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

Stephanie A. Terezakis
Shannon M. MacDonald *Editors*

Target Volume Delineation for Pediatric Cancers

Springer

Practical Guides in Radiation Oncology

Series Editors:
Nancy Y. Lee
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
New York, NY, USA

Jiade J. Lu
Department of Radiation Oncology
Shanghai Proton and Heavy Ion Center
Shanghai, China

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.

More information about this series at http://www.springer.com/series/13580

Stephanie A. Terezakis
Shannon M. MacDonald
Editors

Target Volume Delineation for Pediatric Cancers

Springer

Editors
Stephanie A. Terezakis
Department of Radiation Oncology
Johns Hopkins School of Medicine
Baltimore, Maryland, USA

Shannon M. MacDonald
Department of Radiation Oncology
Massachusetts General Hospital
Harvard University - Medical School
Boston, Massachusetts, USA

ISSN 2522-5715 ISSN 2522-5723 (electronic)
Practical Guides in Radiation Oncology
ISBN 978-3-319-69139-8 ISBN 978-3-319-69140-4 (eBook)
https://doi.org/10.1007/978-3-319-69140-4

Library of Congress Control Number: 2018930342

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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.

Baltimore, MD, USA — Stephanie A. Terezakis
Boston, MA, USA — Shannon M. MacDonald

Contents

Central Nervous System Normal Structures

1

Barbara Fullerton and Shannon M. MacDonald

Contents

B. Fullerton
Department of Otolaryngology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA

Department of Radiation Oncology, Massachusetts General Hospital, Francis H Burr Proton Therapy Center, Harvard Medical School, Boston, MA, USA
e-mail: bfullerton@mgh.harvard.edu

S. M. MacDonald (✉)
Associate Professor, Harvard Medical School, Boston, MA, USA

Department of Radiation Oncology, Massachusetts General Hospital, Francis H Burr Proton Therapy Center, Harvard Medical School, Boston, MA, USA
e-mail: smacdonald@mgh.harvard.edu

S. A. Terezakis, S. M. MacDonald (eds.), *Target Volume Delineation for Pediatric Cancers*, Practical Guides in Radiation Oncology,
https://doi.org/10.1007/978-3-319-69140-4_1

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

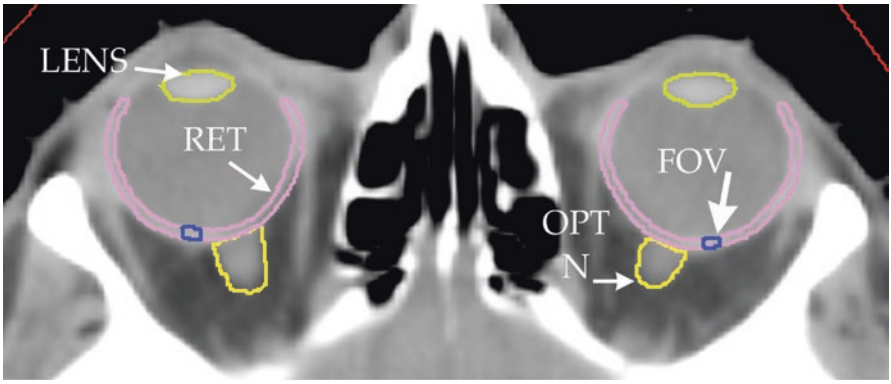


Fig. 1.1 Axial slice from a planning CT. The lens is shown as well as the retina (RET) and its fovea (FOV). The retinal contour, more easily seen in the CT than the MR scan, includes the retina, the choroid, and the sclera. The retinal layer adjacent to the vitreous chamber is too thin to be contoured 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).

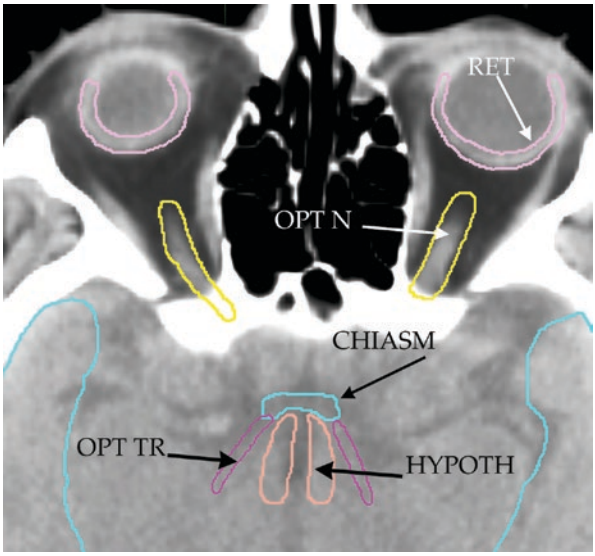


Fig. 1.2 This more inferior axial slice shows the retinas (RET) and the optic nerves (OPT N). The optic nerves are not connected to the eyes in this section and approach the sphenoid bone posterior to the orbit. Because of the angle of the CT scan, the optic nerves are also not connected to the chiasm 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)

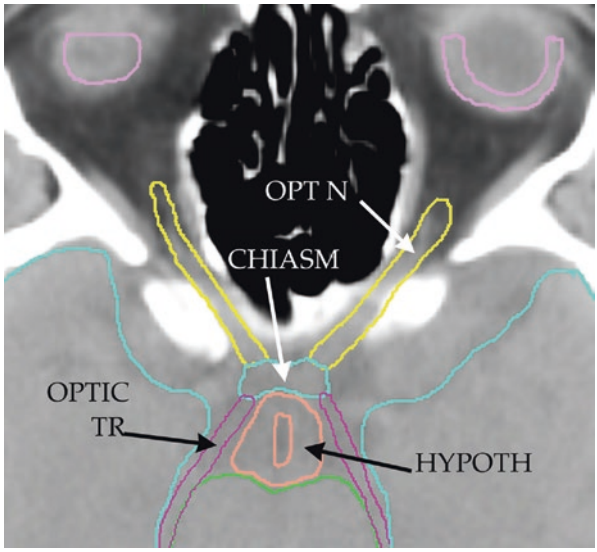


Fig. 1.3 This more inferior axial CT slice shows the optic nerves (OPT N) extending through the optic canal medial to the anterior clinoid processes to join the chiasm. The optic tracts (OPT TR) extend posteriorly from the chiasm to the lateral geniculate nucleus of the thalamus (present in the MR Fig. 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).

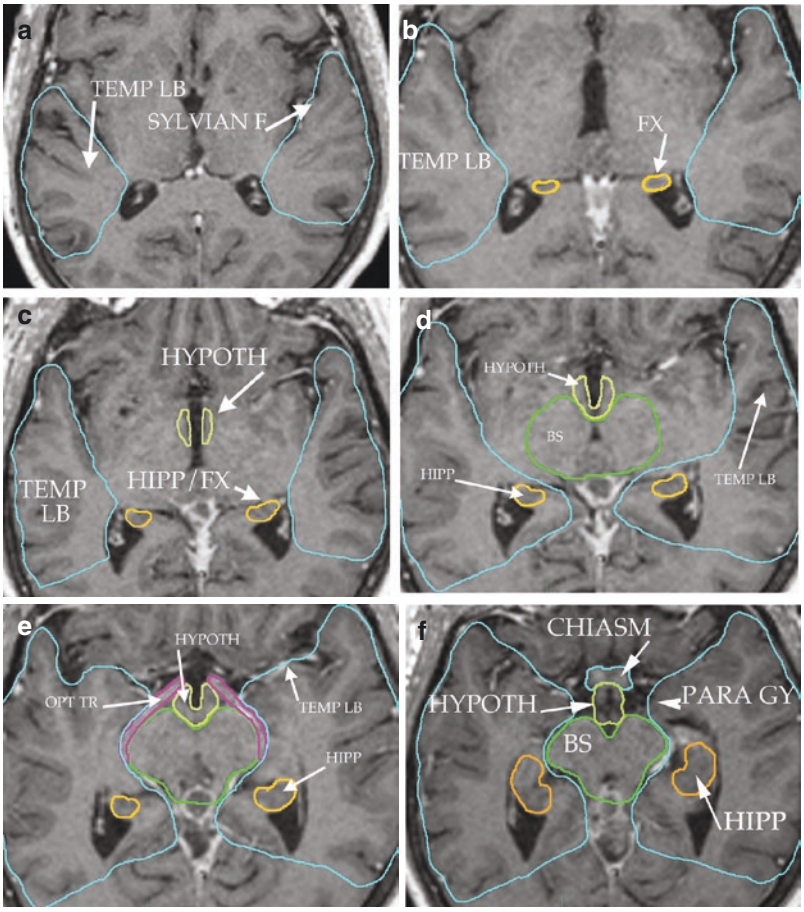
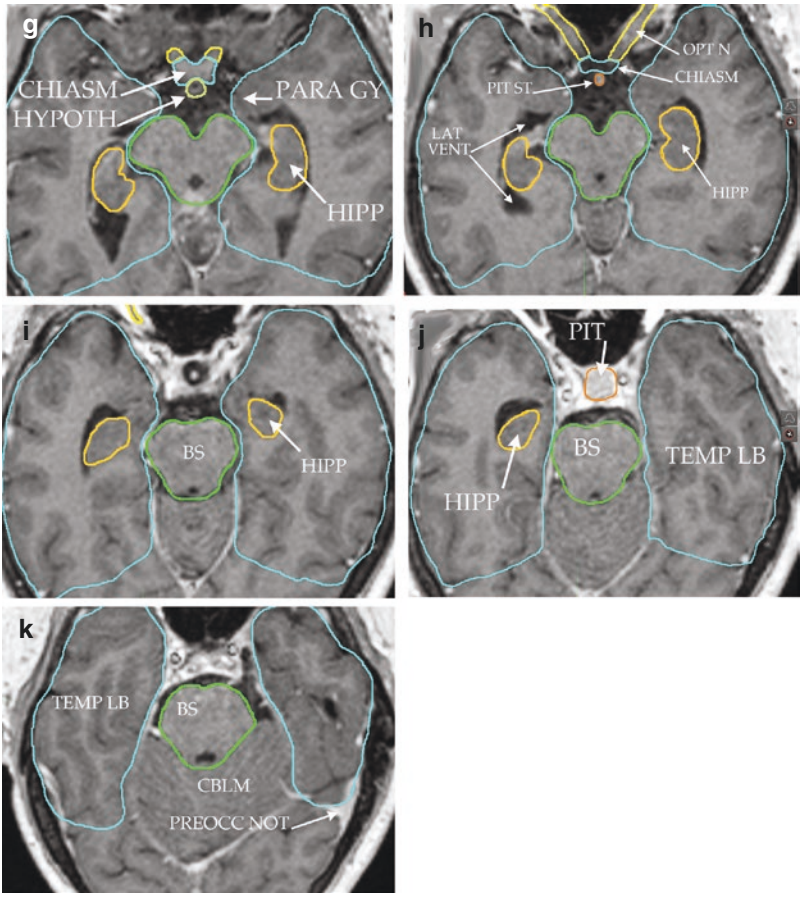


Fig. 1.4 (**a**–**d**) This MR axial series of images was included because many of the anatomical structures are not easily visible in the CT scans. This group of images extends from the superior part of the temporal lobe (**a**) to the inferior part of the temporal lobe where it intersects with the 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

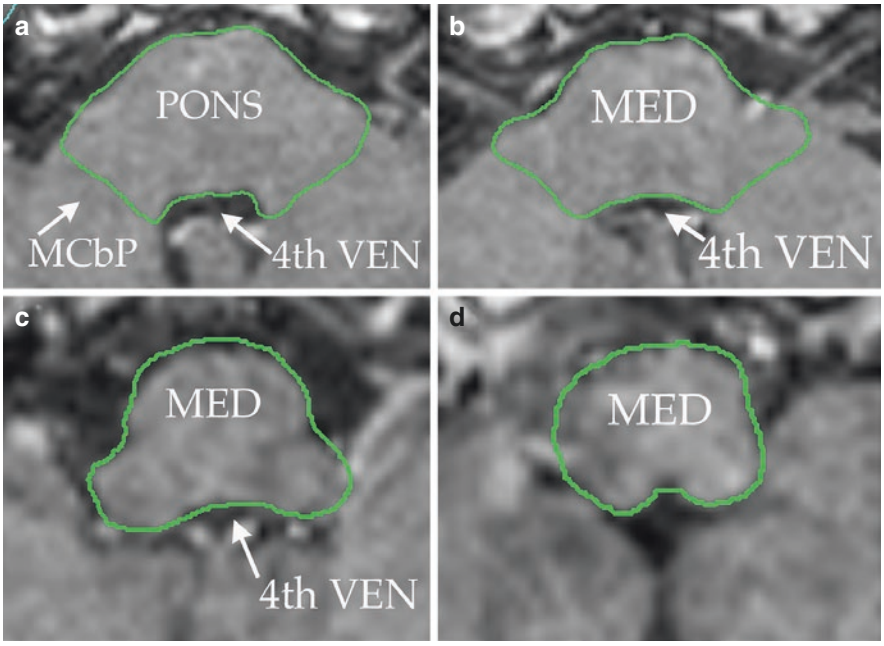


Fig. 1.5 Caudal axial brainstem images. The section in panel (**a**) is at the most caudal level of the pons. The middle cerebellar peduncle (MCbP) forms a large fiber bundle connecting the brainstem to the cerebellum. The fourth ventricle passes over the dorsal surface of the brainstem in panels (**a**, **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

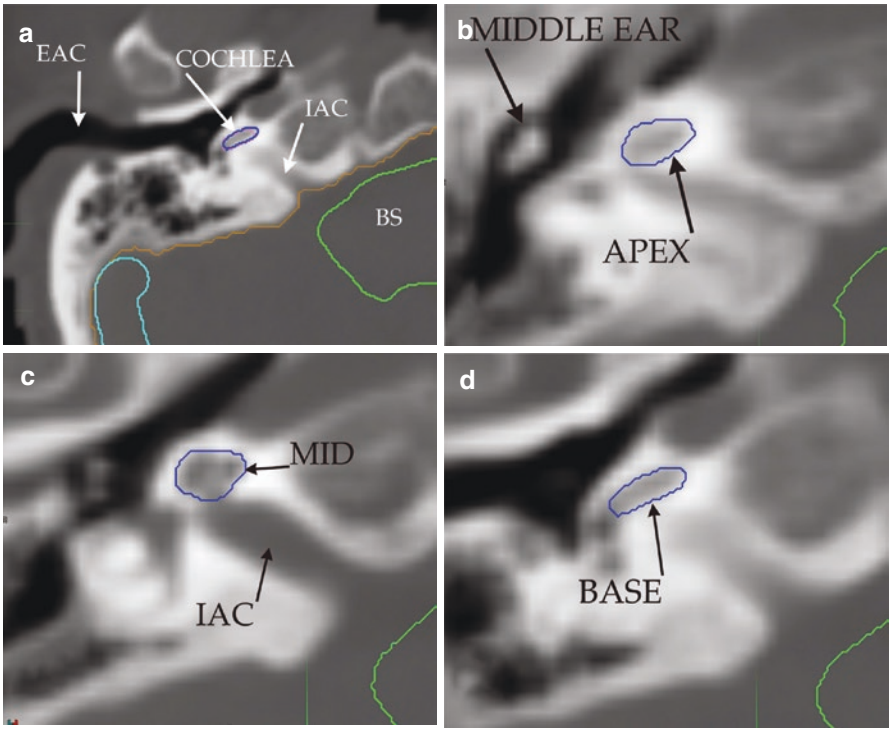


Fig. 1.6 Temporal bone and cochlea. Panel (**a**) shows the overview of the temporal bone in a bone-window axial CT image. The external auditory canal (EAC) is on the left of the image and the internal auditory canal (IAC) is on the right, adjacent to the brainstem (BS). This section is at the level 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.

References

1. Gordon KB, Char DH, Sagerman RH (1995) Late effects of radiation on the eye and ocular adnexa. Int J Radiat Oncol Biol Phys 31:1123–1139
2. Parsons JT, Bova FJ, Fitzgerald CR et al (1994) Radiation retinopathy after external-beam irradiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 30:765–773
3. Monroe AT, Bhandare N, Morris CG et al (2005) Preventing radiation retinopathy with hyperfractionation. Int J Radiat Oncol Biol Phys 61:856–864
4. Constine LS, Woolf PD, Cann D et al (1993) Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 328:87–94
5. Merchant TE, Rose SR, Bosley C et al (2011) Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. J Clin Oncol 29:4776–4780
6. Redmond KJ, Mahone EM, Terezakis S et al (2013) Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study. Neuro-Oncology 15:360–369
7. Indelicato DJ, Flampouri S, Rotondo RL et al (2014) Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. Acta Oncol 53:1298–1304
8. Murphy ES, Merchant TE, Wu S et al (2012) Necrosis after craniospinal irradiation: results from a prospective series of children with central nervous system embryonal tumors. Int J Radiat Oncol Biol Phys 83:e655–e660
9. Giantsoudi D, Sethi RV, Yeap BY et al (2016) Incidence of CNS injury for a cohort of 111 patients treated with proton therapy for medulloblastoma: LET and RBE associations for areas of injury. Int J Radiat Oncol Biol Phys 95:287–296
10. MacDonald SM, Laack NN, Terezakis S (2017) Humbling advances in technology: protons, brainstem necrosis, and the self-driving car. Int J Radiat Oncol Biol Phys 97:216–219
11. Hua C, Bass JK, Khan R et al (2008) Hearing loss after radiotherapy for pediatric brain tumors: effect of cochlear dose. Int J Radiat Oncol Biol Phys 72:892–899

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

N. Esiashvili
Radiation Oncology Department, Winship Cancer Institute, Emory University, Atlanta, GA, USA
e-mail: neisash@emory.edu

S. A. Terezakis, S. M. MacDonald (eds.), *Target Volume Delineation for Pediatric Cancers*, Practical Guides in Radiation Oncology,
https://doi.org/10.1007/978-3-319-69140-4_2