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

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Target Volume Delineation for Pediatric Cancers

Springer

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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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Preface

Optimizing the therapeutic ratio is critical in pediatric radiation oncology to effectively treat benign and malignant diseases while simultaneously decreasing dose to normal structures to reduce the risk of acute and late effects. Being able to achieve therapeutic improvements in radiation therapy is reliant on accurate target volume definition to precisely delineate tumor and critical normal tissues. Accurate target volume delineation has become ever more important as advanced treatment technologies such as proton therapy and image-guided conformal therapies become standard therapeutic options.

It is necessary to understand the specific and unique clinical considerations for multiple pediatric tumors in order to design radiotherapy fields that neither overtreat nor under-treat the disease entity. The clinical target volume (CTV) must be delineated on cross-sectional axial imaging in addition to normal tissues. With certain radiation treatment approaches such as proton therapy, the precise contouring of disease compared to normal structures is essential.

We hope that this text will serve as a comprehensive contouring guide for radiation planning for pediatric diseases in the modern era. Each chapter illustrates different case scenarios to capture the spectrum and diversity that we experience in the pediatrics field. In this age of advanced technologies, we feel that a consistent approach to target delineation is a critical element to provide the optimum treatment for our patients.

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Central Nervous System Normal Structures

1

Barbara Fullerton and Shannon M. MacDonald

Contents

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1.1 Introduction

Recent developments in radiation and neuro-oncology provide the ability to deliver required radiation dose to target volumes for pediatric brain tumors while avoiding sensitive normal central nervous system (CNS) structures uninvolved by tumor. Many CNS target volumes are smaller than in previous years due to better understanding of areas at risk for recurrence or involvement and patterns of spread for a given diagnoses. Advances in neuroimaging and treatment planning software allow for better delineation of tumors and normal neuroanatomy. Utilization of these advances requires accurate delineation of avoidance structures. For optimal avoidance as well as accurate reporting of normal structure tolerance, it is of paramount importance to contour these structures properly. Neuroanatomy is complex and formal education in this area is not at present taught in radiation oncology training. This chapter is included to provide guidance for contouring of pediatric CNS structures.

Structures that will be covered in the chapter include the retinas, optic nerves, optic tracts, optic chiasm, lenses, hypothalamus, cochleae, brainstem (and its components—midbrain, pons, and medulla), temporal lobes, and the hippocampi.

Dose constraint goals are reviewed and toxicities discussed, but we acknowledge that determination of dose to critical structures is highly dependent on tumor location, desired prescription dose to tumor, and the assessed risk-benefit ratio for a given child.

1.2 Visual System

There are several visual structures that may be at risk when delivering radiation for pediatric brain tumors. When thinking about visual toxicity, it is important to consider the actual impact on vision, the patient's visual status at the time of treatment, and competing risks of tumor progression in addition to dose constraints of these structures. For instance, injury to a lens may be surgically repaired. Injury to the optic nerve or retina will cause unilateral vision loss while injury to the chiasm could result in bilateral visual loss. The entire visual apparatus is connected in some way. We usually think of critical structures from anterior to posterior with the anterior being more sensitive in terms of dose.

1.2.1 Lens

The most anterior structure is the lens (Fig. 1.1). The lens is situated between the anterior and the vitreous chambers of the eye with the iris just anterior and surrounding it. The lens is easily seen on CT scan. The lens is very sensitive to the formation of cataracts. Cataracts develop after RT starting with posterior subcapsular opacifications as opposed to anterior opacifications, which are generally seen for cataracts that form as a result of aging. It may take years for cataracts to form following radiation therapy and usually many years to impact vision to the extent that surgical intervention is recommended. This visual loss is considered correctable by surgery and though it is a common surgery, it may be more complex in patients that have had additional ocular problems, especially children that have undergone treatment for retinoblastoma or an eye tumor. These children should be seen by an experienced cataract surgeon. Cataracts

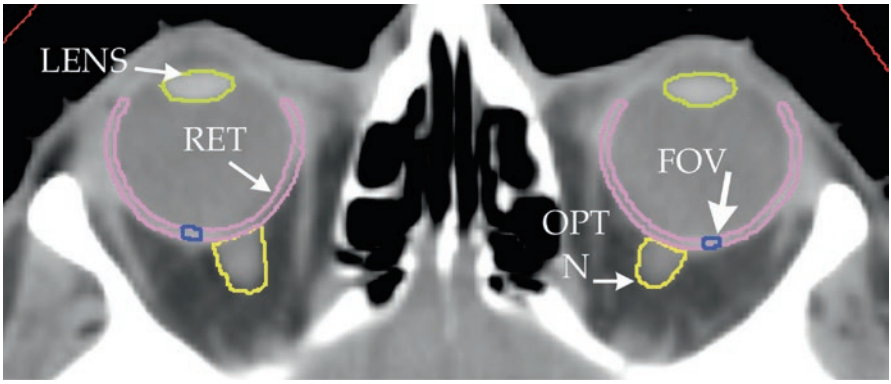


Fig. 1.1 Axial slice from a planning CT. The lens is shown as well as the retina (RET) and its fovea (FOV). The retinal contour, more easily seen in the CT than the MR scan, includes the retina, the choroid, and the sclera. The retinal layer adjacent to the vitreous chamber is too thin to be contoured individually. The fovea (FOV) is indicated just lateral to the optic disk, the region where the optic nerve (OPT N) exits the globe

may develop at single doses as low as 2–3 Gy, and the rate is 80% for a single fraction of 10 Gy TBI but only 10% for this dose delivered at standard fractionation [1].

1.2.2 Retina

The typical retinal contour is seen in Figs. 1.1 and 1.2. Contours of the "retina" include the sclera and the choroid, as well as the retina, since the retina is too thin to contour independently.

Retinopathy is thought to occur at doses of 45 Gy and higher and is due to damage to or reorganizing of small vessels supplying the retina [1]. The appearance on examination is similar to diabetic retinopathy. If a portion of the retina is damaged, the field of vision affected corresponds to the area of the retina damaged. For example, superior retinopathy may affect the inferior visual field (i.e., walking down stairs may be difficult). Retinopathy of the macula or fovea (Fig. 1.1) will lead to central visual loss, which would have a greater effect on overall visual function. Though fovea size is relatively small compared to the rest of the retina, it is the only area of the retina where 20/20 vision is attainable and critical for seeing fine detail and color. The fovea is employed for accurate vision in the direction where it is pointed. It comprises less than 1% of retinal size but takes up over 50% of the visual cortex in the brain.

1.2.3 Optic Nerves, Chiasm, and Optic Tracts

The optic nerves leave the posterior edge of the globe and pass obliquely to the optic canal. At the posterior opening of the optic canal, the internal carotid curves under the edge of the anterior clinoid process (Figs. 1.2 and 1.3, axial images). The optic nerves join the chiasm that is superior to the pituitary gland and anterior to the infundibular stalk (95% of cases).

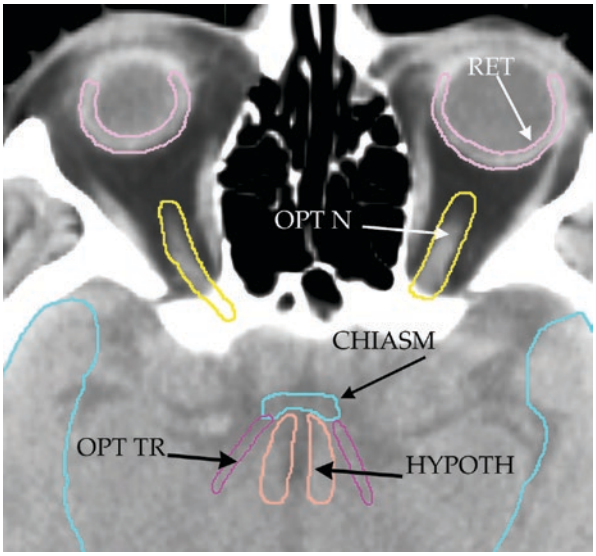


Fig. 1.2 This more inferior axial slice shows the retinas (RET) and the optic nerves (OPT N). The optic nerves are not connected to the eyes in this section and approach the sphenoid bone posterior to the orbit. Because of the angle of the CT scan, the optic nerves are also not connected to the chiasm in this section. The optic tracts (OPT TR) extend posteriorly from the chiasm. The hypothalamus (HYPOTH) is located on either side of the third ventricle as seen also in Fig. 1.4c. The anterior temporal lobes are shown in the most lateral portion of the brain (cyan)

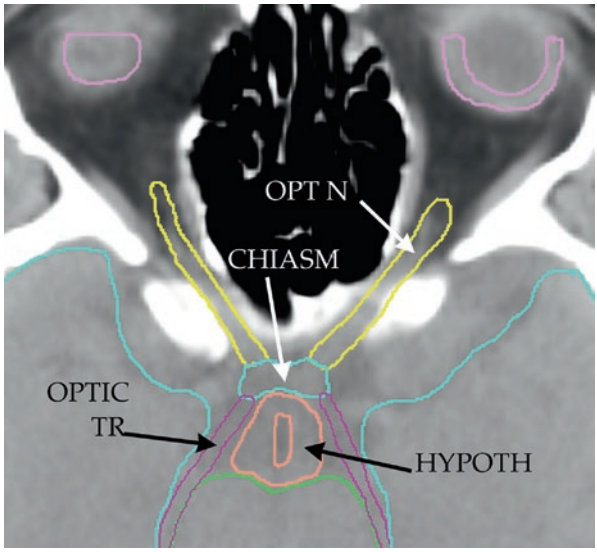


Fig. 1.3 This more inferior axial CT slice shows the optic nerves (OPT N) extending through the optic canal medial to the anterior clinoid processes to join the chiasm. The optic tracts (OPT TR) extend posteriorly from the chiasm to the lateral geniculate nucleus of the thalamus (present in the MR Fig. 1.4e at the terminal end of the optic tracts). The hypothalamus (HYPOTH) is wider at this level than in Fig. 1.2. The third ventricle is located in the center of the hypothalamus

We define the chiasm as the region that is no longer carrying only monocular fibers (Figs. 1.2 and 1.3); it includes the fibers crossing from the two eyes. The temporal retinal field fibers from each eye continue through the chiasm to the optic tract of the same side, while the nasal retinal field fibers cross in the chiasm to the opposite optic tract.

The optic tracts can be in danger of receiving a high dose of radiation, so they are sometimes contoured as well. They pass posteriorly from the chiasm lateral to the hypothalamus and encircle the anterior midbrain (Fig. 1.3), terminating in the lateral geniculate body of the thalamus (Fig. 1.4e). We often contour the optic tracts when vision has already been lost in one eye, in order to spare the remaining visual pathway from a high dose as much as possible.

1.2.4 Visual Impairment

Visual impairment from radiation-induced optic neuropathy can manifest as visual acuity loss or visual field loss depending on the area of the optic pathway affected. Many series report maximum dose, but it is likely that a dose/volume relationship exists, and this may be more meaningful [2, 3]. Though some series report a higher tolerance for the optic chiasm than the optic nerves, others report similar dose constraints. It is also critical to keep in mind that radiation-induced optic neuropathy of one nerve will lead to monocular vision loss, while injury to the chiasm may result in a range from "tunnel vision" to complete vision loss in both eyes. With standard fractionation, an attempt to keep the dose below 50.4 Gy at 1.8 Gy per fraction will minimize risk of injury, but radiation-induced optic injury is unusual for a maximum dose kept below 54–55 Gy. There is less data available for the dose tolerated by the optic tracts. With advanced imaging, the tracts can be contoured, and future research may inform us better of the tolerance of these structures. Damage to the optic tract would result in a field cut for the responsible location.

1.3 Hypothalamus/Pituitary Gland

The pituitary gland is a slightly hypodense structure compared to surrounding structures on CT scan. It is centered in the sella and bordered by the anterior and posterior clinoid processes anteriorly and posteriorly, respectively, and the cavernous sinuses laterally. The infundibular (pituitary) stalk connects the pituitary to the hypothalamus posterior to the chiasm (Fig. 1.4g–j). The most inferior part of the hypothalamus includes the mammillary bodies (Fig. 1.4f). The hypothalamus is situated on either side of the third ventricle (Figs. 1.2, 1.3, and 1.4c–f) and widens superiorly medial to the optic tracts. Ascending superiorly, the hypothalamus narrows and ends at the level of the anterior commissure and massa intermedia connecting the thalamus across the midline (Fig. 1.4c). The usual dividing line between the infundibular stalk and the inferior-most part of the hypothalamus is the presence of the third ventricle (Fig. 1.4g).

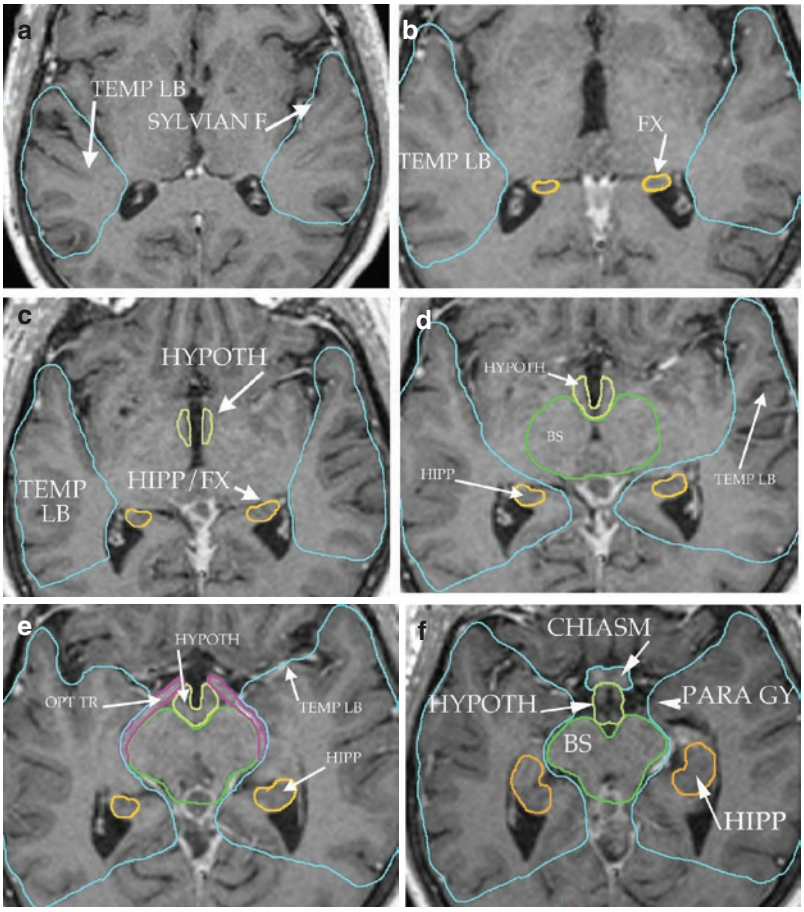
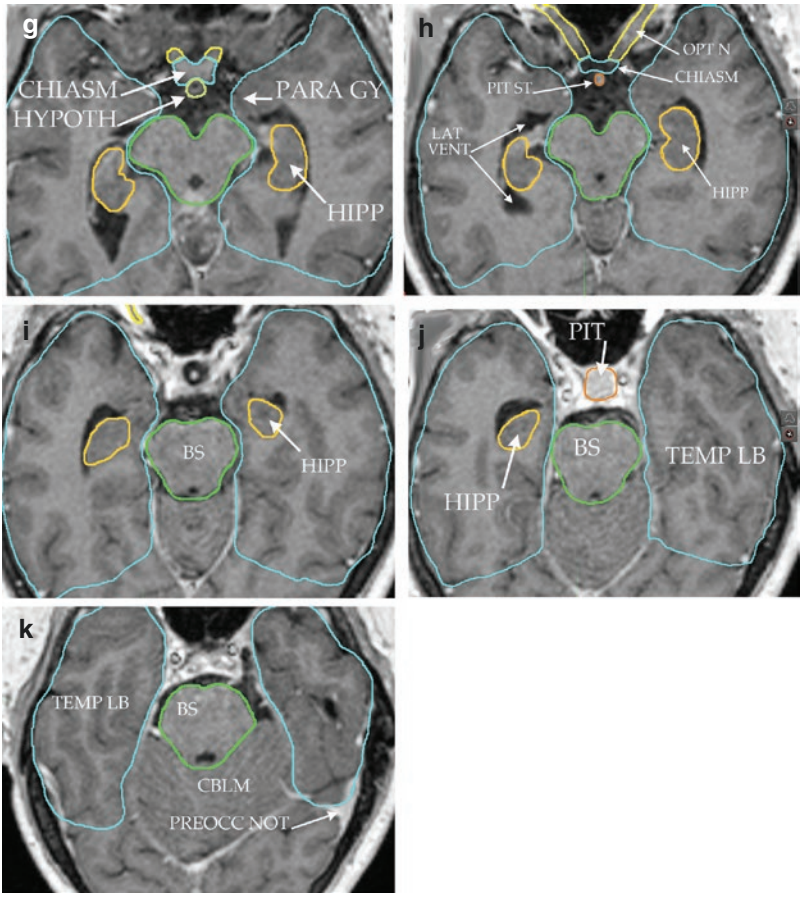


Fig. 1.4 (**a**–**d**) This MR axial series of images was included because many of the anatomical structures are not easily visible in the CT scans. This group of images extends from the superior part of the temporal lobe (**a**) to the inferior part of the temporal lobe where it intersects with the preoccipital notch (**k**). The brain in the figure is slightly asymmetrical, so that the temporal lobe on the (patient's) right is slightly more superior than on the left. (**a**) The temporal lobe arrow on the right points to the transverse gyri of Heschl. The Sylvian fissure (SYLVIAN F) forms the medial boundary of the temporal lobe. Panel (**b**) is at the mid-level of the temporal lobe, and the fornix bundle (FX) from the hippocampus is present at the edge of the lateral ventricle. Panel (**c**) shows the temporal lobe and the transition between the hippocampus and its fornix fibers. The most superior part of the hypothalamus (HYPOTH) can be seen on either side of the third ventricle. (**d**) The temporal lobes are present as is the most superior part of the hippocampus before the fornix fiber bundle continues rostrally. The midportion of the hypothalamus is present; the brainstem (BS) transitions into the thalamus at this level from the midbrain. (**e**) The temporal lobes are wider at this more inferior level and the hippocampi (HIPP) are increasing in size. The temporal lobe label on the left marks the boundary between the temporal lobe and the frontal lobe. The optic tracts (OPT TR) encircle the brainstem (upper midbrain/thalamic) level. The hypothalamus (HYPOTH) is located between the two optic tracts and superior to the interpeduncular fossa. (**f**) The hippocampi are within the main part of the lateral ventricle on both sides and the anterior-medial bulge of the parahippocampal gyrus (PARA GY) is present on both sides. The brainstem (BS) is at the level of the middle of the midbrain. The mammillary bodies are present within the hypothalamus (HYPOTH) and in the space of the interpeduncular fossa. The optic chiasm is present anterior to the hypothalamus.



(**g**) The hippocampi are located more anteriorly as the axial sections move inferiorly. The parahippocampal gyri are still present at this level. The brainstem is at the midbrain level. A short segment of optic nerves are joining the chiasm, and the hypothalamus is continuing from the pituitary stalk inferiorly. (**h**) At this more inferior level, the hippocampi are present, surrounded laterally by the lateral ventricle (LAT VENT). Longer segments of optic nerves are joining the chiasm, and the pituitary stalk is just posterior to the chiasm. The MR slice is only showing a small partial volume of the chiasm. The brainstem is still at the midbrain level. (**i**) The hippocampi (HIPP) are near their inferior limit in the temporal lobes. The brainstem is now at the pontine level. (**j**) The hippocampus is still present on the right side, but not the left. The brainstem is at the level of the pons. The pituitary (PIT) can now be seen in the pituitary fossa. (**k**) At the inferior level of the temporal lobe on the left, the preoccipital notch (PREOCC NOT) divides the temporal lobe from the visual association cortex posteriorly. The brainstem is at the level of the pons

The hypothalamic-pituitary axis is responsible for hormone production. The hypothalamus secretes stimulatory and inhibitory factors signaling the anterior pituitary and synthesizes oxytocin and vasopressin (ADH) stored in the posterior pituitary. Hormones that are produced in the anterior pituitary include growth hormone, gonadotropins, prolactin, cortisol, and thyroid hormone. While radiation can cause

damage to both structures, the hypothalamus is more sensitive to radiation. Radiation impacts hormone production and is considered to be age and dose dependent [4]. Growth hormone deficiency is most common after radiation. The risk is 50% at 5 years for a dose just over 16 Gy [5]. Precocious puberty and thyroid deficiency may be seen at higher doses. Cortisol deficiency is uncommon but may be seen after relatively high doses of radiation. Diabetes insipidus is extremely rare after radiation and is usually attributed to mass effect of tumor or surgery.

1.4 Temporal Lobe

The inferior part of the temporal lobe sits in the middle cranial fossa and is easy to identify in axial CT scans by the bony margins. In the inferior region posteriorly, the preoccipital notch usually marks the division between the temporal lobe and the visual association cortex.

The superior surface of the temporal lobe in the horizontal plane contains obliquely oriented Heschl's gyri (primary auditory cortex); the Sylvian fissure marks the medial boundary.

Images in Fig. 1.4 (a–k) show the extent of the temporal lobe from the superior to inferior extent.

1.4.1 Hippocampus

The hippocampus is considered to be an important part of the temporal lobe. It is important for learning and memory and has the capacity for neurogenesis, especially in younger individuals. There is usually an attempt to limit radiation doses to the hippocampus in the pediatric patients in order not to damage the cellular layers responsible for neurogenesis [6]. The bulk of the hippocampus is located in the inferior temporal lobe along the edge of the lateral ventricle. When contouring the hippocampus in CT images, the lateral ventricle is often a good landmark, since the hippocampus itself may not be well defined.

Figure 1.4 shows the temporal lobe levels with the hippocampus present from superior to inferior extent. There is a fiber tract (fornix) that leaves the main part of the hippocampus to course superiorly and posteriorly, running under the corpus callosum and then continuing anteriorly through the hypothalamus to terminate in the mammillary bodies. The shape of the hippocampus varies somewhat with slightly different angles of the axial plane among individuals.

The temporal lobes and hippocampi are areas of the brain that are important for memory and learning. Though all areas of the brain are considered to be critical and complex neural connections and functions are not completely understood, these areas are proving to be more critical for neurodevelopment. Some tumor locations may make it difficult to avoid these regions of the brain, but it is important to be mindful of their anatomical location and strive to minimize dose to these critical regions when feasible.

1.5 Brainstem

The brainstem is the region between the thalamus and the spinal cord where the cranial nerves connect to provide motor and sensory innervation to the head and neck. There are also major fiber pathways that pass through to connect the spinal cord to the thalamic and cortical regions. The parts of the brainstem are, from rostral to caudal, the midbrain, the pons, and the medulla. The medulla transitions to the spinal cord usually just below the foramen magnum of the skull.

Images showing the midbrain are in Fig. 1.4e–h, the pons in Fig. 1.4i–k and Fig. 1.5a, and the medulla in Fig. 1.5b–d.

The most ventral portion of the midbrain contains the cerebral peduncles, with motor fiber tracts including the corticospinal tract that connect the spinal cord, medulla, and pons with the cortical regions. The ventral brainstem region can receive a high dose when the treatment is centered in the sellar area potentially leading to motor signs and symptoms.

Though rare, radiation injury or brainstem necrosis is one of the most feared complications for pediatric brain tumor patients. The brainstem tolerance is considered by most to be 54 Gy, and every effort should be made to minimize the volume

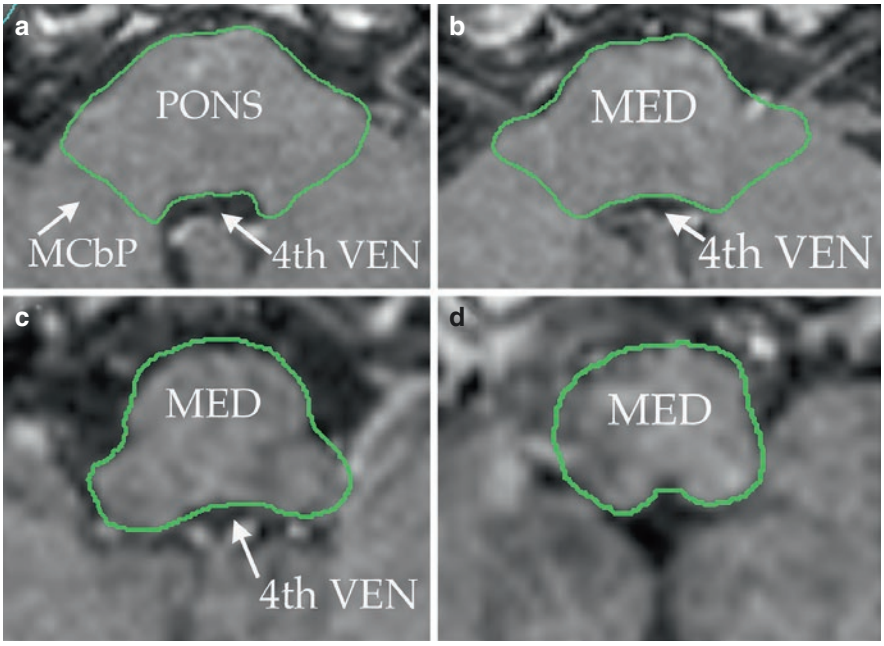


Fig. 1.5 Caudal axial brainstem images. The section in panel (**a**) is at the most caudal level of the pons. The middle cerebellar peduncle (MCbP) forms a large fiber bundle connecting the brainstem to the cerebellum. The fourth ventricle passes over the dorsal surface of the brainstem in panels (**a**, **b**) and transitions to the foramen of Monroe in panel (**c**) at the caudal end of the medulla (MED). Panel (**d**) is the most caudal level through the medulla

of brainstem receiving this dose. Tumor volumes in close proximity requiring higher doses for local control may make this dose limitation challenging to achieve. It is important to discuss this complication with families so they understand the risk and manifestations of these complications. Although very uncommon, this is a potentially debilitating and life-threatening complication of radiation [7–10].

1.6 Temporal Bone: Cochleas

It is critical to restrict the dose to the cochleas in the temporal bone to avoid hearing loss.

The cochlea can be seen most easily in a CT scan with a bone-window setting. Figure 1.6 shows a composite of images of the cochlea in the typical plane. The duct

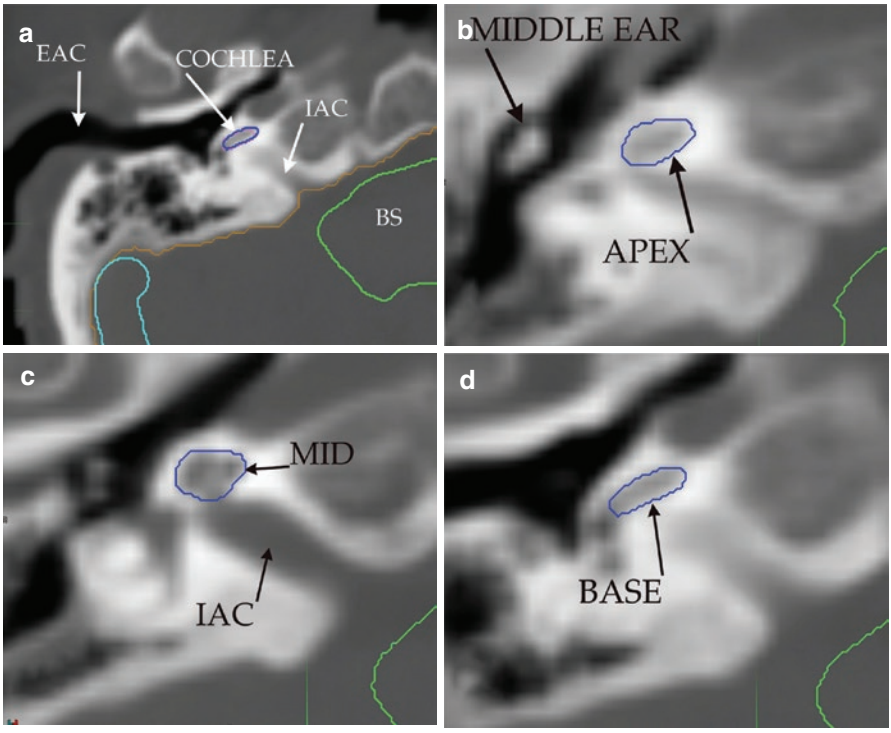


Fig. 1.6 Temporal bone and cochlea. Panel (**a**) shows the overview of the temporal bone in a bone-window axial CT image. The external auditory canal (EAC) is on the left of the image and the internal auditory canal (IAC) is on the right, adjacent to the brainstem (BS). This section is at the level of the basal turn of the cochlea as is panel (**d**). Panel (**b**) is the most superior of the three following levels and is at a level that cuts through the apical turn of the cochlea. The middle ear is seen to the left with the superior portions of the malleus and incus present. Panel (**c**) cuts through the middle of the IAC, and the mid-modiolar section of the cochlea is contoured. The lowest level, panel (**d**), cuts through the basal turn of the cochlea

of the cochlea is coiled and sits in the temporal bone oriented with the small apical turn pointed anteriorly and laterally (Fig. 1.6b). The widest part of the cochlea (the basal turn) where the eighth nerve enters is located more posteriorly and medially, closest to the internal acoustic canal. In the axial sections, the apical turn of the cochlea is more superior (Fig. 1.6b) than is the basal turn (Fig. 1.6d). Functionally, the basal cochlea is the most important region, since more high-frequency processing takes place in this site that is important for speech.

1.6.1 Ototoxicity

Radiation-induced ototoxicity is a well-known side effect of radiation therapy. In adults, hearing loss is uncommon under 45–50 Gy. However, in children hearing loss has been reported with mean doses as low as 35 Gy at a median follow-up of 5 years [11]. It is possible that with follow-up of longer than 5 years, this threshold may be lower. Platinum-based chemotherapy is known to increase the risk of hearing loss, and it is best to be cautious with radiation doses in patients that have baseline hearing loss or additional risk factors for hearing loss. Hearing loss is attributed to damage to sensory cells in cochlea, particularly organ of Corti and basal area.

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Noncentral Nervous System Normal Structures

2

Natia Esiashvili

Contents

2.1 Introduction

There are large number of pediatric tumors affecting the chest, abdomen, pelvis, and extremities. Often they involve a broad anatomical area with multiple vital organs in the tumor vicinity and create a major hurdle for a local control. When targeted with radiation therapy, safe dose delivery to the tumor target without damaging organs at risk can be very challenging especially when using higher doses in young children. There are multiple reports on functional impairments from radiation exposure resulting in acute and late toxicities. Chronic impairment of the heart, lungs, kidneys, liver, gastrointestinal tract, bladder, reproductive organs, etc. can result in not only poor quality of life but even contribute to the mortality of children undergoing cancer

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therapy. Correct identification of organs at risk and understanding of the volume and dose constraints are paramount in the pediatric radiotherapy field. The process of target and normal tissue delineation is the subject to significant levels of inter- and intra-observer variability in both the accuracy and reproducibility of structures [1–6]. In order to report, compare, and interpret the results of radiation treatment adequately, it is extremely important to delineate OARs according to well-defined uniform guidelines. Uncertainties associated with target volumes and organs-at-risk (OAR) definitions, organ motion, and patient set-up errors stand as obstacles to achieving better outcomes in radiotherapy planning and treatment delivery.

Variability in contouring structures may lead to underdosage, causing a decrease in tumor control probability (TCP), or overdose, resulting in an increase in normal tissue complication probability (NTCP). It is believed that minimizing inconsistencies in OAR volume definition will help to improve adequate reporting and interpretation of radiation treatment results. There are studies reporting on the variation in OAR delineation showing that, even in apparently straightforward anatomic structures, such as the heart, esophagus, and spinal cord, inter- and intra-observer variability can be significant [7, 8]. Manual contouring based on simulation CT or slice-by-slice registered diagnostic imaging scan is a gold standard; however, autosegmentation tools based on the use of automated atlas-based segmentation (AABS) algorithms have been explored in recent years [9–16]. Thus, AABS may hold promise for future application in clinical practice to reduce contouring variability. However, it is imperative that when auto-contouring is utilized, the contours must be reviewed and edited by a skilled radiation oncologist with an understanding of the patient's clinical and pathological context.

This chapter is dedicated for describing methods of identifying and contouring/delineation of extracranial normal structures in the pediatric population.

2.2 Head and Neck

Simulation CT scan is typically acquired from the vertex to the upper chest with a slice thickness of 2 mm. Contrast-enhanced CT scans will facilitate contouring of OARs and is strongly recommended.

2.2.1 Head and Neck OAR (Fig. 2.1)

1. Globes (right and left)
2. Lenses (right and left)
3. Lacrimal glands (right and left)
4. Cochlea (right and left)
5. Temporomandibular joints (right and left)
6. Parotid glands (right and left)
7. Submandibular glands (right and left)
8. Oral cavity
9. Thyroid gland

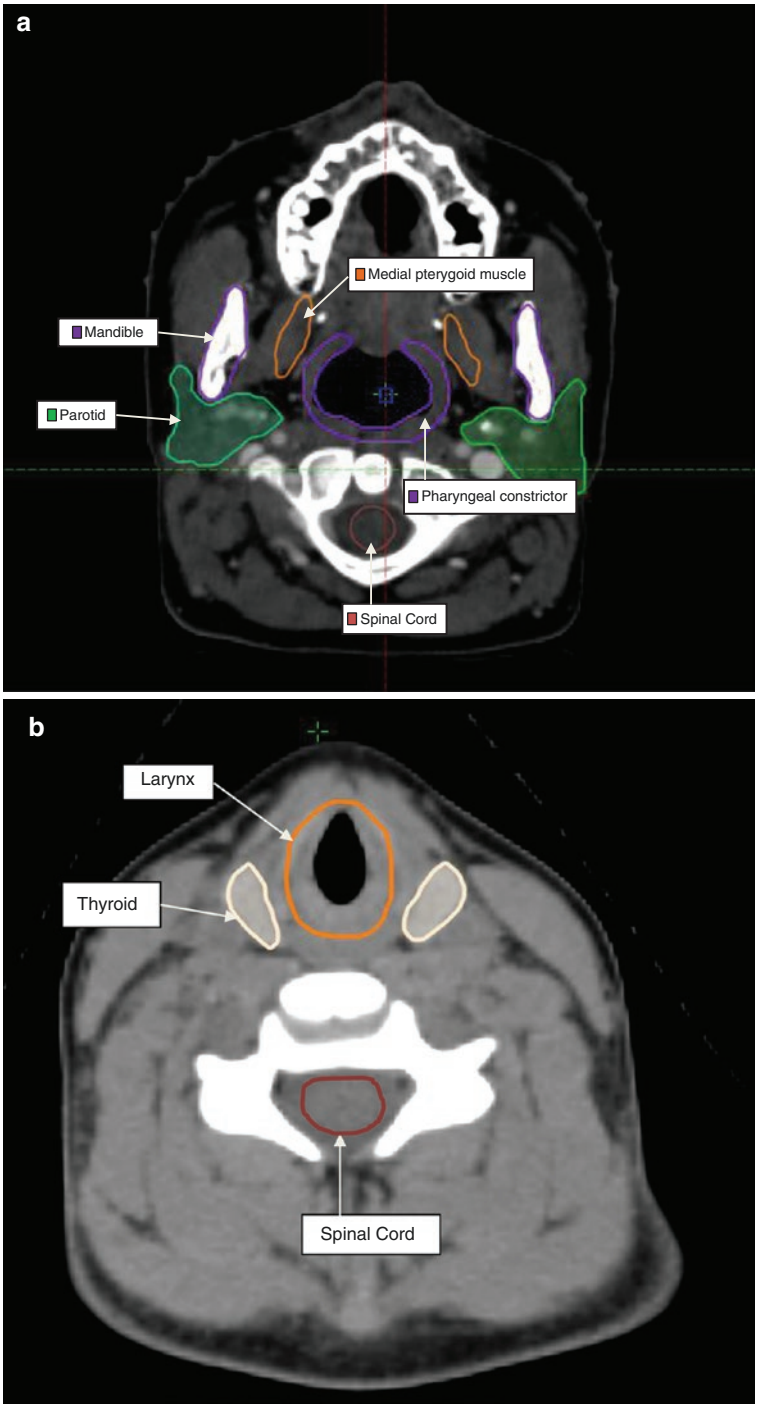

Fig. 2.1 (**a**, **b**) Axial CT image of the head and neck showing contours of organs at risk

10. Glottic-supraglottic larynx
11. Spinal cord
12. Mandible
13. Maxilla
14. Posterior pharyngeal wall and constrictor muscles
15. Cervical esophagus

CT scan currently is the standard for target volume and OAR delineation. Most, if not all, of these organs at risk in head and neck regions are readily identifiable on non-contrast CT, and simulation CT will be appropriate to use. However, it is possible that some structures may be challenging in the absence of contrast or MRI images. For instance, CT-based illustrations could not resolve the difficulties and uncertainties in defining the parts of the tongue with minor salivary glands [17]. Parotid gland tissue extends sometimes laterally from the masseter muscle following the parotid gland duct, and radiation oncologists do not always include this part in the delineation of the parotid gland. Similar discrepancies can be noted for the medial extension in the parapharyngeal space. The evaluation of the parotid gland dose, e.g., the mean parotid dose, may be inaccurate when these parts of the parotid glands are not taken into account.

On CT scan, salivary gland tissues sometimes have similar density values as their surrounding tissues, which may hamper the ability to distinguish salivary gland tissue from adjacent tissues. Magnetic resonance imaging (MRI) may improve the visualization of relevant anatomic structures and CT-MRI fusion may be helpful [18]. Care should be taken to assure fusion is accurate.

It is unclear if other minor salivary glands in the oral cavity should be contoured as OARs. Unfortunately, studies investigating the role of the minor salivary glands lining the oral cavity, in relation to radiation-induced salivary dysfunction or xerostomia, are scarce and only available in adults. A significant association between the dose in the oral cavity, representing the minor salivary glands, and the probability of patient-rated xerostomia has been reported [19]. Delineation of the maxilla, mandible, and temporal mandibular joint (TMJ) is important if we are to improve communication between radiation oncologists and dental care providers and physical therapists regarding radiation and risk to these structures. The maxilla and mandible can be divided into sextants (three segments in both the mandible and maxilla) using bony landmarks [20].

Oral and pharyngeal mucosal DVHs have been studied for predicting the risk of grade 3 oral mucositis and pharyngeal dysphagia. The atlas of complication incidence (ACI) method was found to be useful in selected series in adults, and their contouring should be considered in children receiving high-dose head and neck irradiation (e.g., nasopharyngeal cancer) [21, 22].

2.3 Chest

Simulation CT scan is typically acquired during free breathing and covers the area from the mid-neck to the upper abdomen (level of iliac crest) with a slice thickness of 2 mm. In cases when delineation of more detailed cardiac anatomy is required,

contrast-enhanced CT scan would facilitate contouring and is strongly recommended. Intravenous contrast can also significantly improve ability to distinguish mediastinal tumor from the thymus, blood vessels, and heart structures.

2.3.1 Chest OAR (Fig. 2.2)

1. Lungs
2. Heart (± substructures: right and left atrium, right and left ventricle)
3. Ribs and chest wall
4. Brachial plexus
5. Breasts in females
6. Esophagus
7. Aorta (± other major blood vessels)

2.3.1.1 Lungs

Lung tissues will be projected the most accurately when CT density windows are set up on a lung window and typically that will be the first step prior to contouring lungs. The lung contours are limited to the air-inflated lung parenchyma. Automated contouring tools can be used; however, appropriate thresholds, specific to each CT scan, should be chosen. Reviewing and editing the autocontoured structures are always required. The proximal bronchial tree and vessels should be excluded. When the collapsed lung or fluid is present, they are typically excluded from lung volume.

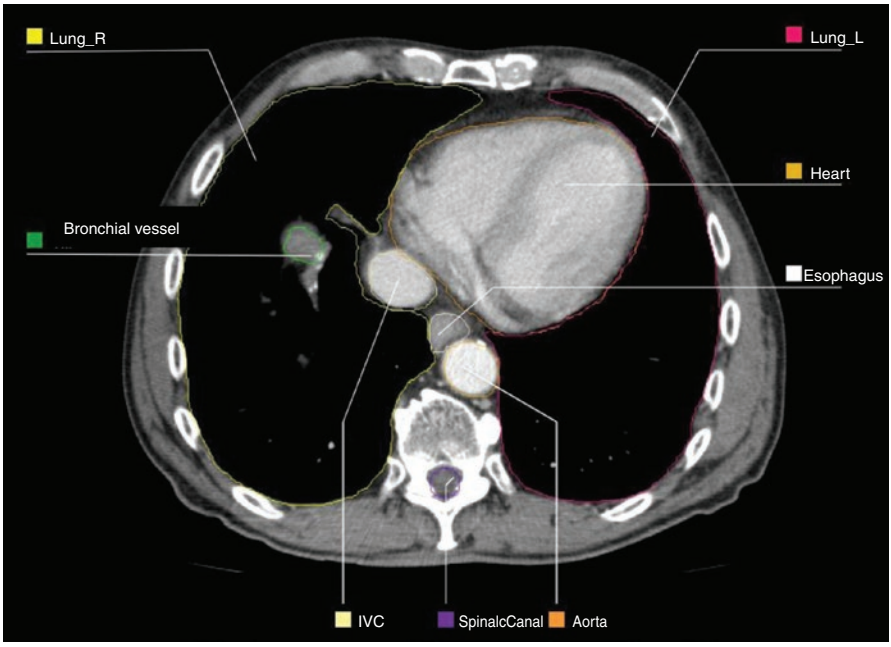

Fig. 2.2 Axial CT image of the chest showing contours of organs at risk

Most protocols define bilateral ("whole lungs") constraints; however, in special circumstances, it may be helpful to apply individual lung dose-volume constraints.

Lung dose-volume histograms are typically calculated based on 3D lung volumes for treatment planning. The use of respiration-correlated 4D-CT simulation for planning provides the opportunity for more accurate assessment of the lung volume as it includes the displacement of the lungs due to respiratory motion. It is better to obtain the CT scans with contrast-enhanced 4-D gated scan using a standard gating device. Lung displacement is most significant in the superior-inferior and anterior-posterior axes during respiration and will be captured with 4D gated minimum intensity projection (*MinIP* lung volumes) (Fig. 2.3). The information on lung motion from 4D CT scans can be incorporated in the planning organ-at-risk volumes (PRVs) [23–27].

2.3.1.2 Heart Subsegments (Fig. 2.3)

Heart subsegments include the whole heart, right atrium, left atrium, right ventricle, left ventricles, left anterior descending coronary artery (LADCA), circumflex artery, right coronary artery, and left coronary artery.

The data on utilization and techniques of delineation of heart structures comes primarily from the adult data [28]. There is evidence that only approximately one-third of the LAD artery could be objectively visualized with current planning CT protocol, and contrast-enhanced imaging may not significantly improve the visualization [29]. Additionally, heart motion can be captured with 4-D and deep inspiration breath-hold [30].

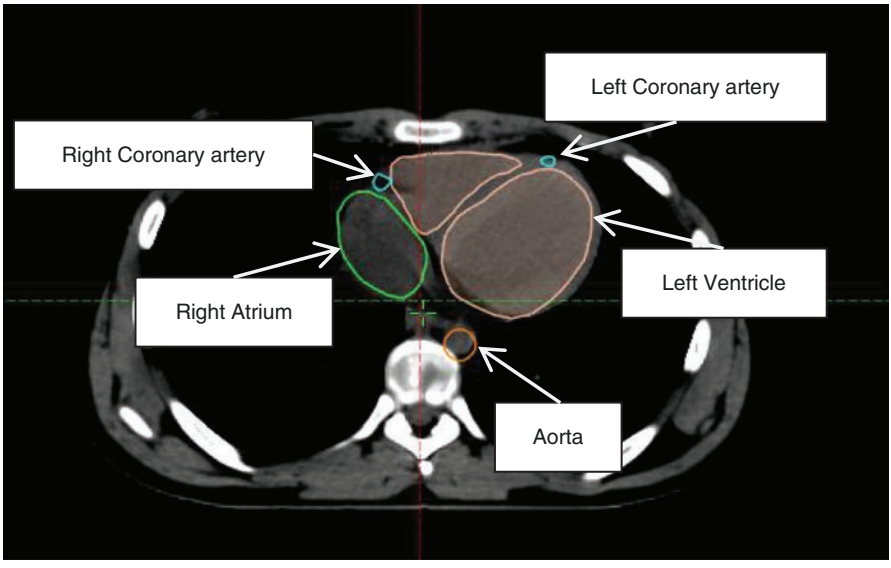

Fig. 2.3 Axial CT image of the chest showing heart contours

2.3.1.3 Major Vessels

The major vessels include the aorta, superior vena cava, and pulmonary artery.

Based on current clinical practice, these structures would be very rarely contoured but may be useful for certain research studies. Contrast CT will provide the best visualization of major blood vessels.

2.3.1.4 Ribs and Chest Wall

When applicable for rare cases of chest cavity or chest wall tumors, the ribs and chest wall will be manually contoured.

2.3.1.5 Brachial Plexus

The brachial plexus originates from the spinal nerves exiting the spinal canal through the neural foramina from the C4–C5 (C5 nerve roots) to the T1–T2 (T1 nerve roots) level. The delineation of the major trunks of the brachial plexus can be facilitated by using the subclavian and axillary vessels as a surrogate. Using high-quality CT scanning with intravenous contrast, it is possible to identify the actual roots and trunks of the brachial plexus directly without the need for a surrogate. The key step is to identify the anterior and middle scalene muscles, subclavian and axillary arteries and veins, and relevant cervical and thoracic vertebrae on the axial CT scan [31, 32].

2.3.1.6 Spinal Cord

Because the spinal cord itself is often not visible on the CT scan, it is usually contoured according to the bony limits of the spinal canal. The contour of the spinal cord can start at the level of foramen magnum and C1 cervical spine intersection and continue to the level at which the spinal cord ends (usually this can be confirmed the best on MRI scan, if available). Most pediatric protocols for treating extracranial tumors do not specify the extent of spinal cord that should be contoured in relation to the target volume for obtaining dose-volume data while some adult studies (NRG) have uniformly included 10 cm above the superior extent of the PTV and continuing on every CT slice to 10 cm below the inferior extent of the PTV.

2.3.1.7 Esophagus

The esophagus should be contoured using mediastinal windowing on CT. The contour usually would begin at the level of cricoid cartilage and include the gastroesophageal junction until it ends at the stomach. Unless gross tumors are located around the esophagus, which is rare in children, routine administration of oral contrast is not recommended, because it could affect the dose calculation and also potentially change the anatomic shape of the esophagus.

2.4 Abdomen

Simulation CT scan is typically acquired during free breathing and covers the area from the mid-chest or upper chest to the pelvic brim with a slice thickness of 2 mm.

2.4.1 Abdominal OAR (Fig. 2.4)

1. Liver
2. Kidneys (right and left)
3. Bowel (small, large, duodenum)
4. Pancreas
5. Spleen

Most abdominal organs, both intraperitoneal and retroperitoneal, are subject to the respiratory motion [33–37]. This may need to be taken into account in certain treatment planning cases, especially when higher dose limits of OARs may be reached. In special treatment protocol cases, a 4-D CT simulation will be helpful for evaluation of organ motion and creating planning organ-at-risk volume (PRV) that will include both internal margin (IM) due to respiratory motion and set-up margin (SM).

2.4.1.1 Liver

The liver is well visualized with non-contrast CT scan, and its contouring can be performed on simulation CT with the window level set as the "abdomen" or "liver." Superiorly the liver is intimately in contact with the diaphragm, and contouring would blend in both structures with the upper edge reaching the inferior edge of the lungs. There is expected respiratory movement of the liver mostly in superior-inferior direction. There is a lack of pediatric age-specific liver respiratory motion data. In cases of high-dose treatment of target volume near or within the liver, 4-D CT scan to capture liver motion will be helpful for careful calculation of liver PRV dose.

2.4.1.2 Kidneys

There is significant evidence of renal displacement with respiratory motion [33–37]. Cone-beam CT study for organ motion found that in the CC direction, the range of movement was 10 mm for the right kidney and 8 mm for the left kidney. Similarly, the liver upper edge range of motion was 11 mm, while the lower edge range of motion was 13 mm [38]. When investigated with 4-D scans, kidney motion was found to decrease linearly with decreasing age and height. The averaged minimal and maximal of renal motion in children younger than 9 years is around 5–9 mm in the ML direction, 4–11 mm in the AP direction, and 12–25 mm in the SI dimension. In children older than 9 years, the same confidence interval reveals a widening range of motion that was 5–16 mm in the ML direction, 6–17 mm in the AP direction, and 21–52 mm in the SI direction [34].

2.4.1.3 Bowel

Most of the evidence around bowel dose-volume effects on acute and late toxicities and methodology of calculating such risks comes from adult data. Subsequently, the methods of contouring of bowel will be mainly extrapolated from experience in adults. There are different contouring methods currently being used: (a) individual small bowel (SB) and large bowel (LB) loops, (b) total bowel (TB, including SB and LB), and (c) peritoneal cavity (PC). This makes dose-volume and toxicity data correlation challenging to interpret. For instance, while some evidence suggests that

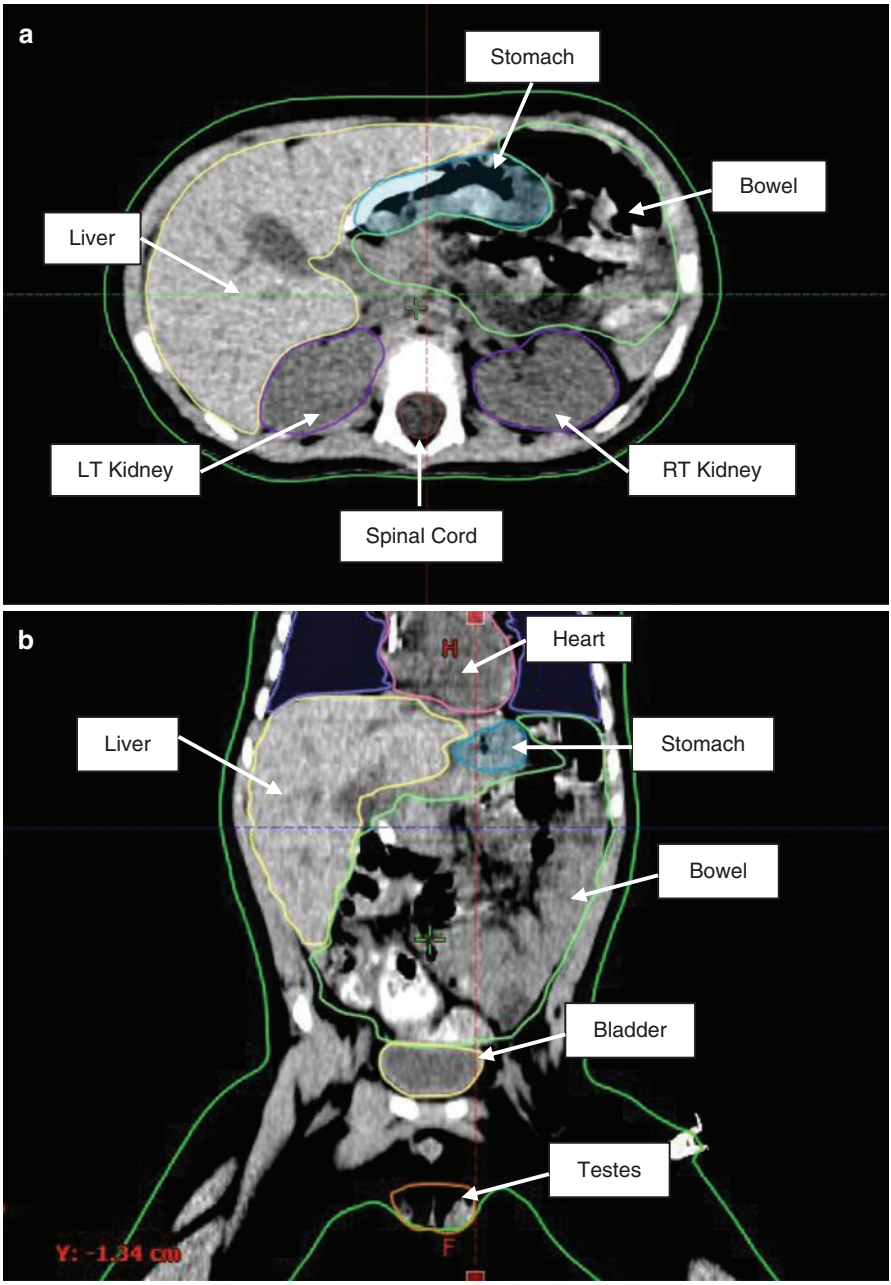

Fig. 2.4 **(a)** Axial CT image of the abdomen showing contours of organs at risk **(b)** Coronal CT image of abdomen depicting organs at risk

PC dose is the most prognostic of acute and late toxicity [39], other studies demonstrated that dose received by small bowel (SB) loops predicted grade 2 and higher chronic GI complication [40]. Contouring of duodenum may be important in high-dose treatments [41]. While total bowel and peritoneal cavity will be relatively easy

to contour on non-contrast scan, per-oral contrast material will be ideal for identifying the small bowel loop.

2.4.1.4 Pancreas

Contouring of the pancreas is not performed routinely; however, it may be carried out in selected cases. The pancreas is located in retroperitoneal space and will be easy to identify on non-contrast simulation CT scan.

2.4.1.5 Spleen

The spleen would be rarely contoured as the OAR but, if needed, is readily identifiable with simulation CT. It is expected that the spleen will move with respiratory motion.

2.5 Pelvis

Simulation CT scan is typically acquired during free breathing and covers the area from the mid- or upper abdomen to the mid-thighs with a slice thickness of 2 mm. Most OAR can be readily visualized without contrast. There should be very little effect from a respiratory motion and typically 4-D scans won't be necessary. Oral contrast can assist in contouring bowel, although will be only indicated in high-dose treatments (e.g., pelvic Ewing's sarcoma, rhabdomyosarcoma).

2.5.1 Pelvic OAR (Fig. 2.5)

1. Bladder
2. Rectum
3. Uterus (in girls)

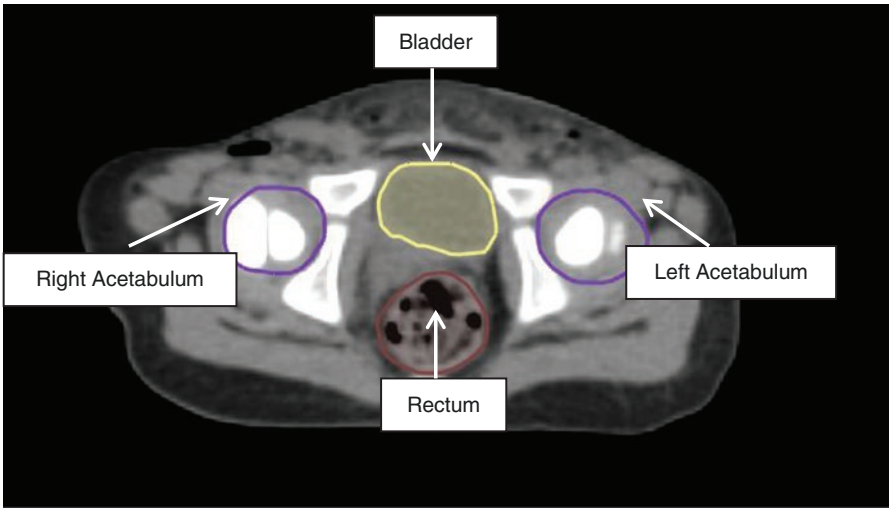

Fig. 2.5 Axial CT image of the pelvis showing contours of organs at risk

4. Ovaries (in girls)
5. Prostate (in boys)
6. Penile bulb (in boys)
7. Testes (in boys)
8. Femur left and right
9. Bowel

2.6 Extremities

Simulation CT scan is typically acquired during free breathing and covers the area above and below the target volume with a slice thickness of 2–5 mm. Contrast is not usually administered as target volumes and OARs will be commonly contoured based on diagnostic MRI images that are registered to planning CT scan.

2.6.1 Extremity OAR (Fig. 2.6)

1. Unaffected bone(s) in the vicinity of target volume
2. Growth plates
3. Joint spaces

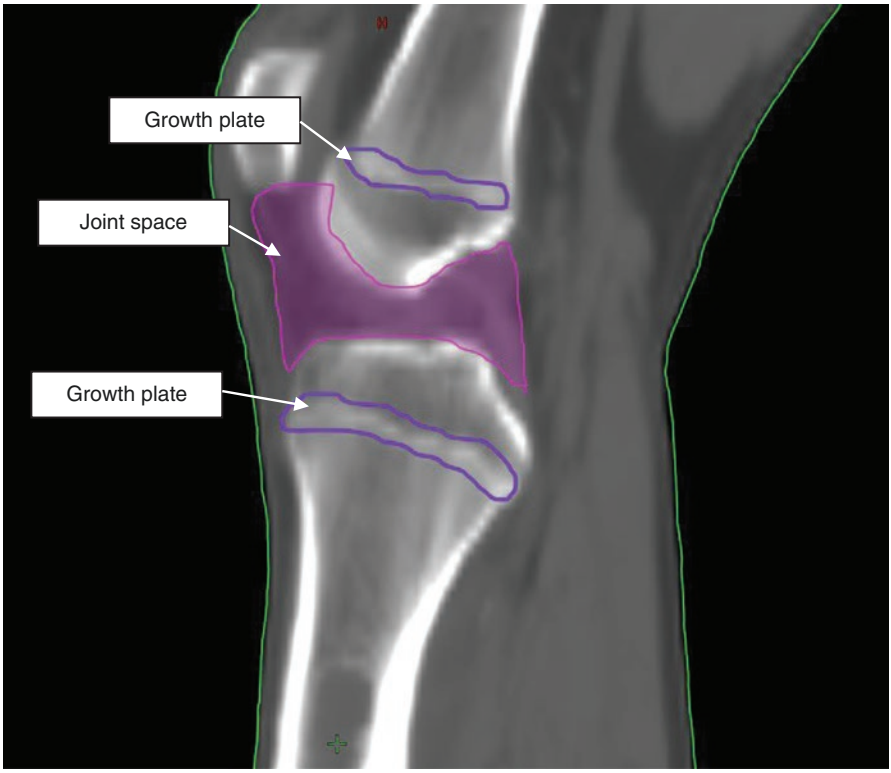

Fig. 2.6 Sagittal CT image of the knee joint showing contours of structures at risk

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Medulloblastoma

3

Ralph Ermoian and Steve Braunstein

Contents

3.1 Background

- Medulloblastoma is the most common malignant embryonal tumor of the central nervous system (CNS), arising in the posterior fossa, most commonly in the fourth ventricle.
- Patients often present with headaches, nausea, vomiting, and ataxia as a result of regional mass effect and cerebrospinal fluid flow obstruction.
- There are approximately 350 cases of medulloblastoma in the United States each year [1].

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Table 3.1 2016 World Health Organization's medulloblastoma subclassifications

Genetic	Medulloblastoma, WNT-activated
	Medulloblastoma, SHH-activated and *TP53*-mutant
	Medulloblastoma, SHH-activated and *TP53*-wildtype
	Medulloblastoma, non-WNT/non-SHH
Histologic	Medulloblastoma, classic
	Medulloblastoma, desmoplastic/nodular
	Medulloblastoma with extensive nodularity
	Medulloblastoma, large cell/anaplasia
	Medulloblastoma (NOS)

3.1.1 Histology

- The World Health Organization has recently reclassified CNS tumors both with respect to other embryonal CNS tumors and subclassifications of medulloblastoma [2].
- Medulloblastoma is now subclassified by either genetic or histology definitions (Table 3.1).
- Although recent retrospective studies have demonstrated profound prognostic value in genetic definitions [3], only histologic definitions of medulloblastoma have been employed in completed prospective multi-institution or cooperative group studies.

3.1.2 Staging

- In addition to maximal safe resection of the primary tumor, the workup for medulloblastoma includes magnetic resonance imaging (MRI) of the brain before and after resection of the tumor, MRI of the spine (preferably before resection to reduce risk of confusing blood from resection for drop metastases), and cerebral spinal fluid (CSF) sampling at least 10 days after primary tumor resection.
- In the past, patients were staged with the Chang [4] staging system which describes the primary tumor site (T-stage) by tumor size and extension, and M-stage by tumor beyond the primary site, including M0 for no evidence of spread, M1 for disease only detected on CSF sampling, M2 for gross supratentorial metastases, M3 for gross metastases in the spinal cord, and M4 for extra-CNS disease. This staging system was developed before the era of three-dimensional imaging. While the T staging is now largely obsolete, the M staging is still employed.
- In ongoing and completed clinical trials, patients 3 years or older with less than 1.5 cm^2 of residual primary tumor in axial imaging and M0 are classified as having standard-risk or average-risk disease. Other patients are considered to have high-risk disease.
- Recent Children's Oncology Group studies have categorized patients with diffuse anaplasia as being high risk, regardless of extent of surgery and metastatic disease status.

3.1.3 Principles of Management

- Historically patients were treated with surgery and radiation to the entire craniospinal axis (CSA) with craniospinal irradiation (CSI) with boosts to the primary site and metastases.
- In the 1990s and 2000s, studies showed that with the addition of chemotherapy including mustard agents, vincristine, prednisone, and cyclophosphamide improved outcomes [5, 6].
- For average-risk patients, the standard of care includes maximal safe resection followed by adjuvant craniospinal irradiation to 23.4 Gy in daily 1.8 Gy fractions, followed by a boost of 30.6 Gy, also in 1.8 Gy fractions. Typically radiation is delivered with concurrent weekly vincristine.
- The recently completed Children's Oncology Group (COG) trial ACNS 0331 demonstrated that average-risk patients can be treated with a boost to the resection bed plus margin rather than the whole posterior fossa without sacrificing disease outcomes. However, the study showed inferior overall survival and leptomeningeal control when reduced-dose CSI of 18 Gy was used in place of 23.4 Gy [7]
- High-risk patients are treated with CSI of 36 Gy with boost to the posterior fossa to 54–55.8 Gy, both in 1.8 Gy fractions. Diffuse spinal metastases call for spine radiation to 39.6 Gy or foci of disease in the spine can be treated to 45–50.4 Gy, depending on whether the lesions are at a level involving the spinal cord or below, respectively. Within limits of feasibility and organ at risk tolerances, brain metastases can be boosted to a total of 54–55.8 Gy in conventional fractionation.
- Radiotherapy should begin within 31 days of surgery, although in some situations radiation is deferred until after high-dose chemotherapy with stem cell rescue, most notably in young patients <3 years old where the toxicities of radiotherapy are most severe during early development. A recent investigation showed equivalent disease outcomes with the latter strategy [8].

3.2 Craniospinal Irradiation Contouring

- The goal of craniospinal irradiation is to treat all spaces where cerebrospinal fluid dissemination can result in tumor deposits. This includes the entire subarachnoid space from the vertex to the bottom of the thecal sac and includes the spinal nerve roots laterally.
- Patients can be simulated prone or supine, with arms down. The neck is hyperextended so that spine fields do not exit through the patient's mouth; when patients are treated with proton radiation with PA fields, the neck may be neutral as there is no concern of exit dose. For patients receiving anesthesia, it is most important to prioritize airway when positioning the head and neck. The head immobilized with a mask and some institutions will use additional immobilization devices for the chest, abdomen, pelvis, and lower extremities.
- The details of the dosimetric planning are beyond the scope of this chapter. However, it would suffice to say there are a variety of techniques that vary in

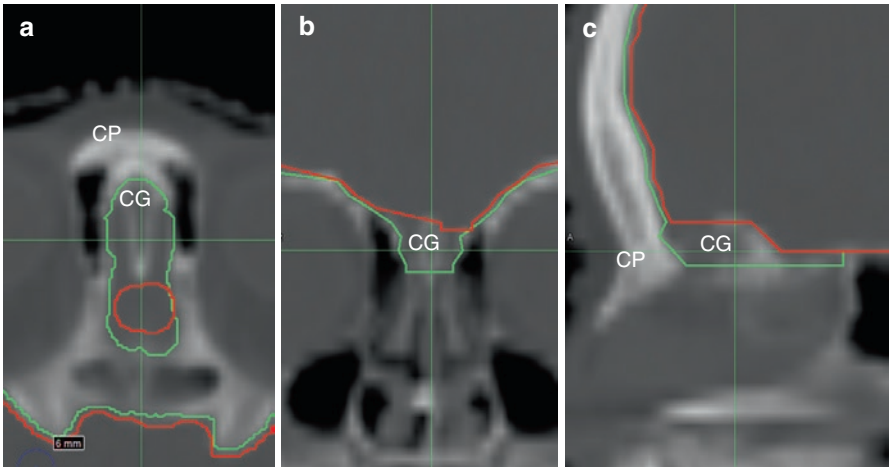

Fig. 3.1 Contours around the cribriform plate in axial (**a**), coronal (**b**), and sagittal (**c**) planes. Suboptimal CTV brain is contoured in red. More optimal CTV brain is contoured in green. *CP* cribriform plate, *CG* Crista galli

patient positioning (prone or supine), planning modality (3D conformal therapy versus intensity-modulated radiation therapy/volumetric arc therapy), and radiation modality (photon versus proton therapy). There are some concerns about increased risk of secondary malignancies in patients treated receiving craniospinal irradiation with volumetric arc therapy compared to 3D conformal therapy [9].

- The clinical target volumes (CTVs)—the spaces actually at risk of disease dissemination—are independent of patient positioning, planning/delivery technique, or modality of therapy.

Critical considerations in delineating the craniospinal CTV include:

- Because planning target volume (PTV) expansions may be different in the brain and spine, clinicians may contour the CTV spine and CTV brain separately.
- It is important not to under-contour the craniospinal CTV. One can change CT settings to bone windows during contouring which will allow the radiation oncologist to contour erring on the side of generous volumes.
- The intracranial compartment includes all of the CSF space surrounding the brain including the prepontine cistern just posterior to the clivus.
- The CSF space around the cribriform plate is critical. This space between the orbits must be contoured with care and to the base of the crista galli. This is often best appreciated on sagittal or coronal views with bone windows, as shown in Fig. 3.1.
- For the inferior extent of the spine fields, most protocols suggest setting beam edge 2–3 cm below the bottom of the thecal sac. The thecal sac can often be seen on both finer cut CT imaging in soft tissue windows and sagittal MRI imaging. The thecal sac typically ends between S1 and S3, and some providers will delineate the "bottom of thecal sac" as a reference point structure. The CTV can then

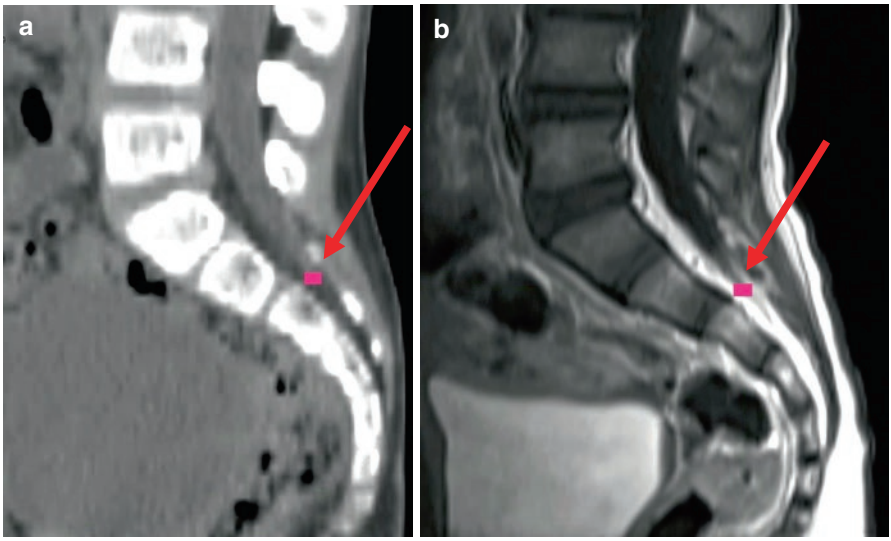

Fig. 3.2 Bottom of the thecal sac is contoured in fuchsia in sagittal CT (**a**) and T1 + gadolinium (**b**) windows

extend 1–2 cm below it. An example is shown in Fig. 3.2. In practice, the inferior edge of the spinal field is rarely higher than S2–S3 space.

- Nerve roots. The CTV should include the neuroforamina at all levels of the spine. As shown in Fig. 3.3, in the sacrum this results in "spade" shape of 3D conformal posterior-anterior (PA) radiation fields but also results in the widening of fields in the cervical spine region.
- One should include pseudomeningoceles in the CTV although one does not need to include surgical tracts.
- The vertebral bodies and bony spine are not part of the CTV because they are not at risk of disease from CSF dissemination.

Craniospinal PTV expansions should be treatment delivery and institution dependent. They may also depend on the type and frequency of image-guided radiation therapy (IGRT):

- In the brain, with daily imaging, CTV to PTV expansions of 3–5 mm are appropriate. In the spine, expansions may vary from 0.5 cm to 1 cm.
- Imaging of the spine varies by technique and affects PTV delineation. While it is standard to check isocenters weekly, clinicians treating with PA spine fields may choose to use image-guided radiotherapy (IGRT) with simple AP KV imaging daily. Patients treated with IMRT or VMAT will also need at least lateral imaging if not cone-beam CT imaging. All of this affects the PTV delineation. Regardless of the type of on-treatment imaging, the clinician must contour the PTVs so the plan is robust not only for uncertainty at the isocenter but also along the full length of the radiation field which may extend 20 or more centimeters from the

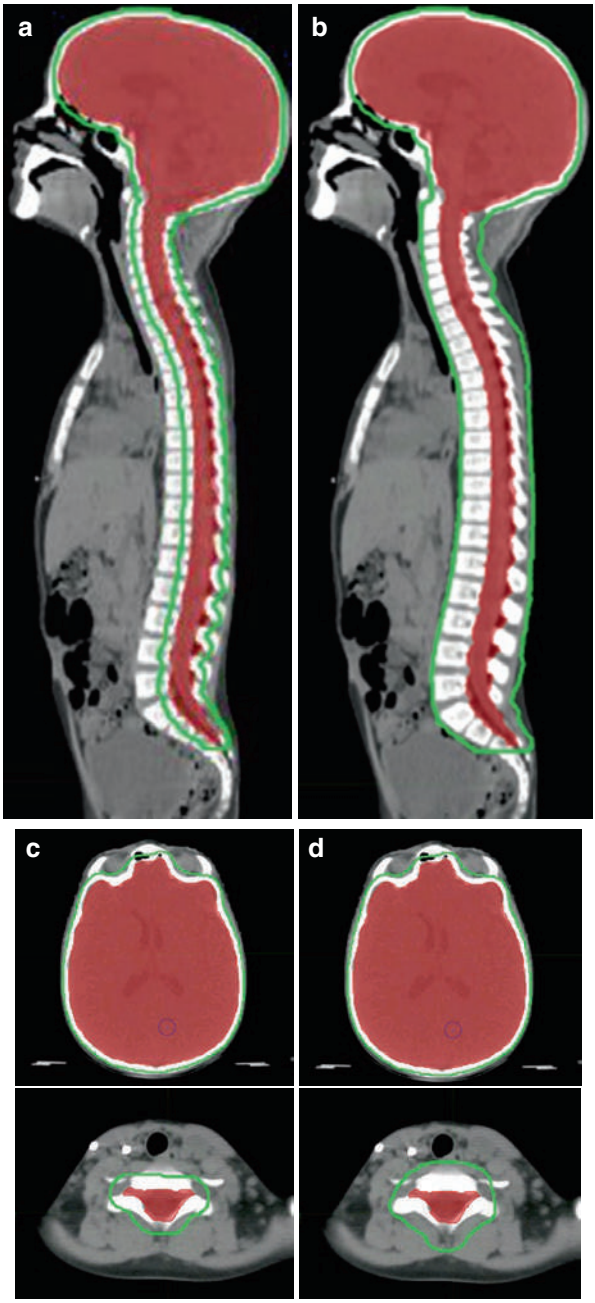

Fig. 3.3 Craniospinal CTV in red and PTV in green contours for patients treated with 3D conformal fields including PA spine fields (**a**, **c**), and IMRT, proton, or off-PA axis spine fields (**b**, **d**)

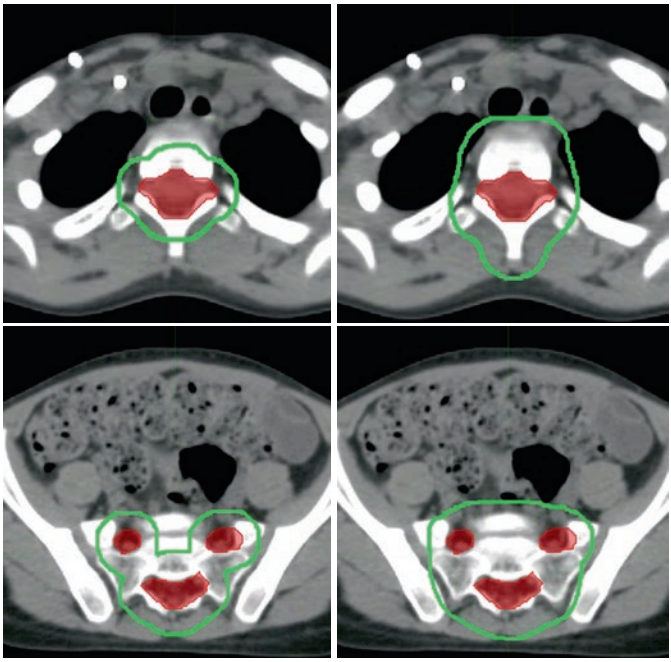

Fig. 3.3 (continued)

isocenter and thus experience potentially large translational movement following small rotational yaw at the isocenter.

- Asymmetric spine growth is a well-known complication resulting from nonuniform radiation dose distribution in spine fields in skeletally immature patients. CTV contouring of the subarachnoid space ensures this is unlikely to be an issue in coronal plane. However, anterior to posterior dose uniformity can be a problem.
- If one is treating with 3D conformal PA fields, the vertebral bodies and pedicles may not need to be contoured because—other than selection of beam energy—there is little to vary in radiation planning to address uniformity concerns.
- However, if planning using IMRT, VMAT, or proton therapy, the vertebral bodies and pedicles should be contoured and targeted. Without doing so, the dosimetrists and planning software may inadvertently create plans that result in clinically unacceptable gradients across vertebral bodies. Some clinicians include them in the spine PTVs and others contour them as separate targeted structures. While there is agreement that very large dosimetric gradients across vertebral bodies should be avoided, there is debate whether the anterior vertebral body needs to receive the full prescription dose or only a high proportion of the prescription dose.

Finally normal tissues should be contoured both to aid in treatment planning and document dose. Structures typically contoured in craniospinal irradiation include the lungs, heart, kidneys, liver, lenses, and thyroid. Some providers will also contour the

esophagus, left ventricle, uterus, ovaries, bladder, bowel, testes and parotid glands. Please refer to Chaps. 1 and 2 for normal structure contour guidelines.

Figure 3.3 shows an example comparing the craniospinal contours in a patient treated with PA spine fields and the same patient treated with target volumes appropriate for IMRT or proton radiation in which the PTV includes the vertebral bodies.

3.3 Focal Boosts to Resection Bed Plus Margins in Average-Risk Medulloblastoma

- As discussed above, ACNS0331 established that average-risk patients can be treated with an involved field boost to the resection bed plus margin. The use of the resection bed plus margin allows reductions of boost targets not just in the portions of the posterior fossa not originally involved by tumor but also in the normal tissue that re-expands into potential spaces after the tumor has been resected.
- The use of treatment planning software that allows fusion of planning studies to MRI imaging is invaluable. Although treatment planning is a team process, it is incumbent upon the radiation oncologists to carefully inspect fusions between MRIs and planning CTs.
- In most modern pediatric treatment centers, the extent of boost targeting is based on MRI imaging. The CTV boost is dependent on the preoperative imaging, postoperative imaging, knowledge of anatomic barriers to spread, information from the operative note, and discussion with neurosurgeons.
- The radiation oncologist needs preoperative and postoperative imaging to contour the resection bed. First, the preoperative imaging defines the initial extent of disease. Once the initial extent of disease is contoured, the resection bed (typically labeled GTV bst 5400) and residual disease can be contoured with fusions of the postoperative MRI imaging and planning CT.

  Critical steps in this process include:

- Establish with certainty—by reviewing imaging, reading operative reports, and discussions with surgeons—the extent of tumor including whether the foramen of Luschka, foramen of Magendie, internal acoustic canal, hypoglossal canal, and cerebral aqueduct was involved in the initial extent of disease.
- Delineating the residual disease with careful attention to gadolinium enhancing series, as well as T2 and FLAIR MRI series. Uncertainties should be resolved in a multidisciplinary manner with the patient's surgeon and other colleagues.
- The inferior extent of tumor will often extend to at least the level of the foramen magnum and at times to C2 or lower.

Once the resection bed has been established, a clinical target volume (CTV bst 5400) can be contoured. The COG trial ACNS0331 used a 1.5 cm geometric expansion, limited by bony anatomy, and the tentorium. Although not studied prospectively, clinicians debate whether a 1.5 cm expansion into the brainstem is necessary when the surgical impression is that the tumor arose from a cerebellar surface such as the floor of the fourth ventricle. However, medulloblastomas can arise from the

surface of the brainstem so one should have a low threshold to generously expand the GTV bst 5400 volume in defining the CTV bst 5400 volume:

- Finally, an institution appropriate PTV expansion is applied. For patients with good immobilization and weekly imaging, 0.5 cm is often used. For patients with daily imaging, a 0.3 cm expansion can be used.
- Organs at risk contoured for the boost scan and also the composite plan should always include the optic chiasm, optic nerves, cochleae, brainstem (midbrain to foramen magnum), cervical cord (typically from foramen magnum to the bottom of C2), and pituitary gland. Additional organs at risk that may be contoured can include the supratentorial brain, hypothalamus, globes, hippocampi, posterior pharyngeal wall, and temporal lobes. Please refer to Chap. 1 for contouring of normal CNS structures.

3.4 Whole Posterior Fossa Boosts in High-Risk Medulloblastoma

- While COG ACNS0331 established the role of resection bed plus margin boosts in average-risk medulloblastoma patients, there has not been a prospective randomized study that establishes the safety of treatment of the involved field in high-risk patients. Therefore the whole posterior fossa is often treated as the boost volume for high-risk medulloblastoma.
- The COG studies and several other protocols have used 55.8 Gy as the boost dose to the whole posterior fossa. Off-study, our recommendation would be 54 Gy so that brainstem tolerance is not exceeded.
- It would be prudent to contour the initial extent of tumor and GTV resection bed in high-risk patients. The whole posterior fossa CTV (CTV pf) is often independent of the resection bed. Nonetheless there are occasions when the CTV pf will depend on the extent of the resection bed, such as when the tumor initially extended past C1–C2.
- The posterior fossa includes all of the cerebellum and the brainstem, the latter of which defines the anterior extent of the posterior fossa. Bony confines of the CTV pf also include the C1 spinal canal inferiorly, the tentorium superiorly, and the occipital and temporal bones anteriorly and laterally. Care should be taken to extend superiorly to the tentorium. Again, there may be instances when the primary tumor resection bed is extensive enough to warrant contouring a CTV pf 5580 beyond these boundaries.
- The same organs at risk should be contoured when planning whole posterior boosts and resection bed plus margin boosts.
- An example case comparing resection bed plus margin versus whole posterior fossa is shown in Fig. 3.4. There are a few subtleties in Fig. 3.4 that should be highlighted. First, the resection bed can continue to collapse after the immediate postoperative MRI. Second, the position of the inferior brainstem and cervical cord may vary between the MRI and planning CT; if there is a variance, contouring should rely on the CT because that reflects the positions of the organs at risk with the patient in treatment position.

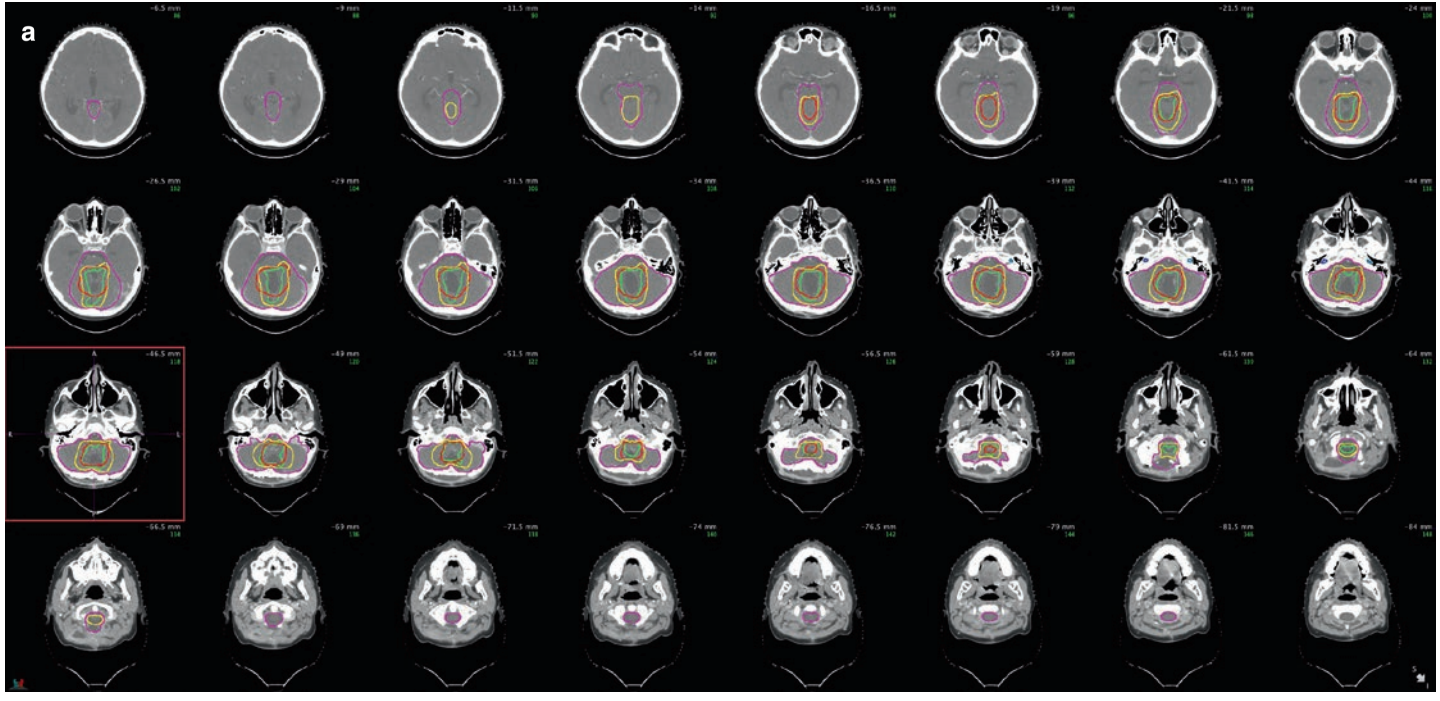

Fig. 3.4 Whole posterior fossa versus resection bed plus margin target volumes in axial (**a**) and sagittal (**b**) planes. Preoperative extent of disease in red, GTV1 bst (resection bed) in green, CTV bst 5400 in yellow, and CTV pf 5580 in fuchsia

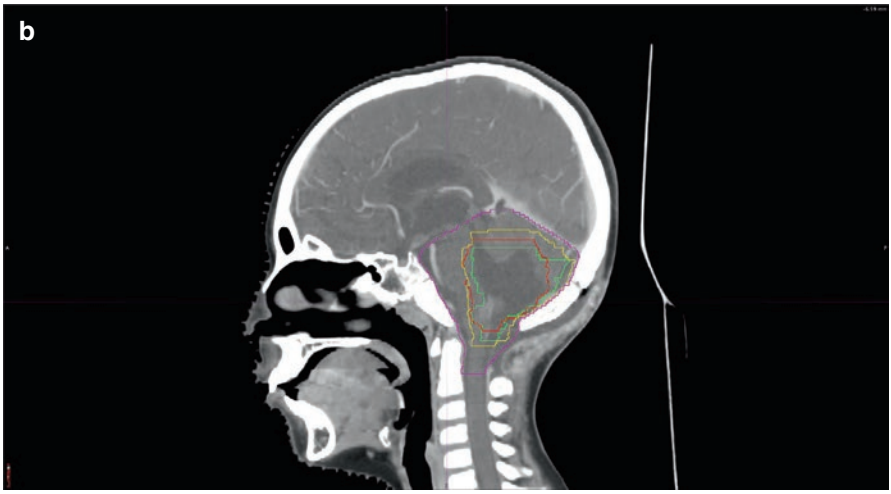

Fig. 3.4 Continued

3.5 Metastases

- Metastases are typically boosted beyond the craniospinal dose levels. The GTV metastasis should be contoured based on MRI imaging. A 0.5 cm to 1 cm geometric expansion—anatomically limited—should be used to contour CTVs for metastatic sites of disease. An institution-defined expansion is then applied to delineate the PTV. When treating boosts in the spine, one must be mindful of dose gradients that could result in asymmetric skeletal hypoplasia.

Figure 3.5 shows an example of GTV, CTV, and PTV for a patient with a drop metastasis.

- Of note, if one is treating metastases with stereotactic radiosurgery, then smaller margins may be applied.

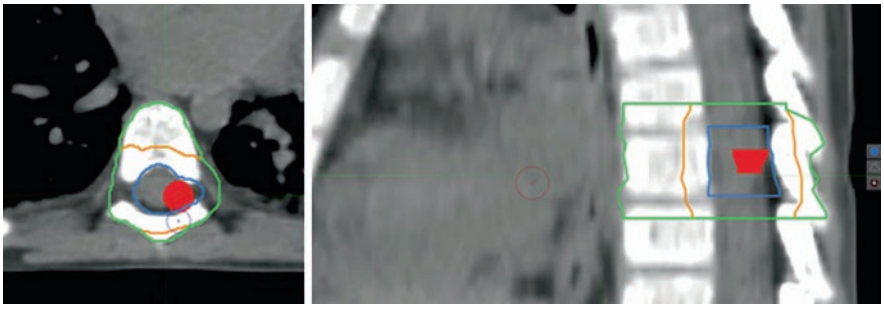

Fig. 3.5 Metastasis boost contours. GTV metastasis in red, CTV metastasis in blue, PTV metastasis (if PA only fields) in gold, PTV metastasis (if treating with IMRT, proton, or off-PA axis fields) in green

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Ependymoma

4

Christine Hill-Kayser

Contents

4.1 Background and Epidemiology

- Ependymoma represents the third most common primary brain tumor in children and accounts for approximately 10% of brain tumors in children and >20% of spinal cord tumors in children [1].
- Ependymoma diagnosis peaks between 0 and 4 years of age, and ependymomas are slightly more common in boys than in girls. Overall, they affect 0.26/100,000 children aged 0–14 years [1, 2].

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Table 4.1 Characterization of childhood ependymoma based on WHO grade

Grade	Types	Characteristics
I	Myxopapillary ependymoma	Arise from filum terminale in conus medullaris
	Subependymoma	Pedunculated, arise within ventricles
II	Ependymoma Cellular[a] Papillary Clear cell Tanycytic	Hypercellular, without vascular proliferation or necrosis
		Papillary structures surrounding vascular cores
		May have cystic components and perinuclear halos
		Elongated cells with spindle-shaped nuclei
	Ependymoma, RELA fusion-positive	Contain oncogenic fusion (RELA-C11orf95) at chromosome 11q13
III	Ependymoma, RELA fusion-positive	Contain oncogenic fusion (RELA-C11orf95) at chromosome 11q13
	Anaplastic ependymoma	Likely to have true ependymal rosettes, vascular proliferation, necrosis, hypercellularity

[a]Cellular ependymoma variant removed from 2016 update of WHO CNS 4th edition because it was considered to overlap significantly with other described variants [3]

- Ependymoma may be further characterized according to histopathology as well as location within the CNS (supratentorial brain, infratentorial brain, spinal cord).
  - The World Health Organization (WHO) separates ependymomas into three groups based on histopathologic grade, with several subclassifications. Subclassifications have been recently modified with a 2016 update of the WHO CNS 4th edition; modifications include incorporation of a genetically defined ependymoma variant (RELA fusion-positive). (Table 4.1) [3].
    RELA fusion-positive ependymoma is the first molecular ependymoma variant to be formally recognized. Over two-thirds of supratentorial ependymomas contain oncogenic fusions between *RELA* (an effector of NF-κB signaling) and an uncharacterized gene, *C11orf95*, involving chromosome 11q13 [4].
  - Additionally, children are affected by these tumors within specific anatomic areas based on age, with mean age 12.2 years for spinal cord ependymomas, 7.8 years for supratentorial tumors, and 5 years for infratentorial tumors [5].
- Ependymomas can disseminate throughout the central nervous system, although this is relatively rare, with <15% of ependymoma tumors being associated with dissemination detected either on imaging or via lumbar puncture [6, 7]
- Surgical resection and focal radiotherapy remain the mainstays of treatment for ependymoma, with the role of chemotherapy remaining investigational.
  - Historically, surgical resection has been regarded as the most crucial aspect of treatment, with improvement in prognosis observed for patients with gross total as compared to incomplete resections [8–10].

4.1.1 Pre-radiotherapy Imaging and Evaluation

- Imaging obtained prior to radiotherapy is essential for radiation planning.
- Often, CT of the head is the first study obtained; this generally demonstrates an isodense or hypodense solid lesion that may have associated cystic components and calcifications [11, 12].

- Initial MRI evaluations should follow and include imaging of brain and spine. Tumors may be solid or associated with cysts and are iso- or hypointense on T1-weighted images and iso- or hyperintense on T2/FLAIR [13]:
  - Supratentorial ependymomas may arise within the cerebral hemispheres or around or within the ventricles.
  - Infratentorial ependymomas most commonly arise within the 4th ventricle, often resulting in dilation of the upper ventricles. Extension into the foramen of Magendie or the foramina of Luschka is common.
  - Spinal cord ependymomas are usually well circumscribed and may cause widening of the spinal cord. Metastatic spread or seeding of the cauda equina may be seen.
- Following initial imaging, patients generally undergo maximal safe resection. This should be followed by postoperative MRI obtained 24–48 h after surgery.
- Disease staging is completed with lumbar puncture obtained 7–10 days after surgical resection.

4.2 Management and Treatment of Intracranial Childhood Ependymoma

4.2.1 Intracranial Ependymoma: Principles of Management

- Maximal safe resection is generally the first step occurrence in management, with gross total resection contributing to rates of overall survival and progression-free survival [2, 14].
- Patients whose tumors cannot be grossly completely resected at the time of first surgery may benefit from a second attempt (second-look surgery), either immediately or after a short course, 1–2 cycles of cisplatin containing chemotherapy (the role of chemotherapy in this setting remains investigational, but this approach is sometimes used to maximize chances of gross total resection if second surgery is not possible or desired immediately following initial subtotal resection).
- Although degree of surgical resection impacts disease-related outcomes, surgical morbidity is an important factor in neurologic recovery, and thus degree of surgical resection must be balanced with morbidity risk [15].
- Surgical resection alone may be considered "on trial" for supratentorial tumors that are completely resected, are grade I or II, and do not communicate with the ventricular system [16].
- Adjuvant radiation for supratentorial ependymoma is indicated for grade III tumors, those that cannot be completely resected and those that have recurred after initial resection and observation.
- Adjuvant radiation is indicated for all infratentorial ependymomas, excluding rare grade I, completely resected tumors which may be treated with surgical resection alone.

4.2.2 Intracranial Ependymoma (Nondisseminated): General Considerations for Radiotherapy

- Radiotherapy for nondisseminated intracranial ependymoma is delivered to the tumor bed and any residual disease, with the goal of eradicating residual disease (microscopic or gross) at the primary tumor site.
  - Although craniospinal irradiation was historically delivered for high-grade tumors, excellent local control has been demonstrated with focal irradiation [17] and is generally considered standard of care for nondisseminated disease.
- Patients should be simulated supine and in a thermoplastic mask or head frame for immobilization.
- Axial CT images should be acquired in 3 mm or smaller increments.
- Some centers may have use of an MR simulator, and MR simulation images are useful for radiation planning. Regardless of presence of MR simulator, MR images obtained preoperatively and within 24–48 h postoperatively should be fused with simulation images.
- Generally, four target volumes are useful to construct for radiation planning: preoperative gross tumor volume (GTV), postoperative GTV, clinical target volume (CTV), and planning target volume (PTV). These volumes are further described in Table 4.2 (Figs. 4.1 and 4.2).
  - In certain circumstances in which the CTV includes an organ at risk, such as the brainstem or optic chiasm, and in which the treating physician intends to deliver a prescription dose that exceeds the constraint for that OAR, a "boost" or "conedown" CTV may be utilized.
- Target volumes may be treated with 3D conformal radiation, intensity-modulated radiotherapy (IMRT), or proton therapy. Beam arrangements should be chosen to minimize dose to organs at risk, including the brainstem, optic chiasm, cochlea, pituitary gland, and hippocampi.
- Radiation dose is a predictor of response, with better outcomes observed in patients who receive at least 5400 centigray (cGy) (V 100, 101). Recent work has demonstrated excellent outcomes after delivery of 5940 cGy [17]; however, in the absence of comparative data and because this dose approaches or exceeds tolerance of several organs at risk within the CNS, a range of 5400–5940 cGy is considered acceptable.

4.3 Management and Treatment of Childhood Spinal Ependymoma

4.3.1 Spinal Cord Ependymoma: Principles of Management

- Spinal cord tumors are relatively rare in children and adolescents, with an overall incidence of 0.26 per 100,000 person-years [18].
  - Ependymomas represent the most common subtype of spinal cord tumor in this age group, and approximately 13% of childhood ependymomas is located within the spinal cord [18].

Table 4.2 Planning target definitions for treatment of intracranial ependymoma

Volume	Description	
Gross tumor volume (GTV)	Preoperative GTV	• Contains gross tumor volume as identified on diagnostic imaging prior to surgical resection
	Postoperative GTV	• Contains tumor cavity and any residual tumor following surgical resection
Clinical target volume (CTV)	CTV	• 1 cm expansion from the postoperative GTV (smaller expansion margins remain investigational) • Should be further expanded to include surfaces of bone and connective tissue that were included in preoperative GTV (i.e., bone and/or tentorial tissue that was in contact with primary tumor) • Excludes extent of preoperative GTV that includes normal brain initially displaced by tumor • Excludes bone • May be cropped to respect anatomic boundaries – for example, the CTV may be cropped at the tentorium, rather than expanding into infratentorial brain only due to uniform expansion • Includes consideration of the following –Image accuracy and quality. CTV should be increased in size to account for uncertainties such as suboptimal fusion of pre- and postoperative images to planning images –Changes in volume since the time of imaging –Adjacent organ dose constraints
	Boost or conedown CTV	• In certain circumstances in which the CTV includes an organ at risk, such as the brainstem or optic chiasm, and in which the treating physician intends to deliver a prescription dose that exceeds the constraint for that OAR, a "boost" or "conedown" CTV may be constructed • This volume should include the initial CTV, but exclude the OARs in question and may be prescribed to receive a higher radiation dose than the initial CTV • When feasible, the conedown CTV should be utilized for dose prescriptions above 5400 cGy, with the initial CTV receiving a minimum dose of 5400 cGy
Internal target volume (ITV)	• Contains the CTV plus an internal margin that accounts for variation in CTV shape, size, and position but is generally not indicated for intracranial tumors which are subject to minimal motion	
Planning target volume (PTV)	• Contains CTV or ITV plus a margin to account for setup uncertainties associated with patient position and beam alignment • CTV-to-PTV expansions are patient- and institution-specific; any recommendations in this chapter or elsewhere must be adjusted to reflect factors unique to the patient and institution	
Organs at risk (OAR)	• Includes uninvolved normal structures at risk of RT-related toxicity for which RT planning or dose may be altered. During treatment of intracranial tumors, these generally include the brainstem, cervical spinal cord, temporal lobes, hippocampi, hypothalamus, pituitary, optic nerves and chiasm, and cochlea	

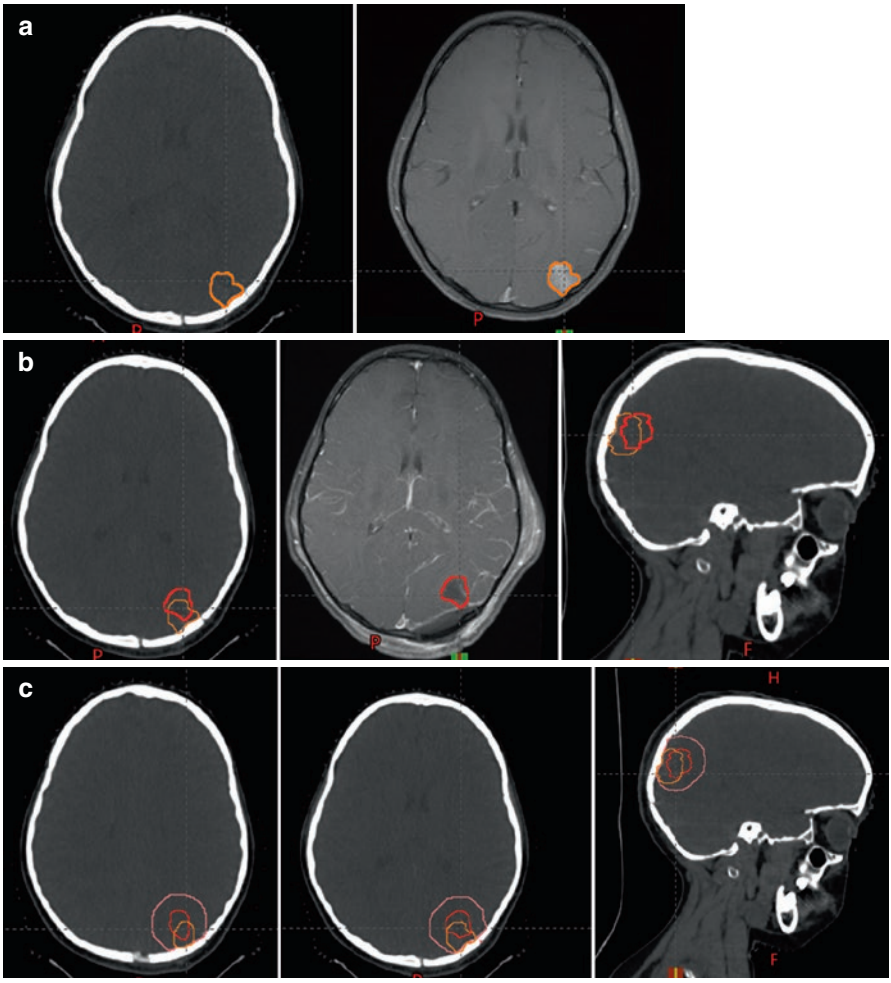
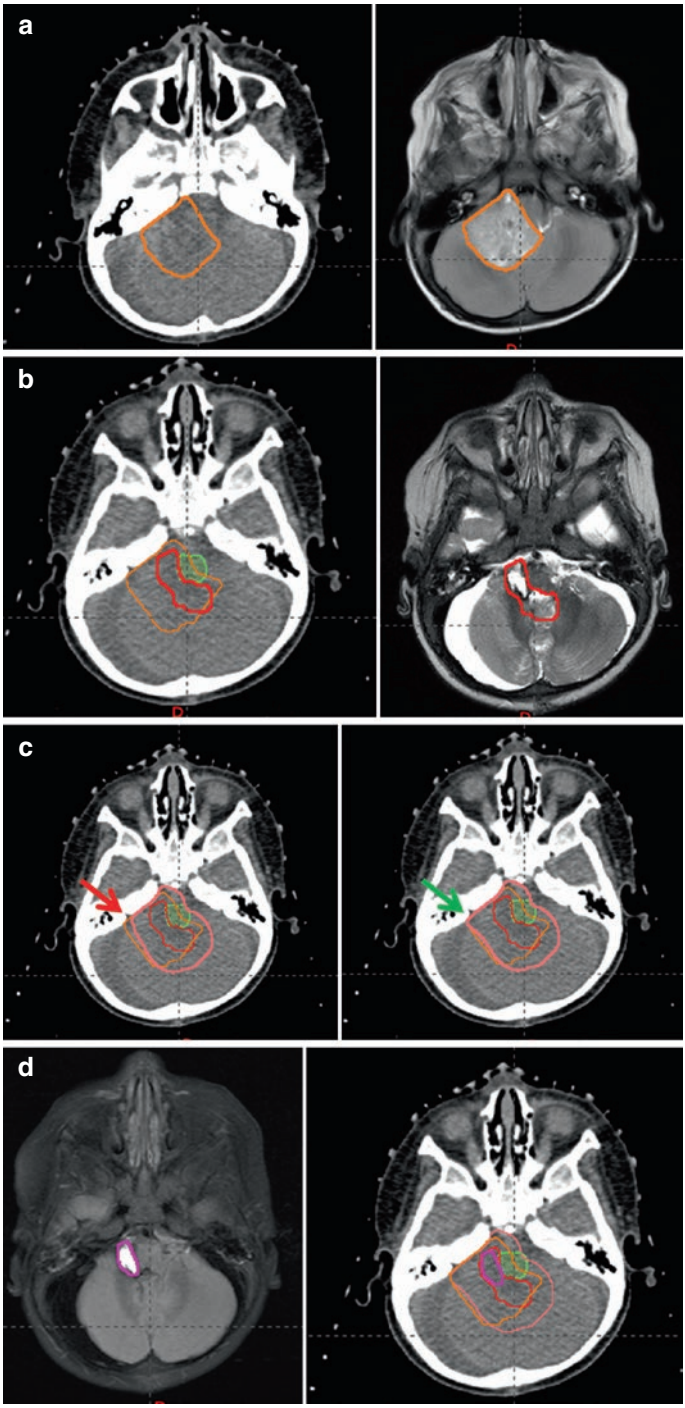


Fig. 4.1 Postoperative radiotherapy planning for localized supratentorial anaplastic ependymoma after gross total resection. Due to location distant from the brainstem, optic chiasm, and other OARs, no conedown is required with total prescription dose of 5940 cGy. (**a**) The preoperative GTV is delineated in orange on the planning CT scan (left). This volume was constructed based on fusion with preoperative MRI scan (right). (**b**) The postoperative GTV is delineated in red on the planning CT scan (left). This volume was constructed based on fusion with postoperative MRI scan (middle) and includes the entire tumor cavity after gross total resection. The relationship between the two volumes is best visualized on the sagittal view (right). (**c**) The CTV is shown in pink as a 1 cm expansion from the postoperative GTV (red). Note that the CTV (orange) is modified to include the dural region that was initially contacting tumor based on the preoperative GTV but is cropped back from bone. PTV (not shown) was constructed with a 3 mm expansion from CTV without cropping or further modification

- Spinal cord ependymomas are most commonly WHO Grade II or I (myxopapillary ependymoma) and are very rarely anaplastic.
  - Grade II and myxopapillary ependymoma are slow-growing neoplasms.
    Long-term follow-up data are limited but suggest that risk of relapse persists out to 15 years [19].
  - Anaplastic ependymomas within the spinal cord are aggressive and highly malignant.
- Staging approach should include MRI scanning of the brain and entire spine, with lumbar puncture included for any patient with anaplastic disease or other concern for dissemination.
- Management strategies for spinal cord ependymoma vary based on location and grade:
  - Grade II tumors are generally intramedullary, involving the true spinal cord (most commonly the cervical cord, followed by the thoracic cord).
    Gross total resection is preferred, although is sometimes performed piecemeal, and favorable outcomes have been achieved with GTR alone [20].
    Adjuvant radiation may be considered after subtotal resection, although close observation with re-resection and radiation in the setting of recurrence is also appropriate.
  - Grade I, myxopapillary ependymomas of the spinal cord most commonly occur in the caudal region and may be resected en bloc.
    Despite their low-grade nature, over 30% of patients develop locally recurrent disease by 5 years after surgical resection, with GTR being associated with improved recurrence-free survival [21, 22].
    Adjuvant radiation is often employed after subtotal or piecemeal resection in attempt to decrease the risk of local recurrence, although data supporting this approach are mixed [21, 22].
  - Anaplastic ependymoma of the spinal cord is a rare entity, and limited data support aggressive treatment with maximal safe resection and adjuvant radiation, regardless of extent of resection.

4.3.2 Spinal Cord Ependymoma: General Considerations for Radiotherapy

- Radiotherapy for nondisseminated spinal ependymoma is delivered to the tumor bed and any residual disease, with the goal of eradicating residual disease (microscopic or gross) at the primary tumor site.
  - Radiation for myxopapillary ependymoma of the caudal region is generally delivered to the tumor bed as well as the distal region of the cauda and to the filum terminale.
- Patients should be simulated supine or prone depending on institutional protocols. A thermoplastic mask should be used for immobilization during treatment of cervical spine; other devices may be used for immobilization of other regions of the spine.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b
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d

- Axial CT images should be acquired in 3 mm or smaller increments.
- Some centers may have use of an MR simulator, and MR simulation images are useful for radiation planning. Regardless of presence of MR simulator, MR images obtained preoperatively and within 24–48 hours postoperatively should be fused with simulation images. MRI fusions of the spine are more challenging than fusions of the brain, and it is sometimes difficult to obtain accurate fusions. Care should be taken to review areas of involvement on all MRIs carefully with a radiologist and assure coverage of the corresponding levels on planning CT.
- Generally, four target volumes are useful to construct for radiation planning: preoperative gross tumor volume (GTV), postoperative GTV (tumor bed + gross disease), clinical target volume (CTV), and planning target volume (PTV). These volumes are further described in Table 4.3.
- Target volumes may be treated with 3D conformal radiation, intensity-modulated radiotherapy (IMRT), or proton therapy. Beam arrangements should be chosen to minimize dose to visceral anterior organs including the esophagus, heart, lungs, bowel, bladder, and organs of fertility.
  - Oocyte banking and/or oopexy should be considered if radiation dose to pelvic organs is expected to exceed 200–400 cGy.
- Organs at risk include the spinal cord and/or cauda and depending on location within the spinal cord, esophagus, heart, lungs, kidneys, bowel, stomach, liver, rectum, and bladder.
- For patients who have not achieved mature bone age, a minimum dose of 2000–2500 cGy should be delivered to the entire vertebral body for any bony vertebra included in the PTV. The rationale for this is to allow for uniform dose to cause growth arrest across the entire vertebral body. If growth arresting dose is delivered to only part of the vertebral body, a kyphosis or scoliosis may result.
  - Age 16 is the average age at which skeletal maturity is reached.

Fig. 4.2 Postoperative radiotherapy planning for localized infratentorial anaplastic ependymoma after subtotal resection. Re-resection was felt to be associated with significant morbidity risk. The planned prescription dose was 5400 cGy to CTV_5400 (pink), with conedown to residual disease (CTV_5940 (magenta)) to a total dose of 5940 cGy due to proximity to the brainstem. (**a**) The preoperative GTV is delineated in orange on the planning CT scan (left). This volume was constructed based on fusion with preoperative MRI scan (right). (**b**) The postoperative GTV is delineated in red on the planning CT scan (left), and its relationship to the preoperative tumor volume (orange) and brainstem (green) can be appreciated. This volume was constructed based on fusion with postoperative MRI scan (right) and includes the entire tumor cavity as well as residual disease after subtotal resection. (**c**) The CTV_5400 is shown in pink as a 1 cm expansion from the postoperative GTV (red) and cropped back from bone. In the panel on the left, note the area of dural contact by tumor that was not initially included in the CTV_5400 based on uniform expansion from postoperative GTV (red arrow). In the right-sided panel, CTV_5400 is manually expanded to include this area, but not areas of normal brain that were displaced by tumor (green arrow). PTV (not shown) was constructed with a 3 mm expansion from CTV_5400 without cropping or further modification. (**d**) The CTV_5940 is shown in magenta as the area of residual tumor after surgical resection on MRI (right). It is shown relative to the other target volumes and brainstem on the left, including postoperative GTV (red), CTV_5400 (pink), and brainstem (green). PTV (not shown) was constructed with a 3 mm expansion from CTV without cropping or further modification

Table 4.3 Planning target definitions for treatment of spinal ependymoma

Volume	Description	
Gross tumor volume (GTV)	Preoperative GTV	• Contains gross tumor volume as identified on diagnostic imaging prior to surgical resection
	Postoperative GTV	• Contains tumor cavity and any residual tumor following surgical resection
Clinical target volume (CTV)	CTV	• 1 cm expansion from the postoperative GTV • Should be further expanded to include surfaces of bone and connective tissue that were included in preoperative GTV • Excludes bone • Includes nerve roots that exit the cord or cauda in the region of tumor and/or tumor bed • For thoracolumbar or caudal tumors, is usually expanded inferiorly to include the thecal sac to the filum terminale, as well as the sacral nerve roots • Includes consideration of the following: – Image accuracy and quality. CTV should be increased in size to account for uncertainties such as suboptimal fusion of pre- and postoperative images to planning images – Changes in volume since the time of imaging – Adjacent organ dose constraints
	Boost or conedown CTV	• 1 cm expansion from postoperative GTV • Includes surfaces of bone and connective tissue that were included in preoperative GTV • Excludes bone • Includes nerve roots • This volume may be modified to allow constraints of spinal cord and cauda to be respected • In certain circumstances, a second conedown CTV may be constructed that contains only residual gross disease
Internal target volume (ITV)	• Contains the CTV plus an internal margin that accounts for variation in CTV shape, size, and position but is generally not indicated for spinal tumors which are subject to minimal motion	
Planning target volume (PTV)	• Contains CTV or ITV plus a margin to account for setup uncertainties associated with patient position and beam alignment • CTV-to-PTV expansions are patient- and institution-specific; any recommendations in this chapter or elsewhere must be adjusted to reflect factors unique to the patient and institution	
Organs at risk (OAR)	• Includes uninvolved normal structures at risk of RT-related toxicity for which RT planning or dose may be altered. During treatment of spinal cord tumors, these generally include spinal cord, brainstem, caudal nerve roots, esophagus, lungs, heart, liver, kidneys, stomach, bowel, bladder, rectum, ovaries, uterus	
Minimum dose structure	• For patients who have not achieved mature bone age, a minimum dose of 2000–2500 cGy should be considered to the entire vertebral body for any bony vertebra included in the PTV. This may be best facilitated by construction of an "involved vertebral body" structure • This structure includes any bony vertebral body that is included in the PTV and is drawn to include the entire bony vertebra (Fig. 4.3d)	

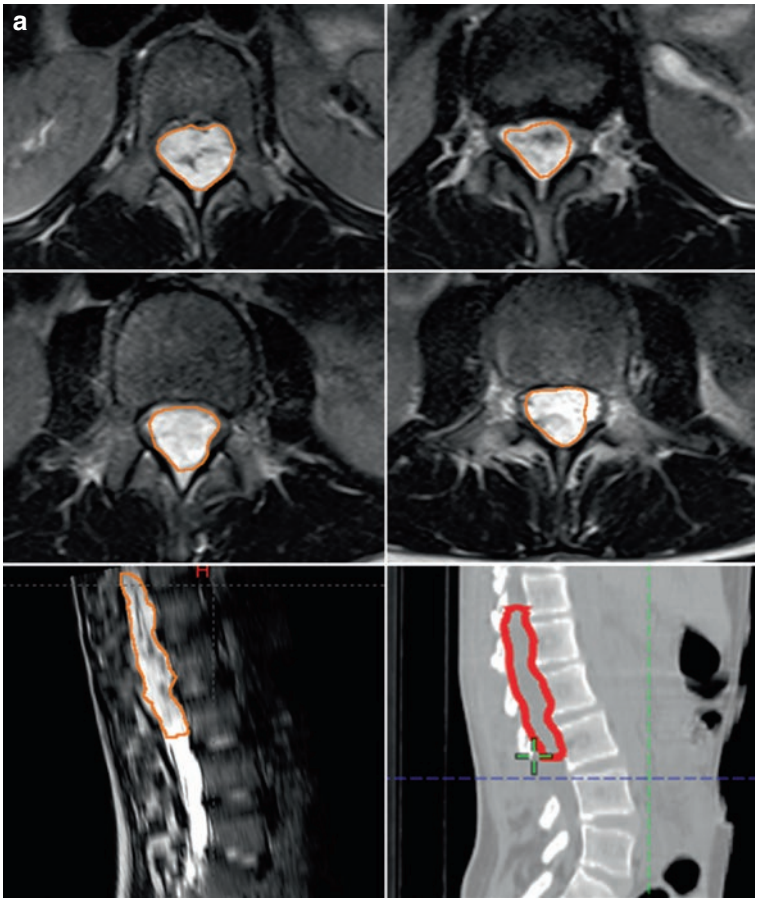

Fig. 4.3 Postoperative radiotherapy planning for localized myxopapillary ependymoma of the thoracolumbar spine after gross total resection. Resection was performed with T11-L3 and partial L4 laminectomy. En bloc resection was not possible; tumor was noted to blend with conus superiorly and to be adherent to nerve roots inferiorly. Because of high risk of residual disease, postoperative radiation was recommended. (**a**) The preoperative GTV is delineated in orange on preoperative MRI scan on axial and sagittal views. This volume is modified to account for anatomic changes and then used to create the postoperative GTV, shown in red on the planning CT scan. (**b**) The CTV1 is constructed as an expansion volume from the postoperative GTV and shown in pink. This volume may be initiated as a uniform expansion but requires significant modification including (1) inclusion of bone and connective tissue surfaces touched by initial tumor, (2) removal of bone, and (3) expansion superiorly and inferiorly to include operative sites and, if desired, the inferior cauda and filum terminale (as shown here). The relationship of the CTV1 to postoperative GTV is shown in sagittal view in the top panel. In the axial slices, the CTV varies depending on vertebral level and includes the thecal sac, nerve roots (red arrows), and operative bed (green arrows). (**c**) The CTV2 (magenta) is constructed as a uniform expansion from the postoperative GTV with removal of bone and expansion to include operative sites. Its relationship to GTV (red) and CTV1 (pink) is shown here. If residual disease is present postoperatively, it may be delineated as a CTV3, to receive further boost dose, based on clinical judgment. In the case shown here, no residual disease was appreciated postoperatively. (**d**) The involved vertebral body structure, prescribed to a minimum dose 2000–2500 cGy, is shown here in aqua, relative to GTV (red), CTVs (pink and magenta), and PTV(navy). This volume should include any vertebral body with any inclusion in PTV. This volume should not be included in a CTV or PTV volume but should be a separate target volume with a minimum prescription dose

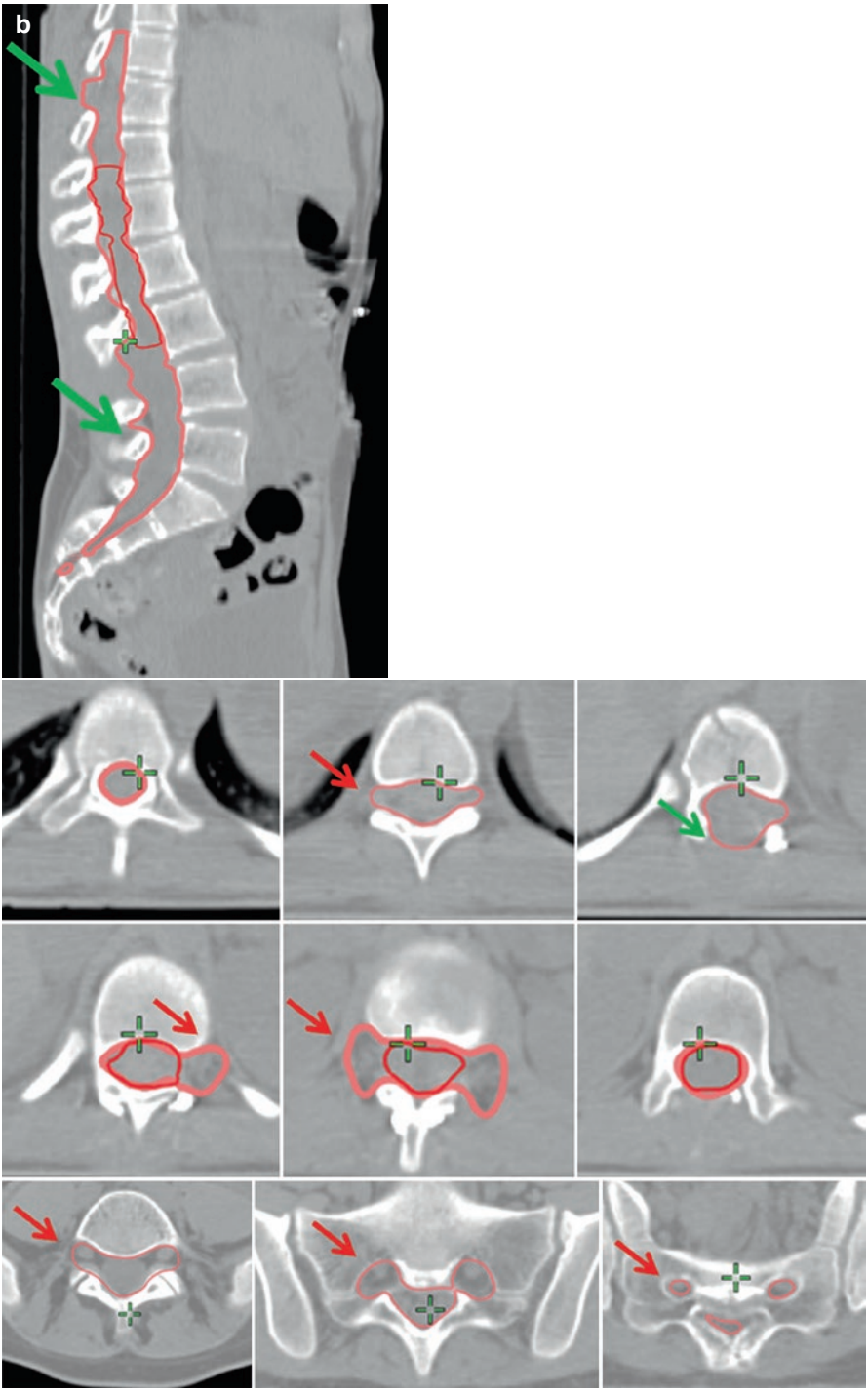

Fig. 4.3 (continued)

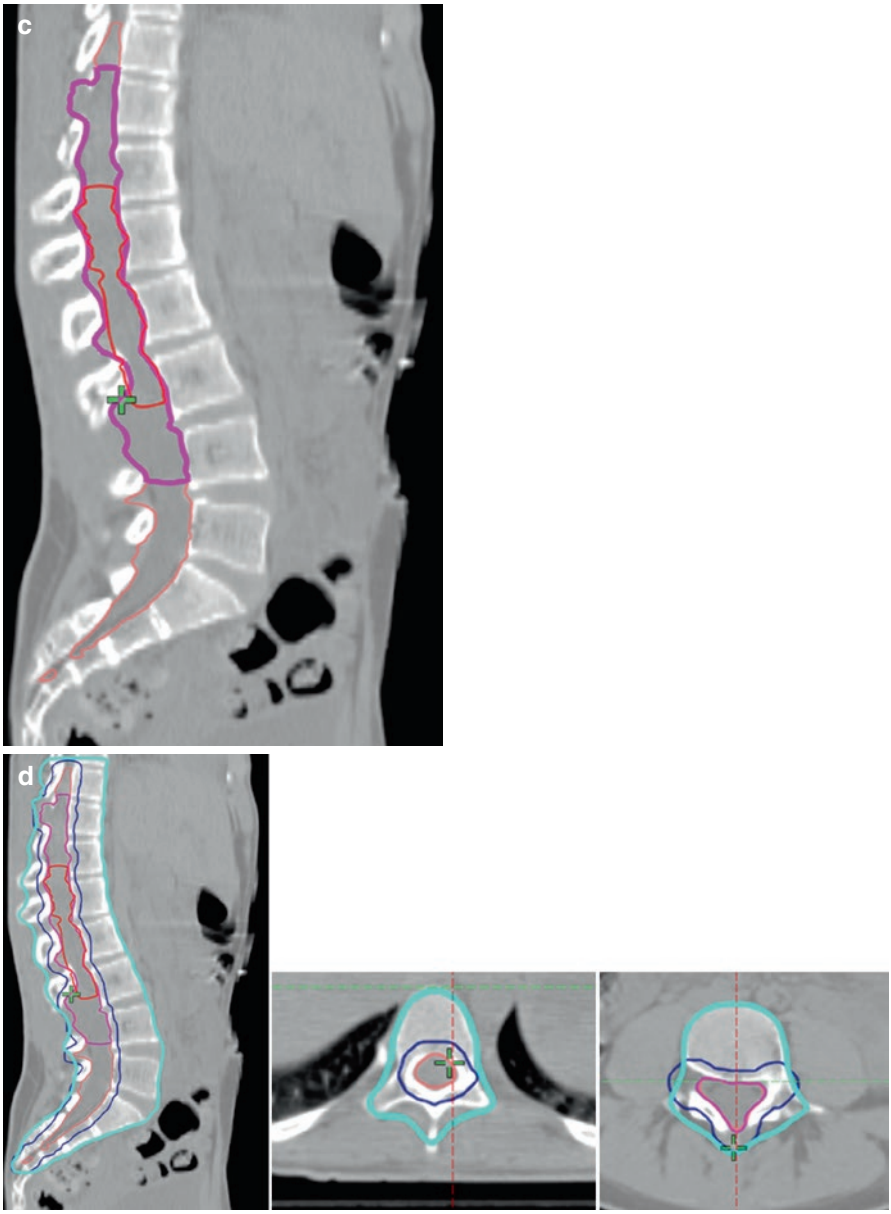

Fig. 4.3 (continued)

  - Patients who are 14–15 years old with stage IV–V Tanner development have very likely achieved skeletal maturity.
  - Patients older than 16 who have not reached sexual maturity may still have significant bony growth to achieve. For these and any other patients for whom skeletal maturity is in question, a radiographic bone age test is useful.
- Radiation treatment planning for spinal cord ependymoma is highly individualized and is made complicated by the proximity of tumors to vital structures, such as the spinal cord and cauda, whose constraints must be respected. The doses discussed below are suggestions; however, they must be adjusted according to individual clinical circumstances as well as clinician and patient assessment of risk/benefit ratios. Because of acceptable variations in dose prescription, target volumes in this section will be referred to as CTV1, CTV2, and CTV3, rather than by their prescription dose.
- The standard dose for grades I–II spinal cord ependymoma is 5400 cGy. Consideration of doses up to 5940 cGy is warranted for rare anaplastic spinal cord tumors. Depending on location within the spinal column, dose delivery will generally require at least one conedown volume:
  - Thoracolumbar or caudal location: The CTV1 may be planned to receive 4500–5040 cGy, which will include the entire tumor bed with an expansion that includes the inferior thecal sac to the level of filum terminale. The CTV2 may be planned to receive 5400 cGy (CTV_5400) and will include only a 1 cm expansion from the tumor bed. In the setting of anaplastic, grade III disease, gross residual disease may be boosted to 5940 cGy depending on clinician judgment. Volumes are further discussed in Table 4.3.
  - Tumors in the cervical or thoracic cord may be treated with a similar method, although clinical judgment may require overall dose reduction of both CTV1 and CTV2 in order to respect spinal cord constraints.

4.4 Special Considerations

4.4.1 Disseminated Ependymoma

- Ependymoma that is disseminated based on lumbar puncture and/or radiographic findings is generally treated with craniospinal irradiation (CSI) to a dose of 3600 cGy. Treatment technique for CSI is described elsewhere in this text.
- Areas of gross disease should then receive boost radiation:
  - Focal brain boost to a total dose of 5400–5580 cGy should be performed after CSI when intracranial tumor is present. The contouring guidelines for intracranial ependymoma may be used to construct these boost volumes.
  - When the spine is diffusely involved with tumor, the entire spine may receive boost of 3960 cGy. When the spine is focally involved, the guidelines for target delineation of spinal cord ependymoma may be employed.

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Suggested Reading

1. Overview of Pediatric Ependymoma: Vitanza NA and Partap S. Pediatric Ependymoma. J Child Neurology 1(13), 2015
2. Overview of spinal cord ependymoma: Benesch M, Frappaz D, Massimino M. Spinal cord Ependymoma in Children and Adolescents. Childs Nerv Syst 28: 2017–2028, 2012

Pediatric Intracranial Germinomas

5

Jonathan W. Lischalk and Shannon M. MacDonald

Contents

5.1 Introduction

- Epidemiology
  - Intracranial germ cell tumors (IGCT) account for 3–5% of pediatric central nervous system malignancies in the United States, though the incidence can be as high as 10–11% in some Asian countries [1].
- Demographics
  - Germinomas are most commonly seen in adolescents aged 10–12 years with 90% occurring before age 20 years. A male predominance is noted for IGCTs, in particular for tumors of pineal gland origin [1, 2].

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Table 5.1 Histological subtypes of IGCTs, tumor marker expression, and prognostication

WHO histologic subtype	β-HCG	AFP	Japanese prognostic group
Pure germinoma	–	–	Good
Germinoma (syncytiotrophoblastic)	+	–	Intermediate
Mature teratoma	–	–	Good
NGGCT			
Yolk sac/endodermal sinus	–	+	Poor
Choriocarcinoma	+	–	Poor
Immature teratoma	±	±	Intermediate
Embryonal	–	–	Poor
Mixed germ cell	±	±	Intermediate/poor

β-HCG beta-human chorionic gonadotropin, *AFP* alpha-fetoprotein, *WHO* World Health Organization

- Histological subtypes
  - IGCTs are broadly classified by the World Health Organization (WHO) into pure germinomas and non-germinomatous germ cell tumors (NGGCT). The majority, two-thirds, are pure germinomas with the remaining one-third NGGCTs [2].
  - NGGCTs are subclassified into [1] embryonal, [2] yolk sac or endodermal sinus, [3] choriocarcinoma, [4] teratoma (immature, mature, and malignant transformed), and [5] mixed germ cell tumor (farraginous components of NGGCT and pure germinoma) [2]. Table 5.1 delineates histologic types with their associated tumor markers and Japanese prognostic group.
- Anatomy and patterns of spread
  - There is an intimate association with midline proximal third ventricular structures, specifically the pineal and suprasellar (e.g., infundibulum and pituitary stalk) regions, which make up nearly two-thirds and one-third of observed IGCTs, respectively. Less common locations include the basal ganglia and thalamus [1, 3].
  - Up to 10% of patients present with bifocal disease, more commonly seen in pure germinomas, which is believed to represent multifocal occurrence of tumors and not metastatic disease. These patients are treated as though they have localized disease [3–5].
  - CSF dissemination occurs in 10–20% of patients [1].
- Prognosis
  - IGCTs treated with standard therapy demonstrate exceptional long-term disease-free survival of >90% and 70–80% for pure germinomas and NGGCTs, respectively [1].
  - The Japanese Pediatric Brain Tumor Study Group Classification categorizes patients into three prognostic groups based on histology for patients that have resection of tumor up front: [1] "good" with a 10-year survival >90%, [2] "intermediate" with a 3-year survival of ~70%, and [3] "poor" with a 3-year survival 10–30% [6]. In the United States and Europe, it is uncommon to perform surgical resection up front for full pathologic evaluation of the tumor.

5.2 Diagnostic Workup, Stratification, and Staging

- Clinical presentation
  - The clinical presentation is dictated by the tumor location with a quicker time course of symptoms usually seen for tumors of the pineal region due to obstruction of the cerebral aqueduct (aqueduct of Sylvius).
  - Pineal tumors: Increased intracranial pressure leading to nausea, vomiting, and headache is a common consequence of the anatomical association with the third ventricular system; Parinaud syndrome can also be seen and is caused by compression of the superior colliculus of the tectum leading to the triad of impaired upward gaze, decreased pupillary light reflex, and convergence nystagmus.
  - Suprasellar tumors: Often lead to endocrinopathies, most commonly diabetes insipidus (DI) and precocious/delayed sexual development, and visual disturbances such as bitemporal hemianopsia [7]. In a patient with DI and a radiologically visible pineal gland tumor, exquisite attention should be placed on identifying occult disease localized within the suprasellar region.
- Radiological workup
  - MRI of the brain with gadolinium (thin cuts through suprasellar and pineal region if possible) is typically first obtained when suspicion for an intracranial process is high in a child. Pure germinoma and NGGCT are radiologically indistinguishable and usually manifest as T1 hypointense and T2 hyperintense lesions [8].
  - MRI of the full spine with gadolinium should be obtained to identify any evidence of disseminated disease.
  - MRI of the orbits should be considered if optic chiasm or optic nerve involvement is suspected.
- Laboratory values
  - Laboratory values are critical in the workup of a suspected IGCT and include alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG) obtained from both serum and CSF. CSF cytology is also crucial in identifying those patients with disseminated disease.
  - Elevations of AFP (≥10 ng/mL or above institutional norm) and/or β-HCG (≥100 ng/mL) are indicative of a NGGCT and preclude the necessity of biopsy. Some pure germinomas (syncytiotrophoblastic variant) can secrete β-HCG without elevation in AFP, and in these cases, confirmatory biopsy is indicated [1].
  - Of note, lumbar puncture for CSF analysis should only be performed under safe conditions, thus may be deferred in cases of severe hydrocephalus. In these scenarios, CSF sampling can be obtained at the time of third ventriculostomy, though the gold standard for workup is CSF obtained by lumbar puncture.
- History of radiation as a diagnostic tool
  - IGCTs are particularly radio- and chemosensitive tumors. Historically, patients fitting the common demographic (i.e., adolescent males) with

suspected IGCTs were treated initially with radiation without biopsy, and if after 10–20 Gy demonstrated a radiological response, the diagnosis of IGCT was made. Of course, this diagnostic method has fallen out of favor, in part due to significant improvements in surgical technique reducing the risk associated with biopsy [8].

- Biopsy and third ventriculostomy
  - Surgery is typically reserved for pathologic confirmation of malignancy, which is requisite when tumor markers are non-diagnostic.
  - Of note, in patients who received neoadjuvant chemotherapy and do not demonstrate a complete response, second-look surgery, if safe, is usually recommended and may lead to surgical resection of any residual tumor.
  - In cases of moderate to severe hydrocephalus, a third ventriculostomy is often prudent whereby a passageway from the floor of the third ventricle to the prepontine cistern is created relieving obstruction and permitting CSF flow. Examination of the ventricular system by endoscopy with biopsy and CSF sampling can also be performed during this procedure [1].
- Staging
  - The modified Chang staging system is used to categorize patients into metastatic (M+) or nonmetastatic (M0) cohorts. Patients with localized disease and negative CSF cytology are considered M0, while all others are considered M+ [9].
  - M+ disease may include any of the following: leptomeningeal or intraventricular metastases on MRI, positive CSF cytology, metastatic disease noted on endoscopy, primary tumor arising within the brain or spine parenchyma, or extensive parenchymal infiltration.
  - Bifocal disease, although categorized both as M0 and M+ in the literature, is more often treated as M0 disease [4].
- Additional studies
  - Baseline opthalmologic, neurospychiatric, and endocrine function tests are also judicious for baseline evaluation.

5.3 Evolution of Radiation Fields

- Historically, pure germinomas were treated with craniospinal irradiation (CSI), often with an intermediate dose to the whole brain and a focal tumor boost achieving outstanding results (10-year overall survival >90%). However, the notable toxicity of CSI prompted exploration of methods of treatment de-escalation in the form of volume and dose reduction with or without chemotherapy augmentation [10, 11].
- The MAKEI 83, 86, and 89 trials found CSI to 36 Gy with a 50 Gy tumor boost (MAKEI 83/86), and ultimately CSI to 30 Gy with a 45 Gy tumor boost (MAKEI 89) resulted in excellent rates of relapse-free survival and overall survival affirming the feasibility of CSI dose reduction [12]. The SIOP CNS GCT 96 took dose reduction one step further showing minimal relapses were achievable with 24 Gy CSI followed by a tumor boost to 40 Gy in both M0 and M+ patients [9].

- A comprehensive review of patterns of relapse for 788 patients with localized pure germinoma treated with definitive radiation alone using varying radiation volumes published in 2005 revealed that the historical treatment of the full neuroaxis may have been excessive. In fact, isolated spinal failures after whole-brain radiation therapy (WBRT) or whole-ventricle radiation therapy (WVRT) were noted in only 3% of cases, with CSI reducing these spinal failures merely 2%. In contrast, focal irradiation alone yielded an unacceptably high rate of relapse at 23% after a median follow-up of 6.4 years [11]. In effect, the data buttressed support for volume reduction from CSI to WVRT but stopped short of focal irradiation alone, at least in the absence of chemotherapy.
- Complete substitution of radiotherapy with chemotherapy (carboplatin, etoposide, and bleomycin) was reported by Balmaceda et al. in 1996 and demonstrated an unacceptable 50% rate of disease progression/recurrence and even more concerning a 10% rate of treatment-related mortality [13].
- Interest then turned to utilizing chemotherapy as an augmentation strategy in effort to reduce the unacceptable number of failures seen with focal radiation alone. The French Society of Pediatric Oncology reported an event-free survival of 93.3% with a median follow-up of 32 months using a combination of chemotherapy (four cycles of alternating carboplatin/etoposide and ifosfamide/etoposide) with focal radiation to 40 Gy [14]. This same treatment algorithm was used in the SIOP CNS GCT 96 for 65 patients with pure germinoma in whom seven patients unfortunately relapsed with six of these occurring in the ventricular region (5-year progression-free survival of 88%) [9].
- In effect, volume reduction to involved-field radiation following chemotherapy was found to lead to unacceptably high rates of ventricular failure for pure germinoma demonstrating a cautionary lower threshold for radiation volume reduction. Thus, having identified a suitable reduced radiation volume (e.g. WVRT), attention has been swung to identifying safe methods of radiation dose reduction. Off protocol, the standard treatment for pure germinoma is chemotherapy with carboplatin and etoposide followed by WVRT to 21 Gy with an involved field boost of 30 to 36 Gy.
- Non-germinomatous germ cell tumors carry an inferior prognosis. ACNS0122 utilized 36Gy CSI with involved field radiation to 54 Gy following six cycles of chemotherapy, and this resulted in a 2-year PFS and OS of 84.4 ± 4% and 93 ± 3%, respectively.
- ACNS 1123 explored radiation dose reduction in both pure germinomas and NGGCTs. In those patients with pure germinomas who obtain a complete response (CR) following four cycles of carboplatin and etoposide, WVRT to 18 Gy with a primary tumor boost to 30 Gy (150 cGy fractions) was delivered. For those with less than a CR, treatment was 24 Gy WVRT followed by a 12 Gy primary tumor boost. For NGGCT cases, neoadjuvant chemotherapy with six cycles of alternating carboplatin/etoposide and ifosfamide/etoposide was delivered. In those who obtained a radiological CR or partial response and normalization of tumor markers, WVRT to 30.6 Gy with a primary tumor boost to 54 Gy (180 cGy fractions) was delivered. This study met early stopping rules for the NGGCT arm, and at present treatment per ACNS 0122 with CSI followed by

involved field radiation is recommended or discussion with a member of the COG CNS germ cell tumor committee is recommended.
- For rare cases of pure germinoma that arise in the basal ganglia or outside of the ventricular system, WBRT is favored over WVRT.

5.4 Treatment Paradigm

- Pure germinoma
  - Localized pure germinoma:
    Neoadjuvant chemotherapy with two to four cycles of carboplatin and etoposide followed by reduced dose radiotherapy is currently the standard of care in the United States. If the patient achieves a CR, recommendation is for 21 Gy WVRT with a primary tumor boost to a total dose of 30–40 Gy. Radiation should begin 3–6 weeks following the last dose of chemotherapy. If a CR is not achieved, verification of pure germinoma histology with a second-look surgery, if safe, is pursued. This is followed by a primary tumor boost to 45–50 Gy [1]. Table 5.2 lists IGCT management recommendations including treatment modality, target considerations, and dose.
    Definitive higher dose radiotherapy is an acceptable alternative for those patients unable to receive neoadjuvant chemotherapy. For example, in cases of suprasellar tumors with associated DI, electrolyte management during chemotherapy may be excessively challenging [15]. In these cases, 24 Gy WVRT is delivered followed by a primary tumor boost to 45–50 Gy.

Table 5.2 IGCT dose fractionation and target management considerations

	Treatment modality	Chemotherapy	Initial target considerations	Initial target RT dose	Primary tumor boost RT dose
Pure germinoma (M0)	RT alone	N/A	WVRT	24 Gy	45–50 Gy
	Chemo + RT[a]	2–4 cycles carboplatin/etoposide	WVRT	21 Gy	30–40 Gy (CR), 45–50 Gy (non–CR)
Pure germinoma (M+)	RT alone	2–4 cycles of carboplatin/etoposide	CSI	24 Gy 21 Gy	45–50 Gy 30–36 Gy (CR)
NGGCT	Chemo + RT[a]	6 cycles of alternating carboplatin/etoposide and ifosfamide/etoposide	CSI	36 Gy	54 Gy

RT radiation therapy, *WVRT* whole-ventricle radiation therapy, *CSI* craniospinal radiation, *M0* without neuroaxis dissemination, *M1* with neuroaxis dissemination, *NGGCT* non-germinomatous germ cell tumor

[a]Response following neoadjuvant chemotherapy will dictate whether second-look surgery is pursued. Pure germinomas achieving a radiological CR and NGGCT achieving resolution of tumor markers and a radiological CR/PR will typically continue on to radiation therapy without surgical intervention

  - Disseminated pure germinoma:
    In cases of disseminated disease (M+), patients are treated with CSI to 24 Gy again followed by a primary tumor boost to 45–50 Gy.
- Non-germinomatous germ cell tumors
  - Due to their poorer prognosis, NGGCTs are managed more aggressively with modern treatment based on the ACNS 0122 protocol. Results with radiation alone have historically been poor (20–40% local control); hence combined modality treatment with chemotherapy is standard [16, 17]. Neoadjuvant chemotherapy in the form of six cycles of alternating carboplatin/etoposide and ifosfamide/etoposide is recommended. Patients are then restaged with MRI and tumor markers. Those with a CR are then treated with CSI to 36 Gy followed by a primary tumor boost to 54 Gy. Those without a CR may benefit from a second-look surgery with resection if feasible. Lower doses/decreased volumes may be appropriate in certain clinical situations but should be discussed with families and/or COG CNS GCT committee members.

5.5 Simulation and Daily Localization

- Treatment techniques include standard three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and proton therapy.
- All patients should undergo contrast-enhanced MRI (1–3 mm slices), both pre- and post-chemotherapy, if applicable. Detailed delineation of the ventricular system in this disease is critical; thus a thin-cut T2 MRI sequence, such as a CISS or SPACE sequence, may be helpful for planning purposes.
- Planning CT scan (≤3 mm slices; preferable 1.25 mm) with or without contrast should be obtained with creation of an aquaplast mask of the head (from the top of head to thoracic inlet) in the supine position with patient arms at their sides. In cases of CSI, setup will be dictated by the capabilities of the treating facility and patient characteristics and may be simulated either in the prone or supine position. CSI cases will require utilization of body immobilization, such as a Vac-Lok bag or Alpha Cradle.
- Patients with IGCTs, if very young, may require general anesthesia for simulation and treatment; thus involvement of the anesthesiologist during simulation to ensure a safe and secure airway during mask formation is critical.
- Daily localization is usually achieved with daily portal images (MV or kV) or daily/weekly cone-beam CT scans but is again dependent on the image guidance capabilities of the treating center.

5.6 Radiation Technique and Target Delineation (See Figs. 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, and 5.8)

- Whole-ventricle radiation therapy
  - The planning CT scan should be fused with the following: [1] pre-chemotherapy T1 and T2 MRI for best delineation of the primary tumor and [2] most recent T2 MRI for delineation of the whole-ventricle volume (WVV). Identification

of the ventricular system is best visualized on the T2 images, but verification of proper fusion and ventricle locations on the planning CT is crucial. Table 5.3 lists recommended target volume definitions and descriptions.

– Boost gross tumor volume (GTV) should first be delineated using the pre-chemotherapy MRI sequence with optimal tumor visualization. GTV should also include sites of residual disease at the time of treatment planning. GTV should exclude normal tissues displaced by pre-chemotherapy tumor, with the exception of areas of parenchymal invasion, which should be included in the GTV. Residual calcifications in pineal gland tumors can often be best visualized by CT.

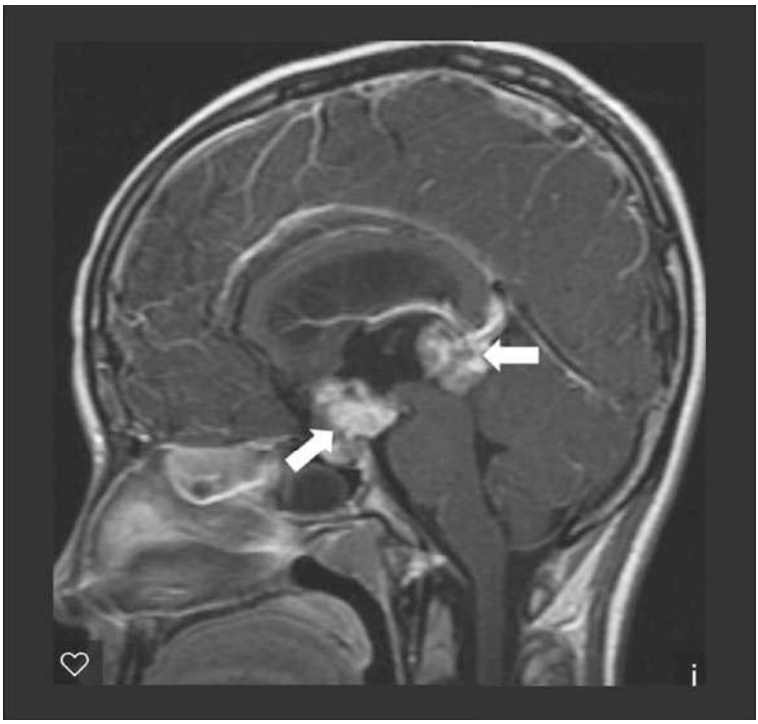

Fig. 5.1 Multiple midline tumor with suprasellar and pineal involvement (white arrows). Most multiple midline tumors are pure germinomas. Treatment includes whole-ventricle radiation followed by an involved field boosts

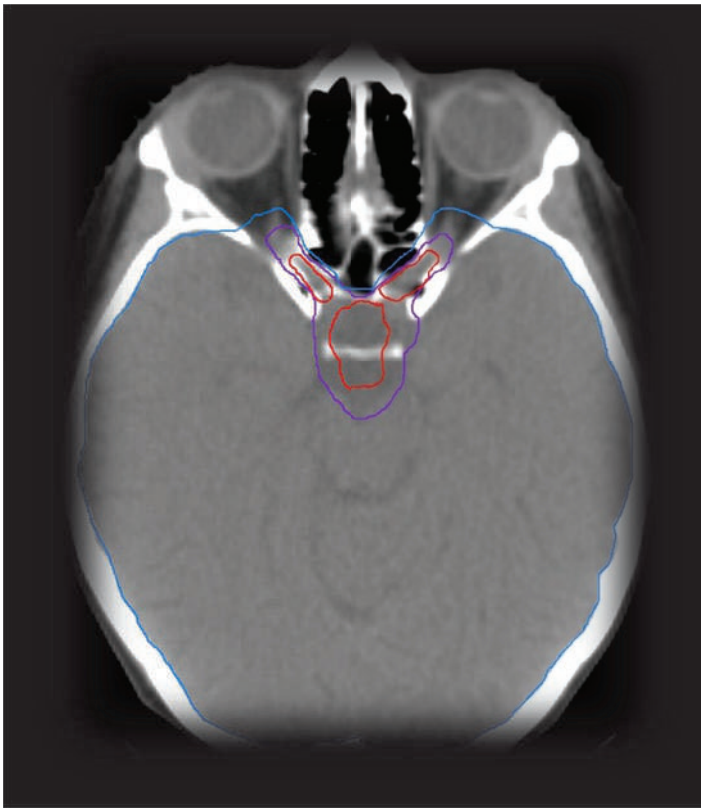

Fig. 5.2 Involved field and whole-brain volume for a child with a non-germinomatous germ cell tumor. GTV involved field in red, and CTV involved field in purple. Whole-brain volume is shown in blue not the extension into the optic nerves. This involved field volume is an example one that extends outside of a standard CSI or WVV underscoring the importance of contouring the involved field at the time of planning CSI or WVV

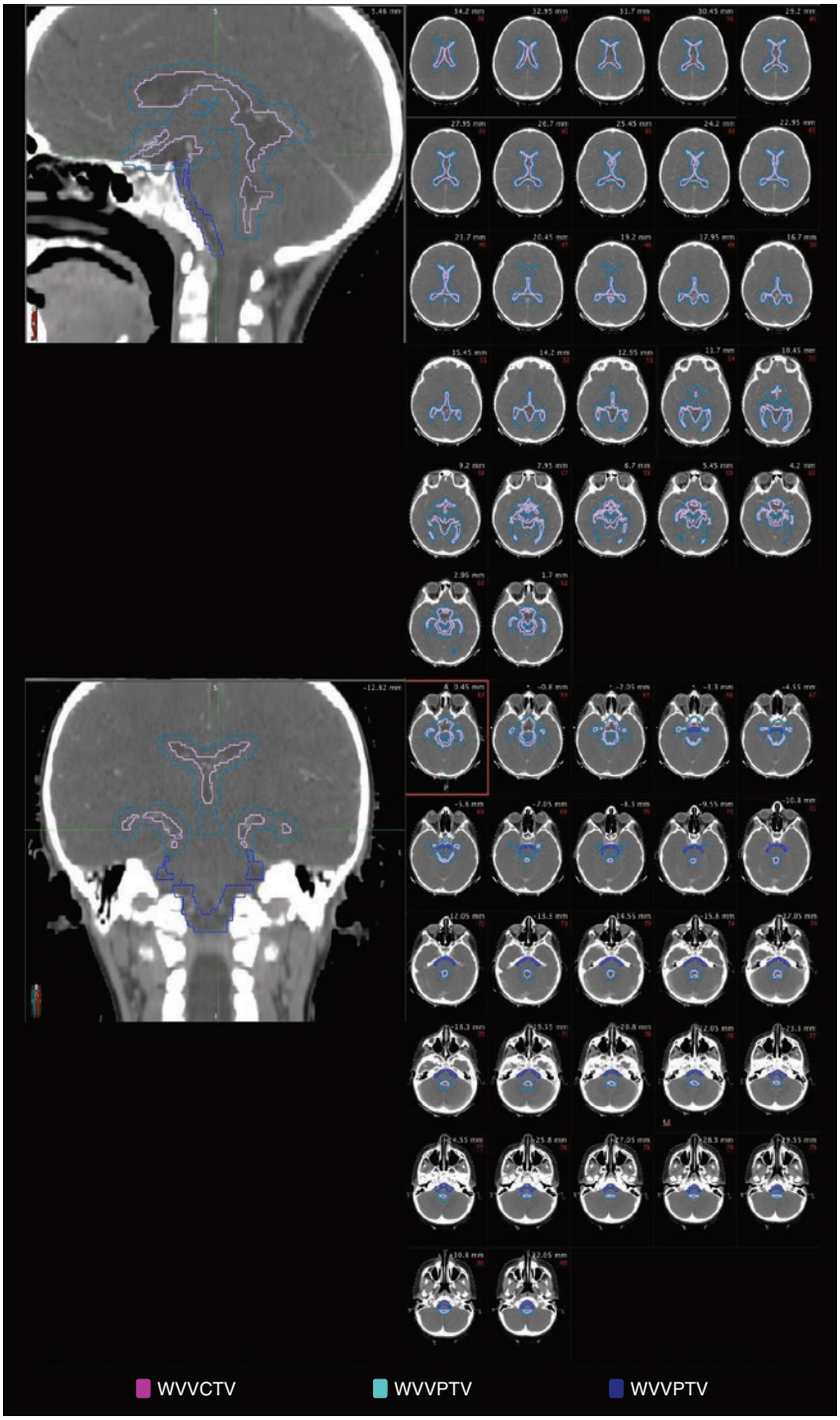

Fig. 5.3 Whole-ventricle volumes per contouring guidelines

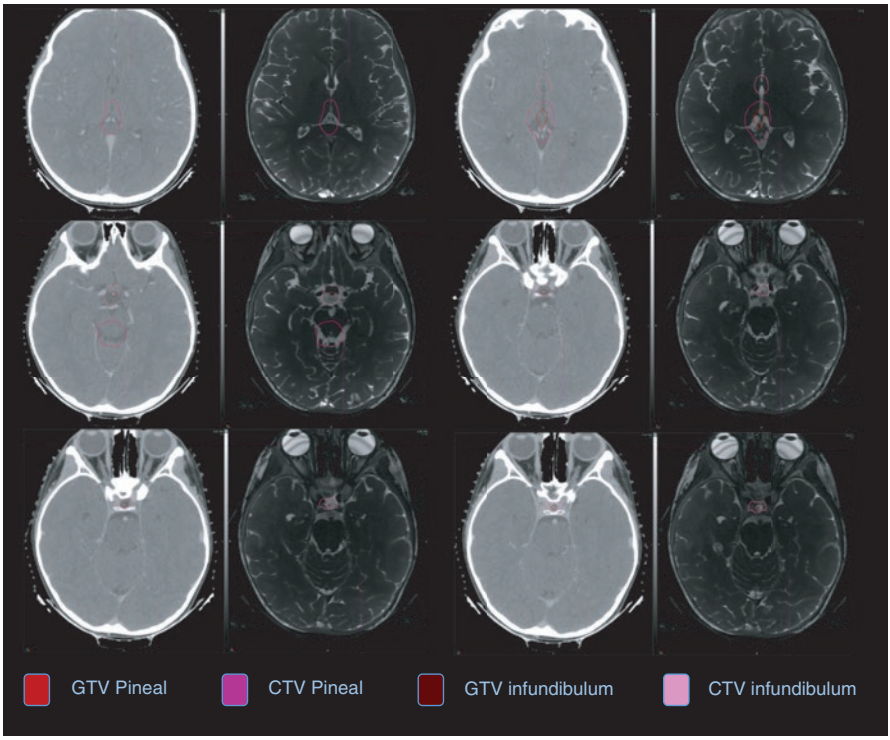

Fig. 5.4 Contours of the involved field boost for a multiple midline tumor. GTV in red. CTV in magenta. Most children receive neoadjuvant chemotherapy (all children with NGGCT and most with pure GCT). The GTV following neoadjuvant chemotherapy should include any area that was in contact with the original tumor volume, and any areas suspicious for residual disease. If tumor infiltration versus displacement is suspected, the volume should include the area of brain with potential infiltration. For cases treated with RT alone, the GTV will be the tumor volume present at the time of planning. Neoadjuvant chemotherapy typically allows for a decreased dose and volume to the area of primary disease as most tumors will have a complete to near complete response to therapy

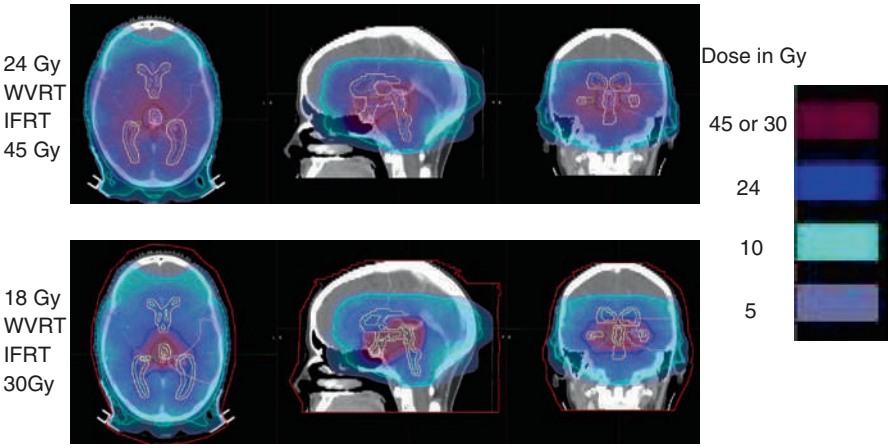

Fig. 5.5 Comparison plans of radiation alone for a bifocal germinoma versus treatment with induction chemotherapy followed by reduced dose radiation on protocol ACNS1123. After four cycles of carboplatin and etoposide and a complete response/minimal residual disease, 18 Gy (rather than 24 Gy) is delivered to the whole-ventricle volume followed by a boost dose to 30 Gy (rather than 45–50 Gy)

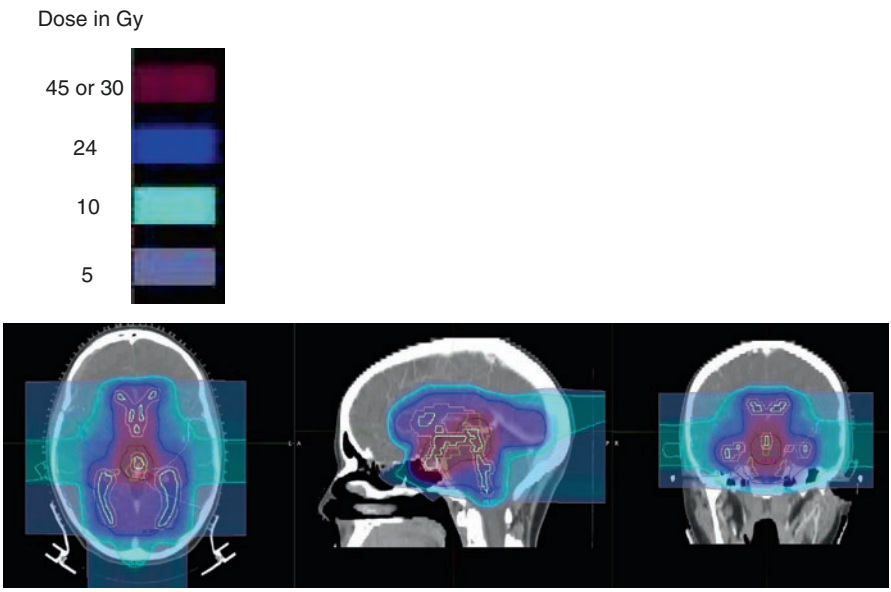

Fig. 5.6 WVV plus boost to both suprasellar and pineal gland regions for a multifocal pure germinoma treated with radiation alone. If neoadjuvant therapy is delivered and a complete response is achieved, reduced doses of RT are used

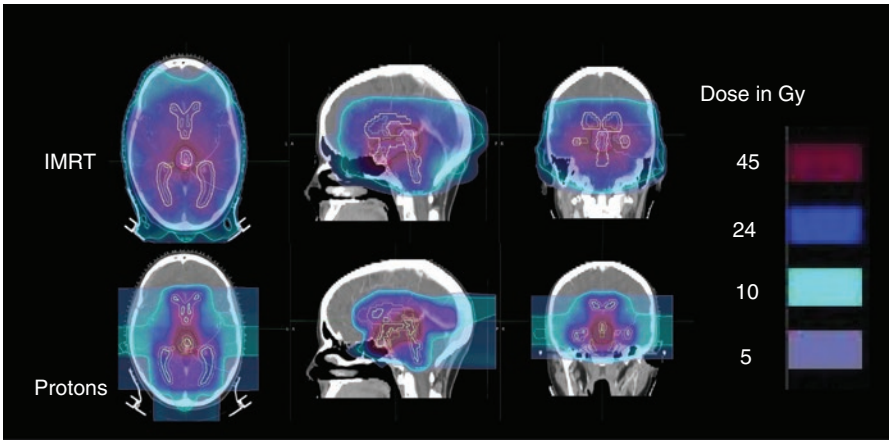

Fig. 5.7 Comparison plans of IMRT versus proton beam for whole-ventricle irradiation followed by an involved field boost. Both are highly conformal plans, however the proton plan delivers a lower integral dose

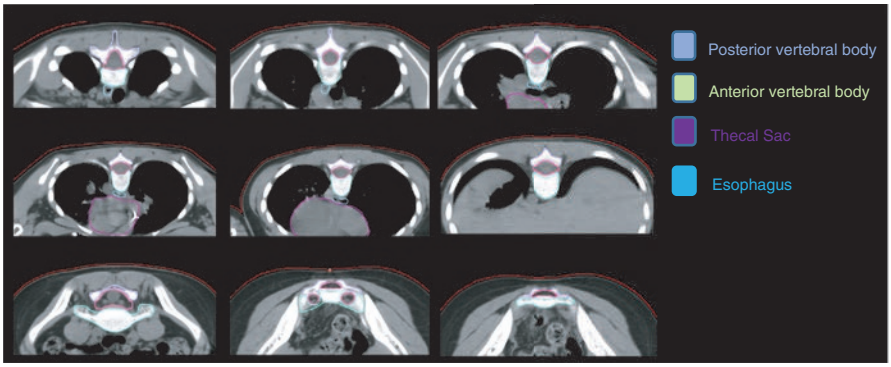

Fig. 5.8 Contours of the thecal sac for CSI planning. CSI is recommended for NGGCT and metastatic pure GCT. For 3D conformal RT, contours may not be necessary. For IMRT, VMAT, or protons, contours must be designed carefully. Attention should be made to deliver an even dose to the vertebral bodies for growing children. Many children diagnosed with GCT are older and may have achieved adequate musculoskeletal development such that partial treatment of vertebral bodies is acceptable

- The boost clinical target volume (CTV) is created by expanding the boost GTV by 5 mm. Ensure the boost CTV is defined up front to ensure this volume is encompassed by the WVVCTV, defined below. Boost PTV is then defined as a 3 or 5 mm expansion from boost CTV and is dependent on daily image guidance at the treating institution.
- The WVV should include the lateral, third, and fourth ventricles with particular attention paid to inclusion of the pineal cisterns and suprasellar region.

Table 5.3 Pure germinoma recommended target volumes

Target volume	Definition and description
Boost GTV	Boost GTV is defined as the pre-chemotherapy primary tumor and sites of post-chemotherapy residual disease
Boost CTV	Boost CTV is defined as a 5 mm expansion from boost GTV
Boost PTV	Boost PTV is defined as a 3 or 5 mm expansion from boost CTV
WVV	WVV should include the lateral, third, and fourth ventricles with particular attention paid to inclusion of the pineal cisterns and suprasellar region as defined by the T2 sequence of the most recently obtained MRI. Inclusion of the prepontine cistern within the WVV is recommended for large suprasellar tumors or those patients who have undergone third ventriculostomy
WVVCTV	WVVCTV includes the boost CTV and WVV
WVVPTV	WVVPTV is defined as a 3 or 5 mm expansion from WVVCTV

WVV whole-ventricle volume

  - Of note, inclusion of the prepontine cistern within the WVV is recommended for large suprasellar tumors or those patients who have undergone third ventriculostomy.
  - The WVV clinical target volume (WVVCTV) is defined as the WVV plus the boost CTV. This volume is expanded by 3 or 5 mm dependent on daily localization to obtain the WVV planning target volume (WVVPTV).
  - Of note, a 5 mm expansion for WVVPTV is preferred if daily image guidance is not utilized.
- Craniospinal irradiation
  - A detailed discussion of CSI may be found in the medulloblastoma section.
  - Specific dose recommendations for CSI have been discussed above and are found in Table 5.3.
- Proton-based planning vs. IMRT-based planning
  - Proton therapy for the treatment of pediatric malignancies has been widely adopted throughout the United States, and essentially its adoption has been spurred by the presumptive reduction in late toxicity afforded by proton therapy.
  - Reduced radiation dose is of particular importance in the pediatric population where long-term survival can lead to concerning late toxicities. For germinoma, however, doses are relatively low.
  - Dosimetric improvements with proton therapy relative to photon therapy in the sparing of the whole brain, temporal lobes, and non-chiasm optic structures have already been documented in the literature, but there is no clinical data at present documenting improvement over IMRT or 3D conformal photon therapy [18]. Table 5.4 demonstrates dose constraints for commmon organs at risk.

Table 5.4 Dose volume histogram recommended constraints (dependent on total dose)

Target structure	DVH constraint
Cochlea (single)	D50% < 20–30 Gy
Brainstem	Max point dose <54 Gy; Mean < 53 Gy
Optic chiasm/ nerves	Max point dose <54 Gy; keep below 50.4 if possible: may be higher for suprasellar NGGCT

DVH dose volume histogram

5.7 Late Toxicity

- Due to the high curability of GCT, close follow-up is critical to identify and treat late toxicity sequelae.
- SEER data indicated GCT survivors have a tenfold increased risk of all-cause mortality, which is driven by a significant increased risk in death from cerebrovascular accidents [19]. Additionally, 25-year follow-up estimates death due to cancer or secondary malignancies at 16% and 6%, respectively.
- Endocrinopathies including hypothalamic obesity, pituitary dysfunction, and growth hormone deficiency may be observed particularly if the primary tumor was localized to the suprasellar region [20].
- Neurocognitive effects can be observed and include deficiencies in working and visual memory, and information processing which have been noted to decline over time [21].

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Craniopharyngioma

6

Anita Mahajan

Contents

6.1 Background

As Harvey Cushing stated, craniopharyngiomas (CPs) are the most "baffling" tumors [1]. Surgery and radiation therapy (RT) offer good local control; however, patients are at risk of a wide variety of tumor- and treatment-related morbidities that affect quality of life and long-term survival [2–5]. Management of CP requires multidisciplinary management with meticulous attention to toxicity reduction. Advances in RT technology lead to better precision and accuracy in treatment planning and delivery that can contribute to reducing toxicities in these vulnerable patients.

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https://doi.org/10.1007/978-3-319-69140-4_6

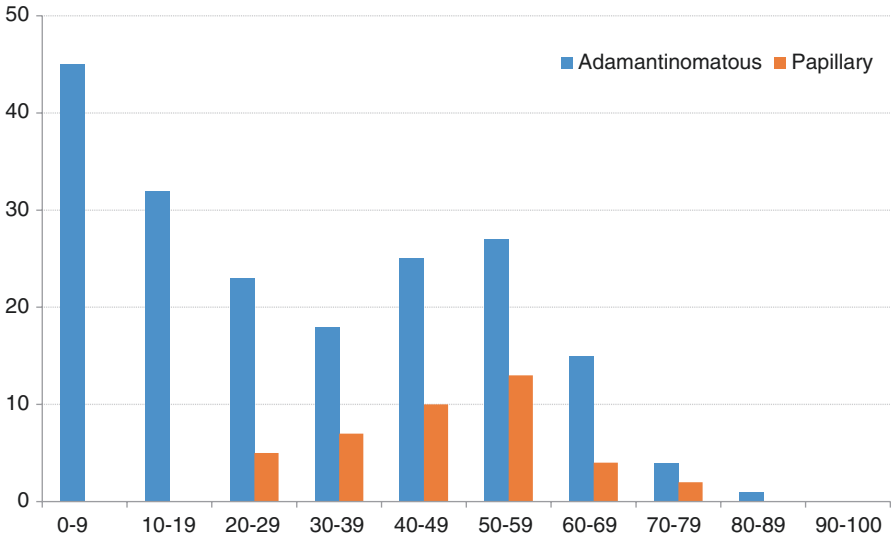

Fig. 6.1 Age distribution of craniopharyngioma subtypes [6]

6.1.1 Epidemiology

- The incidence of CPs is bimodal with a first peak between ages 5 and 14 years and a second peak between 50 and 60 years.
- Males and females are equally affected. CPs constitute 6–10% of all pediatric brain tumors and 54% of all suprasellar masses in children.

6.1.2 Histologic Subtypes

- CPs are WHO grade I tumors which are thought to arise from the epidermoid embryological remnants of adenohypophyseal (Rathke's) pouch that extends from the ectodermal roof to the stomodeum toward the neurohypophysis in the infundibulum-hypophyseal area.
- The cells lining this remnant are thought to give rise to the two subtypes of CP (Fig. 6.1): adamantinomatous CP (ACP) and papillary CP (PCP) [6]. The ACP subtype occurs primarily in childhood and may be from embryonic cell rests of enamel organs along the infundibulum. The PCP subtype occurs almost exclusively in adults and may represent metaplasia within the cellular remnants of Rathke's cleft.
- ACPs are characterized by cystic and solid components with associated calcifications. The cyst wall has three layers: basal layer, internal stellate cells, and the characteristic palisading keratinizing squamous cells ("wet keratin"). Gliosis with Rosenthal fibers, often seen at the infiltrative surface, also distinguishes ACP from PCP. These microscopic fingerlike projections within the gliotic interface of the surrounding brain can make surgical resection of ACP more challenging than for PCP [7–9].

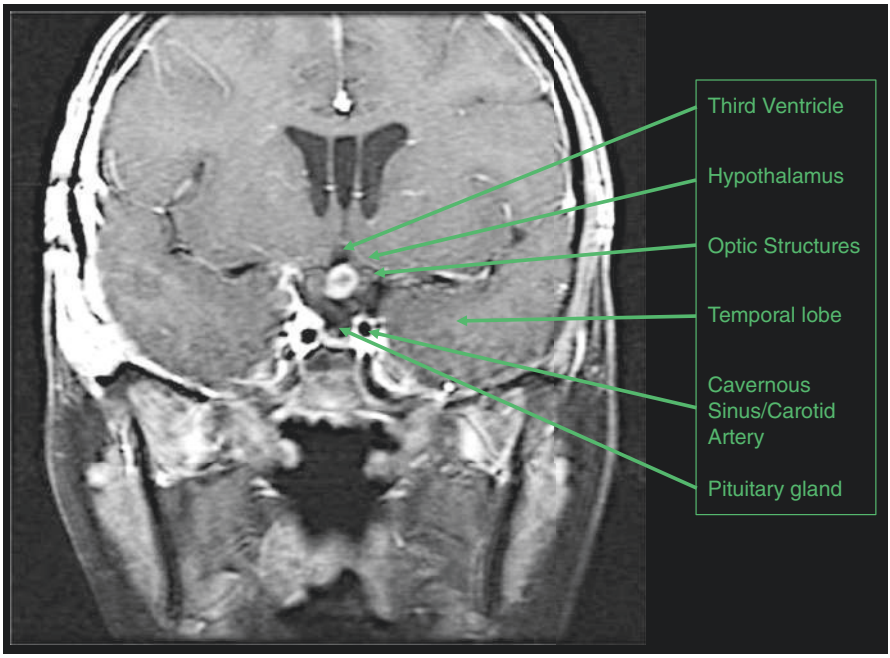

Fig. 6.2 Coronal T1-weighted contrast-enhanced MRI scan demonstrating normal structures in close proximity to small residual craniopharyngioma

- The papillary variant of CP is less likely to be calcified, may be easier to separate from the surrounding brain, is less cystic, has no "wet keratin," and has stratified squamous epithelium with papillary projections of epithelial cords.
- ACPs and PCPs have now been found to have a high incidence of CTNNB1 and BRAF mutations, respectively. These findings are now being investigated for novel management approaches [10].

6.2 Presenting Findings and Anatomic Relationships

- Patients will present with symptoms associated with mass effect on any of the critical structures in proximity to the tumor (Fig. 6.2). A patient may present with several findings including endocrine deficiencies (50–80%, more common in children), visual disturbances (60–85%, mostly in adults), cognitive and personality changes (50%), and signs related to increased intracranial pressure (due to compression or invasion of the third ventricle).
- CPs are often centered in the suprasellar area but can expand in different directions [11, 12]. They are often classified and managed based on the relationship to the optic chiasm: pre-chiasmatic, retro-chiasmatic, or suprachiasmatic. The involvement of the infundibulum and third ventricle should be assessed. Large CPs can extend into the middle cranial fossa with compression of the temporal lobes or into the prepontine cistern with compression of the brainstem.

- At initial presentation, patients should have assessment of intracranial pressure, vision, and endocrine function in order to optimize management strategy.

6.3 Imaging

- Over 50% of CPs have a pathognomonic appearance on CT and MRI imaging which demonstrate a large intrasellar and suprasellar heterogeneous mass.
- Typically ACPs have calcifications visible on non-contrast CT imaging. The solid component and cyst wall will enhance after contrast administration. On T1-weighted MRI imaging, the cyst is hyperintense, homogeneous, and well delineated. The solid component is often isointense with some heterogeneity. After contrast administration, the cyst is usually isointense with the enhancing ring, and the solid component will be hyperintense to the surrounding tissue. On unenhanced and enhanced T1-weighted sagittal images, a compressed pituitary gland can often be identified.
- PCPs typically have a more uniform appearance on CT and MRI imaging.

6.4 Surgery

- The role of surgery has evolved over time. The immediate goals are to relieve elevated intracranial pressure, to reduce mass effect on the optic apparatus, and to establish diagnosis. The surgical approach is customized to the size and location of the CP and may require more than one surgical procedure. The more common approaches include pterional for suprasellar and pre- and post-chiasmatic access, subfrontal for 3rd ventricular and pre-chiasmatic tumors, and transpetrosal for large retro-chiasmatic tumors [13]. Of note, a transsphenoidal approach may not be feasible in children with small or absent sphenoid sinuses.
- Cyst aspiration alone to decompress the optic apparatus often results in reaccumulation of the cyst in approximately 3–6 months.
- A complete resection is associated with local control rates of 70–90%. Surgical morbidities include hypothalamic injury with hypothalamic obesity and/or cognitive dysfunction (50–90%), diabetes insipidus, optic apparatus injury, or hemorrhage (1–12%). If complete resection is feasible with acceptable risks, then that may be the most desirable course of action. If a complete resection is associated with significant risks, more common with ACPs due to their infiltrative "sticky" margins, then a subtotal resection followed by radiotherapy (RT) is more appropriate [14–18].

6.5 Radiotherapy

- Radiotherapy is effective for the management of residual, recurrent, or progressive CPs [19]. Early experience from the Royal Marsden suggested 10-year progression-free survival (PFS) and overall survival (OS) rates of 80% and 77%. Modern techniques have resulted in disease control of 79–84%. Of note, a CP

cyst could reaccumulate temporarily after RT with eventual stabilization with conservative management [20].
- With MRI planning, highly conformal RT techniques, image guidance, and adaptive therapy, the goal to treat only the areas at risk with minimal dose to the adjacent normal structures to reduce toxicity is achievable [21, 22].

6.5.1 Radiotherapy Techniques

- Modern RT delivery technologies including stereotactic setup, image guidance, in-room volumetric imaging, robotic couches, and high dose rate delivery systems justify reduction in intracranial planning target volumes (PTV) to as little at 2 mm [23].
- Intensity-modulated RT (IMRT) and volumetric arc RT (VMAT) allow a highly conformal high dose volume and have been shown to be effective for CP [24–26]. Similarly, proton therapy (PRT) provides the opportunity to reduce the low dose volume and integral dose [27–29]. Intensity-modulated proton therapy (IMPT) may allow both a highly conformal high dose and a low volume low dose for CP [30, 31].
- All of these technical advances can contribute to reduction in RT-related toxicities by reducing radiation dose to normal tissues in proximity to the primary tumor [32]. These techniques should be considered when treating children with CP to allow the best outcomes, and their use requires consistent evaluation and validation.

6.5.2 Planning and Simulation

- Patient position and immobilization should be customized based on treatment technique. Since the vast majority of CPs are treated with fractionated regimens, a high-quality thermoplastic mask with or without fiducials should be formed to allow for sedation if needed with appropriate airway management, reproducibility, comfort, and ease of use. If using arc-based treatments, a strategic head tilt may allow dose reduction to the orbital structures.
- Once appropriate positioning has been achieved, a high-resolution CT scan with slice thickness of 1–1.5 mm through the cranial contents should be obtained. Thin-slice images will allow better visualization of small intracranial structures such as the optic nerves, hippocampus, and cochlea.

6.5.3 Image Fusion

- In the ideal situation, all available diagnostic imaging (MRI and CT) should be evaluated for the pre- and postoperative extension of disease.
- Review of the imaging, operative report, and discussion with the neurosurgeon will augment the delineation of high- and low-risk disease volumes and help distinguish postoperative changes and normal structures.
- A pre-RT high-resolution volumetric planning MRI (1–1.5 mm T1 contrast and T2 weighted in treatment position, if possible) should be obtained to allow better

delineation of normal structures, gross disease, and the postoperative surgical bed adjusted for postoperative anatomic shifts.

- The pre-, post-, and planning MRIs should be fused with the planning CT scan with the fusion optimized in the tumor area. This method allows visualization of normal and target structures on MRI and/or planning CT. Before planning, all structures should be verified on the planning CT to ensure spatial integrity.

6.5.4 Normal Tissue Delineation

- All normal structures in the tumor vicinity should be delineated. If the structure is visible on the planning CT (e.g., optic nerves), then it should be delineated based on then CT images rather than the fused MRI scan to ensure spatial accuracy.
- Typical normal structures to be considered include the eyes, lens, lacrimal glands, optic nerves, optic chiasm, optic tracts, hippocampi, temporal lobes, brainstem, and whole brain. Please refer to Chap. 1 for normal CNS contouring guidelines.
- The optic chiasm delineation can be challenging for many CPs due to its relationship to the tumor. Even if the chiasm cannot be distinguished from the tumor, one should estimate the chiasm location relative to the tumor to avoid dose hotspots on the possible location of the optic apparatus.
- For CP, delineation of the hypothalamus and pituitary gland is less relevant since the tumor has direct involvement of these structures and they are often incorporated into the tumor volumes.

6.5.5 Gross Tumor Volume Delineation

- The gross tumor volume (GTV) should be delineated based on the preoperative, postoperative, and pre-RT imaging with consideration of information from the operative note and neurosurgical input.
- The GTV will include residual enhancing nodules, cysts, and areas of macroscopic residual disease that is reported by the surgeon but not necessarily seen on imaging. It is imperative to evaluate the preoperative tumor characteristics to appreciate possible residual disease that does not have typical imaging appearance or enhancement.
- Because 15% of cystic tumors can enlarge during RT, weekly verification CT or MR imaging can confirm appropriate tumor coverage. For each verification scan, the GTV coverage is redelineated on the new scan, and coverage is objectively assessed. If tumor coverage is inadequate (GTV < 95% and/or PTV < 90%), then an adaptive approach with replanning is performed. Location of critical normal structures should also be evaluated subjectively. As technology and efficiency improve, this process will likely become more automated [33].

6.5.6 Clinical Target Volume

- The clinical target volume (CTV) should encompass any areas of microscopic residual disease. Historically, 1–2 cm CTV margins were added to the GTV; however, this expansion incorporates many normal organs that do not harbor tumor cells.
- Because CPs are not grossly invasive even though ACP can have microscopic fingers in the gliotic capsule, one can restrict the CTV to the surgical bed, adjusted for postoperative anatomic shifts. Using the proposed logic, with modern techniques of MRI-based planning and a multidisciplinary approach, volume reduction of critical structures such as the temporal lobes, bilateral hippocampi, brainstem, and optic nerves is feasible.

6.5.7 Planning Target Volume

- As noted above, the PTV can be reduced to 2–3 mm when using modern treatment delivery techniques and good immobilization for fractionated approaches.
- Table 6.1 summarizes recent literature that defines tumor delineation practices.

Table 6.1 Summary of published literature that included pediatric patients and that describes tumor volume delineation parameters

Authors	Luu—2006	Fitzek—2006	Jalali—2005	Merchant—2006	Coombs—2007
Years	1991–2000	1981–1988	1999–2002	1998–2003	1989–2006
Pt number	16	15 (5 pediatric)	13	28	40 (adult + pediatric)
Technique	PRT—3D	3D PRT/XRT	3DCRT/SCRT	3D XRT	FSRT
Volume	CT	CT	CT/MRI	CT/MRI	CT/MRI
Dose	50.4–59.4 CGE	53.4–67.5 CGE	54 Gy	54–55.8 Gy	52.2 Gy
GTV		Tumor bed, residual	Tumor bed, residual	Tumor bed, residual	Residual
CTV	3 mm		5 mm anat confined	10 mm anat confined	Same as GTV
PTV			5 mm/2 mm	3–5 mm	2 mm
Verification	Daily KV		MR/CT ≥ 1 time	MRI wk. 3 & 5	
Follow-up	Mean 60.2 mo		Median 25 mo	Median 36.6 mo	Median 98 mo
Local control	14/15 controlled	5y 93%, 10y 85%	3y 90.3%	10y 100%	
OS	3 deaths	5y 93%, 10y 72%	0 died	1 died	5y 97%, 10y 89%

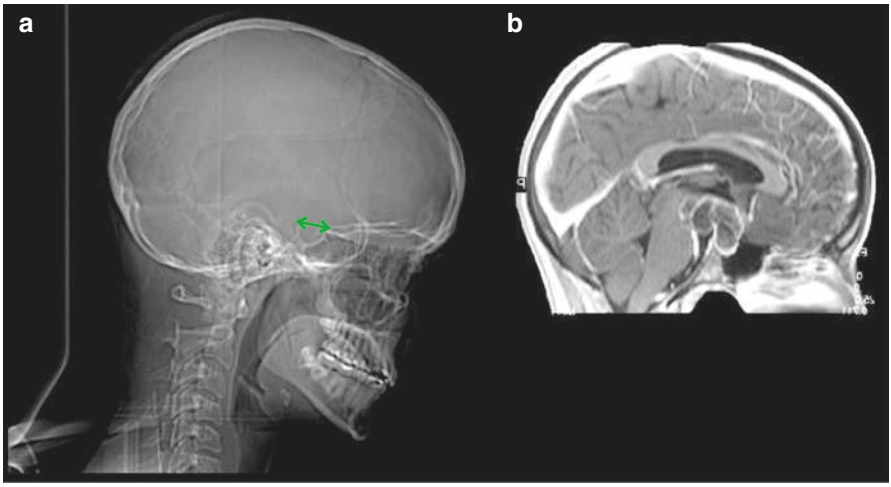

Fig. 6.3 Case 1. (**a**) Lateral topogram with arrow demonstrating an enlarged sella of 13.5 mm. (**b**) Preoperative midline sagittal T1 contrast MRI demonstrating sella, suprasellar, retro-chiasmatic, and prepontine location of cystic tumor

Case 1 Subtotal Resection (Figs. 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, and 6.11) An 18-year-old female with a 2-year history of intermittent headaches associated with vomiting. She then developed poor vision. An ophthalmologist noted evidence of increased intracranial pressure. She was found to have an elevated sodium and urine output suggestive of pre-existing diabetes insipidus, but no other preoperative endocrine deficiencies were noted. She was ultimately diagnosed with a papillary craniopharyngioma.

6.5.7.1 Imaging

CT: Enlarged sella measuring 13.5 mm. Suprasellar lesion with no robust calcifications.

MRI: Complex cystic sellar, suprasellar, and retrosellar mass with extension into the third ventricle. No evidence of hydrocephalus.

6.5.7.2 Operative Procedure

Right orbito-cranial approach to anterior and middle skull base with resection of anterior and middle intradural skull base tumor. The tumor entered between the optic nerves and was debulked. The pituitary stalk was not seen. The tumor was resected from the right ocular motor nerve, medial temporal lobe, right posterior cerebral artery, left optic nerve, left carotid artery, left posterior communicating artery, left posterior cerebral artery, off the front of the brainstem, superior to the basilar bifurcation, from under the chiasm, and off the anterior floor of the hypothalamus and forms the basis of the CTV.

The tumor was markedly adherent to the right posterior communicating artery, posterior floor of the hypothalamus, and at the top of the interpeduncular cistern. Some tumor and tumor capsule was left in these locations which is the basis for the GTV.

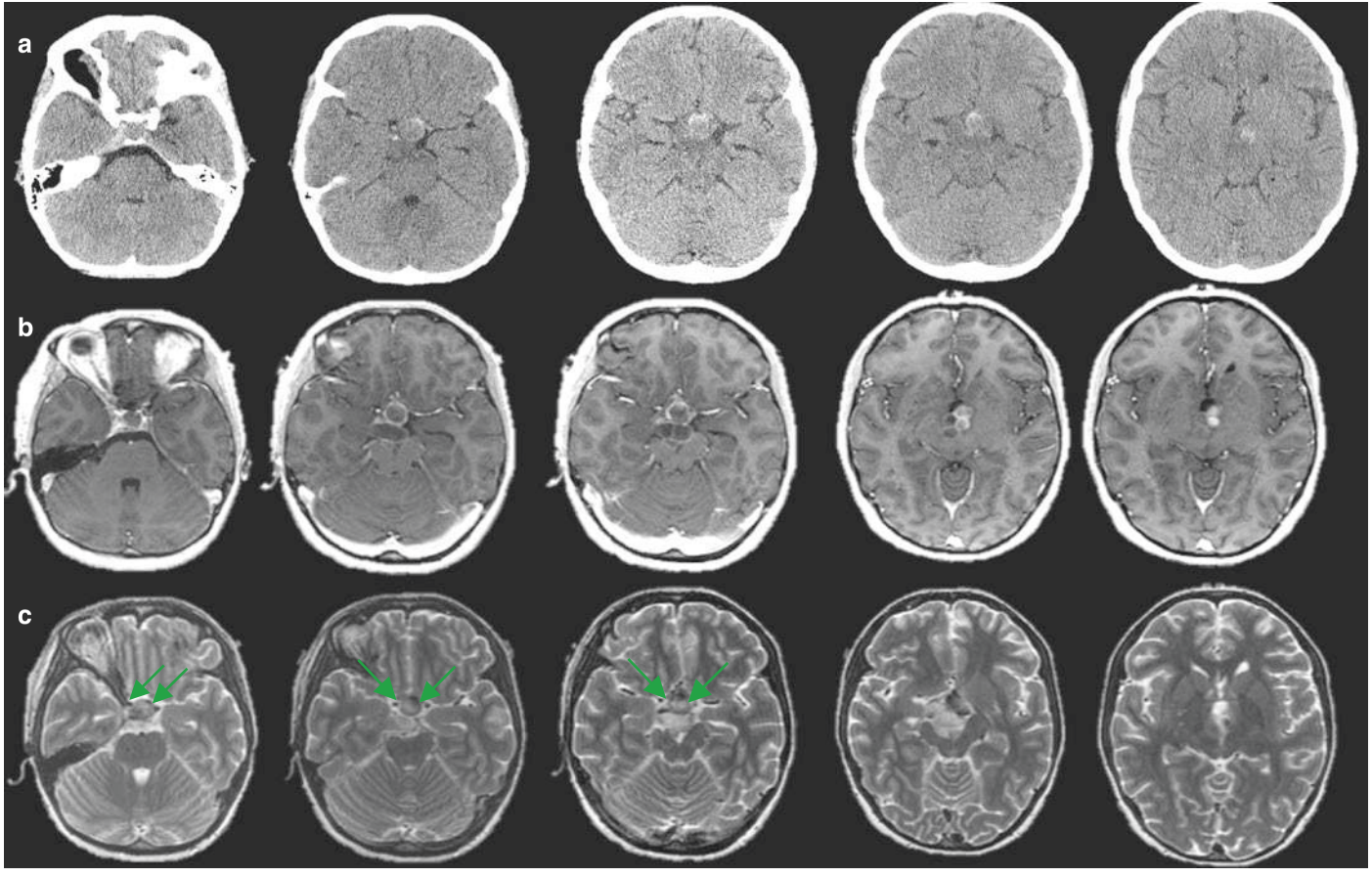

Fig. 6.4 Case 1. Preoperative axial imaging. (**a**) Non-contrast CT scan revealing calcifications within the tumor. (**b**) T1-weighted contrast-enhanced MRI revealing multiloculated cyst wall enhancement and isointense contents. (**c**) T2-weighted MRI scan highlighting location of optic chiasm indicated by arrows

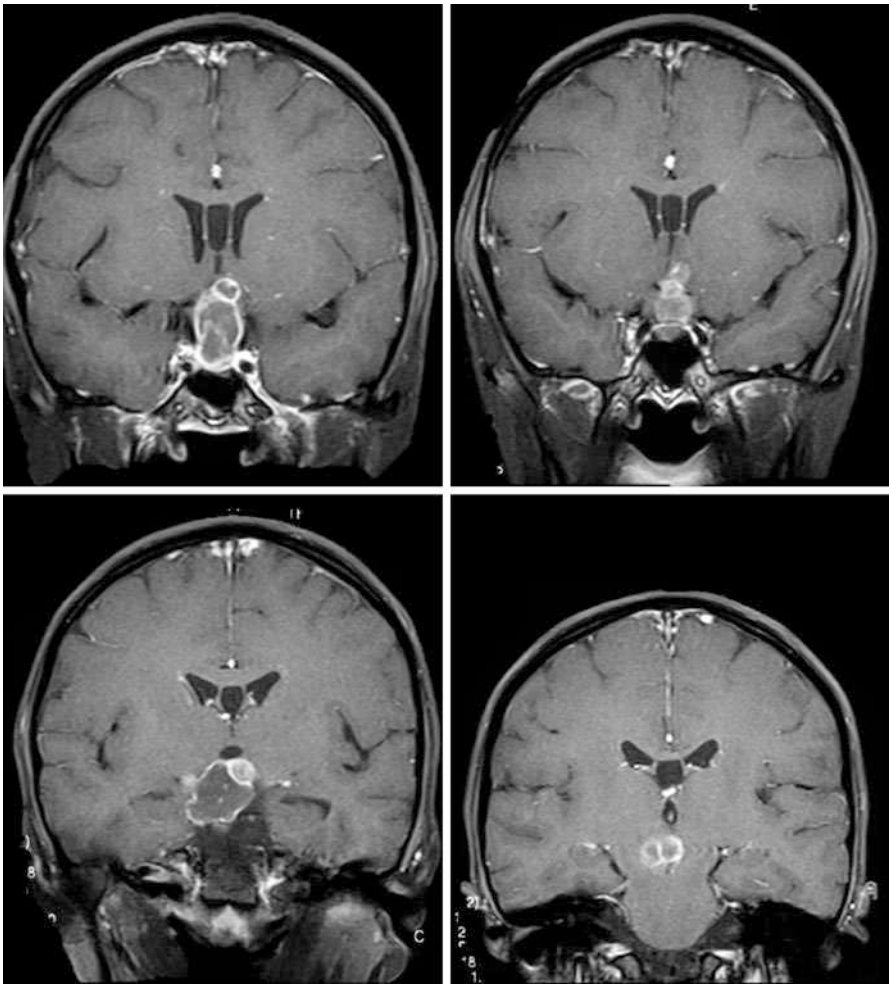

Fig. 6.5 Case 1. Preoperative coronal imaging demonstrating involvement of the hypothalamus and floor of the third ventricle

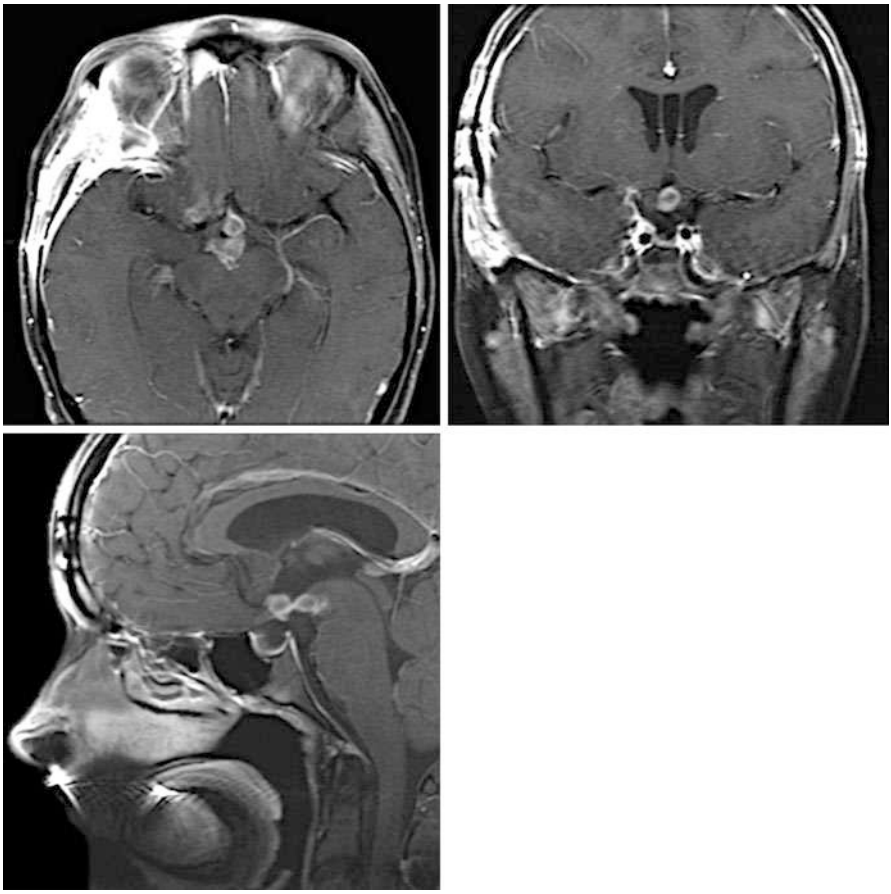

Fig. 6.6 Case 1. Postoperative axial, coronal, and sagittal MRI imaging demonstrating residual enhancing disease in close proximity to the optic apparatus, hypothalamus, and brainstem

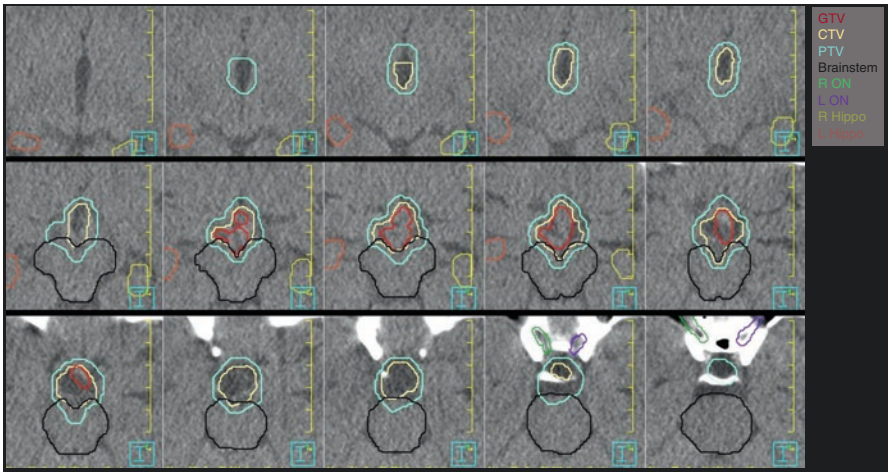

Fig. 6.7 Case 1. Planning CT scan with tumor volumes and adjacent normal structures

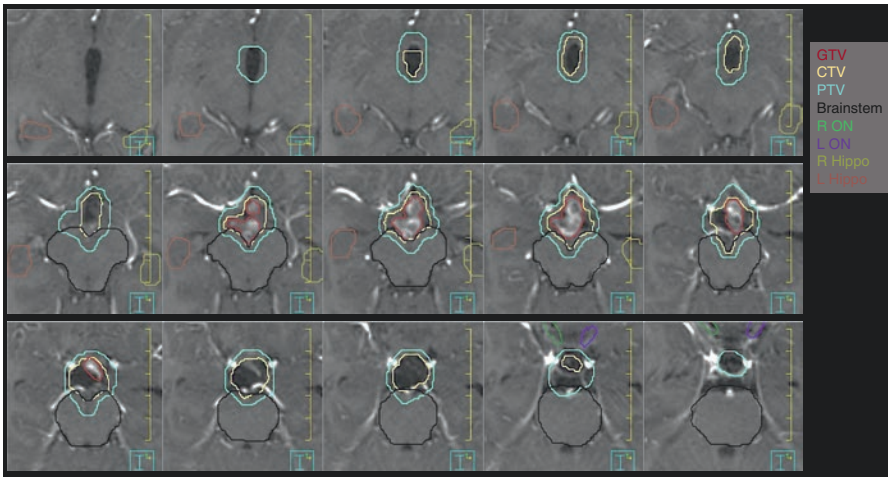

Fig. 6.8 Case 1. Planning MRI with tumor volumes and adjacent normal structures

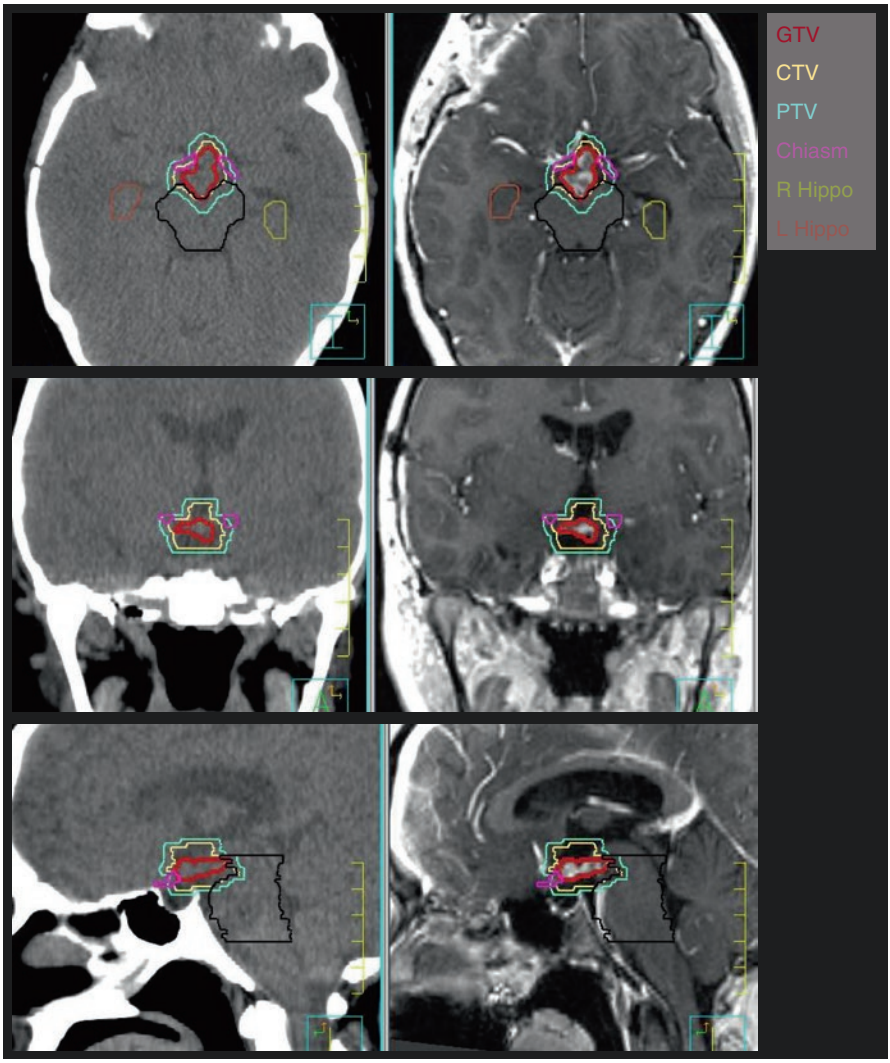

Fig. 6.9 Case 1. Planning CT and MRI axial, coronal, and sagittal reconstructed images with tumor volumes and optic apparatus delineated based on CT image

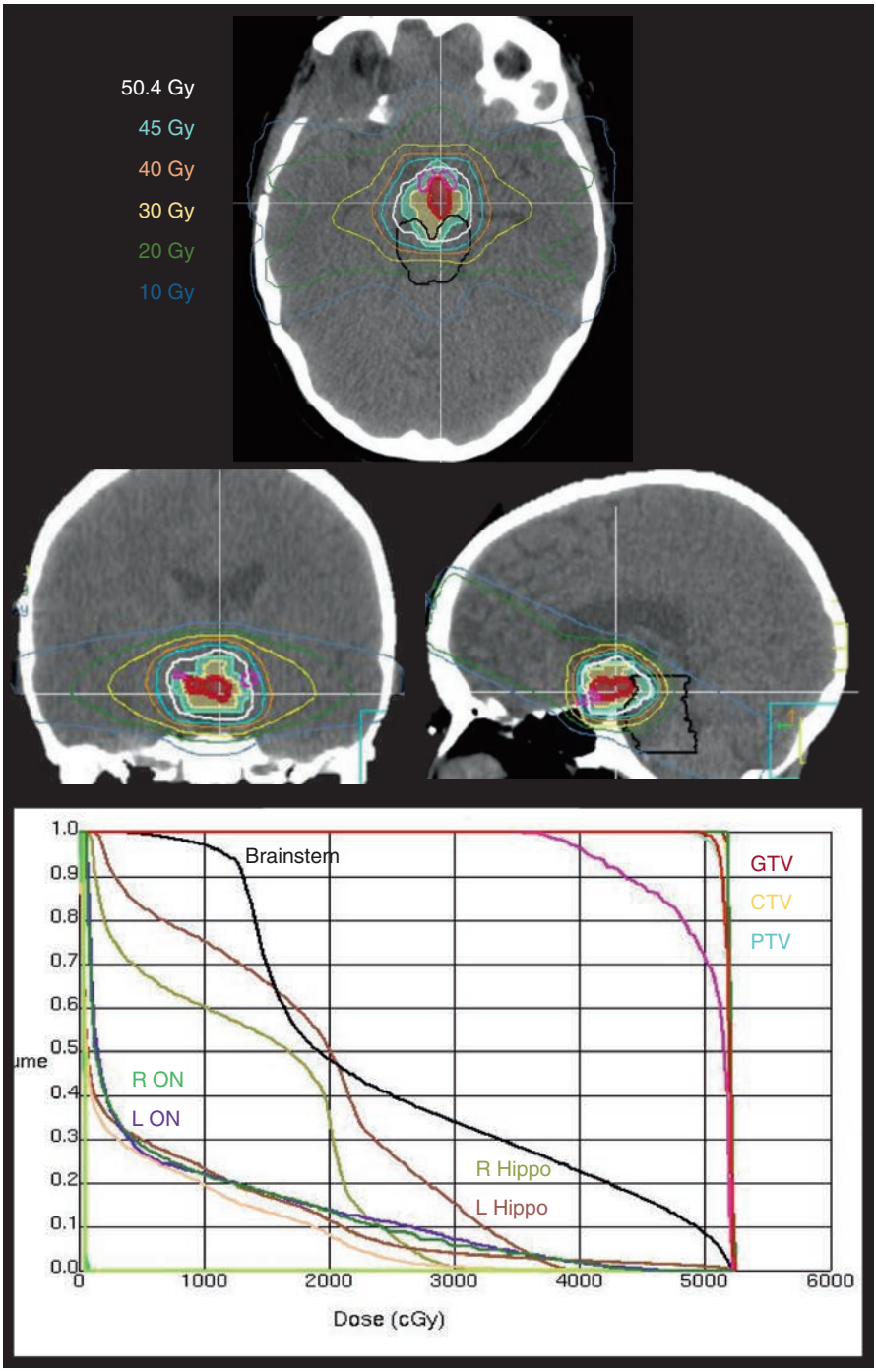

Fig. 6.10 Case 1. Isodoses and dose-volume histogram (DVH) for IMRT plan to deliver 50.4 Gy in 28 fractions

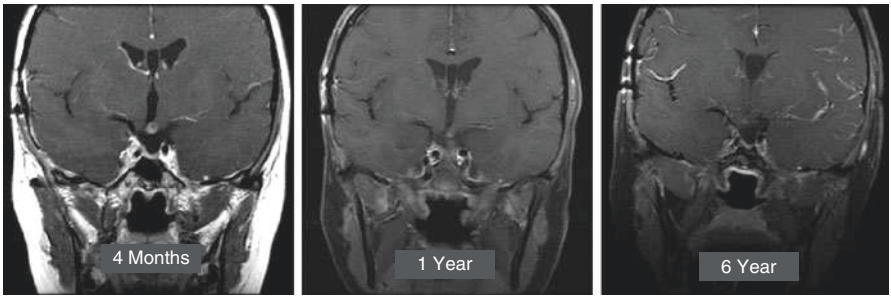

Fig. 6.11 Case 1. Sequential follow-up with no evidence of injury or active disease

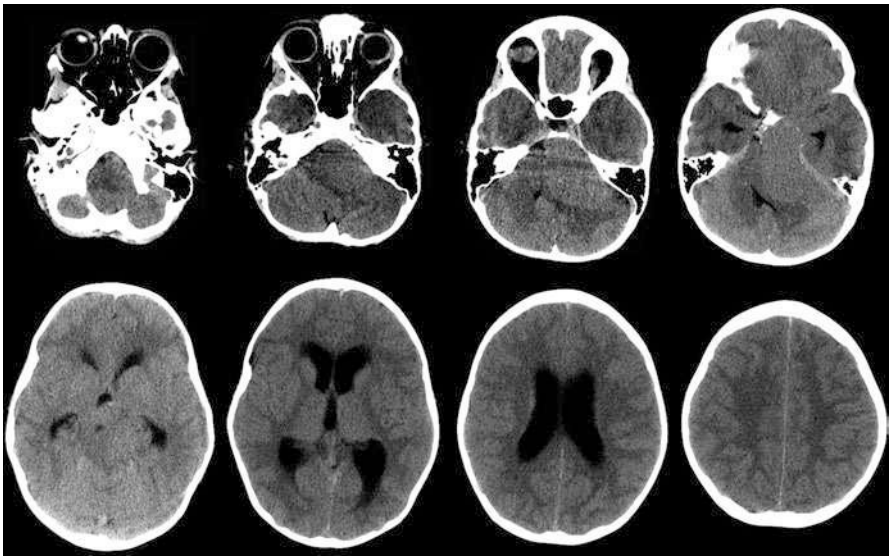

Fig. 6.12 Case 2. Non-contrast CT scan revealing enlarged ventricles, brainstem compression, and a large mass extending from the suprasellar area to left cerebellopontine angle

6.5.7.3 Radiotherapy Planning

GTV: The residual disease as reported from the operative note and the postoperative and RT planning MRI.

CTV: The surgical bed based on the preoperative MRI scan and surgical report.

PTV: 3 mm uniform margin.

Dose and technique: 50.4Gy in 28 fractions with IMRT.

Case 2—Large Tumor (Figs. 6.12–6.19) A 6-year-old girl who presented with a several-year history of a left-sided head tilt and a 2-year history of morning nausea and occasional vomiting. She eventually developed diplopia, left-sided hearing loss, decreased appetite, and ataxia.

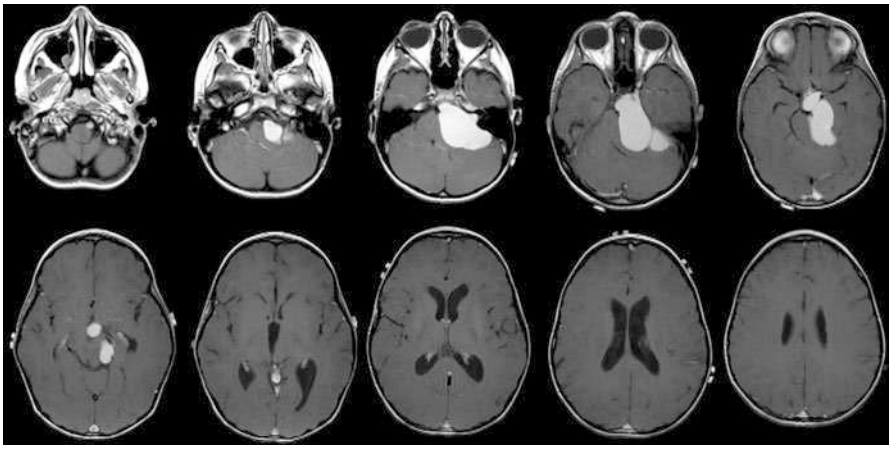

Fig. 6.13 Case 2. T1 weighted, no contrast study showing large cystic mass extending low in the posterior fossa, into the left internal auditory canal and retro-chiasmatic area, and up to the third ventricle

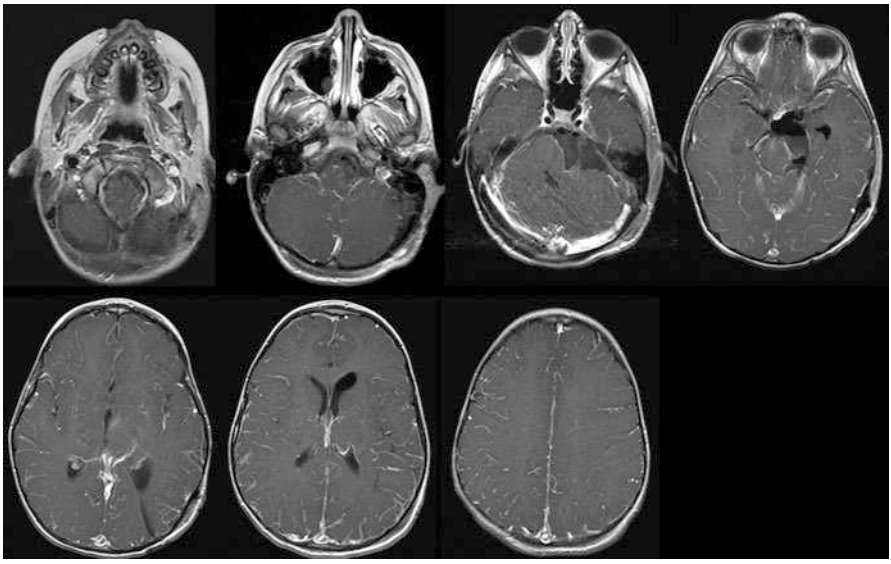

Fig. 6.14 Case 2. Postoperative T1 weighted with contrast axial MRI

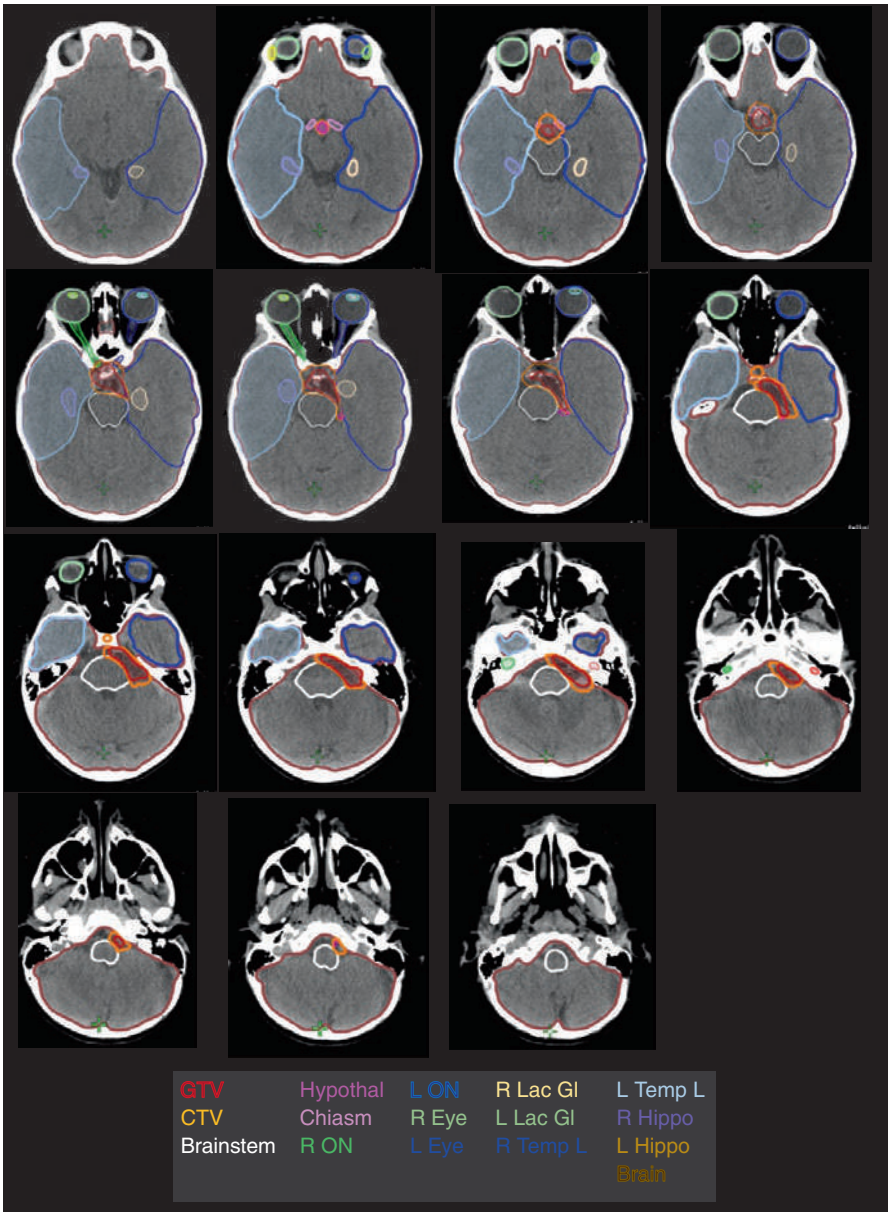

Fig. 6.15 Case 2. Planning CT with target volumes and normal structures delineated

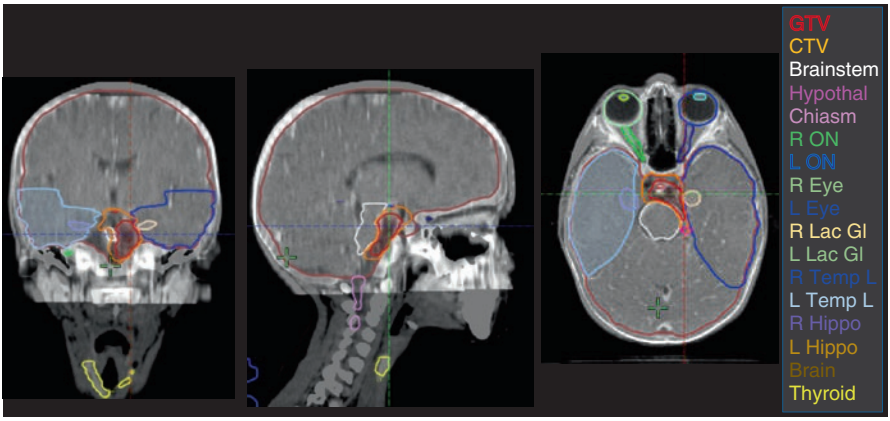

Fig. 6.16 Case 2. Planning CT with MRI fusion superimposed in three planes showing delineated structures

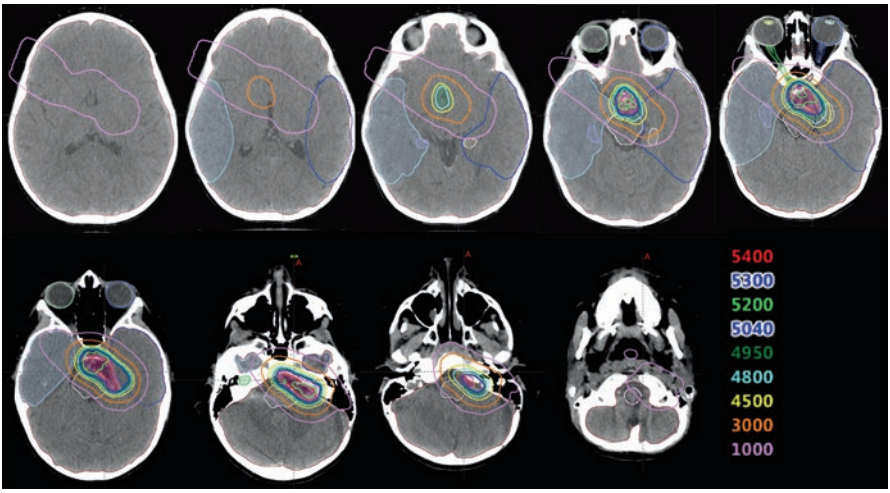

Fig. 6.17 Case 2. Axial isodoses of proton plan delivering 50.4CGE in 28 fractions

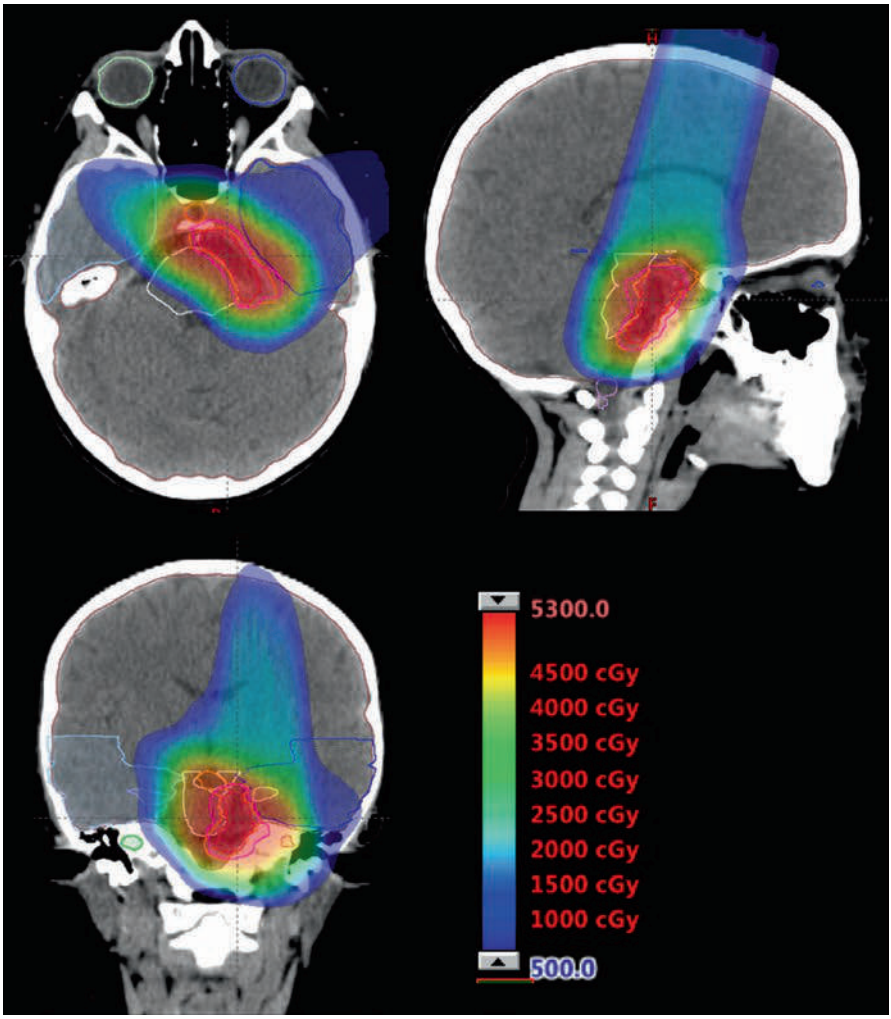

Fig. 6.18 Case 2. (**a**) Color wash isodoses in three planes

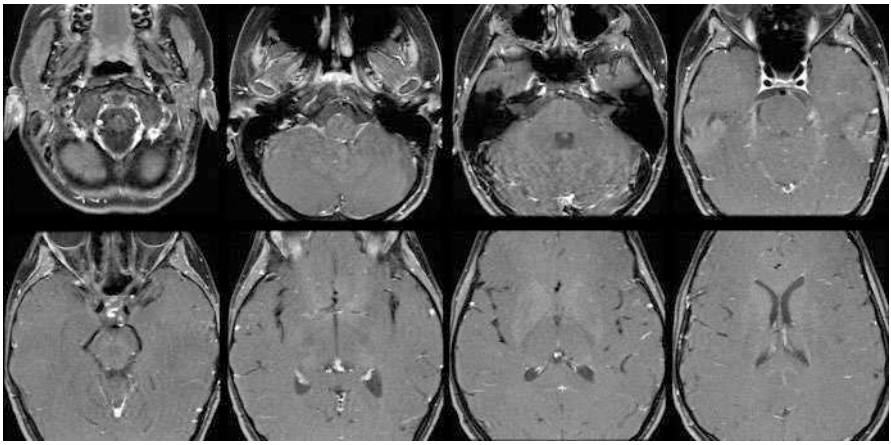

Fig. 6.19 Case 2. MRI 7 years after completion of RT demonstrating stable residual suprasellar mass characterized by heterogeneous signal and enhancement

6.5.7.4 Imaging

- A CT scan revealed a large non-calcified mass extending from the suprasellar area to the posterior fossa with compression of the brainstem and obstructive hydrocephalus. An emergent ventriculostomy was performed. During surgery, the lesion was found to be adherent to the surrounding vessels as well as left-sided cranial nerves VIII and VII, and therefore, a complete resection could not be performed. Pathology was consistent with ACP.
- A postoperative MRI revealed minimal enhancement within the postoperative bed.
- The patient was followed with serial MRIs, and the 4-month postoperative MRI revealed enlargement of a residual cyst. She proceeded to definitive radiation therapy delivered to a dose of 50.4CGE/28 fractions using proton therapy.

Case 3 Recurrent Tumor with Hydrocephalus (Figs. 6.20, 6.21, 6.22, 6.23, 6.24, 6.25, 6.26, and 6.27) A 6-year-old girl who presented with left-sided headaches and progressively worsening crying spells. Scans revealed a cystic suprasellar mass with calcifications for which a subtotal resection and cyst catheter placement and ventriculoperitoneal shunt were performed. Pathology was consistent with ACP. She developed diabetes insipidus postoperatively. Eighteen months later, the patient presented with headaches, nausea, and body aches and was found to have an enlarged cyst and associated hydrocephalus. An MRI revealed enlarged cyst with hydrocephalus. An endoscopic exploration of the suprasellar tumor, cyst fenestration, and drainage was performed. Ophthalmologic exam revealed mild papilledema. Her headaches improved. One month prior to radiotherapy assessment, the patient presented again with recurrent headaches and nausea. MRI revealed interval development of several small cysts along the anterior and superior

aspects of the solid portion. One of the cysts appeared to protrude more mildly into the left foramen of Monro. The ventricles were moderately severely enlarged.

- She underwent a third surgery followed by 50.4 CGE proton therapy in 28 fractions. During radiotherapy, she was noted to have increased hydrocephalus that required intervention and an adaptive planning.

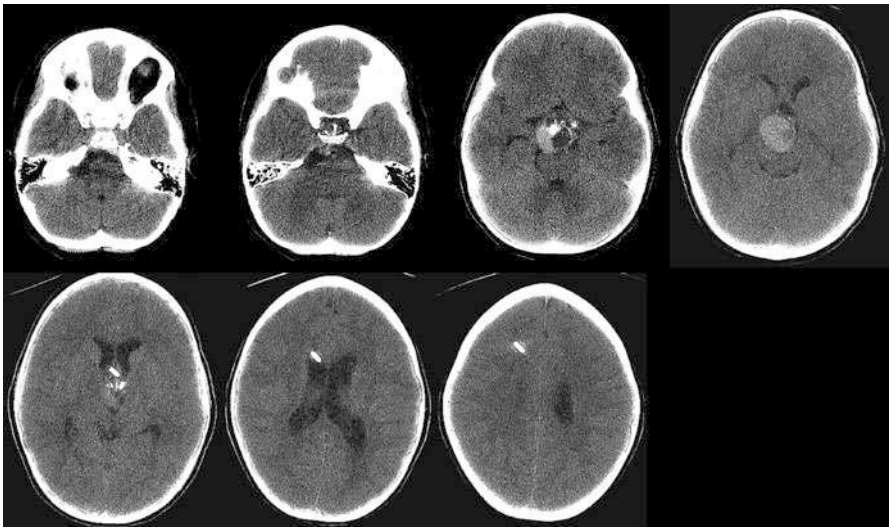

Fig. 6.20 Case 3. Axial non-contrast CT scan of large heterogeneous mixed cystic solid mass. Of note, a shunt catheter has been in place for management of increased intracranial pressure

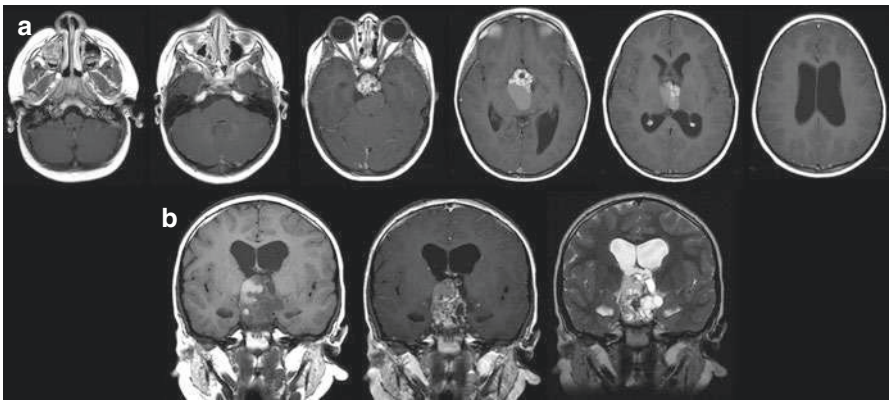

Fig. 6.21 Case 3. MRI scans at the time of diagnosis. (**a**) T1-weighted axial contrast-enhanced MRI scan showing enhancing solid component and hyperintense cystic lesion. (**b**) Coronal views with T1-weighted non-contrast and contrast and T2-weighted images

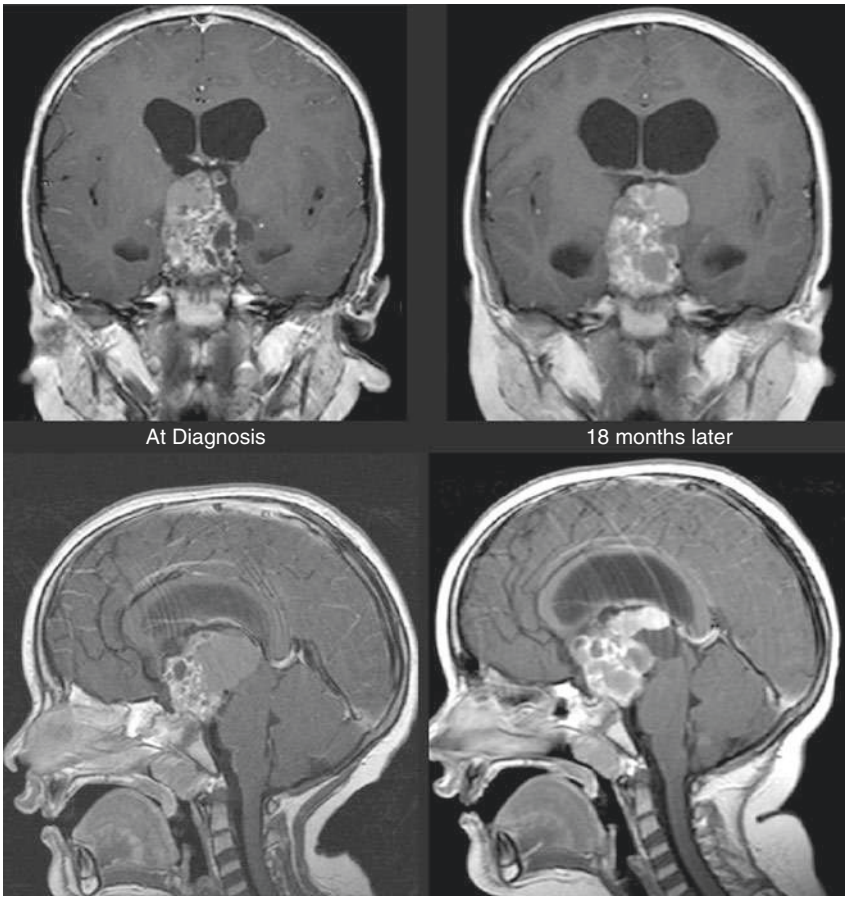

Fig. 6.22 Case 3. Sagittal and coronal MRI images of CP at diagnosis in comparison to 18 months later when cyst enlargement and increased ventricular size were noted

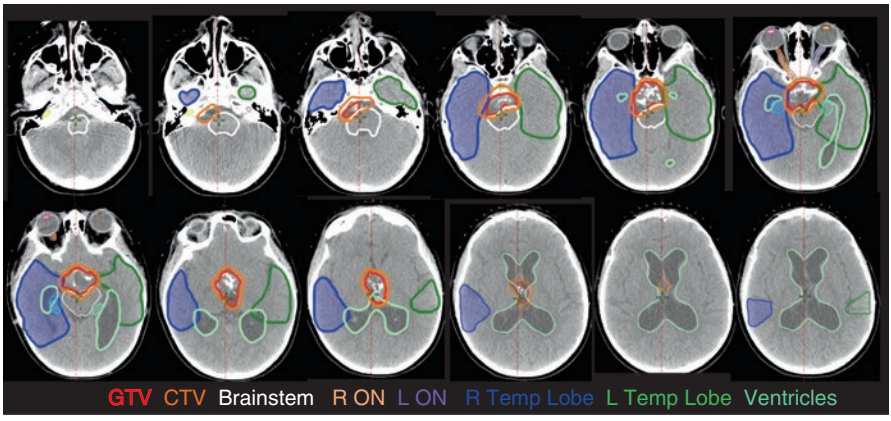

Fig. 6.23 Case 3. Axial planning CT scan of contours for post-op RT planning for progressive ACP

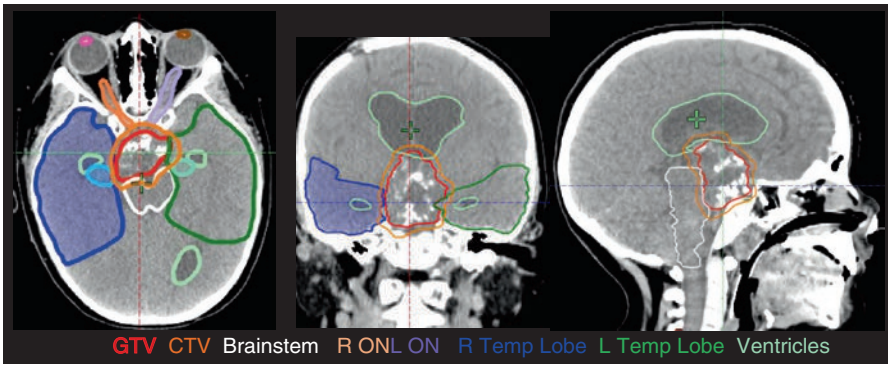

Fig. 6.24 Case 3. Tumor and normal tissue contours seen on three planes with MRI/CT fused images

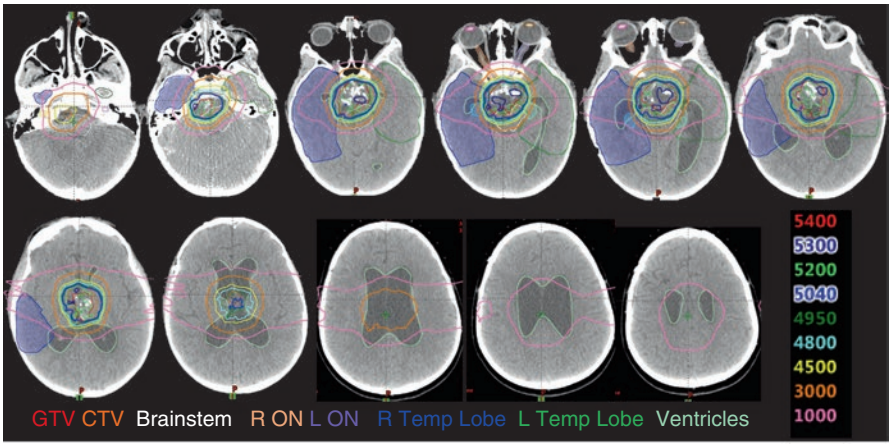

Fig. 6.25 Case 3. Axial CT scan with isodose curves. A final RT dose of 50.4 CGE in 28 fractions was delivered

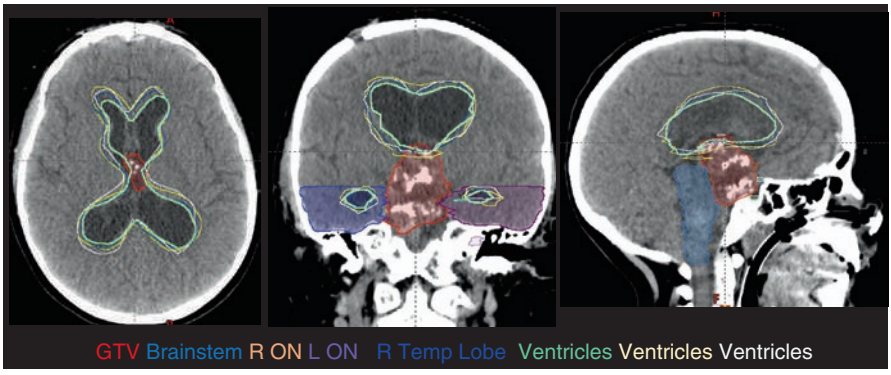

Fig. 6.26 Case 3. Series of verification scans to review the tumor volume revealed ventricular enlargement from 111 cc to 150 cc over 4 weeks requiring surgical manipulation of shunt and replanning

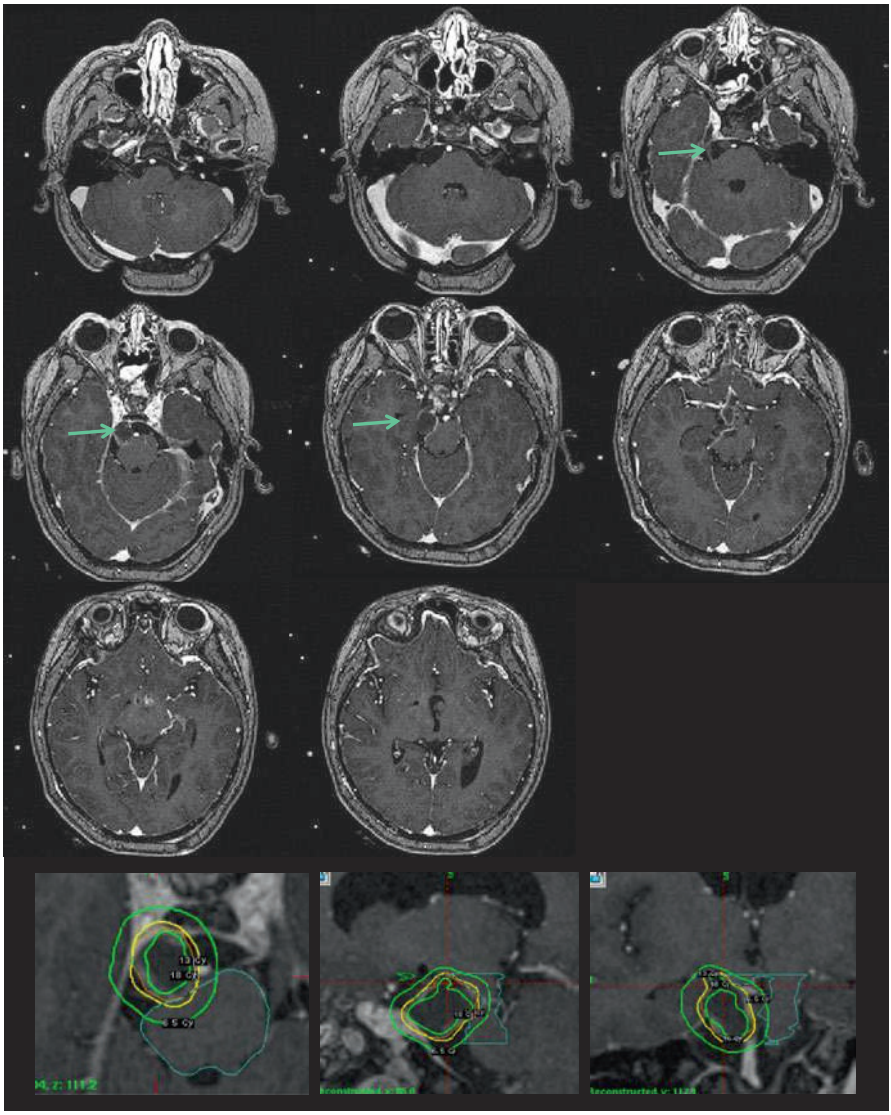

Fig. 6.27 Case 3. Seven years later small cystic inoperable recurrence in prepontine cistern for which 13Gy to 50% with Gamma Knife stereotactic radiosurgery was used to obtain local control. The suprasellar recurrence was considered for surgery

Case 4 Rapidly Enlarging Cyst (Figs. 6.28, 6.29, 6.30, and 6.31) A 14-year-old female noted to have growth delay with a bone age of 10–11. Further workup revealed a small bilateral peripheral visual field defect. An MRI revealed a cystic lesion in the sellar region with extensive suprasellar extension that abutted the optic chiasm. She underwent a transsphenoidal resection with pathology confirming an ACP extensive calcification and islands of wet keratin.

- The planning MRI revealed reaccumulation of the cyst within 6 weeks of surgery. After discussion with referring team and surgeons, it was agreed to proceed with RT with close cyst surveillance during RT.

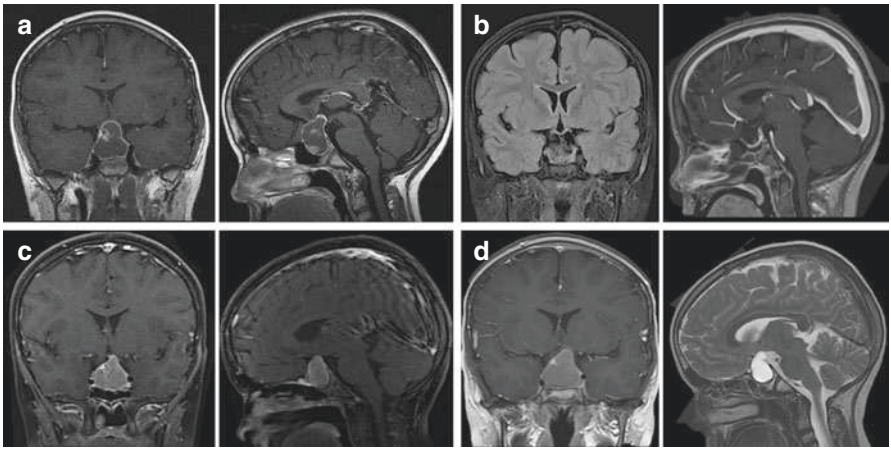

Fig. 6.28 Case 4. Serial coronal MRI scans of patient. (**a**) At diagnosis. (**b**) After initial resection. (**c**) 6 weeks post resection, 1 week pre-RT. (**d**) 1-month post-RT

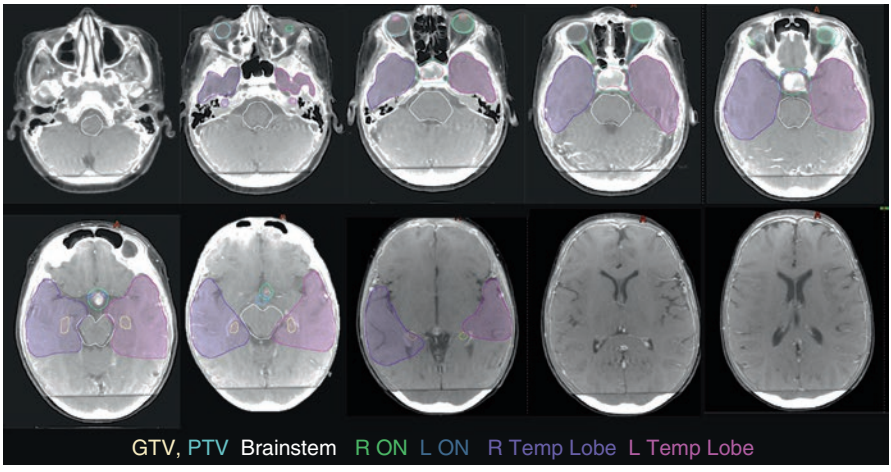

Fig. 6.29 Case 4. Axial CT with MRI fusion and volume delineation

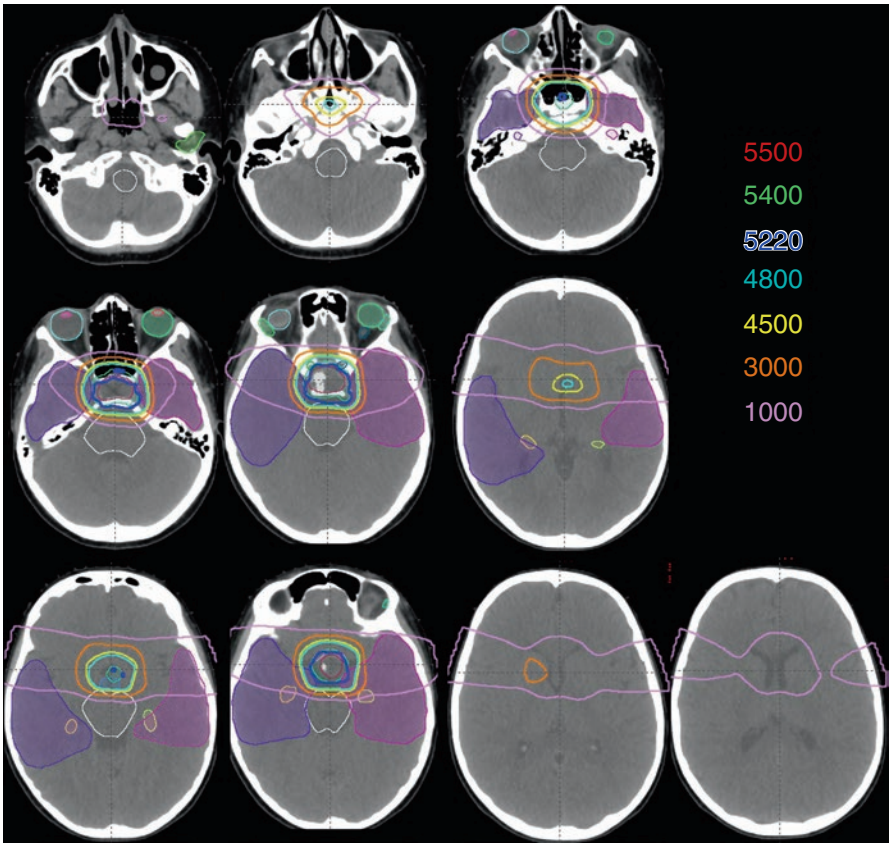

Fig. 6.30 Case 4. Axial CT scans with isodose displayed

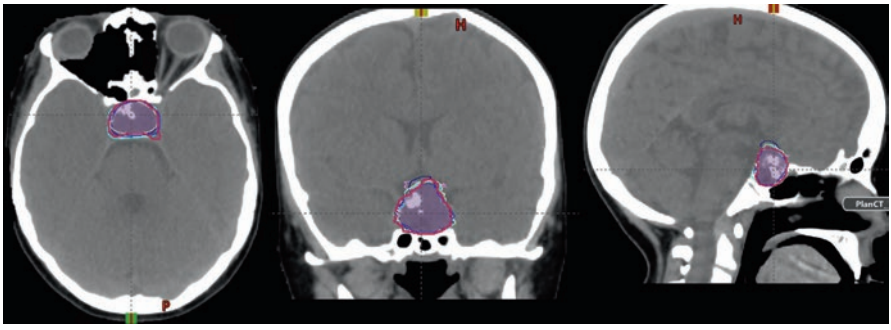

Fig. 6.31 Case 4. Verification weekly CTs with redelineation of GTV to ensure appropriate coverage

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Gliomas in Children

7

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Contents

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https://doi.org/10.1007/978-3-319-69140-4_7

7.1 Introduction

- International Commission on Radiotherapy Units (ICRU) definitions (Prescribing, Recording, and Reporting Photon Beam Therapy, ICRU report 62)

Volume	Description
Gross tumor volume (GTV)	Surgical cavity post-resection and/or macroscopic residual/recurrent tumor. May also include T2/FLAIR abnormality associated with high-grade gliomas
Clinical target volume (CTV)	Tissue considered to harbor subclinical disease. Relies on an understanding of the clinical behavior of the tumor and takes into account the direction of potential tumor infiltration
Planning target volume (PTV)	Allows for geometric and setup uncertainties. Margins vary according to immobilization devices and type and frequency of image guidance

7.2 Background

- Primary CNS tumors are the most common solid cancer in the 0–19-year-age group. According to the Central Brain Tumor Registry of the United States (CBTRUS), the incidence of childhood and adolescent (age 0–19 years) primary malignant and nonmalignant brain and CNS tumors is 5.57 per 100,000, and the incidence of malignant CNS tumors is 3.42 per 100,000. In 2016, there will be an estimated 1800 new cases of glioma diagnosed in the United States in the pediatric population age 0–14 years [1].
- Pediatric gliomas span the full range of clinical and histologic aggressiveness from WHO grade I (pilocytic) astrocytoma to grade IV (glioblastoma).
- Long-term consequences of cranial radiation include neuropsychological effects [2] and neuroendocrine dysfunction, as well as vascular events, late-developing seizure disorders, and secondary malignancies. Moreover, certain patient populations, such as children with NF-1, that are at increased risk for developing gliomas are also at increased risk for late sequelae. However, avoidance of radiotherapy for gliomas results in decreased local control rates, and for many children, radiotherapy remains an important modality of treatment.
- The goal of radiotherapy planning is to deliver a dose adequate to control the tumor while minimizing dose received by normal tissue.
- There are no standard guidelines for target volume definition for pediatric gliomas, and recommendations are derived from single-institution studies and previous clinical trials.
- As technology for imaging has advanced and daily image guidance radiotherapy has become routine, CTV and PTV margins have been adjusted usually to decrease the margins used.

7.3 Imaging

- CT scan of the head is often the first imaging modality used. It is useful for detecting calcifications, acute hemorrhage, and calvarial or skull base involvement [3] and is necessary for radiation treatment planning, as it provides the electron density of tissues required for dose calculation.
- Magnetic resonance imaging (MRI) is, however, the imaging modality of choice for patients with known or suspected brain tumors. It provides better soft tissue definition and the ability to detect small lesions, and there is no radiation dose associated with MRI. Both axial and coronal MR images should be co-registered with the planning CT scan to help define the target volumes [4].
- High-grade gliomas are often hypointense on T1-weighted images and hyperintense on T2-weighted images and can induce significant edema as seen on T2/FLAIR sequences. There is typically post-contrast enhancement on T1 sequences that correlates with areas of increased cellularity, mitotic activity, and neo-vascularity [5].
- In comparison, low-grade gliomas grow more slowly and demonstrate less associated vasogenic edema and less mass effect. Low-grade gliomas are usually isointense to hypointense on T1-weighted MR images and hyperintense on T2-weighted images [3]. With the exception of juvenile pilocytic astrocytomas, they typically do not show post-contrast enhancement.
- The introduction of additional MR sequences such as MR spectroscopy, MR diffusion-weighted and dynamic susceptibility-weighted MR imaging has allowed for the evaluation of tumor biophysiology. MR spectroscopy, for example, provides a measure of tissue metabolism, and typical findings in brain tumors include decreased N-acetyl aspartate (NAA) and increased choline that reflect neuronal volume loss and increased cell turnover, respectively [6].
- While CT and MRI are the primary imaging modalities for target definition of pediatric glioma, functional and metabolic imaging may also be used to determine the potential aggressive nature of the tumor, particularly when patients are unable to undergo biopsy. Fluorine-18 fluorodeoxyglucose (FDG) PET detects increased metabolic activity in tumors. However, glucose metabolism in normal brain tissue is high, and therefore brain tumors may show hypo- or isometabolism in comparison to the normal brain. Carbon-11 methionine PET can be used when available, with the advantage that normal brain tissue demonstrates low uptake. Carbon-11 methionine uptake reflects increased amino acid transport and protein synthesis and therefore is related to cellular proliferation activity [7]. These metabolic studies may be helpful for radiotherapy planning in selected cases.
- CSF dissemination of tumor is seen in approximately 6% of patients with low-grade glioma and 8% with high-grade glioma. Neuro-axis imaging may be appropriate for staging of these patients, especially for tumors located in the midline where the incidence of CNS metastases is greatest [8, 9].

7.4 General Principles

- Patients are positioned supine with arms at their sides. Immobilization is achieved with a thermoplastic mask.
- CT simulation should be done with 1–3 mm slice acquisition from the vertex through the mid-cervical spine.
- Magnetic resonance imaging (MRI) should be used in nearly every case to define target volumes. MRI images are co-registered to the simulation CT scan to delineate gross tumor volume (GTV) and clinical target volume (CTV). Co-registered images typically include T2, FLAIR, and T1 post-contrast sequences in axial and coronal views. When there is no enhancing component of the tumor as may be the case in some low-grade gliomas and in diffuse intrinsic pontine gliomas, the T2 or FLAIR sequence alone is used for target volume delineation. MRI scans with a slice thickness of no greater than 3 mm should be used. Volume-acquired sequences such as SPGR or FIESTA can be helpful for providing greater anatomic detail and can be reconstructed into arbitrary planes for visualization and contouring.
- Areas of FLAIR or T2 signal abnormality can represent infiltrating tumor, edema, or a combination of both. In most cases, these areas of abnormality should be included in the GTV.
- For children who have undergone surgery, the postoperative MRI is usually the most helpful for defining radiotherapy targets, as the intracranial anatomy can change significantly after removal of some or all of a tumor. Also, positional changes in that brain anatomy can evolve further over the few weeks following surgery so that the MRI to be used for radiotherapy planning should be obtained as close to the time of CT simulation and start of treatment as possible.
- Co-registering the preoperative MRI to the postoperative scan can also be helpful. In some instances, non-specific imaging changes on the postoperative MRI can be shown to be outside the area of tumor involvement, as defined on the preoperative MRI, and can be omitted from the radiotherapy target volumes as presumed nonneoplastic surgery-related changes (Fig. 7.1). It is also important to be very certain to include all areas in contact with initial tumor.
- After the GTV is defined and an expansion is done for the CTV, the CTV contour should be constrained to natural barriers to spread including bone, cerebellar tentorium, cerebral falx, and the ventricles (Fig. 7.2).

7.5 Cases

7.5.1 Juvenile Pilocytic Astrocytoma (JPA)

- Pilocytic astrocytomas, WHO grade I, most often arise in the cerebellum and chiasmatic/hypothalamic region.
- JPAs are characterized by slow-growing mixed solid and cystic lesions that generally do not invade brain.
- JPAs are usually well circumscribed and smoothly marginated, except when located in the optic chiasm or optic nerve where the tumor may grow along the optic pathway [10].

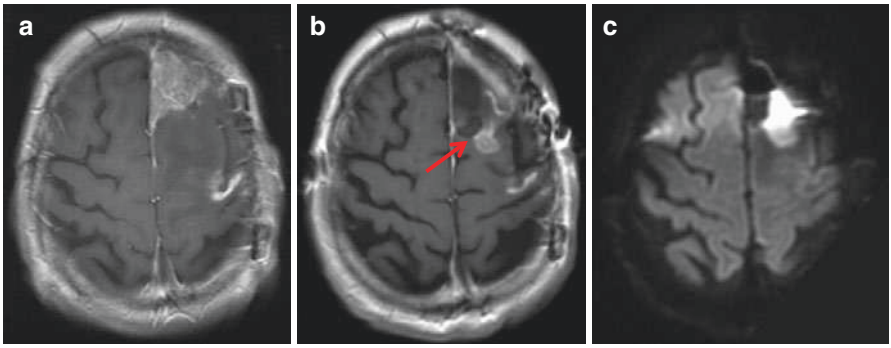


Fig. 7.1 Axial MRI of the head of a child with a left frontal high-grade glioma status-post surgical resection. There is an enhancing lesion along the posterior aspect of the surgical cavity (**b**, *red arrow*) that demonstrates restricted diffusion (**c**). In comparison to the preoperative post-contrast T1-weighted image (**a**), the new area of enhancement lies outside of the initial enhancing component of the disease and represents an area of ischemia following surgical resection. This area of enhancement would not be included in the GTV

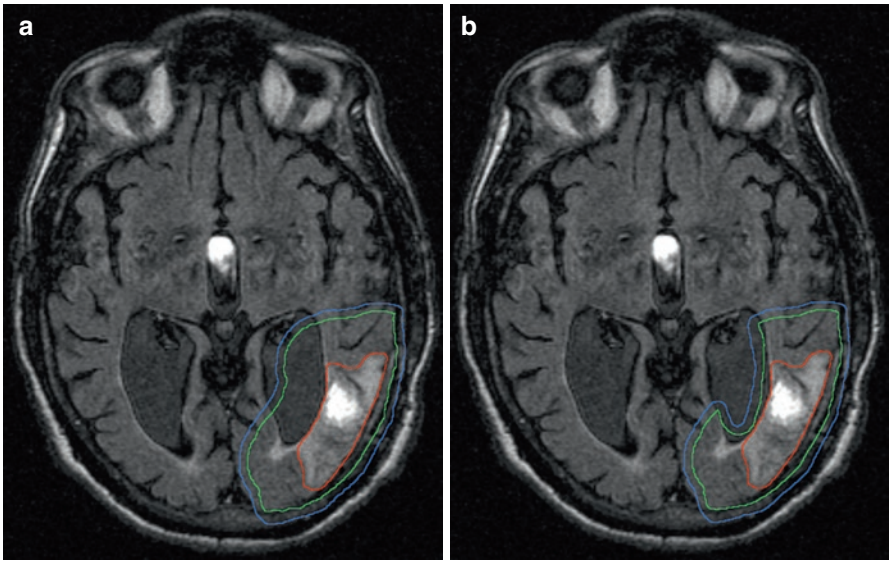


Fig. 7.2 Axial MRI of the head, T2/FLAIR sequence of a patient with high-grade glioma. If the CTV expansion is not limited by the ventricle (**a**), the CTV volume is 150 cm^3, in comparison to 130 cm^3 (**b**) when the CTV is limited at the wall of the ventricle. The use of the larger CTV that includes the ventricle results in a larger integral normal brain dose. Red = GTV, green = CTV (GTV + 1.5 cm), blue = PTV (CTV + 3 mm)

- On MRI, JPAs are typically hypo- or isointense on T1-weighted images and hyperintense on T2-weighted images and show marked enhancement post-contrast injection.
- If a gross total resection is performed, there is no indication for postoperative adjuvant treatment.

- Close follow-up without immediate treatment is usually also appropriate for children with JPAs that have undergone subtotal resection.
- Radiotherapy in the present era is most often indicated in patients with tumors that are unresectable and occur in older children, have progressed after chemotherapy and/or targeted agents, or are in locations that threaten vital functions, e.g., in the brainstem.
- Target delineation (Fig. 7.3):
  - GTV = entire tumor volume seen on gadolinium enhanced T1 MR imaging at time of treatment including tumor cysts and any non-enhancing tumor seen on T2 or FLAIR. Areas of T2 or FLAIR abnormality that can be identified as vasogenic edema are uncommon and usually need not be included.
  - CTV = GTV + 5 mm, limited at natural barriers.
  - PTV = CTV + 3–5 mm.
- Dose: 50.4–54 Gy given in daily fractions of 1.8 Gy 5 days each week.

7.5.2 Low-Grade (Grade 2) Glioma

- Much less common than JPA in the pediatric age group, the majority of low-grade (grade 2) gliomas in children extend into vital areas or arise in deep midline structures, often making complete surgical resection difficult or impossible.
- Surgery is the principal treatment modality, and radiotherapy is used for lesions that either cannot be resected or demonstrate continued growth following surgical resection.
- Target delineation (Fig. 7.4):
  - GTV = entire tumor including any T2 or FLAIR abnormality
  - CTV = GTV + 5–10 mm (10 mm margin may be more appropriate for diffusely infiltrating lesions)
  - PTV = CTV + 3–5 mm
- Dose = 50.4–54 Gy given in daily fractions of 1.8 Gy 5 days each week.

7.5.3 High-Grade Glioma

- High-grade gliomas account for 8–12% of childhood brain tumors.
- Tumors often have irregular and indistinct borders.
- Regions of edema and FLAIR abnormality should be included within the GTV as stereotactic biopsies of these areas have demonstrated the presence of tumor cells [11].
- Surgery is necessary for histologic confirmation and extent of resection correlates with outcome in children.
- Target delineation (Fig. 7.5):
  - GTV1 = enhancing and non-enhancing areas of tumor including MR T2-/FLAIR-weighted imaging abnormality and the resection cavity.

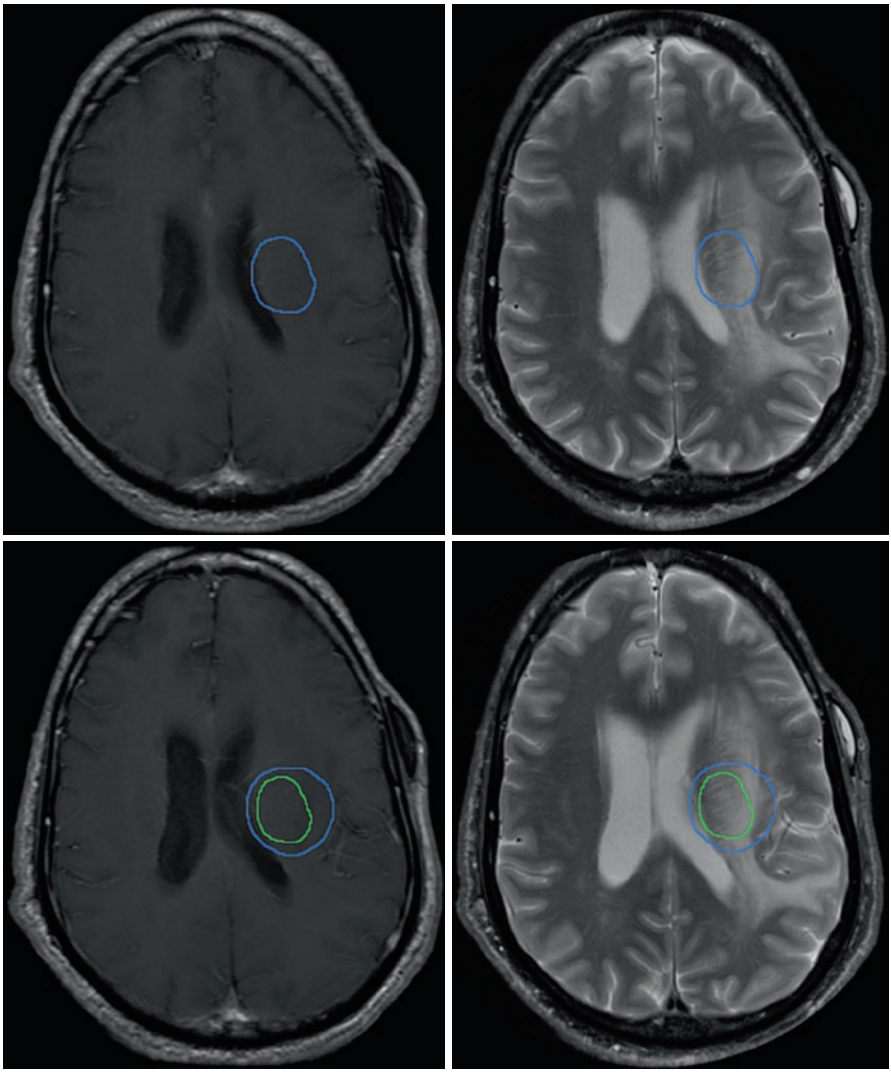
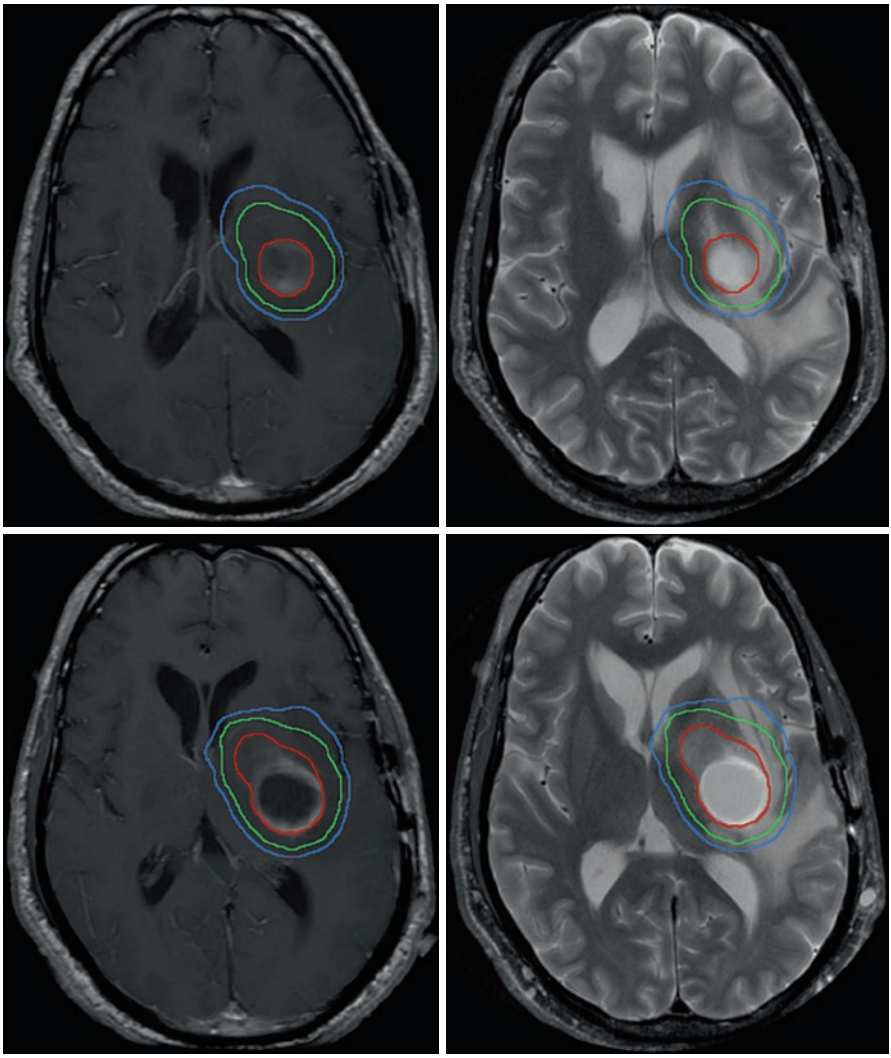


Fig. 7.3 Juvenile pilocytic astrocytoma case. Axial T1 post-contrast images are shown on the left and axial T2-weighted images on the right. Red = GTV which includes both the enhancing disease and the tumor cysts. Green = CTV (GTV + 5 mm). Blue = PTV (CTV + 3 mm)



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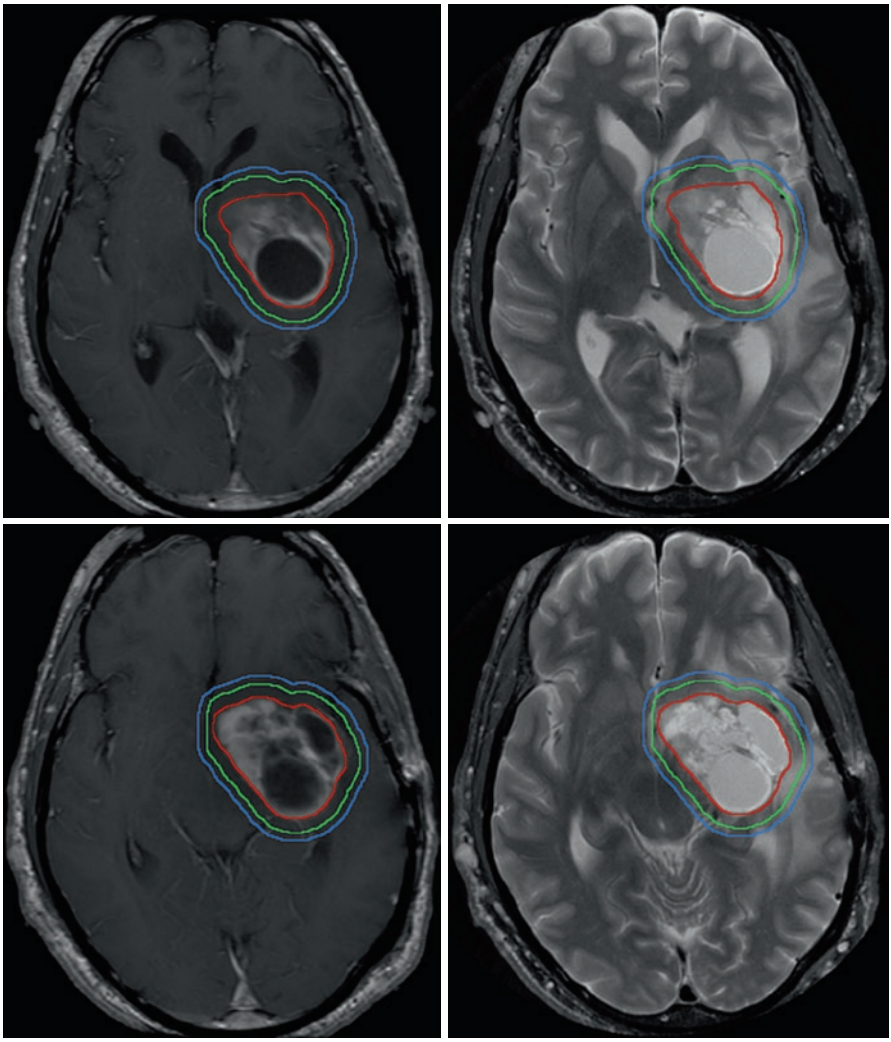

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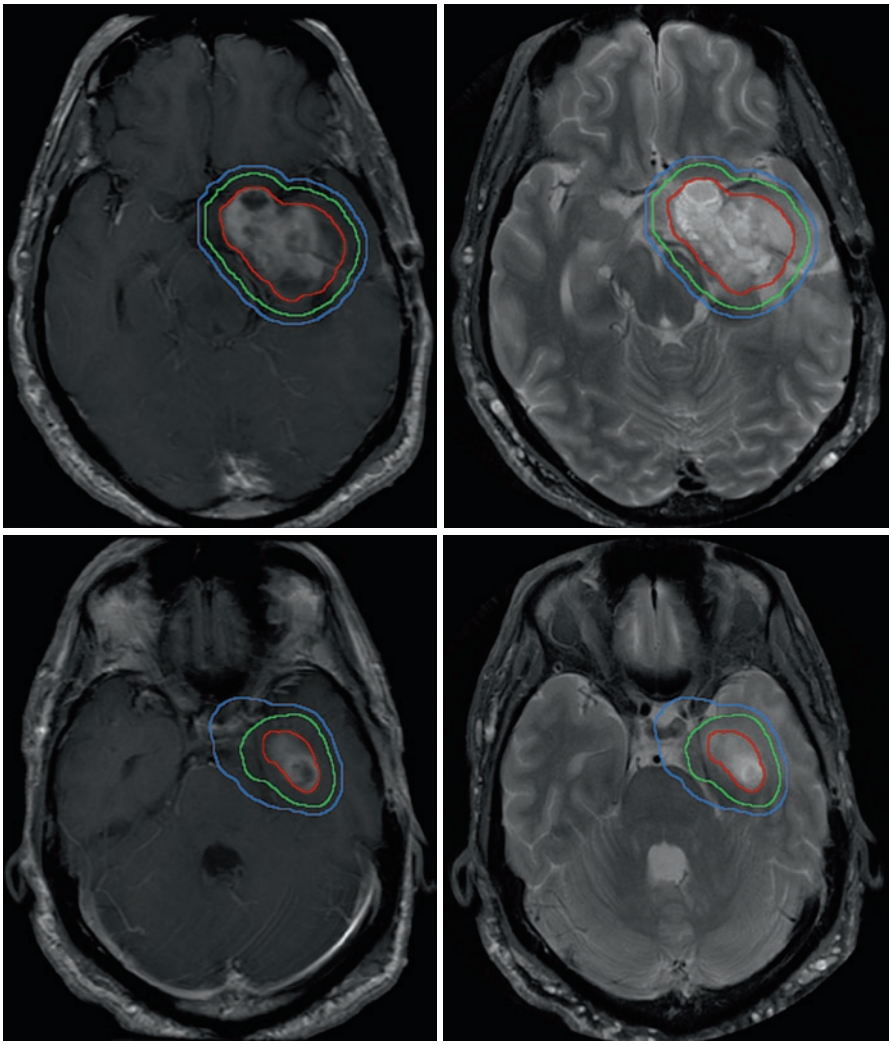

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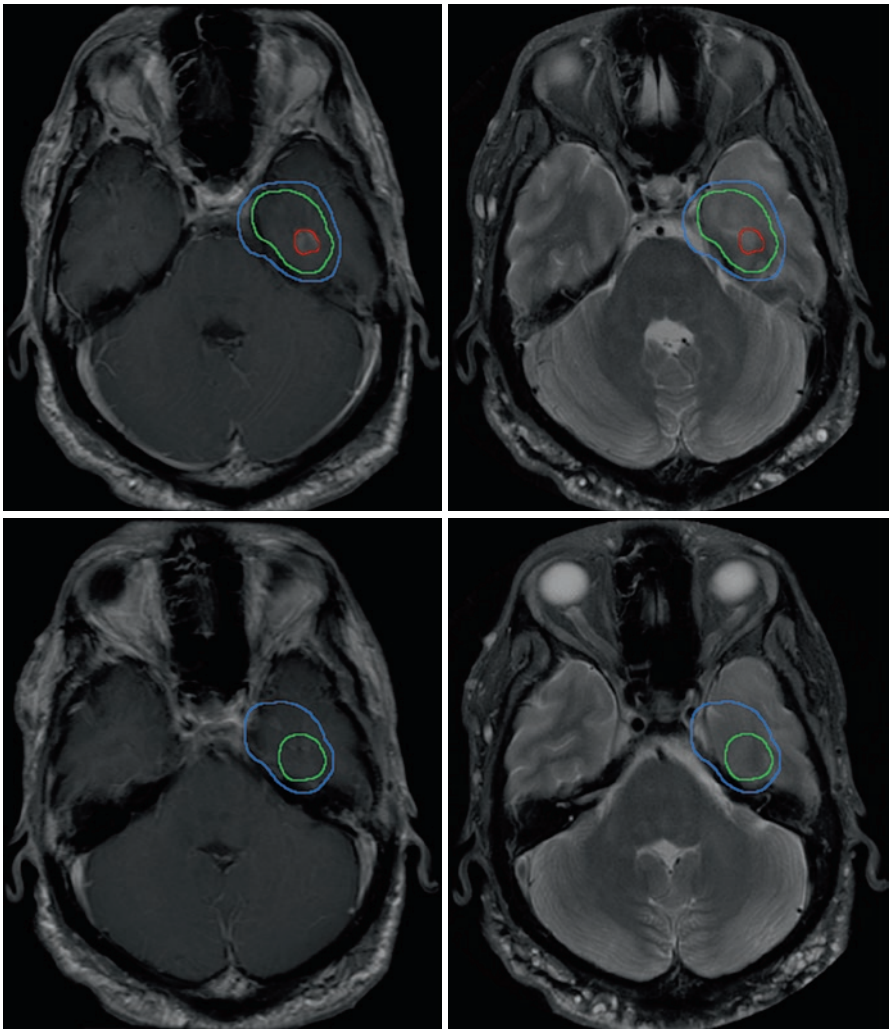

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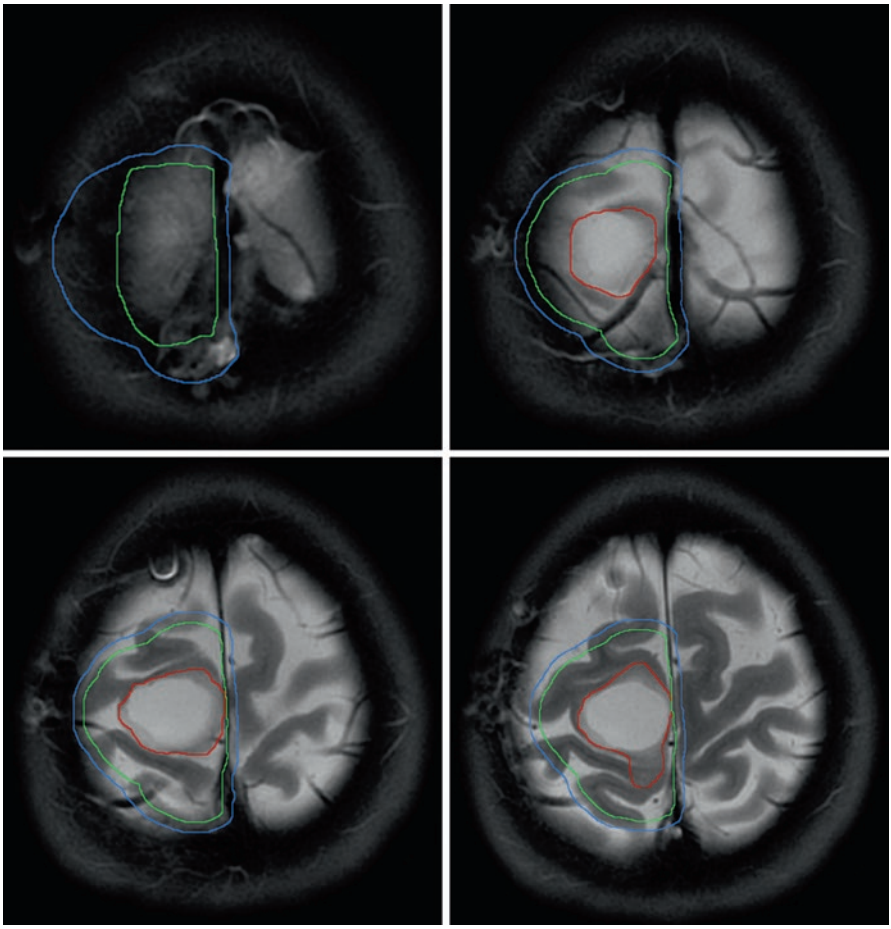
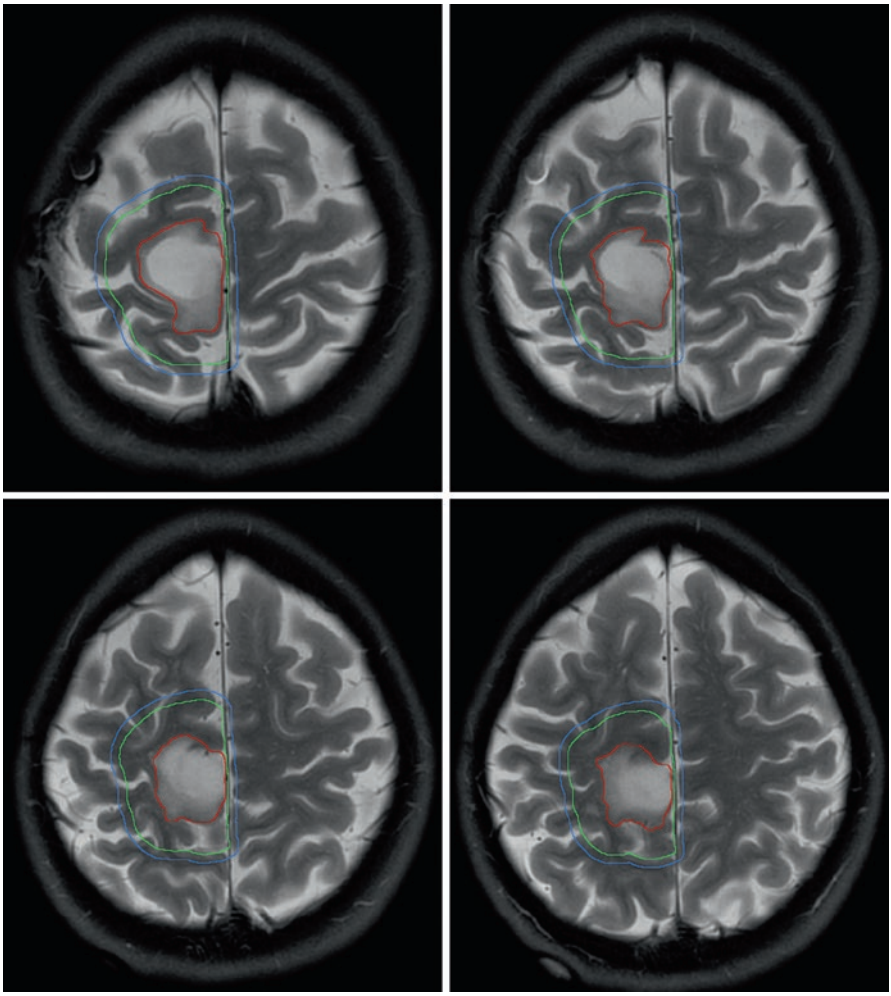


Fig. 7.4 Low-grade glioma case. Axial T2-weighted MRI slices of the head of a patient with a low-grade glioma of the right frontal lobe following incomplete surgical resection. Red = GTV which encompasses both the surgical cavity and residual T2 signal abnormality. Green = CTV (GTV + 1 cm margin). Blue = PTV (CTV + 3 mm)



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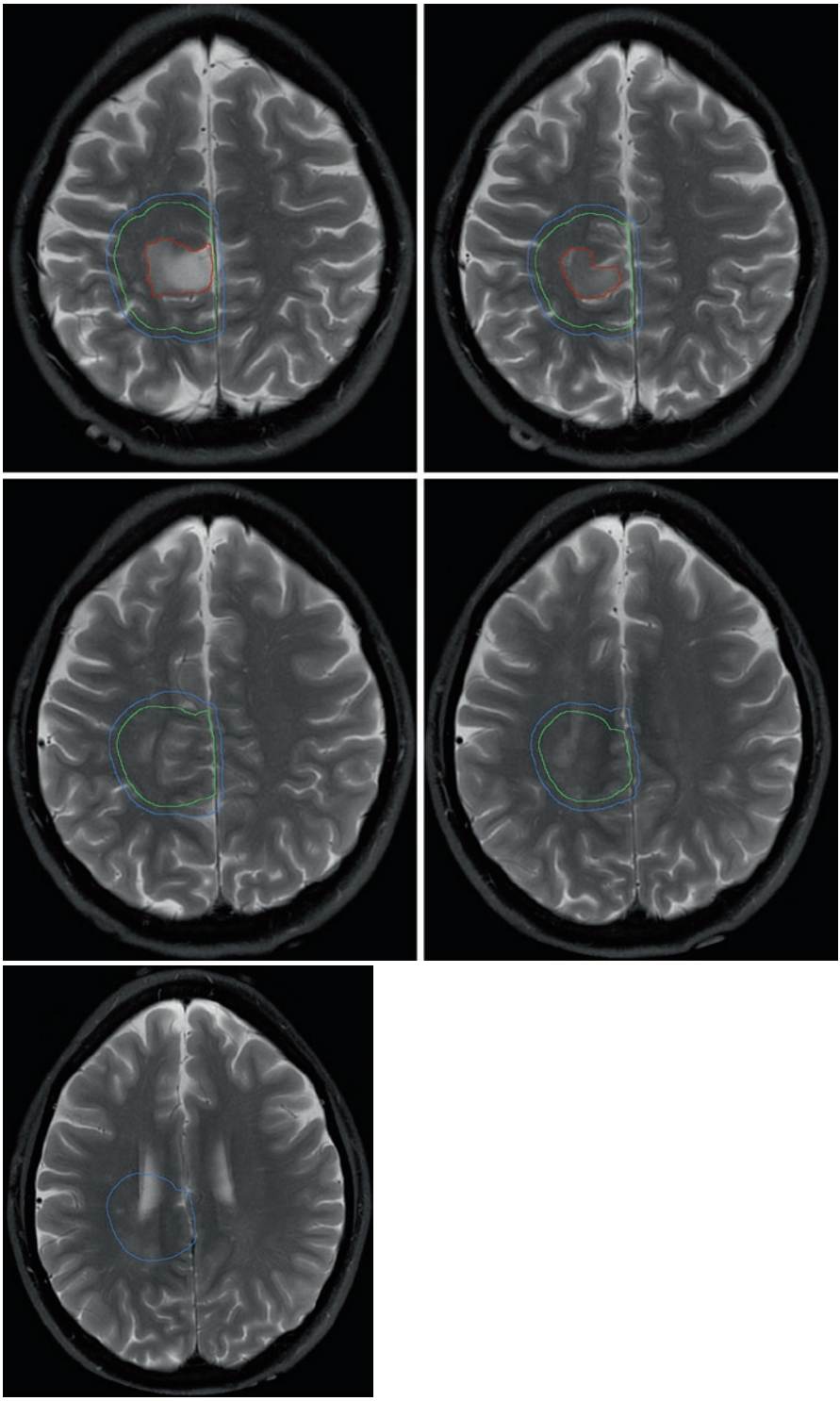

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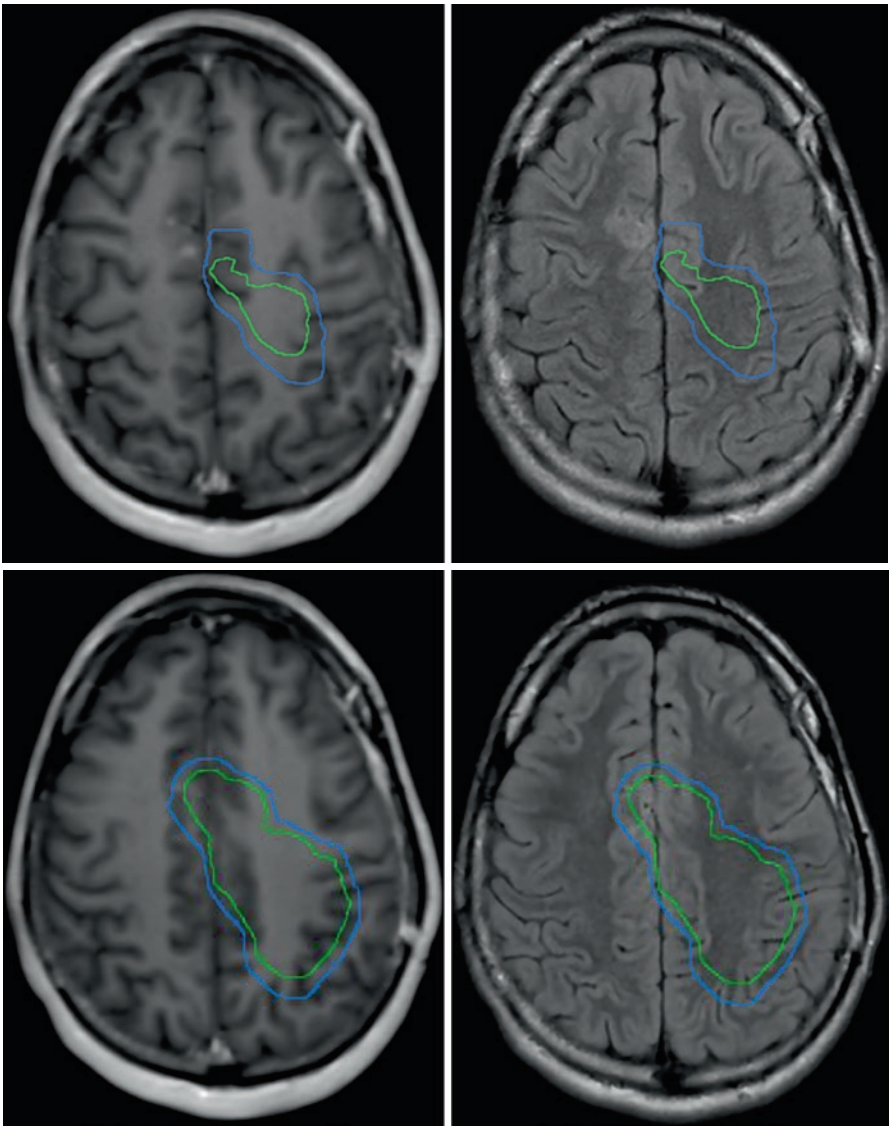
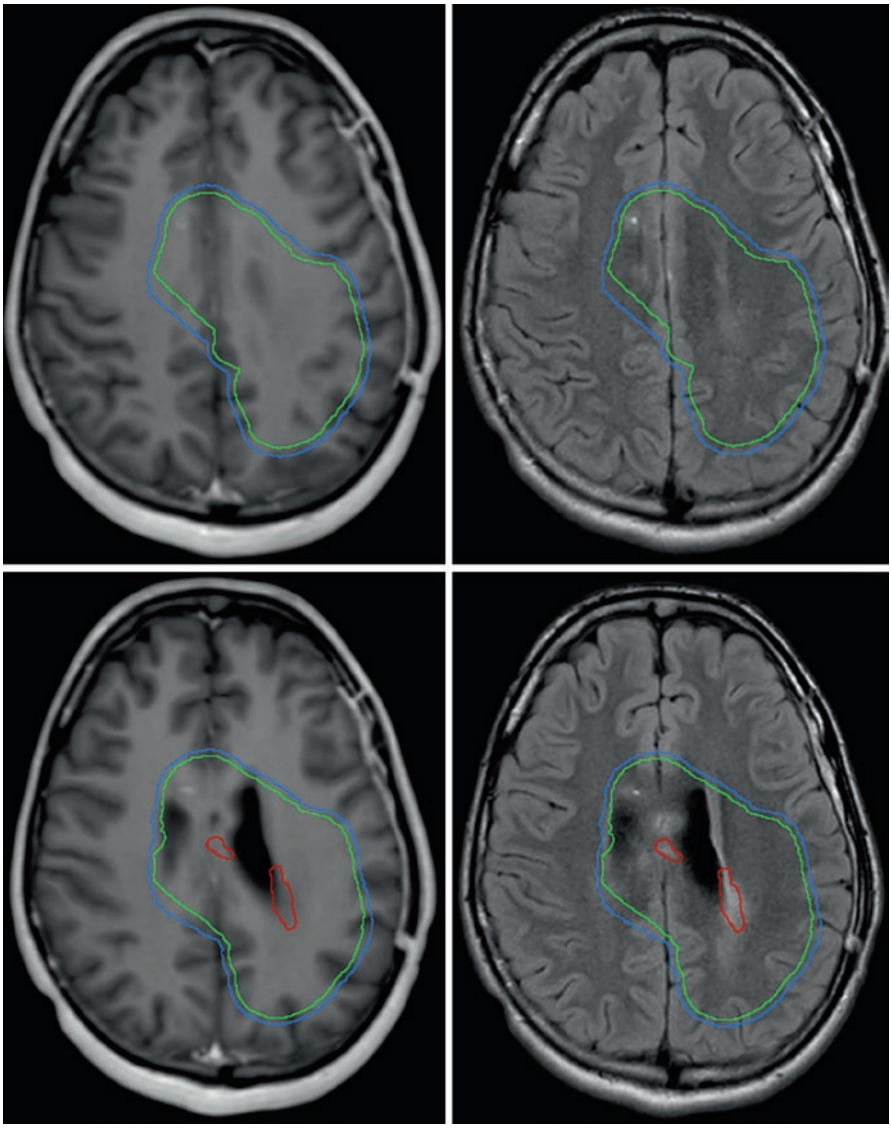


Fig. 7.5 High-grade glioma case. Axial T1 post-contrast MRI is shown on the left and axial T2/FLAIR images on the right. The patient has a large left thalamic glioblastoma status-post subtotal resection. Red = GTV1 which includes both the enhancing component and T2/FLAIR signal. Pink = GTV2 which includes the residual enhancing tumor in addition to the surgical cavity. Green = CTV (GTV1 + 1.5 cm). Blue = PTV (CTV + 3 mm). The GTV1 was felt to be small enough that GTV 2 = GTV 1 and the entire target could be safely treated to 59.4 Gy. Yellow = optic nerves and chiasm. Note that part of the chiasm is within the PTV, but the normal tissue tolerance of this structure should be respected and a "cold" spot allowed within the target to achieve this



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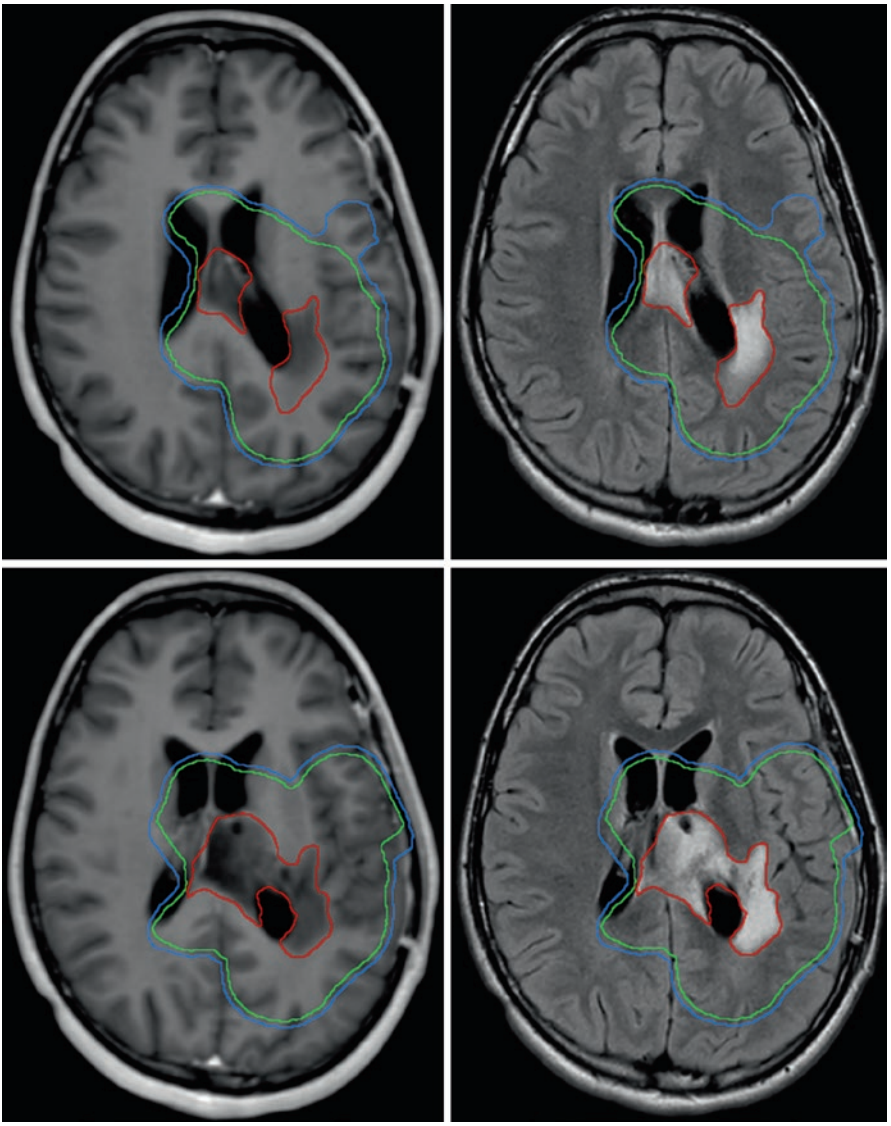

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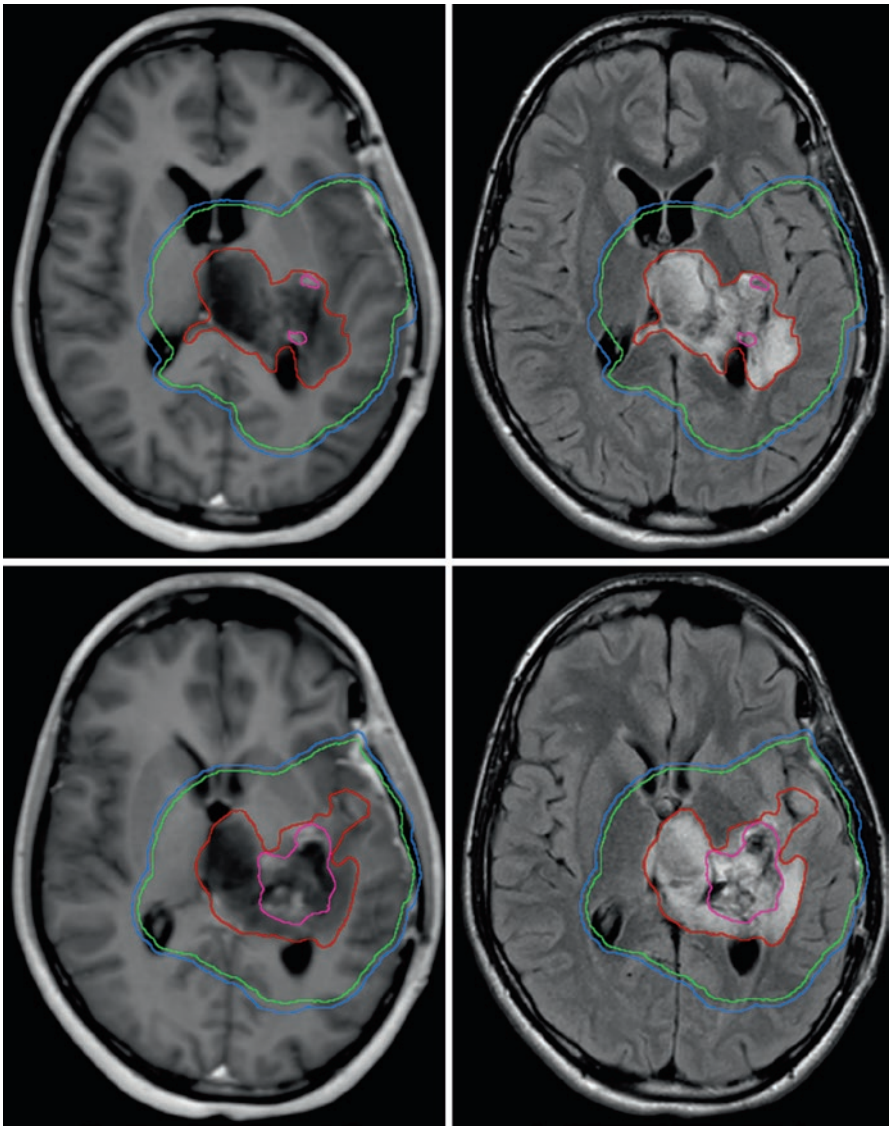

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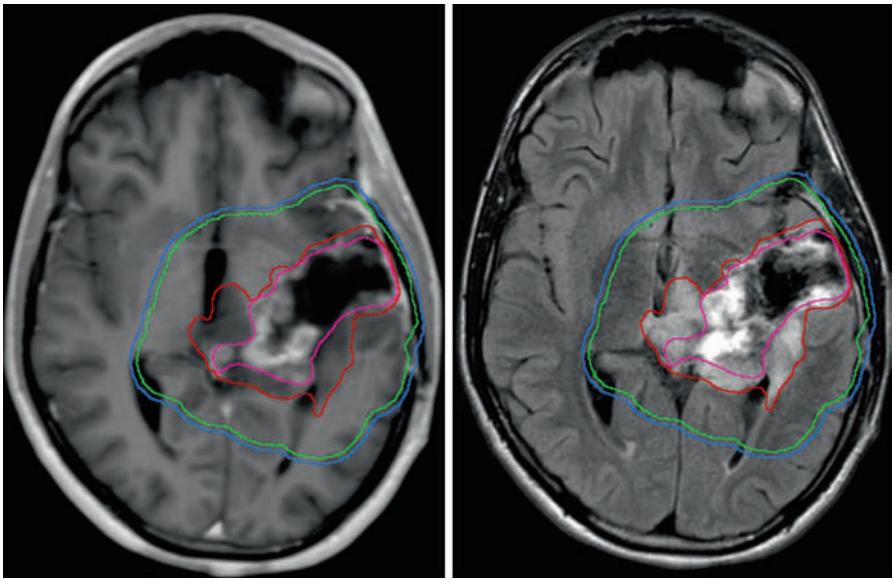

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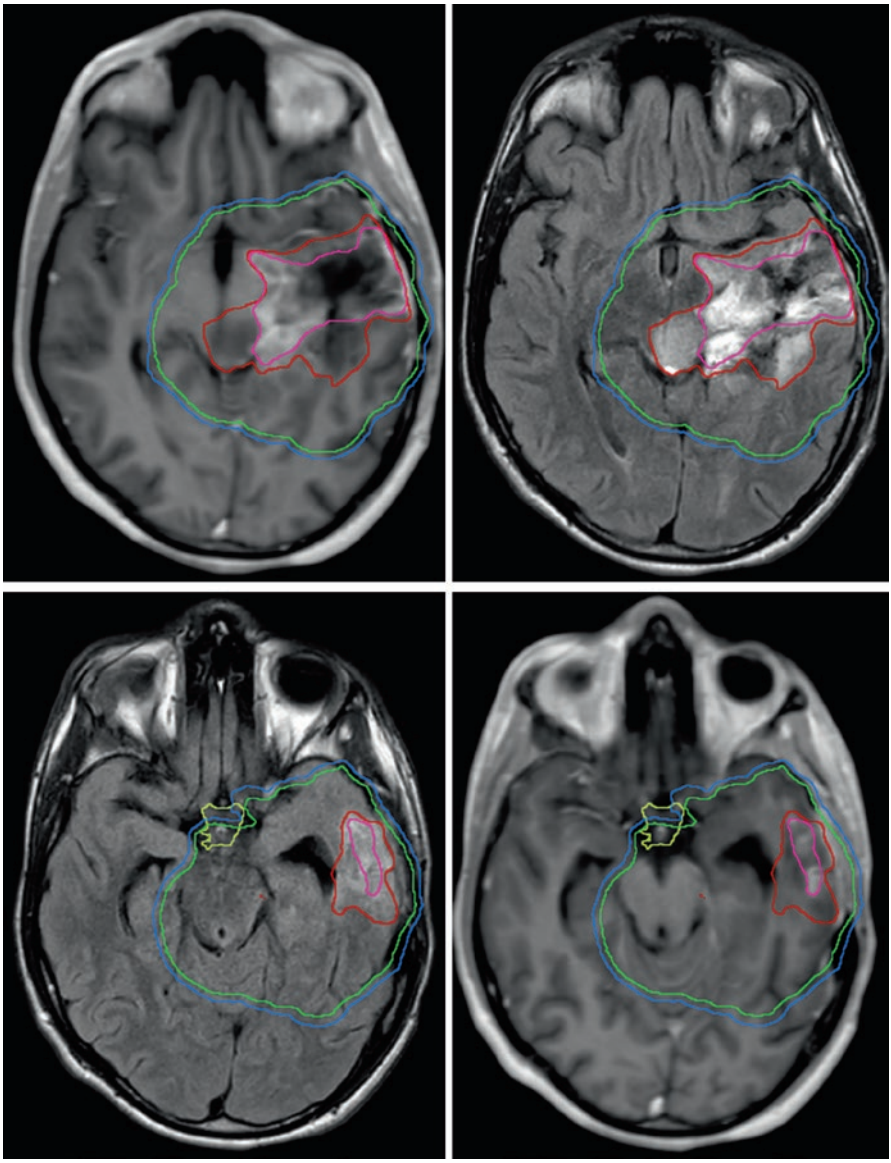

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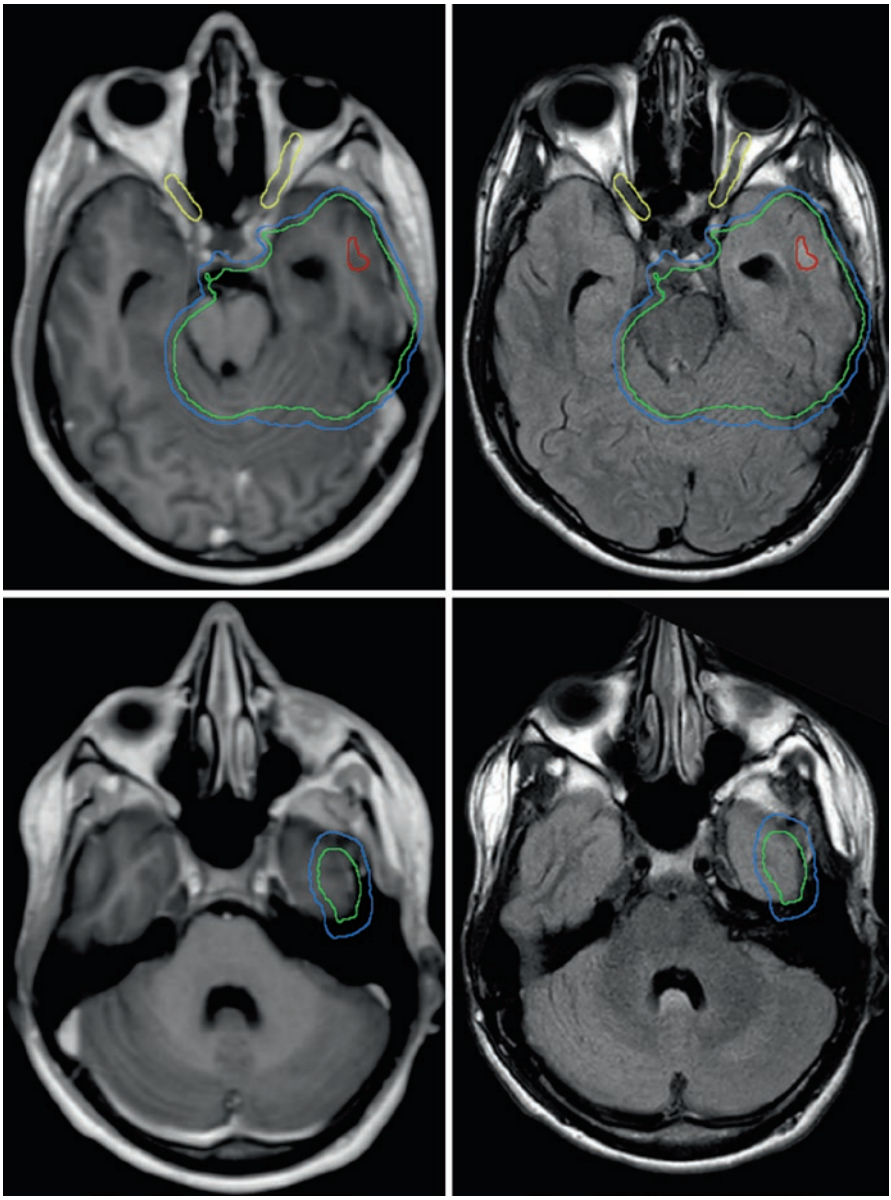


Fig. 7.5 (continued)

  - GTV2 = postoperative cavity after gross total resection or residual tumor as determined by pre- and post-contrast T1-weighted MRI. The GTV2 may equal GTV1 if the PTV1 is relatively small and a dose of 59.4 Gy to this volume is safe.
  - CTV1 = GTV1 + 1.5 cm. (In published literature and previous protocols, CTV margins of 2 cm and even more have been used; however with advancements in imaging for better characterization of the tumor and for target volume delineation, a smaller margin of 1.5 cm is probably appropriate.)
  - CTV2 = GTV2 + 1 cm.
  - PTV1 = CTV1 + 3–5 mm.
  - PTV2 = CTV2 + 3–5 mm.
- Dose: Primary site PTV1 54 Gy in 30 daily fractions followed by an addition 5.4 Gy boost to PTV2 in 3 daily fractions (as per the Children's Oncology Group ACNS0822 protocol).

7.5.4 Diffuse Intrinsic Pontine Glioma (DIPG)

- Brainstem gliomas account for 10–20% of pediatric brain tumors; of these, 50–85% are DIPG.
- Biopsy is not required but is now being performed more frequently to help identify potential targeted therapies.
- The prognosis for children with DIPG is very poor, and since surgical resection is not possible, radiation is the primary treatment modality.
- Tumor recurrence is predominately local. However, leptomeningeal dissemination is seen in a significant minority of patients at disease progression [12, 13].
- Target delineation (Fig. 7.6):
  - GTV = enhancing and non-enhancing tumor (T2/FLAIR abnormality)
  - CTV = GTV + 1 cm (1.5 cm CTV margin has been used in some studies; however, with advances in technology and planning techniques, a CTV margin of 1 cm is recommended in current studies.)
  - PTV = CTV + 3–5 mm
- Dose: 54 Gy in 30 daily fractions.

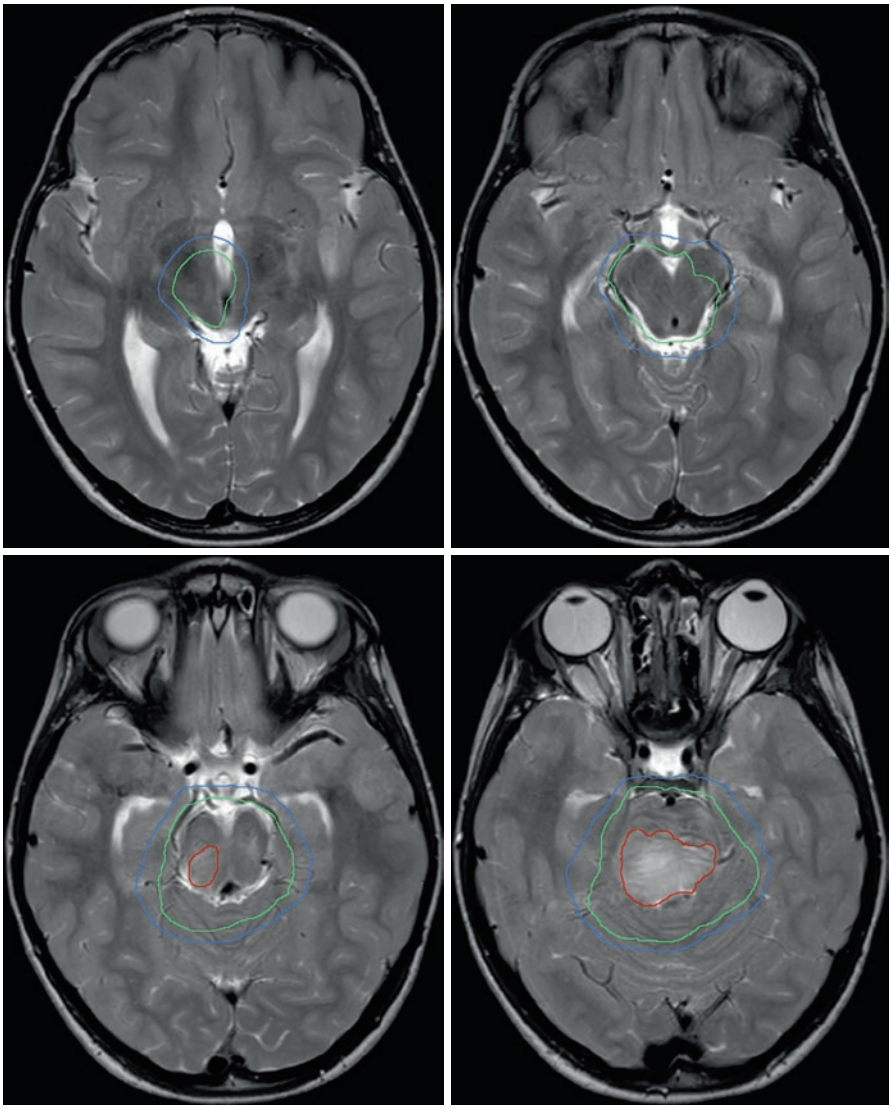
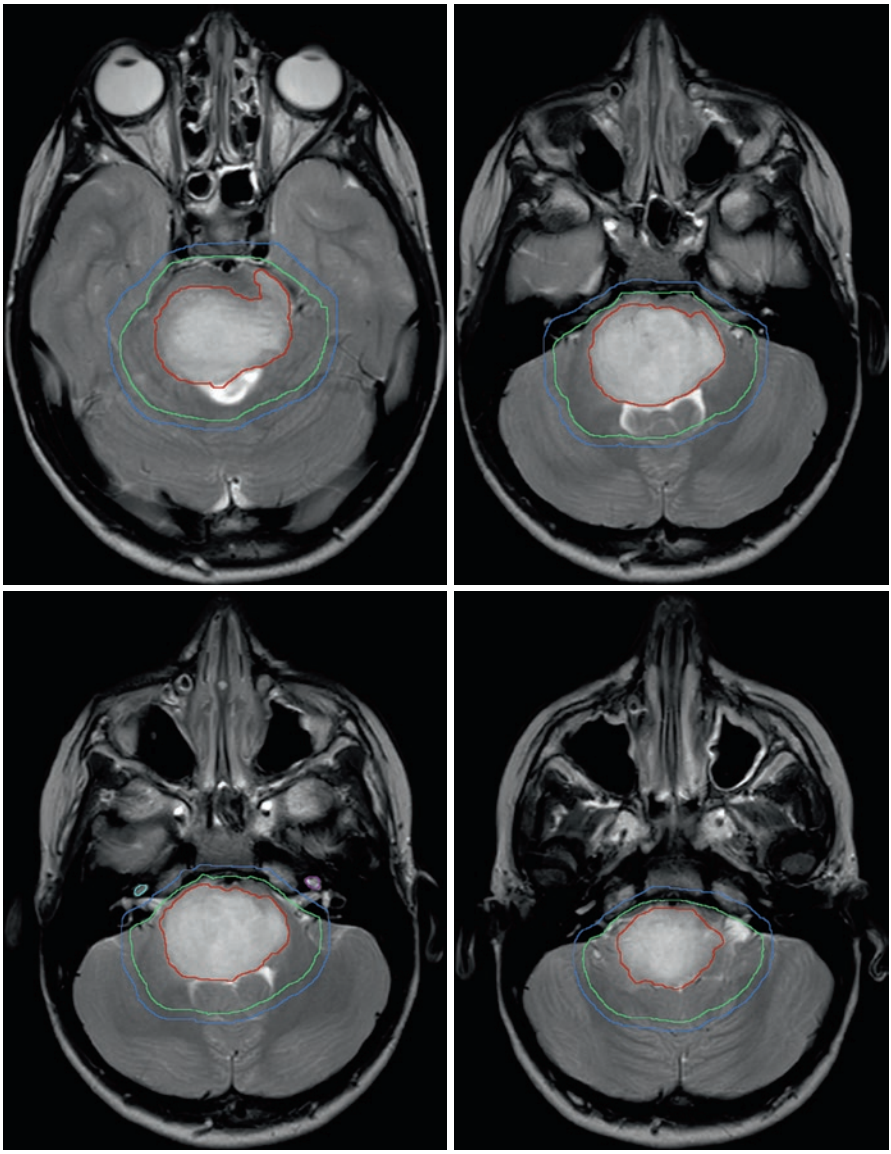


Fig. 7.6 Diffuse intrinsic pontine glioma case. Axial T2-weighted MRI slices of the head of a patient with a DIPG are shown. Red = GTV which includes the T2/FLAIR abnormality and any abnormal enhancement. Green = CTV (GTV + 1 cm). Blue = PTV (CTV + 3 mm). Purple = left cochlea. Teal = right cochlea



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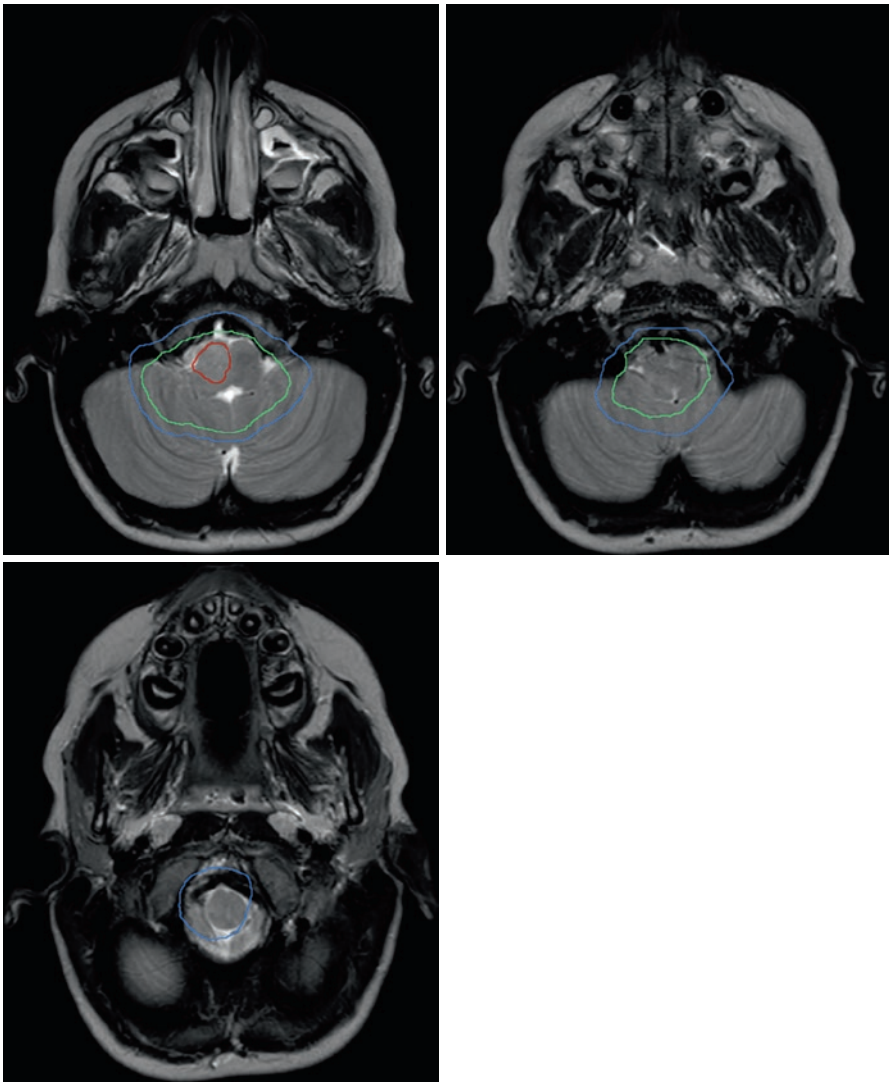

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Rhabdomyosarcoma

8

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8.1 Background

- With roughly 250 new cases each year, pediatric rhabdomyosarcoma (RMS) makes up slightly less than one half of all pediatric soft tissue sarcomas diagnosed within the United States [1].
- Sites of origin are varied and tumors can arise anywhere within the body. Common sites include the head and neck (35%), genitourinary tract (24%), extremities (19%), and elsewhere (22%) [2].
- Treatment for RMS depends on risk group stratification. The intensity of chemotherapy and the use of surgery and/or radiotherapy vary among high-, intermediate-, and low-risk groups, which are determined by primary site, stage, clinical group, and histology.
  - **Primary Site**: The primary sites of origin are categorized as favorable or unfavorable:
    Favorable sites include the orbit, non-parameningeal head and neck, genitourinary tract, and biliary tract.
    Unfavorable sites include bladder, prostate, perineal/perianal and retroperitoneum, trunk and extremity, and parameningeal tumors.
    Tumors that involve two adjacent sites with differing designations of favorability are classified as "unfavorable," so as not to risk delivering inadequate treatment.
  - **Stage**: The staging for pediatric RMS utilizes the tumor, node, and metastasis (TNM) system but also takes into consideration the primary site (Table 8.1).
  - **Clinical Group**: The postsurgical extent of disease prior to the initiation of chemotherapy determines the clinical group in RMS. The group designation represents the tumor extent *before* any chemotherapy has been given, and children who have a delayed surgical resection after chemotherapy has begun are classified as Group III, based on their initial pre-chemotherapy designation (Table 8.2).
  - **Histology**: RMS is segregated into favorable (embryonal, botryoid, and spindle cell) and unfavorable (alveolar) histologic subtypes. Embryonal histology comprises 60–70% of all cases, and alveolar histology is seen in 20% of cases [3]. Two translocations, *PAX3-FOXO1* and *PAX7-FOXO1*, involving the tran-

Table 8.1 Staging for RMS

Stage	Primary site	Tumor extent	Tumor size	Lymph node status	Metastasis
1	Favorable	T1 or T2	*a* or *b*	Any N	M0
2	Unfavorable	T1 or T2	*a*	N0	M0
3	Unfavorable	T1 or T2	*a*	N1	M0
		T1 or T2	*b*	Any N	M0
4	All	T1 or T2	*a* or *b*	Any N	M1

T1 tumors are confined to the anatomic site of origin. *T2* tumors have extension into or fixation to the surrounding tissue. Tumors are classified as "a" if <5 cm and "b" if >5 cm. *N1* clinically involved nodes, *N0* not clinically involved, and *NX* clinical status unknown. *M0* no metastasis, *M1* metastasis present

Table 8.2 Clinical grouping for RMS

Group I	Localized disease that has been completely resected: a. Confined to muscle or organ of origin b. Infiltration outside the muscle or organ of origin
Group II	Complete resection with: a. Microscopic residual disease b. Regional lymphatic spread that has been resected c. Both
Group III	Gross residual disease: a. After biopsy only b. After major resection (greater than 50% resected)
Group IV	Distant metastatic disease present at diagnosis

scription factor *FOXO1* define alveolar genetics. The presence of these translocations portends a worse prognosis, whereas the absence of these translocations in histologically alveolar tumors indicates an outcome similar to embryonal tumors. In the current COG study, ARST1431, *FOXO1* positivity is used to determine risk group and dose [4].

– **Risk Group**: Currently, the RMS risk stratifications used by the Children's Oncology Group (COG) studies separate children into three risk groups (low, intermediate, and high risk). Overall survival varies among the groups and is roughly 98% for low-risk patients, 78% for intermediate-risk patients, and 30% for high-risk patients [5–7]. The current designations for each group are as follows:
  Low risk: Low-risk RMS is defined as nonmetastatic embryonal RMS arising in favorable sites (stage 1) with any clinical group (group I–III) or embryonal RMS arising in unfavorable sites with either completely resected disease (group I) or microscopic residual disease (group II)
  Intermediate risk: Intermediate-risk RMS is defined as nonmetastatic (group I–III) alveolar RMS arising at any site (stage 1–3) or incompletely excised (group III) embryonal RMS arising in an unfavorable site (stages 2 and 3).
  High risk: Patients with metastatic RMS (group IV, stage 4)

8.2 General Principles of Radiotherapy

8.2.1 Tumor Delineation

- Tumor volumes are created using information gathered from physical examination, surgical evaluation, and/or various radiologic studies.
- Comprehensive imaging prior to any treatment as well as at the time of radiation planning is critical to developing an accurate radiation plan.
- Depending on the primary site and disease extent, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), bone scan, or positron emission tomography (PET) may all be utilized.
  – MRI is generally the preferred method of primary site imaging, especially for extremity and parameningeal sites.

  - CT is an acceptable method of primary site imaging for chest, abdominal, or pelvic primaries.
  - PET-CT has been shown to be 77% sensitive and 95% specific for RMS sites of disease outside of the primary and may provide useful information where CT/MRI/bone scan is equivocal [8].
  - Consistent use of the same method of imaging is strongly recommended for assessment of response and serial evaluations.
- Nodal staging via sentinel node biopsy or by surgical evaluation can improve detection over imaging alone and aid in radiation planning in sites at high risk for nodal involvement such as paratesticular and extremity RMS.

8.2.2 Treatment Volumes

- Treatment volumes for pediatric RMS take into consideration visible tumor and involved nodal disease as well as potential sites of occult tumor spread.
- Current guidelines based on the most recent Children's Oncology Group (COG) protocols are given below (Tables 8.3, 8.4, and 8.5).

8.2.3 Radiation Dose

- Radiation is given at 180 cGy per fraction except in the case of large abdomino-pelvic fields or whole lung irradiation, where a dose of 150 cGy is recommended.

Table 8.3 Planning definitions for gross tumor volumes (Adapted from COG guidelines)

Gross tumor volume (GTV)	Description
GTV1 (pre-chemotherapy or pre-surgery GTV)	• GTV1 is the tumor volume at diagnosis as identified by exam and/or diagnostic imaging prior to any chemotherapy or surgical procedure • Pathologically or clinically involved nodal disease is included in the GTV1 • For patients with initial tumors that extend into body cavities (thorax, abdomen, pelvis) and have been resected or have responded to chemotherapy, the GTV1 excludes the volume that extends into the cavity. Examples include the lung, intestine, or bladder that has been compressed (but not invaded) by tumor and has re-expanded following treatment • The GTV1 must include all infiltrative disease detected at initial presentation as well any additional or increased disease seen on the planning imaging (e.g., if there is tumor growth during induction chemotherapy)
GTV2 (post-chemotherapy or surgery GTV)	• The visible tumor volume identified by exam, diagnostic imaging, and/or planning imaging after chemotherapy and/or surgery • GTV2 = GTV1 if there is no change or an increase in the tumor volume after chemotherapy prior to radiation • If there has been resection or a complete response to chemotherapy with no visible tumor left at the primary site, no GTV2 is contoured

Table 8.4 Planning definitions for clinical target volumes (Adapted from COG guidelines)

Clinical target volume (CTV)	Description
CTV1	• The CTV1 = GTV1 + a margin for potential occult tumor, typically 0.5–1 cm but may be larger or smaller depending on the location and risk for adjacent invasion • The volume should not extend outside of the patient or into normal tissues such as the bone or muscle where natural anatomic barriers exist to prevent invasion. Nor should the volume encompass previously displaced organs or tissues that have returned to normal position following chemotherapy or surgery • CTV1 includes the regional lymph node chains for clinically or pathologically involved nodes. Prophylactic coverage of adjacent or draining regional lymph node chains has traditionally not been advised and should not be done unless there is high clinical suspicion for occult involvement. If clinically suspicious, a biopsy to confirm nodal involvement should be done if possible. If a biopsy is not possible, suspicious nodes should strongly be considered for inclusion in the treatment volume • The CTV1 should include the following considerations: – Imaging accuracy and quality with adjustment for uncertainties such as suboptimal image fusions or the absence of adequate pretreatment scans – Changes in tumor volume or patient weight loss since the time of imaging – Patterns of disease spread and potential subclinical involvement
CTV2	• CTV2 is defined as the GTV2 + a margin (typically 0.5–1 cm) and all areas at risk for harboring microscopic disease • As with the CTV1, the CTV2 should be modified to account for specific anatomic barriers to tumor spread and normal tissue re-expansion • If there has been a gross total resection or completed response to chemotherapy with no visible tumor left at the primary site, the CTV2 = GTV1 ± a margin
Internal target volume (ITV)	• The ITV accounts for internal motion (IM), which is the variation in the size, shape, and position of the CTV relative to anatomic reference points due to physiologic processes (bladder filling, respiration, etc.) • The magnitude of the IM is determined by imaging (4D-CT, fluoroscopy, etc.) and is incorporated into the planning target volume (PTV) margins (see Table 8.5) • ITV = CTV + IM • An ITV is not always needed in RMS and may only be pertinent to tumors in or adjacent to sites such as the chest wall, lung, mediastinum, and bladder

Table 8.5 COG planning definitions for planning target volumes

Planning target volume (PTV)	Description
PTV1	• Defined as the CTV1 (or ITV1) plus an institutionally specified margin to account for daily setup variation and uncertainty related to patient immobilization • The PTV margin is typically 0.3 to 0.5 cm which should be uniform in all dimensions • For proton planning, beam-specific PTV expansions will be required
PTV 2	• CTV2 (or ITV2) plus an institutionally specified margin

(continued)

Table 8.5 (continued)

Normal structures	Description
Organ at risk (OAR)	• Normal structures at risk for radiation toxicity which may lead to the planning volume or dose being altered
Planning organ at risk volume (PRV)	• The PRV accounts for treatment uncertainty and motion of the OAR • PRV = OAR + a margin (at least 0.5 cm) to account for physiologic change in the target volume

Special situations	Description
Whole lung irradiation (WLI)	• Children with one or more pulmonary metastases or bilateral pleural effusions can be treated with bilateral WLI • 1500 cGy at 150 cGy/fraction • For children <6 years of age, the dose can be reduced to 1200 cGy at 150 cGy/fraction
Whole abdominal radiation	• 2400 cGy at 150 cGy/fraction

- Patients with gross nodal disease undergoing biopsy alone are considered clinical group III and receive 5040 cGy, while those that are completely resected receive 4140 cGy.
- Clinically proven nodal disease that responds completely to induction chemotherapy should still receive 5040 cGy to the PTV1, though dose reductions to 4140 cGy may be considered if concerns for toxicity to adjacent structures exist.
- A volume reduction after 3600 cGy can be used for patients receiving 5040 cGy if there has been a significant decrease in tumor size after chemotherapy, especially in tumors initially displacing normal structures such as the lung or bladder [9, 10].
  - The PTV1 receives 3600 cGy, and only the PTV2 is treated to the remaining 1440 cGy for a total dose of 5040 cGy.
  - In cases where the total dose will be 3600 cGy or 4140 cGy, a volume reduction should not be used unless the normal tissue dose constraints will be exceeded.
- There is currently an open intermediate-risk COG trial that uses experimental dose escalation and reduction.
- General guidelines for dose limits to OARs are given in Table 8.6.

Table 8.6 General recommendations for dose to organs at risk

Organ	Volume (%)	Dose (cGy)
Optic nerve/optic chiasm	100	5400
Lens	100	1440
Lacrimal gland	100	4140
Retina	100	4500
Cornea	100	4140
Spinal cord	Any volume	4500

Table 8.6 (continued)

Organ	Volume (%)	Dose (cGy)
Lung (bilateral)	20	2000
	100	1500
Heart	100	3000
Liver	50	3000
	100	2340
Kidney (bilateral)	50	2400
	100	1440
Bladder	100	4500
Small bowel	50	4500
Rectum	100	4500

[a]Adapted from the Children's Oncology Group protocol ARST1431 and ARST0531

8.3 Rhabdomyosarcoma Site-Specific Guidelines

- Pattern of spread, risk of nodal involvement, and dose-limiting structures at risk for toxicity can vary significantly between RMS sites.
- Contouring examples and site-specific guidelines are given below.

8.3.1 Orbital Rhabdomyosarcoma

- Patient should be simulated supine with a thermoplastic mask used for immobilization.
- Pretreatment imaging, preferably both CT and MRI, should be fused to the treatment planning CT and used to create the GTV1/CTV1.
- The treatment planning CT and preferably a pre-radiation MRI are used to draw the GTV2/CTV2.
- An example of treatment volumes for a group III orbital RMS is given in Fig. 8.1.
- **Clinical Considerations**:
  - The orbit is defined as the bony cavity that contains the globe, the nerve and vessels, and the extraocular muscles.
  - Relevant OARs include the lens, lacrimal gland, retina, cornea, pituitary gland, optic nerve, and hypothalamus.
  - The entire orbit should not be irradiated in the case of localized orbital tumors.
  - The CTV volumes should not include the globe, as invasion into this structure does not occur. Similarly, without evidence of bony erosion, the orbital bones should also be excluded from the CTV.
  - Care should be taken to limit the dose and volume of orbital bone treated, especially in young children at risk for facial hypoplasia, and for this reason as well as for protection of the other sensitive nearby structures, proton radiation is often utilized.
  - A common site of failure in orbital RMS is the posterior orbit, and the CTV should include coverage of the orbital muscle of origin back to the posterior insertion.

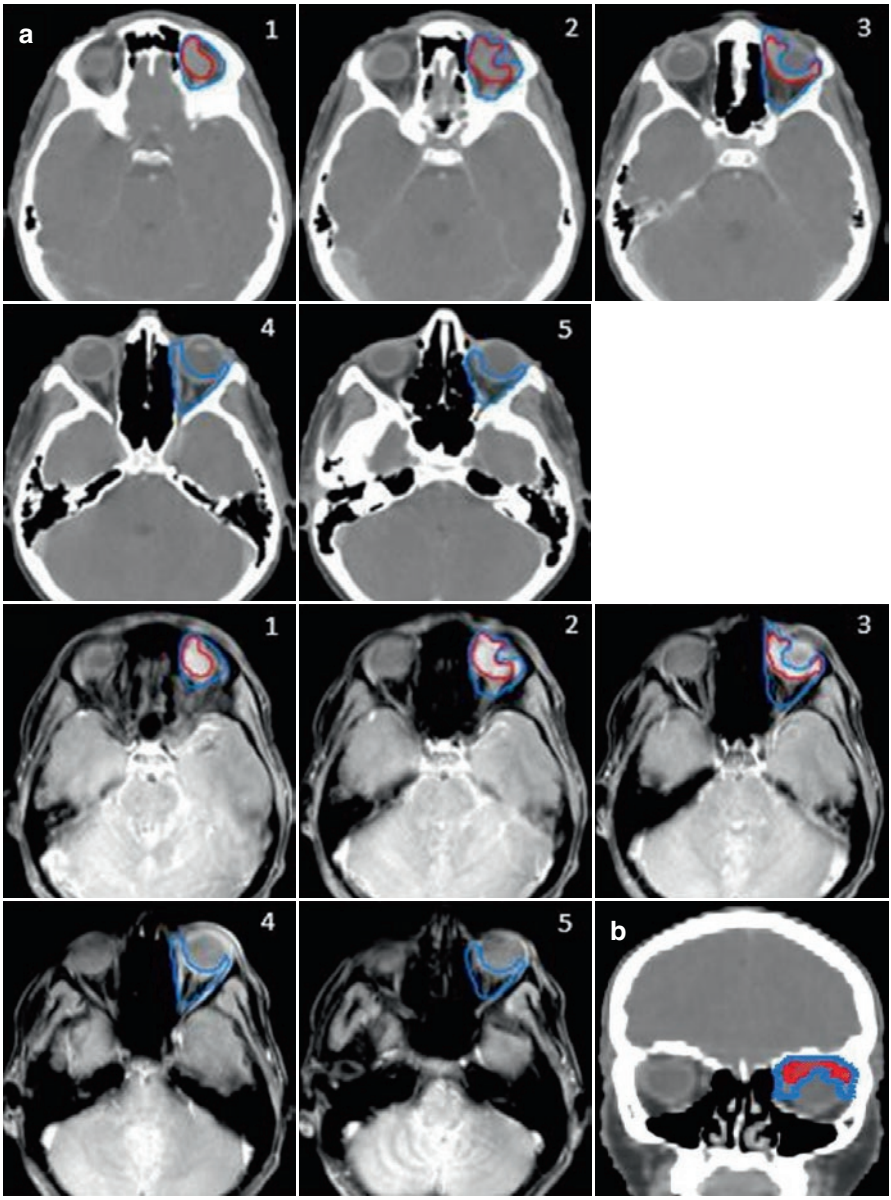

Fig. 8.1 (**a**) Axial slices from a planning CT and post-chemotherapy MRI for a stage 1 group III orbital RMS. The post-chemotherapy GTV (red) and CTV (blue) are shown below. In this case, the gross tumor reduction after induction chemotherapy was minimal, and therefore GTV1 = GTV2 and CTV1 = CTV2 with no reduction after 3600 cGy (A, planning CT; B, T2-weighted MRI). (**b**) Coronal view of the planning CT for a stage 1 group III orbital RMS with the GTV (red) and CTV (blue)

  - A volume reduction after 3600 cGy can be considered for tumors that were initially resected in total or have responded significantly to chemotherapy, with the CTV2 receiving the remainder of the radiation dose.
  - Although the last two low-risk COG protocols have specified a dose of 4500 cGy, the local failure rate in the combined two studies was higher than previous studies. Currently, a dose of 4500 cGy to 5040 cGy is used based on the response of the tumor to initial chemotherapy with doses of 5040 cGy used for partial responses and 4500 cGy used for complete response [11].
- **Uncommon Presentations**:
  - If there has been a complete response to chemotherapy or gross total resection with no visible tumor at the time of radiation, the CTV2 = GTV1.
  - Orbital tumors with extension outside of the orbit and into parameningeal sites are considered parameningeal tumors and should be treated as such with more intensive chemotherapy (such as intermediate-risk regimens) and 5040 cGy.

8.3.2 Parameningeal/Head and Neck Rhabdomyosarcoma

- Patient should be simulated supine with slight neck extension and a thermoplastic mask extending to the shoulders for immobilization.
- Pretreatment imaging, preferably both CT and MRI, should be fused to the treatment planning CT and used to create the GTV1/CTV1.
- The treatment planning CT and preferably a pre-radiation MRI are used to draw the GTV2/CTV2.
- Treatment volumes for a parameningeal RMS are shown in Fig. 8.2.
- For additional cases, please see Chap. 15.
- **Clinical Considerations**:
  - Relevant OARs include the parotid and submandibular glands, thyroid gland, pituitary gland, spinal cord, cochlea, retina, optic nerves and chiasm, and temporal lobes.
  - CNS extension and cranial nerve involvement can occur in parameningeal RMS. A T2-weighted MRI sequence to look at cranial nerves can be useful in patients with high clinical suspicion of cranial nerve involvement.
  - Any radiographic abnormality or clinical symptoms suggesting invasion should be taken seriously with at-risk/involved CNS sites covered in the treatment volumes. The skull base foramina near the primary tumor (such as the inferior orbital fissure, jugular foramen, foramen ovale, and foramen rotundum) should be paid close attention and reviewed for invasion with a radiologist if possible.
  - Careful examination of the foramen ovale is warranted in infratemporal fossa tumors, best seen with a coronal view on MRI. Look for subtle enhancement of the dura at the base of the skull and widening of the foramen on post-contrast scans.
  - Other sites commonly infiltrated by RMS include the cribriform plate and pterygopalatine fossa.

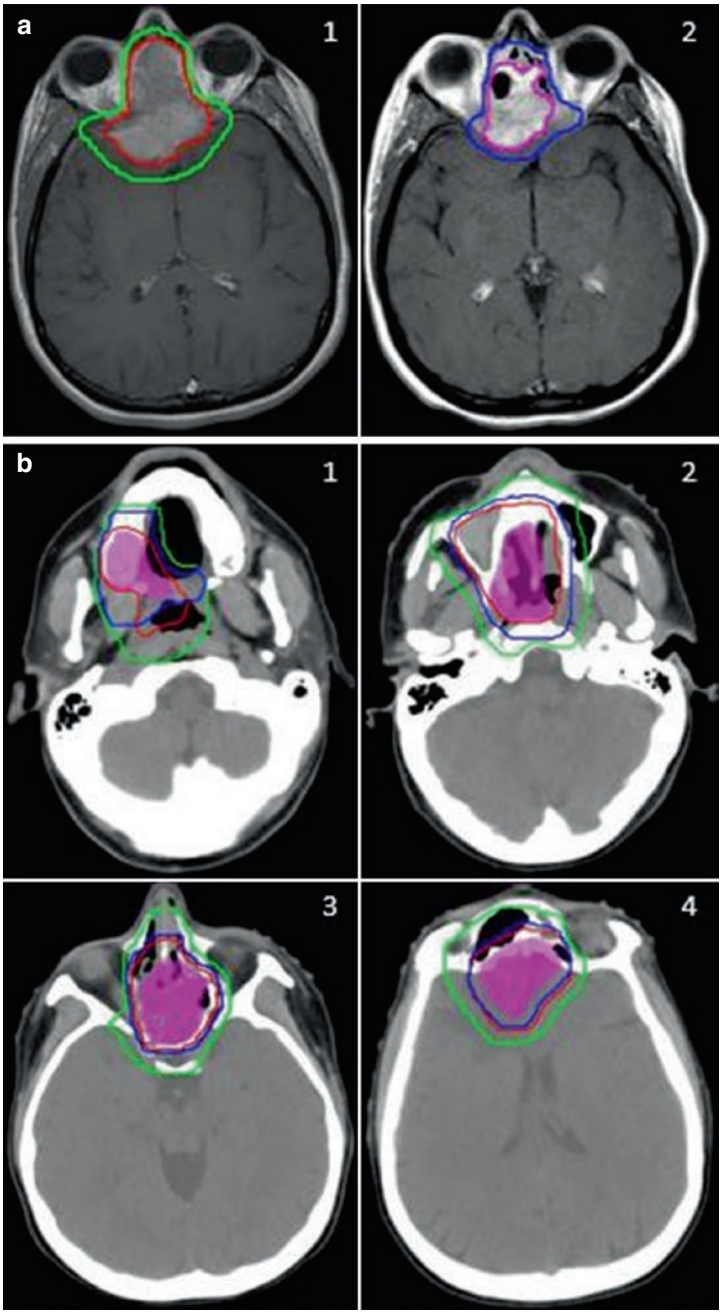

Fig. 8.2 (**a**) Pre-chemotherapy (left) and post-chemotherapy (right) MRIs for a stage 3 group III parameningeal RMS. The GTV1 (red) and CTV1 (green) and GTV2 (purple) and CTV2 (blue) are shown on their respective MRIs. (**b**) Planning CT for a stage 3 group III embryonal parameningeal RMS with intracranial extension showing the GTV1 (red), GTV2 (solid purple), CTV1 (green), and CTV2 (blue). GTV1/CTV1 was treated to 3600 cGy with a cone down to GTV2/CTV2 to 1440 cGy (5040 cGy total)

  - Draining nodal volumes are typically not covered in any N0 patient. In patients with clinically and/or pathologically involved nodes, the involved nodal region and ipsilateral draining nodes are covered in the treatment portal.
  - A volume reduction after 3600 cGy can be considered for tumors that have had a good response to initial chemotherapy and do not invade surrounding structures, with the PTV2 receiving the remaining 1440 cGy.
- **Uncommon Presentations**:
  - Large parameningeal tumors or those with extensive CNS invasion can be challenging to treat, as sensitive adjacent structures often limit the deliverable dose. In such cases, reimaging after 2 weeks and potentially replanning if there has been a tumor reduction can reduce the dose to critical OARs as well as minimize the amount of normal tissue treated.

8.3.3 Extremity Rhabdomyosarcoma

- Patient immobilization should be designed to optimize beam access to the tumor volume and avoid exit dose into uninvolved extremities and torso. A distal forearm or hand primary can be immobilized with the arm above the head.
- CT imaging is useful for delineating lymph node regions, and MRI is preferred for evaluating disease extension. Full MRI or PET imaging of the extremity prior to starting chemotherapy can detect in transit metastasis harbored in the lymphatic vessels but not yet in the nodal basins.
- Surgical evaluation of lymph nodes via sampling or sentinel node biopsy should be done prior to starting chemotherapy, as lymph node involvement can be as high as 30–40% [12]. A PET-CT scan can also be very helpful in identifying occult nodal metastasis.
- Despite the high rate of nodal involvement in extremity RMS, prophylactic coverage of the draining lymphatics is not recommended if imaging and surgical evaluation are negative.
- Because of the increased prevalence of alveolar histology in extremity RMS and the potential for subclinical extension within the muscle compartments, CTV expansions may be expanded in the proximal and distal directions.
- In cases where a complete surgical resection is achieved and histology is alveolar or in the case of an embryonal tumor with positive margins, the CTV1 = CTV2 and the entire volumes are treated to the prescribed dose.
- An example of treatment volumes for an extremity RMS is shown in Fig. 8.3.
- **Clinical Considerations**:
  - Relevant OARs include the bone, joints, lymphatics, and skin.
  - Limb positioning on the treatment planning CT is often quite different compared to the diagnostic images with regard to angle and rotation, and therefore, close attention should be paid to the image fusions with extra margins applied to areas of uncertainty. A pre-radiation MRI after CT simulation using the simulation immobilization can be helpful in generating a high-quality fusion MRI and delineating treatment volumes.

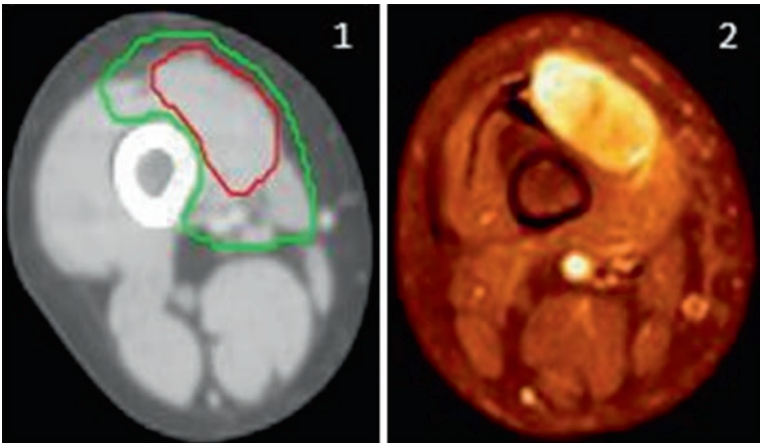

Fig. 8.3 RMS of the thigh. Shown on the left are the GTV (red) encompassing the tumor volume and the CTV (green) with a 1 cm margin tailored to encompass the at-risk muscle compartment and avoid unnecessary soft tissue extension. The planning PET-CT is shown on the right

  - Covered in the target volumes should be all evidence of tumor, including any T2 change indicating peritumoral edema seen on the MRI.
  - Whenever possible, circumferential irradiation of the extremity lymphatics and treatment across joints should be avoided. The CTV can be modified to spare these structures when deemed safe.
  - As in other sites, if there had been significant tumor reduction after initial chemotherapy, a volume reduction at 3600 cGy can be considered.
- **Uncommon Presentations**:
  - In the case of marginally resectable tumors, delayed primary excision may be attempted after initial chemotherapy. Tumors resected after initial chemotherapy are still classified as clinical group III, but the radiation dose can be reduced to 3600 cGy or 4140 cGy.

8.3.4 Rhabdomyosarcoma of the Trunk

- Patients can be immobilized in the supine or prone position, depending on the tumor location (chest wall, paraspinal, abdominal wall, or diaphragm). Arm positioning should be chosen to maximize reproducibility while avoiding entrance and/or exit dose into the contralateral limb.
- Both CT and MRI imaging are useful for delineating disease extension and treatment volumes.
- Surgical resection is preferred when feasible, either at diagnosis or as a delayed primary excision, and radiation is given to all patients except those with small, completely excised embryonal tumors without nodal involvement.
- **Clinical Considerations**:
  - Relevant OARs include the heart, lungs, breast tissue in female patients, spinal cord, liver, kidneys, and bowel.

  - Evaluation of target volume motion with 4D-CT or fluoroscopy should be considered in chest wall, diaphragm, and abdominal wall tumors.
  - In cases where a significant amount of lung or bowel was displaced by the pretreatment tumor and has subsequently returned to normal anatomic position following surgery or chemotherapy, the GTV1 should be modified to exclude those tissues.
  - All areas of pleural involvement should be included in the GTV1 regardless of whether the radiation is delivered pre- or postoperatively.
- **Uncommon Presentations**:
  - In the case of a chest wall tumor with extensive malignant pleural disease, initial treatment with ipsilateral lung radiation may be considered to 1500 cGy followed by a field reduction to the primary site.

8.3.5 Bladder and Prostate Rhabdomyosarcoma

- Patients should be immobilized in the supine position. In males, a clamshell can be used to shield the testes from dose, though this can be technically difficult in young children.
- Both CT and MRI imaging should be utilized for delineating treatment volumes. PET-CT is useful for evaluating lymph node metastases. Typically MRI and CT imaging prior to chemotherapy are most useful in determining the extent of bladder wall involvement.
- Cystoscopy may provide additional information for treatment volume delineation but can underestimate disease extension, as only the mucosa is evaluated in these muscle-derived tumors.
- If surgery is planned, a multidisciplinary discussion including the surgeon prior to the resection is often invaluable. A detailed operative note explaining where tumor was invasive or merely pushing and clips placed in the resection bed to demarcate the extent of involvement and areas concerning for positive margins will improve volume determination.
- In many cases, the tumor bed will be smaller than the primary tumor, as the pushing borders of a large tumor may collapse down after surgery and/or chemotherapy and may be excluded from the radiation treatment volume when deemed safe to do so.
- An example of treatment volumes for a bladder/prostate RMS is shown in Fig. 8.4.
- **Clinical Considerations**:
  - Relevant OARs include the bowel, bladder, pelvic bones and growth plates, femoral heads, and reproductive organs.
  - Target volumes and OARs may shift significantly due to natural variation in the filling of the rectum, bladder, and bowel. CTV margins should take into account these changes.
  - Often tumors in this region arise from the prostate and infiltrate the bladder walls posteriorly and anteriorly. In older children, simulation and treatment with a comfortably full bladder may help to reduce bladder dose and improve reproducibility.

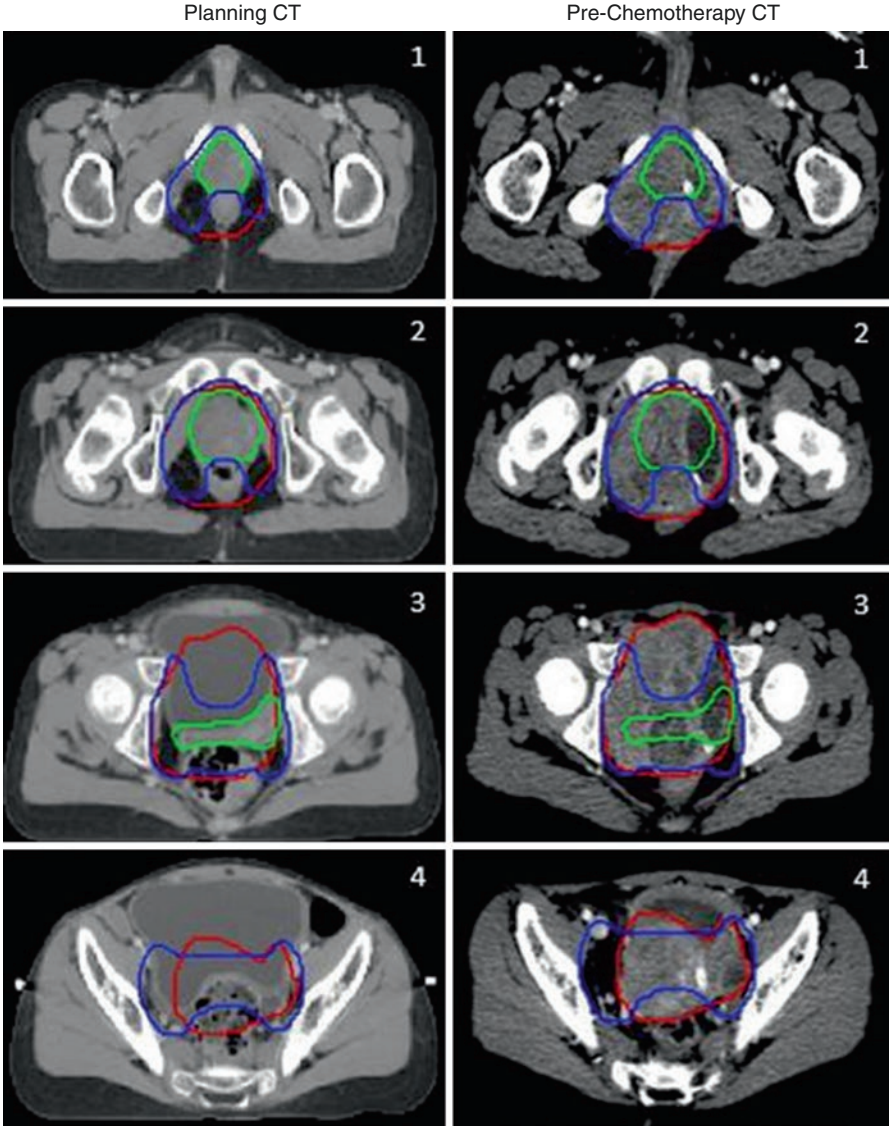

Fig. 8.4 Stage 3 group III embryonal RMS of the prostate. The post-chemotherapy planning CT is shown on the left, and the pre-chemotherapy CT is on the right. The pre-chemotherapy GTV1 (red), post-chemotherapy GTV2 (green), and CTV1 (blue) are shown on both scans. After 3600 cGy, a cone down to the GTV2 plus an anatomically constrained margin 0.5–1 cm was treated to the remaining 1440 cGy (not shown)

  - In young children, IV fluids given in conjunction with sedation can increase bladder volume. During CT simulation, it is helpful to scan early in the simulation and then wait another 10–15 minutes with IV fluids running and repeat the scan. The two scans will give a better idea of potential bladder changes during radiation delivery. An indwelling catheter clamped after bladder filling with an amount determined at the time of simulation may also be considered. Cone beam CT or US may be helpful to assure reproducibility during daily treatments.
  - Sparing of the bladder dome and/or trigone can lead to improved bladder capacity in the future for these patients.
  - Similarly, rectal filling can also be variable and should be examined and/or contoured on prior scans.
  - The CTV should be drawn on multiple simulation scans to ensure that the at-risk volume is adequately covered and OARs are protected in any scenario of bladder and/or rectal filling.
- **Uncommon Presentations**:
  - Occasionally in younger patients, bladder outlet obstruction or ureteral impingement from a large pelvic mass can lead to renal impairment or acute failure. Nephrostomy tube placement prior to treatment may be necessary.
  - When pelvic tumors are very large and do not respond well to chemotherapy by week 9, delayed primary excision should be considered. However, this is very often a complicated surgery with a high risk of morbidity and ideally should be performed by a pediatric urologist and pediatric surgeon.

8.3.6 Paratesticular Rhabdomyosarcoma

- Inguinal orchiectomy is the initial intervention in paratesticular RMS. Boys ten years of age with negative abdominal imaging should undergo retroperitoneal lymph node dissection following inguinal orchiectomy.
- Radiation to the para-aortic nodes is is given to patients with completely resected positive lymph nodes after lymph node dissection (4140 cGy). Any remaining gross disease in the para-aortic chain (unresected gross nodes) are treated to 5040 cGy. In rare instances, radiation can be used to treat the primary site if positive margins remain.
- Patients should be immobilized in the supine position with a custom mold and legs slightly separated (or in a “frog-leg” position if old enough to comply) to provide access to the inguino-pelvic lymph nodes (if needed) and avoid skin reaction from groin folds.
- Both a pelvic CT with contrast and PET-CT are useful for evaluating lymph node metastases, but CT alone has been shown to be unreliable in diagnosing lymph node disease in paratesticular RMS [13]. The risk of lymph node disease is greatest in boys 10 years of age or older, and therefore all boys over 10 years receive a unilateral retroperitoneal lymph node dissection (RPLND). In boys <10 years of age, RPLND is only done in cases where radiographically enlarged nodes are seen. An MRI is typically not needed.

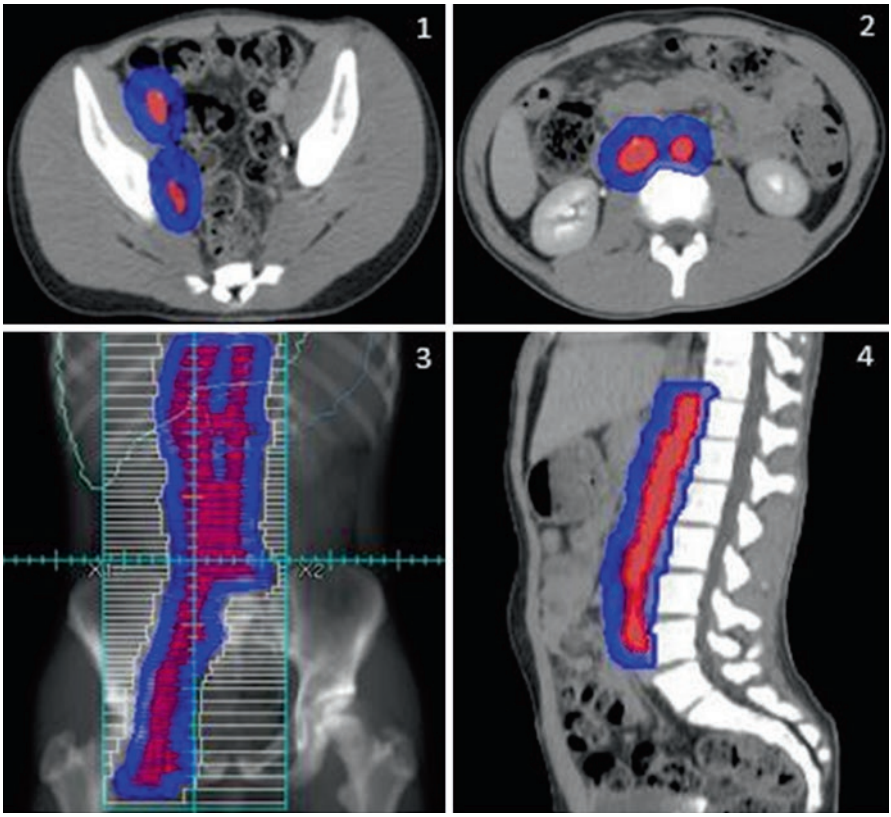

Fig. 8.5 Treatment volumes for a stage 1 group II paratesticular alveolar RMS. After orchiectomy and RPLND with positive nodes, this patient was treated to 4140 cGy

- A discussion on fertility and potential sperm banking for older children should take place prior to treatment. In patients too young to bank sperm, a testicular biopsy to preserve fertility can be considered. These matters should be addressed prior to the start of any chemotherapy.
- An example of treatment volumes for a paratesticular RMS is shown in Fig. 8.5.
- **Clinical Considerations**:
  - Relevant OARs include the bowel, bladder, kidneys, heart, pelvic bones and growth plates, and reproductive organs.
  - Treatment volume should be treated to a 0.5–1 cm anatomically tailored margin around the abdominal aorta and vena cava from T10/11 to L5/S1.
  - Nodal involvement occurs in 20–40% of cases, and the initial pre-chemotherapy imaging should be carefully reviewed for pelvic lymph node involvement.
  - Coverage of the ipsilateral ilioinguinal nodes is controversial but may be considered in patients with bulky para-aortic disease or multiple nodal sites on initial work-up.

- **Uncommon Presentations**:
  - If a trans-scrotal biopsy is performed prior to inguinal orchiectomy, the tumor site is considered to be violated, and the patient is clinical group II. In this case, a hemiscrotectomy can be performed or a smaller resection of the violated scrotal tissue followed by radiation to the hemiscrotum. If radiation is given, the remaining testicle can be transposed laterally into the thigh prior to radiation and then reimplanted into the scrotum at the end of therapy.
  - If a patient has bulky para-aortic adenopathy that cannot be resected safely at the time of diagnosis, RPLND is delayed until after initial chemotherapy with postoperative radiation to follow. If RPLND cannot be done even after chemotherapy, then definitive radiation to 5040 cGy is used.

8.3.7 Pelvic, Genitourinary, and Retroperitoneal Rhabdomyosarcoma

- Perineal/perianal
  - Complete resection in this area is often very difficult.
  - There is a high frequency of alveolar histology and nodal involvement (>50%), especially in children >10 years [14, 15].
  - Prophylactic ilioinguinal lymph node irradiation in children ≥10 years or older is often recommended [13].
  - For children <10 years, thorough nodal evaluation should be carried out, and ilioinguinal lymph regions should be covered in those with radiographically or pathologically confirmed nodes.
- Retroperitoneal
  - Nodal involvement is seen in ~30% of cases [16].
  - Bowel and organs displaced by the tumor that have returned to normal anatomic position following surgery or chemotherapy should not be included in the CTV1 unless microscopic invasion is suspected.
  - All areas of peritoneal or mesenteric involvement should be included in the GTV1 regardless of whether the radiation is delivered pre-or postoperatively.
  - If whole abdominopelvic radiotherapy is required for malignant ascites or diffuse peritoneal involvement, 2400 cGy at 150 cGy per fraction is recommended with appropriate blocking of the kidneys and liver.
- Vaginal/vulvar
  - Omission of RT in group II/III vaginal RMS has led to unacceptable rates of local failure (26–43%) [17]. Therefore, these patients should receive 3600 cGy if CR and 5040 cGy if visible disease remains with a thoughtful RT plan to spare adjacent organs (uterus, bladder, pelvic growth plates, and ovaries should be considered).
  - The risk of vaginal stenosis and infertility in very young females can be quite high, and therefore if doses over 3600 cGy are required, vaginal brachytherapy using an HDR system delivering 5000–6000 cGy over 5–6 days can be considered.

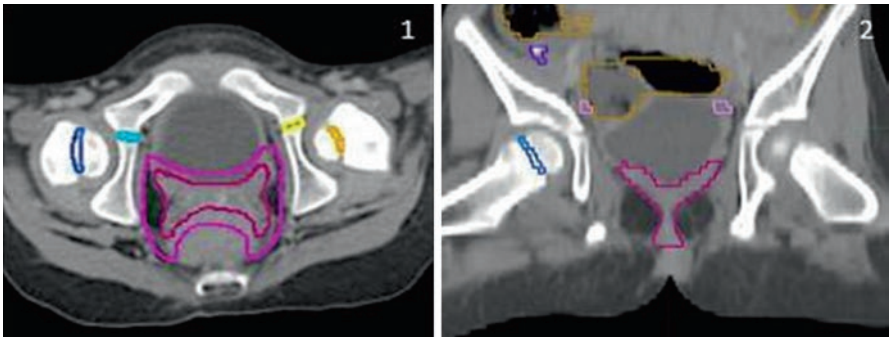

Fig. 8.6 Perineal GTV (red) and CTV (pink) are shown on axial and coronal CT views. Pelvic (light blue and yellow) and femoral (blue and orange) growth plates are also shown

- An example of treatment volumes for a perineal RMS is shown in Fig. 8.6.
- **Clinical Considerations**:
  - Critical OARs include the bladder, pelvic growth plates, uterus, ovaries, and vagina.
  - Legs apart or frog-leg setup is often useful to allow access to ilioinguinal lymph nodes and reduce skin folds in the pelvic area.

8.3.8 Proton Therapy

- Proton therapy may be useful to consider for pediatric RMS patients who develop tumors in close proximity to sensitive OARs.
- At present, a number of dosimetric studies clearly demonstrate that protons have the ability to reduce excess dose to critical structures in the head and neck, pelvis, and other RMS sites, though clinical outcome data showing a clear reduction in toxicity is still absent [18–22].
- Clinical situations where proton therapy may provide a benefit include:
  - Localized orbital tumors where dose to the uninvolved orbit can be minimized
  - Parameningeal tumors in young children or those with CNS invasion to reduce dose to the brain, optic structures, and spinal cord. Lateralized parameningeal and head and neck tumors where dose to the contralateral structures would be omitted
  - Truncal tumors, especially those in the chest wall abutting the heart and lungs and paraspinal tumors adjacent to the kidneys
  - Bladder/prostate tumors where dose to the testes, ovaries, and pelvic growth plates can be omitted or minimized (Fig. 8.7)

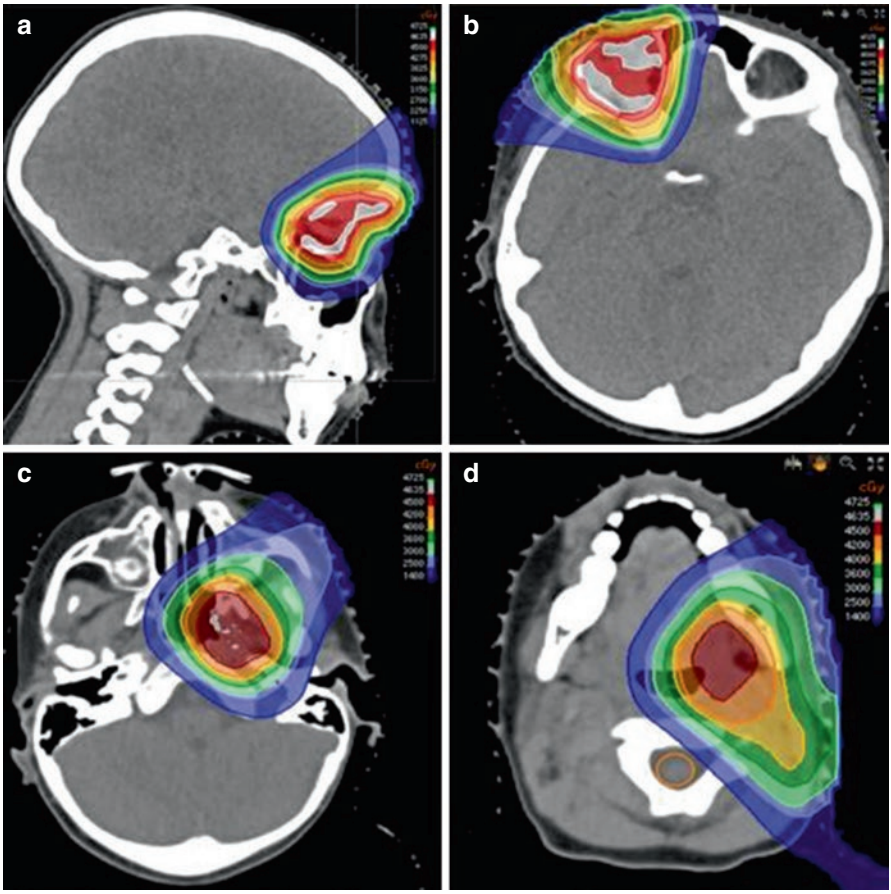

Fig. 8.7 Proton plans for an orbital RMS (**a**, **b**) and a parameningeal RMS (**c**, **d**)

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Ewing Sarcoma and Osteosarcoma

9

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Contents

9.1 Background

- Pediatric bone tumors are treated with multiagent systemic chemotherapy combined with surgery and/or radiation therapy for local therapy.

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9.2 Ewing Sarcoma

- For Ewing sarcoma, radiation therapy is generally used for definitive local therapy when surgical resection is not feasible or would result in significant or unacceptable morbidity (including but not limited to pelvic, spinal, and base-of-skull tumors) [1–6].
- Adjuvant radiation therapy is typically indicated in the setting of positive margins, tumor spill, or poor response to induction chemotherapy [7].
- Definitive and adjuvant radiation ordinarily begin concomitantly with the start of consolidation chemotherapy. When indicated, whole lung irradiation and radiotherapy to sites of metastatic disease are performed after completion of consolidation chemotherapy.

9.3 Osteosarcoma

- For osteosarcoma, the preferred local therapy is oncologic resection with widely negative margins; adjuvant radiation therapy is given for positive margins and in selected patients at high risk for local recurrence (Figs. 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, and 9.8).
- Preoperative radiation therapy should be considered in bone tumor patients with "operable" tumors at high risk for microscopic positive margins.
- Definitive radiation may be considered in inoperable cases. High doses of radiation, on the order of 70 Gy, are generally delivered for these cases.

9.4 General Principles: Target Delineation and Treatment Planning

- Pretreatment and posttreatment imaging should be used for radiation therapy planning, including contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) (and positron emission tomography-computed tomography (PET-CT) when useful).
- Immobilization is dependent on the site of involvement. Custom-molded positioning cushions should be used to immobilize the pelvis and proximal lower extremities. For thoracic primaries, a customized Vac-Lok™ bag (Civco Medical Solutions, Coralville, IA) or Alpha Cradle (Smithers Medical Products Inc., North Canton, OH) is often used; the arms can be positioned above the head with a Vac-Lok™ or wingboard. Head-and-neck and skull-base primaries typically require mask immobilization with shoulder pulls and a bite plate, as necessary.
- Multi-angle photographs of the patient in the treatment position should be included in the CT simulation documentation. Ink skin markers or tattoos for laser alignment are usually necessary.
- Four-dimensional (4D) CT with or without respiratory motion management should be used for thoracic and abdominal primary tumor sites where the target volume and/or normal organs move with respiration.

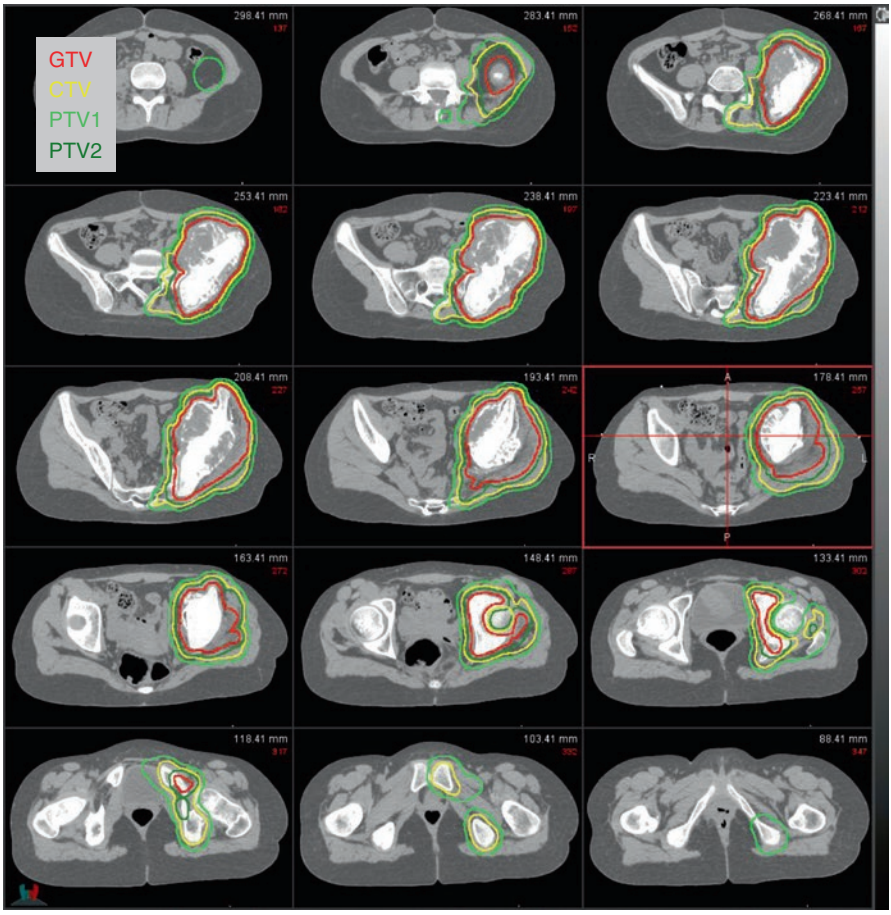


Fig. 9.1 Example of an unresectable left iliac wing T2N0M0 osteosarcoma. CT simulation was performed with 1.0 mm slice thickness. Representative axial slices and target volumes are shown. Note that the CTV expansion has been constrained to the initially infiltrated muscles and for pushing borders into the bowel space. In addition, the CTV did not include the femoral head, which was not involved by the tumor

- For any abdominal or pelvic tumor, patients should be imaged from the diaphragm to pelvis to obtain accurate bowel space dose measurements. For any chest wall or thoracic tumor, imaging should include the entire bilateral lung region to obtain accurate pulmonary dose measurements.
- The tumor should be delineated based on physical examination and using contrast-enhanced CT, MRI, and PET/CT, when helpful. For bone tumors, specific MRI sequence and parameters should be guided by the diagnostic radiologist. Whenever possible, MRI should be obtained in the treatment position.
- Pretreatment diagnostic imaging should be registered to the CT simulation for treatment planning. The preoperative/prechemotherapy tumor volume at presentation should be delineated in all cases.

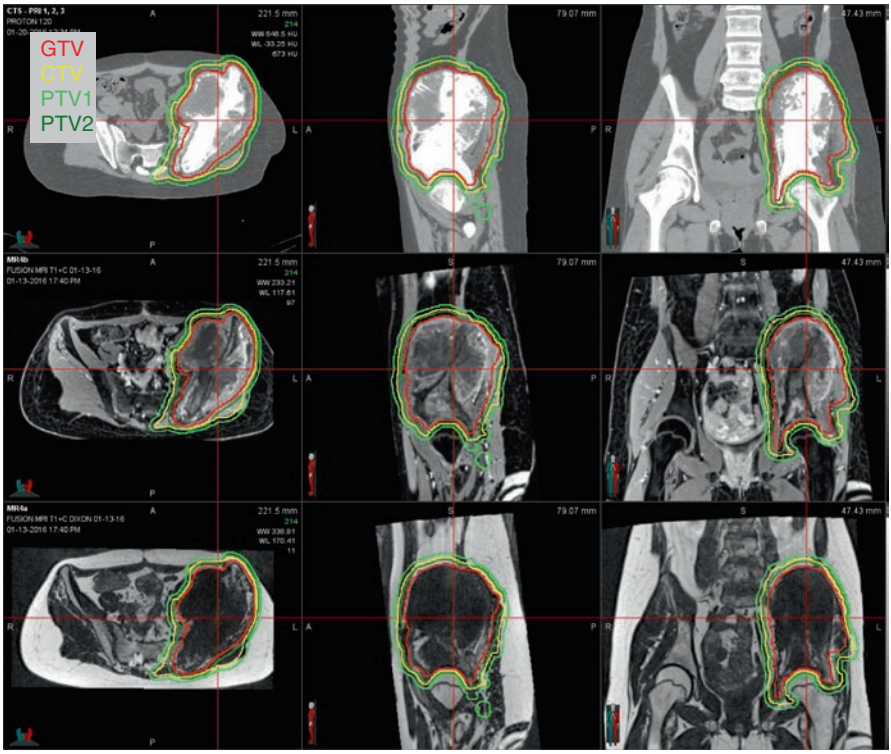


Fig. 9.2 Axial, sagittal, and coronal displays of the target volumes for the unresectable left iliac wing T2N0M0 osteosarcoma. The tumor was delineated using CT (row 1) and diagnostic MRI fusion. Note the utility of the T1-weighted images with contrast (row 2) and fat-suppression T1-weighted images with contrast (row 3) for GTV delineation

- For extremity tumors, the clinical target volume (CTV) should be modified at the discretion of the radiation oncologist to avoid circumferential irradiation of lymphatics and treatment across a joint, *unless* required for tumor coverage. If target volume expansions oblige that the epiphysis of an adjacent bone be irradiated *and* there is no joint space involvement, then a smaller margin may be considered to exclude the adjacent epiphysis.
- Heterogeneity correction is typically used for lung irradiation.

9.5 Ewing Sarcoma

- Approximately 200 cases of Ewing sarcoma are diagnosed in the United States each year. Ewing sarcoma is the second most common pediatric bone tumor.
- More than 80% of patients with localized disease will develop metastases in the absence of chemotherapy.
- Ewing sarcoma typically involves the diaphysis. The most common sites of involvement are the lower extremity (femur, 15–20%, and tibia/fibula, 5–10%), pelvis (20–30%), upper extremity (5–10%), rib (9–13%), and spine (6–8%).

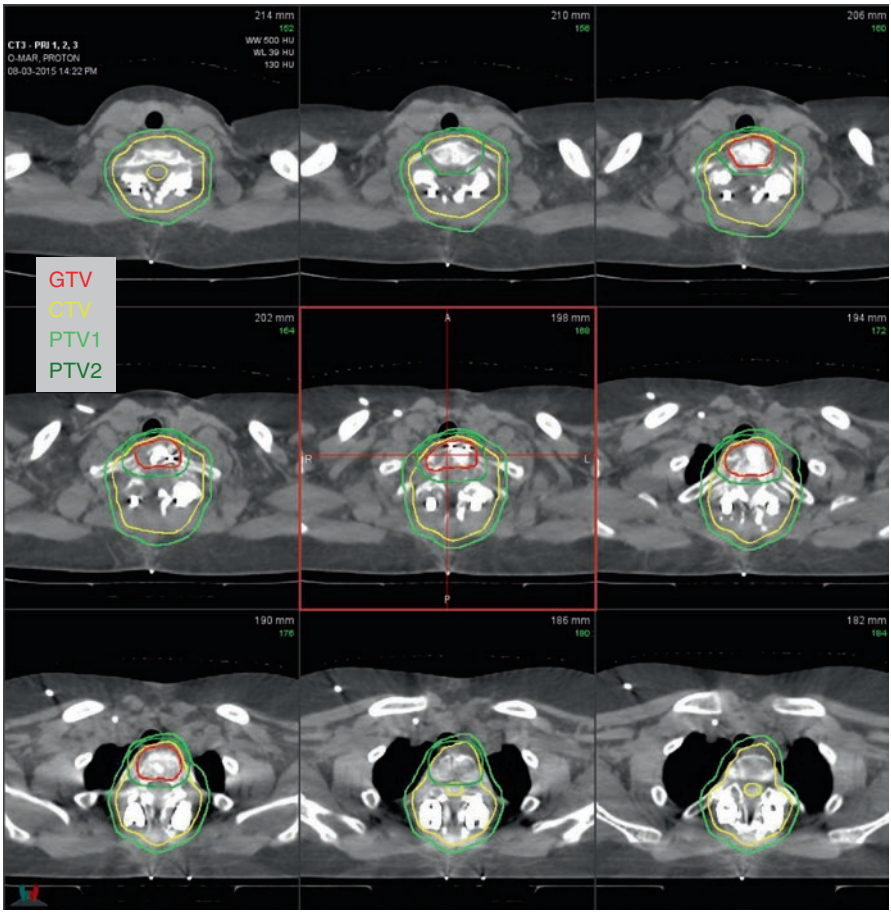


Fig. 9.3 An example of a T1N0M0 grade 3 osteosarcoma of the T1 vertebral body treated with adjuvant radiotherapy after two-part surgical resection by posterior approach and subsequent anterior approach. CT simulation was performed with 1.0 mm slice thickness. Representative axial slices and target volumes are shown. The GTV included the operative bed and did not encompass the scar or operative tracts. Note the significant surgical artifact. MRI was not performed for treatment planning due to magnetic resonance-incompatible hardware

- Local failure rates after primary radiation therapy range from 10 to 25%. Local failure is significantly associated with the primary site (pelvis being worse than extremity), tumor size (<8 cm 10% vs. >8 cm 20%), and other prognostic factors [1–3].

9.5.1 Timing of Radiation Therapy

- Local therapy is typically administered after induction chemotherapy, which consists of six 2-week cycles of chemotherapy (12 weeks) on the current Euro Ewing 2012 and Children's Oncology Group (COG) AEWS 1031 trials.

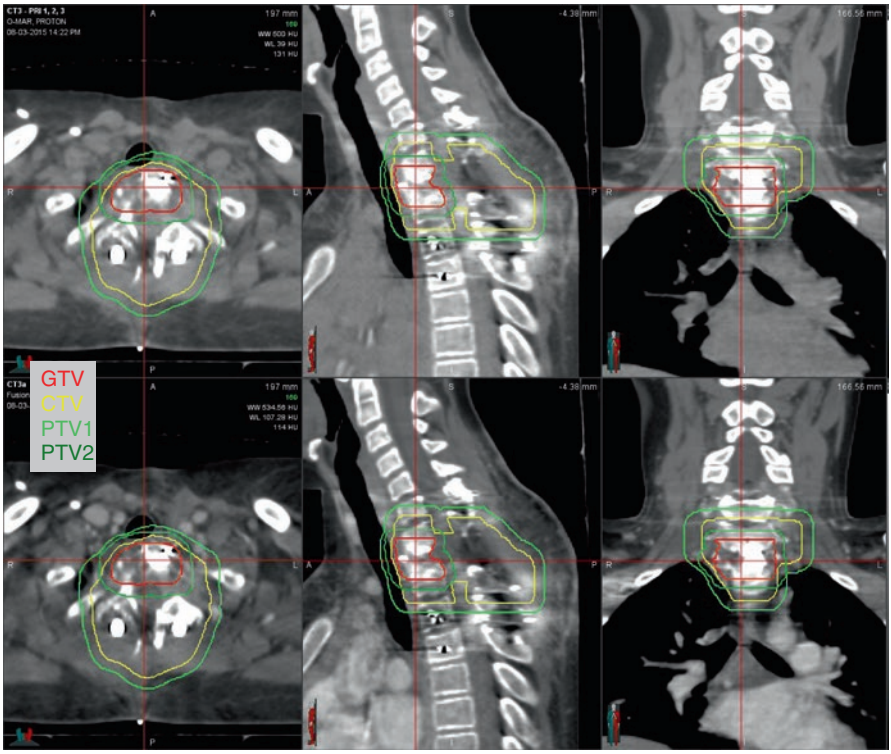
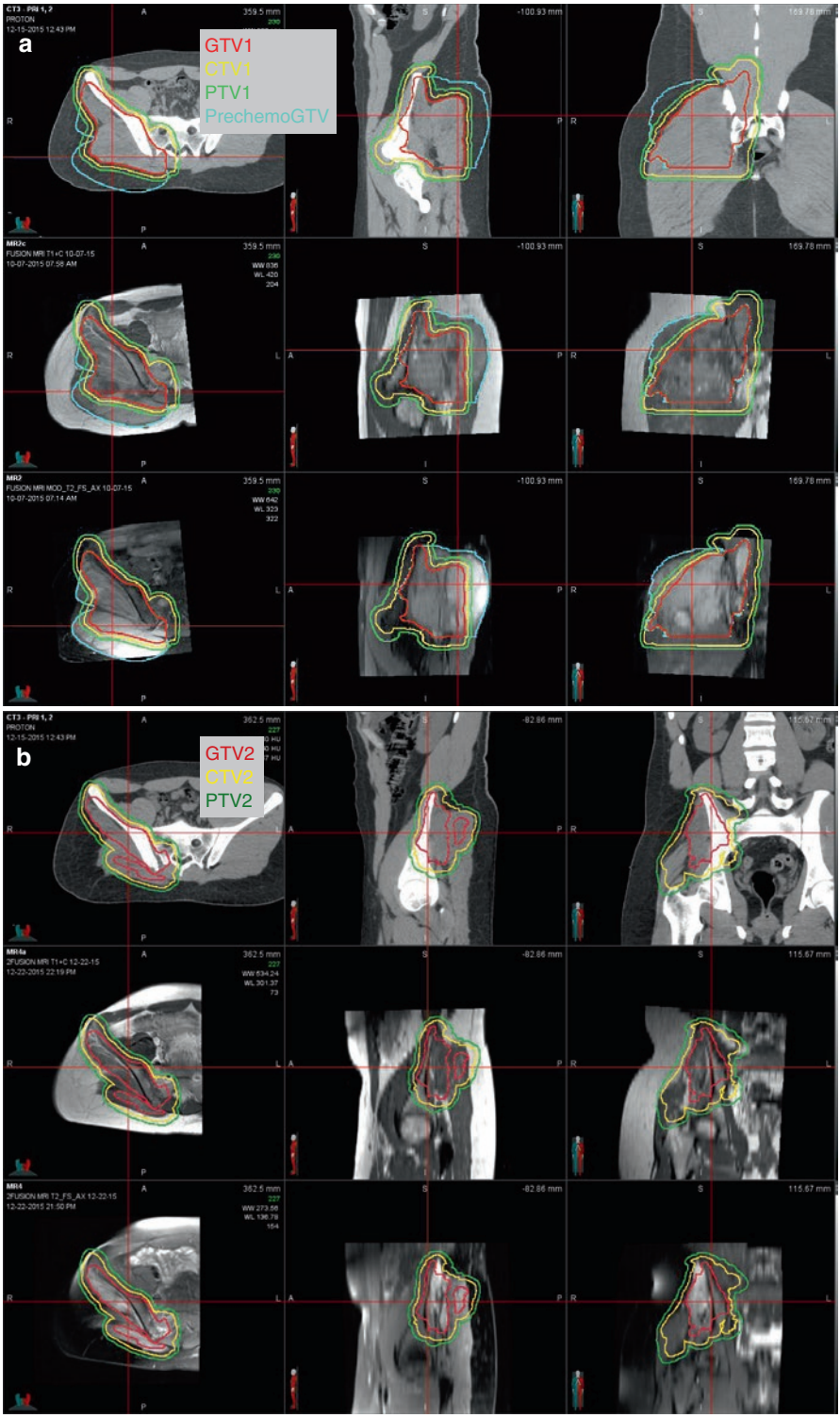


Fig. 9.4 Axial, sagittal, and coronal displays of the target volumes for the resected T1N0M0 grade 3 osteosarcoma of the T1 vertebral body. The tumor was delineated using CT. Preoperative diagnostic MRI was fused to delineate the preoperative GTV (not shown). In this case, a total dose of 61.2 Gy RBE was administered to the high-risk region while respecting spinal cord dose constraints

Fig. 9.5 An example of an unresectable T2N0M0 pelvic Ewing sarcoma of the right ilium involving the gluteal, piriformis, and erector spinae muscles and extending into multiple sacral neural foramina. Target volumes are displayed on a representative axial, sagittal, and coronal frame. The GTV1, CTV1, PTV1, and the prechemotherapy (Prechemo)GTV are shown in (**a**), while GTV2, CTV2, and PTV2 are shown in (**b**). The tumor was delineated using CT (row 1) with diagnostic MRI fusion. T1-weighted images with contrast (row 2) and fat-suppression T2-weighted images (row 3) were used to delineate the PrechemoGTV, GTV1, and GTV2. Note that the GTV1 includes the muscle tissue initially infiltrated by tumor. Due to the response to induction chemotherapy, the size of the involved musculature has decreased, and the GTV1 contour lies within the prechemotherapy extent of disease. The GTV2 includes all initial areas of bone involvement and postchemotherapy residual soft tissue tumor, best identified on MRI


a
GTV1
CTV1
PTV1
PrechemoGTV
b
GTV2
CTV2
PTV2

- When radiation is used as primary or adjuvant therapy for local control of the primary tumor, preoperatively or postoperatively, it will typically begin concurrently with the start of consolidation chemotherapy.
- In general, doxorubicin should not be given during radiation unless specified by the protocol. Ifosfamide/etoposide and vincristine/cyclophosphamide/topotecan can be given concurrently.
- Radiation therapy may be necessary on an emergent basis for patients with spinal cord compromise, acute vision loss, or other function-threatening conditions if the tumor is not amenable to surgical decompression.
- Emergency radiation is expected to be a rare event since most patients will respond quickly and dramatically to chemotherapy.

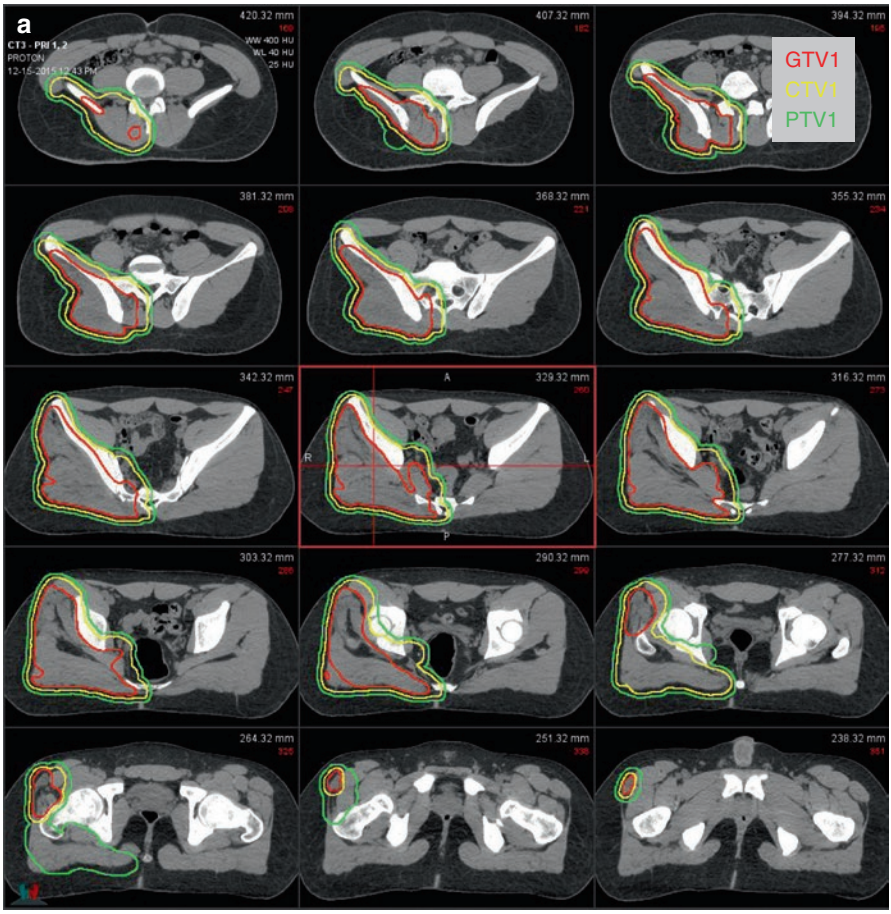


Fig. 9.6 Representative axial slices and target volumes for the unresectable T2N0M0 right iliac Ewing sarcoma with involvement of the pelvic muscles and extension into multiple sacral neural foramina. The GTV1, CTV1, and PTV1 are shown in (**a**), and the GTV2, CTV2, and PTV2 are displayed in (**b**). CT simulation was performed with 1.0 mm slice thickness. CTV1 and CTV2 expansions were edited to account for anatomic barriers to tumor spread

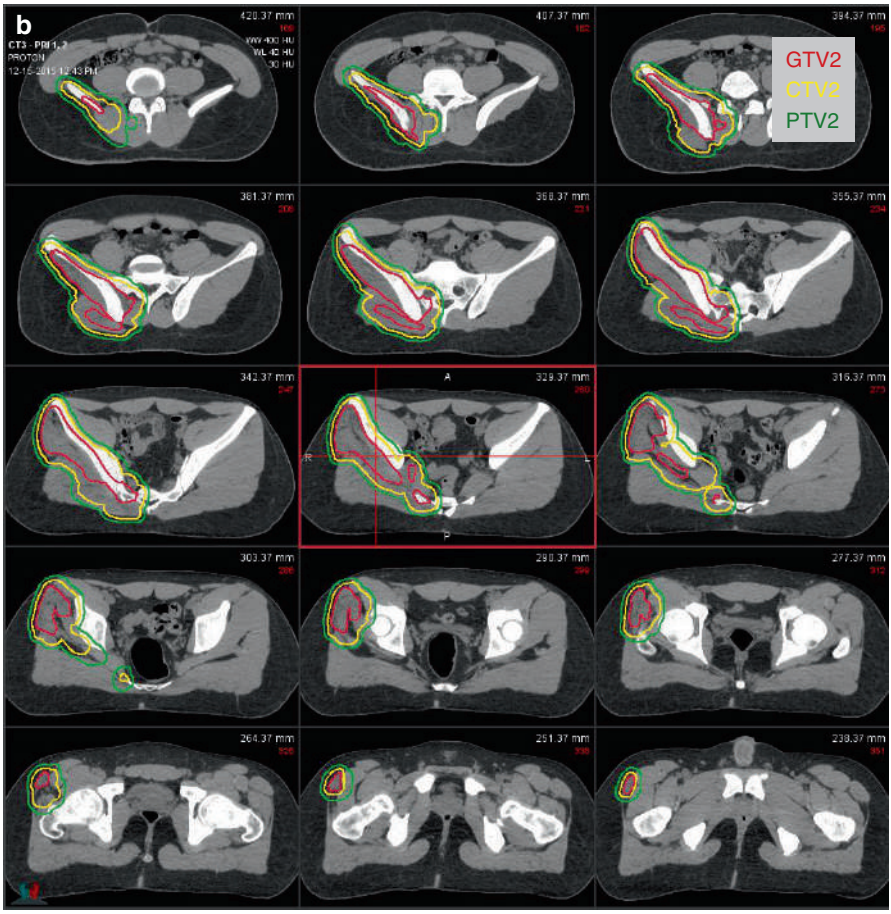


Fig. 9.6 (continued)

- If emergent radiation is initiated, the entire course of radiotherapy for that site should be administered rather than splitting or delaying the treatment until the protocol-specified times for irradiation.
- Adjuvant radiation therapy is typically indicated after surgery for positive margins, tumor spill, and poor response to induction chemotherapy (>10% viable tumors cells) [7].
- For patients with pulmonary metastases, whole-lung irradiation is delivered at the conclusion of chemotherapy. The exception to this rule is when there is a thoracic spinal or chest wall primary tumor that necessitates some lung radiation following induction chemotherapy. In this setting, whole-lung irradiation should immediately precede radiation therapy to the primary site and contribute to the total composite dose.

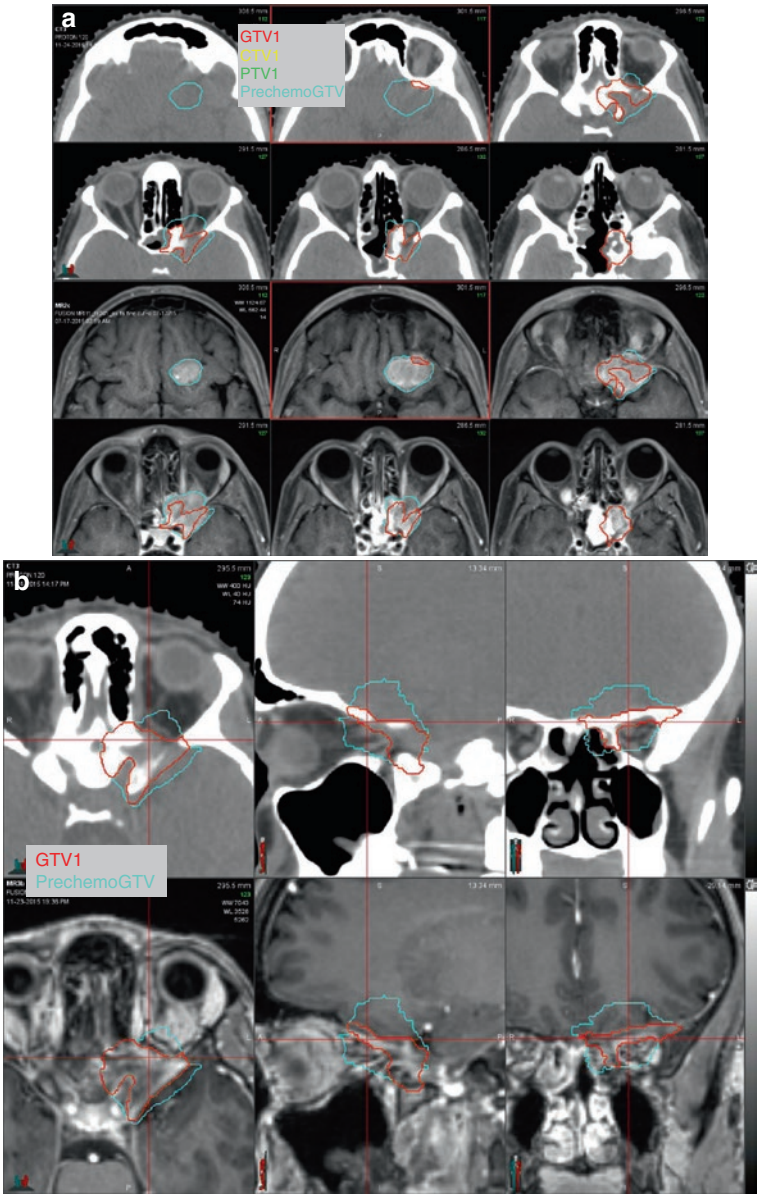


Fig. 9.7 Example of a T1N0M0 left sphenoid wing Ewing sarcoma with involvement of the left orbit and ethmoid and sphenoid sinuses. CT simulation was performed with 1.0 mm slice thickness. Representative axial slices and target volumes are shown on the CT simulation (rows 1 and 2) and *prechemotherapy* T1-weighted images with contrast (rows 3 and 4). GTV1, CTV1, PTV1, and prechemotherapy (Prechemo)GTV are shown in (**a**). An axial, sagittal, and coronal display of GTV1 and the PrechemoGTV are shown on the CT simulation and the *postchemotherapy* T1-weighted MRI with contrast in (**b**). Note the significant regression of the intracranial soft tissue component of the tumor following induction chemotherapy

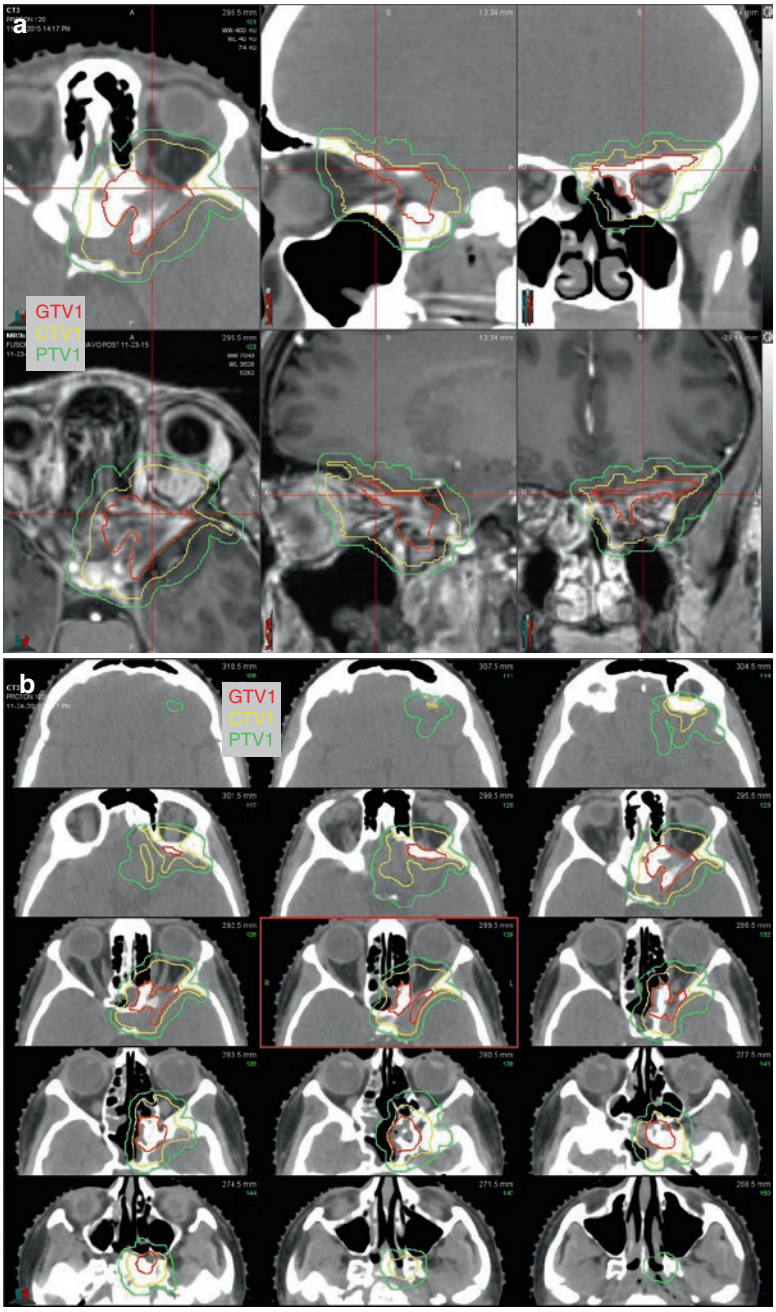


Fig. 9.8 Axial, sagittal, and coronal displays of the target volumes for the T1N0M0 left sphenoid wing Ewing sarcoma are shown in (**a**). The GTV1, CTV1, and PTV1 are displayed. Representative axial slices and target volumes are shown on the CT simulation in (**b**). The CTV1 expansions were edited to account for anatomic barriers to tumor spread, including a *pushing* border along the left temporal lobe of the brain. For skull-base Ewing sarcomas, a total dose of 54 Gy RBE was administered to the high-risk region while respecting normal tissue dose constraints

- Outcomes for metastatic Ewing sarcoma are significantly improved in patients able to receive definitive local therapy to all sites of disease involvement documented at the time of diagnosis. Metastatic sites in the region of the primary tumor can be treated at the time of primary treatment as long as <50% of bone marrow is irradiated. Remaining sites are generally treated at the end of all therapy (similar to whole-lung irradiation).

9.5.2 Target Volumes

- Target volumes are defined using the initial gross tumor volume at presentation (GTV1) and a smaller residual tumor volume after induction chemotherapy and surgery (GTV2) (Tables 9.1, 9.2, 9.3, 9.4, and 9.5).
- Gross target volume includes MRI contrast-enhancing soft tissue and bone tumor, abnormal bone on CT, and changes consistent with infiltration in both soft tissues and bone as seen on T2-weighted MRI.
- Because tumors can extensively infiltrate marrow and surrounding soft tissues, T2-weighted MRI is critical in defining the extent of bone and soft tissue involvement.
- PET/CT is more sensitive and specific for identifying bone involvement and metastatic nodal involvement compared to CT and bone scan. Because bone marrow involvement may be evident on PET, metastatic bone sites should display evidence of bone change on bone scan, MRI, or CT. Off-protocol, definitive treatment doses and volumes are similar to recommendations for the primary site (with the exception of whole-lung as above or whole-abdomen irradiation).
- Whole-lung irradiation for parenchymal lung metastases requires 4D imaging and internal target volume creation or motion management to ensure complete coverage of the lung parenchyma.
- Hemithorax or whole-lung irradiation for positive pleural cytology or pleural involvement must include coverage of lung sulci. Determining the inferior border is still best identified on deep-inspiration lateral radiograph or fluoroscopy and is often at the L1/L2 interspace. 4D simulation alone is inadequate and underestimates the inferior extent of the sulci.
- Deep-inspiration breath-hold for simulation and treatment can reduce the radiation dose to the liver and abdominal contents for both whole-lung and hemithorax irradiation and should be considered in cooperative patients.
- Residual gross disease in the lung after induction chemotherapy must be resected or receive a radiotherapy boost.

9.6 Osteosarcoma

- 400 pediatric osteosarcoma cases are diagnosed in the United States per year. It is the most common pediatric bone tumor.

Table 9.1 Ewing sarcoma target volumes (per guidelines as outlined in AEWS 1031)

Target volume	Description
Initial tumor volume	
GTV1	Gross tumor before surgical debulking and chemotherapy (including unresected enlarged lymph nodes). GTV1 may be modified for tumors with a "pushing margin" into body cavities (e.g., thorax, abdomen, pelvis). If the tumor responded to chemotherapy and normal tissues returned to their natural position, GTV1 excludes the prechemotherapy volume that extended into the cavity. The modified GTV1 *includes* tissue that was initially infiltrated but subsequently responded to chemotherapy. For unresected tumors, GTV1 includes all initial areas of bone involvement* *Because bone involvement at diagnosis is included in the final boost, it is often helpful to define a "bone GTV" that can be combined with the prechemotherapy "soft tissue GTV" or postchemotherapy "soft tissue GTV" to create GTV1 and GTV2, respectively
CTV1	GTV1 + 1 cm (not extending outside of the patient), modified to account for specific anatomic barriers to tumor spread. CTV1 also includes regional lymph node chains for clinically or pathologically involved nodes; for tumors without nodal involvement, regional lymph nodes are not irradiated
PTV1	CTV1 + institutional setup margin according to tumor site
Residual tumor volume	
GTV2	Residual tumor after induction chemotherapy and surgery. For unresected tumors, GTV2 includes all initial areas of bone involvement and postchemotherapy residual soft tissue tumor
CTV2	GTV2 + 1 cm (not extending outside the patient) and areas at risk for microscopic disease, modified to account for specific anatomic barriers to tumor spread
PTV2	CTV2 + institutional setup margin according to tumor site
Special target volumes	
CTV3/ PTV3	Chest wall tumors with ipsilateral pleural nodules and/or pleural fluid involvement are treated with ipsilateral hemithorax irradiation followed by radiation to the primary site and pleural nodules (if applicable)
	Patients with lung metastases at diagnosis require whole-lung irradiation, regardless of the response to chemotherapy. For ipsilateral/whole-lung irradiation, CTV3 is defined as the lung/pleural cavity(ies) plus CTV1. Residual lung nodules should be included as GTV2 and receive a boost if not resected
	Patients with malignant ascites or diffuse peritoneal involvement require whole-abdomen irradiation. For whole-abdomen irradiation, the CTV3 is defined by the abdominal and pelvic cavity plus CTV1. An institutional setup margin is added to form PTV3

GTV gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume

Table 9.2 Ewing sarcoma radiation therapy (RT) dose: primary site (per guidelines as outlined in AEWS 1031)

Radiation sequence	PTV1	PTV2
Primary RT	45 Gy	10.8 Gy
Primary RT (vertebral body)	45 Gy	5.4 Gy
Preoperative RT	50.4 Gy	–
Postoperative RT with *microscopic* residual	50.4 Gy	–
Postoperative RT with gross residual disease	45 Gy	10.8 Gy

PTV planning target volume, *RT* radiation therapy
PTV1 and PTV2, 1.8 Gy per fraction

Table 9.3 Ewing sarcoma radiation therapy dose: pathologically involved lymph nodes (per guidelines as outlined in AEWS 1221)

Involved LNs	PTV1	PTV2
LN resected, separate from primary site	50.4 Gy	–
LN resected, contiguous with primary site	50.4 Gy	–
LN unresected, primary adequately resected	45 Gy	10.8 Gy
LN unresected, primary inadequately resected with microscopic residual	45 Gy	10.8 Gy

LN lymph node, *PTV* planning target volume
PTV1 and PTV2, 1.8 Gy per fraction

Table 9.4 Ewing sarcoma radiation therapy dose: chest wall or abdominal tumors with positive fluid cytology (per guidelines as outlined in AEWS 1221)

Age	PTV1	PTV2	PTV3
≤6 years	32.4 Gy	5.4 Gy	12 Gy
>6 years	30.6 Gy	5.4 Gy	15 Gy

PTV planning target volume
PTV1 and PTV2, 1.8 Gy per fraction; PTV3, 1.5 Gy per fraction

Table 9.5 Ewing sarcoma radiation therapy dose: pleural, pulmonary, or peritoneal nodules (per guidelines as outlined in AEWS 1221)

Age	PTV1	PTV2	PTV3
≤6 years	23.4 Gy	14.4 Gy	12 Gy
>6 years	21.6 Gy	14.4 Gy	15 Gy

PTV planning target volume
PTV1 and PTV2, 1.8 Gy per fraction; PTV3, 1.5 Gy per fraction
PTV3 defined as bilateral lung, hemithorax, or the abdominal/pelvic cavity, depending on the case

- 90% of patients with localized disease will develop metastases without chemotherapy.
- Osteosarcoma most commonly arises in the appendicular skeleton, with 80% of cases arising in the metaphysis of the femur, tibia, and humerus. The most common site of involvement is the femur.

9.6.1 Radiation Therapy Indications

- En bloc oncologic resection with wide negative margins (R0) is the preferred local treatment strategy.
- Most patients will have either surgery alone, surgery followed by postoperative radiation therapy for microscopic positive margins, or radiation therapy alone.
- Adjuvant radiation therapy is typically indicated after surgery for microscopic positive margins. The indication for radiation following close margins or non-oncologic initial surgery is less clear.
- Preoperative radiation should be considered in patients with apparently resectable tumors in selected sites, such as the pelvis and chest wall, which have a high

risk of positive microscopic margins following surgery. *The objective of preoperative radiation therapy should not be to attempt to make an inoperable tumor operable*.

- Definitive radiation therapy should only be considered in selected patients with localized disease for which surgical resection would be especially morbid [8].
- The preferred dose for patients with gross disease in osteosarcoma is >70 Gy and >64.8 Gy for microscopic disease.

9.6.2 Target Volumes (Tables 9.6, 9.7, 9.8, and 9.9)

Table 9.6 Target volumes for preoperative and primary radiation therapy of osteosarcoma

Target volume	Description
GTV	GTV includes gross tumor defined by physical examination, computed tomography, and magnetic resonance at the time of radiation
CTV	GTV + 1.5 cm radial margin (not extending outside of the patient), modified to account for anatomic barriers that limit tumor spread, such as the bone or fascia. For extremity tumors, 1.5 cm radial and 2 cm longitudinal margin are recommended. The CTV also includes all areas at risk for subclinical spread from the GTV and suspicious edema
PTV1	CTV + institutional setup margin according to site
PTV2	GTV + institutional setup margin according to site

CTV clinical target volume, *GTV* gross tumor volume, *PTV* planned target volume

Table 9.7 Target volumes for postoperative radiation therapy of osteosarcoma

Target volume	Description
GTV	Following complete en bloc resection, the GTV includes the operative bed but does not encompass the scar or operative tract, unless felt to be at risk. In the setting of positive margins or gross residual tumor, the GTV also includes gross tumor consisting of the residual postsurgery disease defined by physical examination, computed tomography, and magnetic resonance (T1-weighted, T2-weighted, and FLAIR)
CTV	Two components are combined to form the CTV. GTV + 1.5 cm around the operative bed (not extending outside of the patient), modified to account for anatomic barriers that limit tumor spread, such as the bone or fascia. The CTV also includes tissue that was initially infiltrated by tumor but now has no visible gross disease
PTV1	CTV + institutional setup margin according to site
PTV2	GTV + institutional setup margin according to site
Special target volumes	
CTV3/PTV3	Chest wall tumors with ipsilateral pleural nodules and/or pleural fluid involvement are treated with ipsilateral hemithorax irradiation followed by radiation to the primary site and pleural nodules (if applicable). Patients with lung metastases at diagnosis require whole-lung irradiation, regardless of chemotherapy response. Patients with malignant ascites or diffuse peritoneal involvement require whole-abdomen irradiation. For ipsilateral/whole-lung irradiation, CTV3 is defined as the lung/pleural cavity(ies) plus CTV1. An institutional setup margin is added to form PTV3

CTV clinical target volume, *GTV* gross tumor volume, *PTV* planned target volume

Table 9.8 Osteosarcoma dose: primary site

Radiation sequence	PTV1	PTV2
Primary RT	50.4 Gy	19.8 Gy
Preoperative RT	50.4 Gy	N/A
Postoperative RT with *microscopic* residual	50.4 Gy	14.4 Gy
Postoperative RT with gross residual disease	50.4 Gy	19.8 Gy

PTV planning target volume, *RT* radiation therapy
PTV1 and PTV2—1.8 Gy per fraction

Table 9.9 Osteosarcoma dose: pleural, pulmonary, or peritoneal nodules

Age	PTV1	PTV2	PTV3
≤6 years	23.4 Gy	14.4 Gy	12 Gy
>6 years	21.6 Gy	14.4 Gy	15 Gy

PTV planned target volume
PTV1 and PTV2—1.8 Gy per fraction; PTV3—1.5 Gy per fraction
PTV3 defined as bilateral lung or hemithorax, depending on case scenario

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Non-rhabdomyosarcoma Soft Tissue Sarcomas

10

Lynn Million

Contents

10.1 Background

- Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) account for 4% of childhood malignancies in the USA with an incidence of about 500 cases per year [1].
- Pediatric soft tissue sarcomas are classified according to the World Health Organization as seen in Table 10.1 [2].
- NRSTS has diverse responses to radiation therapy and chemotherapy, precluding single histology trials as have been conducted for rhabdomyosarcomas (RMS).

10.1.1 Evolution of Radiation Fields for Soft Tissue Sarcoma (STS)

- The first US pediatric trial for resected pediatric NRSTS was conducted by the Pediatric Oncology Group (POG) and reported in 1999 [3]. Radiation treatment

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https://doi.org/10.1007/978-3-319-69140-4_10

Table 10.1 WHO classification of tumors of soft tissue: malignant tumors [2]

Tumor category	Subclassification
Adipocytic	Dedifferentiated liposarcoma
	Myxoid liposarcoma
	Pleomorphic liposarcoma
	Liposarcoma, not otherwise specified
Fibroblastic/myofibroblastic	Adult fibrosarcoma
	Myxofibrosarcoma
	Low-grade fibromyxoid sarcoma
	Sclerosing epithelioid fibrosarcoma
Smooth muscle	Leiomyosarcoma
Pericytic (perivascular)	Glomus tumor
	Myopericytoma
	Angioleiomyoma
Skeletal muscle	Embryonal rhabdomyosarcoma
	Alveolar rhabdomyosarcoma
	Pleomorphic rhabdomyosarcoma
	Spindle cell/sclerosing rhabdomyosarcoma
Vascular tumor of soft tissue	Epithelioid hemangioendothelioma
	Angiosarcoma of soft tissue
Chondro-osseous	Soft tissue chondroma
	Extraskeletal mesenchymal chondrosarcoma
	Extraskeletal osteosarcoma
Gastrointestinal stromal	Gastrointestinal stromal tumor, malignant
Nerve sheath	Malignant peripheral nerve sheath tumor
	Epithelioid malignant peripheral nerve sheath tumor
	Malignant triton tumor
	Malignant granular cell tumor
	Ectomesenchymoma
Tumors of uncertain differentiation	Synovial sarcoma NOS (spindle cell and biphasic)
	Epithelioid sarcoma
	Alveolar soft-part sarcoma
	Clear cell sarcoma of soft tissue
	Extraskeletal Ewing sarcoma
	Desmoplastic small round cell tumor
	Extrarenal rhabdoid tumor
	Neoplasms with perivascular epithelioid cell differentiation
	Intimal sarcoma
	Extraskeletal myxoid sarcoma
Undifferentiated/unclassified sarcomas	Undifferentiated spindle cell sarcoma
	Undifferentiated pleomorphic sarcoma
	Undifferentiated round cell sarcoma
	Undifferentiated epithelioid sarcoma
	Undifferentiated sarcoma NOS

[a]Rhabdomyosarcomas will be discussed separately in Chaps. 8 and 15

volumes were generous and included the resection bed plus a 5 cm margin. Boost volumes to areas of residual disease included the reconstructed primary tumor plus a 2 cm margin. Radiation doses were adjusted for age and included: 45–50 Gy for microscopic positive margins and 55–65 Gy for gross residual tumor.

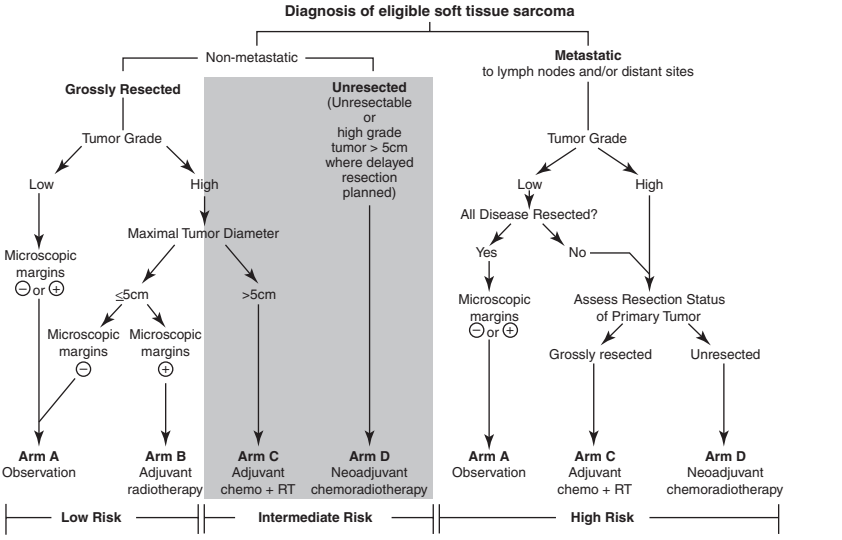
- Large radiation treatment volumes and high-dose irradiation with non-conformal treatment techniques led to irreversible severe musculoskeletal growth abnormalities, subcutaneous fibrosis, and organ injury.
- In 2010, a prospective phase II trial for pediatric high-grade NRSTS study by investigators at St. Jude's showed that a 2 cm margin for CTV expansion of the GTV while avoiding adjacent structures that may act as a barrier to tumor spread, including bone and fascial planes, was adequate for achieving >95% local control in resected tumors [4].
- Adult STS trials conducted by Radiation Therapy Oncology Group (RTOG) have reported significant reduction in long-term musculoskeletal morbidity and excellent local control with limited margins and daily IGRT [5, 6]. RTOG consensus guidelines for preoperative RT included a 3 cm longitudinal and a 1.5 cm radial margin for CTV expansion of GTV [7]. Investigators specified the importance of including suspicious peritumoral edema noted on MRI T1 post-contrast and T2 sequences in the CTV [8].

10.1.2 Pediatric NRSTS Management

- A recently completed Children's Oncology Group (COG) trial for NRSTS validated a risk-based classification scheme that forms the basis of contemporary management of pediatric NRSTS (Fig. 10.1) [9].
- Table 10.2 delineates the radiation therapy dose guidelines used on the COG NRSTS trial, which can be used by radiation oncologists as a guideline for contemporary treatment of NRSTS, and Table 10.3 shows the radiation therapy target volume guidelines. It is important to note that these doses are used with concurrent chemotherapy for patients with intermediate- and high-risk disease.

10.1.3 Indications for Radiation

- Low-grade NRSTS
  - Resected tumors with negative or microscopic positive margins can be observed without adjuvant radiation therapy.
  - Although up to 50% of low-grade tumors may recur after surgery alone, the majority can be successfully retreated with surgery and consideration of adjuvant radiation therapy, thereby precluding the need for radiation and the associated late toxicities.



† Negative microscopic margins defined as the presence of a cuff of non-malignant tissue measuring at least 5mm in all directions surrounding the tumor in the operative specimen. When the tumor abuts fascia or periosteum and the fascia or periosteum is removed in continuity with the tumor specimen, this margin will also be considered negative.

Fig. 10.1 COG risk-adaptive treatment guidelines [9]

Table 10.2 Radiation dose guidelines used on COG NRSTS trial (risk-based treatment for non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)) in patients under 30 years of age: Children's Oncology Group study ARST0332 [9]

	Total dose (Gy)	Dose per fraction (Gy)	PTV1 (Gy)	PTV2 boost (Gy)
Low risk (nonmetastatic)				
Postoperative RT				
– Microscopic margins, high grade, ≤5 cm	55.8	1.8	45.0	10.8
Intermediate risk (nonmetastatic)				
Postoperative RT (arm C)				
– Negative margins	55.8	1.8	45.0	10.8
– Microscopic margins	55.8	1.8	45.0	10.8
Preoperative RT (arm D)				
– Negative margins	45.0	1.8	45.0	0
– Microscopic margins	55.8	1.8	45.0	10.8 (Wk 16)
– Macroscopic margins	64.8	1.8	45.0	19.8 (Wk 16)
High risk (metastatic)				
Postoperative RT (arm C)				
– Negative margins	55.8	1.8	45.0	10.8
– Microscopic margins	55.8	1.8	45.0	10.8
Preoperative RT (arm D)				
– Negative margins	45.0	1.8	45.0	0
– Microscopic margins	55.8	1.8	45.0	10.8 (Wk 16)
– Macroscopic margins	64.8	1.8	45.0	19.8 (Wk 16)

Table 10.3 Radiation target volume guidelines: COG NRSTS trial

Volume		Description
Gross tumor volume (GTV)	GTV1	Defined as the visible and/or palpable disease defined by physical examination, computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET scan), operative notes, and pathology reports. For patients with initial tumors that extend into body cavities (i.e., thorax, abdomen), the GTV1 may require modification. If the tumor has been resected or responded to chemotherapy and the normal tissues have returned to their normal positions, the GTV1 excludes the volume that extends into the cavity. Examples include tumors that compress but not invade the lung, intestine, or bladder that radiographically return to normal anatomic position following surgery or chemotherapy. The GTV1 must include all infiltrative disease detected at initial presentation
	GTV2	For resected tumors, the GTV2 (volume reduction) is defined as the region of positive surgical margins, microscopic or gross residual disease determined by operative note, pathology report, and imaging studies
		For unresected tumors, the GTV2 is defined as the pretreatment residual soft tissue disease following induction chemotherapy
		For partially resected tumors, the GTV2 is defined as the residual soft tissue disease following induction chemotherapy and surgical debulking
Clinical target volume (CTV)	CTV1	Defined as GTV1 + 1.5 cm (but not extending outside of the patient). CTV1 also includes regional lymph node chains that are known to harbor pathologically involved nodes. For some sites, CTV1 is modified to account for specific anatomic barriers to tumor spread
	CTV2	Defined as the GTV2 + 1.0 cm (but not extending outside the patient). For some sites, CTV1 is modified to account for specific anatomic barriers to tumor spread
Planning target volume (PTV)	PTV1	Defined as CTV1 with an additional (minimum) margin of 0.5 cm; however, this margin can vary depending on the institution, type of beam, immobilization methods, and patient cooperation. The PTV1 margin does not need to be uniform in all dimensions, particularly if normal tissues are compromised. Beam-specific PTV1 expansions may be required for proton planning, particularly in the axis of the beam
	PTV2	Defined as the CTV2 with an additional (minimum) margin of 0.5 cm; however, this margin can vary depending on the institution, type of beam, immobilization methods, and patient cooperation. The PTV2 margin does not need to be uniform in all dimensions, particularly if normal tissues are compromised. Beam-specific PTV2 expansions may be required for proton planning, particularly in the axis of the beam

- High-grade NRSTS
  - Resected ≤5 cm tumors with close (≤5 mm) or microscopic positive margins
    Postoperative radiation therapy is recommended.
  - Resected >5 cm tumors with negative or microscopical positive margins
    Postoperative radiation therapy is recommended. Chemotherapy is considered.
  - Borderline resectable or unresected tumors
    Preoperative radiation and chemotherapy are recommended.
    Postoperative boost after neoadjuvant radiation therapy followed by surgery is reserved for those with microscopic positive margins or macroscopic residual disease.

10.2 Target Volume Delineation (See Table 10.3)

10.2.1 Preoperative RT

- Preoperative radiation therapy is indicated for high-grade NRSTS that are borderline resectable or unresectable.
- In general, larger (>5 cm) high-grade tumors will require radiation therapy as part of the overall management plan. Delivering preoperative radiation has the advantage of smaller target volumes and potentially lower radiation doses compared to postoperative RT.
- GTV is identified on the radiation therapy planning CT scan (RTP-CT). Preoperative diagnostic imaging including CT scan, MRI, and PET-CT are reformatted to the RTP-CT scan to aid in distinguishing tumor from normal tissue/edema. MRI or PET-CT obtained in the treatment planning position can further delineate the extent of tumor extension, particularly when there is concern for lymph node involvement, vascular invasion, bone erosion, or organ infiltration. Incisional biopsy scars or biopsy tracts are identified by a radiopaque marker on the RTP_CT so they can be included in the CTV.
- CTV margins include a 1.5 cm radial expansion on the GTV.
  - The CTV is edited to exclude barriers to tumor spread such as bone, organs, fascial planes, and subcutaneous tissues.
  - Biopsy scars should be included in the CTV. Biopsy tracts are more difficult to identify but should be included if possible.
  - CTV expansion should encompass any suspicious peritumoral edema. However, if further expansion of the CTV to encompass edema creates a prohibitively large treatment field or extends beyond a compartment, clinical judgment is used to determine the field borders.
  - Regional lymph nodes that are pathologically involved should be included in the GTV. The entire nodal basin does not need to be encompassed in the CTV.
- PTV margins generally include a 0.5 cm margin for expansion on the CTV except in areas such as the head and neck region where a 0.3 cm margin may be acceptable.
  - PTV margins can vary depending on the institution, type of beam, immobilization methods, and patient cooperation.

  - This margin does not need to be uniform in all dimensions, particularly if normal tissues are compromised. For example, the PTV can be further edited to crop the skin 2–3 mm under the surface if there is no skin or subcutaneous tumor extension. Lowering the skin dose will result in fewer wound-healing problems and a lower risk of late subcutaneous fibrosis.
- Surgery is typically planned for 4–6 weeks after completing preoperative radiation treatment.
  - For resectable tumors with microscopic positive margins, a postoperative boost can be considered. For gross residual disease, a boost is recommended.
  - For unresectable tumors, a definitive dose to a boost volume is recommended.
- Planning the GTV2: postoperative boost volume for resected tumors.
  - The patient is brought back to simulation to plan the postoperative boost after they have recovered from surgery. It is useful to immobilize the patient in the same position that they were treated in preoperatively. This allows for the most accurate reconstruction of the preoperative target volumes, which can be fused with the proposed postoperative target volumes. Although the normal tissues will have shifted into different positions, this will enable assessment of normal tissue dose constraints.
  - The GTV2 is reconstructed to include microscopical positive surgical margins or gross residual disease determined by the operative note, pathology report, and imaging studies. It is helpful for surgeons to place clips in areas concerning for residual disease.
  - The GTV should account for shifting in the anatomic position of normal tissues after surgical resection, and thus, there may be instances where contouring of a GTV2 is not feasible. In this case, a CTV2 is created based on pre- and postoperative imaging, operative report, surgeon's input, pathology reports, clips placed at the time of surgery, and incision seen on the radiation treatment planning RTP-CT.
  - For tumors that are unresectable after a course of preoperative RT, the GTV2 is defined as the residual soft tissue disease following neoadjuvant chemotherapy. If induction chemotherapy was not given or the mass did not respond, the GTV2 is the same as GTV1.
- The CTV2 is defined as the GTV2 + 1.0 cm.
  - Grafts, flaps, and incisions should be excluded from the CTV unless involved with tumor.
  - The CTV2 is edited to exclude barriers to tumor spread such as bone, organs, fascial planes, and subcutaneous tissues.
- The PTV2 is generally defined as the CTV2 + 0.5 cm except in the head and neck region where a 0.3 cm margin is acceptable.
  - This margin does not need to be uniform in all dimensions, particularly if normal tissues are compromised. For example, the PTV can be further edited to crop the skin 2–3 mm under the surface if there is no skin or subcutaneous tumor extension. Lowering the skin dose will result in fewer wound-healing problems and a lower risk of late subcutaneous fibrosis.

10.2.1.1 Thigh

See Figs. 10.2, 10.3, 10.4, 10.5, and 10.6.

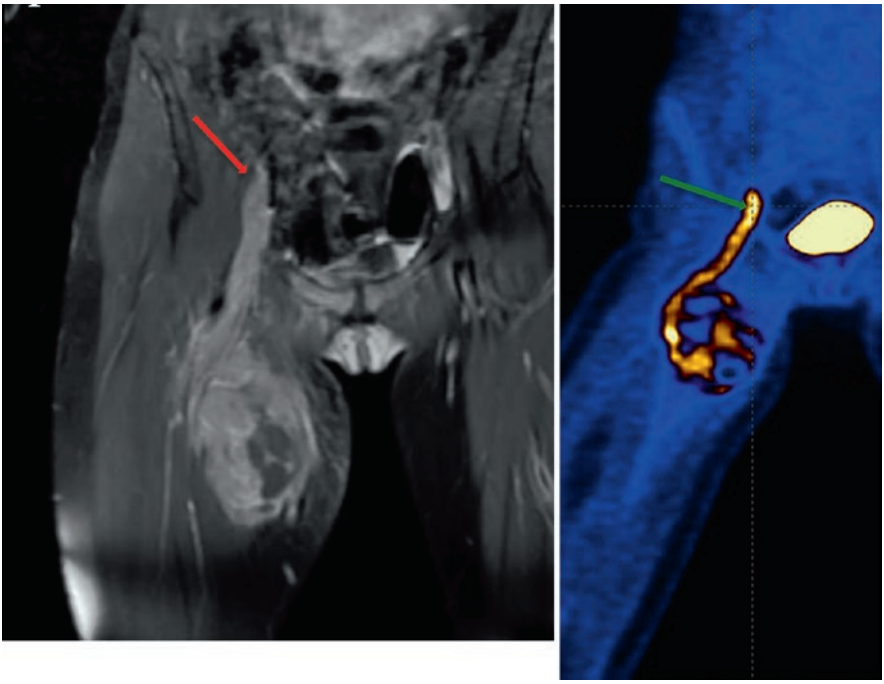
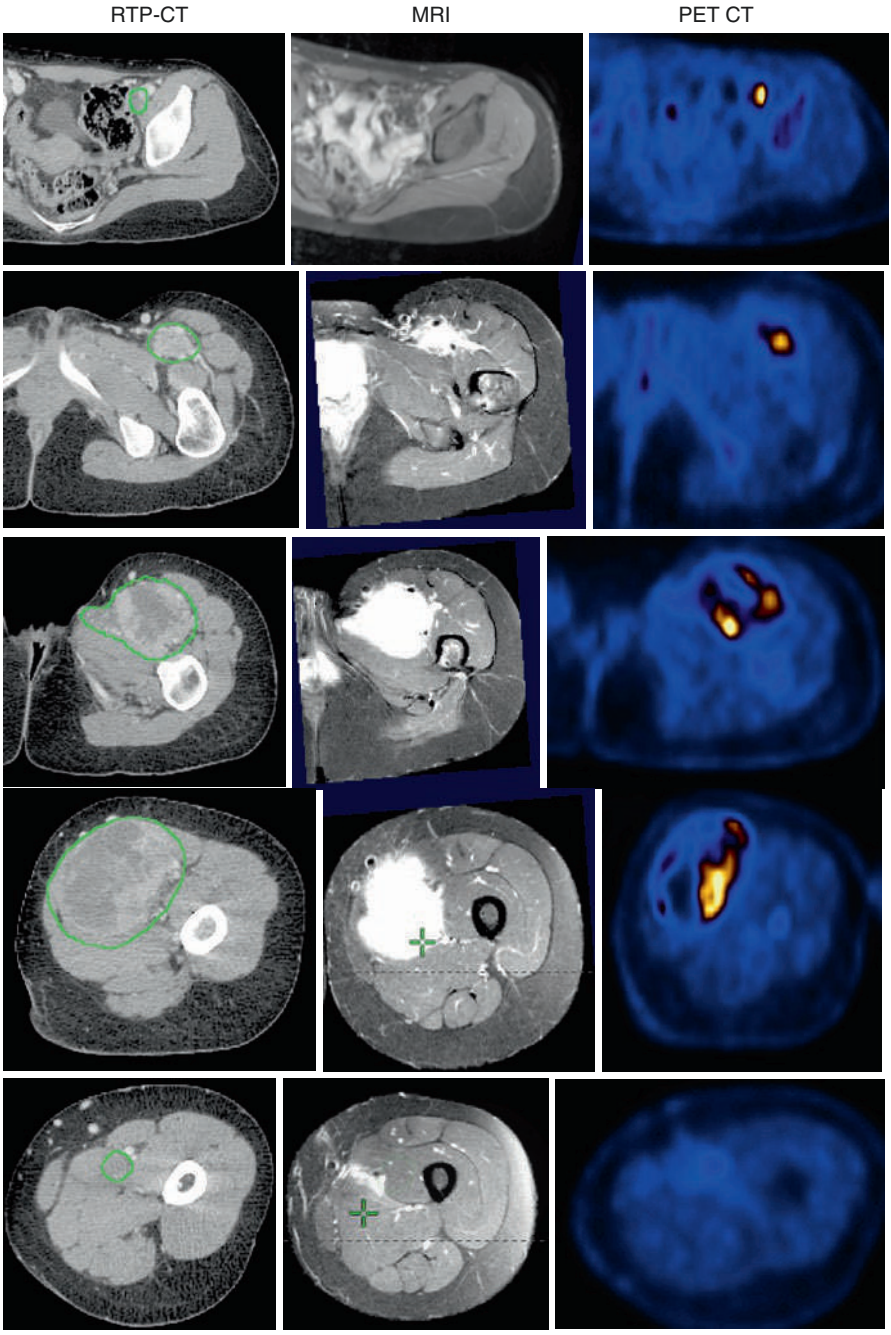


Fig. 10.2 Preoperative coronal MRI and PET-CT images for an adolescent female with synovial sarcoma of the right upper thigh. The patient underwent neoadjuvant chemoradiotherapy with two cycles of adriamycin and ifosfamide followed by 45 Gy in 25 fractions and concurrent ifosfamide at week 1 and 4 of radiation therapy. She then underwent surgery 4 weeks after radiation therapy. The patient was given postoperative RT boost of 10.8 Gy for microscopic positive margins at the medial aspect of the right thigh. MRI (*red arrow*) shows enhancement of the femoral and external iliac vessels. PET-CT (*green arrow*) shows FDG avidity, confirming tumor thrombus in the vessels

Fig. 10.3 Contouring the GTV (*green*). The RTP-CT (*left panels*), MRI (*middle panels*), and PET-CT (*right panels*) are used to contour the GTV. The MRI is reformatted to the RTP-CT. The PET-CT is obtained in the treatment planning position. The patient was positioned feet first in the gantry to ensure the entire mass, and critical organs/tissues from the pelvis to the knee joint were visualized on the radiation therapy planning CT (RTP-CT). IV contrast was used to distinguish tissue planes and define the relationship of tumor to normal tissue


RTP-CT
MRI
PET CT

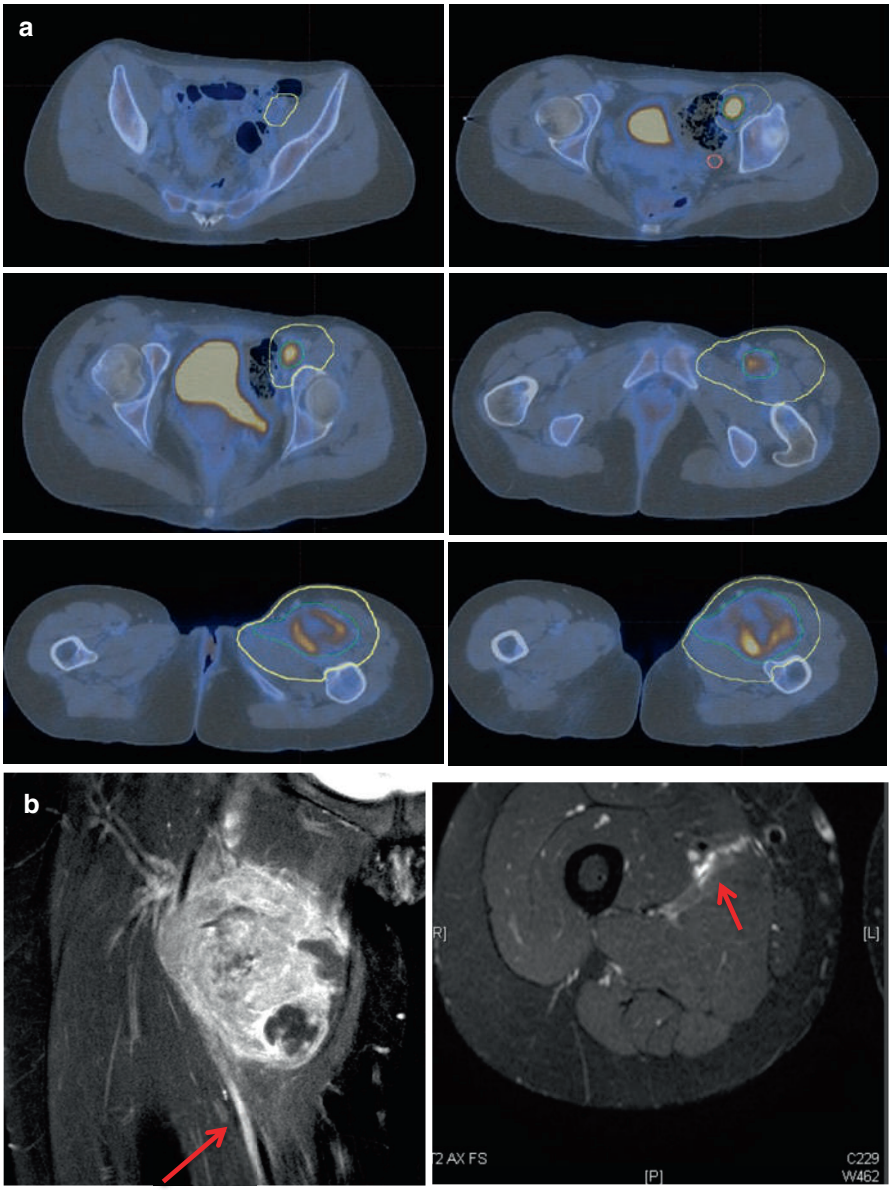


Fig. 10.4 Contouring the CTV (*yellow*). (**a**) The CTV includes a 1.5 cm radial expansion on the GTV and is edited to exclude anatomic borders to tumor spread such as the small bowel, bone, and perineum. The right ovary is marked in orange at the level of the right acetabulum. The fascial plane between the deep muscle compartment and subcutaneous tissues also acts a barrier to tumor spread. As there was no subcutaneous tissue tumor infiltration nor biopsy tract, the CTV expansion was cropped to exclude subcutaneous tissue except in areas where there was potential for uncertainty in daily setup. (**b**) CTV should include suspicious edema as seen on MRI (*red arrows*)

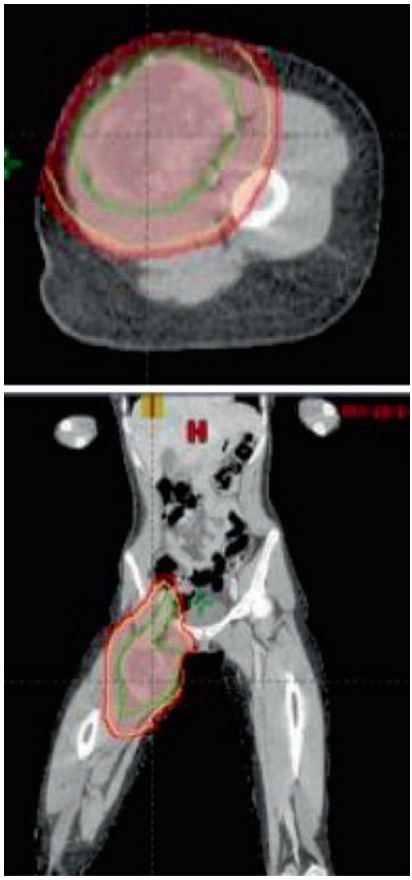


Fig. 10.5 Contouring the PTV (*red*). The PTV includes a 5 mm expansion on the CTV (*yellow*). The PTV is cropped 3 mm under the skin surface

10.2.1.2 Shoulder

See Figs. 10.7, 10.8, 10.9, and 10.10.

10.2.1.3 Abdominal Wall

See Figs. 10.11, 10.12, 10.13, 10.14, and 10.15.

10.2.2 Postoperative Radiation Treatment

- Principles of management
  - Postoperative RT is reserved for (1) resectable tumors that are high grade and ≤5 cm with microscopic positive margins or (2) larger high-grade tumors (>5 cm) that have close or microscopic positive margins.
  - Postoperative RT doses for pediatric patients are lower than doses used for adults with STS and include 45 Gy to the initial target volume with a boost of 55.8 Gy to areas of close/microscopic positive surgical margins. Gross residual disease

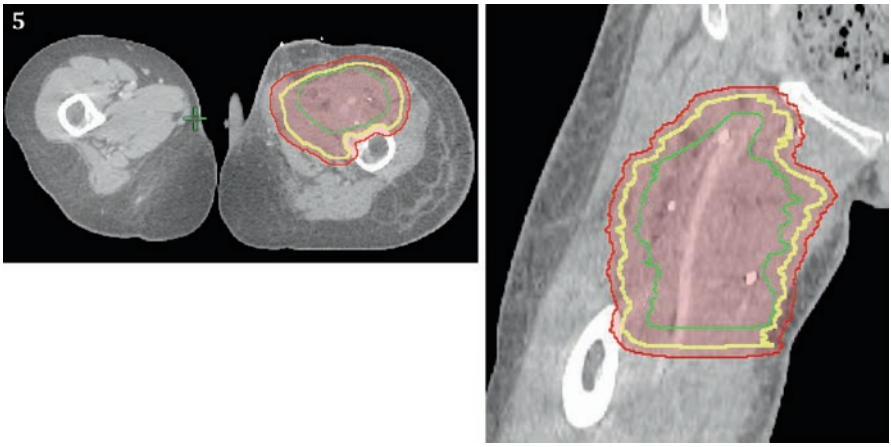


Fig. 10.6 Postoperative boost to the microscopic positive margins at 4 weeks after surgery. The postoperative area with microscopic positive margins (GTV2, *green*) was identified by clips, operative note, and the surgeon's input. The CTV2 (*yellow*) was created by a 1 cm margin for expansion on the GTV2 and edited to exclude bone and subcutaneous tissue. The PTV2 (*red*) included a 0.5 cm margin for expansion on the CTV2

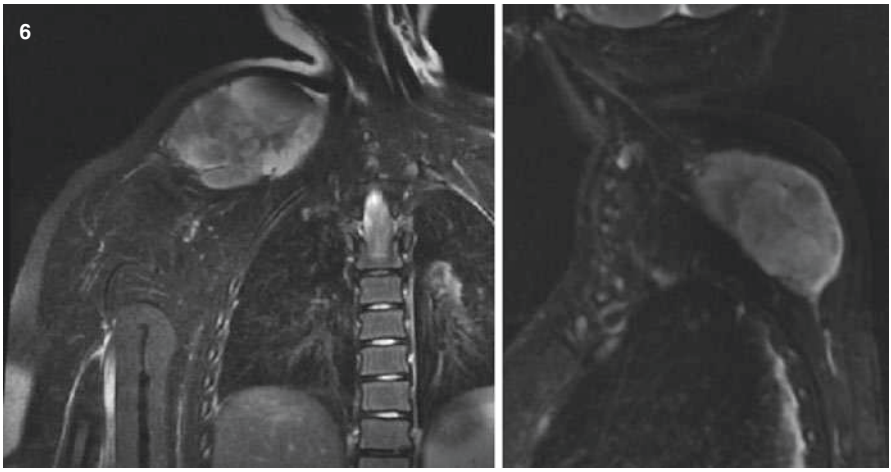


Fig. 10.7 Preoperative MRI and PET of the right posterior shoulder/upper back of an 11-year-old with high-grade undifferentiated soft tissue sarcoma. The patient received neoadjuvant chemoradiotherapy followed by surgical resection. Surgical margins were negative, and a postoperative boost was not recommended

can be boosted to 64.8 Gy total dose. It is important to note that concurrent chemotherapy (ifosfamide) was delivered with postoperative RT on the NRSTS COG clinical trial.

– Contouring target volumes is challenging since tissues shift into a more normal position after surgery, particularly visceral tumors that often extend into body cavities or compress adjacent organs.
– In distinction to preoperative contouring, at least two target volumes are generated for postoperative target volumes: a larger target volume that includes

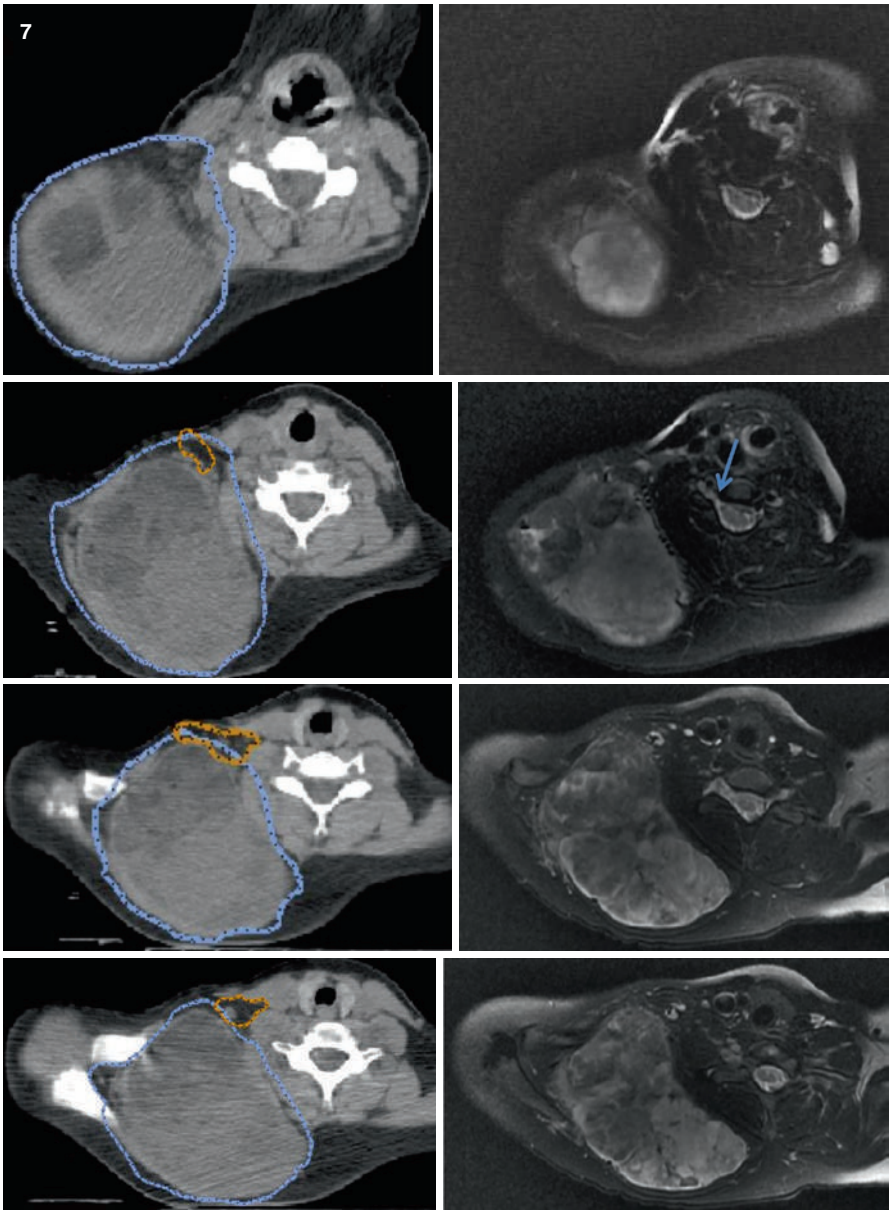


Fig. 10.8 Contouring the GTV (*blue*). The shoulder girdle is one of the most difficult parts of the body to immobilize and accurately recreate daily due to the clavicular, humeral, and scapular articulation. A long mask with Aquaplast was used to immobilize the shoulder while maintaining head and neck alignment. The diagnostic MRI was reformatted to the RTP-CT to align to the spine, brachial plexus, and shoulder joint and helped delineate normal tissues from the tumor. MRI in the treatment position would be an ideal method to delineate the GTV with respect to normal tissues. The exiting nerve roots of the brachial plexus (*gold*) abut the anterior aspect of the mass adjacent to the cervical spine. These nerve roots are best visualized on MRI and contoured as an OAR. The blue arrows show the trajectory of the nerve as it exits the spine and tracts between the anterior scalene and middle scalene muscle. The RTOG brachial plexus contouring atlas is used to contour the brachial plexus [10]

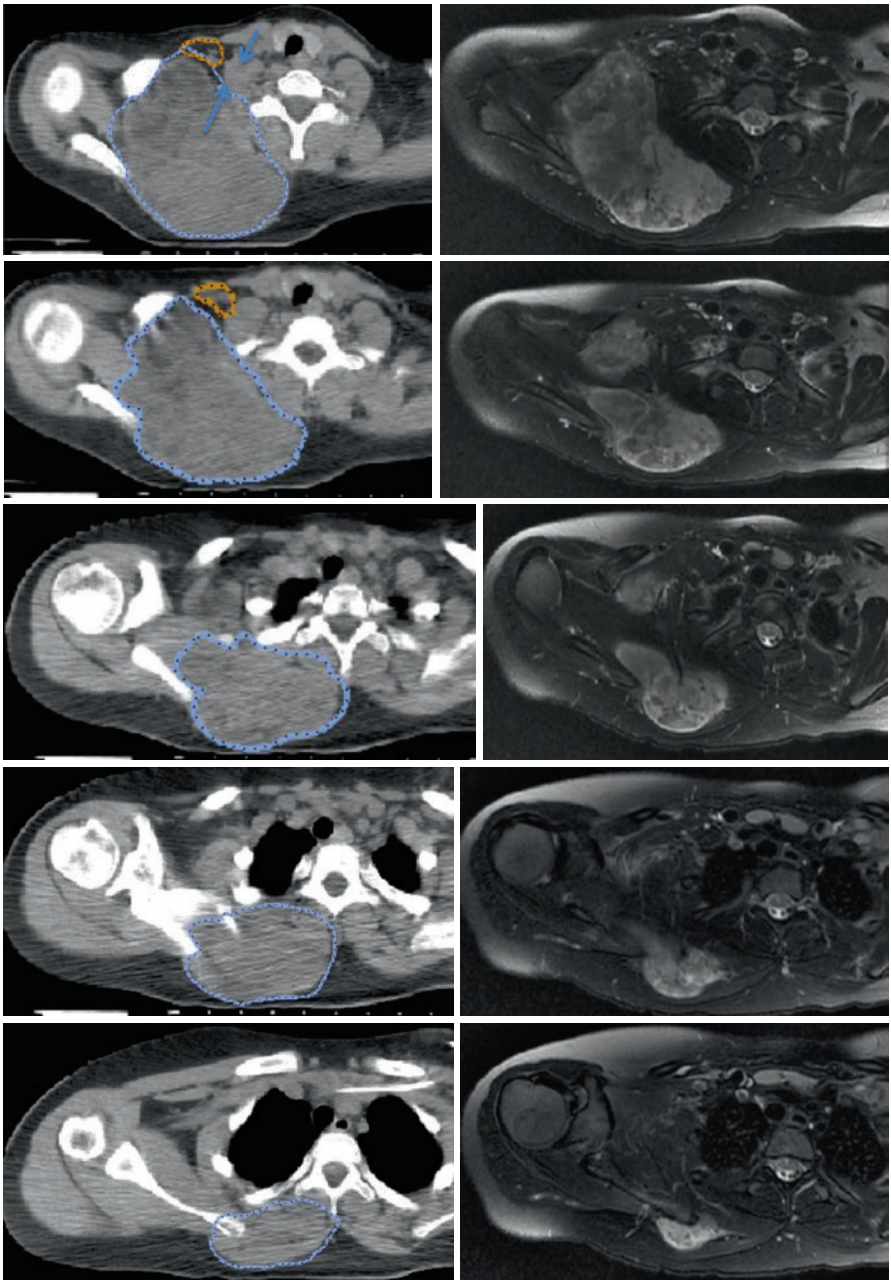


Fig. 10.8 (continued)

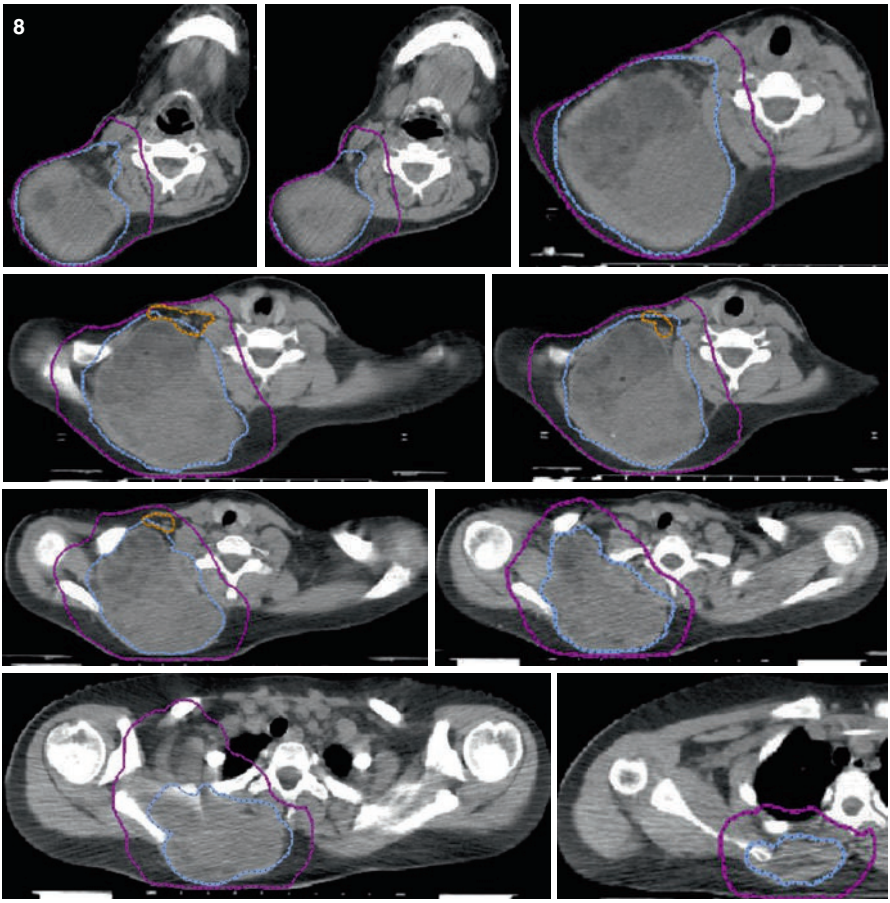


Fig. 10.9 Contouring the CTV (*purple*). A 1.5 cm expansion of the GTV (*blue*) forms the CTV. The CTV is further edited to include the brachial plexus where it abuts the GTV and peritumoral edema but exclude the vertebral body, humeral head, larynx, and lung. The ribs and scapula are included in the CTV as these structures are mobile and prone to daily setup error. In areas where the tumor extends is close to the skin, subcutaneous tissues and skin cannot be excluded from the CTV, which is often the case in younger children with little subcutaneous tissue

the gross tumor volume at diagnosis, operative site, and pathologically involved lymph nodes; a second target volume includes a volume reduction to the area at highest risk for harboring residual tumor.

– The GTV1 is reconstructed using the original tumor volume as seen on preoperative diagnostic imaging. It is then reformatted to the postoperative anatomy and modified to exclude the volume that extends into the cavity or compresses organs that radiographically return to their normal anatomic positions following surgery.
– The GTV2 (volume reduction) for resected tumors is defined as the region of close or microscopic positive margins as determined by the operative note, pathology report, surgeon's input, and imaging studies.

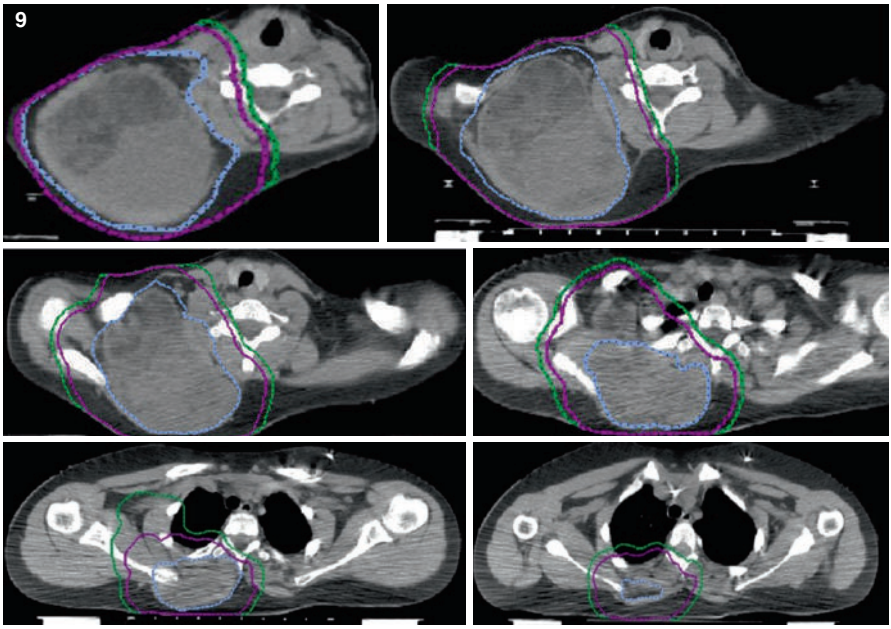


Fig. 10.10 Contouring the PTV (*green*). The PTV included a 5 mm expansion on the CTV (*purple*), except along the skin where the CTV abuts the skin surface. In the head and neck primary sites, a 3 mm expansion is generally sufficient with rigid immobilization. In this case, due to setup uncertainty around the shoulder, a 5 mm expansion was used

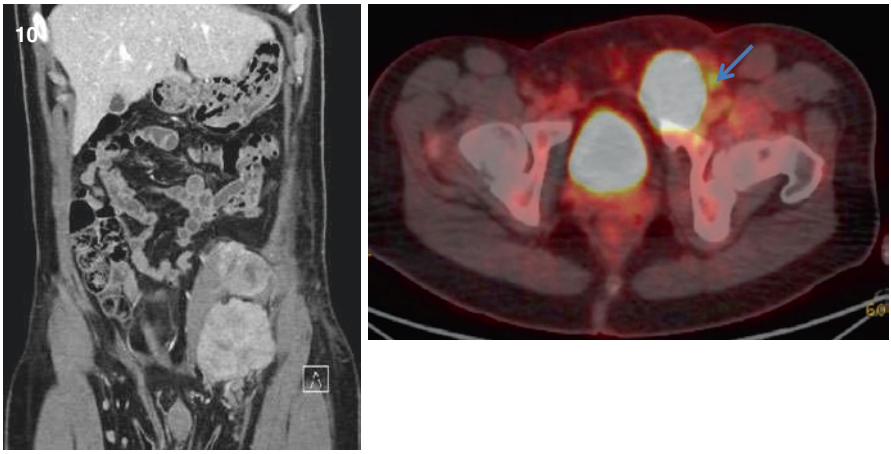


Fig. 10.11 Pretreatment CT of the abdomen/pelvis (*left panel*) shows a multi-lobulated mass of the abdominal wall in a teenage male. Biopsy showed high grade leiomyosarcoma. Axial PET-CT (*right panel*) showed FDG avidity in one inguinal lymph node adjacent to the lower mass (blue arrow). The patient received a course of neoadjuvant chemoradiotherapy including 45 Gy with concurrent ifosfamide

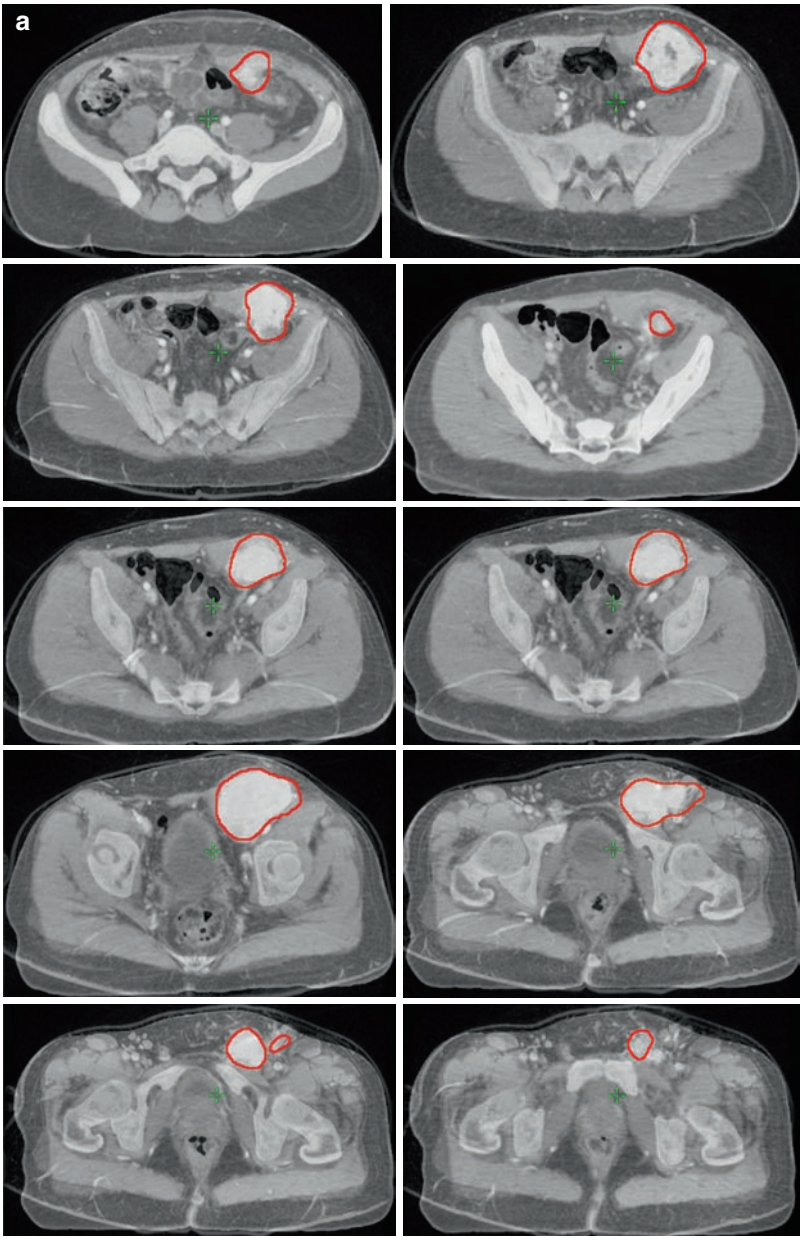
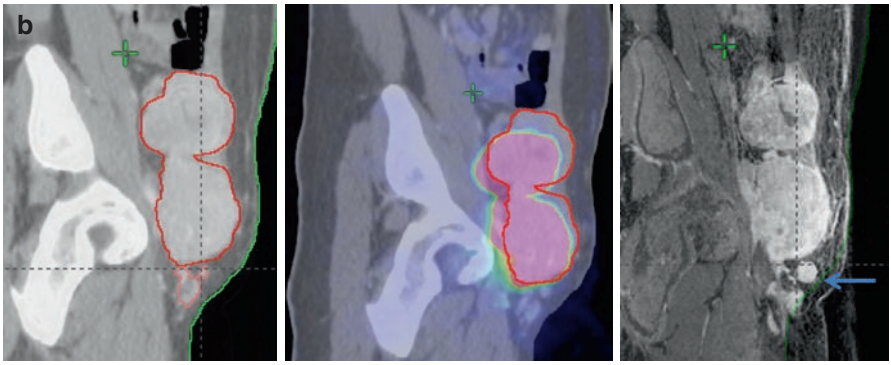


Fig. 10.12 Contouring the GTV (*red*). A RTP-CT scan with IV contrast and 4D scan captured the extent of abdominal movement during respiration. The GTV was contoured using reformatted diagnostic MRI and PET-CT in the treatment position. (**a**) The blended RTP-CT and MRI shows the mass easily visualized on T2 MRI. (**b**) Sagittal RTP-CT (*left*), fused PET-CT (*middle*), and MRI (*right*). On the sagittal MRI, there is a cluster of enhancing lymph nodes (*blue arrow*) distal to the mass that were not FDG avid on PET-CT. These nodes were not included in the GTV but contoured as a separate structure (*orange*) and included in the CTV



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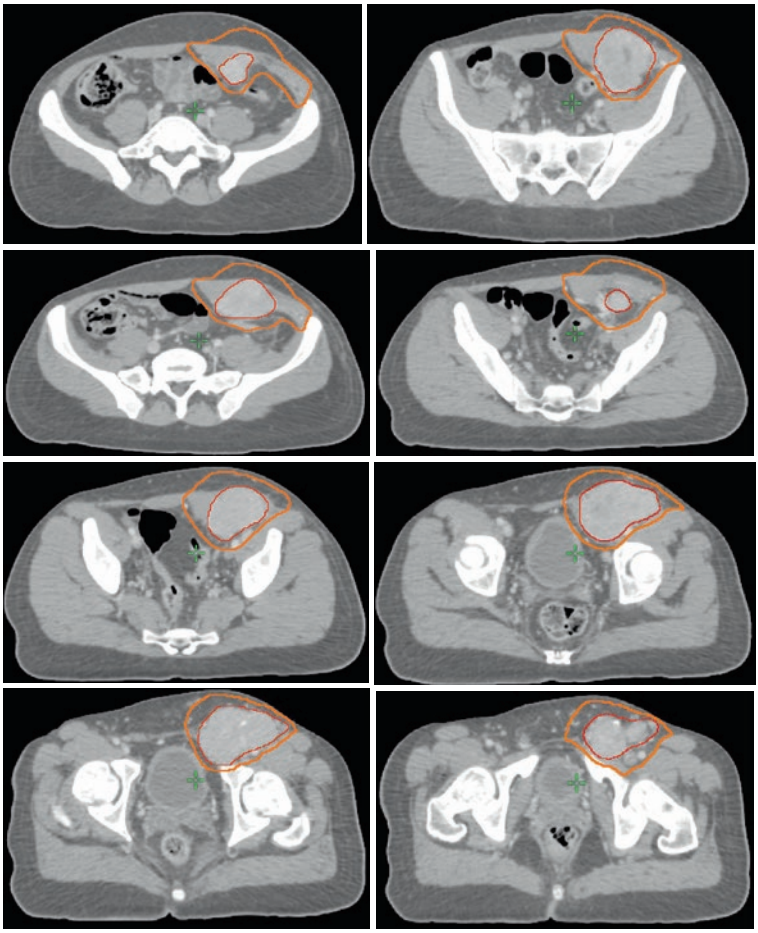
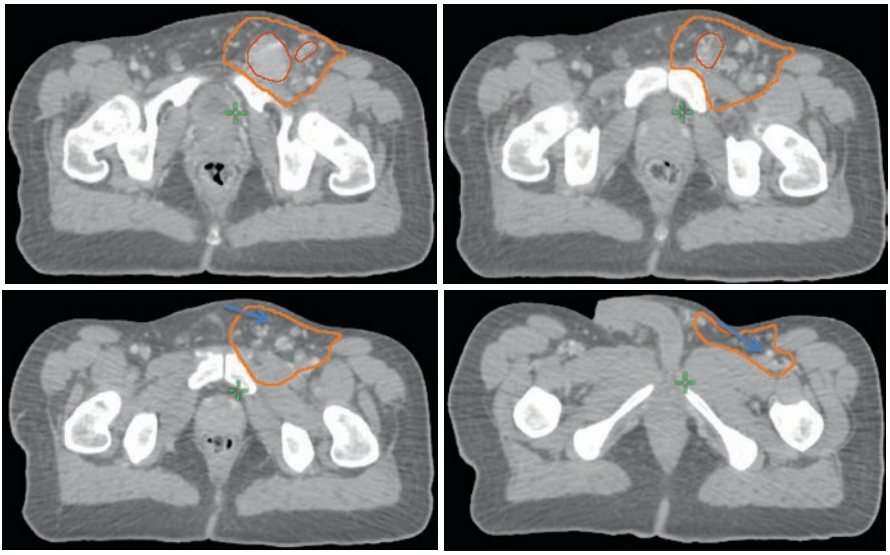


Fig. 10.13 Contouring the CTV (*orange*). After a radial expansion of 1.5 cm on the GTV, the CTV was edited to include suspicious edema along the transverse abdominal wall musculature and adjacent regional nodes that were slightly enlarged but not FDG avid (*blue arrows*). Further editing excluded the small bowel, bladder, genitalia, and bone



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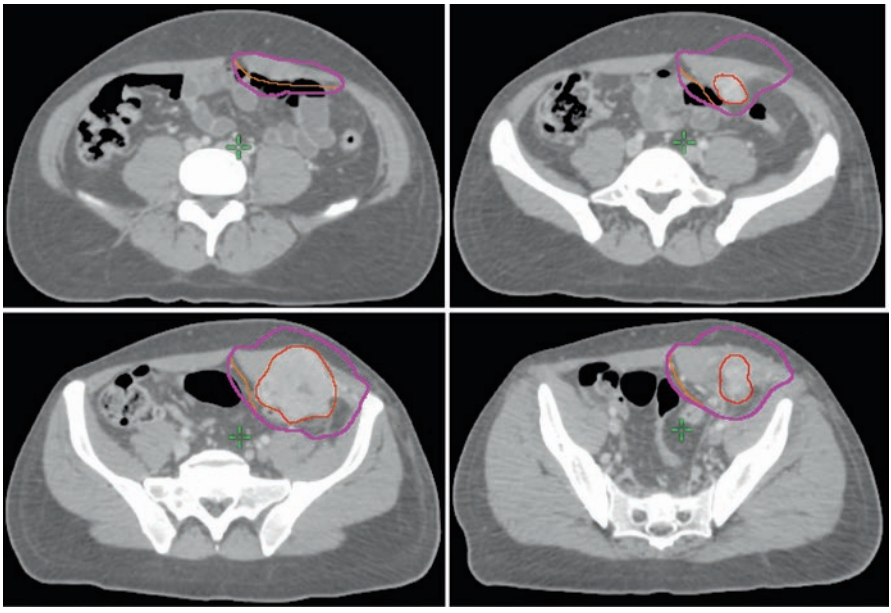


Fig. 10.14 Contouring the ITV (*pink*). The ITV was created to account for abdominal wall motion. The subcutaneous tissue overlying the mass was not cropped back to the fascia to account for abdominal wall motion. However, deep to the abdominal wall, a small ITV expansion into the small bowel was necessary to ensure target coverage during respiration

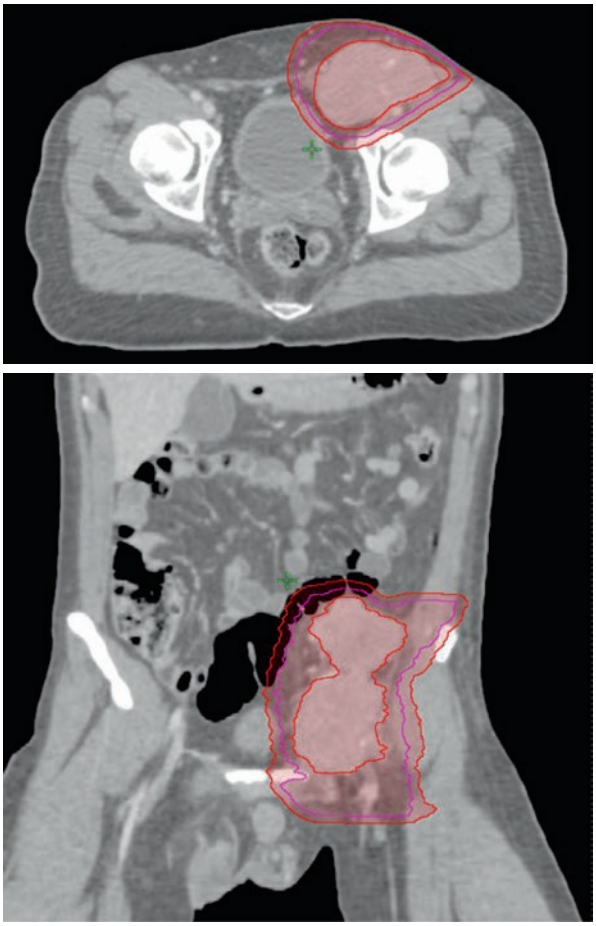


Fig. 10.15 Contouring the PTV (*red*). The PTV was created by a 5 mm expansion on the ITV (*pink*)

- CTV1 is a 1.5 cm expansion on the GTV1 including pathologically involved lymph nodes. CTV1 may need to be further expanded to include the operative bed, seroma, clips, and surgical incision. CTV1 is modified to exclude normal tissues/organs that act as barriers to tumor spread.
- CTV2 is a 1 cm expansion on GTV2.
- PTV1/2 is a 0.5 cm expansion on the CTV1/2.

10.2.2.1 Abdomen

See Figs. 10.16, 10.17, 10.18, and 10.19.

10.2.2.2 Pelvis

See Figs. 10.20, 10.21, 10.22, and 10.23.

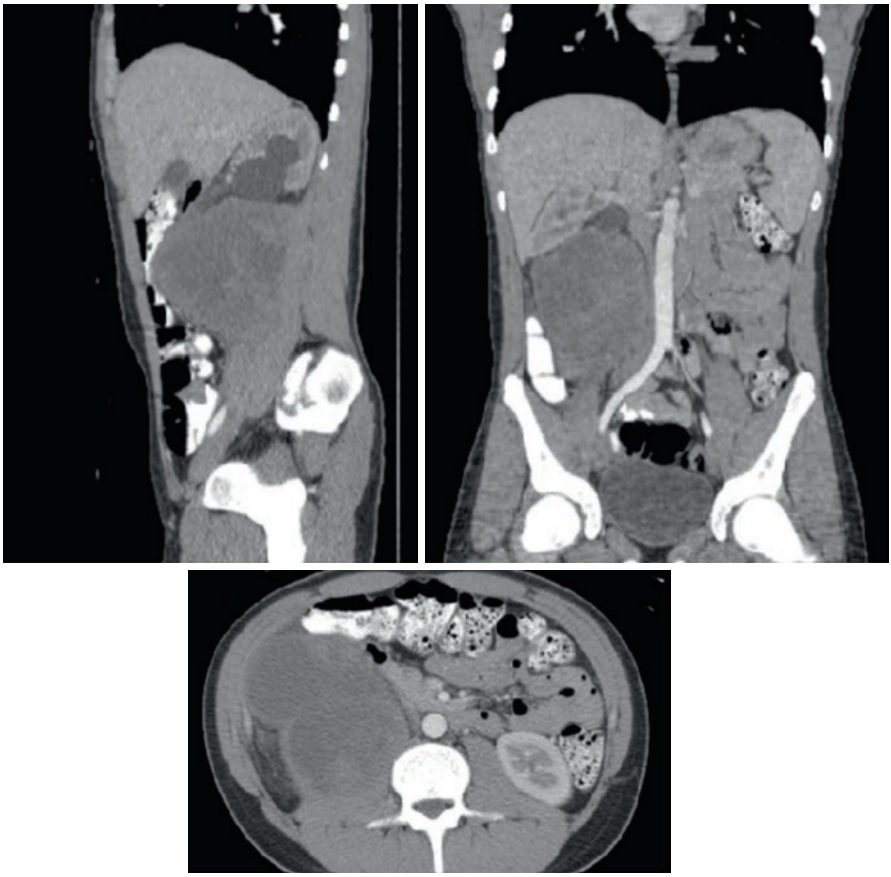


Fig. 10.16 Preoperative CT scan of a high-grade retroperitoneal NRSTS. The patient underwent resection with 1 mm surgical margins. Postoperative radiation therapy was delivered to two volumes: 45 Gy to the initial tumor volume and a boost of 55.8 Gy to areas of close surgical margins

10.3 Plan Assessment

- The decision to use IMRT, protons, or 3D conformal techniques depends on many factors. A large field size, rapidly growing tumor, poor immobilization, and superficial tumors are several reasons that 3D conformal may be favored over IMRT. If motion leads to heterogeneity of tissue or changes in tissue filling (i.e., bowel or lung/soft tissue interface), proton therapy may not be ideal.
- IMRT allows lower doses to the skin and subcutaneous tissues in the preoperative setting and has been associated with fewer wound-healing delays postoperatively [11].
- Respiratory motion should be assessed for sarcomas adjacent to the chest, abdomen, and trunk and accounted for with ITV and/or gating techniques.

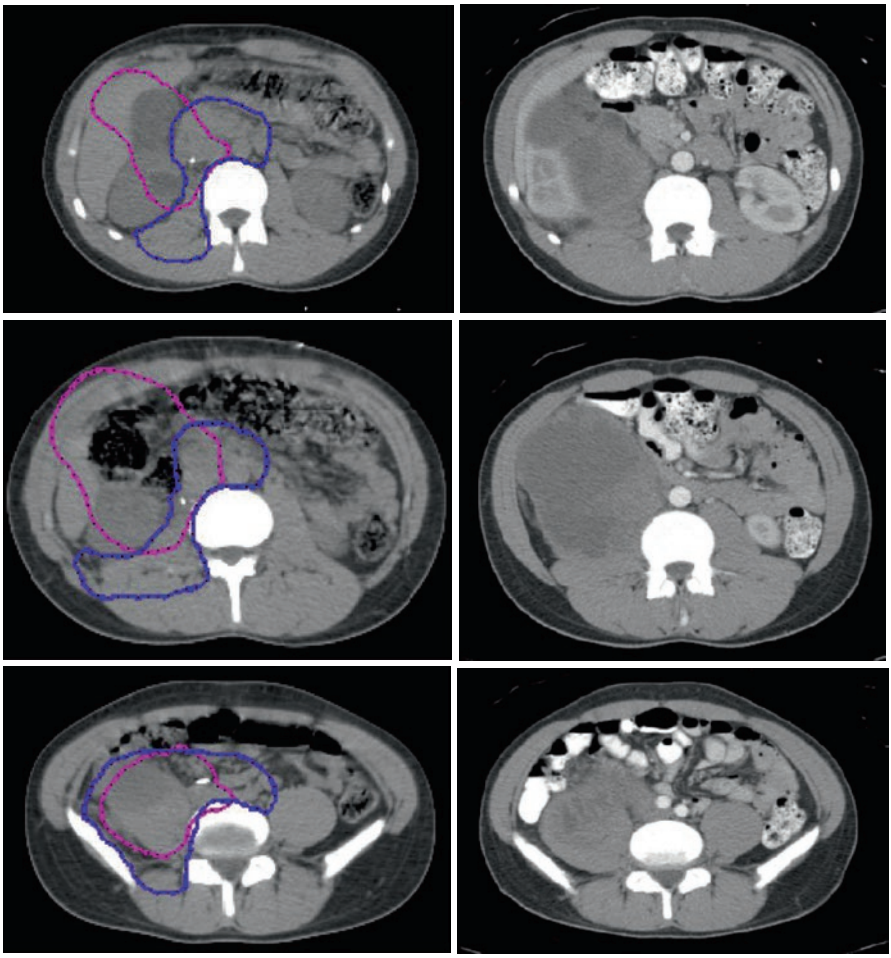


Fig. 10.17 Contouring the GTV (*pink*) and CTV1 (*blue*). The left hand panel shows the post-operative axial image of the RTP-CT with the reconstructed GTV and edited CTV1. The right hand panel shows the corresponding pre-operative axial CT image. The GTV serves as a guide to contouring the CTV1. A 1.5 cm expansion around the GTV provided a starting point to create the CTV1, which was then edited to exclude the small bowel, spine, kidney, liver, and bone and expanded to include clips, postoperative changes, and the psoas muscle where there was infiltration of tumor

- Daily IGRT can significantly reduce late effects for all treatment sites [5]. KV imaging is preferable over MV imaging due to reduced ionizing radiation exposure.
- OAR should be determined by the treatment site. Normal tissue dose constraints can be found in references such as QUANTEC and RTOG protocols.

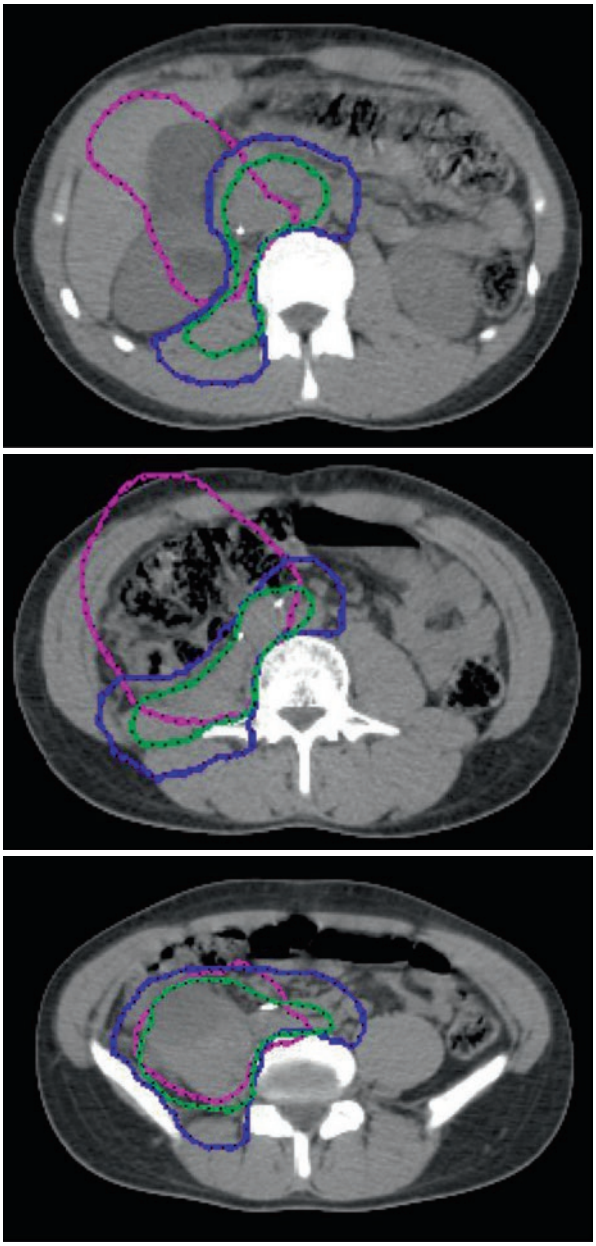


Fig. 10.18 Contouring the CTV2 (*green*). For this patient, the GTV1 and GTV2 are the same (*pink*). The CTV2 included a 1 cm expansion around the GTV. It was then edited to exclude the small bowel, liver, kidney, and bone and further adjusted to not extend outside CTV1

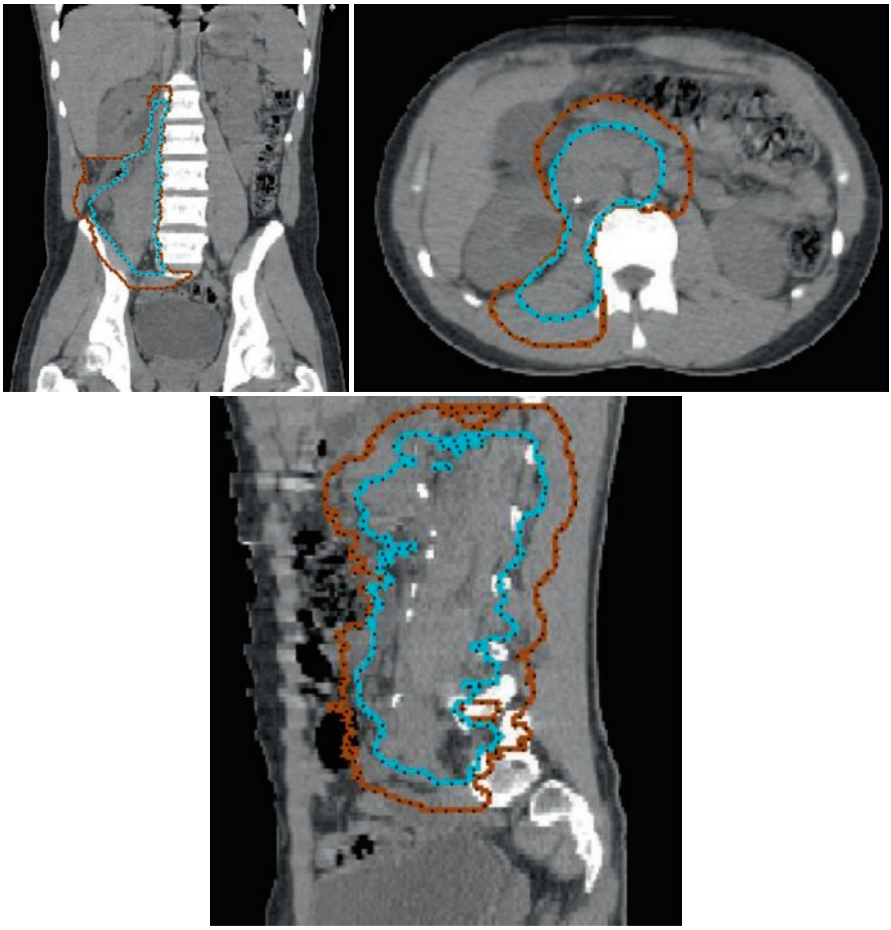


Fig. 10.19 Axial, coronal, and sagittal views of the PTV1 (*brown*) and PTV2 (*light blue*) demonstrate the final volume excluding the liver, kidney, and small bowel but including the operative bed as seen by the clips

- Ovaries and testes should receive doses as low as reasonably achievable (ALARA). Surgical manipulation to move these organs out of the radiation field is recommended. The scatter dose should be calculated to assess the risk for infertility/sterility.
- Bone growth is particularly important in children and young adults. Careful sculpting of target volumes around epiphyseal plates, joints, and vertebral bodies can lessen the risk of bone growth abnormalities.

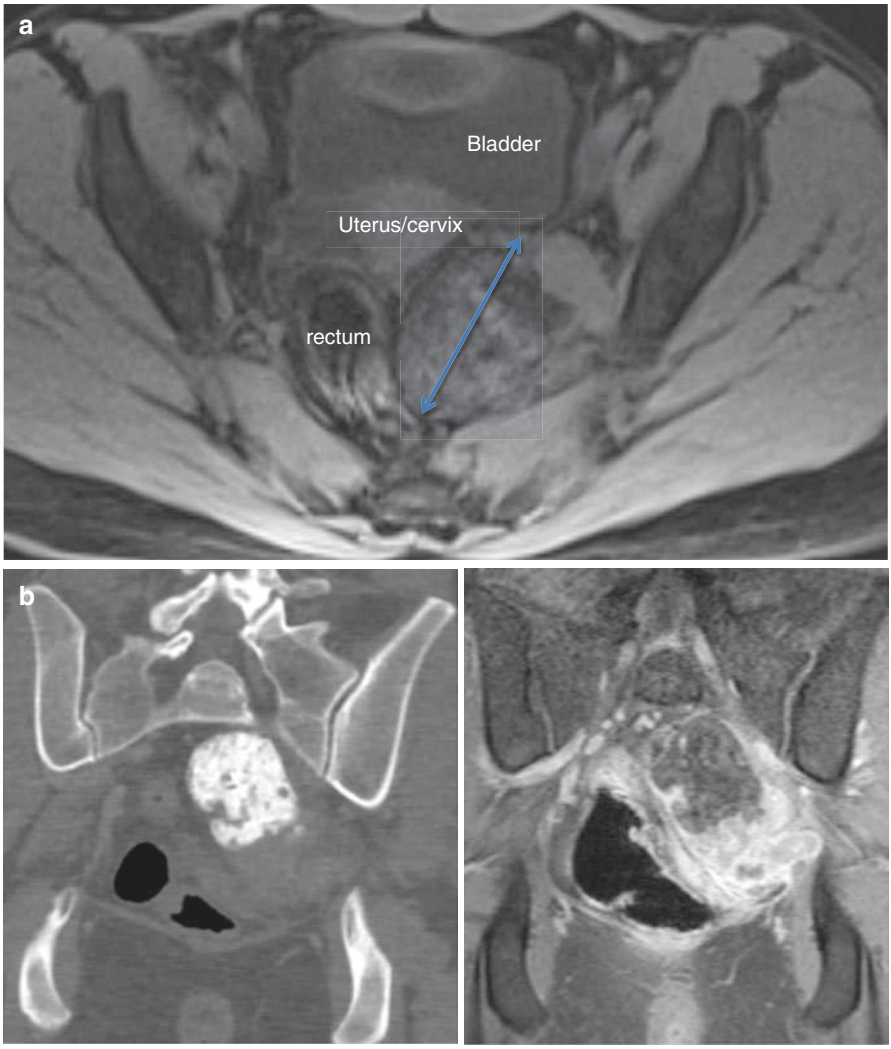


Fig. 10.20 Preoperative imaging of a teen female with high grade NRSTS the mass was resected with microscopic positive margins. (**a**) The axial MRI shows a partially calcified mass arising from the presacral region (*blue arrow*). She underwent surgery with microscopical positive margins abutting the sacral outflow nerve roots. (**b**) Coronal CT (*left*) and MRI (*right*) demonstrate a partially calcified mass with a soft tissue component infiltrating the soft tissues, displacing the bladder, uterus/cervix, and rectum

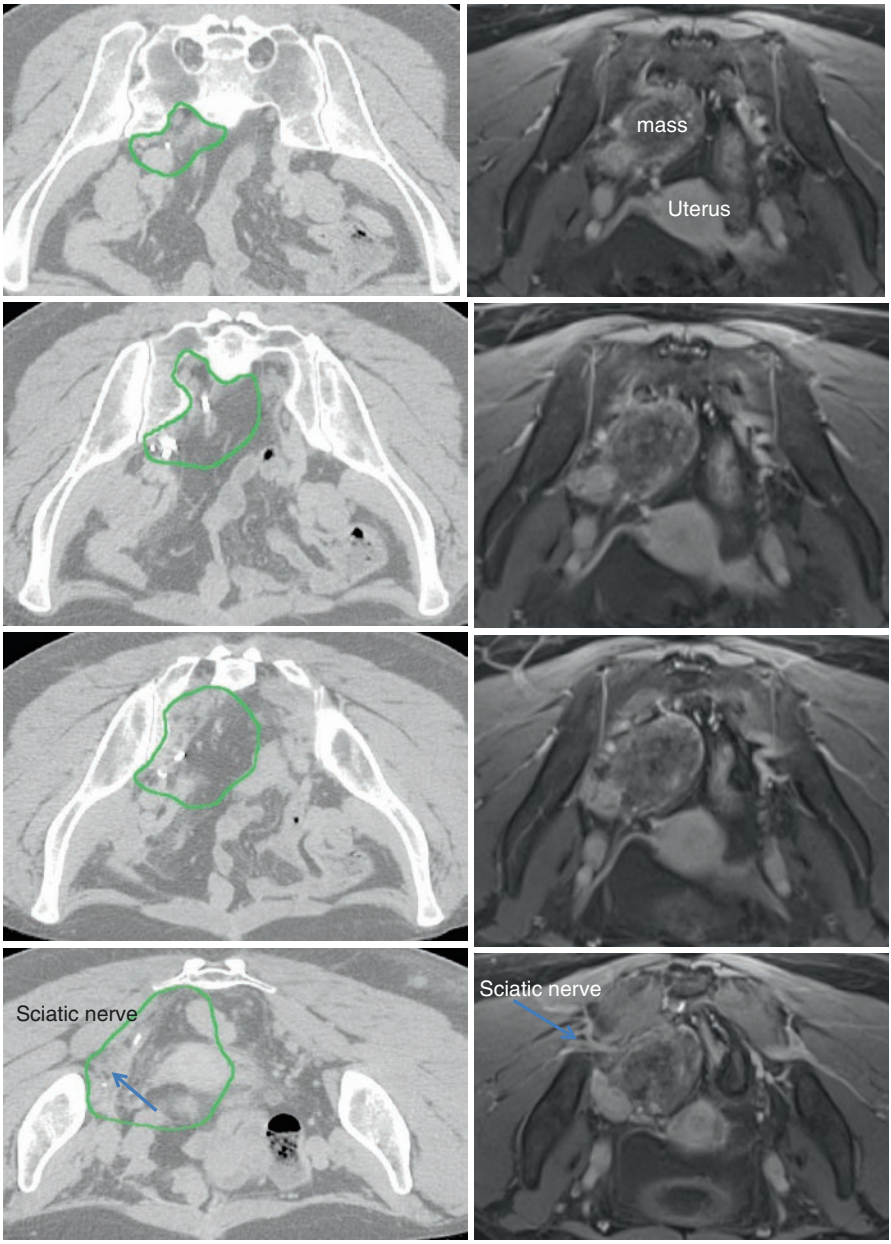
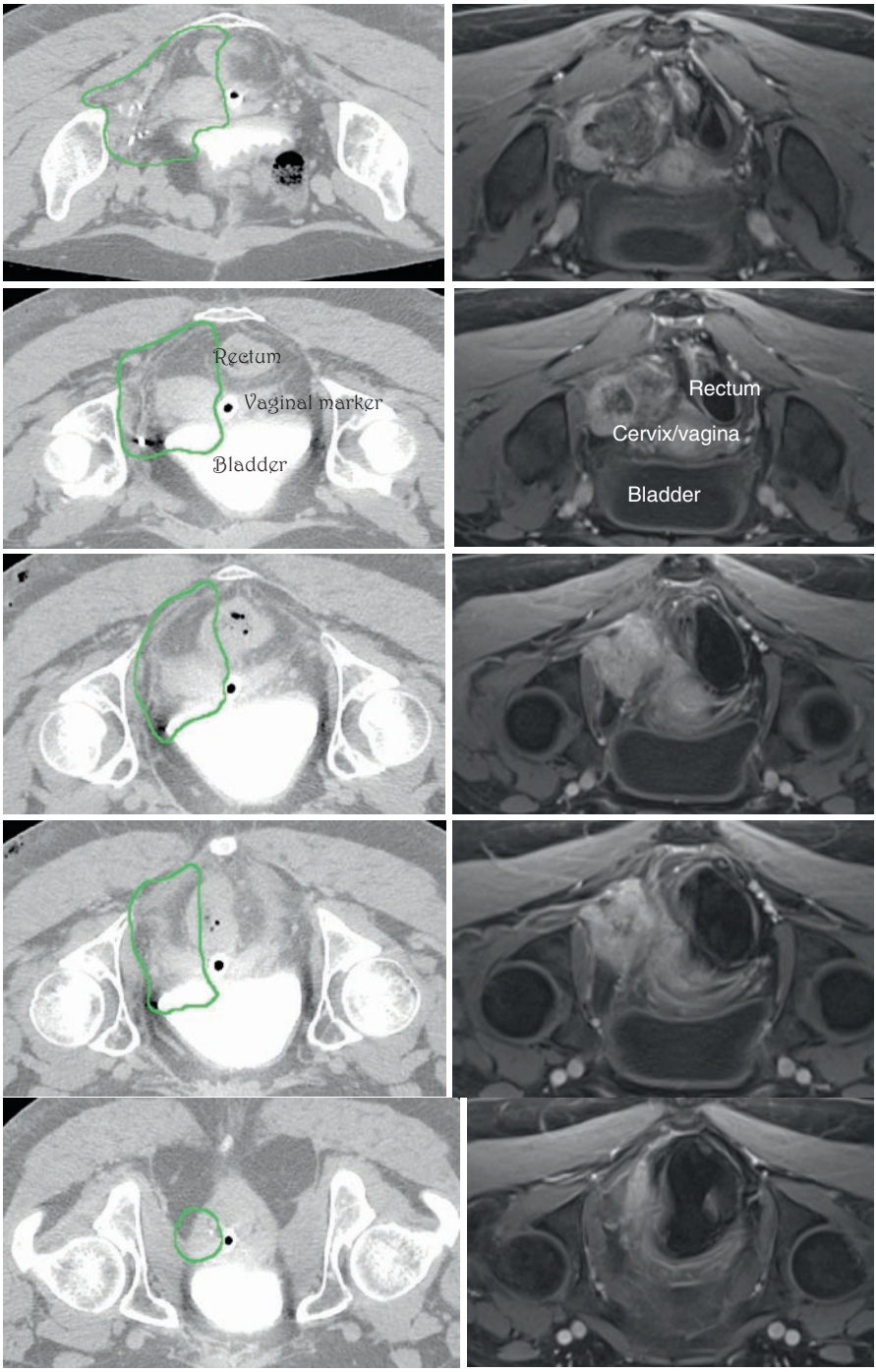


Fig. 10.21 Contouring the GTV. The patient was positioned prone to displace the small bowel out of the radiation field. A vaginal marker was placed at simulation, and the bladder was filled with contrast. The GTV (*green*) was recreated and edited along the medial border where the normal tissues have shifted back to midline including the uterus, vagina, bladder, small bowel, and rectum. The surgeon noted adherence of tumor along the uterus/vaginal wall/bladder and rectal wall, so the GTV partially included the lateral aspect of these structures. The tumor was adherent to the exiting sacral nerve roots so they were tracked as a separate structure from the sacral neural foramen to the sciatic notch (*blue arrow*) and included in the GTV



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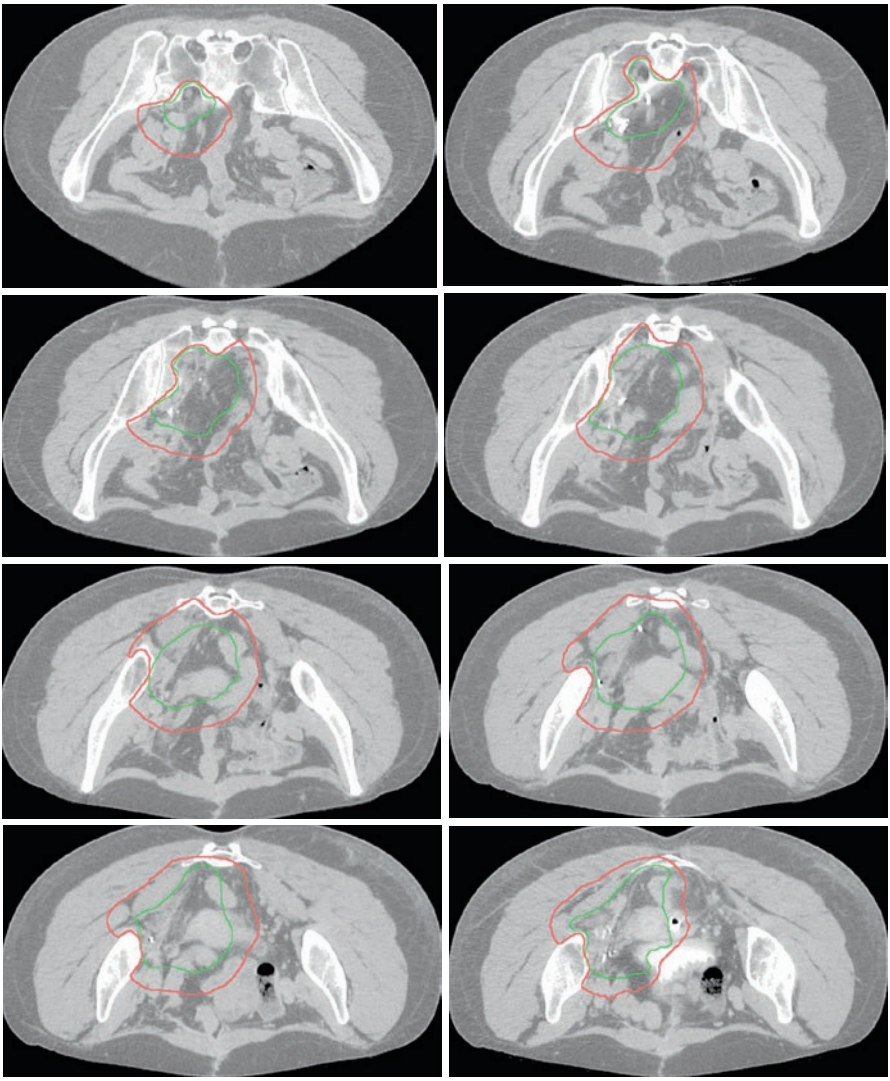
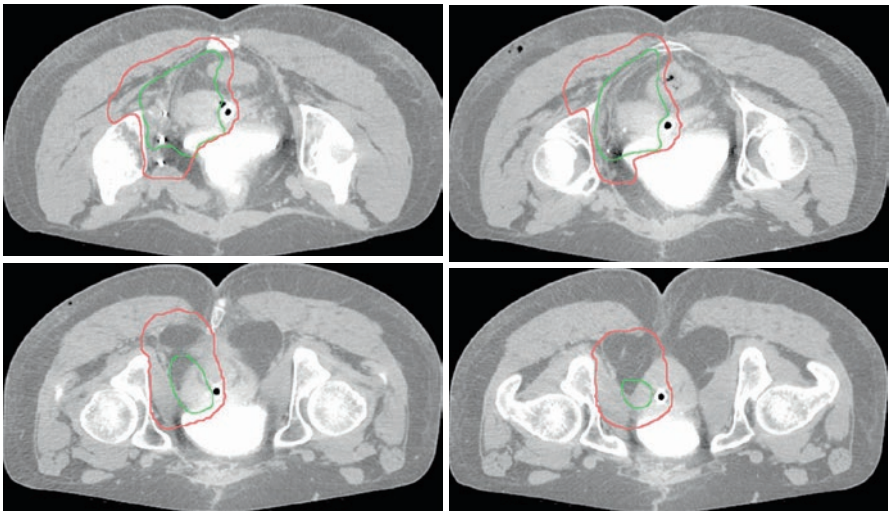


Fig. 10.22 Contouring the CTV1 (*salmon*). The CTV included a 1.5 cm radial expansion of the modified GTV cropping off the bone and edited to exclude normal tissues but include the "at-risk" operative bed that was defined by soft tissue fibrosis and clips. As the tumor was adherent to the adjacent bladder wall, uterus, vaginal wall, and rectum, it was necessary to include a small part of these organs in the CTV

Fig. 10.23 Contouring the CTV2 (*purple*). The boost volume (GTV2) was defined by the surgical clips along the exiting sacral nerve roots and roughly corresponded to the reconstructed GTV1 (*green*). The GTV1/GTV2 was edited to exclude normal tissue such as the small bowel, bladder, uterus, and bone. Fascial planes also function as normal barriers to tumor spread (CTV2). A 5 mm PTV expansion on the CTV2 was used as the planning target volume



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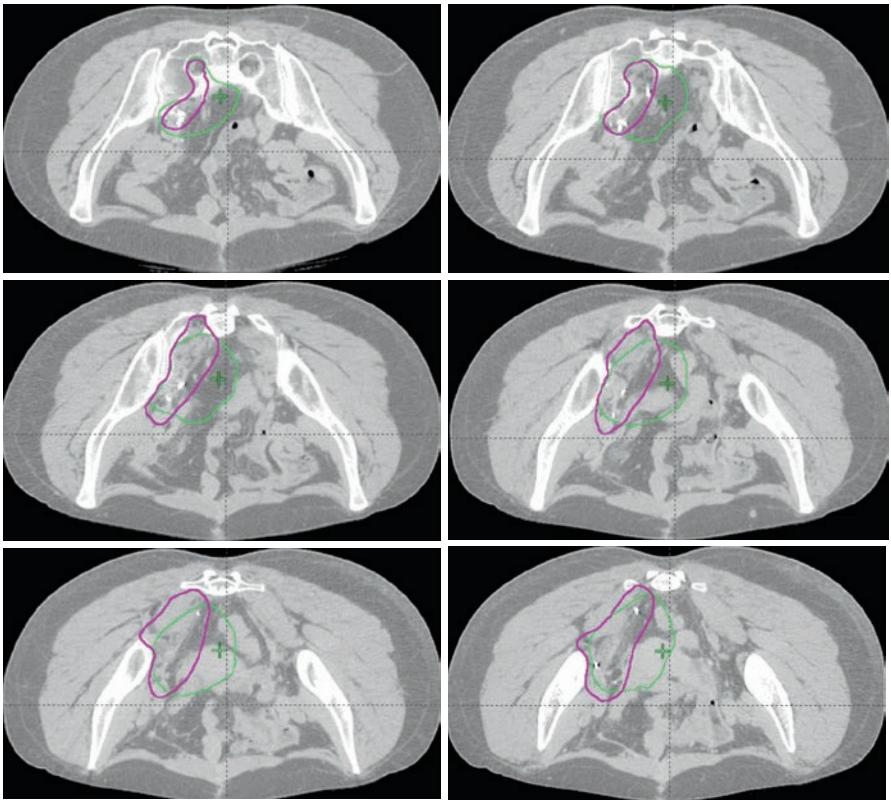

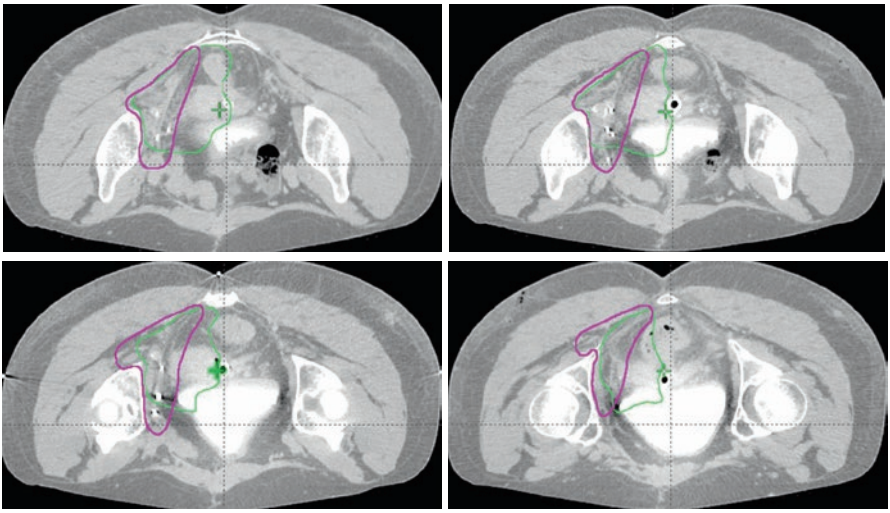

Fig. 10.23 (continued)

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Pediatric Hodgkin Lymphoma

11

Zachary D. Guss, Qinyu Chen, Bradford Hoppe, and Stephanie A. Terezakis

Contents

11.1 Background

- Hodgkin lymphoma (HL) represents approximately 4% of childhood (0–14 years old) malignancies and 15% of adolescent (15–19 years old) malignancies [1]. Bimodal incidence peaks in adolescent and adult age ranges [2].
- The Reed-Sternberg cell, CD15+/CD30+, is a key histologic feature in classic subtypes (nodular sclerosing, lymphocyte-rich, lymphocyte-depleted, and mixed cellular) but not nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), which is CD20+.
- Association with Epstein-Barr virus is highly variable (~30 to 40% in immunocompetent pediatric classical Hodgkin lymphoma, 80% + in immunocompromised patients) [3].

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- The radiation dose range in major pediatric North American trials has been 19.8–25.5 Gy in 1.5–1.8 Gy daily fractions however, higher doses of 30 Gy are being employed among patients with incomplete response following chemotherapy and in relapse studies.

11.2 Staging and Risk Classification

- Staging is per Ann Arbor staging classification for Hodgkin lymphoma.
- Definition of bulk varies by protocol but in many studies includes a mediastinal mass larger than one third of maximal thoracic diameter or contiguous extra-mediastinal nodal aggregate greater than 6 cm in maximum diameter in the axial plane.
- Risk stratification varies per study. In general, recent Children's Oncology Group (COG) trials stratify risk by the following Ann Arbor stages:
  - Low risk: stages IA–IIA without bulk
  - Intermediate risk: IA–IIA with bulk, I–IIAE, I–IIB, IIA, IVA
  - High risk: IIIB, IVB (Stage IIB bulky, IVA are sometimes considered high risk)

11.3 Target Volume Delineation

- Radiation therapy (RT) was historically delivered with extended field and subtotal nodal fields to high doses. This was therapeutic but harbored significant late effects [4–7].
- With the adoption of multimodality treatment paradigms including chemotherapy, involved field radiation therapy (IFRT) evolved to treat the nodal regions superior and inferior to the area of known disease. These classic fields are described by Yahalom and Mauch [8].
- More recently, pediatric protocols have incorporated novel approaches informed by modern diagnostic imaging to include only known nodal disease with a safety margin. Involved node RT (INRT), as defined by the EORTC-GELA [9], uses strict criteria and requires pretreatment diagnostic imaging with the patient in the treatment position. Involved site RT (ISRT) similarly aims to reduce the amount of irradiated normal tissue with less rigid criteria.
- Pediatric Hodgkin lymphoma patients are encouraged to enroll in a clinical trial if one is available. In such a scenario, contouring should be performed according to protocol guidelines.
- Target delineation for several pediatric Hodgkin lymphoma protocols are summarized below (Tables 11.1, 11.2, and 11.3). A representative set of planning objectives and dose constraints is provided in Table 11.4. Illustrative cases are presented in Figures 11.1, 11.2, 11.3, 11.4, and 11.5).

Table 11.1 AHOD0031 planning definitions for IFRT in pediatric Hodgkin lymphoma (a phase III groupwide study of dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin disease)

Volume	Description
Gross tumor volume (GTV)	Contains any lymph node measuring >1.5 cm in a single axis on CT
	Contains any lymph node which is FDG positive at initial diagnosis
Clinical target volume (CTV)	Anatomic compartment containing GTV (see protocol for site-specific recommendations) that contains the original extent of disease
	Fields cannot be adapted to chemotherapy response except in the mediastinum
	Includes contiguous anatomical compartments that contain lymph nodes >1.0 cm in size on CT
Planning target volume (PTV)	Contains CTV plus a 0.5–1.0 cm margin to account for patient motion and setup variability
	Note: *PTV expansions can be modified at the discretion of the treating radiation oncologist*
Organs at risk (OAR)	Includes uninvolved normal structures at risk of RT-related toxicity for which RT planning or dose may be altered
Dose and fractionation	21 Gy in 14 daily fractions

Table 11.2 AHOD0831 planning definitions in pediatric Hodgkin lymphoma (a non-randomized phase III study of response-adapted therapy for the treatment of children with newly diagnosed high-risk Hodgkin lymphoma)

Volume	Description
Gross tumor volume (GTV)	Includes post-chemotherapy radial extent in lateral, anterior, and posterior directions and pre-chemotherapy extent in the superior and inferior directions: Contains the post-chemotherapy volume of disease that was bulky at presentation Includes the post-chemotherapy volume of non-bulky disease with a slow response to chemotherapy Encompasses the post-chemotherapy volume if non-bulky disease at presentation with residual disease measuring ≥2.5 cm in axial diameter at the completion of all chemotherapy in patients with a slow early response (even if that particular site was PET negative)
	Special circumstances: *Note*: *Slow response was defined as any site of disease that is PET positive after the second cycle of chemotherapy*
Clinical target volume (CTV)	Contains entire GTV defined above
	Includes the post-chemotherapy nodal or involved parenchyma regardless of size and response
	Should be 1.0 cm within the anatomic compartment field edge
Planning target volume (PTV)	Contains the CTV plus at least a 0.5 cm margin that account for patient motion and setup variability. Contains the volume receiving 95% of the prescribed dose at least 0.5 cm from the field edge
	Note: *CTV to PTV expansions may be as large as 1.0 cm to ensure adequate coverage determined by the treating radiation oncologist; further modifications as clinical context dictates*
Organs at risk (OAR)	Includes uninvolved normal structures at risk of RT-related toxicity for which RT planning or dose may be altered
Dose and fractionation	21 Gy in 14 daily fractions

Table 11.3 AHOD1331 planning definitions for ISRT in pediatric Hodgkin lymphoma (a randomized phase III study of brentuximab vedotin (SGN-35. IND #117117) for newly diagnosed high-risk classical Hodgkin lymphoma (cHL) in children and adolescents)

Volume		Description
Gross tumor volume (GTV)	Pre-chemotherapy/surgery GTV	Nodal and non-nodal tissues involved with lymphoma prior to any treatment and meet the criteria for requiring RT (large mediastinal adenopathy (LMA) or slow responding lesion (SRL))
	Post-chemotherapy GTV	Imaging abnormalities that persist after all planned chemotherapy
	iGTV	Contains the GTV plus a margin for GTV respiratory motion in patients with moving tumors within the lung for proton therapy planning
Post-chemotherapy clinical target volume (CTV)		Encompasses the entire pre-chemotherapy GTV but must take into account the reduction in axial diameter that has occurred with chemotherapy
		Includes consideration of the following: Expected routes of disease spread Quality of pretreatment imaging Other clinical and imaging factors (e.g., extent of involvement in nearby nodal regions, bulk of disease) Changes in volume since the time of imaging Patient position between diagnostic and treatment
		Contains normal nodal tissue located between two anatomically close (i.e., within 5 cm) sites that are going to be joined and treated by RT as a single volume
		Although there is no rigid CTV expansion, a margin of 1.5 cm above and below lymph nodes involving lymphoma is recommended as a guideline
Internal target volume (ITV)		CTV plus an added margin to account for variation in shape and motion within the patient (e.g., respiratory motion)
		Most relevant for targets within the thorax and abdomen
Planning target volume (PTV)		Includes the CTV and ITV plus a margin to account for geometric variation in daily setup
		Size of expansion, typically 2–7 mm (refer to protocol for specific anatomic sites) should be based on institutional capabilities
Organs at risk (OAR)		Includes uninvolved normal structures at risk of RT-related toxicity for which RT planning or dose may be altered

Table 11.4 Sample dose constraints and target coverage objectives for pediatric Hodgkin lymphoma used at the University of Florida Proton Therapy Institute

Structure		DVH point	Goal	Acceptable range
Target	PTV	Relative dose at 95% volume	100%	$95 \leq D_{95}\% < 100\%$
	PTV	Relative volume at 95% dose	100%	$95 \leq D_{95}\% < 100\%$
	PTV	Relative dose at 99% volume	93%	
	CTV/ITV	Relative dose at 99% volume	100%	
	GTV/IGTV	Relative dose at 99% volume	100%	
OAR	Hearts	Mean absolute dose	15 Gy	$15 \leq D_{mean} < 20$ Gy
	Lungs	Mean absolute dose	14 Gy	$14 \leq D_{mean} < 18$ Gy
	Lungs	Relative volume at 20 Gy	30%	
	Spinal cord	Maximum absolute dose	36 Gy	
	Stomach	Mean absolute dose	10 Gy	$10 \leq D_{mean} < 25$ Gy
	Kidney	Relative volume at 17 Gy	33%	
	Parotid	Mean absolute dose	26 Gy	
	Ventricle left	Mean absolute dose	15 Gy	$15 \leq D_{mean} < 20$ Gy
	Cochlea	Mean absolute dose	30 Gy	$30 \leq D_{mean} < 36$ Gy
	Lacrimal gland	Mean absolute dose	34 Gy	$34 \leq D_{mean} < 41$ Gy
	Larynx	Mean absolute dose	35 Gy	
	Larynx	Maximum absolute dose	45 Gy	
	Oral cavity	Mean absolute dose	35 Gy	
	Ovary	Mean absolute dose	6 Gy	
	Pancreas tail	Mean absolute dose	10 Gy	$10 \leq D_{mean} < 20$ Gy
	Pancreas	Mean absolute dose	10 Gy	
	Parotid	Mean absolute dose	26 Gy	
	Scalp	Relative volume at 30 Gy	5 cc	$V_{30Gy} \geq 5$ cc
	Testes	Mean absolute dose	1 Gy	
	Thyroid	Mean absolute dose	26 Gy	
	Thyroid	Relative volume at 30 Gy	63%	
	Uterus	Mean absolute dose	5 Gy	

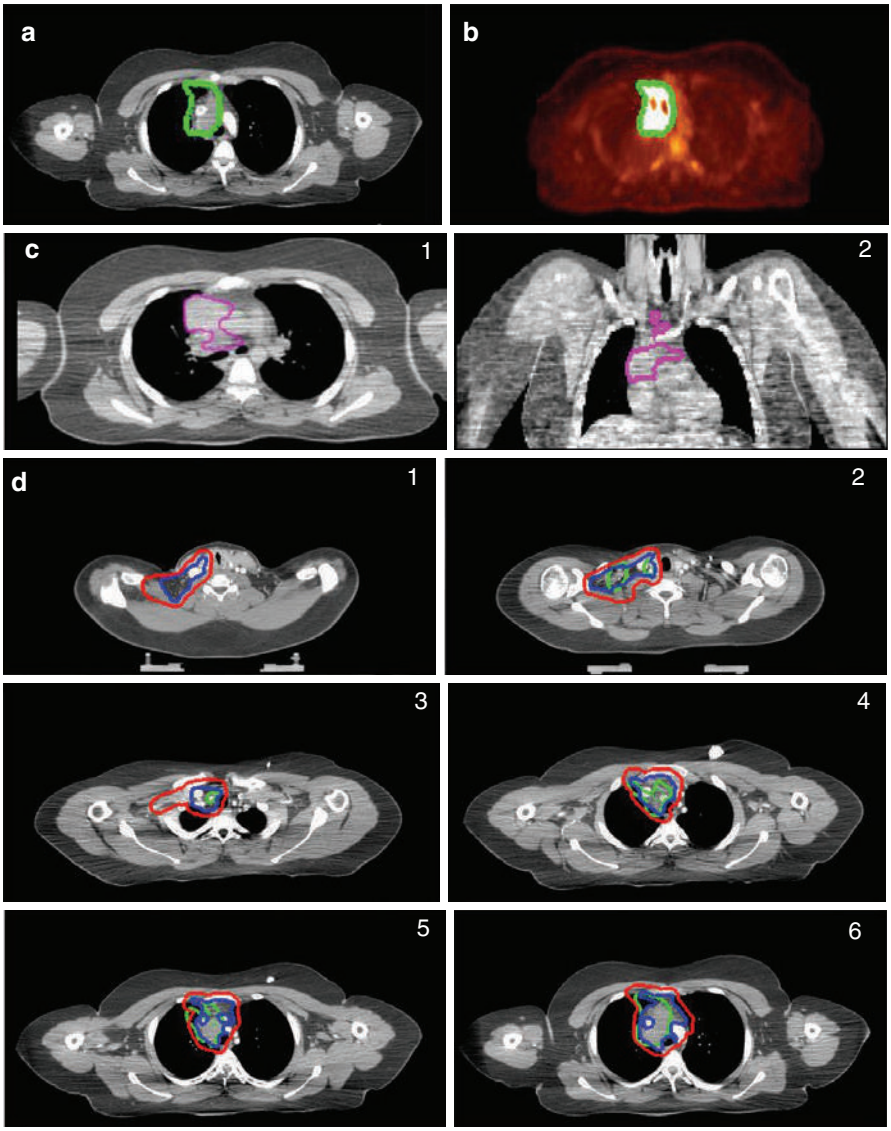

Fig. 11.1 An 18-year-old with nodular sclerosing classical Hodgkin lymphoma with mixed response after chemotherapy. (**a**) On the radiation planning CT, the green contour depicts the pre-chemo gross tumor disease burden. (**b**) Pre-chemotherapy diagnostic PET-CT depicting the pre-chemotherapy gross tumor contoured in green. (**c**) Radiation planning CT with post-chemo GTV contoured in purple. (**d**) Pre-chemo GTV (green), CTV (blue), and PTV (red) depicted on the radiation planning CT

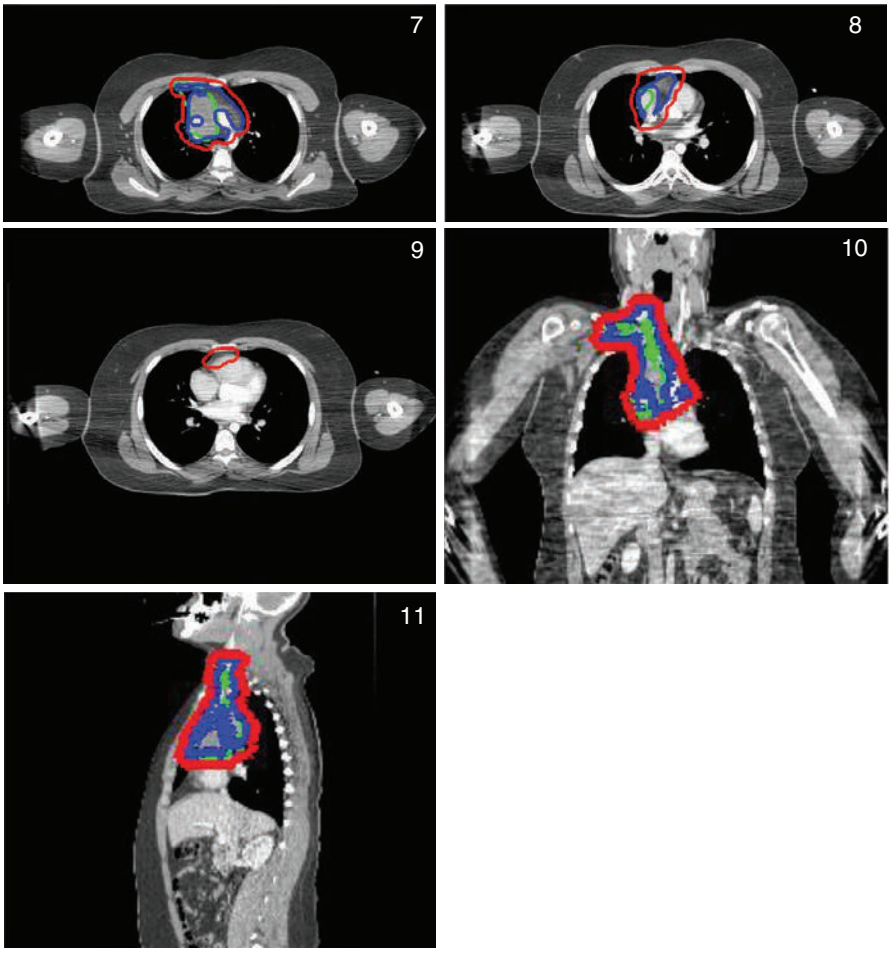

Fig. 11.1 (continued)

11.4 Outcomes and Prognostication

- COG AHOD0031 (intermediate-risk study) analysis showed that relapse rarely emerges solely in a new anatomic site, even after IFRT (0–13% depending on treatment group). Approximately 40–50% of relapses occur inside the radiation field alone, while 95% of relapses have a component of the recurrence in-field [10].
- Patients with a rapid early and complete anatomic response benefited from RT if they had both anemia and bulky limited-stage disease (4-year event-free survival (EFS) 89.3% vs 77.9%) [11].

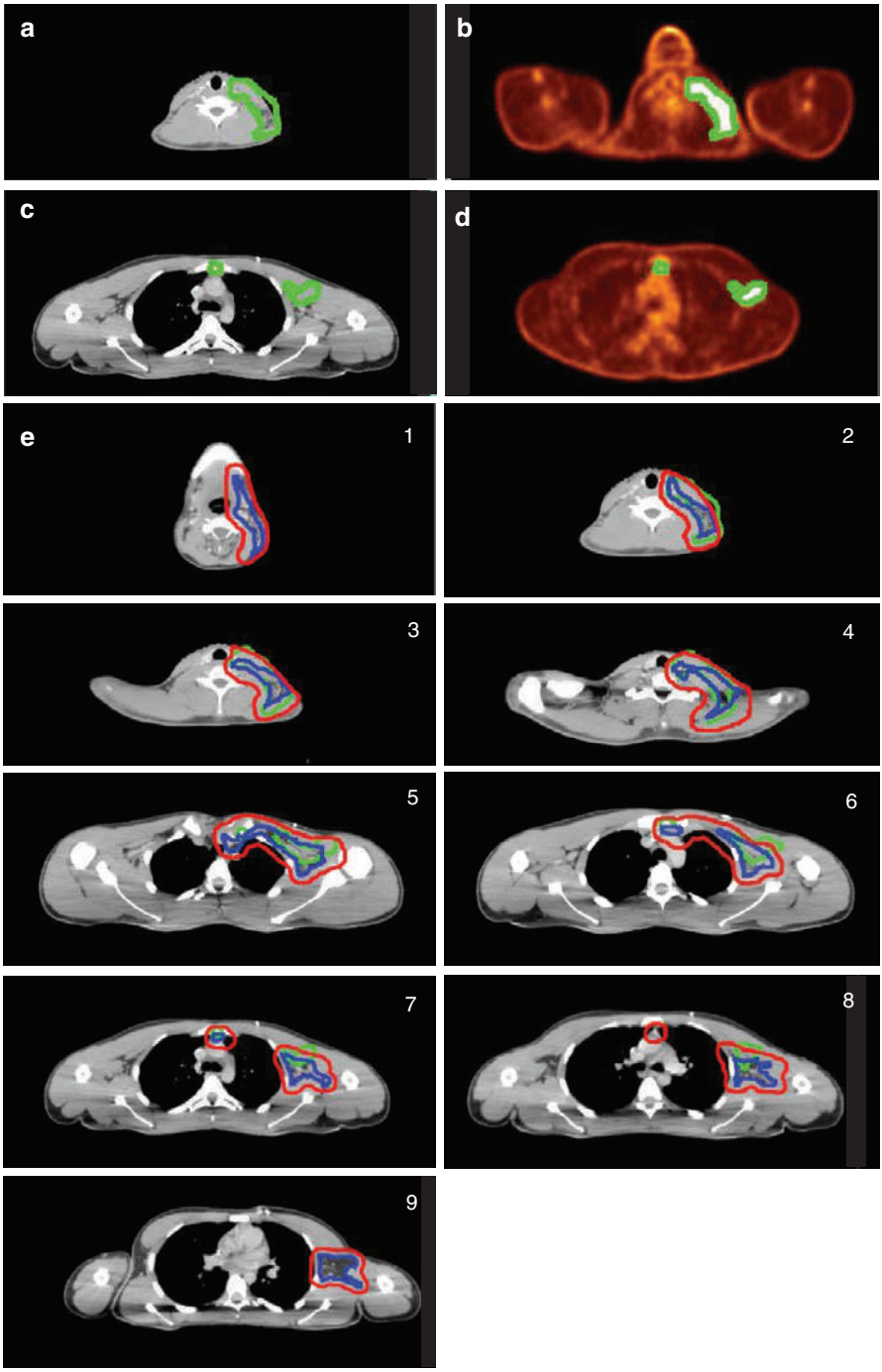

Fig. 11.2 A 17-year-old boy with IIAX Hodgkin lymphoma with rapid early response on PET after two cycles of chemotherapy. (**a**) and (**c**) demonstrate pre-chemo GTV as defined by PET-CT imaging on (**b**, **d**) in green. (**e**) Demonstrates pre-chemo GTV (green), CTV (blue), and PTV (red)

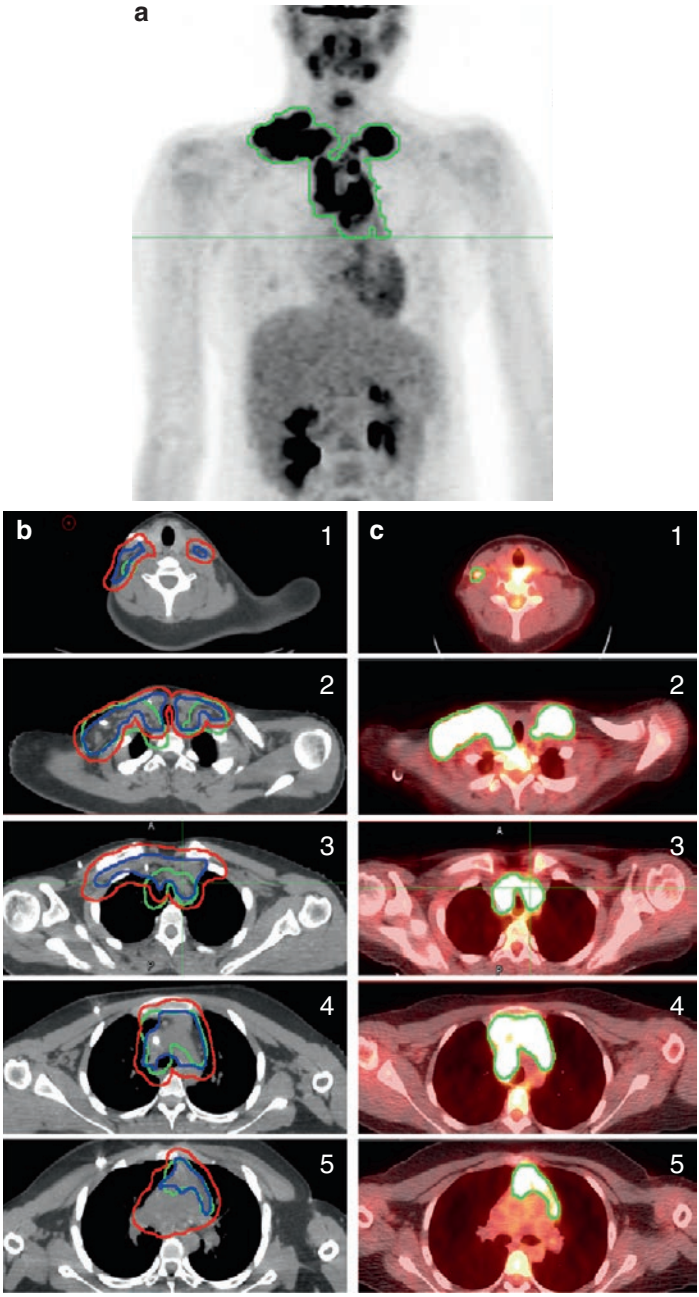

Fig. 11.3 A 15-year-old female with stage IIA bulky nodular sclerosing HL with bulky supraclavicular mass, who presented with anemia. She received four cycles of ABVE-PC chemotherapy with a rapid but not complete response by CT and underwent consolidative ISRT to 21 Gy. (**a**) Coronal PET demonstrating with pre-chemo GTV in green (**b**) Pre-chemo GTV, CTV (blue), and PTV (red) on CT simulation. (**c**) Pre-chemo GTV depicted on axial PET-CT

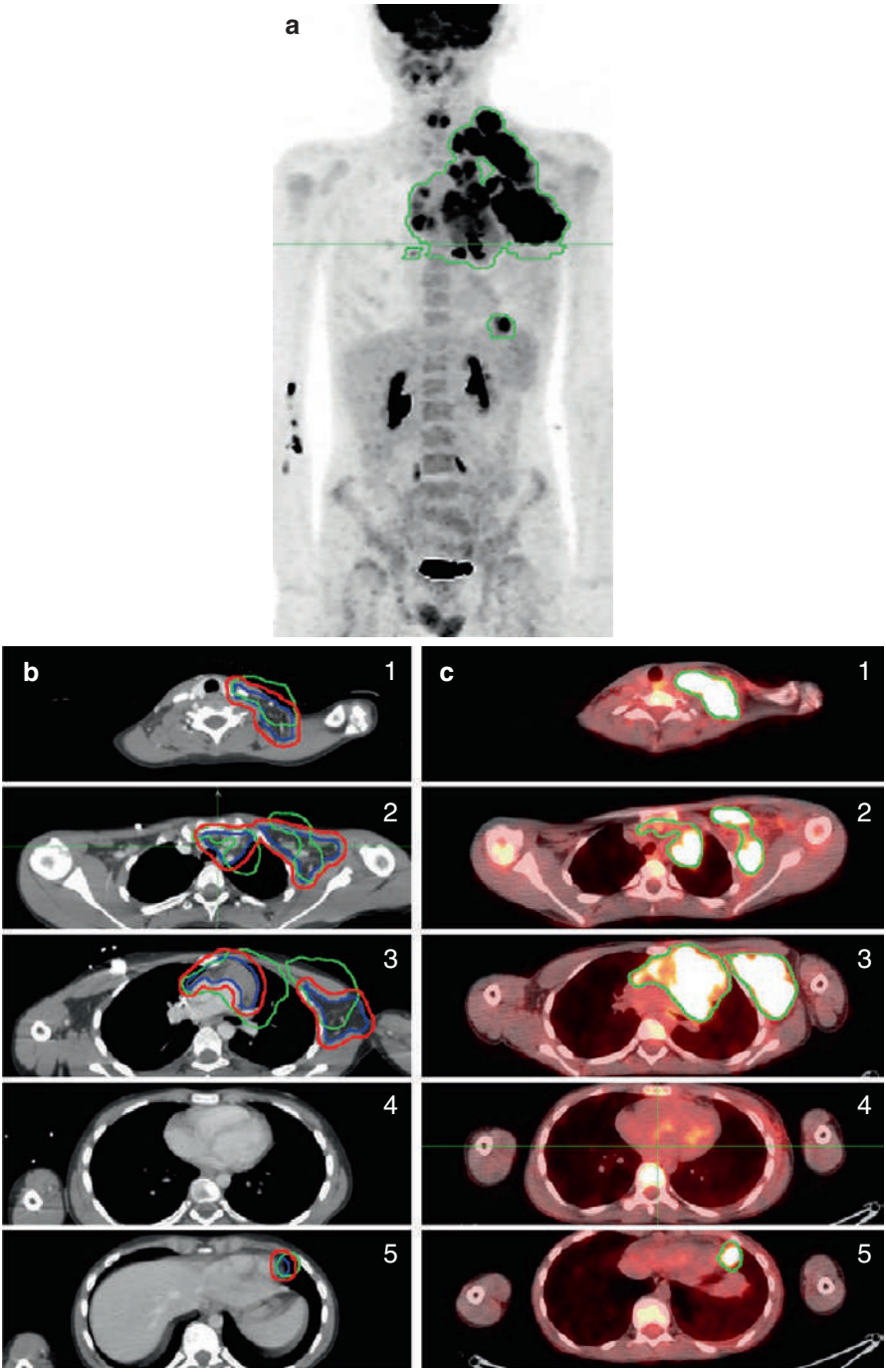

Fig. 11.4 A 14-year-old male with stage IIA bulky mediastinal nodular sclerosing HL. He received four cycles of ABVE-PC chemotherapy with a slow early response but complete response by the end of treatment by PET scan. He received consolidative ISRT to 21 Gy. (**a**) Coronal PET demonstrating with pre-chemo GTV in green (**b**) Pre-chemo GTV, CTV (blue), and PTV (red) on CT simulation. (**c**) Pre-chemo GTV depicted on axial PET-CT

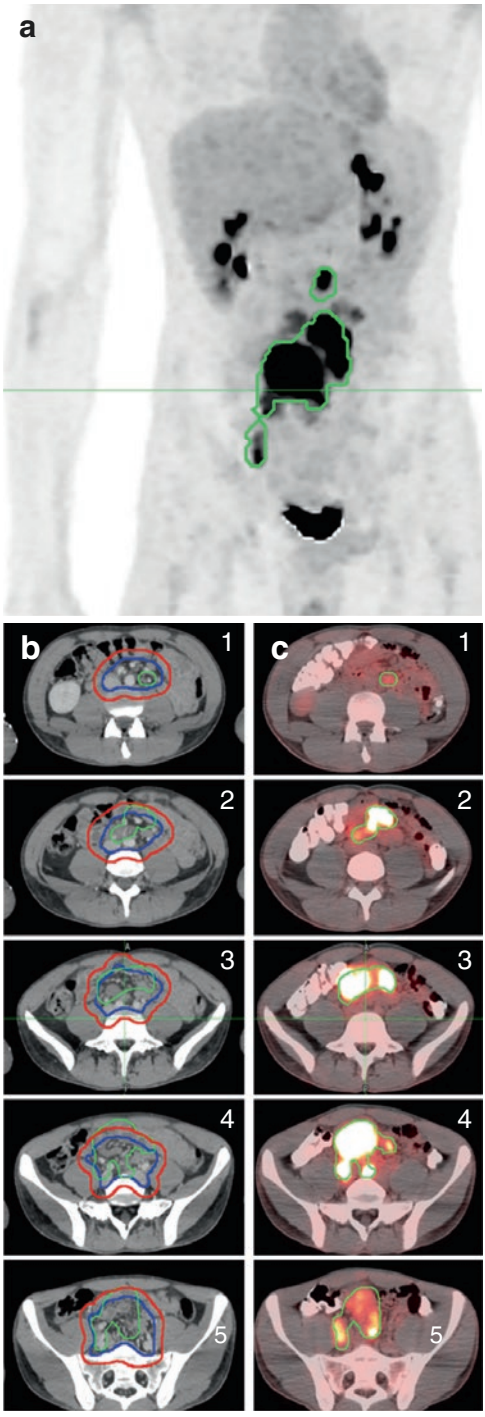

Fig. 11.5 A 17-year-old male with stage IIA bulky nLPHL involving the paraaortic, mesentery, right internal iliac nodal regions, who received four cycles of chemotherapy followed by ISRT to 21 Gy due to incomplete CT response. (**a**) Coronal PET demonstrating with pre-chemo GTV in green (**b**) Pre-chemo GTV, CTV (blue), and PTV (Red) on CT simulation. (**c**) Pre-chemo GTV depicted on axial PET-CT

- Additional analysis of AHOD0031 led to development of Childhood Hodgkin International Prognostic Score (CHIPS) [12]. One point is assigned to each of the following, albumin <3.5, fever, stage IV disease, and bulky mediastinal mass (4 year EFS per group):
  - CHIPS 0: 93.1%
  - CHIPS 1: 88.5%
  - CHIPS 2: 77.6%
  - CHIPS 3: 69.2%
  - CHIPS 4 high risk by default

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Wilms and Other Pediatric Renal Tumors

12

Arnold C. Paulino and John Kalapurakal

Contents

12.1 Background

- Wilms tumor or nephroblastoma is the most common pediatric abdominal, malignant tumor, representing about 5–6% of all childhood cancer.
- The North American approach to these tumors involves initial nephrectomy followed by chemotherapy with or without radiotherapy (RT). In Europe, preoperative chemotherapy followed by surgery and postoperative chemotherapy with or without RT is the usual sequence of treatment. Despite the difference between the two approaches, survival for Wilms tumor is excellent for children in North

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America and Europe with more than 90% alive at 5 years [1]. Most of these patients will have favorable histology subtype with only 10% having anaplastic Wilms tumor.

- In addition to anaplastic histology, loss of heterozygosity (LOH) in 1p and 16q has been associated with worse outcome [2].
- Other renal tumors such as clear cell sarcoma and rhabdoid tumor have been included in studies from the National Wilms Tumor Study (NWTS) and Children's Oncology Group (COG), but they are not subtypes of Wilms tumor.

12.2 Staging and Indications

- Work-up includes a computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of the abdomen and pelvis.
- A CT scan of the chest is ordered to rule out pulmonary metastasis. For patients with clear cell sarcoma and rhabdoid tumor, a bone scan and MRI of the brain are obtained to rule out distant spread.
- The current staging system for Wilms tumor is a modified version of the NWTS staging system (Table 12.1).

Table 12.1 Wilms tumor staging

Staging	Description
Stage I	Tumor limited to the kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection
Stage II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond the kidney, as is evidenced by any one of the following criteria: regional extension of the tumor (i.e., penetration of the renal capsule or extensive invasion of the soft tissue of the renal sinus) and blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor
Stage III	Residual non-hematogenous tumor present following surgery and confined to the abdomen. Any one of the following may occur: Lymph nodes within the abdomen or pelvis are involved by tumor, tumor has penetrated through the peritoneal surface, tumor implants are found on the peritoneal surface, gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination), tumor is not completely resectable because of local infiltration into vital structures, tumor spillage occurring either before or during surgery, tumor is treated with preoperative chemotherapy (with or without a biopsy regardless of type- tru-cut, open or fine needle aspiration) before removal, tumor is removed in greater than one piece, extension of the primary tumor within vena cava into the thoracic vena cava and heart
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region are present
Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease

- Current indications for abdominal RT in favorable histology Wilms tumor include Stage III disease (microscopic margins of resection, gross residual tumor, positive lymph nodes, preoperative rupture, spill, piecemeal resection, peritoneal implants). Some patients with Stage IV disease may need RT to the lungs, liver, and bones.
- Children with pulmonary metastasis will receive lung RT if they have any of these factors: unfavorable histology, presence of non-pulmonary metastasis, presence of LOH 1p and 16q, and incomplete response to 6 weeks of DD4A chemotherapy (vincristine, actinomycin-D, and doxorubicin) with persistent pulmonary nodules [3].
- For patients with clear cell sarcoma of the kidney, all but Stage I tumors receive RT, while for rhabdoid tumors and anaplastic histology Wilms tumor, it is recommended that all patients, regardless of the stage, receive RT.

12.3 Radiotherapy Doses and Treatment Volumes

- Tables 12.2 and 12.3 outline the recommended doses for Wilms tumor, clear cell sarcoma, and rhabdoid tumor.

Table 12.2 General treatment recommendations for favorable histology Wilms tumor

Stage	Chemotherapy	Radiotherapy
Stage I, favorable histology, <550 g tumor and kidney weight, <2 years of age	None	None
Stage I and II, favorable histology, no LOH 1p and 16q	Vincristine and actinomycin-D	None
Stage I and II, favorable histology, LOH 1p and 16q	Vincristine, actinomycin-D and doxorubicin	None
Stage III, favorable histology, no LOH 1p and 16 q	Vincristine, actinomycin-D and doxorubicin	Flank or hemiabdomen irradiation[a]
Stage III, favorable histology, LOH 1p and 16q	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide	Flank or hemiabdomen irradiation[a]
Stage IV, favorable histology who satisfy all of the following: pulmonary metastasis only, no LOH 1p and 16q, complete response in the lungs after 6 weeks of vincristine, actinomycin-D, and doxorubicin	Vincristine, actinomycin-D, and doxorubicin	No lung irradiation Flank or hemiabdomen irradiation depends on local stage[a]
Stage IV, favorable histology who have pulmonary metastasis and any of the following: other sites of distant metastasis, LOH 1p and 16q	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide	Whole lung irradiation Flank or Hemiabdomen Irradiation depends on local stage[a]

[a]If there is preoperative rupture, diffuse spillage of tumor during nephrectomy, positive peritoneal cytology, or peritoneal metastasis, whole abdominal irradiation is recommended

Table 12.3 General recommendations for anaplastic Wilms tumor, clear cell sarcoma, and rhabdoid tumor of the kidney

Stage	Chemotherapy	Radiotherapy
Stage I to III, focal anaplastic, and Stage I diffuse anaplastic	Vincristine, actinomycin-D, and doxorubicin	Flank or hemiabdomen irradiation[a]
Stage II to III, diffuse anaplastic, and Stage IV, focal anaplastic	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide, carboplatin	Flank or hemiabdomen irradiation[a,b,c]
Stage IV, diffuse anaplastic	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide, carboplatin, irinotecan	Flank or hemiabdomen irradiation[a,b,c]
Stage I to III, clear cell sarcoma	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide	Flank or hemiabdomen irradiation for Stages II and III[A]
Stage IV, clear cell sarcoma	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide, carboplatin	Flank or hemiabdomen irradiation[a,b]
Stage I to III, rhabdoid tumor	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide	Flank or hemiabdomen irradiation[a,c]
Stage IV, rhabdoid tumor	Vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide, carboplatin, irinotecan	Flank or hemiabdomen irradiation[a,b,c]

[a]If there is preoperative rupture, diffuse spillage of tumor during nephrectomy, positive peritoneal cytology, or peritoneal metastasis, whole abdominal irradiation is recommended
[b]Whole lung irradiation for lung metastasis in Stage IV patients
[c]Flank or hemiabdomen dose is 10.8 Gy in 6 fractions with the exception of Stage III diffuse anaplastic and children >1 year old with rhabdoid tumor who receive 19.8 Gy in 11 fractions

- Based on the NWTS-3 study, a dose of 1050–1080 cGy to the flank or hemiabdomen will suffice if vincristine, actinomycin-D, and doxorubin are given for Stage III favorable histology Wilms tumor [4].
- On the most recent COG protocols, patients with Stage II and III focal anaplasia, Stage II diffuse anaplasia, Stage II and III clear cell sarcoma, aStage I, II and III (< 12 months old) rhabdoid tumor receive 1080 cGy in 6 fractions to the flank or hemiabdomen, while patients with Stage III diffuse anaplasia and Stage III rhabdoid tumor (> 12 months) receive 1980 cGy in 11 fractions.
- The clinical target volume (CTV) includes the preoperative tumor and kidney volume with a 0.5 cm margin.
- The planning target volume (PTV) includes the CTV with another 0.5 cm margin.
- Patients who do not get up-front nephrectomy will require radiotherapy to the prechemotherapy volume.
- Patients who require whole abdominal irradiation receive 1050 cGy in 7 fractions.
- Indications for whole abdominal irradiation include diffuse spillage of tumor during nephrectomy, peritoneal metastasis, preoperative rupture of tumor, and positive cytology from abdominal/ascitic fluid.

12.4 Outcomes and Prognostication

- The COG AREN0533 study showed patients with pulmonary metastases can have whole lung irradiation (WLI) omitted if they satisfy all of the following criteria: favorable histology, the lung as the only site of distant metastasis, no LOH at 1p and 16q, and complete response of pulmonary nodules on chest CT after 6 weeks of vincristine, actinomycin-D, and doxorubicin. For children who need WLI, the current dose is 1200 cGy in 8 fractions [5].
- Children with pulmonary metastasis from anaplastic Wilms tumor, clear cell sarcoma, and rhabdoid tumor require WLI.
- In about 10% of patients with metastasis, the liver is involved. For solitary hepatic metastasis, surgical resection with negative margins is the treatment of choice.
- In patients with diffuse liver metastasis, the entire liver is irradiated to a dose of approximately 1980 cGy in 11 fractions. Intensity-modulated radiation therapy may be the best way to treat patients with diffuse liver metastases [6].

12.5 Case Presentations

12.5.1 Case 1: Stage IV Favorable Histology Wilms Tumor with Lung and Liver Metastases

See Figs. 12.1, 12.2, and 12.3.

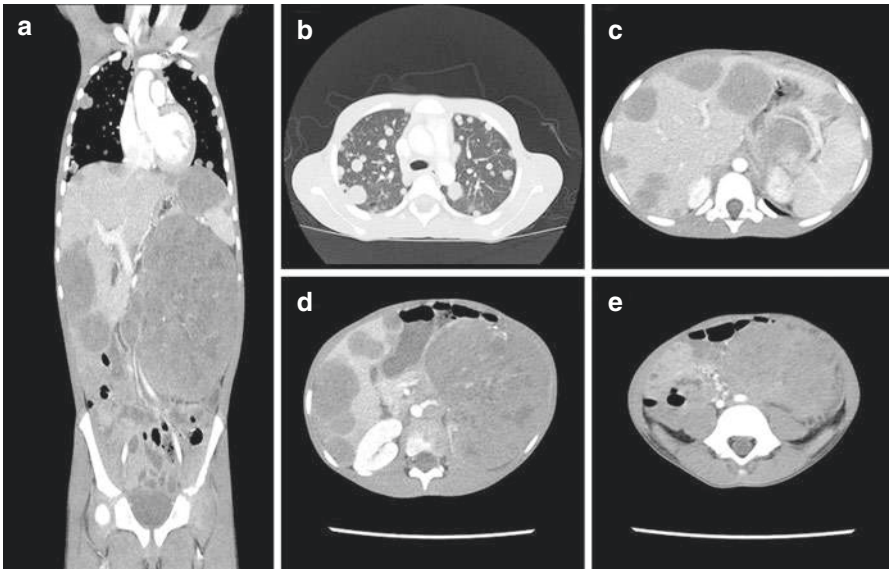


Fig. 12.1 8-year-old girl classified as local Stage II disease with a large left renal mass, liver, and lung metastases after a left radical nephrectomy and preoperative chemotherapy. Favorable histology Wilms tumor with lung and liver metastases (**a**) coronal view, (**b**) axial image of multiple pulmonary nodules, (**c**) multiple liver metastases and superior left renal tumor, (**d**) multiple liver metastases and left renal tumor, (**e**) inferior left renal tumor

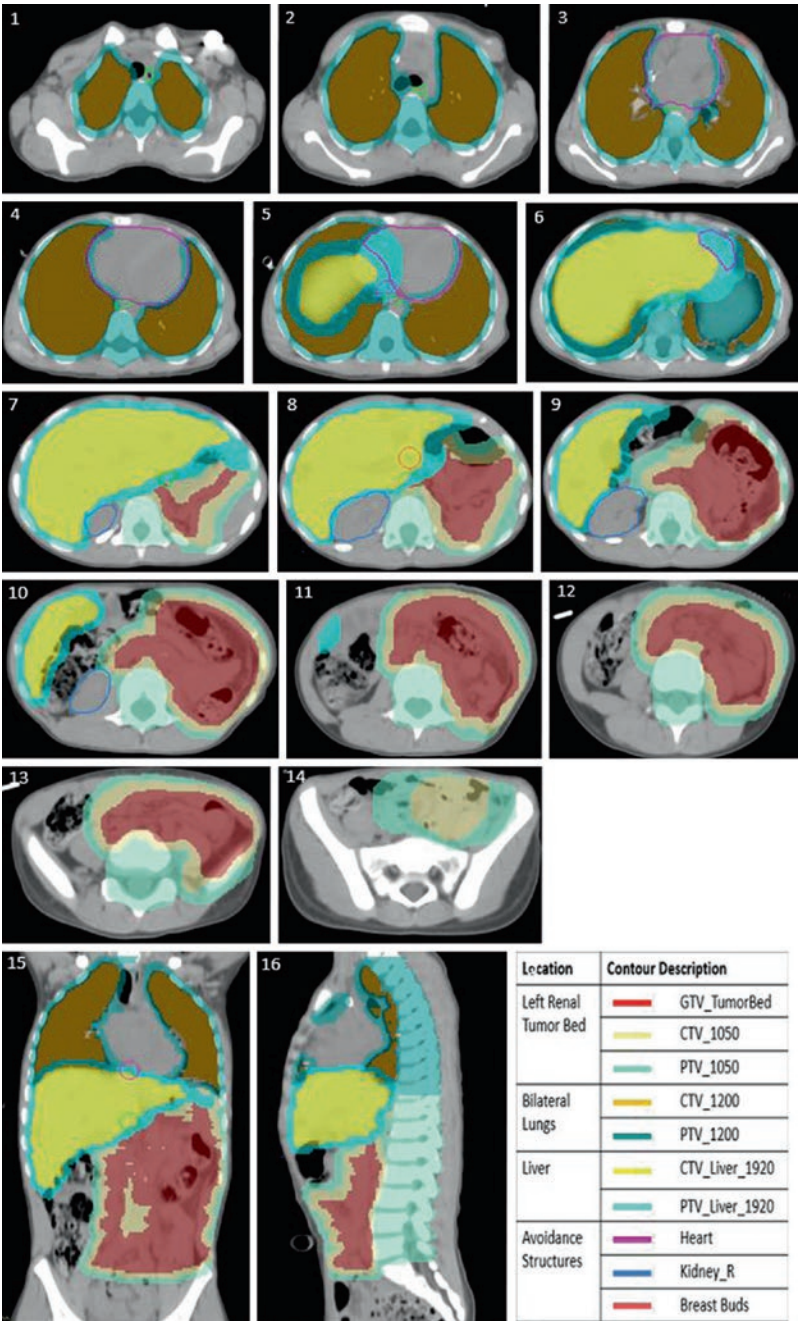


Fig. 12.2 Favorable histology Wilms tumor with lung and liver metastases. The left renal tumor bed, bilateral lungs, and the entire liver were contoured. A 0.5 cm margin around the left renal tumor bed (red) was added to create the CTV 1050 (khaki). The bilateral lungs were contoured on four-dimensional computed tomography and named as CTV 1200 (mustard). The liver was contoured and named as CTV 1920 (yellow). A 0.5 cm margin for the CTV structures was added to create the PTV 1050 (cyan), PTV 1200 (turquoise), and PTV 1920 (sky blue). The prescription dose was 1050 cGy to the left hemiabdomen, 1200 cGy to bilateral lungs, and 1920 cGy to the liver

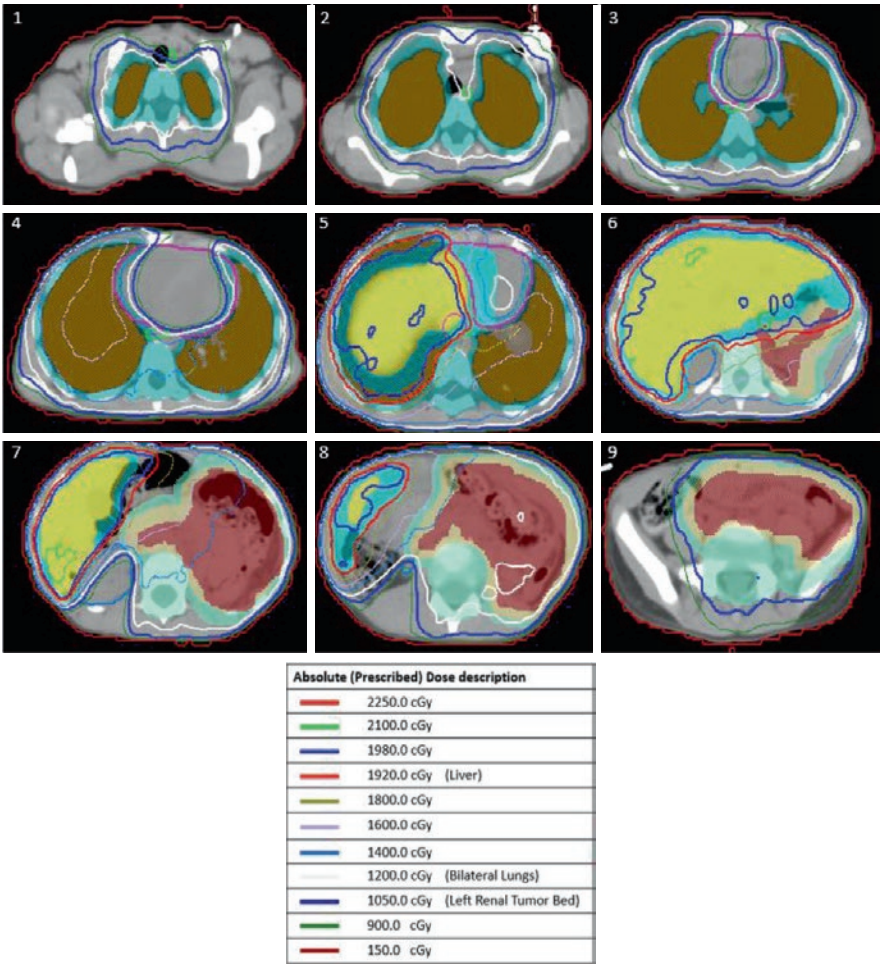


Fig. 12.3 Favorable histology Wilms tumor with lung and liver metastases. Radiotherapy plan showing coverage of the left renal tumor bed, bilateral lungs, and the liver with the prescribed doses. The left renal tumor bed, lungs, and liver were treated concurrently using an IMRT technique at 1.5 Gy per fraction. After a dose of 10.5 Gy, only the lungs and liver were treated with a single fraction of 1.5 Gy. After 12 Gy, only the liver was treated, and the fraction size was changed to 1.8 Gy per day. Total prescribed doses were 10.5 to the left hemiabdomen, 12 Gy to the bilateral lungs, and 19.2 Gy to the liver. In this particular case, IMRT was used to lower the dose to the remaining kidney (blue). IMRT was also used to reduce dose to the heart. Care should be taken to deliver homogeneous dose to the vertebral bodies when using advanced techniques such as IMRT or proton therapy

12.5.2 Case 2: Stage III Favorable Histology Wilms Tumor with Peritoneal Metastases

See Figs. 12.4, 12.5, 12.6, and 12.7.

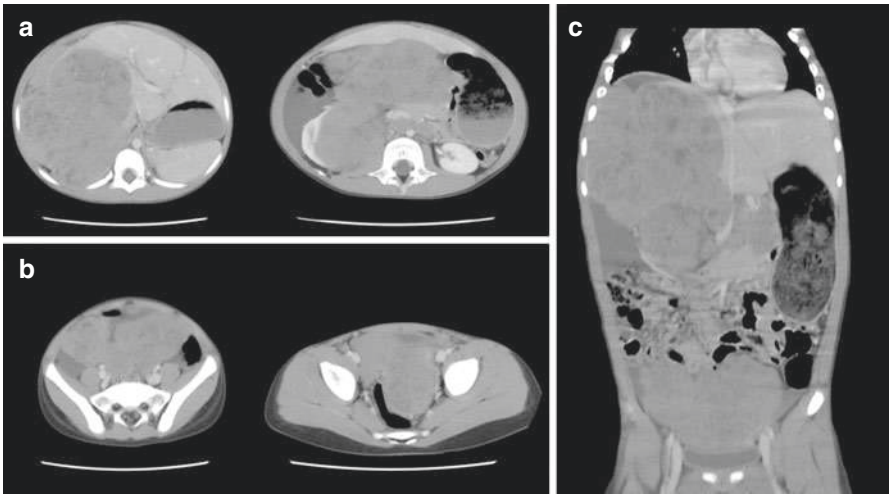


Fig. 12.4 5-year-old girl with a right renal mass and two pelvic masses without any lung metastasis after preoperative chemotherapy and a right nephrectomy and resection of the two pelvic masses. Favorable histology Wilms tumor with peritoneal metastases. (**a**) Axial image of right renal mass, (**b**) axial image of peritoneal metastases in the pelvis, (**c**) coronal image of right renal mass and peritoneal metastases in the pelvis

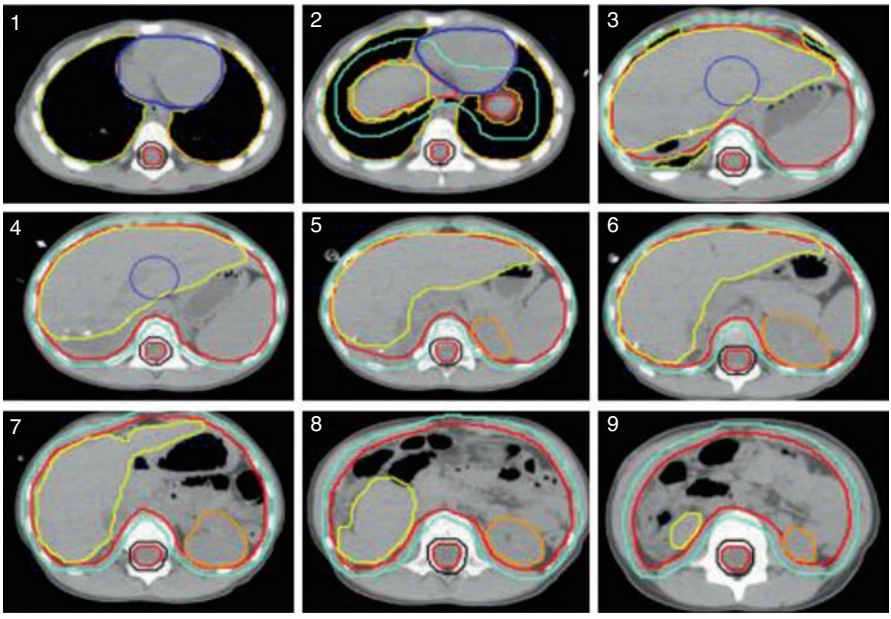
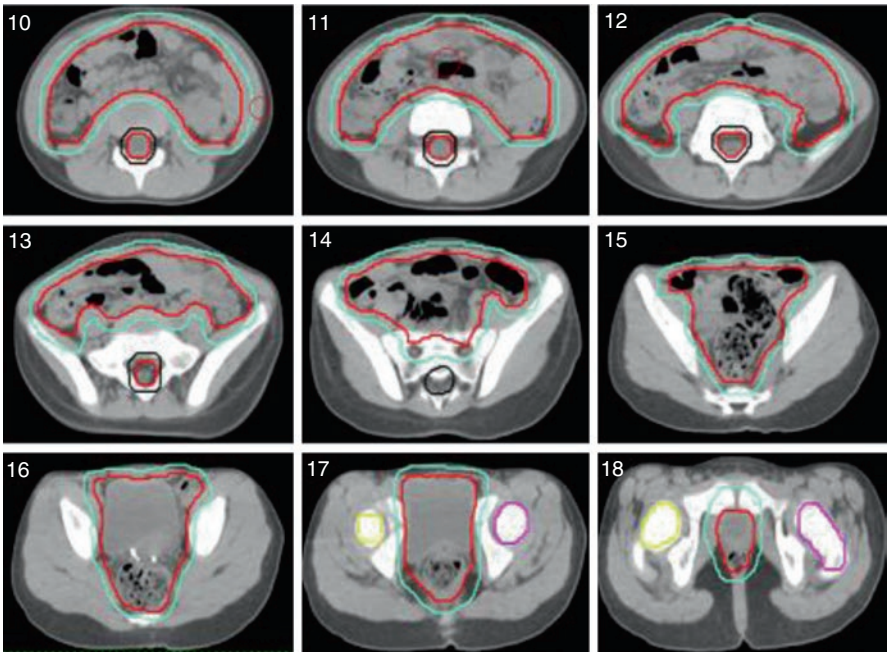


Fig. 12.5 Favorable histology Wilms tumor with peritoneal metastases. Pathology showed favorable histology Wilms tumor with two of five positive paraaortic lymph nodes and negative margins of resection. Both pelvic masses had 90% necrosis. Whole abdominal radiotherapy was recommended. The entire peritoneal cavity was contoured as CTV (red line). A 0.5 cm margin was added to the CTV to create the PTV (aqua line)



Location	Contour Description
Target Volumes	CTV
	PTV
Normal Tissues	Lungs
	Heart
	Kidney_L
	Liver
	Rt_Femur
	Lt_Femur
	Spinal/Canal

Fig. 12.5 (continued)

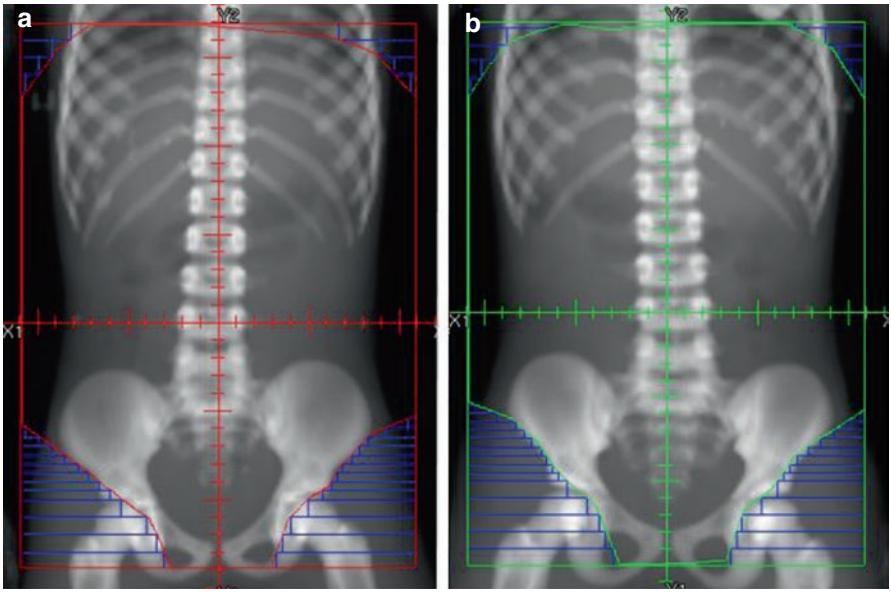


Fig. 12.6 Favorable histology Wilms tumor with peritoneal metastases. AP (**a**)/PA (**b**) Digital reconstructed images of radiotherapy fields for whole abdominal irradiation

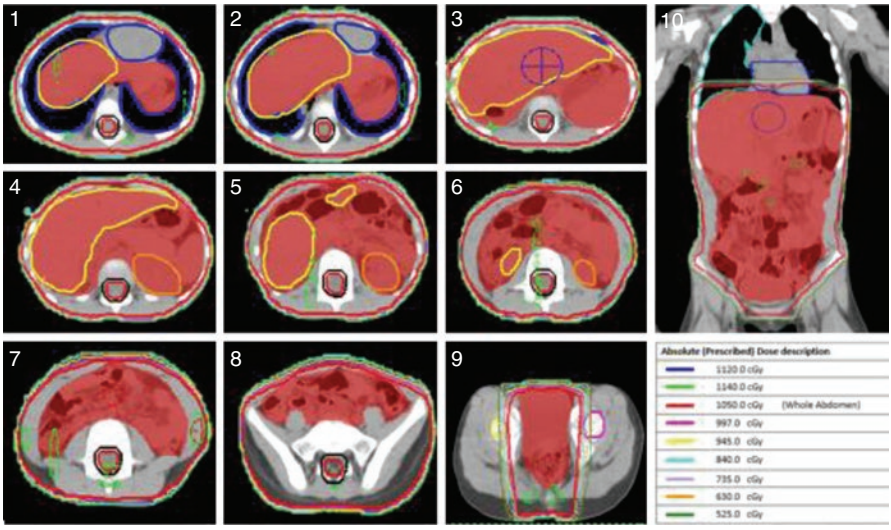


Fig. 12.7 Favorable histology Wilms tumor with peritoneal metastases. Radiotherapy plan showing coverage of the entire peritoneal cavity (red) with 1050 cGy isodose line in 7 fractions (red line)

12.5.3 Case 3: Stage IV Favorable Histology Wilms Tumor with Lung and Ruptured Solitary Liver Metastasis

See Figs. 12.8, 12.9, and 12.10.

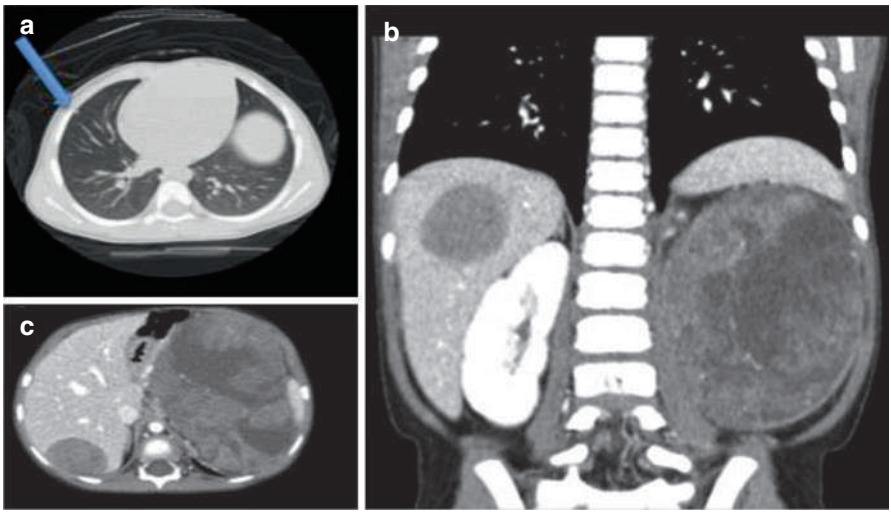


Fig. 12.8 3-year-old male patient with abdominal pain with a left renal mass and a solitary right lung and liver metastasis after nephrectomy and resection of the solitary liver metastasis. Favorable histology Wilms tumor with solitary pulmonary and hepatic metastasis. (**a**) Axial image of solitary right lung nodule (arrow), (**b**) coronal image showing right hepatic metastasis and left renal tumor, (**c**) axial image of solitary hepatic metastasis and left renal tumor

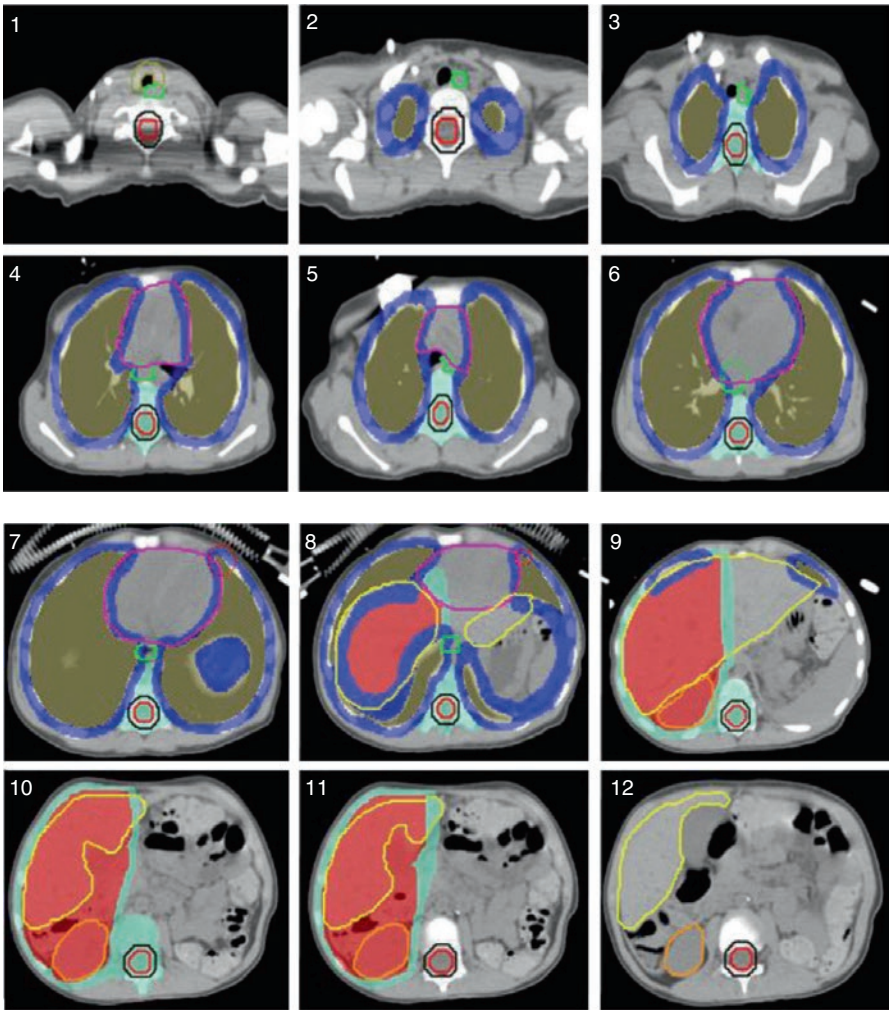


Fig. 12.9 Favorable histology Wilms tumor with solitary pulmonary and hepatic metastasis. The lungs were contoured as CTV lungs (mustard) and the CTV liver spillage bed (red). PTV boost lungs 12 (blue) is 0.5 cm margin around the CTV lungs while PTV 10.5 (turquoise) is 0.5 cm margin beyond the CTV liver spillage bed

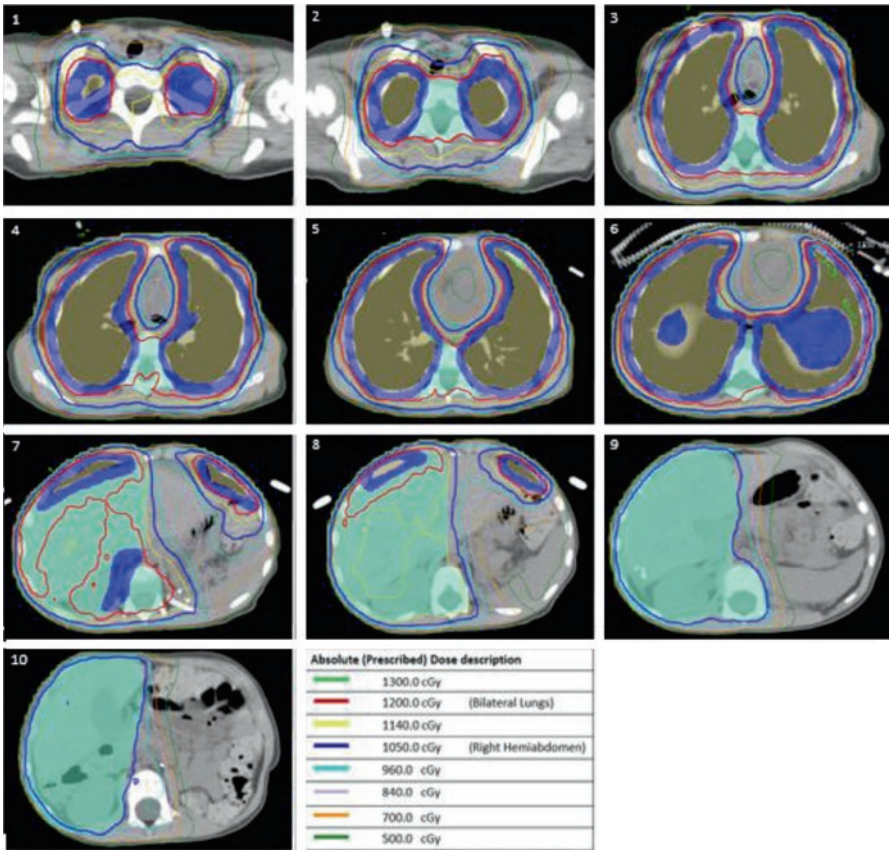


Fig. 12.10 Favorable histology Wilms tumor with solitary pulmonary and hepatic metastasis. The PTV10.5 and PTV boost lungs were treated to a dose of 1050 cGy in 7 fractions, after which a 150 cGy boost was delivered to the PTV boost lung. Radiotherapy plan showing that the lungs are being covered by the 1200 cGy isodose line (red) while the liver spill tumor bed is covered by the 1050 cGy line (blue)

12.5.4 Case 4: Stage II Clear Cell Sarcoma of the Kidney

See Figs. 12.11, 12.12, and 12.13.

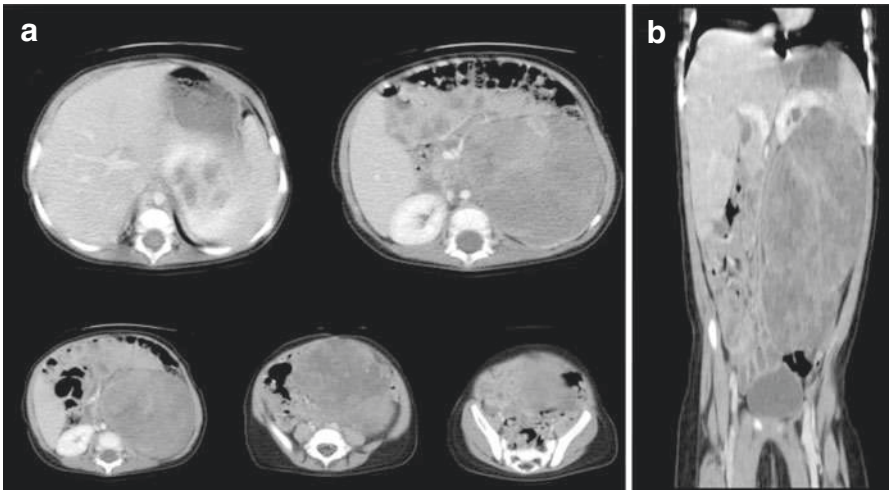


Fig. 12.11 2-year-old girl with non-painful left abdominal mass with clear cell sarcoma of the left kidney. (**a**) Axial images of the left renal mass. Note that in some axial cuts the mass is beyond the contralateral vertebral body. The portion of mass beyond midline is called "tumor overhang" (**b**) coronal image of the left renal mass

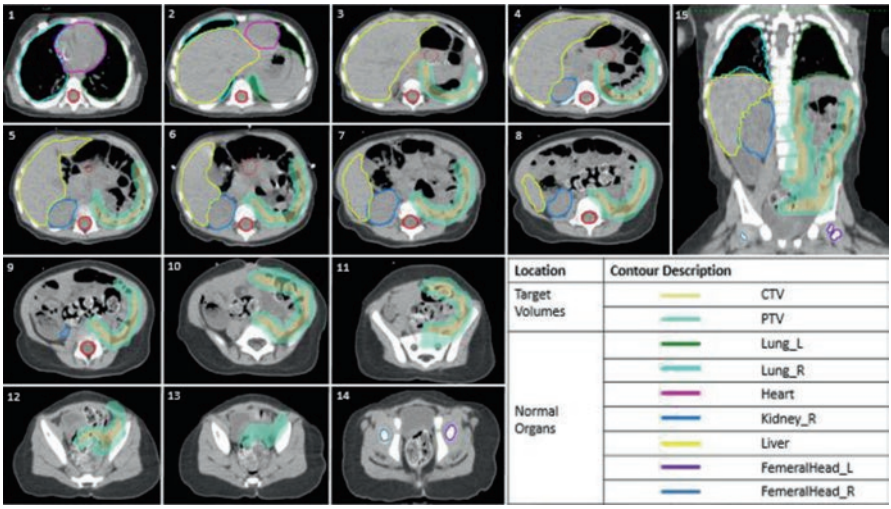


Fig. 12.12 Clear cell sarcoma of the left kidney. The tumor bed was contoured with a 0.5 cm margin and called the CTV (khaki). The CTV was modified medially to avoid treating tumor overhang. A 0.5 cm margin beyond the CTV was added to create the PTV (turquoise)

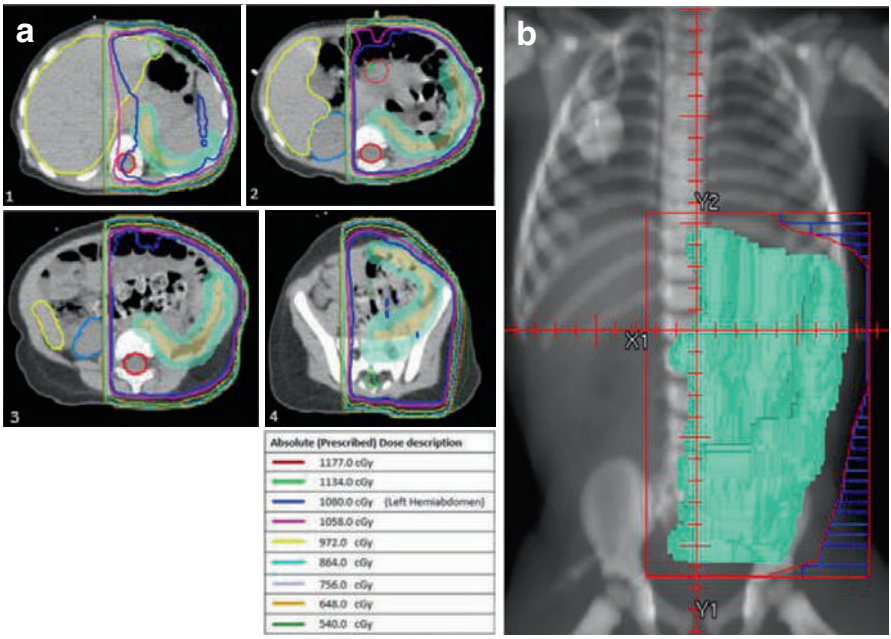


Fig. 12.13 Clear cell sarcoma of the left kidney. (**a**) Radiotherapy treatment plan showing that the renal tumor bed is covered by the 1080 cGy isodose line (blue). Dose-volume histogram shows that the CTV and PTV are receiving the prescription dose. (**b**) Digitally reconstructed radiographic image of the AP field for this patient

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Neuroblastoma

13

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Contents

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13.1 Background

- Neuroblastoma is the most common solid non-CNS malignancy of childhood representing 8–10% of all pediatric cancer, and approximately 650 cases are diagnosed per year in the United States.
- Neuroblastoma is notable for its heterogeneity in behavior, with some cases showing spontaneous regression and others demonstrating dismal outcomes.
- Patients may present with an abdominal mass with or without obstructive symptoms. Children with neuroblastoma tend to have symptoms at presentation in contrast to children with Wilms tumor. It is not uncommon to see systemic symptoms such as fever, weight loss, sweating, flushing, abdominal pain, failure to thrive, and generalized weakness.
- Over 50% of children will have metastases at diagnosis involving the bone, liver, lymph nodes, and skin.
- Bone metastases have the potential to cause pain or refusal to walk, and skin metastases that occur in infants may present with clinical manifestations of blue skin lesions that blanch with pressure due to release of vasoactive catecholamines (referred to as the "blueberry muffin" sign).
- Paraneoplastic syndromes may cause symptoms that include opsoclonus-myoclonus, truncal ataxia syndrome that is attributed to antibody formation to neurons, and diarrhea from vasoactive intestinal polypeptide secretion.
- Workup for neuroblastoma includes CT and/or MRI to evaluate the primary lesion. If feasible, it may be of benefit to obtain both studies at initial diagnosis to best evaluate the initial extent of disease and to determine the best imaging modality for subsequent studies.
- Bilateral bone marrow biopsies and MIBG scan (^{123}I-MIBG) should be obtained to evaluate for metastases. PET/CT and bone scan (with ^{99m}Tc-diphosphonate) may be useful for non-MIBG-avid disease. CT of the chest/abdomen and pelvis should be considered to evaluate for metastatic disease, and MRI or CT of the brain may be useful if large metastases are present. Baseline labs including CBC, CMP, and urinary catecholamines (e.g., vanillylmandelic acid and homovanillic acid, elevated in 90% of patients) should be obtained.
- Pathology is necessary for diagnosis unless urinary catecholamines are elevated since it can provide additional prognostic information. If surgery is performed initially, postsurgical imaging should be obtained to determine the extent of resection.
- Children under 12 months of age are considered to have more favorable outcomes. Recent studies have indicated that this age cutoff can be extended to 18 months for children with favorable histology.
- Past Children's Oncology Group's (COG) studies stratified neuroblastoma into low-, intermediate-, and high-risk groups based on an amalgamation of these prognostic factors.
- Radiation therapy is recommended for children with intermediate-risk disease who progress through chemotherapy, for those who have persistent disease following all treatment, and for children with high-risk neuroblastoma.

13.2 Risk Stratification

- Recognizing biologic pathways in neuroblastoma has improved the ability to treat children with risk-based therapy and altered radiation planning.
- A risk-based approach to therapy is essential due to clinical heterogeneity of neuroblastomas that includes tumors that undergo spontaneous maturation.
- The objective of radiation therapy is to improve disease-free and overall survival while preserving organ function.
- The International Neuroblastoma Staging System (INSS) is based on the extent of disease and the extent of surgical resection (Table 13.1)
- Risk-based groupings have been modified over the history of many clinical trials, and current protocols utilize many different factors to determine very low, low-, intermediate-, and high-risk groups [1] (Table 13.2).
- There are additional prognostic factors including age at diagnosis, MYCN amplification, histology (favorable/unfavorable), and DNA ploidy that have an impact of patient outcome beyond extent of disease. These factors help to determine management as well. Therefore, the next phase 3 COG protocol will utilize the International Neuroblastoma Risk Groups Staging System (INRGSS) to categorize patients (Table 13.2). This system will provide a comparison of patient outcomes based on pretreatment characteristics worldwide, incorporating age, histological status, differentiation, DNA ploidy, MYCN, and the 11q aberration.

Table 13.1 International Neuroblastoma Staging System (INSS)

Stage	Description
I	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically
IIA	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
IIB	Localized tumor with or without complete gross excision with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically
III	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; localized unilateral tumor with contralateral regional lymph node involvement; midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
IV	Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
IVS	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (<10% tumor) in infant younger than 1 year of age

Table 13.2 International Neuroblastoma Risk Group (INRG) consensus pretreatment classification schema

INRG stage	Age (months)	Histologic category	Grade of tumor differentiation	*MYCN*	11q aberration	Ploidy	Pretreatment risk group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	<18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	<18			NA		Hyperdiploid	F Low
	<12			NA		Diploid	I Intermediate
	12 to <18			NA		Diploid	J Intermediate
	<18			Amp			O High
	≥18						P High
MS	<18			NA	No		C Very low
					Yes		Q High
				Amp			R High

GN ganglioneuroma, *GNB* ganglioneuroblastoma, *NA* not amplified, *Amp* amplified

13.3 Guidelines for Radiation Volumes (Table 13.3)

Table 13.3 COG planning definitions for upcoming phase 3 protocol

Volume	Description
Gross tumor volume 1 (GTV1)	Includes disease defined by CT, MR, and MIBG imaging *prior* to surgery but after induction chemotherapy
	Represents the anatomical space confined by normal tissues which contains the highest concentration of residual tumor cells
	Includes additional regions of tumor involvement defined intraoperatively or by pathological report
	Excludes the extent of disease *prior* to chemotherapy or uninvolved lymph node regions
Special situations for GTV	If the GTV was grossly resected at diagnosis, GTV1 will be based on the initial diagnostic tumor volume
	In cases where there is discrepancy between imaging studies and intraoperative findings, the larger volume will define GTV1
	When the primary tumor expands into a body cavity such as the lung or displaces a normal structure (such as the liver without infiltration) and following surgical resection the normal structure now occupies the space previously occupied by tumor, only the rim (<3 mm) of normal tissue that was in contact with the tumor volume should be included within GTV1. This tumor characteristic is referred to as a "pushing border" and excludes volumes that reflect the return of normal structures to their proper anatomic position after surgical resection
Clinical target volume 1 (CTV1)	The CTV1 margin should be an expansion of the GTV1 to encompass microscopic disease and is the GTV1 with an anatomically confined margin of 1.0 cm[a]
	Anatomically CTV1 is defined as the restriction of the volume to encompass only the potential space the tumor came into contact with. It should be modified if the potential space has now regressed based on the loss of the mass effect
	When clear evidence of invasion of an adjacent organ at risk is documented whether by imaging or in the operative report, the CTV1 should not be anatomically confined to the border of that adjacent organ and instead should extend into the region of the organ that is anticipated to likely reflect residual disease
	In general, the intra-abdominal primary site CTV can be modified to exclude the kidney, liver, and vertebral bodies
	Cervicothoracic, pelvic, and head and neck sites should have their CTVs adjusted to exclude uninvolved bone
	The superior and inferior extent of CTV1 should cover the extent to the superior and inferior extent of the presurgical volume
Gross tumor volume 2 (GTV2)	GTV2 is defined as the volume of residual tumor after induction chemotherapy *and* surgery measuring >1 cm^3
	GTV2 includes disease defined by CT, MR, or MIBG imaging
	In locations where a large amount of motion in the target residual disease is possible (as in the region just below the diaphragm with abdominal cases), 4D imaging should be considered in defining an internal target volume (ITV2)

(continued)

Table 13.3 (continued)

Volume	Description
Clinical target volume 2 (CTV2)	CTV2 is the GTV2 with an anatomically confined margin of 1.0 cm[a]
	The CTV2 should be tailored at tissue interfaces where invasion/infiltration is not likely; however, the CTV2 should not be tailored back more than 0.5 cm away from GTV1
Internal target volume 2 (ITV2)	The CTV2 should be modified and expanded to take into account target motion when significant motion is anticipated for the target due to locations adjacent the diaphragm, etc. 4D imaging should can be used for volume definition
	The ITV2 is defined anatomically according to the same definitions listed for GTV2
	ITV2 is the residual gross tumor's motion and the volume adapted to reflect the motion accordingly
Planning target volume (PTV1 and PTV2)	PTV1 is a geometric concept and includes a margin surrounding the CTV1 to account for physiological change or motion in the CTV1 and setup uncertainty
	Movement-prone regions such as the region just under the diaphragm should be considered for a more generous margin
	PTV1 may vary according to immobilization and patient cooperation, although 0.3 cm is the minimum extent of the margin
	See Table 13.5 for specific details

[a]New CTV expansion will be 1 cm based on new Children's Oncology Group (COG) protocol

13.4 General Guidelines for Low- and Intermediate-Risk Neuroblastoma

- Low-risk neuroblastoma is treated with surgery alone unless emergent symptomatic cord compression or respiratory compromise necessitates a short course of chemotherapy or radiation.
- Intermediate-risk patients consist of infants with stage 4 disease without N-MYC amplification, stage 3 disease with favorable biology, or INSS 4S with unfavorable histology or DNA index.
- Generally, radiation is limited to rare situations in which there is clinical deterioration despite chemotherapy and surgery or persistent tumor after chemotherapy and second-look surgery.

13.5 General Guidelines for High-Risk Neuroblastoma

- Radiation therapy will be delivered following five or six cycles of induction chemotherapy, intensified consolidative therapy, and autologous stem cell transplant (ASCT).
- Organ toxicity within the radiation field should have resolved prior to initiating radiation, and it is recommended to start radiation therapy *no sooner than day* + 42 *and by day* + 80 following ASCT.

- Please reference most recent COG protocols for guidelines regarding acceptable levels of organ dysfunction at the time of initiation of radiation therapy.
- In cases in which intensity-modulated radiation therapy (IMRT) or proton therapy planning leads to a dose gradient across the vertebral body such that the vertebral body has a volume > 18 Gy across at least one third of the corpus of the vertebral body, an additional planning pseudo-target may be useful to ensure that the entire vertebral body receives a minimum dose of 18 Gy (see Figs. 13.1 and 13.2). The vertebral body pseudo-target should include the entire corpus and the pedicles. This is done to prevent growth asymmetry since 18 Gy is the threshold for scoliosis [2] (Tables 13.4 and 13.5; Figs. 13.3 and 13.4).

13.5.1 General Principles of Radiation Therapy

- All high-risk patients will be irradiated, and volumetric targeting for radiation therapy planning should be a priority unless in an emergent situation.
- CT (volumetric)-based planning is required to optimize dose to the target volumes while protecting normal tissues.
- CT section thickness should be ≤3 mm.
- Reproducible setups are critical and the use of immobilization devices is strongly encouraged.
- Use of anesthesia is encouraged if necessary for proper positioning.
- Treatment volumes will be based on post-induction imaging (MIBG, CT, and/or MRI) and operative reports.
- PTV is a geometric concept that should account for physiological change or motion and may vary depending on patient motion and immobilization.
- Organs at risk within the irradiated volume should be contoured, but many are site dependent.
- A DVH is necessary to determine target coverage and evaluate dose to normal tissues.
- Simulation and immobilization will be discussed by treatment site.

13.5.2 General Considerations for Proton Radiation Therapy

- When passive scattering or uniform scanning methods are used, the boost PTV for proton therapy will include a margin which is added to the CTV in three dimensions.
- The margin should be consistent with the motion control and setup accuracy for the particular type of treatment at the treating proton center.
- The goal of treatment planning will be CTV coverage of 100% directly with specific measures taken for each specific uncertainty. Specific adjustments will be made to (1) aperture margin definitions, (2) smearing of compensator, (3) range of the individual beams (depth of penetration), and (4) modulation width of the SOBP (spread-out Bragg peak).

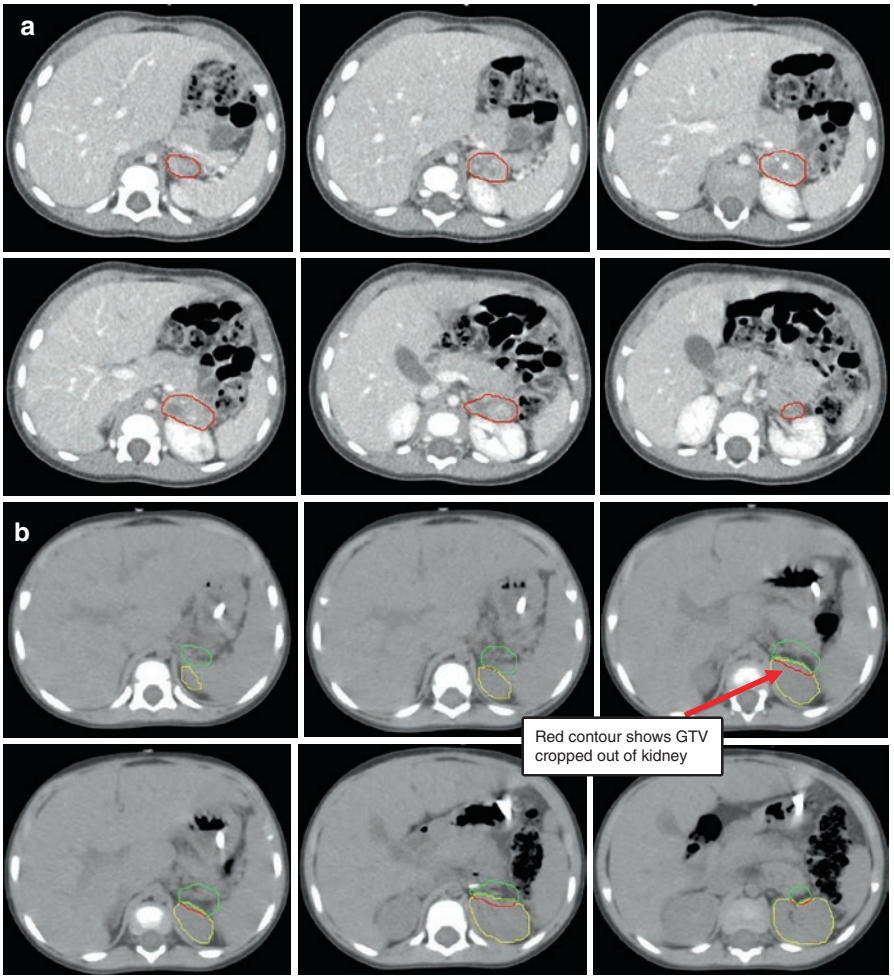


Fig. 13.1 (**a**–**c**) High-risk adrenal neuroblastoma contours. A 2-year-old male with high-risk, N-Myc-positive, adrenal neuroblastoma with metastatic disease treated 50 days post stem cell transplant. Due to a complete response at metastatic sites, he required treatment to the area of post-induction gross disease only. He had a complete resection of primary lesion. (**a**) Patient CT scan post-induction chemotherapy, presurgical GTV (red) is delineated. This is labeled GTV per COG protocol. Preoperative GTV CT scan will be fused to CT simulation, and the volume will be modified based on changes in anatomy and tumor. (**b**) Since the surgical report indicated there was no invasion into the kidney, the GTV (green) was cropped off of the left kidney (yellow). This reflects the volume reduction based on the pushing border (red). When the tumor was removed, the bowel fell in to the previous GTV. If there was question of invasion into the kidney, the GTV volume would be modified to allow only 3 mm of the volume to enter the kidney on the CT simulation scan due to the possibility of microscopic disease remaining in the area. (**c**) Define CTV1 (dark blue) by expanding GTV1 by 1 cm. Modify CTV1 by subtracting the adjacent kidney (yellow), liver, and vertebral body (purple) unless they are involved by disease. Include surgical clips within the CTV after surgery if it is very close to the CTV. CTV will need to be expanded to PTV (light blue) by 0.8 cm; however, this may change depending on the site or available technology (see Table 13.5). Notably new margins will be instituted in the upcoming protocol with a 1 cm instead of a 1.5 cm expansion. In the setting of NB arising from the adrenal gland, it is important to include the vertebral body in the PTV to prevent growth asymmetry

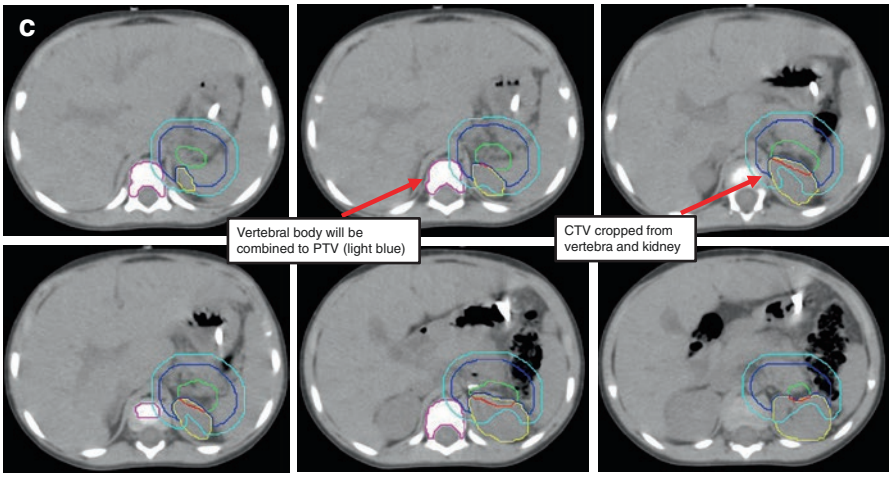


Fig. 13.1 (continued)

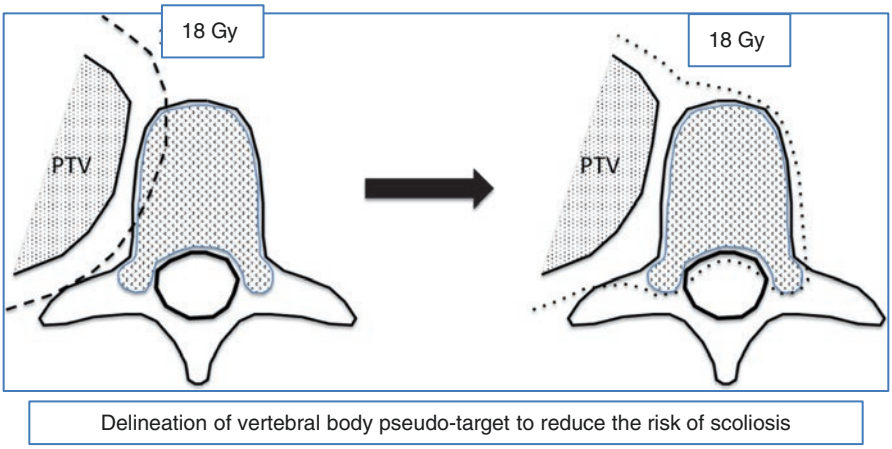


Fig. 13.2 Vertebral body pseudo-target to reduce the risk of scoliosis

Table 13.4 Treatment sites and doses as per Children's Oncology Group protocols

Site/target	Dose
Primary tumor site and initially involved lymph nodes according to imaging criteria or documented by surgery (PTV1)	21.6 Gy delivered in 1.80 Gy fractions
Primary tumor site gross residual disease after surgery (PTV2)	36 Gy (cumulative dose including boost) delivered in 1.8 Gy fractions
Metastatic disease present *after induction* even if resolved on post-consolidation imaging	21.6 Gy delivered in 1.8 Gy fractions
Hepatomegaly leading to respiratory distress	4.5 Gy delivered in 1.5 Gy fractions
Cranio-spinal dose	21.6 Gy delivered in 1.8 Gy fractions

Table 13.5 Suggested PTV margins based on primary site

Primary site	Non-CBCT	CBCT
Head and neck	5 mm	3 mm
Upper paraspinal	5 mm	3–5 mm
Intrathoracic	5 mm	5 mm
Abdomen	5–8 mm	3–5 mm
Lower paraspinal/ pelvic	5 mm	3–5 mm

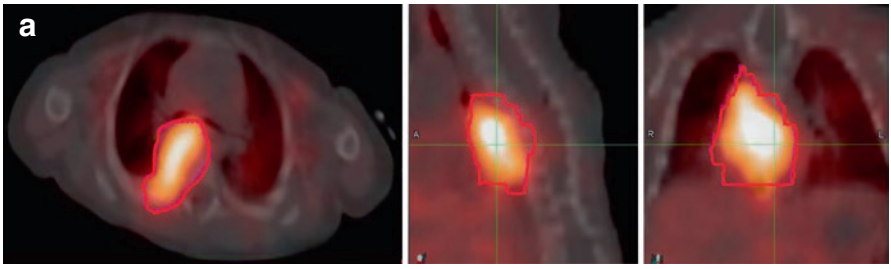
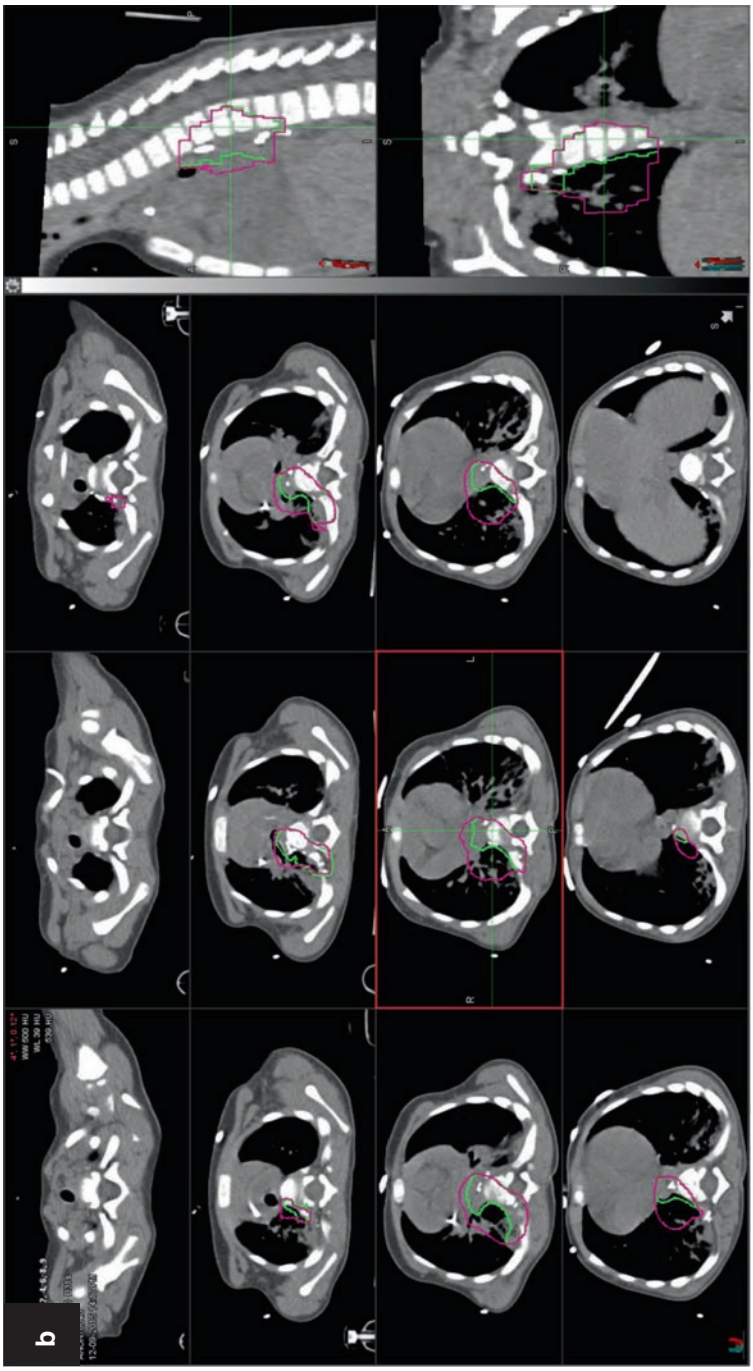


Fig. 13.3 (**a**–**c**) High-risk thoracic neuroblastoma contours. A 2-year-old male with high-risk neuroblastoma of the parasympathetic ganglia in the right thorax. Patient had gross total resection after induction chemotherapy. (**a**) MIBG scan was utilized for initial presurgical target volume delineation prior to CT simulation. Shown is the post-induction, presurgical tumor volume (red) in the axial, sagittal, and coronal planes. These volumes will be fused to the CT simulation for target delineation. (**b**) Shown is the CT simulation after surgery. The GTV 1 defined by the MIBG scan is shown (magenta) but are modified since the primary tumor expanded into the lung without invasion. Since following surgical resection, the normal structure now occupies the space previously occupied by tumor (pushing border); only the normal tissue that was in contact with the tumor volume should be included within GTV1. (**c**) The CTV (turquoise) and PTV (purple) are added to the GTV (green). The CTV was shaved out of the uninvolved bone, lung, and pericardium. Not shown was the addition of the pseudo-target vertebral body volume and addition to the final PTV



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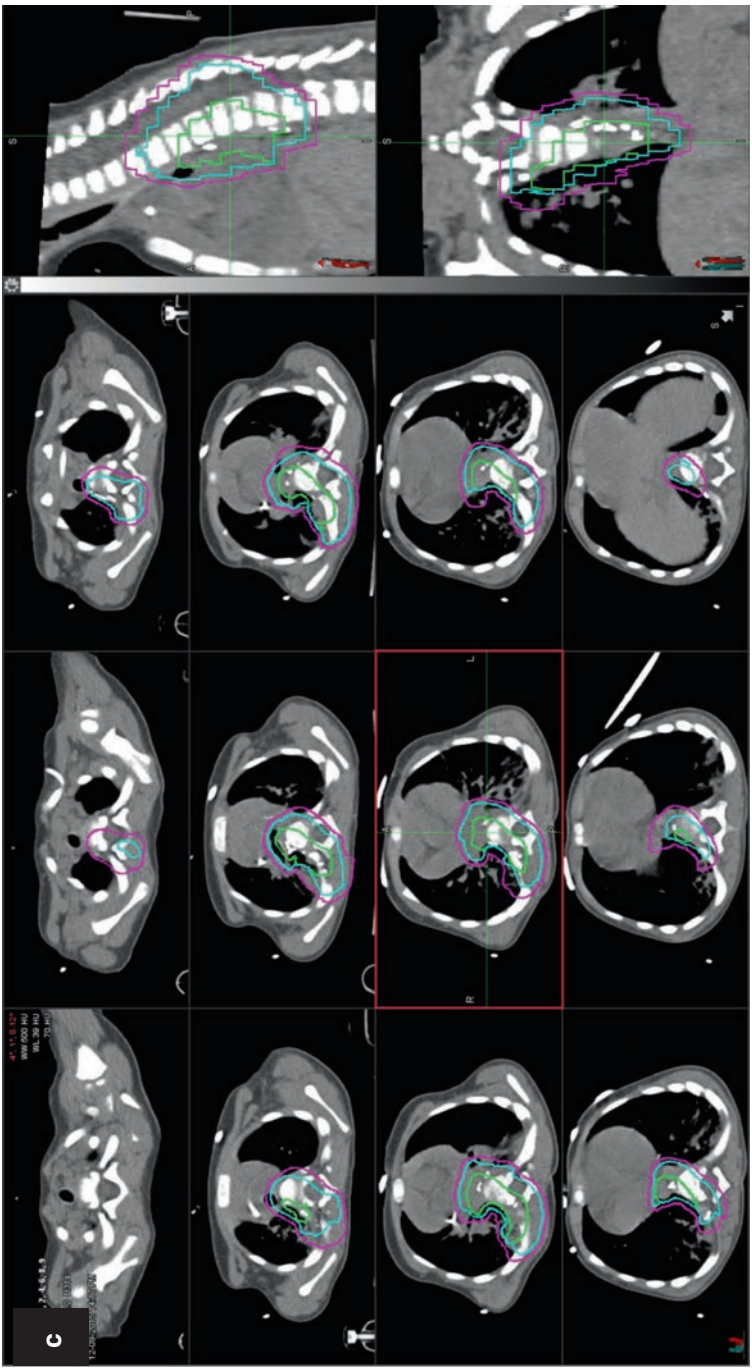

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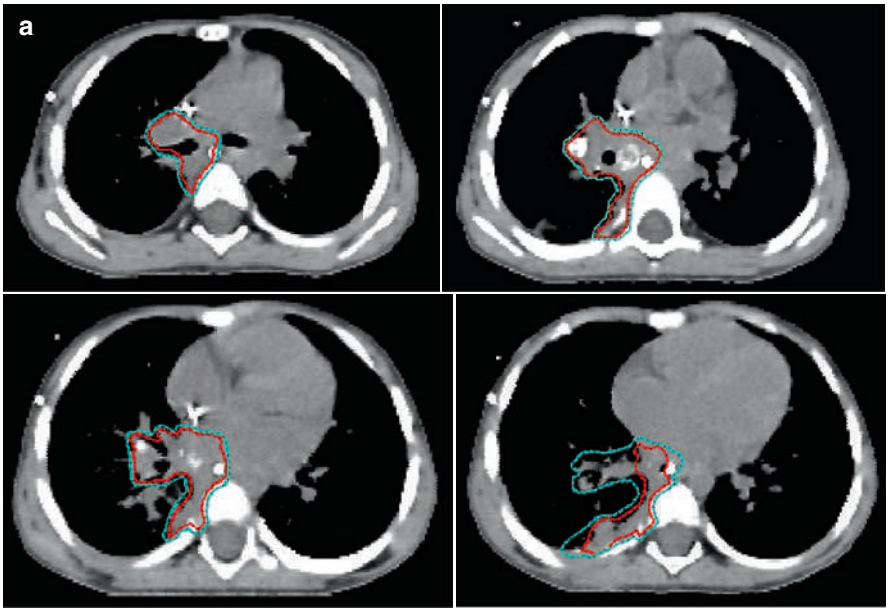
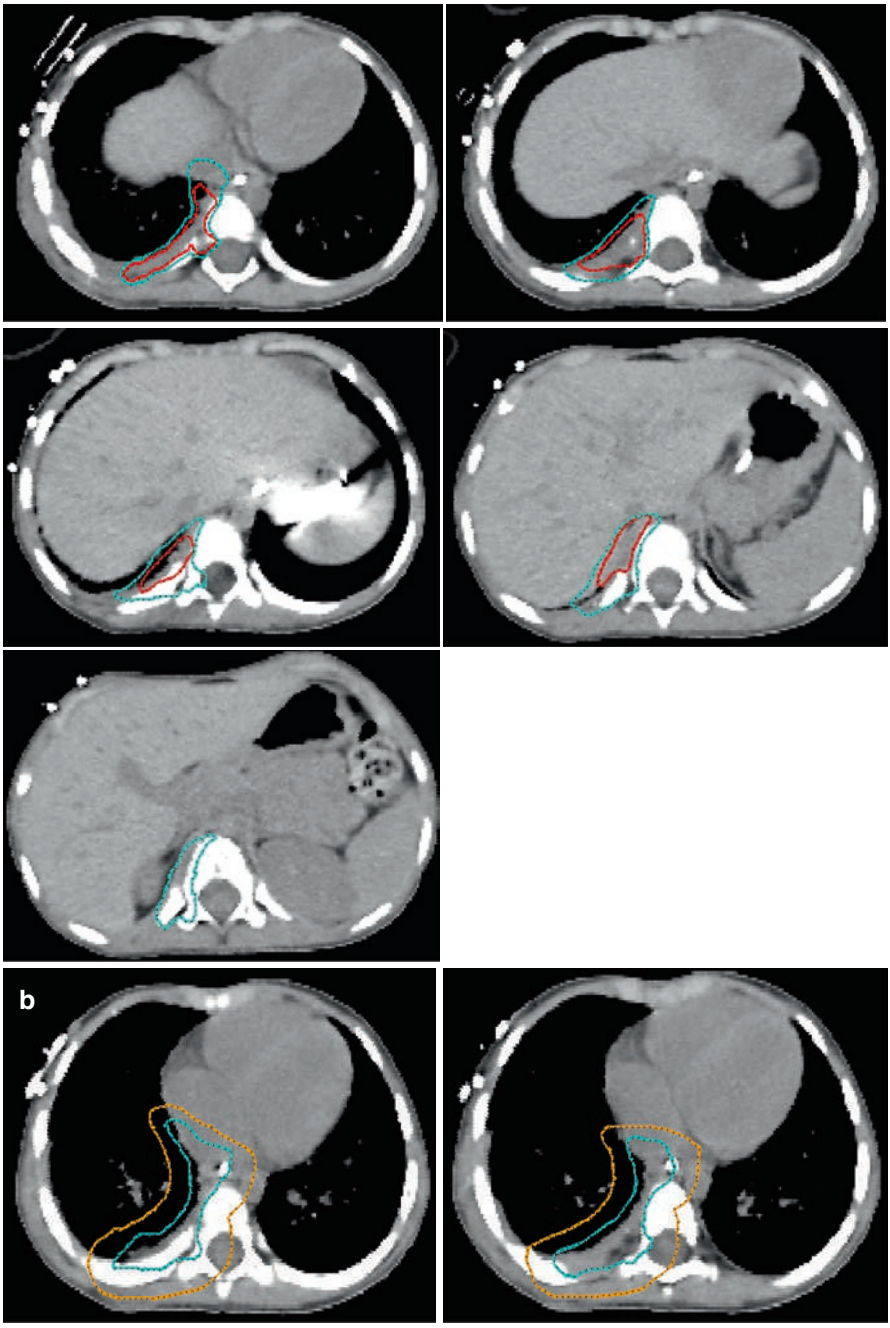


Fig. 13.4 (**a**–**c**) High-risk thoracic neuroblastoma contours. (**a**) A 5-year-old male with metastatic neuroblastoma involving the parasympathetic ganglia in the right thorax. Patient had scintigraphic images demonstrating a MIBG-avid focus corresponding to the soft tissue mass in the right paravertebral location and extending to the right costophrenic recess. The mass extended from the right pulmonary hilar region to the paraspinal region along T8–T12. There was neuroforaminal extension along the T spine most prominent at T9 and T10. The tumor was not completely resected. These images show the GTV 1 (blue) and GTV 2 (red) volumes. Please note that due to the extensive neuroforaminal involvement, GTV1 volumes are generous to include parts of bone. (**b**) The top images show the GTV1 to CTV 1 expansion. (**c**) Images show the GTV 1 to PTV 1 expansion. Please note that CTV 1 was not modified around the vertebral body because of the neuroforaminal involvement. Therefore the vertebral body and pedicles were included in the PTV 1 expansion



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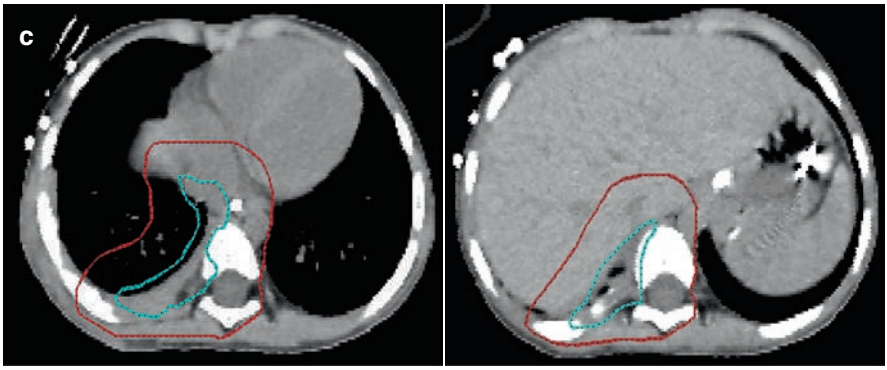

Fig. 13.4 (continued)

- The distal expansion for the PTV should be based on the distal range uncertainty for each beam. A standard expansion will not be used to determine the distal range for the individual proton beams given the unique nature of the range uncertainty in a patient.
- Proton distal target margin = CTV + range calculation uncertainty + setup margin + internal margin
- where
  - CTV = the distal aspect of the CTV
  - Range calculation uncertainty = generally 3.5% of the water-equivalent range of the CTV at max depth
    ≥ 1 mm
  - Setup margin = setup, mechanical, and dosimetric uncertainties
    Protons are relatively unaffected by setup uncertainty in axis of beam.
    Uncertainty in hardware and software has no assigned value available
  - Internal margin = compensates for all variations in site, size, and shape of the tissues contained in or adjacent to the CTV
    ≥ 1 mm

13.5.3 Metastatic Sites

- While the primary site is always irradiated, radiation is only given to those metastatic sites with persistent active disease demonstrated at the time of evaluation prior to consolidation based on persistent soft tissue mass and/or MIBG uptake.
- Sites that are negative on imaging prior to consolidation will NOT be irradiated, even if they had enhanced uptake on MIBG at diagnosis (see Figs. 13.5 and 13.6; Table 13.6).

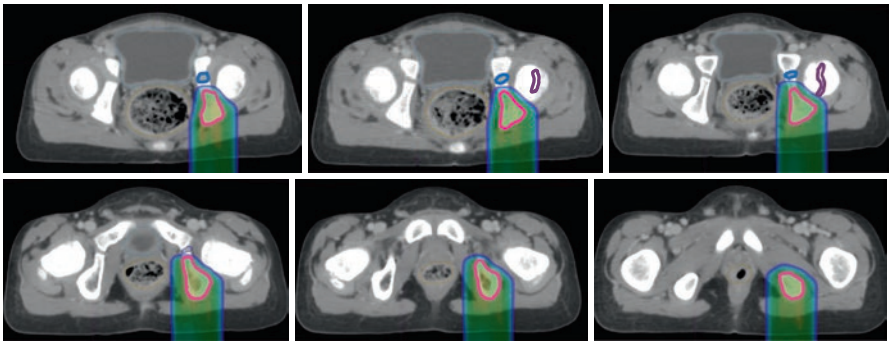

Fig. 13.5 Metastatic thoracic neuroblastoma contours. A 3-year-old male with metastatic neuroblastoma and multiple sites of bony MIBG-avid disease. The only site of post-induction MIBG avidity was a left acetabular metastasis. He received proton RT to the acetabular metastasis to a dose of 21.6 Gy with complete sparing of the growth plates. SOBP is ranged to cover the bone homogenously and does not end prematurely in the mCTV5 (pink). The pelvic (blue) and femoral (purple) growth plates are shown. The growth plates are completely spared

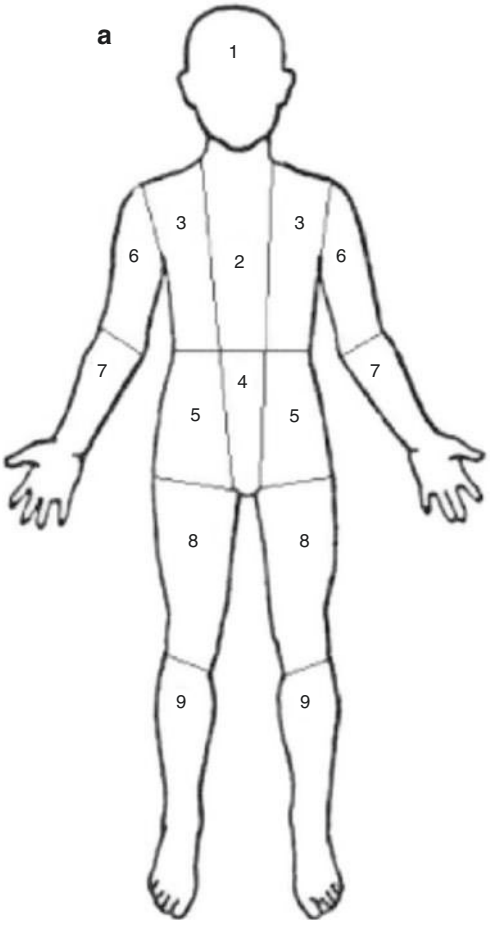

Fig. 13.6 MIBG-123 mGTV identification template

Table 13.6 Metastatic site volume definitions

Site/target	Description
Metastasis gross tumor volume 1 (mGTVx)	The mGTV1x volume is the *post-induction* chemotherapy MIBG-avid disease prior to consolidation *The "x" refers to the anatomical segment designated in the INRG 123I-MIBG scoring system* (see Fig. 13.6)[a]
Metastasis clinical tumor volume 1 (mCTVx)	The mCTV1x is the mGTV1x volume expanded by 1 cm bounded by the mGTV1x volume

[a]This table will be included in the next phase 3 COG protocol

Table 13.7 Suggestions for metastatic site CTV modifications

Treatment site(s)	Methods to anatomically confine CTV
Calvarium	Adjust CTV to avoid extension into the cerebral cortex unless the lesion extends through the skull with suspected dural involvement. In cases where the entire calvarium needs to be treated, a brain-sparing approach should be used [3]
Base of the skull	Adjust CTV to avoid extension beyond bony structures unless there is radiographic evidence of extension into brain tissue. T2-weighted imaging can be useful in delineating the target
Limb	Adjust CTV to avoid circumferential limb treatment, growth plates, and joint spaces (unless involved)
Spine	Adjust CTV to facilitate uniform dose to the entire anterior elements of the vertebral body (regardless of if nonuniformly involved by disease) to minimize the risk of scoliosis. The entire vertebral body should receive >18 Gy if requires partial treatment
Rib	The CTV should be adjusted such that CTV does not extend into the lung parenchyma unless there is strong evidence of parietal pleura involvement

13.5.3.1 Patients with >5 MIBG- or PET-Avid Metastatic Sites Prior to Consolidation

- If the patient had >5 persistently positive metastatic sites identified by MIBG or persistent soft tissue mass with increased FDG-PET uptake prior to consolidation, the appropriate scan should be repeated on day +28 after stem cell transplant.
- Only sites remaining positive will then be irradiated. If there are still >5 MIBG- or PET-positive sites, discussion with COG protocol authors is generally recommended (Table 13.7).

13.6 Emergency Radiation Target Delineation

- Emergent radiation may be administered in several clinical scenarios including respiratory distress and vision loss due to tumor involvement of the liver and orbit, respectively.

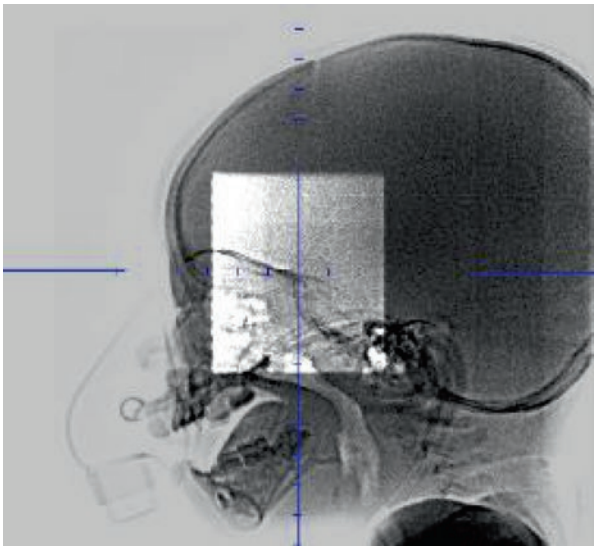

Fig. 13.7 Radiation Portal for acute vision loss. An example of a limited symmetrical field utilized for emergent treatment in a child with rapid onset vision loss

13.6.1 General Considerations for Orbital Treatment

- In emergent situations when simulation is not possible, radiotherapy may be prescribed using a limited symmetrical field for several fractions (see Fig. 13.7).
- In clear cases of vision loss, radiotherapy may be administered over three fractions at 1.5 Gy per fraction.
- Simulation should be done in the supine position with a short thermoplastic mask for immobilization.
- Relevant OARs include the optic apparatus, lens, and lacrimal glands.

13.6.2 General Considerations for Liver Treatment

- The patient should be simulated in the supine position with arms overhead and with a custom mold for immobilization.
- In general, the entire extent of the liver need not be targeted, and the bulk of the volume can be selected for treatment to minimize dose in the abdomen, kidneys, ovaries, and lungs.
- In cases where respiratory distress is present at diagnosis secondary to liver disease, radiotherapy may be administered over three treatments at 1.5 Gy per fraction.

13.7 Plan Assessment

- The dose to the critical organs indicated should be calculated whenever they are included in the radiation field (Table 13.8).

Table 13.8 Normal tissue tolerances[a]

Organ	Dose limit
Contralateral kidney	<25% > 18 Gy
Ipsilateral kidney: whole (100% of the kidney receives <18 Gy)	<75% > 18 Gy
	<100% > 14.4 Gy
	Mean dose ≤18 Gy
Liver	<15% >30 Gy
	Mean dose <15 Gy
Vertebral bodies (if vertebral body is included in PTV)	Minimum dose 18 Gy to the entire corpus and pedicles (see Fig. 13.2)
Bilateral lungs	<30% ≥ 20 Gy
Ipsilateral lung	<30% ≥ 20 Gy
Contralateral lung	<10% ≥ 20 Gy

[a]This table will be included in the next phase 3 Children's Oncology Group (COG) protocol

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Ocular and Orbital Malignancies

14

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Contents

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14.1 Optic Pathway Glioma

14.1.1 Background

Radiotherapy for low-grade gliomas in children has always been controversial due to the high control rates and long potential timeline for the development of late toxicities.

The use of effective cytotoxic regimens like carboplatin and vincristine [1], thioguanine, procarbazine, lomustine, and vincristine (TPCV) [2], and single-agent vinblastine [3, 4] means that radiotherapy may often be delayed to a more favorable age allowing for continued normal development.

Many children who are not surgical cases will ultimately need radiotherapy for disease control, and thus conformal treatment methods are required.

Merchant et al. demonstrated reduced target margin (1 cm CTV) radiotherapy for low-grade gliomas results in excellent disease control and acceptable rates of vasculopathy [5]. ACNS0221 is evaluating the use of 0.5 cm CTV margins for low-grade gliomas, but has not yet been reported.

- Optic pathway gliomas (OPGs) represent a special case of low-grade glioma and often require treatment due to threatened vision. The response rate of OPGs with vision symptoms is substantial, with greater than 75% having either stabilization or improvement in vision with radiotherapy [6].
- Radiotherapy is potentially curative in 80–90% of low-grade gliomas; however, given the potential for late effects, radiotherapy is often used as a last resort after progression following multiple chemotherapy or targeted therapy regimens or when vision is threatened.

14.1.2 Management

- Maximal safe resection is the preferred initial step in management when possible. Even in the setting of residual disease, radiotherapy and chemotherapy are usually avoided until progression.
- Unilateral optic nerve gliomas in patients with absent or impaired vision with no chiasmatic involvement are considered ideal for surgical resection as curative therapy.
- Chiasmatic low-grade gliomas in patients with residual vision or light perception are typically managed with chemotherapy or radiotherapy at progression. At progression or if the tumor is unresectable at diagnosis in a young patient without threatened vision, multiple chemotherapy regimens can be considered.
- Specifically, most providers consider carboplatin and vincristine to be first-line therapy, while more intensive regimens such as TPCV are preferred second or third line. Vinblastine may also be an appropriate treatment alternative.
- Patients with neurofibromatosis represent a special population, and radiotherapy is typically avoided. MRI images and CT images should be 1mm thick as the optic chiasm and other fine structures need to be contoured and fused accurately. Use of MRI data in 3D format yields superior fusion results

14.1.3 External Beam Radiotherapy Dose/Fractionation

- Prescription dose—50.4–54 Gy in 1.8 Gy/fx

14.1.4 External Beam Radiotherapy Target Volumes

14.1.4.1 GTV

- Pilocytic: the entire tumor visualized on gadolinium-enhanced T1 MR imaging performed just prior to the start of irradiation plus any non-enhancing abnormality seen on T2 or FLAIR imaging at that time.
- Non-pilocytic histology: the GTV will often be best identified on T2-weighted or FLAIR images. All tumor cysts should be encompassed by the GTV.

14.1.4.2 CTV

- GTV plus a 5 mm anatomically limited margin (e.g., the CTV will not extend into the calvarium)

14.1.4.3 PTV

- CTV plus a 3–5 mm (depending on institutional experience) margin to account for patient movement (Figs. 14.1 and 14.2)

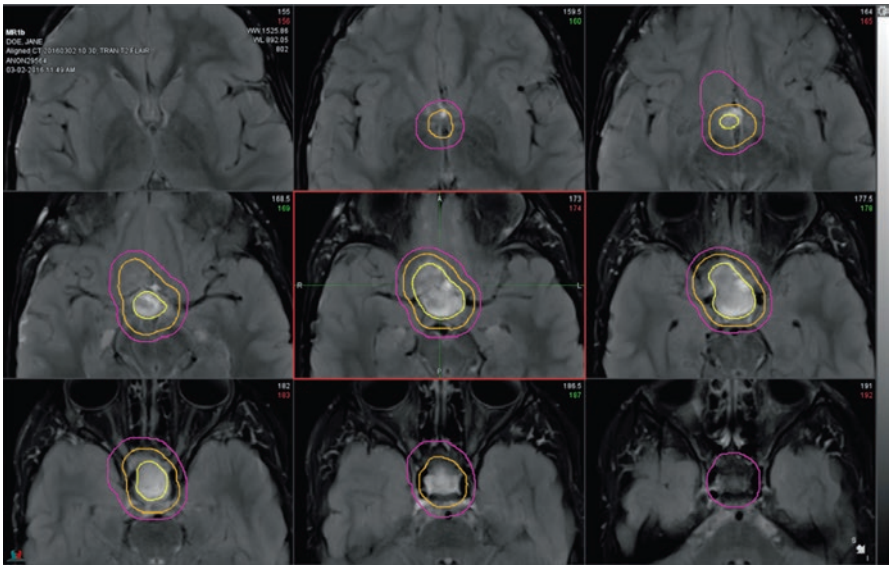

Fig. 14.1 Representative contours for a patient with an optic nerve glioma (GTV, yellow; CTV, orange; PTV, pink) (Image courtesy J.T. Lucas, St. Jude Children's Research Hospital)

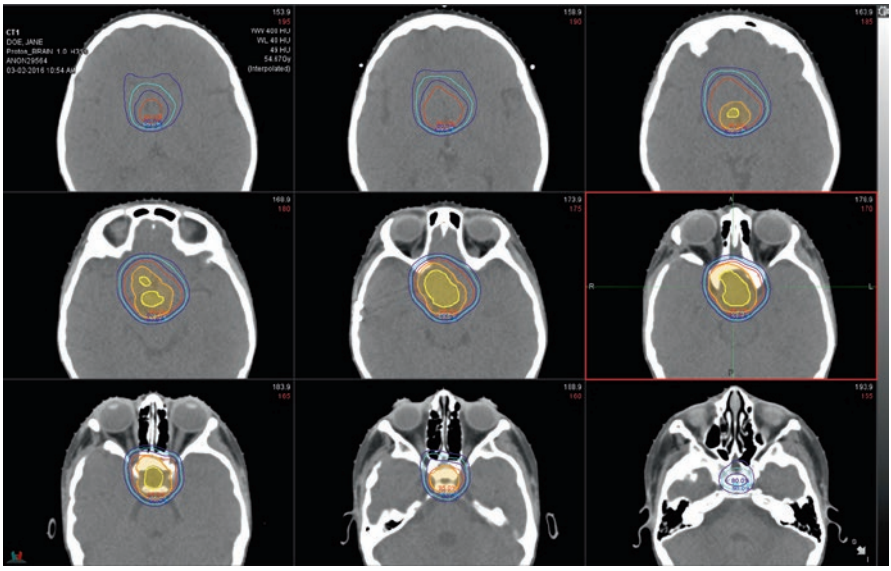

Fig. 14.2 IMPT proton radiotherapy plan for a relapsed locally progressive chiasmatic low-grade glioma. The 95, 80, 65, and 50% isodose lines are indicated in red, deep purple, turquoise, and purple, respectively. The GTV, CTV, and PTV are in yellow, orange, and pink (Image courtesy J.T. Lucas, St. Jude Children's Research Hospital)

14.2 Organs at Risk

- The lens and lacrimal gland are typically only threatened in cases with distal optic nerve lesions and are infrequently dose limiting [7, 8].
- Optic nerves are typically taken to tolerance for at least a portion of their volume along the optic tract. Efforts to avoid excessive hot spots should be made [8–10].
- Chiasmatic optic pathway gliomas represent a special challenge as the hypothalamus, circle of Willis, and medial temporal lobes (hippocampi) are frequently unavoidable.
- Neuroendocrine deficits are virtually guaranteed in these cases necessitating early endocrinology intervention [11].
- The neurofibromatosis population is especially problematic as this population is also at increased risk for second cancers and vasculopathy [11, 12].

14.3 Retinoblastoma

14.3.1 Background

- Radiotherapy for retinoblastoma is generally very effective both applied as an episcleral plaque and as external beam radiotherapy and is generally used as a part of a multimodality approach for patients with residual localized disease following other focal therapy (surgery, laser, diode) or for metastatic disease.

- Episcleral plaque brachytherapy is an excellent means of obtaining disease control and has minimal morbidity [13]. A variety of radionuclides have been used with comparable efficacy, although I-125 is the most commonly used.
- The late effects of external beam radiotherapy necessitate that it be used in primarily high-risk cases when the therapeutic ratio generally favors disease control over concern for morbidity. Late effects can include bony hypoplasia around the orbit [14], retinopathy [15], xerophthalmia [16], prosthesis contracture [personal communication], and second cancers in the heritable retinoblastoma population [17].
- Newer treatment approaches and the use of protons will decrease but not eliminate these risks [18].

14.3.2 Indications for Radiotherapy

- Stage 2 and 3 patients (orbital and/or regional involvement) to initially involved sites.
- Stage 4a and 4b patients to sites initially involved based on response.
- Stage 4a or 4b patients with less than a complete response to induction chemotherapy.
- If less than three metastatic sites, consolidative radiotherapy should be considered pending response.
- Patients with >3 sites will need these regions prioritized, and additional response evaluations following more systemic therapy may be considered to triage limited sites for consolidative radiotherapy.

14.3.3 Timing

- Radiotherapy should start within 42 days of completion of induction chemotherapy for stage 2/3 patients and ASCT for stage 4a/b patients, respectively.

14.3.4 External Beam Radiotherapy Target Volumes

- GTV is the volume of primary tumor and enlarged unresected lymph nodes at diagnosis and is defined by inspection/palpation, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET scan) prior to any surgical debulking or chemotherapy. When the initial tumor volume extends into body cavities (i.e., thorax, abdomen) and has responded to chemotherapy or has been resected, the GTV may require modification. The GTV may be reduced from the original extent and reduced when the pushing border mass effect on parenchymal brain, intestines, etc. is reduced. Regions of initial infiltrative involvement by the GTV at diagnosis must be included.
- The CTV includes the GTV and sites with potential occult tumor involvement including unresected lymph nodes adjacent to the GTV that may be clinically involved. The CTV should be expanded 0.5 cm from the GTV. The CTV should not extend beyond the patient or anatomic boundaries unlikely to represent routes of spread.

  - Extremity Sites: Circumferential treatment of extremity lymphatics and joint irradiation should be avoided.
  - Head and Neck Sites: Radiotherapy dose should be minimized to the brain, cochlea, optic chiasm, and orbit including the eye, eyelid, lacrimal gland, and optic nerve.
  - Orbital Sites: The CTV should not extend outside of the bony orbit, except when there is bony erosion.
  - Chest Wall/Intrathoracic Sites: Displaced lung parenchyma need not be included in the CTV when treatment response following induction chemotherapy or surgical resection has taken place. Pleural involvement sites should be included in the GTV irrespective of response.
  - Intra-abdominal/Retroperitoneal/Pelvic Sites: Displaced bowel may be excluded from the GTV when treatment response is documented, and there was no radiographic evidence of tumor involvement at diagnosis. Peritoneal sites involved at diagnosis should be included irrespective of treatment response. Patients with malignant ascites or diffuse peritoneal involvement should be treated with whole abdominal radiotherapy to 24 Gy at 1.50 Gy per fraction. The kidneys and liver should be blocked/avoided in accordance with tolerance/constraint guidelines.
  - Lymph Nodes: Elective nodal radiotherapy for N0 patients is not recommended. When lymph nodes are clinically or pathologically involved and unresected, the entire lymph node drainage chain should be included in the CTV.
  - Pulmonary Metastases: Whole-lung radiotherapy is recommended for single or multiple pulmonary metastases to a dose of 15 Gy in 1.5 Gy fractions unless the patient is 6 years of age and younger, in which case the child will receive 12 Gy at 1.5 Gy per fraction. Residual disease following chemotherapy may be boosted with a conformal small field radiotherapy to 45 Gy. If only one hemithorax is involved by malignant pleural effusion at diagnosis, only the involved hemithorax will be treated.
  - Metastatic Sites: Radiotherapy is recommended to all incompletely responding metastatic sites. Reevaluation imaging following additional therapy is useful when considering sites in need of consolidation. A CTV is not required for the treatment of metastatic lesions although when there is discrepancy between evaluation imaging in target volume, the larger volume should be treated.
- PTV is the CTV surrounded by a geometric margin to account for variability in setup, breathing, or motion during treatment.
  - The PTV for primary sites should be based on immobilization method and type of image guidance.
  - The PTV for metastatic sites is 1 cm from GTV (Fig. 14.3).

14.3.5 External Beam Radiotherapy Dose/Fractionation

- Stage 2/3 orbital site: 45 Gy in 1.8 Gy/fx.
- Stage 4a with greater than 5 mm pre-radiotherapy residual: 36 Gy in 1.8 Gy/fx.

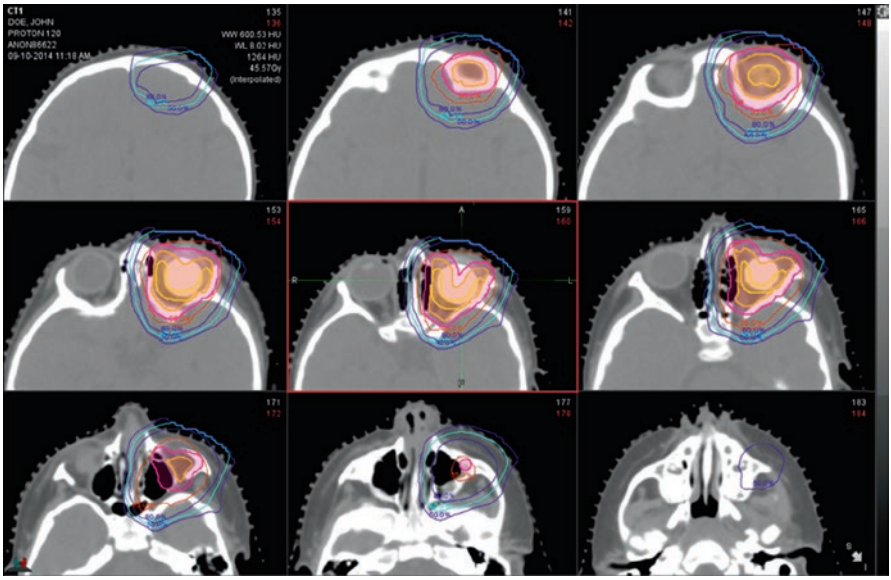

Fig. 14.3 Representative SFUD proton radiotherapy plan following enucleation with placement of prosthesis in a patient with extrascleral extension and a positive optic nerve cut margin. The 95, 80, 65, and 50% isodose lines are indicated in red, deep purple, turquoise, and purple, respectively. The GTV, CTV, and PTV are in yellow, orange, and pink (Image courtesy J.T. Lucas, St. Jude Children's Research Hospital)

- Stage 4b with incomplete response to chemotherapy: Craniospinal radiotherapy to 23.4 Gy if less than 5 years of age or 36 Gy if greater than 5 years of age. Residual spine, cranial, and/or pineal sites will be treated to 36 Gy, 45 Gy, or 50.4 Gy, respectively.

14.4 Plaque Brachytherapy

14.4.1 Indications

- Typically, plaque brachytherapy is delayed till other focal therapy failure has occurred. At this point, many patients may have intravitreous seeding or irregular borders necessitating more than just episcleral plaque brachytherapy. In cases where the size and lack of intraocular spread are permitting, episcleral plaque brachytherapy can offer excellent disease control and functional outcomes (2014).

14.4.2 Plaque Selection/Limitations

- Plaque radiotherapy may be used to treat local recurrences up to 8 mm in thickness and 15 mm in base (Fig. 14.4).

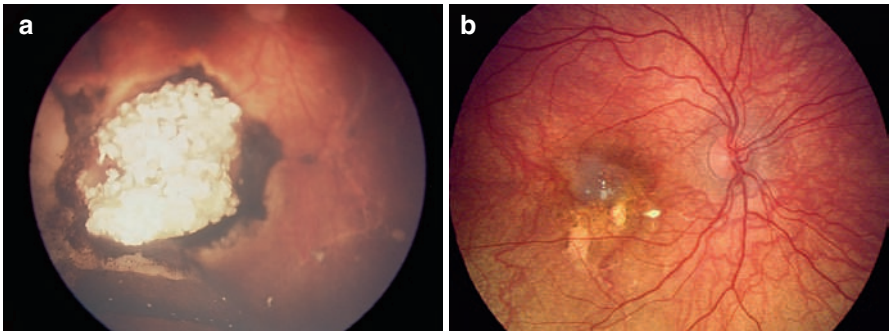

Fig. 14.4 (**a**) Right eye exam under anesthesia demonstrating the inferior temporal portion of the eye with a "fish flesh" area surrounded by calcified tumor. (**b**) Post therapy EUA in a patient following plaque brachytherapy alone demonstrating retinal vascular changes and residual pigmentary abnormalities typical to posttreatment, resolved tumor change (Image courtesy J.T. Lucas, St. Jude Children's Research Hospital)

14.4.3 Plaque Timing

- There should be at least 6 weeks between the last local ophthalmic therapy or systemic therapy and episcleral plaque brachytherapy.

14.4.4 Isotope

- Iodine-125 or ruthenium-106 can be utilized for plaques.

14.4.5 Plaque Size

- The entirety of the tumor base should be covered with plaque with a tumor-free margin of 1–2 mm on all sides except for when the tumor abuts or is within <2 mm of the optic nerve. A "notched" plaque may be useful in these cases. Plaque choice should optimize scatter dose to the patient and coverage (Fig. 14.5).

14.4.6 Radiation Dose

- Prescription point: Prescribed at the apex of the tumor.
- Dose rate: > 0.4 Gy/h but <0.8 Gy/h.
- Tumor thickness: Is defined as the distance from the interior surface of the sclera to the apex of the tumor. The sclera is assumed to be 1 mm thick. Thus, if a tumor is said to be 3 mm thick, the point of dose prescription is 4 mm from the surface of the radioactive plaque, i.e., 3 mm thick tumor +1 mm thick sclera = 4 mm.

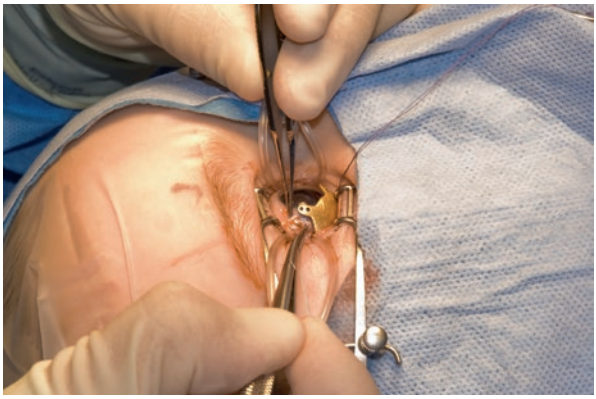

Fig. 14.5 Plaque brachytherapy placement in a patient with an inferior temporal lesion. Typically, 2–3 eyelets are used to tether the plaque to the sclera for a several day treatment application. Commonly, intraocular muscle release may be required to facilitate appropriate placement pending tumor location (Image courtesy J.T. Lucas, St. Jude Children's Research Hospital)

  - If the plaque is placed over one of the ocular muscles, the plaque must be considered to be 1 mm away from the external surface of the sclera, i.e., 3 mm thick tumor +1 mm thick sclera +1 mm muscle thickness = 5 mm. If overlying vitreous seeds are present, the dose is designed to include those seeds.
- Total dose: 30–40 Gy.

14.4.7 Dose to Critical Structures and Other Points of Calculation

The location of the following critical structures, relative to the plaque, is determined by the treating ophthalmologist and radiation oncologist and noted on the retinal drawing or map [19].

- Sclera: The dose to the sclera is estimated and reported at a point on the central axis of the plaque 1 mm from the surface of the plaque. This point is approximately coincident with the internal surface of the sclera near the center of the tumor.
- Optic nerve: The optic nerve will generally be shielded by the lip of the plaque and exposure minimized by careful plaque positioning. The dose to the center of the optic disc is calculated and reported.
- Retina: The dose to the retina opposite the tumor is calculated and reported. The dose is calculated 16 mm from the scleral surface at the base of the tumor measured along a diameter of the globe passing through the apex of the tumor for infants $\leq$6 months of age and 20 mm for patients >6 months of age.
- Lens: The dose to the center of the lens is calculated and reported.

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Pediatric Head and Neck Malignancies

15

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15.1 Background

- Head and neck malignancies account for approximately 5% of all pediatric tumors.
- Although relatively rare, pediatric head and neck malignancies are challenging from a treatment-planning standpoint given proximity to critical structures and developing normal tissue.
- This chapter provides practical contouring guidelines for common pediatric head and neck tumors including malignant tumors such as rhabdomyosarcoma, Ewing sarcoma, salivary gland tumors, and the benign, but locally aggressive, nasopharyngeal angiofibroma.
- Rhabdomyosarcoma and Ewing sarcoma are covered more broadly in Chaps. 8 and 9.

15.2 Rhabdomyosarcoma

15.2.1 Background

- Rhabdomyosarcoma (RMS) accounts for 350 cases of childhood cancer in the USA each year, comprising the most common soft tissue sarcoma in this patient population [1].
- RMS of the head and neck accounts for approximately 25% of all RMS cases, with parameningeal sites being more commonly involved [2].
- RMS of the orbit accounts for approximately 10% of all RMS cases [2].

15.2.2 Histology

- Favorable histologies include embryonal RMS and botryoid or spindle cell variants of embryonal RMS, while alveolar and undifferentiated RMS are unfavorable histologies [2, 3].
- Embryonal histology is the most common histology found in the head and neck region [2, 3].

15.2.3 Staging

- RMS is subclassified into prognostic categories for low-, intermediate-, and high-risk patients based on the probability of treatment failure. Prognostic categories are determined by a combination of histology, clinical group, and stage ([4]; Table 15.1).

15.2.4 Anatomy and Patterns of Spread

- RMS of the head and neck include parameningeal, non-parameningeal, and orbit.
- Parameningeal sites include the infratemporal fossa, middle ear, mastoid, nasal cavity, nasopharynx, paranasal sinuses, parapharyngeal space, and pterygopalatine fossa.
- The incidence of lymph node metastasis is negligible for orbital primaries [5].
- Well-lateralized primary sites of other regions of the head and neck may have involvement of the ipsilateral jugular cervical, preauricular, occipital, or supraclavicular lymph nodes, while central primary sites may have bilateral involvement.
- The incidence of lymph node metastasis has been reported between 7 and 20% for non-orbital RMS head and neck primary sites [5–7].
- The majority of patients with parameningeal RMS primary sites present with either cranial base bony erosion or cranial nerve palsy due to direct local extension, and approximately 25–50% will have intracranial extension [8].

Table 15.1 Rhabdomyosarcoma risk stratification

Histology	Clinical group	Stage	Age	Risk group
Embryonal	I, II, or III	1	All	Low
Embryonal	I or II	2 or 3	All	Low
Embryonal	III	2 or 3	All	Intermediate
Alveolar	I, II, or III	1, 2, or 3	All	Intermediate
Embryonal or alveolar	IV	4	All	High

Reproduced from the National Cancer Institute website: http://www.cancer.gov/types/soft-tissue-sarcoma/hp/rhabdomyosarcoma-treatment-pdq#section/_128

15.2.5 Imaging for Radiotherapy Volume Delineation

- At initial presentation, the patient should undergo imaging with CT with IV contrast and preferably an MR of the head and neck region. PET/CT is recommended but not required.
- In addition, parameningeal sites require an MR brain to assess for intracranial extension and base of skull erosion [8].

15.2.6 Assessment of Lymph Node Status

- FDG PET is recommended for the assessment of lymph node involvement as it has been demonstrated to have sensitivity of 94% and specificity of 100% for detecting nodal disease, in addition to improving the detection of bone, bone marrow, and soft tissue metastases [9].
- FDG PET-detected abnormalities should be confirmed by an additional imaging modality (MR or CT) or through pathological confirmation.
- Patients with head and neck primary sites do not require prophylactic cervical neck lymph node dissection.
- Sampling through an open biopsy is recommended, and in some situations through a needle aspiration, for all clinically or radiographically enlarged lymph nodes.

15.2.7 Treatment Strategy

- Induction chemotherapy followed by concurrent chemoradiotherapy is the current standard of care for any patient with unresectable disease (group III), positive margins, or lymph node involvement (group II) and all patients with alveolar histology based on the improvement in progression-free survival that has been demonstrated with the use of radiotherapy in these groups [10, 11].
- Outcomes for orbital RMS are excellent with the use of definitive radiotherapy and chemotherapy; thus, biopsy alone generally followed by chemotherapy and radiation is the standard of care for orbital stage I, group III disease.
- For RMS non-parameningeal primaries, wide excision is appropriate when feasible, but the possibility of achieving wide margins is generally restricted to those patients with relatively superficial lesions.
- Craniofacial resection for anterior RMS skull-base tumors of the nasal areas, paranasal sinuses, temporal fossa, and other such sites should be reserved to those surgical teams expert in its performance. These regions will generally be unresectable, and radiotherapy will likely be the primary form of local control [12, 13].

15.2.8 Indications for Radiotherapy

- Radiotherapy timing has varied among cooperative group protocols. No benefit has been demonstrated with the early initiation of radiotherapy and beginning

treatment at approximately weeks 9–13 after the initiation of chemotherapy remains the accepted standard for most patients.
- Early radiotherapy for cranial nerve involvement, base of skull involvement, or intracranial extension is no longer recommended, and emergent radiotherapy is reserved for neurologic symptoms such as vision loss or symptomatic cord compression occurring secondary to tumor compression [14].
- Administration of radiosensitizing agents dactinomycin and doxorubicin is generally avoided during radiotherapy.
- Radiotherapy dose varies with surgical group status (Table 15.2).

15.2.9 Simulation

- The patient should be simulated in the supine position with hyperextension of the neck and the use of a long thermoplastic mask extending to the shoulder region for immobilization.
- An anesthesiologist may be necessary for sedation of young children.
- A 3D simulation should be performed. The use of IV contrast and ≤5-mm-thick slices is recommended.
- Use of a bite block may be considered for sparing dose to the uninvolved mucosal surfaces of the oral cavity.
- For orbital primaries, the patient may be asked to keep a steady focused gaze on an external object during treatment in the direction that maximizes treatment to the tumor and reduces dose to the cornea, lens, and/or lacrimal gland.

Table 15.2 Radiotherapy dose according to histology, clinical group, and site

Clinical group	Radiotherapy dose (in 1.8 Gy fraction)	Involved site target volume
Group I, embryonal	0	
Group I, alveolar	36	Pretreatment
Group II, margin+	36	Pretreatment
Group II, lymph node+	41.4	Pretreatment (primary and lymph node chain)
Group III, orbital	45–50.4	Pretreatment, with volume reduction after 36Gy[a]
Group III, non-orbital	50.4[b]	Pretreatment, with volume reduction after 36Gy[a]
Group IV	50.4	As for other groups and including all metastatic sites if safe and feasible

[a]If excellent response to chemotherapy and noninvasive pushing tumor if treating to 50.4Gy; no volume reduction for invasive tumors

[b]The current Children's Oncology Group (COG) protocol ARST1431 for intermediate-risk patients allows an additional boost to a total dose of 59.4Gy for tumors >5 cm and also allows a dose reduction for tumors who have a negative PET or biopsy confirmed pathologic complete response after induction chemotherapy

Reproduced from the National Cancer Institute website: http://www.cancer.gov/types/soft-tissue-sarcoma/hp/rhabdomyosarcoma-treatment-pdq#section/_130

15.2.10 Target Volume Delineation

- All radiotherapy volumes will be at least initially targeting the extent of disease prior to surgical resection and chemotherapy; thus, fusion of CT simulation imaging with imaging studies at presentation including a CT with IV contrast and MR T1 post-contrast-/T2-weighted imaging is imperative for the delineation of the initial gross tumor volume (GTV). Fusion with PET, if available, may also be helpful. Fusion may be limited by differences in neck extension.
- If the tumor has responded to chemotherapy and the normal tissues have returned to their normal positions, the GTV excludes the volume that extends into the normal tissue or cavity. The GTV must include all infiltrative disease detected at initial presentation.
- The clinical tumor volume (CTV) is defined as GTV+ a 1 cm margin in current Children's Oncology Group (COG) protocols. The CTV does not extend outside patient and is anatomically constrained by structures that serve as a barrier to spread (i.e., uninvolved bone), and thus, smaller margins may be used in head and neck primary sites.
- In situations where a pushing rather than infiltrative margin by the tumor is present, reduced radiotherapy volumes can be planned after 36Gy and can be considered for patients whose total dose will be 50.4 Gy. Boost volumes may be planned to encompass any visible or palpable residual tumor at the time of radiotherapy planning as assessed by CT, MR, PET, or physical exam. All sites of infiltrative disease detected at initial presentation (i.e., bone involvement) should be included in the boost volume. In the case of lymph node involvement, the involved lymph node region should be targeted in the CTV, and current COG protocols recommended inclusion of the entire cervical chain.
- In general, elective nodal irradiation is not recommended.
- For surgically resected group II disease, the GTV should include the preoperative tumor volume or involved lymph node confined to the operative bed, excluding normal tissues that may have shifted after surgery. The CTV should include GTV + 1 cm anatomically confined margin and the entire operative bed or involved lymph node region. There are no dose reductions for group II disease.
- Examples of target volume delineation for a stage I, group III orbital RMS case (Fig. 15.1); stage III, group III nasopharynx RMS case with lymph node involvement (Fig. 15.2); and stage III, group III maxillary sinus RMS with no lymph node involvement (Fig. 15.3) are shown.

15.2.11 Treatment Planning

- For orbital primaries, radiotherapy techniques include the use of 3D conformal radiotherapy, IMRT/VMAT, or proton beam therapy [15]. A wedge pair may provide adequate conformality with well-lateralized tumors.
- For other head and neck primary sites, radiotherapy techniques also include IMRT/VMAT or protons [16].

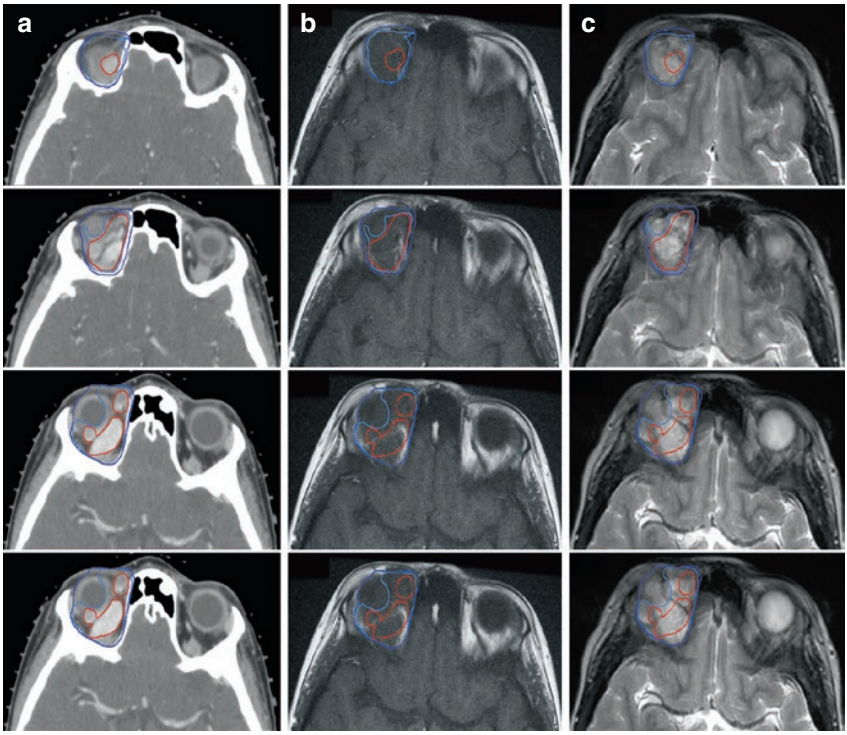
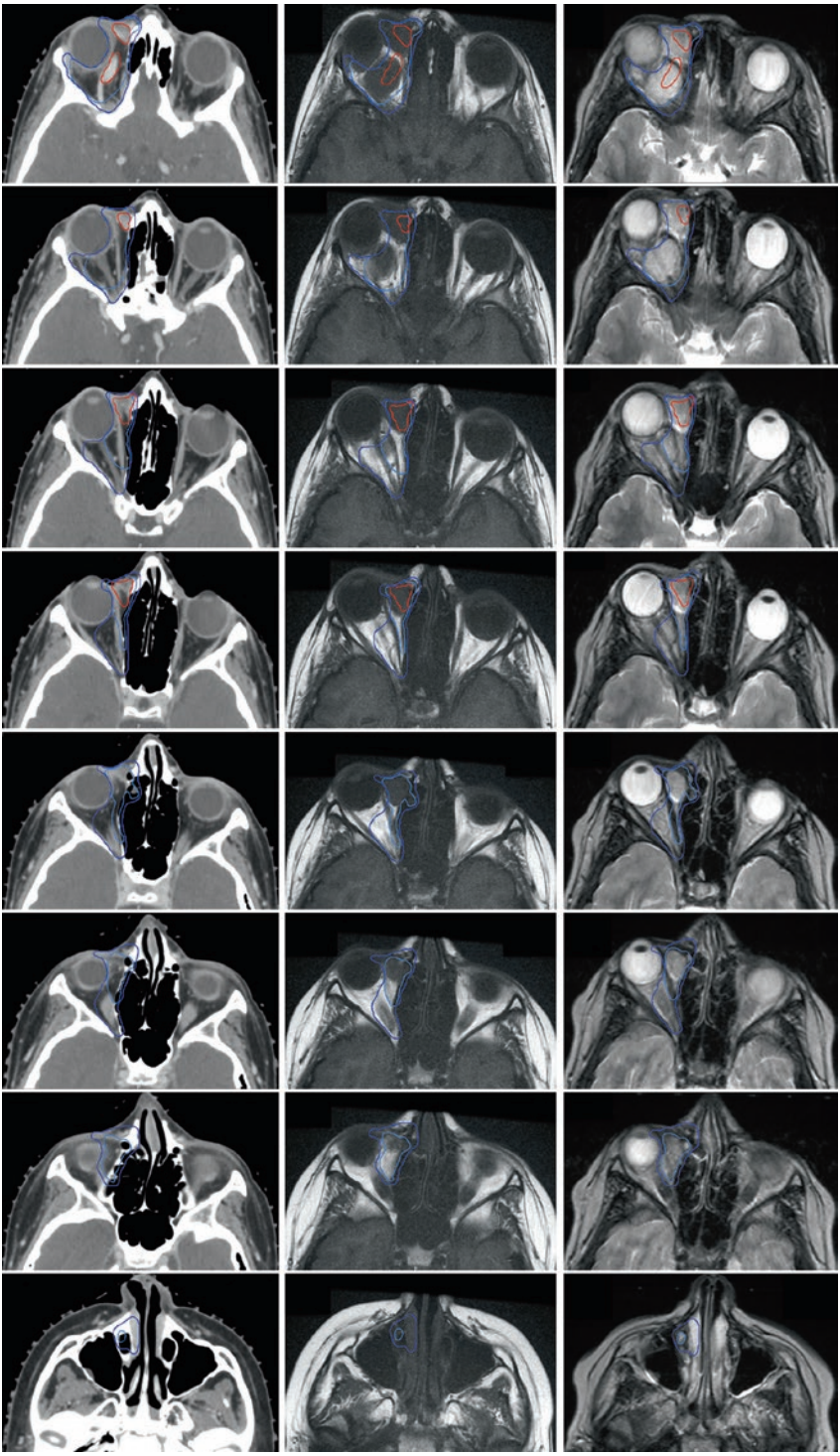


Fig. 15.1 Axial CT simulation planning images (column **a**) and corresponding pre-chemotherapy MR T1 and T2 imaging (columns **b** and **c**, respectively) for a patient with a right-sided orbital embryonal rhabdomyosarcoma stage I, group III, with a good partial response to VAC alternating with VA chemotherapy. Local control with radiotherapy took place at week 12. Pre-chemotherapy MR T1 pre-contrast imaging was chosen in this particular case given better contrast between tumor and orbital fat and, along with MR T2 imaging, was fused with CT planning images. Note that planning accuracy can be limited by the quality of fusion between components. The initial tumor had intraconal and extraconal components and was situated between the superior rectus muscle, optic nerve, and superior oblique. There was involvement of the nasolacrimal duct. There was no intracranial involvement or extension medially into the ethmoid sinus. The extent of tumor on pre-chemotherapy T1/T2 imaging is delineated to form GTV1 (light blue) and CTV1 (dark blue), which does not include the entire orbit but only tumor volume with a margin. The CTV1 included areas at risk of microscopic spread and does not extend outside of the bony orbit when there is no bone erosion present and was contoured on each slice separately taking into consideration anatomic constraints. Tumor present at the time of simulation was delineated to form a GTV2 (light red). A CTV2 (not shown) was delineated and, in this case, represented the extent of pre-chemotherapy disease and was equal to GTV1. Please note that the CTV to PTV margins depend on patient- and institution-dependent factors, and therefore, recommendations for uniform expansions cannot be made. In the case of treatment with proton therapy, no PTV margin is applied. Please note that these are representative slices and not all slices have been included. The patient was asked to keep her eyes slightly open to look to the patient's right-hand side in order to shield the lens and cornea more adequately. In orbital cases, every effort should be made to shield the lens, cornea, and lacrimal gland appropriately



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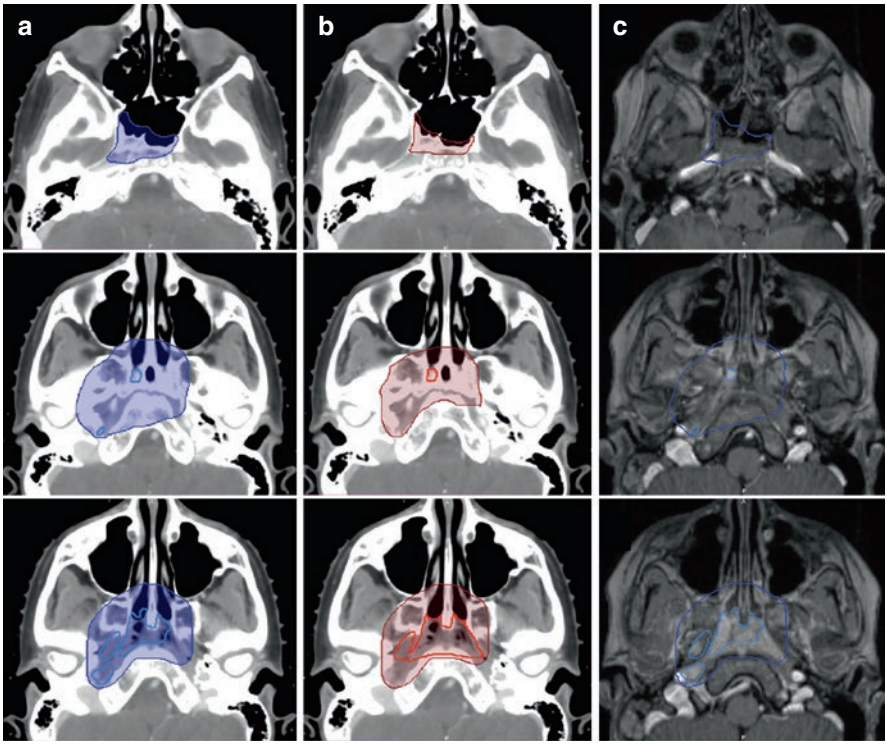

Fig. 15.2 Axial CT simulation planning images (columns **a** and **b**) and corresponding pre-chemotherapy MR T1 post-contrast imaging (column **c**) for a patient with embryonal rhabdomyosarcoma of the nasopharynx stage III, group III with involvement of retropharyngeal and bilateral level II lymph nodes with a near-complete response to VAC alternating with VI chemotherapy. Local control with radiotherapy took place at week 12. MR T1 post-contrast was fused with CT planning images. MR T2 imaging can also be helpful for tumor delineation but is not included here. Note that planning accuracy can be limited by the quality of fusion between components. The initial tumor involved the bilateral nasopharynx and parapharyngeal space with involvement of both right medial and lateral pterygoid plates with extension anteriorly to the nasal cavity and inferiorly to the posterior oral cavity and oropharynx. CT imaging bone windows showed involvement of the hard palate. PET showed avidity of a right-sided retropharyngeal lymph node. The extent of tumor on pre-chemotherapy T1/T2 imaging is delineated to form GTV1 (light blue) and CTV1 (dark blue). The GTV1 excludes normal tissue that returns to normal locations following chemotherapy. Small additional bilateral retropharyngeal lymph nodes and cervical lymph nodes felt to be suspicious for involvement were included in the treatment volume; thus, the entire bilateral retropharyngeal and level II lymph nodes were included in CTV1. The extent of post-chemotherapy residual disease, confined to the right nasopharynx, was delineated to form GTV2 (red) and CTV2 (dark red). In this case, CTV1 was treated to 41.4Gy (RBE) and CTV2 was boosted to a total of 50.4Gy (RBE). Please note that the CTV to PTV margins depend on patient- and institution-dependent factors, and therefore recommendations for uniform expansions cannot be made. In the case of treatment with proton therapy, no PTV margin is applied. Please note that these are representative slices and not all slices have been included. The patient was treated with a bite block to decrease dose to uninvolved mucosal surfaces of the oral cavity

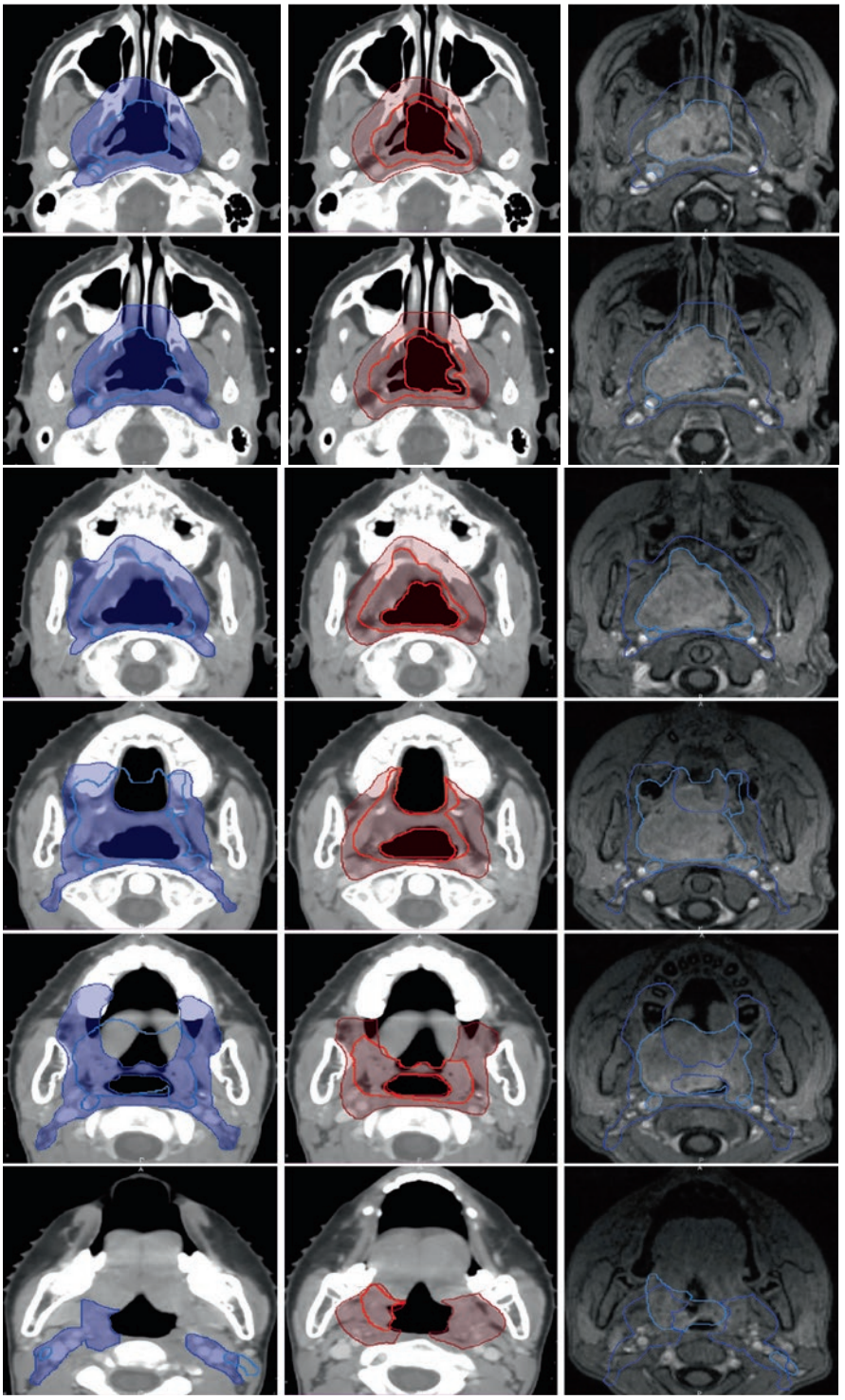

Fig. 15.2 (continued)

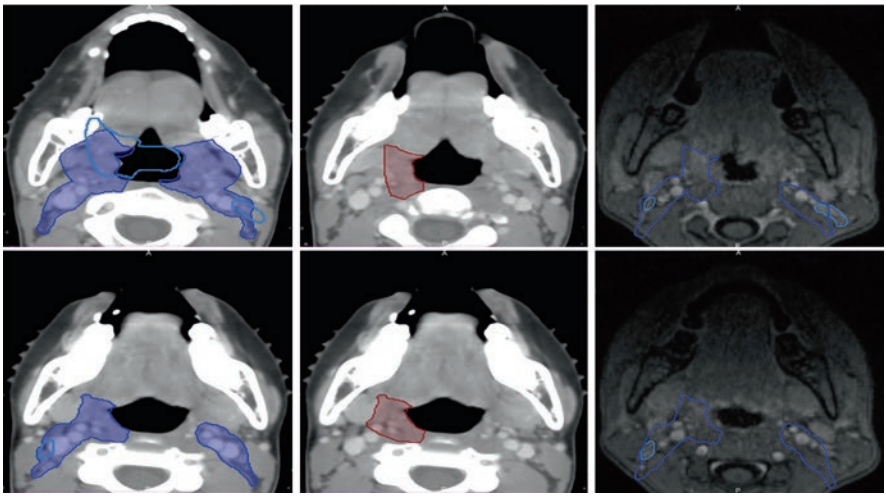

Fig. 15.2 (continued)

- There is no universally applicable planning target volume (PTV) margin, since this will depend on institution practice and the use of image-guided radiotherapy (IGRT).
- When using IMRT or VMAT, it is recommended that the PTV be cropped 3–4 mm away from the skin when uninvolved to avoid excess dose to the skin surface. If target volumes do include the overlying skin, bolus may be required.
- In the case of protons, PTV varies with each individual field and coverage and will require additional adjustment to the lateral margins, smearing of compensator, range of beam (depth of penetration), and modulation (number of required Bragg peaks). Adjustments to any of these will be based on the setup error determined for the particular body site as the individual proton institution.
- In the case of protons, a single beam that stops within a critical organ should not be used.
- Organs within the irradiated volume and organs at risk should be contoured.
- A DVH should be prepared to determine target coverage and to evaluate dose to normal tissue.
- Relevant organs at risk include the spinal cord, optic chiasm, optic nerves and lens/cornea, lacrimal gland, cochlea, brainstem, hypothalamus and pituitary gland, temporal lobes, oral cavity (when uninvolved), parotid and submandibular glands, temporomandibular joint, esophagus, and thyroid gland. Normal tissue constraints for head and neck OARs can be found by references such as QUANTEC [17]. See Table 15.3 for a representative set of dose constraint guidelines included in national cooperative group protocols.

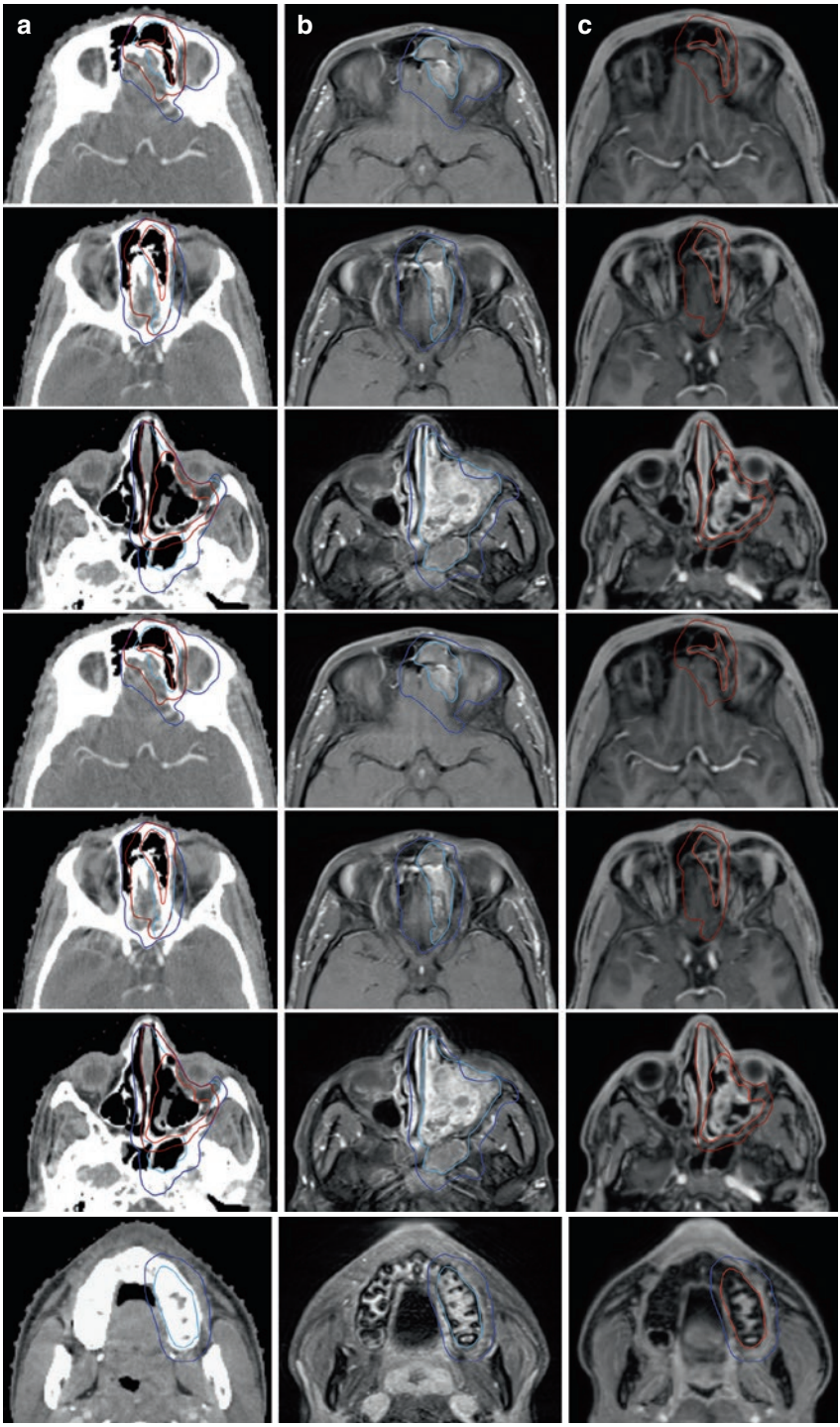
a
b
c

Fig. 15.3 Axial CT simulation planning images (left column) and corresponding initial diagnostic T1 post-contrast fat-suppressed MRI sequence MRI (middle column) and post-induction chemotherapy post-contrast MRI at the time of treatment planning (right column) for a stage III, group III, alveolar RMS of the left maxillary sinus. Initial diagnostic MRI revealed a heterogeneously enhancing expansile mass centered in the left maxillary sinus invading into the left nasal cavity, left pterygopalatine fossa, left orbit through the orbital floor and medial orbital wall, left ethmoid sinus and left frontal sinus with a focal area of dehiscence through the left ethmoid air cells, and cribriform plate suggestive of intracranial extension. There was no evidence of regional lymphadenopathy by MRI or CT with contrast. Biopsy revealed alveolar rhabdomyosarcoma. The patient was treated with VAC/IE chemotherapy. After 9 weeks of chemotherapy, MRI was repeated (right) and revealed significant interval decrease in size of the soft tissue lining the expanded maxillary sinus with resolution of the previous mass effect on the orbit and no further evidence of intraorbital or intracranial extension. The pre-chemotherapy GTV (light blue) was defined on the initial diagnostic MRI (middle). The CTV (dark blue) is defined by a 5–10 mm expansion from the GTV and was anatomically confined by anatomic borders or potential spread and cropped off of normal critical structures that have shifted in place due to decrease mass effect of the tumor after chemotherapy (e.g., the eye). An additional PTV margin of 3 mm was used (not shown) in this case with daily AP and lateral kV on-board imaging for IGRT. This initial tumor volume was treated to 36 Gy in 1.8 Gy per fraction. The post-induction chemotherapy tumor volume (red) was defined on the T1 post-contrast MRI sequence obtained after 9 weeks of chemotherapy (right), and similar CTV margins were used to create the post-induction chemotherapy CTV (dark red). Because the tumor was locally invasive, despite a good response to chemotherapy, the post-induction chemotherapy CTV is only slightly smaller than the initial CTV and is particularly reduced in size where the initial tumor was pushing rather than invasive, such as into the orbit, and all sites of initial gross tumor volume remained covered. Where the post-induction chemotherapy CTV is not shown, it is the same as the preinduction chemotherapy CTV. This volume received an additional 14.4 Gy in 1.8 Gy per fraction to bring the cumulative total dose to 50.4 Gy

Table 15.3 Pediatric head and neck organs at risk dose recommendations

Organ	Volume (%)	Dose (Gy)
Lens[a]	100%	14.4
Spinal cord	Any volume	45
Optic nerve[a]	100%	54
Optic chiasm	100%	54
Lacrimal glands/cornea[a]	100%	41.4
Cochlea[a]	100%	40
Eye[a]	100%	45

Adapted from the Children's Oncology Group (COG) ARST1431 protocol

[a]Denotes a bilateral organ in which both are included in the %

15.2.12 Outcomes

- Long-term failure-free survival for low- and intermediate-risk RMS using multimodality therapy is 85% and 65%, respectively [2].
- Orbital primaries have 98% and 90% rates of local control and overall survival, respectively [13].

- Non-parameningeal head and neck primaries have 90% and 80% rates of local control and overall survival, respectively [2].
- Parameningeal head and neck primaries generally fare the worst with 85% and 75% rates of local control and overall survival, respectively [12].

15.3 Ewing Sarcoma

15.3.1 Background

- Ewing sarcoma (EWS) accounts for 200 cases of childhood cancer in the USA each year, comprising the second most common pediatric bone tumor following osteosarcoma [1].
- EWS can present with osseous or extraosseous involvement.
- Primary EWS of the head and neck region is extremely rare.
- Skull-based EWS comprises 2% of all osseous primaries. Extraosseous EWS of the head and neck accounts for 18% of all extraosseous primaries [18].

15.3.2 Histology and Cellular Classification

- The Ewing family of tumors include Ewing sarcoma and primary neuroectodermal tumors (PNET). Both EWS and PNET are small round blue cell tumors and are treated in the same manner.
- Presence of the translocation involving the EWSR1 gene on chromosome 22 band q12 and any number of partner chromosomes is the hallmark feature in the diagnosis of EWS [19].
- 95% of EWS stain positive for CD99 [20].

15.3.3 Prognosis

- There is no official staging system for EWS, but prognostic factors include size, age, gender, elevated LDH levels [21], presence of metastases [22], site [23], and poor response to chemotherapy [24].

15.3.4 Anatomy and Patterns of Spread

- Common skeletal EWS primary sites of the head and neck include the calvarium, maxilla, and mandible.
- Extraskeletal EWS primary sites of the head and neck may include the paranasal sinuses, oral cavity, and soft tissue of the neck.
- Patients with extraskeletal primary EWS are more likely to have lymph node involvement as compared to patients with skeletal primary EWS.

- The incidence of regional lymph node involvement has been estimated at 12% versus 3% for patient with extraskeletal and skeletal EWS primary sites, respectively [25].

15.3.5 Imaging for Radiotherapy Volume Definition

- At initial presentation, the patient should undergo imaging with a CT with IV contrast, MR of the head and neck region, and bone scan. In addition, PET/CT may be a valuable staging study in Ewing sarcoma for detecting lymph node involvement and metastatic disease and can modify treatment strategy and planning.
- EWS enhances on MR T1 imaging.
- At the completion of induction chemotherapy, the patient should be restaged in a similar manner as was performed at initial presentation. These may be important studies for guiding delineation of boost volumes, if utilized.

15.3.6 Assessment of Lymph Node Status

- Patients with clinically or radiographically suspicious-appearing lymph nodes should preferably undergo open biopsy or, in certain situations, needle biopsy or fine needle aspiration. Elective nodal sampling is generally not recommended.

15.3.7 Indications for Radiotherapy

- Although surgery is the preferred local therapy in patients with Ewing sarcoma, approximately 35% of patients receive radiotherapy as definitive or adjuvant treatment. Local control should aim to eradicate local tumor while best preserving function.
- Local control takes place at week 13, after recovery from the sixth cycle of induction chemotherapy. Timing is the same for definitive or preoperative radiotherapy.
- Radiotherapy is delivered concurrently with consolidation chemotherapy. Adriamycin is held during radiotherapy.
- Definitive radiotherapy may be required for skull-based or facial bone primaries where functional impairment by surgery would be high, but consultation with a surgical oncologist or neurosurgeon experienced in tumors of these sites should be made.
- Preoperative radiotherapy may be given if it is felt to help achieve negative margins with surgical resection. Surgery is generally pursued within 2 weeks of completion of radiotherapy.
- If adjuvant radiotherapy is given, as is the case of microscopic close or residual margins, gross residual disease, or intraoperative tumor spillage, it is scheduled as soon as recovery from surgery permits. It can also be considered in cases of poor tumor response [26].

15.3.8 Simulation

- Please refer to Sect. 2.9 for a discussion of simulation.

15.3.9 Target Volume Delineation

- All radiotherapy volumes will initially target the pre-chemotherapy extent of bone and/or soft tissue disease; thus, fusion of CT simulation imaging with imaging studies at presentation including CT with IV contrast (± bone window) and MR T1 post-contrast-/T2-weighted imaging is imperative. Fusion with PET, if available, can also be helpful. Fusion may be limited by differences in neck extension.
- If the tumor has responded to chemotherapy and the normal tissues have returned to their normal positions, the GTV1 excludes the soft tissue volume that extends into the cavity.
- CTV = GTV + 1 cm but does not extend outside patient and is modified to account for specific anatomic barriers to tumor spread.
- In the case of clinically or pathologically involved lymph nodes, the entire cervical chain should be included in the CTV1. In general, elective nodal irradiation is not recommended.
- In the case of bone involvement, radiotherapy targeting the tumor plus a margin is recommended (i.e., radiotherapy to the entire bone is not necessary).
- GTV2, when implemented, includes delineation of the pre-chemotherapy extent of bone and post-chemotherapy extent of soft tissue disease.
- In the case of an EWS extraosseous head and neck primary with a complete response to chemotherapy or following gross total resection, there will only be a single GTV.
- See Table 15.4 for radiotherapy dosing and target volumes.
- An example of EWS of the nasal cavity (Figure 15.4) is shown.

Table 15.4 Ewing sarcoma radiation dose guidelines

Tumor site/presentation	Clinical tumor volume (CTV1)	Clinical tumor volume (CTV2)
Definitive radiotherapy[a]	45Gy	10.8Gy
Pre-op radiotherapy[a]	36Gy	
Definitive radiotherapy to chain of resected lymph node	50.4Gy	
Post-op radiotherapy—microscopic residual, >90% necrosis		50.4Gy
Post-op radiotherapy—microscopic residual, <90% necrosis	50.4Gy	
Post-op radiotherapy—gross residual	45Gy	10.8Gy

Adapted from the Children's Oncology Group (COG) AEWS1031 protocol
[a]Applies to primary and involved lymph node sites

15.3.10 Treatment Planning

- Please refer to Sect. 2.11 for a discussion of treatment planning.
- Relevant OARs include the spinal cord, optic chiasm, optic nerves, lens/cornea, and cochlea. Normal tissue constraints for head and neck OARs can be found by references such as QUANTEC [17]. See Table 15.3 for a representative set of dose constraint guidelines included in national cooperative group protocols.

15.3.11 Outcomes

- Long-term event-free survival and overall survival for nonmetastatic EWS are 75% and 90%, respectively, and are similar for outcomes for EWS of the head and neck region [27].

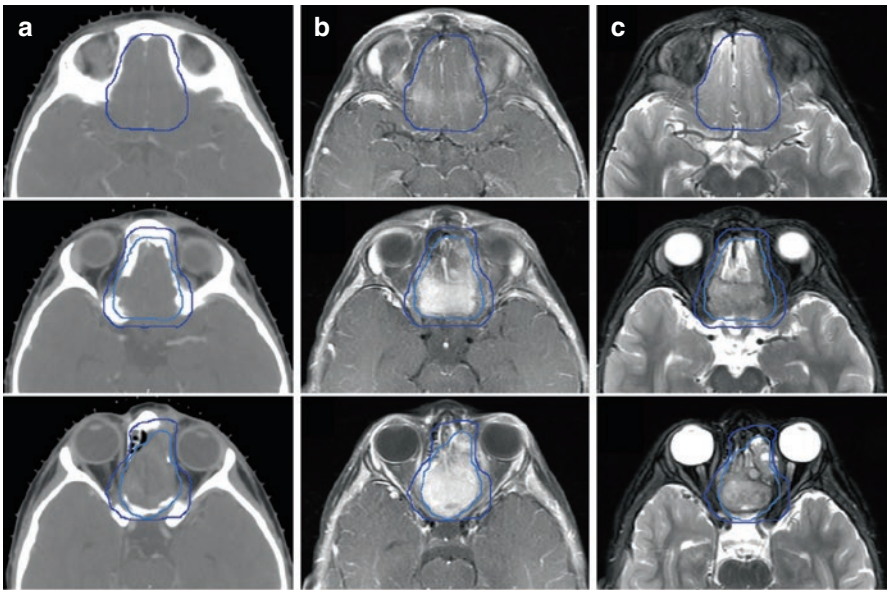

Fig. 15.4 Axial CT simulation planning images (column **a**) and corresponding pre-chemotherapy MR T1 post-contrast and T2 imaging (columns **b** and **c**, respectively) for a patient with an extraosseous Ewing sarcoma of the nasal cavity status post chemotherapy and gross total resection. MR T1 post-contrast and T2 imaging was fused with CT planning images. Note that planning accuracy can be limited by the quality of fusion between components. The initial tumor involved the nasal cavity and bilateral ethmoid air cells, bilateral sphenoid sinuses, bilateral orbit, and left maxillary sinus. There was also intracranial extension with involvement of the dura. The extent of soft tissue tumor on pretreatment T1/T2 imaging is delineated to form GTV (light blue) and CTV1 (dark blue), excluding tissue that returned to normal after treatment. Given gross total resection, there was only a single GTV treated to a total dose of 50.4Gy (RBE). Please note that the CTV to PTV margins depend on patient- and institution-dependent factors, and therefore recommendations for uniform expansions cannot be made. In the case of treatment with proton therapy, no PTV margin is applied. Please note that these are representative slices and not all slices have been included

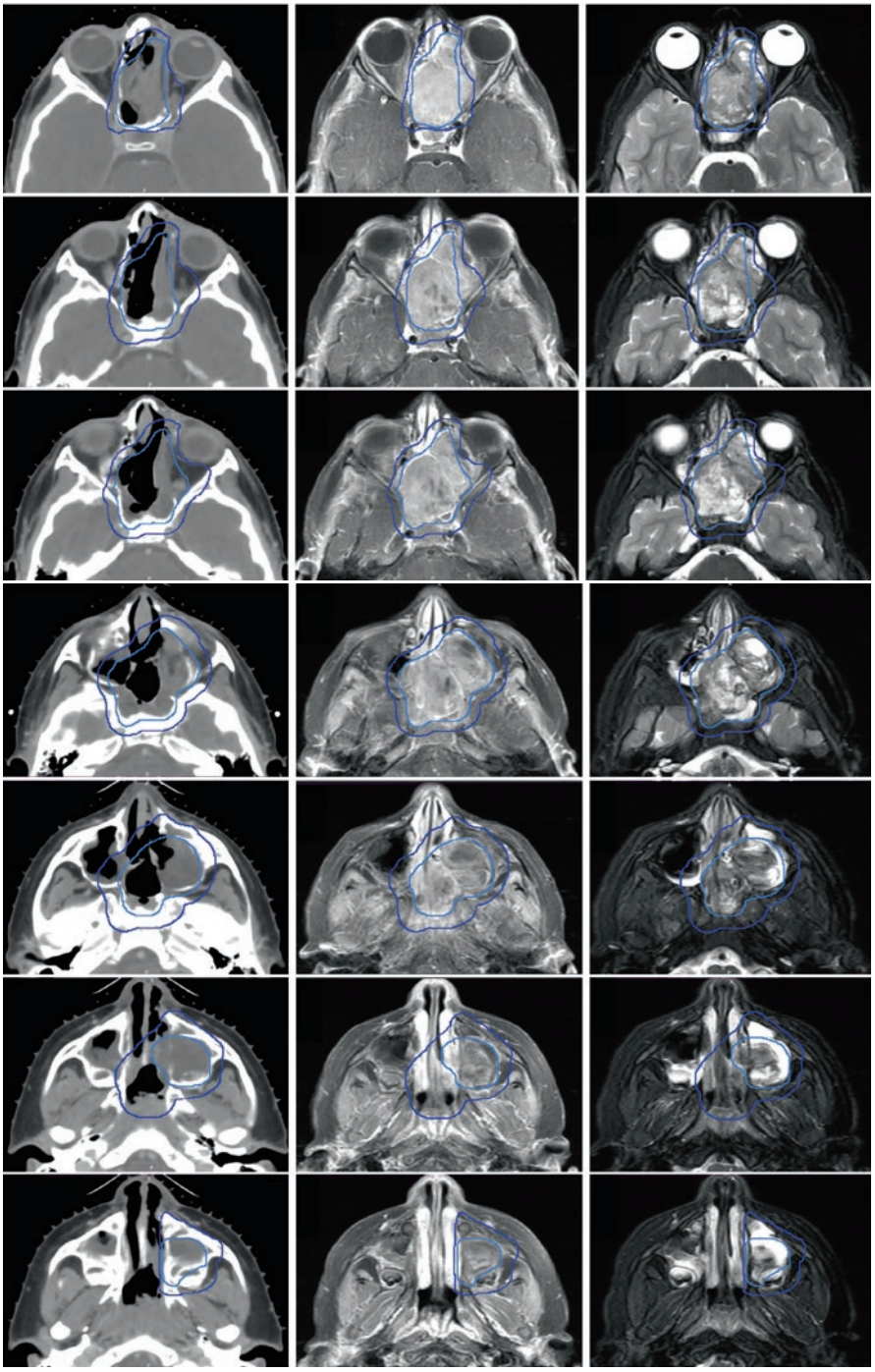

Fig. 15.4 (continued)

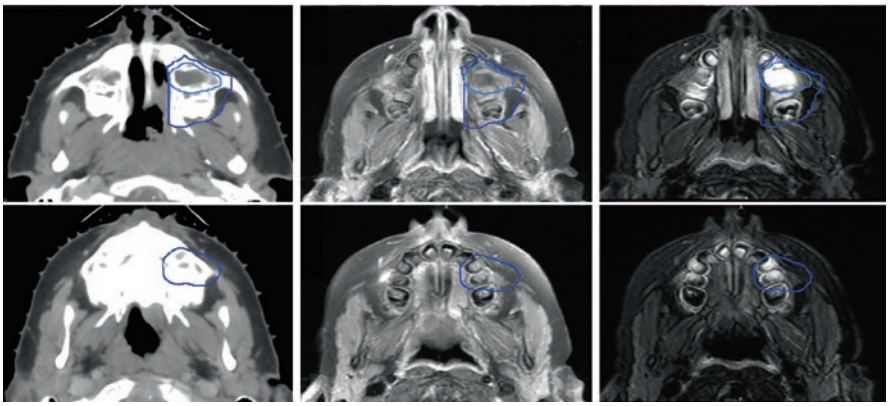

Fig. 15.4 (continued)

15.4 Salivary Gland Tumors

15.4.1 Background

- Malignant salivary gland tumors are rare in the pediatric population, comprising approximately 10% of all pediatric head and neck neoplasms [28, 29].
- The majority of salivary gland tumors are located in the parotid gland with approximately 15% occurring in the submandibular gland or minor salivary glands.

15.4.2 Histology

- The most common histology for malignant salivary gland tumors in children is mucoepidermoid carcinoma followed by acinic cell carcinoma and adenoid cystic carcinoma [29].
- Pleomorphic adenoma is a common benign salivary gland tumor.

15.4.3 Anatomy and Patterns of Spread

- Salivary gland tumors carry a high risk for metastasis to the cervical lymph node chain. Lymph node involvement at diagnosis is present in approximately 25–40% of patients and varies with location and histology; the highest rates are typically seen for mucoepidermoid carcinoma and parotid gland primary site [29, 30].
- Salivary gland tumors also commonly demonstrate perineural involvement and may spread along cranial nerves to the base of the skull.

15.4.4 Imaging for Radiotherapy Volume Definition

- CT with contrast is essential for anatomical imaging of the primary tumor.
- PET/CT and MRI provide additional value if local regional and systemic staging and evaluation of perineural tumor spread.

15.4.5 Treatment Strategy

- The primary treatment for salivary gland tumors is surgical resection and selective neck dissection under the care of a head and neck surgeon.
- Adjuvant radiation therapy is indicated for high-risk features such as positive surgical margins, perineural invasion, lymphovascular space invasion, advanced tumor stage, high-grade histology, and the presence of lymph node metastases as adjuvant radiation has been demonstrated to significantly improve local control for patients with these features [29, 30].
- Elective nodal irradiation, as a component of adjuvant therapy even for those with pathologically negative lymph nodes, has been demonstrated to reduce the risk of nodal relapse for patients with advanced T-stage disease and high-grade histologies such as mucoepidermoid carcinoma, squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma [31].

15.4.6 Simulation

- Please refer to Sect. 2.8 for a discussion of simulation.

15.4.7 Target Volume Delineation

- Fusion of the preoperative diagnostic CT, PET, and/or MRI to the CT simulation for identification of the preoperative tumor volume and any clinically involved lymph nodes prior to surgery is recommended.
- The GTV should include the gross tumor volume as defined on preoperative imaging that is confined to the operative bed and excludes normal tissues that may have shifted during surgery.
- The CTV should include the GTV with a 1 cm anatomically confined margin limited by anatomical barriers of spread and not extending outside of the patient but including the entire operative bed, cervical lymph node regions pathologically involved, and sites of involved cranial nerves.
- Doses used typically follow that used in the adult population with 60 Gy in 1.8–2 Gy per day prescribed to the high-risk CTV as outlined above, while higher doses of 64.8–66 Gy are reserved for positive margins or nodal regions at sites of pathologic extranodal extension.

- A lower-dose volume prescribed to 50–56 Gy in 1.6–2 Gy per fraction should include regions of elective nodal irradiation, surgical scar, other areas adjacent to the primary tumor considered to be at risk for spread, and named cranial nerves at risk for perineural tumor spread.
- An example of adenoid cystic carcinoma of the parotid gland (Figure 15.5) is shown.
- Elective nodal irradiation (ENI):
  - For parotid primary tumors, cervical lymph node levels II–III are at greatest risk for subclinical involvement and should be targeted when elective nodal irradiation is used. Level IV is also often included in ENI for adult patients [32], though risk of isolated nodal relapse in level IV is low [31], and so the risk of the added morbidity of extending the volume in young children should be weighed in consideration of the patients' unique disease characteristics. Level Ib, IV, and V and the retrostyloid space should be considered for inclusion in ENI target volumes in patients who are lymph node positive.
  - For submandibular or sublingual primary tumors, lymph node regions at risk are levels IB–III (± IV per above) with inclusion of the contralateral level I if the ipsilateral level I is involved and the retrostyloid space in lymph node positive patients.
  - Contouring guidelines for CTV definition of LN volumes can be found in the following references [33, 34].
- Perineural Coverage
  - Elective perineural coverage is recommended when there is gross involvement of a named cranial nerve and may also be of benefit in patients' microscopic perineural tumor spread and/or for tumors with high risk of perineural spread such as adenoid cystic carcinoma.
  - Contouring guidelines for CTV definition of nerves at risk for perineural tumor spread can be found in the following references [34, 35].
  - For tumors of the parotid gland, perineural tumor coverage should include the facial nerve to the stylomastoid foramen or through the petrous portion of the temporal bone if known to be involved. There is also risk for spread along the auriculotemporal nerve (a branch of V_3).
  - For tumors of the submandibular gland, perineural tumor spread may occur along the lingual nerve (branch of V3), the chorda tympani of the facial nerve (which eventually joins V3), or the hypoglossal nerve.

15.4.8 Treatment Planning

- Conformal radiotherapy techniques, including 3D conformal photon therapy, IMRT/VMAT, or proton therapy, may be used.
- For parotid bed treatment without elective nodal irradiation or perineural tumor coverage, a 3D conformal wedge pair technique may provide adequate conformality, though the use of more advanced techniques such as IMRT, VMAT, or protons is recommended in most clinical scenarios.
- Please refer to Sect. 2.11 for a detailed discussion of treatment planning.

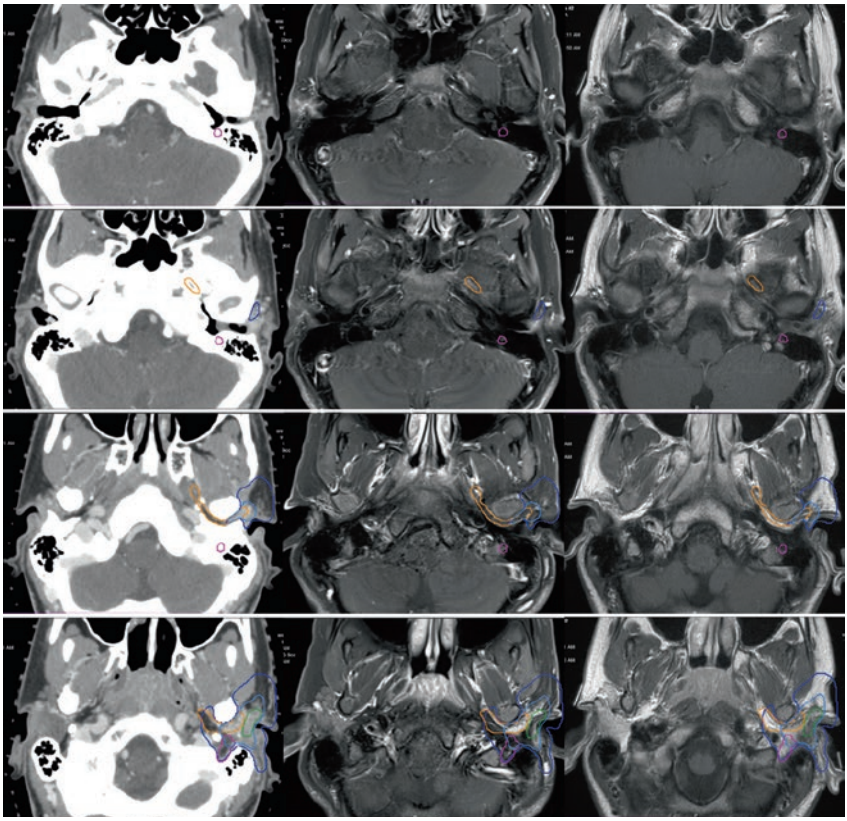

Fig. 15.5 Axial CT simulation with contrast (left) and treatment planning MRI T1 with contrast (middle) and T2-weighted (right) sequences for a teenager undergoing adjuvant radiation therapy for a resected adenoid cystic carcinoma of the parotid gland. At the time of surgery, there was evidence of close margins at less than 1 mm and no lymph node involvement. No high-quality preoperative imaging was available for treatment planning purposes, so postoperative imaging was utilized. The GTV (light blue) is defined as the residual soft tissue and the parotid bed. The CTV (dark blue) is defined by a 1 cm anatomically confined margin. In this case, there was no elective nodal irradiation, but because adenoid cystic histology has a propensity for perineural spread, cranial nerves at risk for perineural spread were included in the initial target volume. The facial nerve (fuschia) is contoured from the petrous portion of the temporal bone through the stylomastoid foramen and into the parotid bed. The mandibular nerve is contoured from the foramen ovale, coursing between the lateral and medial pterygoid muscles, behind the condyle of the mandible and into the parotid bed. The greater auricular nerve (green), which arises from the C2/C3 cervical roots to course around the sternocleidomastoid muscle and arises along the surface of the SCM beneath the platysma to innervate the parotid gland and the overlying skin, is also illustrated within the parotid bed. In this case, the cranial nerves and parotid bed CTV (dark blue) were treated to a dose of 54Gy (RBE) in 1.8Gy per fraction, and then the parotid bed CTV was treated to an additional 10.8Gy (RBE) to bring the cumulative dose to 64.8Gy (RBE), all using 3D conformal passively scattered proton therapy

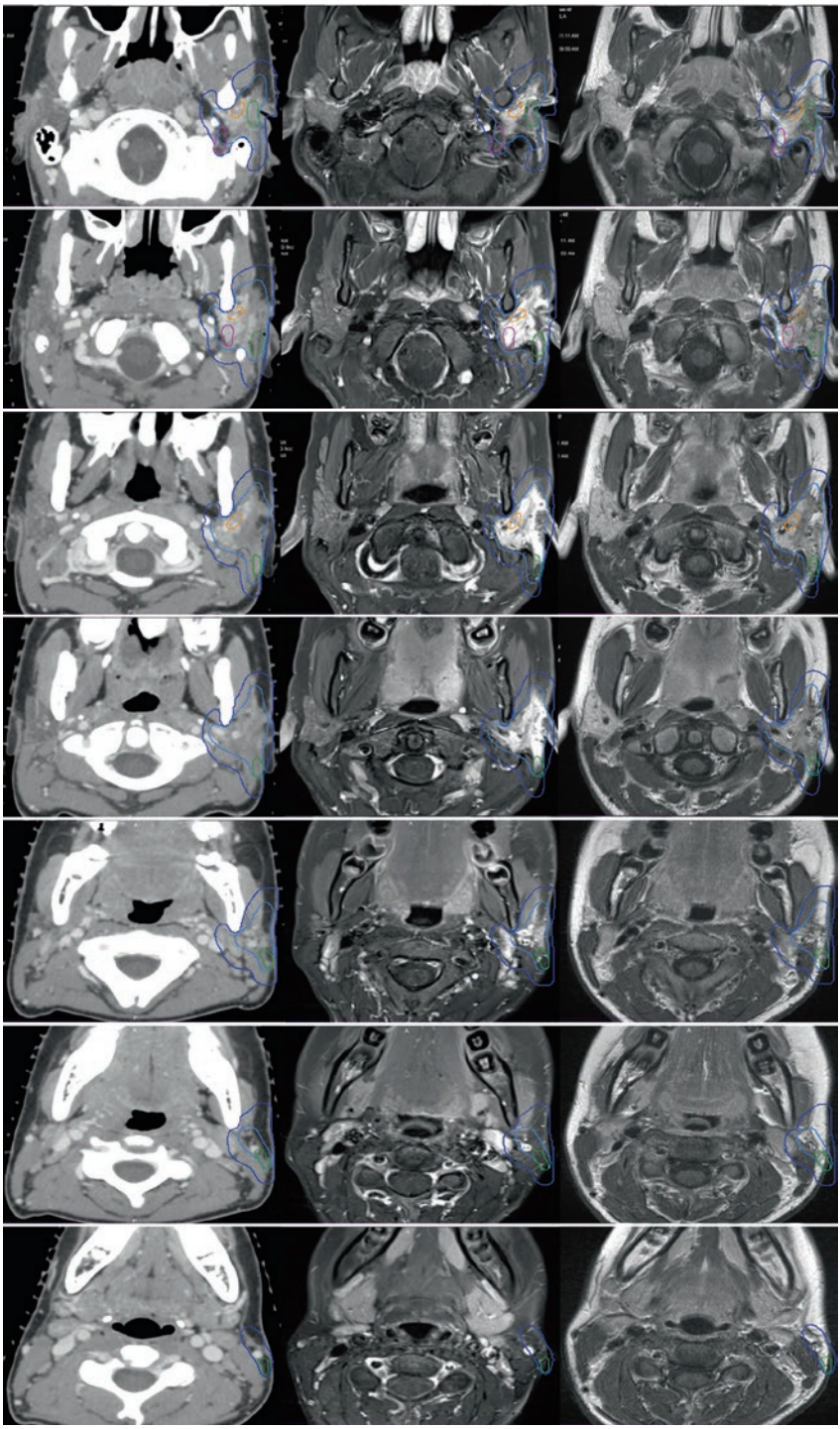

Fig. 15.5 (continued)

15.4.9 Outcomes

- The prognosis for children with salivary gland tumors treated with surgical resection and adjuvant therapy as indicated is good, with reported overall survival rates of 95% at 10 years and greater than 80% at 20 years [29, 36].

15.5 Juvenile Nasopharyngeal Angiofibroma

15.5.1 Background

- Juvenile nasopharyngeal angiofibroma (JNA) is a rare, benign, highly vascularized tumor, which accounts for less than 0.5% of head and neck tumors [37].
- JNA almost exclusively presents in adolescent males and includes symptoms such as nasal obstruction, recurrent epistaxis, and a mass in the roof of the nasopharynx.
- JNA can be locally aggressive and associated with significant morbidity and occasional mortality due to intracranial extension and hemorrhage [38].
- Extranasopharyngeal angiofibroma is extremely rare, occurring more often in older females, and tends to be less vascular and aggressive than JNA [39].

15.5.2 Histology

- JNA is a histologically benign vascular malformation, usually encapsulated and composed of vascular tissue and fibrous stroma.
- JNA is comprised of vessels that are thin walled, lack elastic fibers, and have absent or incomplete smooth muscle, which are prone to hemorrhage.

15.5.3 Staging

- Staging takes into account extension outside of the nasopharynx and involvement of paranasal cavities and the base of skull structures (Table 15.5; [38]).

Table 15.5 Current staging system for juvenile nasopharyngeal angiofibroma (JNA)

Stage IA	Limited to nasal cavity or nasopharynx
Stage IB	Extension to at least one paranasal sinus
Stage IIA	Minimal extension into the sphenopalatine foramen or medial pterygomaxillary fossa
Stage IIB	Full occupation of the pterygomaxillary fossa, lateral or anterior displacement of maxillary artery branches with or without superior erosion of orbital bones
Stage IIC	Extension through the pterygomaxillary fossa into the cheek, temporal fossa or posterior to pterygoids
Stage IIIA	Skull base erosion with minimal intracranial extension
Stage IIIB	Skull base erosion with extensive intracranial extension ± cavernous sinus

15.5.4 Anatomy and Patterns of Spread

- JNA originates in close proximity to the posterior attachment of the middle turbinate near the superior border of the sphenopalatine foramen [40].
- Larger tumors extend beyond the nasopharynx and nasal cavities to intracranial structures by posterior and lateral routes [41].
- Intracranial extension occurs in approximately 20% of cases [41].
- The most common sites of intracranial invasion include the pituitary, anterior, and middle cranial fossa [41].
- Four routes by which intracranial extension occurs have been described and include [42, 43]:
  - Extension from the infratemporal fossa through the floor of the middle cranial fossa
  - Extension from the pterygomaxillary fissure and infratemporal fossa into the superior and inferior orbital fissures, where proptosis and optic nerve atrophy may occur
  - Direct erosion of the sphenoid sinus into the region of the sella turcica and cavernous sinus
  - Rarely, extension from the horizontal lamina of the ethmoids and cribriform plate into the anterior cranial fossa
- The base of the skull is the most frequent site of recurrence [38].

15.5.5 Imaging for Radiotherapy Volume Delineation

- At initial presentation, and following a through history and physical exam focusing on symptoms and cranial nerve deficits, the patient should undergo imaging with CT with IV contrast to identify the presence and extent of bone destruction.
- An MRI with and without contrast with T1 and T2 sequences should be performed to identify the tumor relationship to adjacent soft tissue structures, including the orbits, optic nerves, pterygomaxillary space, buccal and masticator space, carotid arteries, and anterior cranial fossa.
- A biopsy should be avoided unless there is evidence to question a diagnosis of JNA.

15.5.6 Treatment Strategy

- Surgery paired with preoperative embolization is the preferred management of JNA [44].
- There are a variety of surgical approaches available depending on the size and the extent of tumor involvement. An endoscopic approach is preferred for uncomplicated, noninvasive tumors [44, 45].
- Involvement of the base of the skull or intracranial structures may make gross total resection challenging and cause potential morbidity and mortality [41].

- Radiotherapy is a viable treatment strategy for patients who undergo subtotal resection or in the recurrent setting [41, 46, 47].
- Nontraditional treatment approaches include chemotherapy and hormonal manipulation and may be less efficacious than primary surgery or radiotherapy [48, 49].

15.5.7 Indications for Radiotherapy

- Radiotherapy as the primary treatment modality for advanced JNA has resulted in high rates of local control [41, 46, 50].
- Definitive radiotherapy doses have ranged from 30 to 46 Gy in recent series [46, 50].

15.5.8 Simulation

- Please refer to Sect. 2.9 for a discussion of simulation.

15.5.9 Target Volume Delineation

- If surgical resection was performed, radiotherapy volumes will be targeting the extent of disease prior to resection; thus, fusion of CT simulation imaging with imaging studies at presentation including a CT with IV contrast and MR T1 post-contrast-/T2-weighted imaging is imperative for the delineation of the initial gross tumor volume (GTV). Fusion may be limited by differences in neck extension.
- If the normal tissues have returned to their normal positions, the GTV excludes the volume that extends into the normal tissue or cavity. The GTV must include all infiltrative disease detected at initial presentation.
- While there is no agreed upon CTV margins available, given the benign nature of JNA, the clinical tumor volume (CTV) may be reduced to <1 cm, especially around critical structures. The CTV does not extend outside the patient and is anatomically constrained by structures that serve as a barrier to spread (i.e., uninvolved bone), and thus, smaller margins may be used in head and neck primary sites. If an operative bed is present, the CTV will include the entire operative bed.
- Elective nodal irradiation is not necessary.
- Examples of target volume delineation for a large advanced JNA are shown (Figure 15.6)

15.5.10 Treatment Planning

- Please refer to Sect. 2.11 for a discussion of treatment planning.

- In the case of radiotherapy, IMRT or proton beam therapy is preferred in order to maximize target coverage while decreasing dose to surrounding normal tissue [50].
- Relevant OARs include the spinal cord, optic chiasm, optic nerves, lens/cornea, cochlea, hypothalamus, pituitary gland, temporal lobes, and oral cavity. Additional structures contoured as OARs will depend on extent of disease. Normal tissues constraints for head and neck OARs can be found by references such as QUANTEC [17].

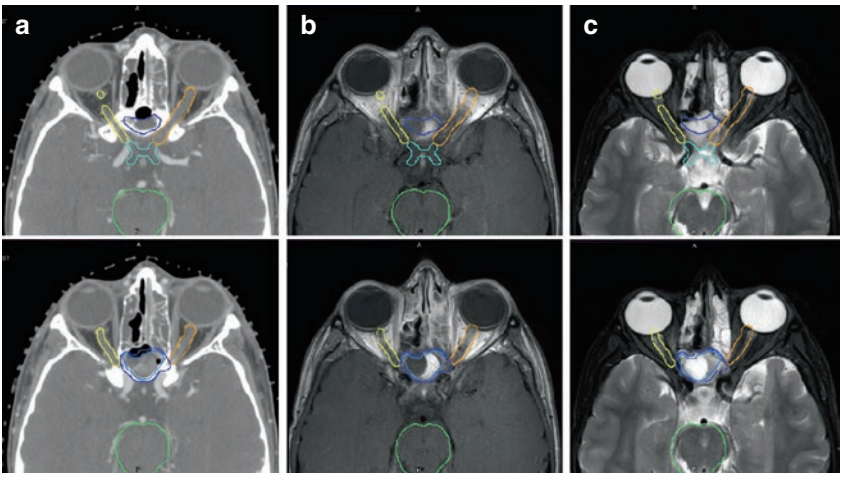

Fig. 15.6 Axial CT simulation planning images (column **a**) and corresponding pre-chemotherapy MR T1 post-contrast and T2 imaging (columns **b** and **c**, respectively) for a teenager with a large juvenile nasopharyngeal angiofibroma stage IIIA status post presurgical embolization and subtotal resection. Presurgical MR T1 post-contrast along with MR T2 imaging was fused with CT planning images. Note that planning accuracy can be limited by the quality of fusion between components. The initial tumor involved the nasopharynx and extended into the left nasal cavity, maxillary and sphenoid sinuses, as well as the left pterygopalatine fossa via the sphenopalatine foramen. There was an extension through the pharyngobasilar fascia to the left foramen lacerum and evidence of erosion of the anterior aspects of the base of skull with extension to the cavernous sinus and left vidian canal. Additionally, there was extension to the sphenoid sinus and floor of the sella turcica. There was post-obstructive opacification of much of the left paranasal cavities. Only subtotal resection was performed given proximity to the internal carotid artery. The extent of tumor on presurgery T1/T2 imaging is delineated to form GTV1 (light blue) and CTV1 (dark blue). The CTV1 was drawn on each slice to consider anatomic constraints, to avoid primarily inflammatory changes. CTV1 also includes the initial extension to the left pterygopalatine fossa. In this case, CTV1 was treated to a total of 41.4Gy (RBE) using passively scattered protons given the large tumor size, multiple treatment interruptions, and severity of bleeding. Given the treatment response and changes in tumor volume which can affect proton dosimetry at the soft tissue-air interface, the patient was re-simulated and replanned at several intervals during treatment. Please note that the CTV to PTV margins depend on patient- and institution-dependent factors, and therefore, recommendations for uniform expansions cannot be made. In the case of treatment with proton therapy, no PTV margin is applied. Please note that these are representative slices and not all slices have been included

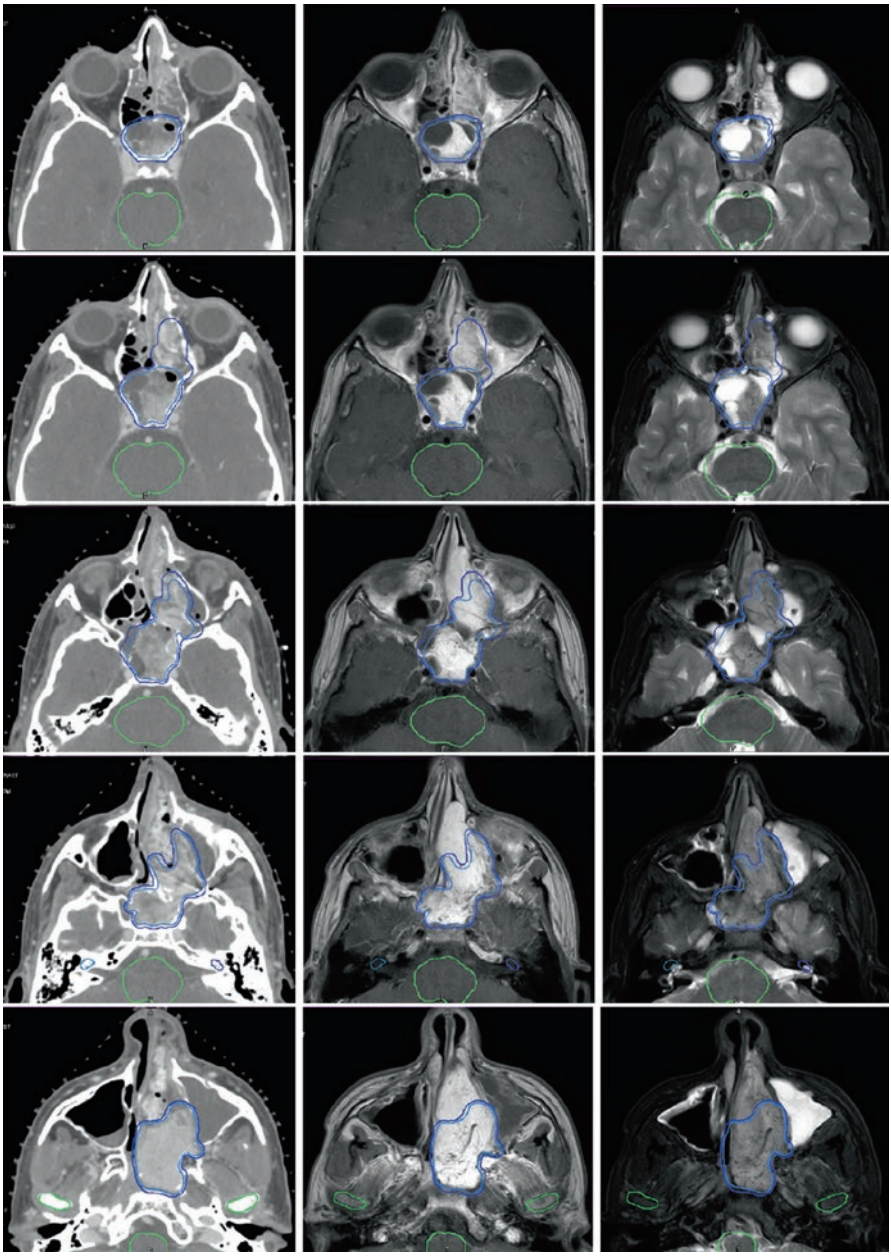

Fig. 15.6 (continued)

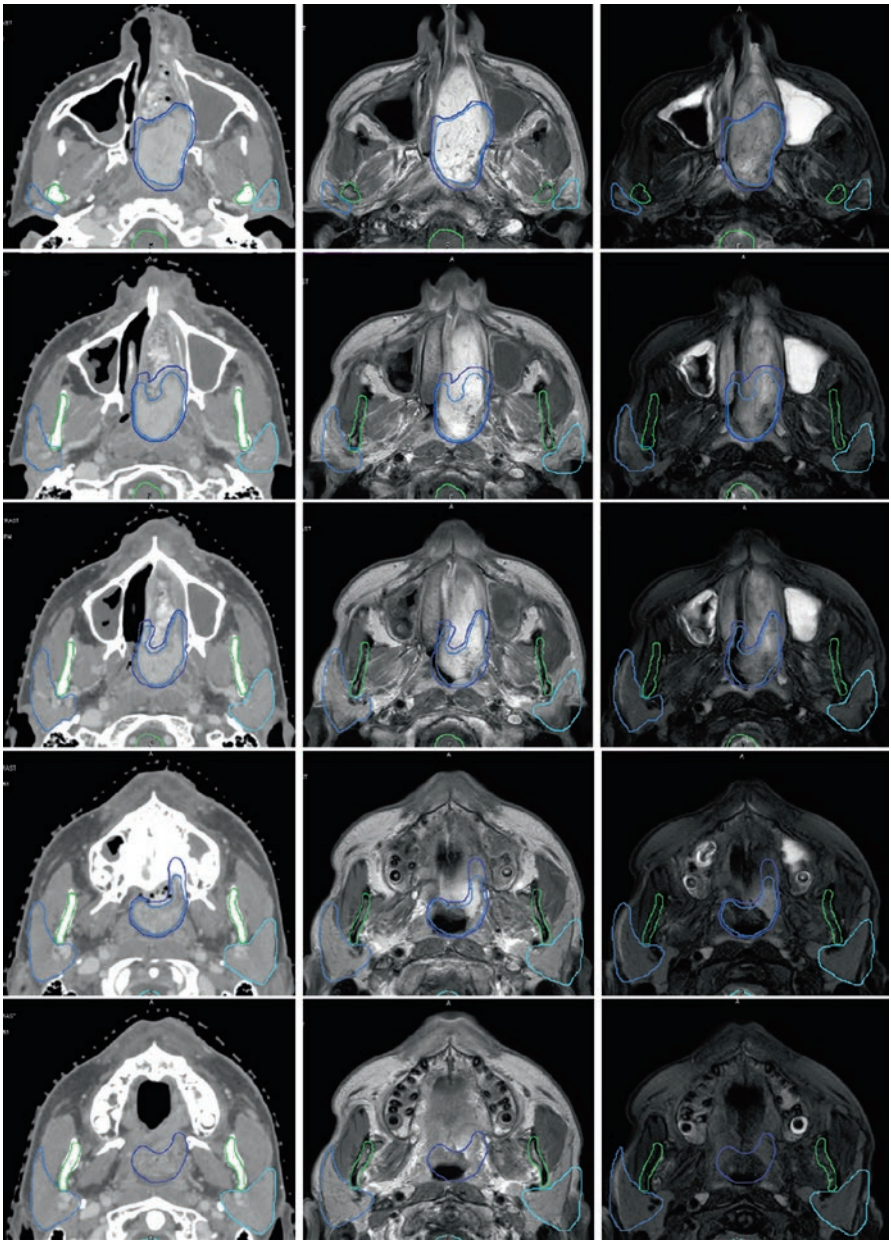

Fig. 15.6 (continued)

15.5.11 Outcomes

- Patients undergoing primary surgical resection alone achieve a disease-free rate of approximately 85–90% [51, 52].
- Similar control rates have been seen in patients treated with primary radiotherapy [41, 46, 50].

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