merged with the planning CT scan. For patients with intact hearing, audiogram should be performed prior to treatment.

7.2 Recommendations for Target Delineation

- Target volumes should be delineated on every slice on MRI. The ipsilateral cochlea should be contoured for patients with functional hearing for minimizing dose during planning. For SRS, usually no planning target volume (PTV) margin is added when using a frame-based system. A minimum margin of 1–2 mm may be added when using a mask-based system. For patients treated with FSRT, a minimum PTV margin of 1–2 mm should be added (Table 7.1, Figs. 7.1 and 7.2).

Table 7.1 Suggested target volumes including GTV, CTV, and PTV

Target volumes	Definition and description
GTV	Enhancing lesion on T1 post-contrast MRI
CTV	No CTV
PTV	Frame-based system: PTV = GTV Mask-based system: PTV = GTV + 1–2 mm

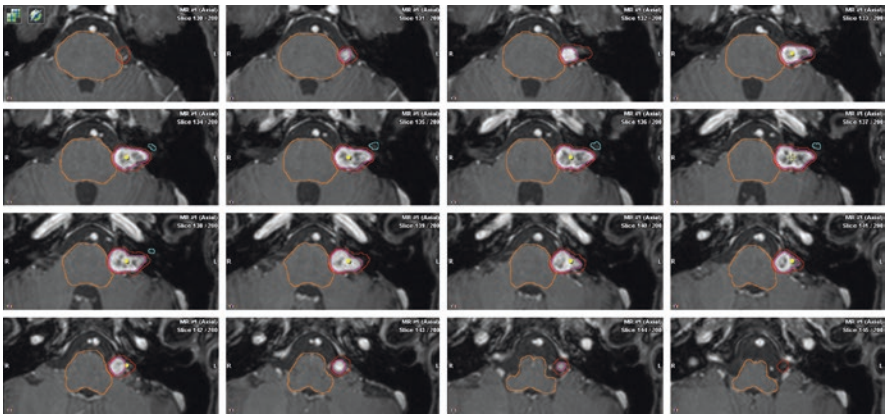

Fig. 7.1 Vestibular schwannoma is best visualized on T1 post-contrast MRI. For mask-based treatment, a 1–2 mm PTV should be added. For a patient with a small vestibular schwannoma, particularly in patient with non-serviceable hearing, SRS is the treatment of choice

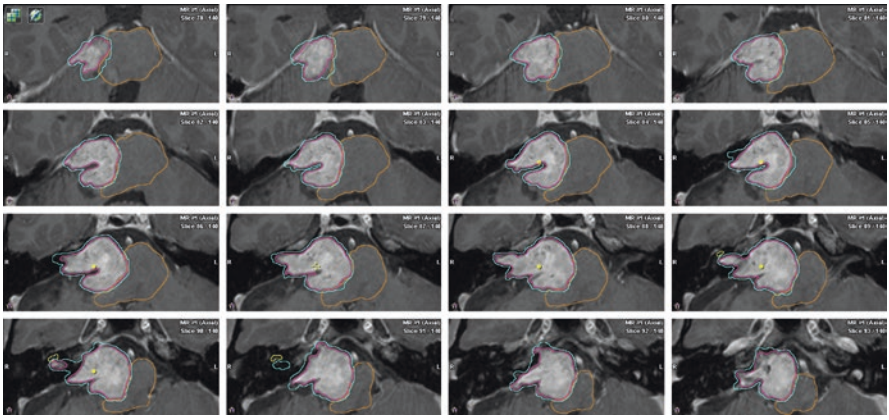

Fig. 7.2 For patients with large vestibular schwannomas, particularly those with significant brain stem compression, FSRT should be used to minimize toxicity. A 1–2 mm PTV margin should be added. The below case example shows a patient with large residual tumor after surgery, who received FSRT treatment to 46.8 Gy in 1.8 Gy fractions

7.3 Dose Prescriptions

- SRS is often used for small VS without brain stem compression. Common prescription dose is 12–13 Gy in single fraction. It is generally prescribed to the 50% isodose line when delivered via Gamma Knife or 70–80% isodose when delivered via a LINAC or CyberKnife (Table 7.2).
- Patients with functional hearing or borderline hearing (Gardner-Robertson value $\leq$2) are good candidates for FSRT at many institutions, in an effort to maximize hearing preservation (Fig. 7.3). The common prescription dose is 46.8–50.4 Gy in 1.8 Gy fractions. Patients with large tumors, particularly those with brain stem compression, are often treated with FSRT (Table 7.2, Fig. 7.2).

7.4 Treatment Planning Techniques

- For FSRT, highly conformal radiation techniques should be used to achieve optimal tumor coverage, with minimum dose to nearby critical structures, including the brain stem and cochlea. 3D conformal radiation, intensity-modulated radiation therapy (IMRT), or volumetric modulated arc therapy (VMAT) with daily image-guided radiation therapy (IGRT) should be used.
- For SRS, different planning techniques may be used based on the treatment platform. Gamma Knife treatment utilizes sphere packing techniques. LINAC-based treatment often uses dynamic arcs, IMRT, or VMAT (Fig. 7.4). The CyberKnife system achieves coverage of the PTV via numerous nodes generated by its dedicated planning system.
- See Tables 7.3 and 7.4 for normal tissue constraints.

Table 7.2 Suggested dose

SRS	12–13 Gy in 1 fraction
FSRT	46.8–50.4 Gy in 1.8 Gy fractions

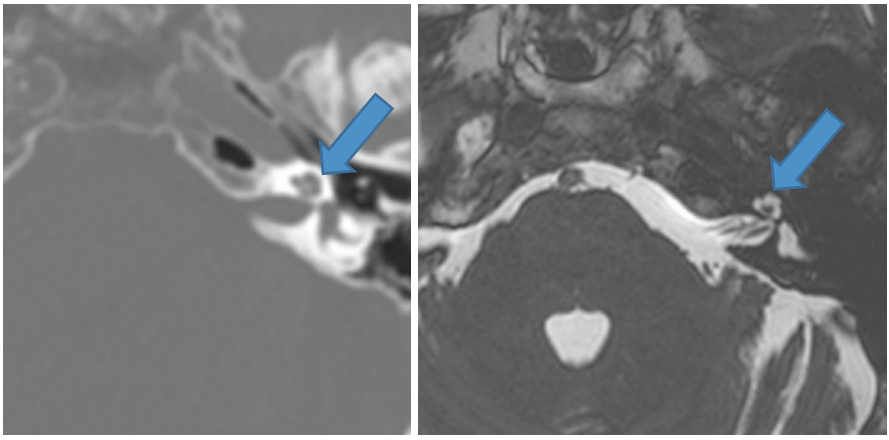

Fig. 7.3 For patients with functional hearing, the ipsilateral cochlea should be contoured, and its radiation dose should be minimized. The cochlea is best visualized on non-contrast CT in the bone window or T2 MRI

Table 7.3 Normal tissue constraints for FSRT

Objects at risk	Suggested dose constraints [1]
Brain stem	Max dose <54 Gy
Cochlea	Mean dose <40 Gy
Spinal cord	Max dose <45 Gy

Table 7.4 Normal tissue constraints for SRS

Objects at risk	Suggested dose constraints [2]
Brain stem	Max dose <12.5 Gy
Cochlea	Mean dose <4.2 Gy (central cochlea)
Spinal cord	Max dose <14 Gy <0.35 cc <10 Gy

7.5 Side Effects

- The acute side effects from SRS are usually mild and transient, including fatigue, headache, nausea, dizziness, and tinnitus. The main late complications are facial weakness, serviceable hearing loss, facial numbness, and brain stem necrosis. Due to the low dose used, the risk of facial nerve/trigeminal nerve injury and brain stem necrosis is in general less than 5–7%. Expansion of a cystic lesion after SRS may lead to compression of the fourth ventricle causing hydrocephalus.

- FSRT is well tolerated; common side effects are fatigue, nausea, dizziness, headache, facial numbness, tinnitus, and hearing loss. The symptoms are usually mild and resolve quickly after finishing radiation treatment. The risk of cranial nerve injury or brain stem injury is negligible.

7.6 Follow-Up

- Surveillance with serial MRI scans every 6–12 months is recommended for follow-up.
- Follow-up should also include close clinical observation to detect early symptoms such as hearing impairment, facial weakness, or facial numbness. Malignant transformation of the treated vestibular schwannoma can occur in rare circumstances many years after treatment and this underscores the importance of long term radiographic follow-up of patients treated with SRS or FSRT.

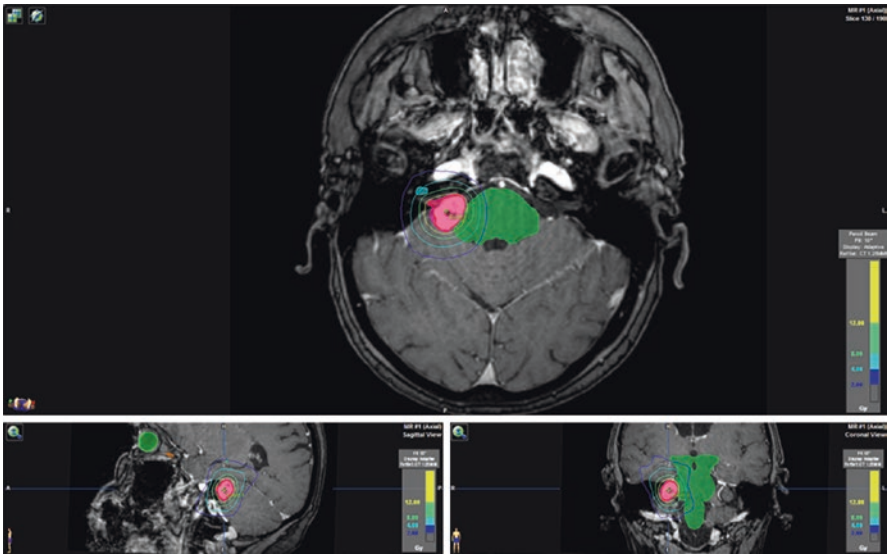

Fig. 7.4 Radiation treatment plan and DVH for SRS for vestibular schwannoma

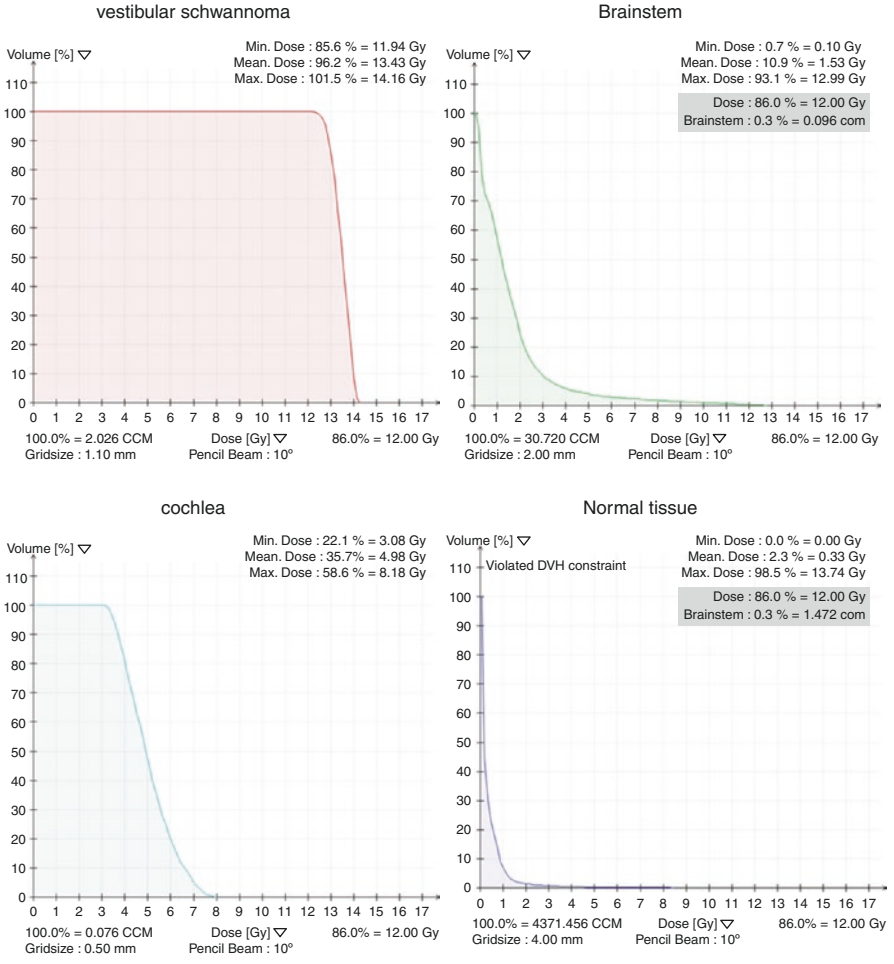

Fig. 7.4 (continued)

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Hemangiopericytoma

8

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Contents

8.1 General Principles of Simulation and Target Delineation

- Adjuvant radiotherapy should be considered for both gross and subtotal resection.
- CT simulation in the supine position with a thermoplastic mask for immobilization and thin slice (1–2 mm) acquisition.
- Obtain volumetric thin slice (1–2 mm) T1 post-gadolinium axial MRI sequences and T2/FLAIR MRI sequences.
- To aid in target delineation, fusion of both preoperative and postoperative MRI, T1 gadolinium +/− T2/FLAIR should be considered with the CT simulation scan (Fig. 8.1).
- Table 8.1 summarizes the suggested target volumes. Figure 8.2 shows an example.

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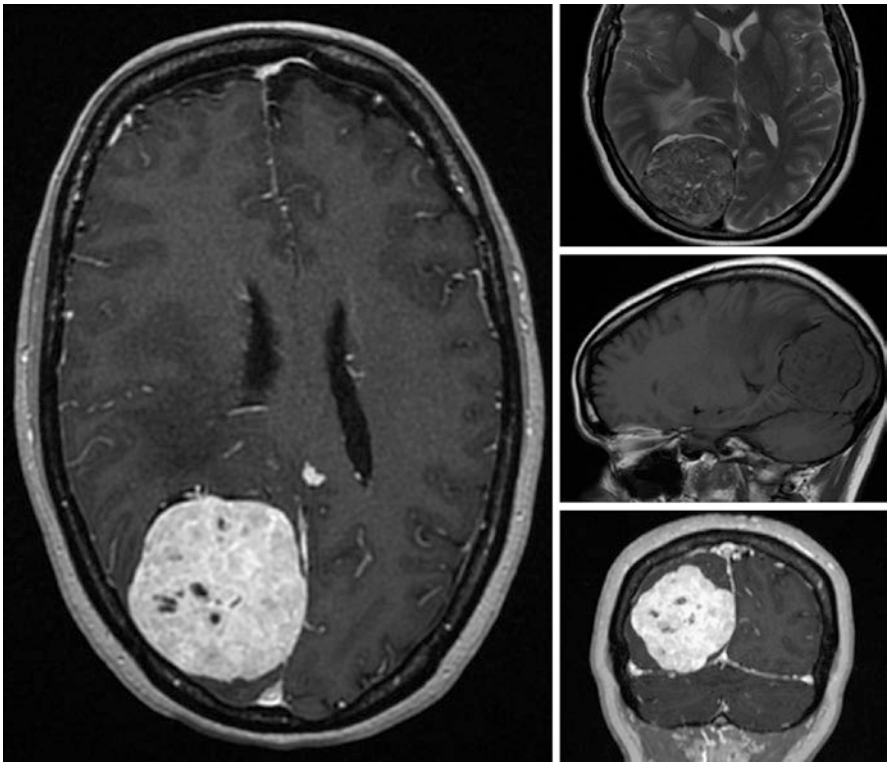


Fig. 8.1 Preoperative MRI for a 57-year-old patient who presented with intermittent headaches and left-sided homonymous hemianopia. Imaging revealed a right parietal occipital extra-axial mass inseparable from the posterior falx measuring 6.3 cm. Left: T1 MRI with gadolinium. Right: Top, axial T2 propeller; middle, sagittal T1 FLAIR; bottom, coronal T1 with gadolinium

Table 8.1 Suggested target volumes

Target volumes	Definition and description
GTV	Gross residual enhancing disease on T1 post-gadolinium images.
CTV	Grade 1: CTV = GTV + 0–0.5 cm. Grades 2 to 3: CTV = GTV + 0.5–2.0 cm and note the CTV should also include the surgical cavity, respecting anatomic barriers to spread including the bone, dura, falx cerebri, and tentorium. The preoperative MRI should be used to guide the extent of surgical cavity delineation along the dura. Some also apply a margin of 0.5–2.0 cm beyond the surgical cavity and more so for grade 3
PTV	PTV = CTV + 0.3–0.5 cm depending on patient positioning, mask fit, image guidance technique.

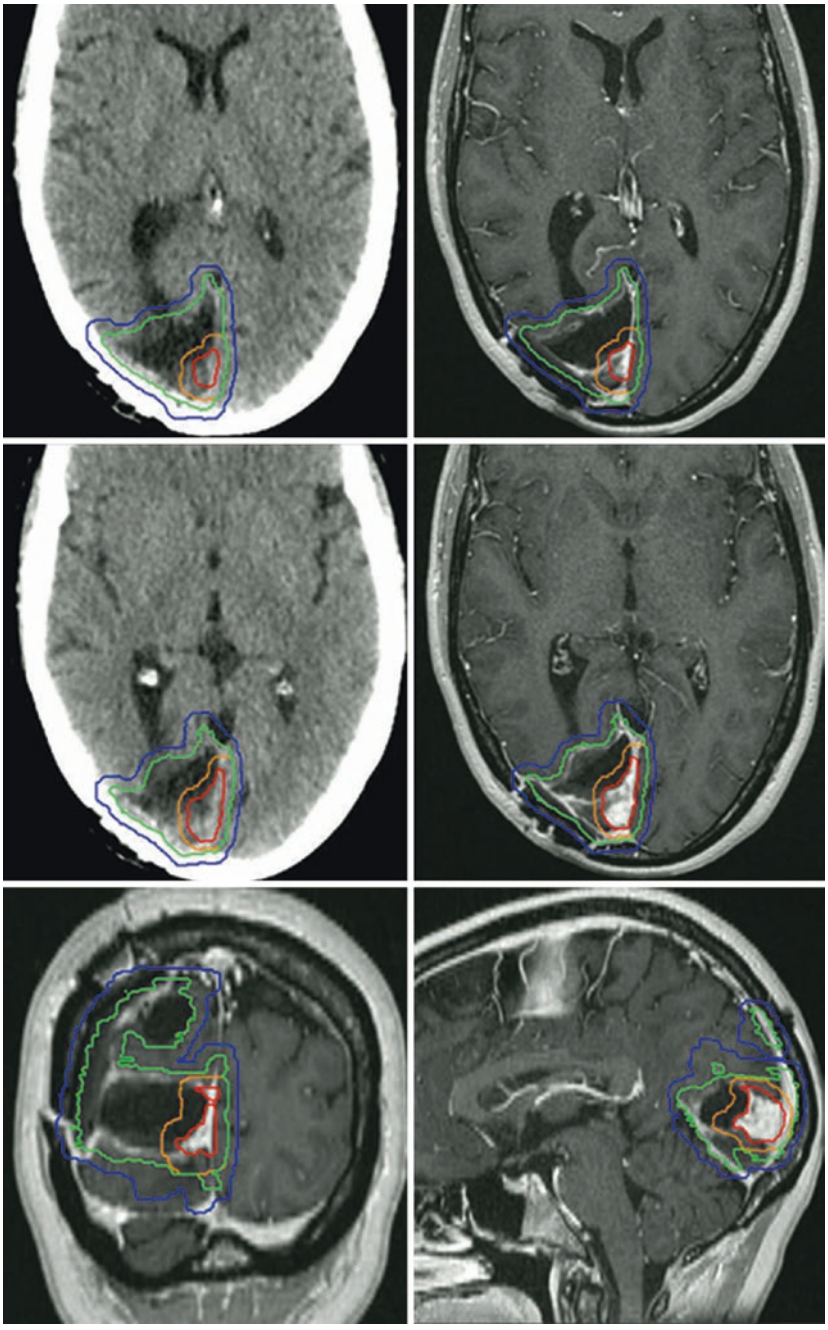


Fig. 8.2 Contours and imaging *after* the patient underwent subtotal resection for WHO grade II hemangiopericytoma. Postoperative MRI revealed focal nodularity suspicious for residual tumor. Postoperative imaging is shown on axial CT (upper and middle left) and T1 MRI with gadolinium on axial (upper and middle right), coronal (bottom left), and sagittal (bottom right) slices. GTV is shown in red, CTV in green, PTV1 in orange, and PTV2 in blue. 70 Gy was prescribed to PTV1 and 64 Gy was prescribed to PTV2 in 35 fractions

8.2 Dose Prescription

- Grade 1: 50–54 Gy in 25–30 daily fractions.
- Grades 2 to 3: 60 Gy in 30 daily fractions or consider a 35-fraction simultaneous integrated boost protocol—residual GTV plus high-dose PTV to 70 Gy in 35 fractions (PTV1) with a 64 Gy volume encompassing the residual GTV, CTV, and low-dose PTV (PTV2). The latter is our in-house practice and data are not yet reported to validate this approach.

8.3 Treatment Planning Techniques (Figs. 8.3 and 8.4)

– 3D-CRT, IMRT, VMAT, or proton therapy may be used.
– Treatment planning objective: Cover 95% of the PTV by 95% of the prescribed dose while respecting OAR constraints.

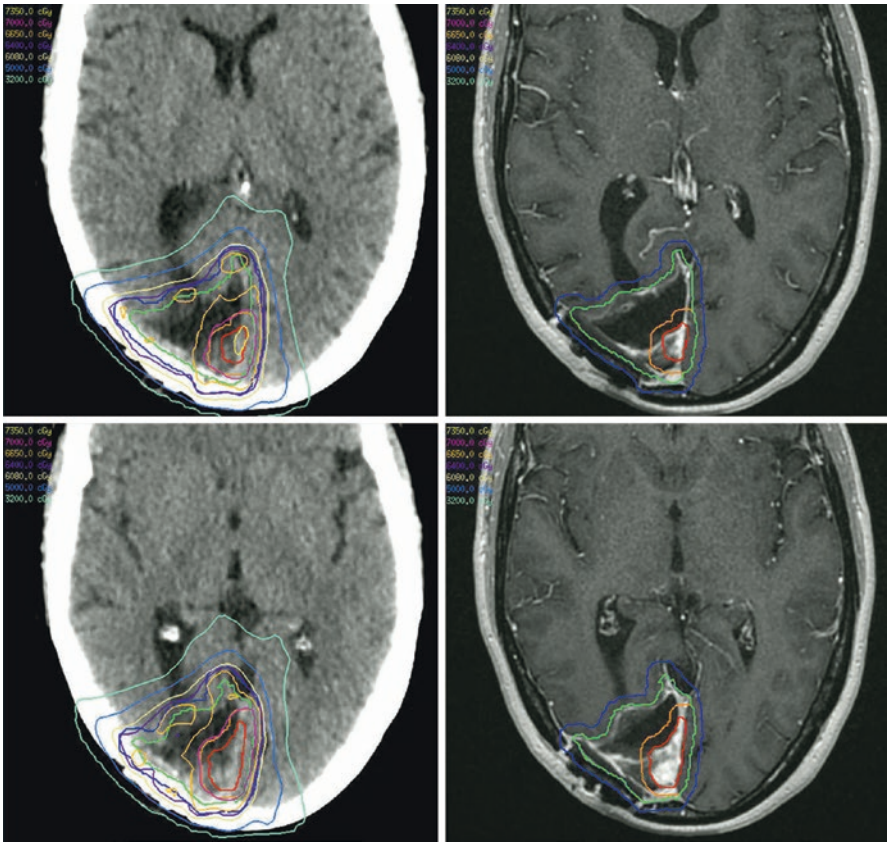
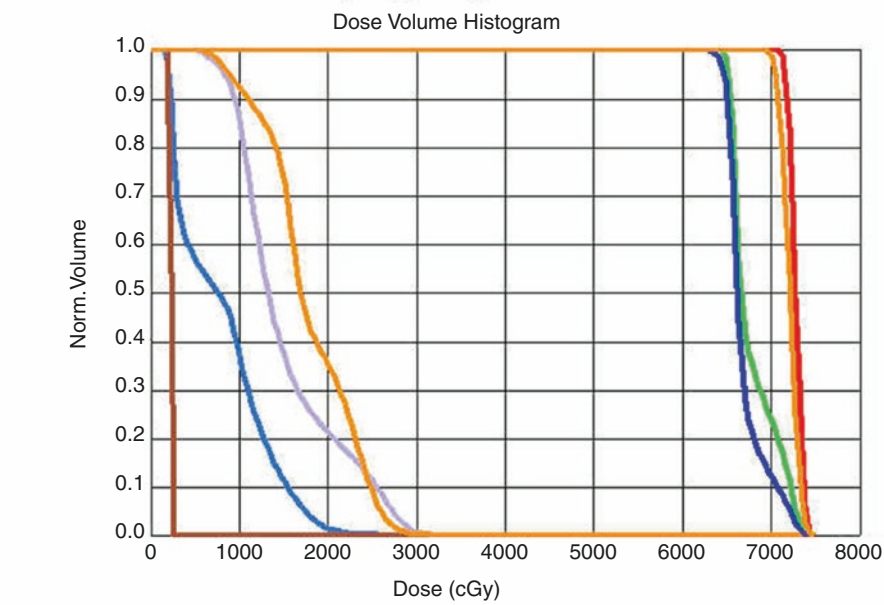


Fig. 8.3 Treatment plan for the case presented in Fig. 8.2. Yellow is the 73.5 Gy isodose line (105% of 70 Gy), pink is the 70 Gy isodose line, orange is the 66.5 Gy isodose line (95% of 70 Gy), purple is the 64 Gy isodose line, light orange is the 60.8 Gy isodose line (95% of 64 Gy), and light blue is the 32 Gy isodose line (50% of 64 Gy)



ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	BRAINSTEM	brai	170.1	2590.4	788.6	528.4
	COCHLEA_R	brai	211.3	254.1	228.5	10.2
	CTV64	brai	6362.7	7492.9	6777.4	257.9
	GTV70	brai	7094.2	7465.8	7273.4	72.0
	HIPPOCAMPUS_L	brai	479.8	3181.3	1516.9	591.8
	HIPPOCAMPUS_R	brai	531.9	3136.9	1782.6	513.5
	PTV64	brai	5961.6	7492.9	6687.2	218.3
	PTV70	brai	6852.1	7492.9	7205.6	95.2

Fig. 8.4 Dose-volume histogram (DVH) for the case described. 97% of PTV2 is covered by 64 Gy and 96% of PTV1 is covered by 70 Gy. 100% of PTV2 is covered by 95% of 64 Gy (60.8 Gy), and 100% of PTV1 is covered by 95% of 70 Gy (66.5 Gy)

Table 8.2 Recommended dose constraints for critical organs at risk for 1.8–2 Gy/day fractionation schemes

Organ at risk	Suggested dose constraints
Optic nerves and chiasm	Dmax <54 Gy
Brain stem	Dmax <54–60 Gy
Cochlea	Mean ≤30–45 Gy
Eyes	Dmax <45 Gy
Lenses	Dmax <10 Gy
Hippocampi	Mean dose <20 Gy if achievable
Pituitary gland	Dmax 30–45 Gy and mean <30 Gy if achievable

Note: Dmax refers to the maximum point dose

Table 8.3 Side effects

Acute	Fatigue, dermatitis, alopecia, headache, cerebral edema causing nausea/vomiting and headaches
Subacute	Somnolence syndrome, cerebral edema
Long-term	Hypopituitarism, hearing loss, cataracts, leukoencephalopathy, neurocognitive deficits, radiation necrosis, and second malignancies

– Daily IGRT with cone-beam CT matching to the bone is recommended.
– Tables 8.2 and 8.3 delineate the dose constraints and side effects, respectively.

Further Reading

Kubicky CD, Sahgal A, Chang EL, Lo SS (2014) Rare primary central nervous system tumors. Rare Tumors 6(3):5449

Chordoma and Chondrosarcoma

9

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Contents

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9.1 Skull Base Clival Chordoma

9.1.1 General Principles of Simulation and Target Delineation

- CT simulation in the supine position with a thermoplastic mask for immobilization and thin slice (1–2 mm) acquisition.
- Obtain volumetric thin slice (1–2 mm) T1 post-gadolinium axial MR images and fat saturation (fat-sat) skull base MR images for target delineation. T2 images are also highly recommended.
- In the case of prior surgery, fuse both the preoperative and postoperative post-gadolinium +/− T2/FLAIR MRIs with the CT simulation scan to help delineate target volumes.
- Target volumes may differ depending on whether surgical debulking has been performed or not and the extent of resection.
- Table 9.1 summarizes target volumes for a sample case of skull chordoma with prior surgery.
- Note: In the event that surgery has not been performed and only a simple biopsy, GTV = gross disease, CTV = GTV + 0.5 cm and typically will include the intracranial surgical track while respecting anatomical boundaries, and PTV=CTV + 0.3–0.5 cm.
- An example is illustrated in Case I.

Table 9.1 Suggested target volumes

Target volumes	Definition and description
GTV	Gross residual tumor on postoperative T1 post-gadolinium images
CTV[a]	CTV1 = resection cavity on postoperative T1 post-gadolinium images +0.5 cm + relevant regions of the clivus[b] + adjacent anatomic compartments at risk of direct spread (i.e., cavernous sinus). Use the preoperative initial tumor extent to ensure any areas in direct contact included in the CTV1 CTV2 = GTV + 0.5 cm Both CTVs should respect anatomic boundaries such as uninvolved bone, dura, and CSF
PTV	PTV1 = CTV1 + 0.3–0.5 cm PTV2 = CTV2 + 0.3–0.5 cm Smaller margins (0.3 mm) are preferred with daily cone-beam CT-based IGRT and 6-degree-of-freedom (6-DOF) positional corrections

[a]For CTV expansion posteriorly, the CTV will not extend into the CSF and will align with the posterior edge of residual tumor or clivus. This allows a little bit of room for maximal sparing of the brain stem

[b]For upper third clival tumors, the inferior clivus can be excluded. For lower third clival tumors, the upper third can be excluded. For middle third tumors, it is debatable but preferred to take the entire clivus as CTV1

9.1.2 Dose Prescriptions

- PTV1: 64–70 Gy in 39 daily fractions
- PTV2: 78 Gy in 39 daily fractions delivered as a simultaneous integrated boost

9.1.3 Treatment Planning Techniques

- Highly conformal treatment plans are necessary using either proton or IMRT/VMAT photon therapy. Carbon ion remains investigational.
- As a general principle, treatment planning aims to cover 95% of the PTV volume by 95% of the prescribed dose while respecting the OAR dose constraints. For complex tumors adjacent to critical OAR like the brain stem, chiasm, and optic nerves (typical for base of skull tumors), coverage may be compromised to protect the OARs. It is not unusual that we obtain 80% of the PTV to be covered by 95% of the prescribed dose or less, as maintaining the upper dose limits to the OAR must be respected.
- Higher than traditionally accepted tolerance limits are required to maximize coverage.
- IGRT using daily cone-beam CT with matching to bones and soft tissue must be employed with photon therapy.
- It is optimal to use a 6-degree-of-freedom (6-DOF) treatment couch or a linac with 6-DOF positional correction ability to maximize treatment delivery accuracy and precision.
- Tables 9.2 and 9.3 show the dose constraints and side effects, respectively.

Table 9.2 Recommended dose constraints for critical organs at risk for 1.8–2 Gy/day fractionation schemes. Note: Higher doses to OARs than what normally would be accepted are necessary for these tumors

Organs at risk	Suggested dose constraints
Optic nerves and chiasm	Dmax 60–62 Gy
Brain stem	Dmax 60–70 Gy
Cochlea	Mean ≤45 Gy Mean ≤55 Gy (for one side if dose to the other cochlea is low, i.e., mean <30 Gy)
Carotid arteries	No hot spots
Spinal cord	Dmax 60–62 Gy
Normal brain tissue	Dmax 78

Note: Dmax refers to the maximum point dose volume

Table 9.3 Side effects

Acute	Fatigue, headache, nausea, and vomiting
Subacute	Somnolence syndrome and alopecia
Long-term	Hypopituitarism, cranial nerve damage, optic nerve/chiasm damage, hearing loss, brain and brain stem radiation necrosis, radiation myelopathy, neurocognitive deficits, second malignancy, and increased risk of cerebrovascular events

Case I: A 59-year-old male presented with CNXII nerve dysfunction and headache. Only minimal safe resection/biopsy was performed to confirm chordoma involving the lower third of the clivus, C1/C2, and occipital condyles. Initial MRI is shown in Fig. 9.1, contours in Fig. 9.2, plan in Fig. 9.3, and the DVH in Fig. 9.4.

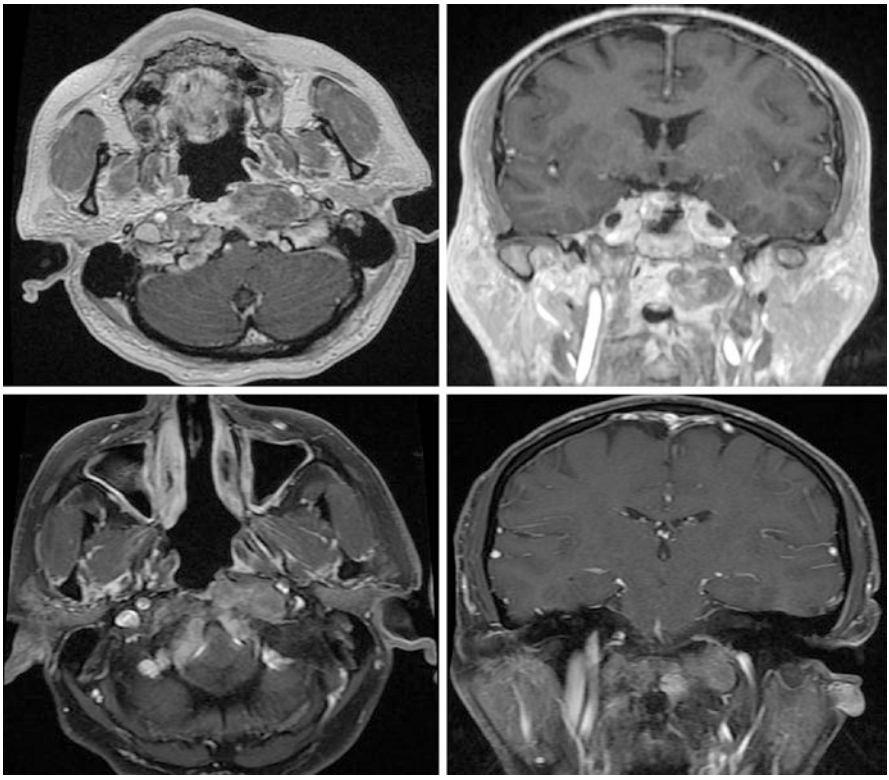


Fig. 9.1 Preoperative MRI for the above case of chordoma of the skull base. Top: T1 MRI post-gadolinium; left is axial view and right is coronal. Bottom: Fat-sat TI post-gadolinium MRI; left is axial view and right is coronal

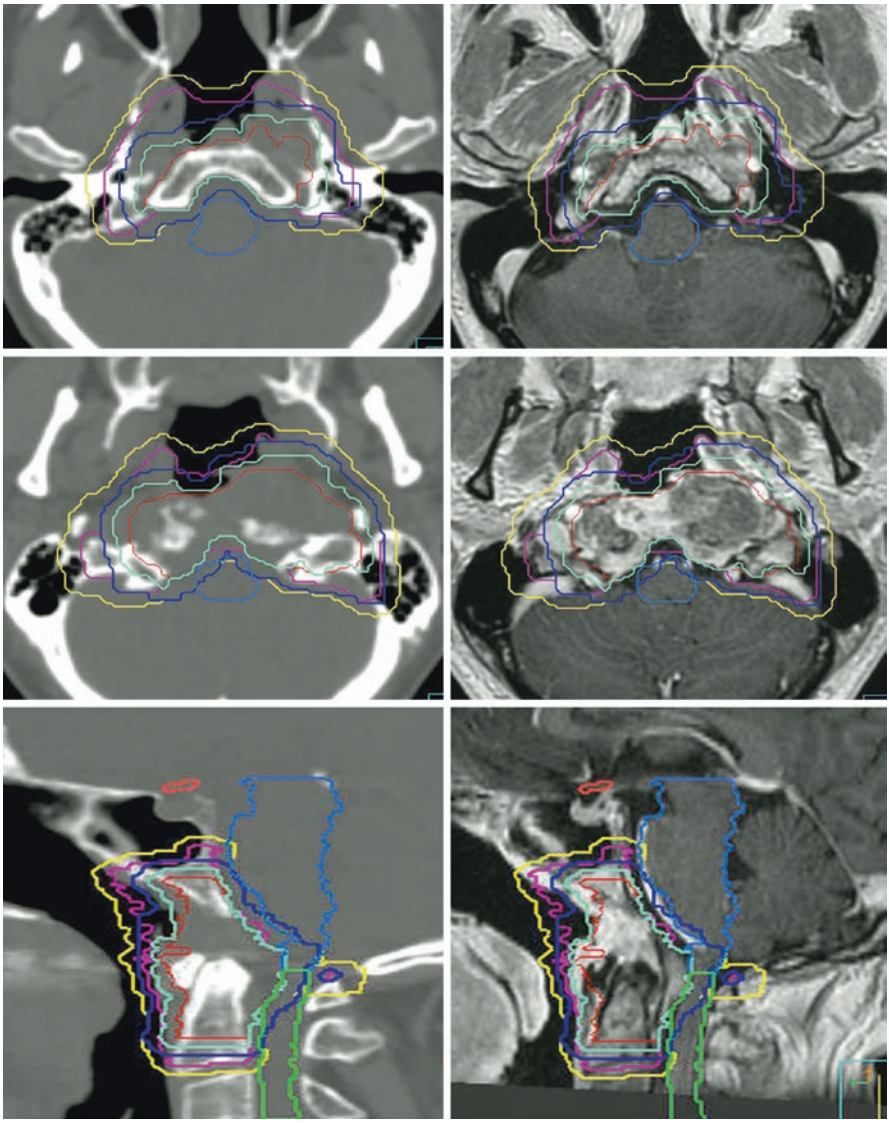


Fig. 9.2 Contours for the same patient with a lower third of skull base chordoma based on the postoperative treatment planning CT and MR images. T1 postoperative post-gadolinium MR images (right) and corresponding CT simulation images (left). GTV in red, CTV1 in pink, CTV2 in cyan, PTV1 in yellow, PTV2 in blue

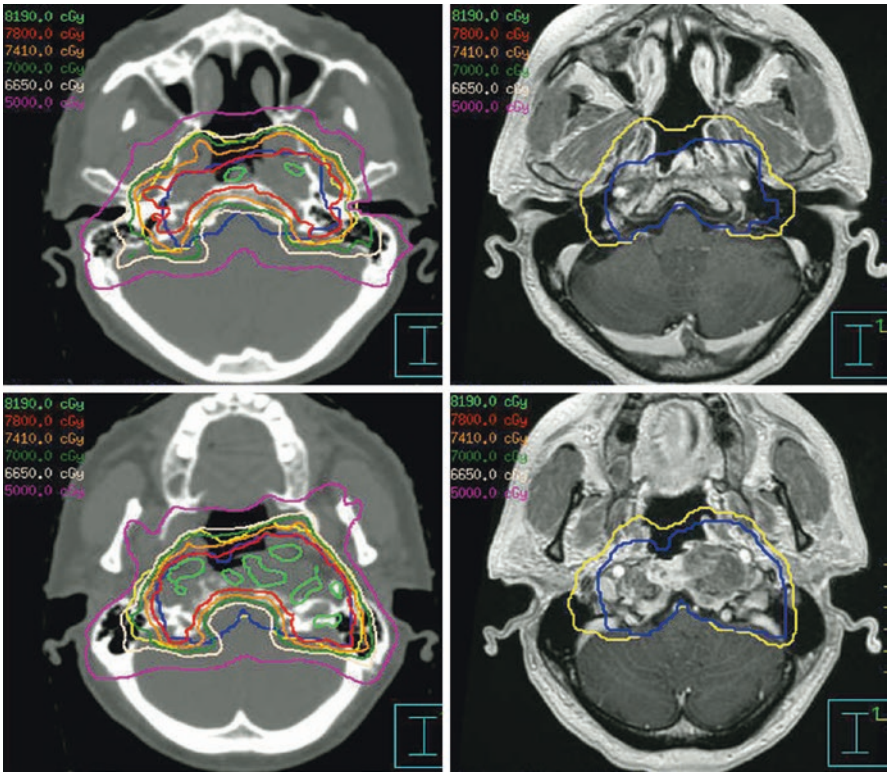
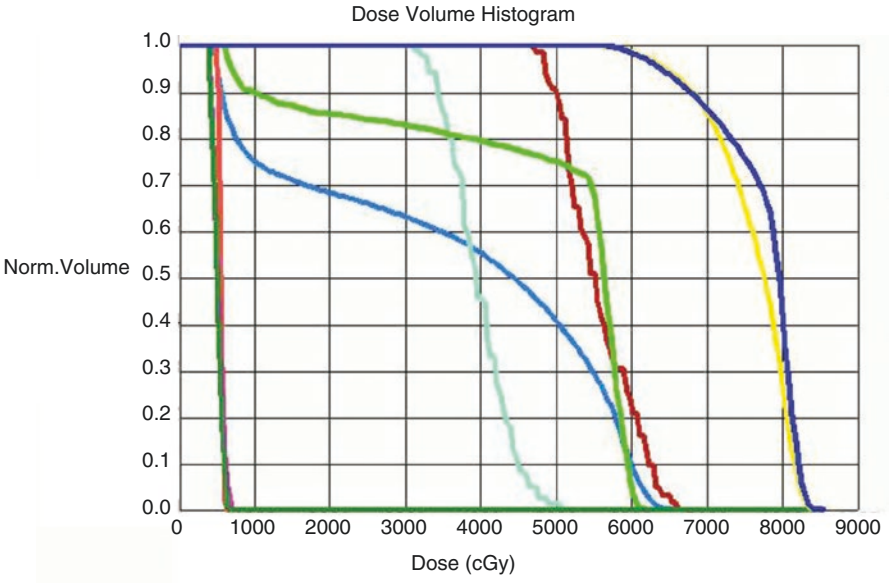


Fig. 9.3 Treatment plan using highly conformal IMRT with selected isodose lines for the above patient with a skull base chordoma. T1 postoperative post-gadolinium MR images (right) and corresponding CT simulation images (left) showing PTV1 in yellow and PTV2 in blue for the same patient as in Fig. 9.1. 70 Gy was prescribed to PTV1; 78 Gy was prescribed to PTV2 in 39 fractions. IMRT was used. Green is the 81.9 Gy (105% of 78 Gy) isodose line, red line is the 78 Gy (100% of 78 Gy) isodose line, orange line is the 74.1 Gy (95% of 78 Gy), forest green is the 70 Gy isodose line, white is the 66.5 Gy isodose line (95% of 70 Gy), and pink is the 50 Gy isodose line



ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	BRAINSTEM	brai	433.5	6590.5	3609.9	2176.5
	COCHLEA_L	brai	4714.0	6583.0	5552.7	476.5
	COCHLEA_R	brai	3119.3	5032.9	3961.1	409.6
	CORD	brai	588.8	6202.7	4802.2	1763.6
	OPTICCHIASM	brai	495.2	609.7	424.3	229.5
	OPTICNERVE_L	brai	391.6	690.3	296.2	257.2
	OPTICNERVE_R	brai	390.3	653.2	292.7	250.6
	PTV70	brai	602.4	8524.7	7597.9	560.3
	PTV78	brai	5249.0	6524.7	7721.2	586.1

Fig. 9.4 Dose-volume histogram (DVH) for the above patient. 95% and 90% of PTV1 (PTV70) and PTV2 (PTV78) are covered by the same dose, 64 Gy and 68 Gy, respectively. 80% of PTV1 and PTV2 are covered by 71 Gy and 74 Gy, respectively, and 70% is covered by 74 Gy and 78 Gy, respectively. Note that coverage was compromised to achieve acceptable dose limits to OARs

9.2 Skull Base Chondrosarcoma

9.2.1 General Principles of Simulation and Target Delineation

- CT simulation in the supine position with a thermoplastic mask for immobilization and 1–2 mm slice thickness.
- Obtain volumetric thin slice (1–2 mm) T1 post-gadolinium axial MR images and fat-sat skull base MR images for target delineation. T2 and FLAIR images are very helpful.
- In the case of prior surgery, fuse both the preoperative and postoperative post-gadolinium +/− T2/FLAIR MRIs with the CT simulation scan to help delineate the target volumes.
- Target volumes may differ depending on whether surgical debulking has been performed or not and the degree of tumor resection.
- Table 9.4 summarizes the target volumes for a sample case of chondrosarcoma with prior surgery. Note in the event that surgery has not been performed and a simple biopsy only then GTV = gross disease, CTV = GTV + 0.5 cm and typically includes the intracranial surgical track while respecting anatomical boundaries, and PTV = CTV + 0.3–0.5 cm.
- An example is illustrated in Case II.

9.2.2 Dose Prescriptions

PTV: 70 Gy in 35 daily fractions.

9.2.3 Treatment Planning Techniques

- Highly conformal treatment plans are necessary using either proton or IMRT/VMAT photon therapy. Carbon ion treatment remains investigational.
- As a general principle, treatment planning aims to cover 95% of the PTV volume by 95% of the prescribed dose while respecting the OAR dose constraints. For

Table 9.4 Suggested target volumes for chondrosarcoma of the skull base after surgical debulking

Target volumes	Definition and description
GTV	Gross residual disease on the postoperative T1 post-gadolinium MRI
CTV	Resection cavity on postoperative T1 post-gadolinium images +0.5 cm + adjacent anatomic compartments at risk of direct spread (i.e., cavernous sinus). Use the preoperative initial tumor extent to ensure any areas in direct contact included in the CTV1
PTV	CTV1 + 0.3–0.5 cm Smaller margins are preferred with daily cone-beam CT-based IGRT and 6-DOF positional corrections

Table 9.5 Recommended dose constraints for relevant organs at risk for 1.8–2 Gy/day fractionation schemes. Note: Higher doses to OARs than what normally would be accepted are necessary for these tumors

Organs at risk	Suggested dose constraints
Optic nerves and chiasm	Dmax 55–60 Gy
Brain stem	Dmax 60–65 Gy
Cochlea	Mean ≤45 Gy Mean ≤55 Gy (for one side if dose to the other cochlea is low, i.e., mean <30 Gy)
Carotid arteries	No hot spots
Spinal cord	Dmax 55–60 Gy
Normal brain tissue	Dmax 78

Note: Dmax refers to the maximum point dose volume

Table 9.6 Side effects

Acute	Fatigue, headache, nausea and vomiting
Subacute	Somnolence syndrome and alopecia
Long-term	Hypopituitarism, cranial nerve damage, optic nerve/chiasm damage, hearing loss, brain and brain stem radiation necrosis, radiation myelopathy, neurocognitive deficits, second malignancy, and increased risk of cerebrovascular events

complex tumors adjacent to critical OAR like the brain stem, chiasm, and optic nerves, coverage may be compromised to protect the OARs. Given the high prescribed doses and critical location of skull base tumors, one should accept higher doses to OARs in order to cover targets effectively.

- IGRT using daily cone-beam CT scan with matching to bones and soft tissue must be employed with photon therapy.
- It is optimal to use a 6-DOF treatment couch or a linac with 6-DOF positional correction ability to maximize treatment delivery accuracy and precision.
- Tables 9.5 and 9.6 show the dose constraints and side effects, respectively.

Case II: A 33-year-old female presented with double vision and cranial nerve V dysfunction. A macroscopic gross total resection was performed and pathology confirmed chondrosarcoma. Preoperative MRI is shown in Fig. 9.5, contours in Fig. 9.6, plan in Fig. 9.7, and DVH in Fig. 9.8.

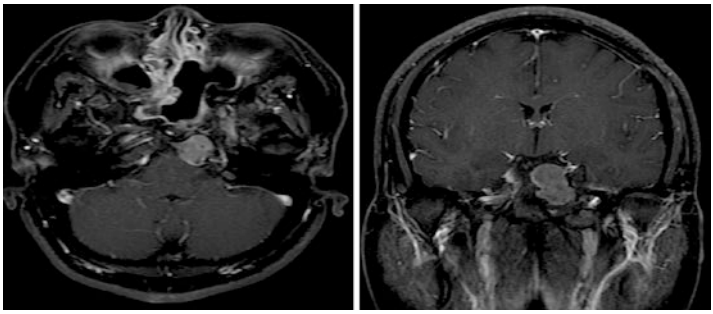


Fig. 9.5 Preoperative MRI for the above case. Fat-sat T1 post-gadolinium MRI: left, axial view; right, sagittal view

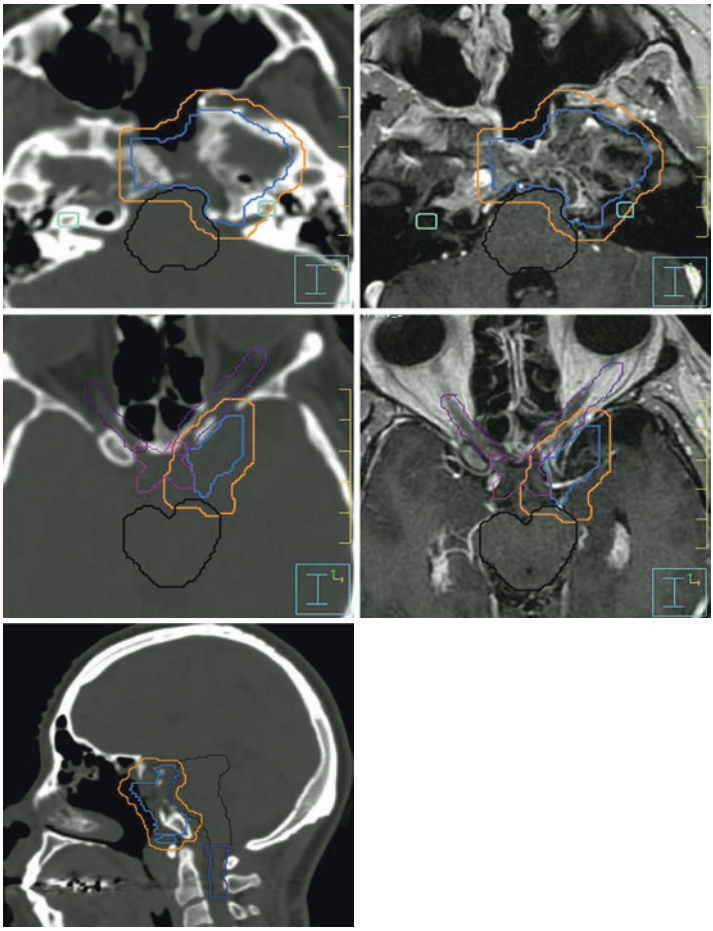


Fig. 9.6 Contours of the above case of skull base chondrosarcoma based on the postoperative treatment planning CT and MR images. CTV in blue and PTV in orange. Top: T1 postoperative post-gadolinium MRI (right) and bone window CT simulation images (left). Bottom: sagittal view of CT simulation scan

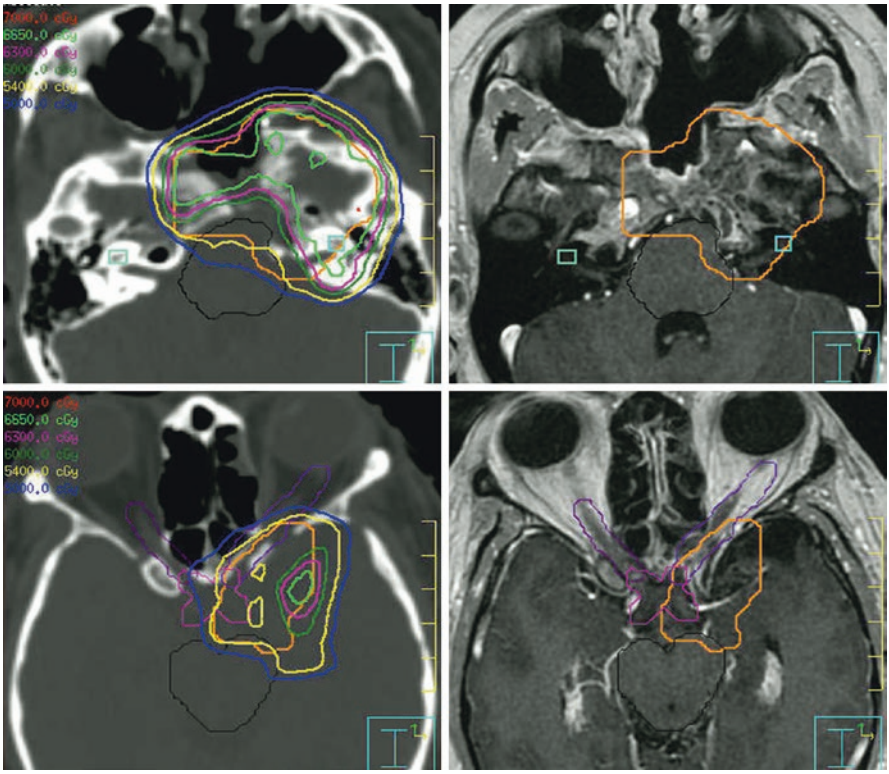
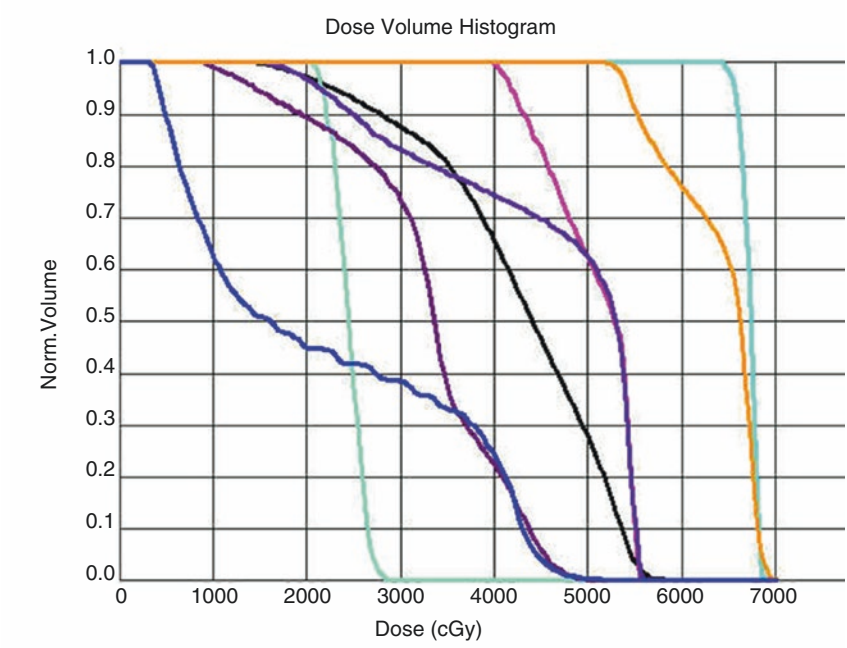


Fig. 9.7 Treatment plan using highly conformal IMRT for the above patient with resected skull base chondrosarcoma. MRI T1 postoperative post-gadolinium (right) showing PTV in orange. CT simulation scan on bone window (left) showing isodose lines. 70 Gy in 35 fractions was prescribed using IMRT. Red is 70 Gy isodose line (100%), green is 66.5 Gy (95%) isodose line, pink is 63 Gy (90%) isodose line, forest green is 60 Gy isodose line, yellow is 54 Gy isodose line, and blue is 50 Gy isodose line



ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. De
	BRAINSTEM	<non-co	1272	5821	4249	974
	COCHLEA_L	<non-co	6437	6861	6719	86
	COCHLEA_R	<non-co	2076	2840	2442	162
	OPTIC CHIASM	<non-co	3938	5575	5059	462
	OPTIC NERVE_L	<non-co	1345	5608	4606	1188
	OPTIC NERVE_R	<non-co	853	4978	3283	874
	PTV	<non-co	4936	7023	6382	487
	SPINAL CORD	<non-co	327	5135	2198	1561

Fig. 9.8 DVH for the above patient with chondrosarcoma of the skull base. 95% of PTV is covered by 65.5 Gy (93.5%) and 90% is covered by 66.5 Gy (95%)

9.3 Spinal Chordoma

9.3.1 General Principles of Simulation, Target, and Organs at Risk Delineation

- CT simulation with near-rigid body immobilization technology and 1–2 mm slice thickness.
- Volumetric thin slice (1–2 mm) MRI with T1, T1 post-gadolinium, and T2 images for target and organ at risk delineation at least one vertebral body above and below the involved spinal segment(s).
- Fuse both the preoperative and postoperative T1 post-gadolinium and T2 MRIs with the CT simulation scan to help delineate the target volume.
- The spinal cord is contoured based on the fused T1 and T2 MR images. Below the cord level (T12-L1), the thecal sac should be contoured. The two structures can overlap within the region of T12 to L1. A 0.15 cm PTV margin is added to the spinal cord contour as a planning organ at risk volume (PRV) and no additional margin applied to the thecal sac. In the case of poor visualization of the cord (i.e., due to metal artifact from surgical instruments), myelogram dye can be inserted prior to the CT simulation scan which is effectively a CT simulation planning myelogram. The central canal (continuation of thecal sac) and nerve roots need to be contoured for cases involving sacral area.
- Table 9.7 summarizes target volumes.
- An example is illustrated in Case III.

9.3.2 Dose Prescriptions

- PTV1: 64–70 Gy in 39 fractions.
- PTV2: 70–78 Gy in 39 fractions as a simultaneous integrated boost.
- Single phase delivering 78 Gy can also be used.

Table 9.7 Suggested target volumes

Target volumes	Definition and description
GTV	Gross residual disease
CTV	CTV1 = GTV + a 0.5 mm margin respecting anatomic barriers + the tumor bed based on both the preoperative and postoperative T1 post-gadolinium MRI. Note the entire hardware apparatus need *not* be included in the CTV. CTV2 = GTV + the entire vertebral segment at risk
PTV	PTV1 = CTV1 + 0.3–0.5 cm PTV2 = CTV2 + 0.3–0.5 cm

9.3.3 Treatment Planning Techniques

- Highly conformal treatment plans are necessary using either proton or IMRT/VMAT photon therapy.
- As a general principle, treatment planning aims to cover 95% of the PTV volume by 95% of the prescribed dose while respecting the OAR dose constraints. To protect critical OAR like the spinal cord/thecal sac, nerve roots, and kidneys, target coverage is typically compromised.
- IGRT using daily cone-beam CT scan with matching to bones and soft tissue must be employed with photon therapy.
- It is strongly suggested to use a 6-DOF treatment couch or a linac with 6-DOF positional correction ability to maximize treatment delivery accuracy and precision.
- Tables 9.8 and 9.9 show the dose constraints and side effects, respectively.

Table 9.8 Recommended dose constraints for relevant organs at risk for 1.8–2 Gy/day fractionation schemes. Note: Higher doses to OARs than what normally would be accepted are necessary for these tumors

Organs at risk	Suggested dose constraints
Cord PRV/thecal sac	Dmax 62–64/64–70 Gy
Kidneys	V20 <32%, V28 <20%, and mean <15–18 Gy
Liver	Mean <30 Gy
Bowel	Individual loops V15 <200 cc Bowel space V45 <195 cc Max dose 64
Lumbosacral nerve roots	Dmax <105% of prescribed dose

Table 9.9 Side effects

Acute	Fatigue, skin reaction, nausea/vomiting, dysuria, loose bowel movement/diarrhea
Long-term	Skin hyperpigmentation or hypopigmentation
Uncommon or rare risks	Myelopathy, neuropathy, kidney dysfunction, lumbar-sacral plexopathy, small bowel obstruction/perforation, and second malignancy

Case III: A 67-year-old female presented with progressive back pain at L2 without signs of radiculopathy or cauda equina syndrome. L2 vertebrectomy with reconstruction and stabilization was performed. Pathology confirmed chordoma. Preoperative MRI is shown in Fig. 9.9, contours in Fig. 9.10, thecal sac and cord contours at a higher level in Fig. 9.11, plan in Fig. 9.13, and DVH in Fig. 9.14. An example of how sacral nerve roots and central canal are contoured is shown in Fig. 9.12 for another sacral chordoma case.

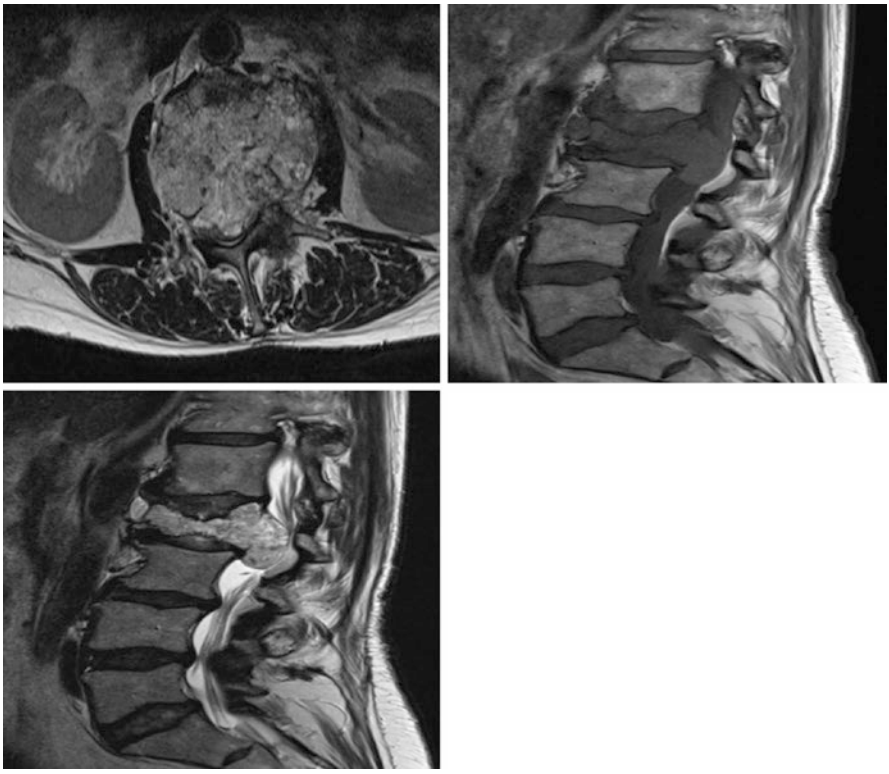


Fig. 9.9 Preoperative MRI for the above case. Top: left is an axial view of TI post-gadolinium MRI; right is sagittal view of T1 MRI. Bottom: T2 sagittal view

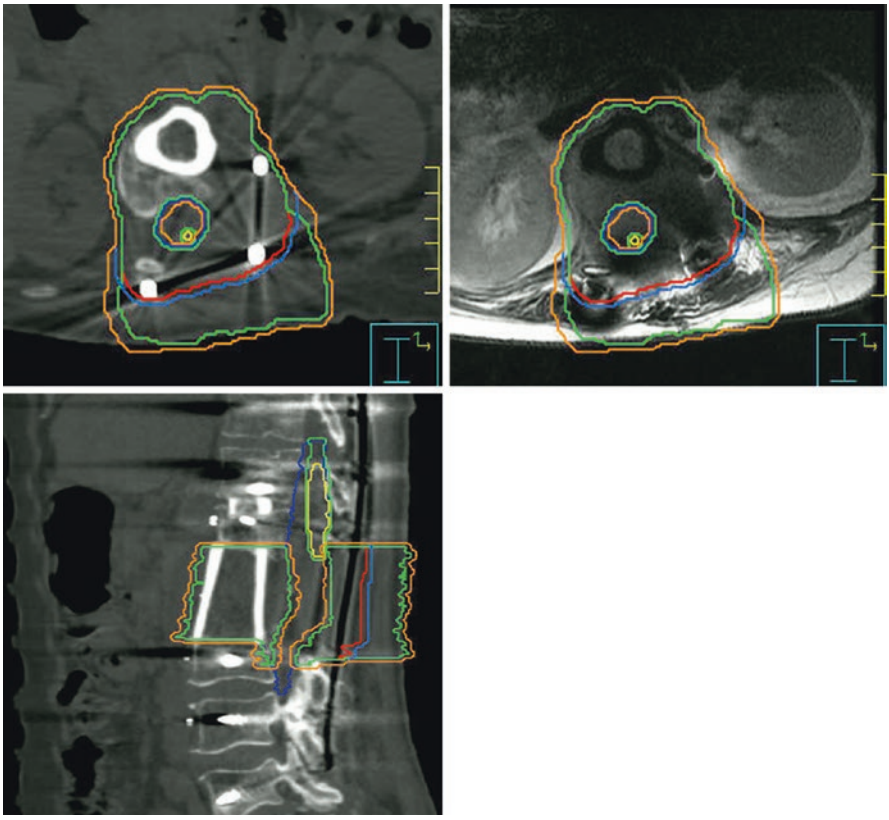


Fig. 9.10 Contours of the above case with spinal chordoma involving L2 based on the postoperative treatment planning CT and MRI. CT simulation scan (left) and postoperative MRI T1 post-gadolinium (right). No GTV (no residual disease), CTV1 in green, CTV2 in red, PTV1 in orange, and PTV2 in blue. Spinal cord in yellow, cord PRV in green, and thecal sac in blue

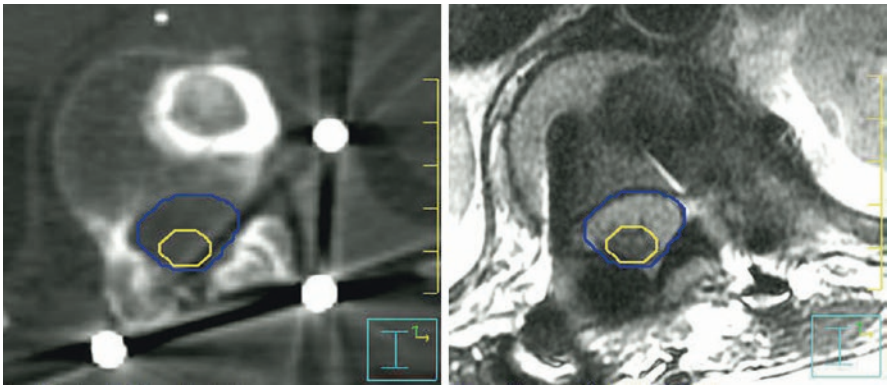


Fig. 9.11 Contours of cord and thecal sac for same case described above. Cord is contoured in yellow and thecal sac in blue

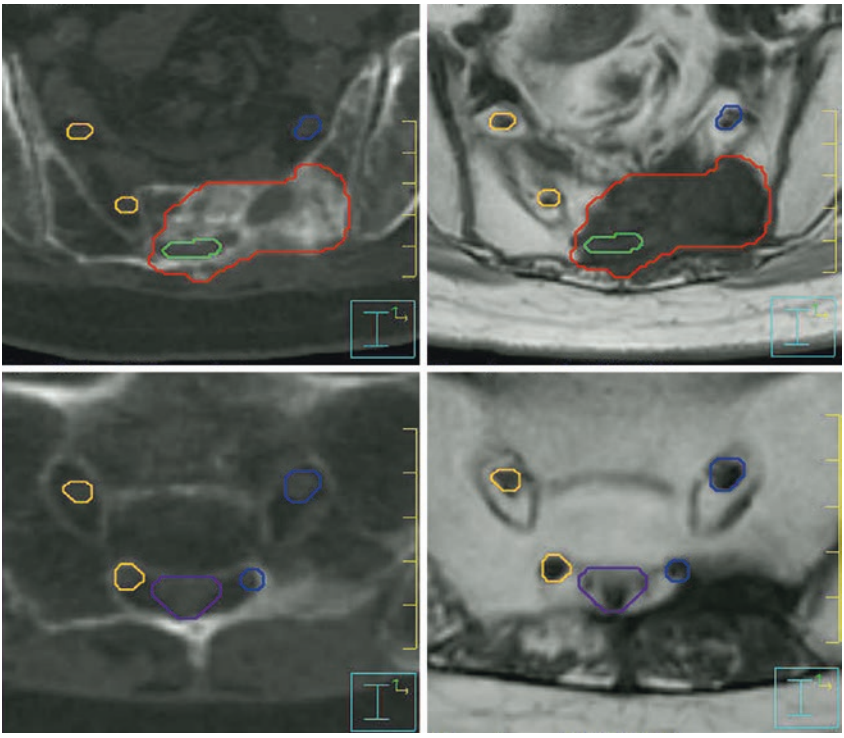


Fig. 9.12 An example of contouring the central canal (continuation of thecal sac) and nerve roots for another case of chordoma involving the sacrum. MRI T1 post-gadolinium (right) and CT simulation scan with bone window (left). Top: GTV in red, central canal (continuation of thecal sac) in green, uninvolved left nerve root in blue, and right nerve roots in orange. Bottom: thecal sac in purple, left nerve roots in blue, and right nerve roots in orange. Note: Involved nerve root was contoured as part of GTV as it cannot be spared

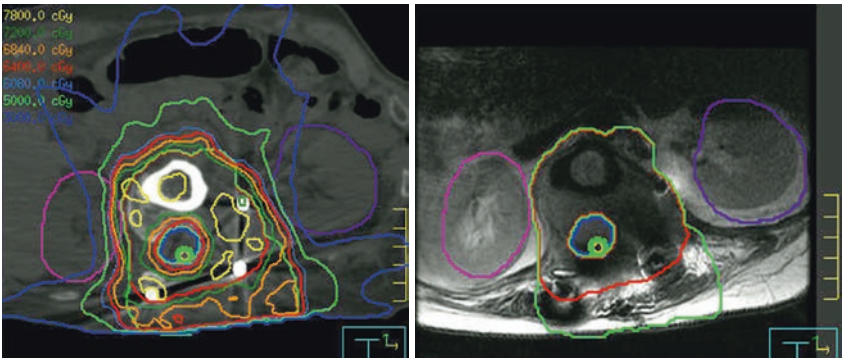
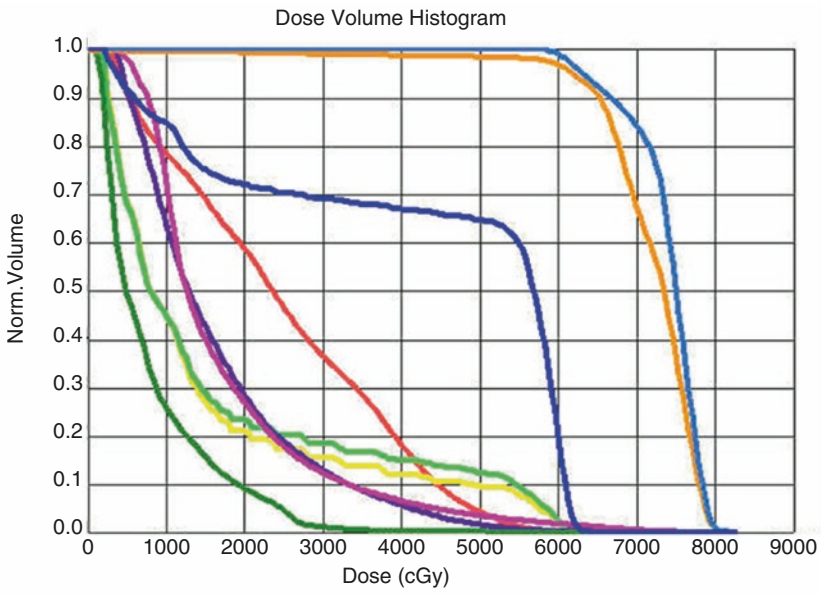


Fig. 9.13 Treatment plan using highly conformal IMRT for the above postoperative case with a spinal chordoma. Green contour is PTV 1 and red contour is PTV2. Thecal sac in blue, cord in yellow, and cord PRV in green. Prescribed dose was 64 Gy to PTV1 and 72 Gy to PTV2 in 39 fractions using IMRT. Yellow is the 78 Gy (108% of 72 Gy) isodose line, forest green is the 72 Gy (100%) isodose line, orange is the 68.4 Gy (95% of 72 Gy) isodose line, red is the 64 Gy isodose line, light blue is the 60.08 Gy (95% of 72 Gy) isodose line, green is the 50 Gy isodose line, and blue is the 30 Gy isodose line



ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.
	BOWEL + stomach	L-Spine	189.5	6181.8	2454.7	1452.1
	CORD	L-Spine	204.2	6146.9	1496.8	1654.0
	CORD prv (1.5mm)	L-Spine	190.7	6194.8	1614.8	1800.8
	KIDNEY LT	L-Spine	343.8	6700.9	1637.6	1133.3
	KIDNEY RT	L-Spine	351.3	7523.7	1719.5	1218.7
	LIVER	L-Spine	72.6	5081.7	781.3	716.1
	PTV 1	L-Spine	--	8196.3	7138.3	890.2
	PTV 2	L-Spine	5443.0	8196.3	7385.8	459.1
	THECAL SAC	L-Spine	201.1	6443.8	4274.6	2252.0

Fig. 9.14 Dose-volume histogram for the above patient with chordoma of L2. 95% of PTV 1 and PTV 2 are covered with 62 Gy and 64 Gy, respectively. 90% of PTV1 and PTV2 are covered by 65 Gy and 67 Gy, respectively

Further Reading

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Ganglioglioma

10

John T. Lucas Jr, Michael D. Chan, and Tamara Z. Vern Gross

Contents

10.1 General Principles of Simulation and Target Delineation (Table 10.1)

- Information on simulation
  - Recommended imaging

    Preoperative as well as postoperative imaging should be obtained. Imaging sequences should include at least T1, T1 with contrast, T2, and FLAIR. Consideration to obtaining either susceptibility-weighted imaging, T2 gradient recalled echo, or T2 star as these sequences can be helpful in delineating the operative bed and distinguishing blood products from residual disease.

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Table 10.1 Target volume guidelines

Target volumes	Definition and description
GTV	The GTV should include the entire operative bed as well as any and all residual contrast-enhancing volume as this may represent gliosis or residual tumor
CTV	The CTV should extend at least 0.5 cm from the operative bed for low-grade gangliogliomas, while 1–2 cm may be more appropriate for high-grade (anaplastic) gangliogliomas. The CTV should be anatomically constrained by barriers for spread such as bone, tentorial or discontinuities in tissue across fissures, ventricles, etc.
PTV	The use of a PTV is recommended for prescription of all photon cases. Typically 0.3–0.5 cm is appropriate. Proton plans are typically prescribed to the CTV with subsequent robust optimization with various combinations of positioning/setup and range uncertainties. The impact of all robustness scenarios should be evaluated in terms of their subsequent impact on target coverage. Positioning uncertainties of 3–5 mm and 3–5% differences in range uncertainty are appropriate for most intracranial cases

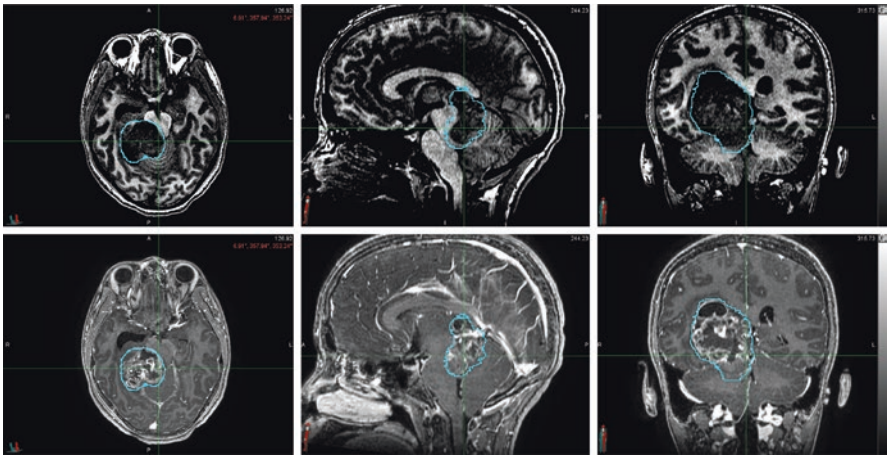


Fig. 10.1 Preoperative tumor volume. Top row: T1 stealth. Bottom row: T1 stealth + contrast. Blue = preoperative tumor volume segmentation

  - Patient positioning
    Supine positioning and immobilization with a short aquaplast mask is recommended. The use of photon vs. proton radiotherapy may dictate head position or the need for other special setup devices like table-associated range shifter, etc.
- Recommendations for target delineation (Figs. 10.1 and 10.2)
  - Imaging sequences and special circumstances
    The T1 and T1 contrast-enhanced studies are most useful for delineation of the operative bed and determining if residual disease is present. Most high-grade gangliogliomas will enhance with contrast on T1, while low-grade gangliogliomas may only partially enhance or not enhance at all. T2 imaging is

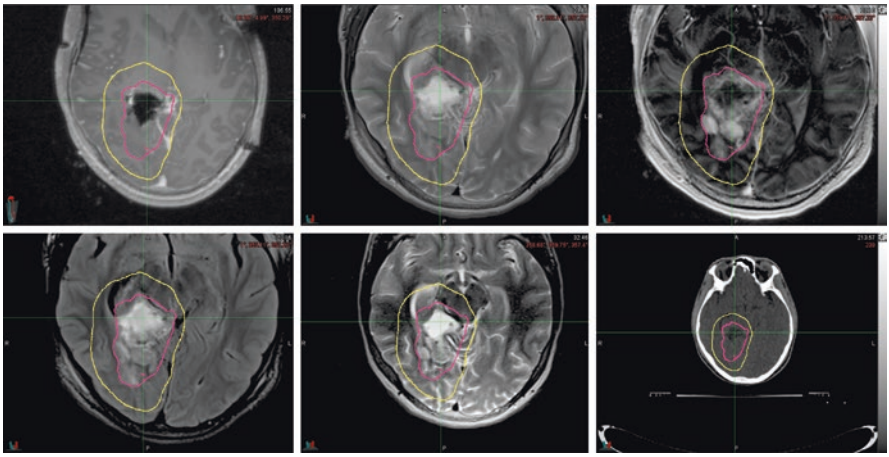


Fig. 10.2 Postoperative treatment volumes. Top row, from right to left: T1 post-contrast, T2, T1 subtraction. Bottom row, from right to left: T2 flair, T2 fast spin echo, CT planning scan. Pink, gross tumor volume; yellow, clinical target volume

useful for delineating the operative bed as it highlights the presence of cerebrospinal fluid within the cavity, while susceptibility-weighted imaging may illustrate regions that the surgeon explored intraoperatively which are not apparent after review of the operative report or the T1 contrast-enhanced study.

– On treatment imaging

Most gliomas can exhibit pseudo-progression which may occur during therapy. Interval imaging at 1–2 week intervals may be useful when smaller disease volumes are utilized to ensure that a marginal miss or insufficient coverage does not occur during the course of therapy from volumetric changes in the tumor.

10.2 Dose Prescriptions

- Recommended doses for ganglioglioma range from 54 to 59.4 Gy depending on tumor grade and presence of residual disease. Most would favor 59.4 Gy for anaplastic ganglioglioma, while 54 Gy would be considered standard for treatment of low-grade ganglioglioma cases after progression on chemotherapy following resection.

10.3 Treatment Planning Techniques (Table 10.2 and Fig. 10.3)

- Modality
  - Protons or 4–6 MV photons are typically utilized for treatment.
- Treatment technique

Table 10.2 Recommended coverage guidelines and dose constraints

Organs at risk	Suggested dose constraints
PTV	D100% = 95%
	V110% ≤ 10%
Cochleae	D50% ≤ 35 Gy—goal
	D50% ≤ 20 Gy—preferred
Optic globes	D50% ≤ 10 Gy—goal
	D10% ≤ 35 Gy—goal
	D50% ≤ 20 Gy—maximum
	D10% ≤ 54 Gy—maximum
Optic chiasm	D50% ≤ 54 Gy—goal
	D10% ≤ 56 Gy—goal
	D50% ≤ 56 Gy—maximum
	D10% ≤ 58 Gy—maximum
Optic nerves	D50% ≤ 54 Gy—goal
	D10% ≤ 56 Gy—goal
	D50% ≤ 56 Gy—maximum
	D10% ≤ 58 Gy—maximum
Spinal cord (superior 6 cm)	D50% ≤ 26 Gy—goal
	D10% ≤ 57 Gy—goal
	D50% ≤ 50 Gy—maximum
	D10% ≤ 59 Gy—maximum
Brain stem	D50% ≤ 61 Gy—goal
	D10% ≤ 63 Gy—goal
	D50% ≤ 62 Gy—maximum
	D10% ≤ 64 Gy—maximum

References for dose constraints per ACNS0423 [1]

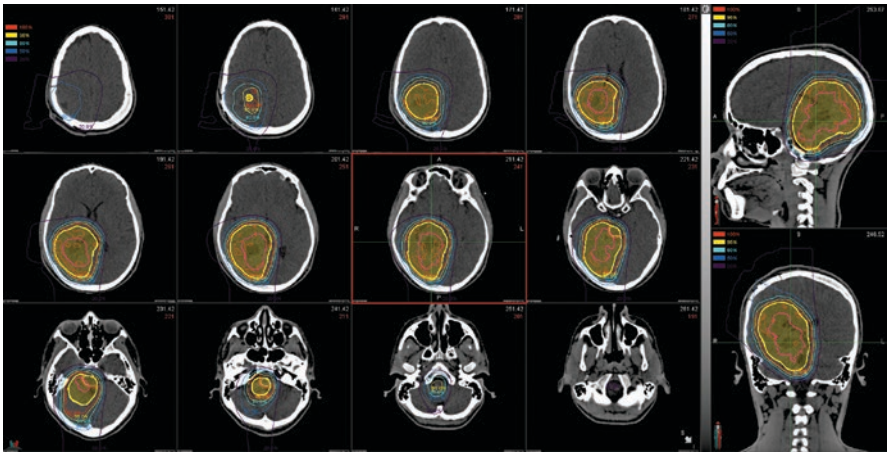
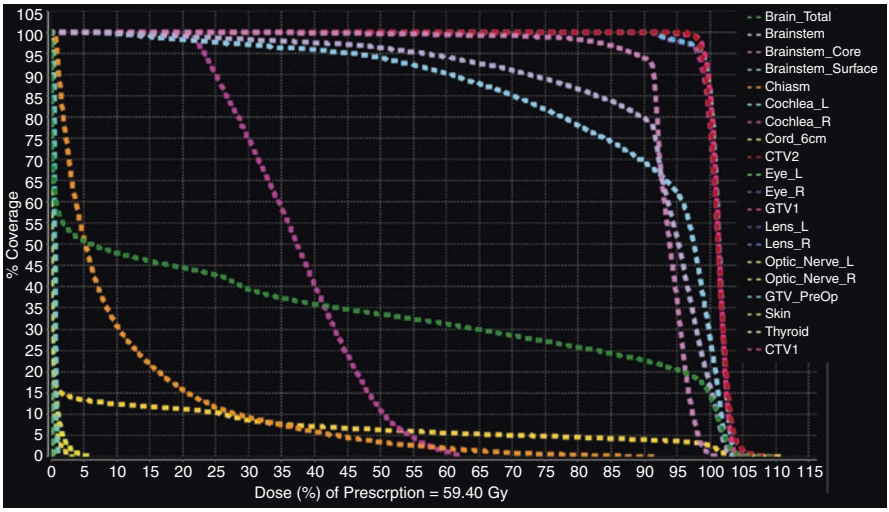


Fig. 10.3 Treatment plan. Isodose lines shown in red, yellow, turquoise, blue, and purple for 100%, 95%, 80%, 50%, and 20%, respectively. Pink, gross tumor volume; yellow, clinical target volume

  - Treatment technique with photons is highly location-dependent although IMRT is increasingly utilized. 3DCRT may be more favorable in situations where integral dose to the brain is of concern. VMAT may offer improved conformality and reduced treatment delivery times over IMRT; however, this may limit certain noncoplanar beam angles. Stereotactic radiosurgery (SRS) may be appropriate at the time of salvage for small focal recurrences or as a boost for residual disease, where further surgery was not possible. Proton therapy is increasingly favored for its dose fall off at depth and reduced integral dose. There are a wide variety of proton delivery methods (passive scatter, pencil beam scanning—single or multiple field optimization, etc.). Concerns over end of range biologic effects may be less pronounced with pencil beam scanning approaches.
- Representative DVH



10.4 Side Effects

- Acute side effects to evaluate during weekly on-treatment visits
  - Hair loss, fatigue, radiation dermatitis, headaches, nausea, seizures
- Late side effects and complications
  - The late effects of focal cranial radiotherapy are highly location-dependent but may include bony hypoplasia, increased soft tissue fibrosis, overlying subcutaneous hypoplasia, endocrine deficits, decline in hearing, neurocognitive and psychological sequelae, vasculopathy, second cancers, necrosis, and decline in vision or cataracts.
- Clinical pearls for addressing those side effects
  - If patients are on steroids at the time of radiotherapy, utilization of gastric prophylaxis (e.g., ranitidine) and evaluation for oral thrush are recommended.

- Topical water-based lotions are recommended for local application over the treated region following (but not before) treatment, three to four times per day depending on the topical lotion utilized.
- As gangliogliomas can be epileptogenic, patients generally are on seizure prophylaxis with levetiracetam during radiotherapy. Exacerbation of seizures during radiotherapy may require increase in anti-epileptic doses, additional anti-epileptic, and/or use of steroids.

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Ependymoma

11

Kenneth K. Wong and Eric L. Chang

Contents

11.1 General Principles of Simulation and Target Delineation (Table 11.1)

- Staging with spine MRI and cerebrospinal fluid sampling is essential to determine if a patient has tumor dissemination.
- CT simulation with a themoplastic mask for immobilization with 1–2.5 mm slice thickness.
- Obtain MRI with T1 pre- and post-gadolinium, T2, and FLAIR for target delineation. Ependymomas often have a mixed pattern of enhancement and may be best visualized on FLAIR sequences.
- Fuse preoperative and postoperative T2/FLAIR and post-gadolinium MRIs to help delineate target volumes.
- If biopsy only, can use preoperative MRI only.

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Table 11.1 Suggested target volumes and doses

Target volumes	Definition and description
GTV1	Residual tumor extent and resection cavity on postoperative T2/FLAIR and T1 post-gadolinium images. Registered preoperative MRIs are helpful for determining residual disease and resection cavity
CTV1	GTV1+ 1 cm. This can be edited around natural boundaries where invasion is unlikely, such as the skull or tentorium (CTV1 is defined as GTV1 + 0.5 mm on COG ACNS0831)
PTV1	CTV1 + 0.3–0.5 cm depending on comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone beam CT)
GTV2	The intent of GTV2 is to administer a boost dose to GTV1 but allow volume reduction to limit dose to the spinal cord, brain stem, and optic chiasm after 54 Gy. If dose constraints can be met, GTV2 may be the same as GTV1
PTV2	GTV2 + 0.3–0.5 cm depending on comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone beam CT). There is no PTV2 for children under the age of 18 months of age at the start of radiotherapy if gross total resection of tumor is achieved

Suggested dose 54.0–59.4 Gy in 1.8 Gy fractions

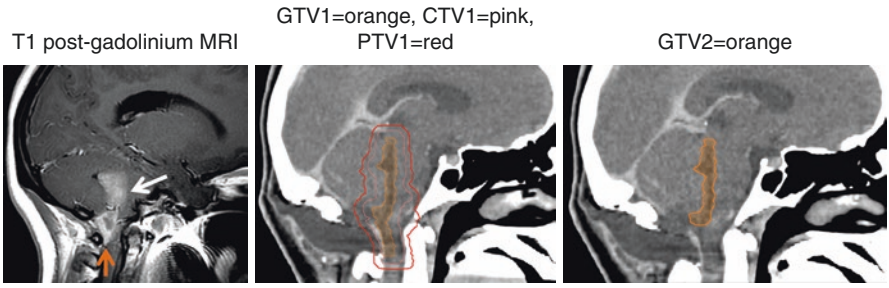

Fig. 11.1 Sagittal images for a patient with WHO grade III anaplastic ependymoma of the fourth ventricle. MRI before gross total resection shows tumor centered in the floor of the fourth ventricle (white arrow) with extension through the foramen magnum to approximately the C2 level (orange arrow). CT simulation with contrast demonstrates initial and boost contours using ACNS0831 guidelines

- If patient has contraindication to MRI, can obtain CT using 1–2.5 mm slice thickness with and without contrast.
- The GTV includes the postoperative residual disease and the edge of the postoperative tumor bed. The edge of any structure in contact with the preoperative tumor should be included, but the surgical tract does not need to be included. The CTV expansion into the brain stem should be limited where invasion or infiltration is not considered likely (Fig. 11.1).
- Contemporary 3D conformal or advanced techniques such as tomotherapy, IMRT, or proton therapy can be considered.

11.2 Dose Prescriptions

- Treatment of the brain after maximal safe resection
  - The current standard doses to the target for intracranial ependymoma are 54–59.4 Gy, and higher doses may be recommended for areas with residual macroscopic disease.
  - The extent of margin for focal radiation therapy continues to be studied with shrinking clinical target volume margins employed on completed and ongoing COG clinical trials.
- Treatment of patients with leptomeningeal dissemination
  - Patients with leptomeningeal dissemination with spinal deposits of intracranial ependymoma generally have a poor prognosis, and treatments should be individualized.
  - Given challenges in the interpretation of CSF cytology in ependymoma, cytology should be repeated in 10–14 days postoperatively to confirm results.

    Craniospinal irradiation is typically indicated after surgery. Target volumes and doses are similar to high-risk medulloblastoma.

11.3 Treatment Planning Techniques

- Contemporary 3D CRT or advanced techniques such as IMRT, VMAT, or proton therapy may be used with the goal of sparing portions of the brain stem, supratentorial brain, hypothalamus, pituitary, optic apparatus, and cochleae (Table 11.2).
- Treatment planning aims to cover 95% of the PTV volume by 95% of the prescribed dose for photon plans and 100% of the CTV volume by 100% of the prescribed dose for proton plans (Fig. 11.2).

Table 11.2 Recommended normal tissue constraints for 1.8 Gy per fraction schemes

Organs at risk	Suggested dose constraints
Optic nerves and chiasm	D50% ≤ 54 Gy and D10% ≤ 56 Gy (goal)[a] D50% ≤ 56 Gy and D10% ≤ 58 Gy (maximum)[a]
Optic globes	D50% ≤ 10 Gy and D10% ≤ 35 Gy (goal)[a] D50% ≤ 20 Gy and D10% ≤ 54 Gy (maximum)[a]
Cochlea	D50% ≤ 35 Gy (goal)[a] D50% ≤ 20 Gy (preferred)[a]
Brain stem (photon)	D50% ≤ 61 Gy and D10% ≤ 63 Gy (goal)[a] D50% ≤ 62 Gy and D10% ≤ 64 Gy (maximum)[a]
Brain stem (proton)	D50% ≤ 52.4 CGE and D0.1cc ≤ 56.6 CGE (goal)[a] D50% ≤ 54 CGE and D0.1cc ≤ 58 CGE (maximum)[a]
Cervical spinal cord (superior-most 6 cm)	D50% ≤ 26 Gy and D10% ≤ 57 Gy (goal)[a] D50% ≤ 50 Gy and D10% ≤ 59 Gy (maximum)[a]

[a]COG ACNS0831 trial [1]

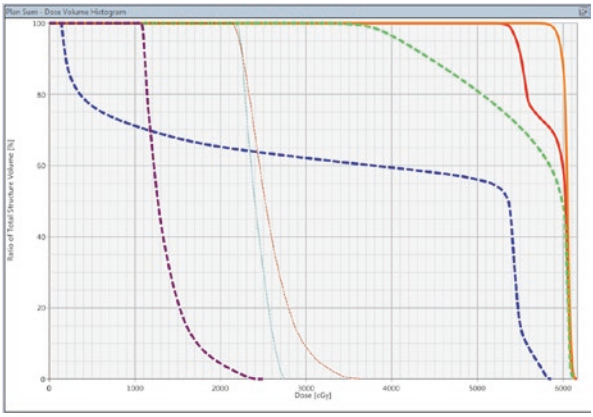

Fig. 11.2 Sample dose-volume histogram for the above patient with WHO grade III anaplastic ependymoma of the fourth ventricle treated with an IMRT plan. PTV2, orange; PTV1, red; brain stem, dashed green; spinal cord, dashed blue; left cochlea, dotted brown; right cochlea, dotted teal; and optic chiasm, dashed indigo

Table 11.3 Side effects

Acute	Hair loss, fatigue, headaches, nausea, diarrhea, fatigue, alopecia, hearing changes, myelosuppression, and cerebral edema causing neurological symptoms
Long-term	Neurocognitive decline, decreased growth, hypopituitarism, hypothyroidism, hearing loss
Uncommon or rare risks	Lhermitte's syndrome, gonadal dysfunction, brain or brain stem injury, secondary malignancies

11.4 Side Effects

Please see Table 11.3.

11.5 Treatment of Recurrence

- While the long-term prognosis for patients with recurrent disease is poor, there is growing evidence that reirradiation is beneficial and has successfully provided local control in carefully selected cases. Patients treated with focal reirradiation remain at risk for development of disseminated metastases or primary site recurrence
- Data in the literature showed that stereotactic radiosurgery can be used for treatment of recurrent intracranial ependymoma; the recurrent tumor, gadolinium enhanced in most cases, alone is targeted, and the typical dose used ranged from 12 to 24 Gy (median 18 Gy) in 1 fraction; the local control rate is 70–80%, but distant failure occurs in at least one quarter of the patients.

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Adult Pilocytic Astrocytoma

12

(Kang) Liang Zeng and Hany Soliman

Contents

12.1 Indications for Radiotherapy

- Surgical contraindications (technically unresectable disease, patient comorbidities, patient refusal)
- Subtotal disease resection
- Adjuvant treatment (a consideration)
- Salvage treatment

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12.2 Radiotherapy Technique (Conventional Radiotherapy)

12.2.1 Simulation, Target Delineation, and Dose Prescriptions (Conventional Radiotherapy)

- CT simulation with 1–1.5 mm slice thickness.
- Immobilization with thermoplastic mask.
- Obtain volumetric thin slice MRI with T1 pre- and post-gadolinium and T2 FLAIR sequences.
- Fuse the planning CT scan with the preoperative and postoperative T2/FLAIR and post-gadolinium MRIs to help delineate the target volume.
- Target volumes are detailed in Table 12.1.
- Techniques to spare critical organs at risk should be considered, including IMRT/VMAT, stereotactic radiotherapy, and/or proton therapy (Table 12.2).
- Treat at a dose of 50–54 Gy in 25–30 fractions.
- Daily cone-beam CT is performed, and all displacements greater than 1 mm are corrected prior to treatment, and all angular displacements greater than 3° require a repeat setup.

Table 12.1 Suggested target volumes

Target volumes	Technique	Definition and description
GTV	*Conventional RT*	Gross tumor, residual tumor, or surgical cavity, contrast-enhancing residual T1 post-gadolinium, with care to be taken to not include the surgical approach areas. T2 FLAIR may be helpful in delineating the GTV, but need not be completely encompassed especially when it is clear that it represents edema
	HSRT	
	SRS	
CTV	*Conventional RT*	Geometric expansion of 0–5 mm around GTV respecting normal tissue boundaries
	HSRT	No expansion
	SRS	No expansion
PTV	*Conventional RT*	3–5 mm geometric expansion
	HSRT	Up to 1–2 mm
	SRS	Up to 1–2 mm

Table 12.2 Recommended normal tissue constraints (conventional radiotherapy)

Objects at risk	Suggested dose constraints
Optic nerves and chiasm	<54 Gy
Orbits	<45 Gy
Lenses	<10 Gy
Brain stem	<54 Gy
Hippocampi and pituitary gland	Beam angles and planning techniques to minimize dose to the hippocampi and pituitary gland

12.3 Treatment Planning Techniques Conventional Radiotherapy)

- Cover 95% of the PTV by 95% of the prescribed dose while respecting OARs.
- In tumors close to critical OAR (e.g., brain stem or optic chiasm or nerves), coverage may suffer to 90% coverage of the PTV by 95% of the prescribed dose on a case-by-case basis.
- Sample contours, plan, and dose-volume histogram are detailed in Figs. 12.1, 12.2, and 12.3.

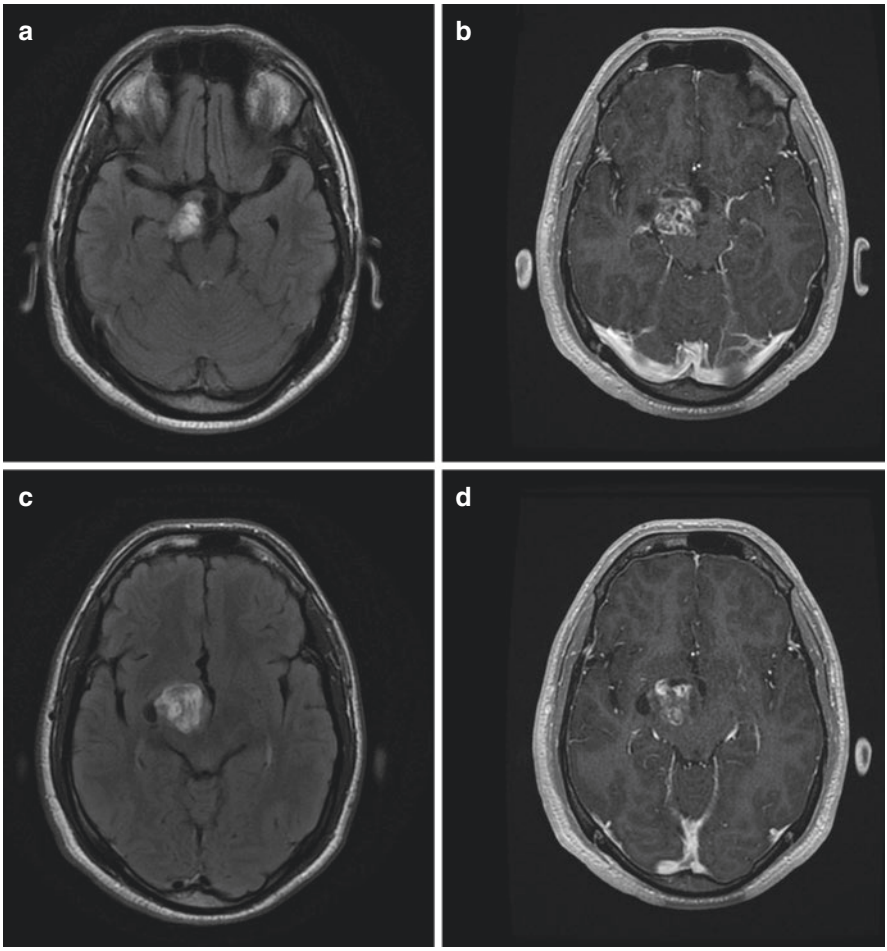

Fig. 12.1 Diagnostic MRI of a 19-year-old patient with pilocytic astrocytoma of the right thalamus post-subtotal resection. (**a**, **c**) Tumor centered in the right thalamus extending anterior to the right midbrain showing a high signal on T2 FLAIR imaging. (**b**, **d**) The same tumor seen on T1-weighted post contrast imaging

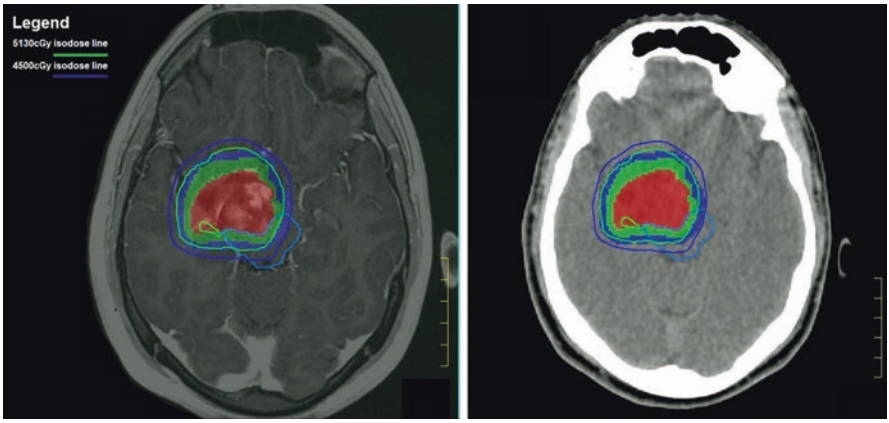

Fig. 12.2 Sample plan for the above patient with pilocytic astrocytoma of the right thalamus. Left: overlaid on diagnostic MRI. Right: overlaid on planning CT scan. The red color wash is the GTV, the green color wash is the CTV, and the blue color wash is the PTV. 95% of the PTV is covered by 5130 cGy (95% of 5400 cGy in 30 fractions). The coverage of the PTV is compromised adjacent to the brain stem to ensure that the brain stem receives less than 5400 cGy. Two isodose lines are shown, green is 5130 cGy, and blue is 4500 cGy

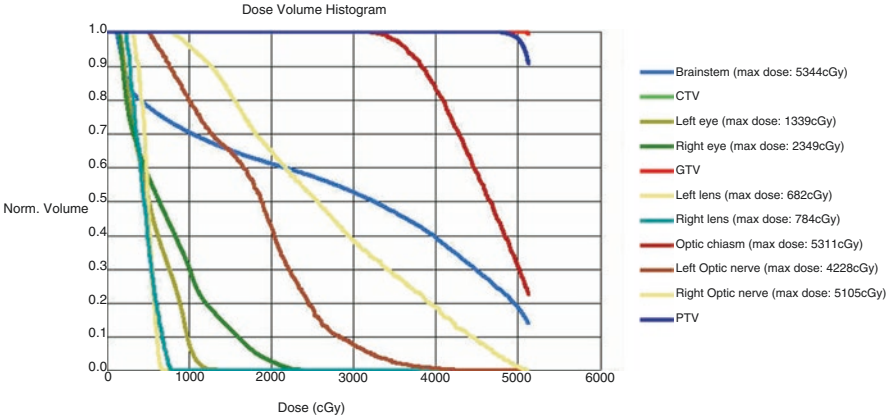

Fig. 12.3 Sample dose-volume histogram for the above patient with pilocytic astrocytoma of the right thalamus

12.3.1 Radiotherapy Technique (Stereotactic Radiosurgery (SRS) and Hypofractionated Stereotactic Radiotherapy (HSRT))

- Indications: Consideration with low-volume local recurrences, surgical contra-indications

12.3.2 Simulation, Target Delineation, and Dose Prescriptions (SRS/HSRT)

- CT simulation with 1–1.5 mm slice thickness.
- Immobilization with thermoplastic mask or stereotactic headframe.
- Obtain volumetric thin slice MRI (1–1.5 mm) with T1 pre- and post-gadolinium and T2 FLAIR sequences.
- Fuse the planning CT scan with the preoperative and postoperative T2/FLAIR and post-gadolinium MRIs to help delineate the target volume.
- Target volumes as listed in Table 12.1 with variations based on technique.
- Linear accelerator-based SRS/HSRT with IMRT/VMAT or Gamma Knife-based SRS/HSRT.
- Dose: Up to 20 Gy in single fraction, similar to brain metastases, or 25–30 Gy in 5 fractions respecting organs at risk and suggested dose constraints as listed in Table 12.3.
- Cone-beam CT is performed for image registration with repositioning thresholds greater than 2° and residual translation <0.1 cm and rotation <1° to begin treatment.

12.4 Treatment Planning Techniques (SRS/HSRT)

- **Stereotactic radiosurgery.**
  - Coverage >98% by prescription isodose
  - Max dose 200% with Gamma Knife
  - Prescribe to 50% with Gamma Knife, 80–90% with linear accelerator-based SRS
- **Hypofractionated stereotactic radiotherapy**
  - PTV: V(100% of prescription) ≥ 98%, max dose 120%.
  - CTV: V(100% of prescription) ≥ 99%.
  - Conformity index of 100% isodose line should be <1.3.

Table 12.3 Recommended normal tissue constraints (single-fraction SRS/five-fraction HSRT)

	Suggested dose constraints	
Objects at risk	Single fraction	Five fractions
Optic nerves and chiasm	<8 Gy	<25 Gy
Retina	<7 Gy	<25 Gy
Lenses	<2 Gy	<8 Gy
Brain stem	<15 Gy	<25 Gy

Table 12.4 Side effects

Acute	• Hair loss • Fatigue • Headaches • Nausea/vomiting • Cerebral edema leading to neurologic deficits
Long-term	• Neurocognitive decline • Hypopituitarism
Uncommon/ rare	• Pseudoprogression, which can lead to neurologic deficits, vision/hearing loss • Secondary malignancies

Table 12.5 Management of neurologic symptoms

Symptom	Management
Seizures	• Education, counseling on immediate management, avoiding heights, swimming alone • Driving restrictions • Antiepileptics
Treatment-related symptomatic edema	• Course of corticosteroids
Motor deficits	• Rehabilitation, occupational therapy/physiotherapy referral • Supportive devices at home

12.5 Follow-Up Care

Patients should be followed closely (every 2–4 months) in the first year after radiotherapy with clinical assessment and imaging (MRI). Visits are prolonged to every 3–6 months during years 1–5 and every 6–12 months from then after. Patients should be monitored for side effects, especially neurological sequelae, in the acute and long-term setting (Tables 12.4 and 12.5).

Further Reading

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Pleomorphic Xanthoastrocytoma (PXA)

13

Anthony Yip, Minh-Phuong Huynh-Le,
and Jona A. Hattangadi-Gluth

Contents

13.1 Background and Epidemiology

- PXA is most commonly a diagnosis in children and young adults [1]:
  - Two-third of patients are <18 years old [2].
  - No significant difference between overall survival in pediatric and adult groups [1].
- Tumor location is typically supratentorial (~98%) and more commonly reported in the temporal lobes [3, 4].

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- Clinical presentation: sudden onset of seizures (80%), cognitive or behavioral change, headache secondary to increased intracranial pressure [2].
- 30% risk of recurrence and 75–80% overall survival rates following primary resection and as needed adjuvant treatment [1]:
  - Poorer prognosis associated with anaplastic PXA: 5-year OS/PFS are 57% and 49% [4].
- For patients younger than 5 years old, a delay in irradiation is suggested if clinical symptoms permit, especially in pediatric patients with Grade II tumors (on average, this delay is 3–5 years from the time of diagnosis).
- Radiation is more often used in a salvage setting; the role of adjuvant radiation is less clear [5].

13.2 Classification Notes from Updated World Health Organization (WHO) 2016 Guidelines

- PXAs comprise less than 1% of astrocytic tumors [2].
- Astrocytomas like PXA have a more circumscribed growth pattern, lack IDH gene family alterations, and frequently have *BRAF* alterations. These characteristics are distinct from the diffuse gliomas [7].
- The descriptive title of "PXA with anaplastic features" is now called "anaplastic PXA" (APXA). Anaplastic PXA (WHO Grade III) is distinct from PXA (WHO Grade II) [7]:
  - Grading: 5 or more mitoses per 10 high-power fields (may/may not have necrosis)
  - Shorter survival time compared to garden variety PXA

13.3 Molecular Pathology

- PXAs have the highest frequencies of *BRAF* V600E mutation in primary CNS neoplasms (60–78%) which are identified with immunohistochemistry via *BRAF* V600E-specific monoclonal antibody [1]:
  - BRAF mutation less commonly seen in APXA (17–65%) [4]
- Recurrent 9p21.3 chromosomal loss [1] encompassing CDKN2A/2B tumor suppressor loci:
  - Loss of p16 expression
- Uncommon to have *IDH1-2* mutation (frequently present in infiltrating gliomas) [1]

Table 13.1 Suggested target volumes including GTV, CTV, and PTV

Target volumes	Definition and description
GTV (gross tumor volume)	All cystic and solid components of the tumor
CTV (clinical target volume)	GTV + 1–1.5 cm. This can be edited around anatomic boundaries such as the bone and dura In pediatric cases, clinical studies of smaller margins (as small as 5 mm for well-demarcated tumors) are ongoing [6]
PTV (planning target volume)	CTV+ 3–5 mm

13.4 General Principles of Simulation and Target Delineation

- Simulation
  - Patient will be simulated in the supine position, arms down and head in neutral position.
  - CT simulation with a thermoplastic head mask extending to the shoulder for immobilization.
- Recommendations for target delineation (Table 13.1)
  - Similar to other low-grade gliomas
  - Fusion of both preoperative and postoperative MRI (T1 post-gadolinium and T2 FLAIR) with CT simulation
  - Example in Fig. 13.1

13.5 Dose Prescriptions

- 50.4–54 Gy in 1.8–2.0 Gy fractions for PXA
- 54–59.4 Gy for anaplastic PXA (WHO Grade III)

13.6 Treatment Planning Techniques

- 3D conformal, IMRT, VMAT, or proton radiation techniques are all acceptable to conform radiation dose to the defined local target volume. Allows greater sparing of neuropsychological function (Figs. 13.2 and 13.3).
- Recommended coverage guidelines: aim to cover 95% of the PTV by 95% of prescribed dose.
- See Table 13.2 for recommended normal tissue constraints.

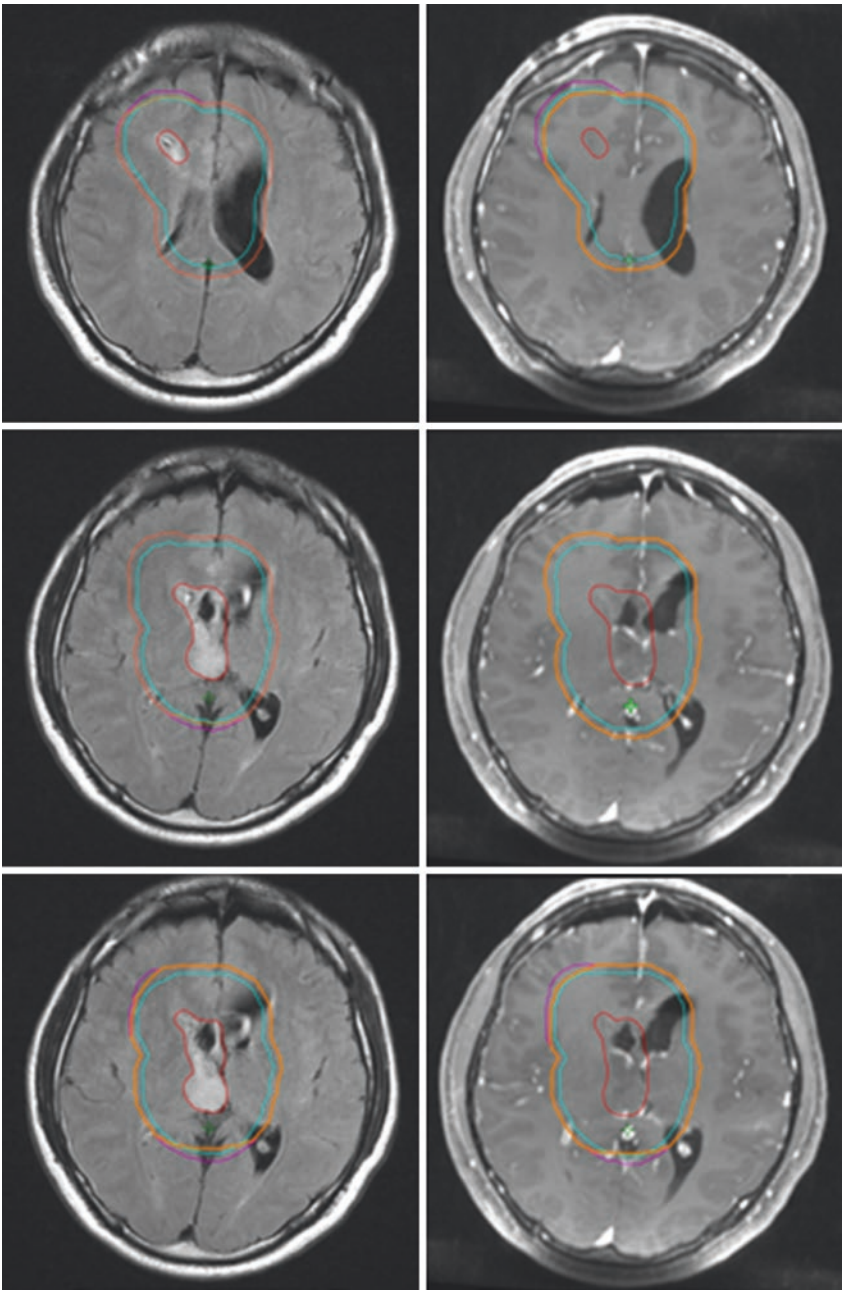

Fig. 13.1 Contours for a 30-year-old man with a resected third ventricular anaplastic pleomorphic xanthoastrocytoma (WHO Grade III). He was treated with 59.4 Gy in 33 fractions via VMAT (initial volume to 50.4 Gy with boost to 59.4 Gy, cropping out critical OARs from the higher-dose PTV). Left, T2 FLAIR images; right, T1 post contrast images. Red, GTV postsurgery; cyan, CTV; magenta, PTV 50.40 Gy; orange, PTV 59.40 Gy

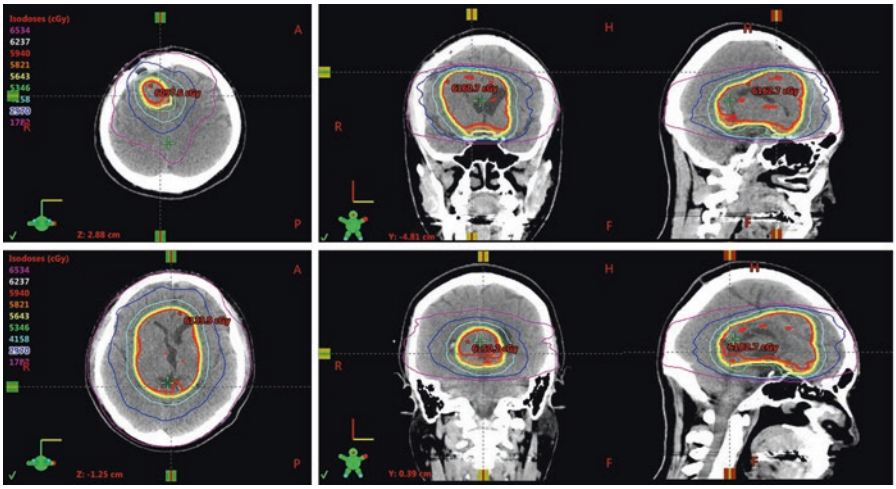

Fig. 13.2 VMAT treatment plan for the aforementioned patient with a resected third ventricular WHO Grade III anaplastic pleomorphic xanthoastrocytoma. Isodose lines: red (100%), orange (98%), yellow (95%), green (90%), cyan (70%), blue (50%), magenta (30%)

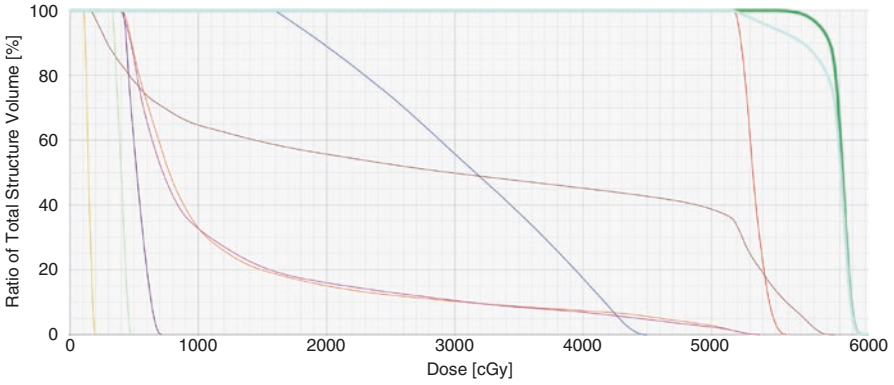

Fig. 13.3 DVH parameters for the aforementioned patient with a resected third ventricular WHO Grade III anaplastic pleomorphic xanthoastrocytoma. Dark green, PTV 59.40; cyan, PTV 50.40; red, optic chiasm; magenta, left optic nerve; orange, right optic nerve; brown, brain stem; dark blue, pituitary; purple, left cochlea; light green, right cochlea; dark yellow, spinal cord

Table 13.2 Recommended normal tissue constraints

Organ at risk	Suggested dose constraints
Optic chiasm and nerves	D_{max} <54 Gy
Brain stem	D_{max} <54 (unless Grade III APXA, then similar to high-grade glioma where D_{max} <60 Gy)
Lens	D_{max} <7 Gy
Retina	D_{max} <45 Gy
Lacrimal glands	D_{max} <30 Gy
Hippocampi	ALARA

13.7 Side Effects

- Acute side effects to evaluate during on-treatment visits include fatigue, hair loss, headaches, nausea, and cerebral edema.
- Late side effects and complications: neurocognitive decline, endocrine dysfunction, long-lasting cerebral edema, radiation necrosis.

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WHO Grades II and III Glioma

14

Lia M. Halasz, Arjun Sahgal, Eric L. Chang, and Simon S. Lo

Contents

14.1 General Principles of Simulation and Target Delineation (Table 14.1 and Fig. 14.1)

- CT simulation with a thermoplastic mask for immobilization.
- Obtain a volumetric thin slice MRI with T1 pre- and post-gadolinium, T2, and FLAIR for target delineation. The gross target volume (GTV) for low-grade glioma is the non-enhancing and enhancing mass which is best visualized on FLAIR sequences and T1 post-gadolinium sequences, respectively.

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Table 14.1 Suggested target volumes

Target volumes	Definition and description
GTV	Tumor extent and resection cavity on postoperative FLAIR and T1 post-gadolinium images. Preoperative MRIs can be helpful in determining residual disease from postoperative edema. For grade III gliomas, a cone down in a two-phase ($GTV_{conedown}$) technique can target the contrast-enhanced tumor.
CTV	GTV + 1.0–1.5 cm. This should be edited around anatomic boundaries such as the bone, tentorium, falx, and dura 1.0 cm for grade II and/or IDH mutant glioma; 1.0–1.5 cm for grade III and/or IDH wild-type glioma. If a cone down is planned after 50.4 Gy for grade III and/or IDH wild-type glioma, the $CTV_{conedown}$ will be $GTV_{conedown}$ + 1.0–1.5 cm.
PTV	CTV + 0.3–0.5 cm depending on comfort of patient positioning, mask fit, image guidance technique (AP/lateral imaging or cone beam CT), and if rotational corrections are being corrected with a 6-degree-of-freedom couch. By the same token, $PTV_{conedown}$ will be 0.3–0.5 cm expansion from $CTV_{conedown}$.

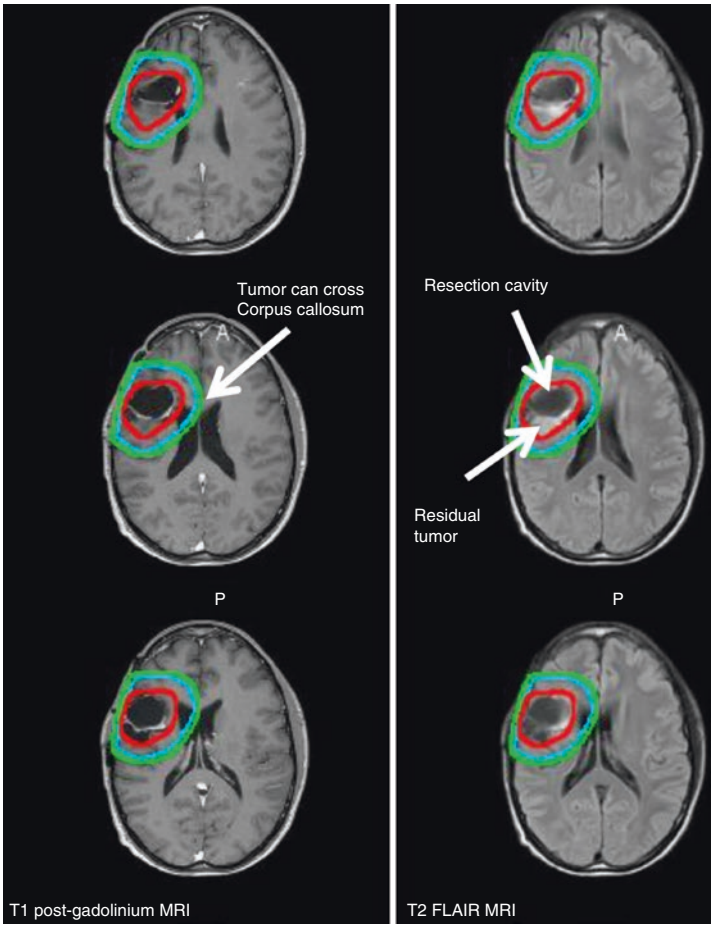

Fig. 14.1 Contours for a patient with WHO grade II oligodendroglioma, with IDH mutation and 1p19q codeletion, of the right frontal lobe. GTV, red; CTV, blue; PTV, green

- Ideally, fuse both the preoperative and postoperative T2/FLAIR and post-gadolinium MRIs to help delineate target volume; however, the postoperative MRI is what determines the volumes.
- If the patient has contraindications to MRI, can use CT with and without contrast, but this is substandard.
- In cases of partial or complete lobectomy, the region anterior to the resection edge where no brain tissue is present does not need to be included in the GTV.
- CTV expansion should respect natural anatomic barriers, including the bone, tentorium, fax, and dura.
- Tumors can cross the corpus callosum, which should be included in CTV expansion.
- 3D conformal, IMRT, or proton therapy can be considered to spare normal brain and hippocampi when possible.

14.2 Dose Prescriptions

- 50.4–60 Gy in 1.8–2.0 Gy fractions.
- Grade II and/or IDH mutant glioma: 50.4–54 Gy.
- Grade III and/or IDH wild-type glioma: 59.4–60 Gy; if there is no contrast enhancement, the PTV will be treated to the full dose; in some centers, if there is contrast enhancement, a cone down will occur after 50.4 Gy.

In the past, 50.4–54 Gy for grade II glioma and 59.4–60 Gy for grade III glioma. With the publication of the *2016 World Health Organization Classification of Tumors of the Central Nervous System*, gliomas are now classified by IDH mutation rather than grade given it has better prognostic value. Though controversy in this area exists, many consider dose dependent on IDH mutation status rather than grade.

14.3 Treatment Planning Techniques

- 3D CRT, IMRT, VMAT, or proton therapy may be used with the goal of sparing the contralateral brain, hippocampi, cochleae, and pituitary if possible (Figs. 14.2 and 14.3).
- Treatment planning aimed to cover 95% of the PTV volume by 95% of the prescribed dose for photon plans and 100% of the CTV volume by 100% of the prescribed dose for proton plans while respecting the OAR constraints. For complex tumors adjacent to critical OAR like the chiasm, brain stem, and optic nerves, coverage may suffer to 90% coverage of the PTV by 95% of the prescribed dose and plan acceptability taken on a case-by-case basis (Table 14.2).

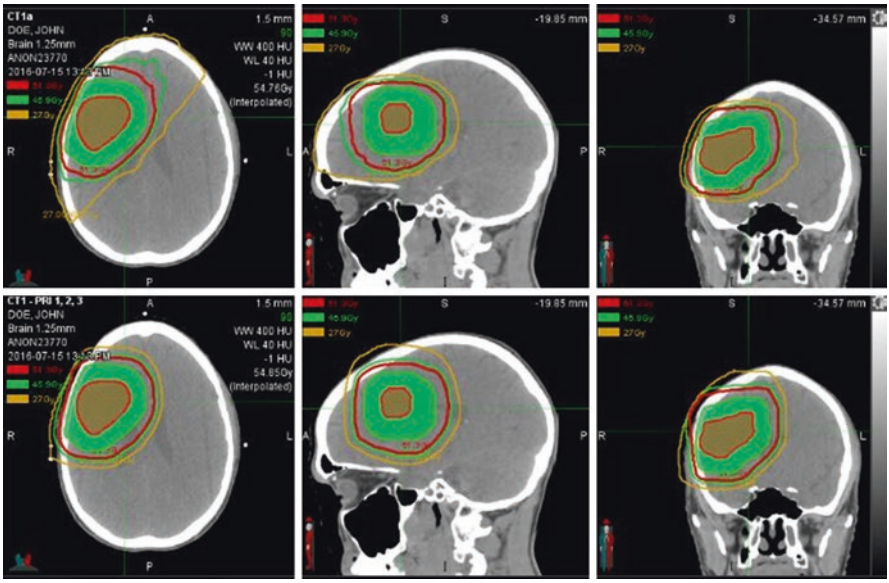

Fig. 14.2 Sample plan for the above patient with WHO grade II oligodendroglioma of the right frontal lobe. IMRT plan is on the top and a proton plan is on the bottom. Red line is 95% isodose line, green is 85% isodose line, and yellow is 50% isodose line

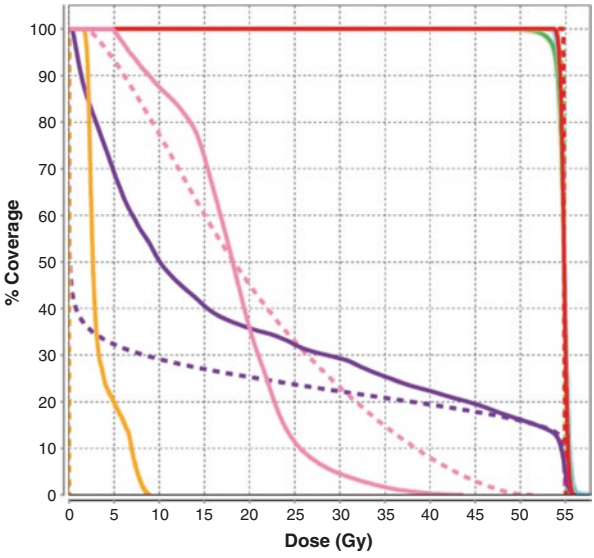

Fig. 14.3 Sample dose-volume histogram for the above patient with WHO grade II oligodendroglioma of the right frontal lobe. IMRT plan, solid line; proton plan, dotted line. GTV, red; CTV, blue; PTV, green; contralateral hippocampus, orange; ipsilateral hippocampus, pink; brain, purple

Table 14.2 Recommended normal tissue constraints for 1.8 Gy/day fractionation schemes

Organs at risk	Suggested dose constraints
Optic nerves and chiasm	<54 Gy [1]
Globe	<45 Gy [1]
Lenses	<10 Gy [1]
Lacrimal glands	<30 Gy, mean <25 Gy without compromising tumor coverage [2]
Brain stem	<54 Gy or <60 Gy, depending on prescription dose
Hippocampi	Beam angles and planning techniques (e.g., IMRT or proton therapy) to minimize dose to hippocampi
Pituitary gland	Beam angles and planning techniques (e.g., IMRT or proton therapy) to minimize dose to pituitary

Table 14.3 Side effects

Acute	Hair loss, fatigue, headaches, nausea, and cerebral edema causing neurological symptoms
Long-term	Neurocognitive decline and hypopituitarism. Radiation necroses 5%
Uncommon or rare risks	Pseudoprogression causing neurological symptoms, vision loss, hearing loss, secondary malignancies

14.4 Side Effects

See Table 14.3.

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Glioblastoma

15

John B. Fiveash and Caleb Dulaney

Contents

15.1 General Principles of Simulation and Target Delineation

- Information on simulation
  - CT simulation with thermoplastic mask for immobilization. Contrast may be of limited value at the time of CT if high-quality MRI is available for image registration.
  - Obtain volumetric thin slice T1 pre- and post-contrast MRI including T2 and FLAIR sequences.
- Recommendations for target delineation (Tables 15.1, 15.2, and 15.3, Fig. 15.1)
  - The target is primarily defined on the postoperative MRI utilized for treatment planning, although registration of the preoperative images may be helpful to assess changing FLAIR/T2 abnormalities or in defining portions of the surgical cavity.

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Table 15.1 Suggested target volumes for glioblastoma with a two-phase approach

Target volumes	Definition and description
GTV_4600	FLAIR or T2 on postoperative MRI; include all of GTV_6000 in this volume
CTV_4600	GTV_4600 plus a variable margin for microscopic involvement. This is typically 0.5–2.0 cm. Exclude tissues from this volume that are at low risk to be infiltrated by tumor (dura, bone, across the falx, into the ventricle, unviolated tentorium)
PTV_4600	CTV_4600 plus a margin for setup error and localization. With daily KV image guidance and a thermoplastic masks, this will typically be 3–5 mm
GTV_6000	T1-enhancing tumor plus postoperative cavity
CTV_6000	GTV_6000 plus a variable margin for microscopic involvement. This is typically 0.5–2.0 cm. Exclude tissues from this volume that are at low risk to be infiltrated by tumor (dura, bone, across the falx, into the ventricle, unviolated tentorium)
PTV_6000	CTV_6000 plus a margin for setup error and localization. With daily KV image guidance and a thermoplastic mask, this will typically be 3–5 mm

Table 15.2 Suggested target volumes for glioblastoma with a single-phase approach (60 Gy in 30 fractions)

Target volumes	Definition and description
GTV_6000	T1-enhancing tumor including the postoperative cavity
CTV_6000	GTV_6000 plus a variable margin for microscopic involvement. This is typically 1.5–2.0 cm. Exclude tissues from this volume that are at low risk to be infiltrated by tumor (dura, bone, across the falx, into the ventricle, unviolated tentorium). If adjacent areas of FLAIR are considered high risk and extend beyond the expansion margin, then this can be taken into the CTV_6000 volume
PTV_6000	CTV_6000 plus a margin for setup error and localization. With daily KV image guidance and a thermoplastic mask, this will typically be 3–5 mm

For patients that cannot have an MRI due to a pacemaker, planning is based upon the postoperative CT, and an additional CTV margin of 1–2 cm should be considered

Table 15.3 Suggested target volumes for elderly glioblastoma as a hypofractionated single-phase approach (40 Gy in 15 fractions)

Target volumes	Definition and description
GTV_4000	T1-enhancing tumor including the postoperative cavity
CTV_4000	GTV_4000 plus a variable margin for microscopic involvement. This is typically 1.5–2.0 cm. Exclude tissues from this volume that are at low risk to be infiltrated by tumor (dura, bone, across the falx, into the ventricle, unviolated tentorium). If adjacent areas of FLAIR are considered high risk and extend beyond the expansion margin, then this can be taken into the CTV_4000 volume
PTV_4000	CTV_4000 plus a margin for setup error and localization. With daily KV image guidance and a thermoplastic mask, this will typically be 3–5 mm

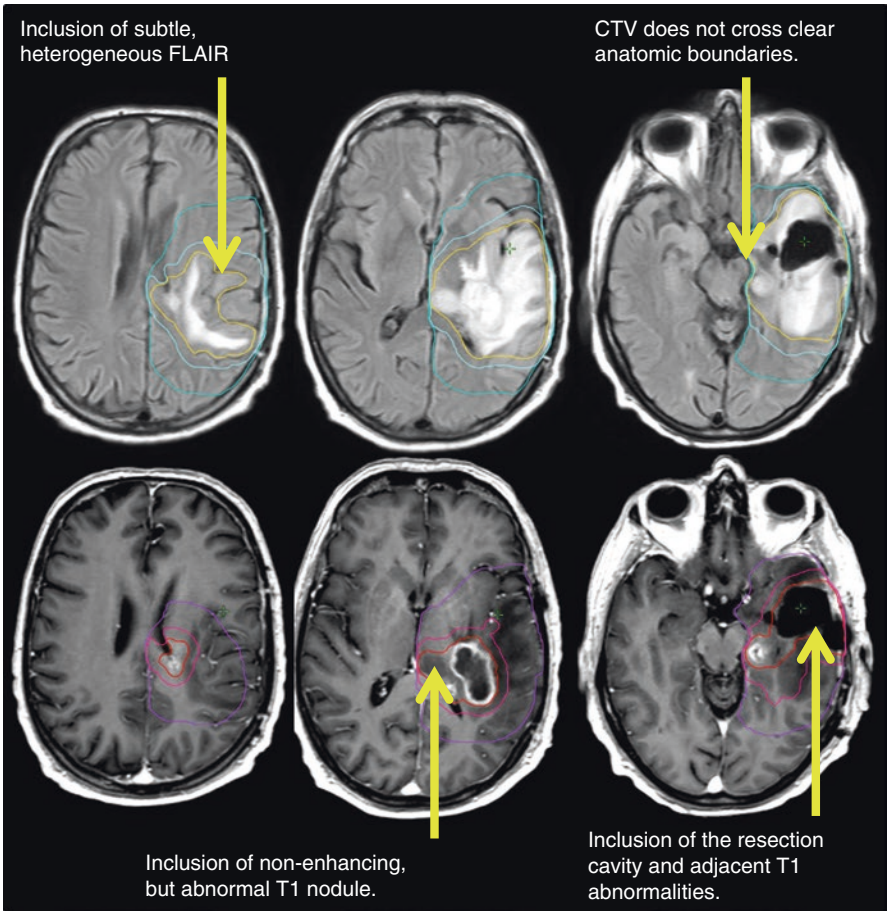

Fig. 15.1 Contours for a patient with WHO IV glioblastoma of the left temporal lobe following partial resection. The upper series shows axial T2-FLAIR images with the T2-GTV in yellow. Two approaches to CTV expansion are shown: Adult Brain Tumor Consortium (ABTC) with 0.5 cm expansion in light blue and Radiation Therapy Oncology Group (RTOG) with 2 cm expansion in green. The lower series shows the same axial slices but on the T1 contrast series with the T1-GTV in red. The ABTC boost CTV (0.5 mm expansion) is in pink. Purple represents both the RTOG boost CTV (2 cm expansion) and the European Organisation for Research and Treatment of Cancer (EORTC) single-phase CTV with 2 cm expansion

- If treatment planning is delayed more than 2–3 weeks following the postoperative MRI, consider obtaining an additional MRI for planning.
- Variation exists in practice between a two-phase approach and a single-phase approach.
- The use of functional imaging in planning GBM remains investigational (e.g., FET-PET avid areas to be boosted).

15.2 Dose Prescriptions

- Either a single- or two-phase treatment is acceptable. If a single phase for treatment is considered for glioblastoma, smaller CTV margins such as 0.5 cm have not been well-studied.
- For two-phase treatment, PTV_4600 should receive 46 Gy in 23 fractions followed by a 7-fraction boost to PTV_6000 for a total of 60 Gy in 30 fractions.
- For elderly or low-performance status patients, consider hypofractionated radiation therapy to 40 Gy in 15 fractions. Another randomized study has investigated 25 Gy in 5 fractions.

15.3 Treatment Planning Techniques

- Patients should receive 3D or IMRT plans. The role of protons for dose escalation is being studied in NRG BN001.
- Goals: PTV D95% $\geq$ 60 Gy, D0.03cc < 64 Gy.
- See Table 15.4.

Assess target coverage on the individual plans and dosimetry of the organs at risk on the sum plan. Generally, do not underdose gross tumor to achieve dose limits to normal tissue. A small portion of the PTV may be underdosed if clinically indicated.

15.4 Side Effects (Table 15.5)

On-treatment visit should include assessment of hematologic function (lymphopenia, thrombocytopenia), steroid toxicity (hyperglycemia, insomnia, oral candidiasis, proximal muscle weakness), and screening for deep venous thrombosis and oral thrush.

Table 15.4 Dose constraints

Organs at risk (in order of importance)	Suggested dose constraints
Optic nerves and chiasm	Dmax <54, up to 60 Gy if needed for tumor coverage
Brain stem below the thalamus	Dmax <54, up to 60 Gy if needed for tumor coverage
Retinae	Dmax <45 Gy
Lens	<10 Gy
Lacrimal glands	Mean <30 Gy
Pituitary	Minimize dose, consider mean <40 Gy

Table 15.5 Side effects

Acute	Hair loss, fatigue, headaches, nausea, and cerebral edema causing neurological symptoms
Long-term	Neurocognitive decline and hypopituitarism. Radiation necrosis (5%)
Uncommon or rare risks	Pseudoprogression causing neurological symptoms, vision loss, hearing loss, secondary malignancies

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Brainstem Glioma

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Tamara Z. Vern Gross, Michael D. Chan, and John T. Lucas Jr

Contents

16.1 General Principles of Simulation and Target Delineation (Tables 16.1 and 16.2)

- Information on simulation
  - Recommended imaging

    Preoperative as well as postoperative imaging should be obtained.

    Imaging sequences should include at least T1, T1 with contrast, T2, and FLAIR.

    CT planning scan section thickness should ideally be ≤5 mm, although ≤2–3 mm remains ideal.

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Table 16.1 Target volume guidelines for low-grade intrinsic brainstem gliomas

Target volumes	Definition and description
GTV	Gross tumor on T2/FLAIR and T1 post-gadolinium images. All tumor cysts should be included in the GTV. Any MR imaging before or after surgical or chemotherapeutic intervention are helpful for identifying the extent of initial tumor involvement and evaluating residual disease
CTV	GTV + 0.5–1 cm expansion. This should be modified depending on initial tumor involvement and areas of suspected invasion and manually constrained by neuroanatomical structures where invasion is not likely (bony calvarium, falx, and tentorium)
PTV	CTV + 0.3–0.5 cm depending on institutional standards, patient immobilization and comfort, and image-guided capabilities (portal imaging vs. cone-beam CT)

Table 16.2 Target volume guidelines for diffuse pontine intrinsic gliomas

Target volumes	Definition and description
GTV	Gross tumor as identified on T2/FLAIR and T1 post-gadolinium MRI sequences. Any MR imaging before or after chemotherapeutic intervention are helpful for identifying extent of initial tumor involvement and evaluating residual disease. DIPG rarely undergo neoadjuvant chemotherapy or surgery; however, if biopsy is performed, this must also be taken into account
CTV	GTV + 1 cm. This should be modified depending on initial tumor involvement and areas of suspected invasion and manually constrained by neuroanatomical structures where invasion is not likely (bony calvarium, falx and tentorium
PTV	CTV + 0.3–0.5 cm depending on institutional standards, patient immobilization and comfort, and image-guided capabilities (portal imaging vs. cone-beam CT)

  - Patient positioning

    Supine positioning and immobilization with a short aquaplast mask are recommended. The use of photon vs. proton radiotherapy may dictate head position or the need for other special setup devices like table-associated range shifter, etc.

- Recommendations for target delineation (Figs. 16.1 and 16.2)
  - Imaging sequences and special circumstances

    Low-grade intrinsic gliomas tend to hypointense on T1-weighted and hyperintense on T2-weighted sequences, varying in degree following gadolinium infusion depending on independent tumor characteristics. Diffuse intrinsic pontine gliomas are expansile tumors that are homogeneously hypointense lesion on T1 and hyperintense on T2. MR T2 and T2 FLAIR are most likely to assist with defining the extent of disease and postoperative tumor bed (if applicable).
  - On-treatment imaging

    Daily cone-beam CT or other stereotactic technique is recommended given the small tumor volumes and commonly pediatric patients that may require sedation and airway protection during treatment.

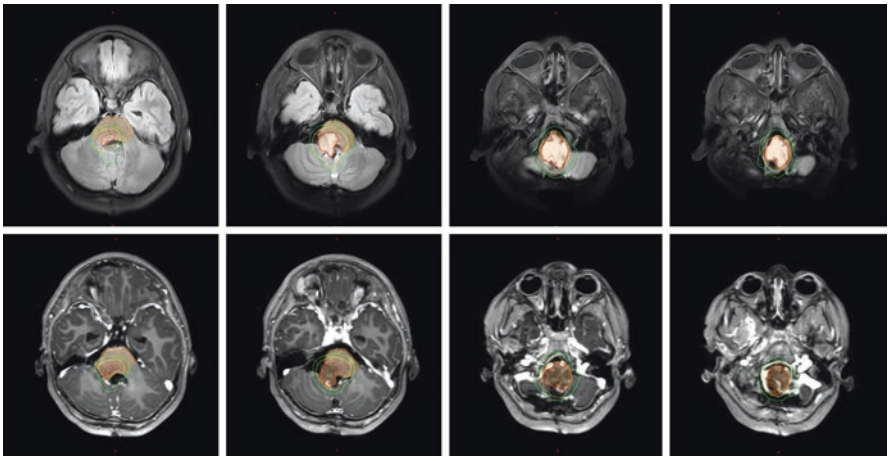

Fig. 16.1 Contours for a patient with low-grade intrinsic ganglioglioma involving the brainstem, WHO grade I. GTV, red; CTV, yellow; PTV, green. Top row, T2 FLAIR axial MRI sequences; bottom row (T1 3D post-contrast axial MRI sequences)

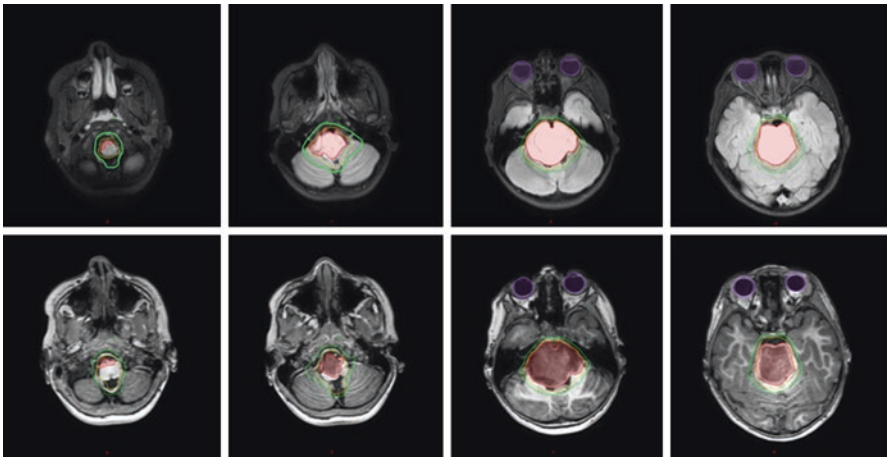

Fig. 16.2 Contours for a patient with a diffuse pontine intrinsic glioma. GTV, red; CTV, yellow; PTV, green. Top row (T2 FLAIR axial MRI sequences); bottom row (T1 3D post-contrast axial MRI sequences)

16.2 Dose Prescriptions

- A dose of 50.4 Gy in 1.8 Gy fractions is generally recommended for low-grade intrinsic brainstem glioma; however, doses ranging from 45 to 50.4 Gy are acceptable depending on the extent of brainstem involvement and ability to meet the dose constraints of the organs at risk.
- A dose of 54.0 Gy in 1.8 Gy fractions is generally recommended for diffuse pontine intrinsic glioma.

16.3 Treatment Planning Techniques (Fig. 16.3 and Table 16.3)

- Modality
  - 4–6 MV photons are typically utilized for treatment. Protons may also be considered.
- Treatment technique
  - Three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), or volumetric modulated arc therapy (VMAT) may be used with the goal of sparing the brain, brainstem, temporal lobes, hippocampi, cochlea, and pituitary/hypothalamic complex if possible.
  - Treatment planning is aimed so that at least 100% of the PTV is covered by 95% of the prescribed dose. Depending on tumor complexity and proximity to organs at risk (brainstem, cochlea, temporal lobes, spinal cord, etc.), achieving 95% coverage of the PTV by 95% of the prescribed dose is acceptable. Furthermore, no more than 10% of the PTV should receive greater than 110% of the prescription dose as determined by the dose volume histogram (DVH).
  - A goal is to achieve uniform dose distributions (utilize wedges, compensators, or any additional techniques).
  - If using proton beam therapy (PBT):

    In patients with focal tumors or low-grade intrinsic brainstem gliomas, consider proton beam therapy, as these children are more likely to achieve a therapeutic benefit by reducing the risk of late toxicities of therapy from reducing radiation dose to normal tissue toxicity while maintaining target volume coverage.

    Because lateral and range expansions may vary for each beam, a single PTV is no longer adequate and should not be used to determine the distal range for the individual proton beams. Instead of prescribing a uniform dose to a PTV, the treatment plan should be created to encompass the CTV in the setting of expected uncertainties. Thus, the distal target margin is based on the distal aspect of the CTV, range uncertainty, setup margin

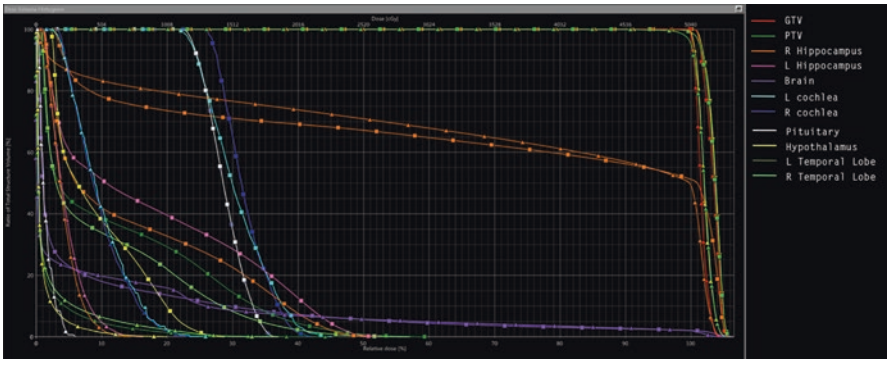

Fig. 16.3 Dose volume histogram diagnosed with low-grade glioma of the brainstem. Proton beam therapy plan, triangle line; VMAT, square line

Table 16.3 Recommended coverage guidelines and dose constraints

Organs at risk	Dose constraints (preferred)
PTV (planning target volume) [1]	Volume receiving 100% dose ≥99%
	Volume receiving 110% dose <10%
Cochlea [1]	Dose received by 50% cochlea ≤20 Gy
Optic globes [1]	Dose received by 90% optic globes ≤5 Gy
	Dose received by 50% ≤10 Gy
	Dose received by 10% ≤35 Gy
Optic nerves [1]	Dose received by 90% (single) optic nerve ≤10 Gy
	Dose received by 50% ≤54 Gy
	Dose received by 10% ≤56 Gy
Optic chiasm [1]	Dose received by 90% optic chiasm ≤10 Gy
	Dose received by 50% ≤54 Gy
	Dose received by 10% ≤56 Gy
Pituitary [2]	Mean <16 Gy
	Volume receiving 30 Gy <50%
Hypothalamus [2]	Mean <16 Gy
	Volume receiving 30 Gy <50%
Brainstem [3]	Mean <44.2 Gy
	Dose received by 0.1 cc brainstem (minus GTV) <56.6 Gy
	Dose received by 90% <44 Gy
	Dose received by 50% <52.2 Gy
	Dose received by 10% <55.4 Gy
Brainstem core [3]	Dose received by 0.1 cc <54.6 Gy
Spinal cord [1]	Volume receiving 50.4 Gy <5 cc
	Dose received by 50% spinal cord <26 Gy

(SM), and internal margin (IM). The IM compensates for all tissue size and shape variation within the CTV. The SM accounts for daily dosimetric and setup uncertainties related to patient positioning, software, and equipment.

16.4 Side Effects

- Acute side effects to evaluate during weekly on-treatment visits
  - Hair loss, fatigue, radiation dermatitis, headaches, nausea, aural fullness, risk of transient edema causing neurological symptoms or resulting in obstructive hydrocephalus.
- Late side effects and complications
  - Temporary or permanent hair loss, injury to the cochlea, causing partial or full hearing loss in one or both ears; hypopituitarism leading to endocrine abnormalities and infertility; neurocognitive decline impacting memory, IQ, and behavior; risk of injury to cranial nerves in the region, which could result in swallowing dysfunction, requiring feeding tube or tracheotomy; injury to the circle of Willis and surrounding vessels, increasing the risk of vasculopa-

thy and stroke; damage to the brainstem and normal brain tissue, which could result in permanent sensory deficit, paralysis, or death; risk of developing secondary malignancies.

- Clinical pearls for addressing those side effects
  - If patients are on steroids at the time of radiotherapy, utilization of gastric prophylaxis (e.g., ranitidine) and evaluation for oral thrush are recommended.
  - Premedicate patients with ondansetron 1 h prior to radiotherapy for prevention of nausea. May need to add a combination of dexamethasone, prochlorperazine, and lorazepam if nausea breaks through prophylaxis.

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Pineal Tumors (PPTID, PTPR)

17

Chia-Lin Tseng and Arjun Sahgal

Contents

17.1 Pineal Parenchymal Tumor of Intermediate Differentiation (PPTID)

17.1.1 General Principles of Simulation and Target Delineation

- No consensus from phase III prospective data to guide adjuvant therapy; focal radiotherapy should be considered to improve local control.
- CT simulation with thin slices (1–2 mm) in the supine position with a thermoplastic mask for immobilization.
- Obtain volumetric thin slice (1–2 mm) T1 post-gadolinium axial MRI sequences and T2/FLAIR MRI sequences.

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Table 17.1 Suggested target volumes

Target volumes	Definition and description
GTV	Gross enhancing tumor or residual postoperative enhancing tumor cavity on T1 post-gadolinium images. Focal cystic and/or hemorrhagic areas may be present and should be included
CTV	CTV = GTV + 0.3–0.5 cm, respecting anatomic boundaries including the bone and dura/falx cerebri/tentorium. The preoperative MRI should be used to guide inclusion of at-risk region
PTV	PTV = CTV + 0.3–0.5 cm depending on patient positioning, mask fit, image guidance technique

- To aid in target delineation, fuse both the preoperative (in the event of prior surgery) and post-gadolinium T1 ± T2/FLAIR MRIs with the CT simulation scan.
- Table 17.1 summarizes the suggested target volumes.

17.1.2 Dose Prescriptions

- PTV: 50–54 Gy in 25–30 daily fractions

17.1.3 Treatment Planning Techniques

- 3D-CRT, IMRT, VMAT, or proton therapy may be used with the goal of sparing the normal brain, hippocampi, and pituitary whenever possible.
- The treatment planning objective is to cover 95% of the PTV volume by 95% of the prescribed dose while respecting the organ-at-risk (OAR) constraints. Large or complex tumors in close proximity to other critical OARs including the chiasm or brainstem may necessitate a compromise in target coverage and should be evaluated on a case-by-case basis.
- Daily IGRT with cone-beam CT matching to the bone is recommended.
- Tables 17.2 and 17.3 summarize the dose constraints and side effects, respectively.

Case I A 62-year-old male presented with confusion, dizziness, and headaches and was found to have obstructive hydrocephalus with an enhancing tumor in the third ventricle with involvement of the pineal gland. A third ventriculostomy was performed with subtotal resection of the tumor, from which the pathology was consistent with a pineal parenchymal tumor of intermediate differentiation, WHO Grade II. Staging MRI spine showed no tumor dissemination. The target contours are illustrated in Fig. 17.1, plan in Fig. 17.2, and dose-volume-histogram (DVH) in Fig. 17.3.

Table 17.2 Recommended dose constraints for critical organs-at-risk for 1.8–2 Gy/day fractionation schemes

Organs-at-risk	Suggested dose constraints
Optic nerves and chiasm	D_{max} <54 Gy
Brainstem	D_{max} <54 Gy
Cochlea	Mean ≤45 Gy
Eyes	D_{max} <45 Gy
Lenses	D_{max} <10 Gy
Hippocampi	Mean dose <20 Gy if achievable
Pituitary gland	D_{max} 30–45 Gy and mean <30 Gy if achievable

Note: D_{max} refers to the maximum point dose

Table 17.3 Side effects

Acute	Fatigue, dermatitis, alopecia, headache, cerebral edema causing nausea/vomiting and headaches
Subacute	Somnolence syndrome
Long-term	Hypopituitarism, hearing loss, cataracts, leukoencephalopathy, neurocognitive deficits, and second malignancies

17.2 Papillary Tumor of the Pineal Region (PTPR)

17.2.1 General Principles of Simulation and Target Delineation

- Rare neuroectodermal tumor with no current consensus regarding adjuvant therapy after surgical resection; focal radiotherapy should be considered to improve local control.
- CT simulation with thin slices (1–2 mm) in the supine position with a thermoplastic mask for immobilization.
- Obtain volumetric thin slice (1–2 mm) T1 post-gadolinium axial MRI sequences and T2/FLAIR MRI sequences.
- To aid in target delineation, fuse both the preoperative (in the event of prior surgery) and post-gadolinium T1 ± T2/FLAIR MRIs with the CT simulation scan.
- Table 17.4 summarizes the suggested target volumes.

17.2.2 Dose Prescriptions

- PTV: 50–54 Gy in 25–30 daily fractions

17.2.3 Treatment Planning Techniques

- 3D-CRT, IMRT, VMAT, or proton therapy may be used with the goal of sparing the normal brain, hippocampi, and pituitary whenever possible.

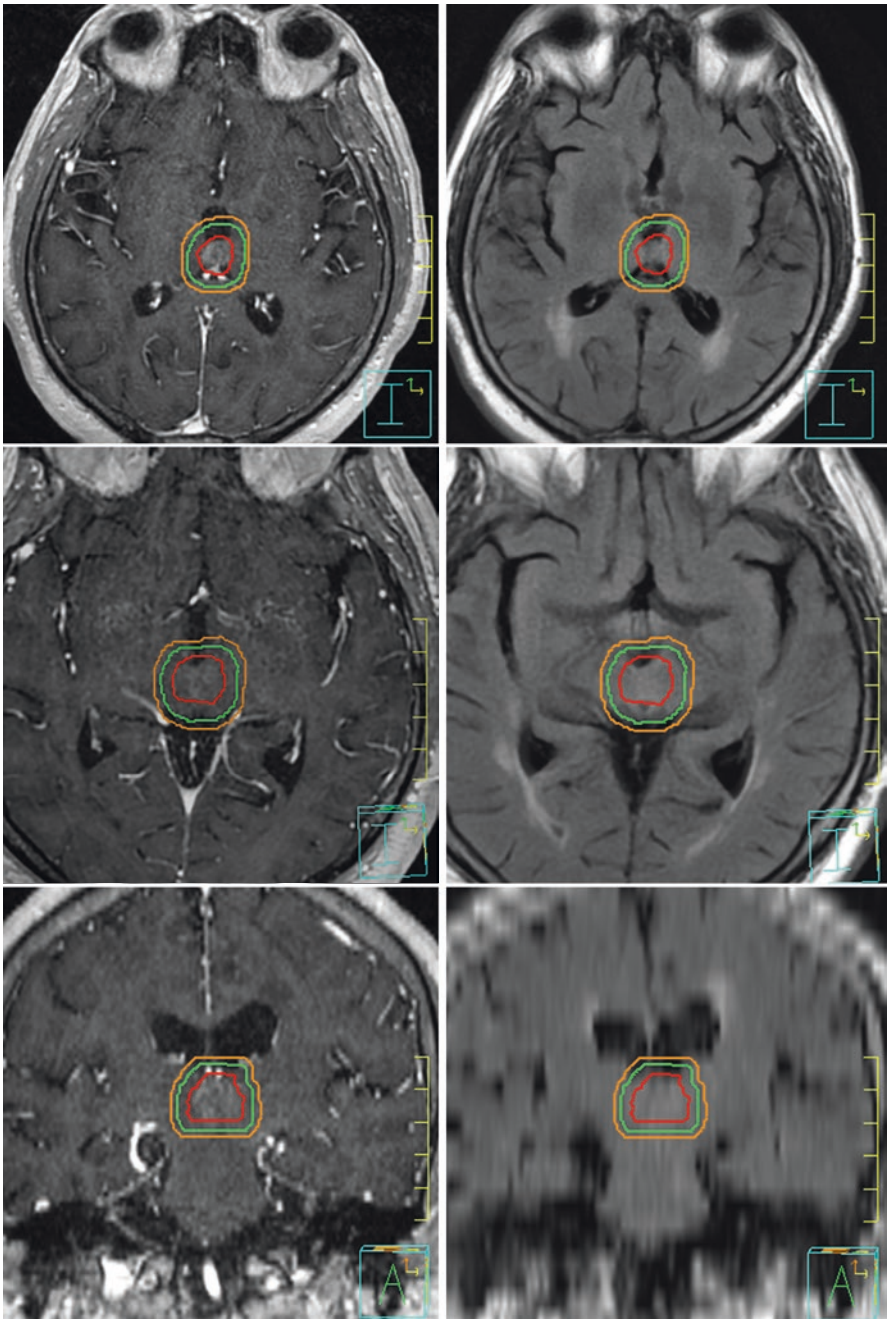


Fig. 17.1 Contours of target based on the T1 post-gadolinium MRI (left) and T2 FLAIR/MRI sequences (right). GTV is shown in red, CTV in green, and PTV in orange

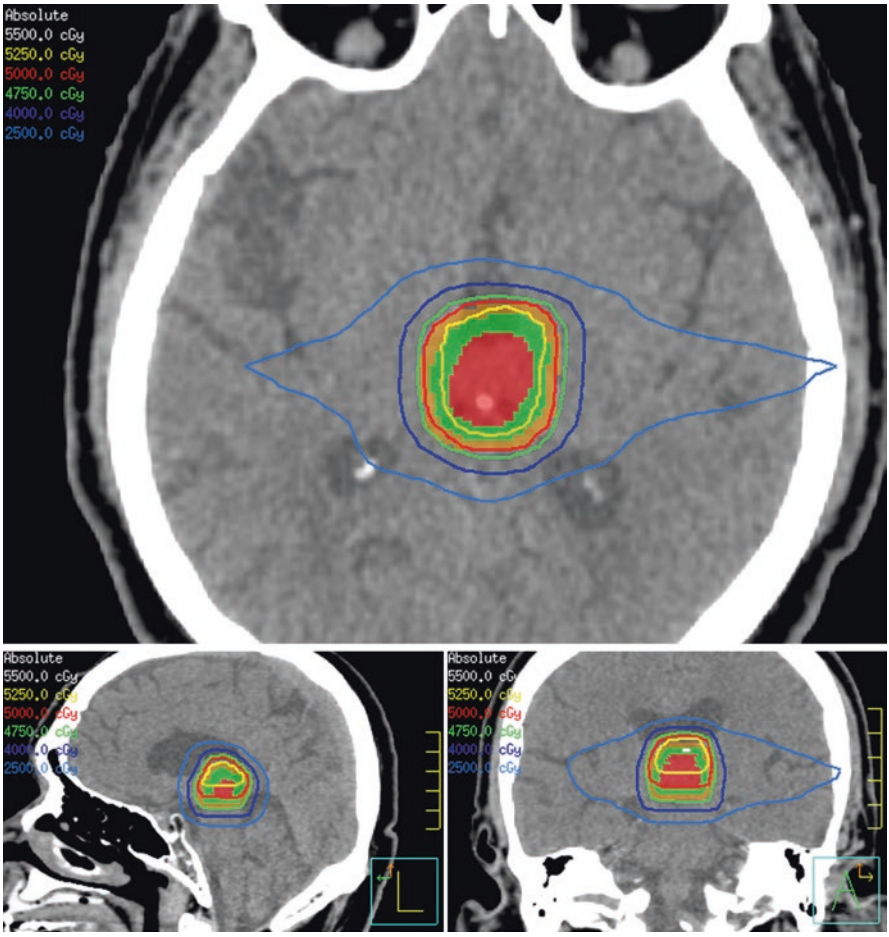
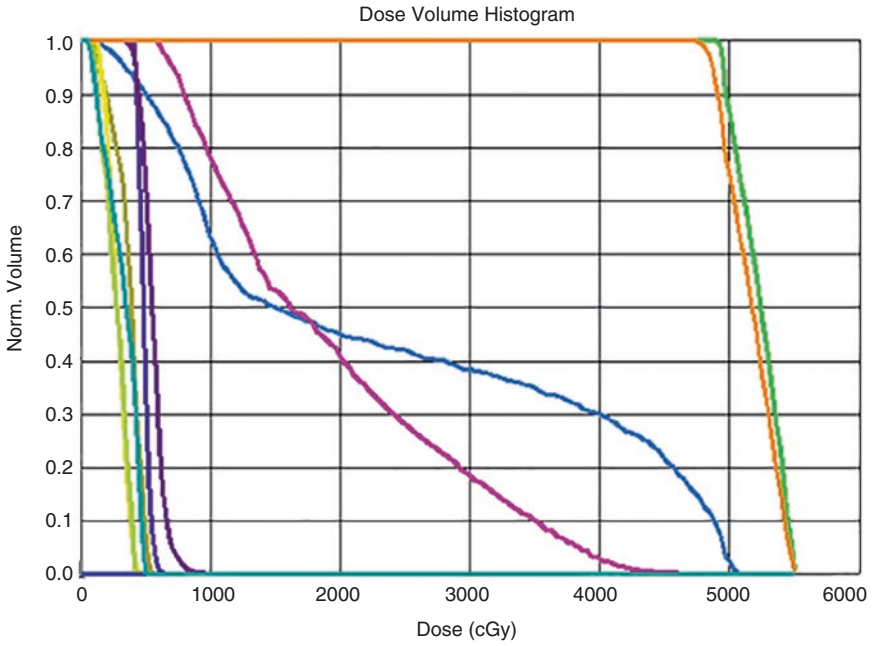


Fig. 17.2 Sample plan with a prescription of 50 Gy in 25 fractions for the illustrative case using an IMRT approach showing selected isodose lines (55 Gy in white, 52.5 Gy in yellow, 50 Gy in red, 47.5 Gy in green, 40 Gy in blue, and 25 Gy in light blue), in the axial (top), sagittal (bottom left), and coronal (bottom right) planes

- The treatment planning objective is to cover 95% of the PTV volume by 95% of the prescribed dose while respecting the OAR constraints. Large or complex tumors in close proximity to other critical OARs including the chiasm or brain stem may necessitate a compromise in target coverage and should be evaluated on a case-by-case basis.
- Daily IGRT with cone-beam CT matching to bone is recommended.
- Tables 17.5 and 17.6 summarize the dose constraints and side effects, respectively.



Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.
	BRAINSTEM	treat	105	5077	2341	1744
	CTV	treat	4847	5508	5226	172
	Eye_L	treat	89	548	368	107
	LENS_L	treat	120	449	281	76
	LENS_R	treat	80	420	268	96
	OPTIC CHIASM	treat	571	4603	1907	1006
	OPTIC NERVE_L	treat	411	663	486	42
	OPTIC NERVE_R	treat	327	948	555	87
	PTV	treat	4640	5508	5164	192
	SPINAL CORD	treat	--	--	--	--
	rt globe	treat	61	505	320	130

Fig. 17.3 Dose-volume histogram (DVH) for the above patient. 99.7% of the PTV is covered by 95% of prescription (47.5 Gy). 85.5% of the CTV is covered by 100% of prescription (50 Gy)

Table 17.4 Suggested target volumes

Target volumes	Definition and description
GTV	Gross enhancing tumor or residual postoperative enhancing tumor cavity on T1 post-gadolinium images. Focal cystic and/or hemorrhagic areas may be present and should be included
CTV	CTV = GTV + 0.3–0.5 cm, respecting anatomic boundaries including the bone and dura/falx cerebri/tentorium. The preoperative MRI should be used to guide inclusion of at-risk region
PTV	PTV = CTV + 0.3–0.5 cm depending on patient positioning, mask fit, image guidance technique

Table 17.5 Recommended dose constraints for critical organs-at-risk for 1.8–2 Gy/day fractionation schemes

Organs-at-risks	Suggested dose constraints
Optic nerves and chiasm	D_{max} <54 Gy
Brainstem	D_{max} <54 Gy
Cochlea	Mean ≤45 Gy
Eyes	D_{max} <45 Gy
Lenses	D_{max} <10 Gy
Hippocampi	Mean dose <20 Gy if achievable
Pituitary gland	D_{max} 30–45 Gy and mean <30 Gy if achievable

Note: D_{max} refers to the maximum point dose

Table 17.6 Side effects

Acute	Fatigue, dermatitis, alopecia, headache, cerebral edema causing nausea/vomiting and headaches
Subacute	Somnolence syndrome
Long-term	Hypopituitarism, hearing loss, cataracts, leukoencephalopathy, neurocognitive deficits, and second malignancies

Case II A 30-year-old male presented with progressive blurry vision, associated with headaches, nausea, and vomiting. MR imaging demonstrated obstructive hydrocephalus associated with a pineal tumor with complex cystic components. A third ventriculostomy and biopsy were performed, with pathology confirming papillary tumor of the pineal region (PTPR), WHO Grades II–III. MRI spine showed no evidence of drop metastases. Preoperative MRI is shown in Fig. 17.4, contours in Fig. 17.5, plan in Fig. 17.6, and DVH in Fig. 17.7.

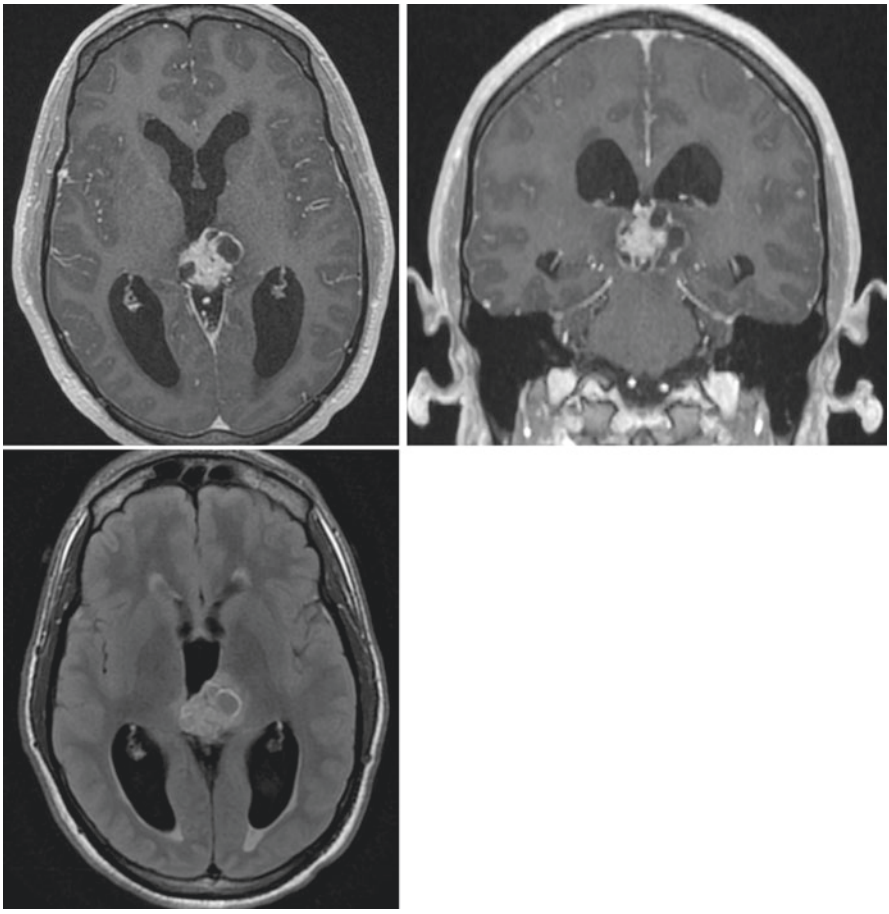


Fig. 17.4 Preoperative MRI for the above case. T1 post-gadolinium MRI is shown at the top (axial on left, coronal on right), and T2/FLAIR axial MRI is shown at the bottom

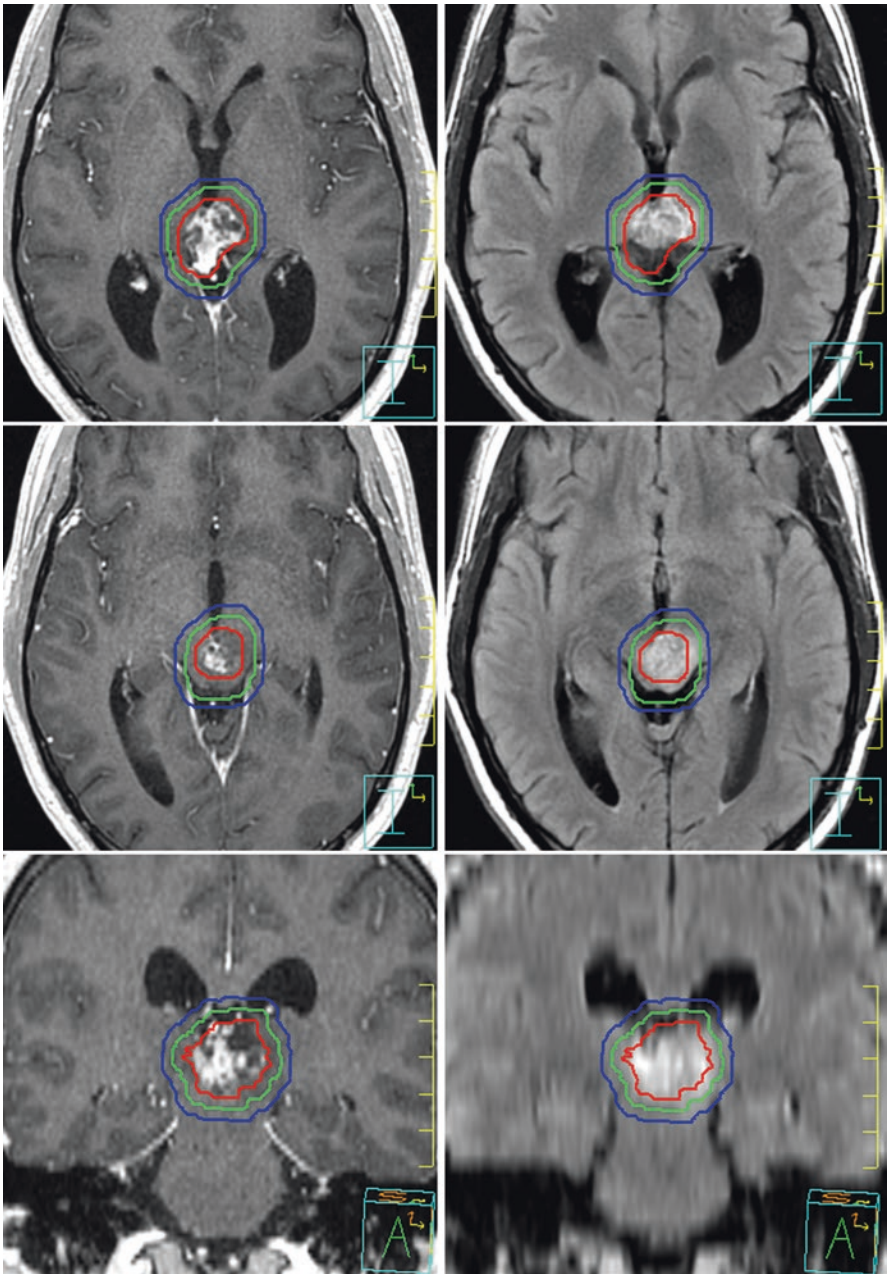


Fig. 17.5 Contours of target based on the T1 post-gadolinium MRI (left) and T2 FLAIR/MRI sequences (right). GTV is shown in red, CTV in green, and PTV in blue

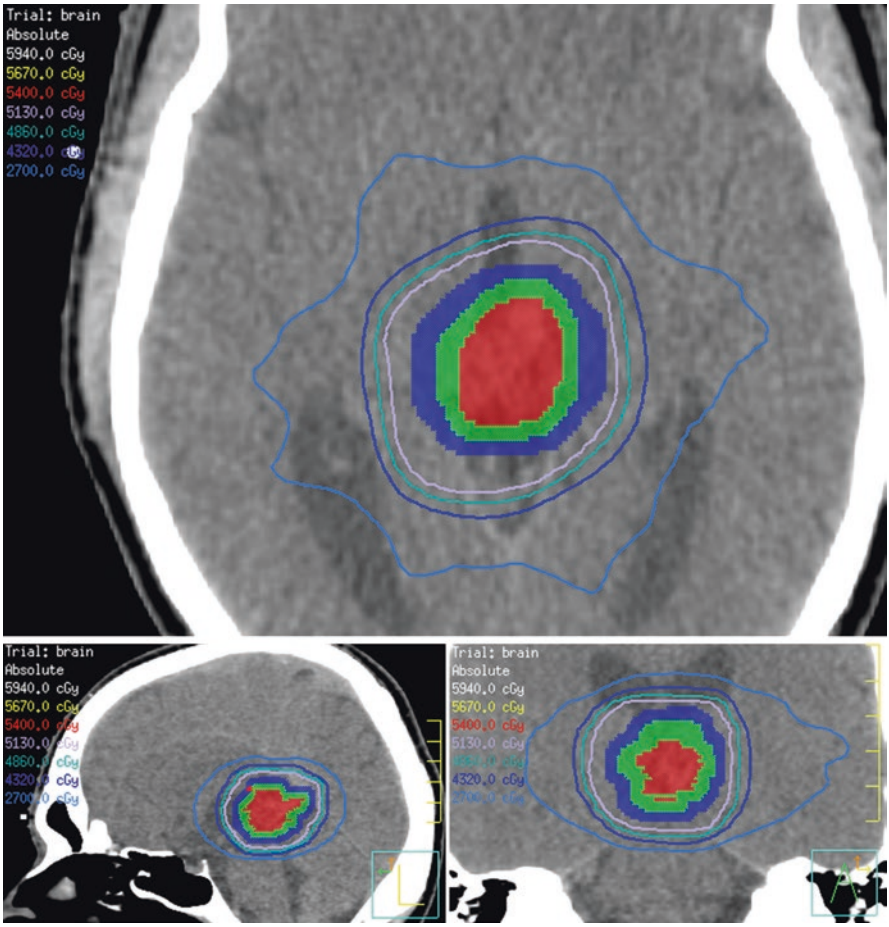
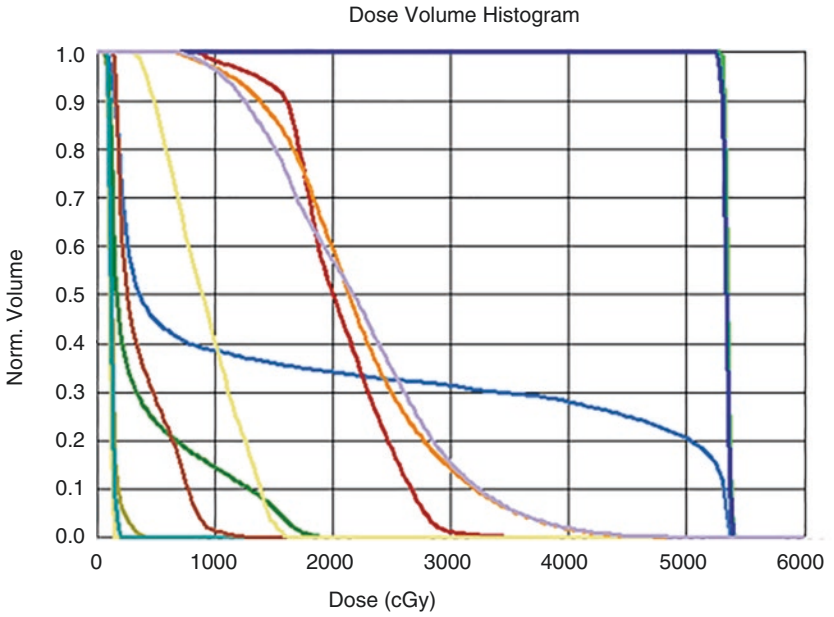


Fig. 17.6 Sample plan with a prescription of 54 Gy in 30 fractions for the illustrative case using an IMRT approach showing selected isodose lines (51.3 Gy in lavender, 48.6 Gy in teal, 43.2 Gy in blue, and 27 Gy in light blue) in the axial (top), sagittal (bottom left), and coronal (bottom right) planes. The plan was optimized for a point maximum of 54 Gy and minimum of 47 Gy to the PTV



Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	BRAINSTEM	brain	87.6	5378.7	1832.9	2150.1
	CTV1	brain	5284.8	5406.7	5348.3	18.5
	Eye_L	brain	45.5	416.5	133.8	43.8
	Eye_R	brain	41.3	1879.3	404.7	462.0
	LENS_L	brain	91.6	131.2	113.4	7.8
	LENS_R	brain	96.8	203.5	123.4	18.5
	OPTICCHIASM	brain	790.2	3464.5	2053.8	441.3
	OPTICNERVE_L	brain	141.7	1244.5	378.3	244.0
	OPTICNERVE_R	brain	286.1	1605.5	912.1	331.3
	PTV1	brain	5215.3	5406.7	5338.9	24.7
	lt hippocampus	brain	607.6	4729.8	2216.0	711.7
	rt hippocampus	brain	619.8	4834.7	2202.7	769.3

Fig. 17.7 Dose-volume histogram (DVH) for the above patient. 100% of the PTV is covered by 95% of prescription (51.3 Gy) with a mean dose of 53.4 Gy

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Adult Medulloblastoma

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C. Jane Cho and Lia M. Halasz

Contents

18.1 General Principles of Simulation and Target Delineation

- See Tables 18.1, 18.2, 18.3 and 18.4.
- Staging with spine MRI and cerebrospinal fluid sampling is essential for determining whether a patient is average-risk or high-risk.
  - Average risk: ≥3 years of age, M0, ≤1.5 cm^2 of residual disease postop and favorable histology.
- Obtain thin slice brain MRI with T1 pre- and post-gadolinium for target delineation. Medulloblastoma heterogeneously enhance on T1 with contrast and can also be visualized on DWI sequence. Fuse both the preoperative and postoperative (within 72 h) MRIs to help delineate target volume.
- Preoperative MRI of the whole spinal canal is ideal. Include both T1 pre- and post-gadolinium to define drop metastases if present and T2 to determine the extent of the cerebrospinal fluid (CSF) space and thecal sac. Postoperative spinal MRI should be obtained at 10–14 days postop to avoid a false-positive result.
  - Spinal MRI should include the whole sacrum.

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Table 18.1 Suggested target volumes for craniospinal irradiation

CTV	Entire CSF space at risk for disease dissemination. Cranial contents including cribriform plate, superior orbital fissure, Meckel's cave, foramen rotundum, foramen ovale, internal auditory meatus, jugular foramen, and hypoglossal canal. Controversy regarding whether to include whole or posterior portion of optic nerves. Spinal canal including intervertebral foramina. Sacral nerve roots do not need to be included. Visualize inferior border of the thecal sac on MRI scan (Figs. 18.1 and 18.2) [1]
PTV	CTV + 0.5–0.7 cm depending on the comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone beam CT)

Table 18.2 Suggested target volumes for tumor bed boost approach

Target volumes	Definition and description
GTV	Residual tumor and resection cavity on postoperative T2/FLAIR and T1 post-gadolinium images. Preoperative MRIs are helpful for determining residual disease and resection cavity
CTV	GTV + 1.5 cm. This can be edited around anatomic boundaries such as the bone, tentorium, dura, and brainstem
PTV	CTV + 0.3–0.5 cm depending on comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone beam CT)

Table 18.3 Suggested target volumes for posterior fossa boost approach

Target volumes	Definition and description
CTV	• Entire posterior fossa including the brainstem. Use sagittal and coronal MRI to assist in identification of the tentorium. Superior: tentorium cerebelli. Anterior: anterior border of the cerebellar folia, brainstem, midbrain • Lateral and posterior: bony walls of the occiput and temporal bones • Inferior: C1–C2 junction
PTV	CTV + 0.3–0.5 cm depending on the comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone beam CT)

Table 18.4 Craniospinal irradiation treatment techniques

3D conformal photons	
Brain field	Often treated with lateral opposed fields with collimator rotation and couch kick to match the spine field divergence and gantry tilt to decrease divergence to the lenses. Borders include flash for superior and posterior borders, 0.5 cm below the cribriform plate, and 1 cm margin anteriorly to vertebral bodies and inferiorly to the middle cranial fossa
Spine field	Superior, C4–C7; lateral, 1 cm margin from the vertebral bodies and fully covered sacral foramina; inferior, 1–2 cm margin inferior to the end of thecal sac which is determined with the T2 sequence of MRI of the spine but is typically located near S2 Feathering can be performed every five fractions or daily with at least three different junctions [2]. A gap of 0–5 mm has been used and the practice is institution-dependent
Protons	
Brain field	Often treated with single PA field, two posterior oblique fields, or opposed lateral fields
Spine field	Posterior fields matched with either feathering junction (uniform scanning) or gradient matching fields (pencil beam scanning) [3]

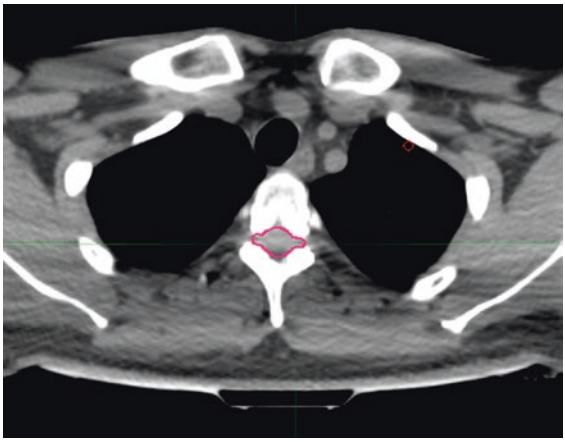

Fig. 18.1 Contours for spine CTV (pink) should include the entire arachnoid space with nerve roots

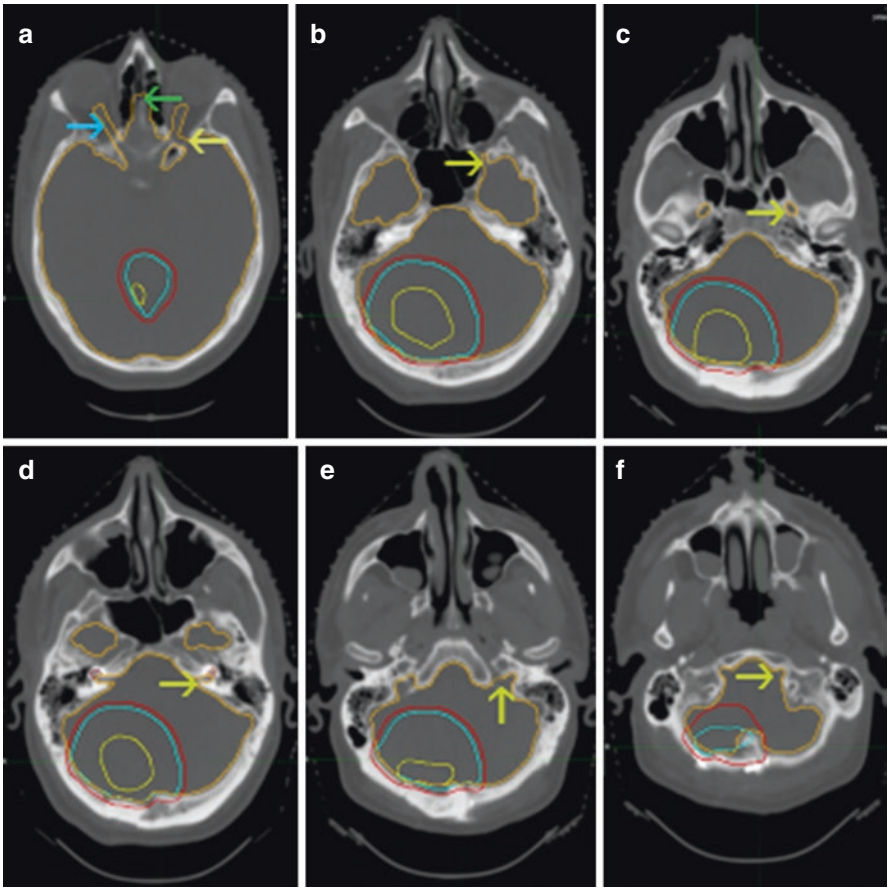

Fig. 18.2 Contours for brain CTV (orange) should include (**a**) superior orbital fissure (yellow arrow) and cribriform plate (green arrow) and consider optic nerve sheaths (blue arrow) (**b**) foramen rotundum, (**c**) foramen ovale, (**d**) internal auditory meatus, (**e**) jugular foramen, and (**f**) hypoglossal canal. Involved field boost contours for average-risk medulloblastoma include GTV (yellow), CTV (teal), and PTV (red)

- If the patient has contraindications to MRI, can use CT with and without contrast.
- CT simulation with a thermoplastic mask and body immobilization for craniospinal irradiation (CSI) with 1–2.5 mm slice thickness:
  - Treatment may be delivered either supine (more comfortable for patient and stable positioning) or prone (advantage is to visualize the spinal junction match lines on the skin, if using traditional CSI technique, but uncomfortable for patient).
  - Hyperextension of the neck can optimally spare the esophagus and larynx.

18.2 Dose Prescriptions

- Treatment of the brain and spinal canal after maximal safe resection
  - Average risk: CSI 23.4–36 Gy and boost to 54–55.8 Gy to tumor bed with margin depending on chemotherapy used. Only consider deescalating from 36 Gy if utilizing Packer regimen for chemotherapy.
  - High risk: CSI 36 Gy in 20 fractions and boost to the posterior fossa or tumor bed with margin to 54–55.8 Gy. Note: Tumor bed boost approach is being increasingly utilized for high-risk medulloblastoma, but has not been established by clinical trials.
- Boost to metastatic lesion
  - Intracranial mets, focal spinal mets below the cord: 50.4 Gy
  - Focal spinal mets above the cord terminus: 45 Gy
  - Diffuse spinal mets: 39.6 Gy

18.3 Treatment Planning Techniques

- *See* Table 18.4 and Figs. 18.3, 18.4 and 18.5.
- 3D CRT, IMRT, VMAT, or proton therapy may be used with the goal of sparing the bone marrow, heart, lungs, kidneys, and bowel for the CSI portion and the supratentorial brain, hypothalamus, pituitary, optic apparatus, and cochleae for the boost portion.
- Treatment planning aims to cover 95% of the PTV volume by 95% of the prescribed dose for photon plans and 100% of the CTV volume by 100% of the prescribed dose for proton plans.
- OARs for 3DCRT or IMRT plans: supratentorial brain, cochlea, hypothalamus/pituitary, eyes, optic nerves, optic chiasm, cervical spinal cord (foramen magnum to top of C2), and skin (Table 18.5).

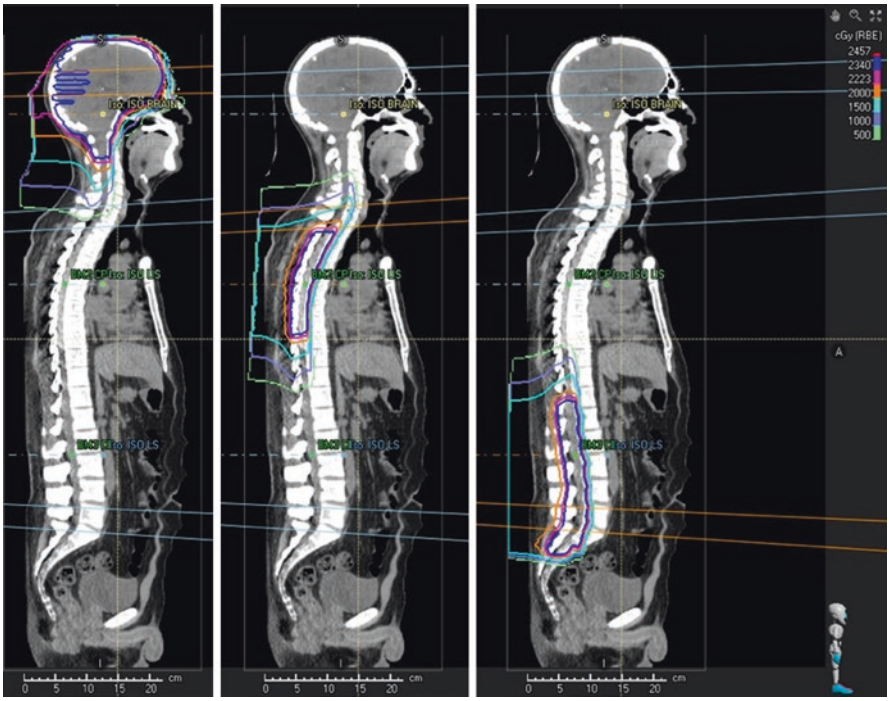

Fig. 18.3 Sample proton plan for the above patient with medulloblastoma utilizing three PA beams that are matched and feathered by overlapping gradients at each junction

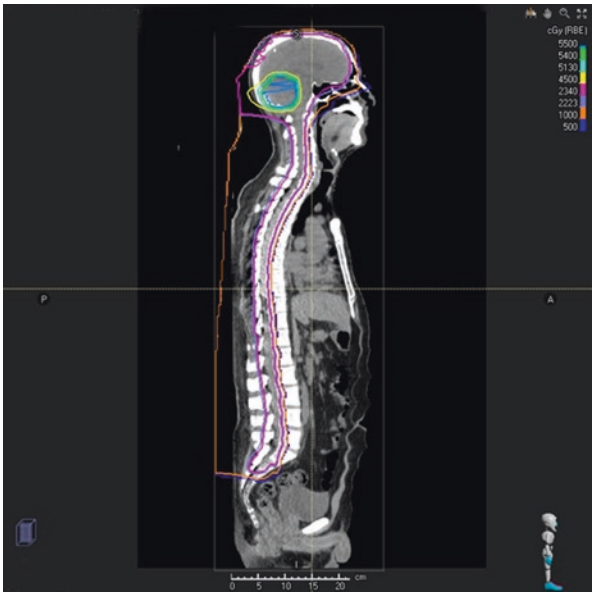

Fig. 18.4 Composite proton plan with gradient matching

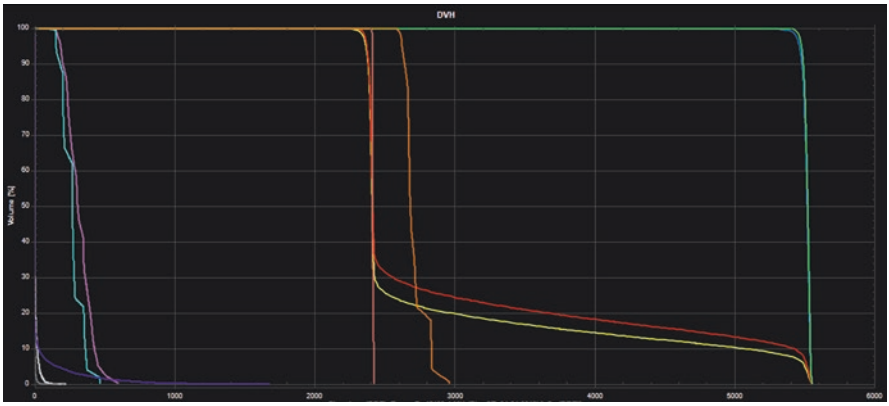

Fig. 18.5 Sample dose-volume histogram for the above patient with medulloblastoma. CTV boost, green; PTV boost, dark blue; CTV craniospinal, red; PTV craniospinal, yellow; cochleae, orang; lenses, teal and lilac; lungs, dark purple; esophagus, white; kidneys, gray

Table 18.5 Recommended normal tissue constraints for 1.8 Gy/day fractionation schemes

Organs at risk	Suggested dose constraints
Spinal cord between C1 and C2 (foramen magnum to top of C2)	V45 Gy <50% [4]
Optic nerves and chiasm	D_{max} <55 Gy
Cochleae	Mean 35 Gy if possible [5]
Brainstem	Brainstem at 0.1 cm^3 <56.6 Gy (acceptable: D0.1 cc ≥56.6 but <58) Brainstem at 50% volume <52.4 Gy (acceptable: D50 ≥52.4 but <54) Brainstem at 10% volume <55.4 Gy (acceptable: D10 ≥55.4 but <56) [6]

Table 18.6 Side effects

Acute	Hair loss, fatigue, headaches, nausea, diarrhea, fatigue, alopecia, hearing changes, myelosuppression, and cerebral edema causing neurological symptoms
Long-term	Neurocognitive decline, decreased growth, hypopituitarism, hypothyroidism, hearing loss
Uncommon or rare risks	Lhermitte's syndrome, gonadal dysfunction, brain or brainstem injury, secondary malignancies

18.4 Side Effects

- See Table 18.6.
- Recommend weekly patient weights and CBC with differential during treatment. Consider daily premedication with ondansetron.

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Intracranial Germ Cell Tumors

19

Lia M. Halasz and Simon S. Lo

Contents

19.1 General Principles of Simulation and Target Delineation (Table 19.1, Figs. 19.1 and 19.2)

- Germinomas make up about 60–70% of all germ cell tumors.
- Non-germinomatous germ cell tumors (NGGCTs) are often mixed tumors that can be composed of yolk sac tumor, embryonal carcinoma, and/or choriocarcinoma. Can include germinoma or teratoma or both.
- Usually occur in the pineal or suprasellar region. Always check both regions for multifocal involvement.
- Staging with spine MRI before surgery or 10–14 days after surgery is essential for determining whether a patient has disseminated disease.
- Lumbar cerebrospinal fluid (CSF) sampling after acute hydrocephalus is addressed is essential for determining whether a patient has disseminated disease.
- Serum and CSF alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) are also essential. Although HCG can be elevated in germinoma with syncytiotrophoblastic giant cells or HCG-secreting germinoma, if the HCG is

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Table 19.1 Suggested volumes

CTVwholeventricle	CTVboost + whole ventricles drawn on CT and thin cut T2 MRI. Include lateral, third, and fourth ventricles with suprasellar and pineal cisterns. Include prepontine cistern if large sellar tumor or s/p endoscopic third ventriculostomy (some always include the prepontine cistern) [1]
PTVwholeventricle	CTV + 0.3–0.5 cm depending on the comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone-beam CT)
CTVcraniospinal	Entire CSF space at risk for disease dissemination. Cranial contents including cribriform plate, superior orbital fissure, Meckel's cave, foramen rotundum, foramen ovale, internal auditory meatus, jugular foramen, and hypoglossal canal. Controversy regarding whether to include whole or posterior portion of optic nerves. Spinal canal including intervertebral foramina. Sacral nerve roots do not need to be included. Visualize inferior border of the thecal sac on the T2 sequence of the MRI scan [2]
PTVcraniospinal	CTV + 0.5–0.7 cm depending on the comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone beam CT)
GTVboost	For boost, take into account pre-surgery and prechemotherapy size on thin cut T1 post-contrast and T2 MRI. Include resection bed and residual disease on thin cut T1 post-contrast, T2 MRI, and planning CT. If pineal lesion is seen on MRI but the patient has diabetes insipidus, assume the suprasellar region has tumor and include in boost volume
CTVboost	GTVboost + 0.5–1.0 cm
PTVboost	CTV + 0.3–0.5 cm depending on the comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone beam CT)

markedly elevated, the patient should be treated as having a mixed germ cell tumor. Elevated serum or CSF concentrations of AFP raise strong suspicion of NGGCT.

- Obtain thin slice MRI brain with T1 pre- and post-gadolinium for boost target delineation and thin slice T2 and CT for ventricle contouring. Utilize the T2 spine MRI to determine the inferior field border and if craniospinal irradiation (CSI) is required. Fuse both the preoperative and postoperative MRIs to help delineate target volume. CT simulation with a thermoplastic mask and body immobilization for CSI with 1–2 mm slice thickness.
  - For CSI, treatment may be delivered either supine (more comfortable for patient and stable positioning) or prone (advantage is to visualize the spine junction match lines on the skin, if using traditional CSI technique, but uncomfortable for the patient).
  - Hyperextension of the neck can optimally spare the esophagus and larynx.

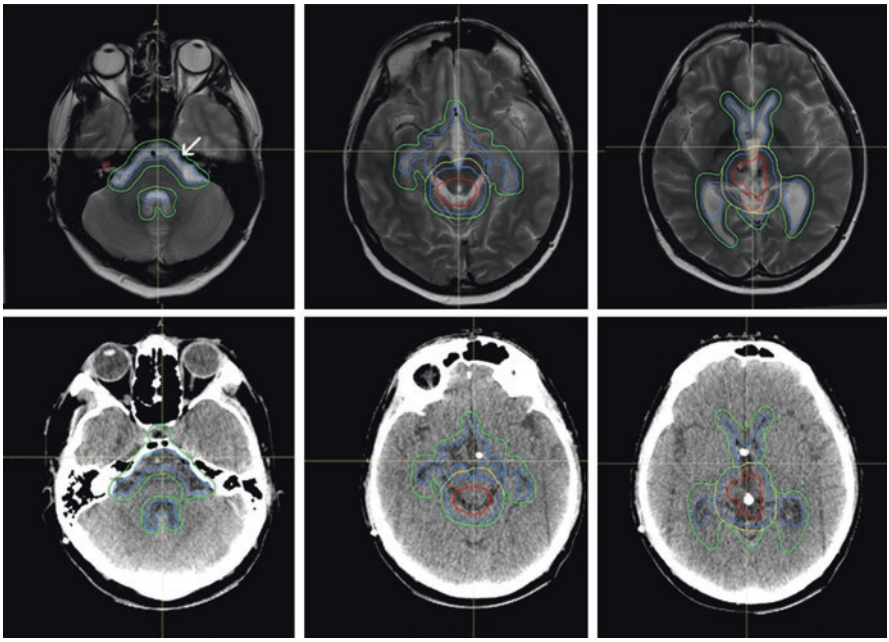

Fig. 19.1 Contours for a patient with germinoma after complete response to chemotherapy. Contours for whole ventricle RT are based on postoperative T2 MRI (upper row) and plan CT (lower row). Blue, CTVwholeventricle; green, PTVwholeventricle; red, prechemotherapy tumor extent. Prepontine cistern indicated by white arrow

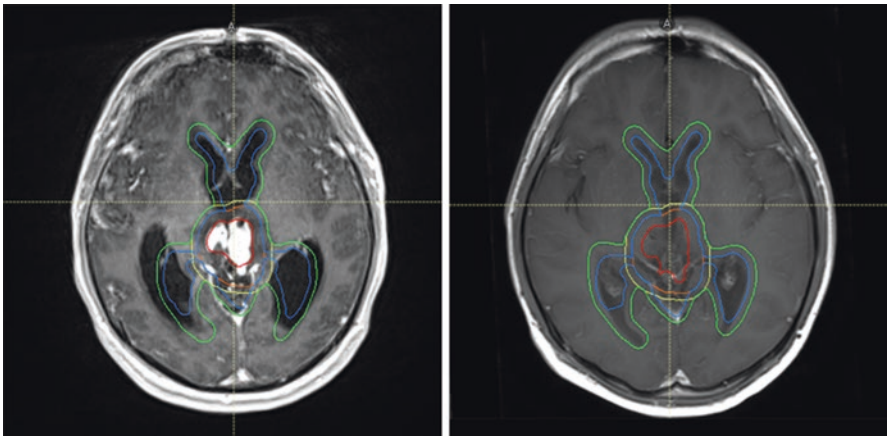

Fig. 19.2 Contours for the boost for the same patient, based on prechemotherapy (left) and post-chemotherapy T1 post-gadolinium (right) MRI. Red, pre-chemotherapy GTV; orange, CTVboost (0.5–1.0 cm expansion on GTV); blue, CTVwholeventricle; green, PTVwholeventricle

19.2 Dose Prescriptions

- M0 germinoma [6, 8]
  - With complete response to chemotherapy: Whole ventricular RT to 23.4–24 Gy in 1.5–1.8 Gy fractions, boost to 36 Gy. ACNS 1123 trial currently utilizing whole ventricular RT to 18 Gy, boost to 30 Gy.
  - With partial response to chemotherapy: Whole ventricular RT to 23.4–24 Gy in 1.5–1.8 Gy fractions, boost to 39.6–40 Gy. ACNS 1123 trial currently utilizing whole ventricular RT to 24 Gy, boost to 36 Gy.
  - With no chemotherapy: Whole ventricular RT to 23.4–24 Gy in 1.5–1.8 Gy, boost to 40–45 Gy.

    Alternatives include the University of Toronto approach: CSI to 25 Gy in 20 fractions with simultaneous integrated boost to 40 Gy in 20 fractions [3].
- M+ germinoma
  - With chemotherapy: Craniospinal RT to 23.4–24 Gy in 1.5–1.8 Gy fractions, PTVboost to 30–36 Gy for complete response and 36–40 Gy for partial response [5].
  - With no chemotherapy: Craniospinal RT to 23.4–30 Gy in 1.5–1.8 Gy, PTVboost to 45–50.4 Gy. Craniospinal RT should be 30–36 Gy if cord diffusely coated.
- M0 and M+ non-germinomatous germ cell tumor
  - Chemotherapy followed by CSI to 36 Gy in 1.8 Gy fractions, PTVboost to 54 Gy. Spinal metastases to 45 Gy [7].

19.3 Treatment Planning Techniques (Figs. 19.3 and 19.4, Table 19.2)

- For whole ventricular RT, IMRT or proton therapy may be used with the goal of sparing normal brain and bilateral cochleae:
  - For proton therapy treatment, generally three beams: right lateral, left lateral, and posterior or superior.
- For CSI, volumetric modulated arc therapy (VMAT), helical tomotherapy, or proton therapy may be used with the goal of sparing the bone marrow, heart, lungs, kidneys, and bowel for the CSI portion:
  - For further information, please see Chap. 18.
- For radiation centers not using the above techniques for CSI, traditional matched cranial and spinal fields can be used. Field junction feathering is highly recommended to minimize hot and cold spots. Gaps of 0–5 mm between the fields have been used, depending on institutional policy. The match between the cranial and upper spinal fields sometimes entails a couch kick (to eliminate divergence into the upper spinal field), a collimator rotation (to match divergence of upper spinal field), and a gantry tilt (to eliminate divergence to opposite lens) for each cranial field.
- Treatment planning aims to cover 95% of the PTV by 95% of the prescribed dose for photon plans and 100% of the CTV by 100% of the prescribed dose for proton plans.

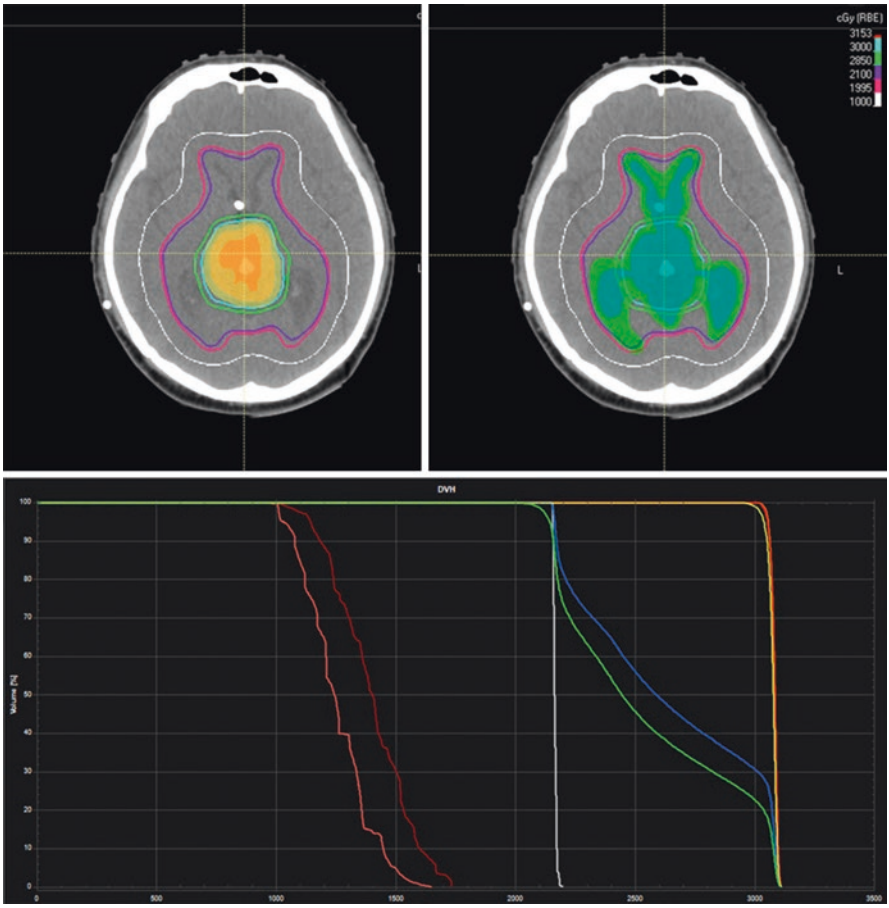

Fig. 19.3 Plan for the same patient with whole ventricles to 21 cobalt gray equivalent (CGE) and boost to 30 CGE plan utilizing proton therapy. Red, GTV; orange, CTVboost; yellow, PTVboost; blue, CTVwholeventricles; green, PTVwholeventricles. DVH shows targets in the corresponding colors described above: cochleae in peach and brown and chiasm on white

19.4 Side Effects (Table 19.3)

For CSI, recommend weekly patient weights and complete blood count with differential during treatment. Consider daily premedication with ondansetron. The exit dose of the spinal fields to the anterior structures is decreased with VMAT, helical tomotherapy, proton therapy, and the risk and extent of the above-listed complications are expected to be less. Dosimetrically, proton therapy has the best marrow sparing capability.

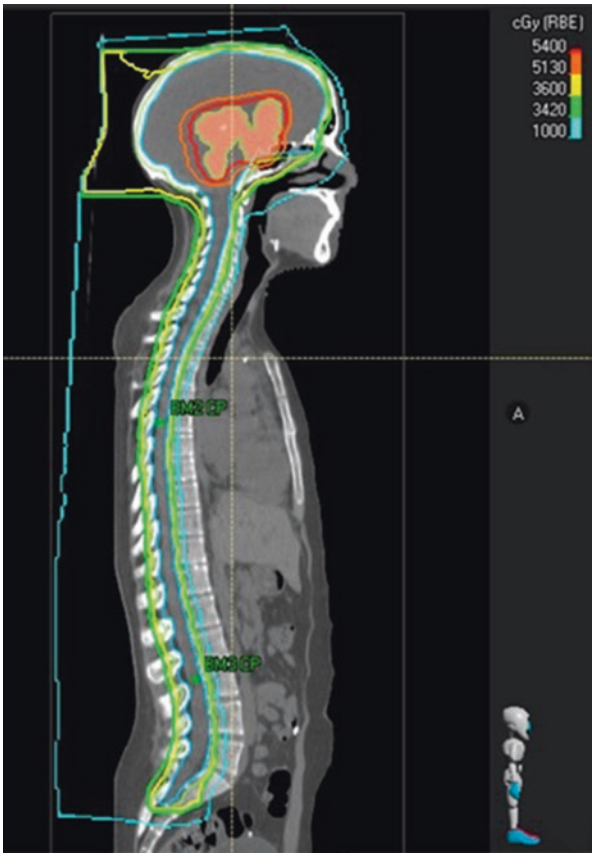

Fig. 19.4 Plan for a patient with non-germinomatous germ cell tumor utilizing proton therapy with gradient matching to deliver craniospinal irradiation to 36 CGE with boost to 54 CGE. Orange, CTVboost; yellow, PTVboost. For further details regarding craniospinal irradiation, please see Chap. 18

Table 19.2 Organs at risk

Organs at risk	Suggested dose constraints
Optic nerves and chiasm	$D_{max} < 55$ Gy
Eyes	$D_{max} < 45$ Gy
Lenses	7–10 Gy
Cochleae	$D_{max} < 35$ Gy (ALARA depending on prescription doses) [4]

Table 19.3 Side effects

Acute	Hair loss, fatigue, headaches, nausea, diarrhea, fatigue, alopecia, hearing changes, myelosuppression, and cerebral edema causing neurological symptoms
Long-term	Neurocognitive decline, hypopituitarism, hypothyroidism, hearing loss, pulmonary dysfunction
Uncommon or rare risks	Lhermitte's syndrome, gonadal dysfunction, brain or brain stem injury, secondary malignancies

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Brain Metastases: Intact and Postoperative Radiotherapy and Radiosurgery

20

Scott G. Soltys, Erqi Pollom, and Iris C. Gibbs

Contents

20.1 General Principles of Planning and Target Delineation (Table 20.1)

- For frameless systems, CT simulation in supine position with a stereotactic headframe thermoplastic mask.
- IV contrast with the simulation CT is preferred to aid in MRI fusion and contour delineation.
- For frame-based systems, MRI performed with skull-fixed coordinate headframe and stereotactic localizer box.
- MRI sequences to include thin slice (preferably volumetric, 0.5–1 mm thick), contiguous (stereotactic) T1 post-gadolinium sequences. See consensus recommendations for MRI protocols [1]:
  - MRI should be obtained on the same day or as close as possible to the day of the CT simulation, particularly in the post-resection setting with potential shift in the brain. Our institutional standard is to repeat the MRI if older than 7–10 days.

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Table 20.1 Suggested target volumes

Structure	Definition and description
Target volumes—intact metastases	
GTV	Tumor extent per T1 post-gadolinium MRI, confirmed by the post-contrast CT images
CTV	Typically 0 mm
PTV	Typically 0 mm; 1 mm may be considered. Margins >1 mm are discouraged [2]
Target volumes—post-resection cavities	
GTV	1. Residual tumor extent per T1 post-gadolinium MRI, confirmed by the post-contrast CT images 2. Involved dura, falx, and tentorium, if present, on the *pre*-resection MRI 3. Resection cavity per the postoperative MRI, including the extent of the resection corridor involved with tumor on the *pre*operative MRI 4. Consider including the entire operative corridor leading to the resection cavity [3] (Our institutional preference is to not include the corridor or additional margin on dura [4])
CTV	Typically a 1–2 mm margin per retrospective data [5], shaved at anatomic barriers to tumor spread such as the falx, calvarium, tentorium
PTV	Typically 0 mm; 1 mm may be considered

- For post-resection cavity SRS, fusion of the *pre-resection* MRI is essential in many cases to ensure correct location and to target any dura involved prior to resection.
- For post-resection cavity SRS, enhancement due to perioperative infarct need not be targeted; the immediate post-resection DWI sequence can reveal if peri-cavity infarct is present, which would enhance weeks later at the time of SRS and should not be confused for enhancing residual tumor.

20.2 SRS Planning Considerations (Tables 20.2, 20.3, and 20.4, Figs. 20.1 and 20.2)

- SRS dose is typically prescribed to cover approximately 97–100% of the PTV.
- The prescription isodose line (IDL) is typically chosen to maximize the dose gradient. This optimal isodose line is target volume and machine-dependent, typically 40–60% for frame-based cobalt units to 65–85% for linear accelerator-based treatments.

20.3 Whole Brain Radiotherapy

- Whole brain radiotherapy (WBRT) may be considered for selected patients with brain metastases.
- Recent prospective trials support a greater use of upfront SRS, with deferral of WBRT:

Table 20.2 Suggested SRS dose for intact metastases

SRS dosing per RTOG 90-05 [6] for intact metastases			
Maximum tumor diameter	**Equivalent spherical volume**	**SRS dose**	
Single-fraction SRS			
0.1–2.0 cm	0–4.2 cm^3	20–24 Gy × 1	
2.1–3.0 cm	4.3–14.1 cm^3	18 Gy × 1	
3.1–4.0 cm	14.2–33.5 cm^3	15 Gy × 1	
Multi-fraction SRS[a]			
2.5–4.0 cm	8.2–33.5 cm^3	8–9 Gy × 3 = 24–27 Gy	
SRS dosing per NCCTG N107C [7] for resection cavities			
Approximate equivalent spherical diameter	**PTV volume**	**SRS dose**	**For cavities larger than 2.5 cm, consider multi-fraction SRS**
0.1–2.0 cm	0.1–4.1 cm^3	20 Gy × 1	
2.1–2.4 cm	4.2–7.9 cm^3	18 Gy × 1	
2.5–3.0 cm	8.0–14.3 cm^3	17 Gy × 1	9 Gy × 3 = 27 Gy
3.1–3.4 cm	14.4–19.9 cm^3	15 Gy × 1	8 Gy × 3 = 24 Gy
3.5–3.8 cm	20.0–29.9 cm^3	14 Gy × 1	8 Gy × 3 = 24 Gy
3.9–5.0 cm	>30.0 cm^3 and <5 cm max	12 Gy × 1	6 Gy × 5 = 30 Gy

[a]Consider multi-fraction SRS for metastases near critical structures or larger than approximately 2.0–2.5 cm maximum diameter [8]

Table 20.3 SRS planning indices and parameters

SRS plan evaluation parameter	Formula	Typical values/notes
Target coverage	Tumor volume covered by the prescription isodose volume (TV_{PIV})/ target volume (TV)	97–100%
Conformity index (RTOG) [9]	Prescription isodose volume (PIV)/ target volume (TV)	Typically 1.05–1.5[a]
Conformity index (Paddick) [10]	Tumor volume covered by the prescription isodose volume $(TV_{PIV})^2$/ target volume (TV)[a] prescription isodose volume (PIV)	Accounts for both undertreatment and overtreatment of the PTV and potential marginal or geographic miss of the target volume by the treatment volume
Homogeneity index	Maximum dose/prescription dose	1.25 (if prescribed to 80% IDL)–2.00 (if prescribed to 50% IDL)
Gradient index [11]	Volume of half of the prescription isodose/volume of the prescription isodose. For example, for a prescription to 50% isodose line, calculate 25% isodose volume/50% isodose volume	Less than 3.0 is preferable

[a]Note: RTOG 90-05 allowed a conformity index of up to 2.0; for ellipsoid brain metastases, lower values are typically achieved with modern planning techniques

Table 20.4 Recommended normal tissue constraints

Organs at risk	Suggested dose constraints (D_{max})
Optic nerve/chiasm [20–23]	10 Gy in 1 fraction 17.4 Gy in 3 (per TG 101 [23]) 20 Gy in 3 fractions (Stanford Institutional Data [20] and HyTEC [22])
Brain stem [24, 25]	12.5 Gy (QUANTEC) Consider higher doses (at least 16–20 Gy in 1 fraction) for brain stem metastases based on prognosis [25] Consider up to 21 Gy in 3 fractions (author's institutional constraints)
Brain parenchyma [26]	12 Gy volume <5–10 cm^3 (QUANTEC)

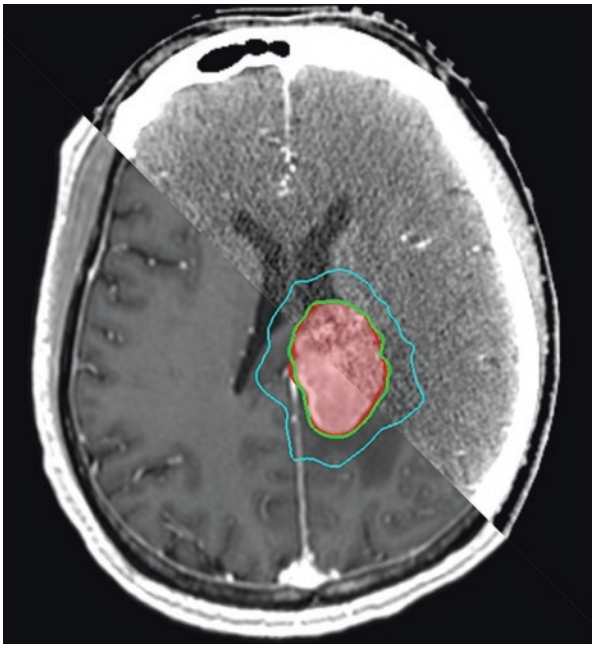

Fig. 20.1 A representative SRS plan for a large intact brain metastasis. The metastasis (red contour), defined by T1 post-gadolinium MRI (lower left) and contrast CT (upper right) fusion, is targeted by the 72% isodose line (green); 36% isodose line (cyan) is also shown. Based on a target maximum diameter of 3.8 cm (volume 17.8 cm^3), 15 Gy in one fraction [6] or 27 Gy in three fractions [8] is typically delivered. SRS indices: conformity index 1.1, homogeneity index 1.4, and gradient index 3.0

- Aoyama (2006) [12]: For intact brain metastases, WBRT + SRS compared to SRS alone had improved local control and distant intracranial control, but no difference in overall survival (the primary endpoint) or neurologic death rate.
- Chang (2009) [13]: For intact brain metastases, WBRT + SRS compared to SRS alone had better intracranial control, but worse neurocognition (the primary endpoint) and overall survival.
- Kocher (2011) [14]: For intact or resected brain metastases, WBRT added to surgery alone or SRS alone had better intracranial control and neurologic death rates, but no difference in duration of functional independence (the primary endpoint) or overall survival, with worse quality of life.
- Yamamoto (2014) [15]: For intact brain metastases treated with SRS alone (without WBRT), overall survival for five to ten metastases was not inferior than for two to four metastases.

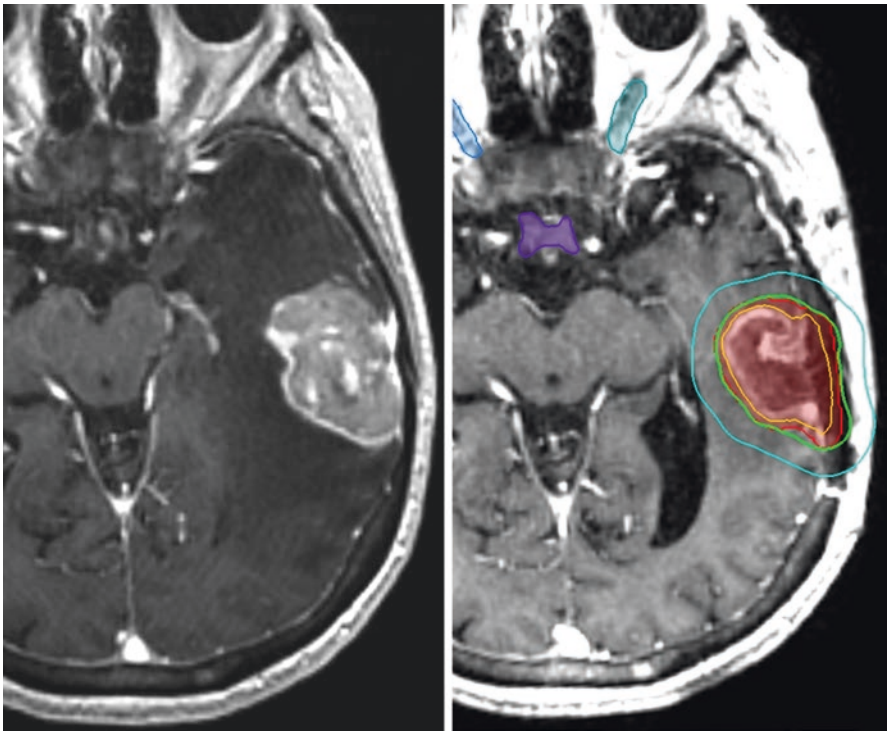

Fig. 20.2 A representative resection cavity SRS plan. The pre-resection MRI (left) is fused with the postoperative MRI (right) and simulation CT. The dura was involved pre-resection and therefore was included in the post-resection GTV (orange contour). A 2 mm CTV margin (red contour) was added. In this specific case, the CTV extends into the bone; however, the CTV may be cropped at barriers to tumor spread (e.g., falx, tentorium, bone). Contouring recommendations exist [3]—the authors' institutional preference does not include the surgical corridor or an extended margin on uninvolved dura. The PTV margin was 0 mm. GTV and PTV were 10.9 and 17.4 cm^3, respectively. Fifteen Gy in one fraction (per N107C) was prescribed to the 76% isodose line. SRS indices: conformity index 1.1, homogeneity index 1.3, and gradient index 2.9

  - Brown (2016) [16]: For intact metastases, WBRT + SRS compared to SRS alone had better intracranial control, but no difference in overall survival and with worse neurocognition (the primary endpoint).
  - Brown (2017) [7]: For resected brain metastases, postoperative WBRT compared to postoperative SRS to the resection cavity had better intracranial control, but no difference in overall survival and with worse neurocognition (the primary endpoint).
- For patients who are best treated with WBRT, prospective data support pharmacologic or technologic means to improve neurocognition:
  - Brown (2013) [17]: For patients treated with WBRT, the addition of the NMDA receptor antagonist memantine failed to statistically ($p = 0.059$) meet the primary endpoint of improved Hopkins Verbal Learning Test-Revised Delayed Recall, but did show improvement in the decline on any neurocogni-

tive test. Many consider this a positive finding, as the trial was underpowered, as only 149 (29%) of patients were evaluable compared to the 442 (80%) expected.

– Gondi (2014) [18]: This single-arm, hypothesis-generating trial found an improvement in neurocognitive decline with hippocampal avoidance WBRT compared to data from a historical comparison trial of WBRT without hippocampal avoidance.
– Brown NRG CC001 [19]: Randomized trial of WBRT + memantine versus WBRT + memantine + hippocampal avoidance-WBRT (HA-WBRT). Those treated with HA-WBRT have better preservation of cognitive function and patient-reported symptoms.

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Brain Metastases: Whole Brain Radiation Therapy

21

C. Jane Cho, Simon S. Lo, and Lia M. Halasz

Contents

21.1 General Principles of Simulation and Target Delineation

- Simulation for simple or 3D conformal whole brain radiation therapy (WBRT) plan (Table 21.1):
  - In a supine position with a head rest
  - CT simulation: from the vertex to the top of the thoracic spine with 2.5 mm slices without contrast, immobilization with a thermoplastic mask
- Simulation for an IMRT plan for sparing hippocampi (Tables 21.2 and 21.3):
  - Slice thickness of CT simulation preferably with 1.25–1.5 mm slices
  - Obtain thin slice MRI brain (axial T1-weighted with contrast, T2-weighted, and axial and coronal FLAIR), and fuse with planning CT
- Consider medical management for symptomatic patients:
  - Corticosteroids (dexamethasone) especially if associated with significant edema and antiepileptics for seizures
  - Systemic agents with brain penetrance

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Table 21.1 Suggested field borders for WBRT

Brain fields using opposed lateral fields for most WBRT	Use gantry rotation and/or MLCs to spare lenses bilaterally Superior, anterior, and posterior borders: 1–2 cm flash Inferior border: 0.5–1 cm margin on the cribriform plate and the floor of the middle cranial fossa and posteriorly at the inferior end plate of the C1 vertebra (Fig. 21.1)
WBRT in the setting of small cell lung cancer and leukemia	Same as above, except consideration of extending the inferior border to the inferior end plate of the C2 vertebra

Table 21.2 Suggested target volumes for IMRT plans for WBRT

CTV	Whole brain using the inner table of the skull outlined using a bony window setting. *Ensure to include the entire frontal lobe, temporal lobes, pituitary fossa, and cribriform plate if targeting the whole craniospinal fluid space* [2]
PTV	CTV + 0.0–0.5 cm depending on the comfort of patient positioning, mask fit, and image guidance technique (AP/lateral imaging or cone-beam CT) *PTV = CTV minus hippocampal avoidance regions per RTOG 0933 [3]

Table 21.3 Potential normal tissue volumes to spare for IMRT plans

Hippocampus [3–5]	Postero-caudal extent: Along the medial edge of the temporal horn, caudal extent of the crescentic-shaped floor of the temporal horn Anterior: Uncal recess of the temporal horn/amygdala Superior: Where the T1-hypointense structure no longer borders the atrium of the lateral ventricle Medial border: Edge of the T1 hypointensity up to the ambient cistern/uncus Postero-cranial: T1-hypointense hippocampal tail (anteromedial to the atrium of the lateral ventricle) *Hippocampal avoidance region*: Generated by 3D expansion of the hippocampal contour by 5 mm (Fig. 21.2)
Lacrimal gland [6–8]	Superior to the lateral rectus muscle, lateral to the superior rectus muscle, within the pre-septal space of the superolateral portion of the orbit
Parotid gland [9, 10]	Anterior: Masseter muscle, posterior border of the mandibular bone, medial and lateral pterygoid muscle Posterior: Anterior belly of sternocleidomastoid muscle, lateral side of the posterior belly of the digastric muscle Lateral: Subcutaneous fat, platysma muscle Medial: Posterior belly of the digastric muscle, styloid process, parapharyngeal space
Scalp	Outer 3–5 mm of the external contour

- Consider prophylactic treatment with memantine to preserve short-term memory/neurocognitive functions per RTOG 0614 trial [1]:
  - Week 1—5 mg in the morning
  - Week 2—Add 5 mg dose in the evening
  - Week 3— Increase the morning dose to 10 mg
  - Weeks 4–24—10 mg in the morning and 10 mg in the evening
  - Dose is lowered to 5 mg orally twice daily if creatinine clearance falls below 30 mL/min
  - Dose is held if the creatinine clearance is less than 5 mL/min with a weekly recheck of laboratory values

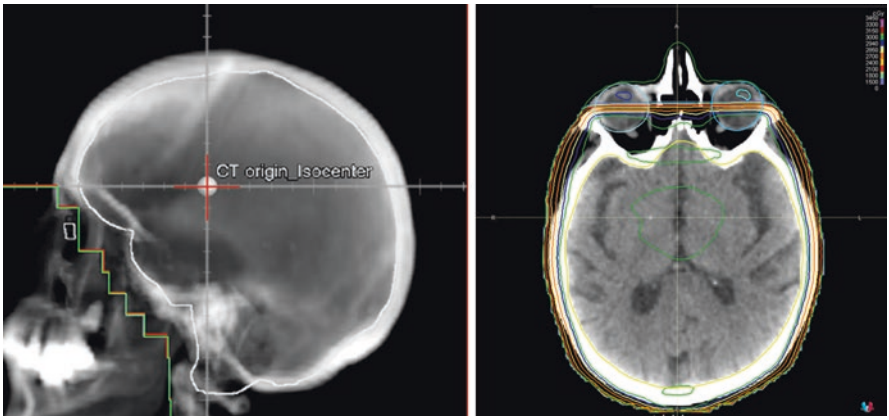

Fig. 21.1 Conventional WBRT field (parallel opposed fields)

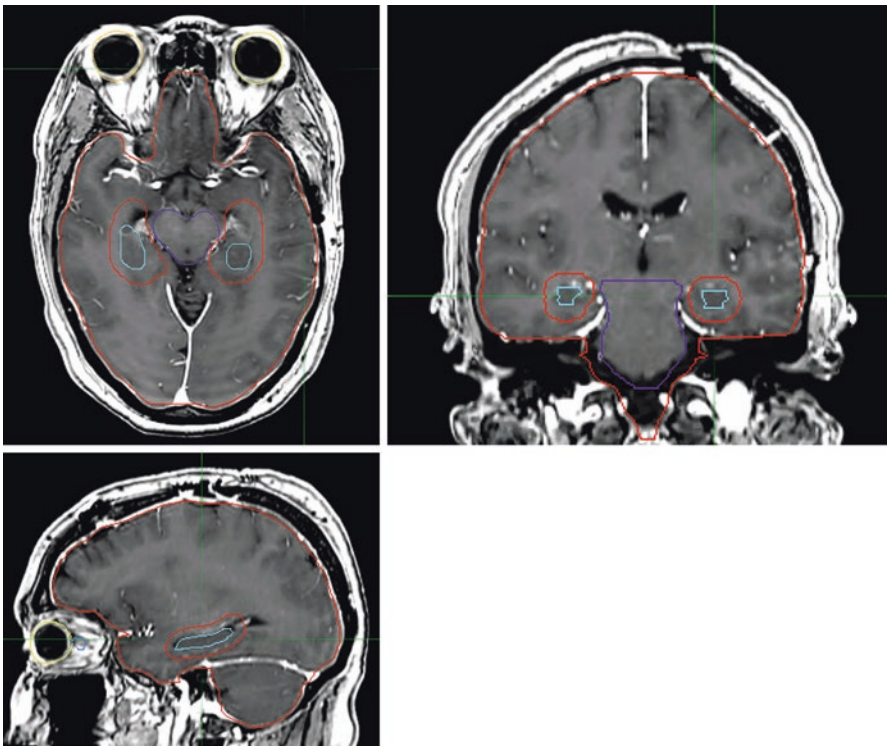

Fig. 21.2 Hippocampi contoured on 3D T1 post-gadolinium MRI imaging. Hippocampi (cyan), brain stem (purple), PTV (red) = whole brain minus hippocampal avoidance area

21.2 Dose Prescriptions

- Most commonly used: 20 Gy in 5 fractions or 30 Gy in 10 fractions (37.5 Gy in 15 fractions not superior to 30 Gy in 10 fractions in outcomes and worse in toxicities [11]).
- Prophylactic treatment of small cell carcinoma: 25 Gy in 10 fractions.

21.3 Treatment Planning Techniques

- Treatment planning aims to cover 95% of the PTV volume by 100% prescription dose.
  - For hippocampal sparing technique (Fig. 21.3): Whole brain PTV D2% ≤37.5 Gy, and D98% ≥25 Gy and V30Gy ≥95% per NRG CC001 [3].
- OARs for IMRT plans may include the optic apparatus (lens, globe, retina, optic nerves and chiasm), lacrimal glands, cochleae, external/middle auditory canals, hippocampi, brainstem, pituitary gland, and scalp (Tables 21.4 and 21.5).

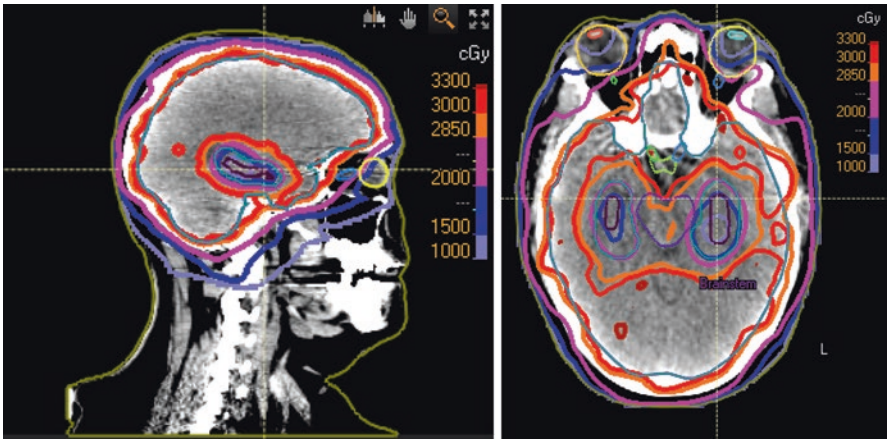

Fig. 21.3 VMAT hippocampal avoidance plan

Table 21.4 Recommended OAR constraints for 3DCRT or IMRT plans using conventional fractionation

Object at risk	Suggested dose constraints for 30 Gy in 10 fractions
Hippocampi (if hippocampal avoidance)	D100% ≤9 Gy [3] D_{max} ≤16 Gy [3]
Optic nerves and chiasm	D_{max} (0.03 cc) ≤30 [3]–33 Gy
Parotid glands	V20Gy <47% [9] (without compromising coverage)
Scalp	Mean <18 Gy [12]

Table 21.5 Potential side effects

Acute	Fatigue, headaches, nausea, alopecia, transient worsening of neurologic symptoms, seizure, otitis, dry or irritated eye
Long-term	Neurocognitive decline (memory loss and difficulty multitasking), hypopituitarism, dry eye, dry mouth, rare chance of visual/hearing impairment, or radiation brain injury

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Primary Spinal Cord Tumors

22

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Contents

22.1 Astrocytoma

22.1.1 General Principles

- Accounts for ~1/3 of primary spine tumors in adults and is more common in the adolescent and pediatric population.
- Maximal safe resection is the primary treatment.
- Decision of adjuvant therapy is dependent on degree of surgery, patient functional status, age, WHO grade, and molecular subtypes.

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- Complete craniospinal imaging needed prior to therapy. Pre-/post-gadolinium-enhanced MRI should be performed. Typically the tumor will be T1 hypointense/T2 hyperintense and will have varied enhancements with gadolinium (Table 22.1 and Fig. 22.1).
- Patients with grade 1 (pilocytic astrocytoma) and grade 2 astrocytoma may be observed following gross total surgical resection. Grade 2 following subtotal resection should be considered for adjuvant therapy.
- Patients with grade 3/4 astrocytoma are appropriate for postoperative adjuvant therapy.

Table 22.1 Suggested target volumes

Target volumes	Definition and description
GTV	Tumor extent and resection cavity on postoperative T2/FLAIR and T1 post-gadolinium images. Preoperative MRIs are helpful for determining residual disease and resection cavity
CTV	GTV + 1–1.5 cm, modified by anatomic boundary of the spinal canal. Tumor-associated syrinx outside of this volume may not require coverage
PTV	CTV + 0.3–0.5 cm depending on patient positioning, immobilization device, and image guidance technique

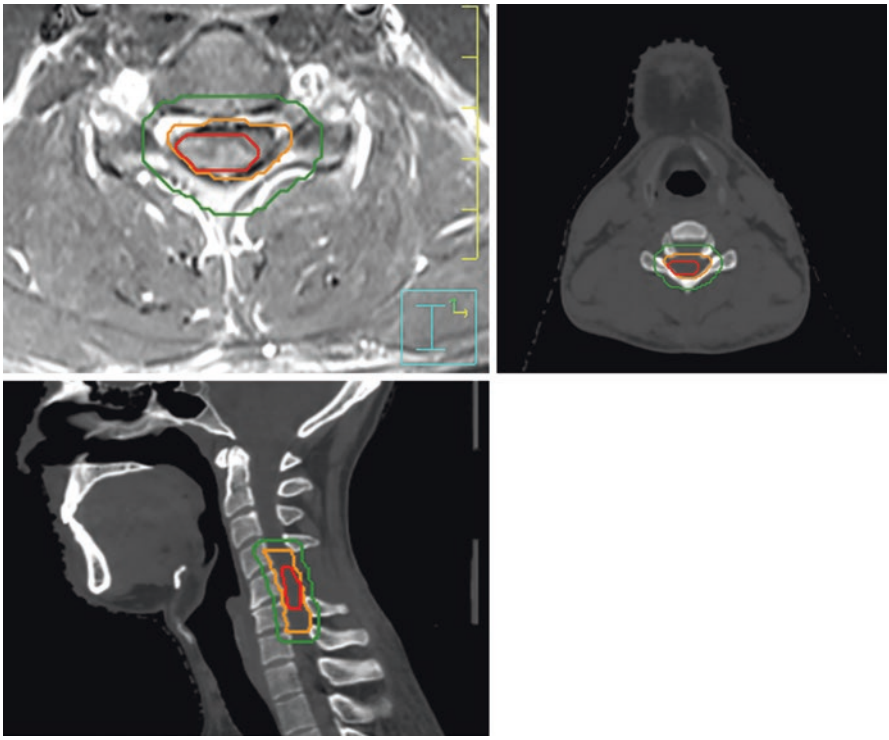

Fig. 22.1 Contours for patient with grade 2 astrocytoma. GTV, red; CTV, orange; PTV, green

22.1.2 Dose Prescription

- 45–50.4 Gy in 1.8 Gy for grades 1 and 2 tumors
- 54.0 Gy in 1.8 Gy for grades 3–4 tumors
- See Fig. 22.2 for example of DVH

22.2 Ependymoma

22.2.1 General Principles

- Most common pediatric spinal cord tumor.
- Classified as grade 1 (subependymoma or myxopapillary ependymoma), grade 2 (ependymoma), or grade 3 (anaplastic ependymoma).
- Entire craniospinal axis evaluation with gadolinium-enhanced MRI is required. Myxopapillary ependymoma may be hyperintense on T1, while non-myxopapillary ependymoma is typically hypointense/isointense on T1. Generally will have homogeneous enhancement with gadolinium (Table 22.2 and Fig. 22.3).

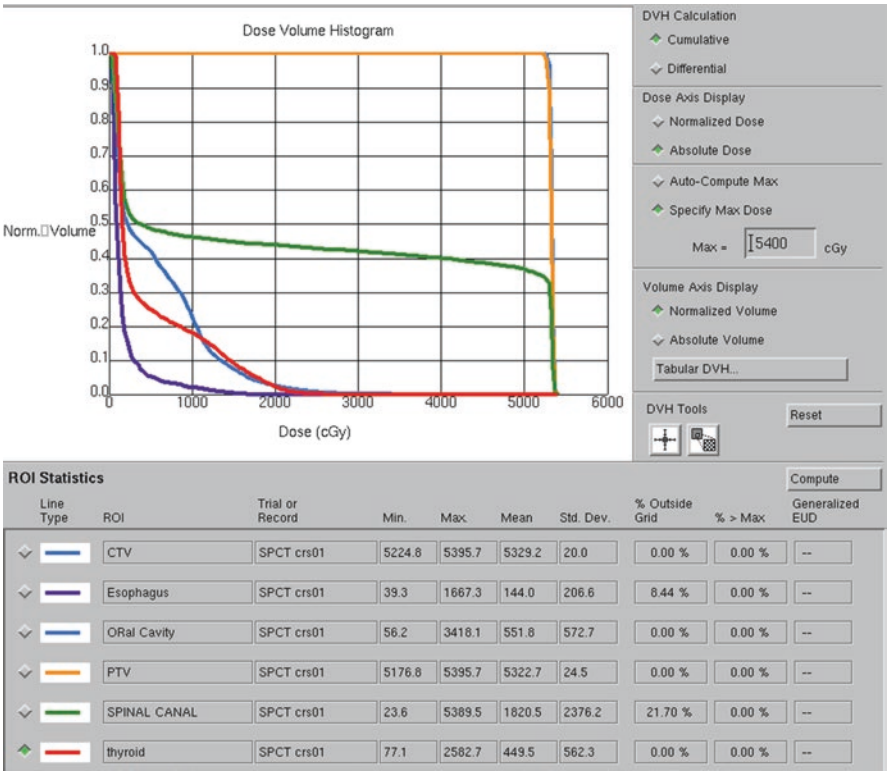

Fig. 22.2 Dose-volume histogram for patient with grade 2 astrocytoma treated with 54 Gy/30 fractions

Table 22.2 Suggested target volumes

Target volumes	Definition and description
GTV	Tumor extent and resection cavity on postoperative T2/FLAIR and T1 post-gadolinium images. Preoperative MRIs are helpful for determining residual disease and resection cavity
CTV—focal	GTV + 1–1.5 cm, modified by anatomic boundary of the spinal canal. Tumor-associated syrinx outside of this volume does not require coverage. Historically defined as two vertebral bodies above/below target volume
CTV—craniospinal	Entire craniospinal axis
PTV	CTV + 0.3–0.5 cm depending on patient positioning, immobilization device, and image guidance technique

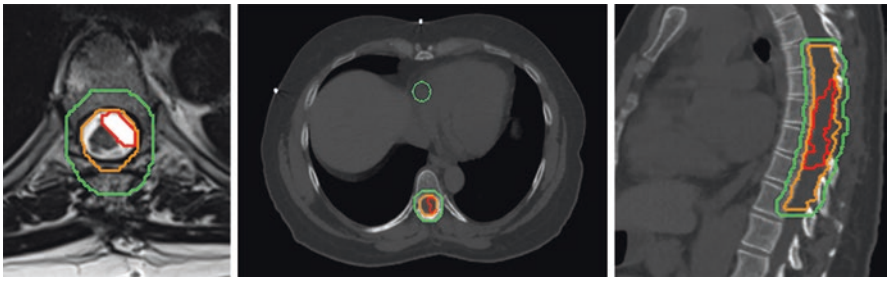

Fig. 22.3 Contours for a patient with WHO grade 2 ependymoma of the thoracic spine. GTV, red; CTV, orange; PTV, green

- If evidence of tumor seeding, focal therapy not appropriate and patient should receive craniospinal treatment.
- Maximal safe resection is the primary treatment.
- Observation is an option after gross total resection for grade 1/2 disease.
- Patients with subtotally resected grade 2 ependymoma and all patients with grade 3 anaplastic ependymoma should be considered for adjuvant radiation.

22.2.2 Dose Prescription

- Focal: 50.4–54 Gy in 1.8 Gy/day.
- Craniospinal: 36 Gy in 1.8 Gy/day followed by boost to gross disease of 18 Gy in 1.8 Gy/day fractions (total dose 54 Gy).
- See Fig. 22.4 for example of DVH.

22.3 Hemangioblastoma

22.3.1 General Principles

- Third most common intramedullary spinal cord tumor.
- Typically found in the cervical or lumbar spine.

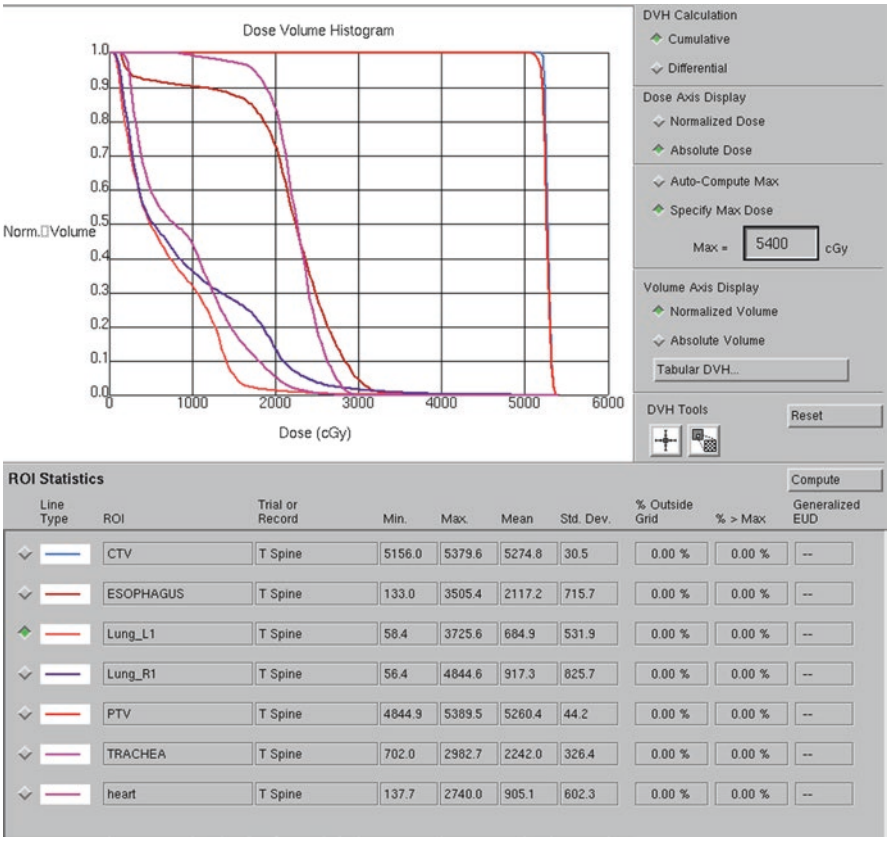

Fig. 22.4 Dose-volume histogram for patient with thoracic ependymoma treated with 54 Gy/30 fractions

- Associated with von Hippel-Lindau (VHL) disease. As such, patients should be screened with brain MRI, CT chest/abdomen/pelvis, and neuro-ophthalmologic evaluation.
- On MRI will typically be hypointense to isointense on T1, isointense to hyperintense on T2, and enhancing with gadolinium. Typically will be a discrete nodule; the entire neuro-axis should be evaluated to rule out other sites of disease (Table 22.3 and Figs. 22.4 and 22.5).
- Management strategies include surveillance, surgical resection, radiotherapy, or stereotactic radiotherapy.

22.3.2 Dose Prescription

- Conventional: 50.4–54 Gy in 1.8 Gy/day
- Radiosurgery: 16–24 Gy in 1–3 fraction(s)
- See Fig. 22.6 for example of DVH

Table 22.3 Suggested target volumes

Target volumes	Definition and description
GTV	Tumor extent as identified on T1 post-gadolinium MRI
CTV—conventional	GTV + 0–1.5 cm, modified by anatomic boundary of the spinal canal. Special care in sacrum to cover the entire cauda equina
CTV—radiosurgery	No CTV applied
PTV—conventional	CTV + 0.3–0.5 cm depending on patient positioning, immobilization device, and image guidance technique
PTV—radiosurgery	GTV + 0.1–0.2 cm depending on patient positioning, immobilization device, and image guidance technique

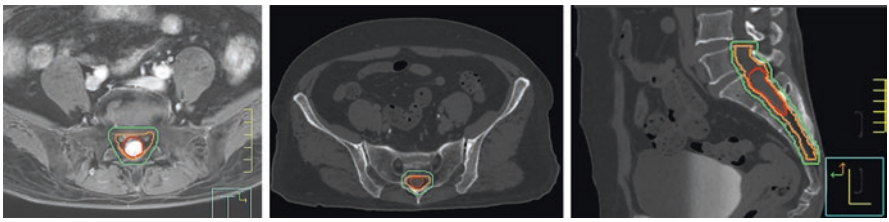

Fig. 22.5 Contours for patient with sacral hemangioblastoma. GTV, red; CTV, orange, PTV, green

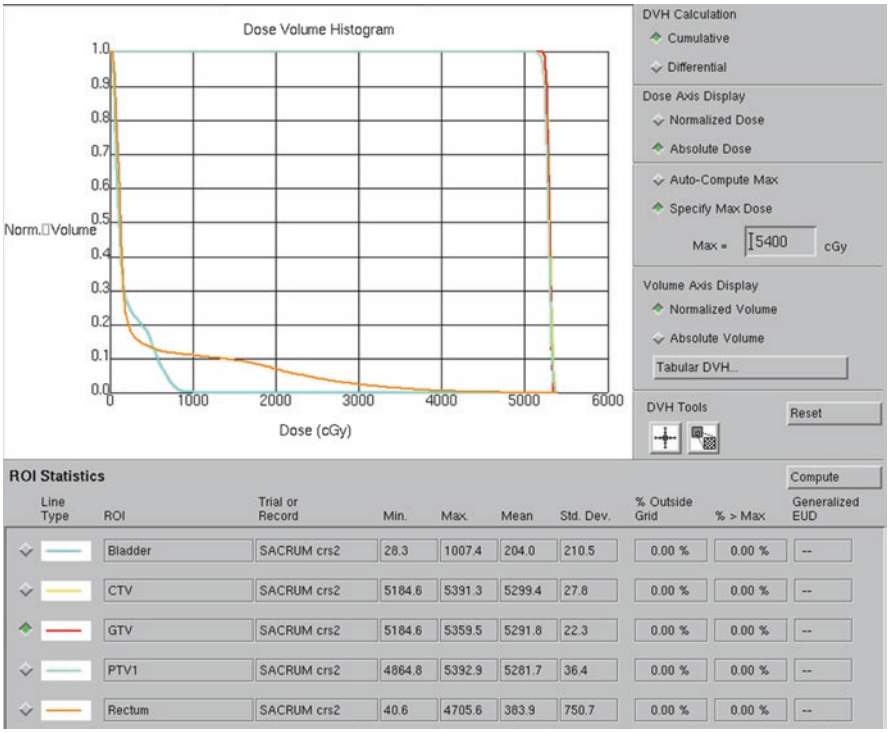

Fig. 22.6 Dose-volume histogram for patient with sacral hemangioblastoma treated with 54 Gy/30 fractions

22.4 General Principles of Spine Radiotherapy Simulation and Target Delineation

- CT simulation with a thermoplastic mask (cervical and upper thoracic spine) or customized immobilization device (lower thoracic, lumbar and sacral spine).
- In general, patients should be simulated in the supine position, though prone position is possible.
- Utilize volumetric thin slice preoperative and postoperative T2/FLAIR and post-gadolinium MRIs to delineate target volume.
- If the patient has contraindications to MRI, can use CT with and without contrast.
- Treatment planning aimed to cover 95% of the PTV volume by 95% of the prescribed dose while respecting the OAR constraints.
- VMAT/IMRT, proton therapy, or tomotherapy should be used to decrease dose to anterior organs at risk. Field junction feathering can be utilized to reduce the risk of overlap.
- See Table 22.4 for dose constraints (Table 22.5).

Table 22.4 Recommended normal tissue constraints

Organs at risk	Suggested dose constraints
Spinal cord	Maximum point dose 54 Gy SRS: 1 fraction, 12.4–14 Gy; 2 fractions, 17 Gy; 3 fractions, 20.3 Gy [1]
Esophagus	ALARA. Consider mean <34 Gy, V50 <40%, V35 <50% [2]
Trachea	ALARA
Lung	ALARA. Consider V20 <30%, mean <7–13 Gy [3]
Bowel	ALARA. Consider V45 <195 cc [4]

Table 22.5 Side effects

Acute	Hair loss, fatigue, headaches, nausea/vomiting, cough, odynophagia, abdominal discomfort, diarrhea, dysuria, hematologic (dependent on where in the spine treatment is applied to)
Long-term	Neurocognitive decline and hypopitutiarism (if treating whole CSI), age-dependent infertility when irradiating the sacrum
Uncommon or rare risks	Myelopathy, persistent myelosuppression, secondary malignancy

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Spinal Metastasis

23

Ting Martin Ma and Kristin J. Redmond

Contents

23.1 General Principles of Planning and Target Delineation

- In the absence of spinal cord compression and/or mechanical instability, either stereotactic body radiation therapy (SBRT) or external beam radiation therapy (EBRT) may be utilized depending on the number of sites, performance status, and life expectancy.
- In the context of spinal cord compression, randomized data has shown that surgical decompression and postoperative radiation increase days of walking compared to radiation alone and are preferred. If nonsurgical candidate, EBRT (e.g., 30 Gy in 10 fx) may be employed, or in select cases (e.g., re-irradiation), SBRT may be utilized.

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- In patients with mechanical instability, surgical stabilization or cement augmentation may be necessary since radiation alone does not stabilize the spine.
- Retreatment of bony metastases may be safely performed in most cases. Normal tissue tolerance should be closely observed and not to be exceeded unless absolutely necessary.

23.2 EBRT

- For reproducibility, in setup, patients are typically positioned in the supine position using site-specific immobilization such as an alpha cradle or aquaplast mask.
- Radiation field depends on the region to be treated and the physical limitations of the patient and positioning. The most common arrangements are AP/PA and posterior oblique fields although three- or four-field techniques are occasionally utilized to reduce dose to adjacent structures such as the esophagus or bowel.
- Laterally the field should cover width of the vertebral body with 2 cm margin, including areas of paravertebral tumor extensions.
- Superiorly/inferiorly, the field should be one vertebral body above and below the targeted disease.
- The spinal cord should be contoured based on the bony limits of the spinal canal, starting at least 10 cm above the superior extent of the PTV down to at least 10 cm below the inferior extent of the PTV.

23.3 EBRT Spinal Cord Dose Scheme and Constraints

- Multiple dosing schemes exist with equivalent survival and function outcomes. 20 Gy in 5 fractions (an example shown in Fig. 23.1) and 30 Gy in 10 fractions are commonly used. Longer fractionation (e.g., 30 Gy in 10 fractions) may improve local control and progression-free survival. For patients with poor performance status or short life expectancy (e.g., <6 months), 8 Gy X1 fraction is appropriate as randomized data suggests equivalent outcomes at 3 months following completion of radiation therapy.

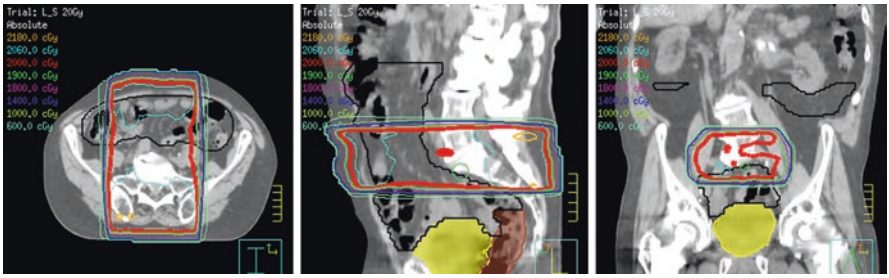

Fig. 23.1 Example of a conventional RT treatment plan (20 Gy in 5 fx) of a 79-year-old man with widely metastatic prostate cancer with pain in the S1 vertebra

- Acceptable coverage of the targeted vertebral levels is typically considered at least 95% of the volume receiving 95% of the prescription radiation dose.
- The prescription dose for conventional RT is lower than the tolerance of the spinal cord, but caution should be taken to minimize hotspots over the spinal canal.

23.4 SBRT

- SBRT is typically used for patients with high-performance status, oligometastatic disease (generally defined as less than three to five sites), radio-resistant disease, and symptomatic disease recurrence in a previous radiation field. A single and solitary spine metastasis is a strong indication for SBRT.
- SBRT has the advantage of bone marrow preservation, patient convenience (fewer fractions), and less interference with ongoing chemotherapy treatments. It can be used with caution as an alternative to surgery in nonsurgical candidates for treatment of patients with epidural extension. SBRT is also utilized following isolated progression after conventional EBRT in cases of diffuse spine involvement. However, in comparison to conventional EBRT, it has higher cost and complexity, longer treatment planning, and treatment times.
- Retrospective series suggest higher rates of local control following SBRT than conventional RT (80–100% vs. 30–60%). Final results and manuscripts are pending from randomized controlled trials including RTOG 0631 comparing single fraction of 8 Gy conventional radiation to 16–18 Gy SBRT in terms of pain relief and quality of life and phase 3 component of SC-24 from the National Cancer Institute of Canada (NCIC) comparing 20 Gy in five-fraction conventional radiation to 24 Gy in two-fraction SBRT in terms of pain control.
- SBRT is being increasingly utilized in lieu of conventional RT postoperatively in the adjuvant setting with excellent local control, although no randomized controlled trials have been published in manuscript form to confirm the superiority of SBRT in this setting.
- Near-rigid immobilization systems (e.g., vacuum-locking bag, dual vacuum-activated immobilization and fixation system, or thermoplastic mask for cervical spine treatments) are used because precise positioning is essential.

23.5 SBRT Target Delineation

- GTV should include the area of gross disease on CT and MRI.
- CTV should include the entire involved bony and epidural disease plus the immediately adjacent segments at risk of microscopic disease extension. Table 23.1 and Fig. 23.2 show consensus contouring guidelines, and Fig. 23.3 shows contours for an example patient.
- When utilizing SBRT in the postoperative setting, consensus contouring guidelines follow the same concept but based on the preoperative extent of disease irrespective of the extent of surgical resection. In cases of preoperative

Table 23.1 Suggested target volumes for intact spine SBRT

Target volumes	Definition and description
Spinal cord	– True spinal cord volume is based on T2-weighted MRI or CT myelogram in cases of inability to accurately visualize the spinal cord on MRI – Spinal cord planning risk volume generally ranges from 0 to 2 mm radial expansion of the true spinal cord. The thecal sac with no expansion should be utilized below the conus
GTV	– Complete delineation of the gross tumor including all bony, epidural, and paraspinal components, using all available clinical information and imaging modalities, including MRI, CT, myelography, plain radiographs, and PET/CT
CTV	– Include abnormal marrow signal suspicious for microscopic invasion – Normal bony expansion into adjacent anatomical compartment (Fig. 23.2) to account for subclinical tumor spread in the marrow space: the entire vertebral body, pedicle, transverse process, lamina, or spinous process was included in the CTV if any portion of these regions contained the GTV – No epidural CTV expansion if without epidural disease – Circumferential CTVs encircling the cord should be used only when the vertebral body, bilateral pedicles/lamina, and spinous process are all involved, or there is extensive metastatic disease along the circumference of the epidural space
PTV	– Uniform expansion around CTV – CTV to PTV margin 1–2 mm depending on detailed institutional analysis of setup error – Subtract spinal cord avoidance structure and adjacent critical structures to allow spacing at the discretion of the physician unless GTV is compromised – Should contain entire GTV and CTV margins

circumferential epidural extension, a "donut-shaped" CTV should be applied, regardless of the extent of residual epidural extension (Table 23.2 and Fig. 23.4). Spinal instrumentation should be excluded from the CTV.

23.6 SBRT Spinal Cord Dose Scheme and Constraints

- No randomized data to guide prescription dose. Reasonable doses include 18–24 Gy in a single fraction, 24 Gy in 2 fractions, 27–30 Gy in 3 fractions, and 30–40 Gy in 4–5 fractions.
- Prescription isodose line varies with treatment technology and intent of an individual treatment but is typically to the 80–90% isodose line for linear accelerator-based systems and 50–80% for robotic systems.
- When given in a single fraction, D10% of the spinal cord (delineated on MRI and 6 mm superior and inferior to the level of CTV) should be no more than 10 Gy. D0.25 cc should be no more than 10, 18, and 22.5 Gy when given in 1, 3, and 5 fractions, respectively. The maximum point doses of 2 Gy biologically equivalent doses (BED) assuming an $\alpha/\beta = 2$ Gy (P_{max} $BED_{2/2}$) that result in 5% or less probability of radiation myelopathy for 1–5 fx SBRT practice are 12.4, 17.0, 20.3, 23.0, and 25.3 Gy, respectively.

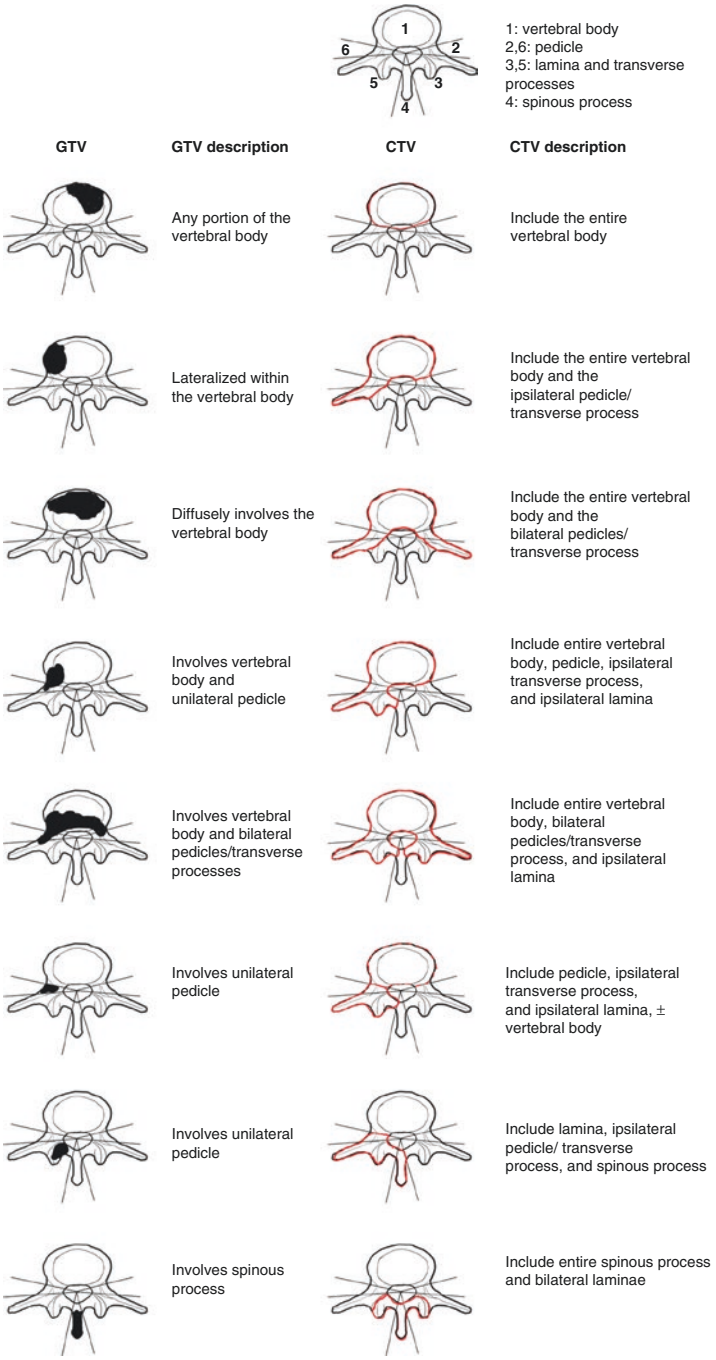

Fig. 23.2 Guidelines for spinal SBRT bony CTV delineation. Red tracings delineate CTV. (Adapted from Cox BW et al. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* 2012 Aug 1;83(5):e597–605)

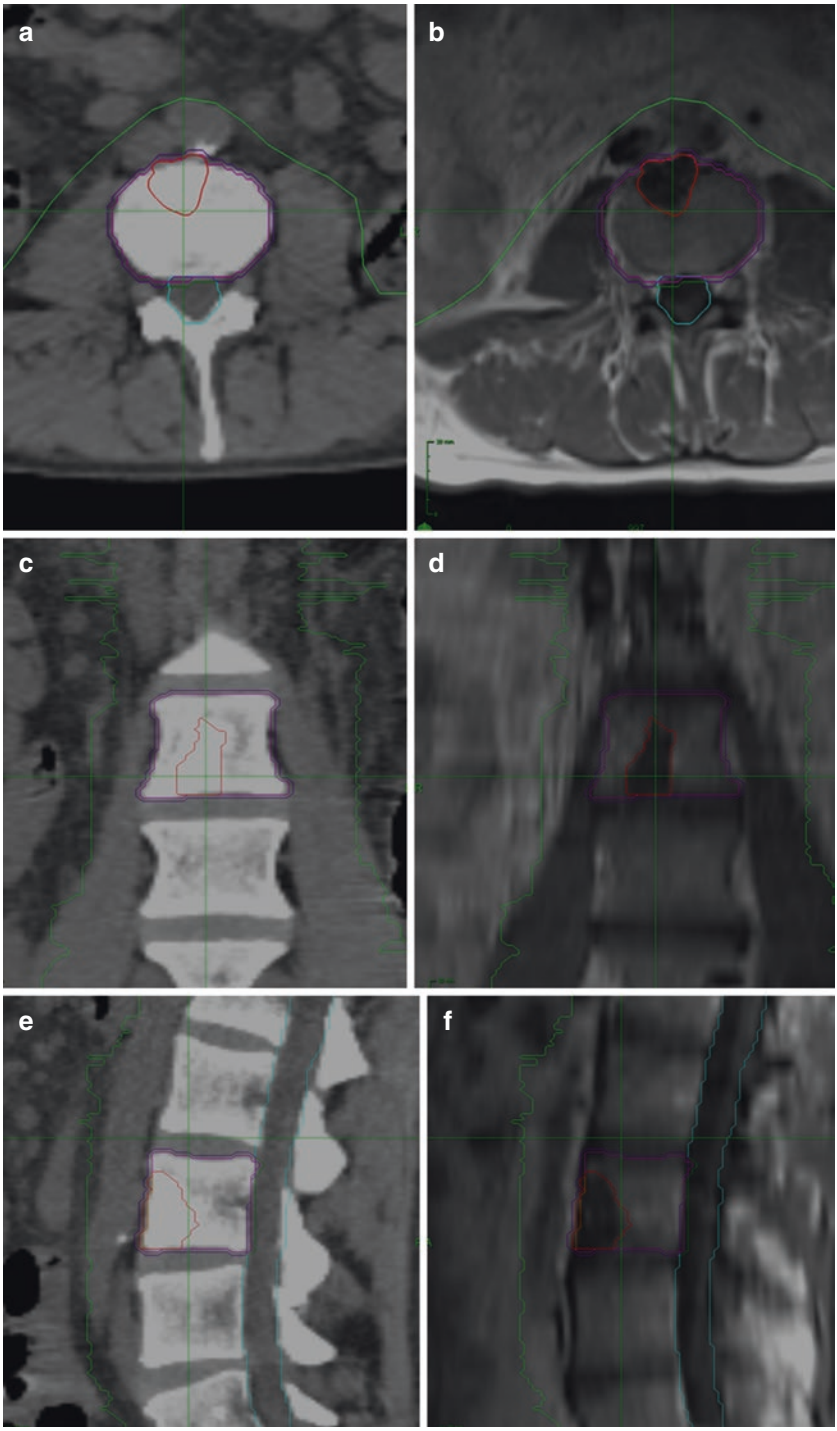

Fig. 23.3 A 47-year-old man with metastatic pancreatic cancer to L3 vertebra. Both CT (**a**, **c**, **e**) and MRI (T1-weighed shown in panels **b**, **d**, **f**) were utilized to delineate GTV (red). CTV is delineated in magenta and spinal cord planning risk volume in turquoise

Table 23.2 Suggested target volumes for postoperative spine SBRT

Target volumes	Definition and description
Spinal cord	– True spinal cord volume is based on T2-weighted MRI or CT myelogram in cases of significant hardware artifact or inability to accurately visualize spinal cord on MRI – Spinal cord planning risk volume generally ranges from 0 to 2 mm radial expansion of the true spinal cord. Alternatively, the thecal sac with no expansion may be utilized
GTV	– Complete delineation of the gross tumor based on postoperative CT and MRI, including residual epidural and paraspinal components of tumor
CTV	– Include the entire GTV and entire anatomic compartment corresponding to all preoperative MRI abnormalities suspicious for tumor involvement (Fig. 23.4) – Hardware and incision not included unless involved – Circumferential CTVs encircling the cord should be used only in cases of preoperative circumferential osseous and/or epidural involvement and can also be considered in cases of near-circumferential epidural disease involvement – Should be modified at reconstructed dural space and to account for changes in the anatomy after surgery – Consider additional anatomic expansions of up to 5 mm beyond paraspinal extension and cranio-caudally for epidural disease
PTV	– Uniform expansion around CTV – CTV to PTV margin of up to 2.5 mm depending on detailed institutional analysis of setup error – Subtract spinal cord avoidance structure and adjacent critical structures to allow spacing at the discretion of the physician unless GTV is compromised – Should contain entire GTV and CTV margins

- Practice patterns from 5 international institutions reported consistent spinal cord limits of 10–11, 15–18, and 20–23.75 Gy for 1, 3, and 5 fractions. The doses were applied to a 1–2 mm expansion of the spinal cord in most centers.
- Re-irradiation with SBRT appeared to be safe when all of the following criteria are met: (1) 5 or more months elapsed after conventional radiation, (2) re-irradiation thecal sac P_{max} $BED_{2/2}$ ≤20–25 Gy, (3) total P_{max} $BED_{2/2}$ ≤70 Gy, and (4) total P_{max} $BED_{2/2}$ accounted for by the SBRT no higher than 50%.
- In the retreatment setting, a lifetime cumulative BED (α/β = 3 Gy) of ≤75 Gy accounting for 25% repair after 6 months and 50% repair after 12 months is reasonable. Cumulative spinal dose in $BED_{2/2}$ ≤135.5 Gy if given >6 months apart with the dose of each course ≤98 Gy may be reasonable.
- Sahgal et al. suggest that reasonable P_{max} $BED_{2/2}$ for 1–5 fx SBRT practice after 20 Gy in 5-fraction conventional radiotherapy are 9, 12.2, 14.5, 16.5, and 18 Gy, respectively. Reasonable P_{max} $BED_{2/2}$ for 1–5 fx SBRT practice after 30 Gy in 10 fx conventional radiotherapy are 9, 12.2, 14.5, 16.2, and 18 Gy, respectively.

23.7 Acute and Late Effects of Spinal Irradiation

- Acute effects:
  - No evidence suggests that radiation induces acute spinal cord toxicity. Single doses of up to 100 Gy have been given without acute effects.

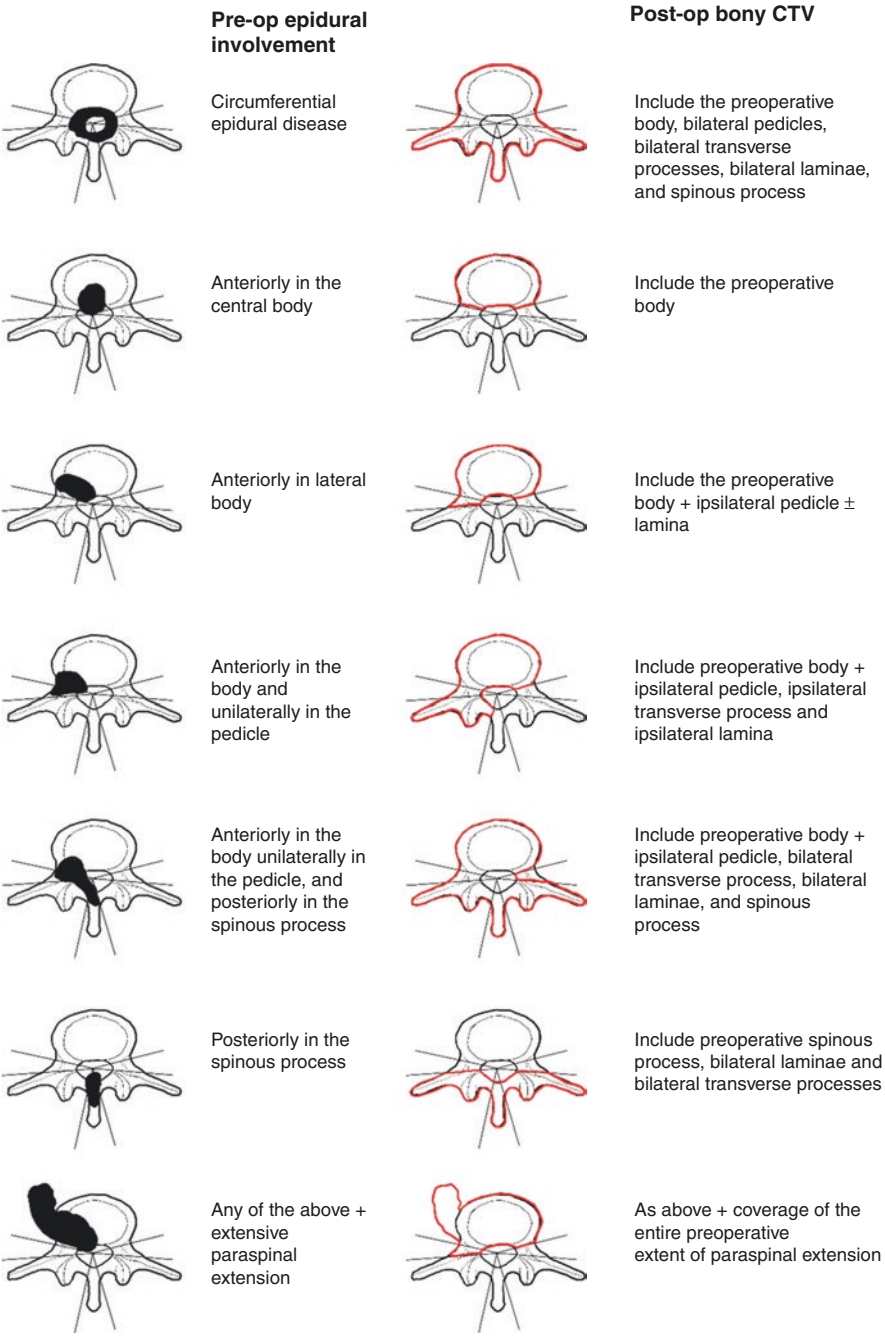

Fig. 23.4 Guidelines for postoperative spinal SBRT bony CTV delineation. Bony CTV was delineated in red. (Adapted from Redmond KJ et al. Consensus Contouring Guidelines for Postoperative Stereotactic Body Radiation Therapy for Metastatic Solid Tumor Malignancies to the Spine. Int J Radiat Oncol Biol Phys. 2017 Jan 1;97(1):64–74)

  - A transient radiation-induced myelopathy may develop in up to 10% of patients 2–6 months after spinal irradiation. This condition is characterized by Lhermitte's sign (shock-like sensation travelling down the spine during neck flexion). It is typically self-limited and does not predict for the subsequent development of chronic progressive myelopathy. Education and reassurance are sufficient.
- Late effects:
  - Chronic progressive myelopathy is an irreversible condition manifesting 6–12 months after irradiation. It is marked by paresis, paresthesia, and sphincter dysfunction. Symptoms are progressive, and there is no established treatment. The risk of developing this condition is proportional to radiation fraction size, total radiation dose, and extent of spinal cord irradiation.
  - Other late effects include lower motor neuron syndrome, which develops 3–25 years after cord radiation and is characterized by progressive weakness of lower extremities without sensory deficits. Telangiectasia and cavernous malformations, which could result in an acute hemorrhage, have also been reported.

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Management of Acute Side Effects of Brain Irradiation

24

Yolanda D. Tseng and Sarah Layman

Contents

24.1 Potential Acute Side Effects of Fractionated Brain Irradiation

See Table 24.1 for timing.

24.1.1 Acute

Common

- Fatigue
- Skin erythema (radiation dermatitis)
- Hair loss, scalp soreness that may precede hair loss

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Table 24.1 Timing of acute side effects of brain irradiation

	Onset from RT start	Anticipated recovery after RT end
Cerebral edema	1–2 weeks	–
Dry mouth	~3 weeks	Weeks to months
Fatigue	2–3 weeks	Weeks to months
Hair loss	3–4 weeks	Weeks to months Follicle D_{50} ~ 40 Gy for permanent alopecia [1]
Irritation of the ear canal	2–3 weeks	Weeks
Mucositis	3–4 weeks	2–4 weeks
Myelosuppression	1–2 weeks	4–6 weeks
Nausea/vomiting	May occur with RT start	Days to weeks
Parotitis	May occur with first 1–2 fractions	Days to weeks after onset
Radiation dermatitis	2–3 weeks	2–4 weeks
Somnolence syndrome	1–6 months	2–3 weeks after onset

Abbreviations: D_{50}, dose at which 50% patients develop toxicity

Less common
- Nausea, vomiting
- Temporary aggravation of brain tumor symptoms (headache, seizures, weakness)
- Myelosuppression: more common with cranial spinal irradiation (CSI) and/or concurrent chemotherapy
- Irritation of the ear canal
  - Conductive hearing loss from serous otitis media
  - Itching
- Eye irritation and dry eye

Uncommon
- Dry mouth, altered taste
- Mucositis: more common with CSI
- Parotitis: fever, swelling, tenderness

24.1.2 Early-Delayed

Less common
- Pseudoprogression

Uncommon
- Lethargy: more common among children, after prophylactic cranial irradiation

24.2 Potential Acute Side Effects of Stereotactic Radiosurgery

24.2.1 Acute

Common
- Nausea, dizziness
- Headache
- Frame placement-related issues
  - Bruising, bleeding, skin laceration
  - Pin site swelling

Less common
- Greater occipital dysesthesias
- Periorbital edema
- Fatigue
- Seizures (24–72 h)

Uncommon
- Skull fracture
- Pin site infection

24.2.2 Early-Delayed

Common
- Fatigue

Less common
- Temporary worsening neurological function
  - Vertigo and worsening hearing for vestibular schwannoma patients
- Pseudoprogression

Uncommon
- Ongoing lethargy

24.2.3 Late-Delayed

Less common
- Acute onset headache and neurological changes due vasogenic edema
  - Consider non-contrast CT scan of the head to rule out hemorrhage

24.3 Potential Acute Side Effects among Patients Receiving Concurrent Temozolomide

Hepatotoxicity
- Monitor liver function tests at baseline and halfway through concurrent treatment.

Myelosuppression
- Weekly complete blood counts.
- Pneumocystis pneumonia prophylaxis:
  - Trimethoprim-sulfamethoxazole PO
  - Pentamidine inhaled
- Hold temozolomide for platelets $<75 \times 10^9$/L, absolute neutrophil count $<1.0 \times 10^9$/L.
- Consider holding RT for severe thrombocytopenia ($<10–20 \times 10^9$/L).

Nausea/vomiting, anorexia
- Ondansetron 8 mg beginning 60 min before temozolomide

24.4 Management of Acute Side Effects

Cerebral edema (headache, nausea)
- Dexamethasone 4–8 mg daily generally adequate, 16 mg daily if significant edema:
  - See "dexamethasone dosing and side effects."
- If concern for intracranial hemorrhage or unresponsive to dexamethasone, work up with non-contrast CT scan of the head.
- For peritumoral edema refractory to steroids (or with significant complications from steroids), can consider bevacizumab versus surgery.

Dry mouth/altered taste
- Baking soda mouthwash (1–3 teaspoons swish and spit PRN)
  - Mix 1 tablespoon baking soda, 1 tablespoon salt, and 1 quart water.
- Chilled carbonated beverages

Fatigue
- Encourage regular physical activity levels.
- Confirm absence of other comorbidities (e.g., anemia, depression).
- Patients may note worsening of fatigue with steroid taper.
- Methylphenidate [CNS stimulant]: 5 mg BID:
  - Can increase based on tolerability by 10 mg/day every 3 days to maximum 40 mg/day.
- Modafinil [CNS stimulant]: 100 mg once daily.

Irritation of the ear canal
- External otitis
  - Cortisporin Otic [neomycin, polymyxin B, hydrocortisone]: 4 gtts to the affected ear.
  - Otitis Externa Mix [1:1 water/white vinegar]: Apply 2–4 gtts to the affected ear.
  - CiproHC Otic [ciprofloxacin, hydrocortisone]: 3 gtts BID for 7 days.
- Eustachian tube edema
  - OTC decongestant (e.g., pseudoephedrine)
  - Short course of steroids (e.g., Medrol dose pack)
  - Rarely requires myringotomy
- Uncomplicated otitis media
  - Amoxicillin 250 mg Q8 hours × 5–7 days

Mucositis
- Baking soda mouthwash (1–3 teaspoons swish and spit PRN):
  - Mix 1 tablespoon baking soda, 1 tablespoon salt, and 1 quart water.
- Minimize spicy foods, alcohol, and tobacco.
- Triple Mix [1:1:1 Benadryl elixir/Maalox/Viscous Xylocaine]: 2 teaspoon PO QID PRN.

Myelosuppression
- Most commonly leukopenia > thrombocytopenia.
- Consider holding RT for severe thrombocytopenia (<10–20 × 10^9/L).

Nausea/vomiting (in order of preference)
- Antiemetics
  - Ondansetron 8 mg Q8 hours PRN with bowel regimen
  - Compazine 10 mg Q6 hours PRN
- Corticosteroids
  - Dexamethasone 4–16 mg daily with proton pump inhibitor prophylaxis
- Ativan 0.5–2 mg Q8 hours PRN

Parotitis
- Ice packs
- Nonsteroidal anti-inflammatory drugs

Pseudoprogression
- Treatment-induced imaging changes (enhancement) seen within 3 months after completion of chemotherapy and RT for high-grade gliomas
- Often asymptomatic

Radiation dermatitis
- Mild reaction: soothing moisturizing lotion or ointments (e.g., Calendula, Aquaphor).
- Moist desquamation (rare):

  - Silvadene cream 1% to affected area TID
  - Domeboro soaks
- Severe reaction (Stevens-Johnson syndrome): uncommonly seen in patients on phenytoin or carbamazepine. Reaction may occur beyond RT fields. Discontinue anticonvulsant.

Seizure (Table 24.2)
- If new seizure, work up with imaging:
  - Start with CT scan of the head without contrast.
  - Consider MRI brain with and without contrast.

Table 24.2 Common antiseizure drugs and comments on use

Drug	Dosing	Comments
Levetiracetam	Start 500 mg BID Can increase to recommended dose 1500 mg BID (increase Q2 weeks by 500 mg/dose)	Fatigue/somnolence
Lamotrigine	If monotherapy, start 25 mg once daily weeks 1 and 2 and 50 mg daily weeks 3 and 4, and then increase by 50 mg/day every 1–2 weeks, max dose usually 225–375 mg/day in 2 divided doses If polytherapy other than valproate, start 50 mg/day weeks 1 and 2 and 50 mg BID weeks 3 and 4, and then increase by 100 mg/day every 1–2 weeks with target dose 300–500 mg/day in 2 divided doses	Rare incidence severe rash (Stevens-Johnson syndrome); stop immediately if concerning rash develops Somnolence Interacts with enzyme-inducing AEDs Avoid use with valproate
Valproate	Start at 15 mg/kg/day Can increase to max 60 mg/kg/day	May interfere with platelet function Teratogenic
Lacosamide	Start 100 mg BID Increase by 50 mg BID weekly to recommended dose 150–200 mg BID	
Topiramate	Start 25 mg BID, and increase weekly by 25 mg BID to max dose 200 mg BID if needed	May increase phenytoin concentration Levels influenced by other AEDs Can help with mood stabilization
Phenytoin	Start 100 mg TID; consider loading dose IV or PO in clinic or hospital setting Titrate up to most effective dose, usually no more than 400 mg daily obtain first level 3–5 days post-initiation of treatment	Levels can be affected by diet, other enzyme-inducing medications Stop immediately if concerning rash develops
Rectal diazepam/ intranasal midazolam	Intranasal midazolam (adults over 50 kg): 10 mg (2 mL) delivered via syringe with attached nasal atomizer Rectal diazepam (gel): 0.2 mg/kg in prefilled syringe. Consider dose reduction in elderly and debilitated	Consider as rescue treatment when patient traveling out of the country

Abbreviations: *AED* anti-epileptic drug

- Monotherapy preferred over polytherapy.
- Prophylactic antiseizure drugs not generally recommended in patients without history of a seizure [3].
- Treat with lowest effective dose.
- Beware of potential interactions between antiseizure drug and other medications.
- Caution patients about state laws regarding driving after loss of consciousness/seizure.

Somnolence syndrome/lethargy
- Usually spontaneously resolves.
- Drowsiness, fatigue, anorexia, transitory cognitive disturbance.
- Consider corticosteroids, especially if associated with signs of increased intracranial pressure.

24.5 Dexamethasone Dosing and Side Effects [2]

Please note, only consider using dexamethasone if there is concern for cerebral edema (i.e., headaches, nausea, loss of neurological function). If started prophylactically or postoperatively, taper during radiation therapy.

Dosing
- Half-life 36–54 h.
- Once or twice daily dosing adequate for maintenance therapy.
- Consider large bolus dose (4 mg TID or QID), and then titrate to lowest required dose once symptoms are controlled.
- Onset within hours.

Common acute/subacute side effects
- Insomnia
- Essential tremor
- Hiccups
- Hyperglycemia
- Immunosuppression/increased risk of opportunistic infection
  - Highest-risk during taper
- Peptic ulcers: prophylactic treatment with a PPI (e.g., omeprazole) recommended for patients with history of previous peptic ulcers, concomitant NSAIDs, and/or elderly
- Steroid myopathy: proximal, 9–12 weeks into treatment
- Increased anxiety, aggression
- Fluid retention, frequent urination
- Osteonecrosis (late effect)

Table 24.3 Suggested dexamethasone tapering guidelines

	Dexamethasone dose	Days
Fast/medium taper	4 mg twice daily	4–7
	2 mg twice daily	4–7
	1 mg twice daily	4–7
	1 mg daily	4–7
	Stop	
Slow taper	4 mg twice daily	7
	2 mg twice daily	7
	1 mg twice daily	14
	1 mg daily	14
	0.5 mg daily	14
	Morning fasting cortisol level	
	If level ≥10 μg/dL, then *stop*	
	If level ≤10 μg/dL, then switch to 20 mg hydrocortisone daily	
	Taper by 5 mg daily every week. Recheck morning fasting cortisol level before stopping	

Taper (see Table 24.3)

- Because of long duration of action, dexamethasone should be tapered every 3–7 days (e.g., 50% reduction Q3–7 days). Consider longer taper if worsening symptoms with each dose reduction.
- Steroid withdrawal syndrome: headache, lethargy, myalgias, arthralgias, loss of appetite, lightheadedness (signs of adrenal insufficiency):
  - Responds to raising dose slightly and tapering more slowly.
- If on steroids for greater than a month, patient may be at risk for adrenal insufficiency. Draw morning fasting cortisol once at 0.5 mg dexamethasone, and if less than 10 μg/dL, consider transitioning to 20 mg hydrocortisone and then reducing more slowly.

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Radiation Necrosis: A Practical Approach

25

Ehsan H. Balagamwala, Martin Tom, Manmeet Ahluwalia, Jonathan Sharrett, and Samuel T. Chao

Contents

25.1 Introduction

- Radiation necrosis is a late complication of radiotherapy to the brain and generally occurs months to years after completion of treatment. Radiation necrosis is frequently confused with pseudoprogression, which is a reversible condition characterized by early delayed radiation injury occurring up to 3 months after

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completion of concurrent chemoradiation [1]. On the other hand, radiation necrosis is largely irreversible and is characterized by a focal pattern demonstrating a circumscribed lesion often with surrounding edema.

- The exact incidence of radiation necrosis is largely unknown due to the challenges in accurate diagnosis. However, the incidence of radiation necrosis is increasing in the era of stereotactic radiosurgery (SRS) and combined modality therapy for primary and metastatic brain tumors. In a prospective randomized trial evaluating low-dose versus high-dose conventionally fractionated radiotherapy for low-grade gliomas, the incidence of radiation necrosis was 2.5% in the 5040 cGy arm as compared to 5% in the 6480 cGy arm [2]. The incidence of radiation necrosis after SRS is approximately 5–10%, with some series reporting a higher rate depending on the criteria used for diagnosis [3].
- Preclinical evidence suggests that vascular injury initiates the process of necrosis. Vascular endothelial cell damage results in fibrinoid necrosis of small vessels which leads to focal coagulative necrosis, as well as oligodendrocyte damage and demyelination. Recent evidence implicates vascular endothelial cell growth factor (VEGF), hypoxia-inducible factor 1α (HIF1α), as well as glucose transporter-1 in the development of necrosis [4–6].
- Radiation necrosis is very challenging to distinguish from tumor recurrence. Symptoms can mimic those of tumor recurrence and can include headache, nausea, vomiting, and somnolence. Risk factors for the development of radiation necrosis include total dose [2], fraction size [7], treatment duration, volume treated [8], concurrent chemotherapy, prior radiation, male sex, and dose homogeneity and conformality of SRS treatments [9]. Recent work has identified biological factors that predict for increased risk of radiation necrosis, including renal cell histology, lung adenocarcinoma histology, HER2-neu amplification, and ALK/BRAF mutational status [10].

25.2 Principles of Diagnosis

- The gold standard for the diagnosis of radiation necrosis is surgical resection and pathologic evaluation. Biopsy alone is not completely reliable due to potential for sampling error. Clinical diagnosis is challenging due to the fact that most published series do not correlate imaging and pathologic findings because of low rates of resection or biopsy.
- Several imaging modalities can be utilized to evaluate patients with concern for radiation necrosis, including magnetic resonance imaging (MRI) with contrast, relative cerebral blood volume (rCBV) as an additional sequence with standard MRI, magnetic resonance spectroscopy (MRS), 18-fluorodeoxyglucose (FDG) positron emission tomography (PET), and thallium-201 (T1) single-photon emission computed tomography (SPECT). Several agents have been utilized with PET imaging, such as carbon-11-methyl-methionine; *O*-(2-[18F]fluoroethyl)-L-tyrosine; 3,4-dihydroxy-6-[18F]fluoro-phenylala-

nine (FDOPA); and 3-*O*-methyl-6-[18F]fluoro-L-DOPA. However, their clinical applicability is limited at this time [3].

- Practical aspects of imaging diagnosis:
  - MRI with perfusion/rCBV [11]: This technique is based on a unique MRI sequence. Cerebral blood volume is postulated to increase in tumor, whereas it decreases in radiation necrosis. Sensitivity of 100% and specificity of 95.2% have been reported. MRI with perfusion/rCBV is the primary imaging modality used at our institution to diagnose radiation necrosis and distinguish it from tumor progression and pseudoprogression. Figure 25.1 demonstrates the salient features of rCBV for the diagnosis of radiation necrosis.
  - FDG PET: This is based on the premise that FDG uptake should increase in tumor and decrease in radiation necrosis. The primary limitation of FDG PET is the widely varying sensitivity and specificity reported in the literature [3].
  - MRS: This technique evaluates the metabolic composition within tissues, including lipids (product of brain destruction), lactate (anaerobic glycolysis), NAA (a neuronal marker), glutamine (a neurotransmitter), creatine (energy metabolism), and choline (cell membrane marker). Adding MRS to a standard MRI adds approximately 15–30 min for data acquisition. With tumor recurrence, NAA increases and lipid decreases. In contrast, with radiation necrosis, lipid increases and choline decreases. With multivoxel MRS, sensitivity and specificity approach 100%; however, its use remains investigational [12]. As this imaging modality is not traditionally covered by the Centers for Medicare and Medicaid Services (CMS), this scan may be an out-of-pocket expense for patients.

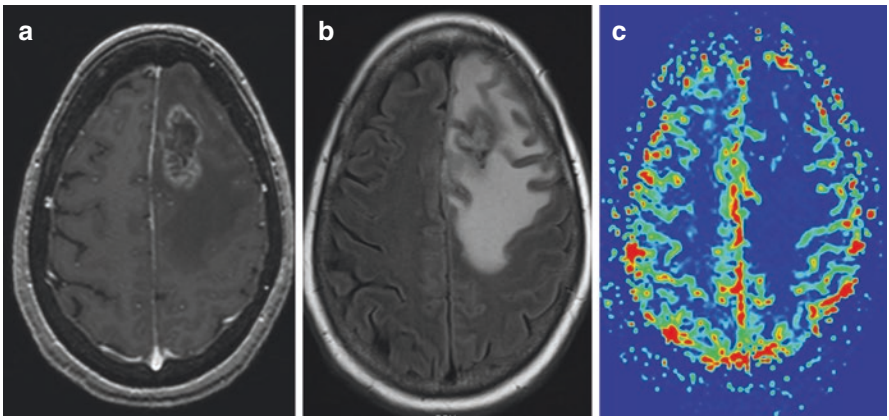

Fig. 25.1 Example of a patient who underwent planned staged cranial stereotactic radiosurgery (12 Gy followed by 15 Gy 1 month apart) for a left frontal brain metastasis from non-small cell lung cancer. Two months after completing radiosurgery and completely tapering off steroids, she developed mild somnolence. MRI showed increasing enhancement (**a**) as well as significant surrounding edema as seen on T2 FLAIR (**b**). The rCBV sequence (**c**) showed reduced blood flow in the left frontal region suggestive of radiation necrosis. Due to the symptomatic progression, she underwent a resection, and final pathology was consistent with radiation necrosis

25.3 Principles of Treatment

- Decisions regarding treatment can be made based on the size of radiation necrosis as well as the symptomatology of the patient. Small lesions in asymptomatic patients can be closely observed. For progressive, asymptomatic radiation necrosis, a combination of pentoxifylline 400 mg three times daily and vitamin E 400 IU three times daily (or 1000 IU once daily) may be considered given its low side effect profile.
- Radiation necrosis is frequently associated with intracranial edema, which is best visualized on the FLAIR MRI sequence. In patients who are symptomatic, corticosteroids such as dexamethasone can be utilized. Dexamethasone dose can be initiated at 4–16 mg total daily dose depending on the severity of symptoms. Due to the long half-life of dexamethasone, we prefer twice daily dosing given with breakfast and lunch. Once symptoms are controlled, we attempt tapering of steroids slowly over the course of 3–4 weeks while closely monitoring the patient's symptomatology.
- In patients with steroid-refractory radiation necrosis, other treatments such as anticoagulants, hyperbaric oxygen, combination of oral vitamin E and pentoxifylline, or bevacizumab can be utilized.
- Hyperbaric oxygen (HBO) is delivered to patients in a chamber with 100% oxygen at 2.5 times atmospheric pressure which increases the amount of oxygen in the blood stream and tissues, thus encouraging new vessels to grow. HBO is given 5 days a week for 30–40 total treatments. Despite the historical use of HBO, data regarding its efficacy are lacking with the strongest evidence for prevention of radiation necrosis rather than for its treatment [13]. In very select cases, HBO may be utilized for the prevention of radiation necrosis. Although considered, it is rarely used for the actual treatment of radiation necrosis in favor of bevacizumab or other therapies which have stronger supporting evidence.
- Vitamin E (1000 IU orally, once daily), in combination with pentoxifylline (400 mg orally, three times daily), can also be used to treat radiation necrosis. Despite the limited data available, the response to treatment is substantial enough to recommend its utility in steroid-refractory patients [14]. Given its favorable side effect profile, it may be considered in an asymptomatic patient with progressive radiation necrosis on imaging. Pentoxifylline should not be utilized in patients who have a history of cerebral or retinal bleeding.
- Given recent evidence implicating VEGF in the development of radiation necrosis, there has been increasing interest in utilizing bevacizumab for the treatment of radiation necrosis. A randomized trial, in addition to our institutional experience, has demonstrated excellent radiographic response as well as a reduction in the duration of dexamethasone treatment [15, 16]. We utilize either a low-dose (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks) or a high-dose (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) regimen. Figure 25.2 shows a typical response to bevacizumab treatment.
- For patients with refractory radiation necrosis, laser interstitial thermal therapy (LITT) can be considered to ablate the necrotic tissue. LITT is a minimally

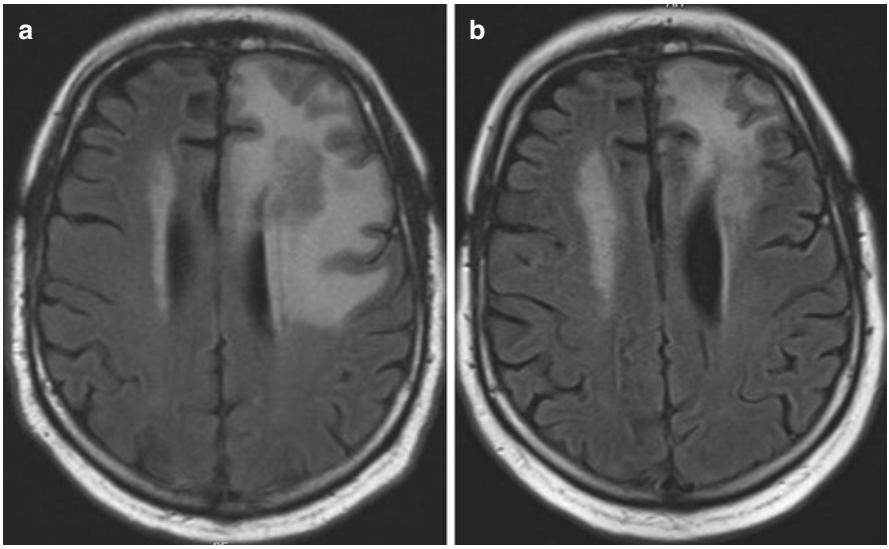

Fig. 25.2 Example of a 73-year-old male who underwent initial surgical resection for a left frontal meningioma followed by radiotherapy for recurrence (5400 cGy in 30 fx). About 16 months after completing radiotherapy, he developed behavioral changes and a decline in the ability to perform activities of daily living as well as evidence of radiation necrosis on MRI brain. He was initially started on dexamethasone which improved his symptoms. However, after 3 months, he developed progressive cognitive changes as well as abnormalities on T2 FLAIR (**a**). He was treated with four doses of bevacizumab (7.5 mg/kg). At last follow-up, his neurologic symptoms improved, and MRI showed significant improvement in T2 FLAIR changes (**b**). He was able to fully taper steroids after completing four doses of bevacizumab

invasive procedure that may be preceded by a biopsy to assist with diagnosis. Initial results are promising for reduction in surrounding edema, improvement in symptomatology, as well as reduction in steroid dependence [17].

25.4 Summary and Conclusions

- Radiation necrosis is a late complication of radiotherapy to the brain and generally occurs months to years after completion of treatment. The risk of radiation necrosis increases with increasing radiation dose.
- Clinical diagnosis of radiation necrosis is challenging with multiple imaging modalities available. At our center, we prefer to use rCBV in addition to a standard series MRI for diagnosis due to the speed with which it can be acquired and its favorable sensitivity and specificity. MRS is also a useful tool; however, its implementation in routing clinical practice is difficult given the prolonged time necessary for image acquisition and cost.
- Small, asymptomatic lesions may be observed closely. Patients with symptomatic lesions as well as those with significant surrounding edema can be treated

with corticosteroids such as dexamethasone. Those refractory to steroids can be considered for bevacizumab. For those patients who are significantly symptomatic or in those in which biopsy confirmation is necessary, LITT can be employed for both biopsy and thermal ablation of the necrosis. Our diagnostic and treatment algorithm is presented in Fig. 25.3.

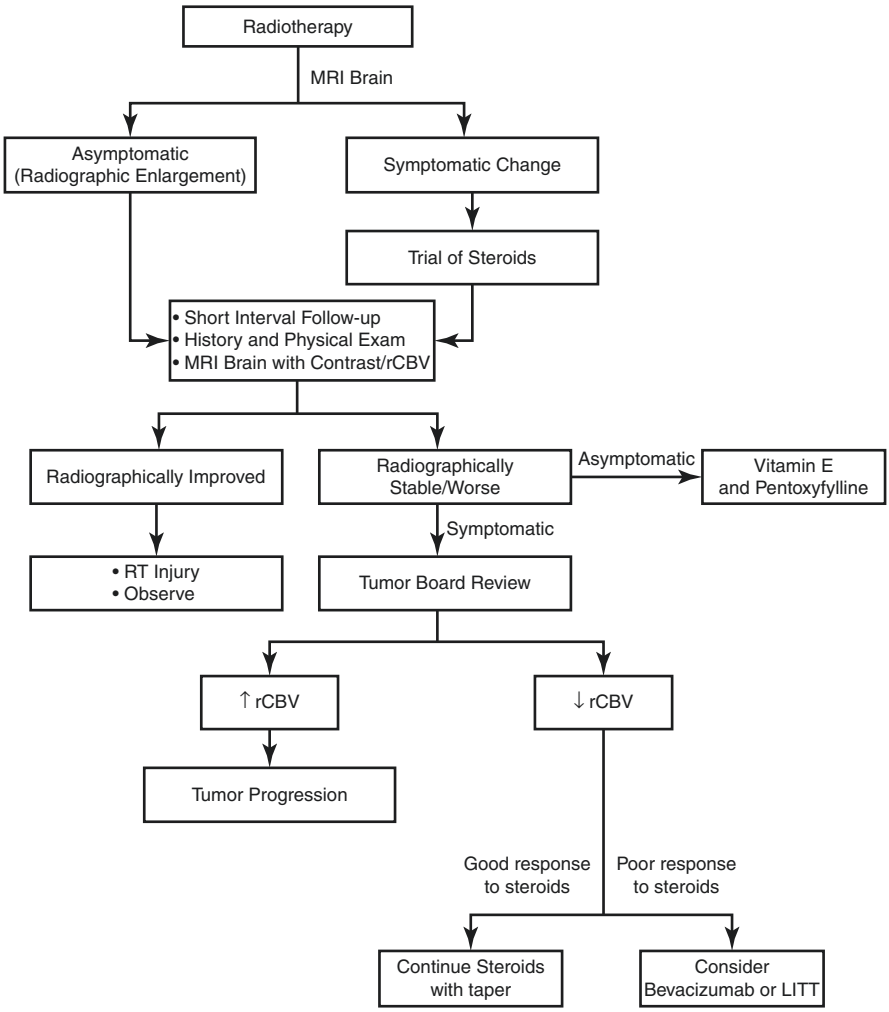

Fig. 25.3 Algorithm for the diagnosis and treatment of radiation necrosis utilized at Cleveland Clinic

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Management of Spine SBRT Adverse Effects

26

Vincent Bernard and Amol J. Ghia

Contents

26.1 Introduction

Toxicities from SBRT are well recognized and can be dichotomized:

- Acute complications: Due to exposure to the anatomic structures proximate to the radiation field
  - Cervicothoracic: Esophagitis/mucositis/dysphagia
  - Lumbar: Nausea/vomiting
  - Sacral: Loose stools
  - Erythema/dermatitis: Rare and mild and generally limited to the treatment site
  - Pain flare
- Late complications
  - Vertebral compression fracture (VCF)

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Table 26.1 Studies regarding pain flare

Paper	Year	Number of patients	Median time to toxicity (months)	Incidence (%)	Outcomes observed
Chiang [2]	2013	41	Most commonly observed at day 1	68.3	Significant predictors of pain flare were high Karnofsky score and cervical and lumbar spine lesions. Dexamethasone effectively reduced pain score during rescue
Pan [1]	2015	210	5 days (0–20 days)	23	Fractionation was significantly correlated with pain flare incidence; those patients receiving one fraction were at greater risk for pain flare than those receiving three or five fractions
Khan [3]	2015	47	N/A	19.2	Patients treated with prophylactic dexamethasone saw a decrease in reported pain flares. A 4 mg dose was most effective at preventing pain symptoms and functional deterioration

- Radiation myelopathy (RM)
- Radiculopathy: ~3–10% particularly in cases with disease within the foramen

26.2 Pain Flare (Table 26.1)

An increase in pain experienced during or immediately after radiation is commonly seen in SBRT compared with conventional radiotherapy (RT):

- *Incidence*: Up to 23–68% of steroid naïve patients. Median time to symptoms of 5 days (range, 0–20 days) after start of treatment [1].
- *Putative risk factors* [2]
  - High Karnofsky performance status
  - Cervical and lumbar spine lesion location
  - Number of treatment fractions (2.4-fold increase in risk with each decrement among 5-, 3-, and 1-fraction treatments)
- *Management*: Typically self-limiting
  - Pain rescue with dexamethasone (4 mg oral BID for the remainder of treatment and tapered over 5 days after SBRT) resulted in significant pain alleviation.
- *Prevention*: We do not routinely administer dexamethasone prophylactically to prevent pain flare. In a prospective observational study, prophylactic treatment with dexamethasone 1 h before and for 4 days following SBRT resulted in a significant decrease in observed pain flares compared to previously untreated published cohorts, 19% and 69% ($p < 0.0001$), respectively [2, 3]. *A prospective randomized clinical trial is evaluating the role of prophylactic dexamethasone in patients receiving spine SBRT.

26.3 Vertebral Compression Fracture (Table 26.2)

Caused by tumor-induced bone demineralization and radiation-induced osteoradionecrosis leading to vertebral instability and fracture [4, 5]:

Table 26.2 Studies regarding vertebral compression fracture

Paper	Year	Number of patients	Median time to toxicity (months)	Incidence (%)	Outcomes observed
Boehling [23]	2012	93	3	20.3	Patients >55yo, baseline VCF, and pain were predictive of VCF
Cunha [5]	2012	90	3.3 (9.5–21.6)	11	Presence of spine deformity, lytic tumors, dose of >20 Gy, and lung and hepatocellular tumors were at higher risk for VCF
Sahgal [10]	2013	252	2.46 (0.03–43.01)	14	Greatest risk exists for those receiving 24 Gy and with baseline VCF, lytic tumor, and spinal deformity which correspond to three of the SINS criteria. Caution is suggested in the use of high-dose single fraction outside of a clinical trial setting
Thibault [24]	2014	37	2	11.4	Patients receiving single-fraction SBRT and the presence of baseline VCF were associated with an increased risk of radiation-induced VCF
Guckenberger [14]	2014	387 lesions	N/A	7.8	VCF with rates as low as 7.8% in a multi-institutional analysis where only 5.8% of patients were treated with single-fraction SBRT. They suggest this evidence supports the idea of fractionated doses leading to fewer rates of VCF
Moussazadeh [12]	2015	278	N/A	36	Authors studied long-term toxicity profiles of patients treated with high-dose single-fraction SBRT. Radiographic fracture rate of 36% was observed, with an intervention rate of 14%
Jawad [7]	2016	541	3 (1–36)	5.7	Those patients with preexisting VCF, solitary metastasis, and prescription dose of 38.4 Gy or more are at greater risk of VCF. MRI target delineation is suggested to lead to decrease risk of VCF

(continued)

Table 26.2 (continued)

Paper	Year	Number of patients	Median time to toxicity (months)	Incidence (%)	Outcomes observed
Boyce-Fappiano [25]	2017	791	2.7	11.9	Significant predictors of VCF risk on multivariate analysis included prior VCF and lytic tumors. It was suggested that the low VCF rates seen in this study were a result of the majority of patients (97%) being treated with 18 Gy or less
Virk [9]	2017	323	13.2 (6.3–28.7)	8	Authors specifically characterized symptomatic VCFs requiring therapeutic intervention contrasting to the incidence of radiographic VCFs in previously published cohorts (8% and 39%, respectively). Higher SINS at the time of SBRT was correlated with earlier fractures

- *Incidence*: Risk of *radiographic* VCF in SBRT is considered higher compared to those patients receiving fractionated RT, 5.7–39% and 3% respectively, with a median time to VCF of approximately 3 months [6–8]. Radiation-related VCF requiring stabilization occurs in <10% of patients receiving dose-escalated single-fraction SBRT [9].
- *Risk factors*
  - Patients receiving high doses per fraction (≥20 Gy) [5, 7, 10]
    Single fractions at 24 Gy with 36–39% radiographic fracture rates, compared to a rate of 21% for those patients receiving 18 Gy in one fraction [11–13].
  - Fractionation
    Fractionated regimens are suggested to confer a lower risk with rates as low as 7.8% [14].
  - Patients with lung and hepatocellular tumors [5]
  - *Spinal instability neoplastic scoring (SINS) system*: See Table 26.3 for the consensus classification system in determining tumor-related instability [10].
- *Management*
  - Optimal management for these patients remains largely unknown as high-quality evidence with a consensus multi-institutional approach is currently lacking.
  - Clinical consequence of radiographic vertebral body fracture is an area of controversy. As such, *most VCFs do not require intervention* [9].
  - Patients with frank mechanical pain (pain worse with sitting/standing/moving and relieved by lying flat) localized to the site of fracture need to be referred for consideration of cement augmentation or percutaneous stabilization.

Table 26.3 Spinal instability neoplastic scoring (SINS) system

SINS component	Description	Score
Location	Junctional (Occ-C2, C7–T2, T11, L1, L5–S1)	3
	Mobile (C3–6, L2–4)	2
	Semirigid (T3–10)	1
	Rigid (S2–5)	0
Pain	Yes	3
	Occasional nonmechanical pain	1
	No	0
Bone lesion	Lytic	2
	Mixed	1
	Blastic	0
Alignment	Subluxation/translation	4
	De novo deformity	2
	Normal	0
Vertebral body (VB)	>50% collapse	3
	<50% collapse	2
	No collapse with >50% VB involved	1
	None of the above	0
Posterolateral involvement	Bilateral	3
	Unilateral	1

The resulting score distribution of 0–18 allows for stratification of those patients at risk, with scores above 7 warranting surgical consultation [15]

- Radiation-related VCFs requiring a stabilization procedure have been reported to occur in 8% of patients, compared to 39% of patients with radiographic fractures, suggesting an overreporting of clinically relevant VCF [9, 11].
- Screening for spinal instability prior to radiosurgery may mitigate early fractures due to SBRT, with those patients with severe instability pain likely to benefit from prophylactic spinal augmentation procedures such as vertebroplasty [7, 12, 16].
- An MD Anderson-based phase 2 study (NCT02387905) is currently underway to evaluate the efficacy of prophylactic vertebral cement augmentation in patients at high risk of developing VCF following spine SBRT.

26.4 Radiation Myelopathy (Table 26.4)

Radiation myelopathy is a rare but potentially devastating consequence of spine SBRT. Clinical experience is sparse, and publications during the early years of spine SBRT detail potential risk factors associated with RM such as cord dose and recent history of prior radiation [21–23].

- *Prevention and management*
  - As there is a clear correlation between dose/fraction and RM risk, it is necessary to balance therapeutic and dose constraints to risk of neurological deficit secondary to uncontrolled tumor progression.

Table 26.4 Studies regarding radiation myelopathy

Sahgal [26]	2012	13 non-RM, 5 RM	5 (3–8)	N/A	Authors developed guidelines for administering reirradiation SBRT. For safe practice after conventional radiotherapy, recommendations include SBRT given at least 5 months after RT, thecal sac P_{max} limit not exceeding 25 Gy with a cumulative EDQ2 of no more than 70 Gy
Sahgal [27]	2013	66 non-RM, 9 RM	12 (3–15)	N/A	Authors developed guidelines for administering SBRT in patients with no prior history of RT. Recommend limiting thecal sac P_{max} volume dose to 12.4, 17.0, 20.3, 23.0, and 25.3 Gy in 1, 2, 3, 4, and 5 fractions, respectively, to achieve a risk of RM of less than 5%

RM radiation myelopathy, *RT* conventional radiotherapy, *VCF* vertebral compression fracture, *EQD2* equivalent dose in 2 Gy fractions

- Rigid immobilization and 3D-3D IGRT with kV imaging and the use of a 6D couch minimize the risk of setup error and resultant toxicity.
- RTOG (RTOG 0631) offers dose constraints performed on a yet published cooperative group spinal SBRT trial that require delineation of normal tissue within 10 cm of the target volume with cord constraints of [17]:
  1. Spinal cord dose 10 Gy to no more than 10% of the partial spinal cord volume
  2. Spinal cord dose 10 Gy to the absolute spinal cord volume less than 0.35 cc
  3. A maximum cord dose of 14 Gy for less than 0.03 cc [17, 18]
- Regardless of the reports to date, cord constraints are largely institution-dependent, but Dmax is generally 10–14 Gy in single-fraction SBRT with no prior history of radiation to the site with an institution-dependent planning organ-at-risk volume (PRV) of 0–2 mm. Prospective and large retrospective series report myelopathy risks of <3% utilizing these constraints in conjunction with appropriate immobilization and IGRT [19–22].
- Guidelines have been reported by Sahgal et al. providing point maximum doses for one- to five-fraction SBRT in the de novo and reirradiation setting.

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Monitoring and Management of Late Effects

27

Karl Cristie F. Figuracion, Lia M. Halasz, and Tresa McGranahan

Contents

27.1 Cerebrovascular Events and Stroke Risk

- *Cerebrovascular disease*
  - *MRI findings*: MRI appearance will differ based on acuity of the stroke.
    Acute lesions are best appreciated on DWI images.
    Subacute images may have contrast enhancement.
    Older ischemic events are only visible on T2 images, or with large vessel strokes; encephalomalacia may also be visible.
  - *Incidence*: 5–10%. High 5-year cumulative stroke recurrence rate (38%).
    Incidences and risk increase over time from radiation therapy (data from childhood cancer survivors).

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- *Stroke types*:
  Transient ischemic attack.
  Ischemic stroke (large vessel or small vessel).
- *Onset*: Large vessel most common 5–6 years after radiation, but the range is 2–25 years after radiation for development of vasculopathy.
- *Treatment*:
  Referral to neurology for evaluation of modifiable stroke risk factors as well as consideration of antiplatelet therapy.
- *Recommendations for surveillance/screening*:
  Supratentorial radiation: Brain vessel imaging with CT or MRI angiogram (CT is preferred method for large vessel evaluation) 5 years after RT, then every 5 years if no cardiac risk factors, or every 3 years if cardiac risk factors.
  Patients with neck or posterior fossa radiation should also have neck vessel imaging 12 months after radiation, and if no vasculopathy is found, then every 3 years.
  - CT angiogram of the neck is preferred due to wider range of carotid evaluation including distal edge of the internal carotid artery.
  - Ultrasound duplex of carotids is a reasonable alternative to avoid contrast and radiation exposure.
- *References* [1–4].

• *Cerebrovascular malformations*
- *Microhemorrhages*
  Cerebral microbleeds are markers of radiation-induced small vessel disease commonly seen following brain radiation.
  Incidence: 40–70% of patients with prior brain radiation and dose related. Higher incidence in patients receiving WBRT than in patients with local therapy.
  Onset: Rate increases significantly 2 years after radiation with increasing incidence with increasing time from radiation.
  Symptoms: Worse executive function and verbal memory.
  Screening: T2*-weighted MRI.
- *Cavernous malformations*
  Thin-walled, dilated, vascular channels without supporting vascular smooth muscle.
  Can be seen with any form of intracranial radiation.
  Onset: Mean latency of 9 years following radiation.
  Symptoms: Typically asymptomatic but are at risk of hemorrhage.
  Treatment: Monitoring is appropriate for most lesions; however, given propensity for hemorrhage, surgery is sometimes required.
- *References* [5, 6].

• *Cardiac vascular complications*
- Patients with thoracic spinal radiation are at risk for cardiovascular injuries including pericardial disease, coronary artery disease, valvular disease, con-

duction disease, cardiomyopathy, and medium and large vessel vasculopathy.
  - *Onset*: Can occur at varying intervals following irradiation.
  - *Recommendations*: Echocardiogram every 5 years after thoracic spine radiation.

27.2 Delayed Cyst Formation

- *MRI findings*: New cyst within the field of radiation
- *Incidence*: Uncommon (10%)
- *Onset*: Median 53 months (range, 37–121 months)
- *Recommendations for surveillance*: Per usual surveillance imaging protocol
- *Treatment*: If symptomatic, neurosurgical intervention
- *Reference* [7].

27.3 Endocrinopathies

- *Incidence*: Common
  - Cumulative incidence increases with follow-up over time.
  - Could also be underreported since screening is not routinely part of surveillance.
- *Onset*: >Median of 2 years from completing RT.
- *Screening recommendations*: Annual lab tests for estradiol/testosterone, TSH, free T4, AM cortisol.
- *Growth hormone deficiency*
  - Incidence: 40–50%.
  - Untreated GHD was significantly associated with decreased muscle mass and exercise tolerance.
  - *Diagnosis*:
    Annual screening is not recommended in adults.
    Tested in the AM: Insulin-like growth factor-1.
  - *Treatment*: Recommbinant human growth hormone.
    Consider referral to endocrinology.
    Growth hormone contraindicated in those who have active malignancy.
- *Estradiol/testosterone deficiency*
  - *Incidence*: 18–22%.
  - Associated with hypertension, dyslipidemia, low bone mineral density, and slow walking; and both deficits, independently, were associated with abdominal obesity, low-energy expenditure, and muscle weakness.
  - *Diagnosis*:
    Males: Low testosterone
    - *Treatment*: Testosterone replacement
    - Consider referral to endocrinology

Females: Low estradiol with amenorrhea in women under 40 years. Can cause infertility
- *Treatment*: Replacement estradiol
- Consider referral to gynecology and endocrinology

- *Hypothyroidism/thyroid-stimulating hormone deficiency*
  - *Incidence*: 60–80% >5 years after radiation, increased with radiation dose to the pituitary, hypothalamic, and thyroid, >16 Gy
  - Increased with chemotherapy (CCNU, bleomycin, and cyclophosphamide)
  - *Diagnoses*:
    Low free thyroxine (T4) coincided with elevated or reduced thyroid-stimulating hormone
    Treatment: Referral to endocrinology for consideration of levothyroxine
- *Adrenocorticotropic hormone deficiency*
  - *Incidence*: 18–43%
  - *Diagnosis*:
    Low 8:00 am cortisol level
  - *Treatment*:
    Hydrocortisone replacement
    - Referral to endocrinology for further management
    - Dose: hydrocortisone 15–25 mg/day dosing
- *References* [8–11]

27.4 Hearing Loss

- *Sensorineural hearing loss*
  - *Definition*: Hearing loss that results to the reduction of the hair cells of the cochlea (inner ear), injury to the nerve that runs from the cochlea to the brain, or a combination of both
    More common side effect than conductive hearing loss
    Can be permanent
  - *Incidence*:
    Varies from 0% to 54% depending on dose, increased incidence >32 Gy
    Exacerbated with the use of chemotherapy especially ototoxic chemotherapy such as platinum agents
    Associated with younger age at RT, higher cochlear radiation dose, cerebrospinal shunting
  - *Clinical presentation and findings*:
    Decreased hearing high-pitched sounds, dizziness, tinnitus, muffled conversations
    No physical abnormality
    Audiogram showing increase in hearing thresholds with no air-bone gap
  - *Onset*: Median is 3 months (range 0.4–13.2 years) but can be gradually progressive.

- *Conductive hearing loss*
  - *Definition*: Typically fluid, tissue, or bony growth, which blocks or reduces the incoming sound. The "blockage" can involve the ear canal, the middle ear, the ear drum, or the bones in the middle ear:
    Medically remedied or are treated by either hearing aids or a bone-anchored hearing aid.
  - *Clinical presentation and findings*:
    Complaints of pressure or pain in one ear or both, difficulty in hearing speech.
    Exam can show fluid in the middle ear, obstruction or tympanic membrane perforation.
    Negative Rinne (BC > AC), Weber localizing to the affected ear.
    Audiogram showing air-bone gap.
- Can be a mix of both conductive and sensorineural hearing loss
  - *Treatment*: Referral to audiology and ENT for consideration of hearing assistance and other therapies
  - *Recommended surveillance*:
    Any IAC tumor should have baseline and annual audiology testing.
    All patients treated with platinum continuing compounds should have baseline audiology testing. If hearing loss is detected, recommend annual hearing evaluation. If negative, every 5 years afterward.
    All brain radiation patients that could have a cochlear dose should be asked annually about hearing changes. If changes are reported, they should be referred for audiology testing.
    Annual hearing screen question, consider annual audiogram for patients at higher risk for hearing loss.
- *References* [12–15]

27.5 Neurocognitive

- *Radiation-induced leukoencephalopathy*
  - *MRI findings/definition*: Cognitive dysfunction associated with diffuse T2-FLAIR white matter hyperintensity after brain irradiation. MRI shows cortical atrophy over time.
  - *Incidence*: Common, increased with longer interval from radiation.
  - *Clinical symptoms*:
    Slow progressive clinical change over time. Gait apraxia, motor slowing, worsening memory and concentration, decrease in executive and behavioral functioning, urinary incontinence.
  - *Onset*: Median time of functional complaints is 36 months (range 6–480 months).
  - *Screening*:
    Annual MOCA (Montreal Cognitive Assessment) to screen for cognitive decline.
    Consider neuropsychology testing for full evaluation of cognitive impairment.

  - *Treatment*:
    Outpatient physical therapy, occupational therapy, and speech therapy
    Employment counseling
    Donepezil: Start with 5 mg PO qhs × 4–6 weeks and then may increase to 10 mg PO qhs
    - Common SE: Nausea, diarrhea, headache, insomnia, dizziness, fatigue
  - *References* [16–19]
- *Acute-late onset CNS impairment (not related to stroke)*
  - *SMART* (stroke-like migraine attacks after radiation therapy) *syndrome*
    Focal stroke-like deficits with or without encephalopathy associated with headaches and/or seizures
    MRI findings: Acute unilateral cortical-subcortical area of hyperintensity and swelling on T2/FLAIR sequence with cortical enhancement ipsilateral to the cerebral hemisphere treated with radiation
    Often reversible
  - *PIPG* (peri-ictal pseudoprogression)
    Transient seizure-related MRI changes that mimic disease progression
    MRI findings: Transient focal cortical and/or leptomeningeal enhancing lesions that normalize 3 months after PPIG episode
    Treatment: Adjustment of antiepileptic medications
  - *ALERT* (acute late-onset encephalopathy after radiation therapy) *syndrome*
    Encephalopathy (which can range from mild to severe) associated with stroke-like deficits with or without headaches, with or without seizures
    MRI findings: Acute multifocal abnormalities in the subcortical and/or periventricular white matter characterized by punctuate enhancement
    Can be permanent
  - Some cases have short-lasting focal deficits that can last 1–12 h without headaches and have no acute MRI abnormalities.
  - *Incidence*: Rare
  - *Clinical presentation* (all combined):
    Constellation of symptoms, including focal deficits (77%), encephalopathy (50%), seizures (35%), and headache (35%)
  - *Onset*: Median of 10 years (can range from 0.75 to 43 years)
  - *Treatment*:
    Dexamethasone
    Seizure management
    Headache management
  - *Reference* [1]

27.6 Psychosocial

- Screen for mood changes with PHQ9 and GAD.
- Ask about financial and employment effects of treatment.
- Ask about support and caregivers.

27.7 Secondary Malignancy

- *MRI findings*: New tumor within the field of radiation
- *Incidence*: Rare
- *Types*: Include (but are not limited to) skin cancer, secondary brain tumor (meningioma, glioma), sarcomas, leukemia, and thyroid malignancy
- *Onset*: >10 years (earlier if treated with chemotherapy)
- *Recommendation*: Minimum effective dose of radiation
  - There is no standard accepted screening; however, continued surveillance, with physical exam, is recommended
- *Reference* [20]: Data also from childhood cancer survivors

27.8 Visual Impairments

- *Xerophthalmia*: Eye dryness, often reported after treatment of patients with malignancies of the orbit and ocular adnexa
  - *Incidence*: Common, up to 39% in some studies [21]
    The incidence and severity vary with the radiation dose to the lacrimal gland.
    Rate of dry eyes increases with doses above 30 Gy.
  - *Onset*: >3 months after radiation effect
  - *Treatment*:
    First line: artificial tears (mild)
    Referral to eye specialist
    Punctal plugs (moderate to severe)
    Prescription eye drops Restasis bid OU or Xiidra bid OU
  - *Reference* [22]
- *Retinopathy*
  - *Definition*: Complications involving the retina
  - *Incidence*: Roughly 12%, increases with higher doses of radiation (>30–45 Gy)
  - *Clinical presentation and findings*:
    Symptom: Decreased in visual acuity.
    Exam: On dilated fundoscopic ophthalmic examination shows presence of dot and/or blot hemorrhages, microaneurysms, cotton wool spots, and macula edema.
  - *Onset*: Median 27 months (15–241 months)
  - *Treatment*:
    Referral to eye specialist.
    Bevacizumab injections have been used.
  - *Recommended surveillance*: Long-term ophthalmic examination follow-up of patients who had orbital radiation therapy.
  - *Reference* [21]
- *Optic neuropathy*
  - *Definition*: Complication involving the anterior visual pathway

  - *Clinical presentation and findings*:
    Visual loss may be unilateral or bilateral, simultaneous or sequential, and irreversible.
    MRI findings: Discrete region of enhancement of the prechiasmatic optic nerve, often accompanied by expansion and T2 hyperintensity in the enhancing segment.
  - *Onset*: Occurs generally between 10 and 20 months after treatment (can range from 3 months to 9 years)
  - *Incidence*: Rare
    Associated with higher doses of RT >54 Gy
    Or single doses to anterior visual pathway or >10 Gy
    Reference [23]
  - *Treatment*:
    Referral to eye specialist
    Minimal data showing effectiveness of steroids, bevacizumab, or hyperbaric oxygen in some cases
  - *Recommended surveillance*: Annual eye exam
  - *References* [23, 24]
- *Cataracts*
  - *Clinical presentation and findings*: Lens opacity, blurry vision, sensitivity to light and glare, decrease night vision
  - *Incidence*: Common (may also be underreported)
    Increases with higher radiation dose to lens
    - 5-year prevalence of 15.2% for lens doses 10–20 Gy and 35.6% for lens doses and 20–60 Gy
  - *Onset*: 27.6 months, range 20–60 months (total body radiation therapy, data from children)
  - *Treatment*:
    Referral to eye specialist for surveillance and surgical management when clinically progresses and worsens
  - *Recommended surveillance*: Clinical exam
  - *References* [22, 25, 26]

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