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

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Yao Yu *Editors*

Target Volume Delineation and Field Setup

A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy

Second Edition

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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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Editors

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ISSN 2522-5715 ISSN 2522-5723 (electronic)
Practical Guides in Radiation Oncology
ISBN 978-3-030-99589-8 ISBN 978-3-030-99590-4 (eBook)
https://doi.org/10.1007/978-3-030-99590-4

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

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Nasopharyngeal Carcinoma

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Irene Karam, Nancy Y. Lee, Quynh-Thu Le, Brian O'Sullivan, Jiade J. Lu, and Ian Poon

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_1

1.1 General Principles of Planning and Target Delineation

- Both physical examination and imaging data are required for accurate delineation of the primary tumor. A detailed endoscopic examination should be performed focusing on the anterior nasal space, nasopharynx, and oropharynx to describe the tumor extension and infiltration.
- Unless there is a contraindication (i.e. pacemaker), patients should undergo a diagnostic contrast-enhanced MRI of the nasopharynx and neck fused to the planning CT scan. Ideally, the MRI should be acquired in the treatment position with the radiation therapy immobilization device. Marrow infiltration of disease is best seen on T1-weighted non-contrast MRI sequence. MRI is critical for delineation of skull base and perineural disease.
- PET/CT should only be used as a guide for delineation of the primary site as it may underestimate or overestimate the true extent of disease, particularly at the skull base.
- PET/CT scan is extremely helpful, particularly for identifying small lymph node metastases. Simulation should be performed in the supine position with the head and neck in the neutral position with a 5-point thermoplastic mask covering from skull with or without the shoulder. The CT simulation (preferably 2–3 mm slice thickness) scan should be acquired with IV contrast typically from vertex to 2 cm below the sternoclavicular joints. In centers that prefer to treat with a beam split technique with a low anterior neck AP or AP/PA fields (N0 patients), thicker slices can be obtained in the low neck.
- EBER status should be obtained from tissue biopsies to assist in the discussion of prognosis. When possible, one can obtain EBV DNA in a CLIA or equivalent certified laboratory.
- Target volumes include gross tumor volumes (GTV) and clinical target volumes (CTV). Accurate selection and delineation of the primary tumor CTV (i.e. CTV_{70}) and subclinical region ($CTV_{54–59.4}$) are of great importance when considering tumor progression and ease of tumor spread along neural pathways and foramina in the IMRT era for NPC. For more dosing options, can refer to NRG HN001 clinical trial. See Tables 1.1 and 1.2.
- Figures 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 demonstrate several examples of target delineation for different nasopharyngeal carcinoma cases.
- For additional dosing options, can refer to NRG HN001 clinical trial or the international consensus guidelines. Sequential no SIB techniques can also be done. The subclinical regional volume can receive 50–54 Gy with a sequential boost to the gross disease of 16–20 Gy to a total dose of 70 Gy.

Table 1.1 Suggested clinical target volumes at the gross disease region

Target volumes	Definition and description
GTV_{70}[a]	**Primary**: All gross disease on physical examination and imaging. Pre-treatment imaging should be carefully scrutinized for invasion of the skull base and perineural spread **Neck**: All nodes ≥1 cm in short axis, with necrotic center; any FDG PET avid nodes; given high likelihood of nodal involvement, contour the lymph node in doubt as GTV
CTV_{70}[a]	**Primary**: $CTV_{70}p = GTV_{70}p + 3–5$ mm [Please note that, at the discretion of the treating radiation oncologist, when there is complete certainty of the $GTV_{70}p$, then $GTV_{70}p$ can be equivalent to $CTV_{70}p$ **without any margin**. Therefore, in this situation, $GTV_{70}p$ is equivalent to $CTV_{70}p$] A 0 mm margin is also acceptable if tumor is in close proximity to critical OARs (i.e. brainstem, spinal cord) If tumor is near the ipsilateral optic nerve, informed discussion of risks and benefits is required. The authors favor coverage of the tumor, sacrificing the ipsilateral optic apparatus, but strictly constraining the contralateral optic nerve and optic chiasm **Neck**: $CTV_{70}n = GTV_{70}n + 3–5$ mm For nodes that are small (i.e. ~1 cm), lower doses of 63–66 Gy may be considered at the discretion of the treating physician [Please note that, at the discretion of the treating radiation oncologist, when there is complete certainty of the $GTV_{70}n$, then $GTV_{70}n$ can be equivalent to $CTV_{70}n$ **without any margin**. Therefore, in this situation, $GTV_{70}n$ is equivalent to $CTV_{70}n$]
PTV_{70}[a]	**Primary**: $PTV_{70}p = CTV_{70}p + 3–5$ mm, depending on daily patient positioning and on treatment imaging. If PTV overlaps with critical OARs (brainstem, spinal cord, brain), compromise of PTV must be accepted **Neck**: $PTV_{70}n = CTV_{70}n + 3$ mm Please note that when the radiation oncologist is certain of the $GTV_{70}p$ or $GTV_{70}n$, these can also be known as $CTV_{70}p$ or $CTV_{70}n$. In other words, $GTV_{70}p = CTV_{70}p$ (without margin) and $GTV_{70}n = CTV_{70}n$ without margin A 5 mm margin can then be added to the $CTV_{70}p$ to name this $PTV_{70}p$. But as stated above, when the target is near critical structures such as brain stem, chiasm, and spinal cord, the PTV margin can be 0 mm. A 3 mm margin can be added to the $CTV_{70}n$ to name this $PTV_{70}n$

[a] Suggested gross dose disease is 2–2.12 Gy/fraction to 69.96–70 Gy in 33–35 fractions

Table 1.2 Suggested clinical target volumes at the high-risk subclinical region

Target volumes	Definition and description
$CTV_{56–59.4}$[a]	**Primary**: $CTV_{56–59.4}p = GTV_{70}p$ + 10 mm (when possible) + whole nasopharynx. In addition, ensure adequate coverage of soft palate inferiorly, posterior nasal cavity (at least 5 mm from choana), posterior maxillary sinuses (ensuring coverage of pterygopalatine fossae where V2 resides), posterior ethmoid sinus when indicated, skull base (foramen ovale, rotundum, lacerum), cavernous sinus to Meckel's cave (if T3–T4; involved side only), pterygoid fossa/parapharyngeal spaces, sphenoid sinus (inferior half if T1–T2; whole if T3–T4), clivus (1/3 if no invasion; whole if invasion; when in doubt, whole clivus should be targeted) Importance of reviewing bone window while contouring on CT scan to ensure coverage of skull base foramina **Neck**: $CTV_{54.12-56}n$ = bilateral retropharyngeal nodes, levels IB, II, III, IV, and V Level IB can be omitted in the N0 neck Level IB can also be omitted in N+ neck at the discretion of the treating radiation oncologist after ensuring there are no suspicious IB lymph nodes Can consider omitting low neck for N0 neck
$PTV_{56–59.4}$[a]	**Primary**: $PTV_{56–59.4}p = CTV_{56–59.4}p$ + 3–5 mm, depending on daily patient positioning and on treatment imaging. When the target is near critical structures like brain stem, chiasm, and spinal cord, the PTV margin can be 0 mm **Neck**: $PTV_{54.12-56}n = CTV_{54.12-56}n$ + 3 mm

[a] High-risk subclinical dose: for 35 fractions: 1.6–1.7 Gy per day; for 33 fractions: 1.64–1.8 Gy per day

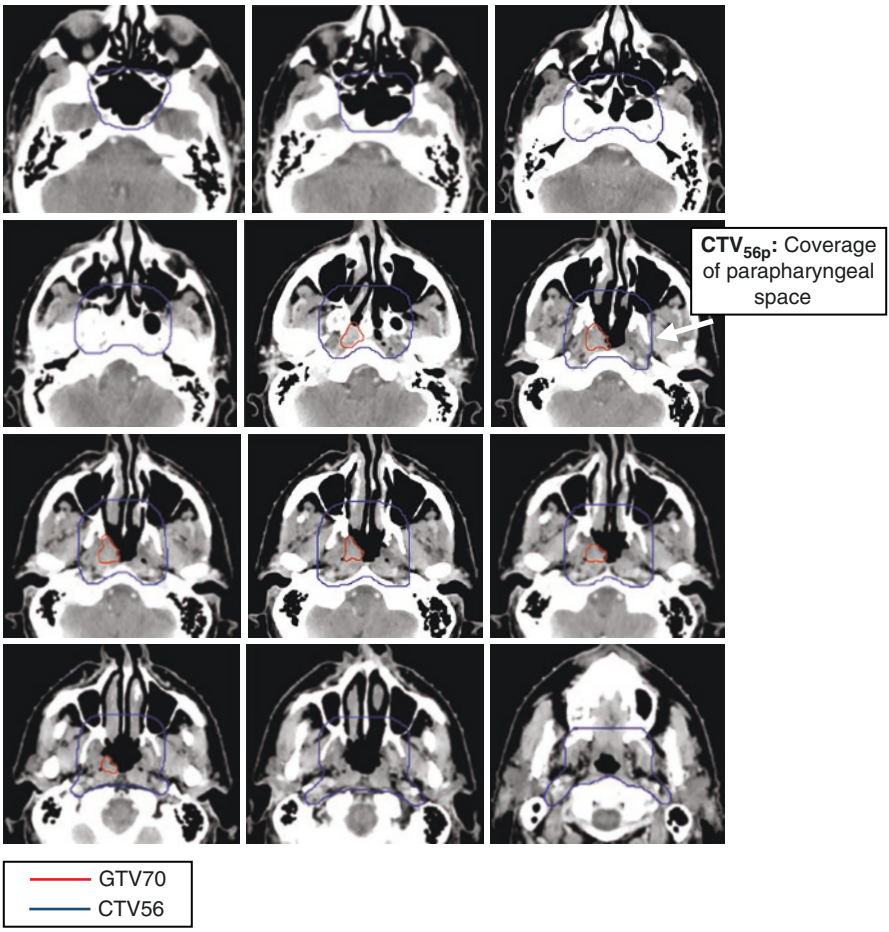


Fig. 1.1 A patient with T1N1 EBV positive nasopharyngeal carcinoma with right-sided level II and III nodes in a cranial to caudal direction. This patient was simulated with a planning MRI scan and PET/CT in the treatment position. Please note that these are representative slices and not all slices are included. The treating radiation oncologist can use the dosing according to institution or protocol guidelines

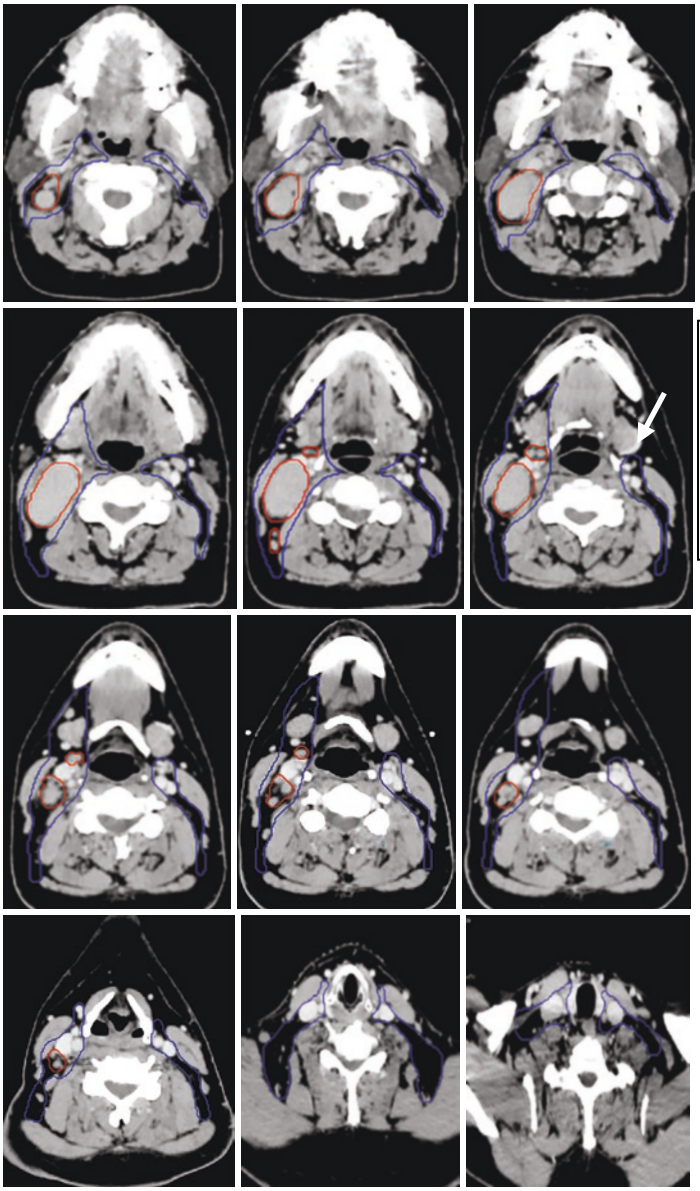
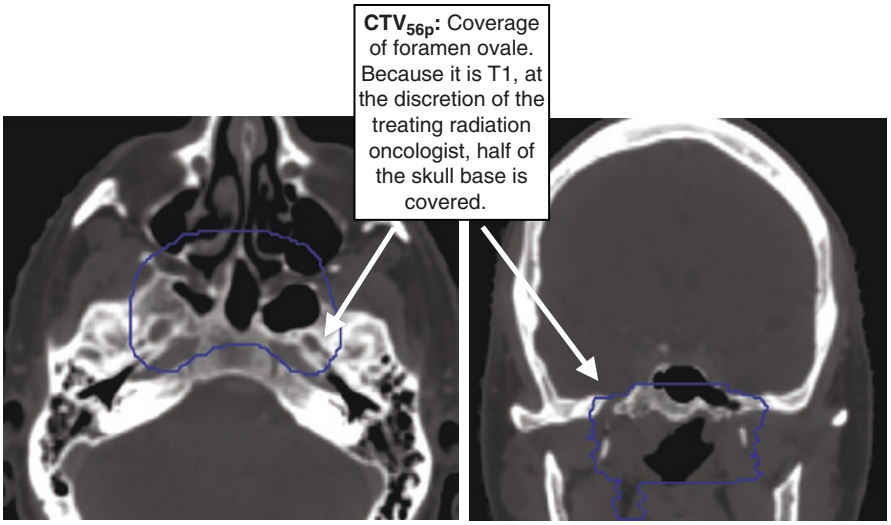


Fig. 1.1 (continued)



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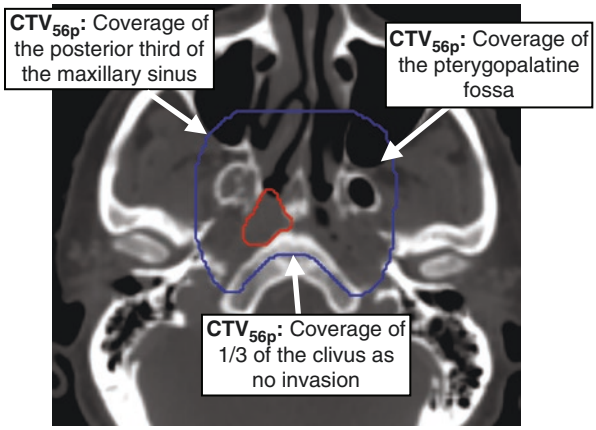


Fig. 1.2 Example of GTV and CTVs displayed on bone windows. The treating radiation oncologist can use the dosing according to institution or protocol guidelines

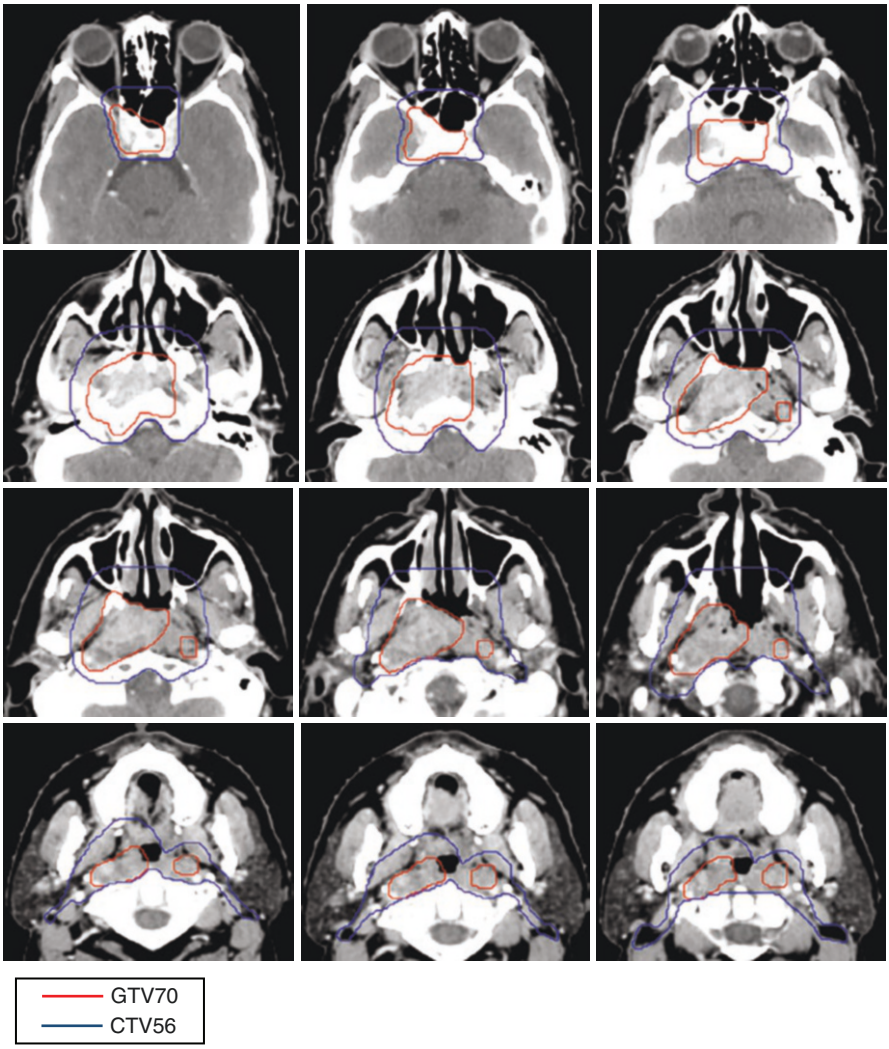
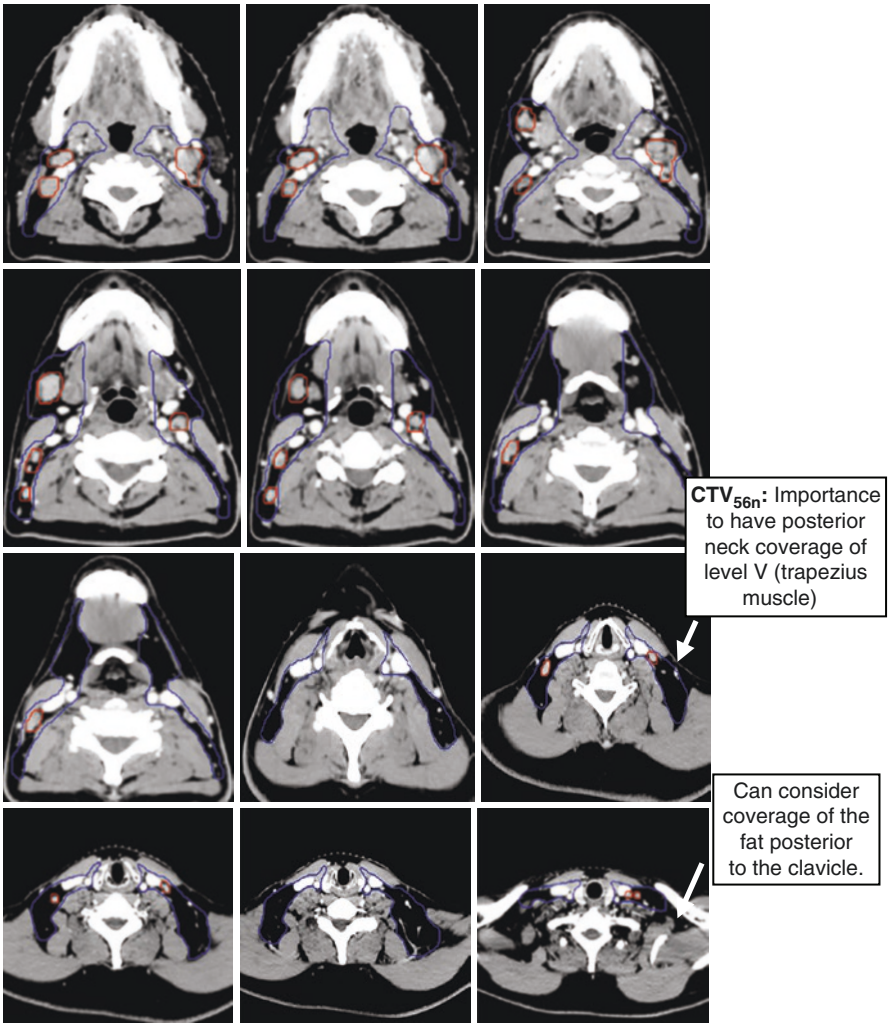


Fig. 1.3 A patient with T4N2 EBV positive nasopharyngeal carcinoma. The treating radiation oncologist can use the dosing according to institution or protocol guidelines



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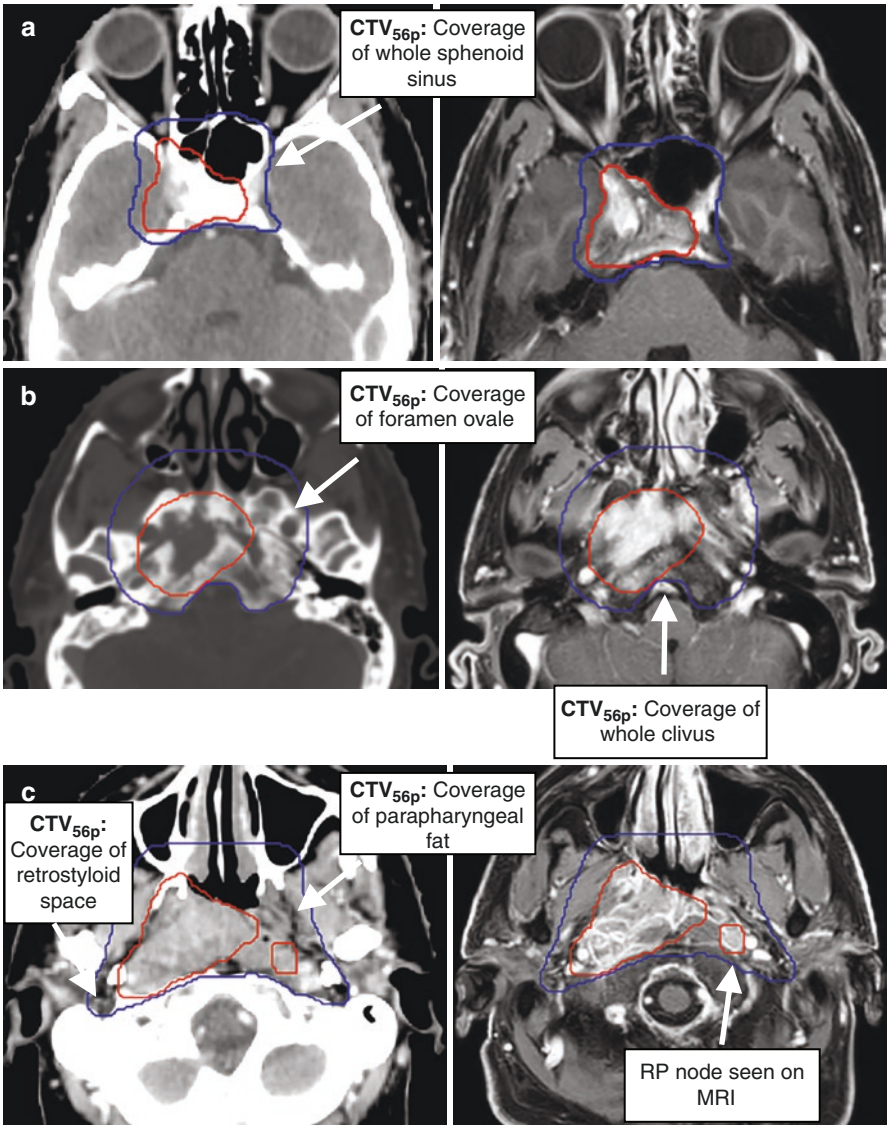

Fig. 1.4 Example of GTV and CTVs displayed on: (**a**) soft tissue window and MRI T1 + GAD, (**b**) bone window and MRI T1 + GAD, (**c**) soft tissue window and MRI + T1 + GAD. The treating radiation oncologist can use the dosing according to institution or protocol guidelines

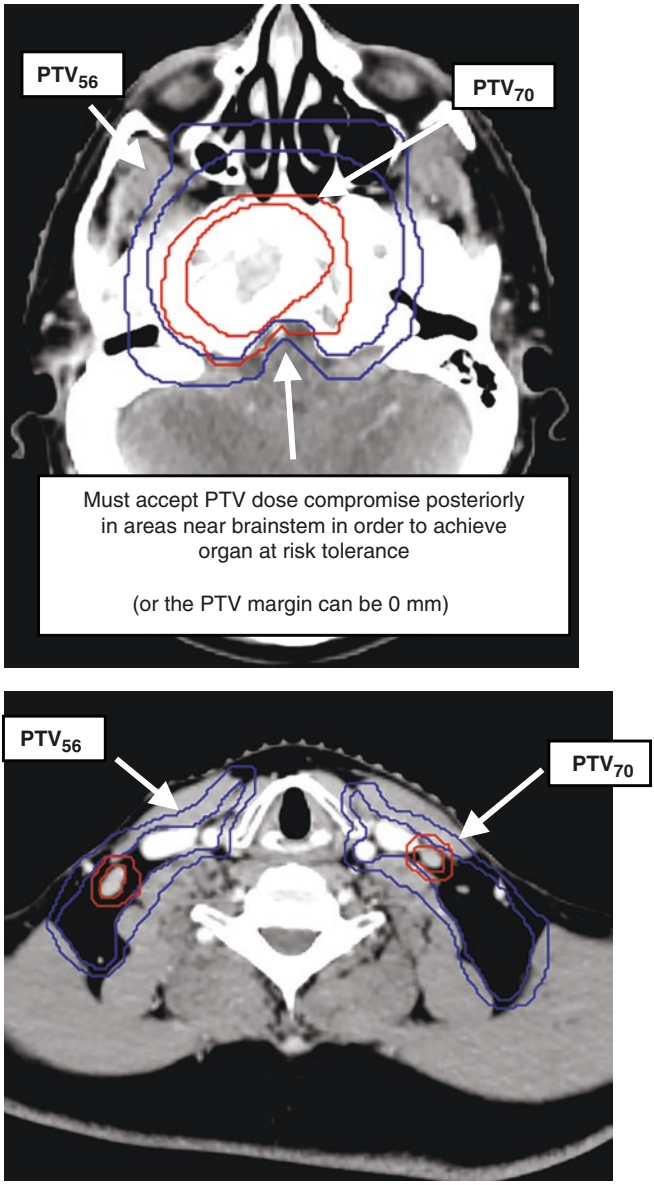

Fig. 1.5 Example of the final 3-mm PTV images. The treating radiation oncologist can use the dosing according to institution or protocol guidelines

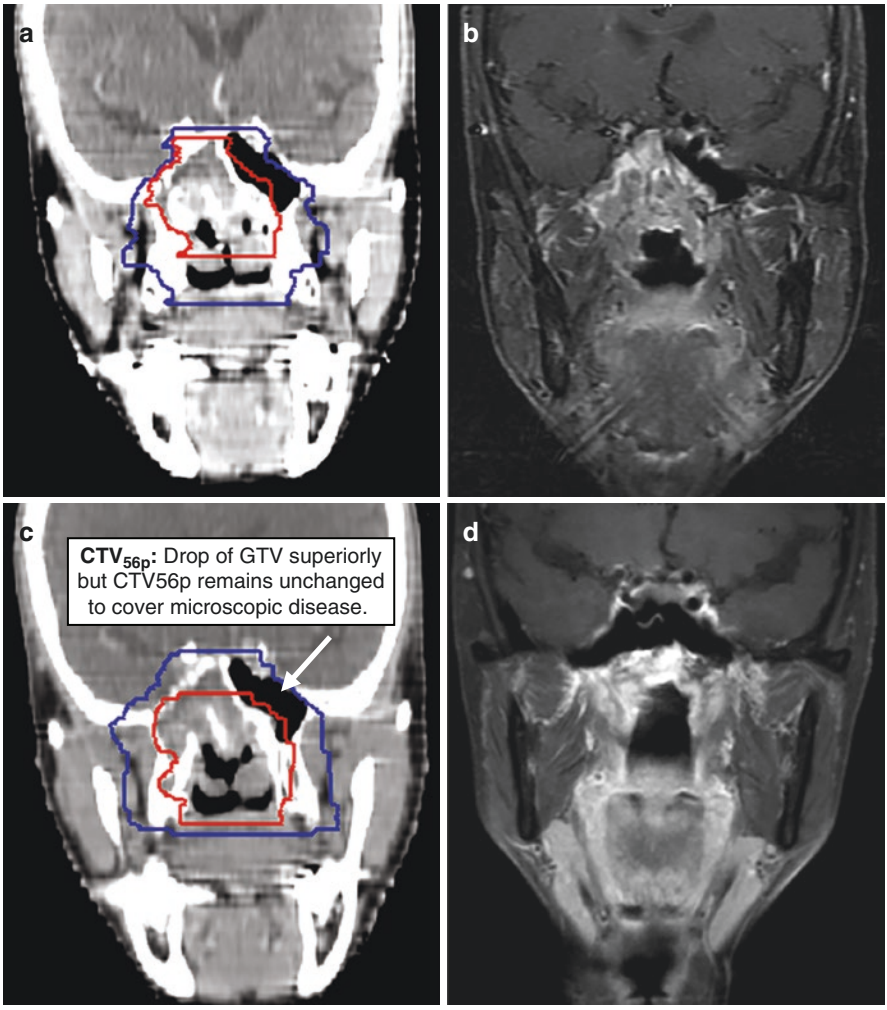

Fig. 1.6 Example of an adaptive nasopharyngeal plan. Patient with cT3N2 NPC who underwent mid-treatment adaptive replanning with MRI simulation showing shrinkage of disease superiorly allowing for reduction of the GTV away from the optic chiasm, and improvement in coverage: (**a**) Phase 1 GTV in red and CTV_{56p} in blue on original CT sim and (**b**) Phase 1 MRI sim T1 post GAD, (**c**) Phase 2 GTV in red and CTV_{56p} in blue on original CT sim, and (**d**) Phase 2 MRI sim T1 post GAD. The treating radiation oncologist can use the dosing according to institution or protocol guidelines

Further Reading

Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol. 2009;27(22):3684–90.

Lee AW, Ng WT, Pan JJ, et al. International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. Radiother Oncol. 2018;126(1):25–36. https://doi.org/10.1016/j.radonc.2017.10.032.

NRG HN001 Clinical Trial Protocol.

Oropharyngeal Carcinoma

2

Zain A. Husain, Jung Julie Kang, Nancy Y. Lee, and Ian Poon

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2.1 Introduction

Oropharyngeal carcinoma comprises primary tumors involving the tonsils, base of tongue, soft palate, or posterior pharyngeal wall. The vast majority of oropharyngeal cancers are squamous cell carcinomas, most of which are associated with the human papillomavirus (HPV). HPV-unrelated cancers are commonly associated with tobacco or alcohol use. HPV-associated head and neck cancers have superior prognosis [1, 2]. Since the last edition of this book, the American Joint Committee

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_2

on Cancer revised staging for oropharyngeal cancer, dividing it into two different systems for HPV-positive and HPV-negative oropharyngeal cancers. Given the prognostic importance of HPV status, viral testing should be performed in all oropharyngeal carcinoma patients. However, de-escalation of therapy based on HPV status should not be performed outside of a clinical trial [3–5]. In this chapter, we outline radiotherapy target delineations with careful consideration of microscopic mucosal spread of the primary tumor as well as knowledge of cervical nodal drainage patterns.

2.2 General Principles of Anatomy and Patterns of Spread

- The oropharynx is a cuboidal space bordered by the oral cavity anteriorly, the nasopharynx superiorly, and the larynx and hypopharynx inferiorly.
- It consists of four subsites: the tonsils, base of tongue, soft palate, and the pharyngeal wall, with the majority of cases arising in the tonsils and tongue base.
- The oropharynx is equipped with a rich lymphatic drainage and lymph nodes are commonly involved.

2.3 Diagnostic Workup Relevant for Target Delineation

- Gross tumor volume delineation of the primary site is best identified by a combination of imaging and physical examination.
- The mucosal and superficial extents of disease are best accessed by visual inspection, palpation, and fiberoptic endoscopic examination. Photographic documentation of disease at the time of consult or simulation is helpful in order to document mucosal extension of disease that may be poorly seen on imaging (Fig. 2.1).

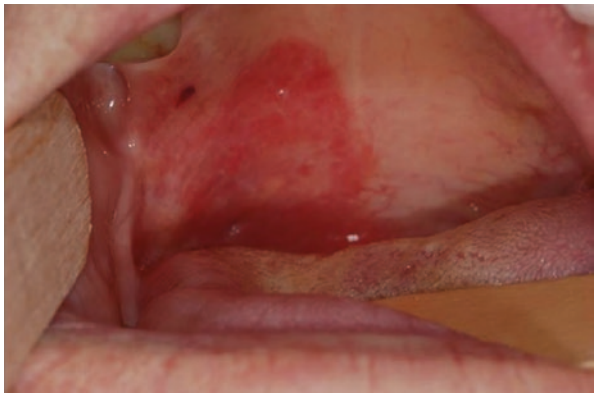

Fig. 2.1 Direct visualization helps demonstrate involvement of the soft palate and evidence of the tumor crossing midline

- While contrast-enhanced CT scans remain the mainstay of diagnostic imaging for this disease, both MRI and PET/CT have well-defined roles.
  - T1-weighted pre-contrast MRI sequences are ideal for the evaluation of fat planes and bone marrow signals.
  - T1-weighted contrast-enhanced MRI sequences may be critical for delineation of the anterior extension of base of tongue tumors and for the assessment of perineural invasion.
  - T2-weighted fat-saturated sequences offer utility for the evaluation of RP nodes and soft tissue extent in the parapharyngeal and pre-epiglottic spaces.
  - FDG-PET provides metabolic information that complements both CT and MRI, and may identify tumor extent missed by CT or MRI.
  - Limitations of FDG-PET include poor spatial resolution and low sensitivity for small-volume lymph node metastases. Thus, the absence of FDG uptake in an otherwise suspicious lymph node should not necessarily be considered reassuring.

2.4 Simulation and Daily Localization

- The patient should be set up in the supine position with head rest with the neck extended. The customized immobilization device (5-point Aquaplast mask) should provide adequate head, neck, and shoulder immobilization. A bite-block and/or mouth guard may be inserted. Patients are instructed not to swallow during scans or during treatment.
- CT simulation with IV contrast using $\leq$3 mm slice thickness encompassing the entire vertex of the skull down through the carina.
- The isocenter is typically placed at the arytenoid cartilages. A low anterior conventional AP neck field can be matched to the IMRT fields.
- MRI and PET images may be registered or fused to the CT simulation scan. The use of immobilization mask during PET scan improves the fusion accuracy, but the use of immobilization mask during the MRI may preclude the use of a dedicated head and neck coil.
- At MSKCC, image guidance is achieved with daily linear accelerator-mounted 2D kV imaging and daily kV and conebeam CT. Conebeam CT can also be used weekly, with daily KV imaging as an alternative strategy. Alternative methods for image guidance may include orthogonal kV imaging (“ExacTrac”) or linear accelerator-mounted MV CT images (“TomoTherapy”).

2.5 Target Volume Delineation and Treatment Planning

2.5.1 Selected IMRT Dose and Fractionation Schemes

- There are many different treatment approaches. At MSKCC, the preferred approach is a sequential technique. Total dose to the gross disease is 70 Gy. For

HPV related tumors, the subclinical regions receive 30 Gy in 2 Gy per fraction followed by a cone down to the gross disease receiving 40 Gy in 2 Gy per fraction. The subclinical region is scrutinized heavily to ensure no gross disease with MRI, CT with contrast, and PET/CT scans. Please refer to our publication, Tsai et al. [6]. For HPV unrelated disease, the initial phase is 60 Gy in 2 Gy per fraction to the gross disease while simultaneously treat 54 Gy in 1.8 Gy per fraction to all subclinical regions. This is followed by a cone down of 10 Gy in 2 Gy per fraction to the gross disease. If a low anterior neck AP field is matched to the IMRT fields, HPV related tumors receive 30 Gy in 2 Gy per fraction to the low neck while the HPV unrelated tumors receive 50 Gy in 2 Gy per fraction to the low neck. Reduced elective doses should only be considered when treating with concurrent cisplatin-based chemotherapy

- Another commonly used radiation technique is the simultaneous integrated boost. Gross disease dose: 70 Gy (2 Gy/fx), high-risk subclinical dose: 56 Gy (1.6 Gy/fx), and low-risk subclinical dose: 50–52.5 Gy (1.43–1.5 Gy/fx). This technique should only be considered when using concurrent chemotherapy.
- Another fractionation schemes such as but not limited to RTOG 0022 [7] or RTOG 1016 [3].

2.5.2 Suggested Target Volumes

- Suggested target volumes for gross disease (Table 2.1) and for subclinical disease (Table 2.2) are presented in the following.

Table 2.1 Suggested target volumes for gross disease

Target volumes	Definition and description
GTV_{70}	Primary: All gross disease as defined by clinical exam and imaging Nodes: all suspicious (>1 cm, necrotic, enhancing, or FDG-avid) lymph nodes. Borderline suspicious nodes can be given less than 70 Gy, i.e. 60–66 Gy for example
CTV_{70}	In areas of excellent visualization GTV_{70} can equal CTV_{70} (no added margin). In situations where there is uncertainty of tumor extent $CTV_{70} = GTV_{70} + 3–5$ mm
PTV_{70}	$CTV_{70} + 3–5$ mm depending on daily set up accuracy and the availability of image guidance

Table 2.2 Suggested target volumes for subclinical disease

Target volumes	Definition and description
General guidelines	As a useful guideline, the primary site $CTV_{subclinical}$ should encompass the GTV_{70} + 1 cm (shaved off of anatomic barriers to spread such as air, bone, and skin)
Tonsil primary, $CTV_{subclinical}$	Ensure adequate margin to the primary tumor ~1 cm. Highly recommend inclusion of pterygoid plates with advanced primary disease (Fig. 2.2). Consider inclusion of the ipsilateral retromolar trigone if tumor spread anterolaterally along the pharyngeal constrictor is suspected
Base of tongue primary, $CTV_{subclinical}$	Glossotonsillar sulcus, vallecula, and the pre-epiglottic space (Fig. 2.3). Ensure a mucosal margin of at least 1.0 cm around the base of tongue primary tumor; anteriorly, this may extend into the oral tongue. MRI is very helpful to ensure accurate delineation of anterior extension of the tumor (Figs. 2.4 and 2.5)
Soft palate primary, $CTV_{subclinical}$	Entire soft palate, superior aspect of tonsillar pillars + fossa, adjacent nasopharynx superiorly to the pterygoid plate. For advanced primaries, consider inclusion of the pterygopalatine fossa. If the pterygopalatine fossa is involved, assessment of the base of skull with MRI is required. Ensure adequate coverage anteriorly, which may require coverage of a portion of the hard palate
Pharyngeal wall primary, $CTV_{subclinical}$	Generous superior and inferior margins given the possibility of skip lesions. In patients with advanced primary tumors, consider extending CTV cranially to include the nasopharynx and caudally to include the hypopharynx
Elective neck nodes, $CTV_{subclinical}$	The nodal regions can be treated to microscopic doses of 54 Gy in 1.8 Gy fractions, 54.12 Gy in 1.64 Gy fractions, 56 Gy in 1.6 Gy fractions, or 59.4 Gy in 1.8 Gy fractions depending on whether these regions are high risk or low risk In node-negative cases, at risk areas include bilateral levels II-IV and lateral retropharyngeal nodes. At MSKCC, we do not routinely treat levels IB or V, unless grossly involved (Figs. 2.5 and 2.6). The exception would be with gross oral cavity extension of disease, in which case IB nodes may be considered at risk (Figs. 2.2 and 2.4) In node-positive cases, the retropharyngeal nodes and retrostyloid nodes should be covered superiorly to the skull base (Fig. 2.4). If there is gross involvement of low-lying nodes, consider coverage of the supraclavicular space (Fig. 2.5) For T1–2, N0–N1 well-lateralized tonsil cancers (at least 1 cm lateral from midline) with no extension to the base of tongue or soft palate, ipsilateral neck treatment is acceptable (Fig. 2.6). The superior extent of coverage for the node-negative neck may begin at the transverse process of C1 or when the posterior belly of the digastric just starts to cross over the internal jugular vein (Fig. 2.6)

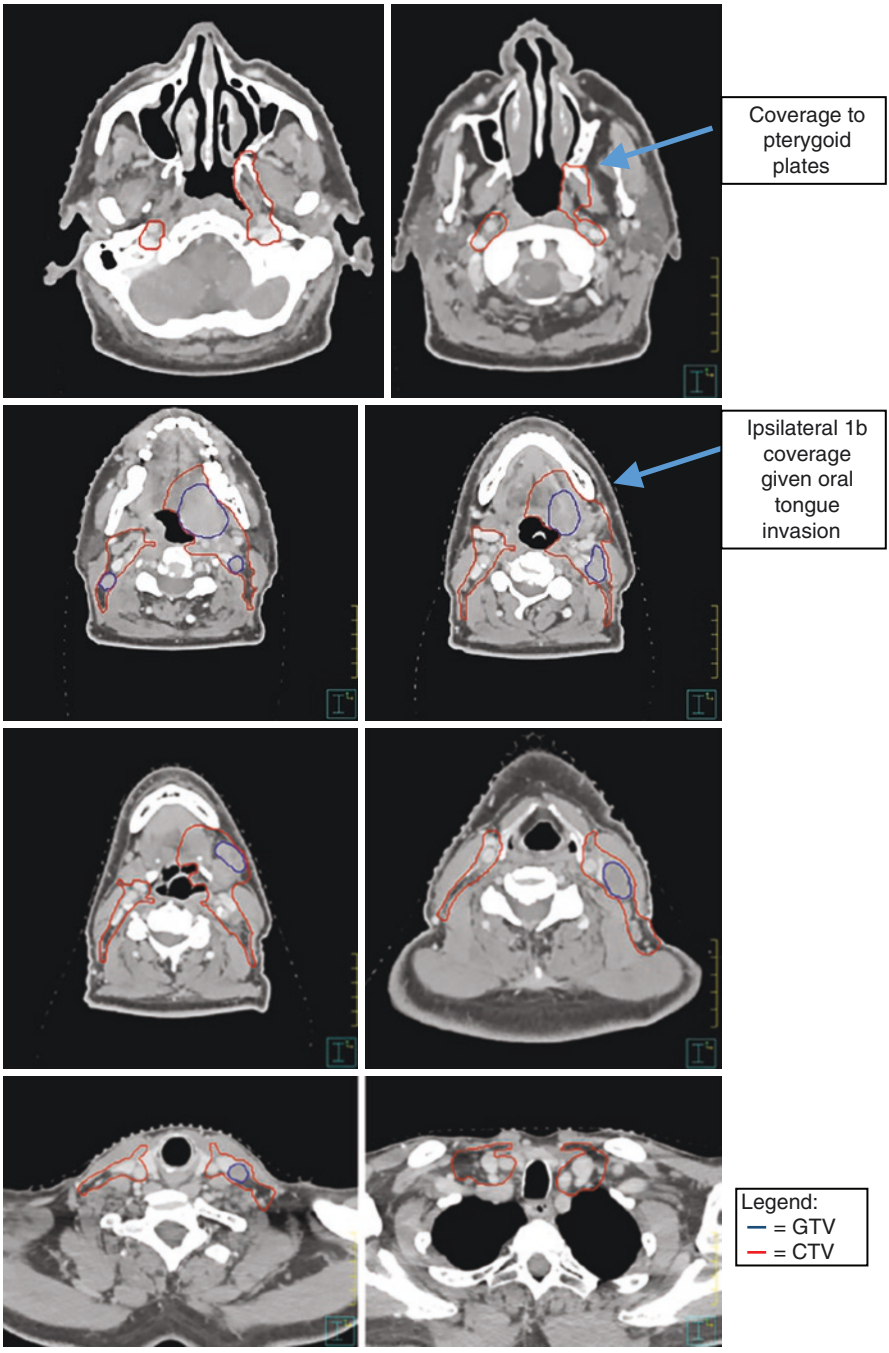

Fig. 2.2 Representative axial slices from a contrast-enhanced CT simulation for a patient with HPV-negative cT4N2 squamous cell carcinoma of the left tonsil

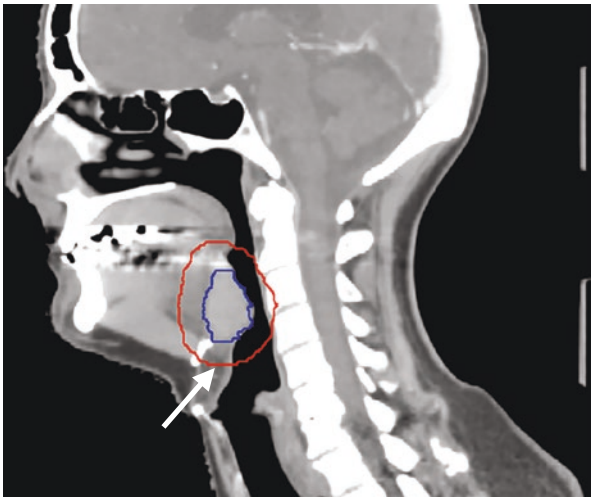

Fig. 2.3 Coverage of the pre-epiglottic space in base of tongue tumors (GTV: blue, CTV: red)

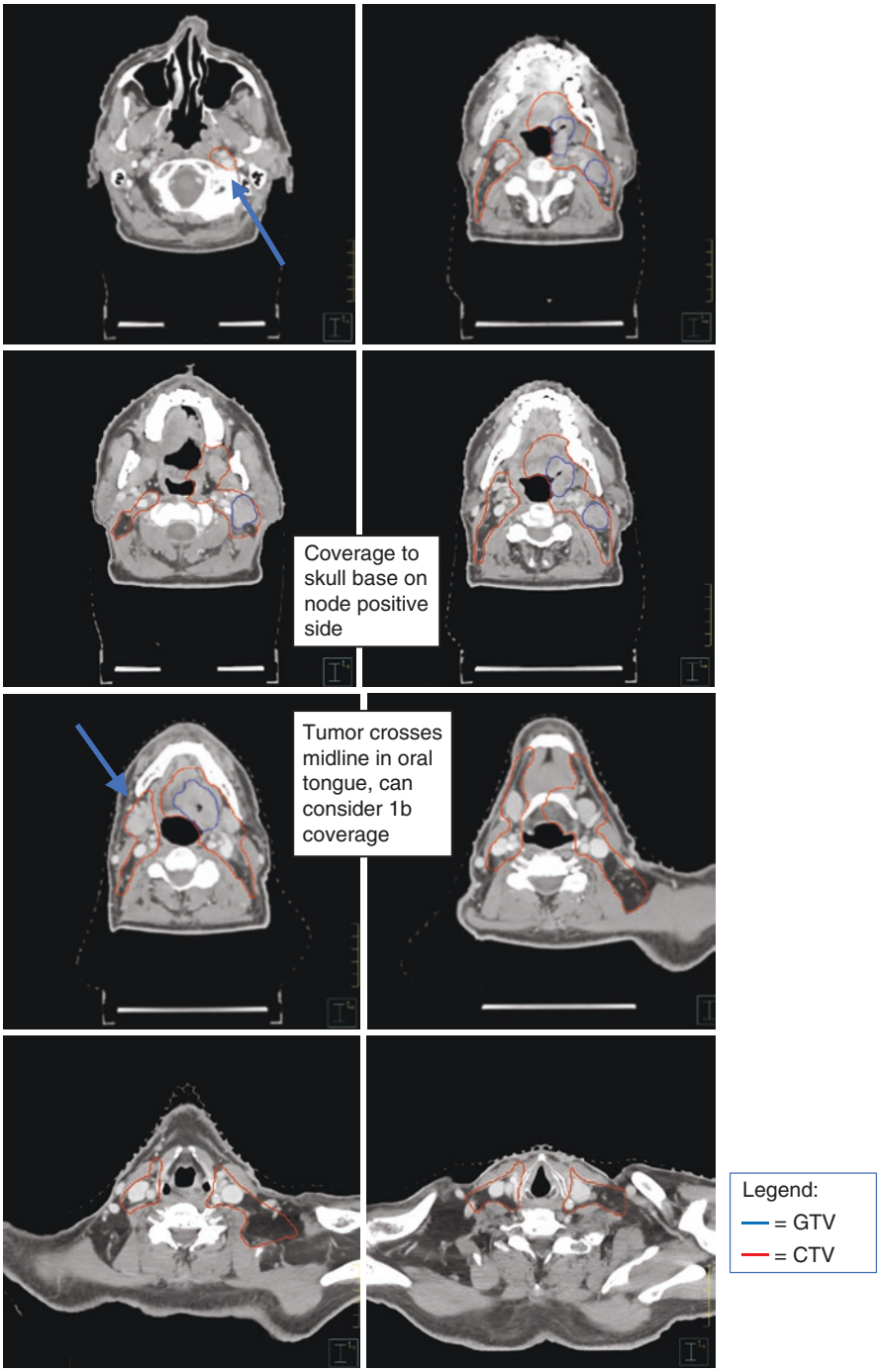

Fig. 2.4 Representative axial slices from a contrast-enhanced CT simulation for a patient with P16-positive, HPV-associated cT4N1 squamous cell carcinoma of the left base of tongue

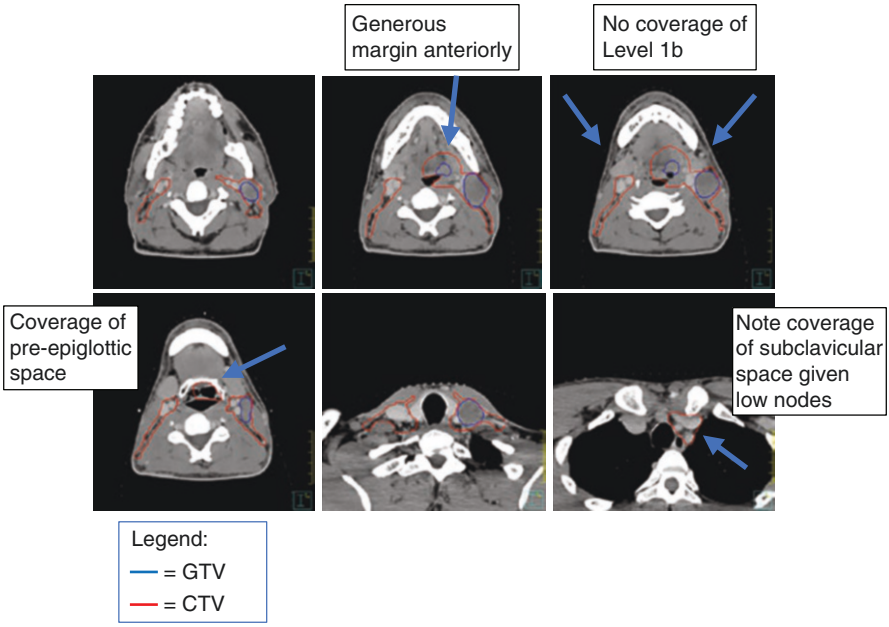

Fig. 2.5 Representative axial slices from a contrast-enhanced CT simulation for a patient with P16-positive, HPV-associated cT1N1 squamous cell carcinoma of the left base of tongue

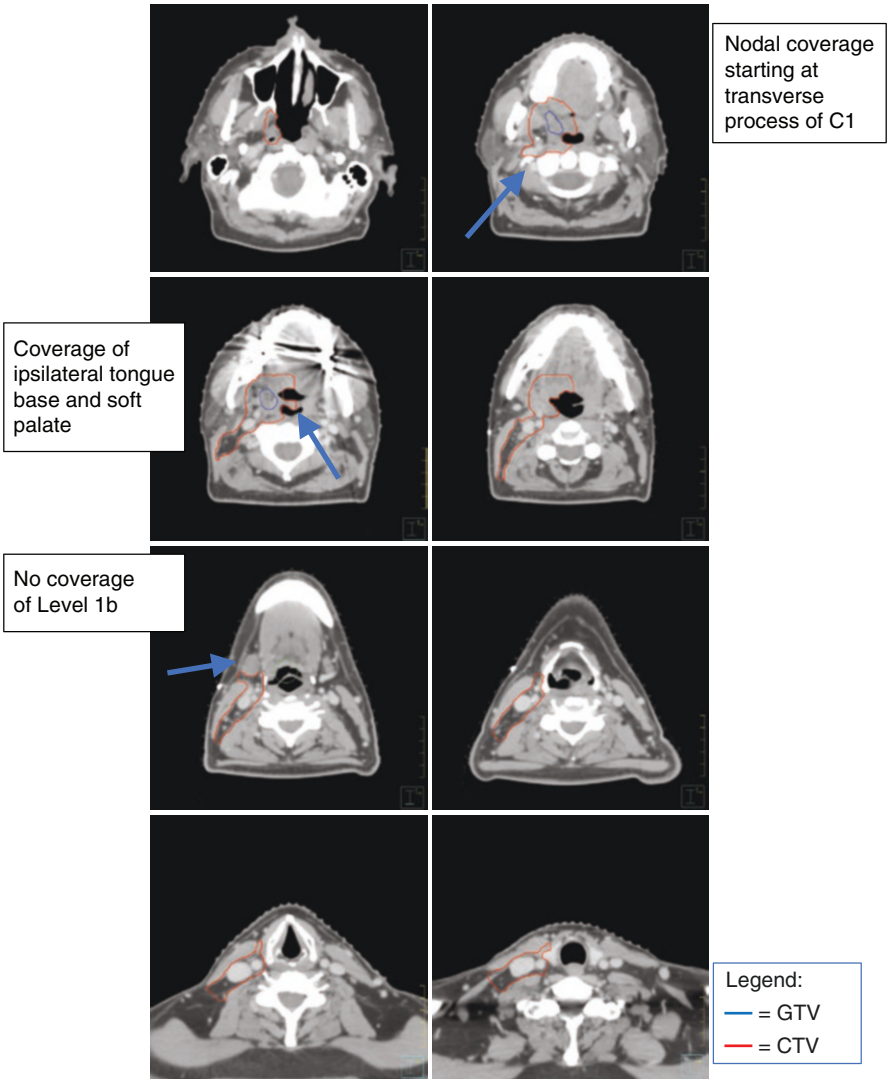

Fig. 2.6 Representative axial slices from a contrast-enhanced CT simulation for a patient with P16-positive, HPV-associated cT2N0 squamous cell carcinoma of the right tonsil (with no evidence of base of tongue or soft palate invasion) to be treated with unilateral radiation. At MSKCC, for tonsil cancers regardless of stage, the ipsilateral subclinical region almost always extend superiorly to include coverage of the ipsilateral pterygoid plate

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Stereotactic Body Radiotherapy for Cancers of the Head and Neck Cancer

3

Dana Keilty, Irene Karam, Nancy Y. Lee, and Ian Poon

Contents

- Advanced Head and Neck Cancer (HNC) is commonly a disease of the elderly and associated with a poor outcomes despite aggressive multi-modality treatments. Select fit elderly patients, despite the expectation of a poor outcome, may choose to undergo radical high-dose radiation to maximize cancer control but with higher rates of toxicity and morbidity. In frail patients, the decision against a prolonged RT course may be based on multiple factors: patient preference (Fig. 3.1), tumor factors (expected morbidity of tumor progression versus the morbidity/mortality risk of treatment and probability of a successful outcome [Figs. 3.2, 3.3, 3.4, 3.5, and 3.6]), life expectancy (influence of age and comorbid conditions [Figs. 3.1, 3.3, 3.4, 3.6, 3.7, 3.8, and 3.9]), tolerance of aggressive

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_3

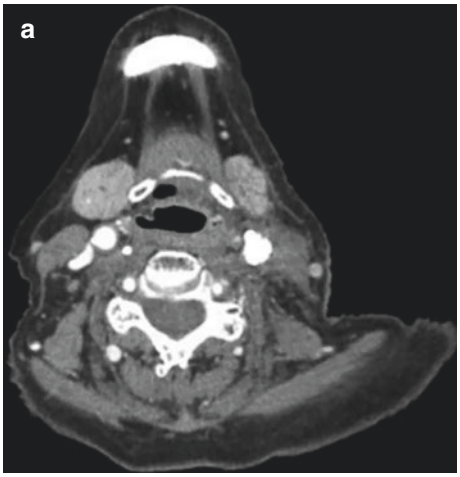
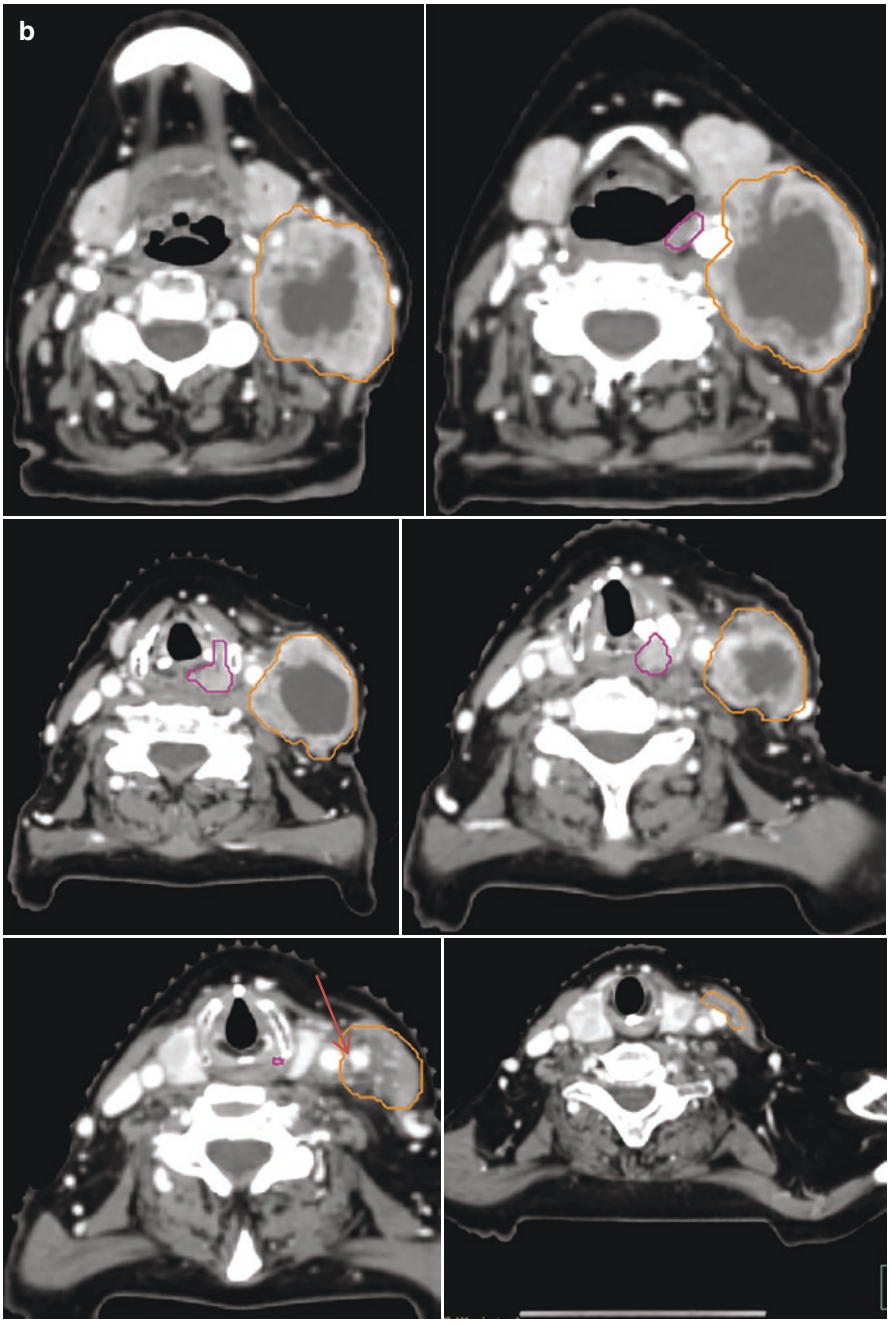


Fig. 3.1 Unresectable piriform sinus tumor. A 73-year-old lady was diagnosed with a T1 N3 squamous cell carcinoma of the left piriform sinus compressing the internal jugular vein. She elected against a protracted radiation course. (**a**) 50 Gy in five fractions, two fractions per week, was prescribed to the GTVn (orange) and 40 Gy in five fractions, two fractions per week, was prescribed to the GTVp (red). Target coverage was not compromised in an attempt to spare the carotid artery (arrow). (**b**) No evidence of disease at 2 years



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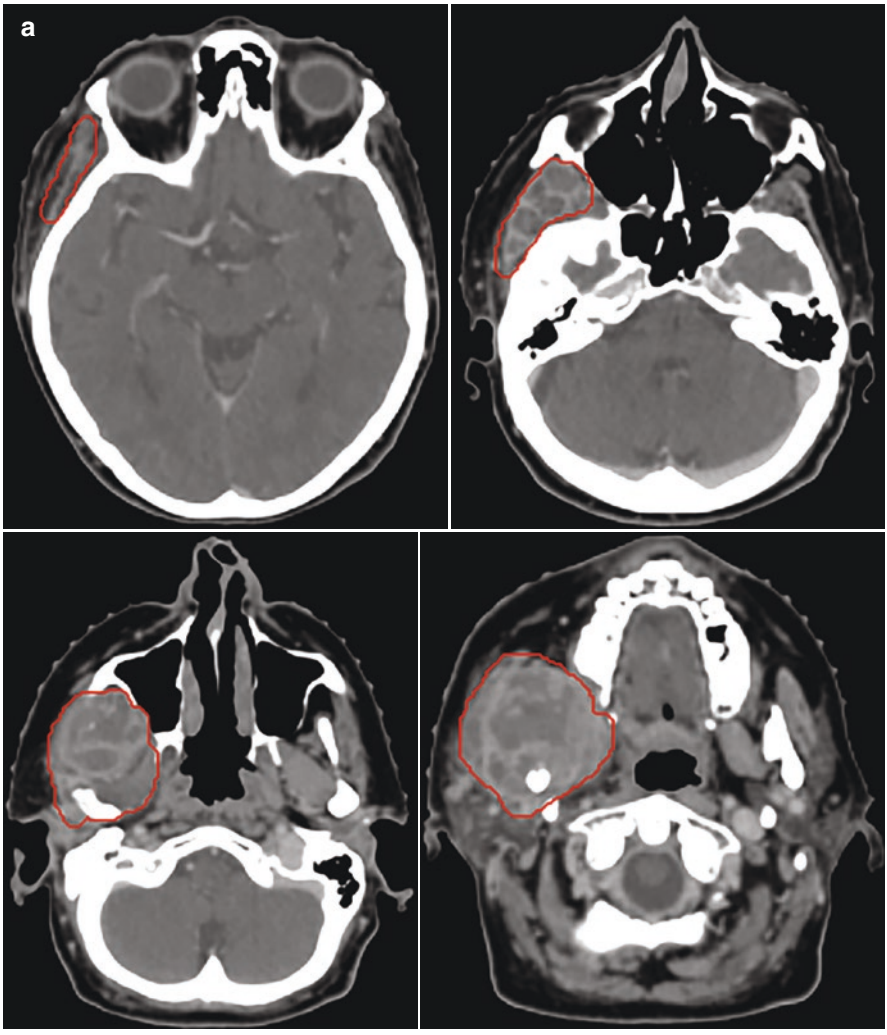
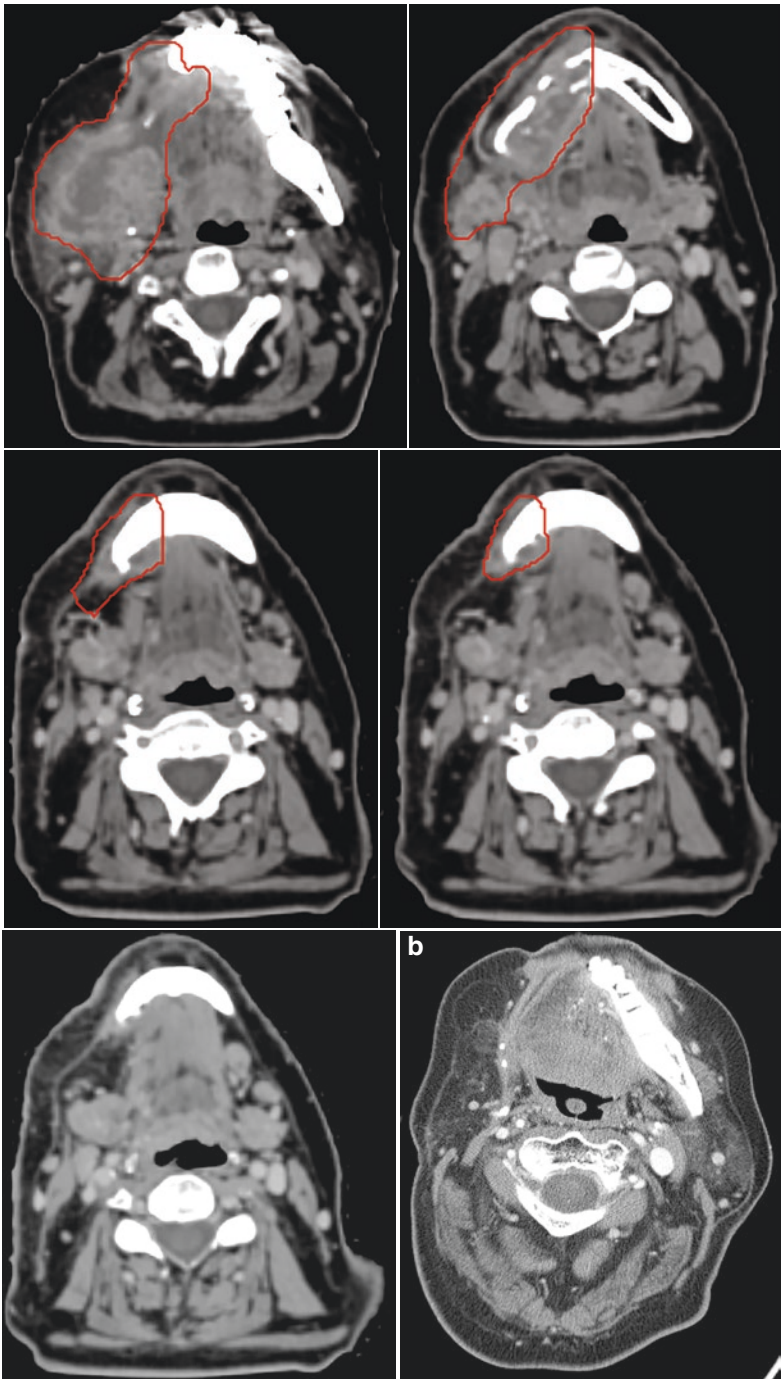


Fig. 3.2 Extensive HNC. A 65-year-old female presented with a painful squamous cell carcinoma of the oral cavity, measuring 6.9 by 4.0 cm, extending from the base of the skull along the infratemporal fossa into the masticator space and the right mandible, causing pathologic fracture and trismus with a mouth opening of 1.5 cm. She received 45 Gy in five fractions, two fractions per week. (**a**) $GTVp_{45}$ is delineated in red. (**b**) Four years later, she can open her mouth 4 cm and remains disease-free



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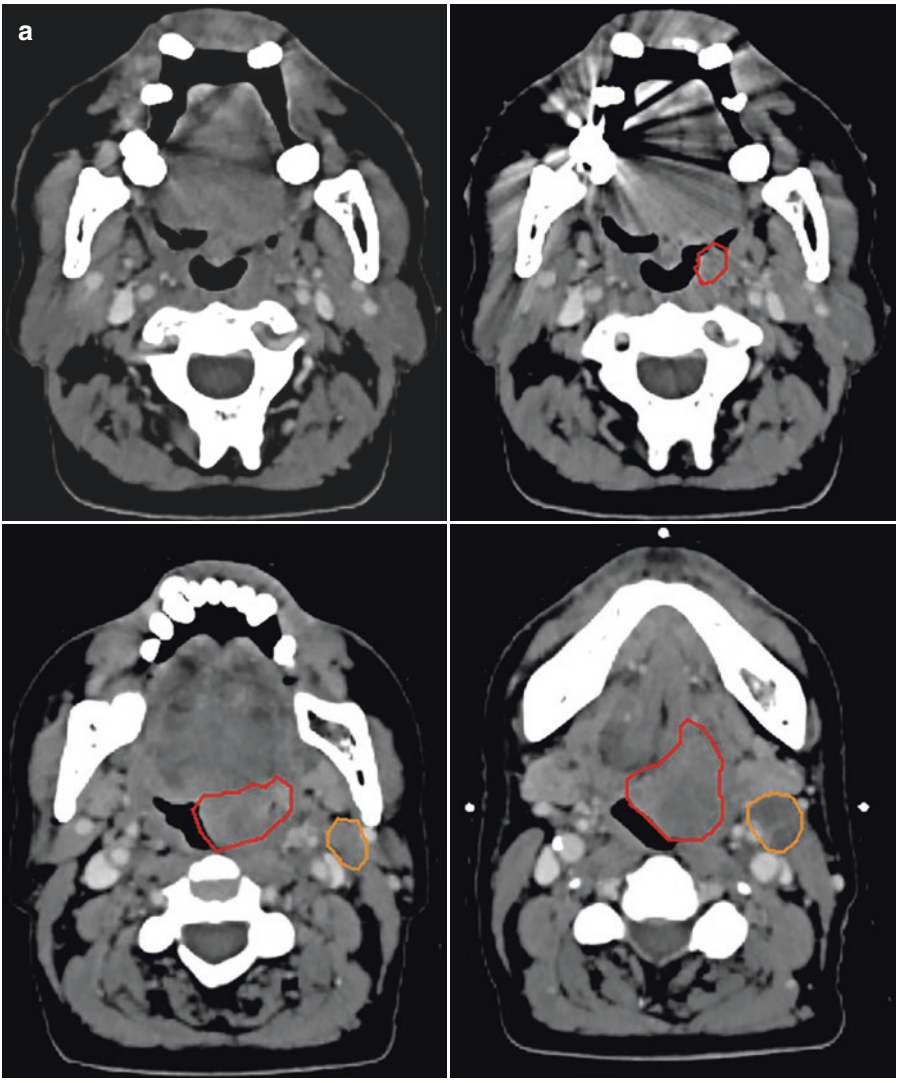
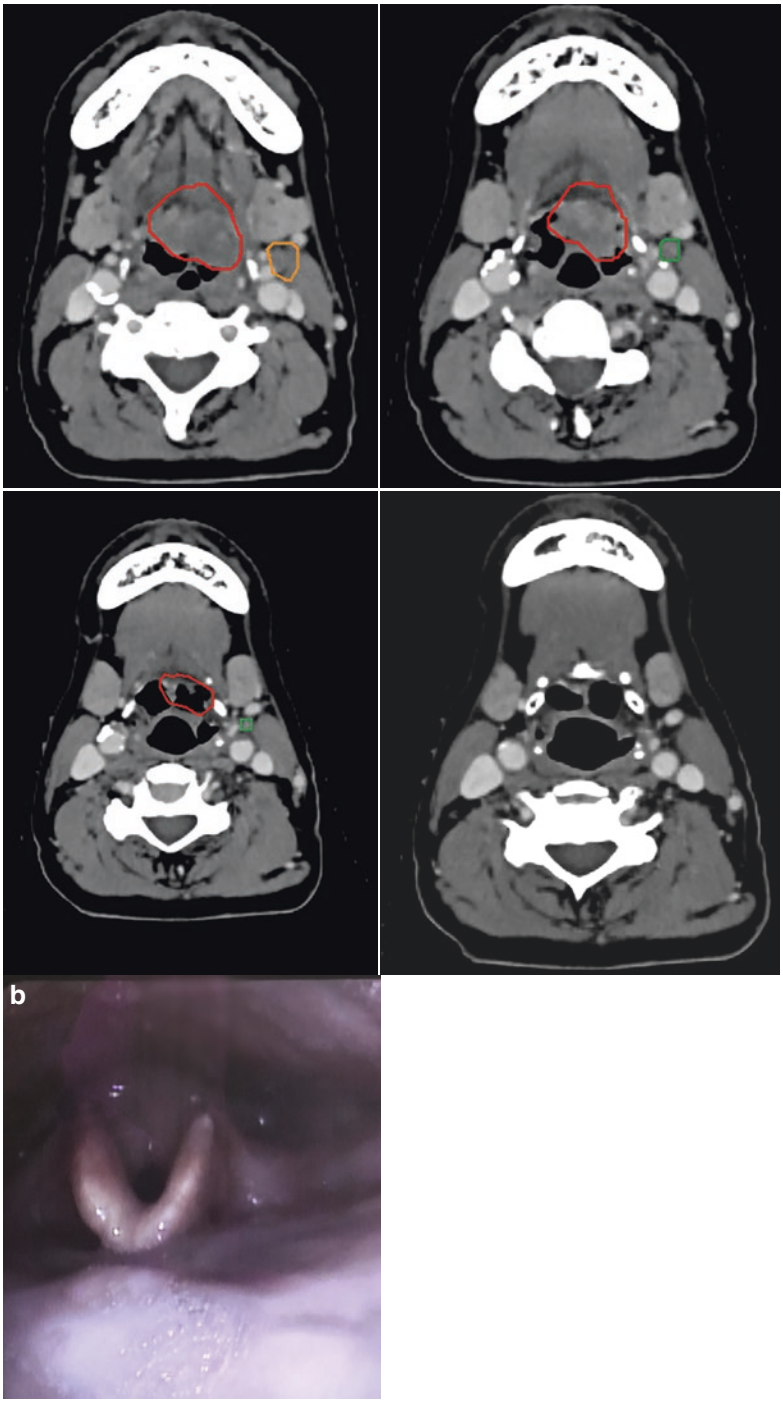


Fig. 3.3 HNC with concurrent life-threatening cancer. A 66-year-old gentleman presented with superior vena cava obstruction from a 10-cm non-small cell lung mass. Palliative radiation and chemotherapy rendered his disease stable for 18 months. Imaging to investigate painful dysphagia showed a 3-cm mass at the left base of tongue crossing the midline and a 3.3-cm left level II lymph node. Flexible nasopharyngoscopy showed the mass extended into the vallecula, displacing the epiglottis. This T2N1 base of tongue cancer was treated with 45 Gy in five fractions, two fractions per week, after which he started second-line lung systemic therapy. (**a**) $GTVp_{45}$ is delineated in red; $GTVn_{45}$ is delineated in orange; $GTVn_{40}$ is delineated in green. (**b**) There is no evidence of disease at 18 months, and he is tolerating all food textures without pain



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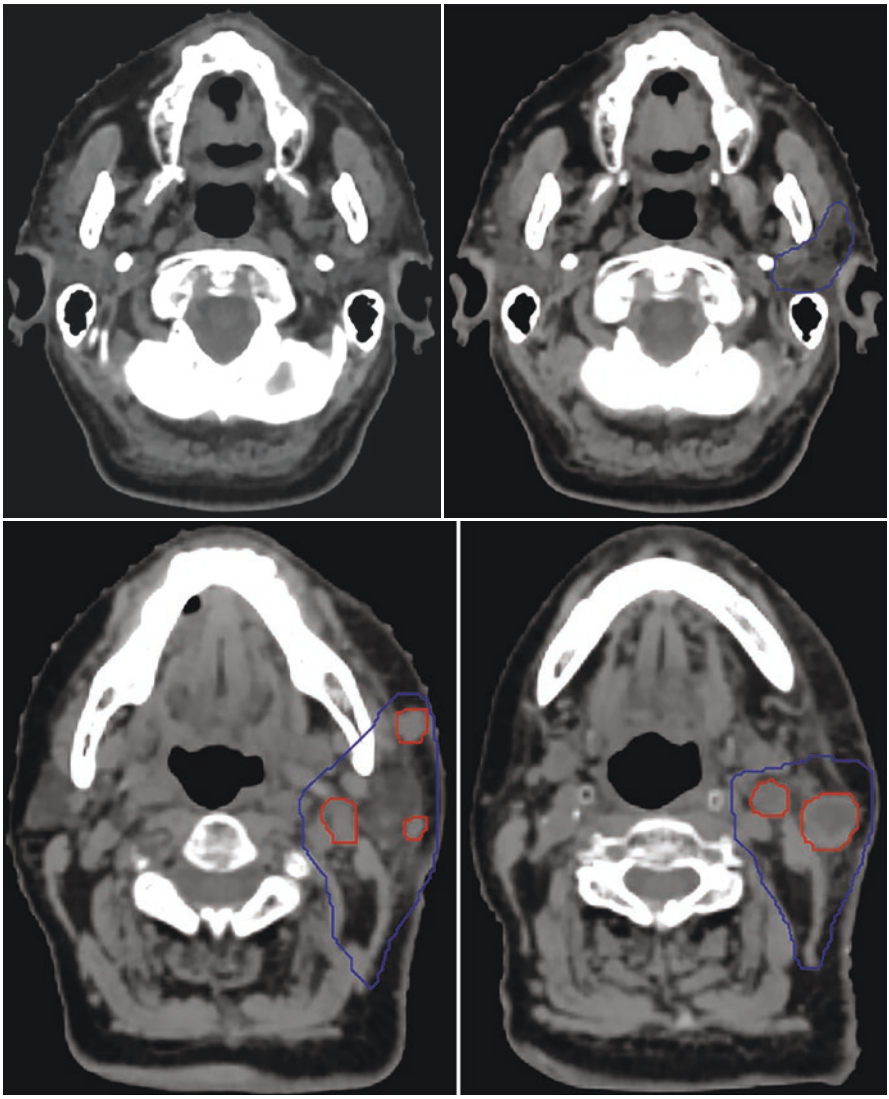
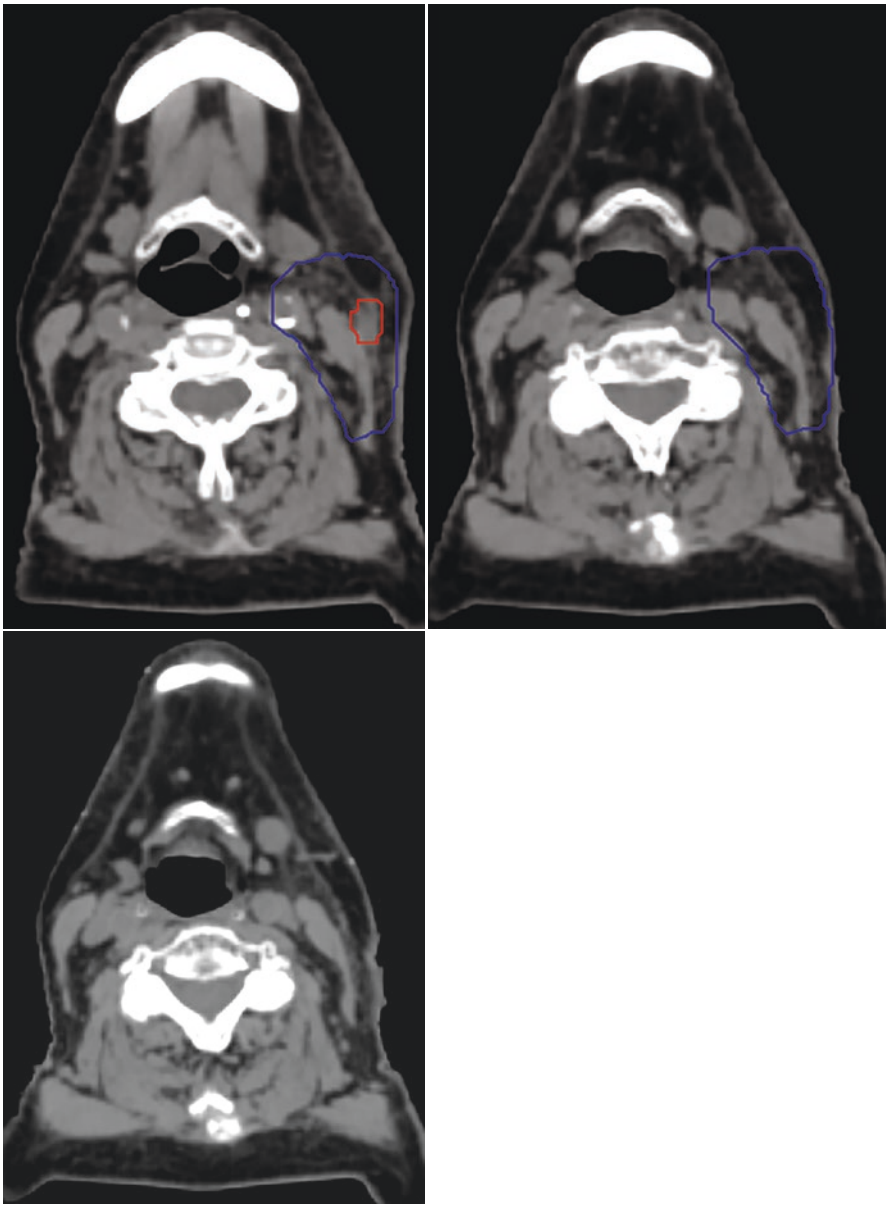


Fig. 3.4 HNC recurrence in centenarian. A 100-year-old female with squamous cell carcinoma of the skin recurred at the parotid and neck nodes. $CTVn_{25}$ (blue) encompasses the nodal basin at high risk of relapse. GTV_{45} is delineated in red. She remained well for 6 months and then recurred regionally, both inside and outside the low-dose field



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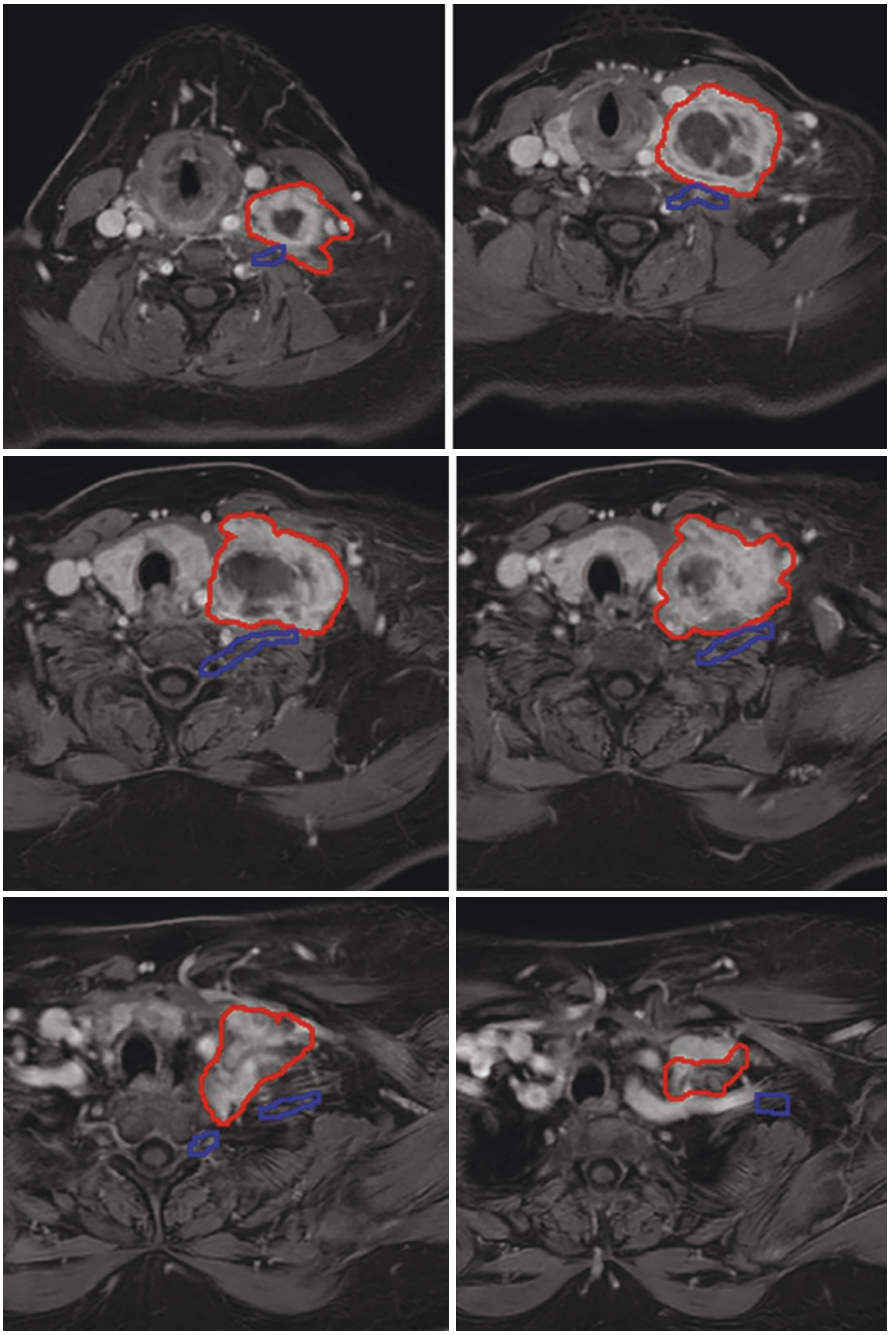


Fig. 3.5 Oligometastatic disease adjacent to brachial plexus. A 55-year-old female presented with an unresectable solitary oligometastatic colorectal cancer at the supraclavicular fossa. This 6-cm node was treated with 45 Gy in five fractions, two fractions per week. The radiation plan was created with MRI simulation to differentiate the GTV (red) from the brachial plexus (blue). The mass recurred 3 years later in the left neck

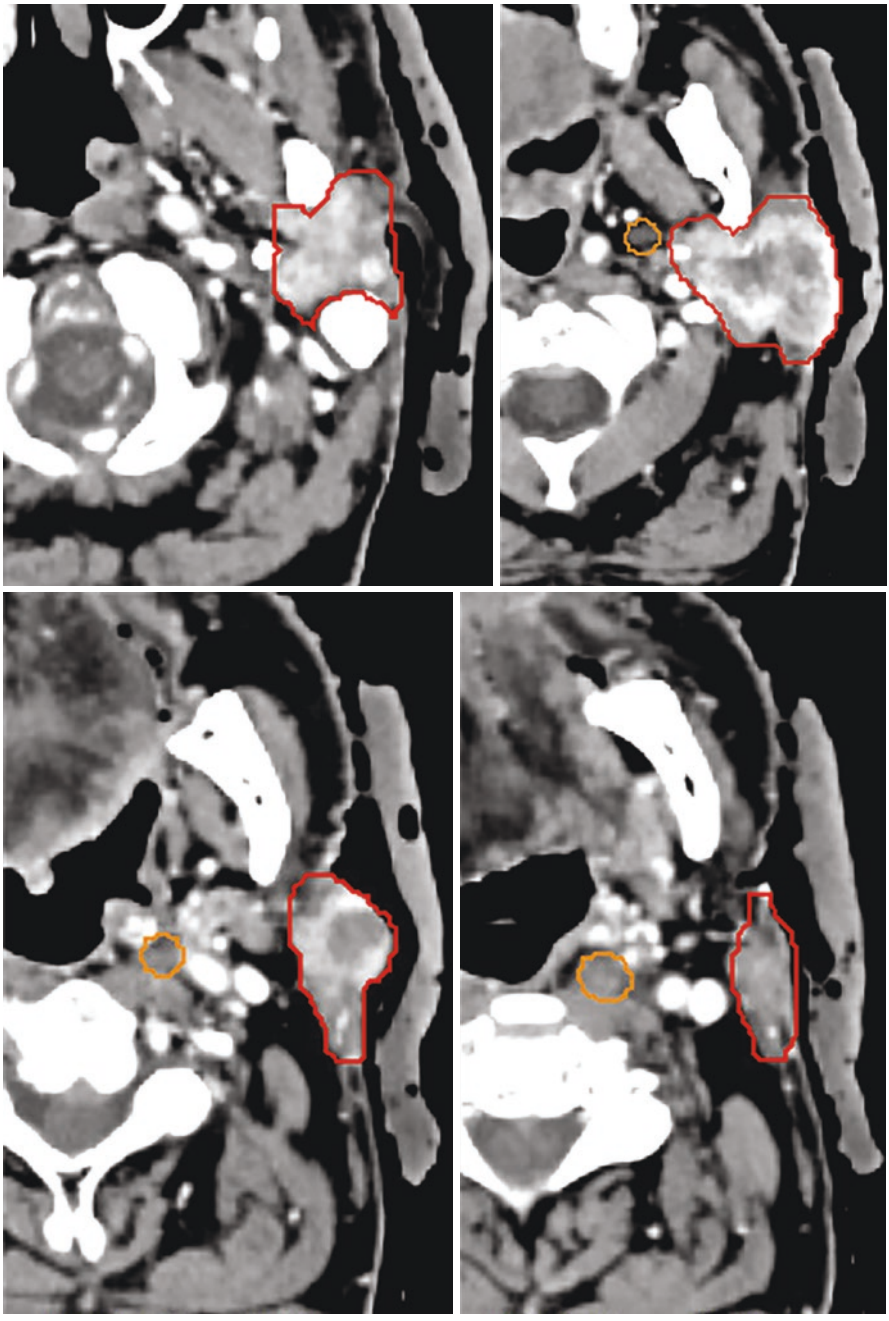
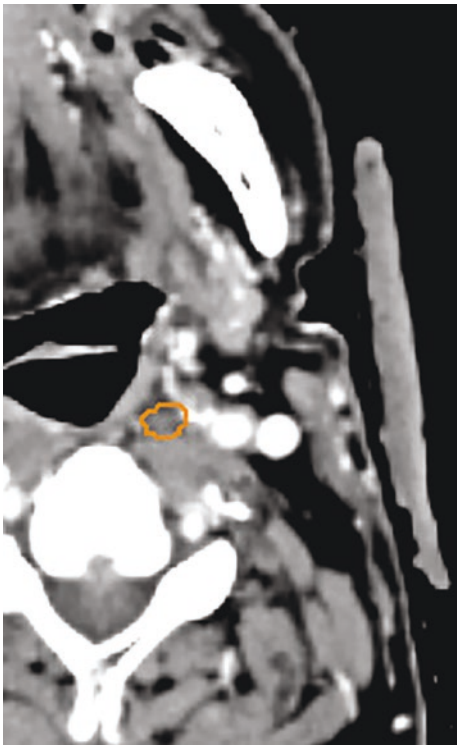


Fig. 3.6 Primary parotid tumor. A 91-year-old gentleman presented with facial nerve palsy secondary to a poorly-differentiated carcinoma in the left parotid (red) with two retropharyngeal nodes (orange). He received 50 Gy in five fractions, two fractions per week. He achieved a complete clinical response and facial nerve function returned. A minor paralytic ectropion of the eye will be treated with canthotomy and canthopexy. There is no evidence of disease at 6 months



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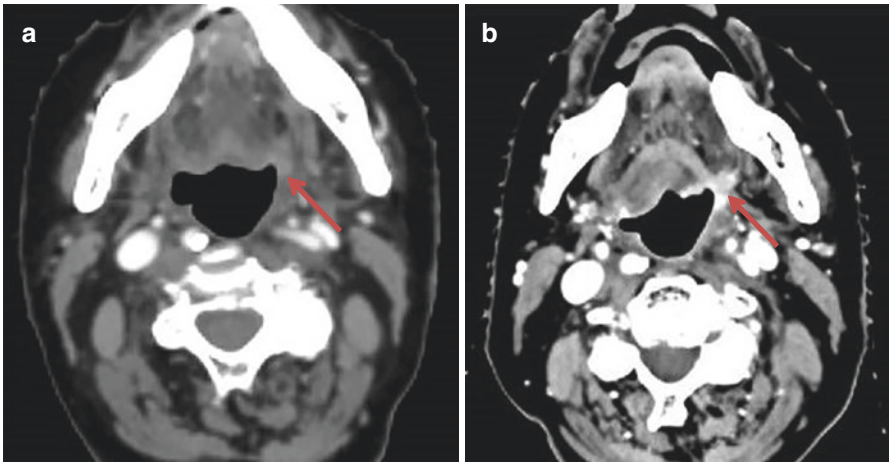


Fig. 3.7 Double-contrast simulation CT when MRI is not available. A 79-year-old lady with a T1N1 squamous cell carcinoma of the base of tongue had single-contrast (80 mL) CT simulation (**a**) that did not adequately visualize the GTV (arrow). (**b**) Double-contrast (160 mL) CT simulation allowed for excellent GTV (arrow) definition

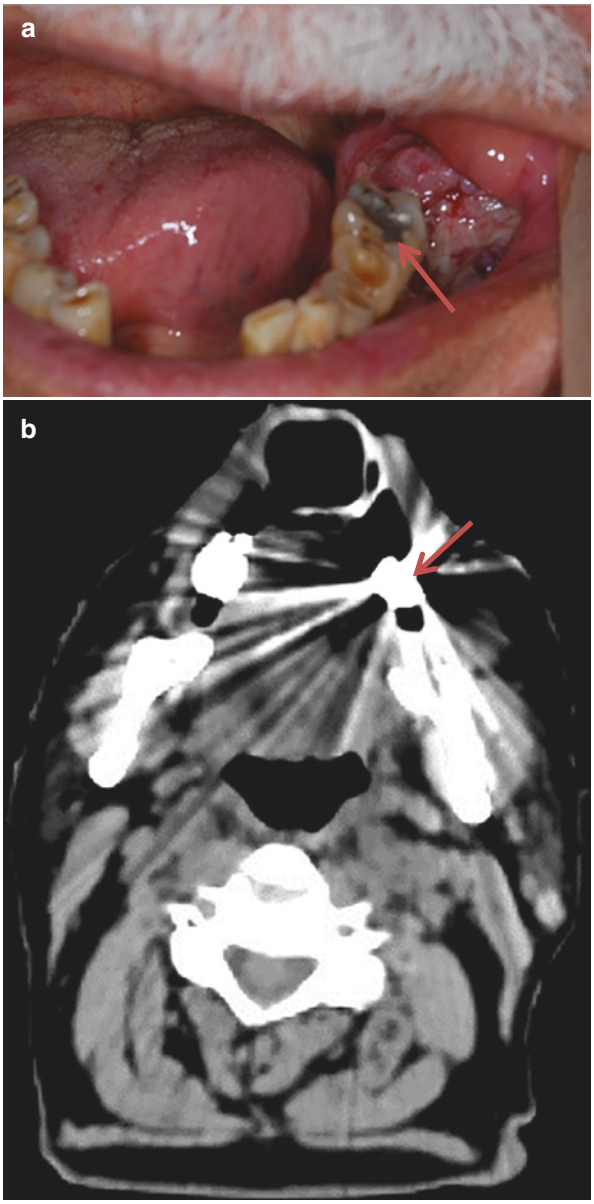
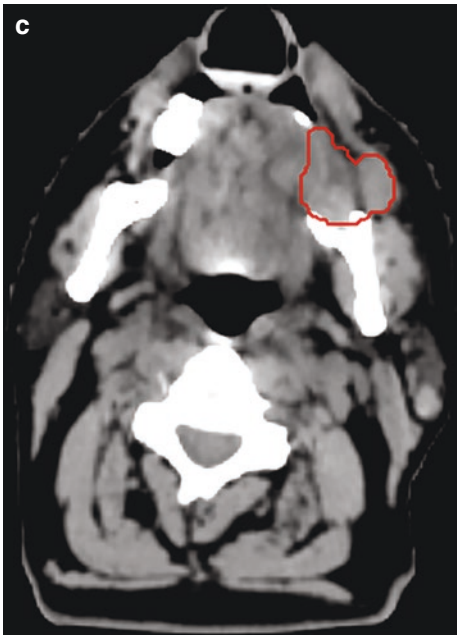


Fig. 3.8 CT artefact removal. An 87-year-old frail gentleman, with an MRI-incompatible pacemaker, was diagnosed with a (**a**) squamous cell carcinoma of the left mandibular gingivobuccal sulcus. (**a**, **b**) Artefact caused by a dental filling (arrow) severely impacted target visualization. (**c**) GTV delineation (red) was made possible by tooth extraction. Alternatively, these can be replaced with non-metal fillings



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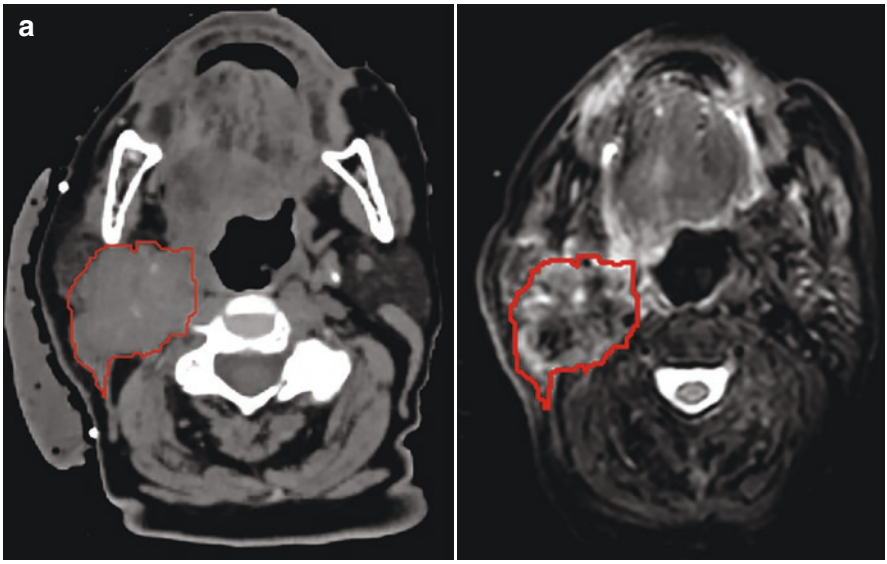

Fig. 3.9 HNC recurrence with discordant post-treatment imaging. An 83-year-old lady treated surgically 3 years previous for a squamous cell carcinoma of the right tongue presented with a painful, right level II nodal mass deep to the parotid and extending into the parotid, parapharyngeal space, and carotid sheath. She was not a candidate for radical chemoradiation. She received 45 Gy in five fractions, two fractions per week. (**a**) GTV (red) delineation was aided by MRI fusion; (CT on the left, MRI on the right). (**b**) While her pain had improved, MRI at 4 months after treatment showed possible progression at T1 (left) but response on T2 (right). (**c**) At 9 months, MRI shows disease stability and the patient is pain-free

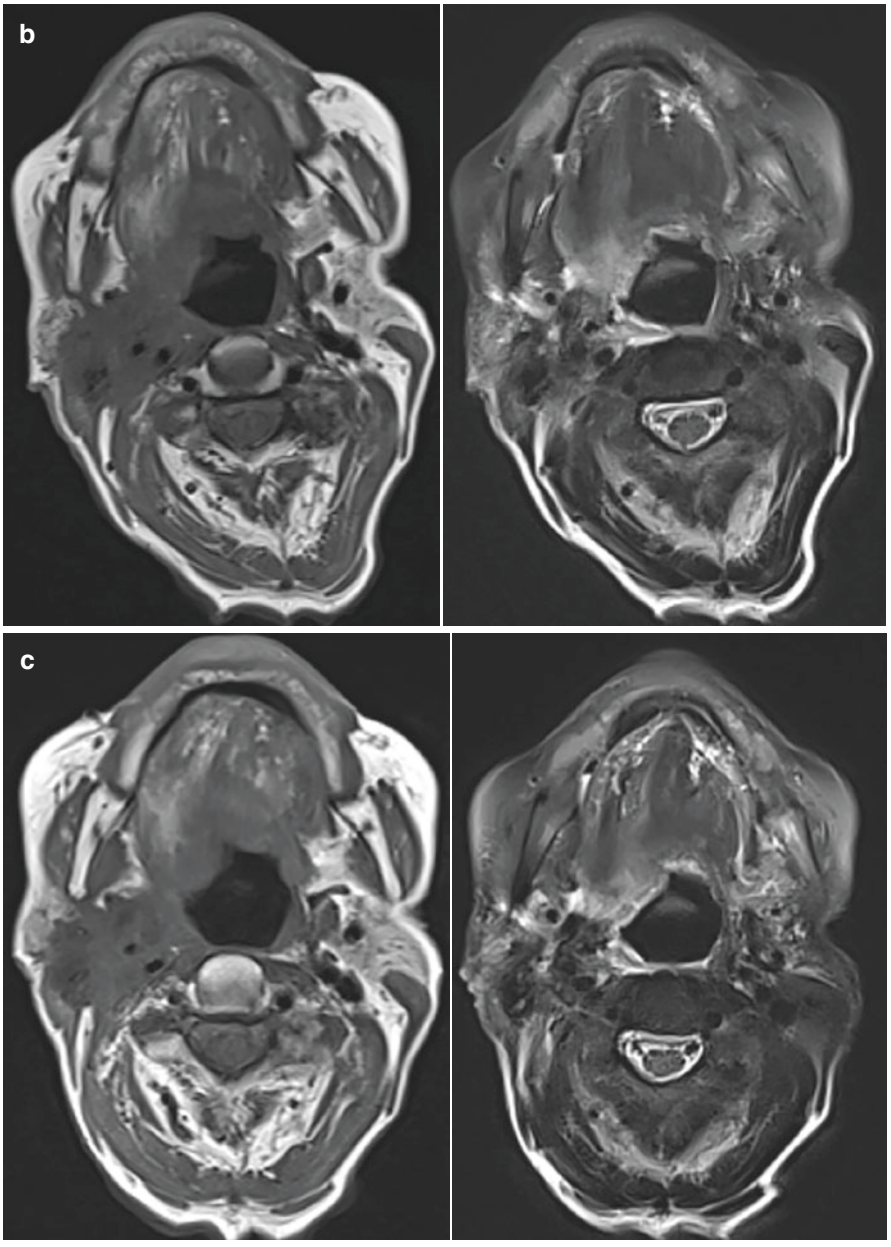

Fig. 3.9 (continued)

treatment based on host (performance status [Fig. 3.8]), and non-host factors (distance from hospital, availability of social/financial/psychological supports). At high volume centers, Head and Neck stereotactic body radiotherapy (SBRT) can be considered as a palliative treatment that may provide more durable local control than standard palliative approaches in patients who are not candidates for standard radical curative treatment. Previously, HN SBRT was primarily considered in re-irradiation, but the greater value of SBRT may be in the un-irradiated setting, where the extended treatment and recovery time of radical therapy may be undesirable or unrealistic for certain patients. SBRT can achieve durable local control [1] with a shortened treatment course and acceptable side effect profile.

- HN SBRT requires a highly experienced multidisciplinary team of medical physicists, dosimetrists, and radiation therapists.
- Accurate GTV delineation is critical for safe HN SBRT. Intraoral photos to document clinical exam details can be valuable. Neuroradiology review can clarify tumor extent and localize radiosensitive organs at risk.
- Contrast-enhanced computed tomography (CT) simulation is required for precise volume definition, with MRI (simulation) fusion greatly improving gross disease visualization. If MRI is not available, double-contrast CT simulation (Fig. 3.7) can be used. Dental fillings that create artefact and impact visualization should be removed for SBRT (Fig. 3.8).
- Five-point thermoplastic mask and daily cone beam CT (CBCT) matching allows for reproducible immobilization and reduction of PTV margins to 3 mm. Toxicity is additionally minimized by eliminating the traditional comprehensive microscopic volumes.
- The standard dose range to the GTV is 40–50 Gy, two fractions per week, with 45 Gy most commonly prescribed. The HN SBRT literature reports radiation prescriptions in the range of 35–50 Gy in 3–8 fractions [1–3, 4]. A high dose and low dose CTV expansion of the GTV is NOT used. A microscopic $CTVn_{25}$ can be created for immediately adjacent at-risk lymph node sites. A microscopic dose is not expanded from the GTV (Table 3.1). A dose-reduced $PTV_{35\text{-}40}$ is created with a 3-mm expansion of the GTV/high-dose CTV.
- The hot spots should lie within the GTV and away from organs at risk. A conformity index of 1.1 of the $GTV_{40–50}$ and $PTV_{35–40}$ is desirable.
- Target coverage must be compromised when in proximity to critical neurological structures (brachial plexus, optic pathways, brain, and brainstem). Dose to the carotid artery, however, should not compromise target coverage, except in re-irradiation [5].
- A strong quality assurance (QA) program is needed. Our center employs a modified Winston–Lutz isocenter alignment test to ensure tolerance within 2.5 mm [6]. Daily CBCT to match to bone and soft tissue is imperative; because the number of CBCTs is minimal, attempts to decrease the CBCT dose are of little value and should not preclude high-quality CBCT images.
- The rate of regression post-SBRT is variable and maximal response is often achieved beyond traditional timelines (>3 months).

Table 3.1 Target volumes

Target volumes	Definition and description
$GTV_{40–50}$	**Primary**: All gross disease on physical exam and imaging, including T1-gadolinium, T1 with fat saturation, and T2 MRI sequences Fusion of contrast-enhanced simulation CT with MRI If patient factors preclude MRI, GTV visualization on simulation CT can be enhanced using double contrast (Fig. 3.8) **Neck lymph nodes**: With necrotic center, or that are PET-avid
$CTV_{40–50}$	With precise GTV delineation, this volume is equal to $GTV_{40–50}$
$PTV_{35–40}$	$CTV_{40–50}$ (equivalent to $GTV_{40–50}$) + 3 mm, with daily CBCT
$CTV_{35–40}$	Suspicious nodes (round, enhancing)
$PTV_{30–35}$	$CTV_{35–40}$ + 3 mm if this volume is near other high-dose volumes and good cone beam match is expected If the above cannot be achieved, $CTV_{35–40}$ + 5 mm equals $PTV_{30–35}$
CTV_{25}	Includes high-risk lymph node basins immediately adjacent to treatment volumes, where repeat radiation to regional recurrence would be difficult
PTV_{25}	CTV_{25} + 3–5 mm

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Larynx Cancer

4

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Contents

4.1 General Principles of Anatomy and Patterns of Spread

- The larynx is divided into three subsites: the supraglottis, glottis, and subglottis.
- The supraglottic larynx includes the ventricles, false vocal cords (FVC), arytenoids, aryepiglottic (AE) folds, and epiglottis (suprahyoid, infrahyoid, and laryngeal surface).
  - Bilateral elective nodal irradiation is warranted for all supraglottic larynx.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_4

- The glottic larynx includes the true vocal cords (TVC), anterior commissure, posterior commissure, and the infraglottic space (0.5 cm inferiorly from the free margin of the true vocal cords).
  - Early-stage (T1–T2 N0) does not require elective nodal irradiation.
  - Advanced (≥T3 or node-positive) glottic cancers require bilateral elective nodal irradiation and small larynx-only fields are inappropriate.
- The subglottic larynx extends from the inferior border of the glottis to the superior border of the trachea.
  - Bilateral elective nodal irradiation including level VI should always be treated due to a propensity for nodal spread.
- TVC mobility must be assessed on laryngoscopy (normal, hypomobile, fixed).
  - A medialized fixed cord indicates recurrent laryngeal nerve injury.
  - A lateralized fixed or hypomobile cord indicates injury to the intrinsic laryngeal muscles and is often seen with laryngeal cancer.
- The paraglottic and pre-epiglottic spaces are connected fat planes with no barriers to spread between then. The paraglottic space is bounded by the thyroid cartilage laterally and the TVCs and FVCs medially. The pre-epiglottic fat space is bounded by the mucosal surface of the vallecula superiorly, hyoid/thyroid strap muscles anteriorly, root of the epiglottis posteriorly, and inferiorly communicates with the paraglottic space.
- A dedicated CT and/or MRI is highly recommended for clinically staged T1–2 glottic larynx to rule out paraglottic extension which changes staging to T3.
- The thyroid cartilage has an inner and outer cortex. Invasion of the inner cortex only signifies T3 disease, while invasion through the outer cortex signifies T4 disease. The degree of invasion can only be assessed through imaging (i.e. CT and/or MRI) with appropriate windowing and must be carefully assessed.
- For true T4 disease, total laryngectomy is the preferred approach, although an organ preservation approach can be considered in select cases.

4.2 Diagnostic Workup Relevant for Target Delineation

- In addition to physical examination with laryngoscopy.
  - Imaging should include a dedicated, thin slice (1–2 mm cuts) high-resolution CT and/or MRI of the larynx with IV contrast. Careful attention should be directed towards evaluation of pre-epiglottic or paraglottic space extension and invasion of the thyroid cartilage.
  - A contrast-enhanced MRI is also helpful for visualizing the locoregional extent of disease. Note that more than 1 cm of base of tongue invasion, was an exclusion criterion for larynx preservation trials (RTOG 91–11).
  - PET/CT is helpful for identifying lymph nodes and metastatic disease.

4.3 Simulation and Daily Localization

- The patient should be simulated supine with head rest with the neck extended in a five-point customized Aquaplast mask that immobilizes the head, neck, and shoulders. A shoulder pull board can be used to lower the shoulders out of the beam angle path.
- For patients with many metal fillings, a custom mouthguard can be helpful to absorb electron scatter and mitigate treatment-related mucositis.
- The CT simulation should use ≤3 mm slices with IV contrast.
- The CT should include the entire vertex of the head through the carina.
- The isocenter is typically placed at the arytenoids if there is no subglottic or hypopharyngeal extension. If either is present, then the isocenter is placed 1 cm inferiorly.
- For postoperative cases, it is helpful to place a radiopaque marker on the scar.
- There are various appropriate IGRT approaches. Daily imaging ideally consists of daily cone beam CT aligned to the larynx. Daily kilovoltage imaging aligned to bone and weekly cone beam CTs are also adequate.
- Patients should be instructed not to swallow during simulation scan, IGRT or during treatment.
- Placement of bolus is needed to ensure adequate anterior coverage of the tumor, especially for those tumors that involve the anterior commissure.

4.4 Target Volume Delineation and Treatment Planning

- The GTV should be delineated using all relevant clinical information derived from laryngoscopy, CT, MRI, and PET (Table 4.1).
- Positive lymph nodes in the neck should be defined as those with central necrosis, extracapsular extension, and/or a short axis diameter >1 cm. For borderline

Table 4.1 Suggested target volumes for gross disease in locally advanced glottic, supraglottic, or subglottic laryngeal cancers

Target volumes	Definition and description
GTV 70	Primary: All gross disease on physical examination and imaging
	Neck nodes: All nodes ≥1 cm or PET positive should be included as nodal GTV. Include borderline lymph nodes in doubt as GTV to avoid undertreatment
CTV 70	Usually same as GTV70 (typically no need to add margin unless there is uncertainty about the extent of gross disease). An additional 0–0.5-cm margin may be to GTV70 to create CTV70
PTV 70	CTV70 + 3–5 mm, depending on reproducibility of daily patient positioning and available IGRT

nodes, those with FDG avidity should be considered disease (Table 4.1). Small nodes that are bean-shaped or exhibit a fatty hilum are more likely benign. Enlarged RP nodes, although unusual in laryngeal cancer, should be considered positive even if small.

- Suggested target volumes are detailed in Tables 4.1, 4.2, and 4.3 (Figs. 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, and 4.7).

Table 4.2 Suggested target volumes for subclinical disease in supraglottic, subglottic, or locally advanced glottic laryngeal cancers

Target volumes	Definition and description
CTV 54–60[a]	CTV 54–60 should encompass the entire GTV
	Includes the entire larynx, from the bottom of the hyoid or the top of the thyroid notch to the bottom of the cricoid cartilage and extend inferiorly when necessary
	High-risk nodal regions include levels II–IV and the retrostyloid space on the involved node-positive neck In the node-positive neck, level II should be treated to the base of skull Level VI should be included if there is subglottic extension or a trach
PTV 54–60[a]	CTV 54–60 + 3–5 mm, depending on immobilization, IGRT, etc.
CTV 54[b]	Levels II–IV of the uninvolved neck In the node-negative neck, the superior border of level II stops where the posterior belly of the digastric muscle crosses the internal jugular vein (or the caudal edge of the lateral process of C1) Level IB and V nodes are not included unless there is gross involvement of nodes at those levels RP nodes may be covered at physician discretion on the side of bulky adenopathy because of retrograde flow Level VII coverage is recommended for subglottic extension or hypopharyngeal involvement
PTV 54[b]	CTV 54 + 3–5 mm, depending on immobilization, localization, etc.

Subclinical disease may be drawn as one CTV or two CTVs (high risk and low risk)
[a] High-risk subclinical dose: 1.8–2 Gy per fraction to 54–60 Gy
[b] Low-risk subclinical dose: 1.54–1.8 Gy per fraction to 54 Gy

Table 4.3 Suggested target volumes for postoperative laryngeal cases

Target volumes	Definition and description
CTV 60[a]	CTV 60 should encompass the entire operative bed, the scar, the stoma, and the node-positive neck (levels II–IV, the retrostyloid space and involved nodal stations)
CTV 54[a]	The node-negative neck Levels VI and VII should be included if there is subglottic extension or a stoma
CTV 66[b]	Areas of positive margins, extracapsular extension, or stoma boost if indicated
PTV	CTV + 3–5 mm, depending on immobilization, IGRT, etc.

Subclinical disease may be drawn as one CTV or two CTVs (high risk and low risk)
[a] Subclinical dose: 1.8–2 Gy per fraction to 54–60 Gy
[b] CTV 66 may be delivered with a sequential cone down or dose painting

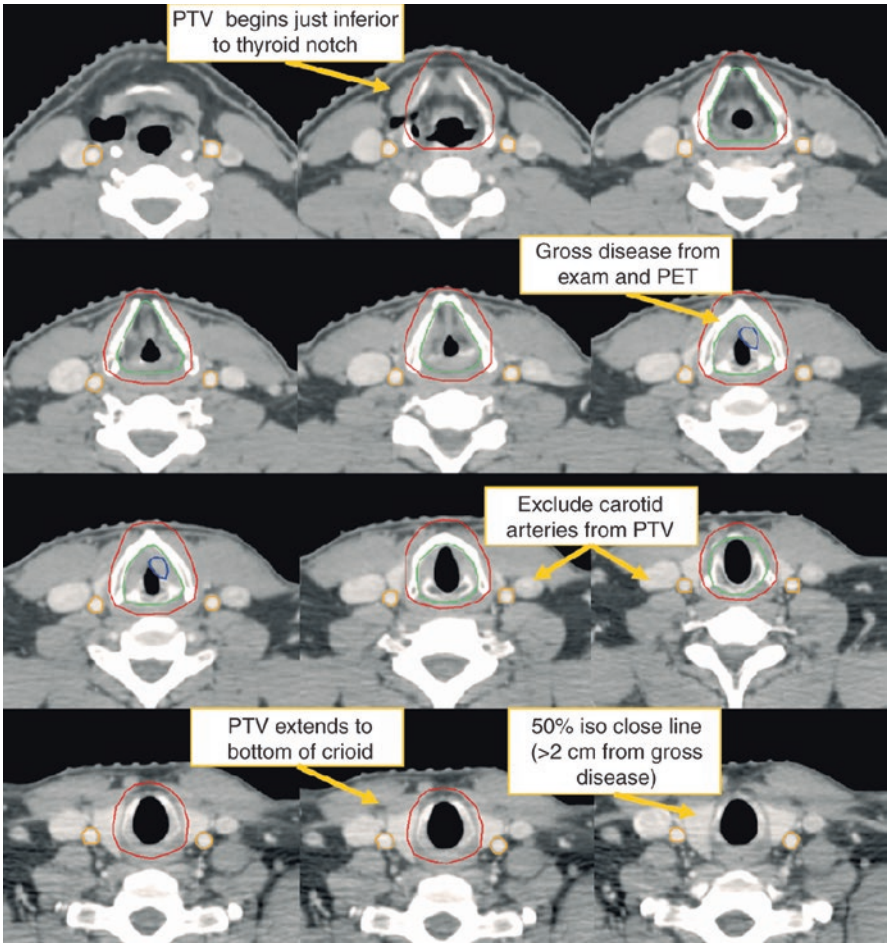

Fig. 4.1 A patient with T1aN0 squamous cell carcinoma of the left vocal cord. Please note that these are representative slices and not all slices are included. *Blue* GTV, *Green* CTV, *Red* PTV. GTV is delineated by laryngoscopy findings only. For T1 larynx tumors, there are typically no CT abnormalities. The entire larynx is delineated as CTV to include both false and true vocal cords, anterior and posterior commissures, arytenoids and aryepiglottic folds, as well as the subglottic region. The PTV extends from thyroid notch to the bottom of the cricoid cartilage. A 5-mm margin added in all directions except posterolaterally was limited to 3 mm to respect the ICA. The *orange circle* is the carotid artery

- **Early stage disease** (T1N0 or T2N0):
  - The CTV should encompass the entire larynx including the anterior and posterior commissures and the arytenoids. We suggest coverage of the entire glottis superiorly from the bottom of the thyroid notch inferiorly to the cricoid cartilage for T1 tumors (Figs. 4.1 and 4.2), and inferiorly to the first tracheal ring for T2 tumors. It is critical to ensure coverage inferiorly as most recurrences tend to be inferior. Ipsilateral cord can be considered.

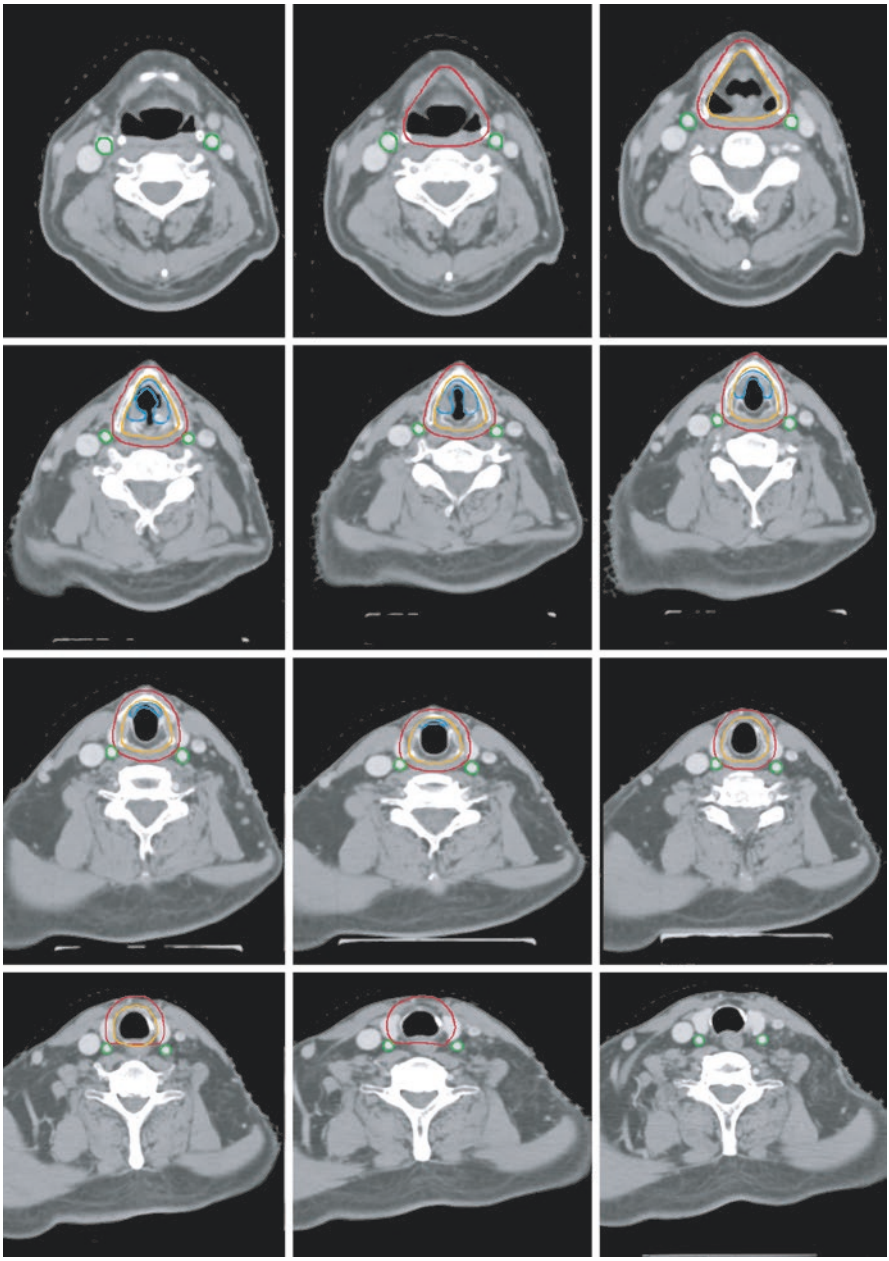

Fig. 4.2 A patient with T1bN0M0 squamous cell carcinoma involving both vocal cords. *Blue* = GTV, *Orange* = CTV, *Red* = PTV

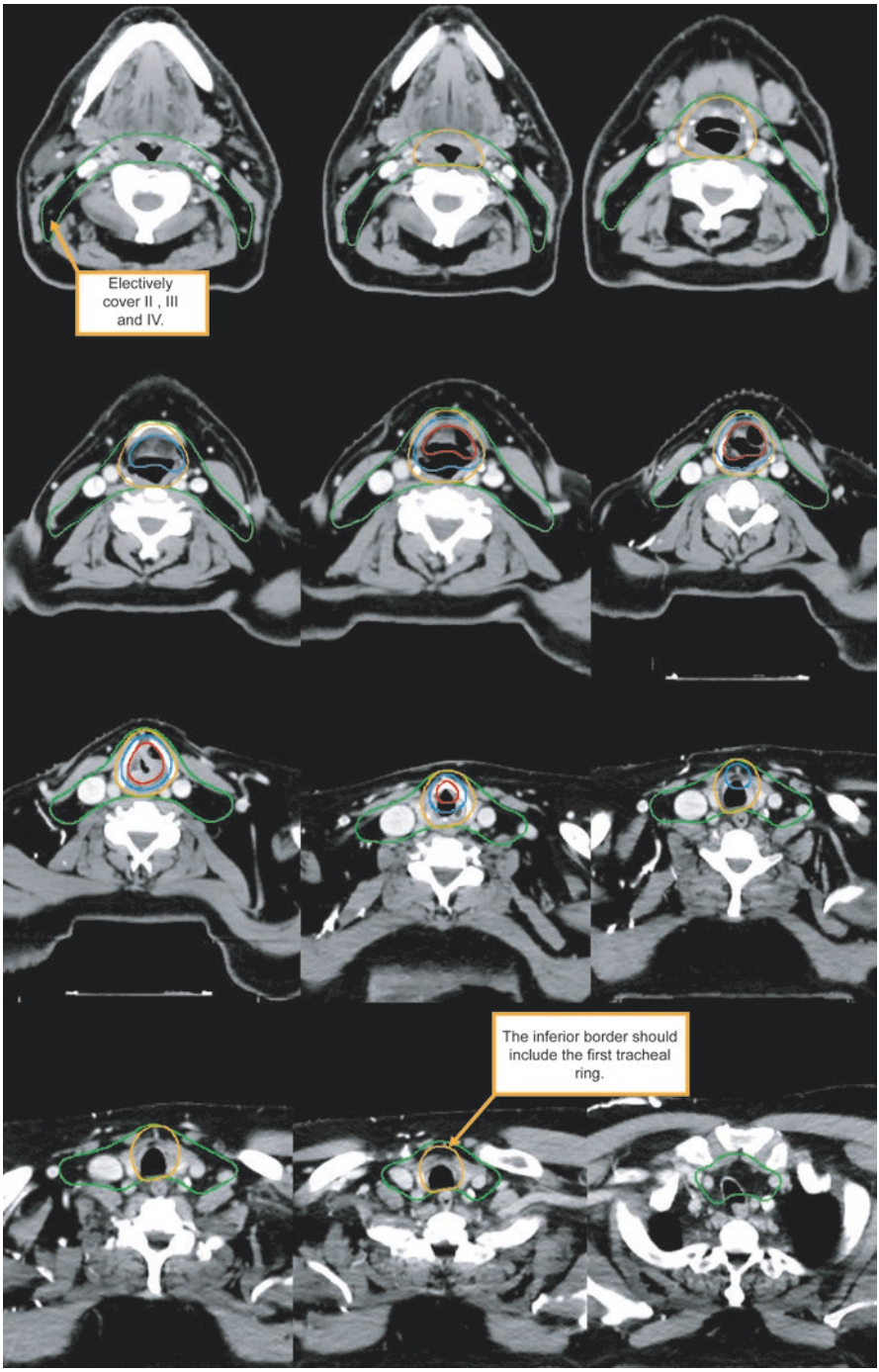

Fig. 4.3 A patient with T2N0M0 left supraglottic squamous cell carcinoma with involvement of left ventricle and true vocal cord, anterior commissure, and anterior aspect of right supraglottic larynx. *Red* = GTV, *Green* = CTV54, *Orange* = CTV60, *Blue* = CTV70. Please note that these are representative slices and not all slices are included

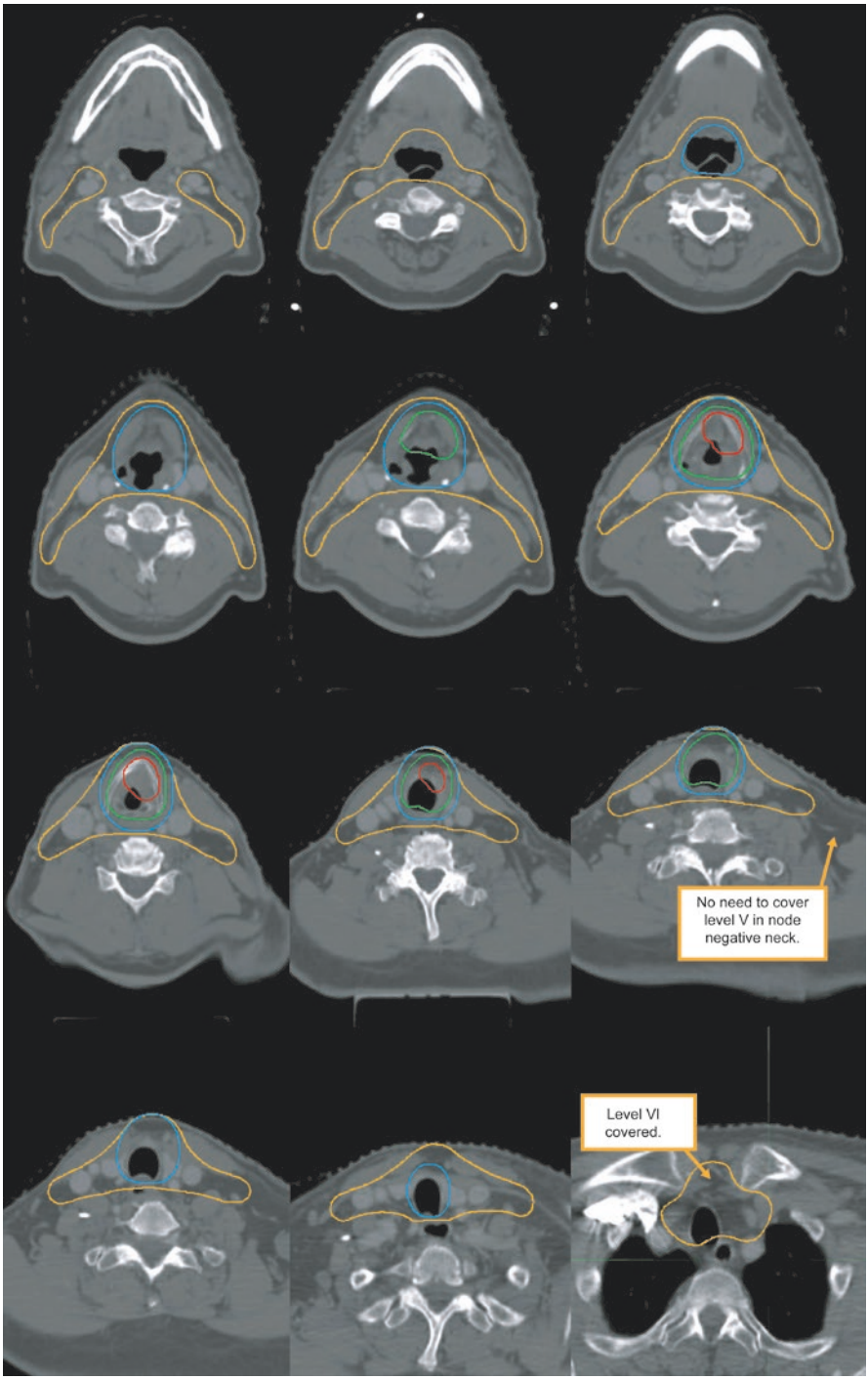

Fig. 4.4 A patient with T3N0M0 squamous cell carcinoma of the left vocal cord with extension to anterior commissure and right cord, with subglottic extension and extension into inner thyroid cartilage. *Red* = GTV, *Orange* = CTV54, *Blue* = CTV60, *Green* = CTV70

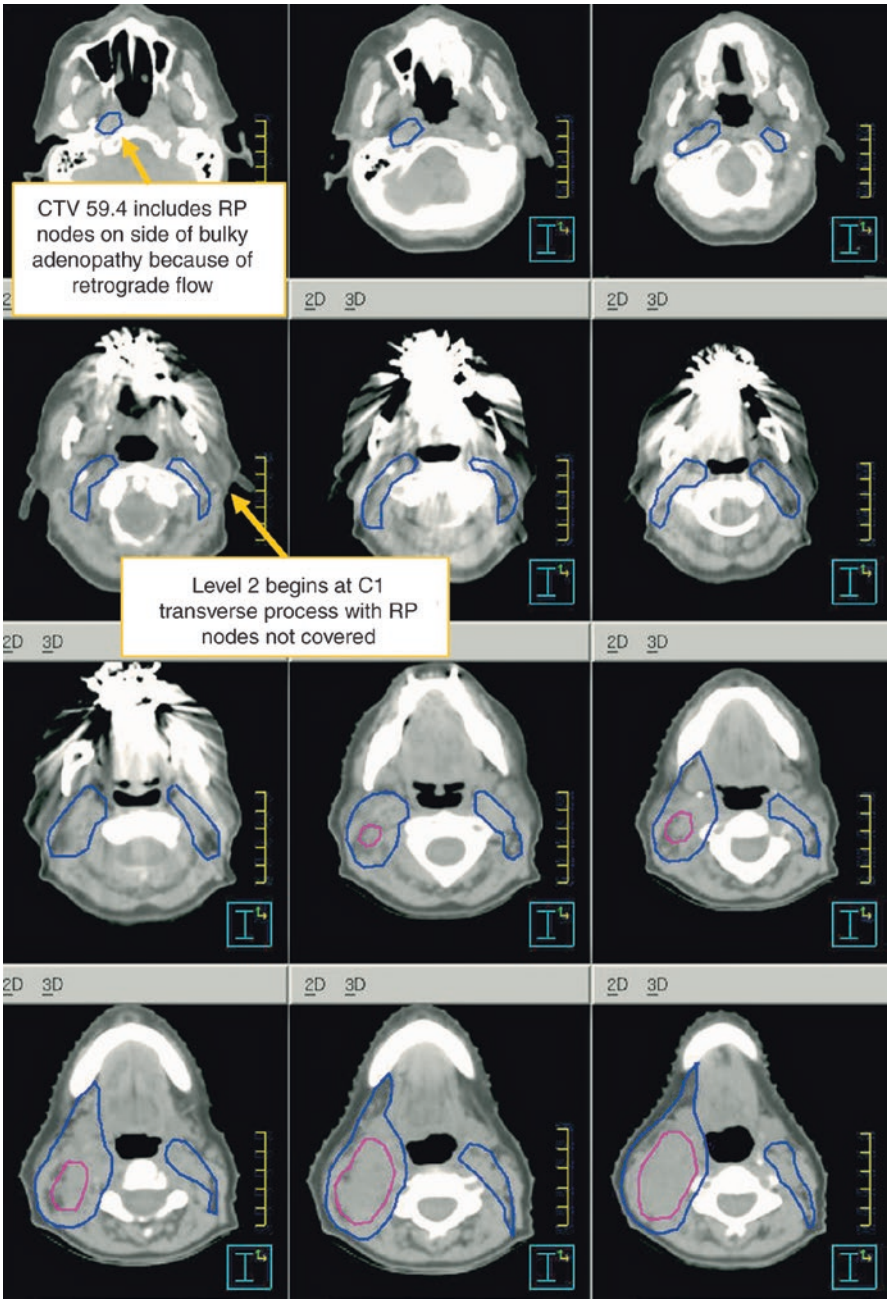

Fig. 4.5 A patient with T2 N2c M0 squamous cell carcinoma of the epiglottis involving right AE fold and bilateral cervical lymph nodes. Please note that these are representative slices and not all slices are included. *Magenta* GTV LN, *Purple* GTV primary, *Blue* CTV 60, *Orange* CTV 54. The treating MD in this case chose to include level IB which can be omitted. In addition, the treating MD did not treat the upper trachea which if indicated should be included

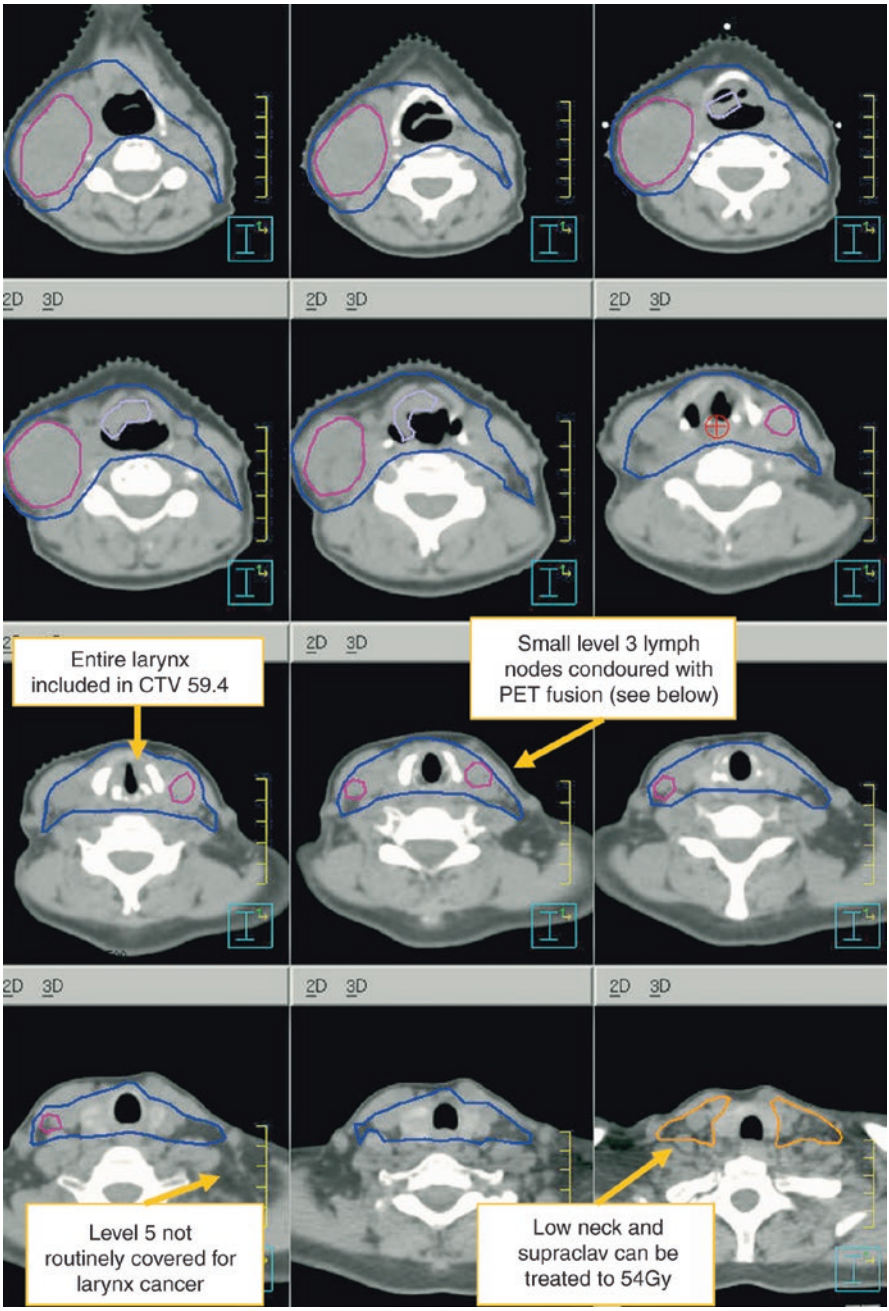

Fig. 4.5 (continued)

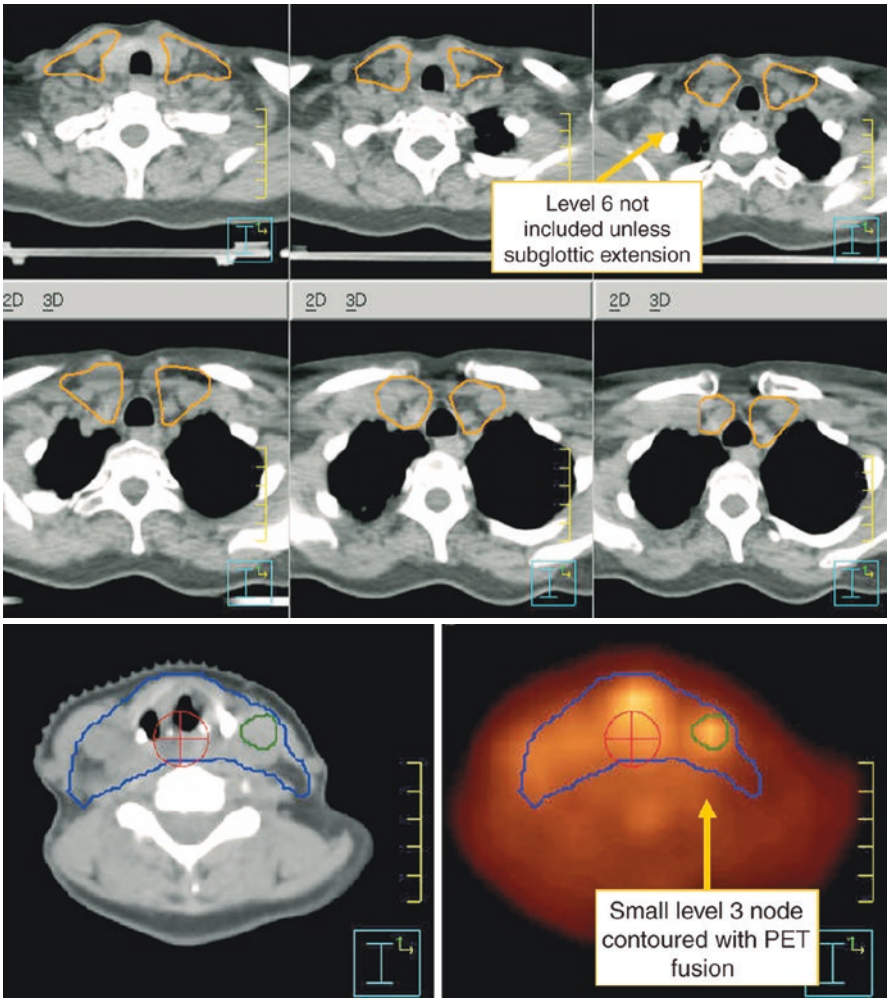

Fig. 4.5 (continued)

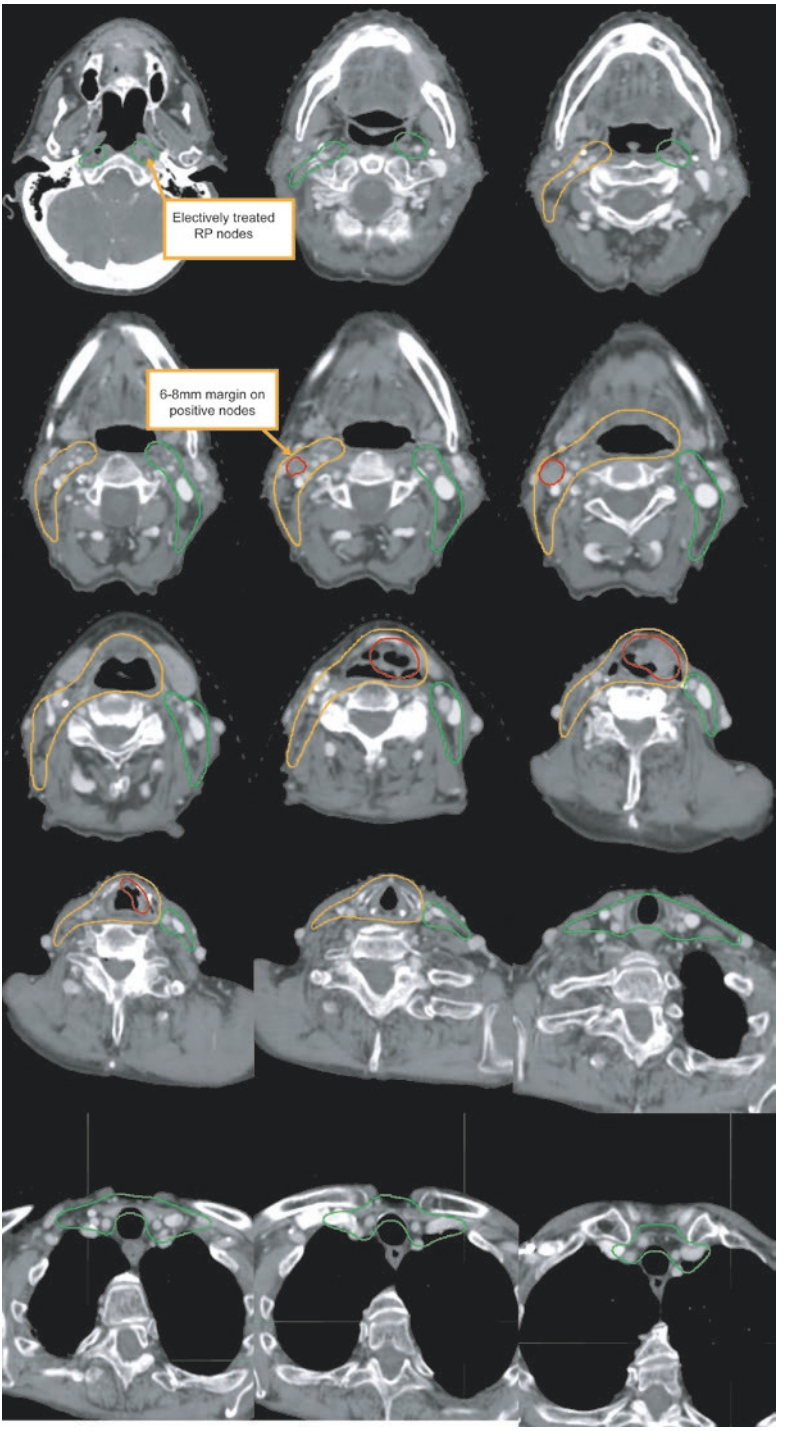

Fig. 4.6 A patient with T3N1M0 supraglottic squamous cell carcinoma with subglottic extension. GTV is in *red*. CTV60 is in *orange*. CTV54 is in *green*

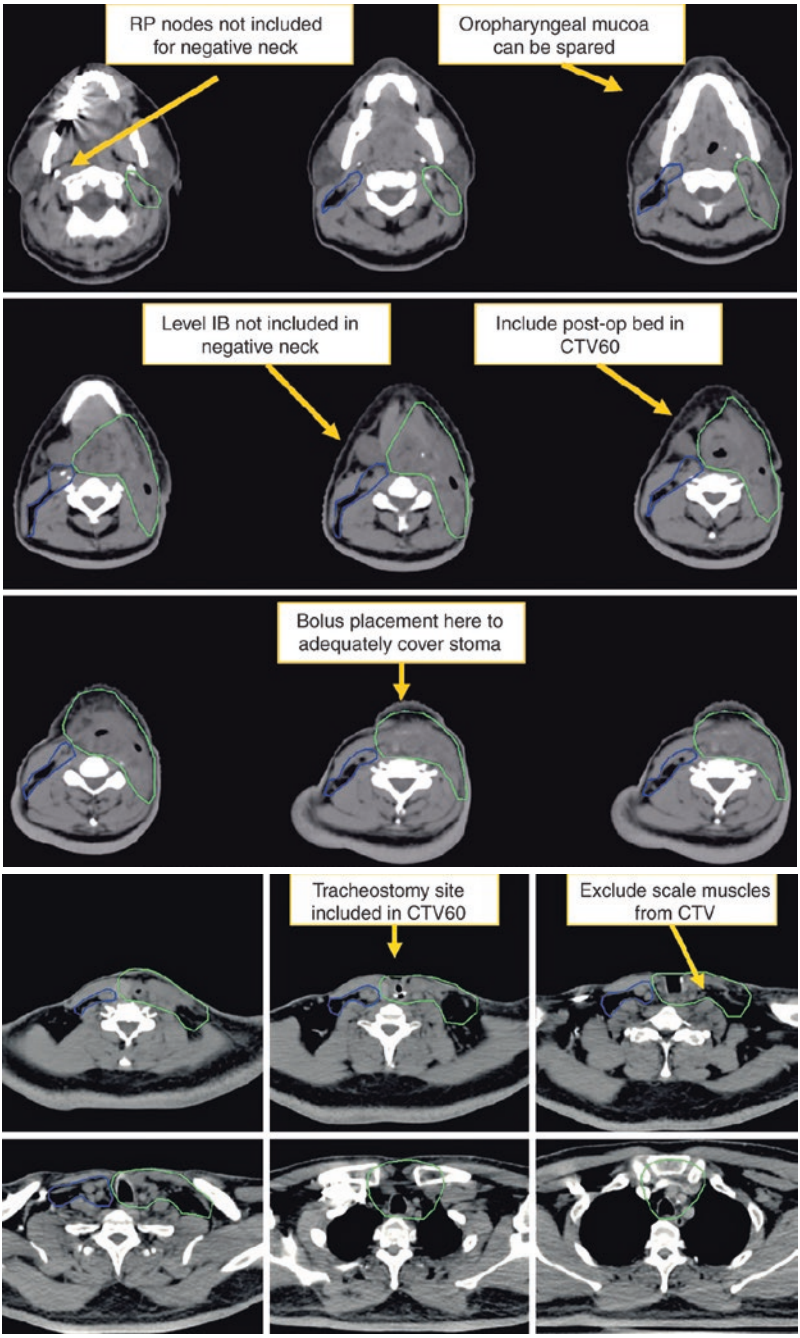

Fig. 4.7 A patient with pT4 N0 M0 squamous cell carcinoma of the left glottis status total laryngectomy and left neck dissection. In the postoperative setting, the high-risk CTV (the entire operative bed) receives 60 Gy in 2 Gy/fraction and the low-risk CTV receives 54 Gy in 1.8 Gy/fraction. *Blue* CTV 54, *Green* CTV 60

- Glottic Larynx.
  Carotid-sparing IMRT should be considered [1–3].
  A CT-based opposed laterals technique is also acceptable. The superior border should extend to the bottom of the hyoid bone or the top of the thyroid notch. The inferior border is the bottom of the cricoid cartilage. The posterior border is the anterior edge of the vertebral bodies. There should be 1 cm flash anteriorly. It may be necessary to angle the beams 5–10° inferiorly to avoid the shoulders. Often 15–30° wedges are used to ensure a homogeneous dos distribution throughout the larynx.
  For T1N0 glottic larynx tumors, we use a dose of 63 Gy in 28 fractions as randomized evidence supports a local control advantage with hypofractionation at 2.25 Gy/fraction [4].
  For T2N0 glottic larynx tumors, there are local control benefits with doses >65 Gy and dose per fraction ≥2.25 Gy [5]. We treat to 65.25 Gy in 29 fractions at 2.25 Gy per fraction. In select cases, treatment with chemoradiotherapy may be acceptable.
- Due to higher risks of occult nodal disease in supraglottic and subglottic cancers, bilateral levels II–IV and in many instances level VI nodal chains should be electively radiated. The superior limit of level II may stop where the posterior belly of the digastric muscle crosses the internal jugular vein (Fig. 4.3).

- **Advanced stage disease** (≥T3 or node-positive disease):
  - Bilateral necks should be included.
    We favor a sequential cone down approach. An initial plan (30 fractions) with a dose-painting approach delivers 54 Gy (1.8 Gy/fx) and 60 Gy (2 Gy/fx) to the low and high-risk subclinical regions, respectively. This is followed by a cone down plan (five fractions) which delivers an additional 10 Gy to gross disease only for a total of 70 Gy over 35 fractions.
    One dose painted IMRT plan is also acceptable. An example fractionation: over 35 days to deliver 2 Gy/fx, 1.8 Gy/fx, and 1.54 Gy/fx to achieve doses of 70 Gy to gross disease, 63 Gy to high-risk subclinical disease, and 54 Gy to low-risk subclinical disease.
  - Extended IMRT plans are favored over the use of a low anterior neck (LAN) field. This is due to the risk of missing gross tumor or high-risk subclinical disease in the low dose region of the match-line.
  - One subclinical or two subclinical (high-risk, low-risk) CTVs may be contoured for microscopic disease (Table 4.2).
    The subclinical primary site CTV should encompass the entire larynx from the bottom of the thyroid notch to the first tracheal ring or extend inferiorly when necessary.
    The subclinical nodal CTV should encompass at least levels II–IV, and in many instances level VI (Fig. 4.4).
    In the elective node-negative neck, the superior border of level II stops where the posterior belly of the digastric muscle crosses the internal jugular vein (this is the superior most extent of an elective neck dissection and corresponds to the caudal edge of the lateral process of C1) (Fig. 4.5).

In the node-positive neck, level II should be treated to the base of skull and the ipsilateral retrostyloid nodes should be included. Cover level VI if there is subglottic involvement or a trach (Fig. 4.6).
See Table 4.2 for recommendations on coverage of levels IB, VII, and RP nodes.

- **Post-operative radiation**: Adverse pathologic features that warrant post-operative radiation as per NCCN v.2020 include positive margins, close margins, extra-nodal extension, pT4 primary, pN2–pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion. Concurrent chemotherapy should be added for extracapsular extension or positive margin.
  - The entire surgical bed, stoma, scar, and dissected node-positive neck should be included in a high-risk CTV to a dose of 60 Gy. Areas of positive margin or extracapsular extension may be boosted to 66 Gy (Fig. 4.7).
  - The undissected node-negative neck can be included in the low-risk CTV to a dose of 54 (Fig. 4.7).
  - The stoma may be boosted to 66 Gy for subglottic extension or if an emergent tracheostomy was performed. Anatomically, a stomal recurrence is a tracheo-esophageal node.
- **Radiation following induction chemotherapy**: In addition to post-chemotherapy targeting, pre-chemotherapy imaging should be fused for target delineation. The high-risk subclinical volume should include the pre-chemotherapy extent of disease and take into consideration the adjacent anatomical sites at risk for microscopic spread. This pre-chemotherapy CTV should be modified for anatomical differences after chemotherapy and exclude natural barriers to spread such as air and bone.
- **Planning**:
  - A PTV margin of 0.3–0.5 cm may be used, depending immobilization and laryngeal motion.
  - For patients with involvement of the anterior commissure, flash and bolus should be used to ensure adequate coverage of the superficial extent of gross or subclinical disease.
  - Care should be taken to limit the heterogeneity to 105% of prescription when treating over the larynx.

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Hypopharyngeal Carcinoma

5

Linda Chen, Yao Yu, and Nancy Y. Lee

Contents

5.1 Anatomy and Patterns of Spread

- The hypopharynx lies between the oropharynx superiorly and cervical esophagus inferiorly. This is a portion of the pharynx that is defined superiorly by the top of the hyoid bone (approximately C4) and inferiorly by the bottom of cricoid cartilage (approximately C6), with the larynx lying anteromedially. As such, hypopharynx tumors have a propensity to disrupt speech and swallow function.
- There are three subsites of the hypopharynx: the paired pyriform sinuses, posterior pharyngeal wall, and the post-cricoid region. Tumors have a tendency for submucosal spread with involvement of multiple sites of hypopharynx, the larynx, and adjacent soft tissue due to minimal barriers between anatomic sites [1]. Patterns of spread for each subsite are outlined in Table 5.1.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_5

Table 5.1 Hypopharyngeal subsite and respective patterns of spread

Hypopharynx subsite	Patterns of spread
Pyriform sinus	• Anteromedially: Arytenoids, aryepiglottic folds, intrinsic laryngeal muscles (which can result in vocal cord fixation), para-glottic space • Posterior: Constrictor muscles, prevertebral tissue • Lateral: Para-glottic space, Thyroid cartilage, and lateral neck • Superiorly: Oropharynx, pre-epiglottic space, thyrohyoid membrane (referred otalgia from the internal branch of superior laryngeal nerve) • Inferiorly: Post-cricoid area • Lymph nodes: Most commonly—RP, II, III. Additional levels at risk: level IV, and level VI (inferior tumors involving the apex)
Posterior pharyngeal wall	• Superiorly: Extension to the oropharynx • Inferiorly: Extension to the cervical esophagus • Posteriorly: Pre-vertebral fascia, retropharyngeal space • Lymph nodes: RP, II–IV
Post-cricoid region	• Anteriorly: Laryngeal invasion (vocal cord fixation) • Superiorly: Pyriform sinuses • Inferiorly: Cricoid cartilage, cervical esophagus • Lymph nodes: II–IV, paratracheal

- Hypopharynx cancers also have a high propensity for lymph node involvement due to an extensive submucosal lymphatic plexus. Bilateral cervical lymph nodes and lateral retropharyngeal lymph nodes are commonly involved [2–6]. Posterior level V involvement, level VI, and superior mediastinal LNs can be involved for post-cricoid region tumors and pyriform sinus tumors that are inferior and involve the apex [2, 5–9]. In patients who are clinically node negative, 30–35% of patients have pathologic lymph node involvement [7]. Level 1b is rarely involved but ranges between 5% and 20% in the node positive neck [2, 6].
- The pyriform sinuses are the most common site of hypopharynx cancer (65–85%) and are paired potential spaces which lie laterally and posteriorly to the larynx [10, 11]. The superior and widest portion of the pyriform sinuses are visualized endoscopically, on either side of the larynx with the medial wall formed by ary-epiglottic fold. The space narrows inferiorly until it reaches the apex at the crico-arytenoid joint, forming the shape of an inverted cone.
- The hypopharyngeal wall (10% of hypopharyngeal cancers) is a continuation of the lateral and posterior pharyngeal wall that lies between the oropharynx superiorly and the cervical esophagus inferiorly. It is composed of mucosa which encloses lateral and posterior constrictor muscles.
- The post-cricoid region (<5%) is the least common site for hypopharyngeal cancers. Mucosa is comprised of the posterior wall of the larynx, spanning from the arytenoids to the cricoid cartilage. Skip metastasis to the cervical esophagus can occur.

5.2 Diagnostic Workup Relevant for Target Volume Delineation

- Pathologically, the vast majority of hypopharyngeal cancers are squamous cell carcinomas. Variants such as verrucous carcinoma, basaloid squamous carcinomas, spindle cell carcinoma as well as minor salivary gland carcinomas comprise a minority of cases.
- Clinical history should focus on tobacco/alcohol use, otalgia (CN X involvement) respiratory function, voice quality as well as baseline swallow function, especially when considering organ preservation for locally advanced tumors.
- Clinical exam should include palpation of the base of tongue (evaluation of pre-epiglottic involvement), evaluation of laryngeal mobility (laryngeal invasion), presence of a thyroid click (absent in posterior lesions which anteriorly displace the larynx), and presence of cervical adenopathy should be evaluated.
- Endoscopic fiber-optic examination should be undertaken to identify whether adjacent mucosal subsites are involved as well as fixation of vocal cords, and is critical for AJCC 8 staging and treatment decision making (Table 5.2). Phonation and valsalva maneuvers during the exam can aid in visualizing the hypopharynx.

Table 5.2 AJCC 8 staging hypopharynx cancer

T1	– Tumor limited to **one subsite** of hypopharynx – Tumor **≤2 cm** or smaller in greatest dimension
T2	– Tumor invades **more than one subsite** of hypopharynx or an adjacent site – Tumor **2–4 cm** – Without fixation of hemilarynx
T3	– Tumor **larger than 4 cm** in greatest dimension – Or with **fixation of hemilarynx** – Or **extension to esophageal mucosa**
T4a	– Tumor invades **thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle or central compartment** soft tissue (pre-laryngeal strap muscles and subcutaneous fat)
T4b	– Tumor invades **prevertebral fascia, encases carotid artery, or involves mediastinal structures**
N0	No regional lymph node metastasis
N1	– Metastasis in a **single ipsilateral lymph node** – **≤3 cm and ENE(−)**
N2a	– Metastasis in a **single ipsilateral node 3–6 cm and ENE(−)**
N2b	– Metastases in **multiple ipsilateral nodes**, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in **bilateral or contralateral lymph nodes**, none larger than 6 cm in greatest dimension and ENE(−)
N3a	Metastasis in a **lymph node larger than 6 cm** in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and **clinically overt ENE(+)**

- Diagnostic, contrast-enhanced CT or MRI should also be utilized to evaluate extent of disease. Special attention to pre-epiglottic or paraglottic space involvement, laryngeal extension, gross cartilage invasion, soft tissue extension, esophageal invasion, and extra-capsular spread [12–15].
- PET/CT can also help to delineate borders, as this is a sensitive modality that can aid in defining extent of disease (i.e. inferior apical tumor boundaries which can be subtle) as well as hypermetabolic malignant cells within lymph nodes [16–18].

5.3 Simulation and Daily Localization

- **Positioning**: Patient should be simulated supine with head rest. The neck should be hyperextended or a shoulder pull board can be used to lower the shoulders out of the beam angle path. Custom immobilization should be used with a thermoplastic mask. In post-operative cases, all surgical scars should be wired.
- **Imaging**: Thin-cut 3 mm CT slices with imaging from the top of the skull down to T5. Intravenous contrast should be administered unless medically contraindicated. Isocenter placement typically at the arytenoids.
- **Localization**: Daily imaging ideally consists of daily cone beam CT aligned to the larynx. Daily kilovoltage imaging aligned to bone and weekly cone beam CTs are also adequate.

5.4 Target Volume Delineation and Treatment Planning

- Intensity modulated radiation therapy (IMRT) planning is recommended. An initial plan (30 fractions) with a dose-painting approach with 54 Gy/1.8 Gy fractions and 60 Gy/2 Gy fractions are used for the low- and high-risk subclinical regions. This is followed by a 10 Gy cone down to gross disease for a total of 70 Gy over 35 fractions. A single dose-painted plan such to 70 Gy over 33–35 fractions is also appropriate (Fig. 5.1).
- Extended IMRT plans are recommended rather than use of a low anterior neck field. This is due to high risk regions or gross disease that are likely be located in the low dose region of the match-line.
- **Early stage disease** consists of T1N0 or T2N0 (AJCC 8) hypopharynx carcinoma. A minority of cases present with early stage disease. Definitive radiation is often preferred for local control, laryngeal preservation, maintenance of speech and swallowing. Due to the high incidence of occult nodal disease, and central location of the hypopharynx, bilateral nodal chains should be included in the target (Figs. 5.1 and 5.2).
- **Advanced stage disease** consists of ≥T3 or node-positive disease (Figs. 5.3, 5.4, and 5.5). Treatment options include definitive chemoradiation, laryngectomy followed by adjuvant therapy, and induction chemotherapy followed by local

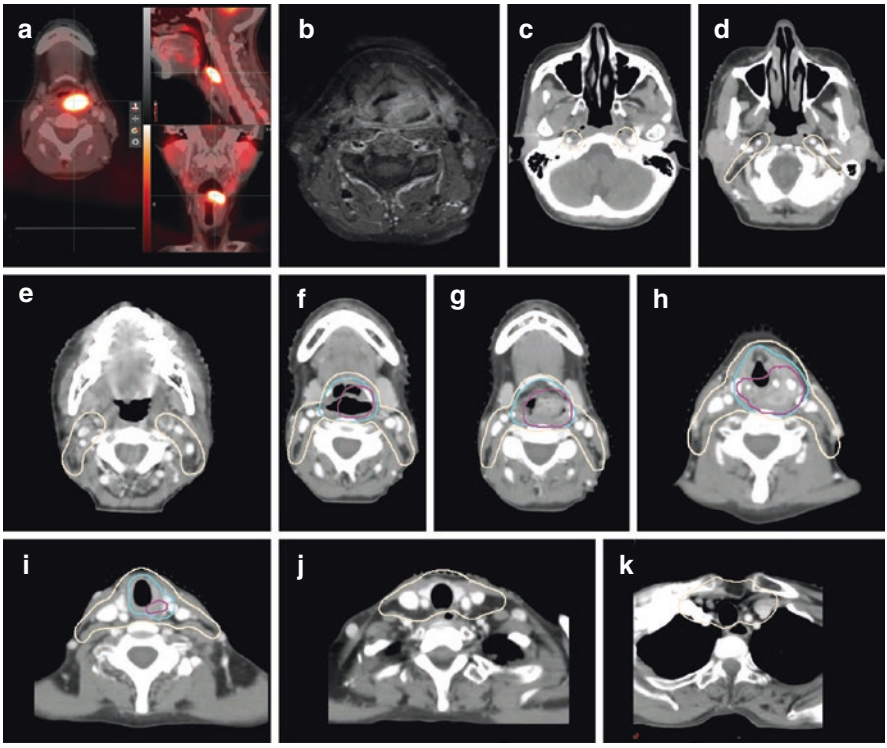

Fig. 5.1 T2N0 left pyriform sinus squamous cell carcinoma treated with definitive radiation in 35 fractions. Patient was treated with simultaneous integrated planning PTV_6996 (magenta), PTV_5940 (aqua), and PTV_5610 (almond) in 33 fractions. (**a**) FDG avid lesion in the left pyriform sinus visualized on PET/CT, extends to midline with inferior margin approaching the post-cricoid region. (**b**) T1-post gadolinium contrast enhance MRI. Mass displaces the left aryepiglottic fold without definitive spread into the supraglottis. (**c**, **d**) bilateral coverage of retrostyloid and retropharyngeal lymph node regions with PTV_5610. (**e**) Continuation of bilateral lymph node coverage of bilateral level 2. (**f**–**i**) Inclusion of larynx from top of the hyoid to bottom of the cricoid, posterior pharyngeal wall, lateral pharyngeal wall in the high-risk subclinical dose in PTV_5940. Bilateral level III covered by PTV_5610. (**j**, **k**) Inclusion of airway 2 cm below the bottom of cricoid, as well as coverage of level IV and VI due to the inferior extent of pyriform sinus tumor in the PTV_5610 low-risk volume. Alternative fractionations are 70 Gy/63 Gy/56 Gy over 35 fractions or a sequential technique

therapy (surgery + adjuvant therapy as indicated, radiation, or chemoradiation). Larynx-preservation strategies are not ideal for patients with advanced T4 disease, poor baseline function, and/or those unlikely to recover baseline function, although can be done in select cases. In the definitive setting, radiation treatment volumes should include gross disease, high-risk subclinical regions, and bilateral neck lymph node regions as outlined in Tables 5.3, 5.4, and 5.5.

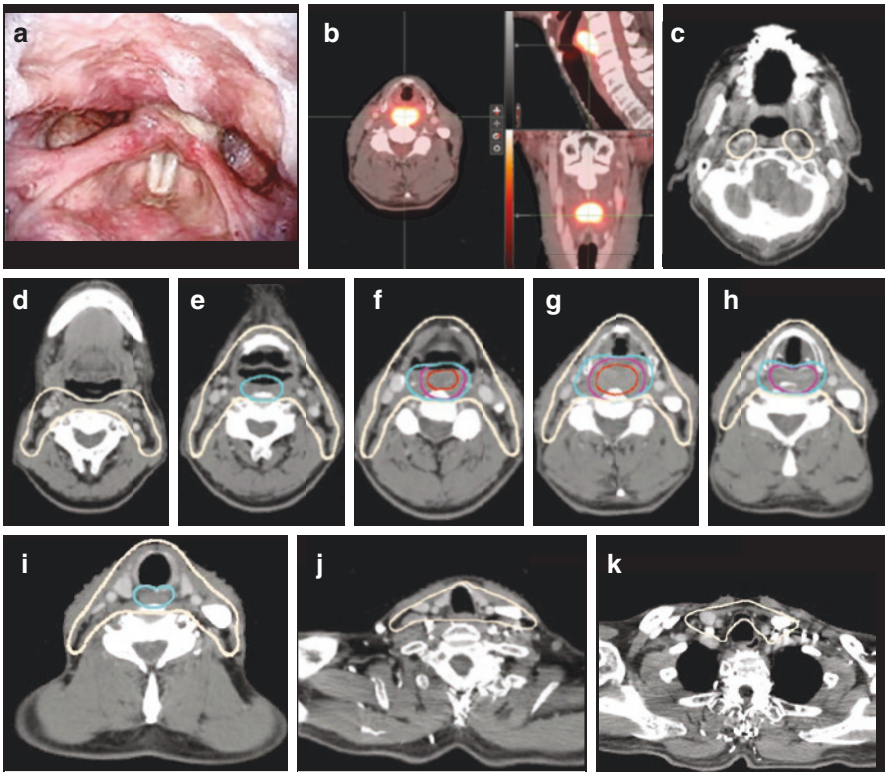

Fig. 5.2 T1N0 squamous cell carcinoma of posterior pharyngeal wall, with submucosal extension inferiorly into the post cricoid region treated with definitive radiation in 33 fractions: PTV_6996 (magenta), PTV_5940 (aqua), PTV_5610 (almond). (**a**) Superior extent of exophytic posterior pharyngeal wall mass as seen on flexible fiberoptic naso-pharyngo-laryngoscopy. On direct exam in the operating room, there is no involvement of the pyriform sinus or post-cricoid mucosa of the larynx. (**b**) FDG-avid mass on PET/CT extending along the posterior pharyngeal wall posterior to cricoid cartilage. (**c**, **d**) Bilateral coverage of lateral retropharyngeal and level II lymph nodes by PTV_5610. (**e**–**h**) PET-avid posterior pharyngeal wall disease with a 5 mm margin covered in PTV_6996. The high-risk subclinical region covered by PTV_5940 includes the gross tumor with 1 cm margin laterally and 2 cm superior/inferior margin. PTV_5940 also includes the entire posterior pharyngeal wall, lateral pharyngeal wall, and pre-vertebral fascia between the hyoid and cricoid. The entire larynx and bilateral level III included in PTV_5610. (**i**–**k**) Coverage of bilateral level IV with PTV_5610. Alternative fractionations are 70 Gy/63 Gy/56 Gy over 35 fractions or a sequential technique

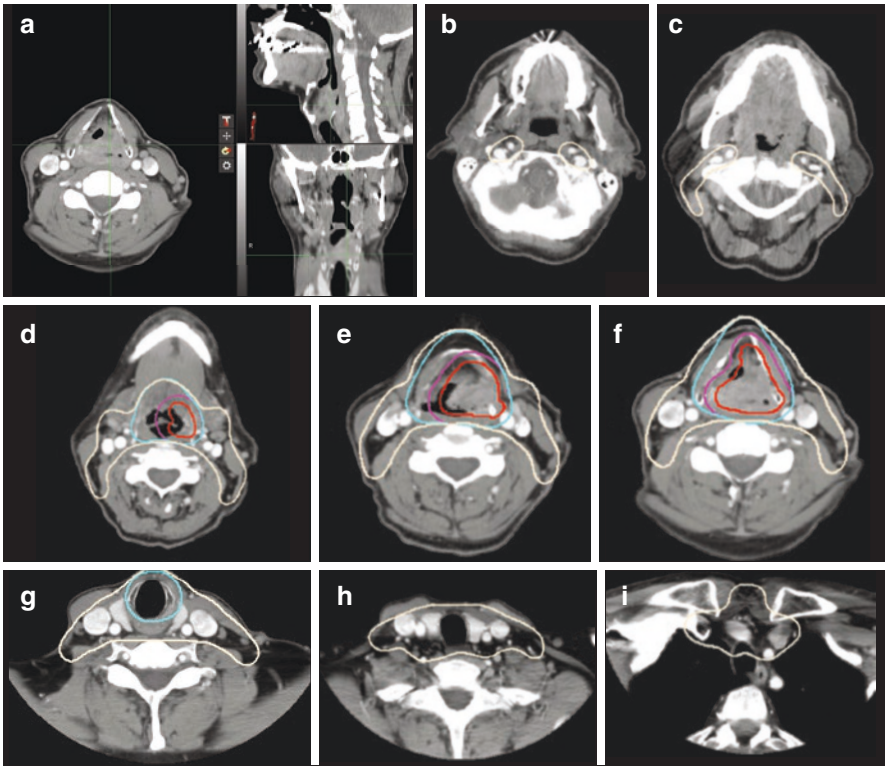

Fig. 5.3 T3N0 squamous cell carcinoma of the pyriform sinus treated with definitive chemoradiation—35 fractions using sequential and serial cone down technique where first phase is 54 Gy in 1.8 Gy per fraction simultaneously 60 Gy in 2 Gy per fraction over 30 fractions with a 10 Gy boost in 2 Gy per fraction: PTV_70 (magenta), PTV_60 (aqua), PTV_54 (almond). (**a**) Pyriform sinus mass extending to the paraglottic space on CT. (**b**, **c**) Bilateral coverage of lateral retropharyngeal lymph nodes and level II. (**d**–**g**) Gross FDG avid disease with a 1 cm lateral margin, as well as the larynx from top of the hyoid to bottom of the cricoid, posterior pharyngeal wall, lateral pharyngeal wall in the high-risk subclinical dose in PTV_60. Bilateral level III treated to 54 Gy. (**h**, **i**) Bilateral Level IV and level VI treated to 54 Gy

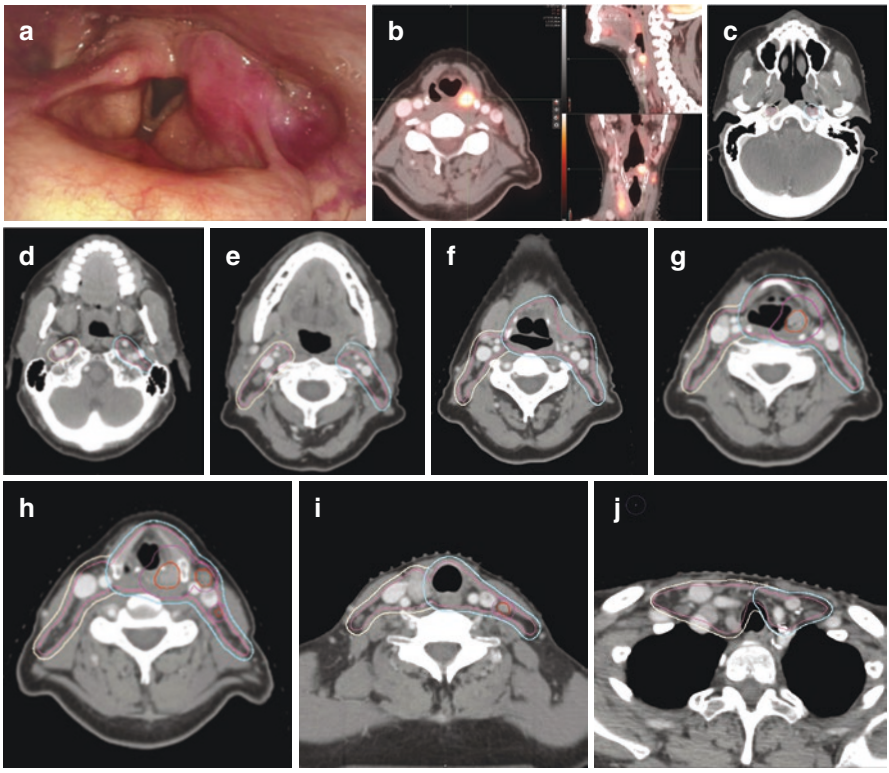

Fig. 5.4 T2N2b squamous cell carcinoma of the pyriform sinus treated with definitive chemoradiation in 35 fractions using sequential and serial cone down technique where first phase is 54 Gy in 1.8 Gy per fraction simultaneously 60 Gy in 2 Gy per fraction over 30 fractions with a 10 Gy boost in 2 Gy per fraction:: PTV_70 (magenta), PTV_60 (aqua), PTV_54 (almond). (**a**) Image obtained from flexible fiberoptic naso-pharyngo-laryngoscopy demonstrates a mass effacing the pyriform sinus as well as the left aryepiglottic fold. (**b**) FDG-avid left pyriform sinus lesion on PET/CT with additional FDG avid left level III and left level IV lymph nodes. (**c**, **d**) Retropharyngeal and retrostyloid lymph node coverage beginning at the skull base. The ipsilateral node-positive neck is treated to 60 Gy, the node-negative neck is treated to 54 Gy for this well lateralized tumor. (**e**) Bilateral coverage of level II. (**f**, **g**) Inclusion of the gross primary tumor with a 1 cm margin, the arytenoids, paraglottic space, larynx from hyoid to cricoid, as well as ipsilateral node positive neck in PTV_60. (**h**–**j**). Inclusion of FDG avid lymph nodes and a 5 mm margin in PTV_70. Bilateral coverage of level III, IV, inclusion of trachea 2 cm below the cricoid, with continuation of PTV_60 to the inferior extent of level IV. Alternatively a simultaneous integrated boost in one plan can be done

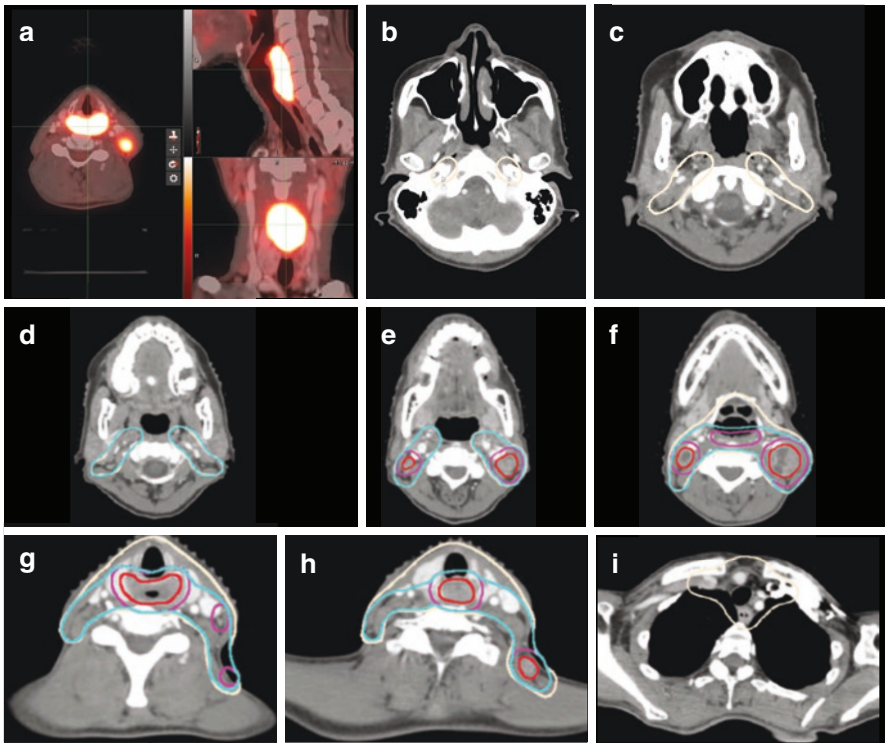

Fig. 5.5 T3N2c squamous cell carcinoma of the posterior pharyngeal wall—treated with definitive chemoradiation in 35 fractions using sequential and serial cone down technique where first phase is 54 Gy in 1.8 Gy per fraction simultaneously 60 Gy in 2 Gy per fraction over 30 fractions with a 10 Gy boost in 2 Gy per fraction:: PTV_70 (magenta, PTV_60 (aqua), PTV_54 (almond). (**a**) PET/CT demonstrates a 4.3 cm posterior pharyngeal wall mass extending inferiorly to the cervical esophagus as well as bilateral FDG avid lymph nodes. (**b**–**d**) Coverage of bilateral lateral retropharyngeal and level II lymph nodes starting at the skull base. (**e**–**i**) Primary tumor and FDG avid lymph nodes treated to 70 Gy. High-risk primary subclinical region (including 2 cm past inferior extent of tumor) as well as bilateral cervical lymph nodes, and left level V covered by PTV_60 given that there is gross nodal disease. The larynx, level VI, and superior mediastinal nodal regions treated to 54 Gy. Alternatively a simultaneous integrated boost in one plan can be done

Table 5.3 Suggested target volumes for the gross disease region[a]

Target volumes	Definition and description
GTV_70	– **Primary**: All gross disease delineated on CT, MRI, or PET – **Lymph nodes**: Lymph nodes ≥1 cm, or suspicious FDG avid lymph nodes
CTV_70	At MSKCC an additional margin for CTV_70 is not utilized routinely. However, if there is uncertainty with regard to extent of disease, a margin can be utilized – **Primary:** GTV_70 + 5 mm margin – **Lymph nodes:** GTV_70 + 3 mm margin (Note: In general GTV_70 = CTV_70 where no additional CTV margin is needed)
PTV_70	– **Primary:** CTV_70 + 3–5 mm margin (based on comfort with daily imaging and set-up error) – **Lymph nodes:** CTV_70 + 3-5 mm margin

[a] Dose suggested for 70 Gy prescribed in 2 Gy fractions. If using a 70/60/54 for gross disease, high-risk and low-risk subclinical regions, respectively, can plan with a simultaneous integrated plan for 60 Gy/2 Gy fractions and 54 Gy/1.8 Gy fractions with a single 10 Gy cone down to PTV70

- **Post-operative radiation**. Adverse pathologic features that warrant post-operative radiation as per NCCN v.2019 include positive margins, close margins, extra-nodal extension, pT3–T4 primary, pN2–pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion. Adjuvant radiation should start ideally within 6 weeks of surgery. The entire surgical bed and dissected node-positive neck should be included in high-risk sub-clinical region (Table 5.4 and Fig. 5.6). The dissected node-negative neck can be included in low-risk sub-clinical region (Table 5.5).
- **Radiation following induction chemotherapy**. In addition to post-chemotherapy targeting, pre-chemotherapy imaging should be fused for target delineation. The high-risk subclinical volume should include extent of pre-chemotherapy gross disease, as well as taking adjacent anatomical sites at risk for microscopic spread into consideration for coverage. This pre-chemotherapy CTV should be modified for anatomical differences after chemotherapy and exclude air and bone.

Table 5.4 Suggested target volumes for the high-risk subclinical region[a]

Target volumes	Definition and description
CTV_60	• **Primary**: GTV_70 with a 1 cm margin + the entire subsite + the larynx (from hyoid to cricoid). Additional adjacent mucosal sits at risk for mucosal or submucosal infiltration should also be taken into consideration for coverage: – **Pyriform sinus**: Arytenoids, paraglottic space, and thyroid cartilage for laterally involved lesions, constrictor muscles or prevertebral muscle if there is posterior involvement, pre-epiglottic space or structures in the oropharynx if there is superior extension, and post-cricoid area for inferior lesions – **Posterior pharyngeal wall**: Pre-vertebral fascia and retropharyngeal space, consider coverage of adjacent oropharynx if there is superior extension, consider coverage of the proximal cervical esophagus if there is inferior extension – **Post cricoid region**: Consider coverage of pyriform sinuses for superior extending lesions, cover the cricoid cartilage if involved, and the proximal cervical esophagus if there is an inferiorly extending lesion • **Lymph nodes**: – Any lymph nodes in CTV_70 should be included – Ipsilateral or node positive neck: Lymph node regions that should be covered include the: lateral retropharyngeal lymph nodes (start at skull base at the entrance of carotid canal), II–IV (with inclusion of the retrostyloid space for superior level II) – For inferior hypopharyngeal tumors, pyriform sinus tumors involving the apex, and advanced T-stage—cover level VI – For midline post-cricoid and posterior pharyngeal wall tumors with an involved lymph node consider bilateral lateral retropharyngeal, II–IV, and VI coverage. For inferior tumors consider paratracheal coverage in the superior mediastinum – Retropharyngeal lymph node coverage in the node positive neck – Consider covering ipsilateral 1B if level II is involved. If posterior level II–IV lymph nodes consider covering level V **Post-operative cases**: Include the entire surgical bed and the bilateral dissected neck inclusive of clips and wired scars. Areas at risk for positive margin or extra capsular spread should be delineated in conjunction with the surgeon and this area can be treated to 66 Gy
PTV_60	CTV_60 + 3–5 mm margin, depending on comfort with daily target localization

[a] Dose suggested for 60 Gy prescribed in 2 Gy fractions. If using a 70/60/54 for gross disease, high-risk and low-risk subclinical regions respectively can plan with a simultaneous integrated plan for 60 Gy/2 Gy fractions and 54 Gy/1.8 Gy fractions with a single 10 Gy cone down to PTV70

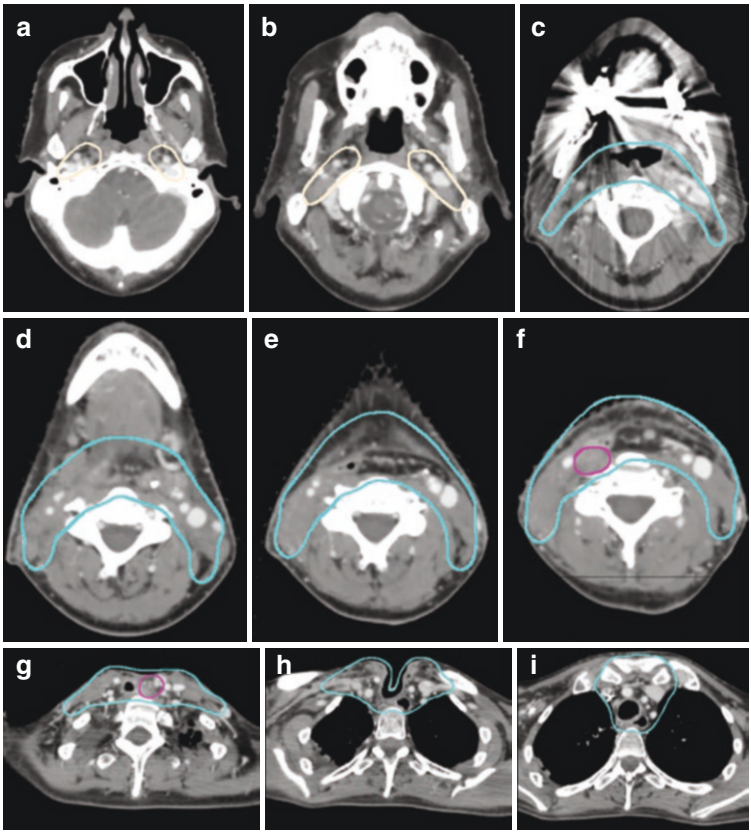

Fig. 5.6 cT3N2c squamous cell carcinoma of the hypopharynx status post-pharyno-laryngectomy, cervical esophagectomy with jejunal reconstruction with positive margins and extranodal extension with 9/52 lymph nodes positive bilaterally. (**a**, **b**) Bilateral retropharyngeal and retrostyloid space covered starting at the skull base. (**c**–**i**) Bilateral level II–IV, level IV covered given extensive nodal disease treated to 60 Gy. The entire surgical bed is included in PTV_60, with area of positive margin and extranodal extension delineated in conjunction with the surgeon and treated to 66 Gy

Table 5.5 Suggested target volumes for the low-risk subclinical region[a]

Target volumes	Definition and description
CTV_54	– **Contralateral or N0 Neck**: Lymph node regions that should be covered include the: lateral retropharyngeal lymph nodes (can start at C1 vertebral body), II–IV (level II can start where the posterior belly of the digastric crosses the internal jugular vein). Exception—in a midline hypopharyngeal tumor where bilateral retropharyngeal nodal region should be included – **Exception**: In midline hypopharyngeal tumors that are node-positive, the contralateral neck is also considered high risk
PTV_54	CTV_54 + 3–5 mm margin, depending on comfort with daily target localization

[a] Dose suggested for 60 Gy prescribed in 2 Gy fractions. If using a 70/60/54 for gross disease, high-risk, and low-risk subclinical regions respectively can plan with a simultaneous integrated plan for 60 Gy/2 Gy fractions and 54 Gy/1.8 Gy fractions with a single 10 Gy cone down to PTV70

5.5 Suggested Reading

- Biau, Gregoire et al. (2019): An updated consensus guidelines of lymph node target volumes for head and neck cancers treated with IMRT/VMAT [19].
- Gupta et al. (2009): Outcome analysis of a large cohort of hypopharynx patients ($n = 501$) treated with a non-surgical approach [20].
- EORTC 24891: 10-year results of EORTC 24891 comparing surgery followed by radiation to induction chemotherapy followed by radiotherapy for hypopharyngeal carcinoma. Laryngeal preservation with induction chemotherapy followed by radiation, does not compromise disease control or survival, and allowed over 50% of survivors to retain their larynx [21].
- Lee et al. (2007): Concurrent chemotherapy and IMRT experience at MSKCC for locoregionally advanced laryngeal and hypopharyngeal cancers [22].
- Prades et al. (2010): A randomized phase III trial comparing induction chemotherapy followed by radiation to concomitant chemoradiation in pyriform sinus carcinoma, demonstrating improved survival with concurrent chemoradiotherapy [23].

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Oral Cavity Cancers

6

Keith Unger, Matthew Forsthoefel, Nadeem Riaz, Allen Chen, and Nancy Y. Lee

Contents

6.1 General Principles of Planning and Target Delineation

- Patients should undergo a comprehensive oral examination, biopsy, and imaging studies for staging and treatment planning. Computed tomography (CT) scan is commonly used to evaluate the local extent of the tumor and regional spread to cervical lymph nodes. CT is particularly valuable for detecting invasion into the mandible, maxilla, and pterygopalatine fossa. MRI is superior to CT in evaluating soft tissue extension and perineural spread. Positron emission tomography (PET) scan is useful for detecting regional lymph nodes involvement and distant disease.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_6

- CT simulation with IV contrast should be performed. A bite block can be placed during simulation and throughout radiation to depress the tongue and protrude the lower lip, as well as to elevate the hard palate. In the case of extranodal extension or when the scar is at risk, tissue-equivalent skin bolus can be used. A wire should be placed on any surgical scars and drain sites. The patient should be immobilized in the supine position with the neck slightly hyperextended using a five-point thermoplastic mask.
- In the definitive treatment setting, the clinical target volumes include the $CTV_{70,}$ which encompasses all known gross disease and is typically identical to the GTV_{70}; the high-risk CTV ($CTV_{59.4–66}$), which includes additional margin around the primary gross disease and high risk nodal levels; and the low-risk CTV (CTV_{54}), which includes nodal levels at lower risk as detailed in Table 6.1.
- In the post-operative setting, the clinical target volumes include the high-risk CTV (CTV_{66}), which includes regions of positive margins or extranodal extension, when present; the intermediate risk CTV (CTV_{60}), which includes the operative bed and high-risk nodal regions; and the low-risk CTV (CTV_{54}), which includes low-risk nodal levels as detailed in Table 6.2.
- Suggested target volumes for specific subsites within the oral cavity are detailed in Table 6.3 (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, and 6.6).

Table 6.1 Suggested target volumes and dosing for definitive treatment of oral cavity cancers

Target volumes[a]	Definition and description
GTV_{70}	Primary: All gross disease on physical examination and imaging
	Neck nodes: All gross disease on physical examination and imaging
CTV_{70}	Same as $GTV_{70,}$ although a 5 mm margin, excluding bone, can be added if there is uncertainty regarding the full extent of gross disease
$CTV_{59.4}$	Primary: Encompass the entire CTV_{70} and the entire anatomic subsite, e.g. if it is an oral tongue cancer, the entire oral tongue should be included in the subclinical target volume; if it is buccal mucosa tumor, the entire buccal mucosa should be included, etc.
	Neck nodes: nodal levels with pathologic involvement and adjacent ipsilateral or contralateral nodal regions at high risk for subclinical disease (site-specific recommendations given in Table 6.3)
CTV_{54}	Ipsilateral and/or contralateral uninvolved nodal levels at low risk for subclinical disease (site-specific recommendations given in Table 6.3)

[a] Subscript numbers represent suggested prescribed doses. PTV_{70} is 69.96 Gy in 2.12 Gy/fraction, $PTV_{59.4}$ is 59.4 Gy in 1.8 Gy/fraction, and PTV_{54} is 54 Gy in 1.64 Gy/fraction; alternative fractionations are 70 Gy in 2 Gy per fraction done in a sequential or simultaneous integrated boost techniques

Table 6.2 Suggested target volumes and dosing for post-operative treatment of oral cavity cancers

Target volumes[a,b]	Definition and description
CTV_{66}	Primary: Regions of soft tissue/bone invasion or microscopically positive margins if present
	Neck nodes: Regions of extracapsular extension if present
CTV_{60}	Primary: Preoperative gross disease and the entire tumor bed and the entire relevant anatomic subsite
	Neck nodes: Preoperative gross disease; entire operative bed; and ipsilateral or contralateral nodal regions at high risk for subclinical disease (site-specific recommendations given in Table 6.3)
CTV_{54}	Ipsilateral and/or contralateral uninvolved nodal levels at low risk for subclinical disease (site-specific recommendations given in Table 6.3)

[a] Subscript numbers represent suggested prescribed doses. PTV_{66} is 66 Gy in 2.2–2.0 Gy/fraction, PTV_{60} is 60 Gy in 2 Gy/fraction, and PTV_{54} is 54 Gy in 1.8 Gy/fraction
[b] If gross residual disease is present, then a GTV should be delineated

Table 6.3 Site-specific guidelines for clinical target delineation of oral cavity cancers

Tumor site	Stage	High-risk clinical target volume ($CTV_{59.4}$ or CTV_{60})[a]	Low-risk clinical target volume (CTV_{54})
Oral tongue, floor of mouth	T1–T4N0	Tumor bed, entire oral tongue, base of the tongue, and bilateral levels I–IV at the physician's discretion regarding whether some levels should be in the high-risk or low-risk target volume[b]	Bilateral levels I–IV at the physician's discretion regarding whether some levels should be in the high-risk or low-risk target volume.[b] Prophylactic overage of level VI when indicated
	T1–T4N1–3	Same as above except to also include level VI nodal regions	Same as above except to also include level VI nodal regions
Buccal mucosa, retromolar trigone, hard palate, gingiva	T1–T2N0	Tumor bed and ipsilateral levels I–IV at physician's discretion[b]	Ipsilateral lymph nodes levels I–IV at physician's discretion[b]
	T3–T4N0	Tumor bed and ipsilateral levels I–IV	Contralateral lymph nodes levels II–IV[c]
	T1–T4N1–3	Tumor bed and ipsilateral levels I–V or bilateral levels I–V if contralateral involved nodes[c]	Contralateral lymph nodes levels II–IV[c] if uninvolved

[a] 66 Gy for microscopically positive margins or extracapsular extension; 70 Gy if gross residual disease
[b] Decision to include in low- or high-risk region based on other tumor features, and at physician's discretion. Level VI is a drainage site for oral tongue cancer, often in patients with node positive disease. Highly recommend including level VI in the target
[c] For buccal mucosa, gingiva, retromolar trigone cancers that are well lateralized, treatment of the contralateral neck can be omitted at the discretion of the treating physician. Hard palate tumors are typically of salivary origin, i.e. adenoid cystic carcinoma where coverage of the track of trigeminal nerves should be included. Given the low nodal spread of these tumors, the neck can be omitted

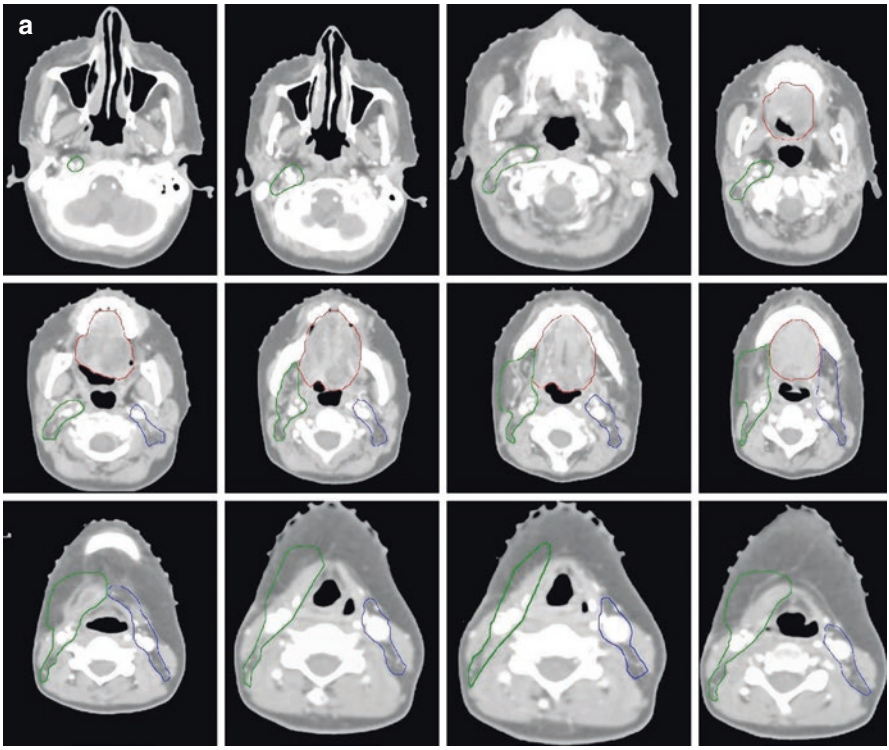


Fig. 6.1 A patient with squamous cell carcinoma of the oral tongue, pathologic stage T3N2b status post-partial glossectomy with microscopically positive surgical margins. (**a**) The high-risk CTV (CTV_{66}) is shown in *red* and encompasses the positive margin. The intermediate-risk CTV (CTV_{60}) is shown in *green*, and the low-risk CTV (CTV_{54}) is shown in *blue*. Neck nodal levels I–V are included on the ipsilateral side and levels I–IV are included on the contralateral uninvolved side. Coverage of level V is recommended for oral tongue primaries, especially after surgical manipulation of the neck and ipsilateral nodal disease. (**b**) Level IA should be covered for oral tongue primaries. The use of bolus and flash is recommended when there are concerns of soft tissue involvement to provide adequate coverage. (**c**) The ipsilateral retrostyloid space is at risk for nodal metastasis, especially with level II nodal involvement. The retropharyngeal nodes are at low risk and are not included. Though not shown in this case, coverage of level VI is highly recommended especially for patients with node positive disease

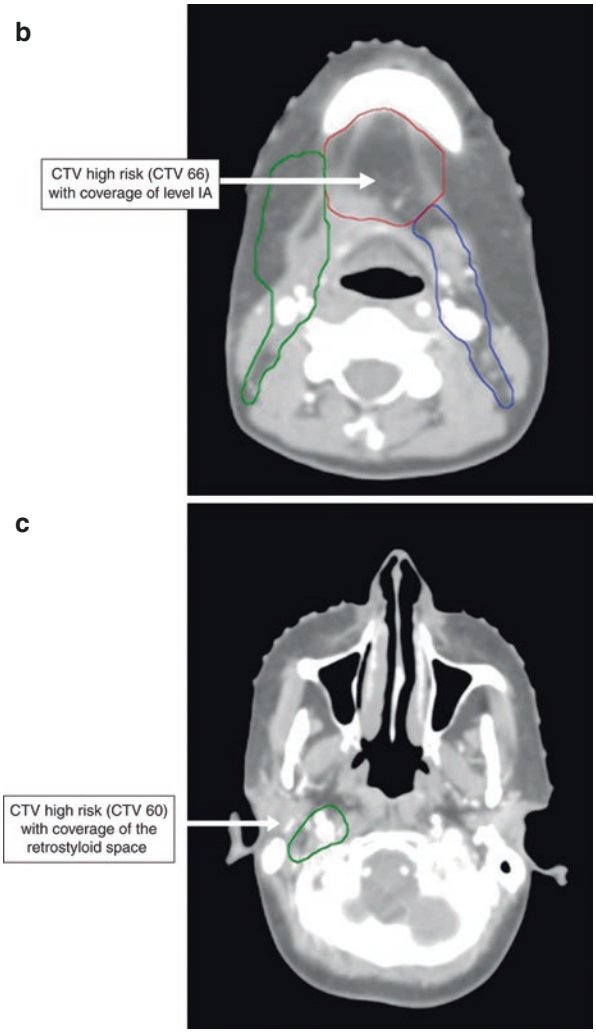


Fig. 6.1 (continued)

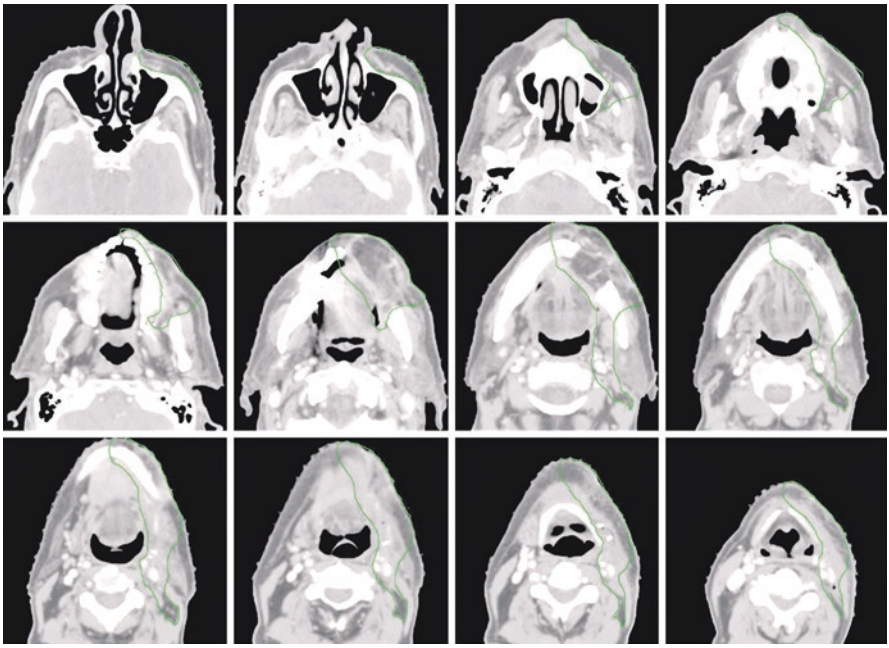


Fig. 6.2 A patient with squamous cell carcinoma of the buccal mucosa, pathologic stage T4aN0 with minimal cortical bone invasion status post-tumor resection, marginal mandibulectomy, and left neck dissection. The surgical margins were widely clear. The high-risk CTV (CTV_{60}) is shown in *green*. Neck nodal levels I–IV are included on the ipsilateral side. The CTV extends cranially to the buccal-gingival sulcus and infratemporal fossa, caudally to the buccal-gingival sulcus and submandibular gland, anteriorly at least to the lip commissure, and posteriorly to the retromolar trigone. Bolus is placed on the skin to provide adequate coverage of the high-risk CTV. Can include ipsilateral parotid if clinically concerned

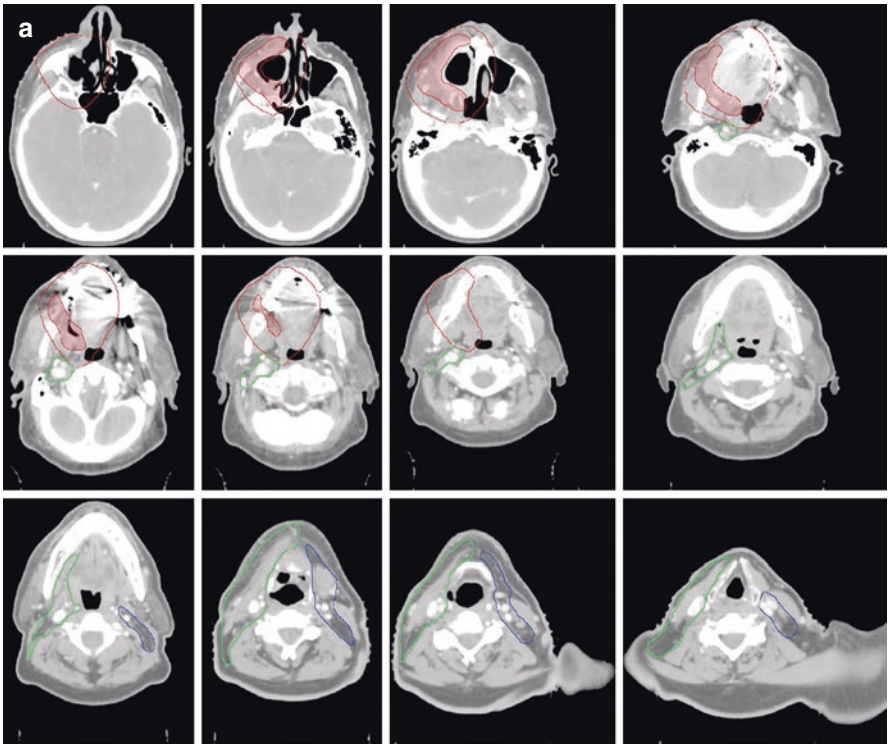
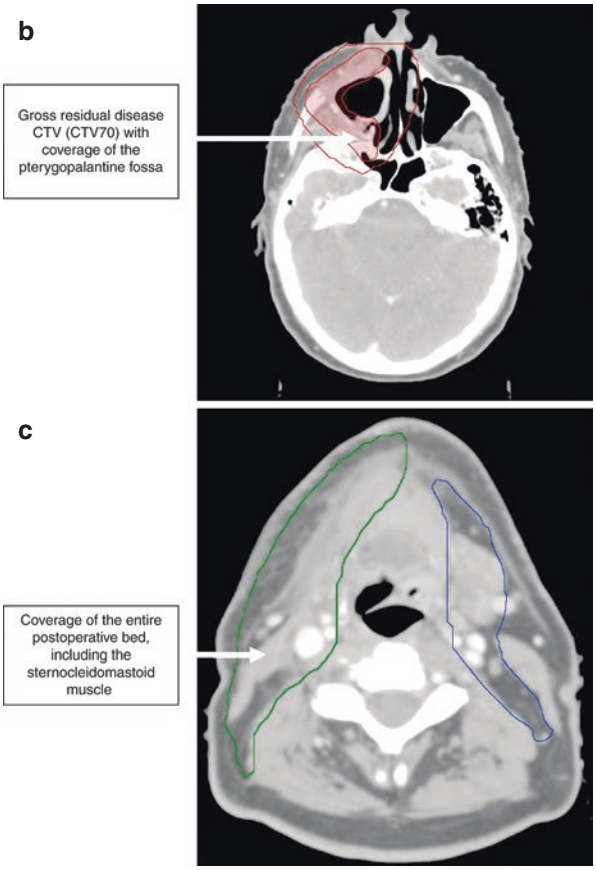


Fig. 6.3 A patient with squamous cell carcinoma of the retromolar trigone, pathologic stage T4aN2b with medial pterygoid involvement, status post-tumor resection with gross residual disease in the tumor bed and right neck dissection. (**a**) The gross disease CTV (CTV_{70}) is shown in shaded *red* and is delineated based on operative findings as well as pre- and post-operative imaging. The high-risk CTV ($CTV_{59.4}$) is shown in *red* in the region of the tumor bed and in *green* in the ipsilateral neck. The low-risk CTV (CTV_{54}) is shown in *blue* and includes the contralateral neck nodal levels IB–IV. (**b**) The pterygopalatine fossa is a gateway for tumor spread to the middle cranial fossa and should be adequately covered, especially with tumor invading the pterygoid muscle. (**c**) Post-operative tumor volumes should include coverage of the entire operative bed based on visualization of tissue inflammation and edema on the planning CT



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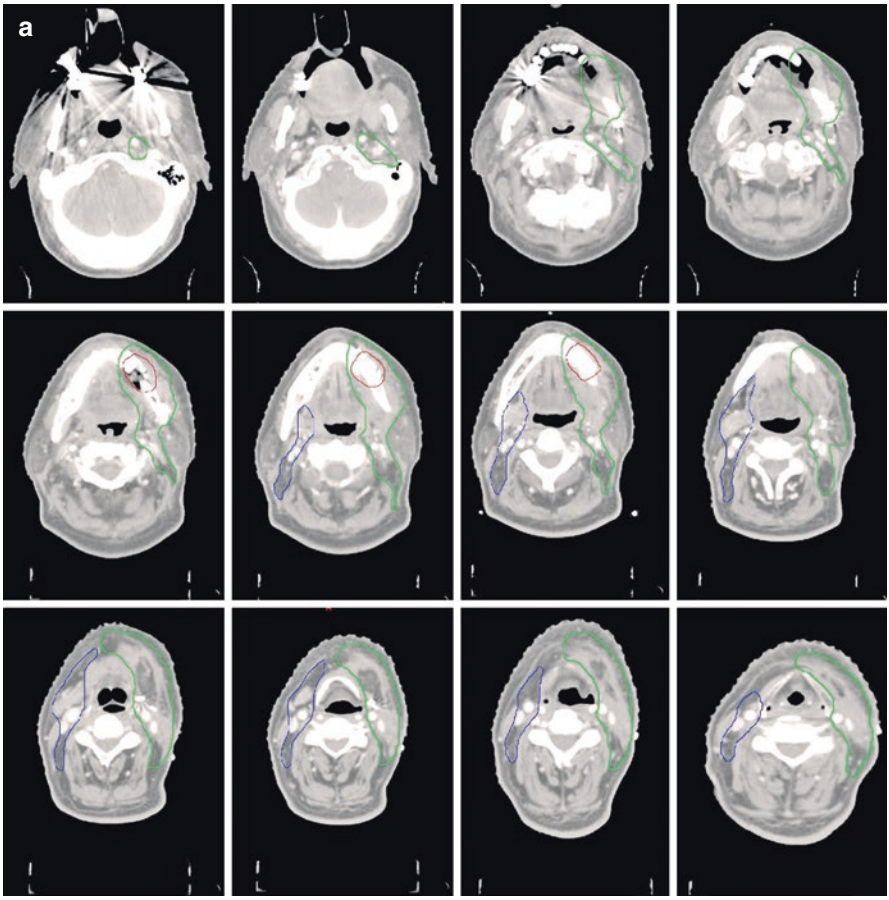
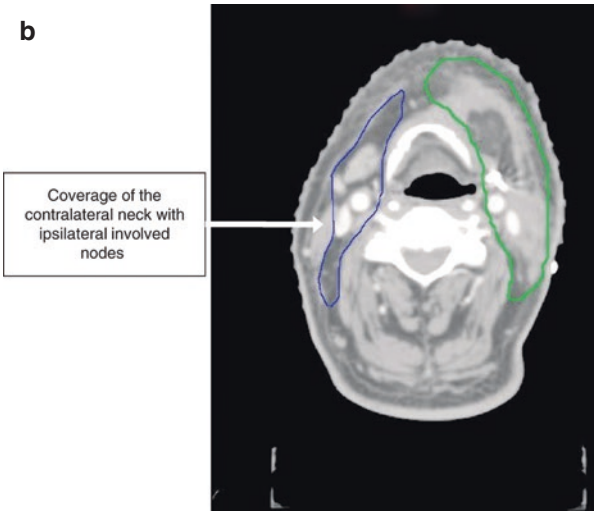


Fig. 6.4 A patient with squamous cell carcinoma of the gingiva, pathologic stage T4aN1 with bone invasion, status post-tumor resection, marginal mandibulectomy, and left neck dissection. (**a**) The high-risk CTV (CTV_{66}) is shown in *red*, and encompasses the region of bone invasion by tumor. The intermediate-risk CTV (CTV_{60}) is shown in *green* and includes the entire operative bed and ipsilateral neck nodal levels I–IV. (**b**) The low-risk CTV (CTV_{54}) is shown in *blue* and includes the contralateral neck nodal levels I–IV. Given Node positive and T4 disease, the contralateral neck was included in the low risk subclinical region



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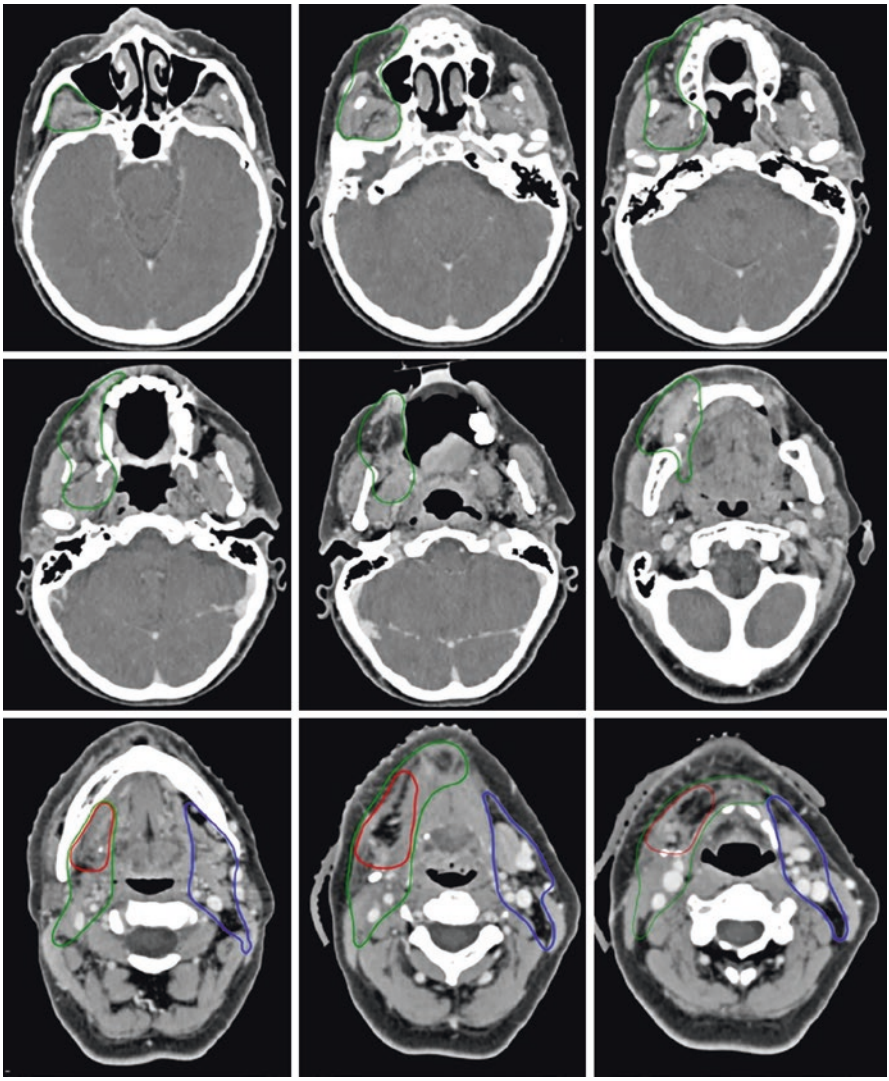

Fig. 6.5 A patient with squamous cell carcinoma of the buccal mucosa, pathologic stage T2N3b status post-tumor resection and right neck dissection with extranodal extension in the nodal level IB. Surgical margins were negative but close along the deep margin. The high-risk CTV (CTV_{66}) is shown in *red* and covers the nodal region with extranodal extension. The intermediate-risk CTV (CTV_{60}) includes the operative bed and entire buccal mucosa. Neck nodal levels I–IV are included on the ipsilateral side. The CTV is extended cranially to the buccal-gingival sulcus and infratemporal fossa at the inferior orbital rim, caudally to the buccal-gingival sulcus and submandibular gland, anteriorly at least to the lip commissure, and posteriorly to the retromolar trigone. Wide margins should be used, even for smaller primary tumors. Bolus is placed on the skin to provide adequate coverage of the high- and intermediate-risk CTVs. The low-risk CTV (CTV_{54}) includes the contralateral neck nodal levels I–III due to the extent of nodal disease present in the ipsilateral neck

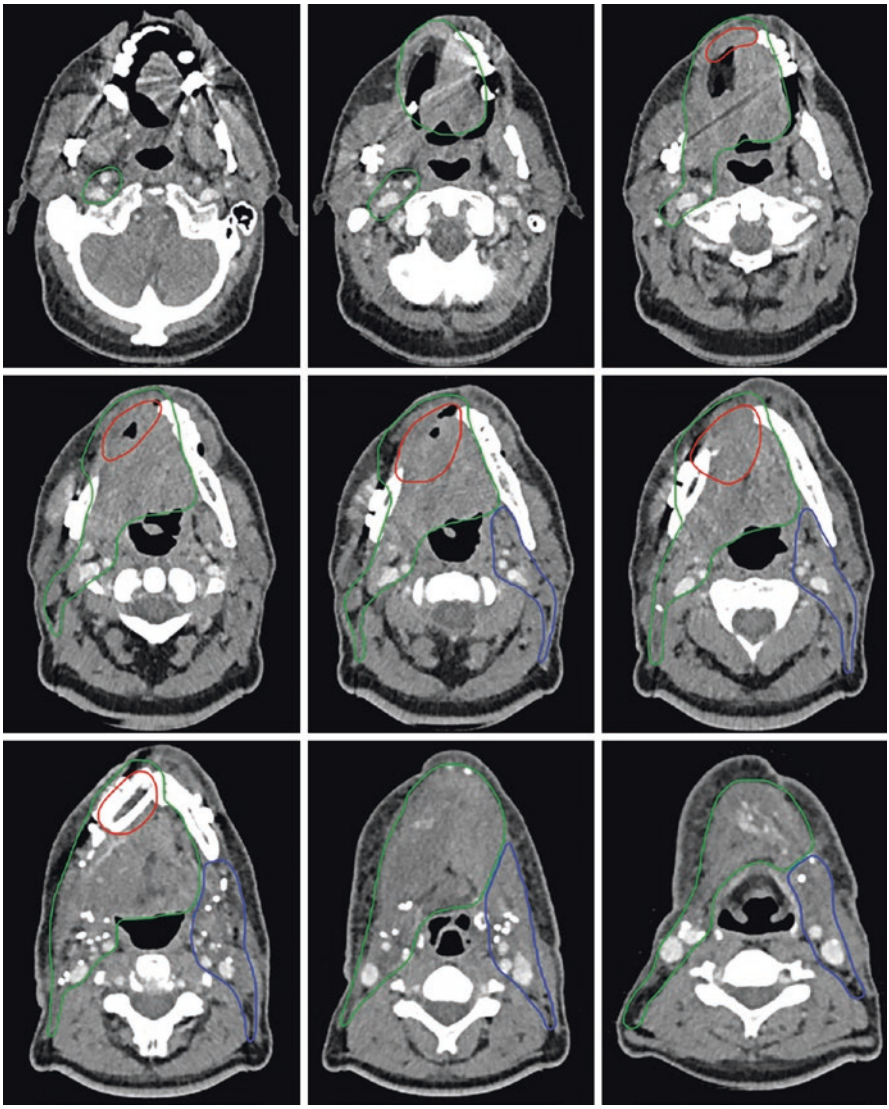

Fig. 6.6 A patient with squamous cell carcinoma of the floor of mouth, pathologic stage T4aN2b with mandibular invasion status post-right hemi-mandibulectomy and bilateral neck. The high-risk CTV (CTV_{66}) is shown in *red* includes the area of extensive bony invasion. The intermediate-risk CTV (CTV_{60}) is shown in *green* and includes the entire operative bed and neck nodal levels I–V on the ipsilateral side. The ipsilateral retrostyloid space is also at high risk for nodal metastasis and should be included in the CTV_{60}, especially with neck nodal level II involvement. The CTV_{60} is also extended to include the entire floor of mouth complex. The low-risk CTV (CTV_{54}) is shown in *blue* and includes the contralateral nodal levels I–IV

Nasal Cavity and Paranasal Sinus Tumors

7

Ming Fan, Yao Yu, Jung Julie Kang, and Nancy Y. Lee

Contents

7.1 General Principles of Anatomy and Patterns of Spread

- Tumors of the paranasal sinuses include diverse histologies with variable behaviors, including squamous cell carcinoma, minor salivary gland adenocarcinoma, adenoid cystic carcinoma, esthesioneuroblastoma (ENB), sinonasal undifferentiated carcinoma (SNUC), small cell neuroendocrine carcinoma (SNEC), melanomas, NUT midline carcinoma, among others.
- Paranasal sinus and nasal cavity are interconnected via multiple ostia and separated only by thin septi, allowing for spread via local extension into adjacent cavities.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_7

  - ENB, SNUCs, and SNECs arise in the superior nasal cavity easily invade the cribriform plate into the anterior cranial fossa. These regions should be encompassed in the target volume.
  - Maxillary sinus cancers may invade the nasal cavity (via the porous medial wall), maxillary gingiva (through the lateral wall of the antrum), infratemporal or pterygopalatine fossa (via posterior spread), orbit (by direct extension superiorly or via the ethmoid sinuses).
- Consider coverage of afferent and efferent cranial nerves for tumors with perineural extension. Generous margins should be given on cranial nerves as microscopic skip metastases are common and recurrences may be difficult to salvage.
  - If cranial nerve involvement is present, it is important to cover the involved nerve(s) back to the skull base.
  - Cranial nerve coverage is strongly recommended for adenoid cystic carcinomas, even in cases without pathologic perineural invasion.
- Elective nodal should be considered in selected cases.
  - Elective neck radiation should be considered for ENB and advanced squamous cell carcinoma (especially if originating from the maxillary sinus or if there is involvement of areas with extensive lymphatic supply such as the nasopharynx, mucosa, skin, cheek, anterior nose, maxillary gingiva or alveolar ridge).
- Suggested target volumes and prescription doses at the gross disease and high- and low-risk regions are detailed in Tables 7.1 and 7.2.
- Figures 7.1, 7.2, 7.3, 7.4, and 7.5 show examples of target delineation based on different clinical cases.

Table 7.1 Suggested target volumes and prescription doses for gross disease

Target volumes	Definition and description
GTV_{70}[a]	All gross disease on physical examination and imaging (CT and MRI). PET can help further define the tumor extent. MRI can help identify perineural invasion, which may be occult on PET
CTV_{70}[a]	Usually identical to GTV_{70}. A 3–5 mm margin may be added if there is uncertainty in primary tumor delineation. Given the proximity to the nearby critical structures, this margin may be as small as 0 mm. In other words, GTV_{70} can equal CTV_{70}
PTV_{70}[a]	CTV_{70} + 3–5 mm depending on setup uncertainty. This can be reduced to 1 mm in areas near critical normal structures, such as the brainstem and optic chiasm

[a] Prescription doses for the GTV are delivered in 1.8–2 Gy fractions to an total dose of 70 Gy

Table 7.2 General principles for target volumes and prescription doses for high- and low-risk subclinical regions

Target volumes	Definition and description
$CTV_{60–66}$[a]	CTV_{60} encompasses regions at high risk for microscopic disease – In the post-operative setting, this should include the resection bed, areas of nodal extension, and all initial preoperative sites of disease. Consider coverage of the entire post-operative bed and flap – In the definitive setting, this should include a 5–10 mm expansion on the primary tumor and covering the relevant anatomic subsite, respecting anatomic boundaries CTV_{66} should be considered for positive margins or areas of extranodal extension. This may be delivered sequentially at 6 Gy in three fractions
$CTV_{50–54}$	$CTV_{50–54}$ encompass the low-risk subclinical regions, including non-violated neck or prophylactic coverage of cranial nerves
$PTV_{60–66}$	$CTV_{60–66}$ + 3–5 mm, depending on setup uncertainty and techniques used for image guidance. The PTV margins can be as small as 1 mm in areas adjacent to critical normal structures
$PTV_{50–54}$	$CTV_{50–54}$ + 3–5 mm, depending on setup uncertainty and techniques used for image guidance

[a] For postoperative cases, the clinical target volume contoured may be an expansion of the preoperative and (when applicable) postoperative GTV, based on the extent and location of the tumor

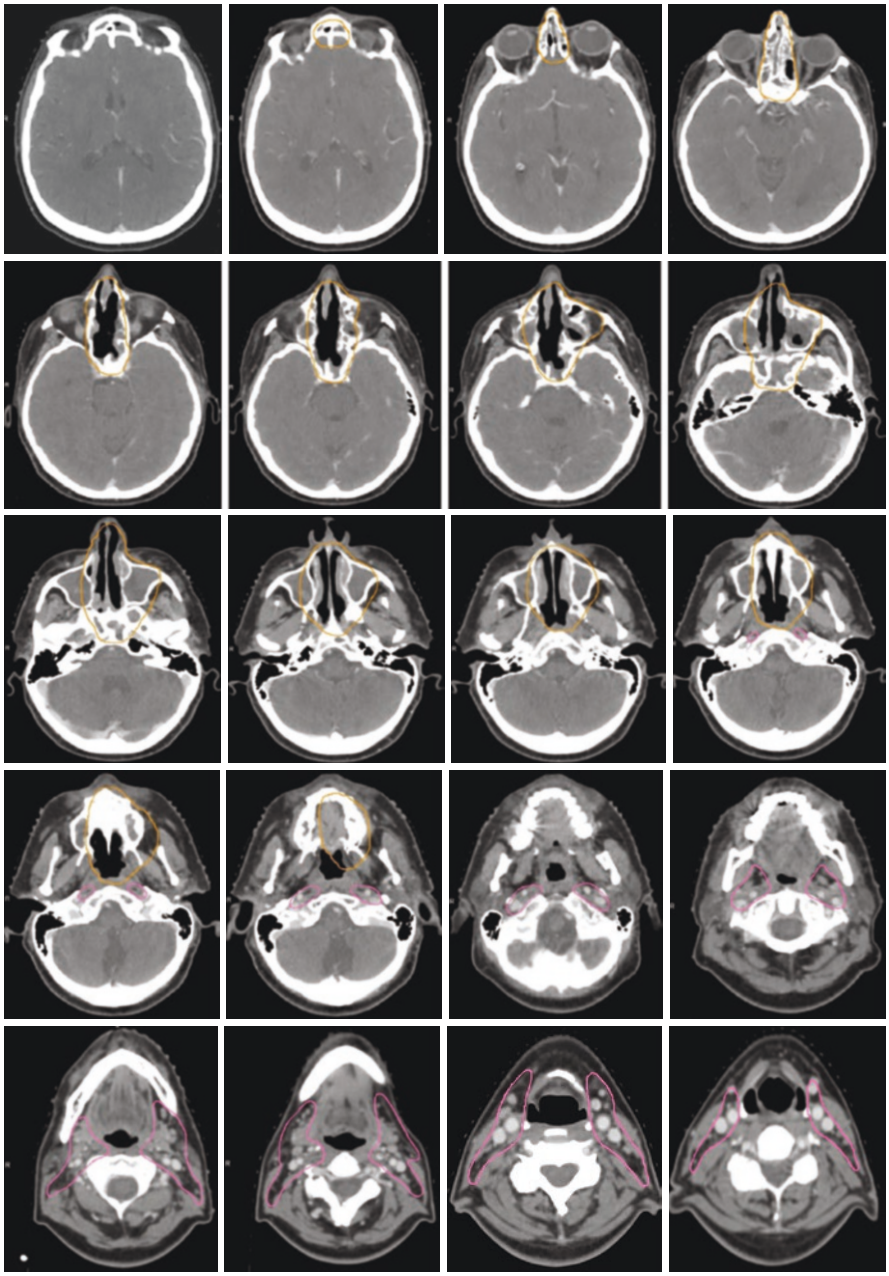

Fig. 7.1 An example of a 61-year-old female patient with a T4aN0M0 SNUC of the nasal cavity. The patient received three cycles of induction chemotherapy followed by endoscopic resection of the tumor. Surgical margins were negative. She then received adjuvant chemoradiation with weekly cisplatin. The primary tumor bed was treated to 60 Gy (CTV_{60}, orange), with the high-risk CTV covering the cribriform plate, ethmoid sinus, sphenoid sinus, and hard palate. Bilateral elective nodal radiation was delivered to RP nodes and Levels 1B–4 (CTV_{54}, pink)

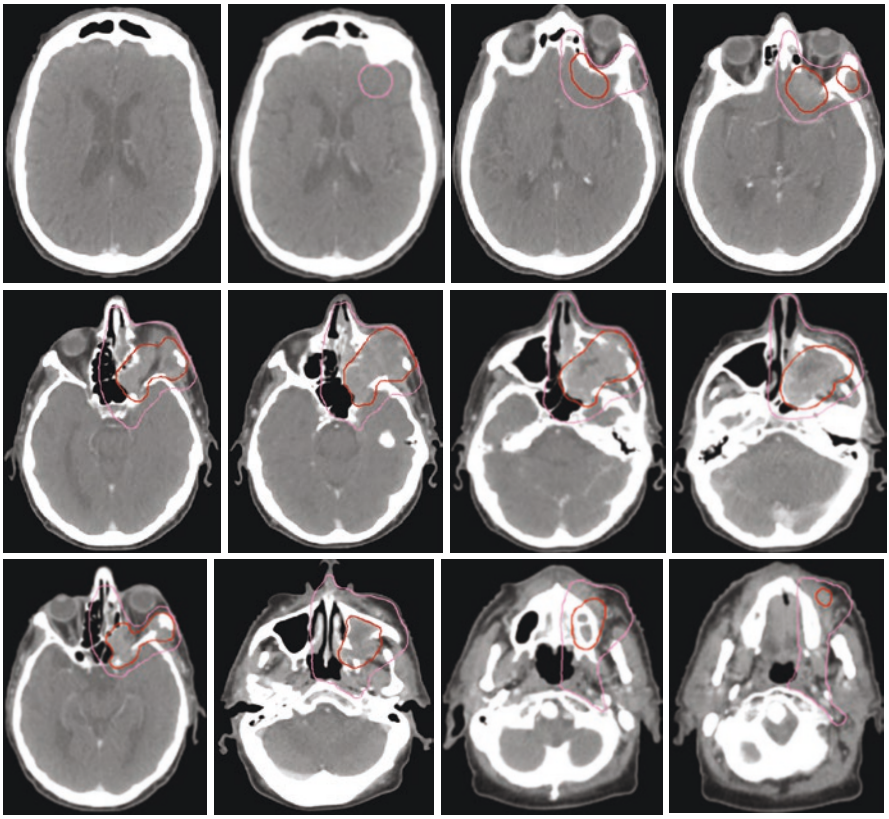

Fig. 7.2 Seventy-four-year-old male with an unresectable T4bN1M0 poorly differentiated SCC of the left maxillary sinus, with invasion of the anterior cranial fossa and cranial nerve involvement. The patient received definitive concurrent chemoradiotherapy. The gross primary tumor and involved lymph node were treated to 70 Gy (GTV_{70}) in red. Subclinical CTV_{50} is noted in pink, encompassing the orbital floor, infraorbital fissure, foramen rotundum, pterygopalatine fossa, infratemporal fossa, and masticator space. $CTV50_{50}$ covers the ipsilateral neck only, given the stage and grade. (Node positive side: retropharyngeal, IB–IV)

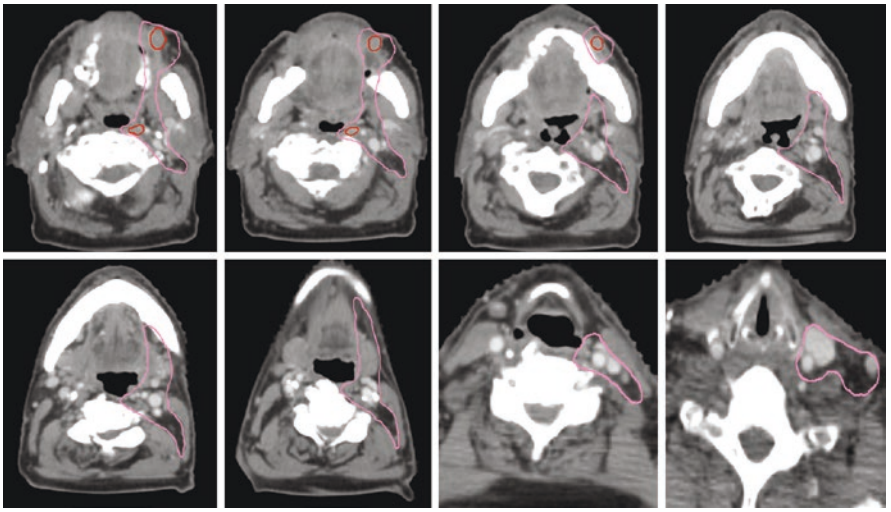

Fig. 7.2 (continued)

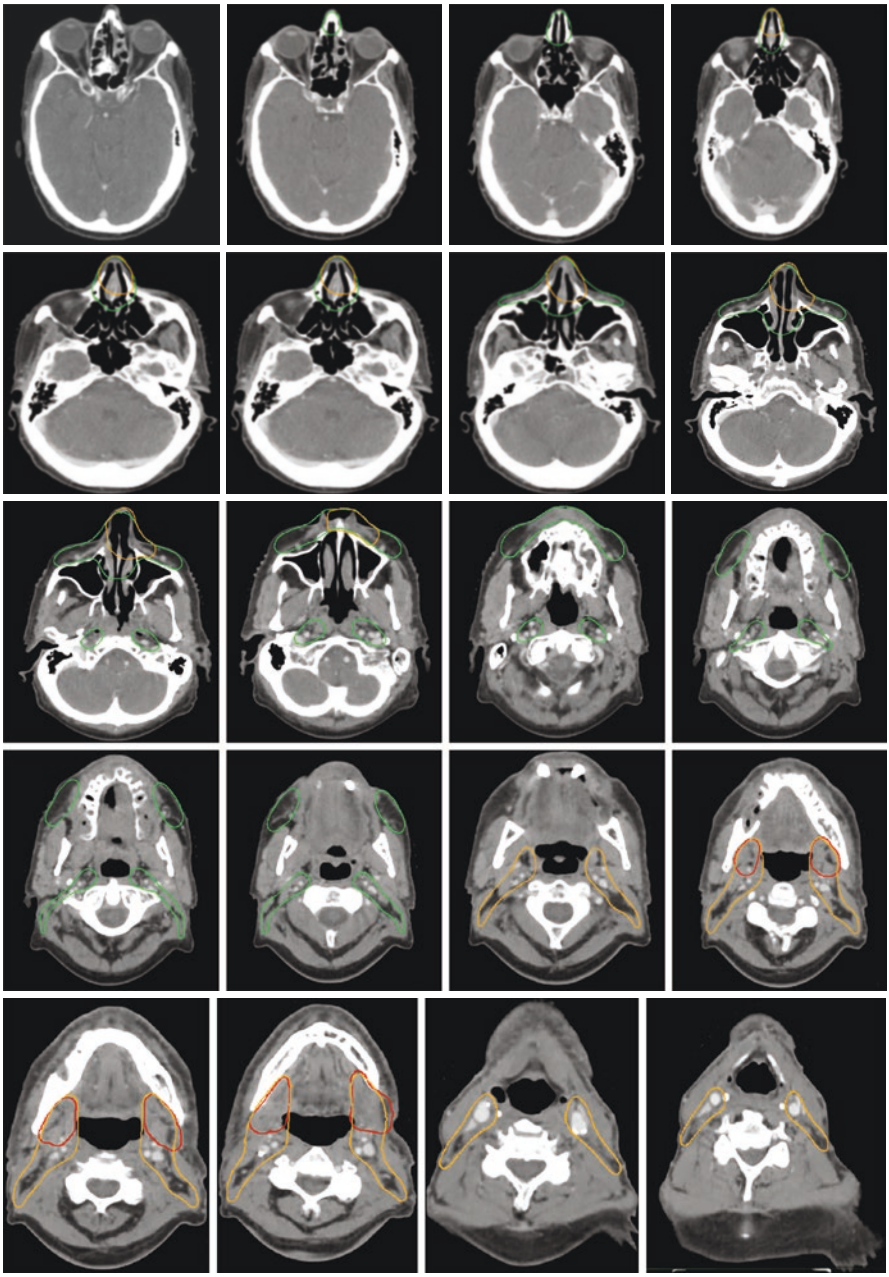

Fig. 7.3 Sixty-six-year-old female with a moderately differentiated SCC of the anterior nasal cavity. The patient underwent endoscopic resection of the primary tumor and bilateral modified radical neck dissection (Level I–IV). Pathology report noted a close surgical margin, and bilateral Level I lymph node metastases, along with extranodal extension. The patient then received adjuvant concurrent chemoradiotherapy. The low-risk CTV_{54} (green) encompasses the nasal cavity, RP nodes, and facial lymph nodes. The high-risk CTV_{60} (orange) encompasses the resection bed, all preoperative macroscopic disease extent, and levels 1B–4. CTV_{66} is noted in red, and covers the regions of extranodal extension

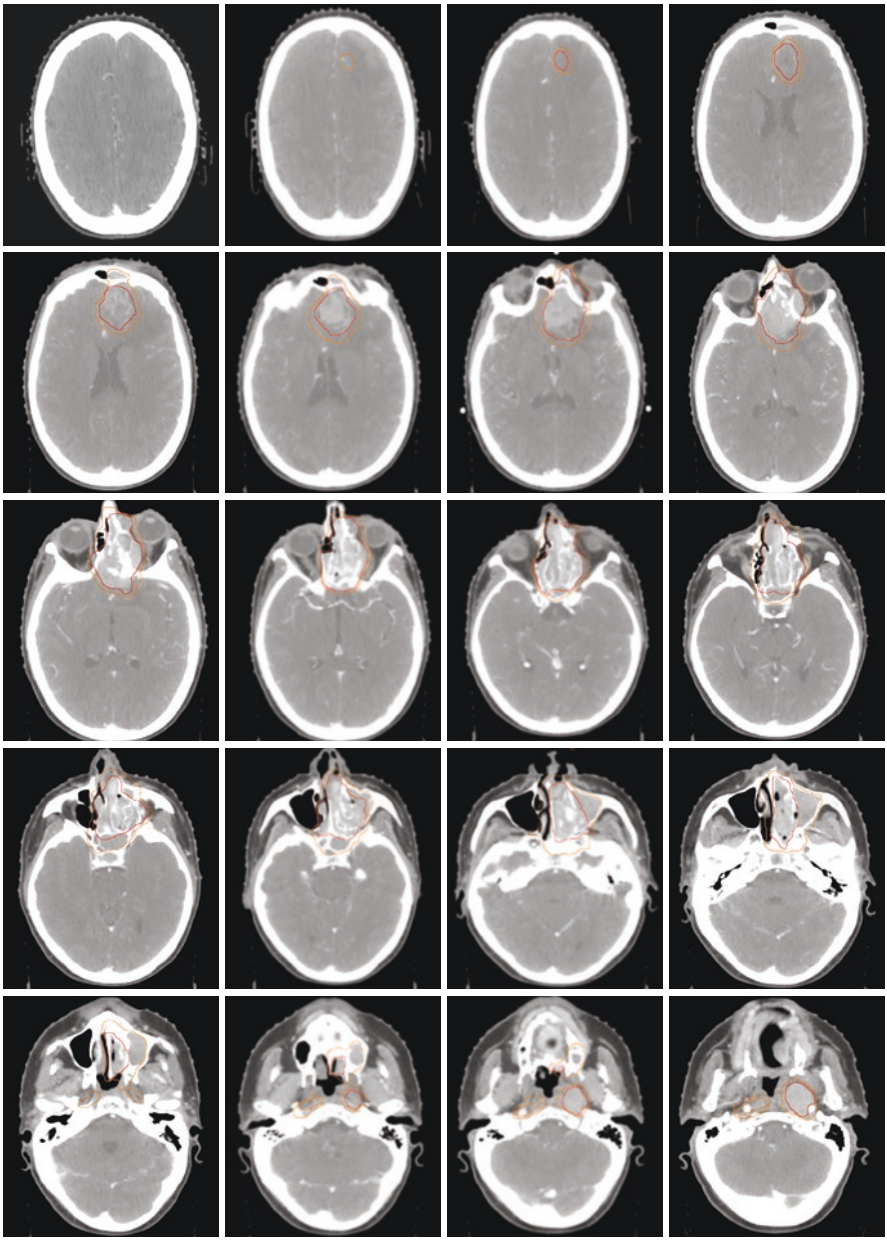

Fig. 7.4 An example of a 59-year-old female patient with a Kadish C esthesioneuroblastoma of the ethmoid sinus. The bulky tumor extended to the frontal lobe and she remained a non-surgical candidate even after three cycles of induction chemotherapy. She was referred to receive definitive chemoradiation. GTV_{70} is noted in red, and covered the primary tumor and involved lymph nodes. CTV_{60} is noted in orange, and encompassed all high-risk areas (cribriform plate, dura, medial maxillary sinus, ethmoid sinus, sphenoid sinus, nasal cavity, pterygopalatine fossa, foramen rotundum) as well as bilateral upper cervical neck (retropharyngeal and Level IB–II). CTV_{54} is noted in green for low-risk elective nodes in Levels III–IV bilaterally

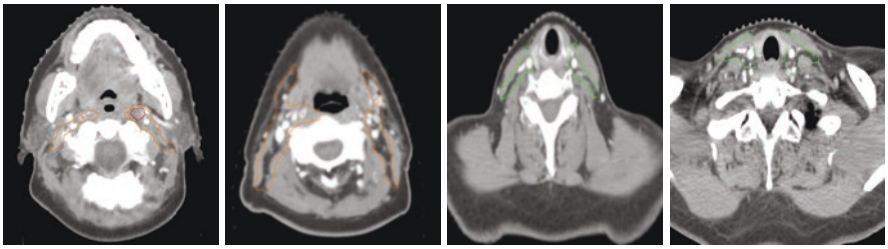

Fig. 7.4 (continued)

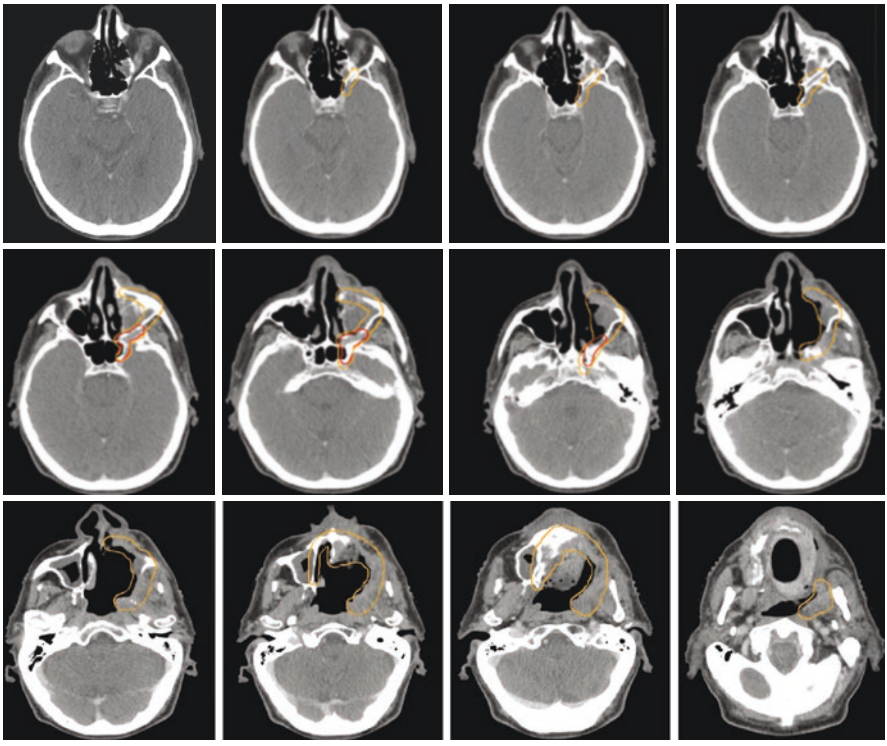

Fig. 7.5 An example of a 77-year-old male patient with a T3N0M0 adenoid cystic carcinoma of maxillary sinus. Patient received maxillectomy and pathologic report noted positive margins. The post-op images revealed patchy residual tumor at the posterior maxillary wall. GTV_{70} is noted in red, which covers the gross residual tumor. CTV_{60} is noted in orange, and covered high-risk areas including nerve courses (superior orbital fissure, inferior orbital fissure, foramen rotundum, pterygopalatine fossa, Vidian canal). The elective neck was not treated in this case due to the pathological type

7.2 Diagnostic Workup Relevant for Target Delineation

- Detailed review of the pre-operative history/symptoms, neurologic examination with emphasis on cranial nerve exam, pre and post-operative imaging, operative report, and pathology report are needed to define target volumes.
- In addition to fiberoptic endoscopy, high-quality diagnostic imaging is critical for tumor localization:
  - Early cortical bone erosion is best visualized on thin slice (1–2 mm cuts) high-resolution CT of the nasal cavity and paranasal sinuses with IV contrast.
  - Soft tissue spread, intracranial extension, perineural invasion, and involvement of the cranial nerve foramina and canals are best visualized on a thin-sliced MRI with IV contrast and fat-suppressed sequences.
  - PET/CT is helpful for identifying lymph nodes and metastatic disease.

7.3 Simulation and Daily Localization

- The patient should be simulated supine with head rest with the neck extended in a five-point customized Aquaplast mask that immobilizes the head, neck, and shoulders. A shoulder pull board can be used to lower the shoulders out of the beam angle path.
- A bite block may be used to push the tongue inferiorly away from the high-dose nasopharynx. For patients with many metal fillings, a custom mouthguard can be helpful to absorb electron scatter and mitigate treatment-related mucositis.
- The CT simulation should use $\leq$3 mm slices with IV contrast.
- The CT should include the entire vertex of the head through the carina.
- The isocenter is typically placed at the arytenoids.
- For postoperative cases, it is helpful to place a radiopaque marker on any scars.
- There are various appropriate IGRT approaches. Daily imaging ideally consists of daily cone beam CT aligned to bone. Daily kilovoltage imaging aligned to bone and weekly cone beam CTs are also adequate.

7.4 Target Volume Delineation and Treatment Planning

- The GTV should be delineated using all relevant clinical information derived from endoscopy, CT, MRI, and PET (Tables 7.1, 7.2 and 7.3).
- The high-risk CTV should encompass all initial sites of disease and potential regions of subclinical tumor spread.
  - All preoperative scans (CT and MRI) should be evaluated to ensure that the initial tumor volume is covered in the high-risk CTV.
  - A detailed review of the operative report and pathology report are necessary to ensure appropriate CTV delineation.
  - MRI should be used in all cases to assist target delineation of the tumor unless medically contraindicated.

Table 7.3 Subsite-specific anatomical considerations for delineation of the primary CTV_{60}–CTV_{66} and CTV_{70}

Maxillary sinus SCC
Superior: Orbital floor/skull base. Coronal MRI can be useful in delineating orbital floor involvement. In cases with intracranial extension, consider a 5 mm dural margin **Inferior**: Hard palate, including at least a 10 mm margin around the initial gross disease **Medial**: Nasal septum for lateralized cases. In cases with medial extension beyond the septum, consider coverage of the entire nasal cavity **Lateral**: Infratemporal fossa, including the masticator space. If there is lateral extension, consider extending coverage along the temporalis muscle **Posterior**: The pterygopalatine fossa and skull base, paying attention to include the infraorbital fissure. The posterior hard palate is innervated from a branch of CN V2. In cases with posterior involvement, cover the courses of CN V2/V3 to Meckel's cave **Nerves**: Branches of the second division of the trigeminal nerve (CN V2), the infraorbital nerve, and the greater palatine nerves
Nasal cavity SCC, ENB, SNUC, SNEC, melanoma
Superior: Cribriform plate, if intact; otherwise include the dural graft. Consider a 5 mm margin along the dura in cases where the cribriform plate is involved or if there is gross intracranial extension **Inferior**: Hard palate **Medial**: Include the entire nasal cavity **Lateral**: Medial border of the ipsilateral maxillary sinus for localized cases **Posterior**: The pterygoid plates, pterygopalatine fossa, ethmoid sinus, and sphenoid sinus **Nerves**: Branches of the olfactory nerve (CN I), and the first and second divisions of the trigeminal nerve (CN V1 and CN V2) including the nasociliary and nasopalatine nerves **SNEC**: See nasal cavity volumes. There is a high risk for metastatic disease. Consider either standard fractionation or treatment to 45 Gy/30 fractions given BID. Elective nodal coverage may be omitted **Nasal cavity mucosal melanoma**: See nasal cavity volumes. There is a high risk for metastatic disease. Consider standard fractionation for larger tumors. For small tumors, treatment to 30–36 Gy in 6 Gy fractions given twice weekly to the primary site only
Ethmoid sinus
Superior: See nasal cavity **Inferior**: Include a 10 mm margin on the initial tumor extent. For early stage tumors, the inferior turbinate is acceptable. For more advanced tumors, include the hard palate **Medial/Lateral**: Nasal cavity, ethmoid sinuses, and the ipsilateral maxillary sinus. In cases where the lamina papyracea has been breached, include the medial rectus. More advanced orbital involvement may require additional coverage **Posterior**: Skull base. Include the sphenoid sinus. The retropharyngeal lymph nodes should be encompassed if the tumor involves the nasopharynx or for N1 disease Nodal metastases are uncommon. Consider elective nodal coverage for large tumors (T4) or high-grade disease (SCC or adenocarcinoma) **Nerves**: Branches of the first and second divisions of the trigeminal nerve (CN V1 and CN V2). Parasympathetic innervation is via the Vidian nerve

- Adenoid cystic carcinomas are highly neurotrophic, so target volumes should encompass the afferent and efferent local nerves to the skull base.
- ENB arise in the superior nasal cavity and tend to invade the cribriform plate and anterior cranial fossa in their early stages, so these regions should be encompassed in the high-risk CTV.

- The surgical approach (midface degloving, lateral rhinotomy, craniofacial resection, or endoscopic resection) should be considered in the field design.
  - If a craniofacial resection has been performed, the frontal graft should be included in the target volume. Surgical fiducial markers can help delineate the tumor bed.
- Elective neck irradiation should be considered at the discretion of the treating physician, depending on primary tumor site and disease extension.
  - Regional nodal drainage patterns include the retropharyngeal nodes, and IB–IV.
  - Level V should be included in cases with nasopharyngeal involvement.
  - Facial node coverage should be considered for nasal cavity tumors.
  - Bilateral nodal irradiation is typically administered as most primaries are midline structures.
  - Unilateral nodal radiation is administered for maxillary sinus cancers.
- Suggested target volumes are detailed in Tables 7.1, 7.2 and 7.3 (Figs. 7.1, 7.2, 7.3, 7.4 and 7.5).
- Planning.
  - We favor a sequential cone down approach. An initial plan (30 fractions) with a dose-painting approach delivers 54 Gy (1.8 Gy/fx) and 60 Gy (2 Gy/fx) to the low and high-risk subclinical regions, respectively. This is followed by a cone down plan (5 fractions) which delivers an additional 10 Gy to gross disease only for a total of 70 Gy over 35 fractions.

Further Reading

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Major Salivary Glands

8

Michelle S. F. Tseng, Ivan W. K. Tham, and Nancy Y. Lee

Contents

8.1 General Principles of Planning and Target Delineation

- Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck region, from the base of skull to the clavicles, should be performed for salivary gland cancer.
- Neoplastic lesions are better visualized and delineated with MRI, given the superior soft tissue contrast in the gland. The T1-weighted images can give an excellent assessment of the margin of the tumor, its deep extent, and its pattern of infiltration. With the addition of fat-saturated, contrast-enhanced T1-weighted

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_8

imaging, perineural spread, bone invasion, or meningeal infiltration can be better visualized.
- CT simulation with intravenous contrast can be performed where the primary tumor is in situ to help guide gross target volume (GTV) delineation. Fusion with diagnostic MRI when available is recommended.
- Suggested target volumes at the gross disease and high-risk regions are detailed in Tables 8.1 and 8.2 (Figs. 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, and 8.9).

Table 8.1 Suggested target volumes at the gross disease region

Target volumes	Definition and description
GTV_{70}[a] (the subscript 70 denotes radiation dose delivered)	Parotid or submandibular primary: all gross disease on physical examination and imaging
	Neck nodes: all nodes ≥1 cm in short axis diameter or nodes with necrotic center
CTV_{70}	Add 5 mm so that GTV_{70} + 5 mm = CTV_{70} Alternatively, GTV_{70} can also be equivalent to CTV_{70} when the treating MD is certain of the target
	For nodes that are small but suspicious for disease (i.e., <1 cm), consider a lower dose of 63–66 Gy
PTV_{70}	Margin specific to treatment center and less if image guidance available
	Typically CTV_{70} + 3–5 mm = PTV_{70}

[a] Suggested dose to gross disease is 2 Gy/fraction to 70 Gy

Table 8.2 Suggested target volumes at the high-risk subclinical region

Target volumes	Definition and description
CTV_{60}	Parotid or submandibular CTV_{60} should encompass the entire GTV or the surgical bed for postoperative patients
	Landmarks for the **parotid** *surgical bed*
	Anterior: masseter muscle
	Lateral: soft tissue of neck
	Medial: styloid process at depth; may need to extend to parapharyngeal fat depending on the extent of parotid gland
	Posterior: mastoid bone
	Landmarks for the **submandibular** *surgical bed* Include the entire surgical bed, all postoperative changes, and use the contralateral submandibular gland as a guide
	Highly consider a boost of 6–10 Gy to residual disease or positive margins. The surgeon should be encouraged to leave clips where possible for localization
	For cases with perineural involvement [1]
	Parotid tumors: Include facial nerve, glossopharyngeal nerve and V3; may need to extend to Meckel's cave
	Submandibular and **sublingual** tumors: Include hypoglossal and lingual nerve; may need to extend to Meckel's cave especially for adenoid cystic carcinoma; may also need to include facial nerve

Table 8.2 (continued)

Target volumes	Definition and description
CTV_{50}	*Clinically node positive tumors*
	Electively irradiate rest of the ipsilateral neck (levels Ib–V) to 50 Gy; can consider omitting level V
	Clinically node negative tumors
	Ipsilateral neck: Include at least levels Ib–III/IV for high-grade or large (T3–4) tumors. Adenoid cystic or acinic cell cancers typically do not require elective nodal irradiation because of the low risk of lymphatic spread
	Contralateral neck:
	Parotid *tumors*: Consider treating when clinically concerned
	Submandibular *tumors*: Consider treating when clinically concerned
PTV_{60}	Margin specific to treatment center and less if image guidance available
	Typically CTV_{60} + 3–5 mm = PTV_{60}

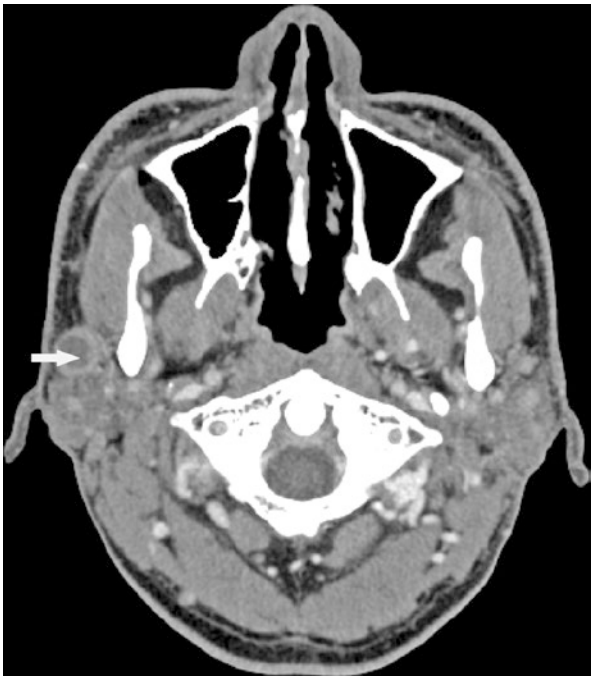

Fig. 8.1 Axial contrast-enhanced CT image of a patient with a history of excision of a cutaneous squamous cell carcinoma (SCC) in the right temporal region, who now presents with an ipsilateral parotid mass, (*arrowed*) confirmed on biopsy to be metastatic SCC

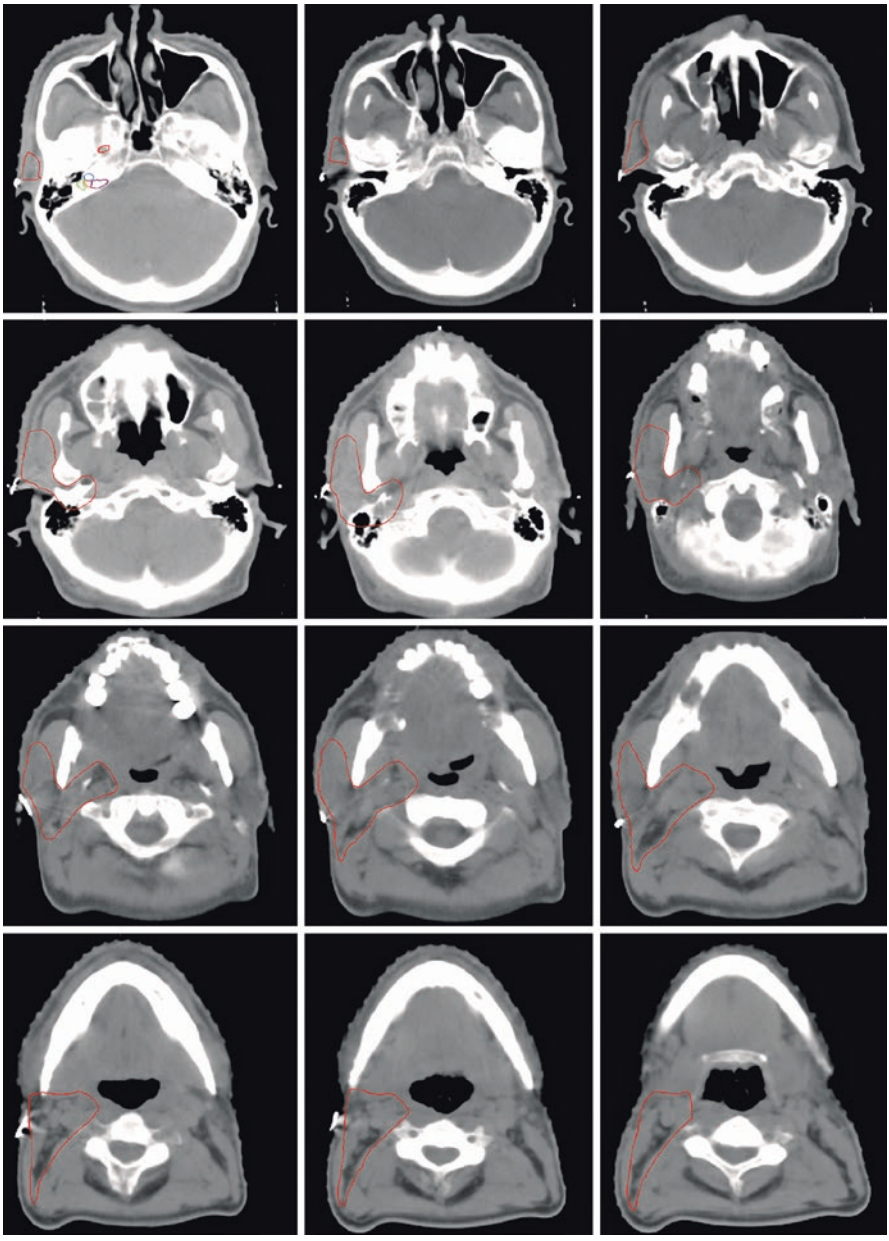

Fig. 8.2 CT simulation with 3-mm slices in a head shell was performed in the same patient following superficial parotidectomy with clear margins. These are representative slices and not all slices are included. Of note, the temporal region where the skin cancer originated should also be included using either electrons matching to IMRT or 3D CRT, or an all-inclusive IMRT or 3D CRT plan, especially if the primary site treatment was less than a year prior. The structures at the base of skull in the first figure are labelled in Fig. 8.3. The orange contour denotes the CTV_{60}

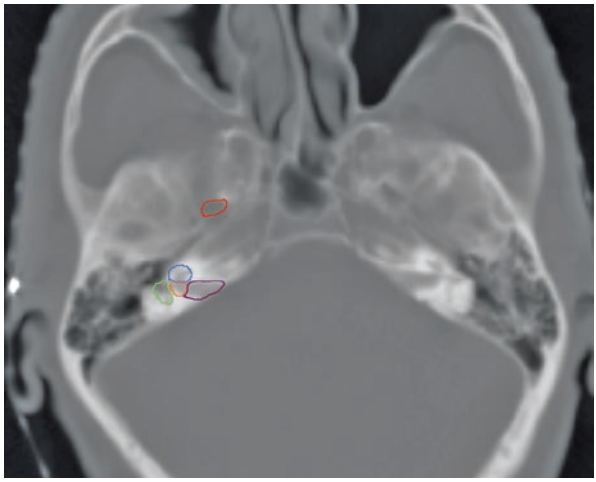

Fig. 8.3 Base of skull Delineation of structures should be done using bone windows. Structures as follows: *red* foramen ovale, *blue* cochlea, *orange* vestibule, *violet* internal auditory canal, and *green* semicircular canals

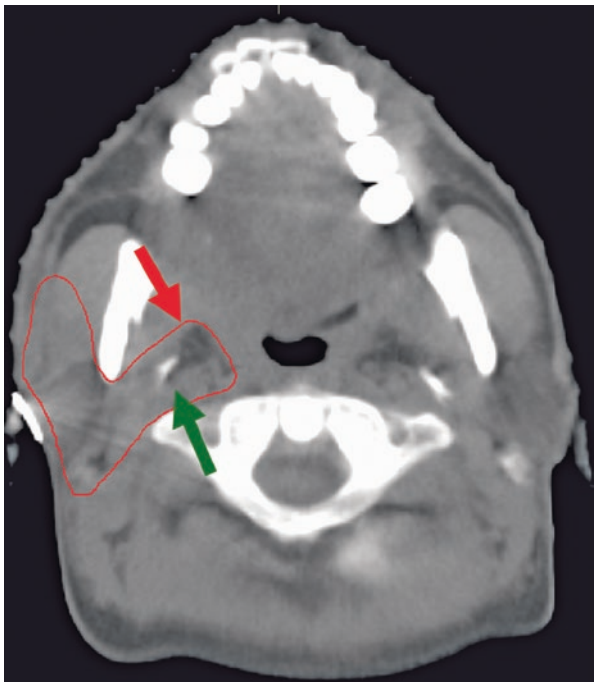

Fig. 8.4 The parapharyngeal space (*red arrow*) is a predominantly fat-filled space extending from the base of skull to the hyoid and should be included for large or deep parotid tumors. The retrostyloid space (*green arrow*) is posterolateral to the styloid process, may contain lymph nodes, and should be included in the CTV_{60}

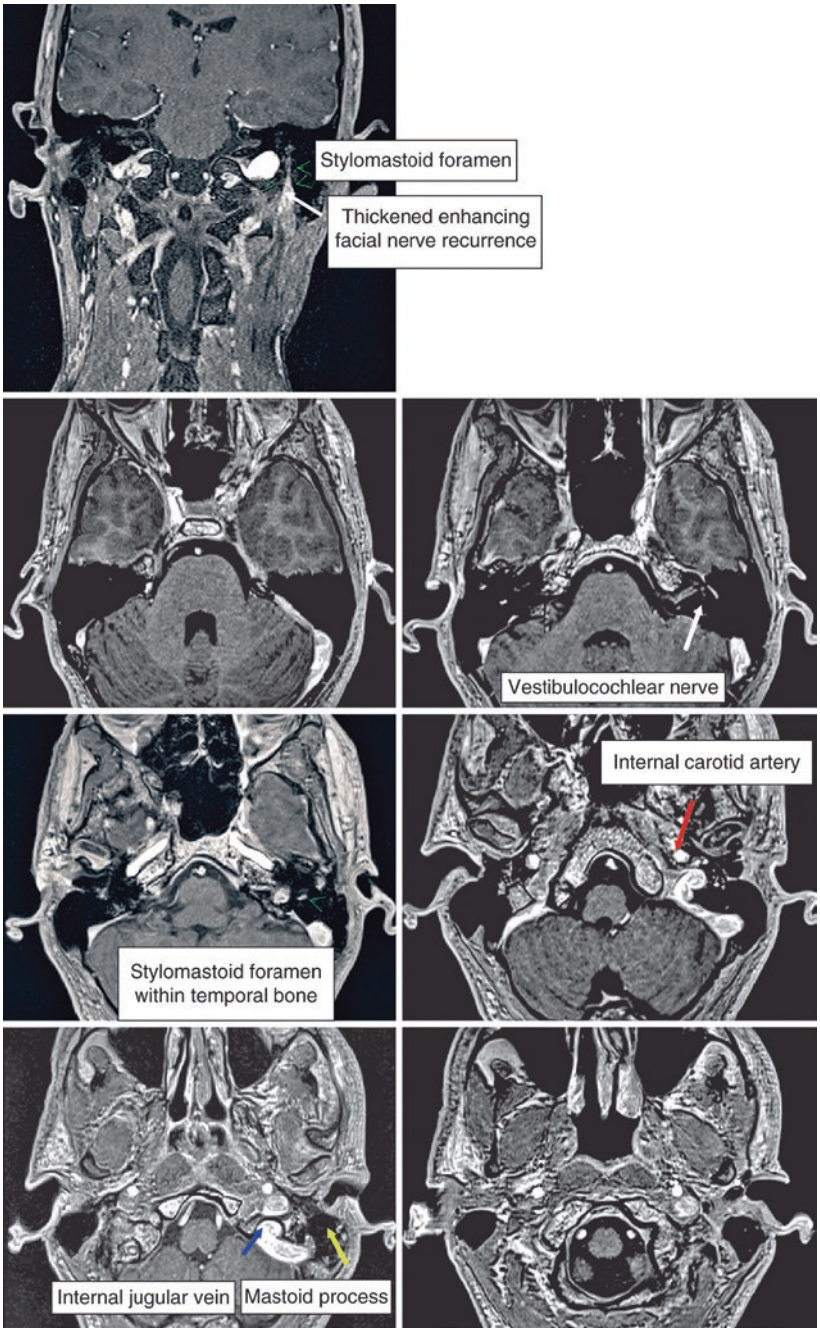

Fig. 8.5 Stylomastoid foramen. Note pattern of perineural recurrence in these T1-weighted contrast-enhanced MRI images, which show recurrent mucoepidermoid carcinoma of the left parotid gland infiltrating the left facial nerve through the stylomastoid foramen (*green arrow heads*). For parotid tumors, include facial nerve when involved or if histology is adenoid cystic carcinoma. Include intra-temporal course of the nerve, via the facial canal, which extends from the internal auditory canal to the stylomastoid foramen

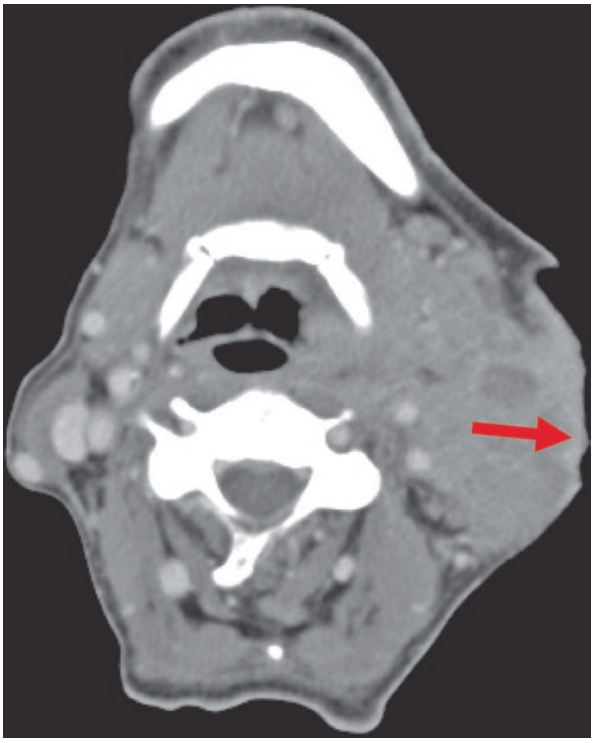

Fig. 8.6 Skin. Include involved skin as a target structure by utilizing a bolus if there is clinical or radiological (*red arrow*) evidence of dermal infiltration. Include the scar in cases with perioperative tumor spillage

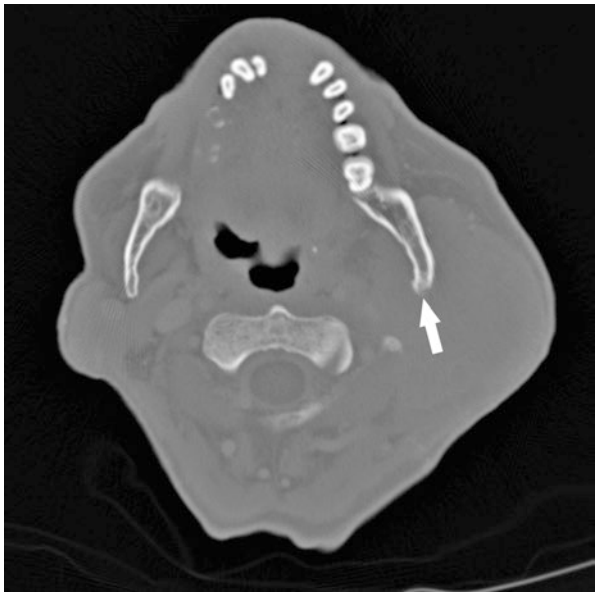

Fig. 8.7 BONE. Assess bone involvement with bone windows on CT scans and include in CTV if required. *White arrow* indicates periosteal reaction at posterior aspect of left ramus of mandible, suggesting involvement

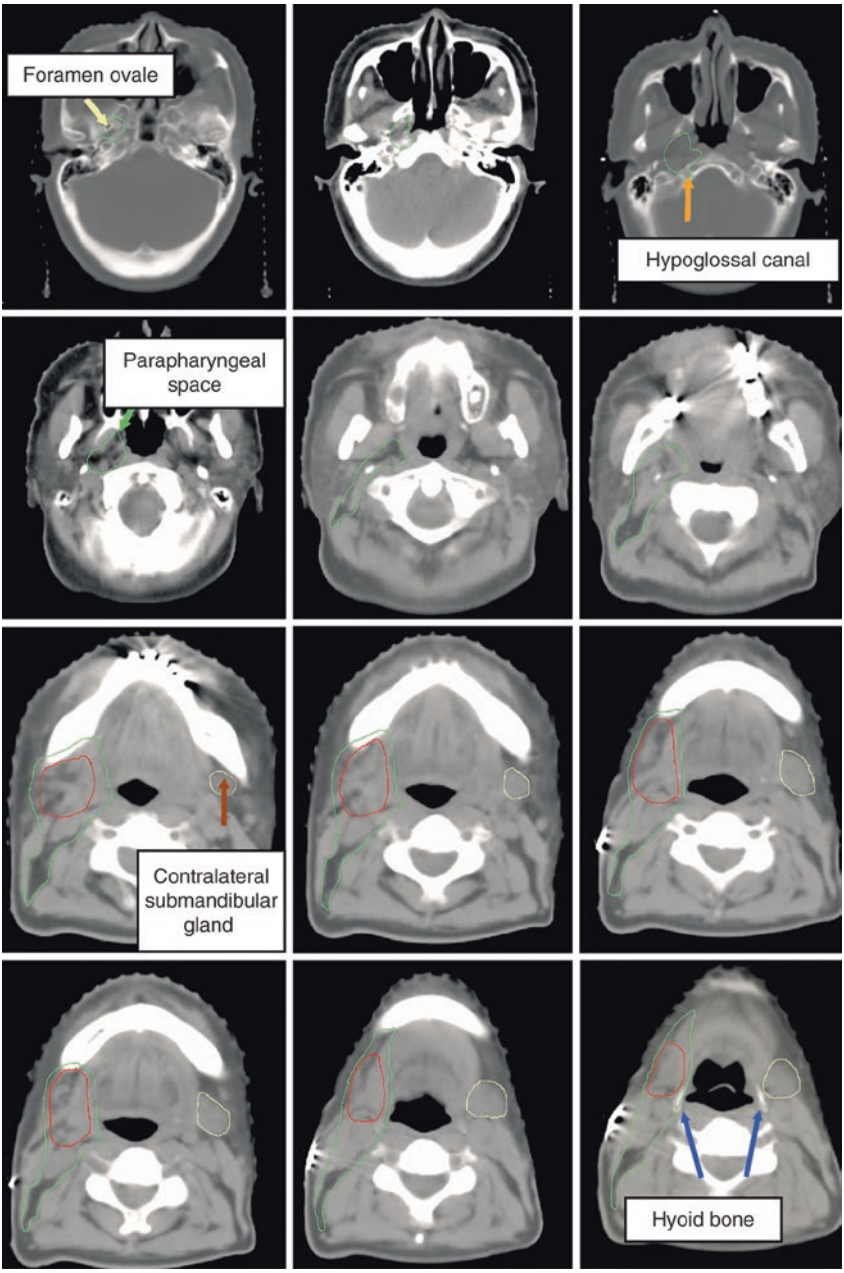

Fig. 8.8 Submandibular gland. Selected CT simulation images of a patient who underwent complete excision of a cT1N1M0 high-grade mucoepidermoid carcinoma of the right submandibular gland with clear margins. Structures as follows: *red* CTV_{60-66} (surgical bed) and *green* CTV_{50-54} (ipsilateral nodal stations and parapharyngeal space to base of skull). Lingual or hypoglossal nerves should be treated to base of skull especially when these named nerves are involved. The lingual nerve originates from the mandibular (V3) branch of the trigeminal nerve at the foramen ovale and courses deep to the lateral pterygoid muscle, then between the medial pterygoid muscle and the ramus of the mandible towards the medial aspect of the submandibular gland before terminating in the tongue

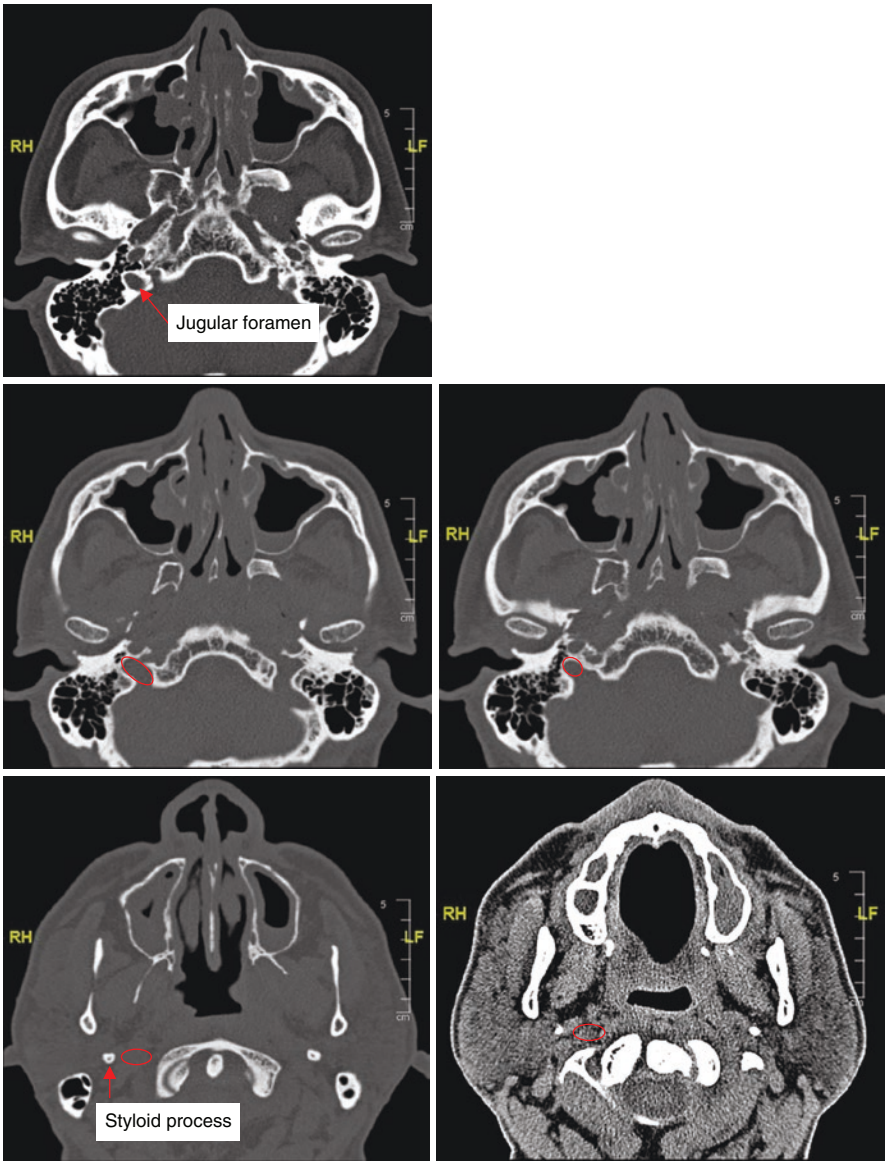

Fig. 8.9 The glossopharyngeal nerve exits the base of skull through the jugular foramen and descends down the neck, anterolaterally to the internal carotid artery, which is medial to the styloid process. It terminates in branches to the pharynx. *Red oval* denotes the course of the glossopharyngeal nerve through different CT images. The last picture uses soft tissue windowing to show the expected location of the glossopharyngeal nerve

Reference

1. Armstrong K, Ward J, Hughes NM, Mihai A, Blayney A, Mascott C, et al. Guidelines for clinical target volume definition for perineural spread of major salivary gland cancers. Clin Oncol (R Coll Radiol). 2018;30(12):773–9.

Thyroid Cancer

9

Kaveh Zakeri, Shyam S. D. Rao, Nadeem Riaz, Nancy Y. Lee, and Robert L. Foote

Contents

9.1 General Principles of Planning and Target Delineation

- In addition to thorough physical examination, adequate imaging studies should be obtained for diagnosis, staging, and planning. The use of iodinated contrast with CT imaging should be avoided if the patient will subsequently require radioactive iodine administration as it can interfere with uptake for up to 6 months. MRI and ultrasound may be valuable in detecting lymphadenopathy or extrathyroidal extension. Unlike most well-differentiated thyroid carcinomas, poorly differentiated or anaplastic thyroid cancer may be FDG-avid.
- CT simulation should be performed to help guide the gross target volume (GTV) delineation, particularly for the lymph nodes. As above, the use of iodinated contrast should be clearly justified as necessary before administered.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_9

- A thermoplastic mask to immobilize the head, neck, and shoulders is preferable to immobilizing only the head and neck region. The head should be slightly extended to lower the dose to the oral cavity.
- Gross disease or tumor bed with positive margins should be treated to 66–70 Gy. At-risk regions should be treated to 54–63 Gy. Patients may be treated in 30–35 fractions with an all-in-one dose-painting IMRT plan or alternatively an initial IMRT course followed by a boost. We recommend clinical target volume (CTVs) be treated with daily fractions sizes between 1.8 and 2 Gy.
- Target volumes include GTV and CTV which should be delineated on every slice of the planning CT. Accurate selection and delineation of CTV for gross disease (i.e., $CTV_{66–70}$) and at-risk subclinical region ($CTV_{54–63}$) is critical for the treatment of thyroid cancer using IMRT.

Suggested target volumes for gross disease and at-risk regions are detailed in Tables 9.1 and 9.2 (Figs. 9.1, 9.2, 9.3, 9.4, and 9.5).

Table 9.1 Suggested target volumes for gross disease

Target volumes	Definition and description
$GTV_{66–70}$[a] (the subscript 66–70 denotes the radiation dose delivered)	Primary: All gross disease on physical examination and imaging
	Neck nodes: All nodes ≥1 cm or with necrotic center
$CTV_{66–70}$[a]	Usually $CTV_{66–70}$ is the same as $GTV_{66–70}$. If a margin is needed due to uncertainty of the gross disease, add 3–5 mm so that $GTV_{66–70}$ + 3–5 mm = $CTV_{66–70}$
	If the GTV is adjacent to the spinal cord, a 1-mm margin is acceptable, as protection of the spinal cord is required
	For suspicious nodes that are small (i.e., <1 cm), a lower dose of 66 Gy (CTV_{66}) can be considered
$PTV_{66–70}$[a]	$CTV_{66–70}$ + 3–5 mm, depending on variability in daily patient positioning. If the CTV is adjacent to the spinal cord, a 1-mm margin is acceptable

[a] Suggested dose for gross disease is 70 Gy. In cases where there is concern for brachial plexus, laryngeal, spinal cord, lung, or esophageal toxicity, 66 Gy may be considered. In postoperative cases with gross resection but significant concern for residual disease based on positive margin(s), the tumor bed or region of concern can be treated to 66 Gy

Table 9.2 Suggested target volumes for at-risk subclinical region

Target volumes	Definition and description
$CTV_{54–63}$[a]	Primary: Should include tracheoesophageal groove and >5-mm margin around any $CTV_{66–70}$
	In the postoperative setting, should encompass tumor bed and tracheoesophageal groove on the involved side(s). If tracheostomy performed, should also encompass tracheostomy stoma to the skin surface
	Optimally, the upper larynx (vocal cords/arytenoid cartilage and above) and posterior esophagus should be excluded, if not adjacent to tumor/tumor bed
	(See Table 9.1, regarding positive margins)
	Lateral Neck regions: Include bilateral nodal levels II–VII. However, coverage of the lateral necks can be omitted when treating the central compartment and the upper mediastinum down to the level of the carina as above. The level I and retropharyngeal nodes are generally omitted unless at risk
$PTV_{54–63}$[a]	$CTV_{54–63}$ + 3–5 mm, depending on variability in daily patient positioning. If the CTV is adjacent to the spinal cord, a 1-mm margin is acceptable

[a] Suggested at-risk subclinical dose: 60–63 Gy. Uninvolved nodal regions may be deemed as low-risk subclinical regions and treated to 54 Gy at the discretion of the treating physician

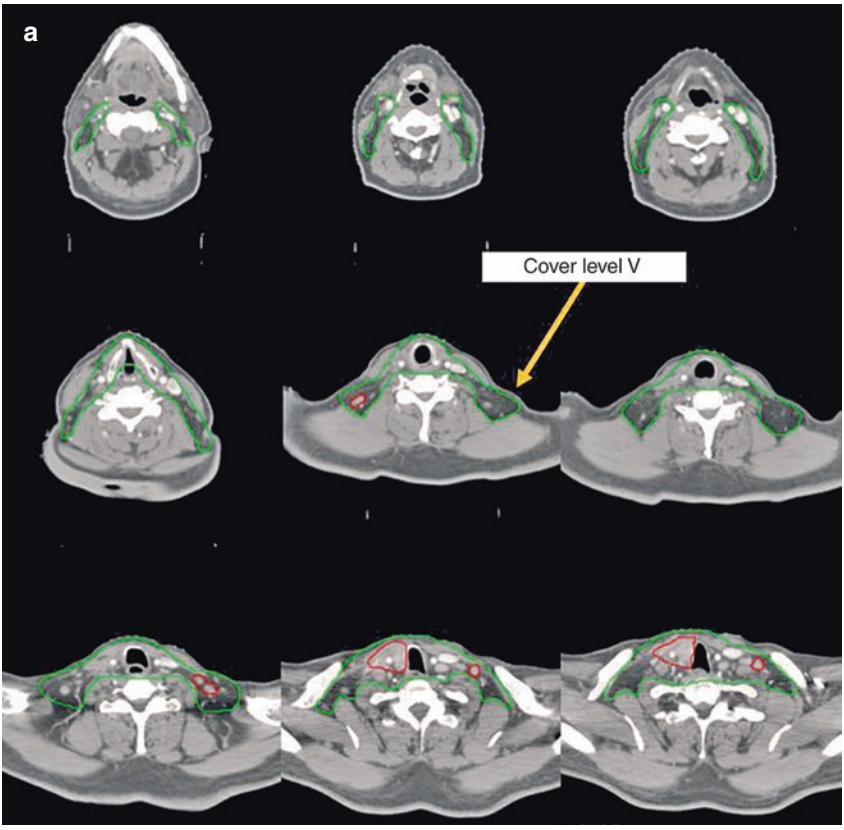


Fig. 9.1 A 58-year-old male with metastatic papillary thyroid carcinoma status post-multiple surgical resections who presented with an unresectable local recurrence and multiple mediastinal lymph nodes. He received definitive chemoradiotherapy to prevent local progression. CTV_{70Gy} is in *red* and CTV_{60Gy} is in *green*. Also, note that these are representative slices and not all slices are included

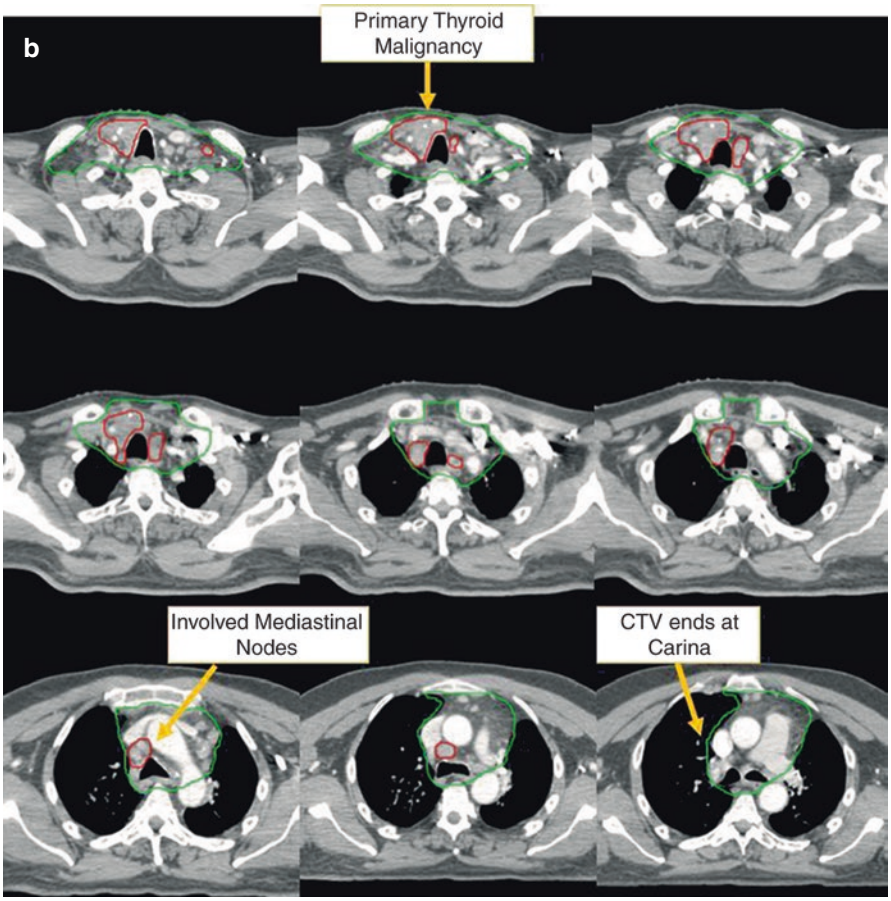


Fig. 9.1 (continued)

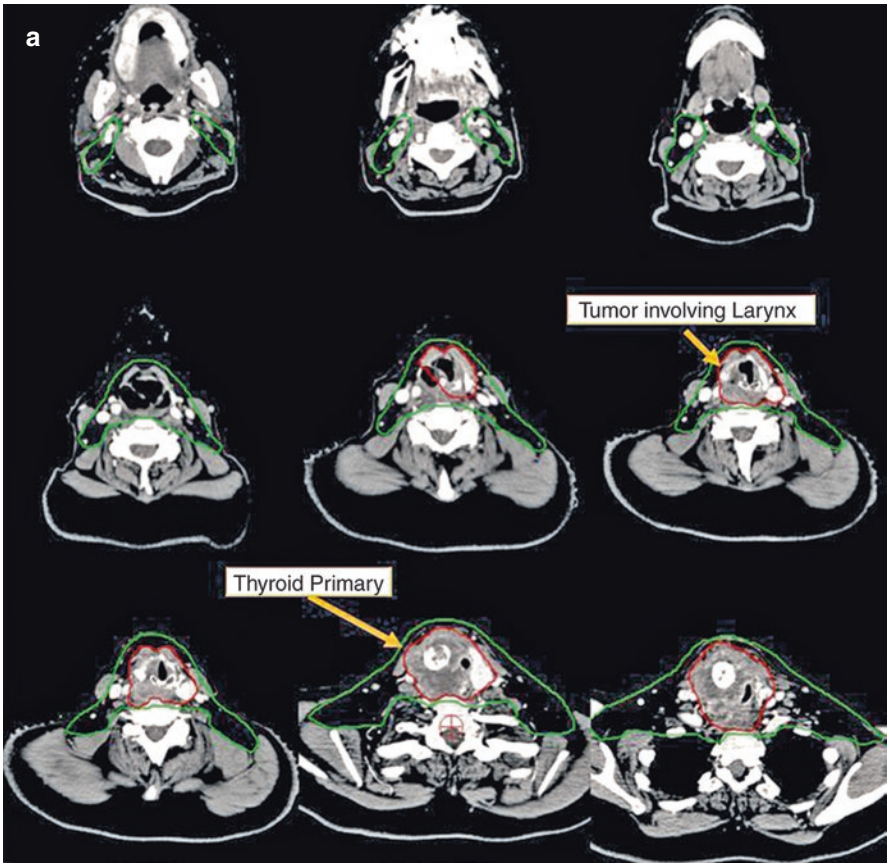


Fig. 9.2 A 73-year-old female with unresectable anaplastic thyroid carcinoma invading the larynx, trachea, and esophagus. She received definitive chemoradiotherapy with concurrent doxorubicin to prevent local progression. CTV_{70Gy} is in *red* and CTV_{60Gy} is in *green*. Although the manubrium is not routinely encompassed in the at-risk volume, it was included for this patient with aggressive bulky anterior neck disease. These are representative slices and not all slices are included

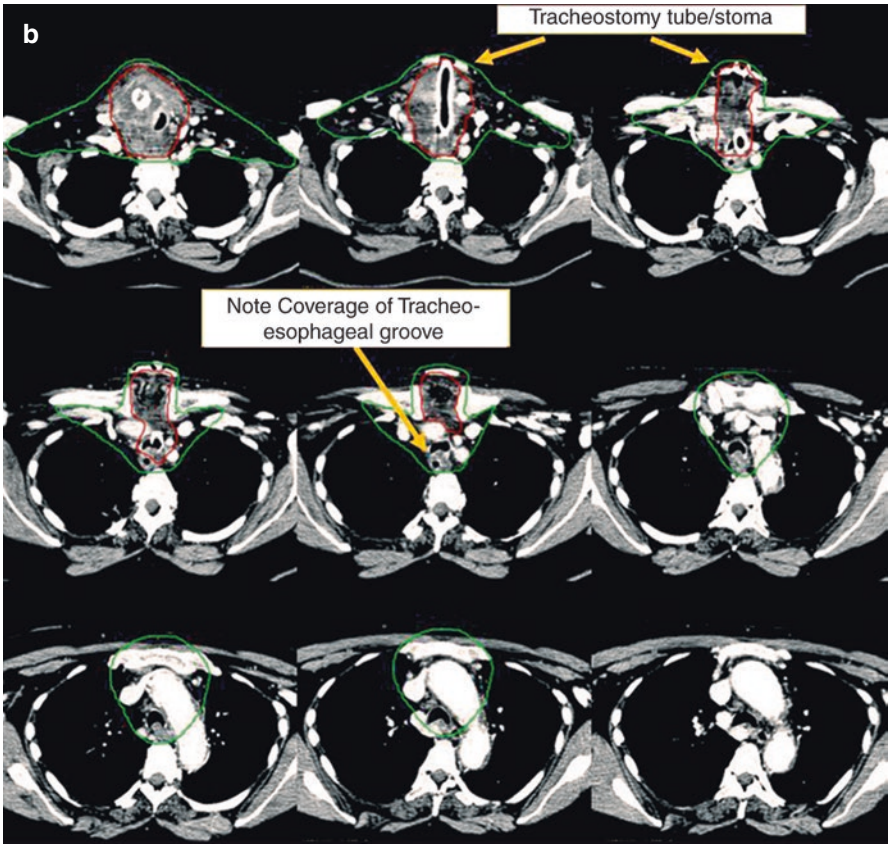


Fig. 9.2 (continued)

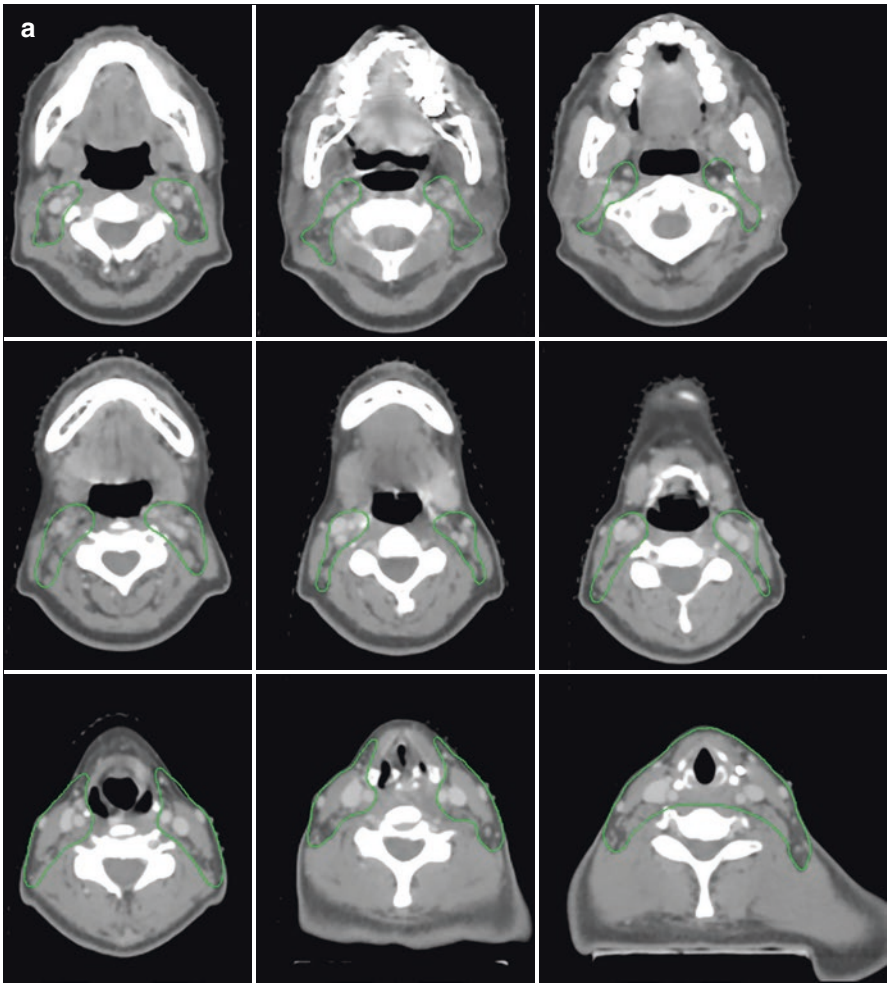


Fig. 9.3 A 50-year-old woman with anaplastic thyroid carcinoma s/p resection with extra-thyroid extension and positive margins but no involved lymph nodes. She received post-operative chemo-radiation. CTV_{70Gy} is in *red* and CTV_{60Gy} is in *green*. CTV_{70Gy} includes the tumor bed and surgical clips. These are representative slices and not all slices are included

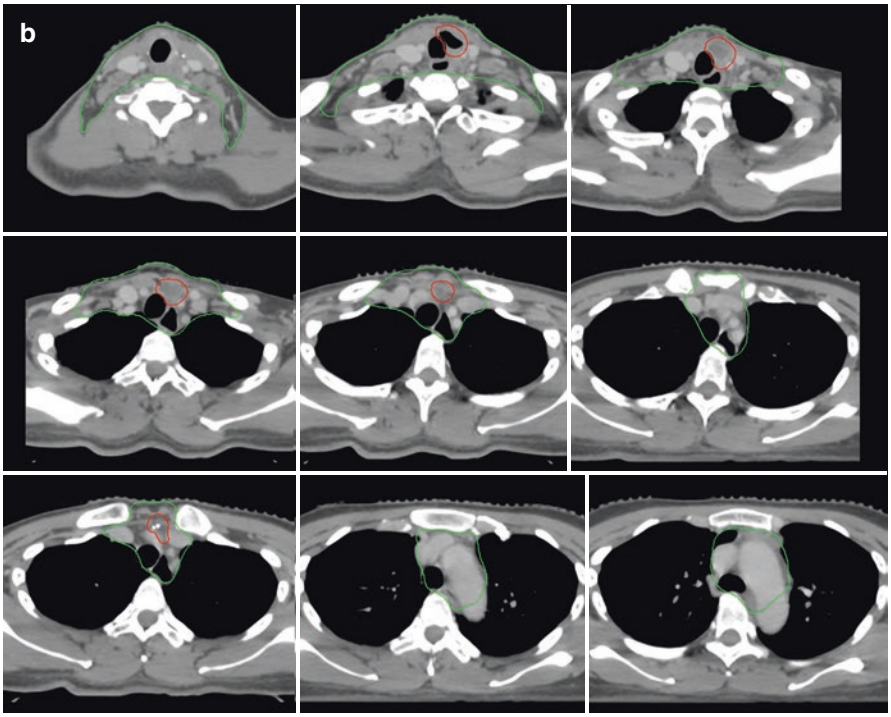


Fig. 9.3 (continued)

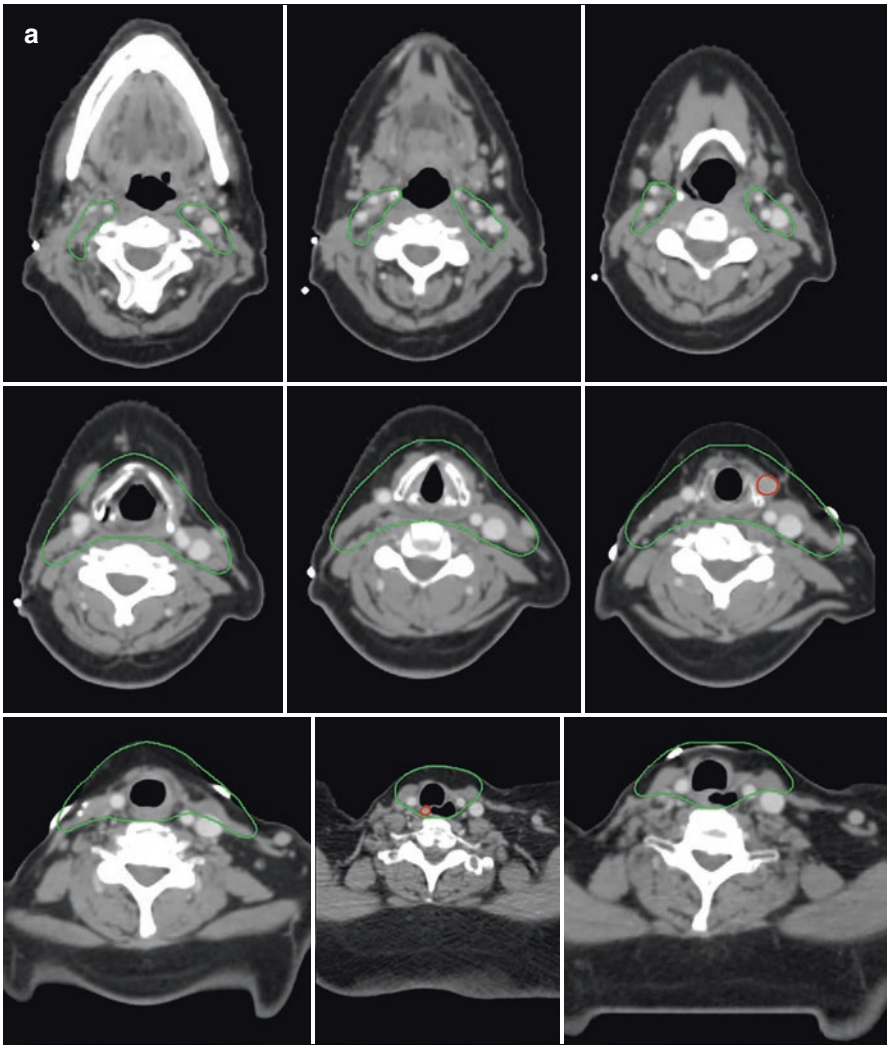
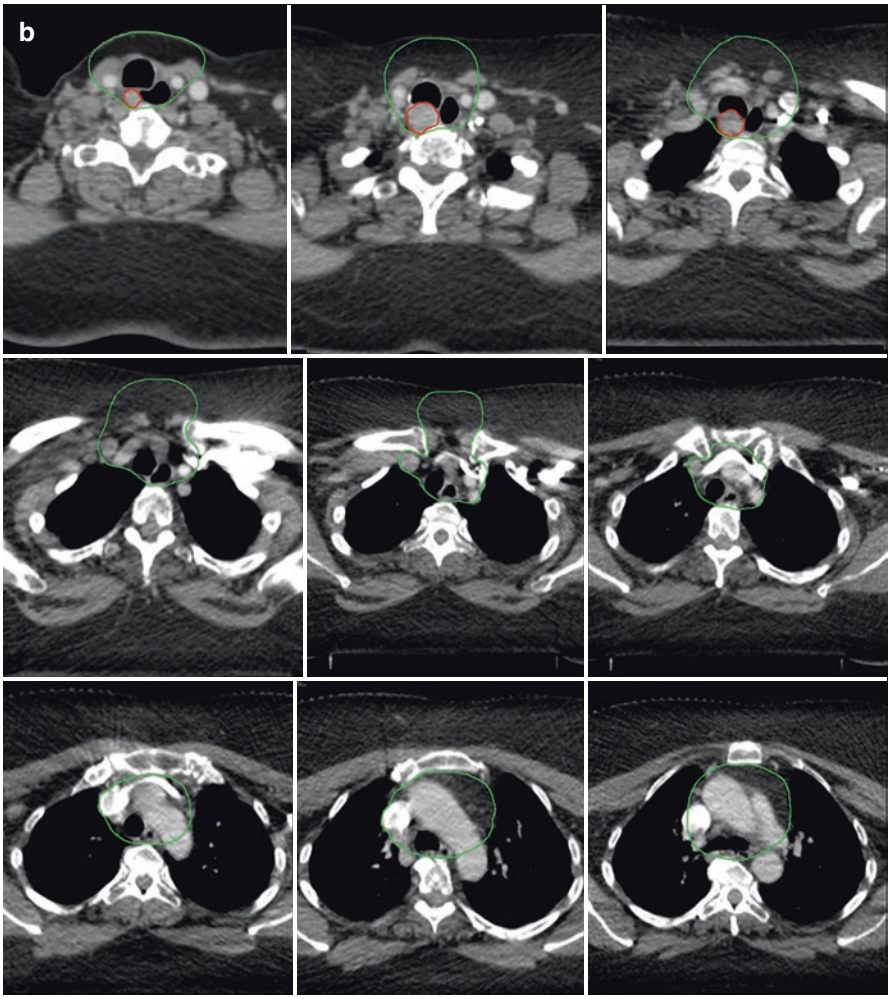


Fig. 9.4 A 61-year-old woman with a multiply recurrent metastatic tall cell variant of papillary thyroid cancer s/p three prior surgeries who presented with a multi-focal recurrence. She was treated with definitive chemoradiation. GTV_{70Gy} is in *red* and CTV_{60Gy} is in *green*. These are representative slices and not all slices are included



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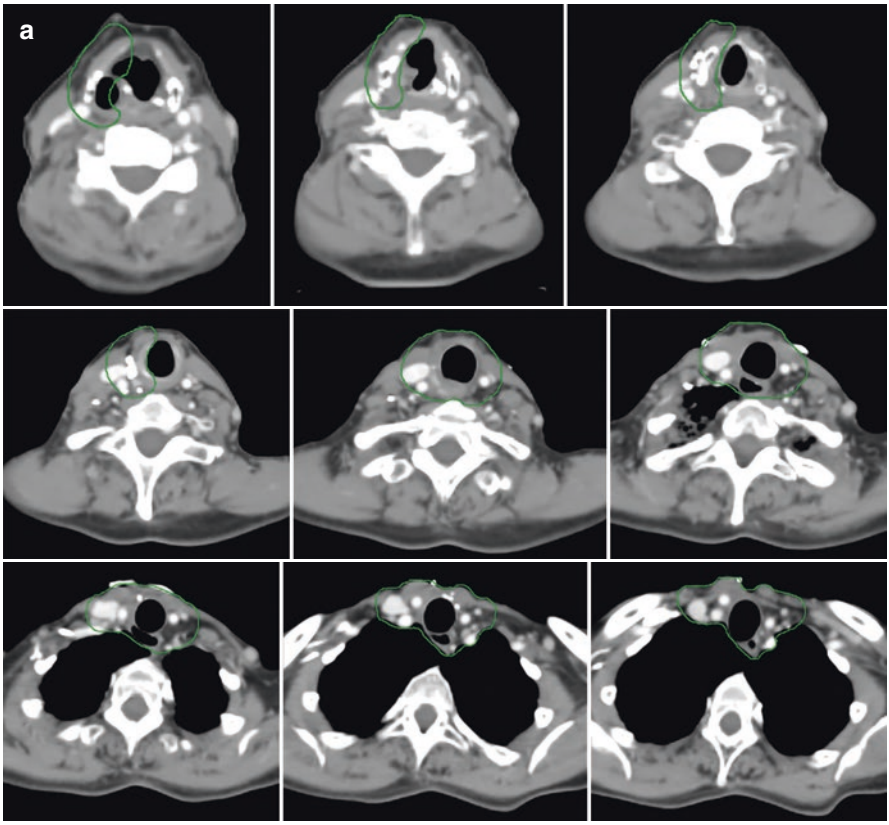

Fig. 9.5 A 69-year-old woman with history of poorly differentiated thyroid cancer of follicular phenotype adherent to trachea and esophagus s/p resection and radioactive iodine who recurred with a right paratracheal mass that invaded the trachea followed by resection and neck dissection. She was treated with adjuvant chemoradiation. CTV_{60Gy} is in *green*. Note that treatment of the lateral neck was omitted given the high risk for recurrence in the central compartment. These are representative slices and not all slices are included

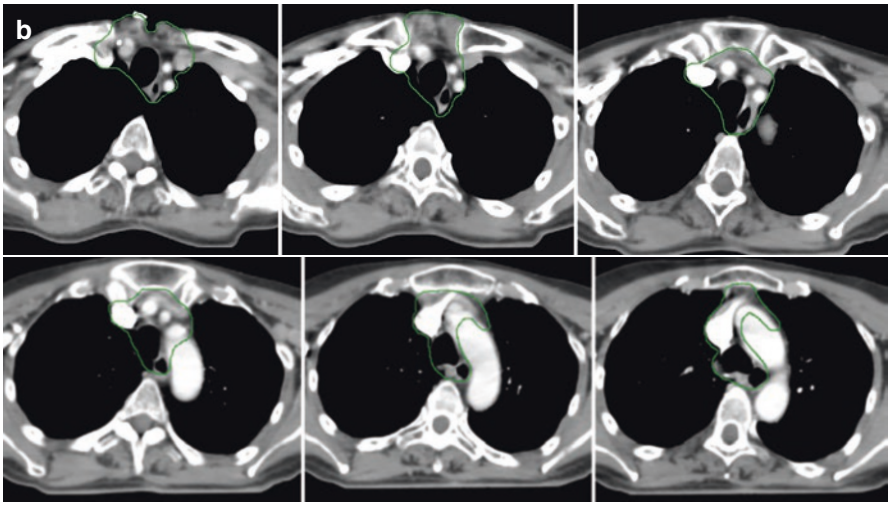

Fig. 9.5 (continued)

Squamous Cell Carcinoma of Unknown Primary in the Head and Neck

10

Daniel Ma, Nadeem Riaz, Allen Chen, and Nancy Y. Lee

Contents

10.1 General Principles of Planning and Target Delineation

- A thorough workup is necessary to rule out a site of origin before proceeding with a diagnosis of an unknown primary. At a minimum, this should consist of a careful physical examination including testing of the cranial nerves; fiberoptic examination visualizing the nasopharynx, oropharynx, larynx, and hypopharynx; and cross-sectional imaging with at least a high-resolution CT scan with contrast. Detailed skin and scalp exam.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_10

- Obtaining a careful patient history is also critical to determine risk factors for cancer and to consider possible infraclavicular primary sources (e.g., thoracic, gynecologic, or gastrointestinal). PET/CT may identify some additional primaries not detected by other methods but should be performed before biopsy to decrease the incidence of false-positive findings. Panendoscopy may also be useful.
- HPV and EBV testing should be performed to help determine possible primary locations. In AJCC eighth edition, HPV and EBV associated nodes are classified as T0 oropharynx or nasopharynx cancers, respectively.
- Directed biopsies of all suspicious lesions in the pharyngeal axis are mandatory; blind biopsies of normal appearing mucosa have traditionally been recommended but are only occasionally helpful in identifying the primary tumor.
- Transoral tongue base mucosectomy (i.e., lingual tonsillectomy) and at least ipsilateral palatine tonsillectomy may detect around 80% of unknown primary cases, particularly among HPV-related cases. Some centers will perform bilateral palatine tonsillectomies and may not perform lingual tonsillectomy.
- For patients with a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and without extranodal extension, consider single modality therapy with either surgery or radiation therapy.
- CT simulation with IV contrast should be performed to help guide delineation of involved lymph nodes.
- If an extended field IMRT plan is used, a thermoplastic mask immobilizing the head, neck, and shoulders is preferable to only immobilize the head and neck region.
- Treatment to the bilateral neck and areas of pharynx at risk for harboring a primary is typically recommended. Some institutions have treated to the ipsilateral neck alone; however, the neck relapse rate and distant metastasis rate appear to be higher than with comprehensive radiotherapy.
- Traditionally, the entire pharynx has been included in treatment. IMRT allows more specific targeting of the portions of the pharynx most likely to contain the original primary site and can better spare normal structures, thereby minimizing side effects.
- The extent of the pharynx to irradiate must be determined on a case-by-case basis and remains an area of active investigation. For instance, irradiating the oropharynx alone may be sufficient for an HPV+ patient, whereas an EBV+ patient especially those with Asian ethnicity may only need treatment to the nasopharynx. The pattern of lymph node spread can further help guide decisions on how much of the pharynx to treat. Some authors have advocated sparing the larynx when there are no low lymph nodes involved. When in doubt, the entire pharynx should be treated.

- For cases that have had full TORS evaluation, emerging data suggests that the pharyngeal axis may be safely spared, although this needs further prospective testing.
- Cervical (levels Ib–V) and retropharyngeal lymph nodes should be included for the node positive neck. For the contralateral neck, nodal levels II–IV and the retropharyngeal nodes should be targeted to a prophylactic dose.
- In the postoperative setting, concurrent chemotherapy should be considered when extracapsular extension is present (ECE). In the definitive setting, advanced nodal disease is a consideration for concurrent chemotherapy.
- Suggested target volumes for gross disease and high-risk regions of the pharynx are detailed in Table 10.1 (Figs. 10.1, 10.2, and 10.3).

Table 10.1 Suggested target volumes

Target volumes	Definition and description
GTV_{70}[a] (the subscript 70 denotes the radiation dose delivered)	All lymph nodes ≥1 cm in short axis, significantly FDG avid, or positive on biopsy. Contour any lymph nodes in doubt as GTV; $GTV_{70} = CTV_{70}$
PTV_{70}[a]	GTV_{70} + 3–5 mm depending on institutional accuracy of daily patient positioning
$CTV_{nasopharynx}$[b]	Extends from the base of skull superiorly to the soft palate inferiorly. Anteriorly extends from the posterior choana to the posterior pharyngeal wall. Laterally ensures adequate coverage on the fossa of Rosenmüller
$CTV_{oropharynx}$[b]	Extends superiorly from the surface of the soft palate to the floor of the vallecula inferiorly (or hyoid bone). Anteriorly, the base of tongue should be covered; however, an additional margin covering the oral tongue is not necessary. Laterally, the tonsils should be covered adequately. Posteriorly, the entire pharyngeal wall should be covered
$CTV_{larynx\&hypopharynx}$[b]	Extends superiorly from the hyoid bone to the bottom of cricoid cartilage
PTV_{mucosa}[b]	A 3–5-mm expansion on the mucosal surface CTVs depending on institutional accuracy of daily patient positioning

Note: If the patient underwent surgery, the postoperative dissected neck should be treated anywhere from 60 to 66 Gy in 2 Gy per fraction

[a] Suggested dose to gross disease is 70 Gy in 33–35 fractions

[b] Suggested dose to mucosal surfaces at risk for harboring a primary is 54–60 Gy

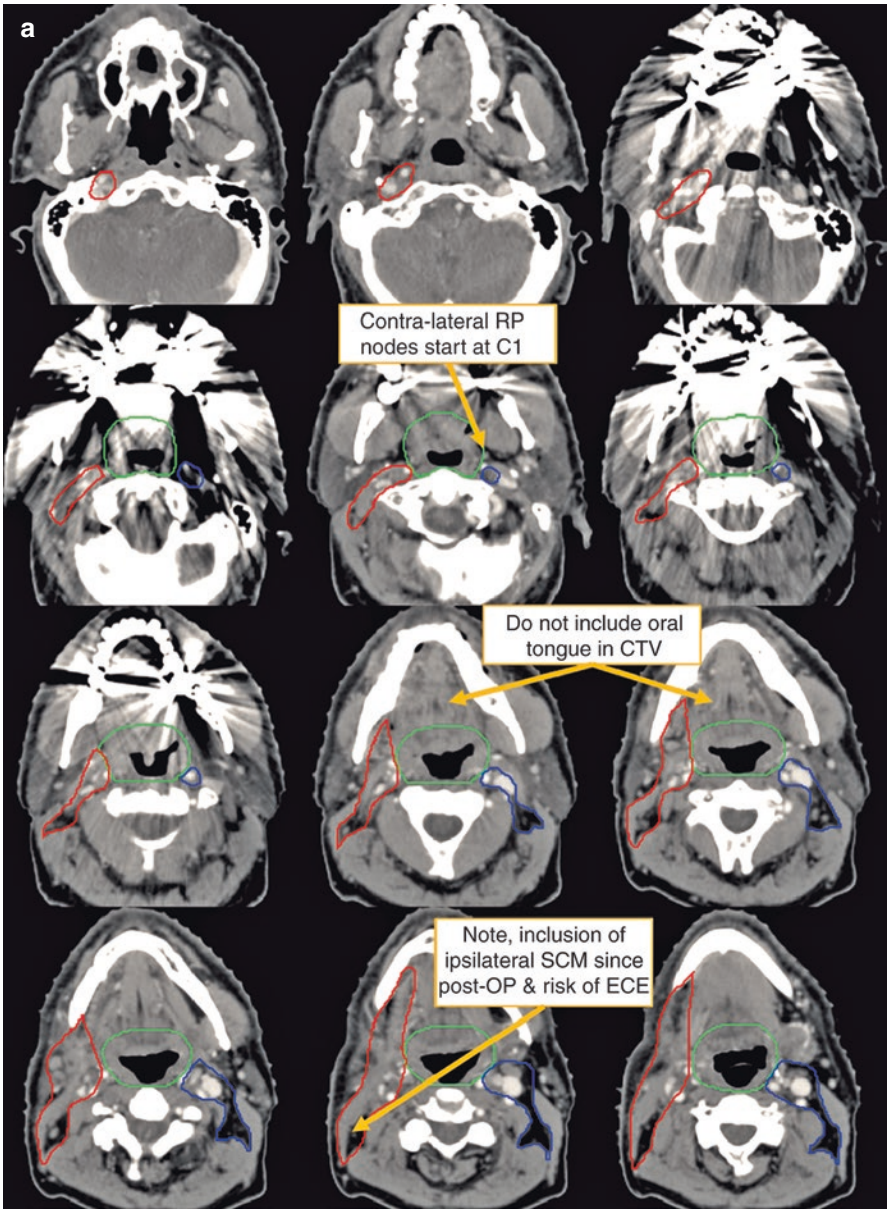

Fig. 10.1 A 62-year-old male with a TxN2a unknown primary referred for postoperative treatment. He underwent bilateral tonsillectomy and a right neck dissection which revealed a single 4.6-cm level II lymph node. Notice the difference in the target delineation in the involved neck versus the contralateral neck. The CTV_{66Gy} is in *red*, the $CTV_{54–60Gy}$ is in *green*, and the CTV_{54Gy} is in *blue*. Please note that these are representative slices and not all slices are included

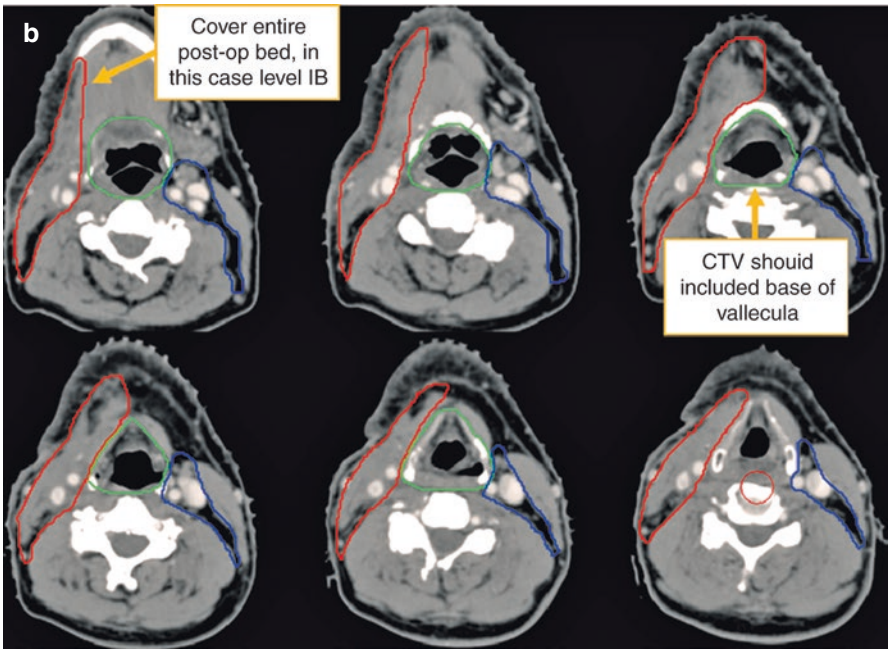

Fig. 10.1 (continued)

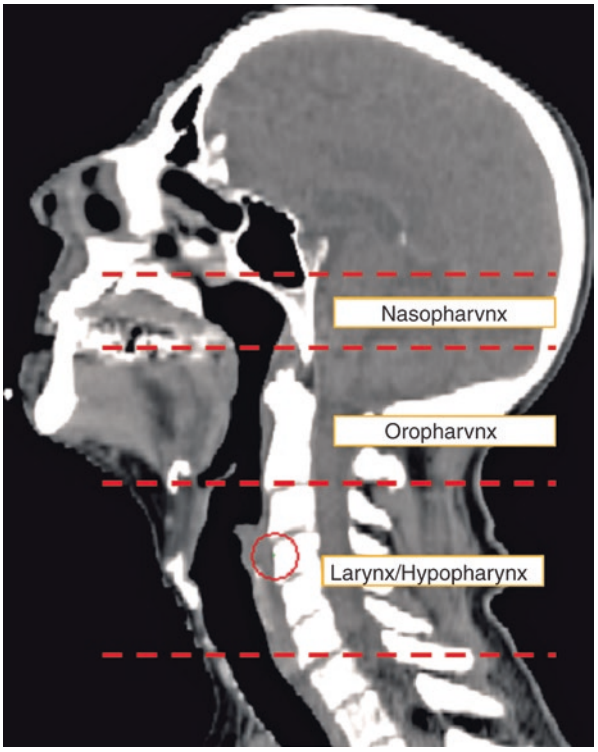

Fig. 10.2 Sagittal image at *midline* demonstrating landmarks delineating nasopharynx, oropharynx, and larynx/hypopharynx. Viewing contours on the sagittal images can ensure adequate coverage of intended target. *Red circle is radiographic iso-center*

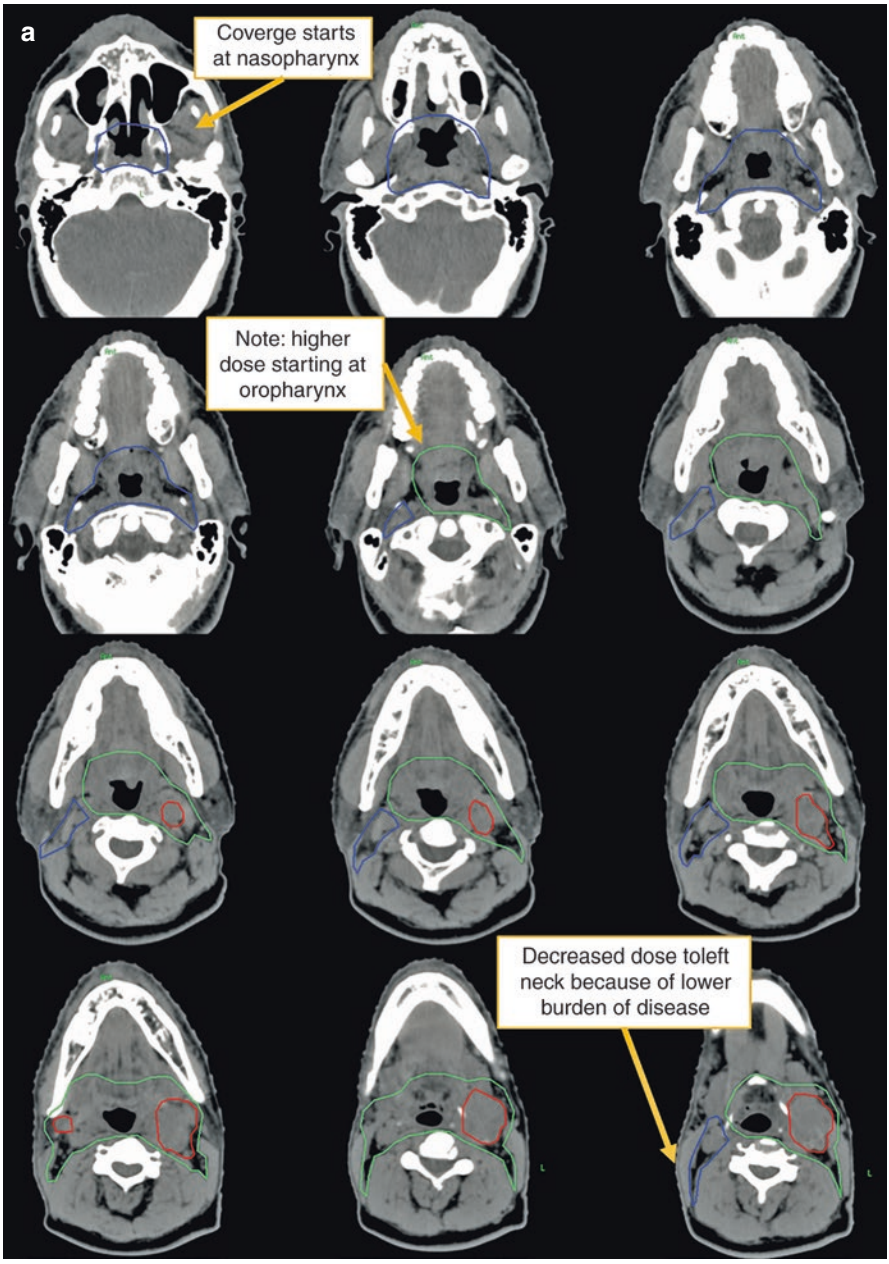

Fig. 10.3 A 50-year-old gentleman with a TxN2c squamous cell carcinoma referred for definitive treatment. An open biopsy of a left-sided lymph node demonstrated extra-nodal extension. HPV ISH and p16 testing were negative. He received definitive chemoradiotherapy. The CTV_{70Gy} is in *red*, the CTV_{60Gy} is in *green*, and the CTV_{54Gy} is in *blue*. Please note that these are representative slices and not all slices are included

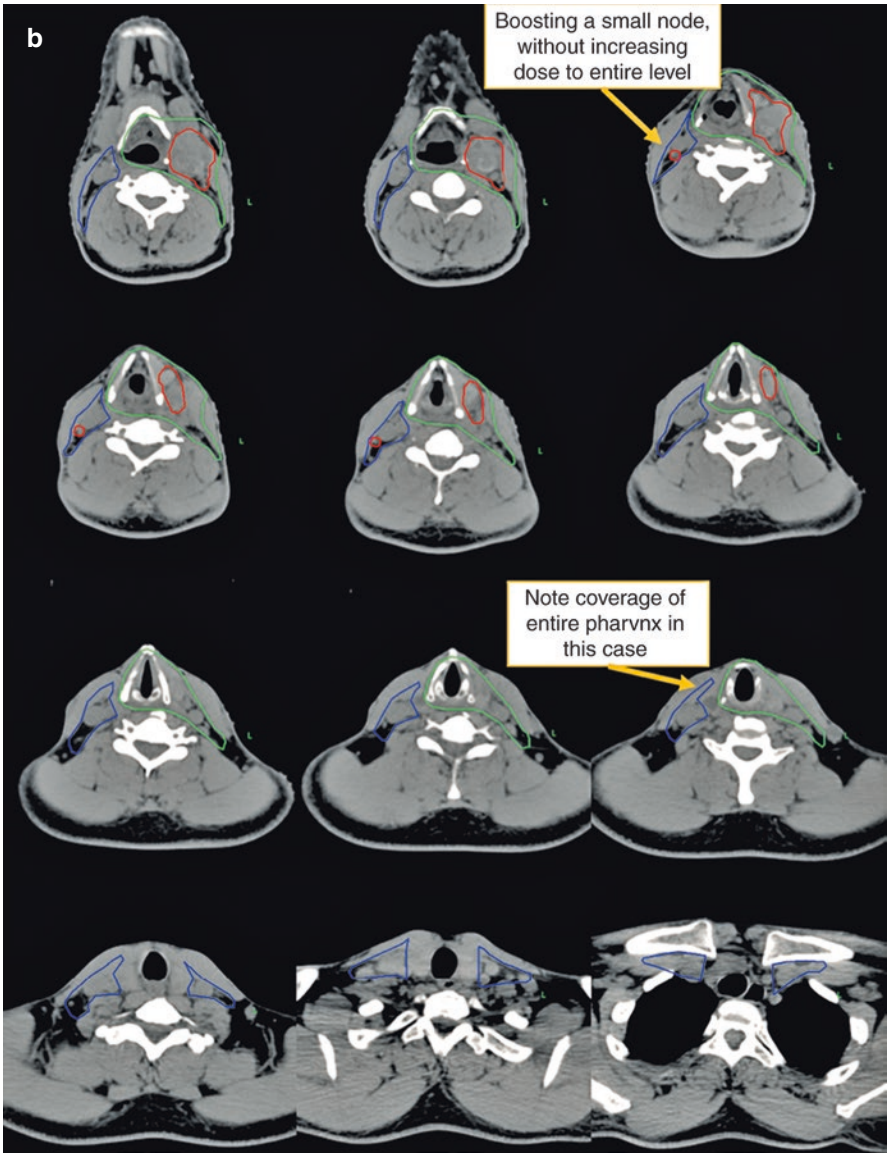

Fig. 10.3 (continued)

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Early Breast Cancer

11

Erin F. Gillespie, Brian Napolitano,
and Shannon M. MacDonald

Contents

11.1 General Principles of Planning and Target Delineation

- Three-dimensional conformal radiation therapy (3D CRT) with appropriate compensation (i.e. field-in-field technique, mixed energy beams) providing homogeneous dose to the breast tissue is the standard technique for adjuvant radiation therapy for early stage breast cancer. The highest level of evidence supports hypofractionated whole breast irradiation.
- A subsequent boost to the tumor bed (lumpectomy cavity) further reduces the risk of local recurrence, but may be omitted in low-risk patients. Boost radiation planning is most often performed using an en face electron beam, with beam energy selection based on the depth to tumor bed plus a margin, not extending beyond the anterior surface of the pectoralis muscles. For a deep tumor bed, mini-tangents can be considered.
- Accelerated partial breast irradiation (APBI), although not yet the standard of care, is an acceptable alternative for select low-risk patients with unifocal disease.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_11

Various treatment techniques can be considered including 3D CRT and intensity modulated radiation therapy (IMRT).

- In addition to thorough physical examination, adequate pre-operative imaging studies and pathological examination should be obtained for diagnosis, staging, and radiation treatment planning.
- All patients should undergo mammogram at diagnosis. Additional imaging commonly includes ultrasound. Although indications for MRI are limited for early-stage disease, images may be available in some patients. Available pre-operative imaging studies should be reviewed prior to radiation planning to ensure adequate margins for whole breast radiation as well as accurate targeting of boost radiation and/or APBI.
- Image-guided biopsy generally confirms a diagnosis of cancer. Surgery consisting of lumpectomy, or segmental excision, alone for ductal carcinoma in situ (DCIS) and lumpectomy and sentinel lymph node biopsy (SLNB) is recommended for early invasive disease. Pathology should be reviewed to ensure adequate margins (no tumor on ink for invasive and 2 mm for pure DCIS, per SSO-ASTRO Consensus Guideline 2016). It is preferred, but not required, for the surgeon to place surgical clips at the time of surgery to assist in delineation of the tumor bed and for radiographic localization prior to radiation delivery; clips can be particularly useful for APBI.
- For whole breast radiation planning, a CT with ≤3 mm slice thickness should be performed in the supine or prone position. For APBI, a CT slice thickness of 1.5–2 mm through the lumpectomy cavity may enable improved delineation of the lumpectomy cavity.
- For supine positioning, the patient should be positioned on a breast board with arms above the head. Deep inspiration breath hold (DIBH) should be considered for patients with left-sided breast cancer to reduce radiation dose to the heart.
- Patients with pendulous breasts may benefit from prone positioning to reduce separation and improve tissue homogeneity in treatment planning, which may reduce acute toxicity. Prone also reduces radiation to lung and may be used for heart-avoidance, though the heart can paradoxically move closer to the treatment field if the tumor bed abuts the chest wall. For prone positioning, patient should be placed prone on a dedicated prone breast board, and care should be taken to ensure that the patient is comfortable as this is very important to facilitate reproducibility. Patients with orthopedic injuries to the back or neck may not be ideal candidates for prone positioning.
- Organs at risk should include the heart and lungs in all cases in order to estimate dose to these critical structures. The heart should be contoured superiorly to the bifurcation of the pulmonary artery, and should include the pericardium and *epi*cardial fat (between the heart muscle and pericardium), but does not need to extend to include *peri*cardial fat outside the pericardium. While the best evidence for cardiac avoidance involves reducing the mean heart dose, data is emerging for importance of radiation dose to the left anterior descending (LAD) and left ventricle (LV) and those structures can also be contoured per published atlases by Feng et al. [1] and Duane et al. [2].
- Target volumes include the breast tissue and lumpectomy cavity for whole breast irradiation. For APBI, lumpectomy CTV and lumpectomy PTV should also be delineated.
- Suggested target volumes are described in Table 11.1 (Figs. 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, and 11.8).

Table 11.1 Suggested target volumes for 3-D treatment planning for early stage breast cancer

Target volumes	Definition and description
Breast	Clinical reference is required for breast tissue delineation. Breast tissue may be wired or borders may be placed clinically at the time of CT. Contour should include all glandular breast tissues. The cranial border should be below the head of the clavicle and at the insertion of the second rib. Caudal border is defined by the loss of breast tissue. Medial border is at the edge of the sternum and should not cross midline. Lateral border is defined by the midaxillary line but is dependent on ptosis of the breast tissue. Anterior border is the skin or a few millimeters from the surface of the skin (for dose reporting), and the posterior border is the pectoralis muscles and muscles of the chest wall. The volume should not include these muscles or the ribs. Borders may extend slightly beyond these definitions to ensure adequate margin on the lumpectomy cavity, particularly in extreme medial or lateral cases
Lumpectomy cavity	Seroma, surgical clips, and notable differences in the glandular breast tissue should be included. Comparison to the contralateral breast may be useful, particularly when fluid and/or surgical clips are not present. All imaging studies should be reviewed prior to planning to assist in delineating this volume. This volume should not extend outside of the breast tissue
Lumpectomy CTV[a]	Lumpectomy cavity with a 1.0–1.5-cm expansion. This volume should not extend outside of the body or into the pectoralis muscles and/or muscles of the chest wall
Lumpectomy PTV[a]	Lumpectomy CTV with a margin based on setup uncertainty and predicted patient motion (generally 0.5–1.0 cm). This volume may extend outside of the patient surface and into the pectoralis muscles and/or muscles of the chest wall. Adjustments to this volume may be necessary for dose-reporting purposes

[a] For APBI only; for whole breast irradiation, the lumpectomy cavity alone is the target for boost

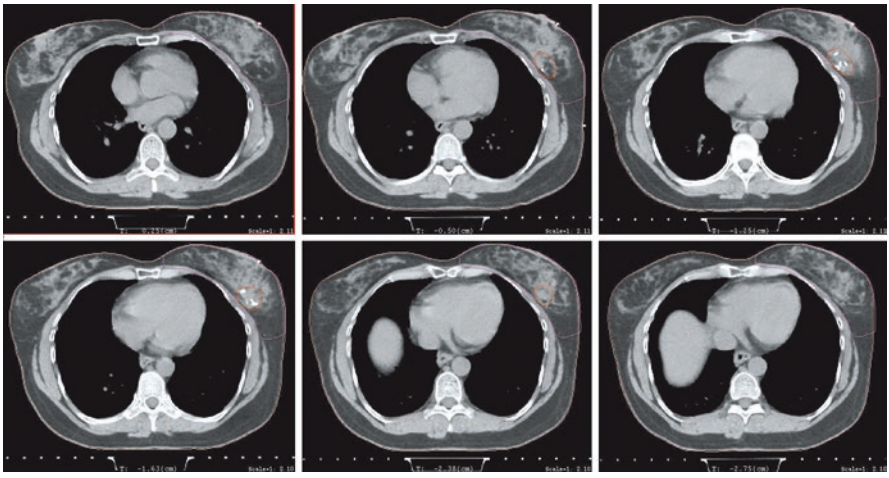

Fig. 11.1 Axial images in the supine position for a woman with left-sided stage I breast cancer

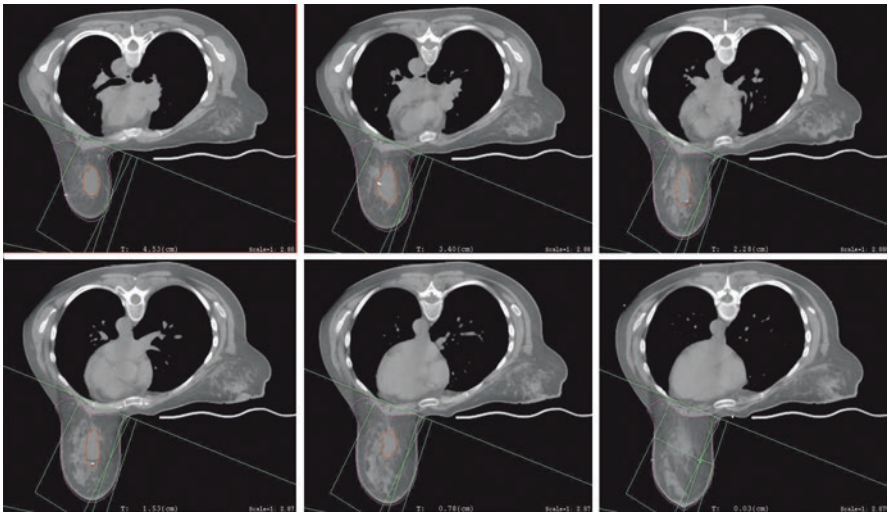

Fig. 11.2 Axial images in the prone position for a woman with left-sided DCIS

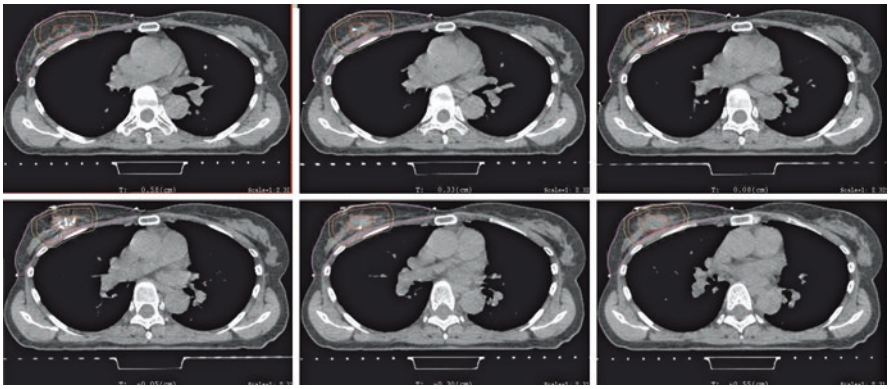

Fig. 11.3 Axial images for APBI. Lumpectomy cavity is based on seroma, clips placed by surgeon, and information from review of mammogram, US, and MRI, when available. CTV is typically a 1.5-cm expansion around the lumpectomy cavity that excludes pectoralis muscle, rib, and chest wall and does not extend outside of the contoured breast tissue. Typically, the CTV does not extend to the skin (restricted to 5 mm from patient surface). PTV is formed by an expansion of approximately 5 mm (depending on institutional setup uncertainty) around the CTV

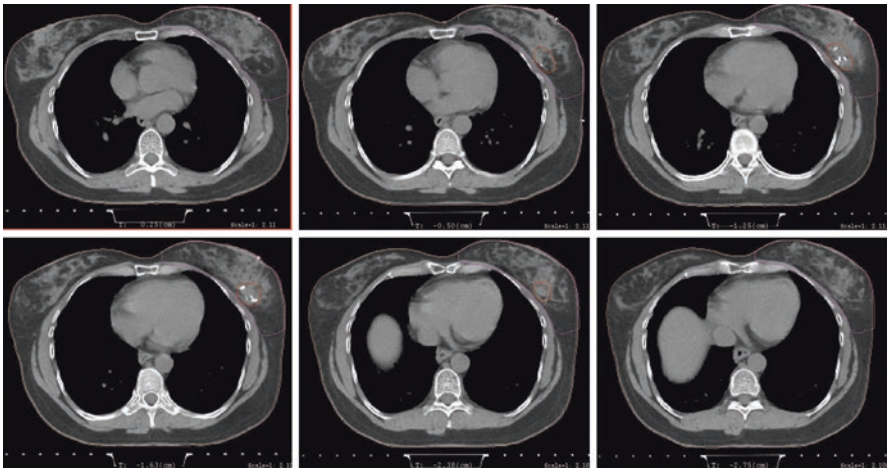

Fig. 11.4 Supine breast plan using tangent fields with a field-in-field technique for homogeneity and a small MLC block for cardiac shielding. Prescribed dose is 42.4 Gy at 2.65 Gy per fraction followed by an electron boost to the lumpectomy cavity to 10 Gy at 2.5 Gy per fraction

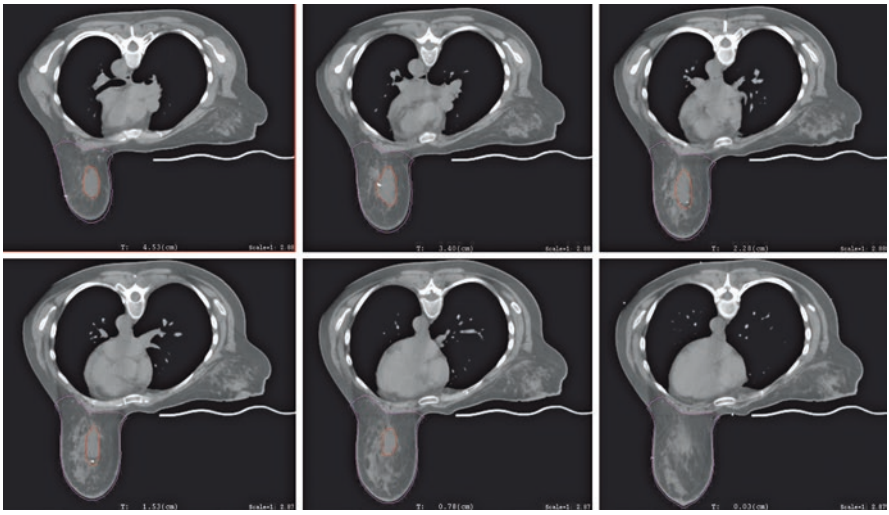

Fig. 11.5 Prone breast plan using tangent fields with a field-in-field technique. Prescribed dose is 42.4 Gy at 2.65 Gy per fraction followed by a mini-tangent photon boost to the lumpectomy cavity to 10 Gy at 2.5 Gy per fraction. The posterior edge of the field should include part of the pectoralis muscle

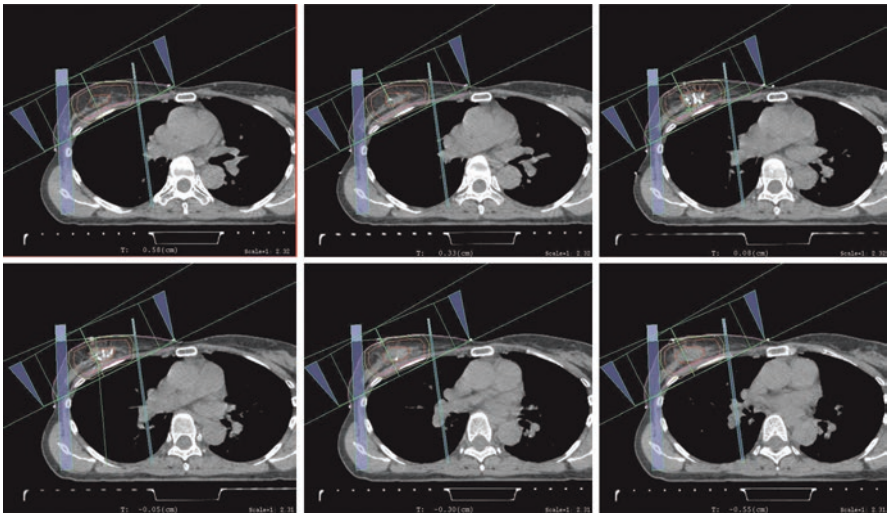

Fig. 11.6 APBI plan using a mini-tangent photon fields in combination with an en face electron field

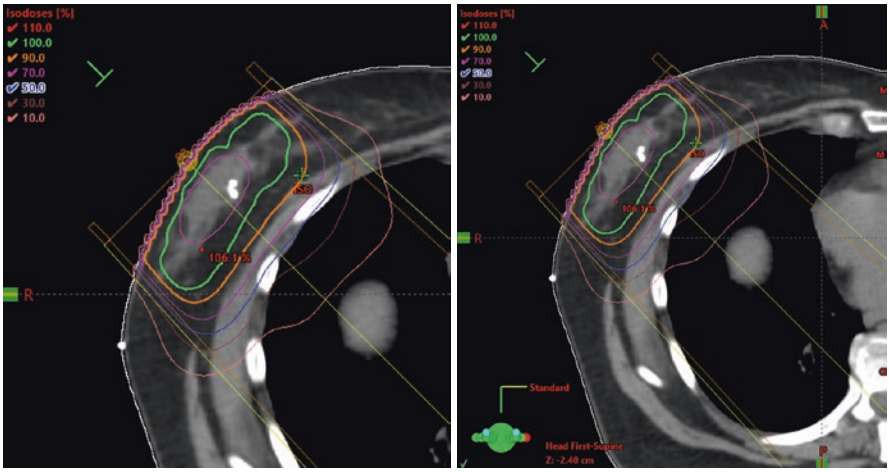

Fig. 11.7 The tumor bed boost in the supine position. Electron energy (12 MEV) is selected to ensure coverage of the 90% isodose line to the anterior surface of the pectoralis muscle

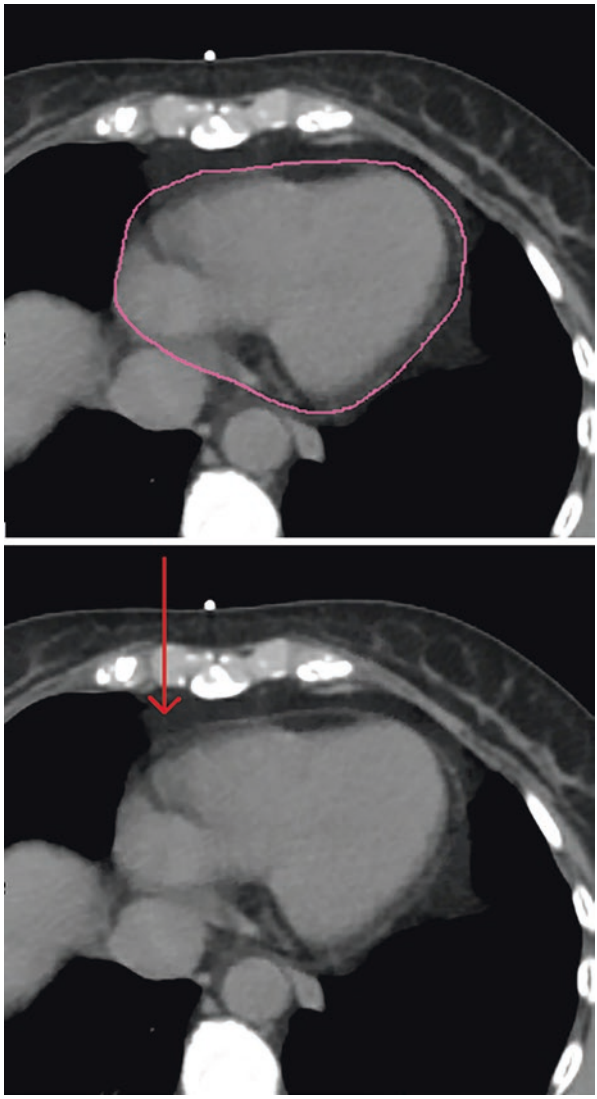

Fig. 11.8 The heart is contoured to include the pericardium but not the pericardial fat (red arrow) that extends outside the pericardium

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Regional Lymph Node Irradiation for Breast Cancer

12

Alice Y. Ho, Samantha A. Dunn, and Simon Powell

Contents

12.1 General Principles of Target Delineation for Regional Nodal Irradiation in Breast Cancer

- Patients undergo CT simulation in the treatment position with both arms extended above their head using breast board immobilization; IV contrast is optional.
- In cases where the patient has an in-tact breast, the borders of the breast and the lumpectomy scar may be wired on the patient's skin prior to scanning.
- Patients are scanned from the cricoid through 5 cm below the clinically marked inferior port edge. The entirety of both lungs must be included.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_12

- The planning target volume (PTV) is defined as any breast tissue or chest wall, ipsilateral level I–III axillary lymph nodes, ipsilateral supraclavicular lymph nodes, ipsilateral interpectoral lymph nodes, and ipsilateral internal mammary lymph nodes (Figs. 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8 and Tables 12.1, 12.2, 12.3).
- Bolus of 3 mm is used daily over the chest wall for all VMAT/IMRT plans. A thicker bolus (1 cm) may be applied in cases of inflammatory breast cancer in which the skin GTV dose is ≥100% of the prescription dose.

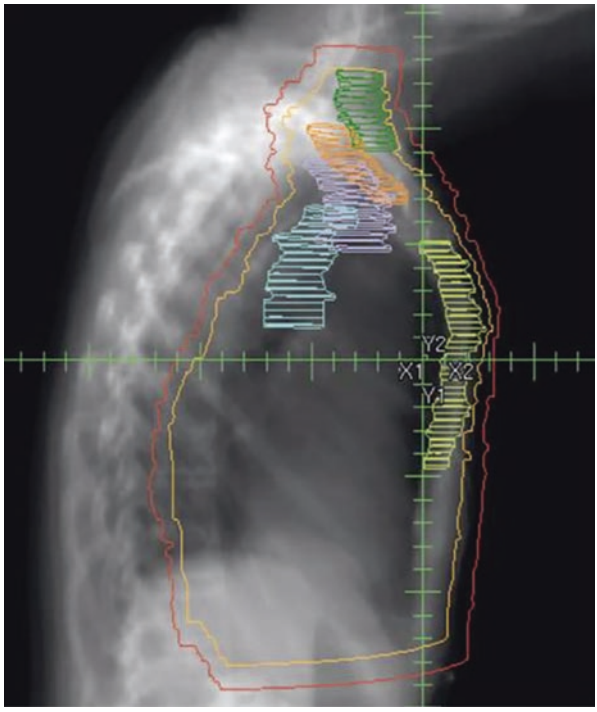

Fig. 12.1 Coronal view. *Red* PTV, *light orange* CTV, *blue* level I lymph nodes, *light purple* level II lymph nodes, *dark orange* level III lymph nodes, *green* supraclavicular lymph nodes, *yellow green* internal mammary nodes (IMN)

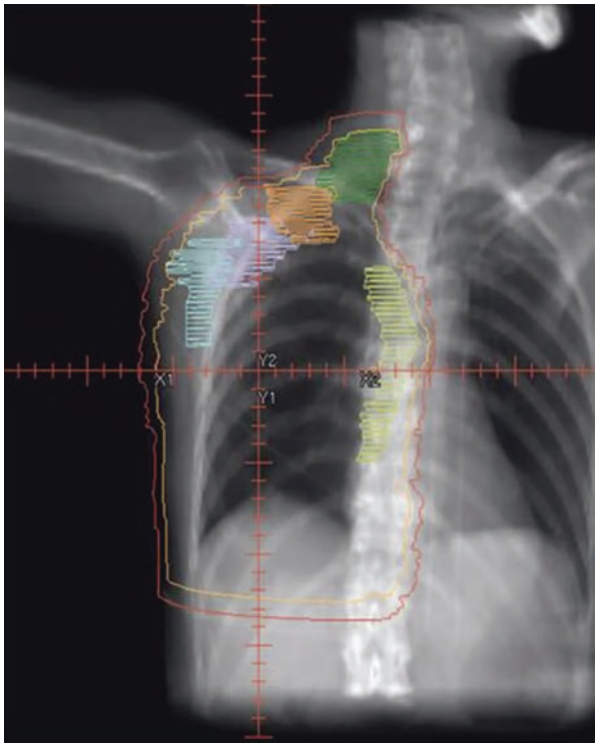

Fig. 12.2 Sagittal view. *Red* PTV, *light orange* CTV, *blue* level I lymph nodes, *light purple* level II lymph nodes, *dark orange* level III lymph nodes, *green* supraclavicular lymph nodes, *yellow green* internal mammary nodes (IMN)

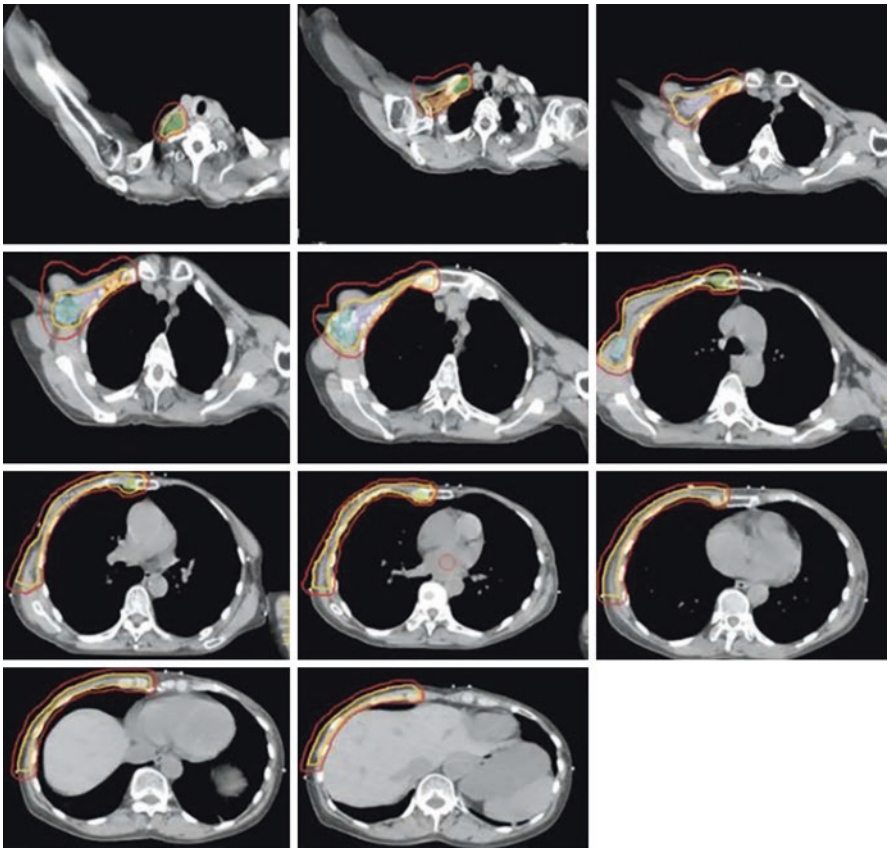

Fig. 12.3 Axial slices in the cranial to caudal direction

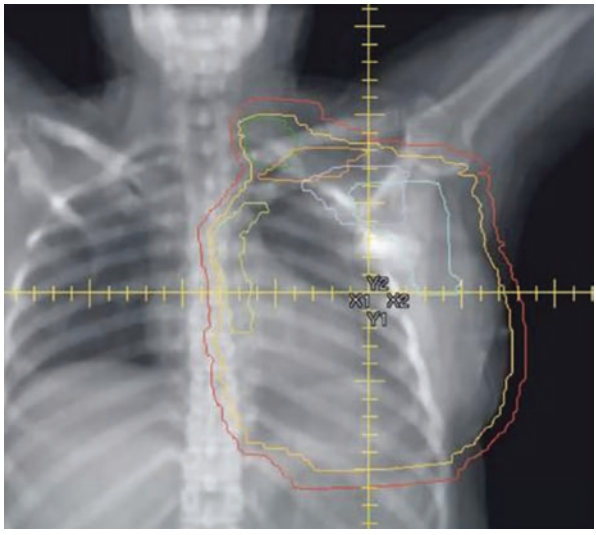

Fig. 12.4 Sagittal view. *Red* PTV, *light orange* CTV, *blue* level I lymph nodes, *light purple* level II lymph nodes, *dark orange* level III lymph nodes, *green* supraclavicular lymph nodes, *yellow green* internal mammary nodes (IMN), *yellow* heart, *dark purple* contralateral breast

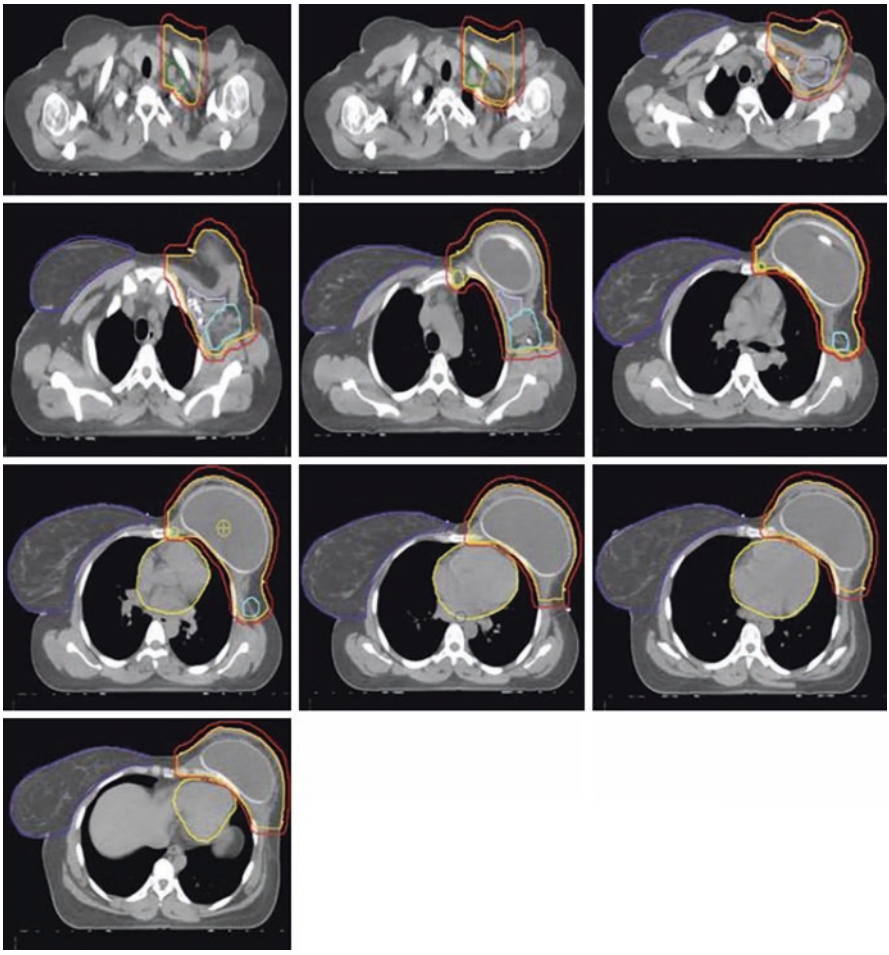

Fig. 12.5 Axial slices in the cranial to caudal direction

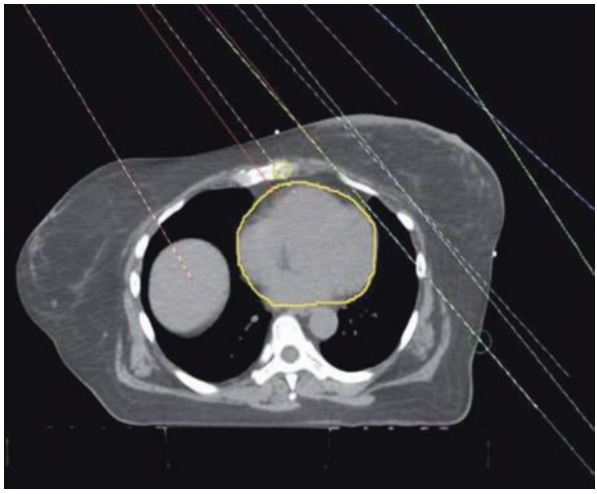

Fig. 12.6 Axial view of three beams: a medial en face electron beam (*red*) matched to two lateral opposing tangent fields (*blue* and *green*)

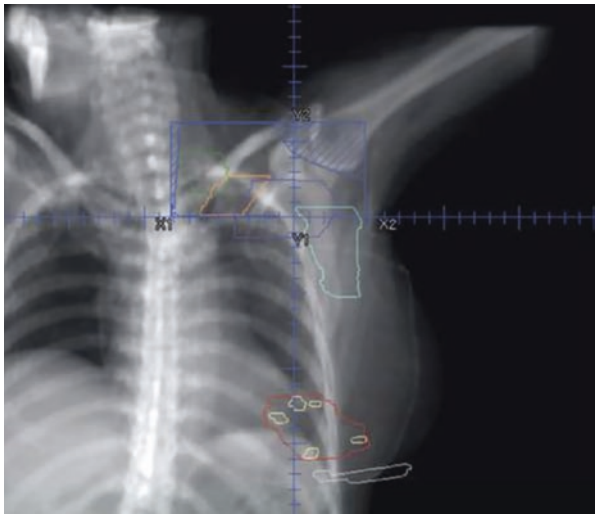

Fig. 12.7 Coronal view of supraclavicular field and lymph node targets

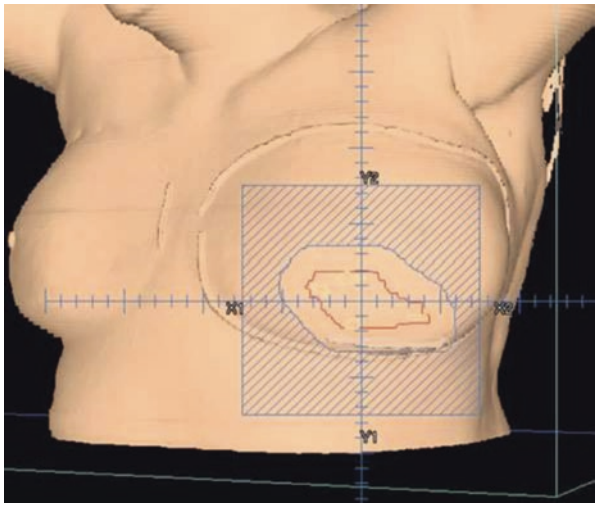

Fig. 12.8 3D view of a boost to the tumor bed: An en face electron field with a custom cutout (*blue*) encompasses the tumor bed (*maroon*), clips (*light green*) and lumpectomy scar (*gray*)

Table 12.1 Suggested target volumes at the gross disease region

Target volumes	Definition and description
Clinical target volume (CTV)	Breast tissue or chest wall as defined by RADCOMP Breast Atlas [1], ipsilateral regional lymph nodes [2], interconnecting lymphatic drainage routes, breast prosthesis (if present) and chest wall musculature/skin to be determined at risk for microscopic disease
Planning target volume (PTV)	A margin of 3–5 mm medially, 5–10 mm laterally, and 3–5 mm posteriorly with the exception of the internal mammary nodes (which should be 0 mm margin posteriorly), and 5–10 mm superiorly, inferiorly, and anteriorly (to include the skin surface) will be added to the CTV. The amount of lung can be trimmed per physician discretion

Table 12.2 Breast VMAT dosimetric planning guidelines

Structure	Parameter	Objective
Target criteria—50 Gy in 25 fractions		
PTV	$D_{95\%}$	≥95%
	$V_{95\%}$	≥95%
	$D_{05\%}$	≤110%
Internal mammary node (IMN)	$D_{95\%}$	≥100%
Normal tissue criteria		
Ipsilateral lung	V_{20Gy}	≤33%
	V_{10Gy}	≤68%
	Mean Gy	≤20 Gy
Contralateral lung	V_{20Gy}	≤25%
Heart	V_{25Gy}	≤25%
	Mean Gy	≤9 Gy[a]; ≤8 Gy[b]
	Dmax	≤50 Gy
Left anterior descending artery (LAD)	Dmax	≤50 Gy
Contralateral intact breast	Mean Gy	≤5 Gy
Contralateral implant	Mean Gy	≤8 Gy
Esophagus	Dmax	≤50 Gy
Thyroid	Mean Gy	≤20 Gy
Brachial plexus	Dmax	≤55 Gy

Table 12.3 Breast IMRT/VMAT dosimetric planning guidelines

Structure	Parameter	Objective
Target criteria—50 Gy in 25 fractions		
PTV	$D_{95\%}$	≥95%
	$V_{95\%}$	≥95%
	$D_{05\%}$	≤110%
Inside implant PVT	$D_{95\%}$	≤120%
Internal mammary node (IMN)	$D_{95\%}$	≥90%

Normal tissue criteria		Non-DIBH	DIBH
Ipsilateral lung	V_{20Gy}	30% (33%)	27% (30%)
	V_{10Gy}	65% (68%)	60% (63%)
	Mean Gy	18 Gy	18 Gy
Contralateral lung	V_{20Gy}	5%	
Heart	V_{25Gy}—left breast	3%	
	Right breast	0.5%	
	Dmax	50 Gy	
	Mean Gy—left breast and IMN $D_{95\%} \geq 90\%$	7 Gy (8 Gy)	6 Gy (7 Gy)
	Right breast and IMN $D_{95\%} \geq 90\%$	4 Gy	
	Left breast and IMN $D_{95\%} \geq 100\%$	8 Gy (9 Gy)	7 Gy (8 Gy)
	Right breast and IMN $D_{95\%} \geq 100\%$	5 Gy	
	If any of the constraints above cannot be achieved	10 Gy (12 Gy)	9 Gy (10 Gy)
Left anterior descending artery (LAD)	Dmax	25 Gy (35 Gy)	
Contralateral intact breast	Mean Gy	6 Gy	
Contralateral implant	Mean Gy	8 Gy	
Esophagus	Dmax	35 Gy (40 Gy)	
Thyroid	Mean Gy	20 Gy	
Brachial plexus	Dmax	55 Gy	
Liver (for right side)	Mean Gy	8 Gy (10 Gy)	
Stomach	Mean Gy	5 Gy	3 Gy
Cord	Dmax	20 Gy	

DIBH deep inspiratory breath hold

12.2 Target and Nodal Volumes for Unreconstructed Right Chest Wall

See Figs. 12.1, 12.2, and 12.3.

12.3 Target and Nodal Volumes for Reconstructed (Tissue Expander) Left Chest Wall

See Figs. 12.4 and 12.5.

12.4 Conventional 3D Conformal Planning

See Figs. 12.6, 12.7, and 12.8.

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Lung Cancer

13

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Contents

13.1 General Principles of Planning and Target Delineation

- Computed tomography (CT)-based planning utilizing conformal techniques and respiratory motion management are the standard of care in the treatment of both NSCLC and SCLC. Three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body radiotherapy (SBRT) each use multiple beam angles and can vary in dose conformality. Thus, each approach requires accurate delineation of target volumes, normal structures, and organs-at-risk (OARs) and evaluation of dose volume histograms during planning. In addition, it is necessary to understand the at-risk nodal levels of the mediastinum, as have been previously published in consensus atlases such as that developed at the University of Michigan [1].

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_13

- *Simulation.* Assessment of respiratory motion, correct patient positioning, and appropriate immobilization during radiation simulation are vital to radiation planning. Patients should ideally be simulated with their arms above their head to maximize the number of beam arrangements that can be utilized. A four-dimensional (4D) simulation should be performed to assess for internal motion.
- In addition to the target volume, the following normal structures should be contoured when in proximity to the treatment field: heart, lungs, spinal cord, esophagus, chest wall, great vessels, proximal bronchial tree (PBT), and the brachial plexus for superiorly located tumors or high paratracheal/supraclavicular lymph node involvement using available atlases [2]. The liver should be contoured for right lower lobe tumor located close to diaphragm. For low lying left lower lung tumors or left pleural tumor, the spleen may receive significant radiation. Consensus guidelines for contouring the brachial plexus are available [3] and should be referenced for accurate contouring.
- For both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) in the setting of gross disease, an involved field approach is widely accepted based on prior publications demonstrating a low rate of failure in elective nodal regions [4, 5] and a randomized trial showing improved outcomes with an involved field vs. elective nodal approach [6]. Therefore, elective nodal regions should not routinely be covered if the treating physician is confident in the understanding of the sites of active disease.
- Physicians should delineate targets utilizing a combination of the physical examination, a CT scan with contrast, a positron emission tomography, and evaluation of the mediastinum with either a mediastinoscopy or endobronchial ultrasound (EBUS).
- The gross target volume is defined as macroscopic disease. There are two potential approaches for expanding the GTV to subsequent target volumes. The first technique is performed by delineating the GTV and then assessing for internal motion, a structure called the iGTV. The iGTV is then expanded to create the iCTV and further expanded to yield the PTV. The second technique involves an expansion of the GTV to the CTV, followed by a further expansion to the ITV to account for internal motion, followed by a PTV expansion for daily variations in patient position and movement. This approach is also used in the post-operative setting, where there is no GTV or iGTV.
- For early stage NSCLC, standard treatment margins from the iGTV to iCTV are 0–0.2 cm. The PBT should be consistently contoured. This structure includes the distal 2 cm of the trachea, the carina, the right and left mainstem bronchi, and the lobar bronchi. We define an area 2 cm beyond the PBT radially as the no-fly zone (NFZ). Doses for SBRT are variable depending on the location and extent of the lesion, with the primary criteria being achievement of a biologically equivalent dose (BED) of >100 Gy.
- For locally advanced NSCLC (stage II–III), a margin from the iGTV to the iCTV of 0.5–0.8 cm is typically used, based on prior histologic analyses [7]. PTV margins are dependent on estimation of setup error, often 1.0–1.5 cm if no assessment of management for internal motion or daily image-guided radiation therapy (IGRT), such as kV imaging or cone-beam CT scan; 0.5–1.0 cm if either 4D CT

planning or CBCT, but not both; 0.3–0.5 cm from CTV (or iGTV) to PTV for 4D CT planning and with kV/CBCT guidance, which is preferred. The standard dose in the chemoradiation setting is 60 Gy in 30 fractions.

- In the postoperative scenario for NSCLC, there is no clear consensus as to target delineation. Historically, large fields were used including the tumor bed, involved lymph node levels, the bilateral mediastinum, ipsilateral bronchial stump, and supraclavicular lymph nodes for superiorly located tumors. This approach is now rarely used since the adoption of CT planning and comprehensive mediastinal lymph node dissection. Many institutions, including our own, now use a limited approach to treating the mediastinum, encompassing the involved lymph node regions and the ipsilateral bronchial stump, with consideration of inclusion of one lymph node level above and one level below the involved region. This approach is similar to that used in the Lung ART trial [8]. Generally, a CTV (no GTV present), ITV, and a PTV with an ITV to PTV expansion of approximately 0.5 cm are defined, contingent on available IGRT techniques.
- For SCLC, a "standard" GTV to CTV margin has not been well defined. Margins of 0.5–1.0 cm are acceptable, often to include the ipsilateral hilum. We recommend that the CTV to PTV margin follows similar guidelines as that for NSCLC as noted above. Standard doses for limited stage SCLC are 45 Gy in 1.5 Gy fractions or 66–70 Gy in 2.0 Gy fractions.
- Recommended target delineation does not differ significantly between limited and extensive stage SCLC, the latter being in the context of consolidative or palliative treatment. An involved field technique is utilized in both scenarios, with standard doses as depicted in Table 13.1. Standard doses for consolidation thoracic radiation typically range from 30 to 45 Gy in ten fractions.
- Standard treatment doses for NSCLC and SCLC are depicted in Table 13.1. Dose constraints are dependent on the total dose and the number of fractions delivered and guidance is provided in the *Quantitative Analyses of Normal Tissue Effects*

Table 13.1 Appropriate radiation treatment regimens for lung cancer

Lung malignancy scenario	Accepted treatment doses
NSCLC, stage I stereotactic body radiation therapy (SBRT)—peripheral	Variable—include 54 Gy in 18 Gy fractions, 48 Gy in 12 Gy fractions, 50 Gy in four fractions, and 50 Gy in five fractions
NSCLC, stage I SBRT—central	Variable—include 50 Gy in five fractions, 70 Gy in ten fractions, 60 Gy in eight fractions
NSCLC, stage II–III standard fractionation	60 Gy in 2 Gy fractions daily
Postoperative	50–54 Gy in 1.8–2.0 Gy fractions—R0 resection 54–60 Gy in 1.8–2.0 Gy fractions—R1 resection 60 Gy in 2.0 Gy fractions (consider concurrent chemotherapy)—R2 resection
SCLC, limited stage	45 Gy in 1.5-Gy fractions BID with chemotherapy OR 66–70 Gy in 2.0-Gy fractions daily
SCLC, extensive stage	30–45 Gy in 3.0 Gy fractions for consolidative chest radiation

in the Clinic publication [9]. The stages cited in are as per the eighth Edition Staging by the American Joint Committee on Cancer [10] (Table 13.1 and Figs. 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7).

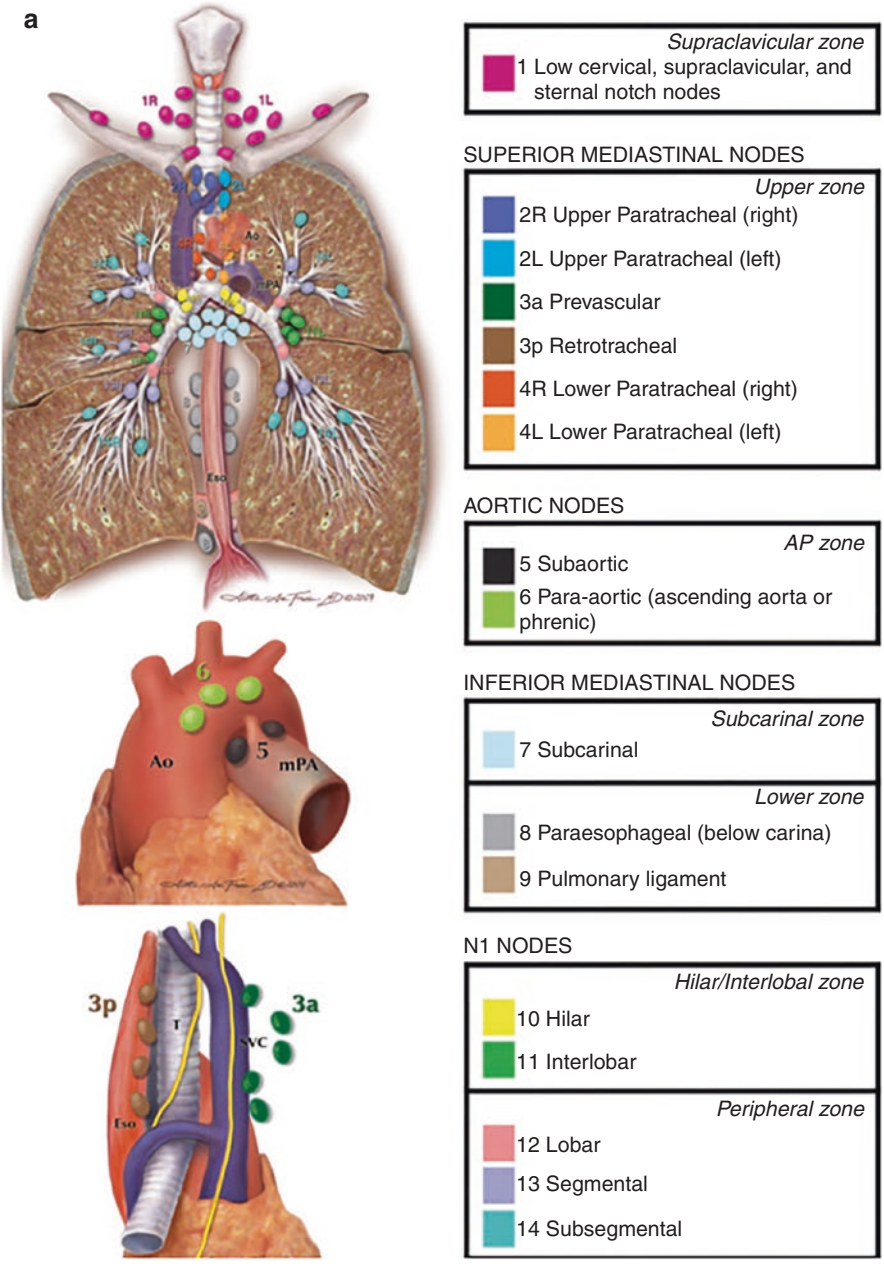


Fig. 13.1 (**a**) Lymph node stations. (Reproduced with permission from [11].) (**b**) Risk of lymph node involvement by tumor location. (Adapted from [12])

b

Involved Node Station	Lobe Involved by Primary Tumor			
	Right Upper (n=45)	Right Middle/ Lower (n=36)	Left Upper (n=35)	Left Lower (n=8)
Upper Mediastinum (1)	9%	3%	0%	0%
Paratracheal (2)	40%	31%	3%	0%
Prevascular, retrotracheal, pretracheal (3)	73%	47%	29%	0%
Lower paratracheal (4)	36%	28%	17%	13%
Subaortic (5)	–	–	71%	13%
Para-aortic (6)	–	–	43%	25%
Subcarinal (7)	36%	69%	20%	38%
Paraesophageal (8)	9%	11%	3%	50%
Pulmonary ligament (9)	2%	6%	6%	13%

Fig. 13.1 (continued)

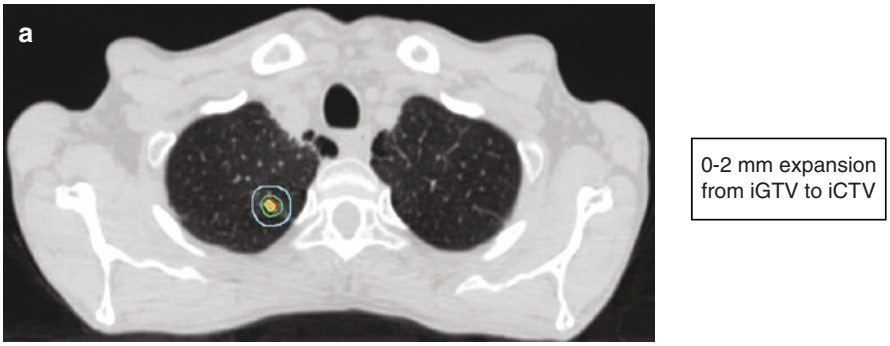
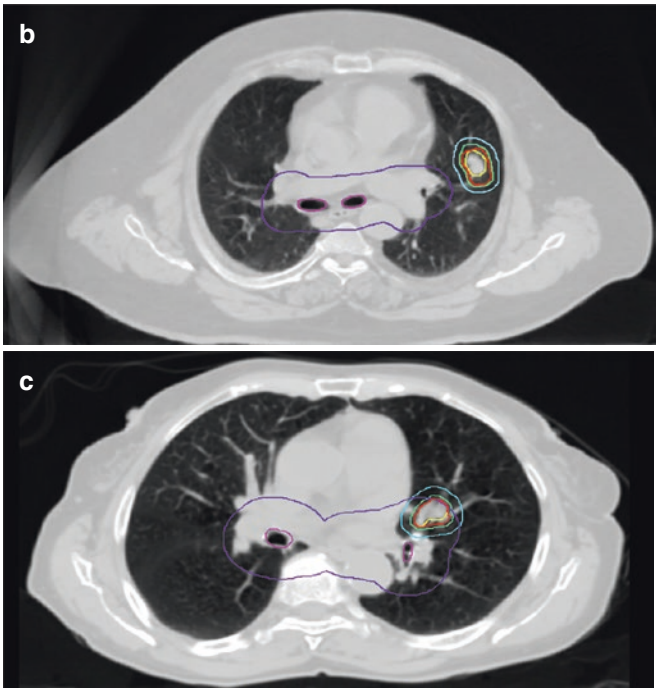


Fig. 13.2 Early stage NSCLC [cT1N0] treated with SBRT. (**a**) A peripheral tumor treated with 54 Gy in three fractions. (**b**) A lesion in a medically inoperable patient approaching the pulmonary tree, receiving 48 Gy in four fractions. (**c**) A central lesion encroaching on the bronchi receiving 50 Gy in five fractions. Generally, we constrain the maximum point dose to the PBT at 55 Gy. GTV (*yellow*); iGTV (*red*); iCTV (*green*); PTV (*sky blue*); proximal bronchial tree, PBT (*pink*); no fly zone, NFZ (*purple*)



0.5 cm expansion from iCTV to PTV

2.0 cm expansion from PBT to NFZ

Fig. 13.2 (continued)

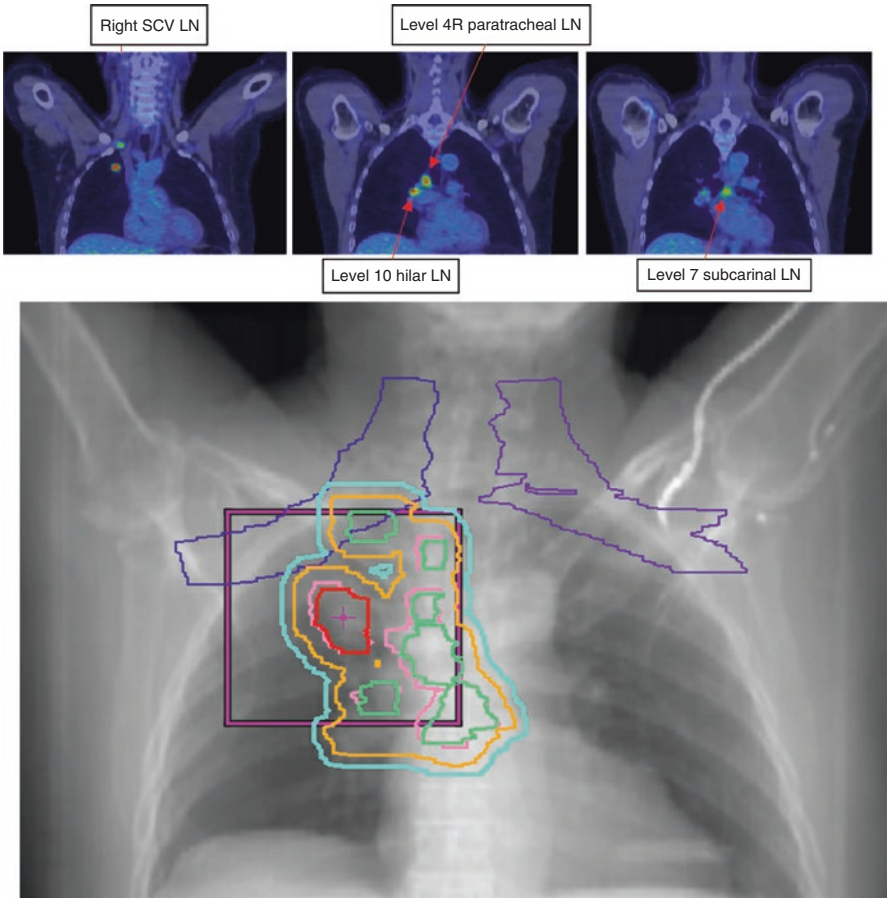
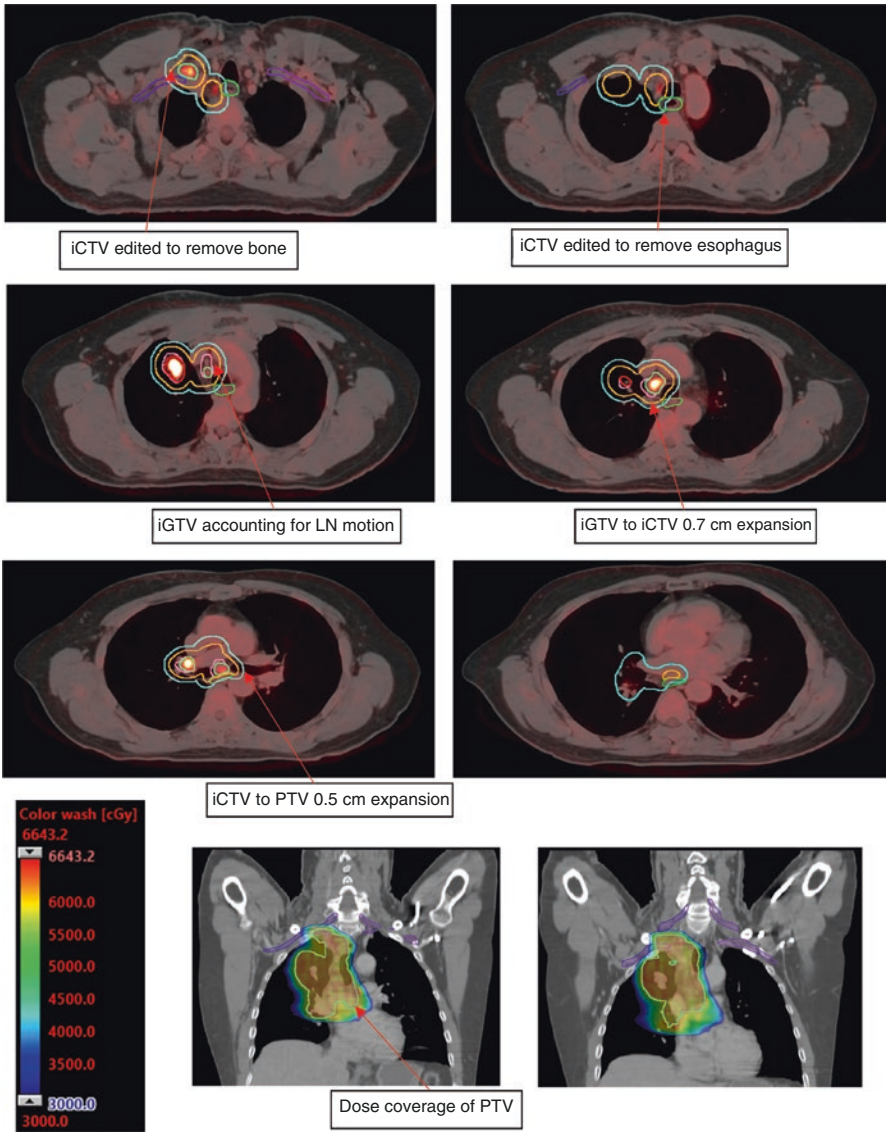


Fig. 13.3 Locally advanced NSCLC [cT1cN3M0] (IIIB). The patient had a 2.3-cm right upper lobe tumor with right hilar, subcarinal, precarinal, paratracheal and right supraclavicular lymphadenopathy. Lung windows on CT scan are utilized to delineate the primary tumor and hilar region. Nodal stations delineated through assessment of PET/CT scan, CT scan with contrast, and endobronchial ultrasound. The patient received 60 Gy in 30 fractions. GTV primary tumor (*red*); GTV lymph nodes (*light green*); iGTV primary and lymph nodes (*pink*); iCTV (*orange*); PTV (*aqua*); brachial plexus (*purple*). Locally advanced NSCLC [cT1cN3M0] (IIIB). GTV tumor (*red*); GTV nodes (*light green*); iGTV (*pink*); iCTV (*orange*); PTV (*aqua*); brachial plexus (*purple*); esophagus (*dark green*)



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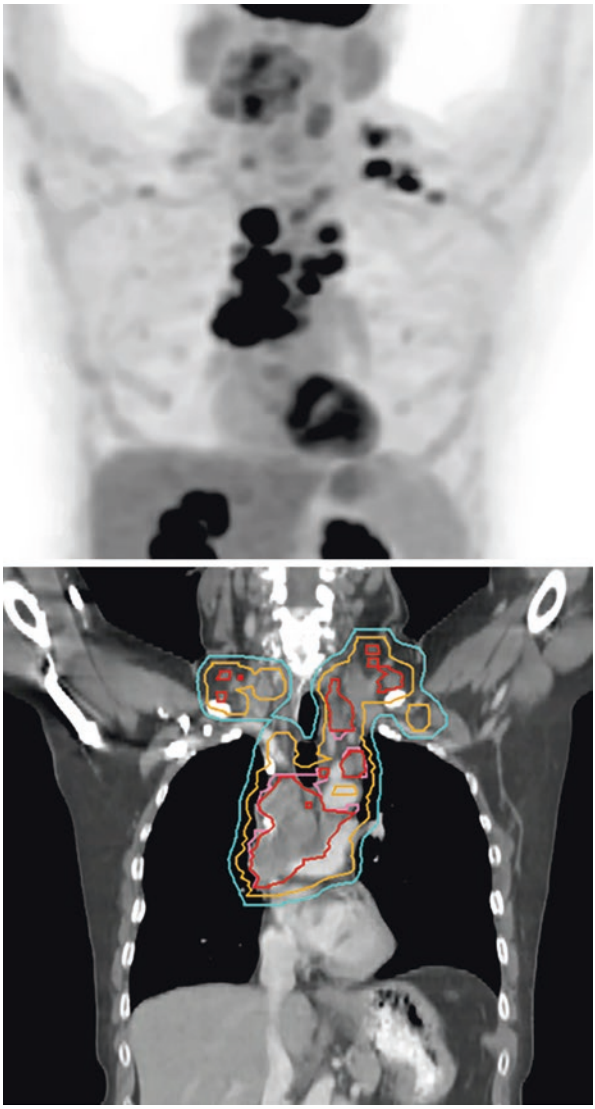
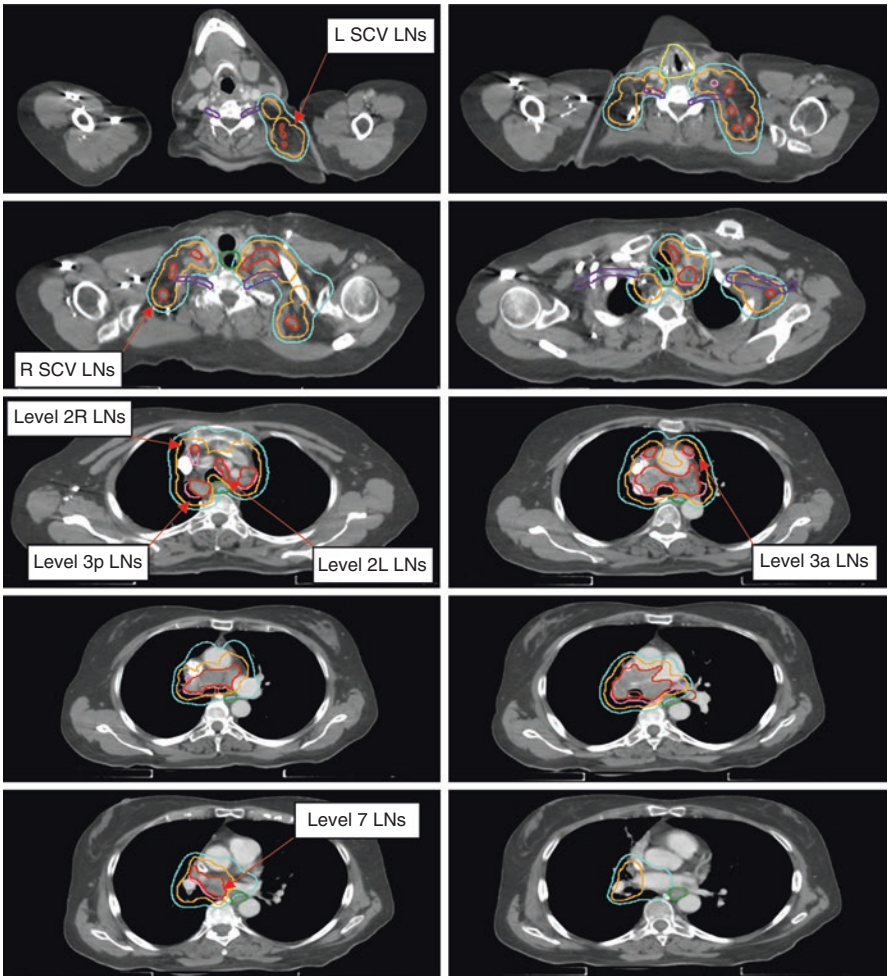


Fig. 13.4 Locally advanced lung adenocarcinoma [cT4N3M0] (IIIC). The patient presented with SVC syndrome and was found to have a large right hilar/suprahilar mass compatible with a primary lung tumor vs. adenopathy and extensive mediastinal adenopathy including bilateral supraclavicular metastasis. The patient was treated to 60 Gy in 30 fractions. GTV (*red*); iGTV (*pink*); iCTV (*orange*); PTV (*aqua*). Locally advanced lung adenocarcinoma [cT4N3M0] (IIIC). GTV (*red*); iGTV (*pink*); iCTV (*orange*); PTV (*aqua*); brachial plexus (*purple*); esophagus (*dark green*); larynx (*yellow*)



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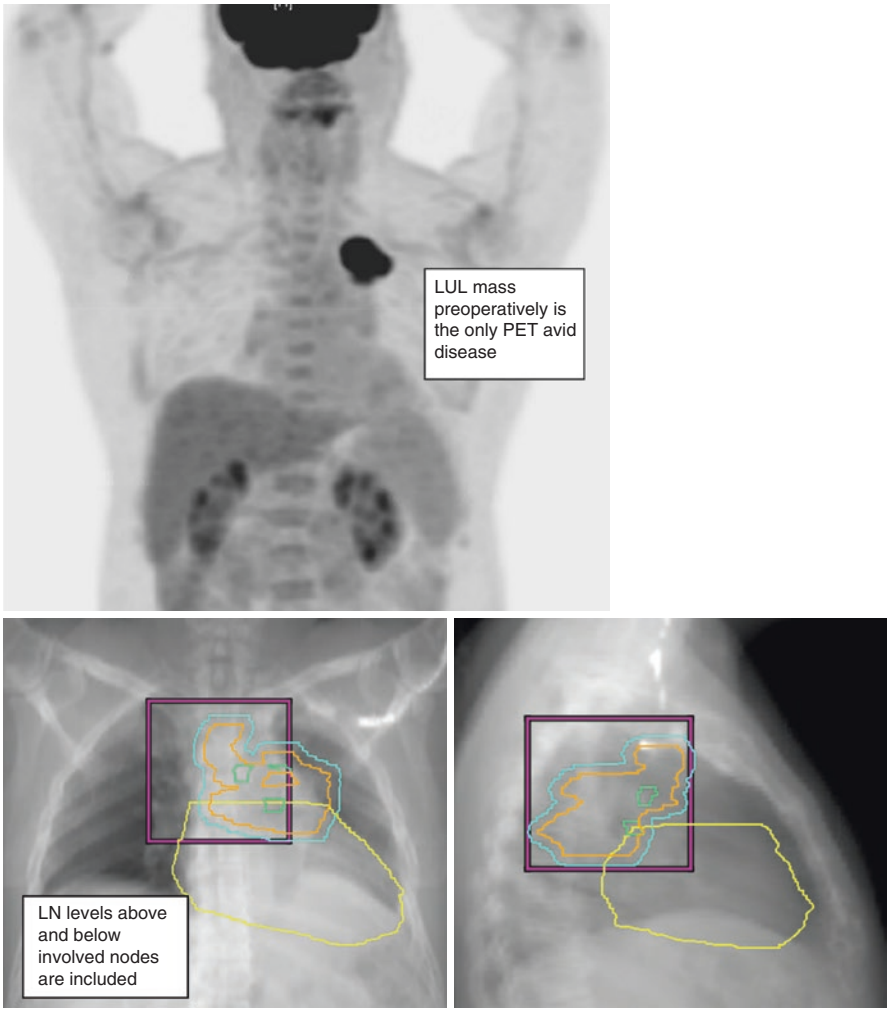
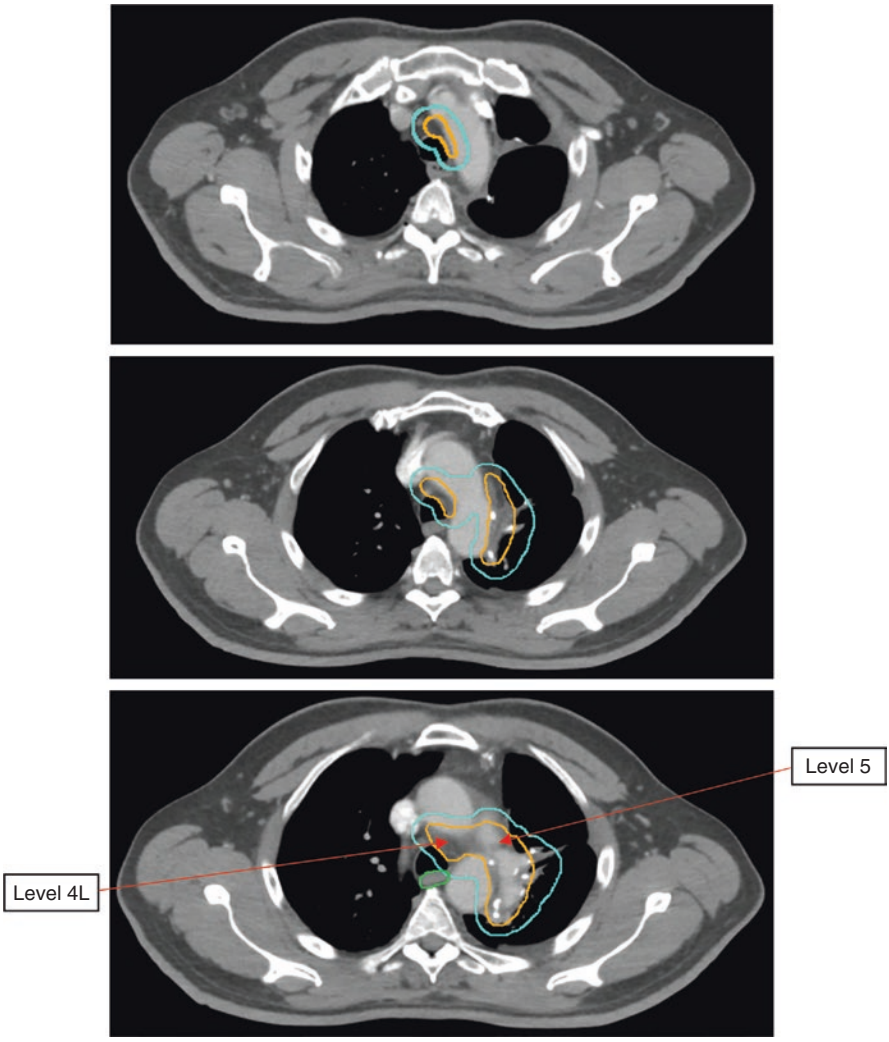


Fig. 13.5 Postoperative radiation for NSCLC. The patient had a 5.8-cm LUL tumor with EBUS showing involved level 4L nodes [cT3N2]. The patient received neoadjuvant chemotherapy. Pathologic findings from surgery showed negative margins, with levels 5 and 10L positive for malignancy. A limited field including the tumor bed, levels 4L, 5, 7, the ipsilateral bronchial stump is covered per the Lung ART guidelines. The prescription dose was 1.8 Gy × 30 fractions = 54 Gy. CTV (*orange*); PTV (*aqua*); involved LNs (*light green*); heart (*yellow*). Postoperative radiation for NSCLC. CTV (*orange*); PTV (*aqua*); esophagus (*dark green*). Postoperative radiation for NSCLC. CTV (*orange*); PTV (*aqua*); esophagus (*dark green*)



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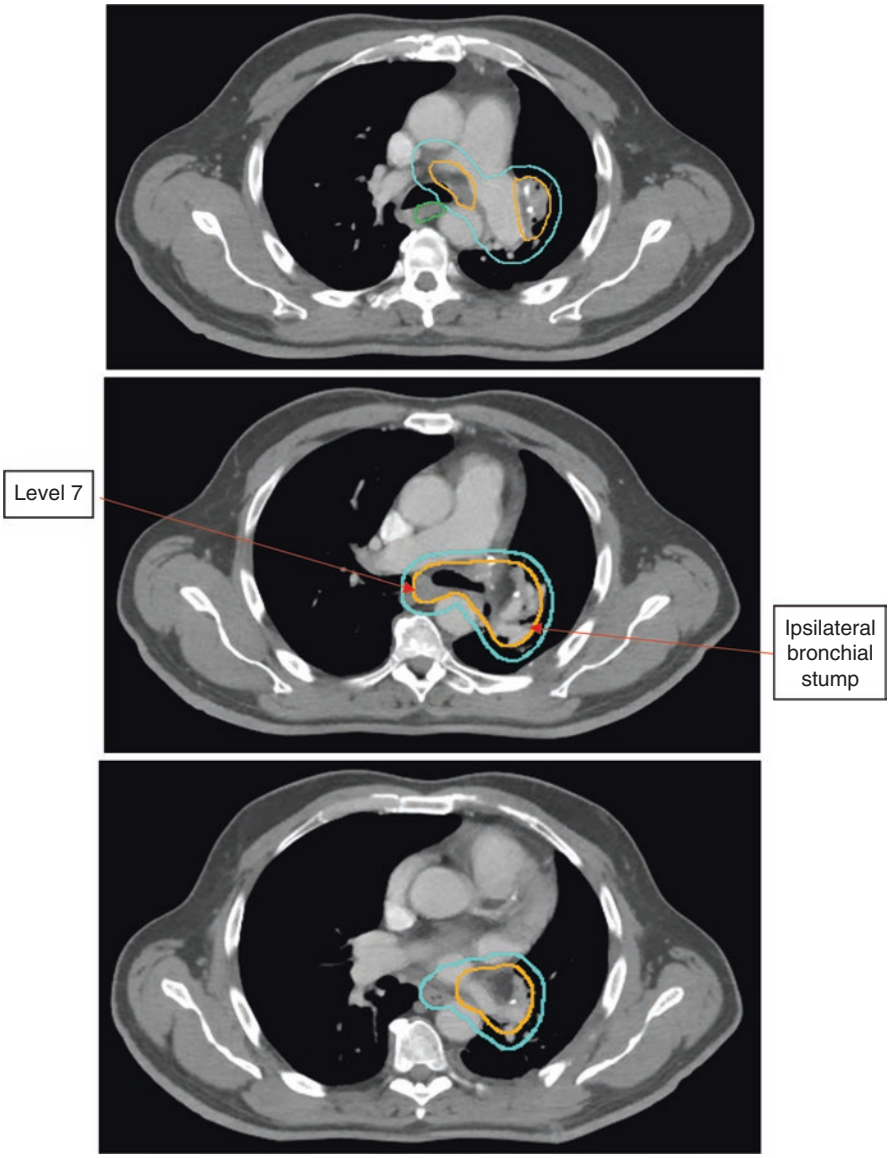

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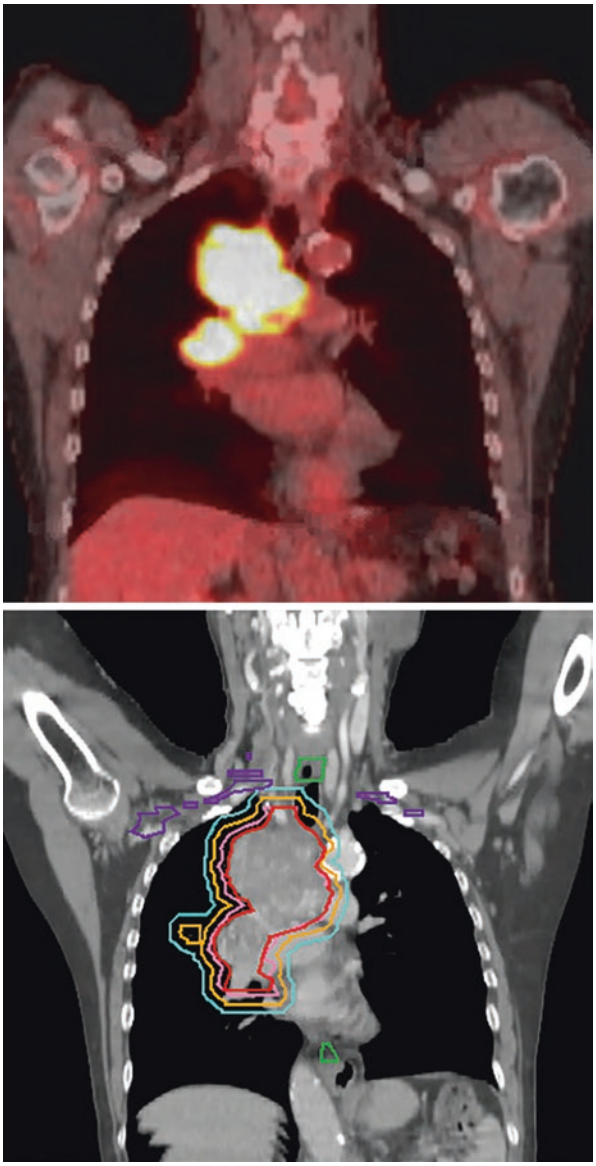
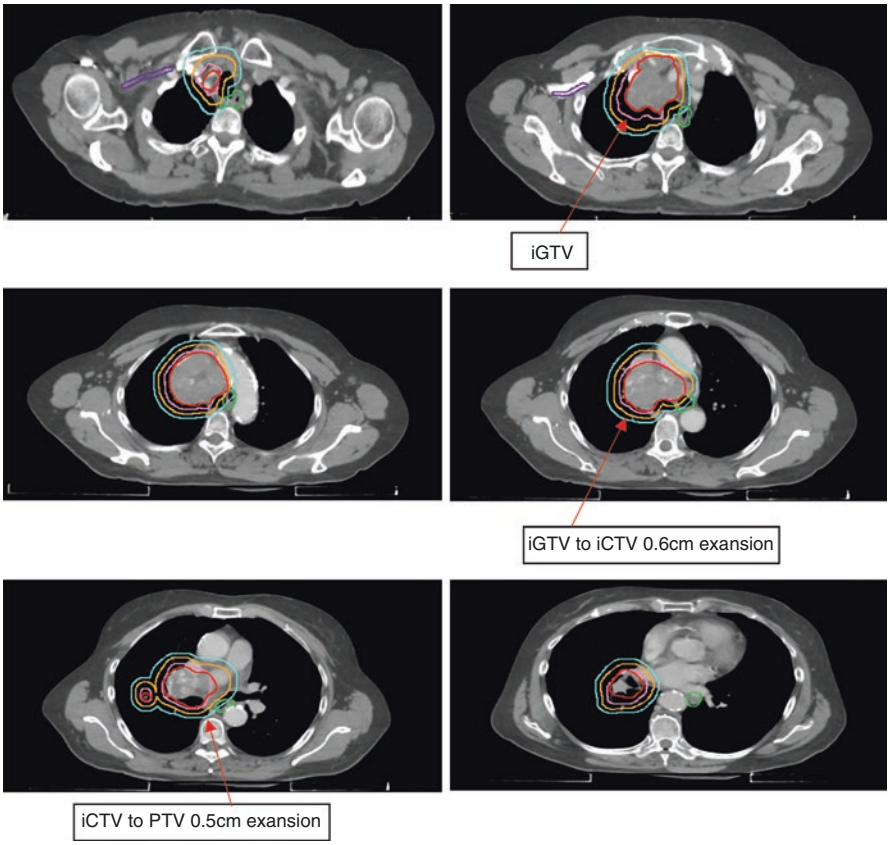


Fig. 13.6 Small cell lung cancer. The patient was found to have right paratrachael and right hilar masses showing cT2N2 limited-stage SCLC, with involvement of the anterior mediastinum and contiguous involvement of the right hilum and precarinal lymph nodes. An involved nodal approach was used, with coverage of the appropriate mediastinal and hilar regions. The prescription dose was 1.5 Gy × 30 fractions BID = 45 Gy. GTV (*red*); iGTV (*pink*); iCTV (*orange*); PTV (*aqua*); brachial plexus (*purple*); esophagus (*dark green*). Small cell lung cancer. GTV (*red*); iGTV (*pink*); iCTV (*orange*); PTV (*aqua*); brachial plexus (*purple*); esophagus (*dark green*)



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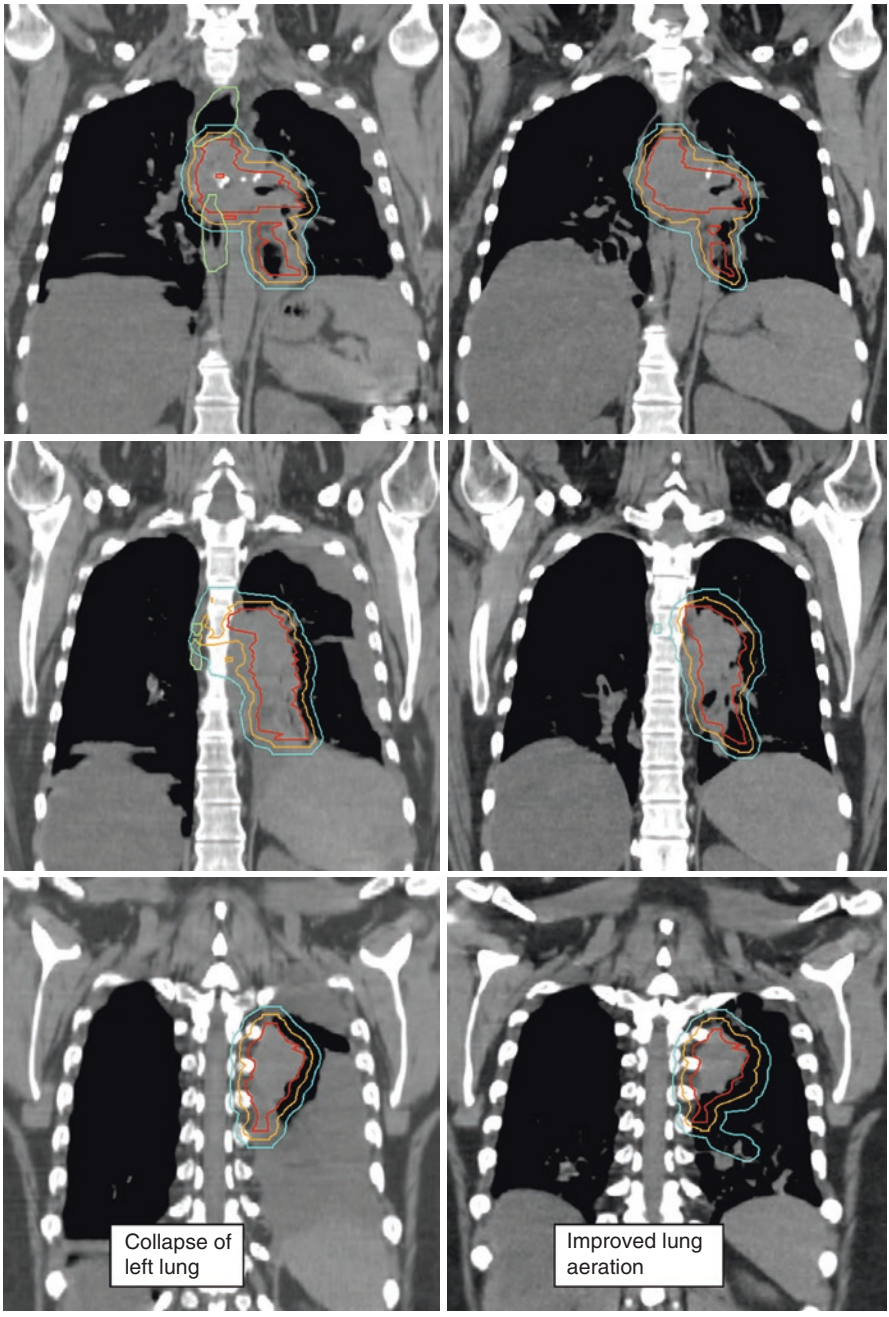

Fig. 13.7 Metastatic pulmonary lesion. The patient presented with an obstructive lesion (left) and was treated with 45 Gy in 15 fractions. During treatment, the patient improved and through CBCT it was noted that they required adaptive re-planning to account for changes in the lung anatomy (right). GTV (*red*); CTV (*orange*); PTV (*aqua*); esophagus (*green*)

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Esophageal Cancer

14

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Contents

14.1 General Principles of Planning and Target Delineation

- The standard of care in radiotherapy for esophageal cancer involves computed tomography (CT)-based planning with conformal techniques. Both intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3D-CRT) use multiple beam angles and allow for variation in dose conformality. Thus, both approaches require accurate delineation of target volumes, normal structures, and organs-at-risk (OARs) as well as evaluation of dose volume histograms during treatment planning. Because the esophagus begins in the neck at the lower border of the cricoid cartilage and anterior to the sixth cervical vertebra and descends through the mediastinum passing through the diaphragm into the abdomen, it is necessary to understand the anatomy of the neck, brachial plexus, mediastinum, lungs, heart, spinal cord, normal esophagus, and heart. A contouring atlas has delineated these structures and can be referenced [1].

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_14

- *Simulation*. Ideally, patients are simulated with their arms above their head to maximize the number of beam arrangements that can be used without having beams pass through the arms. For distal or GE junction tumors, measures should be taken to account for respiratory motion such as four-dimensional (4D) CT scanning, respiratory gating, or breath-hold techniques. In addition, when tumors involve the distal esophagus or GE junction, patients should be nil per os (NPO) for at least 2–3 h prior to simulation and each treatment to limit daily variation in anatomy from gastric and bowel gas. For IMRT, intravenous contrast at the time of simulation can better delineate nodal fields.
- Using a 40 cm standard distance from the incisors to the GE junction, the cervical esophagus extends from the incisors to approximately 15–20 cm, the upper or proximal thoracic esophagus extends from 18–20 to 25 cm, the mid or distal thoracic esophagus extends from 25 to 30–32 cm, and the abdominal esophagus extends from 30–32 to 40 cm.
- When contouring esophageal cancer, it is helpful to address esophageal malignancies by their anatomic subdivision: upper-mid esophagus tumors (including malignancies of the cervical esophagus), thoracic esophagus tumors, and gastroesophageal (GE) junction tumors. Tumors that span multiple esophageal subdivisions can follow the contouring guidelines of all involved subsets. Regardless of location of the tumor within the esophagus, the entire lungs should be contoured for proper DVH analysis. In malignancies of the upper esophagus, the brachial plexus and larynx should be contoured. In malignancies of the lower esophagus, the heart, the liver, the kidneys, the stomach, and adjacent bowel should be delineated [2].
- The following target structures should be delineated: gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). At our institution, we routinely define an ITV, the volume encompassing the internal motion of the GTV as observed on the 4DCT. The ITV is then expanded to a CTV, followed by a PTV.
- Physicians should delineate the GTV with reference to CT and positron emission tomography (PET) imaging, as well as findings on upper endoscopy and endoscopic ultrasound. The endoscopic ultrasound can be used to better stage the depth of invasion of the esophageal tumor and to classify small peri-esophageal lymph nodes that are difficult to classify with CT or PET scan. A bronchoscopy is recommended if a tumor is superior to the carina to rule out the presence of a tracheoesophageal fistula, which may delay radiotherapy.
- Standard ITV to CTV expansions are 1 cm radially to encompass the peri-esophageal lymph nodes and 3–4 cm in the superior-inferior direction (oriented along the esophageal mucosa) to account for submucosal spread and the possibility of skip lesions. The expansion to CTV can be limited to 0.5 cm in areas overlapping the heart and uninvolved liver, assuming appropriate motion management techniques. Because a 4 cm caudad margin for distal esophagus and GE

junction cases would include large volumes of stomach or abdominal viscera, only 2 cm margin to CTV along clinically uninvolved gastric mucosa is recommended, unless treating with preoperative-intent doses (≤4500 cGy) in which case a 4 cm or greater gastric margin may be appropriate, particularly for tumors with significant gastric extension. The uninvolved vertebral bodies and kidneys are excluded from CTV. For involved lymph nodes, a GTV to CTV margin of 0.5–1.0 cm can be utilized. If there are grossly involved periesophageal nodes, then the CTV should cover at least 1 cm cephalad to the involved nodes. An expansion of 0.5 cm from CTV to PTV is recommended. These recommended margins can be adjusted depending on the motion assessment technique and one's confidence in having accurately covered the extent of disease.

- Regional lymph nodes should be included in the CTV according to the location of the primary tumor within the esophagus. For proximal thoracic and cervical esophagus tumors, bilateral supraclavicular nodal basins are included. They are bounded cranially at the lower edge of the cricoid cartilage, and they are bounded anteriorly, posteriorly, and laterally by the sternocleidomastoid muscle. For proximal thoracic tumors, mediastinal lymph nodes are included in addition to the peri-esophageal nodes encompassing the entire trachea, levels 2 and 4, with extension towards the sternum and clavicular heads to encompass level 3. For distal tumors, the CTV should include the celiac nodes, which are bounded on the right by the lateral aspect of T12, on the left 0.5–1 cm beyond the lateral aspect of the aorta, posteriorly by vertebral bodies, and anteriorly by the pancreas. For distal tumors, it is not necessary to include the superior mediastinal nodal stations electively, other than overlap with the aforementioned cranial expansions. For GE junction tumors, CTV should include para-aortic and the gastrohepatic ligament nodes in a volume bounded by the liver on the right, the stomach on the left.
- When GE junction tumors significantly overlap the gastric cardia, it is unclear whether they have a gastric origin rather than a esophageal origin. To overcome this ambiguity, the Siewert–Stein classification defines GE junction tumors according to their epicenter relative to the GE junction: type I lesions have an epicenter 1–5 cm above the junction, type II lesions have an epicenter from 1 cm proximal to 2 cm distal to the junction, and a type III lesions have an epicenter 2–5 cm below GE junction. A reasonable cutoff for esophageal cancer is Siewert type II, and, in fact, the eighth edition AJCC staging system now defines esophageal tumors as those whose epicenter extends no more than 2 cm into the gastric cardia [3]. For Siewert Type II tumors, some or all of the splenic hilum and greater curvature nodal region may be included. Based on prevailing guidelines for gastric cancers, a diagnostic laparoscopy, J-tube placement, preoperative chemoradiation [4] or postoperative chemoradiation [5] can be considered. (Table 14.1 and Figs. 14.1, 14.2, 14.3, 14.4).

Table 14.1 Summary of recommendations for contouring esophageal cancers

Esophagus subdivision	Definition	ITV to CTV margin	CTV to PTV margin	Elective nodal coverage	Dose
Cervical	Incisors to approximately 15–20 cm	3 cm superior and inferior (oriented along mucosa), 1 cm radially	0.5 cm	Periesophageal, supraclavicular, ± anterior mediastinal	50.4 Gy in 1.8 Gy per fraction, with consideration of boost to 60–70 Gy for SCC
Upper thoracic	From 18–20 cm to approximately 25 cm	3 cm superior and inferior (oriented along mucosa), 1 cm radially	0.5 cm	Periesophageal, supraclavicular, ± anterior mediastinal	50.4 Gy in 1.8 Gy per fraction
Lower thoracic	From 25 cm to approx. 37 cm	3 cm superior and inferior (oriented along mucosa), 1 cm radially	0.5 cm	Periesophageal	50.4 Gy in 1.8 Gy per fraction (definitive) 41.4–50.4 Gy in 1.8 Gy per fraction (pre-operative)
Abdominal (GE junction)	From approx. 37 to 42 cm	3 cm superior (along esophageal mucosa) and 1–2 cm inferior (along gastric mucosa) for 50.4 Gy dose. For preoperative-intent doses (≤4500 cGy) ≥ 4 cm gastric margin may be appropriate	0.5 cm	Periesophageal, gastrohepatic ligament (i.e. paracardiac and left gastric stations), celiac axis, ± splenic hilum	50.4 Gy in 1.8 Gy per fraction (definitive) 41.4–50.4 Gy in 1.8 Gy per fraction (pre-operative)

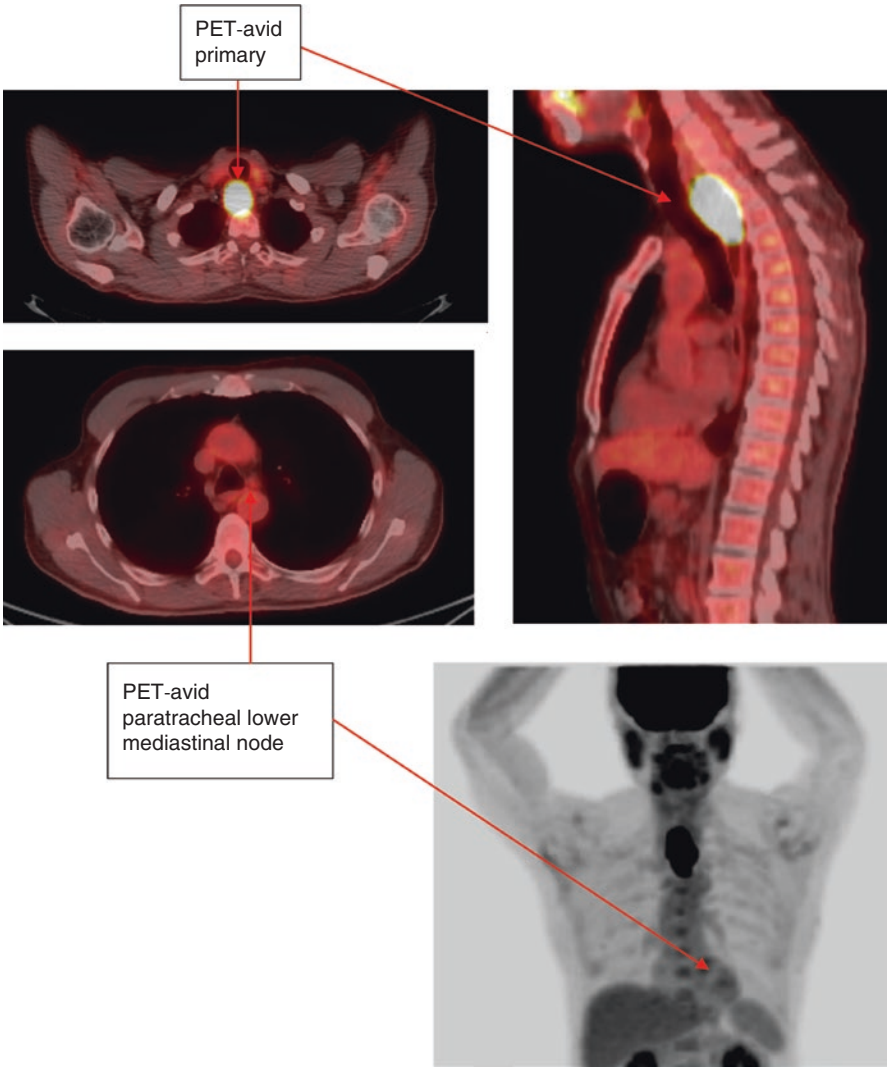


Fig. 14.1 Sixty-nine-year-old with SCC of the cervical/upper thoracic esophagus. PET scan images showing FDG avid primary and mildly avid paratracheal lymph nodes. EGD showed an ulcerating, submucosal mass 15–23 cm from the incisors. Sixty-nine-year-old with SCC of the cervical/upper thoracic. Brachial plexus (purple); larynx (*yellow*); GTV esophagus (*red*); GTV nodes (*green*); CTV (*orange*); PTV 54 Gy (*aqua*); PTV 60 Gy (*dark blue*)

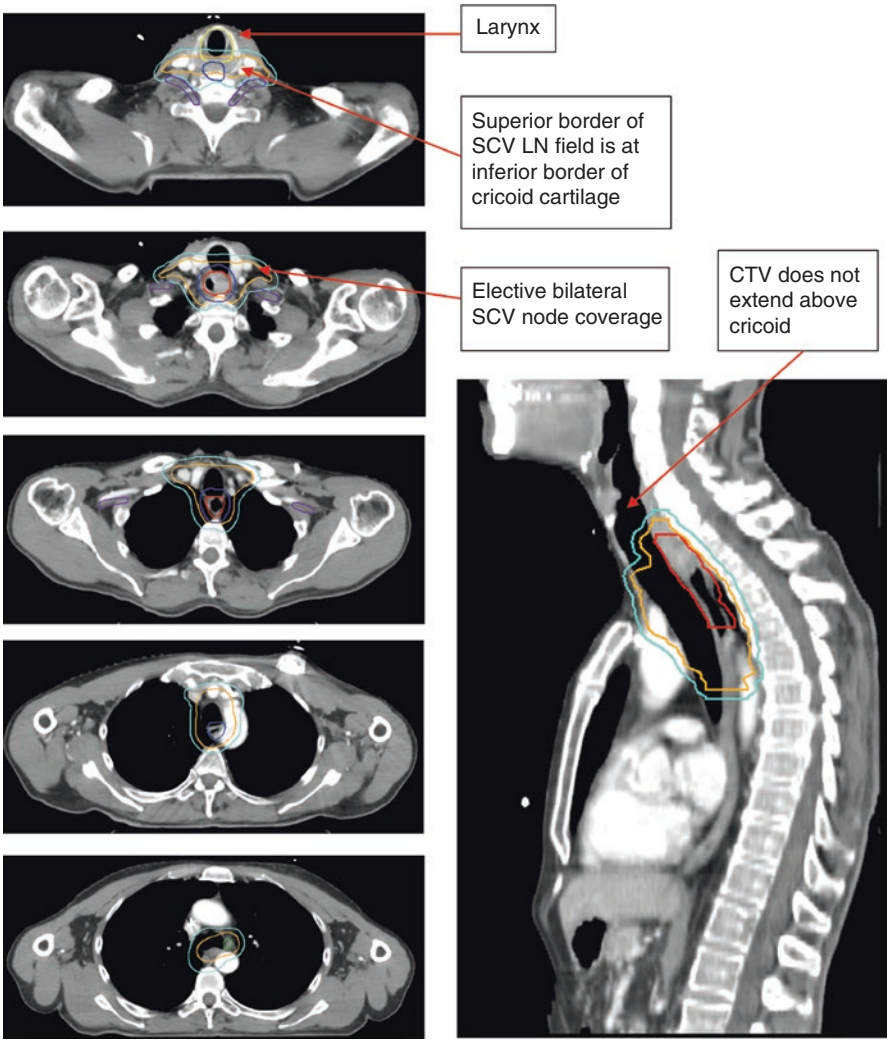


Fig. 14.1 (continued)

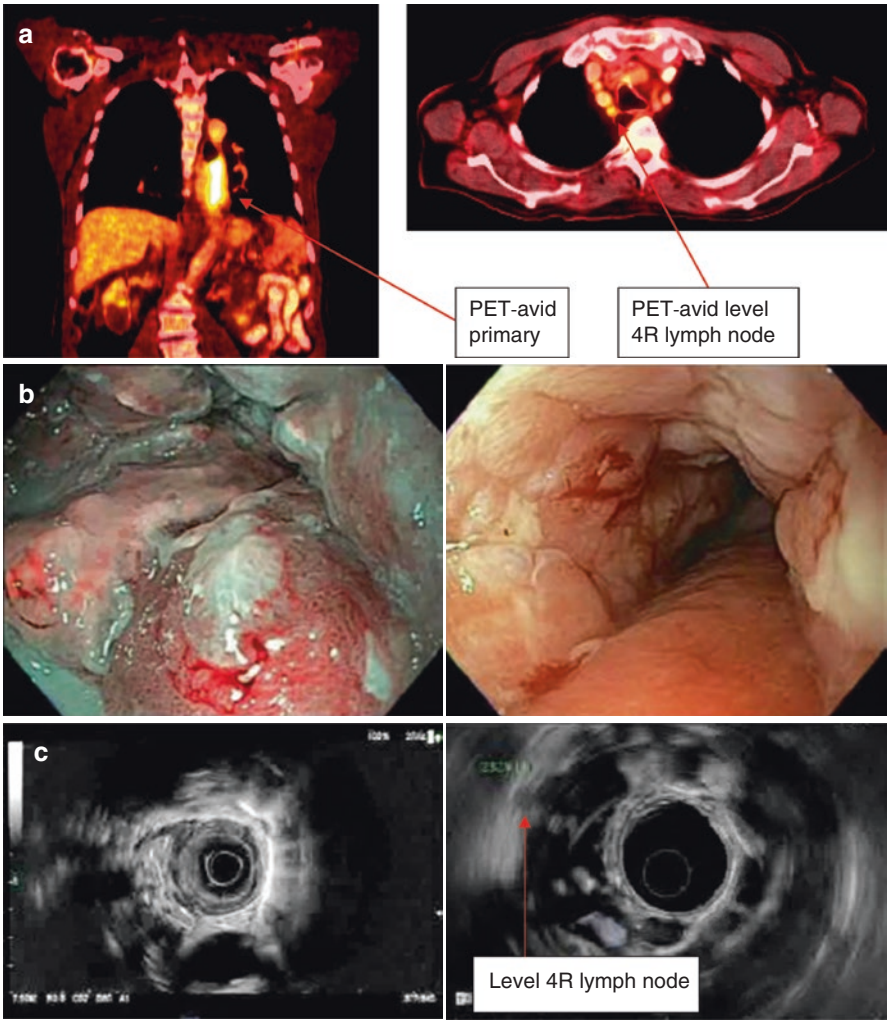
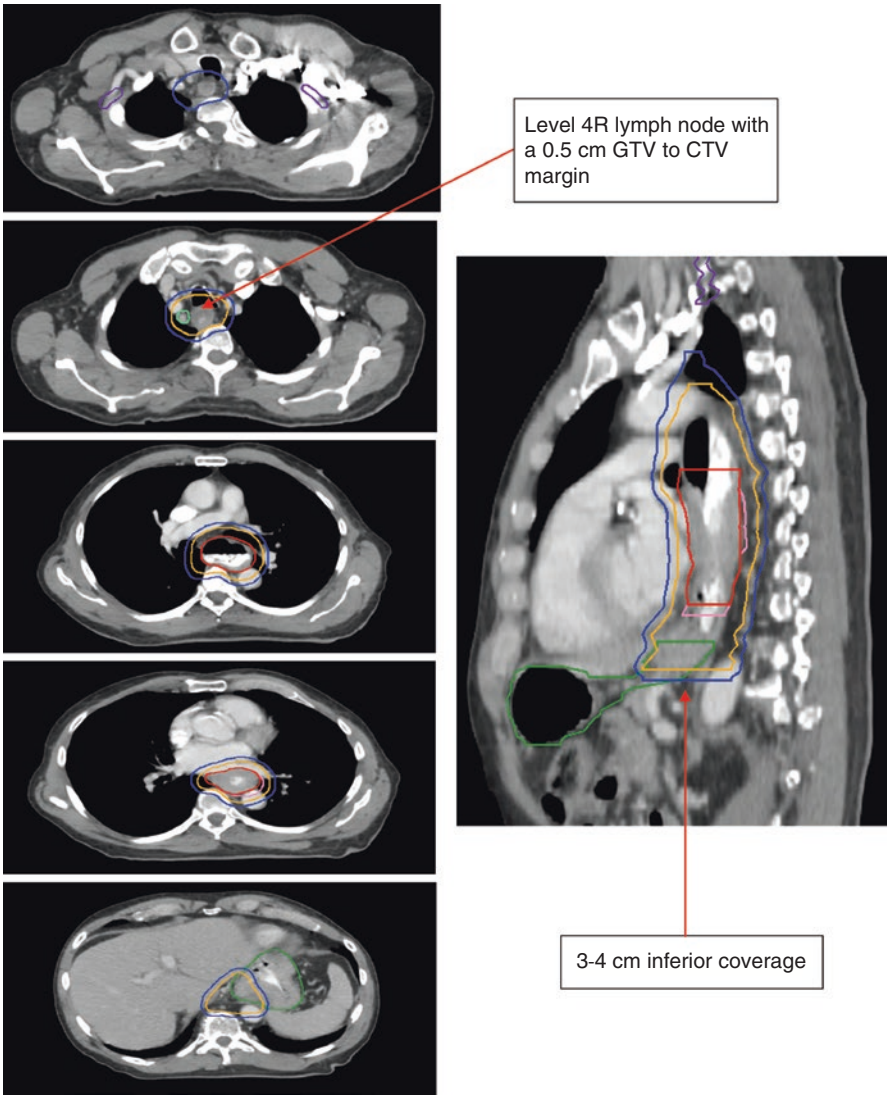


Fig. 14.2 Eighty-one-year-old with a lower thoracic esophageal adenocarcinoma [uT3N1]. (**a**) PET imaging showing the primary and level 4R paratracheal lymph node. (**b**) Endoscopy showing partially obstructing and circumferential esophageal adenocarcinoma 31–35 cm from the incisors. (**c**) EUS showing T3 primary disease and suspicious level 4R lymph node. Eighty-one-year-old with a lower thoracic esophageal adenocarcinoma [uT3N1]. Brachial plexus (*purple*); stomach (*dark green*); GTV esophagus (*red*); ITV (*pink*); GTV nodes (light *green*); CTV (*orange*); PTV 50.4 Gy (*dark blue*)



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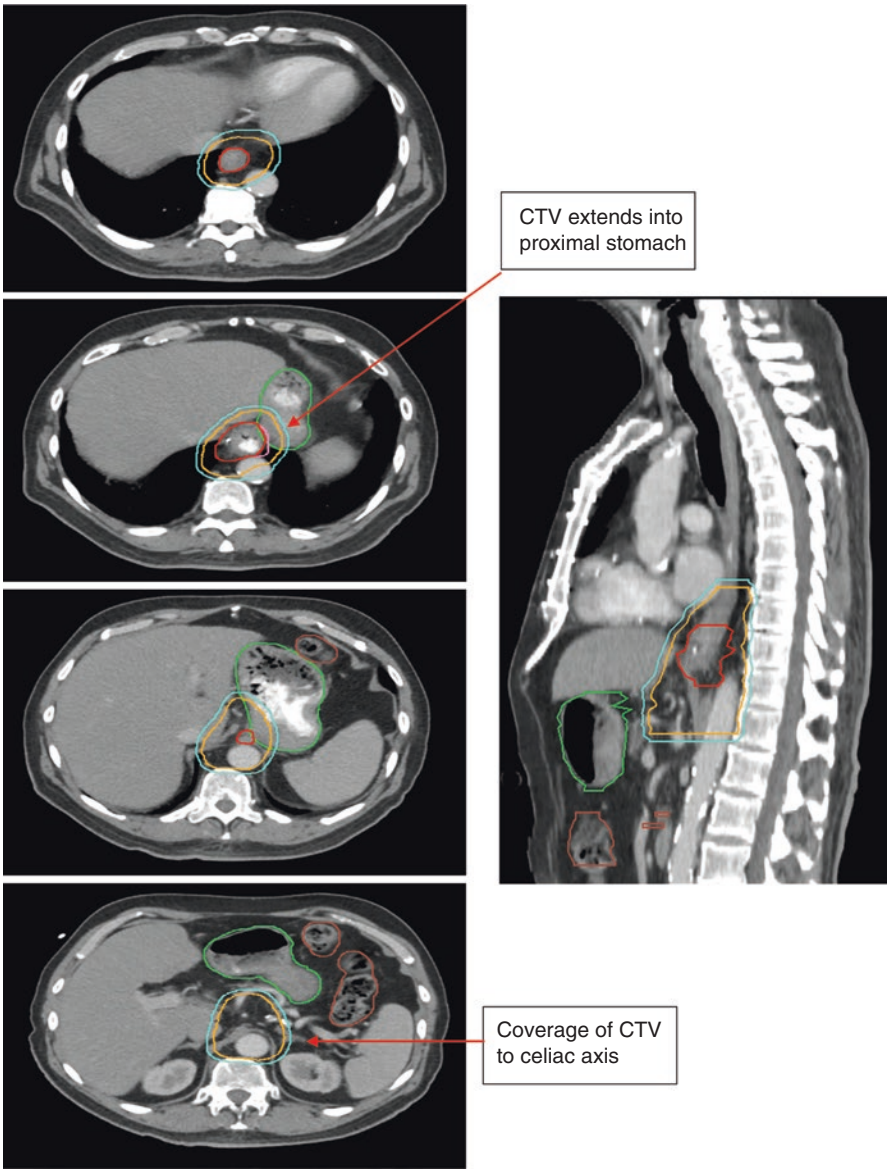

Fig. 14.3 Seventy-five-year-old with gastroesophageal junction adenocarcinoma [uT3N0]. Stomach (*dark green*); large bowel (*brown*); GTV esophagus (*red*); CTV (*orange*); PTV 50.4 Gy (*aqua*)

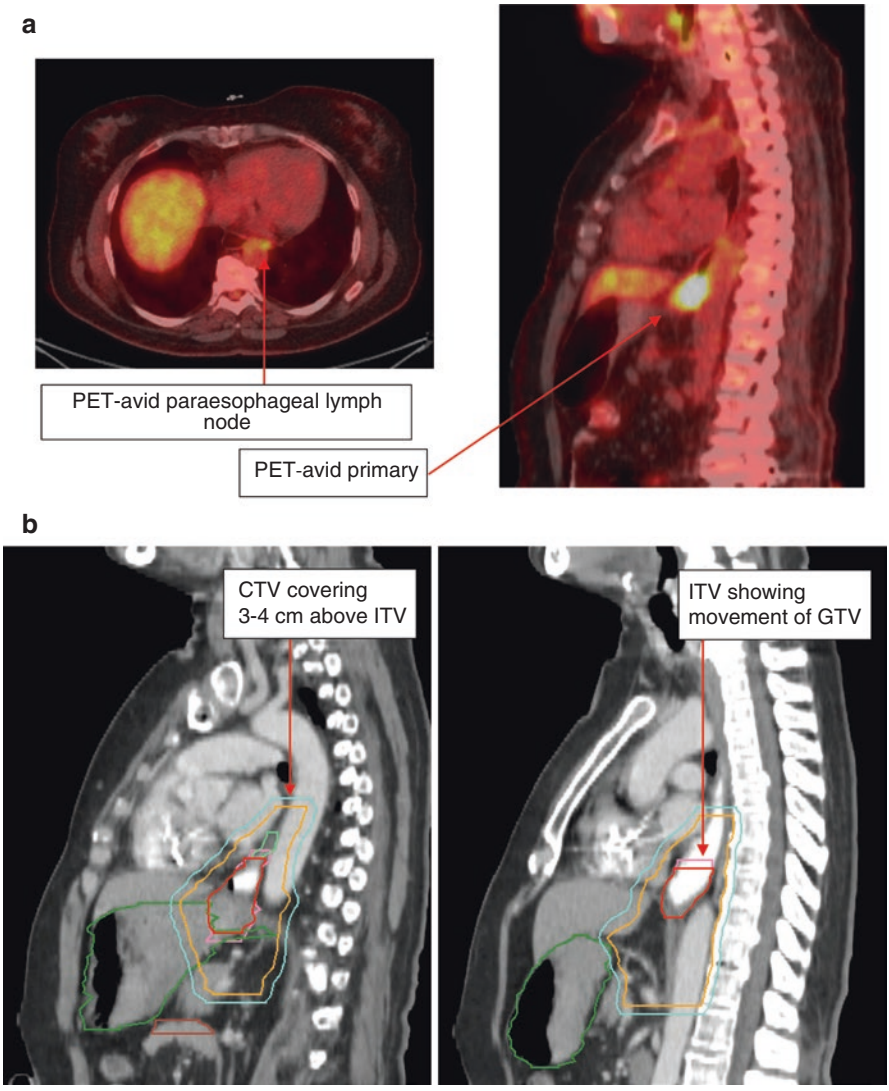

Fig. 14.4 Fifty-nine-year-old with adenocarcinoma of gastroesophageal junction [uT3N2]. (**a**) PET imaging showing FDG-avid paraesophageal nodes and primary located at 36–40 cm from the incisors. (**b**) Sagittal planning CT with contours. Stomach/duodenum (*dark green*); GTV nodes (*light green*); GTV esophagus (*red*); ITV (pink); CTV (*orange*); PTV 50.4Gy (*aqua*). Fifty-nine-year-old with adenocarcinoma of gastroesophageal junction [uT3N2]. Stomach/duodenum (*dark green*); GTV nodes (*light* green); GTV esophagus (*red*); CTV (*orange*); PTV 50.4 Gy (*aqua*)

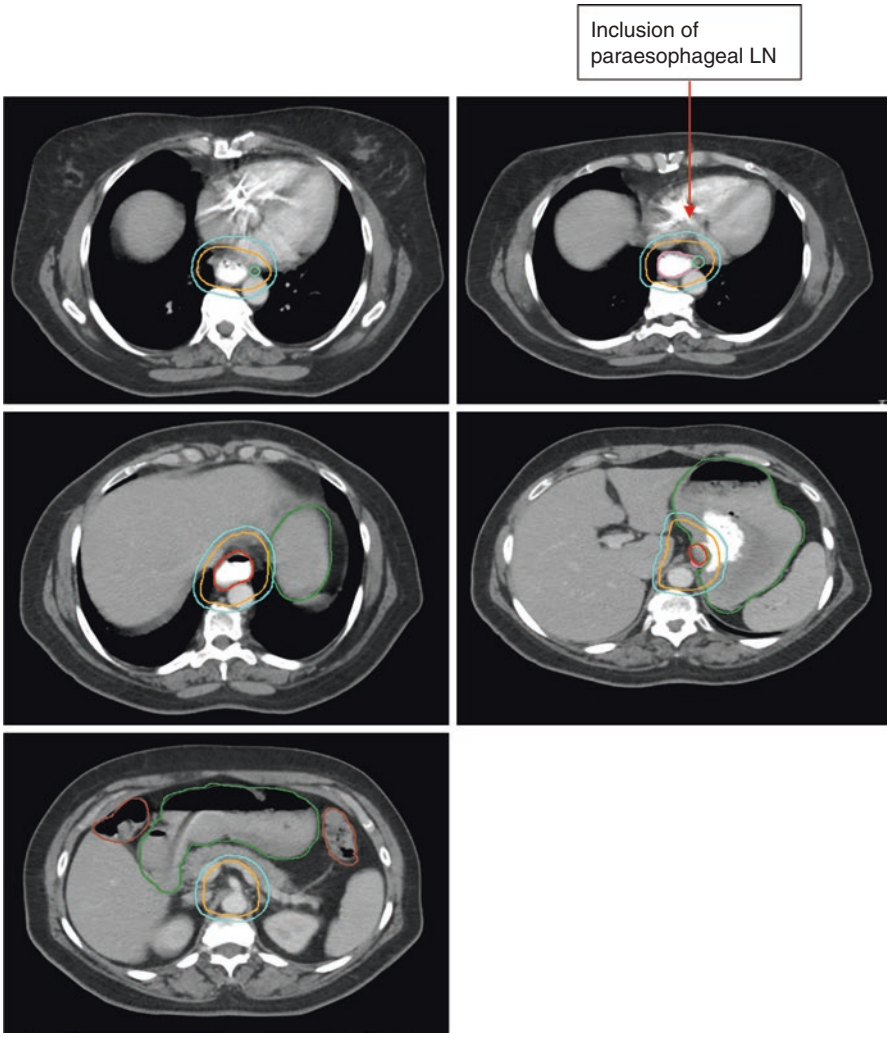

Fig. 14.4 (continued)

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Gastric Cancer

15

Jeremy Tey, Jiade J. Lu, and Ivy Ng

Contents

15.1 Anatomy and Patterns of Spread

- The stomach begins at the gastro-esophageal junction and ends at the pylorus. The greater curvature forms the left and convex border of the stomach, and the lesser curvature forms the right and concave border of the stomach. It is divided into four parts: the cardia, fundus, body, and antrum. Its wall is divided into five

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_15

layers: mucosa, submucosa, muscularis externa, subserosa, and serosa (Fig. 15.1a).

- It is covered with peritoneum and is closely related to the left lobe of the liver, spleen, left adrenal gland, superior portion of the left kidney, pancreas, transverse colon, and major blood vessels including the celiac axis and superior mesenteric artery (Fig. 15.1b).
- Regions of stomach and the probability of gastric carcinoma, according to the primary location: tumours arising from gastro-esophageal junction, cardia, and fundus account for ~35%; from the body, ~25%; from antrum and distal stomach, ~40%.
- **Local extension**:
  - The tumour can invade locally with direct involvement of the liver, duodenum, pancreas, transverse colon, omentum, and diaphragm.
  - Proximal tumours may spread upwards to involve the oesophagus.
  - Perineural invasion can occur.
- **Regional lymph node metastases** (Fig. 15.2 and Table 15.1):
  - Lymph node involvement is seen in up to 80% of cases at diagnosis.
  - Lymph node involvement depends on the origin of primary disease.
  - Proximal/gastro-esophageal junction tumours may spread to lower paraoesophageal lymph nodes.
  - Tumours of the body can involve all nodal sites.
  - Tumours of the distal stomach/antrum may involve periduodenal and porta hepatic lymph nodes.

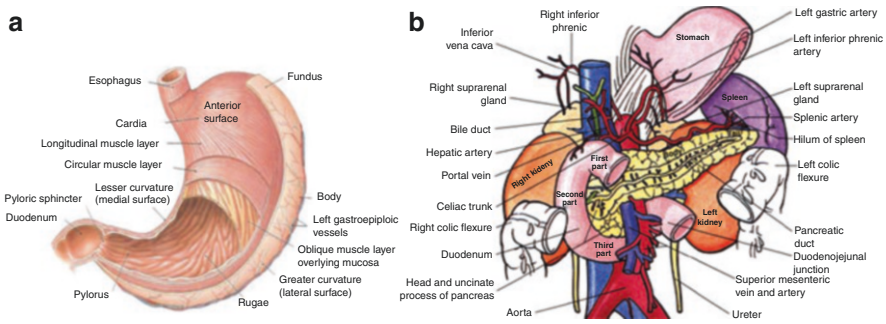

Fig. 15.1 Anatomy and relations of stomach

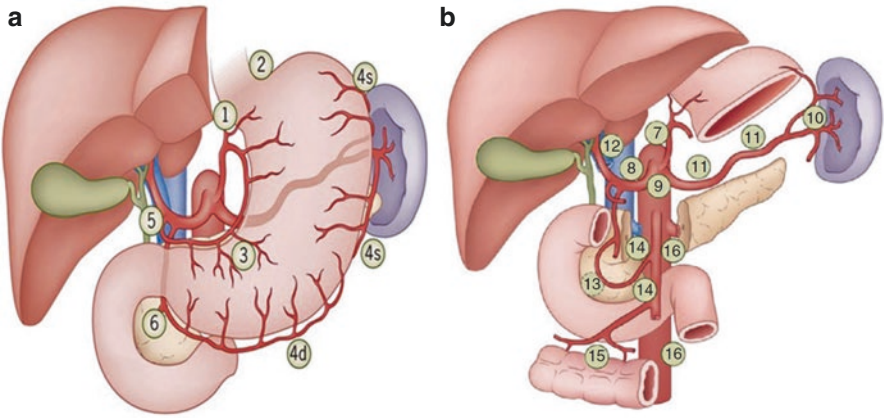

Fig. 15.2 Lymph node groups surrounding the stomach

Table 15.1 Lymph node stations commonly involved in gastric cancer (Japanese Research Society for the Study of Gastric Cancer—JRSGC)

N1	1	Right cardial nodes
	2	Left cardial nodes
	3	Nodes along lesser curvature
	4	Nodes along greater curvature
	5	Suprapyloric nodes
	6	Infrapyloric nodes
N2	7	Nodes along left gastric artery
	8	Nodes along common hepatic artery
	9	Nodes along celiac axis
	10	Nodes at the splenic hilus
	11	Nodes along splenic artery
N3	12	Nodes in the hepatoduodenal ligament
	13	Nodes at the posterior aspect of pancreatic head
	14	Nodes at the root of mesenterium
N4	15	Nodes in the mesocolon of transverse colon
	16	Para-aortic lymph nodes

Source: Figure and table adapted from Hartgrink, Van De Velde (2005) Status of extended lymph node dissection: Journal of Surg Oncol 90:153–165. Used with permission from Wiley Inc.

15.2 Diagnostic Workup Relevant for Target Volume Delineation

- Prior to radiotherapy planning, it is imperative to review surgical and pathology reports, and discuss with the surgeon to identify the areas considered to be the highest risk for recurrence; type of operation, i.e. total vs. partial gastrectomy, needs to be noted.
- Preoperative CT scans should be reviewed to identify location of primary tumour and involved regional lymphatics.
- 18-Fluodeoxyglucose (FDG) PET alone is not adequate diagnostic imaging modality for preoperative staging of gastric cancer as diffuse and mucinous tumour subtypes have low FDG uptake.
- Consider pre-radiation quantitative renal perfusion study to evaluate relative bilateral renal function.
- Post-operative diagnostic CT scan with oral and intravenous contrast is required with the identification of the following:
  - Oesophagus and gastric remnant.
  - Anastomosis (gastrojejunal, oesophagojejunal).
  - Duodenal stump.
  - Portal hepatis.
  - Splenic hilum.
  - Pancreas.
  - Coeliac artery and superior mesenteric artery.
- Type of surgery performed depends on location of tumour and histology pattern (Fig. 15.3).

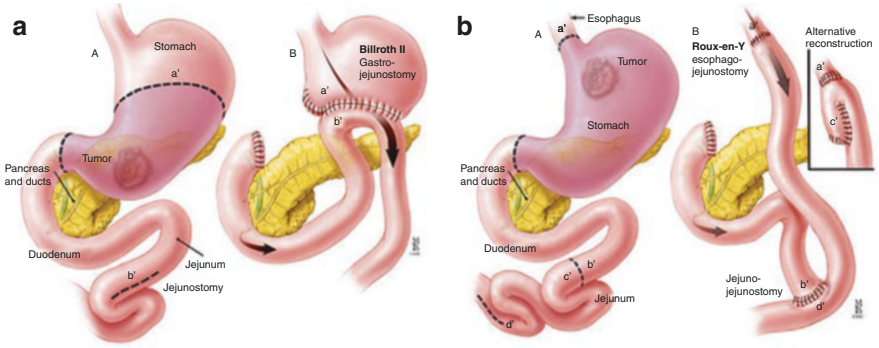

Fig. 15.3 Types of gastric cancer surgery

15.3 General Principles of Planning and Target Delineation for Adjuvant Radiation for Adenocarcinomas of the Gastro-Esophageal Junction and the Stomach

- Patients should be fasted for 2–3 h before CT simulation and before treatments.
- Radiotherapy planning CT scans of 3–5 mm thickness should be obtained with patient in the supine position with arms overhead, from top of diaphragm (for stomach) or carina (for tumour involving GE junction or cardia) to the bottom of L4.
- Immobilisation with a vacuum bag such as VacLok® is recommend for treatment with intensity modulated radiotherapy (IMRT).
- Intravenous contrast is preferred to demonstrate blood vessels and guide clinical target volume (CTV) delineation, particularly for lymph nodes; preoperative CT scans should be used to aid identification of preoperative tumour volume and nodal groups to be treated.
- CTV for adjuvant radiation therapy for gastric cancer depends on the position of the primary disease as well as the status of lymph node metastasis. Suggested target volumes for CTV coverage depending on subsite are detailed in Tables 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8 and Fig. 15.4.

Table 15.2 Target volume definition and description

Target volumes	Definition and description
GTV	Gross residual disease defined by CT imaging and surgical findings
PTV (residual disease)	GTV/positive margins + 1.5 cm. Cone down boost after 45 Gy to a total dose of 50.4–54 Gy in 1.8 Gy/fraction
CTV_{45}	Coverage of nodal groups according to subsite (see Tables 15.5, 15.6, 15.7, and 15.8). Also includes remnant stomach, anastomosis (gastrojejunal, oesophagojejunal), duodenal stump
PTV_{45}	CTV_{45} + 1 cm margin. A larger margin may be required for organ motion and setup uncertainties

Table 15.3 General considerations for clinical target volume

Target volumes	Definition and description
Duodenal stump	Should preferably be covered in patients who have had a partial gastrectomy for distal/antral tumours
	Should not be covered in patients with proximal/cardia tumours who have had a total gastrectomy
Anastomosis	Gastrojejunal anastomosis (partial gastrectomy for tumours of the distal stomach) Oesophagojejunal anastomosis (total gastrectomy for tumours of proximal stomach or GE junction) should be treated
Para-aortic nodes	Should be included for the entire length of the CTV
Paraoesophageal nodes	4 cm margin of the oesophagus should be included in the clinical target volume for tumours of the gastro-esophageal junction

Table 15.4 General guidelines of impact of T and N category on inclusion of remaining stomach, tumour bed, and nodal sites within radiation fields

AJCC eighth edition TN category	Remaining stomach	Tumour bed	Nodes
T1-2N0 (not into subserosa)	No	No	No
T2N0 (into subserosa)	Variable	Yes	No
T3N0	Variable	Yes	No
T4N0	Variable	Yes	Variable
T1-2N+	Yes	No	Yes
T3-4N+	Yes	Yes	Yes

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Table 15.5 Recommended target volumes depending on stage and site of primary tumour in stomach: Gastro-esophageal (GE) Junction

Site of primary and stage	Remaining stomach[a]	Tumour bed volumes[a]	Nodal volume
GE Junction	If allows exclusion of 2/3 right kidney	T stage dependent	N stage dependent
T2N0, invasion of subserosa	Variable, dependent on surgical pathological findings[b]	Medial left hemidiaphragm; adjacent body of pancreas	None or PG, PEN
T3N0	Variable, dependent on surgical pathologic findings[b]	Medial left hemidiaphragm; adjacent body of pancreas	None or PG, PEN, CN, MN[c]
T4N0	Preferable but dependent on surgical pathologic findings[b]	As for T3N0 plus site(s) of adherence with 3–5 cm margin	Nodes related to site(s) of adherence ± PG, PEN, CN, MN
T1-2N+	Preferable	Not indicated for T1, as above for T2 into subserosa	Proximal PG, PEN, CN, MN
T3-4N+	Preferable	As for T3N0, T4N0	As for T1-2N+ and T4N0

PG perigastric, *CN* celiac, *PEN* perioesophageal, *MN* mediastinal

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[a]Use preoperative imaging (CT, barium swallow), surgical clips, and post-operative imaging (CT, barium swallow)

[b]For tumours with >5 cm margins confirmed pathologically, treatment of residual stomach is optional, especially if this would result in substantial increase in normal tissue morbidity

[c]Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2) and at least 10–15 nodes are examined pathologically

Table 15.6 Recommended target volumes depending on stage and site of primary tumour in stomach: cardia/proximal third of stomach

Site of primary and stage	Remaining stomach[a]	Tumour bed volumes[a]	Nodal volume
Cardia/ Proximal third of stomach	Yes, but spare 2/3 of one kidney, usually right	T category dependent	N category dependent, spare 2/3 of one kidney
T2N0, invasion of subserosa	Variable, dependent on surgical pathological findings[b]	Medial left hemidiaphragm, adjacent body of pancreas ± tail	None or PG[c]
T3N0	Variable, dependent on surgical pathological findings[b]	Medial left hemidiaphragm, adjacent body of pancreas ± tail	None or PG Optional: PEN, CN, MN[c]
T4N0	Variable, dependent on surgical pathological findings[b]	As for T3N0 plus site(s) of adherence with 3–5 cm margin	Nodes related to site(s) of adherence ± PG, CN, MN
T1-2N+	Preferable	Not indicated for T1	PG, CN, splenic, SP, ± MN, PD, PH[d]
T3-4N+	Preferable	As for T3N0, T4N0	As for T1-2N+ and T4N0

PG perigastric, *CN* celiac, *SP* suprapancreatic, *PH* porta hepatis, *PD* pancreaticoduodenal, *PEN* perioesophageal, *MN* mediastinal

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[a]Use preoperative imaging (CT, barium swallow), surgical clips, and post-operative imaging (CT, barium swallow)

[b]For tumours with >5 cm margins confirmed pathologically, treatment of residual stomach is optional, especially if this would result in substantial increase in normal tissue morbidity

[c]Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2) and at least 10–15 nodes are examined pathologically

[d]Pancreaticoduodenal and porta hepatis nodes are at low risk if nodal positivity is minimal (i.e. 1–2 positive nodes with 10–15 nodes examined), and this region does not need to be irradiated. Perioesophageal and mediastinal nodes are at risk if there is oesophageal extension

Table 15.7 Recommended target volumes depending on stage and site of primary tumour in stomach: body/middle third of stomach

Site of primary and stage	Remaining stomach[a]	Tumour bed volumes[a]	Nodal volume
Body/mid third of stomach	Yes, but spare 2/3 of one kidney	T category dependent	N category dependent, spare 2/3 of one kidney
T2N0, invasion of subserosa	Yes	Body of pancreas ± tail	None or PG Optional: CN, splenic, SP, PD, PH[b]
T3N0	Yes	Body of pancreas ± tail	None or PG Optional: CN, splenic, SP, PD, PH[b]
T4N0	Yes	As for T3N0 plus site(s) of adherence with 3–5 cm margin	Nodes related to site(s) of adherence ± PG, CN, splenic, SP, PD, PH
T1-2N+	Yes	Not indicated for T1EEEEE	PG, CN, splenic, SP, PD, PH
T3-4N+	Yes	As for T3N0, T4N0	As for T1-2N+ and T4N0

PG perigastric, *CN* celiac, *SP* suprapancreatic, *PH* porta hepatis, *PD* pancreaticoduodenal, *PEN* perioesophageal, *MN* mediastinal

[a]Use preoperative imaging (CT, barium swallow), surgical clips, and post-operative imaging (CT, barium swallow)

[b]Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2) and at least 10–15 nodes are examined pathologically

- Three areas must be identified as CTV for adjuvant radiotherapy: the gastric tumour bed, the anastomosis or stumps, and the regional lymphatics.
- In addition, the hepatogastric ligament should preferably be treated in all cases as it is at high risk of recurrence. It represents the part of the lesser omentum that runs between the lesser curvature of the stomach and liver, and contains the left and right gastric nodes that are not always completely removed at surgery.
- The benefits of IMRT have been suggested by many publications. If used, tumour bed and subclinical target volumes including lymphatic draining regions should be delineated.
- Planning Target Volume (PTV): CTV + margin considering organ motion and setup uncertainties. A minimum expansion of 1 cm is suggested.
- A total dose of 45 Gy in 25 fractions is recommended for adjuvant radiotherapy with concurrent chemotherapy, using high energy (≥6 MV) photons. Boosts to 50.4–54 Gy for positive margins or residual disease should be given, if doses to surrounding critical organs are within tolerance.

Table 15.8 Recommended target volumes depending on stage and site of primary tumour in stomach: antrum/pylorus/distal third of stomach

Site of primary and stage	Remaining stomach[a]	Tumour bed volumes[a]	Nodal volume
Pylorus/distal third of stomach	Yes, but spare 2/3 of one kidney, usually left	T category dependent	N category dependent, spare 2/3 of one kidney
T2N0, invasion of subserosa	Variable, dependent on surgical pathological findings[b]	Head of pancreas ± body, first and second portion of duodenum	None or PG Optional: CN, SP, PD, PH[c]
T3N0	Variable, dependent on surgical pathological findings[b]	Head of pancreas ± body, first and second portion of duodenum	None or PG Optional: CN, SP, PD, PH[c]
T4N0	Variable, dependent on surgical pathological findings[b]	As for T3N0 plus site(s) of adherence with 3–5 cm margin	Nodes related to site(s) of adherence ± PG, CN, SP, PD, PH
T1-2N+	Preferable	Not indicated for T1	PG, CN, SP, PD, PH Optional: Splenic hilum
T3-4N+	Preferable	As for T3N0, T4N0	As for T1-2N+ and T4N0

PG perigastric, *CN* celiac, *SP* suprapancreatic, *PH* porta hepatis, *PD* pancreaticoduodenal, *PEN* perioesophageal, *MN* mediastinal

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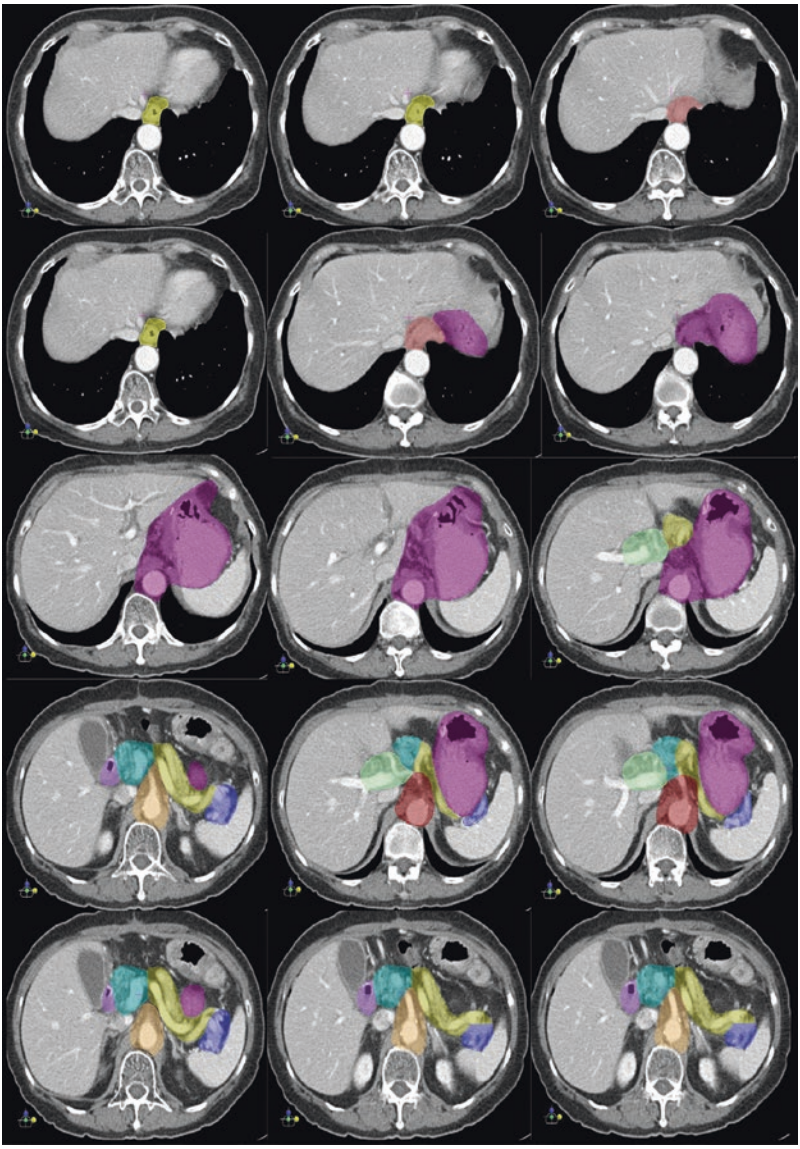
[a]Use preoperative imaging (CT, barium swallow), surgical clips, and post-operative imaging (CT, barium swallow)

[b]For tumours with >5 cm margins confirmed pathologically, treatment of residual stomach is optional, especially if this would result in substantial increase in normal tissue morbidity

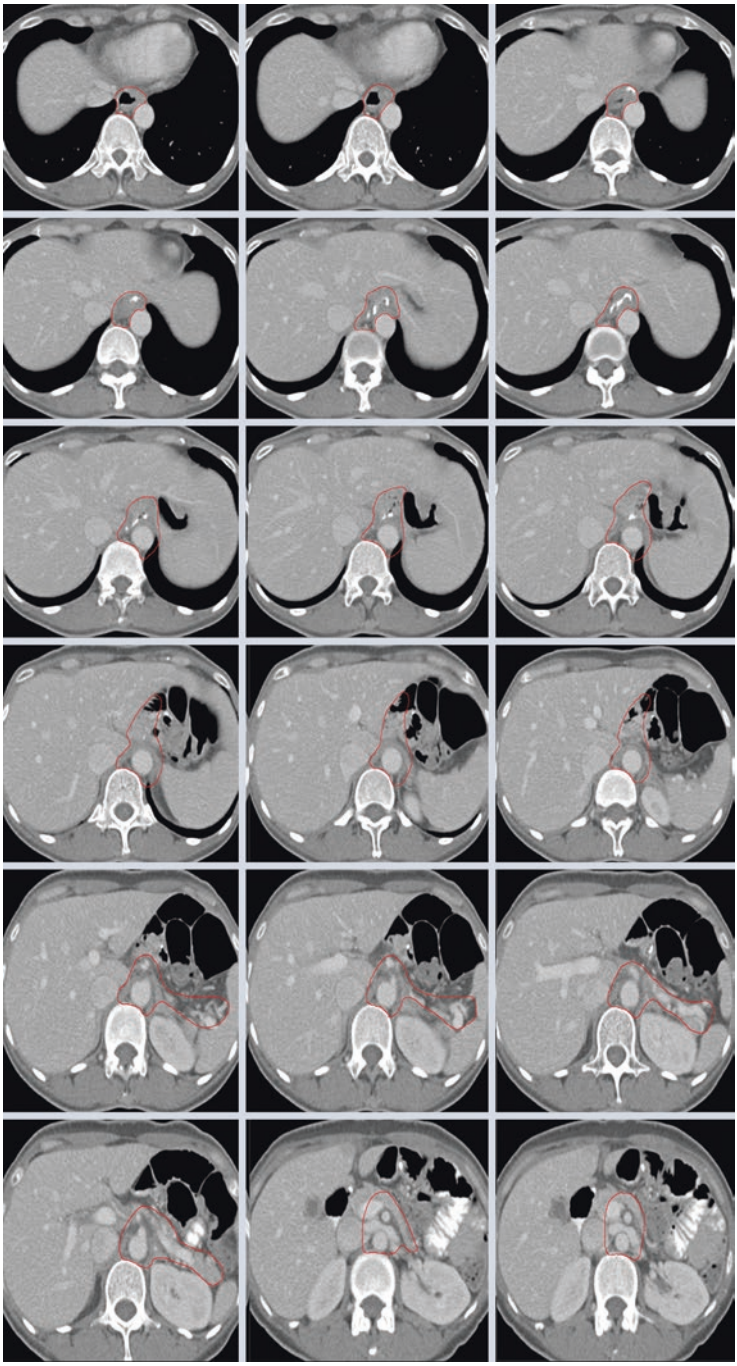
[c]Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2) and at least 10–15 nodes are examined pathologically

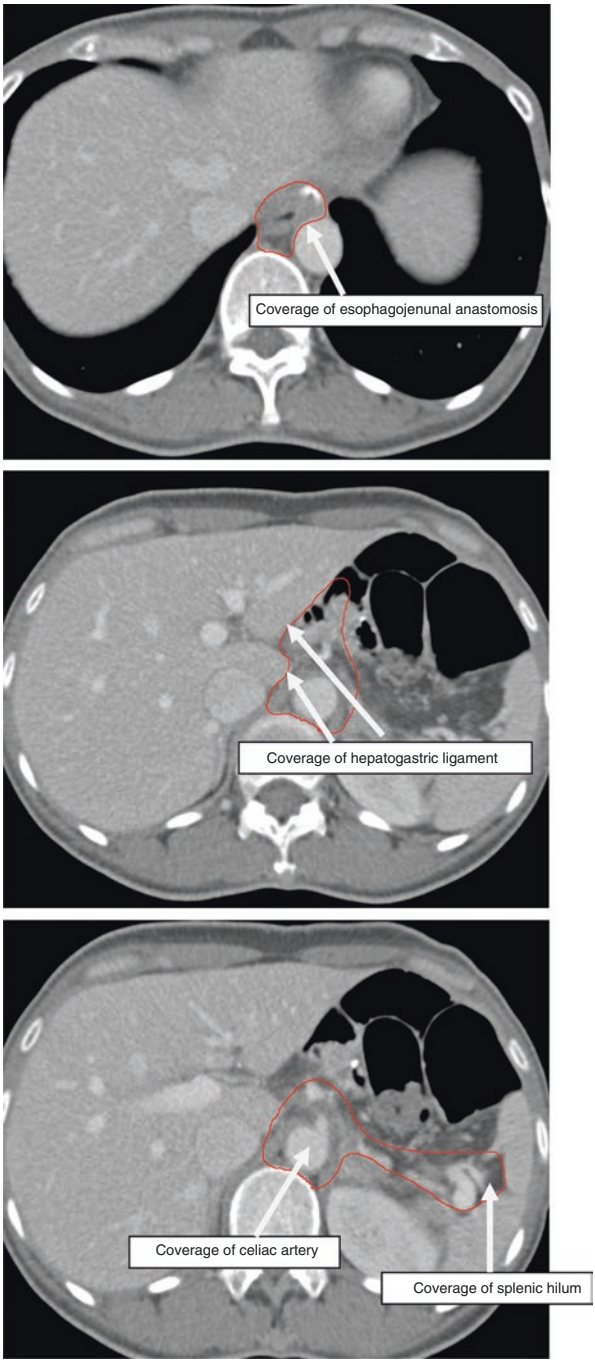


	Paraesophageal Nodes			Splenic Hilar Nodes
	Periesophageal Nodes			Pancreaticoduodenal Nodes
	Gastric remnant/perigastric Nodes			Celiac Nodes
	Portahepatic Nodes			Superior mesenteric nodes
	Nodes along the splenic artery			Duodenum

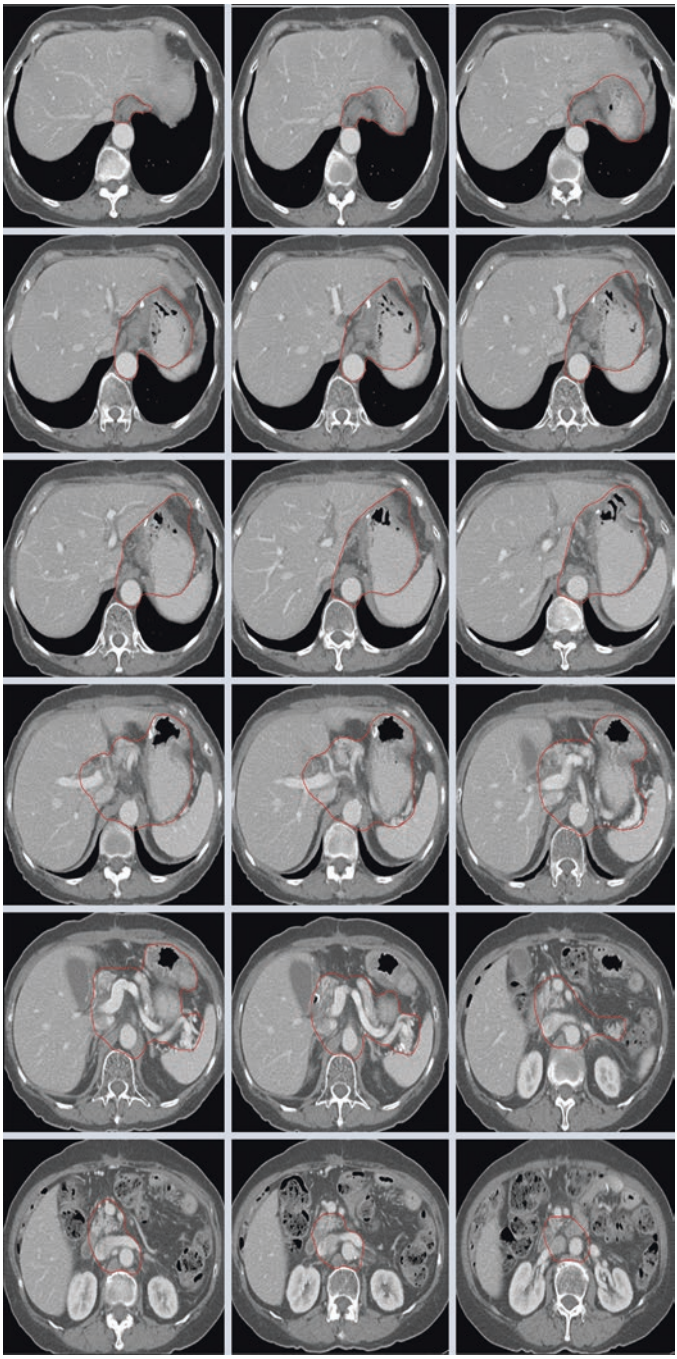
Fig. 15.4 Nodal distribution and clinical target volumes for adjuvant radiotherapy for gastric cancer

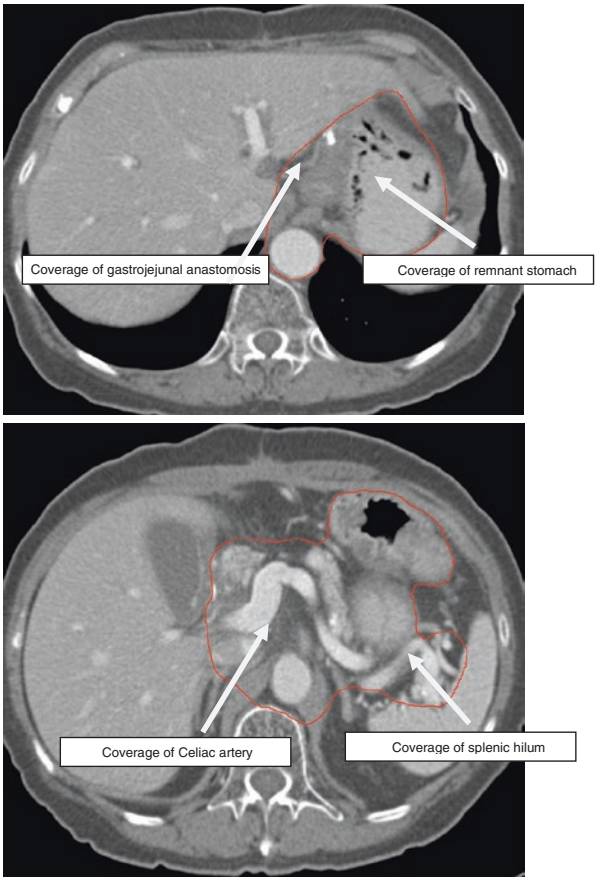
15.4 Clinical Target Volumes for a Patient with T1N1M0 Adenocarcinoma of the Gastric Cardia Post Total Gastrectomy



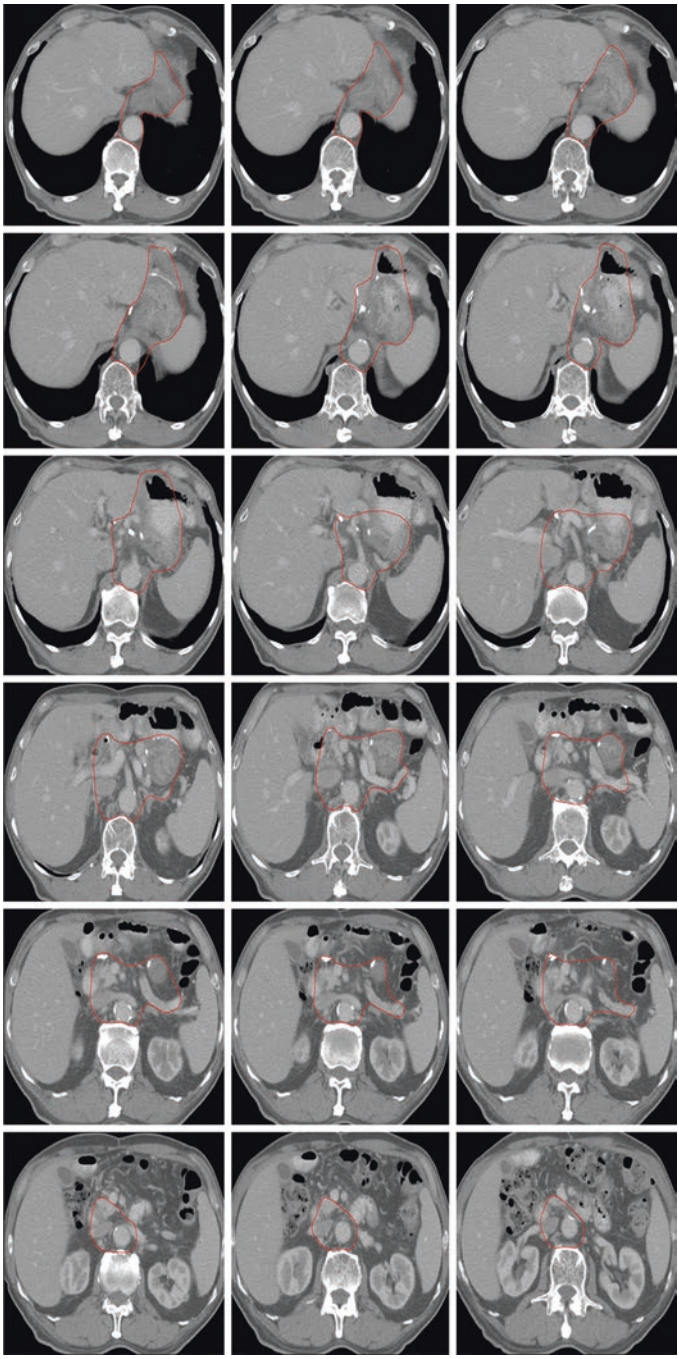

Coverage of esophagojenunal anastomosis
Coverage of hepatogastric ligament
Coverage of celiac artery
Coverage of splenic hilum

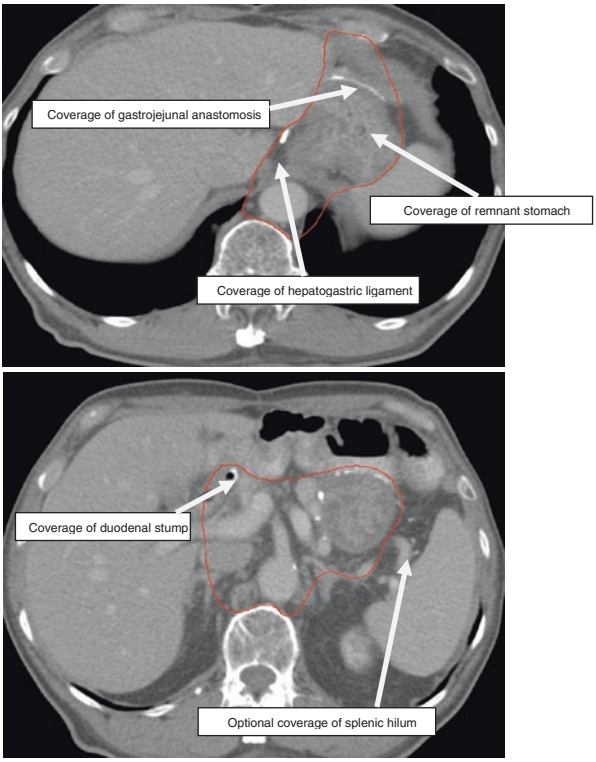
15.5 Clinical Target Volumes for a Patient with T3N3M0 Adenocarcinoma of the Gastric Body Post Distal Gastrectomy




Coverage of gastrojejunal anastomosis
Coverage of remnant stomach
Coverage of Celiac artery
Coverage of splenic hilum

15.6 Clinical Target Volumes for a Patient with T2N1M0 Adenocarcinoma of the Antrum/Pylorus Post Distal Gastrectomy





15.7 Plan Assessment

- In advanced cases, we typically prioritise normal structure constraints, specifically spinal cord, kidneys, and liver over full coverage of the tumour.
- Ideally, when using 3D conformal technique, 100% of PTV_{45} should receive ≥42.75 Gy (95% of prescribed dose) as per ICRU 62. If using IMRT, 98% of PTV should receive ≥42.75 Gy (95% of prescribed dose) as per ICRU 83.
- Critical normal organs at risk (OAR) surrounding the CTV need to be outlined. Dose constraints are outlined in Table 15.9.

Table 15.10: From the above trials, it may be argued that adjuvant chemoradiotherapy should be reserved for patients with involved margins, pT3 or T4, less than D2 resection. In ARTIST trial, patients with node-positive disease benefited from addition of radiotherapy but this benefit was not demonstrated in ARTIST II.

Table 15.9 Dose limitations of OAR in radiation therapy for upper abdominal malignancies

OAR	Dose limitation	End point	Rate (%)
Spinal cord	• Dmax = 50 • Dmax = 60 • Dmax = 69	Myelopathy	• 0.2 • 6 • 50
Whole liver	• Mean dose 30–32 • Mean dose <42	Classical RILD	• <5 • <50
Small intestine	• V45 < 195 cc (Entire potential space within peritoneal cavity)	Grade ≥ 3 acute toxicity	• <10
Heart	• Mean dose <26 (Pericardium) • V30 < 46% (pericardium) • V25 < 10% (whole heart)	Pericarditis Long-term cardiac mortality	• <15% • <15% • <1
Bilateral whole kidneys	• Mean dose <15–18 • Mean dose <28	Clinically relevant renal dysfunction	• <5 • <50

Table 15.10 Treatment approaches

Trials	Year	*N*	Arms			OS (%)	OS median	HR	Notes
Adjuvant chemoradiotherapy (CRT)									
INT0116 [8]	2001, 2012	556	1: Surgery			41 (3-year)	27 months	1.32 $P = 0.005$	10% D2 surgery
			2: Surgery	→	Adjuvant CRT (5FU)	50	36 months		
ARTIST [9]	2012, 2015	458	1: D2 surgery	→	Adjuvant Chemo (XP) × 6 cycles	73 (5-year)	NR	NS	All R0 resection; No SS OS difference; Improved DFS for node-positive disease and intestinal histology
			2: D2 Surgery	→	XP x 2 cycles → CRT → XP × 2 cycles	75	NR		
ARTIST II [10]	2021	546	1: D2 surgery	→	S1 for 1 year	3-Year DFS 65	NR	S1 vs. SOX: 0.692 $P = 0.042$	All node-positive Adjuvant SOX or SOXRT effective in prolonging DFS compared to adjuvant SOX alone
			2: D2 surgery	→	SOX × 6 months	74	NR		
			3: D2 surgery	→	SOX × 2 months → S1/RT → SOX × 4 months	73	NR	SOX vs. SOXRT: 0.724 $P = 0.074$	

(continued)

Table 15.10 (continued)

Trials	Year	*N*	Arms					OS (%)	OS median	HR	Notes
Perioperative											
MAGIC [11]	2006	503	1: Surgery					23 (5-year)	18 months	0.75 $P = 0.009$	Chemo: ECF
			2. Chemo	→	Surgery	→	Chemo	36	30 months		
CRITICS [12]	2018	788	1: Chemo	→	Surgery	→	Chemo	41 (5-year)	43 months	NS	Chemo: ECF or ECX NS difference in OS or toxicity
			2: Chemo	→	Surgery	→	Adjuvant CRT	41	37 months		
Adjuvant chemotherapy											
ACTS-GC [13]	2007	1059	1: Surgery					70 (3-year)		0.68 $P = 0.003$	East asian population
			2: Surgery	→	Chemo (S1)			80			
CLASSIC [14]	2012	1035	1: Surgery					70 (5-year)	NR	0.66 $P = 0.0015$	China, South korean, Taiwan
			2: Surgery	→	Chemo (CapeOx)			78	NR		
Neoadjuvant											
TOPGEAR			1: Chemo	→	Surgery						Recruiting
			2: ChemoRT	→	Surgery						
CRITICS II			1: Chemo	→	Surgery						Recruiting
			2: Chemo	→	ChemoRT	→	Surgery				
			3: CRT	→	Surgery						

N number of recruited patients, *OS* overall survival, *DFS* disease-free survival, *HR* hazard ratio, *SS* statistically significant, *NS* not statistically significant, *NR* not reported, *S1* tegafur/gimeracil/steracil, *ECF* epirubicin/cisplatin/5-FU, *ECX* epirubicin/cisplatin/xeloda

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Pancreatic Cancer

16

Marsha Reyngold and Christopher Crane

Contents

16.1 General Principles of Target Delineation and Planning

- Intensity modulated radiation therapy (IMRT) is becoming a standard technique for treatment of pancreatic adenocarcinoma in a variety of settings (neoadjuvant, adjuvant, and definitive). 3D-CRT may be appropriate for palliation and in the neoadjuvant setting, as long as the appropriate volume can be treated to the target dose while respecting normal tissue constraints. Ablative approaches in the definitive setting require the use of stereotactic body radiotherapy (SBRT) or image-guided techniques.
- IV contrast-enhanced pancreatic protocol simulation CT helps with accurate target and organ-at-risk delineation for all settings. Unless contraindicated, it is particularly useful for treating in the context of surgically altered anatomy and is critical for doses exceeding 50 Gy in EQD2. Typical pancreas protocol IV contrast administration consists of two phases with 150 cc of iodinated contrast medium administered at the rate of 5 cc/s with 35 s (late arterial) and 90 s (portal venous) delay from start of scan.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_16

- Motion management helps to lower doses to organs at risk (OARs) while maximizing target coverage and is required for any ablative approaches. Gating (whether deep-inspirational breath hold or expiratory gating) is preferred, but an internal target volume (ITV) approach may be used as an alternative based patient factors and available technology. Gating requires metal fiducials or metal stent.
- Patients are immobilized in a custom alpha-cradle with arms extended above the head if tolerable.
- Suggested target volumes and relevant OARs are listed in the following tables, organized by setting/dose.
- Ablative and non-ablative fractionation schemes may be appropriate in a particular setting based on the treatment intent, available technology, and patient anatomy.
- Treatment of **high-risk resectable or borderline resectable** disease with preoperative intent requires lower doses, and therefore, less complex technology, but attention should be paid to adequate margins to fully encompass all microscopic disease as well as radiographically occult extension of disease along the vasculature (Table 16.1). Fractionation schemes including 25 Gy in 5 fractions, 30 Gy in 10 fractions, 36 Gy in 12 fractions, and 50.4 Gy in 28 fractions may be appropriate.
- **Unresectable tumors** should be treated with ablative doses (BED10 $\geq$ 100 Gy) if motion management techniques and image-guidance are available (Table 16.2). The choice of the fractionation scheme is often driven by the available technology. However, it is critical that the trend for fewer fractions, which is in part driven by the resource-intensive nature of stereotactic planning and delivery, is balanced by radiobiologic and dosimetric considerations and results in a dose that is ablative (BED10 $\geq$ 100 Gy) [1]. Due to the proximity of the radiosensitive luminal GI tract OARs to the target, the ability to achieve an ablative dose often requires hypofractionated courses that exceed five fractions. We recommend

Table 16.1 Target volumes for treatment in the neoadjuvant setting for borderline resectable disease (see Fig. 16.1)

Target volumes	Definition and description
GTV	all gross disease on imaging, including the primary tumor (typically hypointense), paying particular attention to the extension along the vessels, and all suspicious nodes
ITV-optional	If using the ITV approach, use the guidelines for GTV delineation on all phases of the 4D-CT
CTV	Given the infiltrative nature of PDAC, adequate margin is critical, and should include at least 1 cm uniform expansion on all gross disease + coverage of CA and SMA basins + additional margin along vessels if there is any uncertainty regarding tumor extension + coverage of splenic hilum for body/tail lesions + optional coverage of porta hepatis basins for head of the pancreas lesions
PTV	PTV margin is based on the motion management technique used (if any) and should be at least 0.5 cm. For cases treated with free breathing (FB) and without an ITV, expansions of 1–1.5 cm in the superior-inferior dimension is recommended

Table 16.2 Target volumes for neoadjuvant/definitive setting for unresectable disease (see Fig. 16.2)

Target volumes	Definition and description
GTV	All gross disease on imaging, including the primary tumor (typically hypointense), paying particular attention to the extension along the vessels, and all suspicious nodes
ITV-optional	If using the ITV approach, use the guidelines for GTV delineation on all phases of the 4D-CT
$CTV_{high\ dose}$	Corresponds to GTV or ITV if used without additional margin
$CTV_{microscopic\ dose}$	Given the infiltrative nature of PDAC, adequate margin is critical, and should include at least 1 cm uniform expansion on all gross disease (to ensure coverage of **peripancreatic** nodes) + coverage of **CA** and **SMA** basins + splenic hilum basin (body/tail lesions only) + additional margin along vessels if there is any uncertainty regarding tumor extension Optional: Coverage of the porta hepatis basin (for head of the pancreas tumors)
$PTV_{high\ dose}$	Uniform expansion 0–0.5 cm followed by **subtraction** of any overlapping critical OAR with additional safety margin as below. **Ablative doses are preferred when possible** • For 56 Gy in 28 fractions, or 33 Gy in 5 fractions Subtract stomach and small bowel without additional margin • For 50 Gy in 10 fractions, 67.5 Gy in 15 fractions or 75 Gy in 25 fractions Subtract stomach and small bowel with an additional uniform expansion margin of 0.5 cm. Can use 0.7 cm for long interface between the target and the given OAR (see Fig. 16.2)
$PTV_{microscopic\ dose}$	PTV margin is based on the motion management technique used (if any) and should be at least 0.5 cm. For cases treated with FB and without an ITV, expansions of 1–1.5 cm in the superior-inferior dimension is recommended
Notable OAR volumes	**Applicable for doses ≥ 60 Gy in 25 fractions (or BED equivalent)**
Stomach-proximal duodenum PRV	Stomach and duodenum segments 1 and 2 + 0.3 cm (0.5 cm for long interface between target and OAR)
Small bowel PRV	All other small bowel + 0.3 cm (0.5 cm for long interface between target and OAR)

See [1] for more detailed information on contouring for ablative cases

75 Gy in 25 fractions for tumors within 1 cm of the OARs and 67.5 Gy in 15 fractions for tumors more than 1 cm. 50 Gy in five fractions may be selectively used for tumors >2 cm away from the OARs. Extensive contact between tumor and OARs may preclude effective target coverage with the treatment dose. In those cases (either as determined after attempted ablative treatment planning or empirically judged based on the experience of the treating radiation oncology), non-ablative treatments of 50.4–56 Gy in 28 fractions or low dose SBRT approach of 33Gy in 5 fractions may be used.

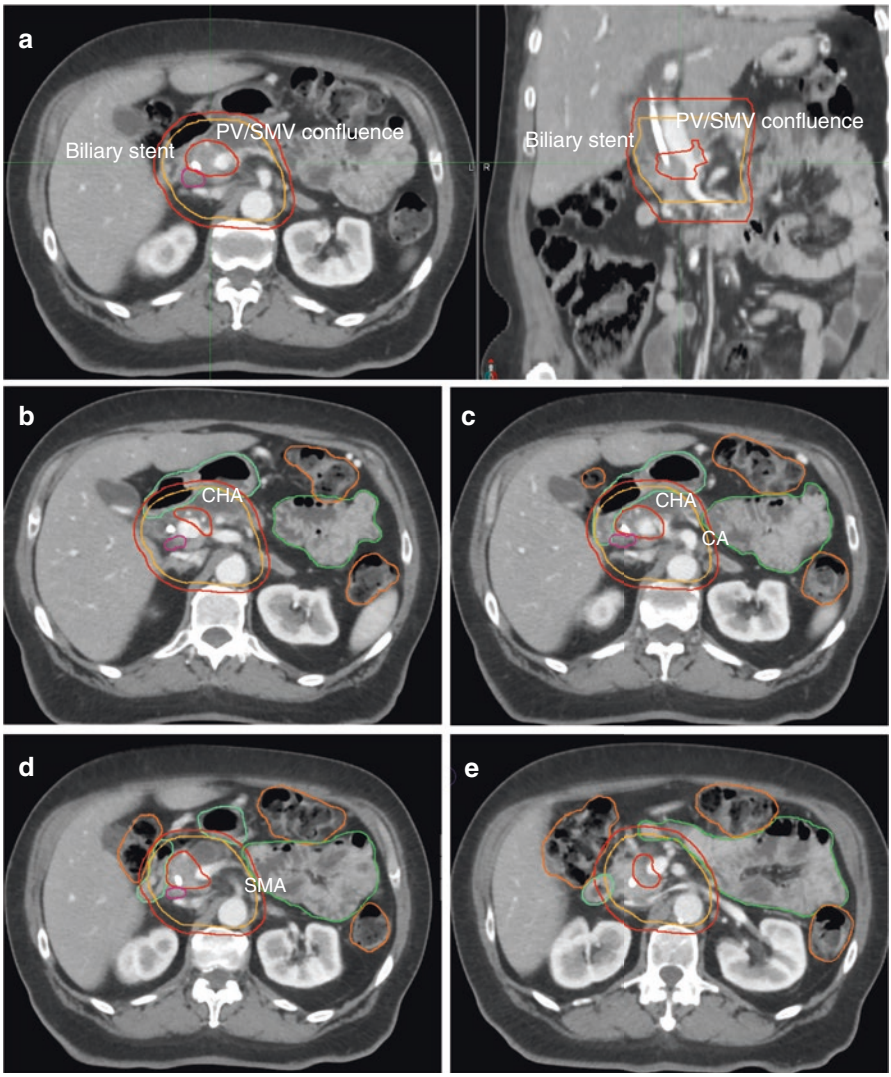

Fig. 16.1 Volumes for a 2.9 cm adenocarcinoma in the head of the pancreas causing biliary and pancreatic duct dilatation s/p placement of the plastic biliary drain, partial encasement of the PV/SMV and possible abutment of the common hepatic artery (CHA) with a 1.6 × 1.1 cm portacaval node treated with pre-operative intent. Volumes shown include GTV (red), GTV node (maroon), CTV (gold), PTV (red), stomach/proximal duodenum (light green), small bowel (dark green), large bowel (orange). (**a**) Axial and coronal views at the isocenter. Note asymmetrical margins with 1.5 cm superior-inferior margin to account for diaphragmatic motion used for treatment with free breathing. (**b**–**e**) Axial slices from most superior to most inferior aspects of the GTV. Given some haziness around CHA it was included in the GTV (**b**). CTV includes peripancreatic, CA (**c**), SMA (**d**, **e**) and porta hepatis nodes

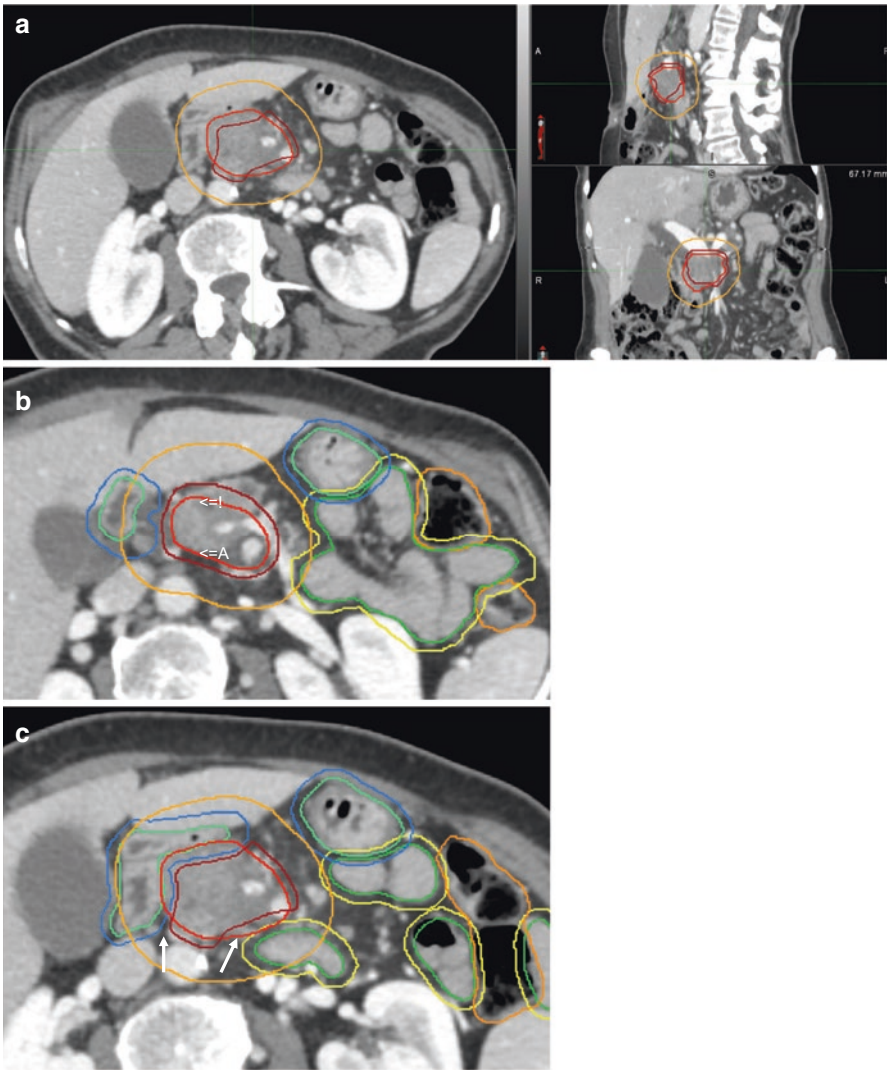

Fig. 16.2 Volumes for a 3.8 cm pancreatic head tumor with near occlusion of the SMV, abutment of PV and tumor tracking along the SMA to the celiacomesenteric trunk treated definitively with 75 Gy in 25 fractions with daily CBCT guidance and DIBH. Volumes shown include GTV (red), PTVhigh dose (maroon), PTVmicroscopic dose (gold), stomach/proximal duodenum (light green), stomach/proximal duodenum PRV (blue), small bowel (dark green), small bowel PRV (yellow) and large bowel (orange). (**a**) Axial, sagittal and coronal views at the isocenter obtained in the arterial phase. Note the restricted margins compared to pre-op case. (**b**, **c**) Axial slices showing target and OAR contours. (**b**) Given the infiltrative nature of PDAC over-contouring of the GTV to include the surrounding pancreas parenchyma may be reasonable, especially when supported by additional diagnostic imaging and/or other sources of data. (**c**) In regions of direct contact or close proximity of the GTV to a critical OAR, the PTV is designed to exclude the OAR with an additional safety margin that exceeds PRV expansion margin (arrows)

- For **adjuvant** field design, the RTOG 0848 contouring atlas provides a stepwise contouring approach based on identifiable regions of interest (ROI) that were chosen on the basis of ease of identification and reproducibility on imaging studies [2]. However, smaller fields targeting the post-operative bed, CA and SMA may be appropriate in clinical scenarios with dose-limiting OARs (Table 16.3).
- Suggested dose constraints are listed in Table 16.4.

Table 16.3 Target volumes for treatment in the adjuvant setting (see Fig. 16.3)

Target volumes	Definition and description
GTV	Not applicable
CTV	Post-operative bed and pancreatojejunostomy (PJ) Nodal basins including peripancreatic, CA, SMA, paraaortic, PV (head tumors), and splenic (body/tail) RTOG 0848 stepwise contouring approach to create CTV from ROIs ROIs: • **CA** (proximal 1–1.5 cm) • **SMA** (proximal 2.5–3 cm) • Portal vein (**PV**: starts at confluence of SMV and splenic vein) • **PJ** • **Aorta** (superiorly to most cephalad of CA, PV, or PJ contours; inferiorly to bottom L2, or as low as L3 to cover pre-op GTV) • **Tumor bed** (based on review of pre-op imaging, pathology report, surgical clips if placed for that purpose only) Expansions: • Expand PV, PJ, CA, SMA by 1.0 cm • Expand aorta by 2.5–3.0 cm on the right, 1.0 cm on the left, 2–2.5 cm anteriorly, 0.2 cm posteriorly **CTV** = Expansions 1 + 2, confirm that tumor bed is encompassed
PTV	PTV margin is based on the motion management technique used (if any) and should be at least 0.5 cm. For cases treated with FB and without an ITV, expansions of 1–1.5 cm in the superior-inferior dimension is recommended

Table 16.4 Suggested dose constraints

Rx	Small bowel	Small bowel PRV	Stomach and duodenum	Stomach and duodenum PRV	Large bowel	Esophagus	Common bile and hepatic ducts	Liver*	Cord	Kidneys
3 fractions	Dmax ≤23 Gy **G** Dmax ≤27 Gy **L** (30 Gy if PTV overlap) **L** D5cc ≤ 21 Gy	D2cc ≤23 Gy **G** D2cc ≤27 Gy **L**	Dmax ≤23 Gy **G** Dmax ≤27 Gy **L** (30 Gy if PTV overlap) **L** D5cc ≤21 Gy **L**	D2cc ≤23 Gy	Dmax ≤25 Gy **G** Dmax ≤30 Gy **L** D5cc ≤ 25 Gy **L**	Dmax ≤25 Gy	Dmax ≤40 Gy	700cc <15 Gy **L** Dmean <16 Gy **L**	Dmax <18 Gy V15 Gy <10cc	Each: V15 Gy <67% **G** Both: V10 Gy <50% **L** *Single kidney*: V10 Gy <33% **L**
5 fractions	Dmax ≤28 Gy **G** V20 Gy = 100cc **G** Dmax ≤30 Gy **L** (33 Gy if PTV overlap) **L** D5cc ≤25 Gy **L**	D2cc ≤28 Gy **G** D2cc ≤30 Gy **L**	Dmax ≤28 Gy **G** Dmax ≤30 Gy **L** (33 Gy if PTV overlap) **L** D5cc ≤25 Gy **L**	D2cc ≤28 Gy	Dmax ≤30 Gy **G** Dmax ≤33 Gy **L** D5cc ≤30 Gy **L**	Dmax ≤30 Gy	Dmax ≤55 Gy	700cc <15 Gy **L** Dmean <16 Gy **L**	Dmax <18 Gy V15 Gy <10cc	Each: V15 Gy <67% **G** Both: V10 Gy <50% **L** *Single kidney*: V10 Gy <33% **L**
8–10 fractions	Dmax ≤40 Gy **L**	D2cc ≤40 Gy	Dmax ≤40 Gy **L**	D2cc ≤40 Gy	Dmax ≤45 Gy **L**	Dmax ≤45 Gy	Dmax ≤70 Gy	700cc <20 Gy **L** Dmean <20 Gy **L** V20 Gy <33% **G**	Dmax <35 Gy	Each: V20 Gy <33% **G** Both: V20 Gy <50% **L** *Single kidney*: V20 Gy <33% **L**

(continued)

Table 16.4 (continued)

Rx	Small bowel	Small bowel PRV	Stomach and duodenum	Stomach and duodenum PRV	Large bowel	Esophagus	Common bile and hepatic ducts	Liver*	Cord	Kidneys
12–14 fractions	Dmax ≤40 Gy **L** V36 Gy = 40cc **G**	D2cc ≤40 Gy	Dmax ≤40 Gy **L** V36 Gy ≤40cc **G**	D2cc ≤40 Gy	Dmax ≤45 Gy **L**	Dmax ≤45 Gy	Dmax ≤70 Gy	700cc <20 Gy **L** Dmean <20 Gy **L** V20 Gy <33% **G**	Dmax <35 Gy	Each: V20 Gy <33% **G** Both: V20 Gy <50% **L** *Single kidney*: V20 Gy <33% **L**
15 fractions	Dmax ≤45 Gy **L** V37.5 Gy ≤40cc **G**	D2cc ≤45 Gy	Dmax ≤45 Gy **L** V37.5 Gy ≤ 40cc **G**	D2cc ≤45 Gy	Dmax ≤50 Gy **L**	Dmax ≤50 Gy	Dmax ≤70 Gy	700cc <24 Gy **L** Dmean <24 Gy **L**	Dmax <35 Gy	Each: V20 Gy <33% **G** Both: V20 Gy <50% **L** *Single kidney*: V20 Gy <33% **L**
25–28 fractions	Dmax ≤60 Gy **L** V50 Gy ≤40cc **G**	D2cc ≤60 Gy	Dmax ≤60 Gy **L** V50 Gy ≤40cc **L**	D2cc ≤60 Gy	Dmax ≤65 Gy **L**	Dmax ≤65 Gy	Dmax ≤80 Gy	700cc <28 Gy **L** Dmean <28 Gy **L**	Dmax <45 Gy	Each: V20 Gy <33% **G** Both: V20 Gy <50% **L** *Single kidney*: V20 Gy <33% **L**

L—Limit, indicating a dose that cannot be exceeded under any circumstances; **G**—Guideline, indicating a suggested constraint when coverage is not compromised, compromised

*If no cirrhosis, otherwise use lower constraints

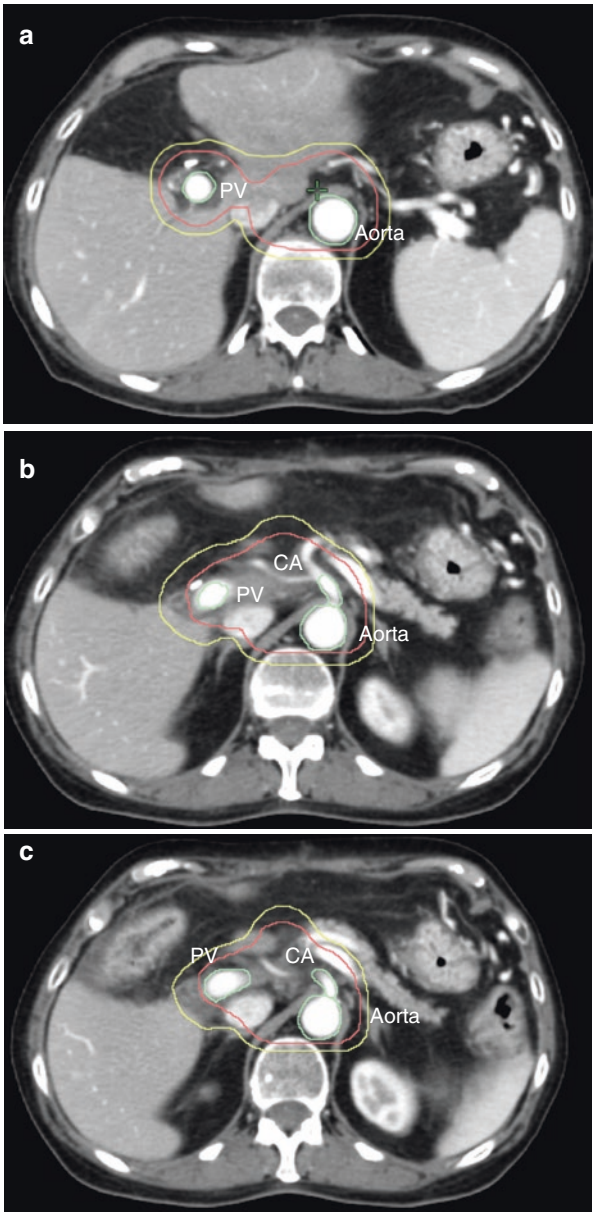

Fig. 16.3 Volumes for a patient with pT3N1 adenocarcinoma of the head of the pancreas s/p pancreaticoduodenectomy. Volumes shown include ROIs designated in the contouring atlas (light green), CTV (pink) and PTV (yellow). (**a**–**f**) Representative axial slices are shown. (**g**) Representative parasagittal and corresponding axial slices illustrate superior and inferior aspects of the PTV

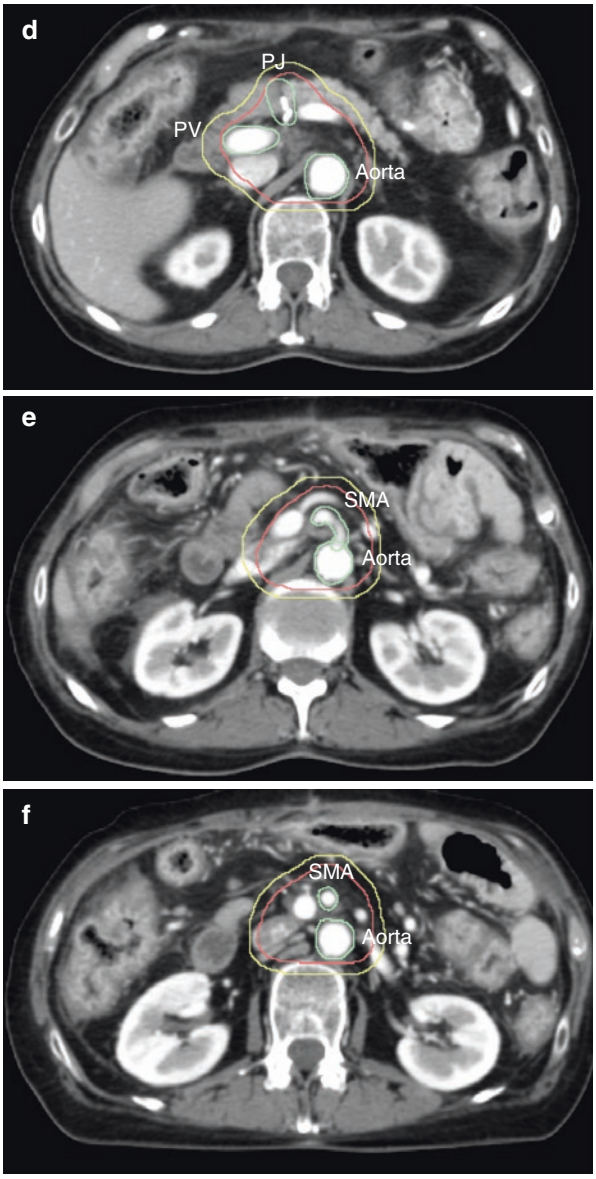

Fig. 16.3 (continued)

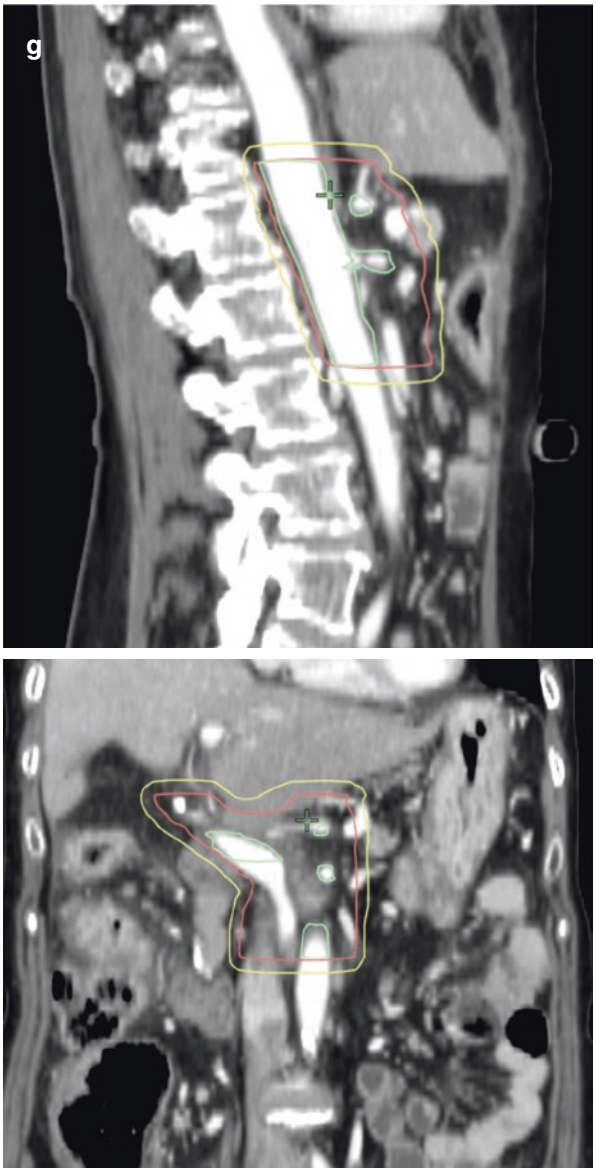

Fig. 16.3 (continued)

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Hepatocellular Carcinoma

17

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_17

17.1 General Principles of Planning and Target Delineation

- Step-and-shoot intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy, with limited number or range of gantry angles to reduce low-dose spread of normal liver, have been the standard techniques for HCC. SBRT with ≤5–6 fractions is preferable in cases with safe bowel sparing, available facilities of high dose rate, adequate immobilization, and image guidance. Hypofractionated treatment is sometimes used due to the proximity of targeted tumor to luminal gastrointestinal tissues.
- In addition to a history and physical, laboratory examinations, a liver function assessment and imaging studies should be obtained for diagnosis, staging, and planning. Patients should undergo a contrast-enhanced (preferably tri-phasic [arterial, portal-venous, and delayed phases]) computed tomography (CT) scan of the liver, with 3–5 mm slice thickness. Multi-phase dynamic magnetic resonance imaging (MRI) scans can be used if the required breath hold for image acquisition is possible or CT contrast is contraindicated. With image fusion, MRI scans may be complimentary to CT scans for target delineation. Positron emission tomography (PET) images with 18F-fluorodeoxyglucose (18F-FDG) or other tracers, such as 11C-acetate and 11C-choline, may be helpful in localizing the viable tumor(s) of individual cases such as patients with residual/recurrent tumor(s) at previous lipiodol retention and/or radiofrequency ablation areas.
- Half-body or whole-body immobilization with respiratory control is needed for better reproducibility. Devices such as a vacuum bag or chest board may be used to immobilize a patient, preferably with arms up, during simulation and used throughout the course of treatment. This will enable reproducibility and allow spatial freedom of beam directions. The systems for immobilization should be made of materials not attenuating radiation doses and should not interfere with the gantry positions that may be required for coplanar and non-coplanar beams.
- Respiratory motion management using a number of techniques is frequently needed to minimize imaging artifacts from changes in liver positioin due to breathing. Active breath hold helps reduce the treated volume and is preferable to patients who can hold breath for more than 30 s. Abdominal compression is used for patients who could not tolerate breath hold and might result in deformation of abdomen or organ shape. Delineation of target volumes is most often done on multi-phasic, multi-modality images, obtained in breath hold (i.e., similar to diagnostic images for HCC). Image-guided radiation therapy (IGRT) is required to account for changes in the intra-/inter-fractional liver position. In patients who cannot tolerate breath control, the use of passive abdominal compression devices combined with four-dimensional CT (4DCT) provides information about internal organ motion and can compensate for liver position changes. Gated treatment takes longer duration for the selected inspiratory or expiratory window and may also be useful for patients that cannot tolerate breath control.
- CT simulation with IV contrast to obtain multi-phase imaging is required. This should be obtained with the patient in the treatment position and respiratory coordination. Fusion of the different phase images and/or diagnostic images will aid in the delineation of gross tumor volume (GTV). Usually the viable HCC is

best visualized (brightest) on the arterial-phase CT scan, with less enhancement seen relative to the liver on venous and delayed phase images. Portal-phase CT scan is used with the intrahepatic vessel distribution for anatomical boundaries of treated tumor, especially with the deformed liver shape under immobilization and respiratory control. Tumor invasion into the vascular structures is best observed on portal-venous phase CT scan. The extent of tumor invasion to inferior vena cava is better demonstrated on delayed-phase CT scan.

- Under specific circumstances for SBRT, only visible tumor will be targeted as GTV. More commonly, GTV would be enlarged to constitute the clinical target volume (CTV) based on the clinical risk of microscopic spread within the boundary of liver parenchyma, such as around previous radiofrequency ablation zone or embolized zone. CTV may fluctuate in size and position because of respiratory motion and organ dynamics. Suggested CTV for high-risk regions are detailed in Table 17.1 (CTVmacroscopic and CTVmicroscopic) (Figs. 17.1, 17.2, 17.3, and 17.4).

Table 17.1 Suggest target volumes at the GTV and CTV regions

Target volumes	Definition and description
GTV[a]	Liver tumor: Intrahepatic enhancing tumor on arterial-phase contrast CT with washout on venous- or delayed-phase CT
	Lipiodol retaining tumor: Lipiodol (white) contiguous to the enhancing tumor
	Ablated refractory tumor: Arterial enhancing tumor adjacent to the hypodense ablated zone
	Vascular tumor thrombus: Arterial enhancing thrombus with washout on venous-phase CT
CTVmacroscopic[a]	Liver tumor: The intrahepatic enhancing tumor on arterial-phase contrast CT
	Embolized zone contiguous to the enhancing tumor included in GTV
	Arterial enhancing tumor adjacent to the hypodense ablated zone
	Arterial enhancing vascular tumor thrombus
CTVmicroscopic (elective)[b] (optional according to clinical indication/protocol)	3–5 mm margin around intrahepatic GTV[c]
	2–3 mm margin around the tumor thrombus GTV within the vessel
	Bland thrombus adjacent to tumor thrombus GTV
	Radiofrequency ablation zone adjacent to GTV
	Embolized zone not directly adjacent to the GTV
	CTV should not cross natural barriers such as the surface/boundary of the liver
PTV	CTV (or GTV/CTVmacroscopic) + 5–20 mm (may be asymmetric), depending on immobilization and respiration control
	The internal organ motion and the setup error form the basis of PTV
	4DCT acquired from all respiratory phases may help define PTV and cover the extent of internal organ motion

[a]GTV/CTVmacroscopic. For example, to be treated to 45–54 Gy in 3–6 fractions. Note that the "safe" dose may need to be reduced if limited by normal tissues

[b]Elective/microscopic CTV. For example, to be treated to 24–30 Gy in 3–6 fractions. Note that author L.A.D. does not routinely recommend a microscopic CTV around the GTV

[c]The additional margin around the intrahepatic GTV may be treated to macroscopic/higher doses if safe

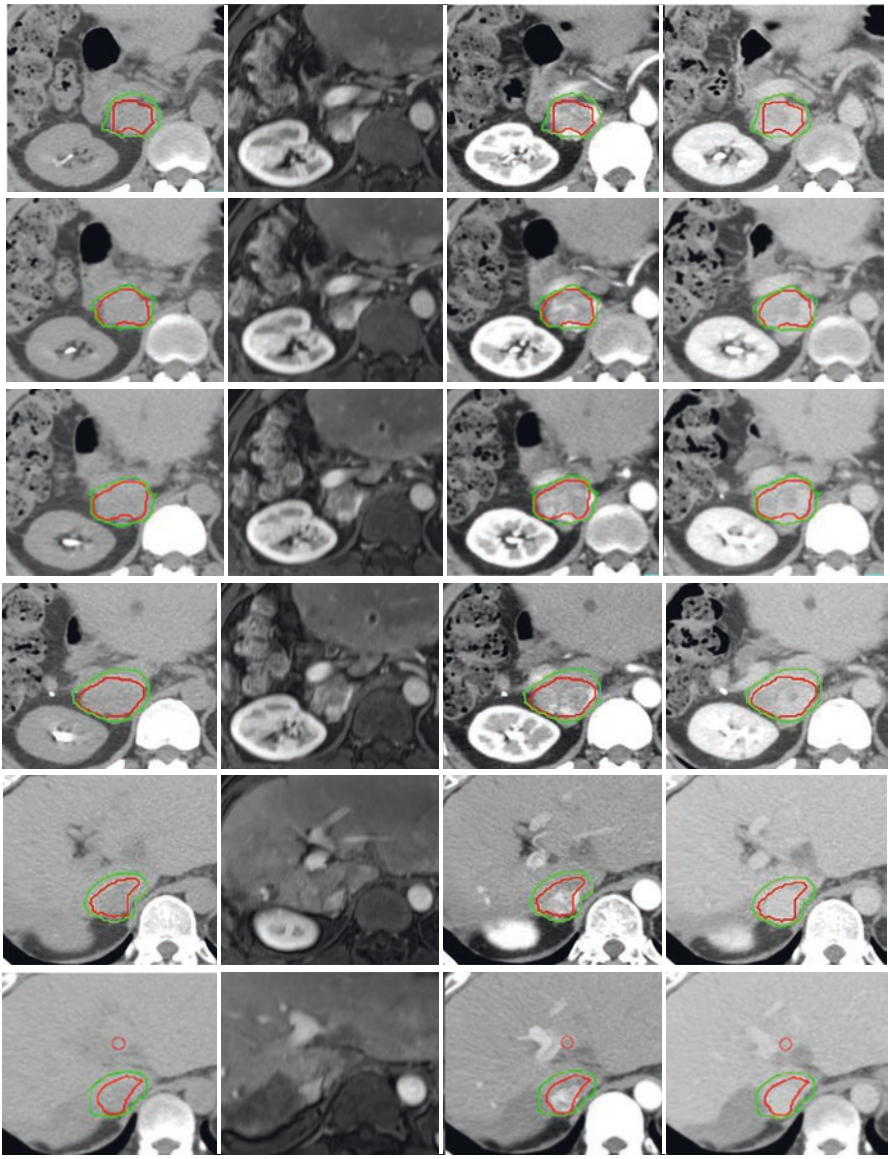

Fig. 17.1 Residual hepatocellular carcinoma after transcatheter arterial chemoembolization and radiofrequency ablation. Tri-phasic contrast-enhanced CT simulation (from left to right: no contrast phase, T1-weighted contrast-enhanced MRI image, arterial phase and venous [delayed] phases), obtained with breath-hold coordination for liver immobilization. The GTV (in red) includes the contrast enhancing tumor and the invaded IVC thrombosis. The CTV (in green) includes a 5-mm margin within liver boundary and 3-mm intravascular margin around the GTV

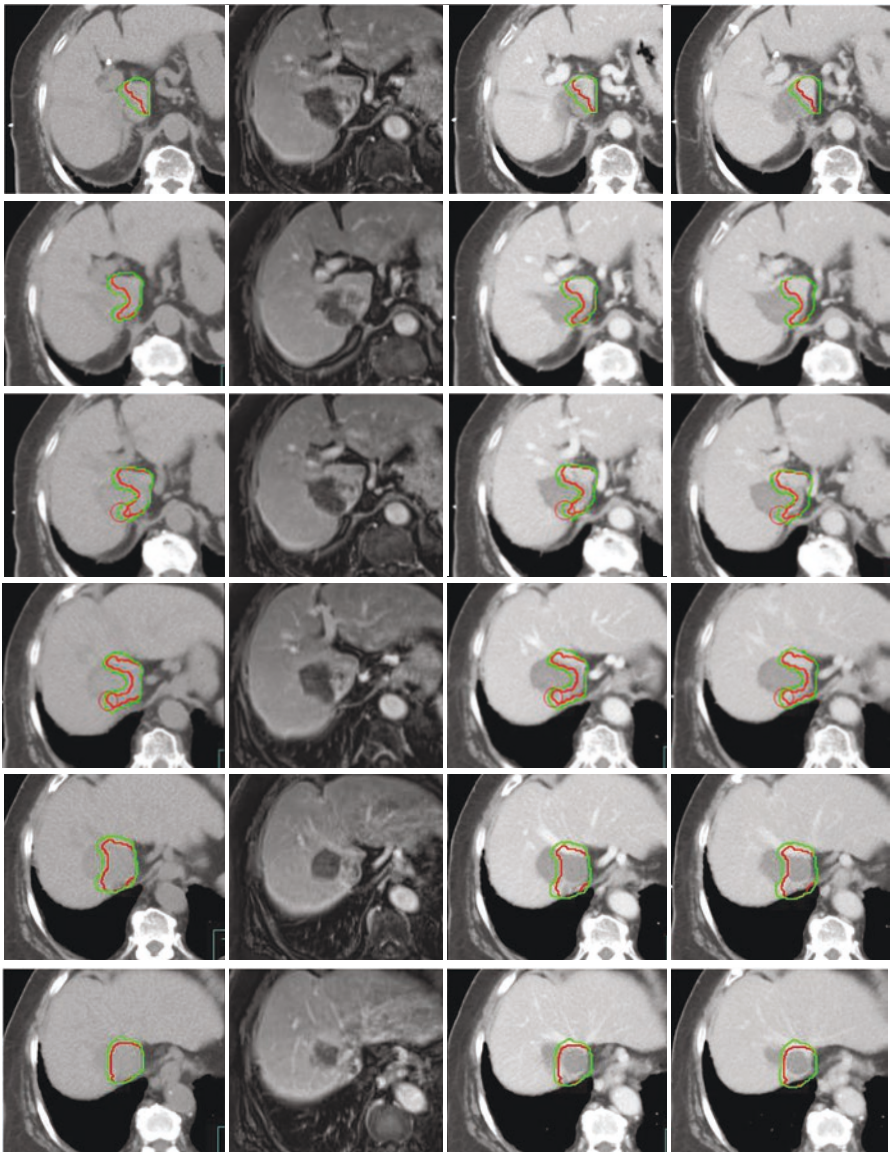

Fig. 17.2 Recurrent hepatocellular carcinoma with partial inferior vena cava (IVC) thrombosis after repeated radiofrequency ablation (RFA). Tri-phasic contrast-enhanced CT simulation (from left to right: no contrast phase, T1-weighted contrast-enhanced MRI image, arterial phase and venous [delayed] phases), obtained with breath-hold coordination for liver immobilization. The CTV (in green) includes the contrast enhancing tumor and the tumor thrombus (GTV in red) as well as a 5-mm margin around the GTV within liver boundary and previous radiofrequency ablated zone (if clinically needed)

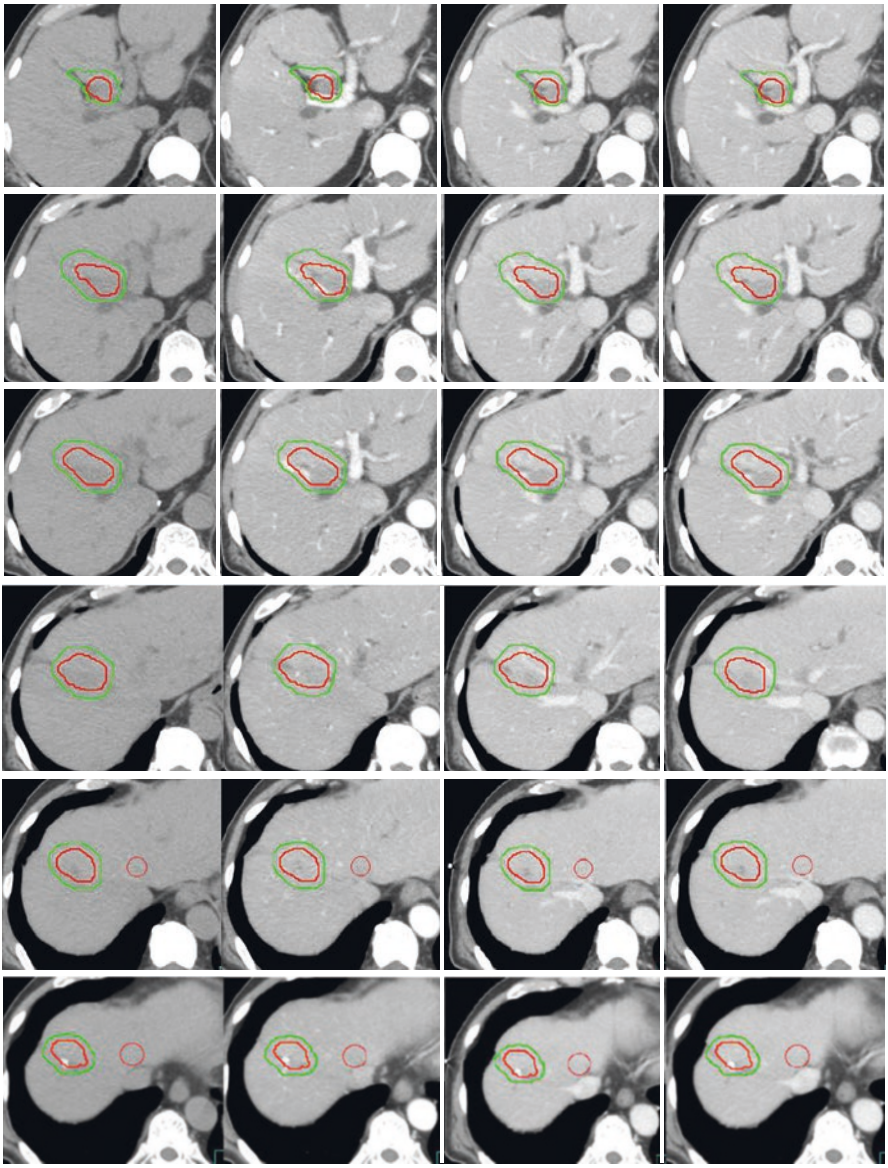

Fig. 17.3 Recurrent hepatocellular carcinoma after surgery and radiofrequency ablation (RFA) with high risk of bile duct injury by RFA. Tri-phasic contrast-enhanced CT simulation (from left to right: no contrast, arterial, portal, and venous [delayed] phases), obtained with breath-hold coordination for liver immobilization. The CTV (in green) includes the contrast enhancing tumor (GTV in red) and a 5-mm margin of liver parenchyma and 3-mm margin of intra-vascular space around the GTV

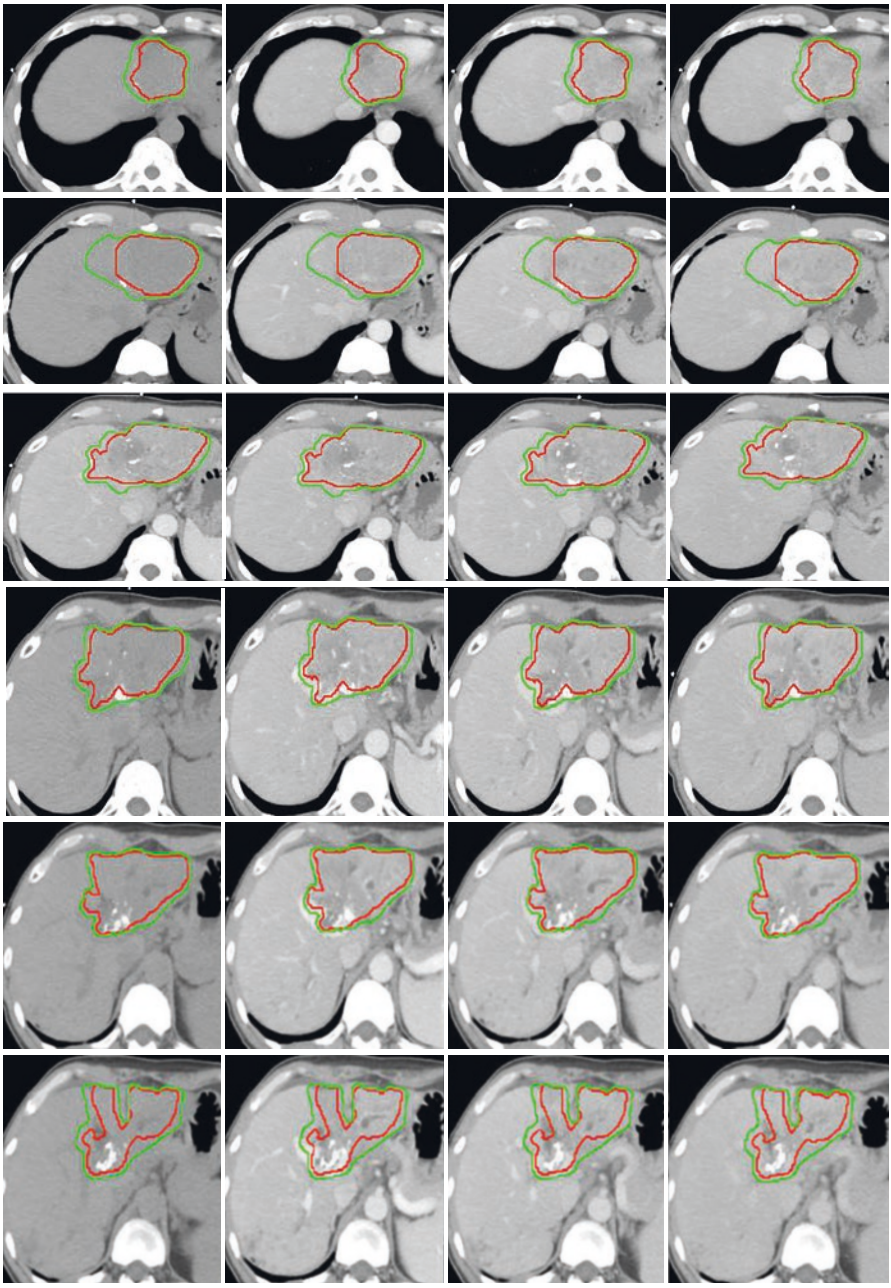

Fig. 17.4 Hepatocellular carcinoma refractory to sorafenib treatment with progression of portal vein and middle hepatic vein thromboses. Tri-phasic contrast-enhanced CT simulation (from left to right: no contrast, arterial, portal, and venous [delayed] phases), obtained on breath-hold coordination for liver immobilization. The CTV (in green) includes the contrast enhancing tumor (GTV in red) and a three-dimensional 5-mm margin around the GTV within liver boundary

Further Reading

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Rectal Cancer

18

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_18

18.1 Diagnostic Workup Relevant for Target Volume Delineation

- Physical exam is an important part of the staging and treatment planning process. For palpable tumors, note the distance to the anal verge. Sphincter function should be noted at the time of exam.
- For low-lying tumors, direct visualization is necessary to determine the relationship to the dentate line, as the dentate line is not palpable.
- Endorectal ultrasound (EUS) can be used to determine the depth of invasion of the primary tumor, as well as to assess the status of nearby lymph nodes, but it may under or over stage patients in approximately 20% of cases.
- MRI is now a standard imaging modality for preoperative staging to detect invasion into the mesorectal fat (T3) or adjacent structures (T4), to assess lymph node status, verify distance from the anal verge, and to assess operability with negative margins (Fig. 18.1).
- PET/CT can be helpful for delineating gross disease (Fig. 18.2). However, areas of low radiotracer uptake on PET/CT should not supercede physical, endoscopic, or CT/MRI findings.

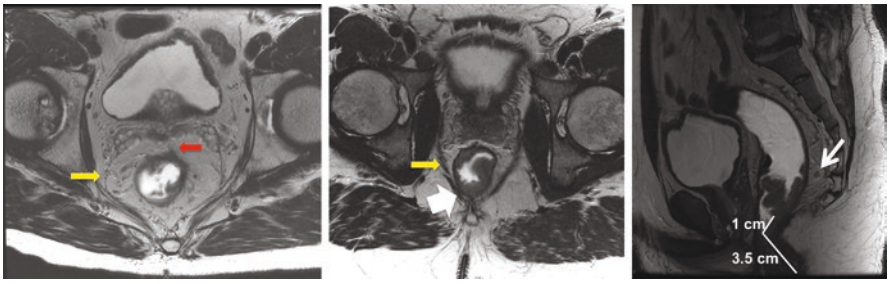

Fig. 18.1 Axial T2-weighted sequences without fat suppression for staging of rectal cancer. The mesorectal fat surrounds the rectum and is enclosed within the mesorectal fascia (yellow arrows). In the left panel, the tumor was staged as an early T3 tumor with minimal invasion into the perirectal fat. The distance from the mesorectal fascia is more than 1 cm (red arrow). In the middle panel, a more extensive example of a T3 tumor is shown with a tumor that approaches within 2 mm of the mesorectal fascia (large white arrow). In the right panel, a sagittal view is shown. A mesorectal lymph node is visible (thin white arrow). The estimated distance of the tumor from the anal verge is 4.5 cm

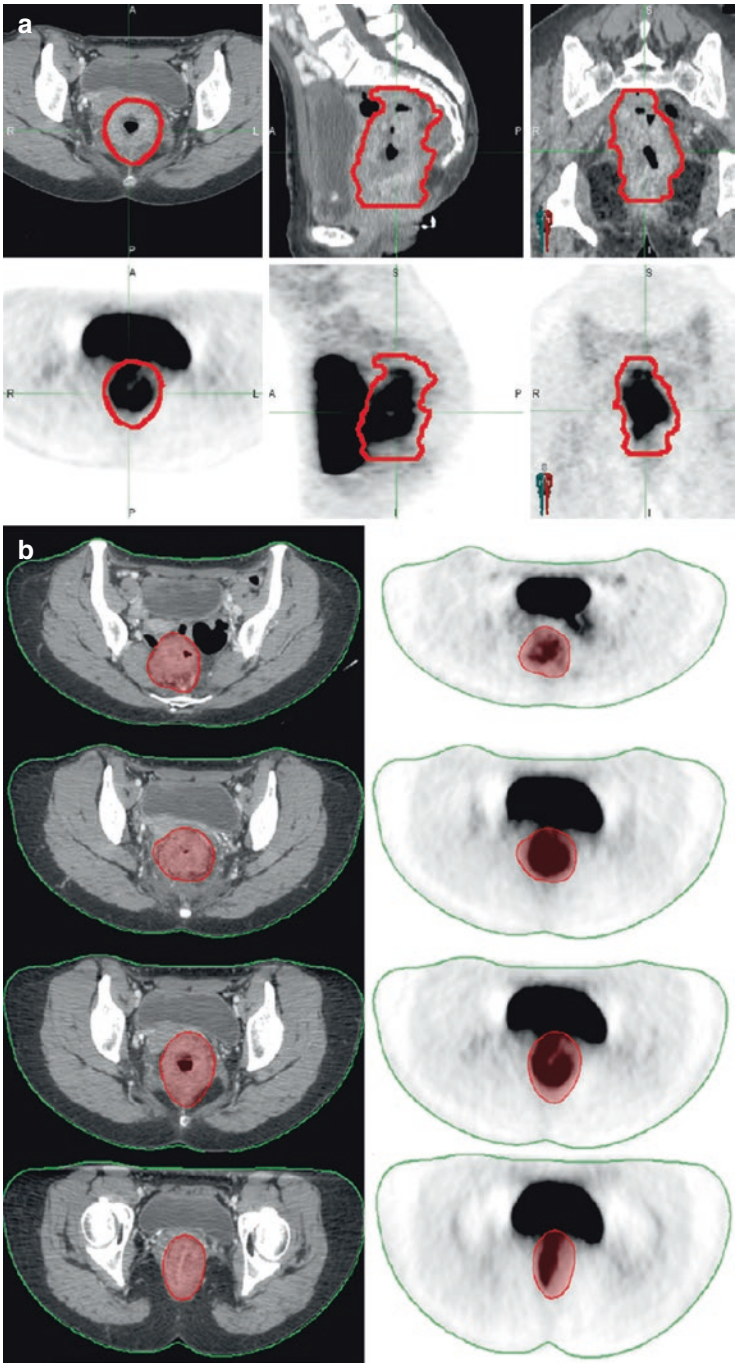

Fig. 18.2 A patient with clinical T4N0 rectal adenocarcinoma, with invasion into the cervix. Co-registered CT and PET images illustrate the utility of PET in target volume delineation. (**a**) The GTV (red) is seen on representative axial, sagittal, and coronal views, on both the treatment planning CT and PET. (**b**) Additional axial slices of the co-registered CT and PET are shown

18.2 Simulation and Daily Localization

- Most patients treated with 3D conformal radiotherapy can be simulated prone on a belly board to displace bowel. If IMRT is planned, we recommend supine positioning in a body mold to ensure setup reproducibility. A radio-opaque marker can be placed at the anal verge, and surgical scars should be wired.
- CT simulation with intravenous contrast and ≤3 mm slice thickness. Oral contrast may be helpful to delineate small bowel. PET/CT simulation or fusion with diagnostic PET/CT or MRI may aid in target delineation.
- Bladder filling/emptying may be considered, particularly if IMRT is used. A full bladder may limit the volume of bowel in the pelvis, whereas an empty bladder may be more reproducible.
- We recommend image guidance with daily orthogonal kilovoltage imaging and weekly cone-beam CT scans (to assess soft tissue) to verify alignment during treatment, depending on setup reproducibility.

18.3 Target Volume Delineation and Treatment Planning

- Prior to the cone-down volume, conventional 3D conformal radiotherapy for rectal cancer involves a PA field and two opposed lateral fields (Figs. 18.3 and 18.4).
- Traditional borders for the PA field are: *superior*—L5/S1 interspace; *inferior*—the inferior edge of the obturator foramen or 3 cm below the GTV, whichever is more distal; *lateral*—1.5–2 cm lateral to the pelvic brim.
- Borders for the lateral fields include: *superior*—same as PA field; *inferior*—same as PA field; *anterior*—posterior margin of the pubic symphysis (bony landmark for internal iliac nodes) for T1–T3 disease or at least 1 cm anterior to the

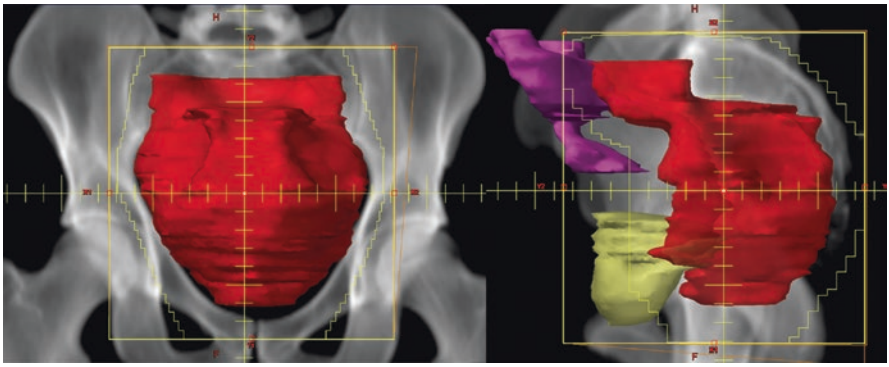

Fig. 18.3 Standard fields for a clinical T3N1b rectal cancer treated with preoperative long-course chemoradiotherapy. A 3D conformal three-field plan is used. The PA field (left panel) and left lateral field (right panel) are shown. The CTV-SR is shown in red. The patient was simulated prone on a belly board, allowing the small bowel (purple) to fall anteriorly away from the CTV. The bladder is shown in yellow

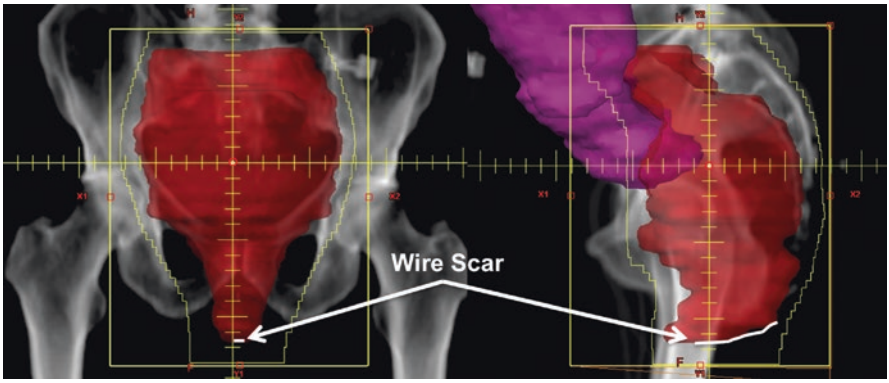

Fig. 18.4 Standard fields for a pathologic T3N2a rectal cancer treated with postoperative long-course chemoradiotherapy following an abdominoperineal resection. A 3D conformal three-field plan is used. The PA field (left panel) and left lateral field (right panel) are shown. The CTV-SR is shown in red. The field includes the perineal scar with margin. The patient was simulated prone on a belly board, allowing the small bowel (purple) to fall anteriorly away from the CTV. Note that more small bowel is in the pelvis in the postoperative setting

anterior edge of the pubic symphysis (bony landmark for external iliac nodes) for T4 disease; *posterior*—1 to 1.5 cm posterior to the posterior edge of the bony sacrum.

- With CT-based planning, the borders described above can be modified to ensure adequate coverage of the planning target volumes (PTV). Target volumes including primary and nodal gross tumor volumes (GTV), clinical target volumes (CTV), and the PTV should be delineated on every applicable slice of the planning CT.
- The primary gross tumor volume (GTV-P) is defined as all gross disease on physical examination, endoscopy, and imaging.
- The nodal GTV (GTV-N) includes all visible perirectal, mesorectal, and involved iliac lymph nodes. Include any lymph node in doubt as GTV_N in the absence of a biopsy. For low-lying rectal tumors, attention should be paid to the inguinal lymph nodes (Fig. 18.10). For tumors with anterior invasion into adjacent organs, attention should also be paid to the external iliac lymph nodes.
- The high-risk CTV (CTV-HR) should include the GTV with a minimum 1.5–2 cm superior and inferior margin, as well as the entire rectum, mesorectum, and presacral space (Table 18.1).
- The standard-risk CTV (CTV-SR) should cover the entire CTV_{HR}, mesorectum, and bilateral internal iliac lymph nodes. The CTV-SR should also include the bilateral external iliac and obturator nodes for patients with T4 tumors with anterior organ involvement (bladder, cervix, prostate). If the primary tumor extends inferiorly into the anal canal, the bilateral external iliac and inguinal lymph nodes should be included into CTV-SR (Table 18.1) (Figs. 18.5, 18.6, 18.7, 18.8, 18.9, and 18.10).

Table 18.1 Suggested target volumes for gross and microscopic disease in the preoperative setting (Figs. 18.5, 18.6, 18.8, 18.9, and 18.10)

Target volumes	Definition and description
Gross tumor volume (GTV)	Primary (GTV-P): all gross disease on physical examination, endoscopy, and imaging Regional lymph nodes (GTV-N): all visible perirectal, presacral, and involved iliac nodes. Include any lymph node in doubt as GTV in the absence of a biopsy. For low-lying rectal tumors, attention should also be paid to the inguinal nodes
High risk clinical target volume (CTV-HR)	CTV-HR should cover the GTV-P and GTV-N with 1.5–2 cm margin expansion superiorly and inferiorly, excluding uninvolved bone, muscle, and air. For grossly involved external iliac or inguinal nodes, a minimum 10–15 mm GTV to CTV margin should be included Include the entire rectum, mesorectum, and presacral space in the transverse plane at these levels. A 1–2 cm margin into adjacent organs (e.g., bladder, prostate, cervix) should be added for T4 tumors Visible mesorectal nodes on CT, MRI, and PET/CT should be included
Standard risk clinical target volume (CTV-SR)	Include the CTV_{HR}, entire mesorectum, and bilateral internal iliac lymph nodes. Include the external iliac and obturator nodes for T4 tumors with anterior organ involvement. Include the externa lilac and inguinal lymph nodes in cases with anal canal involvement *Superior*: Rectum and mesorectum, up to the L5/S1 interspace or 2 cm superior to gross disease, whichever is most cephalad *Inferiorly*: Pelvic floor or at least 2 cm inferior to gross disease, whichever is most caudad *Lymph nodes:* To cover the internal iliac nodes, a 0.7–cm margin around the internal iliac vessels should be drawn (excluding muscle and bone) To cover the external iliac nodes (for T4 lesions), an additional 1 cm margin anterolaterally around the vessels should be drawn. Any adjacent small nodes should be included For tumors that extend into the anal canal, the bilateral inguinal nodes should be covered (Table 18.4) A 1.8-cm wide volume between the external and internal iliac vessels should be drawn to cover the obturator nodes *Anterior*: A margin of 1–1.5 cm should be added into bladder to account for changes in bladder and rectal filling
Planning target volume (PTV)	Each CTV should be expanded by 0.5–1 cm, depending on the physician's comfort level with setup accuracy, frequency of imaging, and the use of IGRT

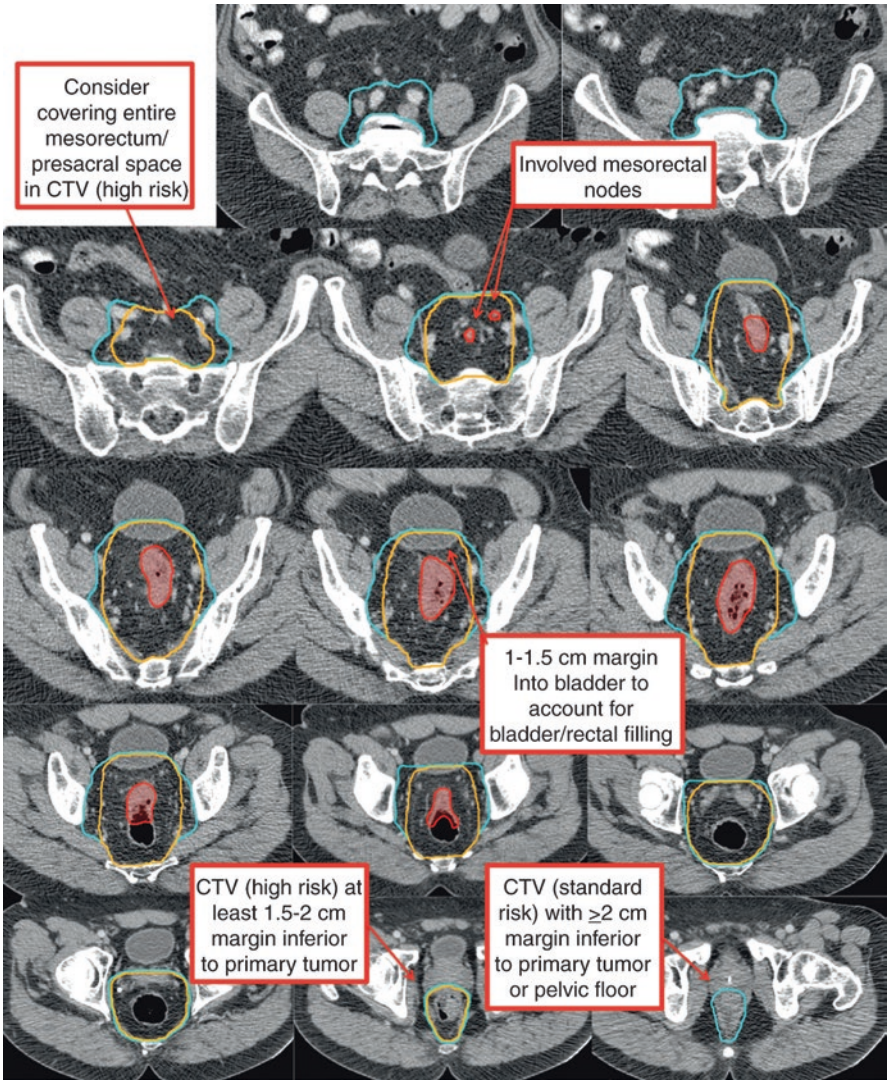

Fig. 18.5 Representative images for a patient with clinical T3N1b rectal adenocarcinoma treated with preoperative long-course chemoradiotherapy. This patient was simulated prone (note the anterior displacement of the small bowel) with PET/CT simulation and 2.5 mm slice thickness. The CT images are rotated 180° for viewer orientation. CTV-SR (cyan), CTV-HR (orange), GTV-N (red, shaded), and GTV-P (red, shaded) are shown

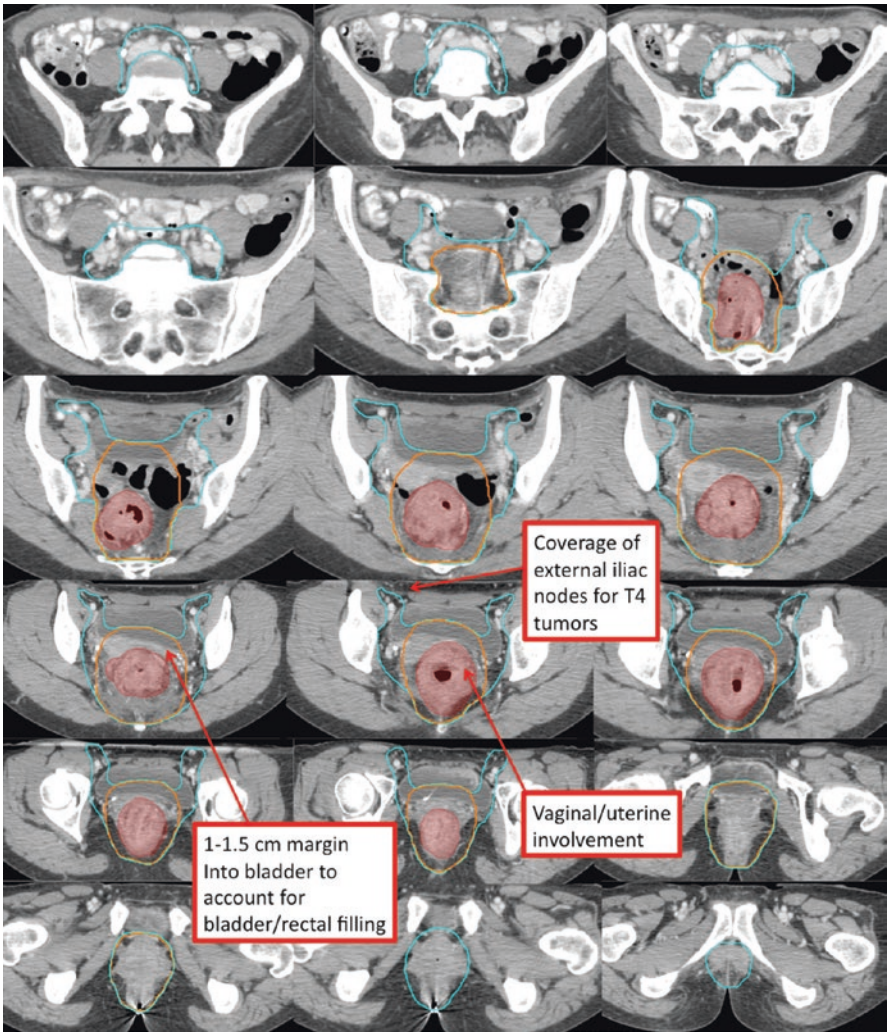

Fig. 18.6 Representative images for a patient with clinical T4N0 rectal adenocarcinoma with gross invasion into the cervix treated with preoperative long-course chemoradiotherapy. CTV-SR (cyan), CTV-HR (orange), and GTV-P (red, shaded) are shown. Note that in this case, the CTV-SR covers the external iliac nodal region due to T4 disease

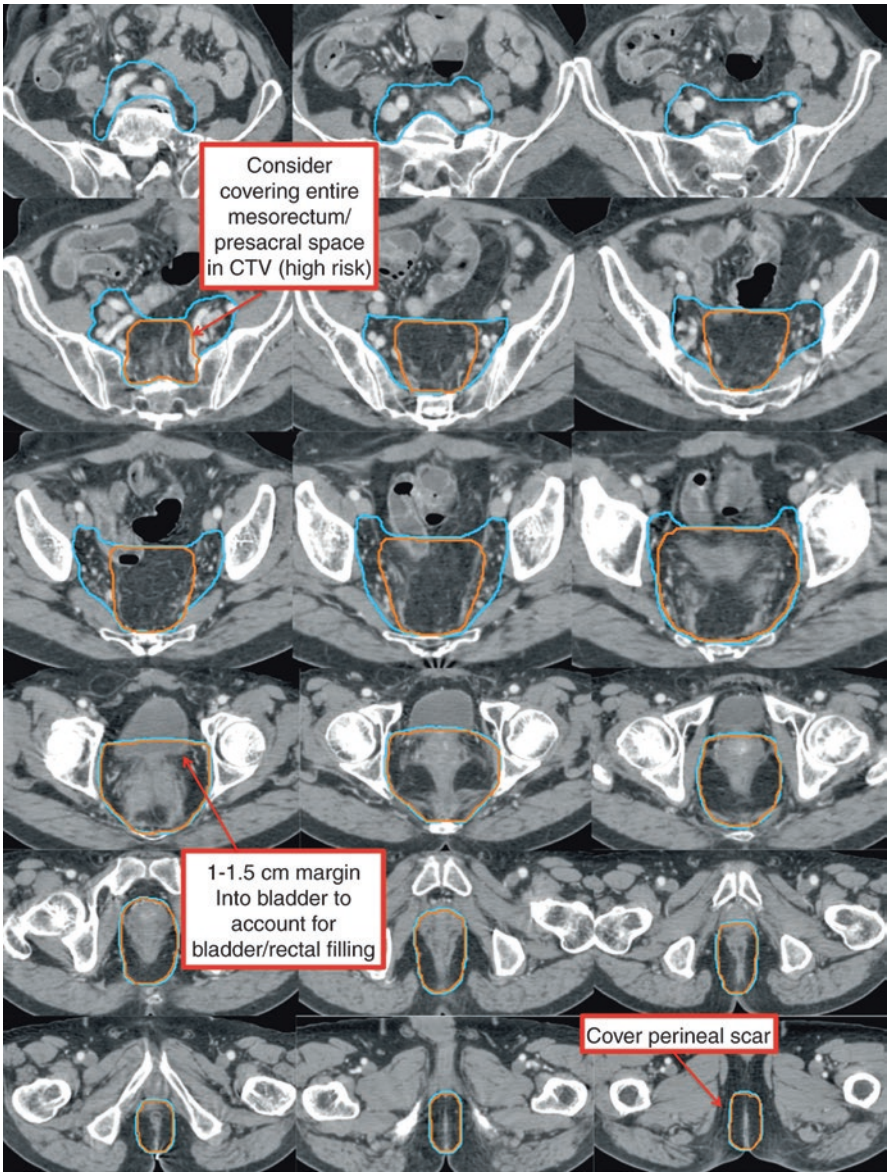

Fig. 18.7 Representative images for a patient with pathologic T3N2a rectal adenocarcinoma treated with postoperative long-course chemoradiotherapy. This patient underwent an abdominoperineal resection (APR) without preoperative chemoradiotherapy. The primary tumor extended from 2–5 cm from the anal verge. The patient was simulated prone. The CT images are rotated 180° for viewer orientation. CTV-SR (cyan) and CTV-HR (orange) are shown. In this case, due to the absence of small bowel near the postoperative bed, the GTV-HR was boosted to a total dose of 55.8 Gy. However, if a portion of bowel was near the boost volume, the dose could be reduced

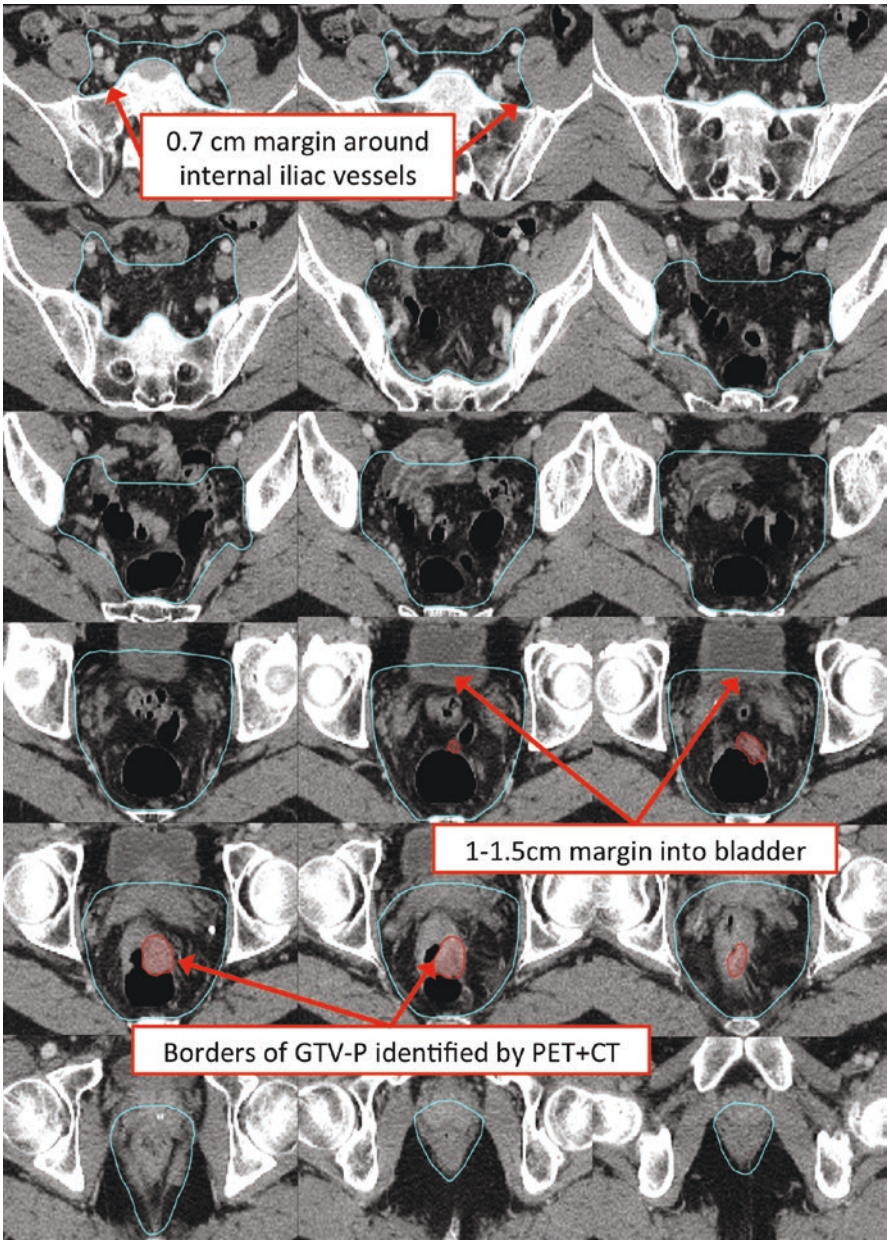

Fig. 18.8 Representative images for a patient with clinical T3N0 rectal adenocarcinoma treated with short-course preoperative radiotherapy. This patient was simulated prone (note the anterior displacement of the small bowel) with PET/CT simulation with 2.5 mm slice thickness. The CT images are rotated 180° for viewer orientation. CTV-SR (cyan) and GTV (red, shaded) are shown

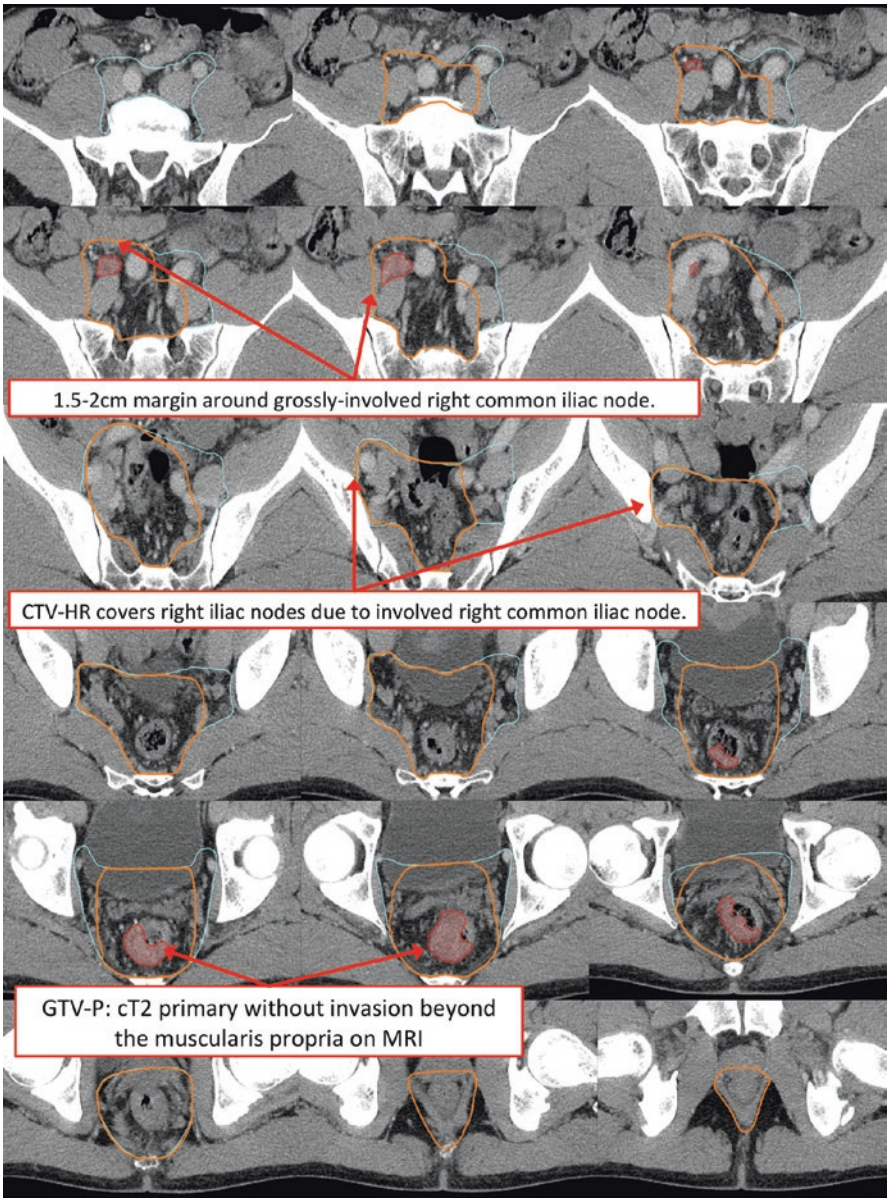

Fig. 18.9 Representative images for a patient with clinical T2N0M1a rectal adenocarcinoma with a 2 cm non-regional right common iliac lymph node confirmed by PET/CT. This patient underwent preoperative long-course chemoradiotherapy. CTV-SR (cyan), CTV-HR (orange), GTV-N (red, shaded), and GTV-P (red, shaded) are shown

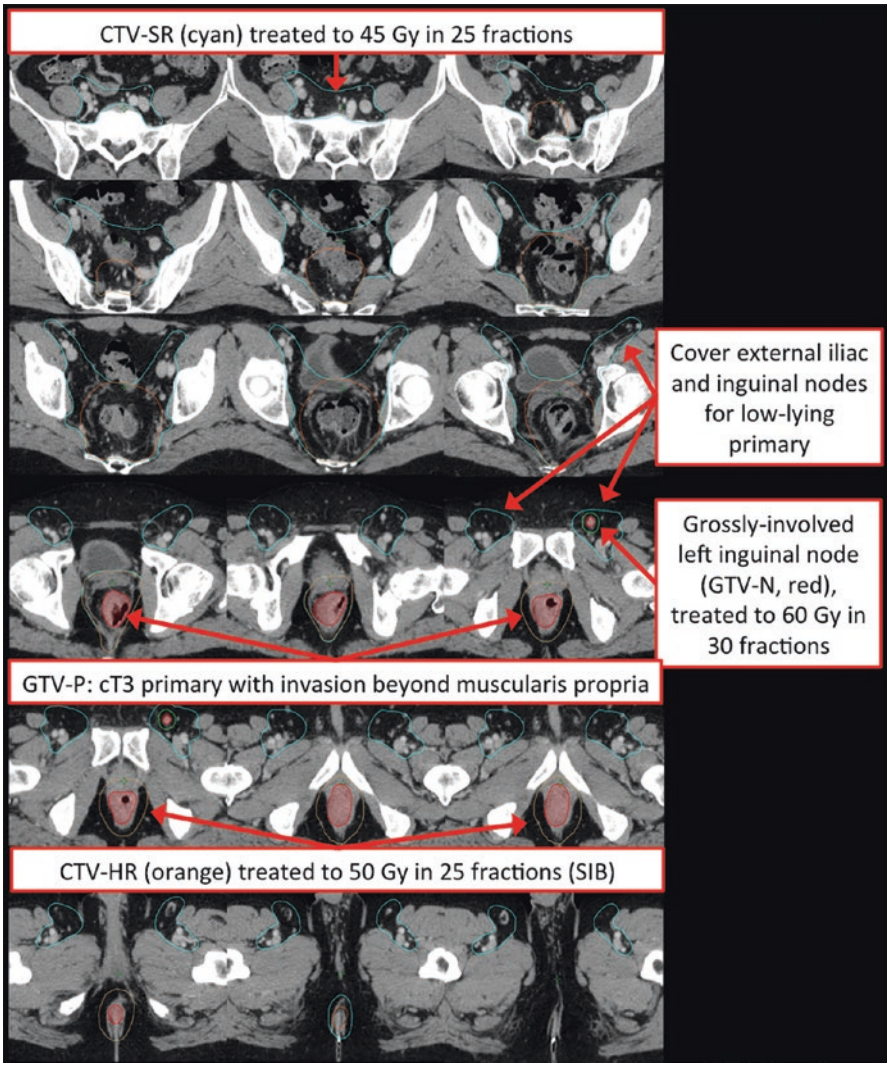

Fig. 18.10 Representative images for a patient with clinical T3N2a low-lying rectal adenocarcinoma (2 cm superior to the anal verge) with a grossly involved left inguinal lymph node confirmed by PET/CT. The patient underwent preoperative long-course chemoradiotherapy with IMRT for coverage of the bilateral external iliac and inguinal nodes. CTV-SR (cyan), CTV-HR (orange), GTV-N (red, shaded), GTV-P (red, shaded), and CTV-N (green, 10 mm GTV-N to CTV-N margin) are shown

- Target volume delineation in the postoperative setting is similar to the preoperative setting. In the setting of abdominoperineal resection, the entire surgical bed, including the perineal scar, should be included (Table 18.2).
- The RTOG anorectal contouring atlas provides a detailed consensus contouring descriptions of three elective CTVs that should be considered in patients with rectal and anal cancers. CTV-A includes the perirectal, presacral, and internal

Table 18.2 Suggested target volumes in the postoperative setting (Fig. 18.7)

Target volumes	Definition and description
Clinical target volume for gross disease or positive margin (CTV-P)	Areas of known microscopically involved margin or macroscopic residual disease plus a 1–2 cm margin, excluding uninvolved bone, muscle, or air
High risk clinical target volume (CTV-HR)	Remaining rectum (if applicable), mesorectal bed, and presacral space axially at these levels, excluding uninvolved bone, muscle, or air. For undissected grossly involved external iliac or inguinal nodes, a minimum 10–15 mm GTV to CTV margin should be included
Standard risk clinical target volume (CTV-SR)	Include the CTV-HR, entire mesorectum, and bilateral internal iliac lymph nodes. Include the external iliac and obturator nodes for T4 tumors with anterior organ involvement. Include the externa lilac and inguinal lymph nodes in cases with anal canal involvement *Superior*: Remaining rectum and mesorectum (usually up to L5/S1) with at least 1 cm margin superior to the anastomosis, whichever is most cephalad *Inferior*: Pelvic floor or at least 1 cm below the anastomosis or rectal stump, whichever is most caudad. In cases following abdominoperineal resection, the surgical bed extending down to the wired perineal scar should be included *Lateral:* 0.7-cm margin around the internal iliac vessels, excluding muscle and bone To cover the external iliac nodes (for T4 lesions), an additional 1 cm margin anterolaterally around the vessels should be drawn. Any adjacent small nodes should be included For tumors involving the anal canal, the bilateral inguinal nodes should be covered (Table 18.4) A 1.8-cm wide volume between the external and internal iliac vessels should be drawn to cover the obturator nodes *Anterior*: 1–1.5 cm margin should be added into bladder to account for changes in bladder and rectal filling
Planning target volume (PTV)	Each CTV should be expanded by 0.5–1 cm, depending on the physician's comfort level with setup accuracy, frequency of imaging, and the use of IGRT

iliac regions and should be covered in all patients with rectal cancer. CTV-B includes the external iliac nodes (covered only for primary rectal tumors that invade into adjacent organs (T4 disease) or extend inferiorly into the anal canal). CTV-C includes the inguinal region (covered only for primary rectal tumors that extend inferiorly into the anal canal). A detailed description of CTV-A is provided in Table 18.3.

- More recent international consensus guidelines suggest a common set of pelvic subsites/subvolumes that differ from the terminology of the RTOG anorectal contouring atlas. In particular, major distinctions include recommendations for including the abdominal (cranial) presacral space, ischiorectal fossa, anterior vs. posterior (obturator vs. internal iliac) lateral lymph nodes, and the cranial border for the lateral lymph nodes. Based on these guidelines, consideration may be made for omitting the lateral lymph nodes superior to the cranial border of the

Table 18.3 Description of the borders of CTV-A in the RTOG anorectal contouring atlas

Clinical target volume	Key highlights
CTV-A: lower pelvis	*Inferior*: 2 cm below gross disease, including the entire mesorectum down to the pelvic floor *Lateral*: does not need to extend more than a few millimeters beyond the levator muscles unless there is tumor extension into the ischiorectal fossa. For T4 tumors, should include 1–2 cm margin around identified areas of invasion
CTV-A: mid-pelvis	Includes the rectum, mesorectum, internal iliac region, and 1 cm margin into the bladder for daily variation in bladder filling *Posterolateral*: Extends to the pelvic sidewall muscles or bone (when muscles are absent) *Anterior*: at least 1 cm into the posterior bladder. Should also include at least the posterior portion of the internal obturator vessels Recommend 7–8 mm margin in soft tissue around the internal iliac vessels. CTV should be trimmed off uninvolved muscle and bone
CTV-A: upper pelvis	*Superior (perirectal component)*: Should be at the rectosigmoid junction or at least 2 cm cephalad to macroscopic disease in the rectum/perirectal nodes, whichever is most cephalad. The entire length of the rectum should be included *Superior (nodal coverage)*: should be at the bifurcation of the common iliac vessels into the external/internal iliacs, approximately at the sacral promontory Recommend 7–8 mm margin in soft tissue around the internal iliac vessels, but at least 1 cm anteriorly, especially if vessels or small nodes are seen in this area. CTV should be trimmed off uninvolved muscle and bone

mesorectum for T3N0 tumor without invasion of the mesorectal fascia, and for omitting the anterior lateral lymph nodes for T3N0-1 tumors in select scenarios.

- The Australasian GI Trials Group Atlas describes seven elective regions to be considered when treating anal cancer, some of which are applicable for rectal cancers: mesorectum, presacral space, internal iliac nodes, ischiorectal fossa, obturator nodes, external iliac nodes, and inguinal nodes. Table 18.4 is a summary of the definitions of these regions.
- There are multiple acceptable approaches to dose prescription for rectal cancer. In the preoperative setting, the most common prescription dose is 45 Gy at 1.8 Gy/fraction to the PTV_{SR}, followed by a sequential cone-down boost of 5.4 Gy at 1.8 Gy/fraction to a total of 50.4 Gy to the PTV_{HR}. For clinical T4 tumors, the PTV_{HR} may instead be boosted to a total dose of 54–55.8 Gy in 30–31 fractions. Grossly involved lymph nodes that will not be resected (e.g., inguinal) should be boosted to approximately 60 Gy in 30 fractions, whereas nodes that will be resected can be treated to 50.4 Gy (Table 18.5).
- The 3D conformal technique uses opposing lateral fields with a PA field (Figs. 18.3 and 18.4). If treating external iliac lymph nodes with this technique, the anterior border of the lateral fields should be approximately 1 cm anterior to the anterior border of the pubic symphysis.
- When treating with IMRT, simultaneous integrated boosts can be considered. Table 18.4 lists several suggested dose and fractionation schemes for various settings.

Table 18.4 Description of the borders used in defining the elective nodal regions from the Australasian GI Trials Group Contouring Atlas

	Mesorectum	Presacral space	Internal iliac nodes	Ischiorectal fossa	Obturator nodes	External iliac nodes	Inguinal nodes
Cranial	Recto-sigmoid junction	Sacral promontory (L5/S1 interspace)	Bifurcation of common iliac arteries (L5/S1 interspace)	Apex formed by levator ani, gluteus maximus, and obturator internus	3–5 mm cranial to obturator canal	Bifurcation of common iliac artery	Level where external iliac artery leaves bony pelvis to become femoral artery
Caudal	Anorectal junction (levators fuse with external sphincter)	Inferior border of coccyx	Level of obturator canal or level where there is no space between obturator internus and midline organs	Anal verge	Obturator canal, where obturator artery exits the pelvis	Between roof of acetabulum and superior pubic rami	Lower edge of ischial tuberosities
Posterior	Presacral space	Position at anterior border of sacral bone; should include sacral hollow	N/A	Transverse plane joining anterior edge of medial walls of the gluteus maximus muscle	Internal iliac nodes	Internal iliac nodes	Muscle boundaries

(continued)

Table 18.4 (continued)

	Mesorectum	Presacral space	Internal iliac nodes	Ischiorectal fossa	Obturator nodes	External iliac nodes	Inguinal nodes
Anterior	Men: bladder and seminal vesicles (mid-pelvis), prostate and penile bulb (lower pelvis) Women: uterus, cervix, vagina, and bladder Internal margin of 1 cm added to anterior mesorectal border on slices containing bladder, seminal vesicles, or uterus for daily variation	1 cm anterior to the sacral border, encompassing any lymph nodes	Obturator internus muscle or bone in the lower pelvis; in the upper pelvis, 7 mm margin around the internal iliac vessels	Level where obturator internus, levator ani, and anal sphincter muscles fuse; inferiorly, at least 1–2 cm anterior to anal sphincter muscles	Anterior extent of obturator internus	7 mm margin anterior to the external iliac vessels	Minimum 2 cm margin on the inguinal vessels, including any visible nodes
Lateral	Medial edge of levator ani (lower pelvis), internal iliac nodes (upper pelvis)	Sacro-iliac joints	Medial edge of obturator internus muscle or bone (lower pelvis); iliopsoas muscle (upper pelvis)	Ischial tuberosity, obturator internus, and gluteus maximus	Obturator internus	Iliopsoas muscle	Medial edge of sartorius or iliopsoas
Medial	N/A	N/A	Mesorectum and presacral space (lower pelvis); 7 mm margin around internal iliac vessels (upper pelvis)	N/A	Bladder	Bladder or 7 mm margin around vessel	1–2 cm margin around the femoral vessels

Table 18.5 Suggested dose and fractionation schemes for rectal cancer

	PTV-SR	PTV-HR
Preoperative T3 or N+	45 Gy at 1.8 Gy/fx, OR 45 Gy at 1.8 Gy/fx (SIB)	50.4 Gy at 1.8 Gy/fx (CD), OR 50 Gy at 2 Gy/fx (SIB)
Preoperative T4 N0-2b	45 Gy at 1.8 Gy/fx, OR 45.9 Gy at 1.7 Gy/fx (SIB)	54–55.8 Gy at 1.8 Gy/fx (CD), OR 54 Gy at 2 Gy/fx (SIB)
Preoperative (short course) T3-4 or N+	25 Gy at 5 Gy/fx	
Postoperative (negative margins)	45 Gy at 1.8 Gy/fx, OR 45.9 Gy at 1.7 Gy/fx (SIB)	54–55.8 Gy at 1.8 Gy/fx (CD), OR 54 Gy at 2 Gy/fx (SB)
Postoperative (gross disease or positive margin)	45 Gy at 1.8 Gy/fx, OR 45.9 Gy at 1.7 Gy/fx (SIB)	54–59.4 Gy at 1.8 Gy/fx (CD), OR 54–60 Gy at 2 Gy/fx (SIB and/or CD)

fx fraction, *CD* (sequential) cone-down, *SIB* simultaneous integrated boost

- With growing interest in total neoadjuvant therapy, patients may receive systemic therapy prior to radiation. Until further outcome data are available, the pre-chemotherapy primary and nodal tumor volumes should be used to define target volumes. Nodes that were initially suspicious for involvement should be included in the boost volume, and threatened radial margins prior to chemotherapy should be included in the high-dose volumes even in the setting of a major or complete response to chemotherapy.

18.4 Plan Assessment

- Ideally, at least 95% of each PTV should receive 100% of the prescription dose. In addition, the maximum dose in the PTV should be <110%.
- When evaluating plans with a sequential boost to gross disease, each individual plan should be scrutinized before the "plan sum" to assess for hot spots or undercoverage of each individual PTV.
- The organs-at-risk include the small bowel, large bowel, bladder, femoral heads, iliac crest, and external genitalia. Uniform consensus guidelines for contouring the small and large bowel, bladder, and femoral heads are available from an RTOG consensus panel. Suggested dose constraints from QUANTEC and RTOG 0822 are listed in Table 18.6.

Table 18.6 Dose constraints for organs-at-risk

Organ-at-risk	Constraints
Small bowel	QUANTEC V15Gy < 120cc (individual loops) V45Gy < 195cc (entire potential space within peritoneal cavity) RTOG 0822 V35Gy < 180 cc V40Gy < 100 cc V45 Gy < 65 cc Dmax < 50 Gy
Bladder	QUANTEC Dmax < 65 Gy V65Gy < 50% RTOG 0822 V40Gy < 40% V45Gy < 15% Dmax < 50 Gy
Femoral heads	RTOG 0822 V40Gy < 40% V45Gy < 15% Dmax < 50 Gy

Further Reading

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Anal Cancer

19

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Contents

19.1 Anatomy and Patterns of Spread

- The anal canal is about 4 cm in length and extends from the anorectal ring proximally (palpable border of the anal sphincter and puborectalis muscle) to the anal verge distally.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_19

Table 19.1 Lymphatic drainage of the anal canal

Location of primary tumor	Draining lymphatics
Distal anal canal, perianal skin, and anal verge	Superficial inguinal Femoral External iliac
Anal canal just proximal to dentate line	Internal pudendal Hypogastric Obturator Inferior and middle hemorrhoidal
Proximal anal canal and distal rectum	Perirectal Superior hemorrhoidal

- The anal verge is the junction of the nonkeratinized squamous epithelium of the distal anal canal and the keratinized hair-bearing perianal skin.
- Embryologically, the dentate line (or pectinate line) is formed by the junction of the endoderm proximally and the ectoderm distally, leading to important differences in both histology and lymphatic drainage.
- The dentate line demarcates the transition from the columnar epithelium of the proximal anal canal to the squamous epithelium of the distal anal canal.
- Squamous cell carcinomas that arise proximal to the anal verge are managed as anal canal cancers, whereas squamous cell carcinomas that arise distal to the anal verge are managed as perianal skin cancers.
- The primary draining lymphatics of the anal canal include the perirectal, internal iliac (hypogastric), and superficial inguinal lymph nodes. The pattern of drainage depends on the location of the primary tumor within the anal canal (Table 19.1).

19.2 Diagnostic Workup Relevant for Target Volume Delineation

- Physical examination is an important part of the staging and planning process, and should include detailed assessment of the characteristics of the primary tumor (size, location relative to anal verge, anal sphincter function, invasion of adjacent structures via pelvic examination) as well as an assessment of inguinal lymph nodes.
- Inguinal lymph nodes that are suspicious for metastatic involvement but borderline in size should be biopsied to confirm metastasis, as nearly 50% of suspicious nodes are related to reactive hyperplasia.
- PET/CT is recommended both for staging and treatment planning to assist in delineating extent of gross disease (Fig. 19.1).
- Areas of low uptake on PET should not supersede physical examination findings or abnormalities seen on CT or MRI.

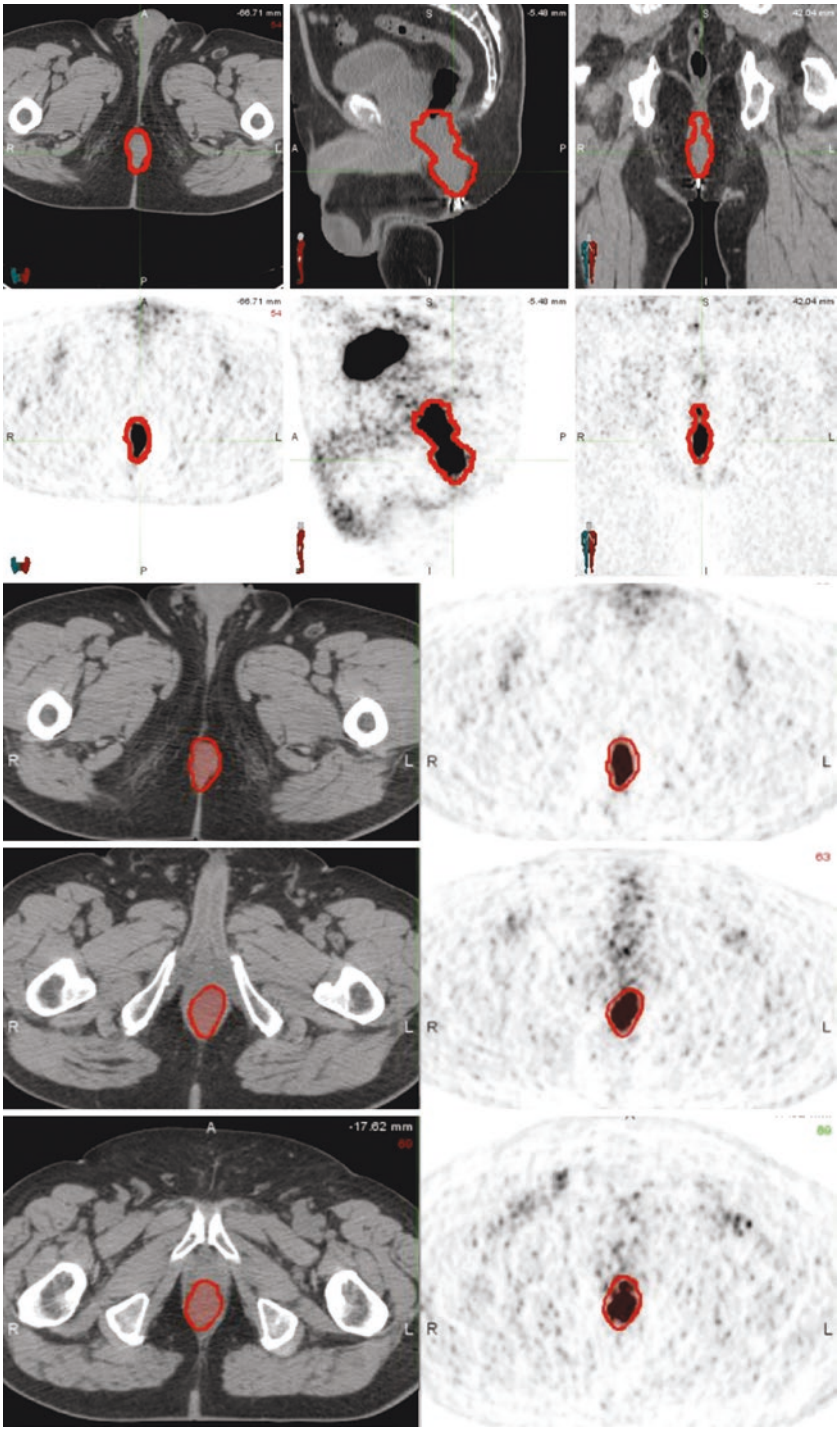

Fig. 19.1 An example of delineating the GTV-P (red) using the co-registered simulation CT and diagnostic PET on representative axial, sagittal, and coronal images. In the lower three panels, additional axial slices of the co-registered CT and PET are shown

19.3 Simulation and Daily Localization

- The patient should be simulated supine with arms on chest in a body mold. Prone positioning with a belly board can be used to allow for anterior displacement of the bowel, but this is not as reproducible and complicates bolus placement. A radiopaque marker should be placed at the anal verge.
- CT simulation with intravenous contrast and ≤3 mm slice thickness should be performed to delineate the pelvic blood vessels and gross tumor volume. If PET/CT is available, a PET/CT fusion should be performed to aid in target volume delineation. MRI may also be useful.
- Bladder filling/emptying should be considered. A full bladder may keep bowel from migrating into the pelvis, while an empty bladder may be more reproducible.
- We recommend image guidance with daily orthogonal kilovoltage imaging and weekly cone-beam CT scans (to assess soft tissue) to verify alignment during treatment. Cone beam CTs may be done more frequently if there is significant variation in bladder and/or rectal filling.

19.4 Target Volume Delineation and Treatment Planning

- Conventional 3D conformal radiotherapy for anal canal cancers is complex due to the need to irradiate the pelvis and inguinal lymph nodes. The "thunderbird" technique was historically the most common method used to treat anal cancer. An example of the thunderbird technique compared to an IMRT plan is shown in Fig. 19.2. A detailed description of thunderbird technique variations is described by Gilroy et al. [1]

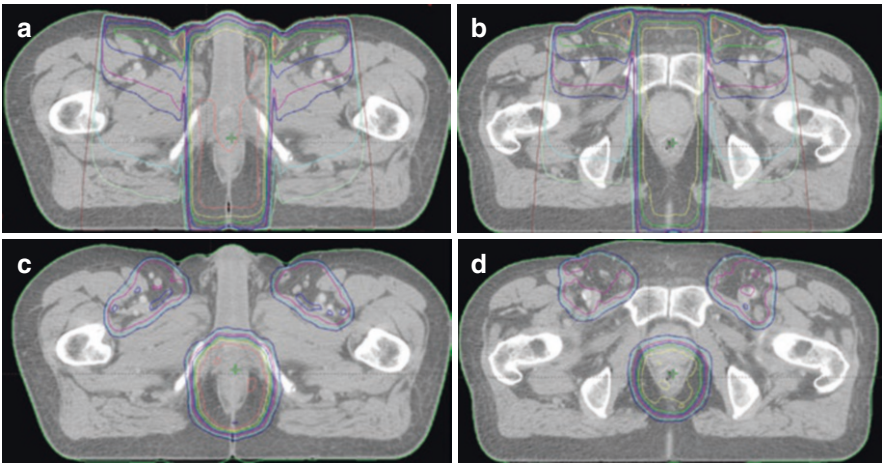

Fig. 19.2 Dose distributions for a photon/electron thunderbird technique (panel (**a**) and (**b**)) and intensity-modulated radiotherapy plan (panel (**c**) and (**d**))

- RTOG 0529 has established the feasibility of IMRT in a multi-institution setting and demonstrated lower rates of grade 2 or higher hematologic toxicity and lower rates of grade 3 or higher gastrointestinal or dermatologic toxicity when compared to historical controls in the RTOG 9811 trial, which utilized 3D conformal radiotherapy [2, 3]. However, accurate target volume delineation is critical, as delineation that is non-compliant with consensus guidelines is associated with an increased risk of disease recurrence (Table 19.2) [4–6].

Table 19.2 Suggested target volumes for gross and microscopic disease

Target volumes	Definition and description
Gross tumor volumes (GTV-P, GTV-N)	Primary (GTV-P): all gross disease on physical examination and imaging Regional nodes (GTV-N): all nodes ≥1.5 cm, PET-positive, and/or biopsy-proven. Include any lymph nodes in doubt as GTV-N in the absence of biopsy. Lymph nodes that are ≤3 cm (GTV-Na) may be distinguished from those that are >3 cm (GTV-Nb)
Clinical target volumes for gross disease (CTV-P, CTV-N)	CTV-P is the GTV-P with a 1.5–2.5 cm margin expansion excluding uninvolved bone, muscle, or air. The CTV-N is the GTV-N with a 1.0–1.5 cm margin expansion excluding uninvolved bone, muscle, or air
High risk clinical target volume (CTV-HR)	Should cover CTV-P, CTV-N, the entire mesorectum, perirectal lymph nodes, and bilateral internal iliac lymph nodes inferior to the inferior border of the sacroiliac joint. If the inguinal or external iliac nodes are involved, these regions should be included in CTV-HR. Similarly, the upper internal iliac nodes should be included if involved To cover the internal iliac nodes, a 0.7-cm margin around the internal iliac vessels should be drawn (excluding muscle and bone) [4, 7] To cover the external iliac nodes (for either inguinal or external iliac node-positive disease), an additional 1 cm margin anterolaterally around the vessels should be drawn. Any adjacent small nodes should be included [4, 7] To cover the inguinal nodes (for inguinal or external iliac node-positive disease), the entire inguinal compartment should be contoured, including small vessels and adjacent lymph nodes bounded by muscle and bone (Table 19.4). A 1.8-cm wide volume between the external and internal iliac vessels should be drawn to cover the obturator nodes [7] Anteriorly, a margin of 1–1.5 cm should be added into bladder to account for changes in bladder and rectal filling [4, 8]
Low risk clinical target volume (CTV-LR)	Should cover the uninvolved internal iliac lymph nodes superior to the inferior border of the sacroiliac joint, as well as the uninvolved external iliac and inguinal lymph nodes To cover the internal iliac nodes, a 0.7-cm margin around the internal iliac vessels should be drawn (excluding muscle and bone) [4, 7] To cover the external iliac nodes, an additional 1 cm margin anterolaterally around the vessels should be drawn. Any adjacent small nodes should be included [4, 7] To cover the inguinal nodes, the entire inguinal compartment should be contoured, including small vessels and adjacent lymph nodes bounded by muscle and bone (Table 19.4)
Planning target volumes (PTV)	Each CTV should be expanded by 0.5–1 cm, depending on the physician's comfort level with setup accuracy, frequency of imaging, and the use of IGRT

Table 19.3 Elective nodal regions described in RTOG anorectal contouring atlas [4]

Clinical target volume	Key highlights
CTV-A (perirectal, presacral, internal iliac regions)	Lower pelvis: The inferior border should be 2 cm below gross disease, including the entire mesorectum. The volume does not need to extend more than a few millimeters beyond the levator muscles unless there is extension into the ischiorectal fossa Mid pelvis: Includes the rectum, mesorectum, internal iliac nodes, and 1 cm margin into the bladder for daily variation in bladder filling. Posterolaterally, the volume extends to the pelvic sidewall muscles or bone (when muscles are absent). At minimum, the posterior portion of the internal obturator vessels should be included. A 7–8 mm margin in soft tissue around the internal iliac vessels should be drawn. The volume should be trimmed off uninvolved muscle and bone Upper pelvis: The most superior extent should be at the bifurcation of the common iliac vessels into the external/internal iliacs, approximately at the sacral promontory Recommend 7–8 mm margin in soft tissue around the internal iliac vessels, but at least 1 cm anteriorly, especially if vessels or small nodes are seen in this area. CTV should be trimmed off uninvolved muscle and bone
CTV-B (external iliac region)	The border between the inguinal and external iliac region is somewhat arbitrary. The consensus was that the border should be set at the level of the inferior extent of the internal obturator vessels (bony landmark: the upper edge of the superior pubic rami) Recommend 7–8 mm margin in soft tissue around the iliac vessels, but at least 1 cm anteriorly, especially if vessels or small nodes are seen in this area. CTV should be trimmed off uninvolved muscle and bone
CTV-C (inguinal region)	The most inferior extent should be 2 cm below the saphenous/femoral junction. The border between CTV-B and CTV-C is approximately the upper border of the superior pubic rami The entire inguinal compartment should be contoured, including small vessels and lymph nodes. CTV should be trimmed off uninvolved muscle and bone

- Detailed contouring atlases available include the RTOG anorectal contouring atlas and the Australasian GI Trials Group Atlas [4, 5].
- The RTOG anorectal contouring atlas describes three CTV regions that should be included for all patients with anal canal cancer [4]. CTV-A includes the perirectal, presacral, and internal iliac regions. CTV-B includes the external iliac nodes. CTV-C includes the inguinal region. Table 19.3 provides a more detailed description of these regions.
- The Australasian GI Trials Group Atlas describes seven elective regions to be considered when treating anal cancer: mesorectum, presacral space, internal iliac nodes, ischiorectal fossa, obturator nodes, external iliac nodes, and inguinal nodes [5]. Table 19.4 is a summary of the definitions of these regions.
- Disagreement exists among anal cancer contouring guidelines (RTOG, AGITG, BNG) with respect to contouring the inguinal lymph nodes. Recent data indicate that 10–29% of involved inguinal lymph nodes appear to be situated outside of recommended nodal borders [9]. To adequately cover this nodal chain, a 2 cm

Table 19.4 Description of the borders used in defining the elective nodal regions from the Australasian GI Trials Group Contouring Atlas [5]

	Mesorectum	Presacral space	Internal iliac nodes	Ischiorectal fossa	Obturator nodes	External iliac nodes	Inguinal nodes
Cranial	Recto-sigmoid junction	Sacral promontory (L5/S1 interspace)	Bifurcation of common iliac arteries (L5/S1 interspace)	Apex formed by levator ani, gluteus maximus, and obturator internus	3–5 mm cranial to obturator canal	Bifurcation of common iliac artery	Level where external iliac artery leaves bony pelvis to become femoral artery
Caudal	Ano-rectal junction (levators fuse with external sphincter)	Inferior border of coccyx	Level of obturator canal or level where there is no space between obturator internus and midline organs	Anal verge	Obturator canal, where obturator artery exits the pelvis	Between roof of acetabulum and superior pubic rami	Lower edge of ischial tuberosities
Posterior	Presacral space	Position at anterior border of sacral bone; should include sacral hollow	N/A	Transverse plane joining anterior edge of medial walls of the gluteus maximus muscle	Internal iliac nodes	Internal iliac nodes	Muscle boundaries

(continued)

Table 19.4 (continued)

	Mesorectum	Presacral space	Internal iliac nodes	Ischiorectal fossa	Obturator nodes	External iliac nodes	Inguinal nodes
Anterior	Men: bladder and seminal vesicles (mid-pelvis), prostate and penile bulb (lower pelvis) Women: uterus, cervix, vagina, and bladder Internal margin of 1 cm added to anterior mesorectal border on slices containing bladder, seminal vesicles, or uterus for daily variation	1 cm anterior to the sacral border, encompassing any lymph nodes	Obturator internus muscle or bone in the lower pelvis; in the upper pelvis, 7 mm margin around the internal iliac vessels	Level where obturator internus, levator ani, and anal sphincter muscles fuse; inferiorly, at least 1–2 cm anterior to anal sphincter muscles	Anterior extent of obturator internus	7 mm margin anterior to the external iliac vessels	Minimum 2 cm margin on the inguinal vessels, including any visible nodes
Lateral	Medial edge of levator ani (lower pelvis), internal iliac nodes (upper pelvis)	Sacro-iliac joints	Medial edge of obturator internus muscle or bone (lower pelvis); iliopsoas muscle (upper pelvis)	Ischial tuberosity, obturator internus, and gluteus maximus	Obturator internus	Iliopsoas muscle	Medial edge of sartorius or iliopsoas
Medial	N/A	N/A	Mesorectum and presacral space (lower pelvis); 7 mm margin around internal iliac vessels (upper pelvis)	N/A	Bladder	Bladder or 7 mm margin around vessel	1–2 cm margin around the femoral vessels

Table 19.5 Suggested dose and fractionation schemes for anal canal cancer

Target volume	RTOG 9811 [3]	RTOG 0529 [2]/Transaustralian [5]
PTV-P	T1N0: 45–50.4 Gy at 1.8 Gy/fraction T2N0: 50.4 Gy at 1.8 Gy/fraction N+ or T3-T4: 54–59.4 Gy at 1.8 Gy/fraction	T1N0: Not included on RTOG 0529 T2N0: 50.4 Gy at 1.8 Gy/fraction N+ or T3-T4: 54 Gy at 1.8 Gy/fraction
PTV-N	54–59.4 Gy at 1.8 Gy/fraction	50.4 Gy at 1.68 Gy/fraction if node ≤3 cm 54 Gy at 1.8 Gy/fraction if node >3 cm
PTV-HR	45 Gy at 1.8 Gy/fraction	T2N0: 42 Gy at 1.5 Gy/fraction N+ or T3-T4: 45 Gy at 1.5 Gy/fraction
PTV-LR	30.6–36 Gy at 1.8 Gy/fraction Alternatively, 40 Gy at 1.6 Gy/fraction SIB may be used	A low-risk PTV was not used on RTOG 0529

radial margin around the femoral vessels, 1 cm radial margin around the saphenous/femoral junction, and 3 cm medial/lateral margin along the lower inguinal ligament is necessary. The caudal border of the inguinal CTV should be the level of the anal margin.

- There are multiple techniques and methods of dose prescription for anal cancer, and the exact dose and fractionation will vary based on which technique is used. The current recommendations are based on the treatment plan used in RTOG 9811 [3] (Table 19.5).
- Figure 19.3 shows a case example of a clinical T2N0 anal canal cancer treated with definitive chemoradiotherapy with an IMRT plan. The PTV-LR and PTV-HR were treated simultaneously to 40 Gy (1.6 Gy/fx) and 45 Gy (1.8 Gy/fx) in 25 fractions, respectively. Then, the PTV-P was boosted sequentially to 50.4 Gy (1.8 Gy/fx) in 28 total fractions.
- Figure 19.4 shows a case example of a clinical T3N1a anal canal cancer with bilateral inguinal nodal involvement treated with definitive chemoradiotherapy with an IMRT plan. The PTV-LR and PTV-HR were treated simultaneously to 40 Gy (1.6 Gy/fx) and 45 Gy (1.8 Gy/fx) in 25 fractions, respectively. Then, the PTV-P and PTV-N were boosted sequentially to 54 Gy (1.8 Gy/fx) in 30 total fractions.
- Figure 19.5 shows a case of a pathologic T1 (1.0 cm) clinical N0M0 squamous cell carcinoma of the perianal skin (anal margin), which was resected with a 0.1cm close margin. The patient was treated with postoperative radiotherapy to the postoperative bed and inguinal lymph nodes alone with an IMRT plan. The PTV-HR and PTV-P were treated simultaneously to 45 Gy (1.8 Gy/fx) in 25 fractions. Then, the PTV-HR was boosted sequentially to 55.8 Gy (1.8 Gy/fx) in 31 total fractions.

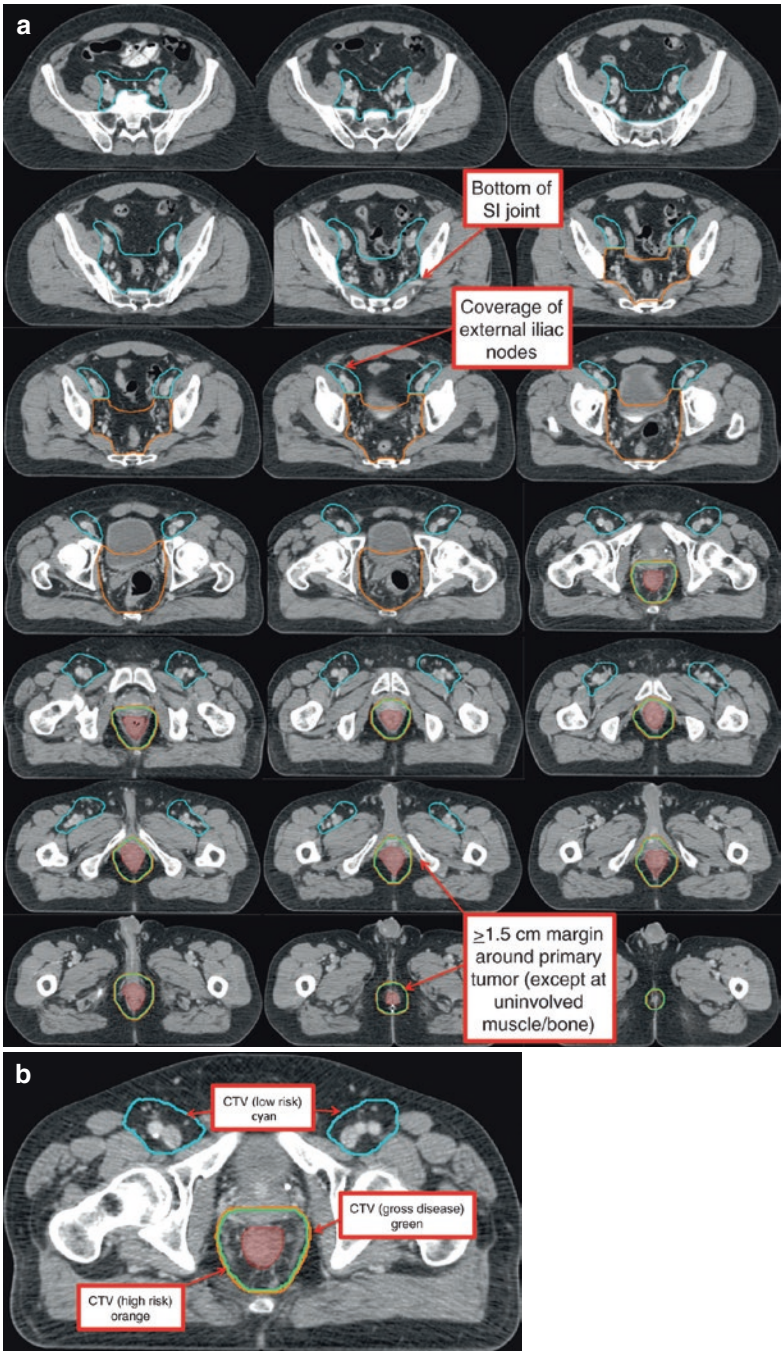

Fig. 19.3 (**a**) Representative images of a patient with T2N0 anal canal cancer treated with definitive chemoradiotherapy. This patient was simulated supine using PET/CT simulation with a 2.5 mm slice thickness. CTV-LR (cyan), CTV-HR (orange), CTV-P (green), and GTV-P (red, shaded) are shown. (**b**) Magnified image of the lower pelvis showing CTV-LR (cyan), CTV-HR (orange), CTV-P (green), and GTV (red, shaded)

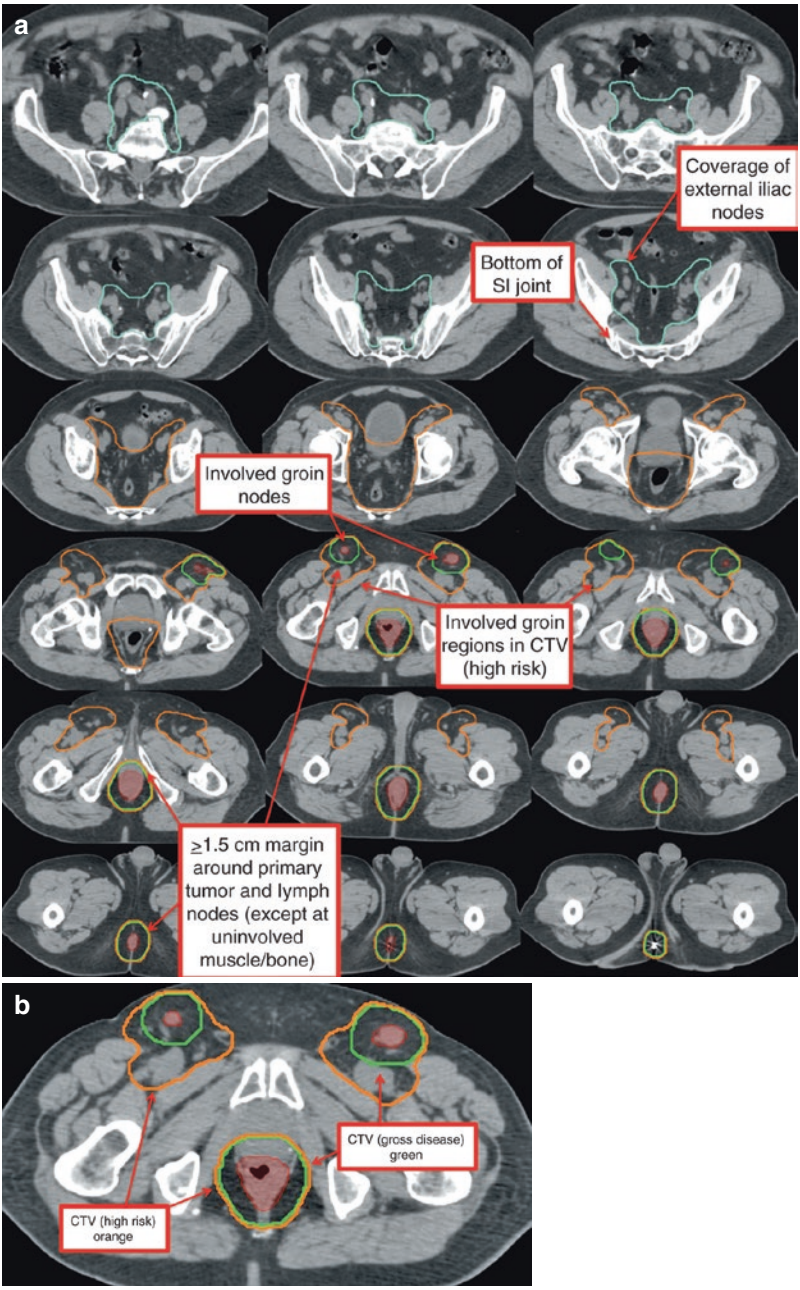

Fig. 19.4 (**a**) Representative images of a patient with T3N1a anal canal cancer with bilateral inguinal lymph node involvement. This patient was simulated supine using PET/CT simulation with a 2.5 mm slice thickness. CTV-LR (cyan), CTV-HR (orange), CTV-P and CTV-N (green), and GTV-P and GTV-N (red, shaded) are shown. Note that the bilateral inguinal and external iliac nodes are included in CTV-HR due to bilateral inguinal involvement. (**b**) Magnified image of the lower pelvis showing CTV-HR (orange), CTV-P (green), CTV-N (green), GTV-P (red, shaded), and GTV-P (red, shaded)

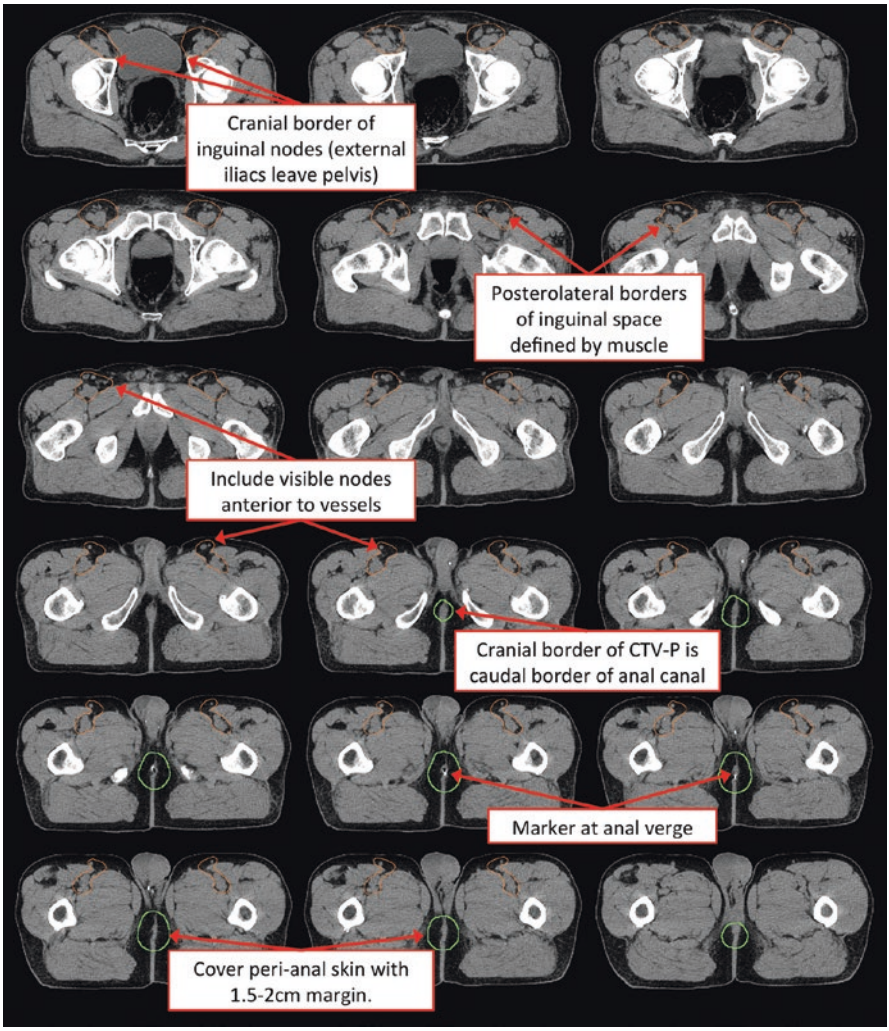

Fig. 19.5 Representative images of a patient with a pathologic T1 (1.0 cm) clinical N0M0 squamous cell carcinoma of the perianal skin (anal margin), which was resected with a 0.1 cm close margin. This patient was simulated supine using CT simulation with a 2.5 mm slice thickness. The perianal surgical bed with a 1.5–2 cm margin (CTV-P, green) and at-risk inguinal lymph nodes (CTV-HR, orange) were treated given concern for microscopic residual disease and the potential for nodal metastasis

19.5 Plan Assessment

- Ideally, at least 95% of each PTV should receive 100% of the prescription dose. In addition, the maximum dose in the PTV should not exceed 10%.
- When evaluating plans with a sequential boost to gross disease, each individual plan should be scrutinized before the "plan sum" to assess for hot spots or under-coverage of each individual PTV.
- The organs-at-risk include the small bowel, large bowel, bladder, femoral heads, iliac crest, and external genitalia. Uniform consensus guidelines for contouring the small and large bowel, bladder, and femoral heads are available from an RTOG consensus panel [10]. Suggested dose constraints from QUANTEC and RTOG 0529 are listed in Table 19.6 [2, 11].
- Pelvic bone marrow is emerging as an important organ-at-risk with respect to minimizing acute hematologic toxicity in patients receiving concurrent chemo-

Table 19.6 Dose constraints for organs-at-risk

Organ-at-risk	Constraints
Small bowel	QUANTEC V15Gy < 120 cc (individual loops) V45Gy < 195 cc (entire potential space within peritoneal cavity) RTOG 0529 V30Gy < 200 cc V35Gy < 150 cc V45Gy < 20 cc Dmax < 50 Gy
Large bowel	RTOG 0529 V30Gy < 200 cc V35Gy < 150 cc V45Gy < 20 cc
Bladder	QUANTEC Dmax < 65 Gy V65Gy < 50% RTOG 0529 V35Gy < 50% V40Gy < 35% V50Gy < 5%
Femoral heads	RTOG 0529 V30Gy < 50% V40Gy < 35% V44Gy < 5%
Iliac crest	RTOG 0529 V30Gy < 50% V40Gy < 35% V50Gy < 5%
External genitalia	RTOG 0529 V20Gy < 50% V30Gy < 35% V40Gy < 5%

radiotherapy for anal cancer [12–14]. Currently, the pelvic bones serve as a surrogate for the pelvic bone marrow. Delineation of the pelvic bone marrow structure is described by Mell et al. [15]. The pelvic bone marrow structure consists of 3 sub-sites: the lumbosacral spine, the ilium, and the low pelvis.

- We suggest that potential dose constraints for the pelvic bone marrow should include mean dose <28 Gy, V10 <90% and V20 <75%. However, these constraints have not been validated prospectively and should not supercede other planning objectives. The lumbosacral spine may be the most active sub-site of the pelvic bone marrow [12, 13, 16], and limiting dose to this site may be sufficient to reduce hematologic toxicity.

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Postoperative Therapy for Cervical, Vaginal, and Endometrial Cancer

20

Karen Tye, Loren K. Mell, and Dominique Rash

Contents

20.1 Introduction

Intensity-modulated radiation therapy (IMRT) has become the treatment of choice for adjuvant radiotherapy for patients with gynecological cancers, particularly cervical and endometrial malignancies [1–3]. A Phase III randomized trial comparing patient reported outcomes and quality of life (QOL) scores in patients who received pelvic radiation with IMRT versus 3D conformal radiation therapy demonstrated significant reduction in acute GI and GU toxicity as well as better QOL with IMRT. Additionally, IMRT has been demonstrated to reduce the volume of irradiated bone marrow in cervical and endometrial cancer patients who undergo postoperative pelvic radiotherapy (RT), producing a clinically significant reduction in acute and chronic toxicity [4, 5].

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_20

Target delineation is an essential component of IMRT treatment in cervical and endometrial cancer patients. Multiple consensus guidelines for clinical target volume (CTV) delineation have been published in recent years [6–9]. The treatment paradigm varies by disease site:

- For cervical cancer, surgery is preferred over radiation therapy for early stage disease. Radiation therapy is delivered following surgery in patients with high-risk features such as size ≥4 cm, lymphovascular space invasion (LVSI), deep cervical stromal involvement, positive margins, or locally advanced disease including parametria or lymph node involvement [10, 11].
- For endometrial cancer, treatment consists of upfront surgery, consisting of a total abdominal or laparoscopic hysterectomy and bilateral salpingo-oophorectomy (TAH or TLH-BSO) when possible. Radiation therapy is delivered following surgery in women with adverse pathologic features including high-grade disease deep myometrial invasion, cervical stromal extension, and regional lymph node involvement [12].

Postoperative RT is recommended for endometrial cancer patients at high risk for recurrence in the lymph nodes, including stage I-II non-endometrioid histology or grade 3 endometrioid adenocarcinoma with deep myometrial invasion [13–15]. Whole pelvis RT is strongly considered for patients with stage III–IV disease to reduce the risk of pelvic and para-aortic recurrences [16–19].

A phase III randomized trial comparing vaginal cuff brachytherapy (VCB) and chemotherapy to pelvic RT alone for high-intermediate and high-risk early stage endometrial cancer patients did not demonstrate superiority with the addition of chemotherapy to VCB compared to pelvic RT [20]. Acute toxicity was greater with chemotherapy. As such, whole pelvis RT remains an effective, well-tolerated and appropriate adjuvant treatment in high-risk early stage endometrial carcinomas of all histologies.

Traditionally, most endometrial cancer patients undergoing adjuvant RT received pelvic irradiation. However, low risk, early stage patients undergoing surgical staging who are found to have negative nodes may undergo vaginal brachytherapy alone [21]. For additional details, please refer to the chapter on image guided brachytherapy.

20.2 Diagnostic Workup Relevant for Target Volume Delineation

- All gynecologic cancer patients should undergo a complete history and physical examination including a pelvic exam and evaluation of the inguinal and supraclavicular lymph nodes as part of initial diagnosis and staging. Standard radiographic workup in these patients includes a computed tomography (CT) scan to assess the extent of local disease involvement and sites of extrauterine spread.

- During the pelvic exam, special attention should be given to evaluation of the vaginal vault, rectovaginal septum, and bilateral parametria and sidewalls. Exam under anesthesia is indicated if patient discomfort prohibits a thorough examination.
- Patients suspected to have urinary bladder or rectal involvement should undergo cystoscopy or rectosigmoidoscopy.
- Positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) of the pelvis are useful in selected patients to delineate any residual gross tumor volume or involved lymph nodes. PET/CT is of particular use in diagnostic workup of cervical cancer, to assess for para-aortic nodal spread and distant metastasis [22].

20.3 Simulation and Daily Localization

- Gynecologic cancer patients undergoing postoperative pelvic IMRT are simulated in the supine position. Immobilization of the lower body (and upper body in the setting of extended field radiation), such as with a cradle or Vac-Lok device, is recommended.
- CT simulation with $\leq$3 mm slice thickness is the recommended simulation approach and is performed with (comfortably) full and empty bladder scans which can be fused to generate an integrated target volume (ITV).
- Intravenous contrast is recommended to identify the patient's vasculature as a surrogate for the lymph nodes, unless medically contraindicated.
- Consider use of oral contrast to opacify the small bowel as a critical organ at risk.
- Patients are encouraged to empty their rectum the morning of simulation and for daily treatment. Use of rectal enema may be considered.
- An internal vaginal marker to identify the apex of the vagina and an introitus marker are standard.
- Whenever possible, it is desirable to simulate patients in both the empty and full bladder state, to account for changes in target position due to bladder filling and emptying, such as with an internal target volume (ITV) (Fig. 20.1). Patients should be treated consistently in either a full bladder or empty bladder state to minimize the impact of bladder filling on target motion.
- Daily orthogonal planar imaging (MV or kV) is recommended for setup.
- Weekly imaging with cone beam CT (CBCT) should be done at minimum to verify treatment setup; daily CBCT to monitor variations in bladder and bowel filling can also be done.

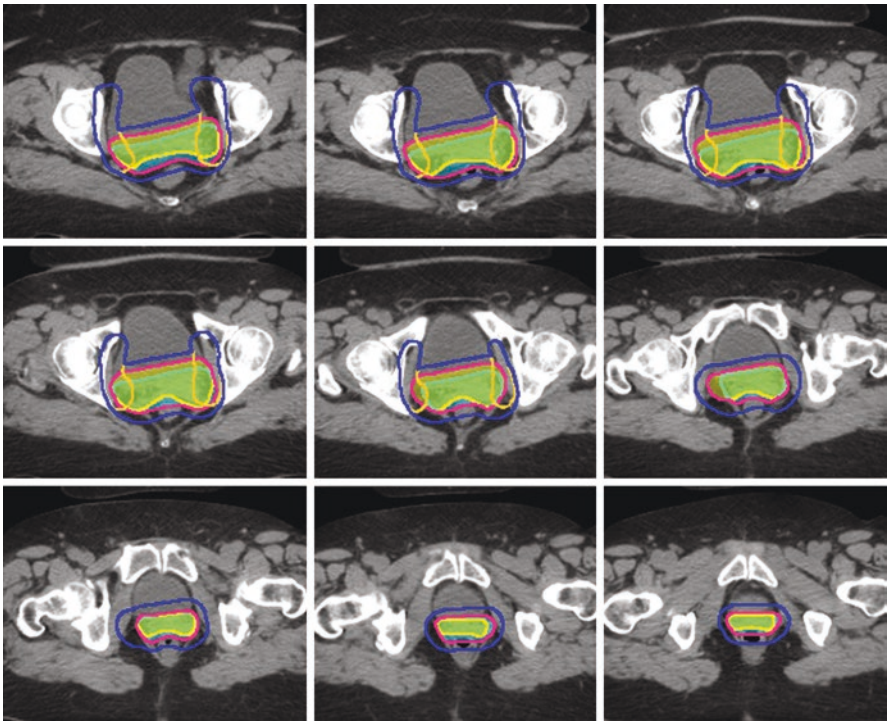

Fig. 20.1 An example of internal target volume (ITV) to planning target volume (PTV) expansion. Target volumes are drawn both on a scan with a full bladder (cyan) and empty bladder (yellow) then combined to make an ITV (red), which is then expanded and included in the PTV (dark blue)

20.4 Target Volume Delineation and Treatment Planning

- Delineated target volumes in cervical and uterine cancer patients undergoing adjuvant pelvic IMRT include multiple CTVs (CTV_1, CTV_2, and CTV_3), to allow for anisotropic CTV to PTV expansions (Fig. 20.2). See Table 20.1 for a detailed description of these components, which were used on TIME-C randomized clinical trial.
- Regarding CTV_1, the anterior portion of the uterosacral ligament is removed during a radical hysterectomy. Consequently, the mesorectal fascia is used as a surrogate structure for the posterior border of the vaginal cuff and parametrium CTV [10].
- Vaginal boost can be considered if at higher risk for recurrence due to factors such as cervical stromal invasion, supracervical hysterectomy, extensive LVSI, or extensive vaginal involvement.

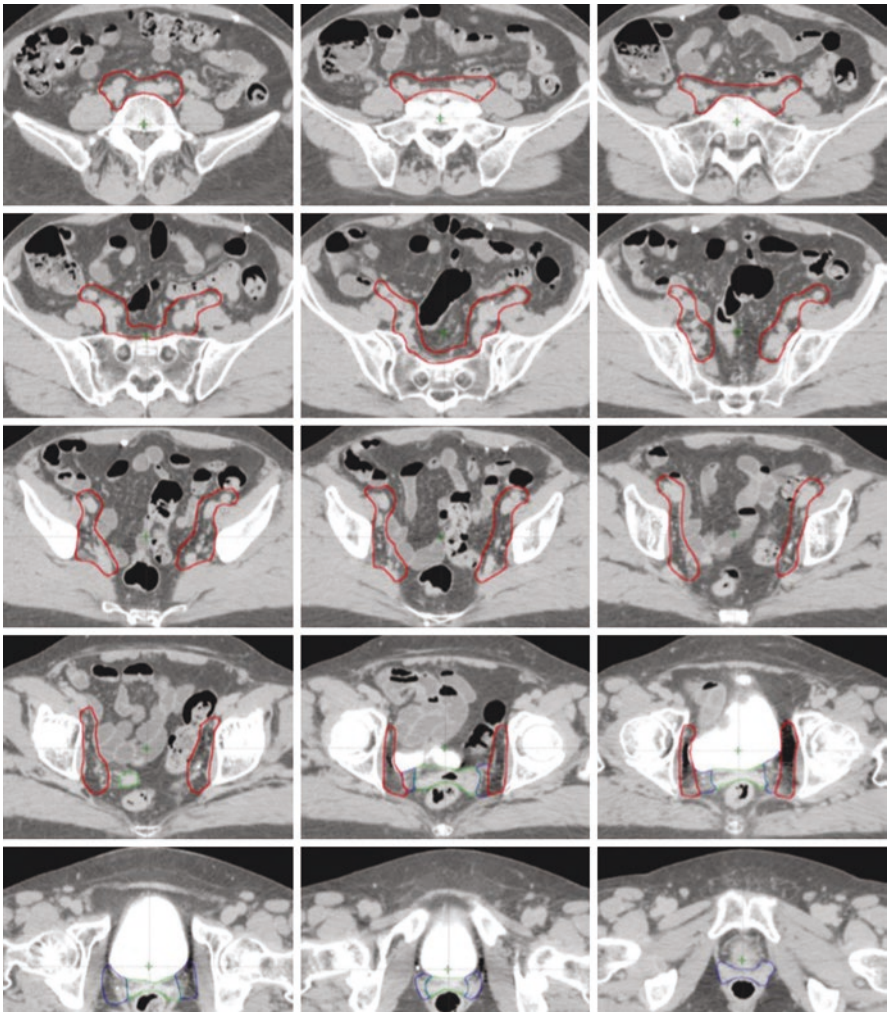

Fig. 20.2 A patient with International Federation of Gynecology and Obstetrics (FIGO) stage IB1 cervical cancer who underwent a radical hysterectomy and pelvic lymphadenectomy. Pathology revealed deep cervical stromal invasion as well as 3 of 15 positive nodes. She was treated with adjuvant intensity-modulated pelvic radiation therapy and concurrent cisplatin. Three clinical target volumes (CTV) are shown: CTV_1 (green), CTV_2 (blue), and CTV_3 (red)

- In endometrial cancer patients, CTV_3 is modified to include the presacral region when there is cervical stromal invasion (Fig. 20.3).
- Extended field RT (i.e., pelvic-para-aortic fields) are often used when patients have pathologic involvement of para-aortic or high common iliac nodes. In this case, the upper border of the CTV may extend to the T12-L1 or L1-L2 interspace, or the renal vasculature (Fig. 20.4).

Table 20.1 Target volumes used in cervical/endometrial cancer patients undergoing postoperative pelvic IMRT

Target volumes	Definition and description
GTV	Not applicable in most settings unless patient is found to have residual gross disease at the time of radiation treatment
CTV_1	Vaginal cuff
	Includes any fat and soft tissue anterior and posterior to the vaginal cuff between the bladder and rectum
CTV_2	Paravaginal/parametrial tissues, proximal vagina (excluding the cuff)
CTV_3	Includes common iliac[a] and external and internal iliac nodal regions
	The common iliac and external and internal iliac regions are defined by including the pelvic vessels plus a 7-mm expansion (excluding bone, muscle, and bowel) as well as all suspicious lymph nodes, lymphoceles, and pertinent surgical clips
	Soft tissues between the internal and external iliac vessels along the pelvic sidewall are included
	Presacral nodes: The presacral area consists of the soft tissues anterior (minimum 1.0 cm) to the S1–S2 vertebrae
	Upper extent: 7 mm inferior to L4–5 interspace
	Lower extent: superior aspect of femoral head (lower extent of external iliacs) and paravaginal tissues at level of vaginal cuff (lower extent of internal iliacs)
	Cervical: In patients with suspected uterosacral involvement, the entire presacral region is included Endometrial: The presacral region is included for patients with cervical stromal involvement
	Inguinal nodes: In cases with distal 1/3 vaginal involvement, inguinal nodes will be contoured continuously from external iliac nodes to 2 cm caudal to the saphenous/femoral junction
PTV_1	CTV_1 + 15 mm
PTV_2	CTV_2 + 10 mm
PTV_3	CTV_3 + 7 mm

IMRT intensity-modulated radiation therapy, *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume. The final PTV is then generated by the union of the PTV_1, PTV_2, and PTV_3: $PTV = PTV_1 \cup PTV_2 \cup PTV_3$

If an ITV approach is used, CTV_1 and CTV_2 should be contoured on both the empty and full bladder scans and subsequently fused to generate an ITV. A 7 mm expansion on the ITV can be used to generate the PTV, which will be combined with PTV_3 for the final PTV

[a] To the level of L4–5 which will not include the entire common iliac nodal region in many patients; for patients undergoing extended field radiation for involved para-aortic disease, CTV3 should be extended to the level of the renal hilum or 2–3 cm above the highest involved node

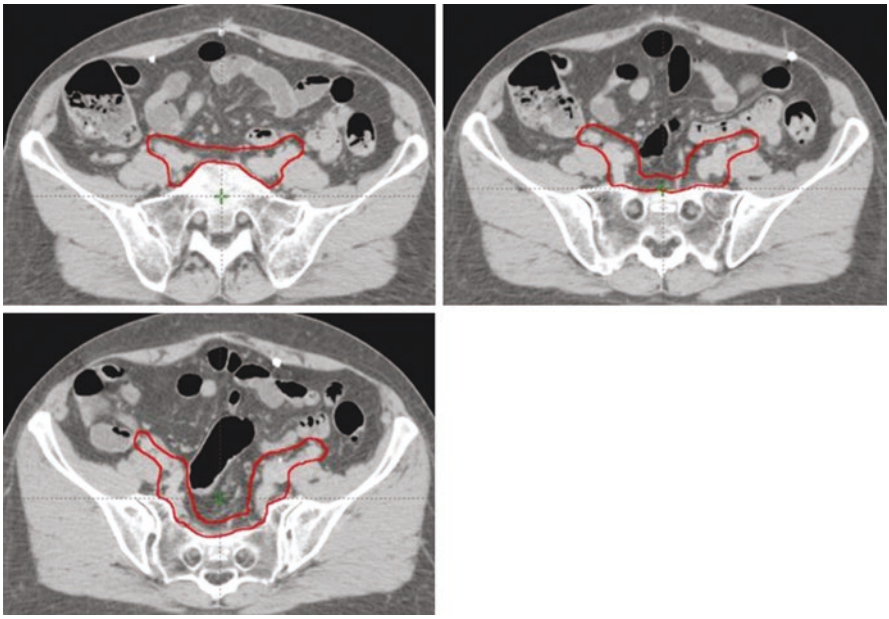

Fig. 20.3 The clinical target volume (CTV_3) (red) is modified in endometrial cancer patients with cervical stromal invasion to include the presacral region

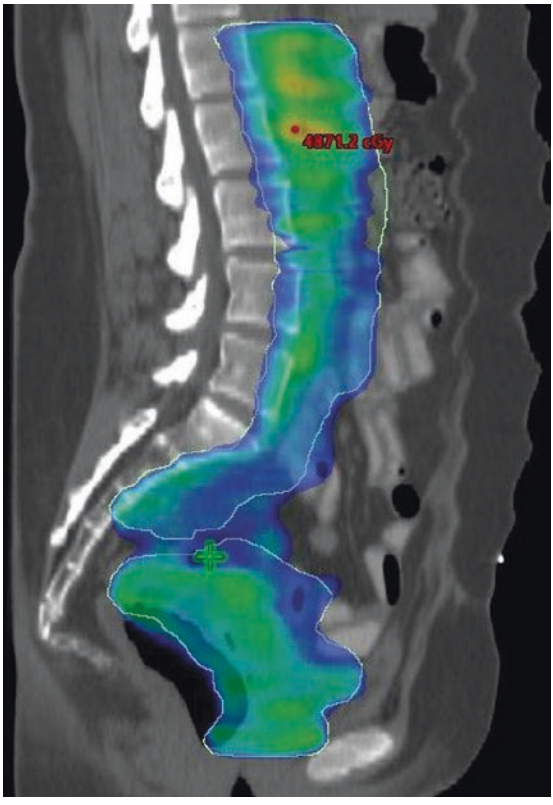

Fig. 20.4 Sagittal cross-section of a planning computed tomography with overlaid prescription isodose in colorwash in a patient with endometrial cancer undergoing postoperative extended field radiation therapy. Planning target volume is shown in light green, extending to the superior border of L1

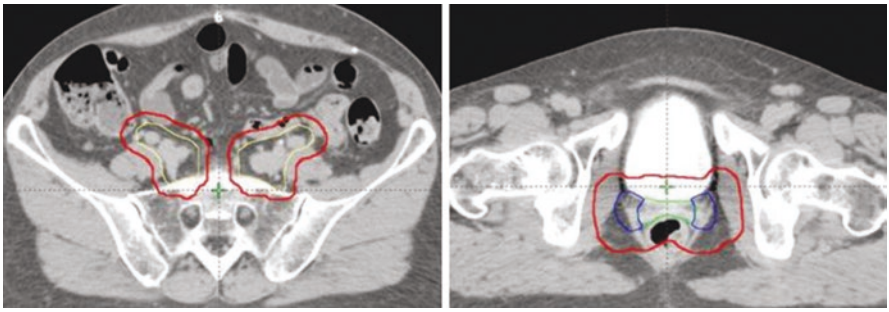

Fig. 20.5 Several planning target volumes (PTV) are generated in the postoperative endometrial cancer patient described in Fig. 20.3. The final PTV used for treatment planning is generated by combining PTV_1, PTV_2, and PTV_3 (and internal target volume (ITV), if defined). The resultant PTV (red) is shown in the figure encompassing CTV_1 (green), CTV_2 (blue), and CTV_3 (yellow)

- Modified extended fields with upper borders between L4-L5 and L1-L2 may be used in patients with extensive pelvic nodal or high common iliac nodal involvement.
- Planning target volumes (PTVs) are created for each CTV (see Table 20.1 for CTV to PTV margins), and the final PTV used for treatment planning is generated by combining the individual PTVs (Fig. 20.5). Different CTV to PTV expansions are used for each CTV component based on its degree of internal organ motion and setup uncertainty.
- A boost of 5–15 Gy may be added for gross nodal disease or parametrial involvement; this may be done sequentially or by an integrated boost (Fig. 20.6).

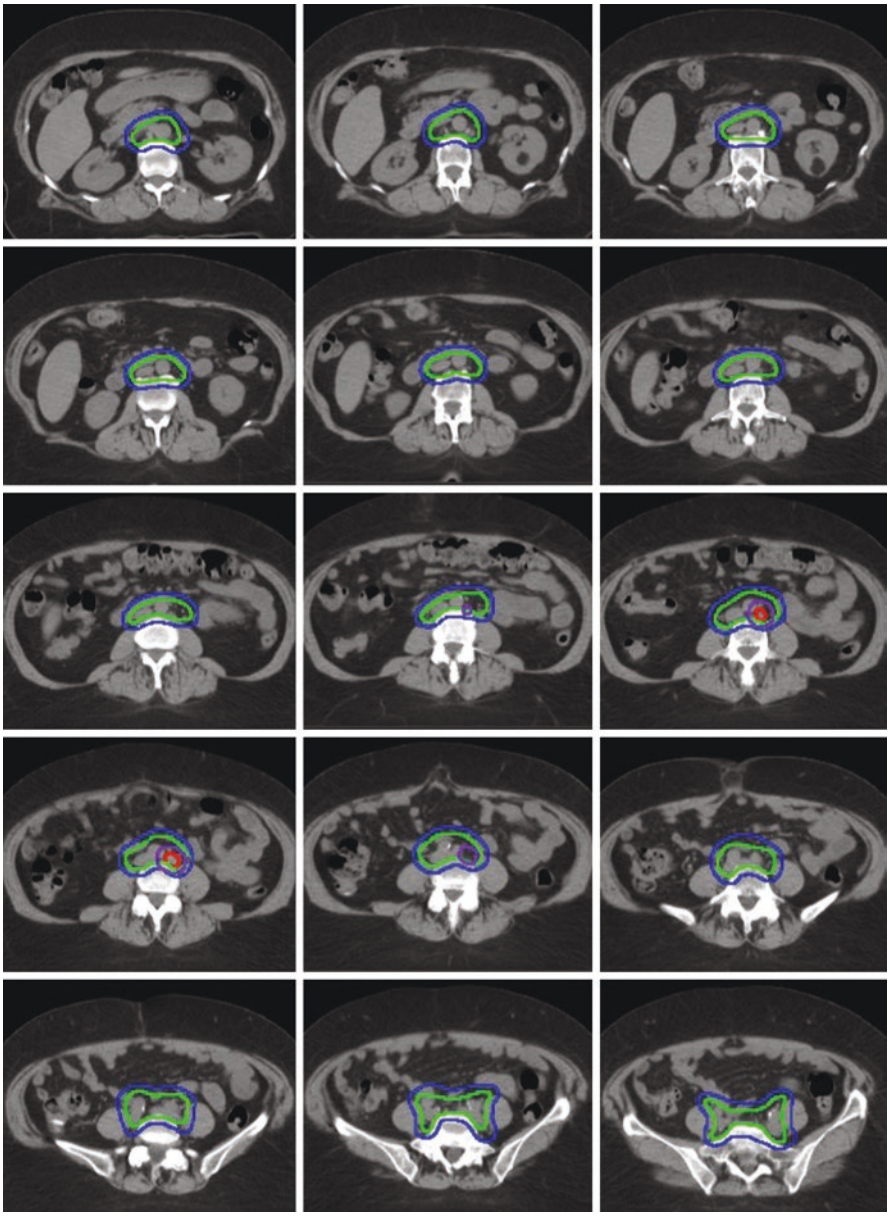

Fig. 20.6 A patient with FIGO stage IB endometrioid adenocarcinoma s/p robotic assisted laparoscopic hysterectomy who was found at the time of CT simulation to have an enlarged para-aortic lymph node. She was treated with extended field IMRT. An ITV technique was used. The superior border of CTV3 (green) was modified to include the renal hilum and the GTV of gross nodal disease is contoured (red). This was given a planned SIB boost 5940 cGy with 4760 cGy in 28 fractions to the other nodes

20.5 External Beam Plan Assessment

- Ideally at least 95% of the PTV should receive 100% of the prescription dose and ≥99% of the PTV will receive ≥90% of the prescription dose.
- The dose maximum should occur within the PTV and dose areas >100% of the prescription dose outside of the PTV should be minimized.
- Organs at risk (OAR) used in treatment planning include the bowel, bladder, and rectum and femoral heads. In patients undergoing adjuvant chemotherapy, the pelvic bone marrow (BM) should be included as this technique has been shown to help reduce the risk of hematologic toxicity [2] (Fig. 20.7). See Table 20.2 for detailed descriptions for delineation of the OARs as well as dose constraints used in gynecological cancer patients undergoing pelvic IMRT treatment planning.
- The bowel contour should include the entire peritoneal space encompassing the bowel such that the superoinferior boundaries extend 1.5 cm superior to the caudal aspect of the PTV and inferiorly to the rectosigmoid junction. In the anterior-posterior direction, the bowel should be delineated from the anterior abdominal wall to the most posterior extent of bowel. The bilateral bowel edges serve as the left-right boundaries.

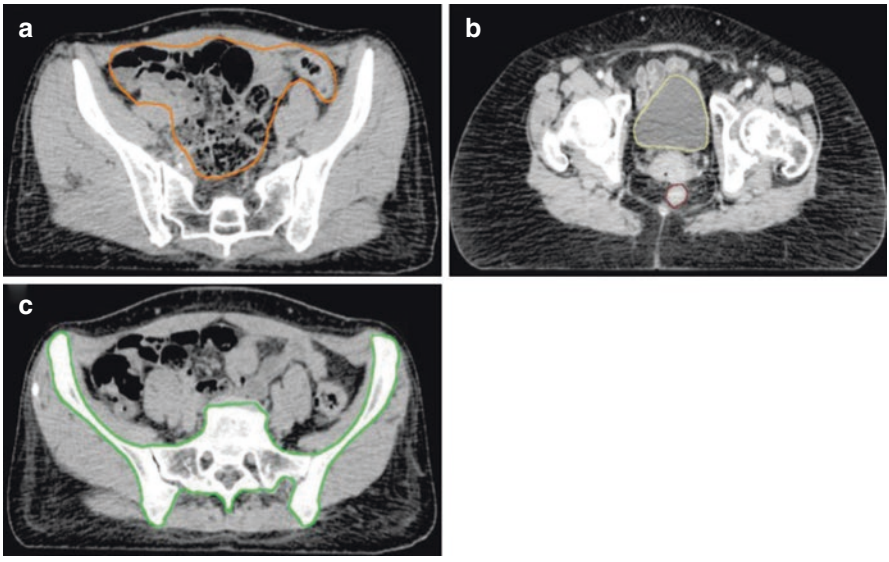

Fig. 20.7 Contours for organs at risk including bowel ((**a**), orange), rectum ((**b**), brown), bladder ((**b**), yellow), and bone marrow ((**c**), green) on representative computed tomography slices

Table 20.2 Organ at risk (OAR) and dose constraints from University of California San Diego guidelines and TIME-C protocol

Organ	Definition and description	Dose constraints
Bowel	Outermost loops of bowel from the level of the L4–5 interspace to the sigmoid flexure. Includes the sigmoid colon and ascending/descending colon present in the pelvis	V35 Gy < 35% V45 Gy < 200 cc
Rectum	Defined by the outer rectal wall from the level of the sigmoid flexure to the anus	V45 Gy < 50%
Bladder	Defined by the outer bladder wall	V45 Gy < 35%
Bone marrow	The pelvic bones serve as a surrogate for the pelvic bone marrow. Regions included are the os coxae, L5 vertebral body, entire sacrum, acetabulae, and proximal femora The superior extent of the contour should be at the level of the superior border of L5 or the iliac crest (whichever is more superior) Inferior extent: ischial tuberosities	V10 Gy < 90% V20 Gy < 75% V40 Gy < 37%
Femoral heads	Entire femoral head excluding the femoral neck	V30 Gy < 15% V50 Gy < 5%
Kidneys	The outer organ contour should be delineated and filled in, treating the right and left kidneys as a solid continuous structure	V18 Gy < 50%
Spinal cord	The spinal cord will be contoured from the level of T10/T11 to the L1/L2 interspace	Dmax < 45 Gy
Duodenum	The duodenum should be contoured and filled in, treating the organ as a solid continuous structure, from the distal stomach to the jejunum	V40 Gy < 50% V55 Gy < 5 cc

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Definitive Therapy for Cervical, Vaginal, and Endometrial Cancer

21

Casey W. Williamson and Loren K. Mell

Contents

21.1 Introduction

IMRT is fast becoming a widely used radiation approach for definitive treatment of gynecologic cancers. Although no large randomized trials comparing IMRT to conventional techniques have been conducted for this population, evidence from numerous phase II trials and controlled studies support the effectiveness and reduced toxicity with IMRT in patients with an intact uterus. Moreover, phase III protocols

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_21

have begun to incorporate IMRT as a standard treatment approach for definitive therapy, indicating its widespread acceptance. However, 3D conformal techniques remain in common use for this population, and delineation of targets and organs at risk (OARs) are also important for defining fixed beam arrangements and evaluating the dosimetry with conventional treatment plans. In contrast to the postoperative setting, application of IMRT in patients with an intact uterus is complicated by even greater mobility of targets and OARs. Moreover, treatment intensity is generally higher, with radiation often given with concurrent chemotherapy and followed by brachytherapy and/or nodal boosts, with higher overall doses delivered. Thus, normal tissue dose is a particularly critical factor in determining both treatment tolerance and risk for high grade late complications. Advanced technologies play a prominent role in defining targets and OARs in this context, which remains an active area of investigation.

21.2 General Principles of Workup, Imaging, and Staging

- All patients should undergo a complete history and physical examination with attention on pelvic exam to size and location of tumor, extent of vaginal extension, and presence of urethral, parametrial, and/or sidewall involvement. Exam under anesthesia may be necessary if patient is unable to otherwise tolerate a thorough examination.
- If there is clinical suspicion for bowel or bladder involvement, pelvic MRI and proctosigmoidoscopy and/or cystoscopy are indicated.
- Dynamic contrast-enhanced MRI is the optimal method for detecting cervix invasion and myometrial invasion, with an accuracy of 85–93% [1], and has been shown to be superior to CT and physical examination for determining tumor size and extent of invasion [2].
- The sensitivity of MRI for detecting lymph node metastases is 27–66% with specificity 73–94% in surgically staged patients [3]. However, PET/CT is preferable if available, with sensitivity and specificity for assessing regional lymph node metastases ranging from 50–100% and 87–100%, respectively [3].
- Radiologic workup with whole-body PET/CT is preferred for patients with at least International Federation of Gynecology and Obstetrics (FIGO) stage IB disease, given its greater sensitivity than CT [4], and is now admissible for FIGO staging purposes [5].
- FIGO has published staging systems for cervical, endometrial, and ovarian cancers [5, 6]. There are also TNM staging systems produced by the American Joint Committee on Cancer [7].

21.3 CT Simulation for Treatment Planning

- CT simulation should be obtained with the patient in a supine position with a customized immobilization cradle to minimize treatment setup error. Scans should be obtained with slice thickness $\leq$3 mm.

- The degree of bladder and rectal fullness at simulation should ideally replicate that which will be observed during daily treatment. Empty and full bladder scans may be fused to generate an integrated target volume (ITV).
- Treatment can be delivered with either a (comfortably) full or empty bladder and it is recommended to use a consistent bladder filling state (i.e., always full or always empty) for both the simulation scan used for treatment planning, and for daily treatment. Treatment with an empty bladder may be more reproducible and reduces the absolute variation in bladder volume, whereas treatment with a full bladder can displace bowel from the treatment field and improve bowel dosimetry [8].
- Bowel preparation with an enema can be used to achieve simulation with an empty rectum.
- Given that the patient's pelvic vasculature serves as a surrogate for lymph node location, simulation with intravenous contrast is recommended, unless medically contraindicated.
- Tools for improving target volume delineation include placement of fiducial markers prior to CT simulation or placing radiopaque markers in the vaginal apex and introitus at the time of simulation.
- Patients with disease involving the distal one-half of the vagina (or vaginal primary) should also receive bilateral inguinal RT, in which case CT simulation can be performed in the "frog-leg" position to minimize skin fold toxicity.

21.4 General Principles of Target Delineation

- IMRT is increasingly used as a standard modality for gynecologic malignancies in the definitive setting. Evidence demonstrates excellent outcomes and an improved toxicity profile, with improvements in gastrointestinal (GI) and hematologic toxicities, as well as reduced risk of pelvic fractures, compared to 3D conformal techniques [9–15].
- Multiple ongoing clinical trials utilize IMRT, with their respective protocols delineating specific treatment planning requirements [16–20].
- Fusion of pre-treatment PET/CT with CT simulation is recommended to assist in delineation of gross tumor volume (GTV).
- See dedicated sections below for target delineation for cervical, vaginal, and endometrial cancers, respectively, with definitions described in Table 21.1. These recommendations are derived from the protocol for the multi-institutional cooperative group phase III NRG-GY006 clinical trial [16]. Note there are varying standards across trials and institutions.
- Accurate target delineation is of critical importance for IMRT planning. International consensus guidelines for contouring definitive cervix cases have been published [21].
- Interactive online sample cases are available on educational websites, such as eContour [22], to assist with contouring.
- An MRI study using injected iron oxide particles suggested that 95% of pelvic (common iliac, internal iliac, medial and anterior external iliac, and obturator)

Table 21.1 Target delineation for cervical cancer (per NRG-GY006 protocol) [16]

Name	Details
GTV	All visible gross disease as assessed by clinical information, physical examination, radiographic studies, endoscopic examination, and biopsy results
CTV1	GTV + cervix + uterus
CTV2	Parametria and upper third of the vagina (or upper half if the vagina is clinically involved)
CTV3	Common, external iliac, internal iliac, and presacral lymph nodes. The upper border should start the aortic bifurcation (approximately L4–L5 interspace). Presacral nodes should be included to the S2–S3 interspace; below this point this nodal volume can be separated into two structures. External iliac nodes should be included to the top of the femoral heads. If there is distal vaginal involvement, the inguinal nodes should be included (from the external iliac nodes to 2cm caudal to the saphenous/femoral junction). If para-aortic nodes are involved, an extended field should be used, extending the superior border to the L1/L2 interspace or 3cm cranial to gross disease. CTV3 should be obtained by placing a 7mm margin around the vessels with inclusion of any adjacent visible lymph nodes, lymphoceles, or surgical clips. This volume should be modified to exclude bone, muscle, and bowel, and should not extend inferior to the ischial tuberosities
CTV_boost	Gross pelvic lymph nodes. If the patient will receive a parametrial boost, this area should be included
ITV	If an ITV approach is to be used, CTV1 should be delineated on both the full and empty bladder scans and combined to generate the ITV
CTV_4500 or CTV_4760	CTV1 + CTV2 + CTV3 + ITV
PTV1	CTV1 + 15 mm uniform expansion
PTV2	CTV2 + 10 mm uniform expansion
PTV3	CTV3 + 5 mm uniform expansion
PTV4	ITV + 7 mm uniform expansion
PTV_boost	CTV_boost + 5 mm uniform expansion
PTV_4500 or PTV_4760	PTV1 + PTV2 + PTV3 + PTV4 + PTV_boost. This should be trimmed up to 3 mm from the skin surface, if necessary, to spare skin. The CTV should be fully encompassed by the PTV

lymph nodes are located within 7 mm of the pelvic vasculature [23]. However, inguinal nodal basins should be delineated using an anatomic compartment approach given greater range of potential lymph node location with respect to the vessels [24].

- Common problems with target delineation observed in multi-center trials include:
  - Inadequate margin around the vasculature/clinical target volume (CTV) that is too close to the vessels
  - Insufficient coverage around the internal iliac vasculature inferior and posterior in the pelvis
  - Insufficient coverage around the obturator vasculature inferior and anterolaterally in the pelvis
  - Insufficient coverage of the presacral region
  - Unnecessary extension of the CTV into the sacral hollows

21.5 Organs at Risk

- Standard organs at risk (OARs) include the bowel, rectum, bone marrow, bladder, and femoral heads. Recommended dose constraints for these structures are outlined in Table 21.2.

Table 21.2 Organ at risk definition (per NRG-GY006 protocol) [16]

OAR	Description	Dose constraints		
All patients		Dosimetric parameter	Per protocol	Variation acceptable
Bowel space	Bowel space should be contoured beginning from the axial slice 1cm above the superior-most slice containing PTV (if not present at this level, then beginning from its most superior extent) and extending to its most inferior extent in the pelvis. The distal descending colon and sigmoid colon should not be included. The volume should include the outermost extent of bowel loops plus any space within the abdominal cavity the bowel may occupy. Individual loops of bowel should not be separately contoured. Rectum should be contoured separately (next row)	V45 (cc) DMax (Gy) D30% (Gy)	≤200 ≤59.4 ≤40	≤250 ≤62.1 ≤50
Rectum	The outer rectal wall should be contoured and filled in and treated as a solid continuous structure, spanning the level of the sigmoid flexure to the anus	D50% (Gy) D60% (Gy) DMax (Gy)	≤45 ≤30 ≤50	≤54 ≤50 ≤55
Bone marrow	The outer bone contour should be delineated and filled in, treated as a solid continuous structure. The os coxae, L4 and L5 vertebral bodies, entire sacrum, acetabulae, and proximal femora should be included. The inferior-most extent should be the level of the ischial tuberosities	Dmean (Gy) V10 (%) V20 (%)	≤27 ≤85.5 ≤66	≤29 ≤90 ≤75
Bladder	The outer wall of the entire bladder should be contoured and filled in, treating the organ as a solid continuous structure	D50% (Gy) DMax (Gy)	≤45 ≤50	≤55 ≤57.5
Femoral heads	The outer contours of bilateral femoral heads should be delineated and filled in, treated as solid continuous structures, not including the femoral necks	D15% (Gy) DMax (Gy)	≤30 ≤50	≤50 ≤55
Extended field patients [17]				
Bilateral kidney	The outer organ contour of each kidney should be delineated and filled in, treated as a solid continuous structure	D50% (Gy)	≤18	≤20
Spinal cord	Should be contoured from T10/T11 to the L1/L2 interspace	D0.03cc (Gy)	≤45	≤47.5
Duodenum	Should be contoured from the outer border and filled in from the distal stomach to the jejunum	D0.03cc D50% (Gy)	≤56 ≤40	≤60 ≤50
Liver	Should be contoured from the outer border and filled in	D50% (Gy)	≤25	≤30

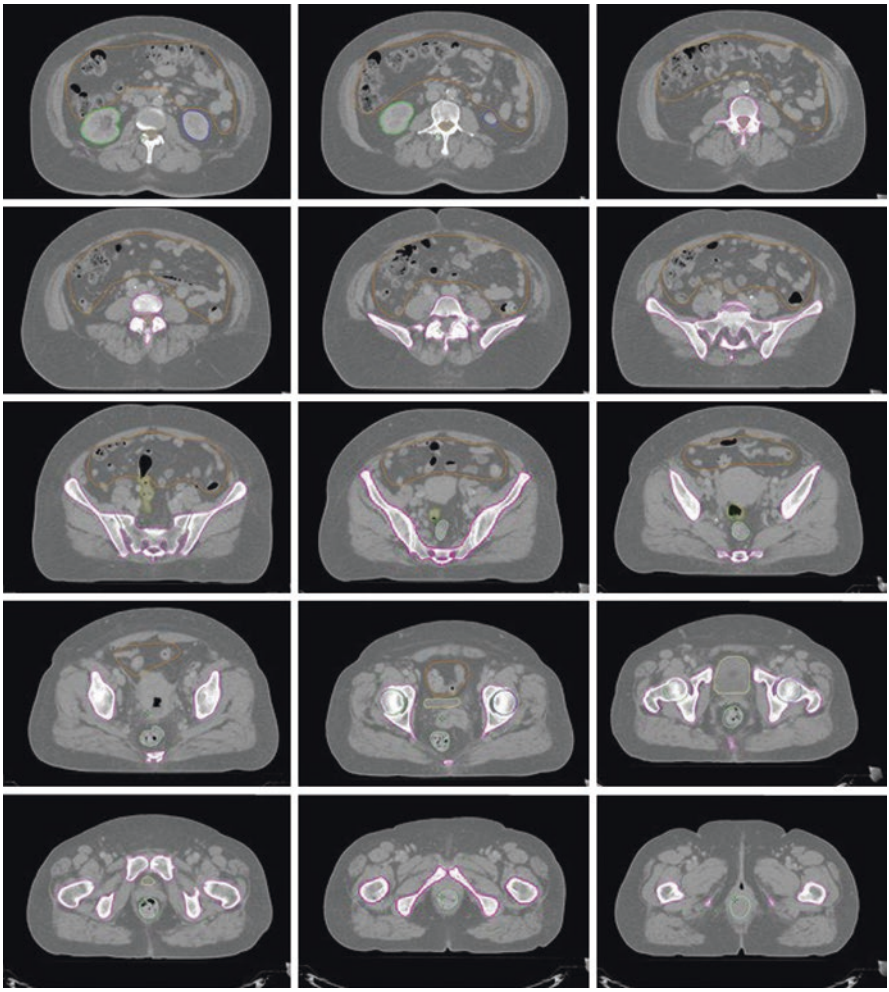

Fig. 21.1 Organs at risk for pelvic IMRT: Representative slices from a patient with FIGO IIIC2 cervical cancer (starting superiorly from the L2/L3 interspace). Contoured are the bladder (yellow), rectum (light green), sigmoid (light brown), bone marrow (pink), bowel space (orange), left kidney (blue), right kidney (green), left formal head (blue), right femoral head (green), spinal canal (orange)

- Figure 21.1 shows representative axial CT slices with OARs contoured for a patient with FIGO IIIC2 cervical cancer treated with extended field RT.
- Normal tissue complication probability (NTCP) modeling studies have established validated dose constraints for bowel [25] and bone marrow [26] in cervical cancer patients undergoing chemoradiotherapy.
- IMRT has been shown to reduce GI toxicity [10, 11] and hematologic toxicity [11], and may improve patient-reported GI and urinary toxicity.

- PET/CT can be used to segment active subregions of bone marrow, where dose accumulation has been correlated with higher rates of hematologic toxicity [27]. Moreover, this approach can reduce the overall bone and bone marrow dose [28]. Sparing metabolically active marrow with IMRT has been found to reduce neutropenia and improve chemotherapy tolerance in prospective clinical trials [11, 29].

21.6 Plan Assessment

- Ideally, at least 95% of the PTV should receive 100% of the prescription dose, and ≥99% of the PTV should receive at least 90% of the prescription dose.
- The dose maximum should occur within the PTV and dose areas >100% of the prescription dose outside of the PTV should be minimized.
- Knowledge-based planning workflows are useful to help achieve optimal dosimetry for more complicated IMRT plans in patients with cervical cancer [30].

21.7 Image-Guided Treatment Delivery

- Patients treated with conventional beam arrangements should undergo at least weekly imaging with MV ports.
- Daily bony imaging with kV or cone beam CT (CBCT) can facilitate reduction of planning margins to 5 mm around the nodal CTV [31, 32].
- Patients treated with IMRT should undergo image guidance with at least weekly CBCT. CBCT with each fraction is recommended, whenever feasible, to check for large variation in target position due to changes in rectal or bladder filling or uterine motion.

21.8 Cervical Cancer

- Regional lymphatic spread typically follows a stepwise pattern by spreading to pelvic nodes before para-aortic nodes. The cervix drains the paracervical lymph nodes which in turn drain into the obturator, internal iliac, and external iliac basins, followed by common iliac and para-aortic nodes.
- Patients with lesions involving the distal vagina are at risk for inguinal nodal metastases.
- Delineated target volumes include a GTV and multiple clinical target volumes (CTVs). See Table 21.1 for detailed descriptions of these volumes.

- If para-aortic nodes are involved, an extended field technique should be employed by extending the cranial border of CTV superiorly to the L1/L2 interspace or 3 cm cranial to the superior-most involved node.
- PTVs are created for each CTV and the final PTV used for treatment planning is the combination of all PTVs. Different CTV-PTV expansions are used for each CTV component based on its degree of internal organ motion and setup uncertainty (29), which have been validated in a separate cohort [30]. Figure 21.1 shows representative axial CT slices for a patient with FIGO IIIC2 disease.
- A typical dose prescription is 45 Gy in 25 fractions to the node-negative pelvis, or 47.6 Gy in 28 fractions if there is nodal disease, with a simultaneous integrated boost (SIB) to involved nodes to 59.4 Gy.
- The nodal boost dose and/or dose per fraction may need to be reduced to respect bowel tolerance; note there are acceptable variations in dose prescription in practice.
- A parametrial boost may be added at the discretion of the treating physician for parametrial involvement as long as that side is not to receive a SIB within the parametrial boost field. Conventional AP/PA fields for a parametrial boost include the sacroiliac joints (upper border), bottom of the obturator foramen (lower border), and obturator internus muscle (lateral borders) with a 4–5 cm midline block. A typical dose prescription is 6–10 Gy in 3–5 fractions.
- Brachytherapy boost is standard towards the end of or following the completion of EBRT. See the following chapter for further discussion.
- Figure 21.2 shows sample slices from the CT simulation scan for a patient with IB1 cervical cancer treated with pelvic IMRT.
- Figure 21.3 shows sample slices from the CT simulation scan for a patient with IIIC2 cervical cancer treated with extended field IMRT.

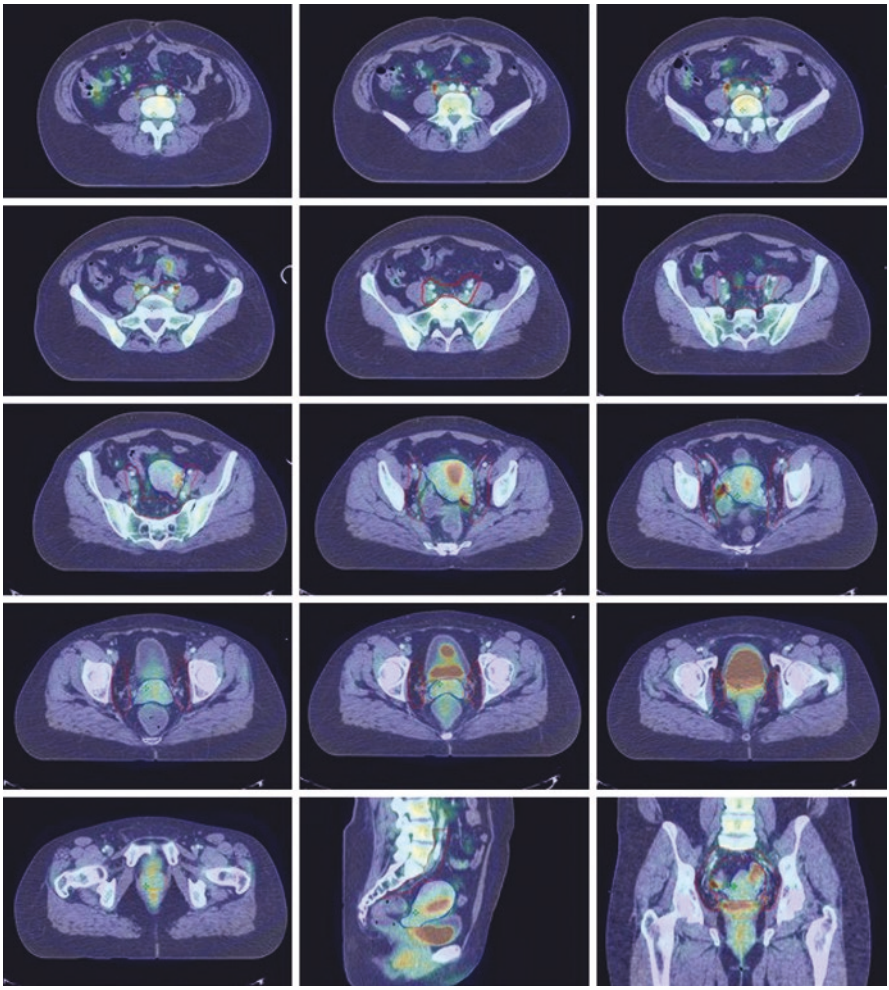

Fig. 21.2 Representative slices from the CT simulation plan for a patient with FIGO IB1 cervical squamous cell carcinoma who had undergone a large size cold knife cone biopsy. The patient's pre-treatment PET/CT was fused to the planning CT. Shown are CTV1 (blue), CTV2 (orange), and CTV3 (red). She received 45 Gy in 25 fractions to the pelvis with concurrent cisplatin followed by an HDR intracavitary boost of 28 Gy in 4 fractions

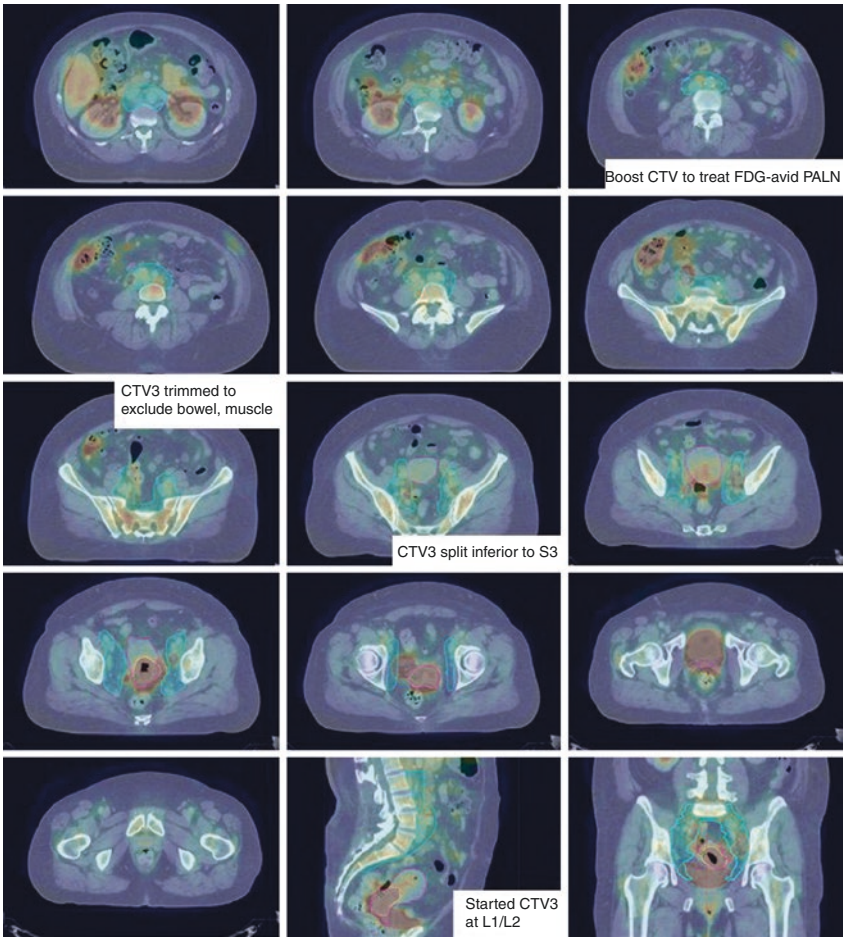

Fig. 21.3 Representative slices from the CT simulation scan for a patient with FIGO IIIC2 cervical squamous cell carcinoma with parametrial involvement and PET/CT-positive para-aortic lymph nodes. Planning was done on an empty bladder and the PET/CT was fused to the planning CT scan. Shown are the primary GTV (yellow), nodal GTV (orange), CTV1 (pink), CTV2 (purple), and CTV3 (cyan). The prescribed plan was for 47.6 Gy in 28 fractions to the pelvis with an SIB boost to gross nodes to 59.4 Gy although bowel tolerance limited the boost dose to 58 Gy for bowel-adjacent nodes to be followed by HDR brachytherapy boost

21.9 Vaginal Cancer

- Vaginal cancer primaries are a relatively rare entity, as any tumor involvement of either cervix or vulva results in classification of cervical or vulvar cancer, respectively. There is a lack of prospective data to guide management specifically for vaginal cancers. The recommended treatment approach is individualized and often follows guidelines for cervical cancer.
- Definitive RT, consisting of EBRT and brachytherapy, is an excellent treatment option for stage I disease, although definitive surgery is an option for select

patients with non-bulky, distal, non-urethral disease. Definitive chemoradiation therapy is a standard for stages II-IVA [33–35].

- The standard EBRT approach is pelvic RT with coverage of the entire vagina.
- Patients with disease involving the distal one-half of the vagina should receive bilateral inguinal RT.
- Temporary fiducial markers can be used to delineate the vaginal apex and introitus at the time of CT simulation.
- A typical EBRT dose prescription is 45 Gy in 25 fractions to the pelvis and entire vagina, typically followed by a brachytherapy boost (e.g., 6 Gy × 4 fractions).
- Figure 21.4 shows sample slices from a CT simulation for a patient with stage IVA (T4N0M0) squamous cell carcinoma of the distal posterior vagina with rectal involvement, treated with pelvic IMRT.

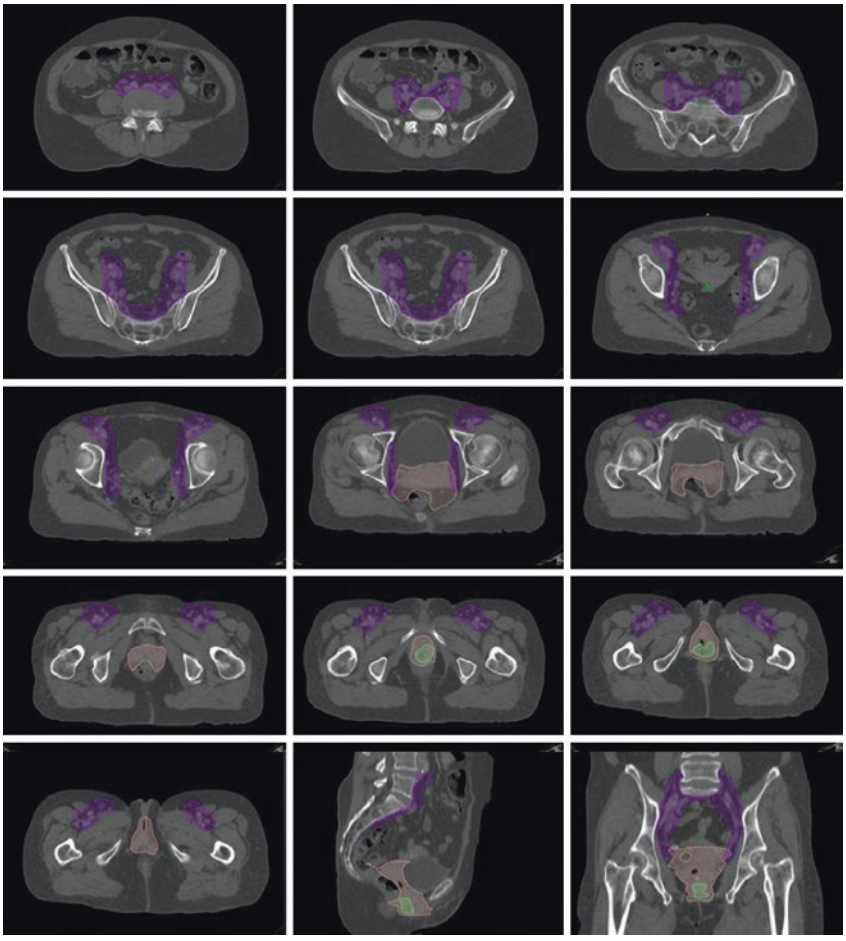

Fig. 21.4 Representative slices from CT simulation scan for a patient with a stage IVA (T4N0M0) squamous cell carcinoma of the distal posterior vagina with concern for rectal involvement. Contours shown are CTV1 (light green), CTV2 (orange), and CTV3 (purple). The pelvis received 45 Gy in 25 fractions, followed by an HDR brachytherapy boost of 21.5 Gy in 3 fractions

21.10 Endometrial Cancer

- The uterus is bordered anteriorly by the bladder and posteriorly by the rectum. It is covered by peritoneal reflections and is divided into the fundus, isthmus, and cervix.
- The uterine wall consists of an outer smooth muscle layer (the myometrium) and an inner layer of glandular epithelium (endometrium).
- The uterus is supported by five ligaments: broad, round, cardinal, uterosacral, and vesicouterine.
- Nodal areas at risk for uterine cancer patients include the obturator, external iliac, internal iliac, common iliac, and para-aortic lymph nodes.
- Lesions involving the uterine fundus can spread directly to the para-aortic nodes.
- The incidence of pelvic and para-aortic lymph node involvement varies according to risk categories (low, medium, and high), as well as tumor size and depth of invasion, as defined in the Gynecologic Oncology Group (GOG) 33 trial [36]
- Hysterectomy is standard treatment for patients who are surgical candidates, with consideration for adjuvant RT based on pathologic risk features.
- For medically inoperable patients, standard treatment is definitive RT with brachytherapy, with or without EBRT. EBRT alone can be considered for patients who are ineligible for or refuse brachytherapy [37–39]. Patients with recurrent disease may also be candidates for EBRT.
- For patients to be treated with EBRT + brachytherapy, a standard EBRT dose is 45 Gy in 25 fractions.
- For patients treated with EBRT alone, pelvic RT can be followed by a cone-down boost to the uterus and cervix. SBRT can be considered if the patient is unable to receive brachytherapy.
- Target delineation is similar to pelvic RT for cervical cancer (Table 21.1).
  - GTV includes all gross disease based on all available clinical and radiologic data.
  - The CTV is divided into three subregions: CTV1, CTV2, and CTV3
    a. CTV1: GTV + entire uterus
    b. CTV2: paravaginal/parametrial tissues plus 3cm of the proximal vagina
    c. CTV3: same as in the postoperative setting (see postoperative chapter)
  - In patients with distal one-third vaginal involvement, the inguinal nodes should be contoured continuously from the external iliac nodes to 2 cm caudad to the saphenous/femoral function.
  - If para-aortic nodes are involved, an extended field technique should be employed by extending the cranial border of CTV3 in a similar fashion to that described in Table 21.1.
  - Each CTV should be expanded differentially to form PTV1, PTV2, and PTV3 (15 mm, 7–10 mm, and 5–7 mm margins, respectively).
- An additional boost of 5–15 Gy may be added for gross nodal disease or parametrial involvement, which may be done with an SIB or a sequential approach.
- Figure 21.5 shows a pre-treatment MRI from a patient with medically inoperable FIGO stage IB endometrial cancer demonstrating deep myometrial invasion.
- Figure 21.6 shows sample slices from the CT simulation scan for the same patient who was treated with definitive radiation therapy.

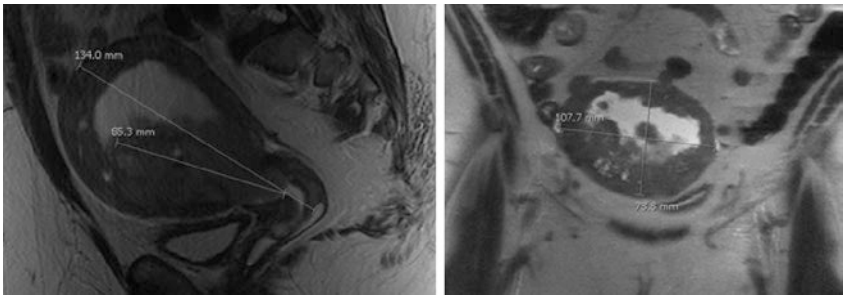

Fig. 21.5 Sagittal (left) and coronal (right) pre-treatment pelvic MRI from a patient with a medically inoperable FIGO IA endometrial cancer with a 7.0 × 4.7 × 0.5 cm mass in the anterior body/lower uterine segment involving more than 50% of the myometrium and extending into the upper cervix

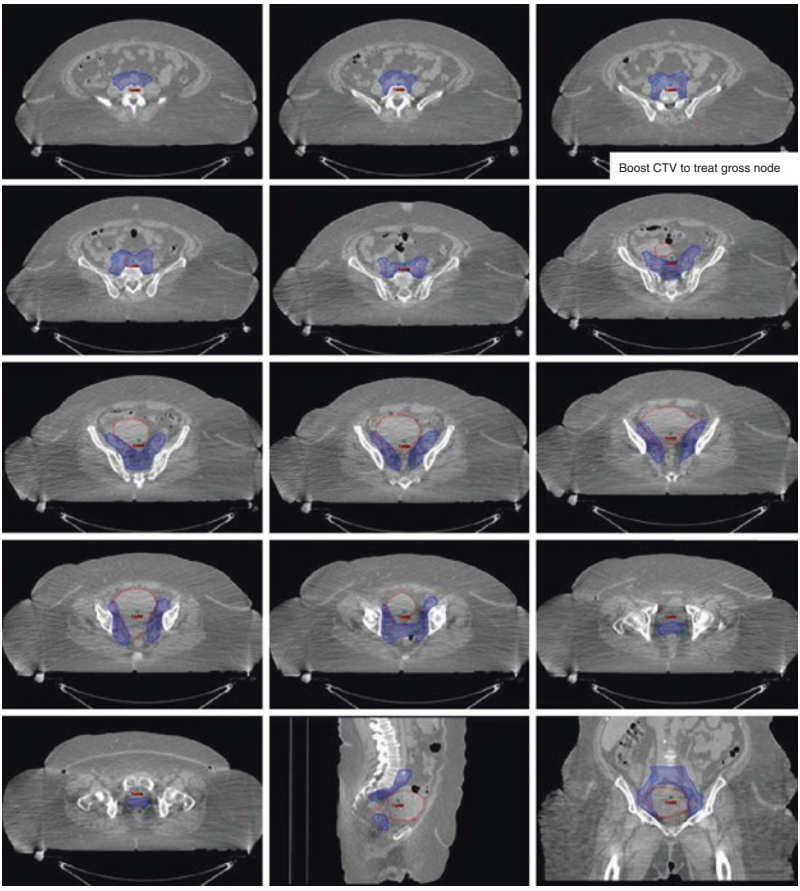

Fig. 21.6 Representative slices from CT simulation scan for a patient with FIGO stage IB medically inoperable endometrial cancer with pelvic adenopathy (same patient as Fig. 21.5). The pre-treatment pelvic MRI was fused to the CT simulation scan. Shown are CTV1 (red), nodal CTV (dark blue), and CTV Boost (light blue). She received 50.4 Gy in 28 fractions to the pelvis with a boost to the suspicious pelvic lymph node to a total of 56.4 Gy and an HDR brachytherapy boost of 20 Gy in 5 fractions with an intracavitary applicator

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Image-Guided Brachytherapy

22

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Contents

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_22

22.1 General Principles

- All patients should undergo a complete history and physical examination including a pelvic examination during initial diagnosis and staging. Standard radiographic workup in these patients includes a contrast-enhanced computed tomography (CT) scan, PET/CT and/or pelvic MRI to assess the extent of local disease involvement and sites of metastatic spread.
- Brachytherapy treatment planning and delivery guidance is given by the American Brachytherapy Society (ABS) [1] and GEC-ESTRO [2–4].
- Applicator choice should consider histopathologic diagnosis, tumor size, topography, extension to nearby organs, and response to radiotherapy or chemoradiotherapy when applicable.
- Brachytherapy is the standard central boost technique for cervical and uterine cancer patients and other techniques including stereotactic body radiotherapy (SBRT) are options only in the context of a clinical trial or in patients who refuse brachytherapy.
- All patients should be counseled on long-term toxicities of brachytherapy and use of a vaginal dilator if not having regular vaginal intercourse.
- Follow-up should be coordinated within a multidisciplinary team.

22.2 Cervical Cancer

- The use of brachytherapy in definitive treatment improves local control, disease-free survival (DFS), and overall survival (OS) [5–7].
- Brachytherapy should be initiated Week 3–5 of external beam radiation (EBRT).
- Total treatment time should be 56 days or less.
- In the postoperative setting, patients with a positive vaginal margin should receive brachytherapy following EBRT.

22.2.1 Initial Evaluation and Applicator Choice

- Full history and physical exam
- Labs: CBC, CMP (chemistry, LFTs, BUN, Cr)
- Radiographic studies:
  - Contrast-enhanced CT chest/abdomen/pelvis at diagnosis
  - Whole body PET/CT recommended at diagnosis
  - Pelvic MRI (along with cystoscopy and/or sigmoidoscopy) at diagnosis if concerns regarding bladder and/or rectal invasion
  - Pelvic MRI recommended for brachytherapy planning in patients with larger (>4 cm) tumors

- Brachytherapy applicator dependent on tumor size, parametrial extension, vaginal extension:
  - Intracavitary alone: tumor size <4 cm, <1 cm vaginal involvement, non-bulky parametrial disease
  - Hybrid intracavitary/interstitial: tumor size 3–5 cm, parametrial disease, irregular tumor topography, difficulty meeting organs-at-risk (OAR) constraints
  - Interstitial alone: tumor size >5 cm, >1 cm vaginal involvement, bulky parametrial disease, difficulty meeting OAR constraints
- Transabdominal or transrectal ultrasound (US) can be used to guide tandem placement.
- Transrectal US can also be useful in cases where a tandem tract needs to be created or to guide needle placement for hybrid/interstitial cases.
- Additional considerations for patients with pre-existing fistula(s):
  - Vesico-vaginal fistula: consider diverting nephrostomy tubes
  - Rectovaginal fistula: divert prior to initiation of radiation

22.2.2 Implant Evaluation

- Thin-slice CT or MRI with applicator for 3D treatment planning.
- Tandem should be placed in cervix and uterus.
  - If using ring, the ring should be flush against the cervix.
  - If using ovoids, tandem should bisect the ovoids.
  - Ensure vaginal packing does not displace ring or ovoids
- If using interstitial needles, review for tumor coverage and proximity to critical structures.

22.2.3 Volume Delineation

- Target structures and OAR delineation for intact cervical cancer are in Table 22.1.
- Ensure full dose coverage of uterus in cases with uterine extension.

Table 22.1 Intact cervical cancer brachytherapy target volumes and OARs (Figs. 22.1 and 22.2)

Structure	Description
GTV	Macroscopic tumor at time of brachytherapy seen on MRI
HRCTV	GTV, cervix, macroscopic extension or parametrial involvement at time of brachytherapy
IRCTV(3)	HRCTV + 1 cm margin, can include initial disease extension at diagnosis (often used in Europe, less commonly used in the United States)
Bladder	Contour outer bladder wall
Rectum	Contour outer rectal wall from above the anal sphincter to level of transition into the sigmoid
Sigmoid	Contour outer sigmoid wall from rectosigmoid flexure to 2 cm superior to uterus and parametria

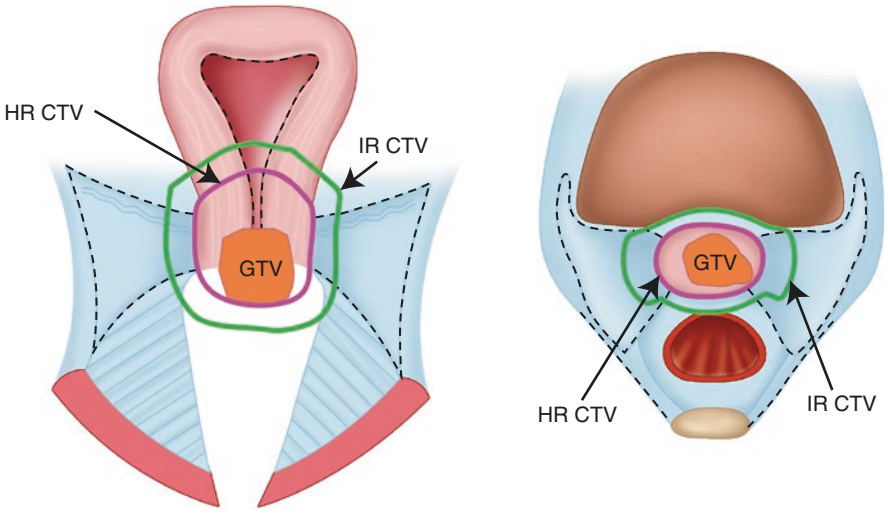

Fig. 22.1 Suggested image-guided brachytherapy target volumes from the Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (Haie-Meder et al. [2]). HRCTV high-risk clinical target volume, IRCTV intermediate-risk clinical target volume, GTV gross tumor volume. (Used with permission)

- If using CT for planning, target volumes often overestimate extent of disease.
- If using MRI for planning, definition of the GTV is possible.

For postoperative cervical cancer with a positive vaginal margin, the upper 1/3 of the vagina should be treated.

22.2.4 Treatment Planning

- Common dose and fractionation schedules for intact cervical cancer are in Table 22.2.
- Postoperative cervical cancer with positive vaginal margin is typically treated with EBRT to 45 Gy in 25 fractions followed by vaginal cuff brachytherapy to 15 Gy in 3 fractions dosed to the surface of the upper vagina.
- Planning dosimetry goals are in Table 22.3.

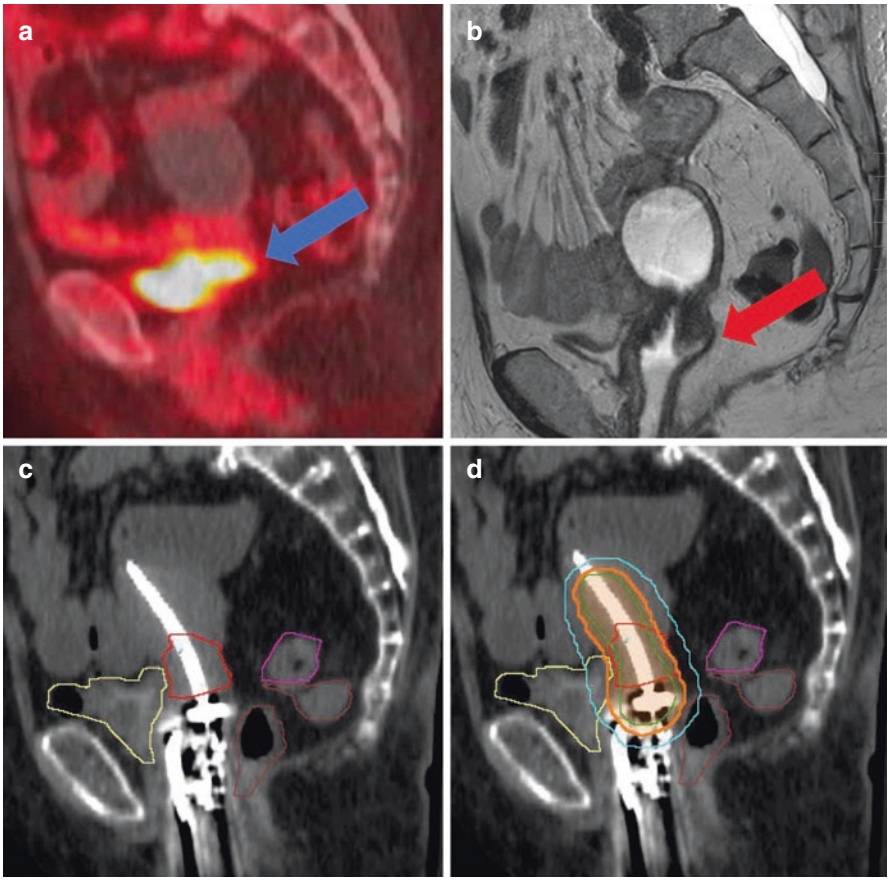

Fig. 22.2 FIGO IIB cervical cancer. Sagittal views of (**a**) PET/CT with FDG-avid tumor posterior to bladder (blue arrow) and (**b**) T2-weighted pelvic MRI showing posterior cervical tumor (red arrow). (**c**) Tandem and ovoids applicator with HRCTV in red, rectum in brown, sigmoid in magenta, bladder in yellow. (**d**) Applicator with dose distribution. 1050 cGy in green, 700 cGy in orange, 400 cGy in cyan

Table 22.2 Intact cervical cancer HDR EQD2 for common dose and fraction schedules

Total EBRT (Gy)	# HDR fractions	HRCTV dose per fraction (Gy)	Total HRCTV dose (Gy)	Total HRCTV $EQD2_{10}$ (Gy)
45	4	7.0	28.0	83.9
45	5	5.5	27.5	79.8
45	5	6	30	81.8
45	3	8.0	24.0	80.3

Dose contribution from EBRT is assumed to be prescription dose (45 Gy) and doses are cumulative EQD2 (α/β = 10 for target, α/β = 3 for normal tissues) for HDR and physical doses for PDR/LDR

Table 22.3 Cervical cancer brachytherapy target volume and OAR goals

Structure	Dosimetric parameter	Ideal Goal $EQD2_3$ (Gy)	Maximum constraint $EQD2_3$ (Gy)
HRCTV ($EQD2_{10}$)	$D_{90\%}$ (Gy)	≥80	–
Bladder	D_{2cc} (Gy)	≤80	≤90
Rectum	D_{2cc} (Gy)	≤65	≤75
Sigmoid	D_{2cc} (Gy)	≤70	≤75

22.3 Endometrial Cancer

- Brachytherapy can be used in the postoperative adjuvant, recurrent, and medically inoperable settings for uterine cancer.
- Upfront surgery is standard for patients who have operable endometrial cancer.
- Lymph node assessment should be considered in patients with FIGO grade 2–3 disease, >2 cm gross disease intraoperative, and/or >50% myometrial invasion.

22.3.1 Postoperative Adjuvant Treatment

- Adjuvant radiation therapy reduces risk of local recurrence in patients with adverse pathologic features including high-grade disease, deep myometrial invasion, cervical stromal extension, LVSI, and regional lymph node involvement [8–12].
- Treatment recommendations for adjuvant therapy are in Table 22.4.
- Vaginal brachytherapy should commence within 12 weeks of surgery, only after pelvic exam to assess for cuff healing.
- Vaginal brachytherapy boost following EBRT should commence within 2 weeks of finishing EBRT.

22.3.1.1 Initial Evaluation and Applicator Choice

- Full history and physical exam
- Labs: CBC, CMP (chemistry, LFTs, BUN, Cr)
- Radiographic studies:
  - Clinical stage I patients do not require routine imaging workup
  - Contrast-enhanced CT chest/abdomen/pelvis for patients with locally advanced disease

22.3.1.2 Implant Evaluation

- Thin-slice CT with applicator for 3D treatment planning.
- Vaginal cylinder should be largest diameter tolerated by patient.
- Verify applicator is flush with apex of the vaginal cuff and achieves mucosal contact.
- Verify vaginal length.

Table 22.4 Adjuvant treatment recommendations for endometrial cancer

AJCC stage	GRADE	LVSI	PLND	Cervical involvement	Chemo	Pelvic EBRT	Brachytherapy
IA	1	Any	Any	N/A	No	No	No
	2	No	Any	N/A	No	No	No
		Yes	Any	N/A	No	No	Yes
	3-Adeno	Any	Any	N/A	No	No[a]	Yes
	3-PS/CC	Any	Any	N/A	No/Yes	Yes	No
		Any	Any	N/A	Yes	No	Yes
IB	1	No	Any	N/A	No	No	No
		Yes	Any	N/A	No	No	Yes
	2	No	Any	N/A	No	No	Yes
		Yes	Any	N/A	No	No	Yes
	3-Adeno	No	Any	N/A	No	No[a]	Yes
		Yes	Any	N/A	No	Yes	No
	3-PS/CC	Any	Any	N/A	Yes	Yes	No
		Any	Any	N/A	Yes	No	Yes
II	1–2	No	No	Yes	No	No	Yes
		Yes	No	Yes	No	Yes	Yes
	1–2	No	Yes	Yes	No	No	Yes
		Yes	Yes	Yes	No	No	Yes
	3-Adeno	Any	Any	Yes	No	Yes	Yes
	3-PS/CC	Any	Any	Yes	Yes	No	Yes
		Any	Any	Yes	Yes	Yes	Yes
IIIA	1	Any	Any	No	Yes	No/Yes	No
		Any	Any	Yes	Yes	Yes	Yes
	2–3	No	Any	No	Yes	Yes	No
		Yes	Any	Any	Yes	Yes	Yes
		Any	Any	Yes	Yes	Yes	Yes
IIIB	Any	Any	Any	Any	Yes	Yes	Yes
IIIC1	1	Any	Any	No	Yes	Yes	No
		Any	Any	Yes	Yes	Yes	Yes
	2–3	No	Any	No	Yes	Yes	No
		Yes	Any	Any	Yes	Yes	Yes
		Any	Any	Yes	Yes	Yes	Yes
IIIC2	1	Any	Any	No	Yes	N/A	No
		Any	Any	Yes	Yes	N/A	Yes
	2–3	No	Any	No	Yes	N/A	No
		Yes	Any	Any	Yes	N/A	Yes

LVSI = lymphovascular space invasion, PLND = pelvic lymph node dissection, PS = papillary serous histology, CC = clear cell histology

EFRT depends on uterine risk factors and LN status/risk of involvement

[a] Denotes patients eligible for GOG 249 and pelvic RT should be considered

22.3.1.3 Volume Delineation

- Brachytherapy alone: upper 1/3 to 1/2 of vagina depending on tumor characteristics
- Brachytherapy following EBRT: upper 1/3 to 1/2 of vagina

22.3.1.4 Treatment Planning

- Common dose and fractionation schedules for postoperative endometrial cancer are in Table 22.5.

Table 22.5 Common dose and fractionation schedules for postoperative endometrial cancer

(A) Vaginal cuff brachytherapy alone schedules			
Prescription point	# Fractions	Dose per fraction (Gy)	
0.5 cm Depth from vaginal surface	3	7	
	4	5.5	
	5	5	
	6	2.5	
Vaginal surface	4	8.5	
	5	6	
	6	4	
(B) Vaginal cuff brachytherapy boost schedules after EBRT (See Fig. 22.3)			
EBRT dose and fractionation	Prescription point	# HDR fractions	Dose per fraction (Gy)
45 Gy in 25 fractions	Surface	3	5
50.4 Gy in 28 fractions	Surface	2	6

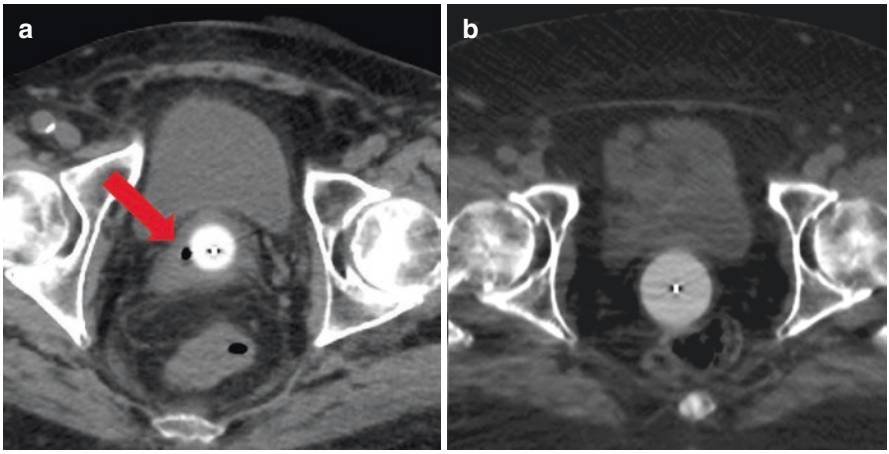

Fig. 22.3 Vaginal cuff brachytherapy applicator with (**a**) small air gap (red arrow) at apex and (**b**) without air gaps

Table 22.6 Inoperable uterine cancer definitive radiotherapy recommendations

AJCC stage	Grade	EBRT	Brachytherapy
I	1	No	Yes
	2–3		Yes
II	Any	Pelvic RT	Yes
IIIC1	Any	Pelvic RT	Yes
IIIC2	Any	EFRT	Yes

22.3.2 Medically Inoperable Endometrial Cancer

- Definitive radiotherapy consisting of brachytherapy +/− EBRT is standard treatment.
- EBRT alone is not preferred, and should only be offered to patients who refuse or are ineligible for brachytherapy.
- Treatment recommendations for definitive therapy are in Table 22.6.

22.3.2.1 Initial Evaluation and Applicator Choice

- Full history and physical exam.
- Labs: CBC, CMP (chemistry, LFTs, BUN, Cr).
- Radiographic studies: Pelvic MRI at baseline recommended to determine full extent of disease.
- Patients with uterine width <4 cm may be treated with a tandem and cylinder or tandem and ring.
- Patients with uterine width >4 cm will require a double tandem applicator.

22.3.2.2 Implant Evaluation

- Thin-slice CT with applicator for 3D treatment planning.
- For single tandem, ensure tandem is in the uterus and reaches fundus.
- For double tandem, ensure tandems are in the uterus, ideally with tips in the bilateral cornu for optimal dose distribution.

22.3.2.3 Volume Delineation

- Use MRI to guide GTV delineation.
- CTV should include the entire uterus, cervix, and upper 1–2 cm of the vagina.

22.3.2.4 Treatment Planning

- Common dose and fractionation schedules for postoperative endometrial cancer are in Table 22.7.

22.3.3 Locally Recurrent Endometrial Cancer

- For patients without prior radiotherapy or with an out-of-field recurrence, salvage radiotherapy is recommended for vaginal or pelvic recurrences.

Table 22.7 Common dose and fractionation schedules for inoperable uterine cancer

(A) Brachytherapy alone schedules			
# HDR fractions	Dose per fraction (Gy)	$EQD2_{10}$ (Gy)	
4	8.5	52.4	
5	8	60	
5	7.3	52.6	
6	6.4	52.5	
6	6	48	
(B) Brachytherapy boost schedules following EBRT (See Fig. 22.4)			
EBRT dose and fractionation	# HDR fractions	Dose per fraction (Gy)	$EQD2_{10}$ (Gy)
45 Gy in 25 fractions	2	8.5	70.5
	3	6.5	71.1
	3	6.3	69.9
	4	5.2	70.6
	5	5	75
50.4 Gy in 28 fractions	2	6	65.6
	6	3.75	75.3

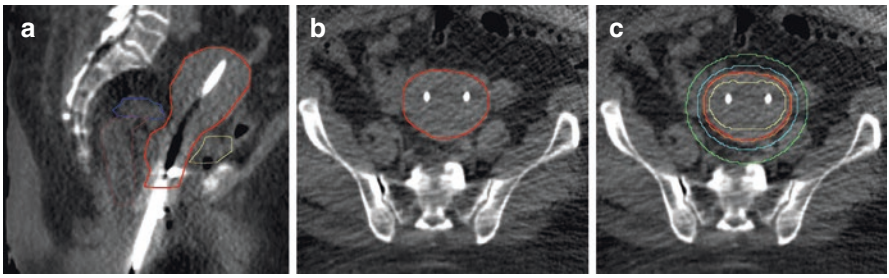

Fig. 22.4 Medically inoperable endometrial cancer with Y applicator brachytherapy following EBRT. (**a**) Sagittal view with applicator in place. HRCTV in red, rectum in brown, sigmoid in blue, bladder in yellow. (**b**) Axial view with applicator in place and HRCTV in red. (**c**) Axial view with dose distribution. 780 cGy in yellow, 520 cGy in orange, 390 cGy in cyan, 260 cGy in green

  - EBRT: 45 Gy in 25 fractions.
  - Brachytherapy: total EQD2 of 70–80 Gy.
  - For patients previously treated with pelvic radiation who present with a vaginal recurrence, salvage surgery could be considered. If surgery is unable to be performed, salvage radiotherapy may consist of reduced-dose EBRT and brachytherapy +/− chemotherapy.
  - Reduced-dose EBRT: 30.6–36 Gy in 17–20 fractions.
  - Brachytherapy dosing depends on normal tissue tolerance and prior dose.
- For patients previously treated with pelvic radiation who have a non-vaginal pelvic recurrence, salvage radiotherapy may consist of reduced-dose EBRT and/or SBRT +/− chemotherapy.

  - Reduced-dose EBRT: 30.6–36 Gy in 17–20 fractions.
  - Consider boosting gross disease with EBRT or SBRT depending on normal tissue tolerance and prior dose.

22.4 Vaginal Cancer

- Brachytherapy as a part of definitive organ-preserving treatment improves overall survival [13].
- Definitive radiation is the preferred approach for patients with Stage I disease, with surgery as an option in select non-bulky stage I patients with distal non-urethral disease.
- Definitive chemoradiation is the preferred approach for stage II-IVA.

22.4.1 Initial Evaluation and Applicator Choice

- Full history and physical exam.
- Labs: CBC, CMP (chemistry, LFTs, BUN, Cr).
- Radiographic studies:
  - Contrast-enhanced CT chest/abdomen/pelvis for initial staging
  - Pelvic MRI (along with cystoscopy and/or sigmoidoscopy) at diagnosis if concerns regarding bladder and/or rectal invasion
- Interstitial brachytherapy is the standard approach, with exception of very small tumors with thickness $\leq$5 mm where intracavitary applicators may be considered.
- Transrectal US can help guide interstitial needle placement and avoid placing needles into bowel.
- Perform digital rectal exam at conclusion of interstitial procedure to ensure no catheters are perforating rectum.

22.4.2 Implant Evaluation

- Thin-slice CT or MRI with applicator for 3D treatment planning.
  - Diluted contrast can be placed into bladder and rectosigmoid region to assist with organ visualization.
- If using interstitial needles, review for tumor coverage and proximity to critical structures, especially rectum and bowel.

22.4.3 Volume Delineation

- Pelvic MRI can help determine superior and paravaginal extent to disease.
- Target structures and OAR delineation for vaginal cancer are in Table 22.8.
- Vaginal target volumes depend on the extent of initial involvement, treatment response, and presence of multifocal disease or discontinuous spread.

22.4.4 Treatment Planning

- Common dose and fractionation schedules for vaginal cancer are in Table 22.9.
- Planning dosimetry goals are in Table 22.10.
- Total dose goal should be 70–80 Gy depending on location within the vagina and surrounding normal structures, such as the urethra. For example, the proximal vagina dose could be 75–80 Gy, but the distal vaginal dose should be decreased to 70–75 Gy.
- For patients with multifocal spread or discontinuous disease, it is reasonable to treat the entire vaginal length to an equivalent dose of 60 Gy and boost areas of gross residual tumor to 70–80 Gy.

Table 22.8 Primary vaginal cancer brachytherapy target volumes and OARs

Structure name	Description
GTV	Macroscopic tumor at time of brachytherapy seen on MRI
HRCTV	GTV + 1 cm margin in lateral, inferior, and superior directions
IRCTV	HRCTV + microscopic extension in vagina (includes all initial disease)
Bladder	Contour outer bladder wall
Rectum	Contour outer rectal wall from above the anal sphincter to level of transition into the sigmoid
Sigmoid	Contour outer sigmoid wall from recto-sigmoid flexure to 2 cm superior to uterus and parametria

Table 22.9 Common dose and fractionation schedules for primary vaginal cancer

EBRT dose and fractionation	# HDR fractions	HRCTV dose per fraction (Gy)	HRCTV $EQD2_{10}$ (Gy)
45 Gy in 25 fractions	3	7	74.1
	4	6	76.3
	5	4.5–5.5	71.5–79.8
	9	3	76.8
	10	3	73.6
50.4 Gy in 28 fractions	3	7	79.4
	5	4–5	72.9–80.9

Table 22.10 Primary vaginal cancer brachytherapy target volume and OAR goals (See Fig. 22.5)

Structure	Dosimetric parameter	Ideal goal $EQD2_3$ (Gy)	Maximum constraint $EQD2_3$ (Gy)
HRCTV ($EQD2_{10}$)	$D_{90\%}$ (Gy)	Lower 1/3 Vagina: 70–75	–
		Upper 2/3 Vagina: 75–80	
Bladder	D_{2cc} (Gy)	≤80	≤90
Rectum	D_{2cc} (Gy)	≤65	≤75
Sigmoid	D_{2cc} (Gy)	≤75	≤75

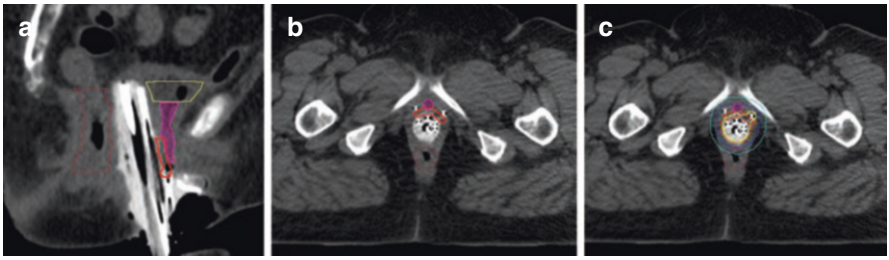

Fig. 22.5 Distal vaginal cancer with interstitial implant. (**a**) Sagittal view with applicator in place. HRCTV in red, rectum in brown, urethra in magenta, bladder in yellow. (**b**) Axial view with applicator in place. (**c**) Axial view with dose distribution. 600 cGy in yellow, 500 cGy in orange, 300 cGy in blue, 200 cGy in cyan

22.5 Vulvar Cancer

- Concurrent chemoradiotherapy is the preferred approach for stage II-IVA, with consideration of brachytherapy boost for patients with vaginal extension or who poorly tolerate the initial phase of EBRT.
- Brachytherapy is not standard in treatment of stage I disease except in medically inoperable patients.

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Vulvar Cancer

23

Allison E. Garda, Loren K. Mell, and Ivy A. Petersen

Contents

23.1 Introduction

Vulvar cancer is one of the most complex disease sites to treat with radiation therapy, due to the large treatment volumes and relatively high rates of morbidity, particularly with intensive chemoradiation for advanced stages. Intensity modulated radiation therapy (IMRT) is now widely used in the community and in

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_23

contemporary clinical trial protocols, due to reduced rates of morbidity and high treatment efficacy in most published series compared to historical techniques. Publication of consensus contouring guidelines has advanced the quality of treatment delivery, and evolving treatment planning recommendations have helped standardize approaches across institutions.

23.2 General Principles

- The treatment of vulvar cancer consists of upfront surgery, typically radical vulvectomy or wide local excision in select patients with small well-lateralized tumors. Most patients undergo lymph node evaluation with either inguinofemoral dissection or sentinel lymph node biopsy, particularly those found to have tumor invasion >3 mm, lymphovascular space invasion (LVSI) and/or high-grade disease.
- Radiation therapy (RT) is typically delivered following surgery in patients with high-risk features including LVSI, tumor invasion >5 mm, surgical margins <8 mm, microscopically positive margins, grade 3 disease, and/or positive lymph nodes [1–3]. Data suggests smaller margins (e.g., <5 mm) may be used as indication for adjuvant therapy [4–6].
- Patients presenting with unresectable disease are candidates for preoperative RT [7, 8]. At many centers, these patients also receive concomitant chemotherapy [9–11]. Patients with unresectable locally advanced disease have high rates of clinical and pathologic response to chemoradiation [12], which is an area of active investigation in a recently completed prospective Phase II clinical trial [13].
- The standard RT approach in vulvar cancer patients consists of pelvic-inguinal irradiation. Brachytherapy has a limited role in vulvar cancer patients, apart from women with a positive vaginal margin or those with medically inoperable disease.

23.3 IMRT for Vulvar Cancer

- Given the large volumes irradiated and the growing experience using intensity-modulated RT (IMRT) in patients with gynecologic cancer, IMRT is receiving increasing attention in the treatment of vulvar cancer. The recently completed Gynecology Oncology Group (GOG) 0279 trial of definitive chemoradiation in locally advanced disease mandates IMRT [13].
- Dosimetric and preliminary clinical studies have reported superior normal tissue sparing and lower rates of acute and chronic toxicities in patients with vulvar cancer receiving IMRT compared to those undergoing conventional approaches [14–17]. Long-term outcome in these patients, however, remains limited.
- Consensus recommendations for contouring and treatment planning, including a pictorial contouring atlas, have been published [18].

23.4 Simulation

- Patients with vulvar cancer undergoing IMRT should be simulated in the supine position using a modest frog-leg position with customized immobilization of the upper and lower body, with the goal of reducing skin folds.
- Since the patient's vasculature serves as a surrogate for the lymph nodes, it is helpful to perform an IV contrast-enhanced computed tomography (CT) simulation.
- The anus should be marked with a fiducial marker at the time of simulation.
- To assist in delineation of the tumor, radiopaque wire is used to identify gross disease or surgical scars.
- It is advisable to simulate all patients with 0.5–1 cm bolus placed over the vulva, particularly in patients treated preoperatively or with gross disease. Bolus over the groins should be considered in cases of clinically evident skin involvement.
- Simulation scans should be obtained with full and empty bladder and an internal target volume (ITV) should be generated [19] for locally advanced cases, especially in those with vaginal, urethral, and/or anal involvement. If rectum is distended >3.5 cm at the time of simulation, simulation should be repeated after bowel preparation.

23.5 Image Registration

- In patients undergoing preoperative or definitive radiotherapy, positron-emission tomography (PET)-CT is helpful for delineation of the gross tumor volume (GTV).
- Gadolinium-enhanced pelvic MRI with and without vaginal gel is useful to help delineate the full extent of primary tumor and evaluate relationship between tumor and adjacent normal tissues.

23.6 Target Delineation

- Delineated target volumes in vulvar cancer patients include a gross tumor volume (GTV) (in preoperative or definitive setting) and two clinical target volumes (CTV). CTV_1 encompasses the GTV (if applicable), uninvolved vulvar tissue, and adjacent soft tissues. CTV_2 includes the pelvic and inguinofemoral lymph nodes bilaterally. CTV_3 includes boost volumes to either primary and/or nodal disease. Each CTV is then expanded to create planning target volumes (PTVs).
- See Table 23.1 for a detailed description of target volumes.
- See Table 23.2 for a description of boost target volumes.
- See Figs. 23.1 and 23.2 for pictorial atlas of contours in the definitive and postoperative setting, respectively.

Table 23.1 Target volumes used in vulvar cancer patients undergoing IMRT

Target volumes	Definition and description
GTV	Primary tumor defined on physical exam, CT or PET/CT imaging (preoperative/definitive only)
	Pelvis and inguinal lymph nodes: All nodes ≥1.5 cm, biopsy proven, and/or with FDG avidity
CTV_1	GTV plus remaining uninvolved vulva and adjacent soft tissues as indicated below:
	If GTV extends beyond vulva, CTV_1 includes this region plus 1-cm margin
	If primary tumor involves vagina: gross disease plus 3 cm of vagina
	If primary tumor involves anus, anal canal, or bladder: gross disease plus 2 cm of anus or bladder
	If primary tumor is periurethral: gross disease plus 2 cm of urethra
	If primary tumor extends to mid or proximal urethra: entire urethra and bladder neck included
	If primary tumor is preclitoral: gross disease plus 2 cm and cover suspensory ligament of the clitoris (extends to pubic bone)
	Bone and muscle should be excluded unless directly involved by tumor
	If no skin involvement, CTV_1 should be cropped from the skin by 3–5 mm
CTV_2	Bilateral pelvic and inguinofemoral lymph node regions
	The pelvic lymph nodes (common iliac,[a] external iliac, internal iliac, and obturator nodal regions) are defined by including the pelvic vessels plus a 7 mm expansion excluding uninvolved bone, muscle, and bowel
	The presacral area should be included in patients with vaginal involvement and consists of the soft tissues anterior (minimum 1.0 cm) to the S1–S3 vertebrae
	In patients with anal/rectal involvement, the perirectal lymph nodes should also be included
	Inguino-femoral lymph node compartment begins superiorly where the external iliac artery leaves the bony pelvis to become the femoral artery with the inferior border 2 cm below the sapheno-femoral junction or at the level of the lesser trochanter; laterally, medial border of the iliopsoas; medially, lateral border of adductor longus or medial end of pectineus; posteriorly, iliopsoas muscle laterally and anterior aspect of the pectineus muscle; medially and anteriorly, the anterior edge of the sartorius muscle. No margin is added posterior or lateral to femoral vessels. Any visualized lymph nodes in adjacent fat/soft tissues should be included.[b]
PTV_1	CTV_1 + 5–10 mm[c]
PTV_2	CTV_2 + 5–7 mm[c]

The final PTV is then generated by the union of the PTV_1 and PTV_2: $PTV = PTV_1 \cup PTV_2$ and may be needed to be cropped back from the skin surface in the inguinal nodal region

IMRT intensity-modulated radiation therapy, *GTV* gross tumor volume, *PET* positron-emission tomography, *CT* computed tomography, *CTV* clinical target volume, *PTV* planning target volume

[a] To the level of L4–5 which will not include the entire common iliac nodal region in many patients. At some centers in patients with negative pelvic lymph nodes, the common iliacs are not included, and the upper extent of the treatment volume is limited to the bottom of the sacroiliac joints

[b] The inguino-femoral lymph nodes should be considered as a region or compartment, rather than a margin around vessels

[c] This expansion to PTV assumes daily image guidance with CBCT matched to soft tissues. Consider increasing margins to 1 cm if daily cone beam CT (CBCT) is not used

Table 23.2 Target volumes used for boost to primary tumor and involved lymph nodes

Target volumes	Definition and description
GTV	Primary tumor defined on physical exam, CT or PET/CT imaging
	Pelvis and inguinal lymph nodes: All nodes ≥1.5 cm, biopsy proven, and/or PET avidity
CTV_3	$GTV_{primary}$ + 2 cm and anatomically confined to CTV_1
PTV_3	CTV_3 + 5–7 mm[a]
	GTV_{node} + 5 mm[a]

GTV gross tumor volume, *PET* positron-emission tomography, *CT* computed tomography, *CTV* clinical target volume, *PTV* planning target volume

[a] This expansion to PTV assumes daily image guidance with CBCT matched to soft tissues. Consider increasing margins to 1 cm if daily CBCT is not used

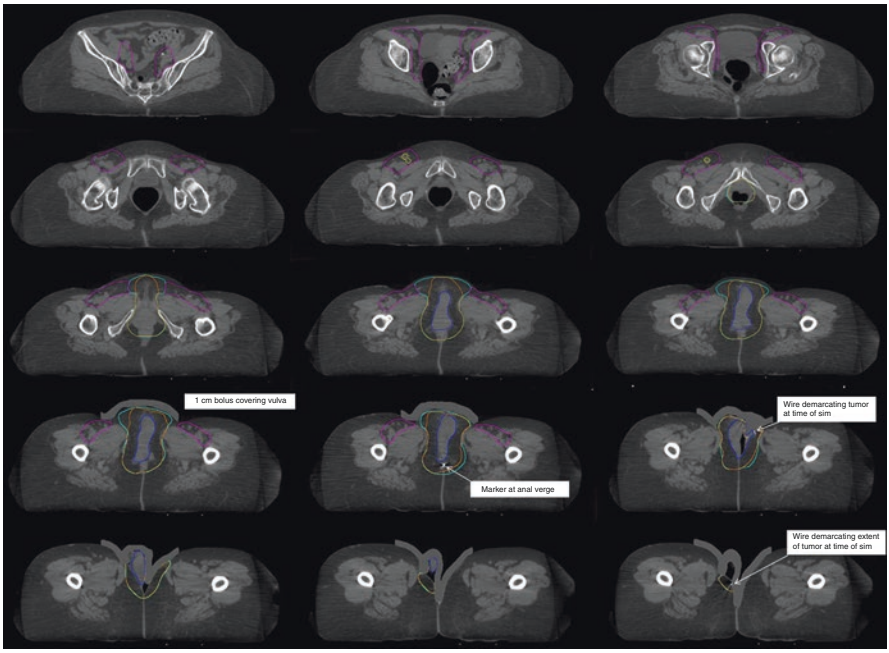

Fig. 23.1 Definitive radiotherapy. The patient had FIGO Stage IIIB vulvar cancer confined to the vulva, which was deemed unresectable based on proximity to the urethral meatus and vagina, and two FDG-avid right inguinal lymph nodes. She was treated with definitive IMRT and concurrent chemotherapy. The GTV for the primary lesion is outlined in blue. CTV_1 (cyan) includes the entire vulva, excluding adjacent bone and muscle. CTV_2 (magenta) includes the pelvic and inguinal-femoral lymph nodes. The pelvic lymph nodes and primary were treated to 45 Gy in 25 fractions. The bilateral inguinal-femoral regions were treated to 50 Gy in 25 fractions. PTV_3 included the FDG-avid right inguinal lymph nodes (yellow) plus 5 mm and was treated with a simultaneous integrated boost to 62.5 Gy in 25 fractions. CTV_3 (orange) was the primary GTV plus 2 cm expansion confined to CTV_1 and was treated with a sequential boost of 14 Gy in 7 fractions (total dose 64 Gy in 32 fractions). PTV expansions were all 5 mm due to use of daily CBCT

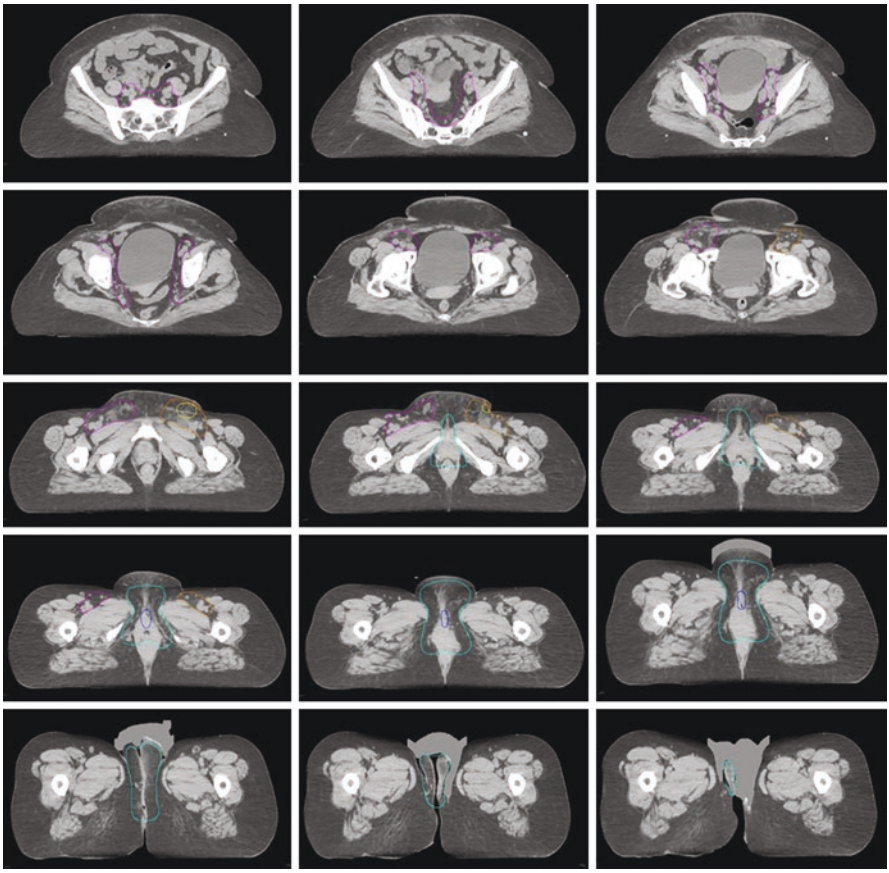

Fig. 23.2 Postoperative radiotherapy. The patient had FIGO Stage IIIA vulvar cancer (preoperative primary outlined in blue). She underwent wide local excision, dissection of grossly enlarged left inguinal lymph node (preoperative node outlined in yellow), and bilateral sentinel lymph node dissection at an outside institution. Final pathology showed a 4 cm moderately differentiated squamous cell carcinoma with 0.4 cm depth of invasion without lymphovascular space invasion. Pathologic margins were 7 mm. A 3 cm left non-sentinel inguinal lymph node was involved without extranodal extension. Two right and one left sentinel lymph nodes were negative for malignancy. She was treated with adjuvant IMRT and concurrent chemotherapy. Pelvic and right inguinal-femoral lymph nodes (magenta) were treated to 45 Gy, vulva (cyan) was treated to 50 Gy, and left inguinal-femoral lymph nodes (orange) were treated to 55 Gy, all in 25 fractions. PTV expansions were all 5 mm due to the use of daily CBCT

- Figure 23.3 depicts contours from consensus guidelines [18] and indicates the extent of variation in target delineation amongst clinicians with expertise in IMRT. Note that a contouring atlas is available on the NRG Oncology website [20].

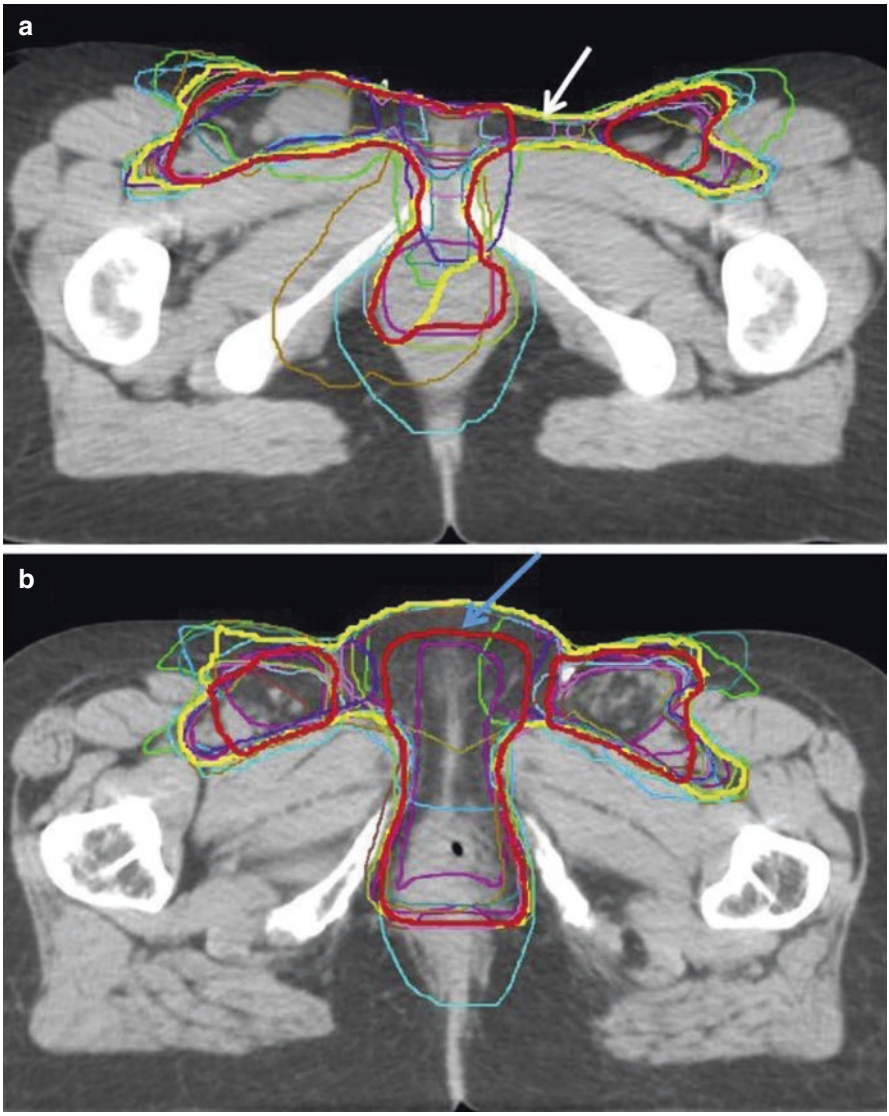

Fig. 23.3 Consensus contour (yellow), modified consensus contour (red), and individual contours from 14 different physicians for a locally advanced vulvar case (case 1) (**a**) and postoperative case (case 2) (**b**). The modified consensus contour was retracted from the space between the vulva and groin (white arrow) and skin surface (blue arrow) when it was believed to be at low risk. (From Gaffney et al. [18], reproduced with permission)

23.7 Prescription Recommendations

- Table 23.3 provides suggested dose and fractionation schemes.
- A primary site boost is typically given sequentially with IMRT, direct electron field, or interstitial brachytherapy, depending on response and location of disease.
- When using a sequential boost for definitive treatment, consider rescanning and adjusting the target volume prior to starting the boost phase of treatment.
- Using IMRT, grossly involved lymph nodes can be boosted using a simultaneous integrated boost (SIB). A common SIB scheme involves delivery of 45 Gy in 25 fractions to the pelvis, with 2.25 Gy per fraction to positive pelvic lymph nodes (plus PTV margin) and 2.5 Gy per fraction to positive inguinal lymph nodes (plus PTV margin).

Table 23.3 Suggested dose fractionation schemes

Radiotherapy timing	PTV_1	PTV_2	PTV_3
Preoperative	45–50.4 Gy/25–28 fractions	45–50.4 Gy/25–28 fractions	57.6 Gy/32 fractions [12]
Definitive	45–50.4 Gy/25–28 fractions	45–50.4 Gy/25–28 fractions	Primary:
			59.4–70.2 Gy/33–39 fractions
			Lymph nodes[a]:
			59.4–70.2 Gy/33–39 fractions
Adjuvant	45–50.4 Gy/25–28 fractions[b]	45–50.4 Gy/25–28 fractions	Gross residual disease:
		For ENE:	64–66 Gy/32–33 fractions
		54–64 Gy/30–32 fractions	

PTV planning target volume, *ENE* extranodal extension

[a] If using simultaneous integrated boost to lymph nodes, use EQD2 dose equivalent in 25 fractions

[b] Consider higher dose for close/positive margins or lymphovascular space invasion

23.8 Organs at Risk

- See Table 23.4 for detailed descriptions of the organs at risk (OARs) used in vulvar cancer and Table 23.5 for dose constraints for OARs.
- Organs at risk used in the treatment planning process typically include the bowel, bladder, rectum, anus, and bilateral femoral heads. In women undergoing chemotherapy, the pelvic bone marrow (BM) may also be included.
- Small bowel constraints are given priority over coverage of the lymph node SIB volume.

Table 23.4 Organs at risk (OAR) in radiotherapy for vulvar cancer

Organ	Definition and description
Bowel bag	Abdominal contents excluding muscle and bones. Inferiorly, contours start at the most inferior small or large bowel loop or above the anorectum, whichever is most inferior. Extend contours at least 2 cm above the superior most portion of the PTV
Rectum	Outer wall of the rectum contoured beginning inferiorly at the level of the ischial tuberosity and superiorly to where the rectum loses its round shape and connects anteriorly with the sigmoid
Anus	Outer wall of the anus contoured inferiorly from the anal verge identified by radiopaque marker placed at time of simulation to the level of the ischial tuberosity in the axial plane. The anal canal is approximately 4 cm in length
Sigmoid	Bowel contoured inferiorly where the anorectum contour ends and ending when connecting to the ascending colon laterally
Bladder	Outer bladder wall contoured inferiorly from the bladder base and ending superiorly at the bladder dome
Bone marrow	Pelvic bones serve as a surrogate for the pelvic bone marrow
	Regions included are the os coxae, L5 vertebral body, entire sacrum, acetabulae, and proximal femora
Proximal femurs	Femoral head and neck contoured inferiorly from the lowest level of the ischial tuberosities and superiorly to the top of the ball of the femur, including the trochanters

PTV planning target volume

Table 23.5 Normal tissue dose constraints for vulvar cancer radiotherapy

Critical structure	Recommendation[a]
Small bowel	Max ≤52 Gy[b]
	≤30% to receive ≥40 Gy
	<195 cm^3 to receive ≥45 Gy
Rectum	≤80% to receive ≥40 Gy
Anus	≤80% to receive ≥40 Gy, Max ≤65 Gy[c]
Bladder	≤35% to receive ≥45 Gy
Femoral heads	≤50% to receive ≥30 Gy
	≤35% to receive ≥45 Gy
	≤5% to receive ≥44 Gy
Bone marrow	≤37% to receive ≥40 Gy
	≤90% to receive ≥10 Gy
	≤80% to receive ≥20 Gy

PTV planning target volume

[a] Based on constraints from RTOG 1203 [21] and RTOG 0529 [22], as recommended in consensus guidelines [18], and currently in use at Mayo Clinic in Rochester, MN

[b] Small bowel is given priority over coverage of the PTV (pelvic lymph node boost) volume

[c] May not be met in case of tumors immediately adjacent to or involving the anus

23.9 Image-Guided Radiation Therapy

- Daily image guidance typically includes a combination of kV and/or CBCT imaging. CBCT is preferred for daily localization and matching with soft tissue.

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Advanced Technologies and Treatment Techniques for Gynecologic Malignancies

24

Casey W. Williamson, Whitney Sumner, and Loren K. Mell

Contents

24.1 General Principles

- Outcomes for locoregionally advanced gynecologic malignancies remain suboptimal and toxicities can limit treatment delivery. Methods to intensify treatment and to reduce toxicity are both needed.
- Intensity-modulated RT (IMRT) has become an accepted standard modality for definitive and postoperative external beam RT (EBRT) for cervical and endometrial cancer although there is still some controversy regarding routine implementation given limited prospective, randomized data.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_24

- Daily image-guided IMRT (IG-IMRT) improves localization of the targets and the organs at risk (OARs) and can enable more conformal treatment plans while maintaining tumoricidal doses.
- Adaptive re-planning can account for changes in tumor and patient anatomy throughout the treatment course to potentially further improve target coverage and reduce dose to OARs.
- Bone marrow-sparing IMRT can reduce hematologic toxicity.
- SBRT can be used as a boost for definitive therapy for patients who are ineligible for brachytherapy or who refuse brachytherapy. SBRT can also enable delivery of high dose RT to previously irradiated areas or to localized areas of recurrence or limited sites of metastasis.
- Proton therapy may reduce toxicity due primarily to rapid dose fall-off distal to the target although high quality directly comparative data with conventional RT and/or IMRT are limited.

24.2 Image Guidance

- IMRT allows for sophisticated and conformal treatment planning which can reduce the volume of irradiated area. However, this requires accurate delineation of target structures and OARs as well as appropriate management of organ motion and setup uncertainty. Pelvic organs are in motion both during and between treatment fractions.
- IG-IMRT has been associated with improvement in both hematologic and gastrointestinal toxicity compared to IMRT alone [1, 2]
  - Daily on-board orthogonal kV images can be used to align bony anatomy at the time of treatment to the initial positioning at computed tomography (CT) simulation.
  - Cone-beam CT (CBCT) can be acquired daily and allows for improved identification of rectal and bladder filling status in comparison to the time of simulation. With application of a shape model-based planning target volume (PTV) expansion strategy and image guidance with daily CBCT, target coverage within the 95% isodose cloud is excellent [3].
  - Figure 24.1 shows an example of pre-treatment daily CBCT identifying changes in bladder and rectal filling resulting in movement of the uterine fundus outside the PTV.

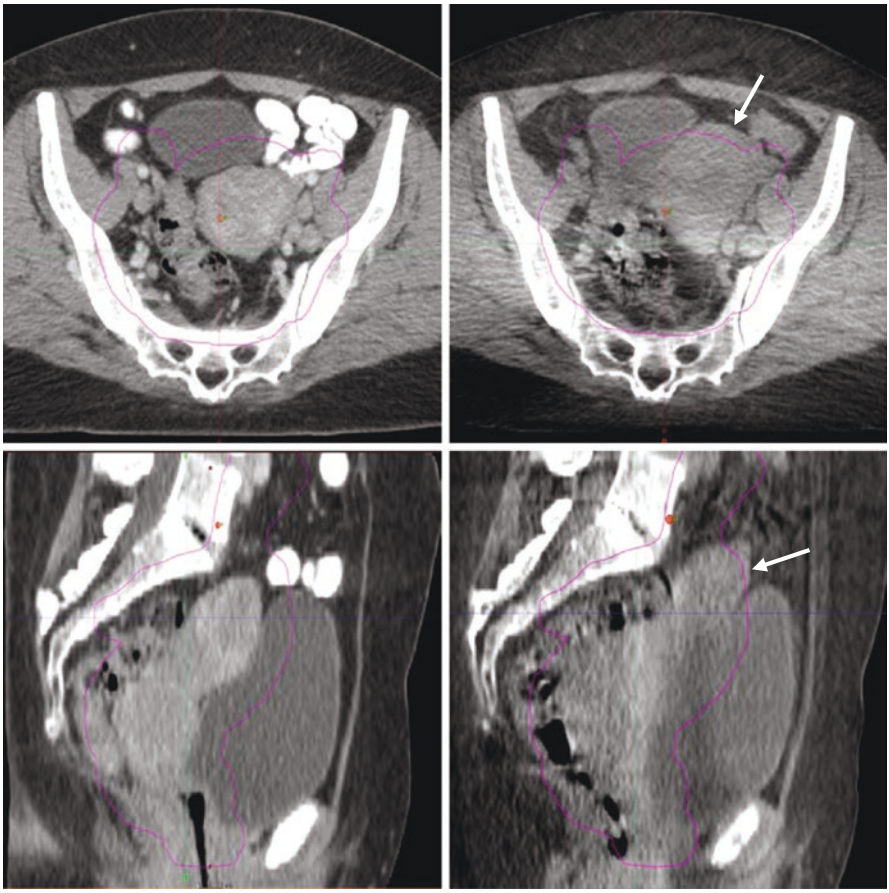

Fig. 24.1 Comparison between patient anatomy and coverage of the planning target volume (PTV, pink line) at the time of CT simulation (left column) and on cone-beam CT before one of the patient's daily treatments (right column). The patient received treatment for a FIGO 2009 IIB cervical cancer with pelvic and para-aortic involvement. Changes in filling status of the bladder and rectum resulted in a portion of the uterine fundus falling outside the PTV (white arrow)

24.3 Bone Marrow-Sparing IMRT

- IMRT can be used to spare bone marrow for patients undergoing pelvic RT and has been shown to reduce hematologic toxicity [2, 4].
- A variety of approaches have been implemented
  - PET/CT-based IG-IMRT can be used by contouring pelvic bones and defining active bone marrow as regions within bones with standardized uptake volume (SUV) greater than the mean SUV within bones, then applying dose constraints to the bone marrow [2, 5].

Pelvic bone marrow constraints, with hard constraints based on NTCP modeling: [6]
- Soft constraint: mean ≤27 Gy, V10(%) ≤85.5%, V20(%) ≤66%
- Hard constraint: mean ≤29 Gy, V10(%) ≤90%, V20(%) ≤75%

Active bone marrow constraints:
- Soft constraint: mean ≤28.5 Gy, V10(%) ≤90%, V20(%) ≤70%
- Hard constraint: mean ≤30 Gy, V10(%) ≤90%, V20(%) ≤75%

– An atlas-based approach is also feasible and offers an advantage if PET/CT is unavailable [5].
– Another option in the absence of PET/CT is to demarcate bone marrow as the low-density regions within bones on the simulation CT and to then apply dose constraints [4].

24.4 Adaptive Re-planning

- Adaptive re-planning can be subdivided into three major categories: offline between treatment fractions, online immediately prior to a treatment fraction, or in real-time during treatment delivery.
- Several adaptive strategies have been proposed and can be considered
  – A "plan-of-the-day" technique which generates a patient-specific library of treatment plans corresponding to different target volumes and organ motion, with pre-treatment CBCT used to select the library plan most similar to the target and OAR configuration each day.
  – Scheduled re-planning can be done with weekly magnetic resonance imaging (MRI).
  – Deformable image registration can be used to model accumulated dose to targets and OARs.
- Offline adaptive RT (ART)
  – Offline ART, e.g., generating a new treatment plan between treatment fractions, should be considered for patients who experience significant weight loss or substantial change in target size.
  – Repeat simulation may be required if re-planning cannot be performed on imaging acquired in the treatment room.
  – Deformable image registration can be utilized to create new plans based on pre-treatment imaging and/or interim diagnostic imaging (e.g., MRI, positron emission tomography (PET)/CT).
  – Advanced treatment planning systems can allow for automated dose monitoring and dose-volume metrics that can be reviewed offline to guide decision-making regarding the need for re-planning.
- Online ART
  – Variation in rectum and bladder filling can lead to both target and OAR displacement that may not be captured on CT simulation.
  – Emerging technologies allow for integration of iterative CBCT for dose calculation and daily re-planning based on pre-treatment imaging [7] or for MRI-based online re-planning [8].

24.5 Proton Therapy

- Proton therapy takes advantage of a relatively gradual dose build-up and a sharp dose fall-off distal to the target compared to photons.
- Protons may therefore allow for decreased dose to OARs, particularly distal to incident treatment fields as well as decreased integral dose while preserving adequate dose to the targets.
- Treatment of para-aortic nodes and re-irradiation are additional scenarios in which proton therapy may present advantages over IMRT.
- Dosimetric and early clinical studies suggest improvement in dose to nearby normal structures including bowel, bladder, and bone marrow with protons compared to IMRT [9].
- Protons may also allow for improved ovarian sparing in pre-menopausal women, e.g., sparing one ovary to a mean dose of <15 Gy [10].
- For definitive management, target dosing should be the same as with photon therapy (accounting for an assumed relative biological effectiveness (RBE) of 1.1 for protons).
- See the definitive EBRT chapter for gross tumor volume (GTV) and clinical target volume (CTV) delineation. PTVs are beam-specific based on range uncertainty. Avoid beam arrangements that result in critical structures in the field distal to the target. Figure 24.2 shows sample images from a patient treated with intensity-modulated proton therapy (IMPT).
- Proton therapy can be considered as a boost alternative for patients who are unable to receive brachytherapy, as protons can have dosimetric advantages in the bladder, bowel, femoral heads, and the rectum compared to VMAT. For example, the boost CTV can be determined using MRI obtained after 3 weeks of chemoradiation and a dose of 30 Gy/Gy equivalent in 5 fractions then administered in lieu of brachytherapy [11].
- However, it should be noted that high quality prospective evidence is lacking at present and the link between improved dosimetry and clinically meaningful reduction in toxicity and/or the ability to deliver intensified therapy remains unproven.

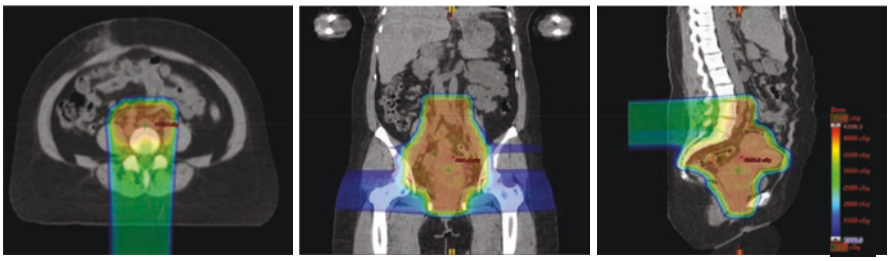

Fig. 24.2 Representative cross-sectional images of an intensity-modulated proton therapy (IMPT) plan for a 39-year-old woman with FIGO 2009 IIB cervical cancer with involvement of pelvic nodes. The patient had a history of active lupus nephritis leading to hemodialysis and she was referred for proton therapy given concern for increased risk of radiation-induced bowel injury. The pelvis received 39.6 Gy in 22 fractions and the gross nodal disease was boosted to a total of 51.6 Gy. She then received a brachytherapy boost of 30 Gy in 4 fractions. Dose is shown in color wash with legend in absolute dose (bottom right)

24.6 Stereotactic Body Radiation Therapy (SBRT)

24.6.1 Cervical Cancer

- For patients with locoregionally advanced cervical cancer, standard of care is daily fractionated EBRT with concurrent cisplatin-based chemotherapy followed by a brachytherapy boost with a final 2 Gy equivalent dose (EQD2) dose to the target of 80–95 Gy.
- SBRT is a specialized EBRT modality which allows for high doses to be delivered in 1–5 fractions. Target visualization, accurate tumor and OAR delineation, and high-fidelity setup with image guidance are crucial.
- Lymph nodes can be boosted with SBRT [12].
- SBRT can also be considered in the setting of re-irradiation for recurrent disease or for treating limited sites of metastasis [12–15].
- Some patients are not candidates for brachytherapy due to severe medical comorbidities and some patients refuse brachytherapy, especially patients at risk for posttraumatic stress disorder [16].
- SBRT can allow for conformal delivery of a high dose boost
  - However, a recent phase II trial investigating the use of SBRT (28 Gy in 4 fractions) as a replacement for brachytherapy closed prematurely due to concern for higher than expected toxicity and lower than expected 2-year local control, progression-free survival, and overall survival [17]. Brachytherapy remains the standard of care for eligible patients.
  - A five-fraction regimen (e.g., 27.5 Gy in 5 fractions) following 45 Gy to the pelvis could also be considered for patients who will not receive brachytherapy, which results in an EQD2 of 80 Gy ($\alpha/\beta = 10$). Figure 24.3 shows images from a patient treated with an SBRT boost following EBRT.

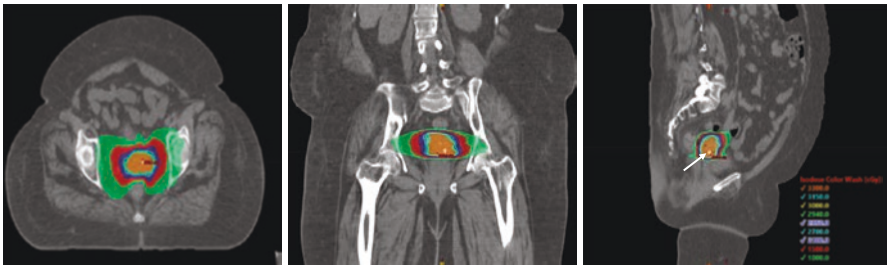

Fig. 24.3 Representative images from a stereotactic body radiation therapy (SBRT) boost given in lieu of brachytherapy for a 52-year-old woman with FIGO 2009 IB1 cervical cancer who was not a surgical candidate and not a candidate for brachytherapy due to comorbidities. She received external beam radiation to the pelvis to 45 Gy in 25 fractions followed by an SBRT boost of 30 Gy in 5 fractions. Dose is shown in color wash with legend in absolute dose (bottom right). Fiducial markers were placed prior to simulation (white arrow)

- Determination of dose and fractionation should take into account target size, prior RT to the area, and tolerance of nearby OARs. For a 5 fraction regimen, dose per fraction is typically in the 4–8 Gy range [18, 19]. Fractions of 8–15 Gy per fraction have also been reported [20, 21].
- Total EQD2 should be calculated for the treated area.

24.6.2 Endometrial Cancer

- SBRT has also been considered as an alternative modality for boost delivery in the setting of postoperative endometrial cancer [22–24].
- Lymph nodes can also be boosted with SBRT as above.
- Re-irradiation or metastasis-directed SBRT can also be considered.
- A retrospective series of patients with recurrent, persistent, or oligometastatic foci treated with a median 24 Gy (range 10–50) in a median of 4 (range 1–6) fractions showed 1 year and 3 year local control rates of 80% and 68%, with more favorable control in smaller tumors [25]. The rate of grade ≥2 toxicity was 4.3% with only one grade 3 event and no grade 4 or 5 toxicities.

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Prostate Adenocarcinoma

25

Daniel Gorovets, Brandon S. Imber, Neil Desai, and Michael J. Zelefsky

Contents

25.1 General Principles of Planning and Target Delineation

- Intensity-modulated radiation therapy (IMRT) is the standard technique for external beam radiation therapy (EBRT) for prostate adenocarcinoma. IMRT is used in both the definitive setting (alone or combined with brachytherapy) and post-operatively (adjuvant or salvage). Various fractionation schemes exist; however, all approaches rely on accurate target delineation and image-guided treatment delivery to maximize tumor control and minimize toxicities. This chapter will describe common treatment approaches and provide walk-throughs of typical scenarios in the radiotherapeutic management of prostate cancer.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_25

- Following pathological confirmation, initial case workup includes digital rectal examination, urinary and erectile function scores, and relevant labs (i.e. PSA +/− additional studies if ADT is planned). At MSKCC, mpMRI is recommended for all patients (unless contraindicated) to identify potentially undersampled high-grade disease, determine prostate volume, define the dominant tumor size/location, evaluate extent of extra-prostatic disease (EPE) and seminal vesicle invasion (SVI), as well as identify gross disease requiring dose escalation post-operatively.
- Choice between various treatment regimens depends on factors such as NCCN risk group, MRI findings, age, comorbidities, urinary function, and patient preference.
- Simulation: At MSKCC, MR-only simulation and treatment planning as described by Tyagi et al. is preferred for all definitive treatments and for post-op gross local recurrences. Alternatively, a 2 mm slice thickness CT simulation can be fused with a 3 T MRI in the treatment position to help delineate the prostate CTV.
  - For definitive treatments, three fiducial markers (base, mid-gland, apex) +/− rectal spacer (if no posterior EPE) are placed at least 5 days prior to sim. If dose escalation is planned for suspected post-op gross local recurrences, fiducial markers can be placed at the time of biopsies.
  - Empty rectum: Low fat-low residue diet, fiber supplement, and simethicone are started 1 week before sim and continued through treatment; An enema is administered 3 h before sim +/− treatments as needed.
  - Full bladder: 16 oz of water 45 min prior to sim + treatments.
  - To delineate the urethra as an avoidance structure, a Foley catheter is placed for stereotactic body radiation therapy (SBRT) sims and when EBRT is combined with a brachytherapy boost. Alternatively, MR-based urethral delineation can be used as described by Zakian et al.
  - Position: Supine with leg/pelvis immobilization. SBRT setups should be validated and may include frame or frameless systems. At MSKCC, patients are immobilized with a thermoplastic mold that extends from mid-abdomen to mid-thigh and conforms to the inner leg. A knee cushion is used to provide additional stability.
  - Sim Borders: L2 to mid-femur.
  - Isocenter: Prostate or prostate bed; if treating lymph nodes: top of femoral heads.
- Image fusion of MRI to simulation CT can be improved by matching of the bladder/prostate interface (often affected by “pitch” variations between MRI/CT) as well as bony anatomy and fiducials (requires specific MRI sequence, such as T1 SPGR or 3D BFFE).
- Clinical target volumes (CTV) should be delineated on every slice of the planning CT or MRI. Planning target volumes (PTV) depend on fractionation scheme, image guidance, and institutional standards. A general description of target volumes and margins is indicated in Table 25.1.
- Volume walk-throughs: see Figs. 25.1, 25.2, 25.3, 25.4, and 25.5.

Table 25.1 Suggested target volumes for EBRT and contouring concepts

Treatment setting	Protocol	Fractional dose	MSKCC regimen[a]	PTV margin[b]	CTV description
Definitive	Conventional	180–200 cGy	81–86.4 Gy in 45–48 fractions	6 mm except 5 mm posterior	CTVpros: entire prostate +/− SV depending on risk of invasion (Fig. 25.1)
	• Rarely used at MSKCC				• Refer to diagnostic mpMRI to ensure gross tumor and EPE included in CTV
	Moderately Hypofractionated	240–300 cGy	70.2 Gy in 26 fractions	5 mm except 3 mm posterior	• Axial T2 MRI is most useful to delineate CTV; prostate borders are defined by the capsule and SVs are clearly visualized
	• Default EBRT option at MSKCC if not brachytherapy or SBRT candidate		• if treating pelvic nodes, see below		• Begin contours mid-gland where prostate borders/capsule are most easily identifiable
			55 Gy in 20 fractions in low-vol M1 setting		• Lateral boundary: within levator ani
	Ultra-hypofractionated (SBRT, SABR)	>500 cGy	40 Gy in 5 fractions, delivered every other day		• Anterior boundary: anterior fibromuscular stroma (AFS)
	• Low and intermediate risk with good urinary function				• Posterior boundary: rectum interface or rectal spacer
					• Inferior boundary: identify apex relative to GUD (i.e. CT slice above "hourglass" of McLaughlin et al.)
					• Superior boundary: bladder interface +/− proximal 5–10 mm or entire SVs
					• Check sagittal and coronal planes and/or 3D structure for quality assessment (Fig. 25.2)

(continued)

Table 25.1 (continued)

Treatment setting	Protocol	Fractional dose	MSKCC regimen[a]	PTV margin[b]	CTV description
Post-op (adjuvant or salvage)	Conventional	180 cGy ± boost to gross disease	72 Gy in 40 fractions +/− boost to 78 Gy	6 mm except 5 mm posterior	Prostate fossa CTV within RTOG guidelines (Fig. 25.3):
					• Inferior boundary: ~10 mm below VUA (last with urine). Do not extend CTV into penile bulb
					• Anterior boundary: pubic symphysis; above symphysis, taper off bladder gradually over 4 slices
					• Posterior boundary: anterior rectal wall or mesorectal fascia
					• Lateral boundary: levator ani and obturator internus
					• Superior boundary: extend ~1–2 cm above the pubic symphysis to include SV remnants, but not necessary to encompass all hemostatic clips
					• Check sagittal and coronal planes and/or 3D structure for quality assessment (Fig. 25.4)

Pelvic nodes (either definitive or post-op)	Conventional	180 cGy ± SIB to gross disease	45 Gy in 25 fractions +/− SIB to 56.25 Gy	8 mm on elective pelvis	Modified RTOG (see Fig. 25.5):
			46.8 Gy in 26 fractions +/− SIB to 57.2 Gy	5 mm on nodal GTV	• Target regions: common iliac, external iliac, internal iliac, obturators, pre-sacral
					• No bowel or muscle in CTV
					• Start at aortic bifurcation
					• External iliacs end at top of femoral head
					• Internal iliacs/obturators end at superior aspect of pubic symphysis
					• Pre-sacrals extend from top of S1 to bottom of S2
					• If gross nodal disease to boost, fuse diagnostic image (i.e. MRI or PET) that best demonstrates GTV to ensure accurate target delineation

[a] Doses provided here are specific to current practices at MSKCC. Prescriptions should be based on doses validated for efficacy and safety with the treatment planning and setup allowances specific to each institution's practice

[b] MSKCC PTV margins are based on our institutional standards for image-guided IMRT. Daily pre-treatment kVs are matched to fiducials (definitive) or bone (post-op), and CBCTs are performed at least weekly for soft tissue evaluation. For hypofractionated treatments, kVs and CBCTs are done daily, and intra-fraction motion management is used to monitor/correct prostate position during treatment delivery

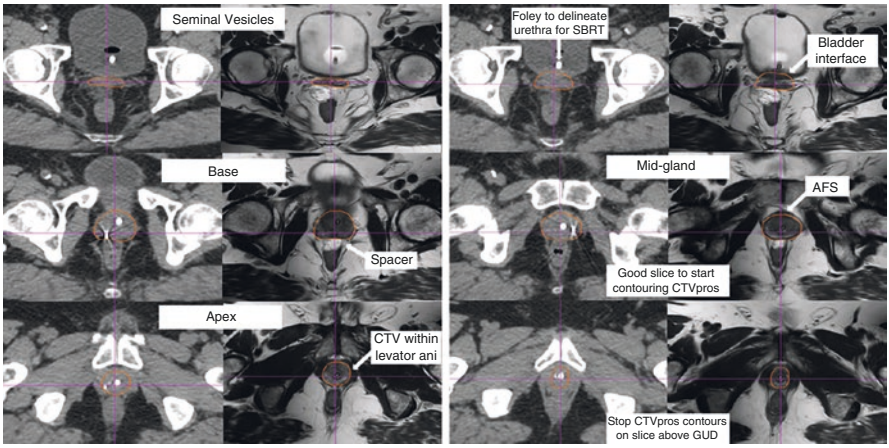

Fig. 25.1 Definitive prostate CTV (*orange*) delineation. This series of representative images from a 2-mm slice thickness CT simulation (left) fused with a T2 MRI (right) demonstrates general boundary discrimination. It begins at the SVs and proceeds caudally to the apex. Not all slices are shown. Note that hydrogel rectal spacer is best visualized on T2 MRI, however, Atluri et al. demonstrated that the addition of iodinated contrast can facilitate MRI-independent spacer delineation

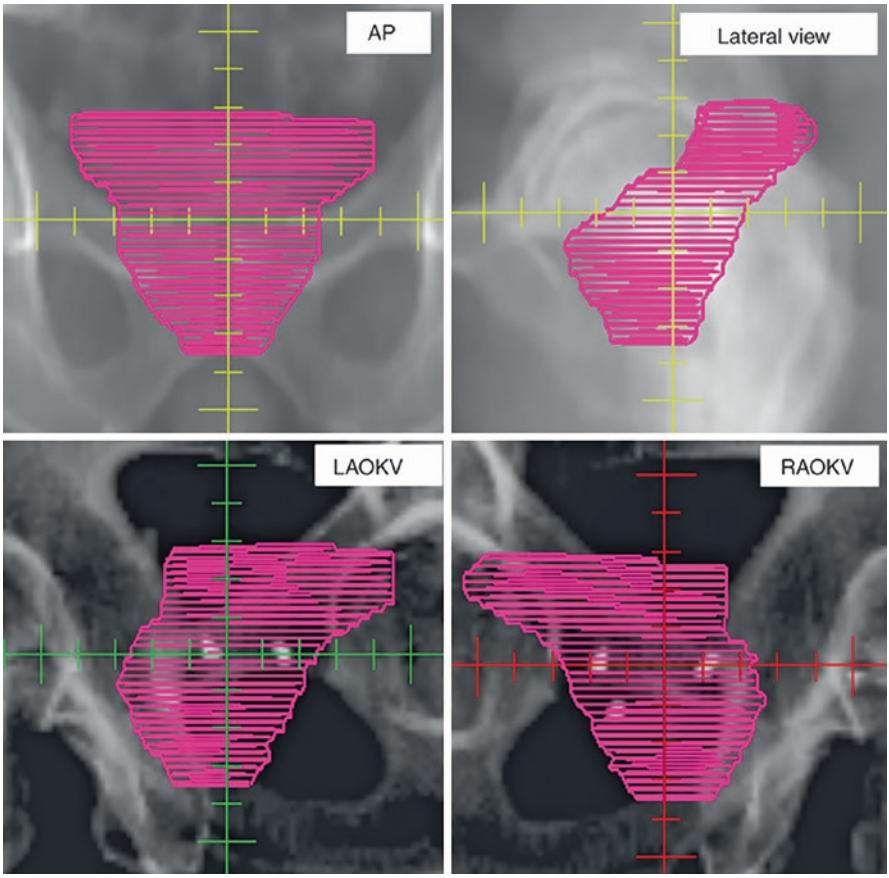

Fig. 25.2 Three-dimensional projection of CTV in various views for quality assessment. Note the appearance of a relatively globular gland underneath a winged structure representing the seminal vesicles superiorly. Cross-referencing of these projections to axial contours allows for detection of common misinterpretations of anatomy, i.e., extending too far into the GUD will produce extension of the pedestal structure inferiorly. Moreover, gross irregularities in the overall structure may reflect overcorrection from slice to slice that is not anatomically faithful, especially when averaging organ deformation and motion during treatment

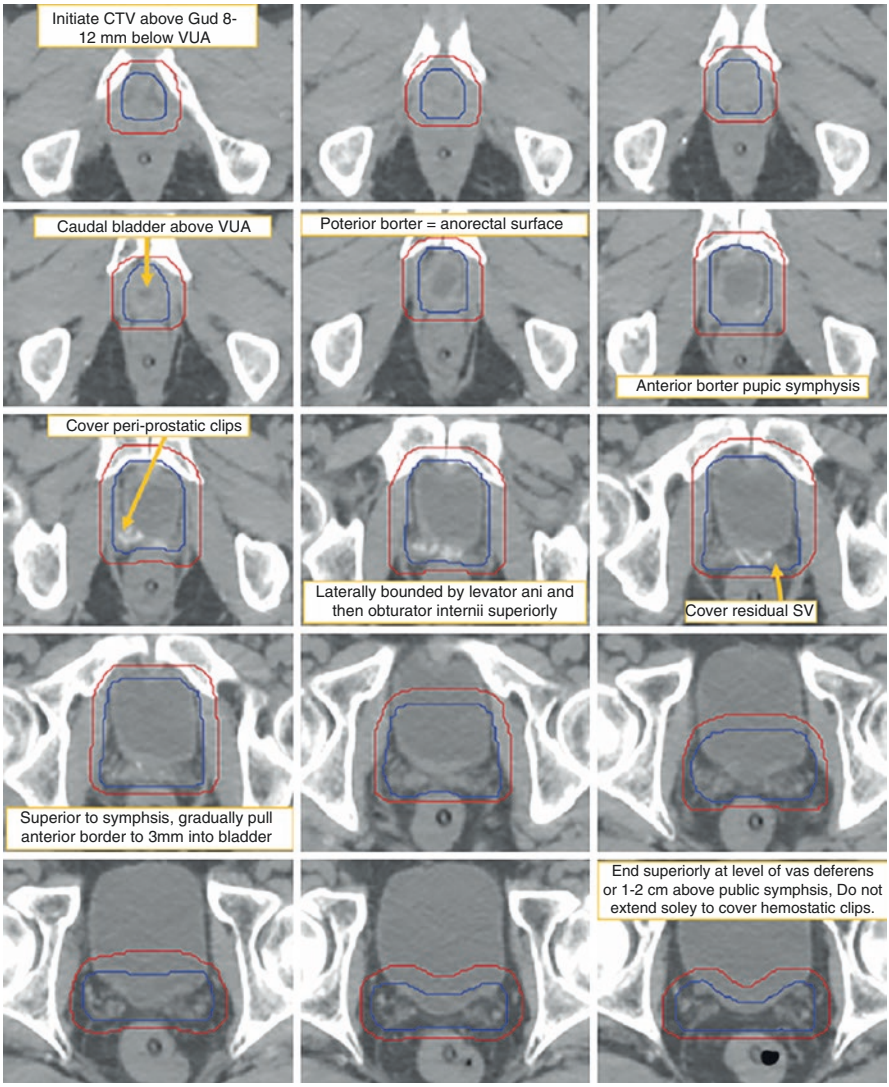

Fig. 25.3 Post-prostatectomy target delineation. Representative images from 2-mm slice thickness simulation CT with full bladder protocol begin caudally and proceed cranially. Note that manual modification of the PTV (*red*) after expansion is shown alongside the initial CTV (*blue*). This helps avoid overdosing the rectum by excessive draping of the "dumbbell" shape cranially at the anterolateral rectum

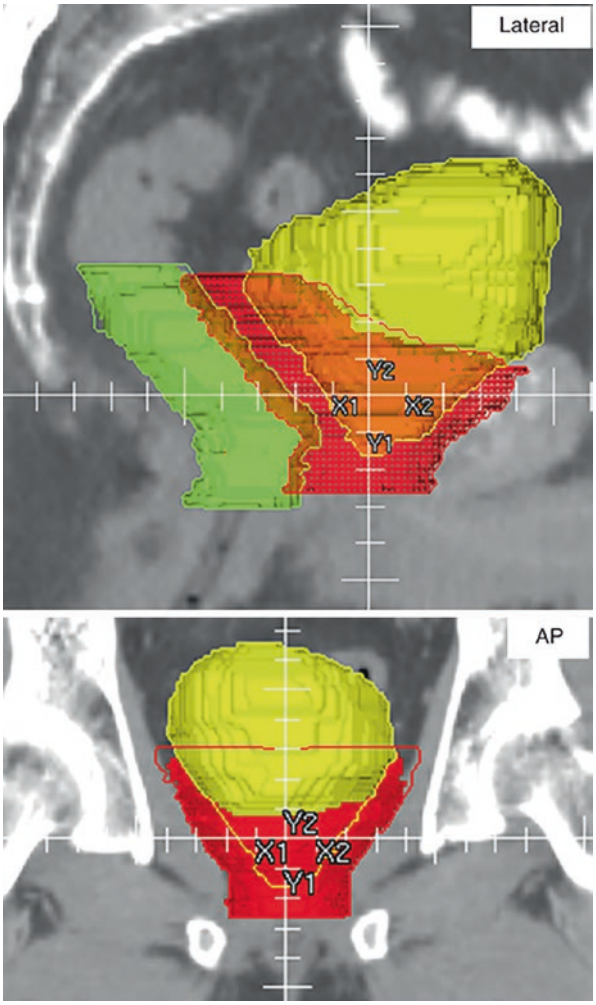

Fig. 25.4 Three-dimensional projection of PTV in orthogonal views for quality assessment. As opposed to an intact prostate treatment plan, the contours for a post-operative plan will necessarily approximate the bladder and rectum to cover areas of potential microscopic residual disease. These areas include the anterior perirectal space, the vesicoureteral anastomosis (VUA), and the new spaces created at the posterior bladder interface with the pelvic floor and VUA. The overlap of PTV margin with rectum (*green*) and bladder (*yellow*) is highlighted here. A gradual tapering of the anterior PTV boundary superior to the pubic symphysis is ensured by inspection of the 3D projection. Smoothing out this transition avoids abrupt changes in dose distribution that are susceptible to errant targeting based on day-to-day changes in bladder volume despite a full bladder protocol

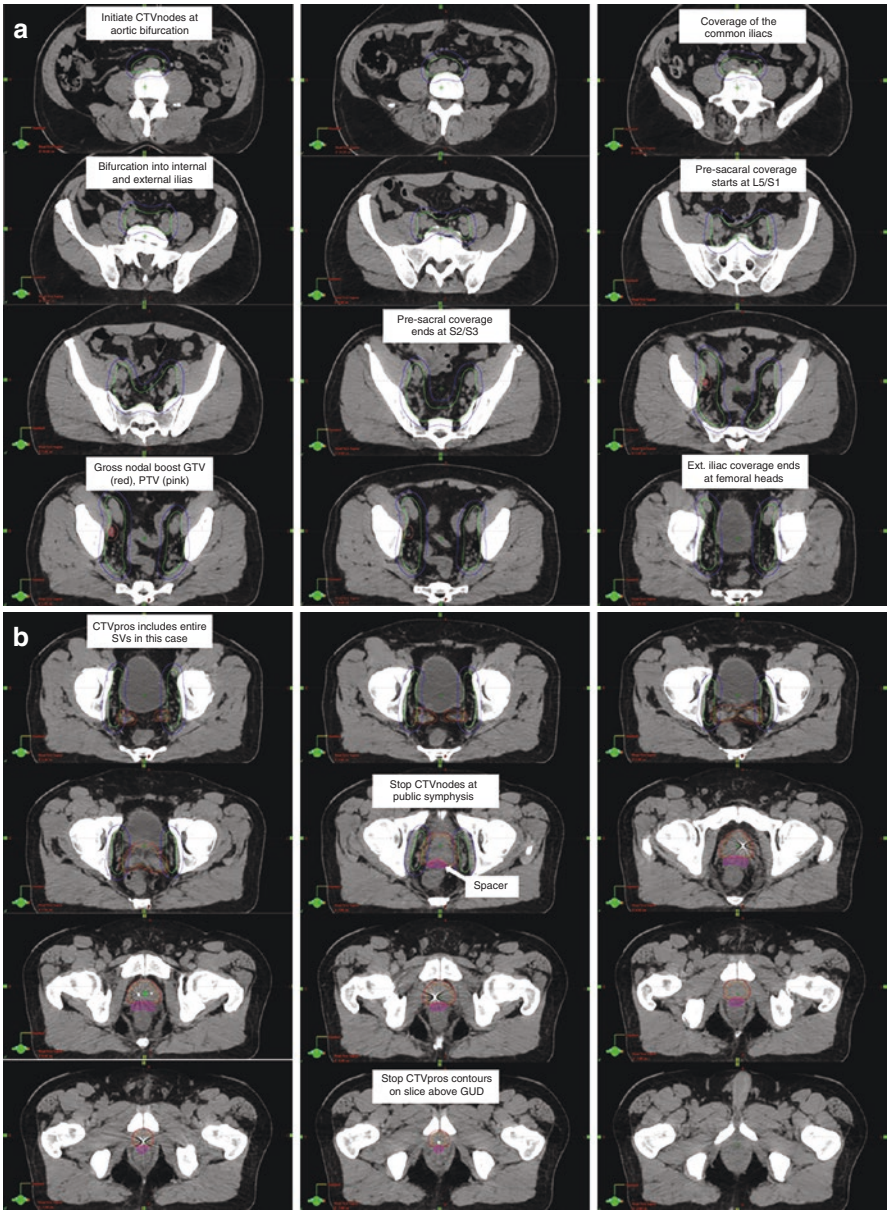

Fig. 25.5 (**a**, **b**) Pelvic lymph node target delineation. Representative images from a 2-mm slice thickness CT simulation scan are provided beginning cranially and proceeding caudally. Note that a 3 T MRI in the treatment position was fused to help delineate the CTVpros (*orange*) and rectal spacer (*magenta*). This patient had regional lymph node disease (T1cN1M0, GS 4 + 4, PSA 22) treated with moderately hypofractionated IG-IMRT and 2 years of Lupron and Abiraterone. Radiation consisted of 26 fraction dose-painting: elective pelvis to 4680 cGy (CTVnodes: *green*; PTVnodes: *blue*), gross right pelvic lymph node to 5720 cGy (GTVboost: *red*; PTVboost: *pink*), and prostate/SVs to 7020 cGy (CTVpros: orange; PTVpros: red)

Further Reading

Atluri PS, et al. Addition of iodinated contrast to rectal hydrogel spacer to facilitate MRI-independent target delineation and treatment planning for prostate cancer. Pract Radiat Oncol. 2019;9(6):e528–33.

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Bladder Cancer

26

Ariel E. Marciscano and Marisa A. Kollmeier

Contents

26.1 General Principles of Planning and Target Delineation

- Organ-preservation with bladder-sparing trimodality therapy (TMT) is a standard definitive treatment option for node-negative, muscle-invasive bladder cancer (MIBC). TMT involves maximal, and ideally complete, TURBT followed by concurrent chemoradiotherapy [1–3]. For node positive bladder cancer, systemic chemotherapy is the mainstay of therapy; however, for patients with disease confined to the pelvis/para-aortic nodes, chemoradiation is a reasonable therapeutic option.
- RTOG/NRG protocols have classically used three-dimensional conformal radiation therapy (3D-CRT). Future NRG studies, including the phase III SWOG/NRG 1806 study (NCT03775265), permit intensity-modulated radiation therapy (IMRT) for concurrent chemoradiotherapy.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_26

- The use of IMRT is increasingly utilized to minimize dose to adjacent normal tissue, especially bowel—particularly, when dose constraints cannot be achieved with 3D-CRT-based planning. When using IMRT, it is essential to account for organ motion which may be accomplished by image-guidance.
- There is no consensus on optimal field design [4, 5] (whole bladder +/− prostate, partial bladder, elective nodal coverage) or dose/fractionation regimen (daily fractionation [6], BID hyperfractionation [6, 7], hypofractionation [8]).
- Definitive treatment should include the use of radiosensitizing therapy for all eligible patients. Various chemotherapy regimens [1, 6, 7] and hypoxia-modifying agents [9] have been studied. In general, the most commonly used radiosensitizers are cisplatin, fluorouracil (5 FU)/mitomycin C, or gemcitabine.
- The use of adjuvant radiotherapy for high-risk bladder cancer following radical cystectomy is under investigation [10, 11]. In general, this approach is most appropriate for pT3, pN+, and/or positive surgical margins. Additionally, the use of intraoperative radiation therapy may be appropriate for some cystectomy-eligible patients with locally advanced disease who are anticipated to have a need for adjuvant local therapy due to positive surgical margins.
- Organs at risk (OARs) include: small bowel, large bowel, rectum, and femoral heads.

26.2 Three-Dimensional Conformal Radiation Therapy (3D-CRT)

- Recent RTOG studies (0712, 0926) have included a small pelvic field (defined as CTV_{4140}) which includes the entire bladder, prostate and prostatic urethra (in men), proximal urethra (in women), and regional lymphatics followed by a cone down to a whole bladder field (defined as CTV_{6120}) which includes the entire bladder and any gross tumor volume. Protocol OAR constraints are displayed in Table 26.1.
- The small pelvic field is generally planned as a four-field box arrangement (Table 26.2, Fig. 26.1).
- The whole bladder field is generally planned as a four-field box or parallel opposed laterals (Table 26.2).
- A randomized study comparing standard whole-bladder radiation therapy versus reduced high-dose volume radiation therapy (RHDVRT) reported no significant reduction in late toxicity and non-inferiority of locoregional control with RHDVRT as compared with whole-bladder radiation therapy [12]. A two-phase sequential boost or single-phase concomitant boost approach can be used for RHDVRT (Fig. 26.2).

Table 26.1 Doses constraints for 3D-CRT selective bladder preservation

RTOG 0712/0926 OAR constraints for 3D-CRT-based selective bladder preservation	
Rectum	$V30_{Gy} < 50\%$ (0712) or $V55_{Gy} < 50\%$ (0926)
	$V55_{Gy} < 10\%$ (0712)
Femoral heads	$V50_{Gy} < 20\%$ (0712)
	Dmax < 45 Gy (0712, 0926)
Small bowel	$D45_{Gy} < 300\ cm^3$

Table 26.2 Field design for 3D-CRT selective bladder preservation

Small pelvic field	Designed to cover entire bladder and regional pelvic nodes as well as prostate/prostatic urethra in men and proximal urethra in women using four-field box arrangement
	AP/PA fields: Superior extent to S1/S2 junction (anterior) and inferior extent 1 cm below obturator foramen. Laterally, extend field 1.5 cm beyond bony pelvis (at widest diameter). Block femoral heads
	Parallel opposed lateral fields: Same superior/inferior extent as AP/PA field. Anteriorly, 1 cm anterior to symphysis pubis or 1.5 cm anterior to CTV whole bladder volume. Posteriorly, extend 3 cm beyond CTV whole bladder volume (see below). Consider anterior block to minimize dose to small bowel
	Recommend contouring of pelvic nodes to ensure standard fields encompass intended lymphatics at risk, adjust borders as necessary
Whole bladder field	**CTV whole bladder** field includes entire bladder and any gross tumor volume (GTV)
	PTV whole bladder includes 0.5 cm isotropic expansion on CTV whole bladder with exception of 1.5 cm superiorly
	Field design for whole bladder may consider four-field box or opposed lateral field to optimize target coverage and OAR sparing, multi-leaf collimation to optimize conformality

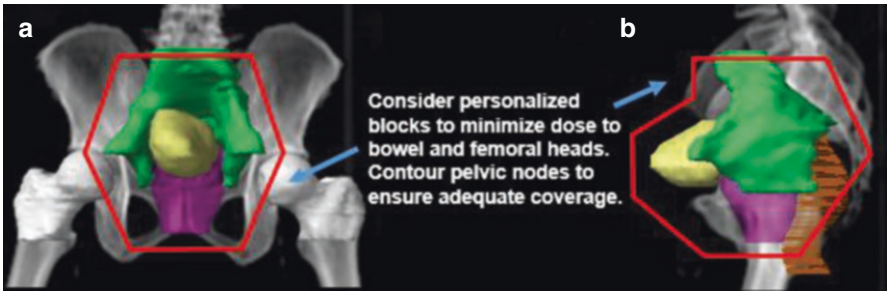

Fig. 26.1 AP (**a**) and lateral (**b**) DRR images for 3D-CRT small pelvic field for selective bladder preservation. Field design outlined in red; targets and organs at risk as follows: bladder (yellow), prostate/seminal vesicles (magenta), pelvic nodes (green), rectum (brown), femoral heads (white)

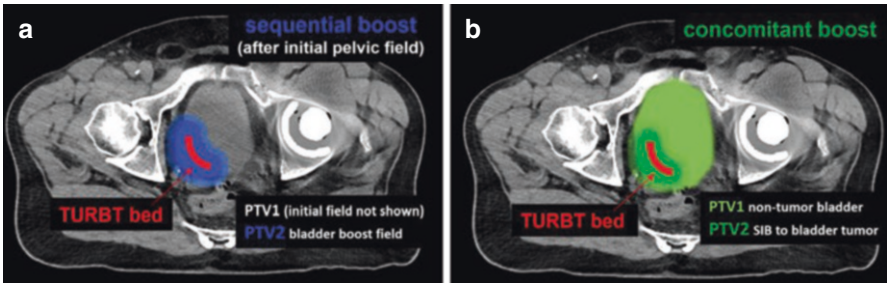

Fig. 26.2 Schematic representation of target delineation for reduced high-dose volume radiation therapy (RHDVRT) per BC2001 randomized non-inferiority trial via (**a**) two-phase bladder-boost "cone down" technique or (**b**) single-phase simultaneous integrated boost (SIB) technique

26.3 Intensity-Modulated Radiation Therapy (IMRT)

- Target volumes with IMRT are similar to 3D-CRTand include the whole bladder, prostate, and prostatic urethra in men/proximal urethra in women with or without nodal coverage.
- Daily bladder target motion variability introduces significant uncertainty that must be accounted for with PTV margin, daily setup, and image-guidance.
- In addition to accounting for consistency in bladder filling volume, it is also critical to assess variability in adjacent organs at risk (OARs). The daily variation in the positioning of the small/large bowel in the superior, anterior, and lateral directions as well as the position of the large bowel/sigmoid and rectum in the posterior and lateral orientations.
- IMRT offers a reduction in dose to OARs directly adjacent to the high-dose PTV, including the small and large bowel.
- IMRT offers an opportunity to optimize sparing of normal bladder for partial bladder/reduced volume irradiation and potentially permit dose-escalation to the TURBT bed [13–15].
- Please see Table 26.3 for summary of target volumes for IMRT for bladder cancer.
- Please see clinical vignettes and IMRT-based treatment fields for patients with localized MIBC including (1) initial pelvic field (Fig. 26.3) and sequential bladder boost (Fig. 26.4); or (2) bladder-only field (Fig. 26.5).
- Common conventional dose-fractionation prescriptions are: 64–66.6 Gy delivered in 32–37. Elective treatment of the regional nodes (including CTV bladder) is generally 39.6–45 Gy delivered in 1.8 Gy fractions prior to sequential bladder boost of 19.8–21.6 Gy in 1.8 Gy fractions.

Table 26.3 Field design for selective bladder preservation using intensity-modulated radiation therapy (IMRT) planning

Initial pelvic field	• Designed to cover entire bladder and regional pelvic nodes as well as prostate/prostatic urethra in men using four-field box arrangement
	• **GTV** = any gross disease and/or tumor bed as defined by fiducials or post-TURBT imaging
	• **CTV bladder** = whole bladder (including GTV) + prostate/prostatic urethra (men) or proximal urethra (women)
	• **PTV bladder** = CTV bladder + 1.5 cm
	• **CTV pelvis** = includes bilateral pelvic nodal regions (perivesical, internal iliac, external iliac, presacral, distal common iliac)
	• **PTV pelvis** = CTV pelvis + 8–10 mm on vessels (corresponding to nodal regions)
	• If electing to treat pelvic nodes combine PTV bladder + PTV pelvis to create composite PTV for initial pelvic field
Bladder-boost field	• **GTV/CTV bladder boost** = any gross disease and/or tumor bed as defined by fiducials or post-TURBT imaging
	• **PTV bladder boost** = CTV + 1 cm isotropic expansion

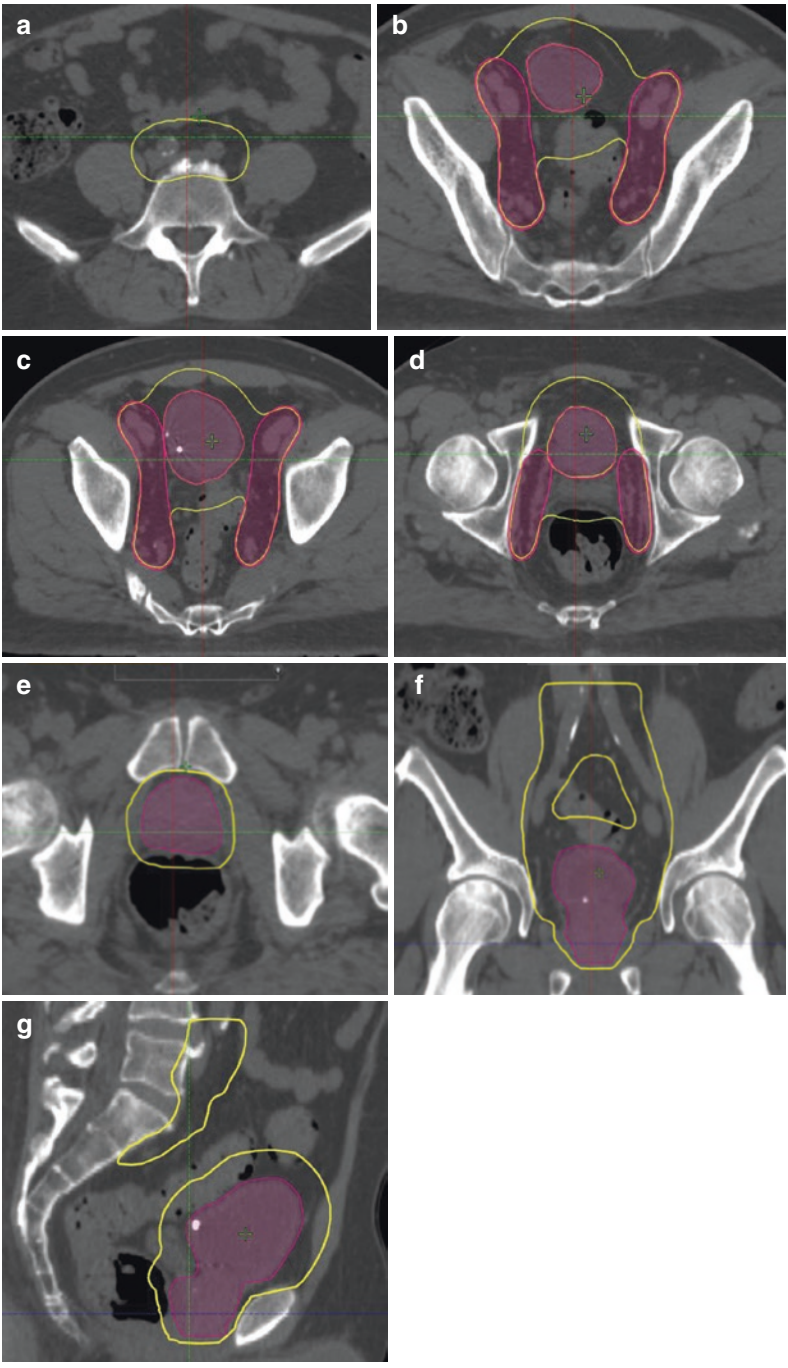

Fig. 26.3 Initial pelvic IMRT field for 56-year-old gentleman with cT2N0 high-grade urothelial muscle-invasive bladder carcinoma involving right posterolateral bladder wall. Representative images of initial pelvic field with targets and PTV contoured in axial (**a**–**e**), coronal (**f**) and sagittal (**g**) plane

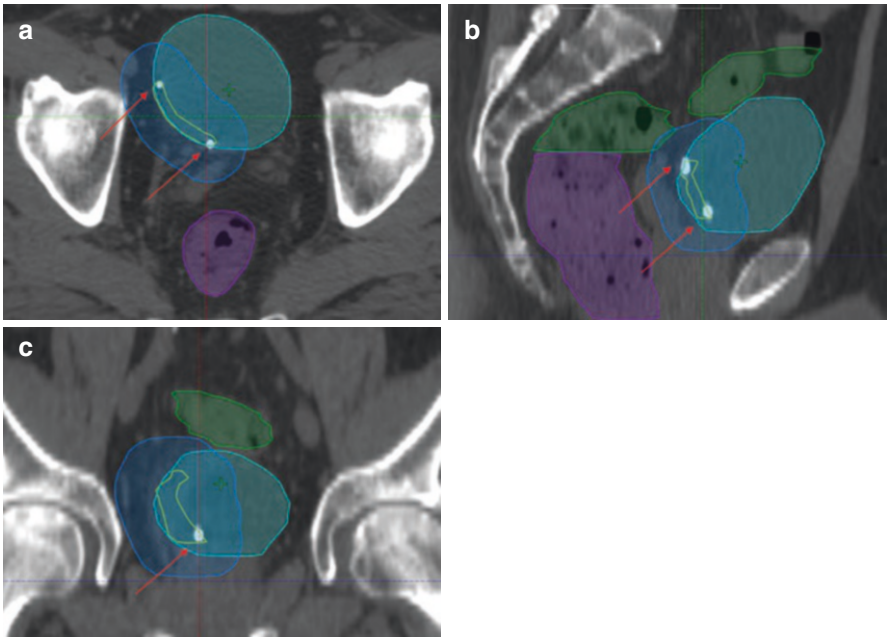

Fig. 26.4 Bladder-boost pelvic IMRT field for 56-year-old gentleman with cT2N0 high-grade urothelial muscle-invasive bladder carcinoma involving right posterolateral bladder wall. Bladder = cyan. TURBT bed = yellow. PTV boost = blue. Rectum = magenta. Bowel = green. Arrows = fiducials. (**a**) axial (**b**) sagittal and (**c**) coronal plane

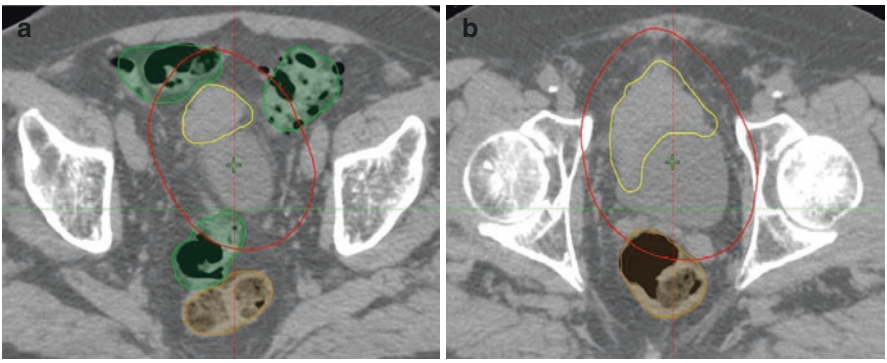

Fig. 26.5 Concurrent chemoradiation with bladder-only IMRT for 82-year-old man with locally advanced, unresectable muscle-invasive disease at right anterolateral bladder wall. PTV = red. GTV = yellow. Bowel = green, Rectum = orange. Prostate = blue. Axial (**a**–**c**), coronal (**d**), and sagittal (**e**) representative CT slices with targets contoured for IMRT-based bladder-only treatment

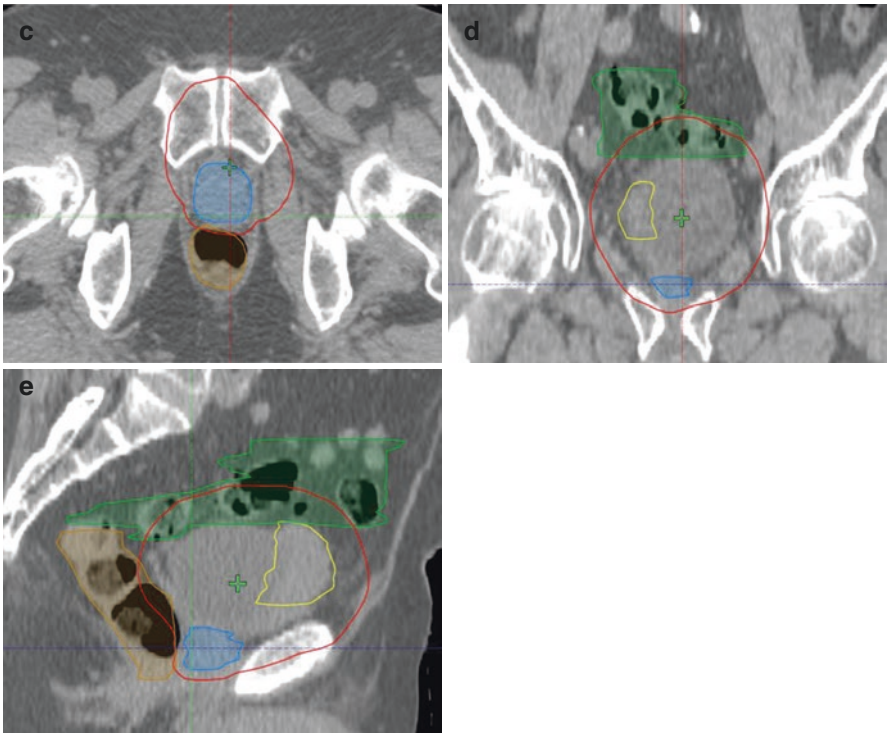

Fig. 26.5 (continued)

26.4 Simulation and Planning

- CT-based simulation in supine position with appropriate pelvic immobilization device is recommended.
- Reproducible bladder filling and verification with image-guidance is critical to effective and safe delivery of IGRT for MIBC [16].
- Image-guidance may vary by institution. For the initial phase, daily KV imaging matched to bone and at least weekly CBCTs to verify bladder position are performed. For the boost phase, daily KV imaging matched to fiducials and/or CBCT daily is appropriate. When fiducials are not present, daily CBCT is recommended for the boost phase.

26.5 MSKCC Guidelines

- At our institution, definitive trimodality therapy generally involves maximal TURBT with bladder mapping and placement of gold fiducial markers placed at the periphery of the TUR bed.
- Following TUR with fiducial placement, a CT-based simulation is performed with empty bladder. The choice of an empty bladder is for both consistency and reduction of the initial bladder target volume. Oral contrast is used to delineate bowel. IV contrast for simulation purposes should be used with caution in patient with compromised renal function or those planned for nephrotoxic chemotherapy.
- During Week 3–4 of concurrent chemoradiation, a CT-based re-simulation is performed with full bladder in order to plan the cone down phase. The choice of a full bladder is to displace bowel and uninvolved bladder walls from bladder boost target.
- The prescription for the initial phase of treatment is 4500 cGy delivered in 25 daily fractions (180 cGy/fraction) and the targets for the initial phase of treatment are: bladder (whole), prostate/prostatic urethra, regional pelvic nodes (obturators/perivesical, external iliac, internal iliac, presacral, common iliac [to aortic bifurcation]).
- The prescription for the cone down phase of treatment is 2160 cGy delivered 12 daily fractions (cumulative dose to PTV boost is 6660 cGy over 37 fractions). The target for the cone down phase of treatment includes the TURBT bed as defined by the fiducial markers with a 1 cm margin.
- In selected patients, hypofractionated regimens (55 Gy over 20 fractions) may be used. Target volumes include the bladder/prostatic urethra and any gross tumor with a 1.5 cm circumferential margin with daily CBCT for image-guidance. Radiosensitizing chemotherapy is utilized when clinically appropriate. Selected patients may include those with poor performance status or very elderly patients, cystectomy-ineligible patients with multifocal disease, or palliation for locally advanced disease.
- For node-positive patients, the initial phase may include a simultaneous integrated boost (SIB) to dose-escalate gross adenopathy. Generally, a SIB dose of 5625 cGy delivered in 25 daily fractions (225 cGy/fraction) to gross nodal disease (PTV = GTV + 5 mm margin) respecting normal tissue tolerance is appropriate. See Figs. 26.6 and 26.7 for case example of locally advanced node positive bladder cancer.

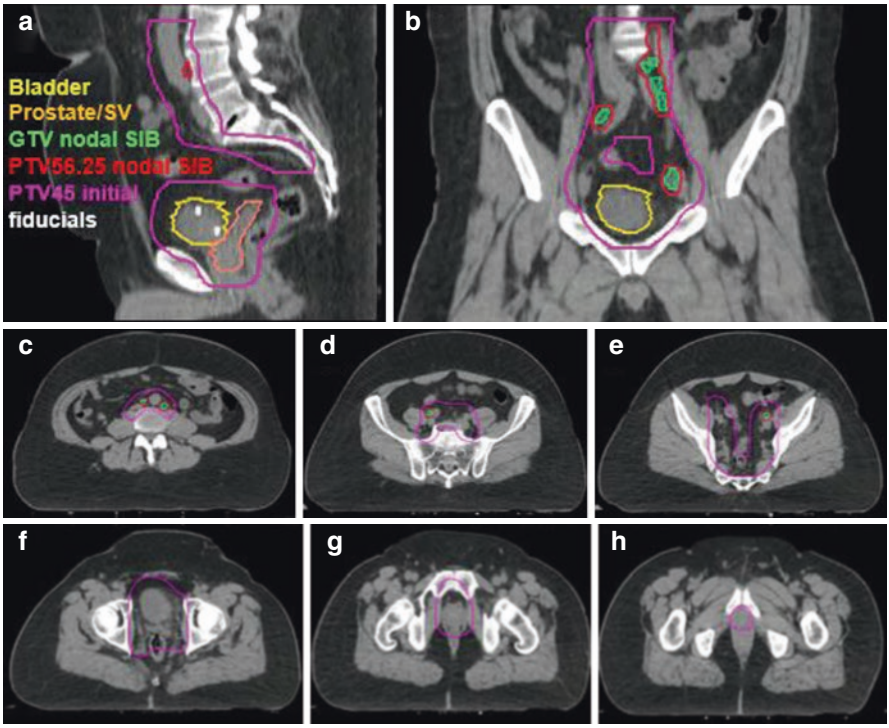

Fig. 26.6 Initial pelvic fields with simultaneous integrated boost for 51-year-old male with cT2N+ locally advanced urothelial bladder carcinoma w/ 5.0 × 2.8 cm mass along left posterolateral wall s/p maximal TURBT. Sagittal (**a**), coronal (**b**), and axial (**c**–**h**) CT slices with targets contoured for IMRT-based treatment

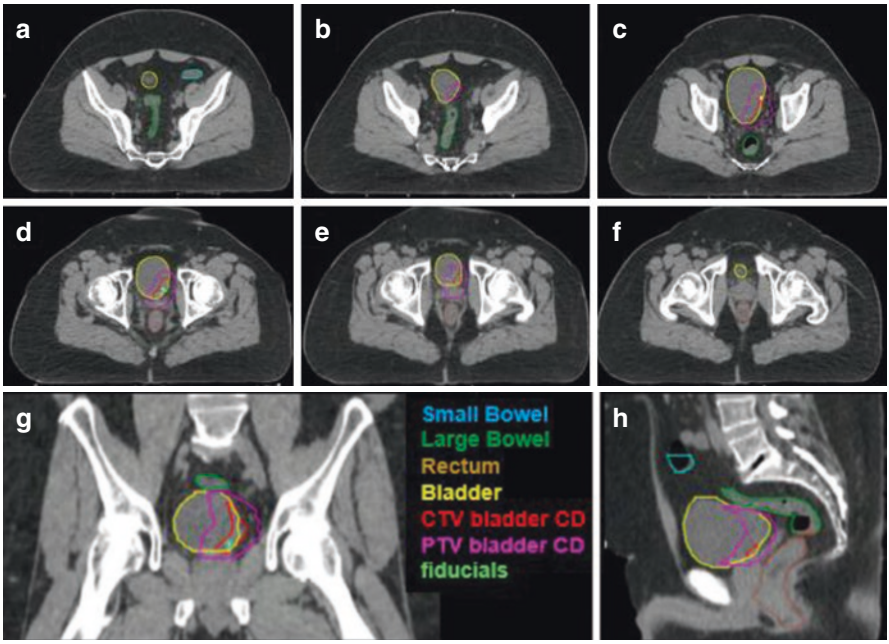

Fig. 26.7 Bladder-boost fields for 51-year-old male with cT2N+ locally advanced urothelial bladder carcinoma w/ 5.0 × 2.8 cm mass along left posterolateral wall s/p maximal TURBT. Axial (**a**–**f**), coronal (**g**), and sagittal (**h**) CT slices with targets and organs at risk contoured for IMRT-based bladder boost

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Testicular Seminoma

27

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Contents

27.1 General Principles of Planning and Target Delineation

- In almost all cases, initial management of testicular cancer involves a radical inguinal orchiectomy. Post-operative management depends on histological subtype and extent of disease.
- Post-operative radiation is generally only considered for pure seminomas (most common type of testicular germ cell tumor, highly radiosensitive) and rarely considered for non-seminomatous germ cell tumors (less common, less radiosensitive).
- Prior to any treatment, adequate workup should be performed to ensure pure seminoma, including detailed history and physical exam, serum tumor markers (AFP, β-hCG, and LDH), chemistry panel, testicular ultrasound, and CXR [1]. Following radical inguinal orchiectomy for a pure seminoma, serum tumor markers should be repeated, and additional staging studies should be performed

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_27

including CT chest/abdomen/pelvis +/− brain MRI (if indicated). All patients planned for testicular cancer treatment should be offered fertility evaluation and sperm banking.

- Laterality of testicular seminoma and prior surgery influences pattern of spread [2].
  - Right sided seminoma tends to drain to the paracaval, precaval, and aortocaval nodes.
  - Left sided seminoma tends to drain to the lateroaortic and preaortic nodes.
  - Pelvic, external iliac or inguinal nodes may be at risk in patients with prior scrotal or inguinal surgery [3].
- Patients with stage I pure seminoma have several options. Generally, post-orchiectomy surveillance is strongly preferred. However, based on results from MRC TE 10 [4] and TE18 [5], those patients with stage I seminoma who refuse surveillance can receive adjuvant radiotherapy to para-aortic lymph nodes alone (i.e., PA strip, see Table 27.1 and Fig. 27.1) to a dose of 20–25.5 Gy unless there is prior inguinal or scrotal violation. Another non-inferior adjuvant option is 1–2 cycles of carboplatin [1, 8].
- Patients with stage II pure seminoma can be treated using a dogleg field (see Table 27.2 and Figs. 27.2 and 27.3) to either 30 Gy (stage IIA) or 36 Gy (stage IIB) [1]. Alternatively, primary chemotherapy can be used, typically consisting of etoposide/cisplatin +/− bleomycin for 3–4 cycles.
- At our institution, standard radiation simulation parameters for testicular seminoma include a 2 mm slice thickness CT with the patient positioned supine with arms up. An alpha cradle is used for immobilization. IV contrast is often used for stage II patients to help delineate gross nodal disease. If the patient has a staging

Table 27.1 Suggested target volumes for stage I testicular seminoma

Target volume	Definition based on CT imaging and vascular anatomy (see Fig. 27.1)	Definition based on anatomic landmarks
CTV	• Contour inferior vena cava and aorta from 2 cm below top of kidney superiorly down to the bifurcation of iliac vessels inferiorly	• Superior border: top of T11 (*Note*: some sources recommend top of T12) [6]
	• Expand IVC contour by 1.2 cm and aorta contour by 1.9 cm	• Inferior border: bottom of L5
	• Combine the two volumes and then subtract off of bone, muscle, and bowel	• Lateral borders: edge of transverse processes (typically 10 cm width); For left sided seminoma: nodal mapping studies suggest that it is optional to cover the left renal hilum [7].
PTV [20–25.5 Gy in 1.5–2.0 Gy per fraction]	• Expand the final CTV by 0.5 cm + 0.7 cm to block edge	

See [6] for more detailed information

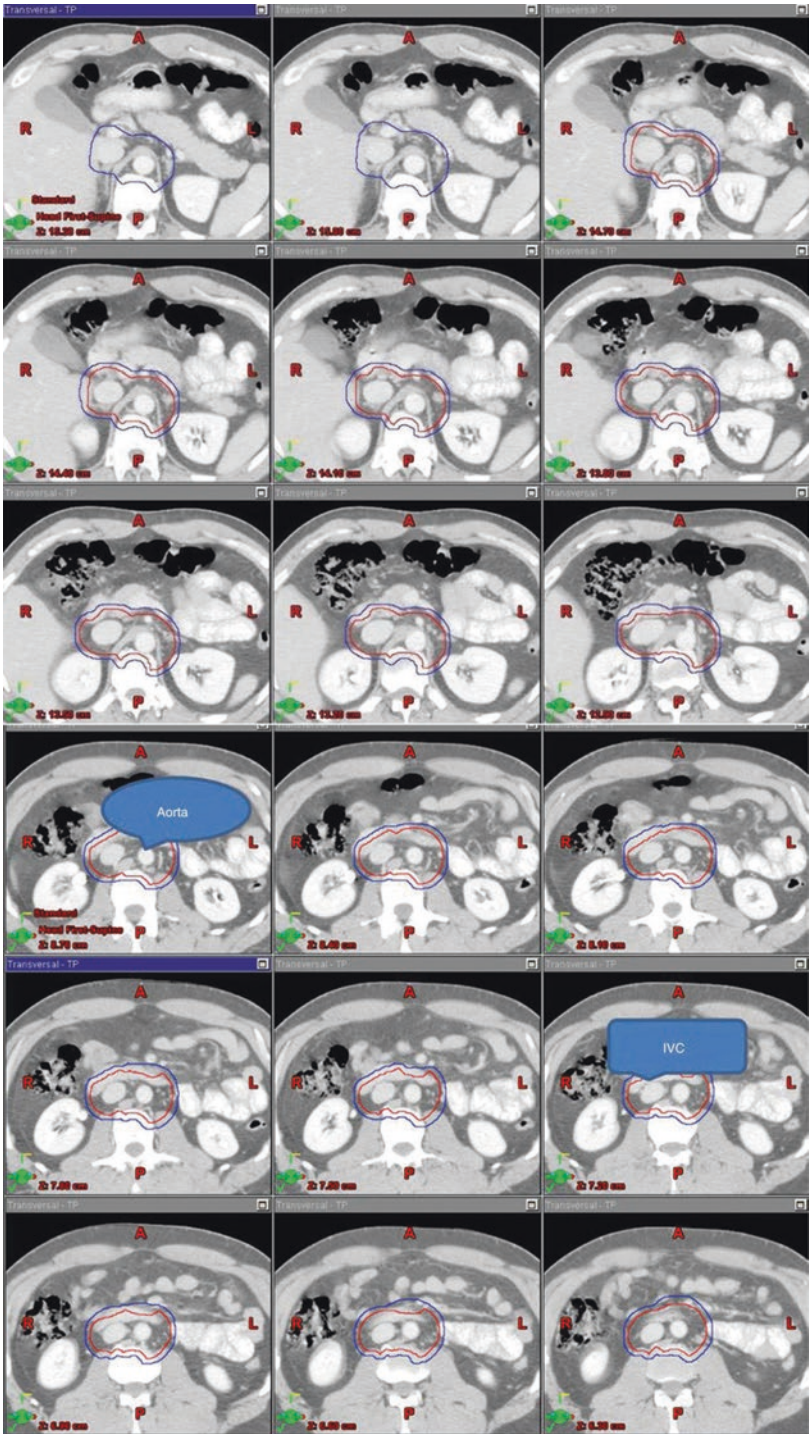

Fig. 27.1 Volumes for clinical stage I seminoma based on vascular anatomy. Volumes for clinical stages IA, IB, and IS (CTV = red, PTV = blue); slices are superior to inferior

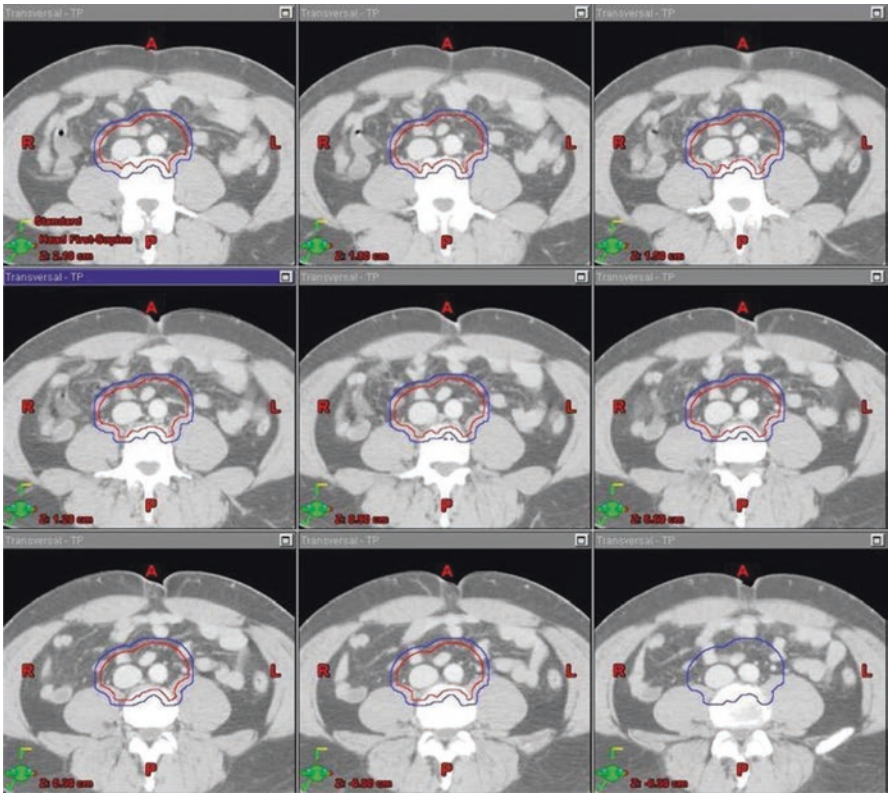

Fig. 27.1 (continued)

PET scan, this can also be fused with the simulation CT scan. The contralateral intact testicle should be shielded with a clamshell.

- 3D-CRT is the standard treatment approach for seminoma with AP/PA fields based on bony anatomic landmarks or vascular anatomy. A general description of target volumes and margins is indicated in Tables 27.1 and 27.2. See [6] for more detailed information.
- In the case of prior inguinal or scrotal surgery, the ipsilateral inguinal and iliac regions should be included in the field. If there was penetration of the scrotum, consider electron boost to the scrotum and scar.

Table 27.2 Suggested target volumes for stage II testicular seminoma

Target volume and dosing	Definition based on CT imaging and vascular anatomy (see Fig. 27.2)	Definition based on anatomic landmarks
$CTV_{initial}$	• Create $CTV_{vessels}$: Same IVC/aorta contours and expansions as per Table 27.1. Next, contour common iliac vessels, proximal internal iliac vessels (until takeoff of superior gluteal), and external iliac vessels down to the upper border of the acetabulum and expand by 1.2 cm respecting anatomic boundaries	• Superior border: top of T11 (*Note*: some sources recommend top of T12) [6]
	• Create CTV_{nodes}: Contour gross nodal disease (GTV) and expand by 0.8 cm respecting anatomic boundaries	• Inferior border: top of the acetabulum (*Note*: some sources recommend middle or bottom of the obturator foramen) [6]
	• Combine $CTV_{vessels}$ and CTV_{nodes} to form $CTV_{initial}$	• Lateral border: tips of transverse processes of lumbar vertebra (typically L3 with consideration of kidney location) and extending to cover lateral acetabular edge at inferior extent of the field
$PTV_{initial}$ [20–25.5 Gy in 1.5–2.0 Gy per fraction]	• Expand $CTV_{initial}$ by 0.5 cm + 0.7 cm to block edge	• For left sided seminoma: nodal mapping studies suggest that it is optional to cover the left renal hilum [7]
$PTV_{conedown}$ [Boost volume to receive total of 30–36 Gy in 2 Gy per fraction] (see Fig. 27.3)	• Expand CTV_{nodes} by 0.5 cm + 0.7 cm to block edge	• Ensure 2 cm margin on all visible gross adenopathy

See [6] for more detailed information

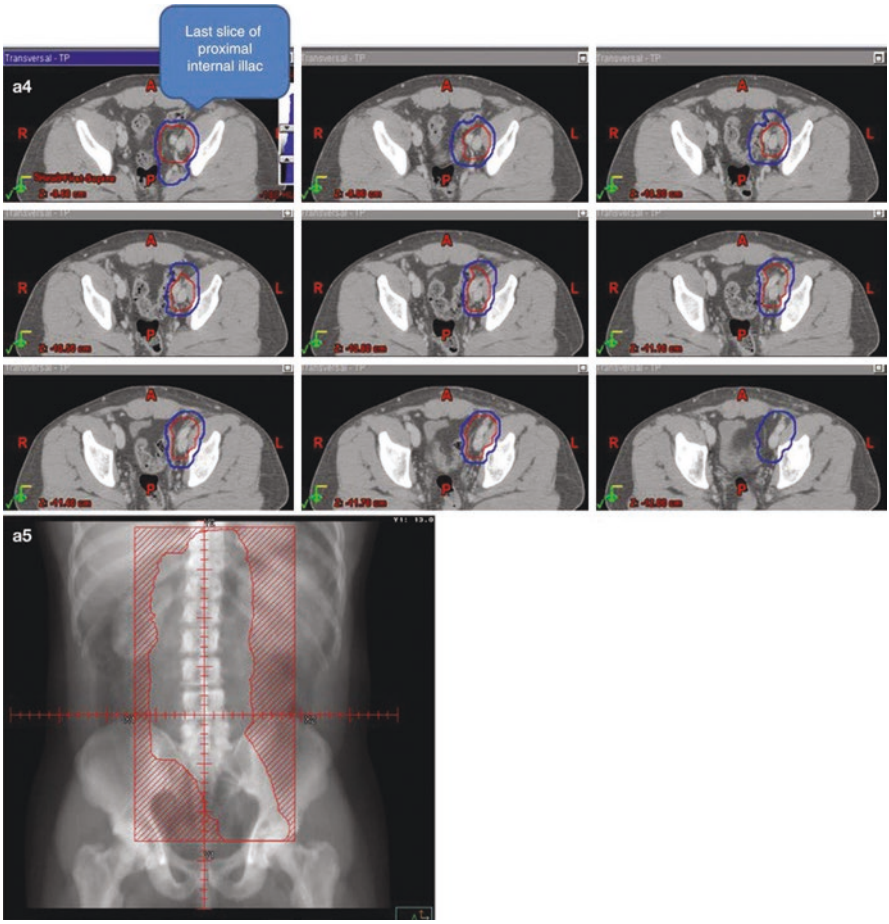

Fig. 27.2 Inferior portion of dogleg field based on vascular anatomy. Initial dogleg field with CTV in red and PTV in blue with slices projected superior to inferior. Note that the superior portion of the field is as per Fig. 27.1

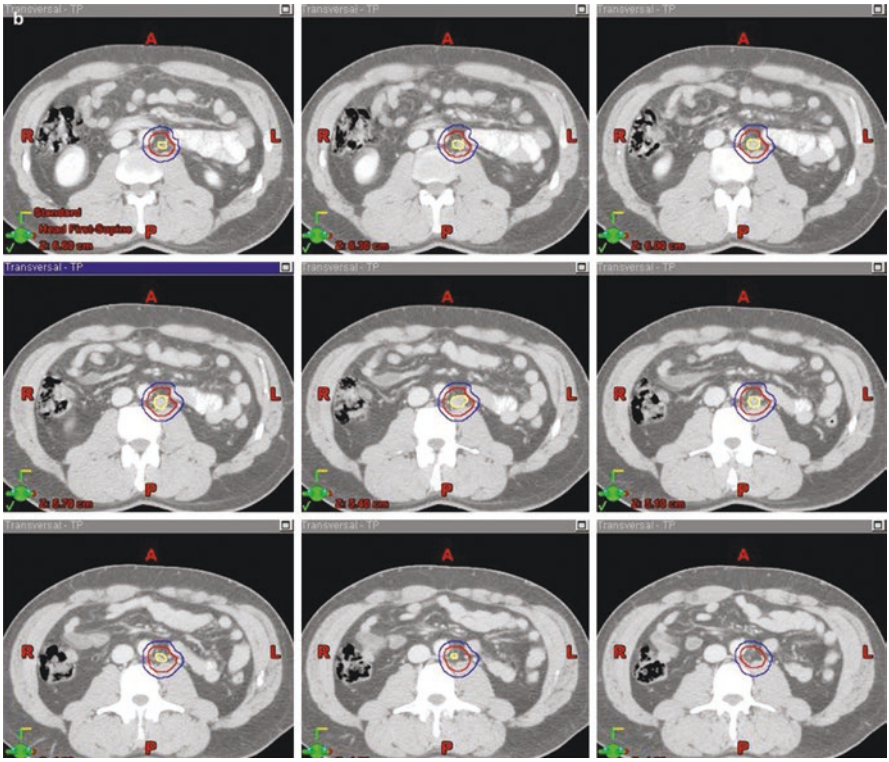

Fig. 27.3 Boost volumes. Example boost contours for a male with stage IIA disease. Note that GTV = yellow, CTV = red, PTV = blue, and that slices are superior to inferior

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Brain Metastases

28

Christophe Marques, Julie Jang, Fahad Momin, Michael Reilly, and Eric L. Chang

Contents

28.1 Whole Brain Radiation Therapy Versus Stereotactic Radiosurgery

- The choice of whole brain radiation therapy (WBRT) versus stereotactic radiosurgery (SRS) is beyond the scope of this manual, but depends on a number of factors, including number and volume of brain metastases and performance status. Several prognostic tools, including molecular graded prognostic assessment, are available to aid in decision-making.
- Generally, SRS offers better preservation of neurocognitive function and quality of life, whereas WBRT improves the distant and overall control rates of intracranial metastases.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_28

28.2 WBRT: General Principles of Planning and Target Delineation

- See Table 28.1 for clinical scenarios and variations in technique. Dose fractionations are included in Table 28.2.
- Strategies to preserve neurocognitive function include addition of memantine and/or hippocampal avoidance WBRT (HA-WBRT).
- Non-contrast treatment-planning CT scan from vertex to upper cervical spine (axial slice thickness ≤2.5 mm) is performed with the patient supine and head in neutral position, using a thermoplastic mask for immobilization, with field of view 600 mm.

Table 28.1 Suggested WBRT fields

	Conventional WBRT	Leptomeningeal disease	Lymphoma/leukemia	Scalp sparing	HA-WBRT
Clinical scenario	• Diffuse brain metastases (numerous or "too many to count")	• Leptomeningeal disease	• CNS prophylaxis for ALL	• Cosmetic outcome is a priority (technique may result in a "reverse Mohawk")	• Diffuse brain metastases (numerous or "too many to count")
	• PCI for SCLC		• CNS leukemia (high-risk)		• PCI for SCLC • Exclusion: lesion is within 5 mm from hippocampus
Fields	3D-CRT with lateral opposed beams rotated slightly off-axis (RAO/LAO) to avoid divergence into the lenses				IMRT/VMAT
Target volumes and margins	Entire cranial contents	Entire cranial contents	Entire cranial contents	Entire cranial contents	CTV: whole brain parenchyma to foramen magnum
		+ optic nerves	+ optic nerves		PTV: CTV minus (hippocampi + 5 mm expansion), no setup margin
		+ retroorbital region	+ retroorbital region		Normal structure constraints:
		+ lamina cribosa	+ retina		Brain metastases:
			+/− whole globe if ocular involvement		• hippocampi D100% ≤9 Gy, Dmax ≤16 Gy

Table 28.1 (continued)

	Conventional WBRT	Leptomeningeal disease	Lymphoma/leukemia	Scalp sparing	HA-WBRT
Field edges	*Sup*: 2 cm flash			MLC edge set at outer table of the calvarium	• optic nerves and chiasm Dmax ≤30 Gy
	Post: 2 cm flash +/− posterior neck MLC block to protect soft tissue				PCI for SCLC: • hippocampi D100% ≤7.5 Gy, Dmax ≤13.5 Gy
	Inf: bottom of C1				• optic nerves and chiasm Dmax ≤25 Gy
	Ant: MLC block from 2 cm flash to anterior aspect of C1, blocking parotid and lenses				
	Cover temporal lobes and cribriform plate				
		Cover temporal lobes and cribriform plate with additional margin 8–10 mm for penumbra and daily setup	Cover temporal lobes and cribriform plate with additional margin 8–10 mm for penumbra and daily setup		
			Cover posterior 1/3 of the globes if no ocular involvement on slit lamp examination or entire bilateral globes if ocular involvement		

Table 28.2 WBRT dose and fractionation

Clinical scenario	Dose and fractionation
WBRT, LMD	30 Gy in 10 fractions (most common), 37.5 Gy in 15 fractions (RTOG), 30 Gy in 12 fractions, 20 Gy in 5 fractions (poor prognosis)
WBRT reirradiation	20–25 Gy in 10 fractions and a time interval of at least 4–6 months
PCI fort SCLC	25 Gy in 10 fractions (most common)
CNS prophylaxis for ALL	12 Gy in 8 fractions
CNS leukemia (high-risk)	≥18 Gy in 9–10 fractions (dose based on intensity of systemic therapy)

- 3D-CRT with opposed lateral photon beams of energy 6 MV is used typically with a multileaf collimator (MLC) block (Figs. 28.1 and 28.2).
- For hippocampal avoidance, inverse-planned IMRT relies on a planning CT scan fused to a gadolinium contrast-enhanced MRI scan (using the three-dimensional spoiled gradient sequence with axial slice thickness 1.25–1.5 mm to define the hippocampal avoidance region) (Fig. 28.3) [1].
- Orthogonal films for setup verification are done weekly with MV imaging. Daily kV is usually reserved for IMRT-based WBRT.

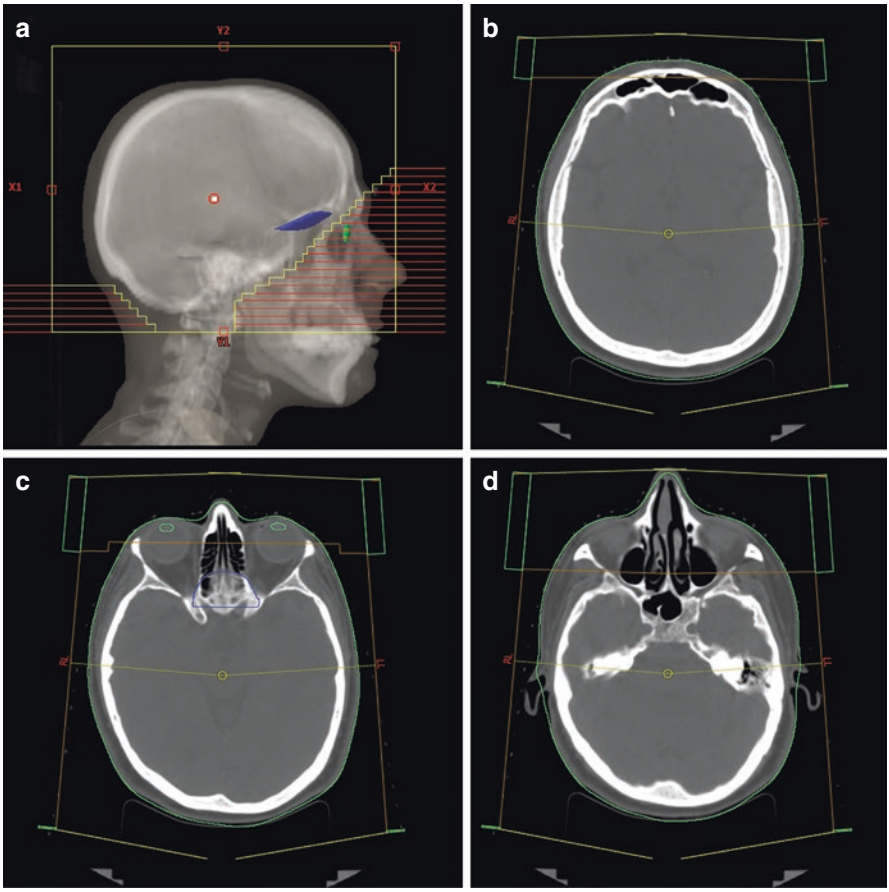

Fig. 28.1 Standard WBRT fields as described in Table 28.1 with lateral opposed beams rotated slightly off-axis (RAO/LAO) to avoid divergence into the lenses. (**a**) Beam's eye view showing coverage of the cribriform plate (blue) with MLCs blocking the lenses (green), (**b**) mid-cranium axial view illustrating coplanar anterior field edges, (**c**) axial view showing adequate coverage of the cribriform plate and avoidance of the lenses, (**d**) axial view illustrating adequate coverage of the temporal lobes. Note: the isocenter can also be placed midline at the level of the canthus, allowing no beam divergence to the eyes or lenses

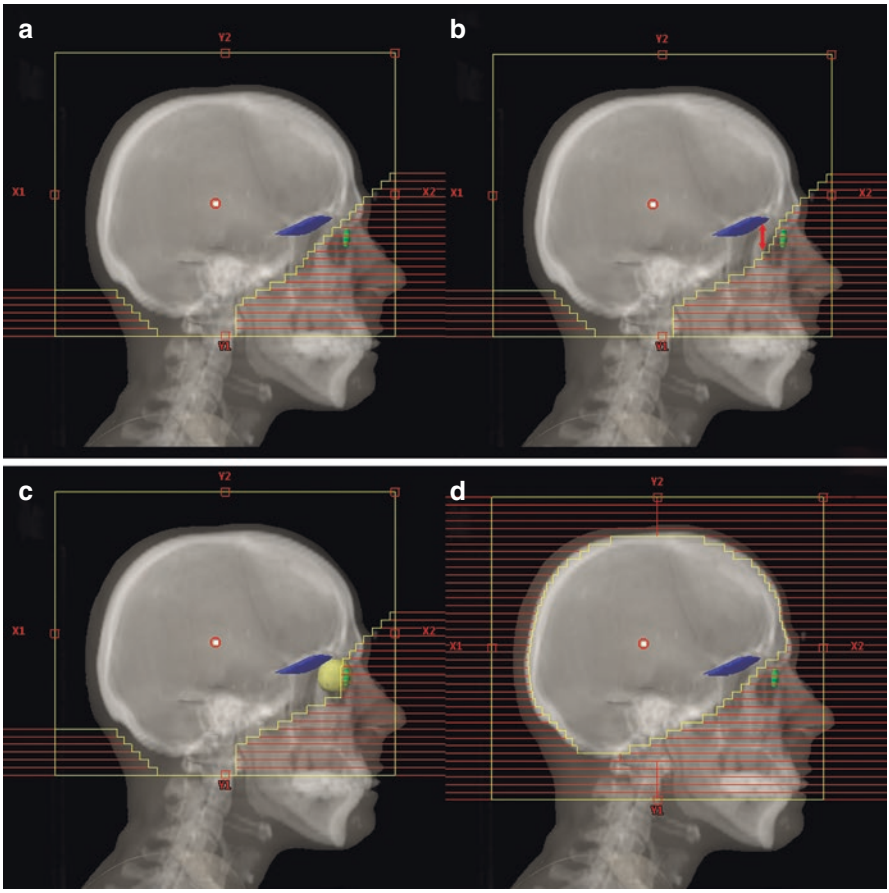

Fig. 28.2 Variations of the standard WBRT fields accounting for differing clinical situations as described in Table 28.1. (**a**) Conventional WBRT, (**b**) larger fields used for leptomeningeal disease with red arrow showing greater distance from the cribriform plate compared to (**a**), (**c**) fields covering the posterior orbits for CNS leukemia/lymphoma, (**d**) scalp-sparing technique with MLC edges set at the outer table of the calvarium

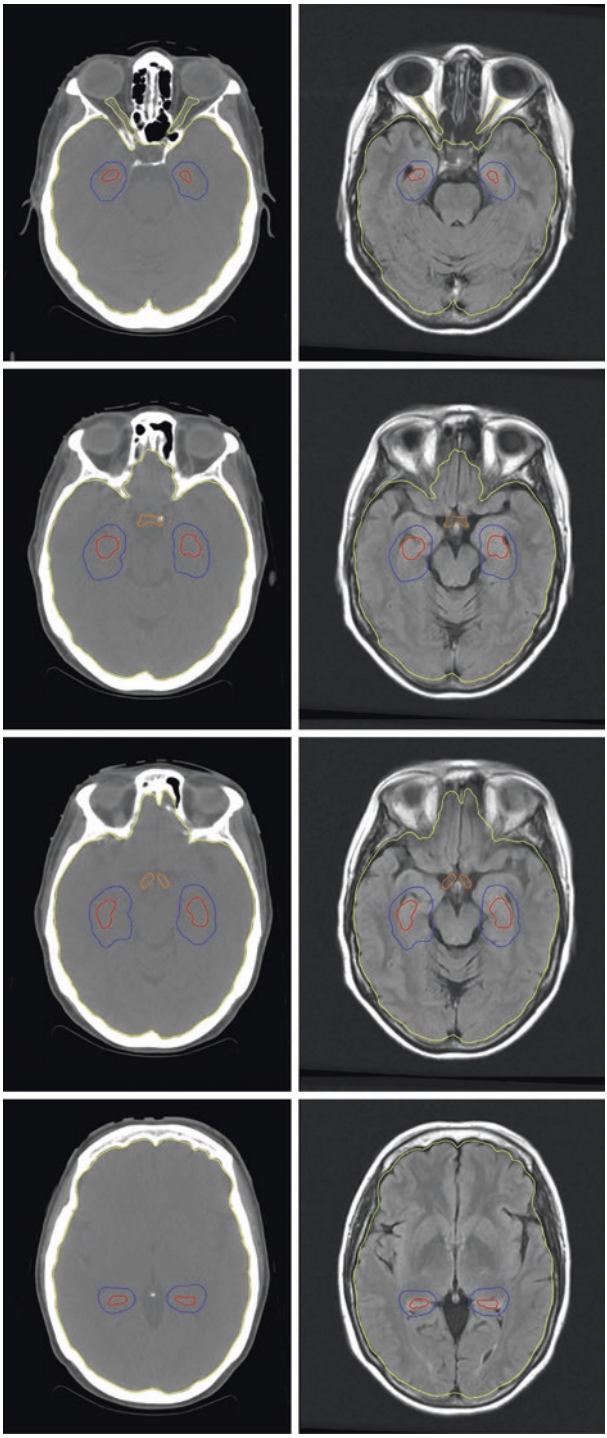

Fig. 28.3 Hippocampal avoidance WBRT illustrated with axial slices of CT and fused postcontrast three-dimensional spoiled gradient MRI from the caudal to cranial direction. Per RTOG 0933 contour guidelines, only the subgranular zone (SGZ) portion of the hippocampi is contoured (red) and a 5 mm volumetric expansion margin (blue) is applied to create a hippocampal avoidance zone. The PTV consists of the entire brain tissue (yellow) minus the 5 mm expanded hippocampi (blue). Also shown are the optic nerves (yellow) and chiasm (orange)

28.3 SRS: General Principles of Planning and Target Delineation

- Clinical scenarios employing SRS include single-fraction and fractionated SRS (2–5 fractions) for intact brain metastases and post-resection cavity (Table 28.3, Figs. 28.4 and 28.5). Dose fractionation depends on target size or volume and distance from critical structures (Table 28.4).
- Instruments include the frame-based or frameless cobalt-based Leksell Gamma Knife® or LINAC-based systems.
- Target volume delineation and treatment planning using a volumetric contrast-enhanced T1-weighted MRI scan (1–2 mm slices) is preferred (or contrast-enhanced CT scan if unable to tolerate MRI or patient has an incompatible implanted device). A thin-slice CT is acquired and co-registered for LINAC-based SRS.
- For LINAC-based SRS, daily imaging is required.

Table 28.3 Suggested SRS target volume delineation using two different methods [2, 3]

Target	GTV	CTV
Unresected brain metastases	Contrast enhancing lesion on T1-weighted sequence MRI	GTV + 0 mm
Postoperative gross total resection cavity (method 1) [2]	n/a	• 2 mm expansion margin around the resection cavity borders visualized on postcontrast MRI
Postoperative gross total resection cavity (method 2) [3]	n/a	• Entire contrast enhancing region, surgical cavity, and surgical tract seen on postoperative MRI
		• 5–10 mm margin along the bone flap beyond the initial region of preoperative tumor contact (if initial tumor was in contact with the dura)
		• 1–5 mm margin along the bone flap (if initial tumor was NOT in contact with the dura)
		• 1–5 mm margin along the venous sinus (if initial tumor was in contact with a venous sinus)

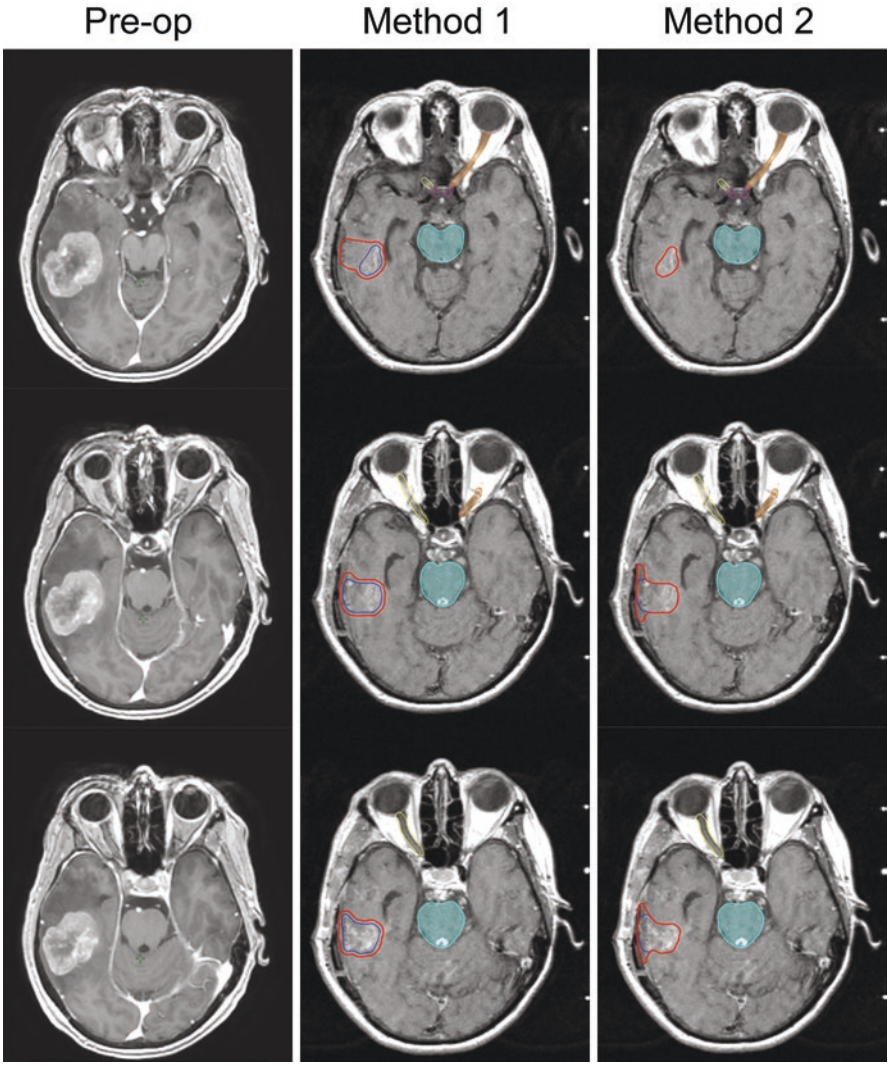

Fig. 28.4 Single-fraction SRS to a 24 mm left temporal lobe surgical cavity, after gross total resection of a 33 mm metastasis from primary rectal cancer with preoperative dural contact but no venous sinus contact. Method 1 shows the contours as described by Soltys et al. [2], CTV delineation (red) = MRI T1 post-gadolinium enhancement and surgical cavity (blue) + 2 mm uniform expansion margin. Method 2 shows the contours as described by Soliman et al. [3], CTV delineation (red) = MRI T1 post-gadolinium enhancement, surgical cavity, and surgical tract (blue) + 10 mm margin along the bone flap. Single-fraction SRS was chosen due to the small cavity size (<3 cm) and sufficient distance from delicate brain structures. Patient was treated using Leksell Gamma Knife® by Elekta, hence PTV = CTV + 0 mm expansion margin. Contoured structures shown include the right optic nerve (yellow), left optic nerve (orange), and the brainstem (cyan)

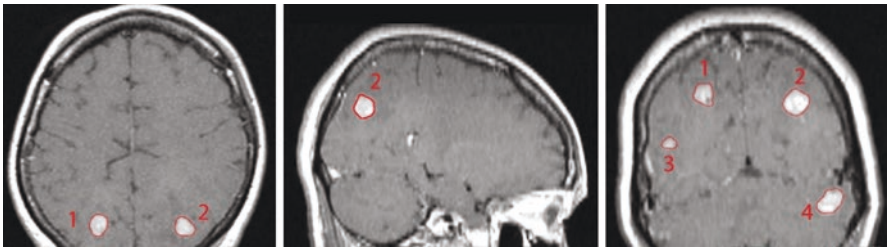

Fig. 28.5 Multiple isocenter single-fraction SRS to new brain metastases from primary breast cancer, ranging from 6 to 20 mm (volume ranging from 0.07 to 1.92 cm^3) in a patient who received prior WBRT 30 Gy in 10 fractions. Lesion 1 is located in the right parietal lobe, lesion 2 in the left parietal lobe, lesion 3 in the right temporal lobe, and lesion 4 in the left cerebellum. Single-fraction treatment was chosen due to the smaller tumor sizes (less than 3 cm) and sufficient distance from delicate brain structures. For all lesions, GTV delineation (red) = MRI T1 post-gadolinium enhancement. Patient was treated using Leksell Gamma Knife® by Elekta, hence PTV and CTV used 0 mm expansion from GTV

Table 28.4 SRS dose and organ at risk constraints for different fractionation schemes (based on Alliance A071801 trial) [4]

	1 Fraction	3 Fractions	5 Fractions
PTV dose (postop cavity)	20 Gy (<4.2 cm^3)	27 Gy (<30 cm^3)	30 Gy (≥30 cm^3 to <5 cm)
	18 Gy (≥4.2 to <8.0 cm^3)		
	17 Gy (≥8.0 to <14.4 cm^3)		
	15 Gy (≥14.4 to <20 cm^3)		
	14 Gy (≥20 to <30 cm^3)		
	12 Gy (≥30 cm^3 to <5 cm)		
PTV dose (unresected metastases)	24 Gy (<1 cm)	27 Gy	30 Gy
	22 Gy (≥1.0 to <2.0 cm)		
	18 Gy (≥2.0 to <3.0 cm)		
	15 Gy (≥3.0 to <4.0 cm)		
Brainstem constraint	V12 Gy < 1 cm^3	23.1 Gy max	28 Gy max
		V18 Gy < 0.5 cm^3	V23 Gy < 0.5 cm^3
Optic apparatus constraint	9 Gy max	17.4 Gy max	23 Gy max
		V13.8 Gy < 0.2 cm^3	V20 Gy < 0.2 cm^3

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Benign Tumors of the CNS

29

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Contents

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_29

29.1 General Principles of Radiotherapy Planning and Target Volume Delineation

- In the management of patients with benign primary brain tumors, a detailed history, neurologic-focused physical examination, appropriate laboratory investigations (including assessment of hormonal function), visual field and visual acuity testing, audiometric assessment, and baseline neurocognitive function are all key to determine the appropriate treatment modality. Maximal safe surgical resection, with an objective of a gross total resection, remains the standard-of-care for patients who are medically operable and have surgically accessible tumors. Multidisciplinary care is highly recommended for all patients with benign primary brain tumors.
- Definitive radiation therapy is used for patients with a variety of primary brain tumors, including pituitary adenomas, meningiomas, and vestibular and non-vestibular schwannomas. The radiation therapy approach to more aggressive variants of these tumors or malignant tumors is discussed elsewhere in this textbook.
- A variety of radiotherapy techniques are used in patients with benign primary brain tumors, including 3D-conformal radiotherapy (3D-CRT), fractionated stereotactic radiosurgery (FSRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), as well as proton beam radiotherapy (PBT).
- Accurate delineation of the target volumes as well as the key organs-at-risk (OARs) is key to individualizing the best treatment option for each patient and creating an optimal radiotherapy treatment plan. Essential to this process is the ability to obtain treatment planning MR images close to the time of CT simulation with sequences that best allow for visualization of the tumor (i.e. T1-post contrast or FLAIR images) as well as normal anatomy (i.e. T1 images to delineate the hippocampus or 3D T2 or CISS sequences to delineate cranial nerves).

29.2 Patient Positioning, Immobilization, and Simulation

- Patients with benign primary brain tumors are typically simulated in the supine position with arms extending parallel to the body and shoulders in a natural position.
- For patients undergoing CT simulation and treatment, an indexed 3-point thermoplastic mask is used for immobilization; however, a 5-point thermoplastic mask can be used for patients with base-of-skull tumors or with tumors close to the optic apparatus in which neck positioning can be reinforced with the extended mask.
- For patients undergoing MRI simulation and treatment, a clam shell mask is used.
- The head and chin are placed in a neutral position, unless specific instructions for base-of-skull positioning are required.
- Axial CT simulation images are obtained at 1 mm slice thickness (SRS, FSRT, or PBT) or 2 mm slice thickness (3D-CRT, IMRT, or VMAT) through the entire head of the patient and down to the level of the shoulders.

- Co-registration of diagnostic MR imaging is strongly recommended for target volume delineation for primary brain tumors, unless there is a clear medical or clinical contraindication.
- IV contrast is used, unless medical or clinical contraindication, to delineate primary tumors, resected tumor cavities, or to aid with fusion to pre-treatment MR imaging.

29.3 Normal Structures

- OARs are delineated on the treatment planning CT scan with aid of pre-treatment MR imaging.
- Planning risk volumes (PRVs) can be created for tumors abutting nearby critical organs for aid in dosimetric planning and dose assessment at the time of plan evaluation.
- A list of normal contours delineated for most benign primary brain tumors is provided in Table 29.1.
- Examples of contours of key OARs for primary intracranial cases are provided in Figs. 29.1, 29.2, 29.3 and 29.4.

Table 29.1 List of suggested organs-at-risk for primary brain tumors

• Brain
• Uninvolved brain (brain—GTV or CTV, depending on clinical scenario)
• Brainstem (brainstem core, brainstem surface)
• Spinal cord
• Right cochlea
• Left cochlea
• Right globe
• Left globe
• Right lens
• Left lens
• Right optic nerve
• Left optic nerve
• Optic chiasm
• Right retina
• Left retina
• Right lacrimal gland
• Left lacrimal gland
• Right temporal lobe
• Left temporal lobe
• Right hippocampus
• Left hippocampus
• Hypothalamus
• Pituitary

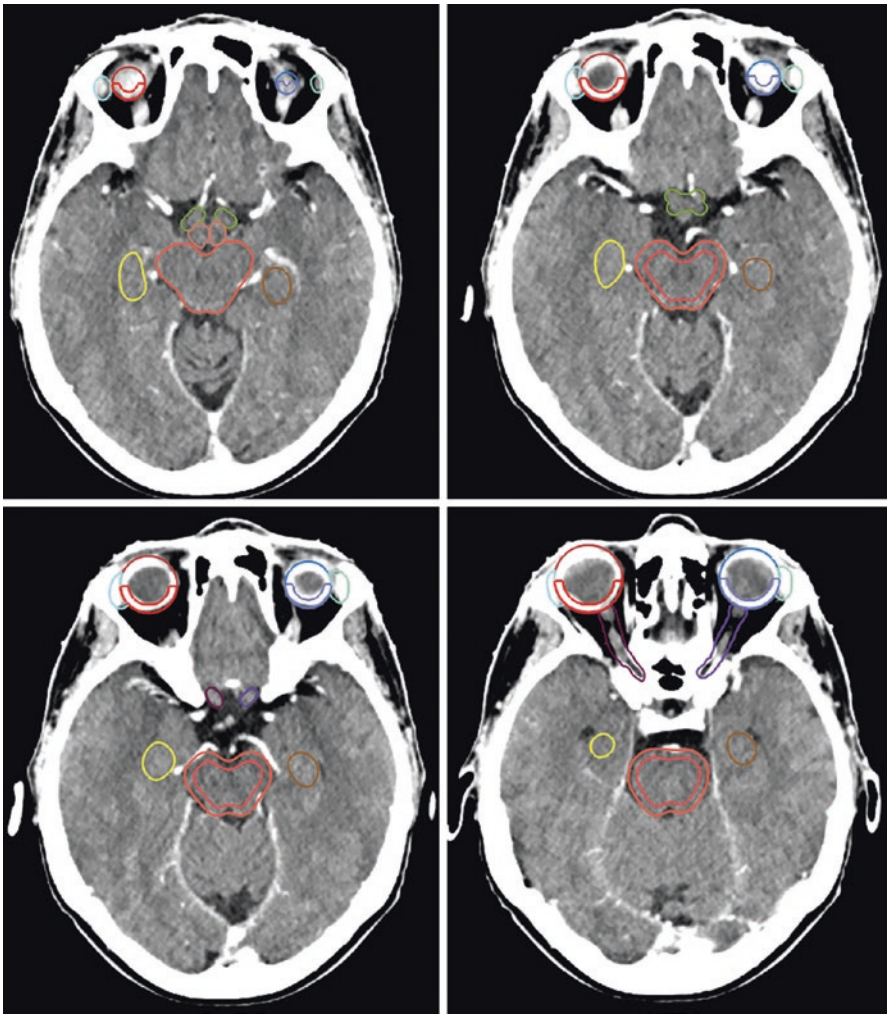

Fig. 29.1 Representative slices of a CT simulation (brain window/level) for a patient demonstrating key OARs to delineate for patients with primary brain tumors. Structures best delineated using this contrast setting include the brainstem, optic chiasm, and intracranial components of the optic nerves. Additionally, this helps to visualize the retinal component of the globe. The right hippocampus is in yellow and the left hippocampus in brown; these are delineated using an axial T1 MRI but visualized on the CT scan (see corresponding Fig. 29.4). The brainstem is in pink and separated into a brainstem core and a brainstem surface (typically a 3 mm peripheral rind). The hypothalamus (dark brown) is located in front of the brainstem and behind the optic chiasm (olive green). Each of the optic nerves (right magenta and left in purple) approximates the respective globe contours. The lacrimal glands (teal) are located on lateral aspect of each of the globes

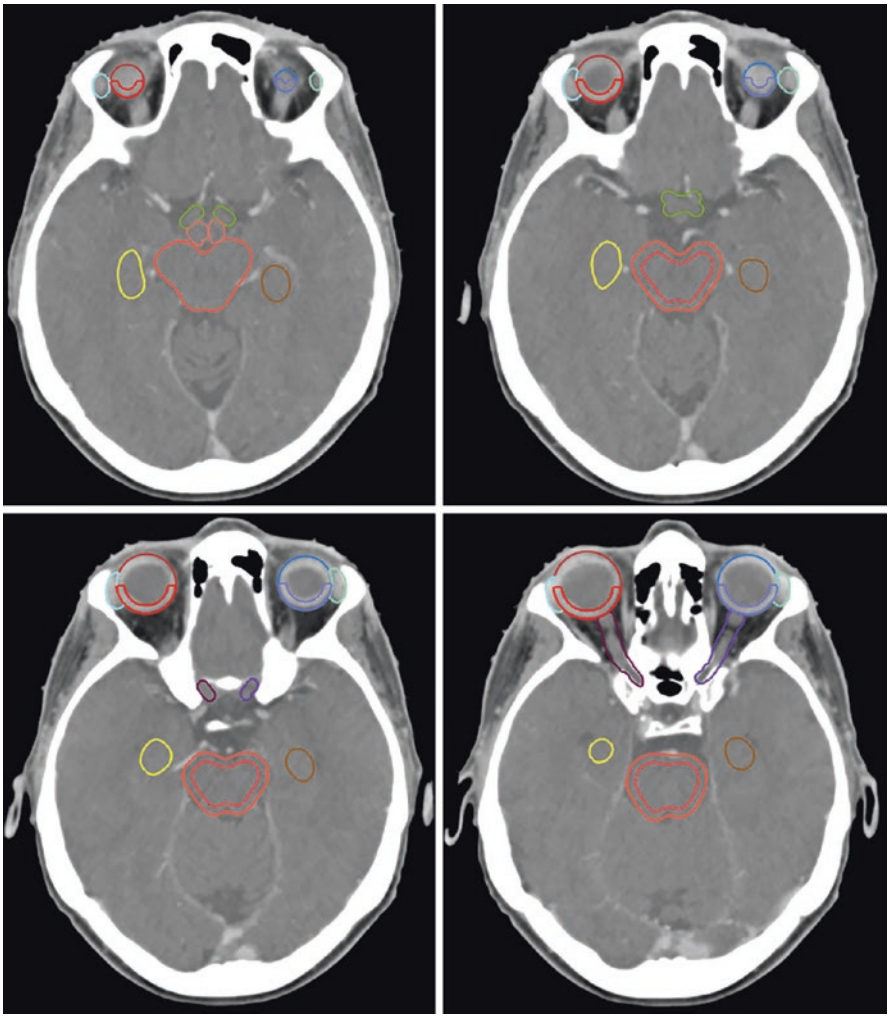

Fig. 29.2 Representative slices of the CT simulation for patient in Fig. 29.1 demonstrating key OARs to delineate for patients with primary brain tumors (soft tissue window/level). Structures best delineated using this contrast setting include the optic nerves as they traverse the optic canals as well as the orbital components of these nerves (right optic nerve in magenta and left optic nerve in purple), as well as the globes and lacrimal gland

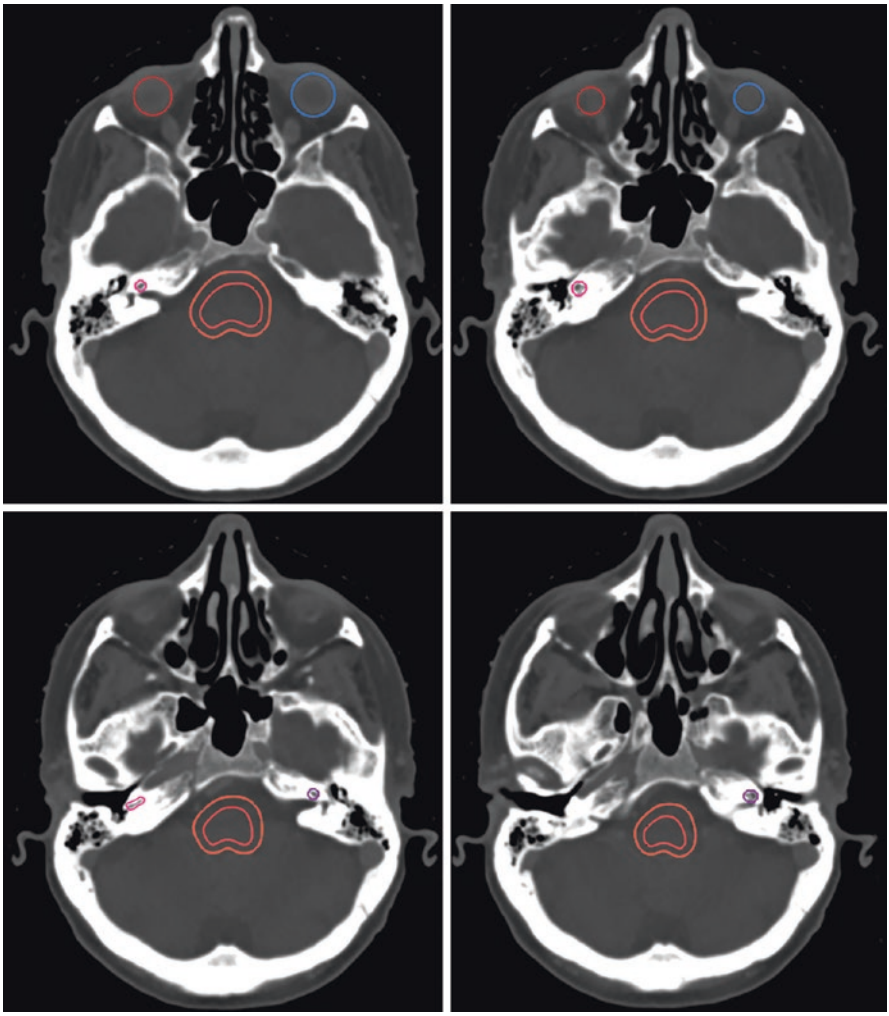

Fig. 29.3 Representative slices of the CT simulation (bone window/level) demonstrating the right and left cochlea, which are best identified and delineated. Based on the patient's head position, these structures may not be located on the same axial slices as shown in this example

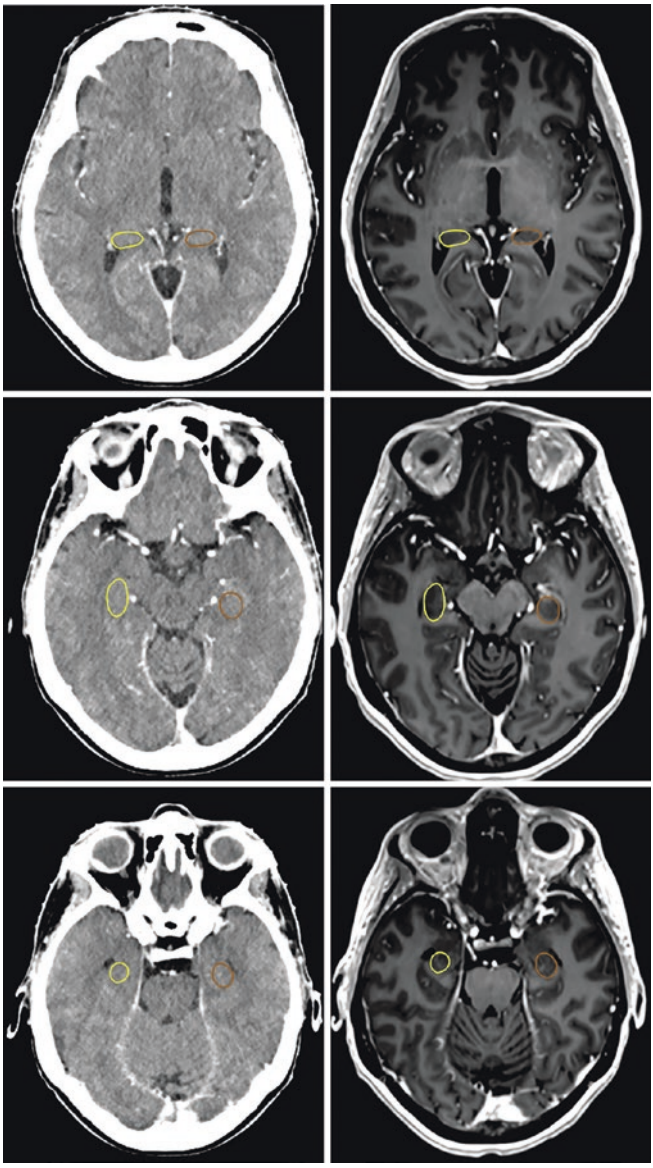

Fig. 29.4 Representative slices of the CT simulation (brain window/level setting) and treatment planning MRI (T1 post-contrast) used to delineate the right (yellow) and left (brown) hippocampus for treatment planning. It is important to note that these contours represent the subgranular zone of the hippocampus (not the entire structure) and can be visualized as hypointense gray matter. The superior-most slice begins where the hypointense gray matter borders the atrium of the lateral ventricle and approximates the splenium of the corpus callosum, while the inferior-most slice ends at the inferior extent of the temporal horn of the lateral ventricle

29.3.1 Low-Grade Astrocytic and Oligodendroglial Tumors

Patients with low-grade diffuse astrocytomas (IDH-mutated) and oligodendrogliomas should undergo maximal safe resection for diagnosis and molecular characterization. Gross total resection should be attempted if this can be safely performed.

- Patients are treated with conventionally fractionated radiation therapy to a dose of 54 Gy in 30 fractions (Table 29.2 and Fig. 29.5); chemotherapy is recommended for patients with grade 2 or higher tumors with certain high-risk features.
- Multi-modality therapy is recommended for IDH-wild type tumors (akin to malignant gliomas given their natural history and prognosis).
- Stereotactic radiosurgery is not recommended for these tumors in the upfront setting, except for select patients with pilocytic astrocytomas.

Table 29.2 Recommended target volumes for astrocytic and oligodendroglial tumors

Tumor type	GTV definition	Suggested CTV expansions	PTV expansions
Grade I pilocytic astrocytoma	For unresected tumors, the GTV will be delineated by the post-contrast T1 MRI For resected tumors, the GTV will include the post-operative cavity	0–0.5 cm, reduced around natural anatomic barriers to tumor spread	0–0.3 cm, depending on the radiotherapy technique and daily patient positioning technology 0–1 mm: SRS or HSRT 1–3 mm: Conventionally fractionated radiotherapy
Ganglioglioma	For unresected tumors, the GTV will be delineated by the post-contrast T2 or FLAIR MRI For resected tumors, the GTV will include the post-operative cavity and residual tumor	1 cm, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology
Grade II low-grade diffuse glioma (DH-mutated)	For unresected tumors, the GTV will be delineated by the post-contrast T2 or FLAIR MRI For resected tumors, the GTV will include the post-operative cavity and residual tumor	1 cm, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology

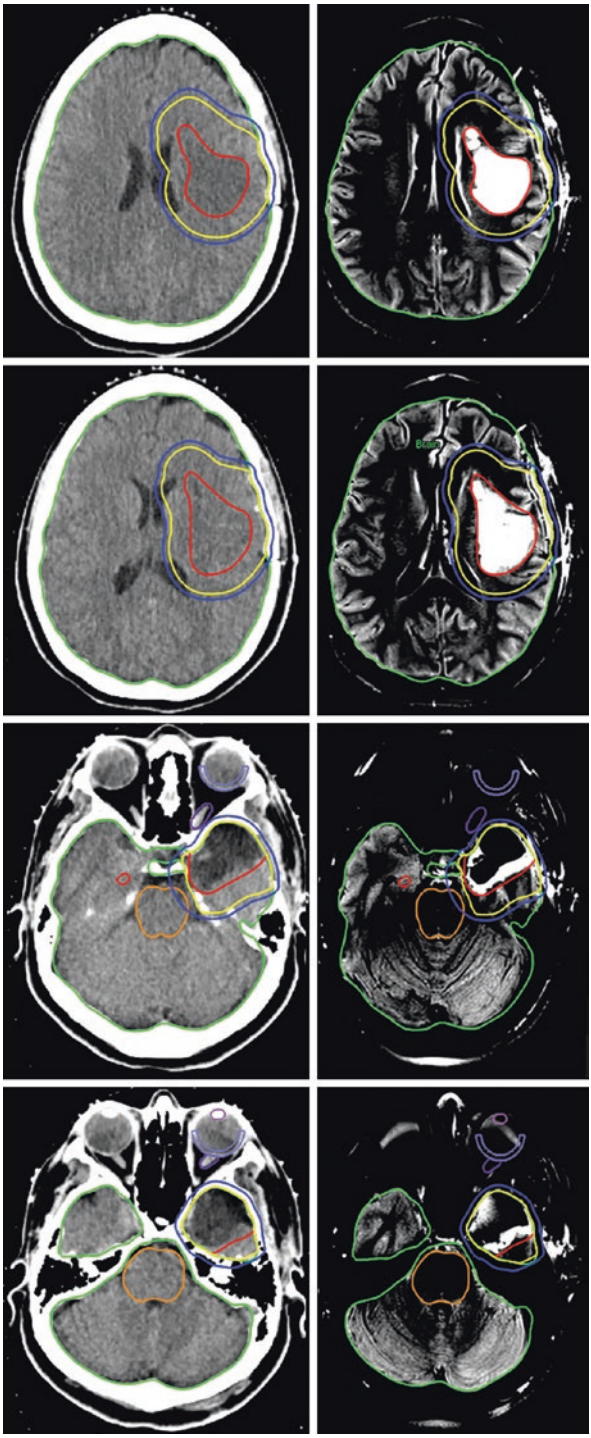

Fig. 29.5 Representative treatment planning CT images (brain window/level) and corresponding MR images (post-contrast FLAIR) for a patient with an oligodendroglioma after a left frontotemporoparietal craniotomy with partial resection with involvement of the left insula and portions of the operculum as well as extending into the left centrum semiovale. The GTV (red) was outlined using the FLAIR residual disease and the post-operative cavity. A 1.0 cm expansion was used to generate the CTV (yellow), with anatomic restriction out of the posterior fossa, skull, and other midline structures, and a 0.3 cm expansion to generate the PTV (blue)

29.3.2 Meningioma

- Meningiomas represent the most common primary intracranial tumors in adults and a majority (>70%) are benign and can be treated definitively with radiotherapy (Table 29.3).
- For patients with Grade 1 meningiomas who undergo subtotal resection in areas at high-risk for symptomatic progression, adjuvant therapy can be considered. For the remainder, repeat surgery and radiation therapy are considered in the setting of disease recurrence.
- In addition to the use of a treatment planning MRI for target volume delineation, CT evaluation is strongly recommended to decide whether to include any periosteal and bone changes within the GTV (Table 29.4 and Figs. 29.6, 29.7 and 29.8).

Table 29.3 Recommended techniques and dose/fractionation schedules for Grade 1 meningiomas

Radiation technique	Suggested dose/fractionation
SRS	14–16 Gy in 1 fraction
FSRT	20–24 Gy in 4 fractions 25 Gy in 5 fractions
Conventionally fractionated radiotherapy	52.2–54 Gy at 1.8–2 Gy/fraction 50.4 Gy at 1.8 Gy/fraction for optic nerve sheath meningiomas

Table 29.4 Recommended target volumes for Grade 1 meningiomas

Tumor type	GTV definition	Suggested CTV expansions	PTV expansions
Grade 1 meningioma (unresected)	Tumor delineated on planning MRI and CT simulation	0–0.5 cm, reduced around natural anatomic barriers to tumor spread	0–0.3 cm, depending on the radiotherapy technique and daily patient positioning technology 0–1 mm: SRS or HSRT 1–3 mm: Conventionally fractionated radiotherapy
Grade 1 meningioma (recurrent)	Post-operative cavity, residual enhancing tumor including suspicious dural and/or bone involvement, and prior dural attachment	Anatomically constrained 0–0.5 cm expansion	0–0.3 cm, depending on the radiotherapy technique and daily patient positioning technology 0–1 mm: SRS or HSRT 1–3 mm: Conventionally fractionated radiotherapy

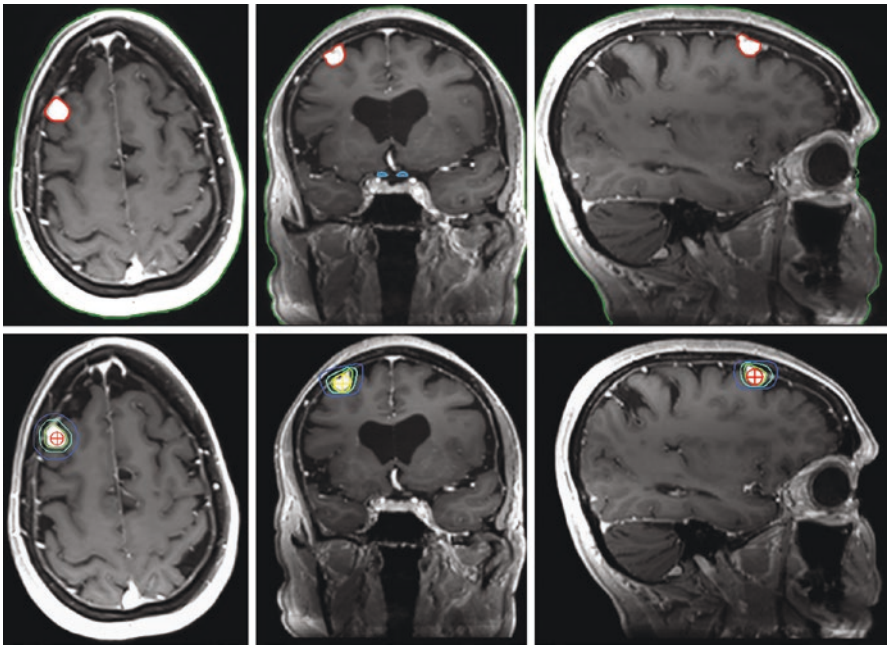

Fig. 29.6 Representative treatment planning MR images (axial, coronal, and sagittal T1 post-contrast) for a patient with a right frontal convexity extra-axial homogenously enhancing meningioma. The delineated tumor in red represents the GTV and no CTV or PTV expansions were added as this patient was treated with single fraction frame-based SRS. The bottom row of images displays the prescription isodose line (green) of 14 Gy as well as the 8 Gy (teal) and 4 Gy (blue) isodose lines

29.3.3 Vestibular and Non-Vestibular Schwannoma

- Patients with vestibular or non-vestibular schwannomas can be treated with radiation therapy in the definitive setting, as adjuvant treatment for patients with partially resected tumors, or rare cases for those with recurrent disease (Table 29.5 and Figs. 29.9 and 29.10).

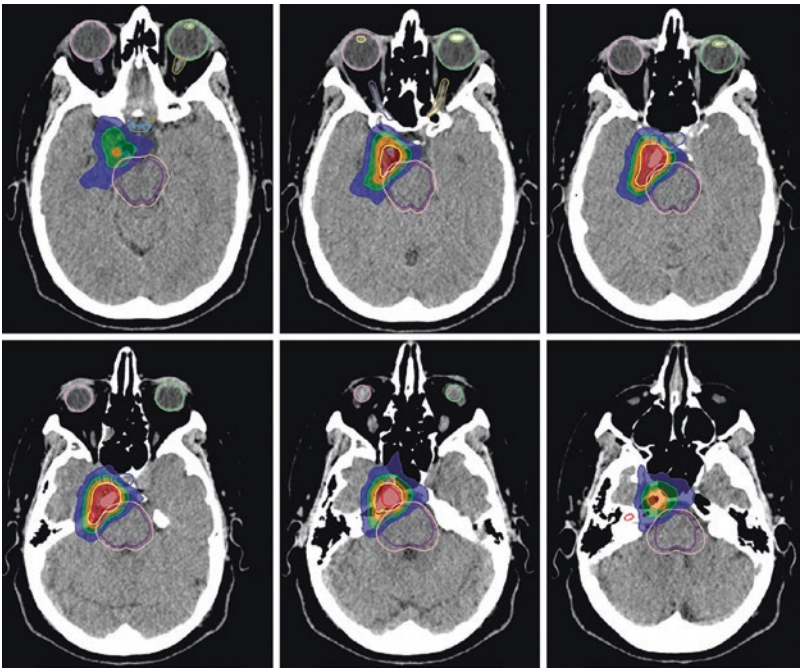

Fig. 29.7 Representative treatment planning CT images (brain window/level) for a patient with a right cavernous sinus meningioma treated to a dose of 52.2 Gy in 29 fractions. The GTV is outlined in red and was delineated using a treatment planning MRI; a 2 mm margin was added to create the PTV (yellow). Colorwash isodose lines are overlayed, including the prescription dose (52.2 Gy, dark red) and 45 Gy (orange), 30 Gy (green), and 15 Gy (blue). Key organs-at-risk are also delineated, including the brainstem (purple), chiasm (light blue), adjacent cranial nerves (blue), carotid artery (dark blue), and right cochlea (coral)

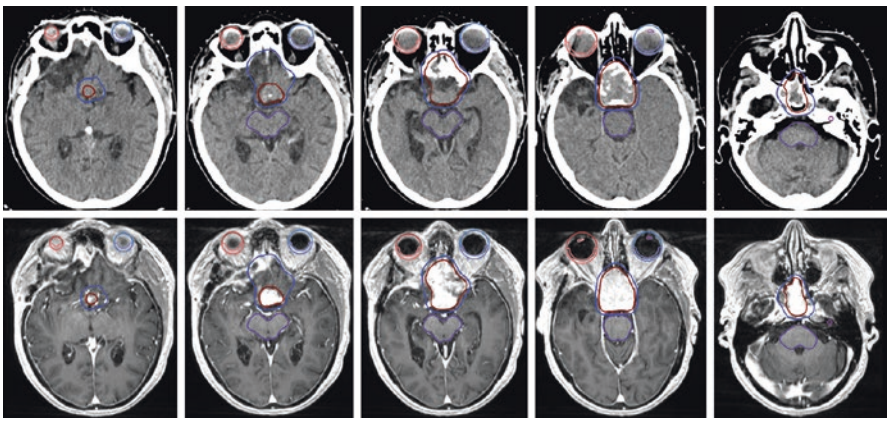

Fig. 29.8 Representative treatment planning CT images (brain window/level) and corresponding MR images for a patient with a massive sellar and suprasellar Grade 1 meningioma, with significant residual disease after attempted debulking. The tumor is outlined in maroon and a 3 mm expansion was used to create the PTV. Organs-at-risk visualized in these slices include the brainstem (purple) as well as both globes

Table 29.5 Radiotherapy techniques and target volumes for vestibular and non-vestibular schwannomas

Radiation technique	Suggested dose/ fractionation	Relevant target volumes
SRS	12–13 Gy in 1 fraction	GTV: Tumor as delineated on planning MRI and CT simulation CTV: None PTV: Technique dependent, typically 0–1 mm
FSRT	20 Gy in 4 fractions 25 Gy in 5 fractions	GTV: Tumor as delineated on planning MRI and CT simulation CTV: None PTV: Technique dependent, typically 0–1 mm
Conventionally fractionated radiotherapy	46.8–54 Gy at 1.8–2 Gy/fraction	GTV: Tumor as delineated on planning MRI and CT simulation CTV: None PTV: Technique dependent, typically 0–3 mm

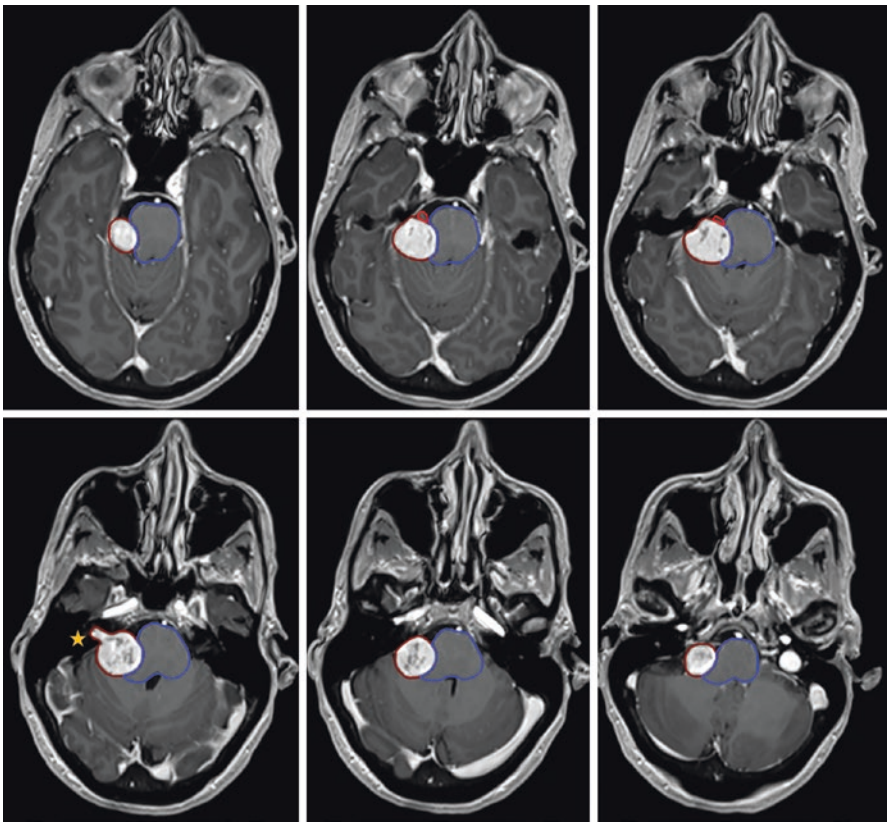

Fig. 29.9 Representative treatment planning MR images (axial T1 post-contrast) for a patient with a right cerebellopontine angle vestibular schwannoma (brown). The tumor compresses the right middle cerebellar peduncle and right side of the pons as well extends into the fundus of the internal auditory canal (orange star). Of note, there is compression of the brainstem (blue) and also compression of the right cisternal trigeminal nerve (red) as well as moderate partial effacement of the fourth ventricle. In this case, GTV is brown and no CTV or PTV expansions were used

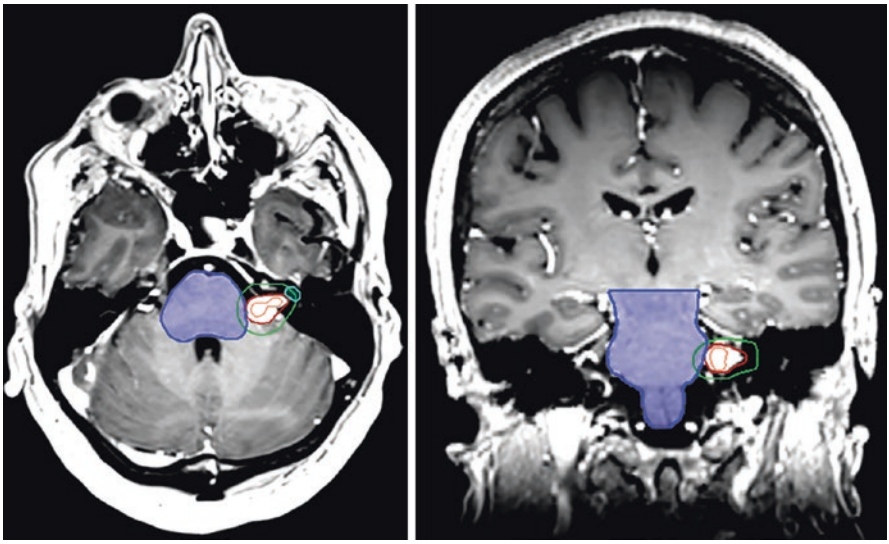

Fig. 29.10 Representative axial and coronal treatment planning MR images (T1 post-contrast) for a patient with a left cerebellopontine schwannoma. Note that the tumor extends into the internal auditory canal. Key organs-at-risk are delineated including the brainstem (blue) and cochlea (teal). The tumor is covered by the prescription isodose line (12.5 Gy, dark red) as well as a higher isodose line (20 Gy, orange) in the center of the tumor and the lower isodose line (5 Gy, green)

Table 29.6 Recommend techniques and dose/fractionation schedules for pituitary adenomas

Radiation technique	Suggested dose/fractionation
SRS	Non-functional: 15–16 Gy in 1 fraction
	Functional/secretory: 18–25 Gy in 1 fraction (preferred >20 Gy) based on optic nerve/chiasm tolerance
Conventionally fractionated radiotherapy	Non-functional: 45–50.4 Gy at 1.8–2 Gy/fraction
	Functional/secretory: 54–55.8 Gy at 1.8–2 Gy/fraction

29.3.4 Pituitary Tumors

- Non-functional pituitary adenomas are typically treated with SRS, HSRT, or conventionally fractionated radiation therapy in the adjuvant or salvage setting, after resection (Table 29.6).
- Functional pituitary adenomas may be treated with hormonal therapy, or resection, depending on the tumor subtype, prior to consideration of radiation therapy.
- High-resolution, thin-slice MR images of the pituitary gland in the coronal and sagittal planes are useful when delineating the target volumes (Table 29.7 and Figs. 29.11, 29.12 and 29.13). Due to the differential enhancement patterns of adenomas and the normal pituitary gland, tumors are best seen in the early phase of the gadolinium-enhanced dynamic imaging and appear as a hypointense lesion against the hyperintense background of the normally enhancing pituitary gland.

Table 29.7 Recommended target volumes for pituitary adenomas

Tumor type	GTV definition	Suggested CTV expansions	PTV expansions
Unresected Focal residual Focal recurrent disease	Tumor delineated on planning MRI and CT simulation	0–0.5 cm, reduced around natural anatomic barriers to tumor spread	0–0.3 cm, depending on the radiotherapy technique and daily patient positioning technology 0–1 mm: SRS or HSRT 1–3 mm: Conventionally fractionated radiotherapy
Resected with residual or recurrent disease	Tumor delineated on planning MRI and CT simulation	0–0.5 cm, reduced around natural anatomic barriers to tumor spread and to pre-operative disease extension	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology

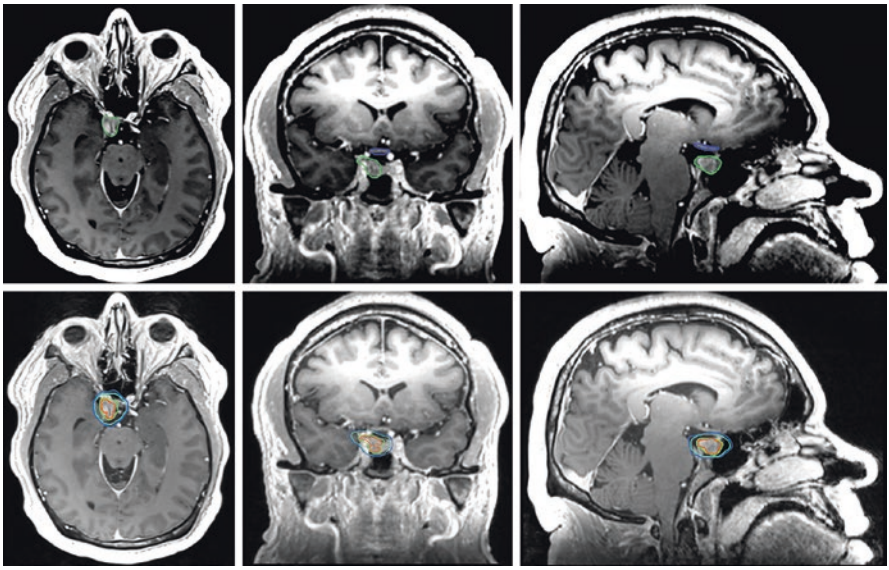

Fig. 29.11 Representative axial, coronal, and sagittal treatment planning MR images (T1 post-contrast) for a patient with a growth-hormone secreting pituitary adenoma (top row). The tumor is outlined in green (GTV, no PTV expansion) abuts the medial margin of the right cavernous carotid and extends between the loops of the cavernous carotid laterally with cavernous sinus involvement superiorly. The optic chiasm is delineated in blue. This patient was treated with SRS to a dose of 24 Gy in 1 fraction with corresponding isodose lines for the prescription dose (24 Gy, green), 30 Gy (orange), 10 Gy (teal), and 8 Gy (blue). The dose to the chiasm, optic nerves, and brainstem was less than 8 Gy, each

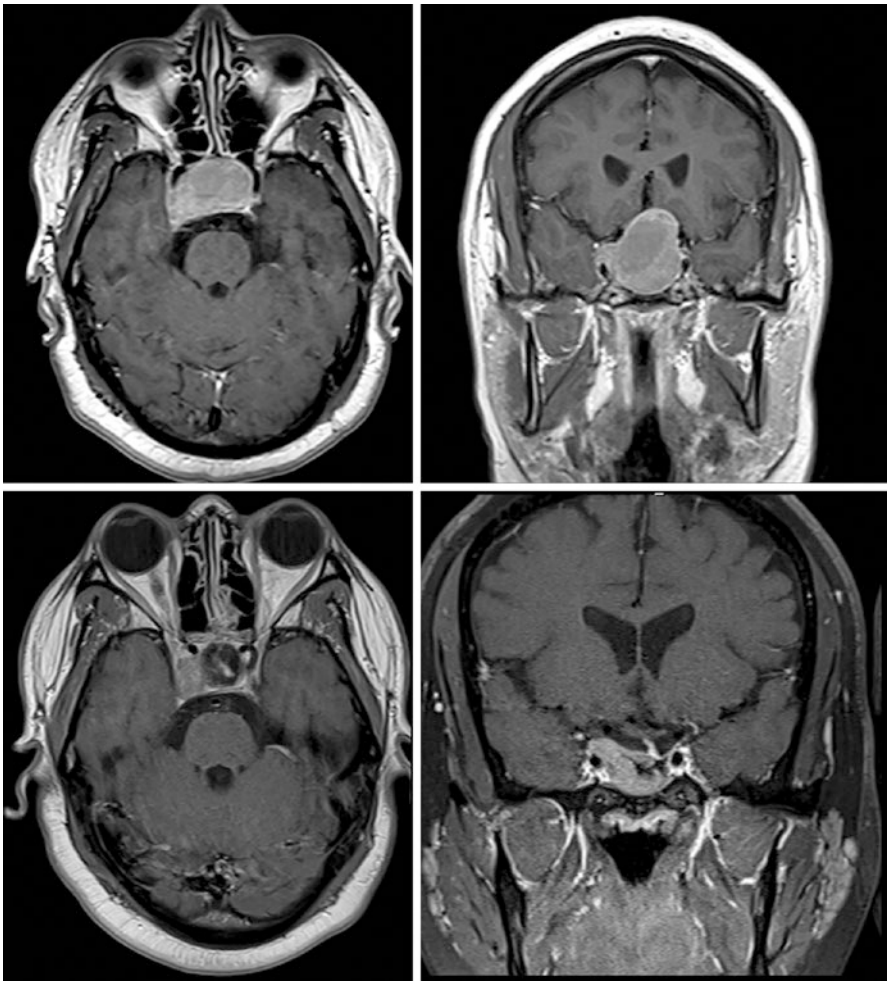

Fig. 29.12 Pre-operative axial and coronal MR images (T1 post-contrast) for a patient with a non-secretory pituitary adenoma (top row) centered in the sella and extending into the suprasellar cistern displacing the optic chiasm and invading into the right cavernous sinus. Post-operative axial and coronal MR images (T1 post-contrast) after resection demonstrate residual tumor in the sella and right cavernous sinus

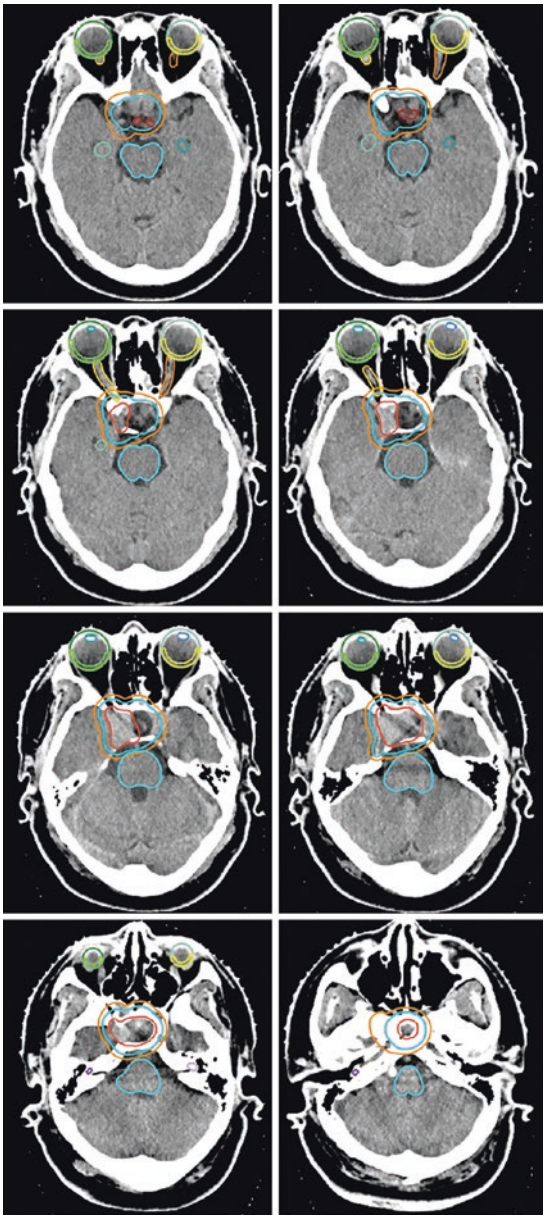

Fig. 29.13 Representative treatment planning CT images (brain window/level) for a patient with a non-secretory pituitary adenoma after resection (see Fig. 29.12 for pre- and post-operative MR images). The GTV is outlined in coral with a 0.5 cm, anatomically restrained margin in teal, expansion for the CTV, and a 0.3 cm margin expansion for the PTV. Key organs-at-risk are delineated on the slices, including the brainstem (light blue), optic chiasm (red), and right and left optic nerves (light and dark orange)

Knowledge of the type of implanted material (muscle vs. fat vs. rotational nasal septal flap) is useful to differentiate tumor from implanted material.
- For patients with macroadenomas, it is important to assess the extent of invasion into the cavernous sinus, and when this is difficult to visualize, it is recommended to include the entire cavernous sinus in the GTV.

29.3.5 Glomus Tumors/Paraganglioma

- Glomus tumors represent rare neuroendocrine tumors that can occur at the skull base, head and neck, thorax, and abdomen and are typically named based on their origin site.
- Treatment options include embolization, resection, and radiation therapy with high local control rates (Table 29.8).
- Depending on the site of origin, careful assessment of the patient's diagnostic MR and CT imaging is needed when delineating the target volume to detect potential invasion into the tympanic cavity, jugular foramen, petroclival region, cavernous sinus, or hypoglossal canal.
- In addition to the use of a treatment planning MRI for target volume delineation, CT evaluation is strongly recommended to assess for potential bony erosion (Table 29.9 and Figs. 29.14 and 29.15).

Table 29.8 Recommended techniques and dose/fractionation schedules for glomus tumors/paragangliomas

Radiation technique	Suggested dose/fractionation
SRS	14–16 Gy in 1 fraction
FSRT	25 Gy in 5 fractions
Conventionally fractionated radiotherapy	50.4–54 Gy at 1.8–2 Gy/fraction

Table 29.9 Recommended target volumes for glomus tumors/paragangliomas

GTV definition	Suggested CTV expansions	PTV expansions
Tumor delineated on planning MRI and CT simulation	0–0.5 cm, reduced around natural anatomic barriers to tumor spread	0–0.3 cm, depending on the radiotherapy technique and daily patient positioning technology 0–1 mm: SRS or HSRT 1–3 mm: Conventionally fractionated radiotherapy

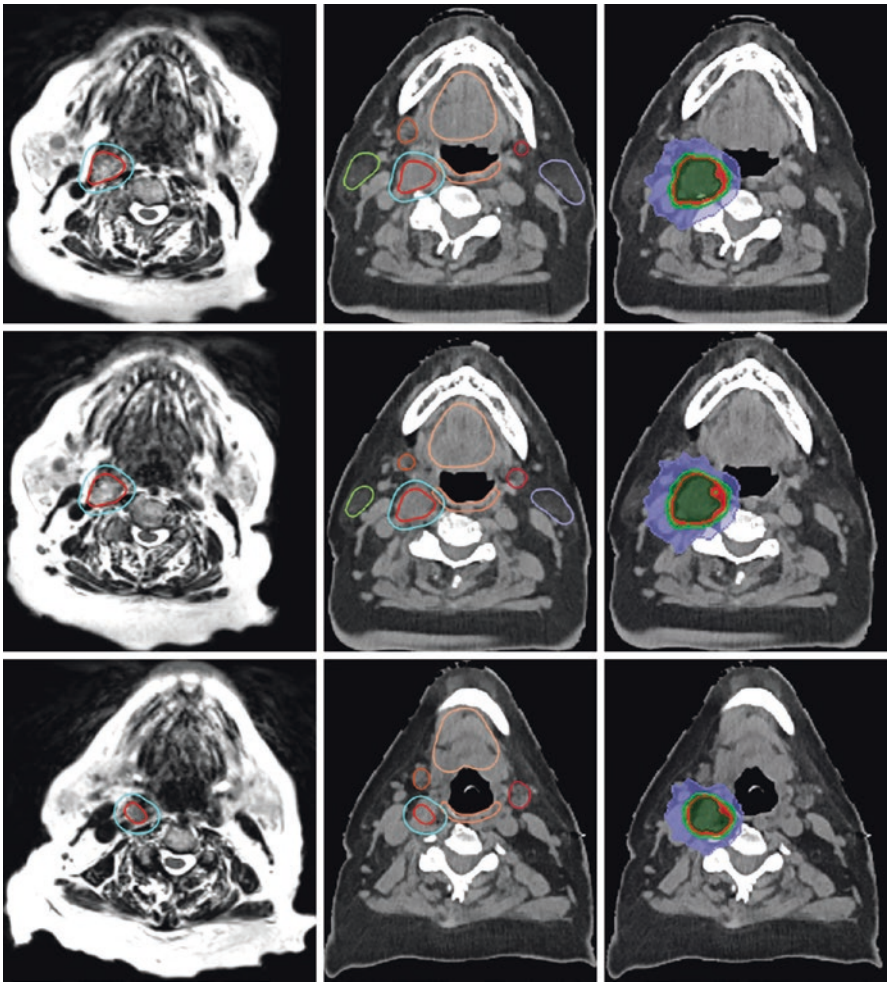

Fig. 29.14 Representative treatment planning MR images (first column, T2-weighted SPACE sequence), treatment planning CT images (second column, soft tissue window/level), and dosimetric treatment plan for a patient with a right-sided glomus tumor centered at the carotid bifurcation with splaying of the internal and external carotid arteries. The GTV (red) was delineated using the treatment planning MRI co-registered to the treatment planning CT scan with a 3 mm expansion used to create the PTV (turquoise). This elderly patient was treated to a dose of 25 Gy in 5 fractions and colorwash isodose lines are overlayed (third column), including the prescription dose (25 Gy, red), 110% isodose volume (27.5 Gy dark green), 80% isodose volume (20 Gy, light green), and 50% isodose volume (12.5 Gy, purple). Key nearby organs-at-risk, including the parotids, submandibular glands, oral cavity, and oropharyngeal wall are visualized on selected slices

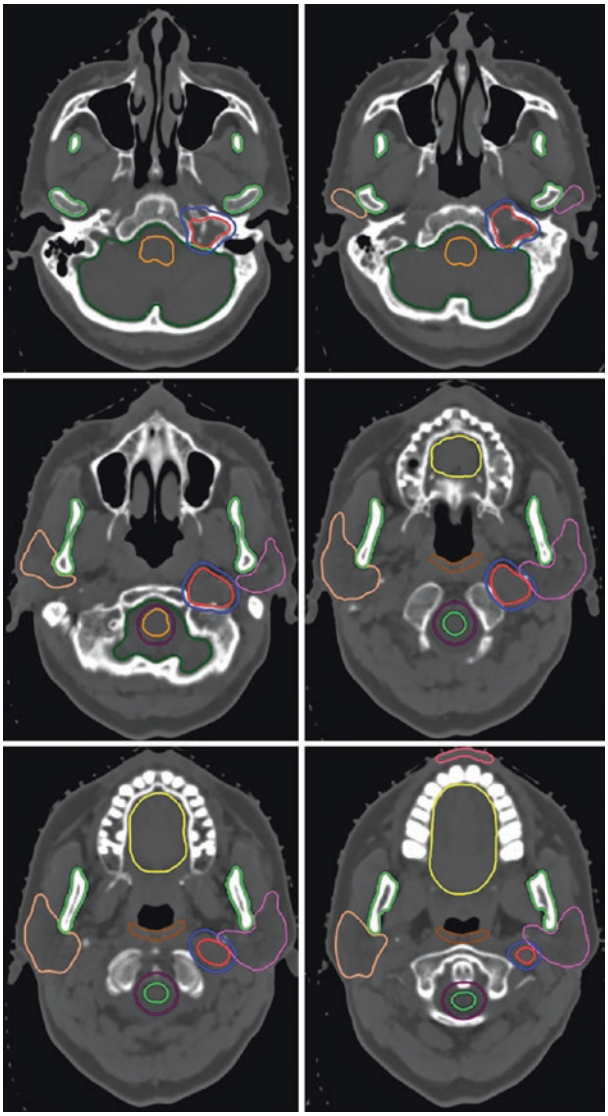

Fig. 29.15 Representative treatment planning CT images (bone window/level) for a patient with a recurrent left-sided glomus tumor after embolization and resection, with recurrent disease centered in the left jugular bulb, treated to a dose of 54 Gy in 30 fractions. Co-registration of the patient's MR images at initial diagnosis and at the time of recurrence was used to generate the GTV (red) which consisted of the initial extent of disease at first diagnosis, post-operative changes and tumor bed, and recurrent disease, with coverage to the skull base. A 0.3 cm margin expansion was used to create the PTV (blue). Key organs-at-risk are delineated on the slices, including the brainstem (orange), mandible (green), left parotid (pink), right parotid (light orange), spinal cord with PRV (green and violet, respective), oropharyngeal wall (brown), oral cavity (yellow), and lips (pink)

Malignant Tumors of the CNS

30

Rupesh Kotecha, Samuel T. Chao, Erin S. Murphy, and John H. Suh

Contents

30.1 General Principles of Radiotherapy Planning and Target Volume Delineation

- In the management of patients with malignant primary brain tumors, a detailed history, neurologic-focused physical examination, appropriate laboratory investigations (including assessment of hormonal function as well as baseline blood

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_30

counts for patients undergoing chemotherapy), visual field and visual acuity testing, audiometric assessment, and baseline neurocognitive function are all important. Maximal safe surgical resection, with an objective of a gross-total resection, remains the standard-of-care for patients who are medically inoperable and have surgically accessible tumors.

- Definitive radiation therapy is used for patients who undergo a biopsy alone and adjuvant radiotherapy for the majority of patients after resection. The radiation therapy approach to benign variants of these tumors is discussed elsewhere in this textbook.
- A variety of radiotherapy techniques are used in patients with malignant primary brain tumors, including 3D-conformal radiotherapy (3D-CRT), fractionated stereotactic radiosurgery (FSRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), as well as proton beam radiotherapy (PBT).
- Accurate delineation of the target volumes as well as the organs-at-risk is key to determining the best treatment option for each patient and creating an optimal radiotherapy treatment plan. Essential to this process is the ability to obtain treatment planning MR images close to the time of CT simulation with sequences that best allow for visualization of the tumor (i.e. T1-post contrast or FLAIR images) as well as normal anatomy (i.e. T1 images to delineate the hippocampus or 3D T2 or CISS sequences to delineate cranial nerves).

30.2 Patient Positioning, Immobilization, and Simulation

- Patients with malignant primary brain tumors are typically simulated in the supine position with arms extending parallel to the body and shoulders in a natural position.
- For patients undergoing CT simulation and treatment, an indexed 3-point thermoplastic mask is used for immobilization; however, a 5-point thermoplastic mask can be used for patients with base-of-skull tumors or with tumors close to the optic apparatus in which neck positioning can be reinforced with the extended mask.
- For patients undergoing MRI simulation and treatment, a clam shell mask is used.
- The head and chin are placed in a neutral position, unless specific instructions for base-of-skull positioning are required.
- Axial CT simulation images are obtained at 1 mm slice thickness (SRS, FSRT, or PBT) or 2 mm slice thickness (3D-CRT, IMRT, or VMAT) through the entire head of the patient and down to the level of the shoulders.

- Co-registration of diagnostic MR imaging is strongly recommended for target volume delineation for primary brain tumors, unless there is a clear medical or clinical contraindication.
- IV contrast can be used to delineate primary tumors, resected tumor cavities, or to aid with fusion to pre-treatment MR imaging.

30.3 Normal Structures

- Organs-at-risk are delineated on the treatment planning CT scan with aid of pre-treatment MR imaging.
- Planning risk volumes (PRVs) can be created for tumors abutting nearby critical organs for aid in dosimetric planning and dose assessment at the time of plan evaluation.
- A list of normal contours delineated for most primary brain tumors is provided in Table 30.1.
- Examples of contours of key organs-at-risk for primary intracranial cases are provided in the "Benign Tumors of the CNS chapter" Figs. 30.1, 30.2, 30.3 and 30.4.

Table 30.1 List of suggested organs-at-risk for primary brain tumors

• Brain
• Uninvolved brain (brain—GTV or CTV, depending on clinical scenario)
• Brainstem (brainstem core, brainstem surface)
• Spinal cord
• Right cochlea
• Left cochlea
• Right globe
• Left globe
• Right lens
• Left lens
• Right optic nerve
• Left optic nerve
• Optic chiasm
• Right retina
• Left retina
• Right lacrimal gland
• Left lacrimal gland
• Right temporal lobe
• Left temporal lobe
• Right hippocampus
• Left hippocampus
• Hypothalamus
• Pituitary

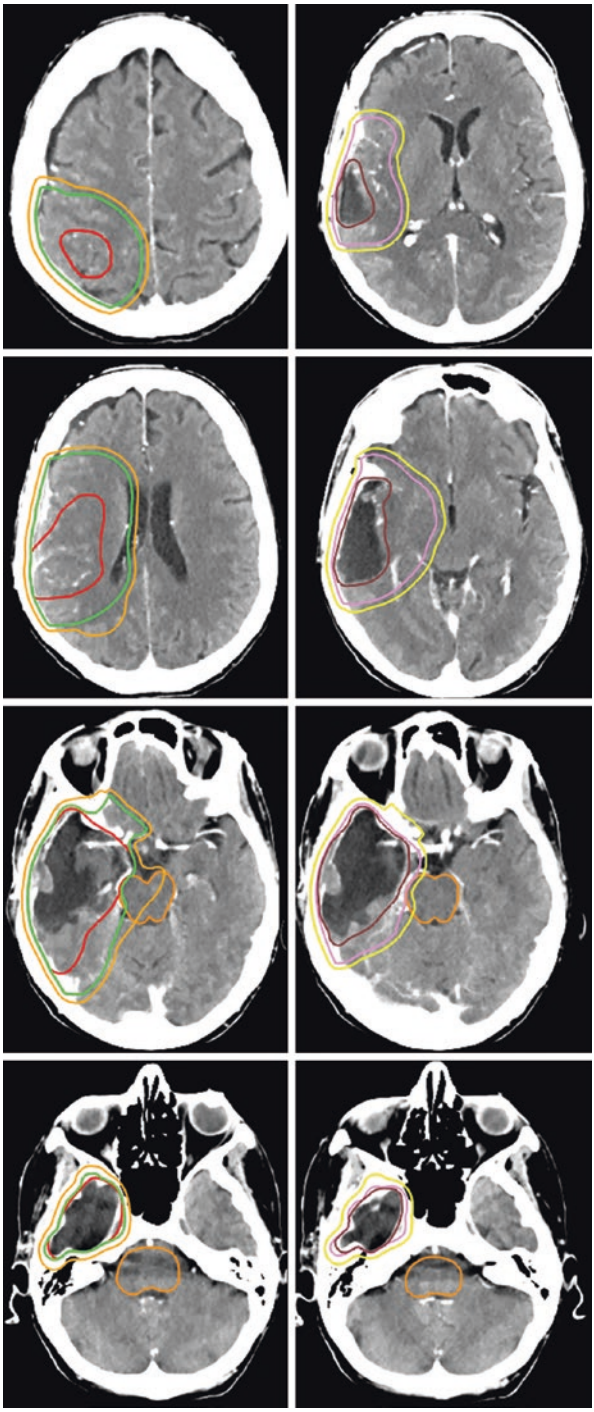

Fig. 30.1 Representative slices of a contrast-enhanced treatment planning CT for a patient with a right temporal anaplastic astrocytoma, with a satellite right parietal lesion. Treatment planning MRIs (not shown) were co-registered to the planning CT to generate the target volumes. Two sequential radiotherapy volumes were used in this patient, the first (PTV1, orange) to 50.4 Gy and the final volume (PTV2, yellow) to 59.4 Gy. The GTV1 (red) was delineated using the post-contrast FLAIR image, with a 1.5 cm anatomically constrained expansion used to create the CTV1 (green) and 0.3 cm expansion created for the PTV1 (orange). The GTV2 (brown) was delineated using the post-contrast T1 image and included the resection cavity, with a 1 cm anatomically constrained expansion used to create the CTV2 (pink) and 0.3 cm expansion created for the PTV2 (yellow). Note that the anatomically constrained expansions do not cross midline, extend into the pre-pontine cistern, skull, or extend past the tentorium into the posterior fossa

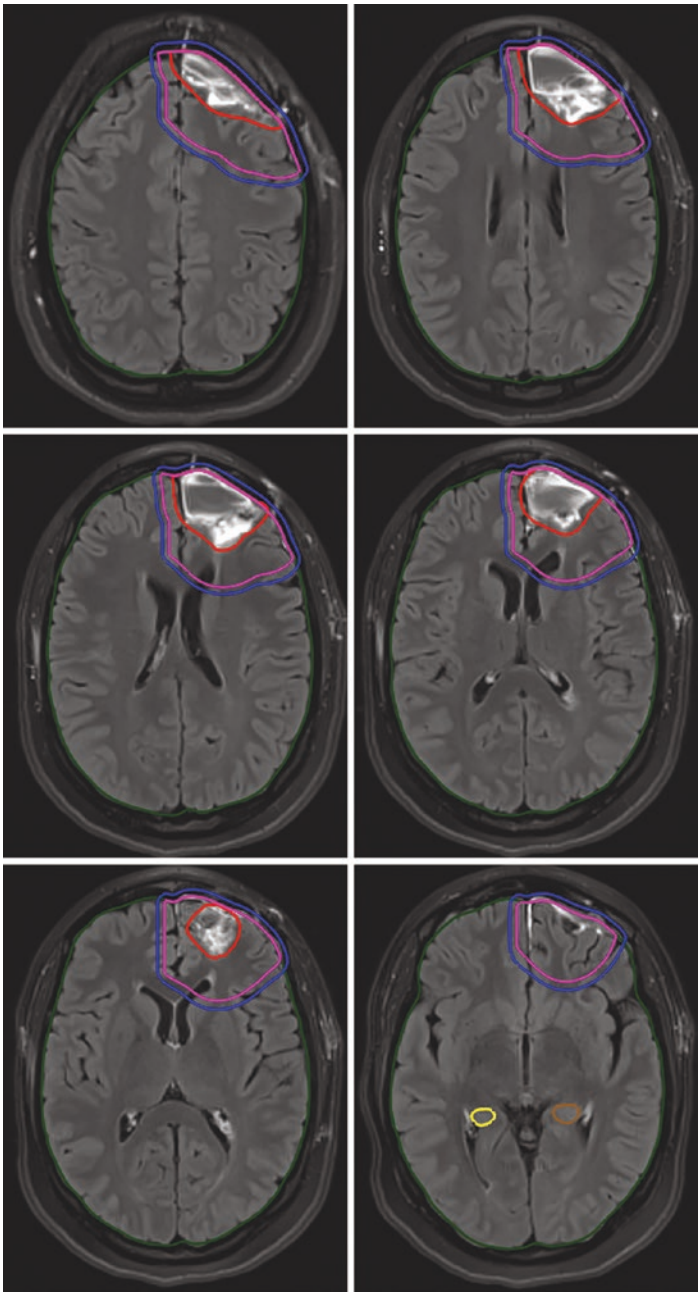

Fig. 30.2 Representative slices of the treatment planning MRI (post-contrast FLAIR) for a patient with a left frontal non-enhancing anaplastic astrocytoma after gross-total resection. This patient was treated to a dose of 59.4 Gy in 33 fractions. The GTV (red) was delineated using the post-contrast FLAIR image and included the resection cavity. A 1.5 cm anatomically constrained expansion used to create the CTV (pink) and 0.3 cm expansion created for the PTV (blue). Of note, the left (brown) and right (hippocampal) contours are seen on the inferior most treatment planning image presented (although these were delineated on a co-registered T1 post-contrast MRI)

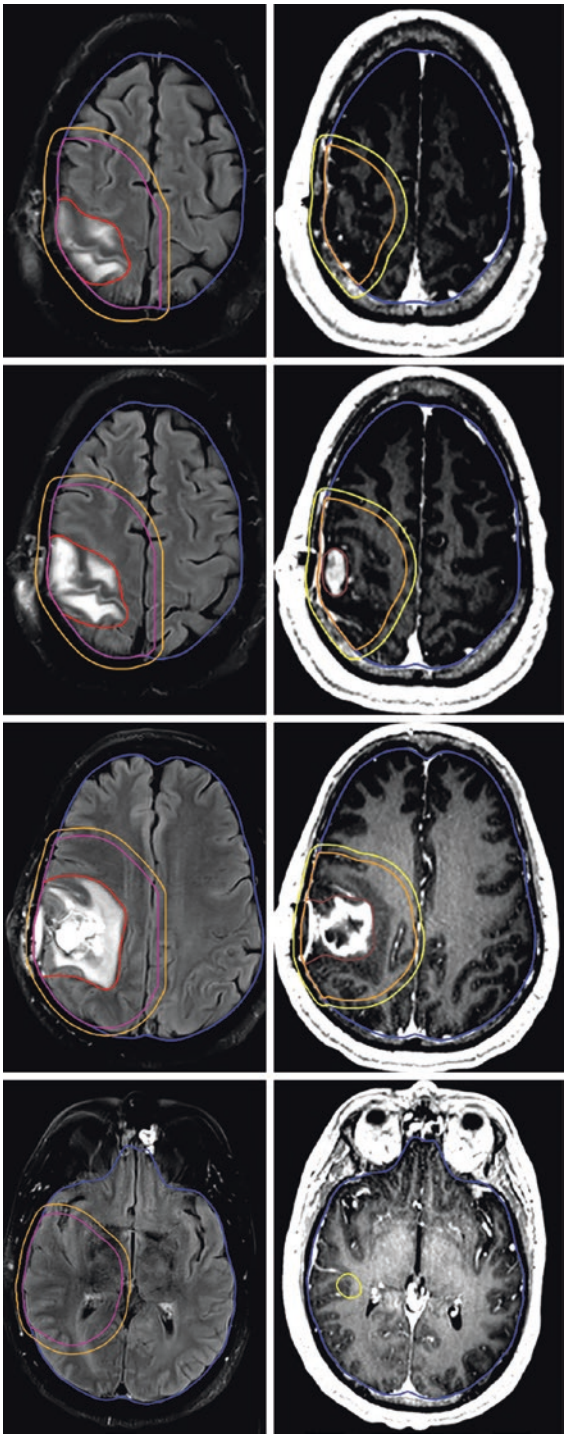

Fig. 30.3 Representative slices of the treatment planning MRI (post-contrast FLAIR and post-contrast T1) for a patient with a right parietal glioblastoma after a subtotal resection. Two sequential radiotherapy volumes were used in this patient, the first (PTV1, orange) to 46 Gy and the final volume (PTV2, yellow) to 60 Gy. The GTV1 (red) was delineated using the post-contrast FLAIR image, with a 2 cm anatomically constrained expansion used to create the CTV1 (pink) and 0.3 cm expansion created for the PTV1 (orange). The GTV2 (brown) was delineated using the post-contrast T1 image, with a 2 cm anatomically constrained expansion used to create the CTV2 (orange) and 0.3 cm expansion used to create the PTV2 (yellow)

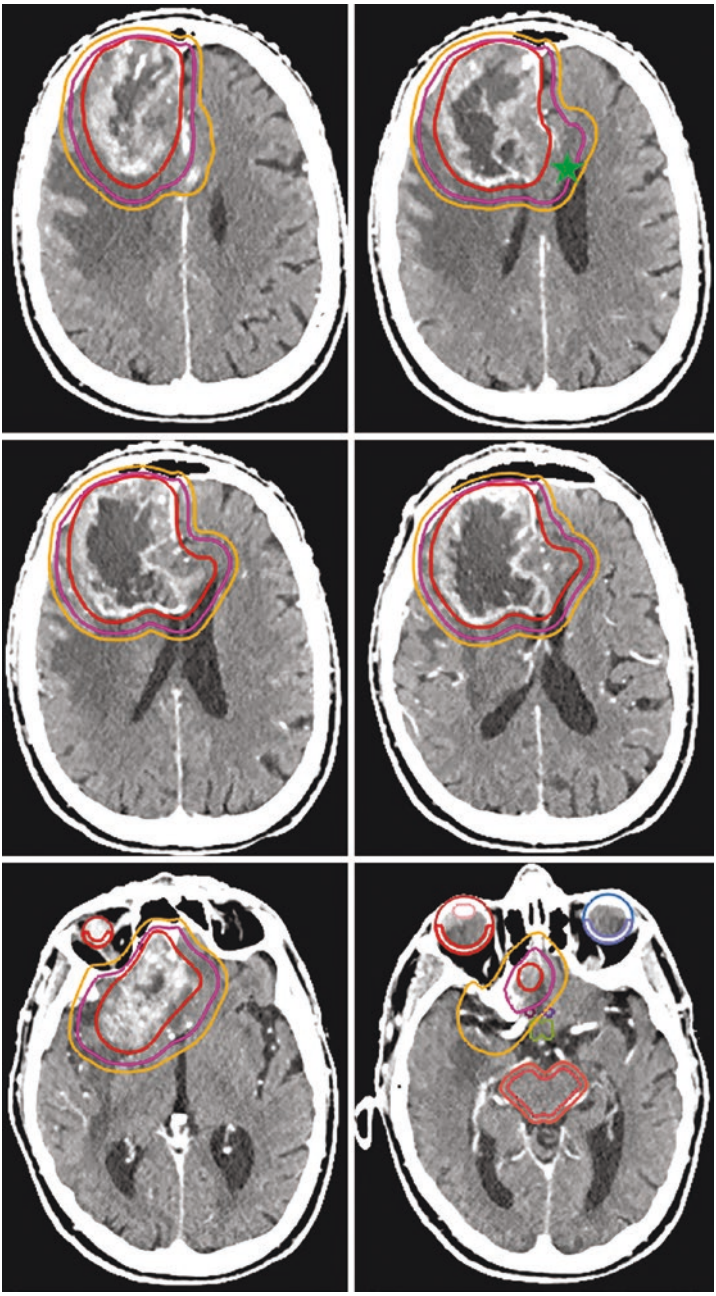

Fig. 30.4 Representative slices of a contrast-enhanced treatment planning CT for an elderly, poor-risk patient with a large glioblastoma centered in the right frontal region treated with a hypofractionated course of radiotherapy alone. The GTV (red) was delineated using the post-contrast T1 MRI co-registered to the planning CT scan. A 0.5 cm margin was used to create the CTV (pink), and although anatomically constrained, importantly, it includes tracks at risk for potential contralateral tumor spread such as the genu of the corpus callosum (green star). A 0.3 cm expansion was used to create the PTV (light orange). Representative organs-at-risk including the bilateral globes, retina, optic nerves, chiasm, and brainstem are also visualized on certain slices

30.4 High-Grade Glioma

- Patients with high-grade astrocytoma and oligodendroglioma undergo maximal safe resection for diagnosis and molecular characterization as well as to safely remove as much gross disease as feasible.
- Patients are treated with conventionally fractionated radiation therapy to a dose of 59.4–60 Gy along with chemotherapy, either in the concurrent or adjuvant setting (Table 30.2 and Figs. 30.1, 30.2 and 30.3).
- Poor-risk, elderly, or frail patients with high-grade gliomas can be treated with hypofractionated radiotherapy schedules, including 40.05 Gy in 15 fractions or

Table 30.2 Recommended target volumes for high-grade glioma

Tumor type	Recommended dose/ fractionation	GTV definition	Suggested CTV expansions	PTV expansions
Anaplastic glioma (enhancing tumor)	Sequential Cone Down: PTV1: 50.4 Gy at 1.8 Gy/fraction PTV2 59.4 Gy at 1.8 Gy/fraction Simultaneous Integrated Boost: PTV1: 54.45 Gy at 1.65 Gy/fraction PTV2: 59.4 Gy at 1.8 Gy/fraction	GTV1 is defined by the T2 or FLAIR volume GTV2 is defined by the post-operative cavity and residual tumor by the post-contrast T1 MRI	CTV1 is defined by a 1.5 cm expansion, reduced around natural barriers to tumor spread CTV2 is defined by a 1.0 cm expansion, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology
Anaplastic glioma (non-enhancing tumor) IDH-wild type diffuse astrocytoma	PTV1: 59.4 Gy at 1.8 Gy/fraction	GTV is defined by the post-operative cavity volume and residual tumor by T2 or FLAIR	CTV is defined by a 1.5 cm expansion, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology
Glioblastoma	PTV1: 46 Gy at 2 Gy/ fraction PTV2: 60 Gy at 2 Gy/ fraction (sequential cone down) PTV1: 50–51 Gy at 1.67–1.7 Gy/fraction PTV2: 60 Gy at 2 Gy/ fraction (simultaneous integrated boost)	GTV1 is defined by the T2 or FLAIR volume GTV2 is defined by the post-operative cavity and residual tumor by the post-contrast T1 MRI	CTV1 is defined by a 2 cm expansion, reduced around natural barriers to tumor spread CTV2 is defined by a 2 cm expansion, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology

Table 30.2 (continued)

Tumor type	Recommended dose/ fractionation	GTV definition	Suggested CTV expansions	PTV expansions
Gliosarcoma	PTV1: 46 Gy at 2 Gy/ fraction PTV2: 60 Gy at 2 Gy/ fraction (sequential cone down) PTV1: 50–51 Gy at 1.67–1.7 Gy/fraction PTV2: 60 Gy at 2 Gy/ fraction (simultaneous integrated boost)	GTV1 is defined by the T2 or FLAIR volume GTV2 is defined by the post-operative cavity and residual tumor by the post-contrast T1 MRI	CTV1 is defined by a 1.5–2 cm expansion, reduced around natural barriers to tumor spread CTV2 is defined by a 1.5–2 cm expansion, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology

25 Gy in 5 fractions, with reduced margins (0.5–1 cm), with or without chemotherapy (Table 30.2 and Figs. 30.4, 30.5, 30.6).

- Treatment paradigms for patients with gliosarcoma mirror those for those with glioblastoma (Fig. 30.7).

30.4.1 Meningioma and Hemangiopericytoma

- Meningiomas represent the most common primary intracranial tumors in adults with fewer than 30% of tumors classified as atypical (WHO grade II) or malignant (WHO grade III).
- Adjuvant radiation therapy can be considered for patients who undergo a gross-total resection of WHO grade II meningioma and is recommended for patients who undergo a subtotal resection (Table 30.3 and Fig. 30.8).
- For patients with a WHO III meningioma, adjuvant radiation therapy is recommended for all patients regardless of the extent of resection (Table 30.3 and Fig. 30.9).
- Given that grade II and III meningiomas can involve bone and brain, it is important to note on image review and target volume delineation that skull and normal brain are not necessarily a natural barrier to tumor spread. For example, margins should include normal brain if there is brain invasion noted as part of operative or pathology findings.
- Adjuvant radiation therapy is recommended for patients who undergo resection of a hemangiopericytoma.

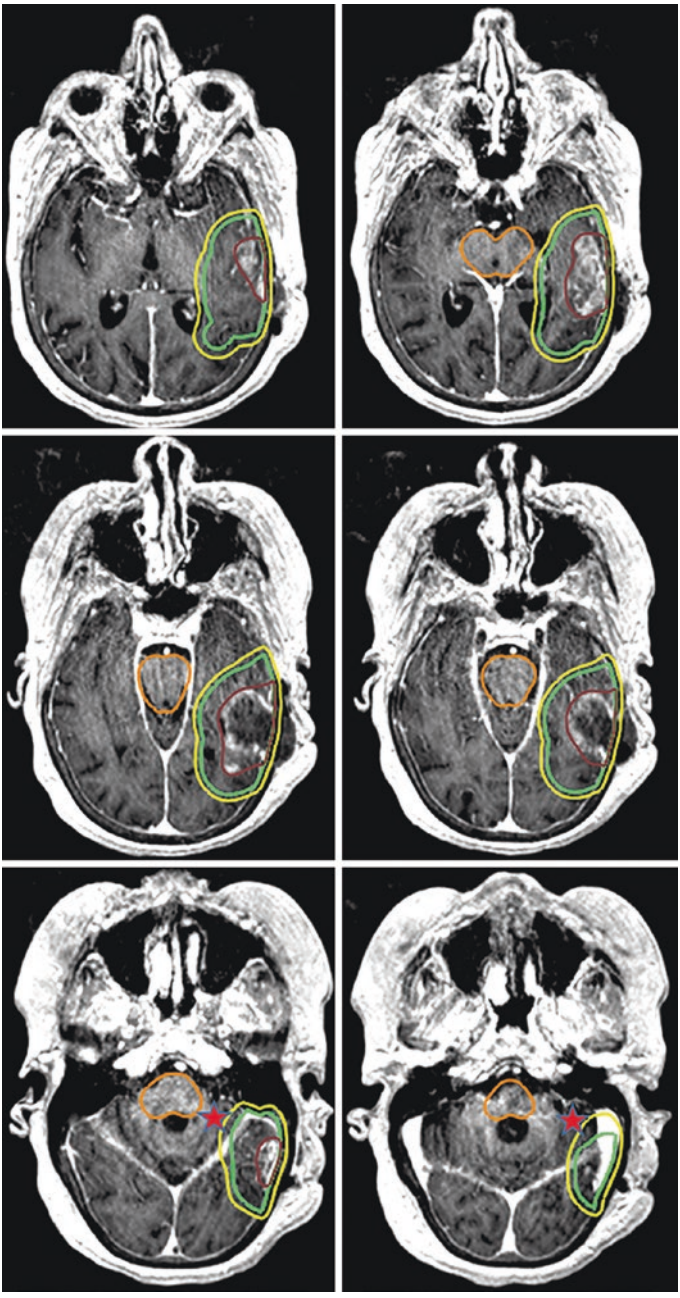

Fig. 30.5 Representative slices of the treatment planning MRI (post-contrast T1) for an elderly, poor-risk patient with a left posterior temporal glioblastoma. This patient did not any significant FLAIR volume extending outside of the contrast-enhanced tumor. Therefore, the patient was treated to a dose of 40 Gy in 15 fractions to a single volume. The GTV (brown) was delineated using the post-contrast T1 and included the resection cavity, residual tumor, and nearby satellite nodule. A 1.0 cm anatomically constrained expansion was used to create the CTV (green) and 0.3 cm expansion used to create the PTV (yellow). Note that the CTV is anatomically restricted from crossing the tentorium (red star)

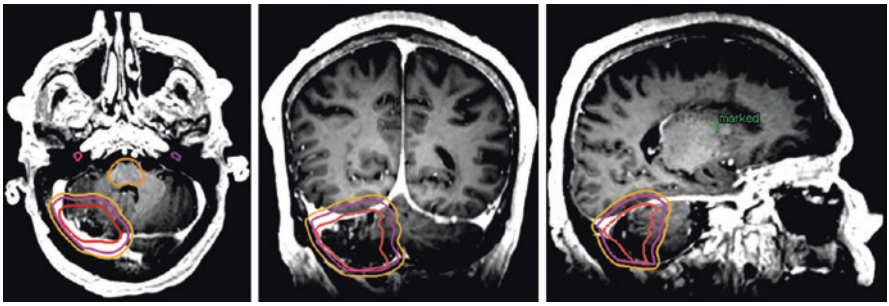

Fig. 30.6 Representative slices of the treatment planning MRI (post-contrast T1) for an elderly, poor-risk patient with a right cerebellar glioblastoma. This patient was treated to a dose of 30 Gy in 5 fractions. The GTV (red) was delineated using the post-contrast T1 and included the resection cavity following gross-total resection of the tumor. A 0.5 cm anatomically constrained expansion was used to create the CTV (pink), and 0.3 cm expansion was used to create the PTV (light orange). Of note, the cochlea and brainstem are visible on the axial MRI

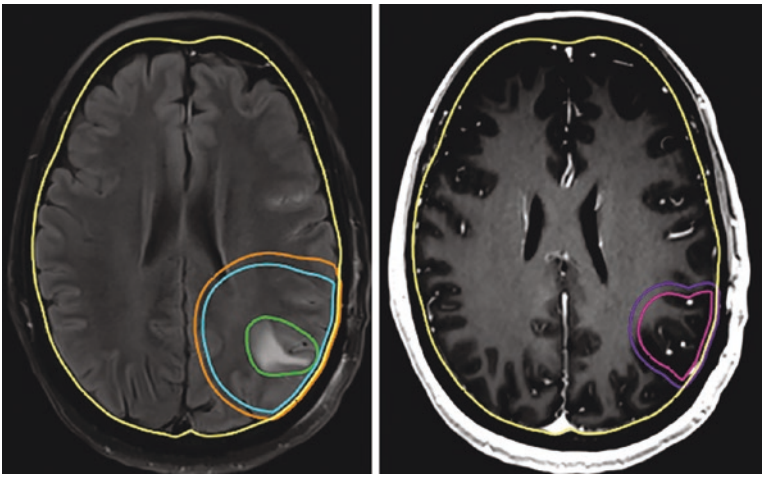

Fig. 30.7 Representative slices of the treatment planning MRI (post-contrast FLAIR and post-contrast T1) for a patient with a left temporal occipital gliosarcoma after gross-total resection. Two radiotherapy volumes were used in this patient, the first (PTV1, orange) to 46 Gy and the final volume (PTV2, purple) to 60 Gy. The GTV1 (green) was delineated using the post-contrast FLAIR image, with a 1.5 cm anatomically constrained expansion used to create the CTV1 (turquoise) and 0.3 cm expansion used to create the PTV1 (orange). The GTV2 (red) was delineated using the post-contrast T1 image, with a 1.5 cm anatomically constrained expansion used to create the CTV2 (pink) and 0.3 cm expansion used to create the PTV2 (purple). The brainstem is contoured in blue

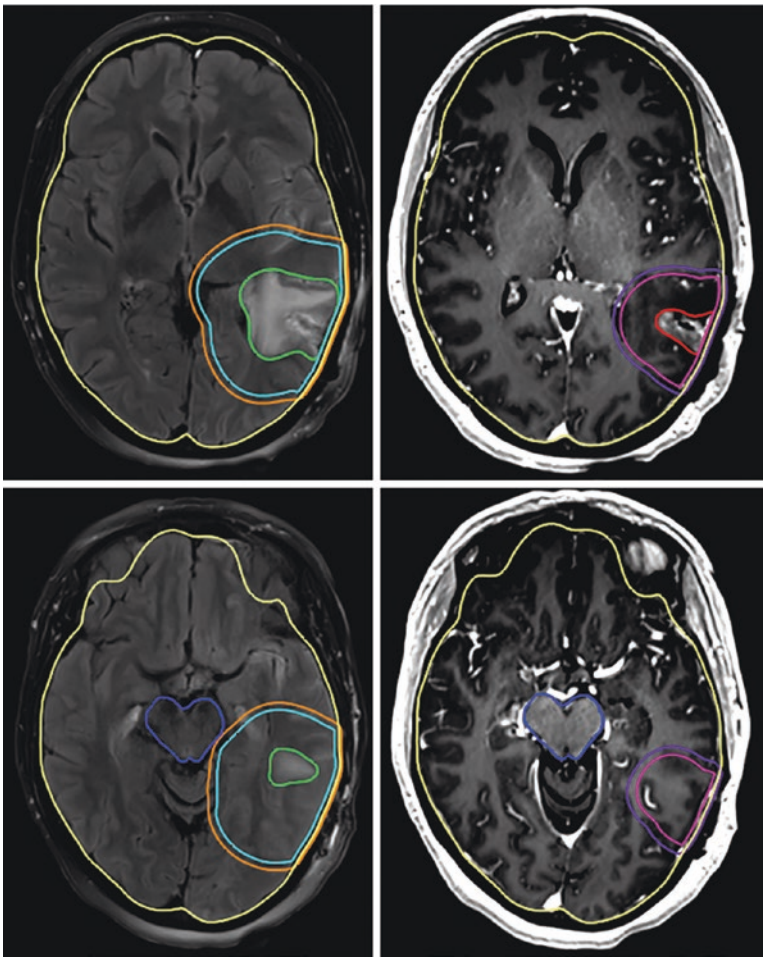

Fig. 30.7 (continued)

Table 30.3 Recommended target volumes for grade II/III meningioma and hemangiopericytoma

Tumor type	Recommended dose/ fractionation	GTV definition	Suggested CTV expansions	PTV expansions
Grade II meningioma (upfront)	PTV: 54–59.4 Gy at 1.8 Gy/fraction	GTV is defined by The post-operative cavity, residual tumor including suspicious dural and/or bone involvement by the post-contrast T1 MRI	CTV is defined by a 0.5 cm expansion, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology
Grade II meningioma (recurrent)	PTV: 54–59.4 Gy at 1.8 Gy/fraction	GTV is defined by The post-operative cavity, residual tumor including suspicious dural and/or bone involvement by the post-contrast T1 MRI. Evaluation of prior dural attachment at initial diagnosis is also recommended	CTV is defined by a 0.5–1.0 cm expansion, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology
Grade III meningioma (upfront or recurrent)	PTV: 59.4–60 Gy at 1.8–2 Gy/ fraction	GTV is defined by The post-operative cavity, residual tumor including suspicious dural and/or bone involvement by the post-contrast T1 MRI. Evaluation of prior dural attachment at initial diagnosis is also recommended	CTV is defined by a 1–1.5 cm expansion, reduced around natural barriers to tumor spread	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology
Hemangiopericytoma	PTV: 59.4–60 Gy at 1.8–2 Gy/ fraction	GTV is defined by The post-operative cavity, residual tumor including suspicious dural and/or bone involvement by the post-contrast T1 MRI	CTV is defined by a 1.5 cm expansion, reduced around natural barriers to tumor spread, but include entirety of involved bone	0.3–0.5 cm, depending on frequency of IGRT, radiotherapy technique, and daily patient positioning technology

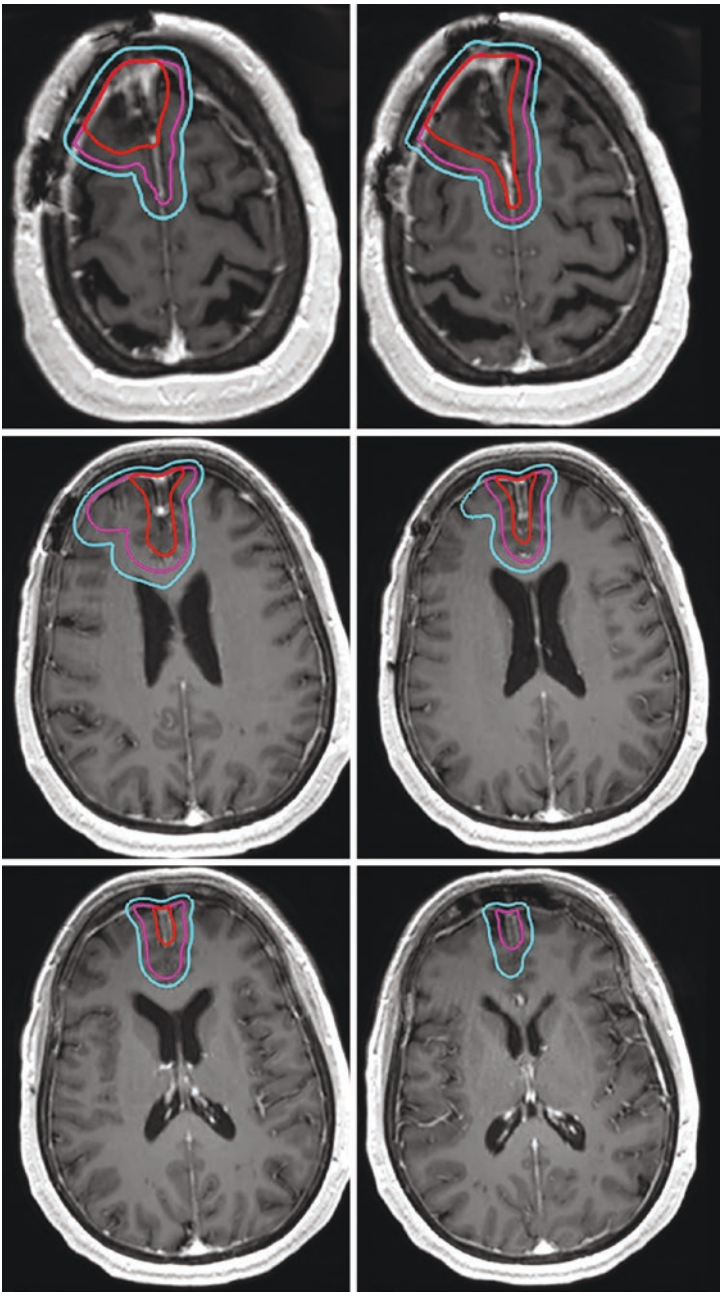

Fig. 30.8 Representative slices of the treatment planning MRI (post-contrast T1) for a patient with an atypical (WHO grade II) parafalcine meningioma. Outlining the pre-operative extent of disease, including dural attachments is critical to delineating the post-operative target volumes for radiotherapy treatment planning. The post-surgical bed, original dural attachments, and residual nodularity at the medial margin of the surgical cavity involving the falx were included in the GTV (red). A 0.5 cm anatomically constrained margin was used to generate the CTV (pink) and a 0.3 cm expansion used to create the PTV (turquoise)

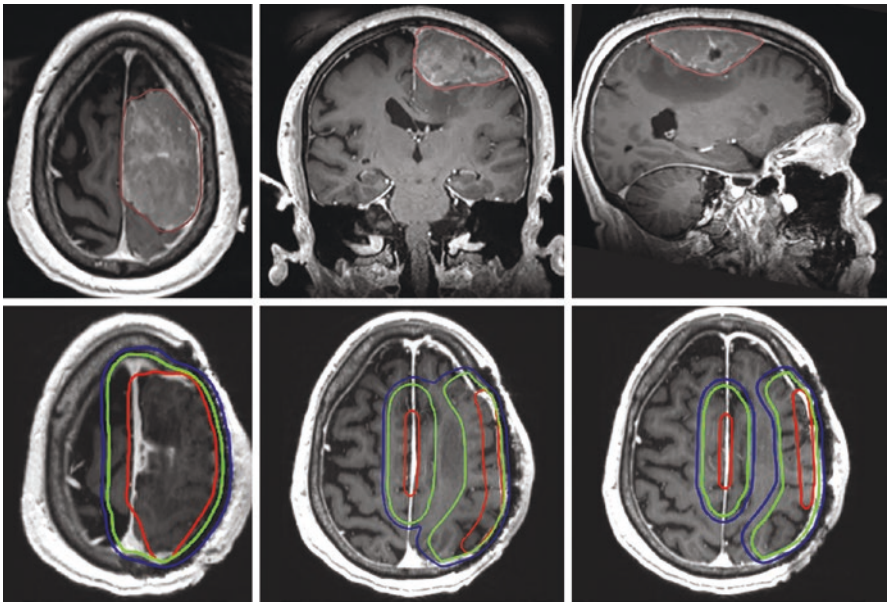

Fig. 30.9 Axial, coronal, and sagittal T1 post-contrast MRI for a patient with a large left fronto-parietal parasagittal convexity malignant meningioma (WHO III) (top row). Outlining the pre-operative extent of disease, including dural attachments (brown) is critical to delineating the post-operative target volumes for radiotherapy treatment planning. Representative slices of the post-operative treatment planning T1 post-contrast T1 MRI (below) show the post-surgical bed and original dural attachments included in the GTV (red). A 1.0 cm anatomically constrained margin was used to create the CTV (green) and a 0.3 cm expansion used to create the PTV (blue)

Hodgkin and Non-Hodgkin Lymphoma

31

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Contents

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_31

31.1 General Principles of Tumor Volume Delineation and Field Setup

- Delineation and field setup for radiation therapy (RT) for both Hodgkin (HL) and non-Hodgkin lymphoma (NHL) depend on the origin of the disease, the quality and patient positioning of pre-chemotherapy imaging, the use and response to systemic chemotherapy, as well as the extent of disease.
- Extended-field radiation therapy (EFRT) was historically used as definitive management without chemotherapy. With combined modality therapy allowing for reduction of treatment field size, involved-field radiation therapy (IFRT) then became standard therapy to treat smaller fields resulting in lower doses delivered to normal tissues compared to EFRT.
- With the most recent effective curative regimens despite shrinking radiation fields, involved-site radiation therapy (ISRT) which further reduced volumes based on 3-dimensional (3D) anatomy, focusing on the original extent of disease with a margin to account for imaging limitations, has become the recommended standard [1–3].
- ISRT has emerged over the past decade due to ongoing efforts to minimize late effects of treatment and improve the quality of life of survivors [4].
- In practices where patients are seen by the radiation oncologist prior to diagnostic imaging, involved-node radiation therapy (INRT) technique may be employed. The principles of target volume delineation for INRT and ISRT are similar, with differences in the quality and accuracy of pre-chemotherapy imaging suggesting that the margins for ISRT should be larger to allow for uncertainties in contouring the clinical target volume (CTV). INRT is the common approach in Europe where optimal imaging is available, including a pre-chemotherapy PET-CT scan acquired in the same position as the radiotherapy treatment positioning [5–8]. As it is not yet a routine practice that optimal pre-treatment imaging is available, ISRT is the standard practice in most healthcare systems in North America.
- Treatment doses to various subtypes of Hodgkin and non-Hodgkin lymphoma differ based on their histology, stage, and response to chemotherapy and are therefore out of the scope of this chapter on target volume selection/delineation and field setup.

31.2 Principles of Involved-Site and Involved-Node Radiation Therapy

- Below is a summary of published guidelines for defining INRT and ISRT treatment volumes [1–3, 5].

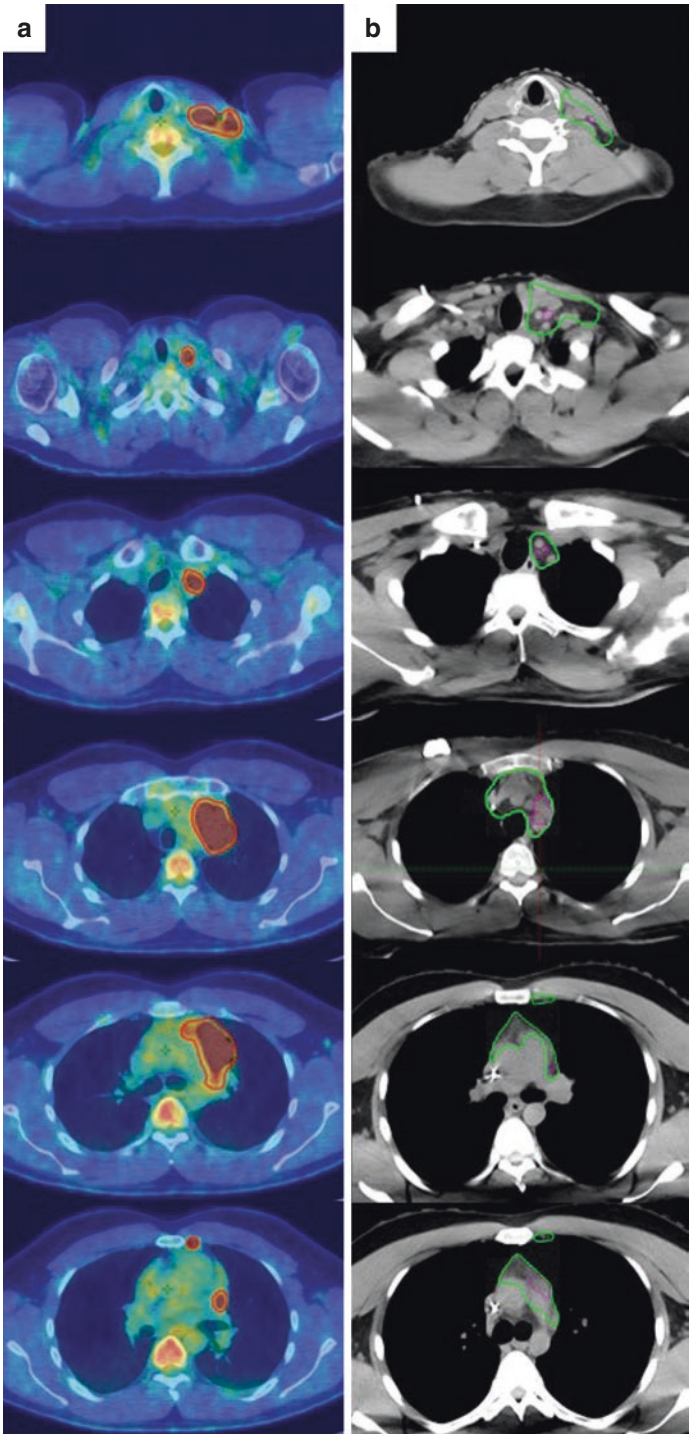
- ISRT simulation must be based on a 3-dimensional simulation (CT simulator, PET/CT simulator, or a magnetic resonance imaging simulator). If the patient's medical conditions permit, IV contrast should be used for accurate identification of the vessels.
- When radiation therapy is performed as consolidation after chemotherapy, the pre- and post-chemotherapy FDG-PET and CT should be ideally fused with the simulation CT in the RT planning system.
- ISRT planning incorporates the standard definitions and nomenclature as outlined in the International Commission on Radiation Units and Measurements (ICRU) Report 83, with consideration of whether radiation therapy is used as a primary modality or as consolidation therapy [9].
- The gross tumor volume (GTV), CTV, internal target volume (ITV) when relevant, and planning target volume (PTV) should be delineated as follows using all the available imaging information including pre-chemotherapy imaging (contrast-enhanced CT and PET-CT as shown in the clinical examples discussed throughout this chapter).
- Pre-chemotherapy GTV.
- Post-chemotherapy GTV.
- CTV: A volume encompassing the superior and inferior extent of the pre-chemotherapy GTV with the radial extent respecting and avoiding overtly uninvolved, normal structures (i.e. lungs, kidneys, muscles) based on clinical judgment. The CTV should also take into account the differences in pre-chemotherapy and post-chemotherapy imaging positioning and fusion accuracy, pattern of spread of disease, changes in the volume of disease since imaging, risk of subclinical involvement, and nearby structures. Typically, the superior and inferior extent of the CTV often extends 1–2 cm beyond the pre-chemotherapy GTV extent to account for these uncertainties. Nodal volumes that are more than 5 cm apart can be treated as separate fields.
- ITV: Target motion should be accounted for using an ITV as defined in the ICRU Report 83 as the CTV with a margin to consider organ motion for an individual patient [9]. A 4D CT simulation can be useful to obtain the ITV margins. If unavailable, 1.5 to 2 cm margins may be necessary in the chest or upper abdomen where respiratory movement can be significant.
- PTV: This margin should account for uncertainty in setup based on patient factors or immobilization that varies across institutions.
- The CTV for ISRT will generally be larger than that for INRT due to the lack of optimal imaging information.

- Radiotherapy may be used as a single modality for definitive treatment of certain indolent, early-stage NHLs, and early-stage nodular lymphocyte-predominant HL. In these scenarios, the CTV should be more generous given the concern of a larger extent of subclinical disease without pre-treatment with chemotherapy [1–3].
- For a reference of historical IFRT field borders, please refer to the chapter on HL and NHL in the previous edition of this handbook [10].

31.3 Case-Based Examples for Target Delineation

- Early-stage Hodgkin lymphoma (Fig. 31.1).
- Advanced-stage Hodgkin lymphoma (Fig. 31.2).
- Nodular lymphocyte-predominant Hodgkin lymphoma (Fig. 31.3).
- Early-stage Diffuse Large B-cell Lymphoma of the Head and Neck (Fig. 31.4).
- Follicular lymphoma of the groin (Fig. 31.5).

Fig. 31.1 A 27-year-old male with Stage IIA, non-bulky, favorable-risk, nodular sclerosing Hodgkin lymphoma involving the left supraclavicular and mediastinal lymph node regions was treated with 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). A post-chemotherapy PET demonstrated a complete metabolic response (Deauville 2). Since he met criteria for the German Hodgkin Study Group H10, he was treated with 20 Gy of radiation therapy following completion of 2 cycles of ABVD. For target delineation, the pre-chemotherapy PET/CT was registered to the simulation CT. For target delineation, the pre-chemotherapy PET/CT was registered to the simulation CT. (**a**) Axial slices from cranial to caudal extent of his disease on pre-chemotherapy PET/CT with gross disease (pre-chemo GTV) contoured in red. (**b**) Corresponding axial slices in his post-chemotherapy simulation CT demonstrate the slight change in anatomy between scans due to the different arm positioning, hyperextended neck, and five-point mask retracting his shoulders at the time of simulation, differences that are accounted for by an ISRT contouring approach. The small volume post-chemotherapy residual disease (post-chemo GTV) is shown in pink and the ISRT CTV in green. This patient was treated with a breath-hold technique, so there is no expansion on the CTV to account for respiratory motion. Radiation therapy was prescribed to the CTV plus an institutionally specified PTV margin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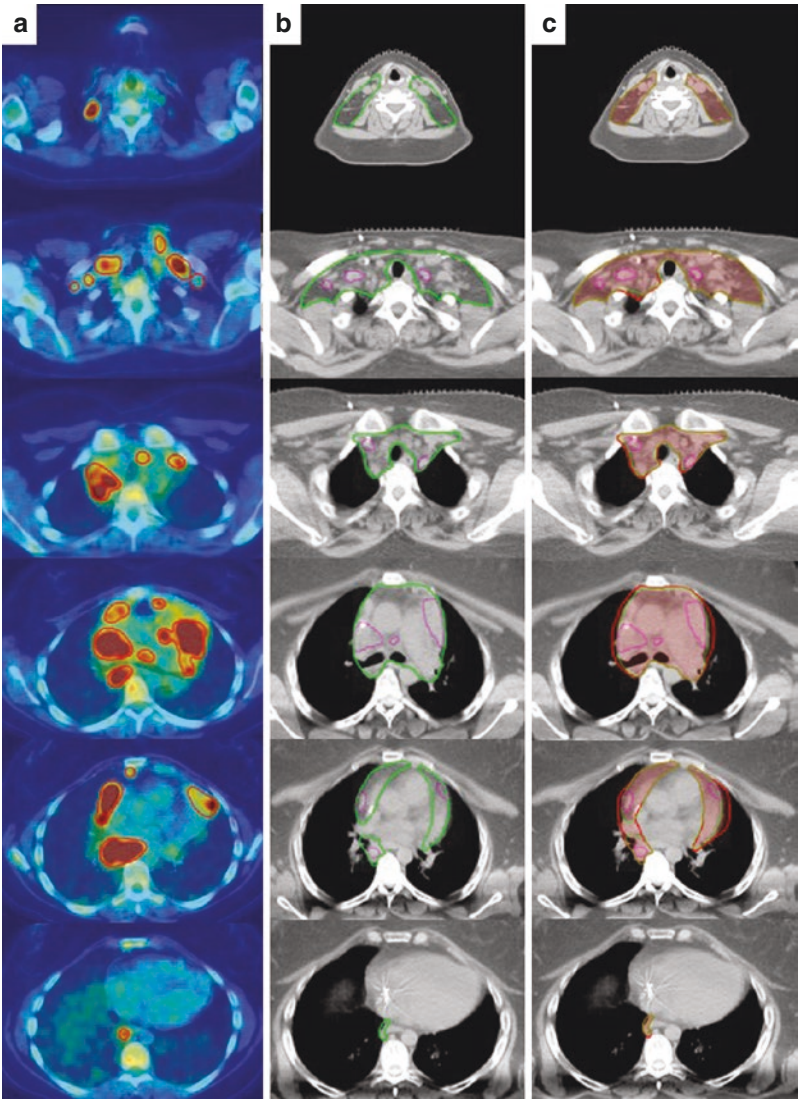

Fig. 31.2 A 31-year-old woman with Stage IIB with bulk nodular sclerosing Hodgkin lymphoma involving the cervical, supraclavicular, mediastinal, and bilateral hilar nodal regions received 2 cycles of ABVD and interim PET/CT demonstrated a complete metabolic response (Deauville 2). She received an additional 4 cycles AVD (Bleomycin dropped due to pulmonary toxicity) and subsequently was treated with consolidation radiation therapy due to initial bulky disease at presentation. For target delineation, the pre-chemotherapy PET/CT was registered to the simulation CT. (**a**) Axial slices from cranial to caudal extent of her disease on pre-chemotherapy PET/CT with gross disease (pre-chemo GTV) contoured in red. (**b**) On post-chemotherapy simulation CT, note the slight change in anatomy between scans due to the hyperextended neck and five-point mask retracting her shoulders at time of simulation, differences that are accounted for by an ISRT contouring approach. The small volume post-chemotherapy residual disease (post-chemo GTV) is shown in pink and the ISRT CTV in green. (**c**) The final ITV in red is shown overlaying the CTV in green and post-chemo GTV in pink, accounting for changes in anatomy due to respiration captured using 4-D CT at time of simulation. Radiation therapy was prescribed to the ITV plus an institutionally specified PTV margin

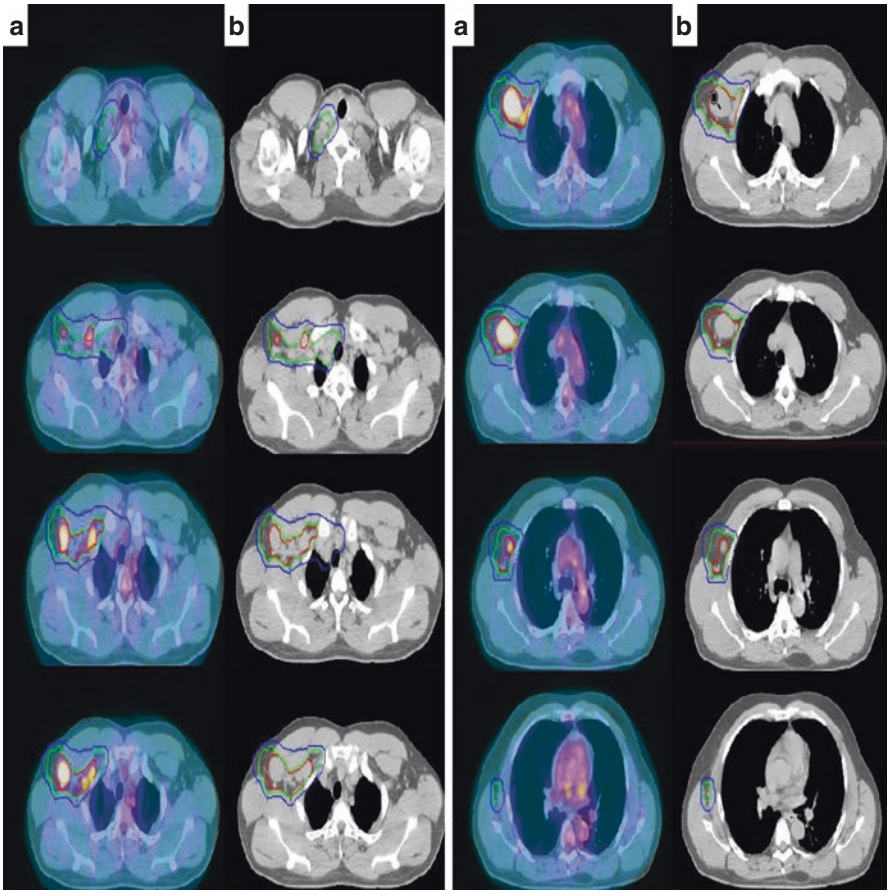

Fig. 31.3 A 61-year-old man with Stage IIA nodular lymphocyte-predominant Hodgkin lymphoma involving the right supraclavicular, subpectoral, and axillary lymph node regions treated with definitive radiation therapy alone. Patient was simulated with arms up, utilizing a wingboard. (**a**) The diagnostic PET/CT was registered to the simulation CT. (**b**) Corresponding axial slices of his simulation CT are shown with respect to the diagnostic PET/CT. Gross disease is contoured in red and the ISRT CTV in light green. Radiation therapy was prescribed to the institutionally prescribed PTV margin (blue)

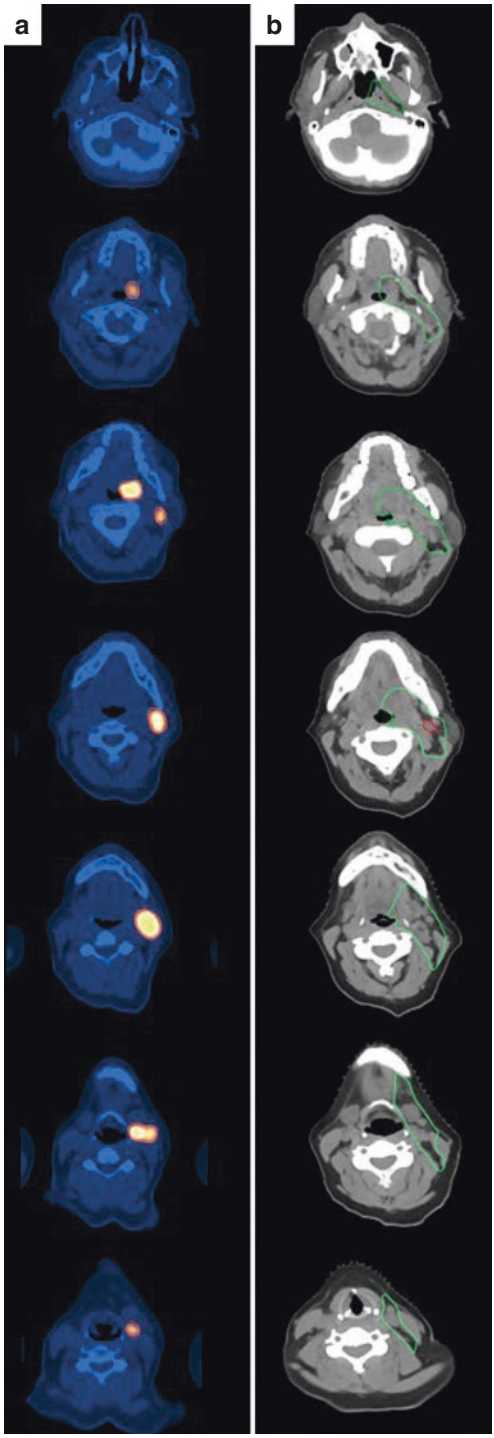

Fig. 31.4 A 47-year-old woman with Stage IIA non-bulky, favorable diffuse large B-cell lymphoma of the left tonsil and left neck (level 2, 5.6 cm) received 3 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and subsequently presented for consolidation radiotherapy. She was simulated with her neck in extension and immobilized using a 5 point aquaplast mask. For target delineation, the pre-chemotherapy PET/CT was registered to the simulation CT. (**a**) Axial slices from cranial to caudal extent of her disease on pre-chemotherapy PET/CT demonstrate the gross disease (pre-chemo GTV) contoured in red. (**b**) Corresponding axial slices in her post-chemotherapy simulation CT demonstrate small volume post-chemotherapy residual disease (post-chemo GTV) contoured in red and the ISRT CTV contoured in green, covering the entire left tonsil and left neck nodal level of the involved lymph node, including 1–2 cm superior and inferior to the pre-chemotherapy extent of disease

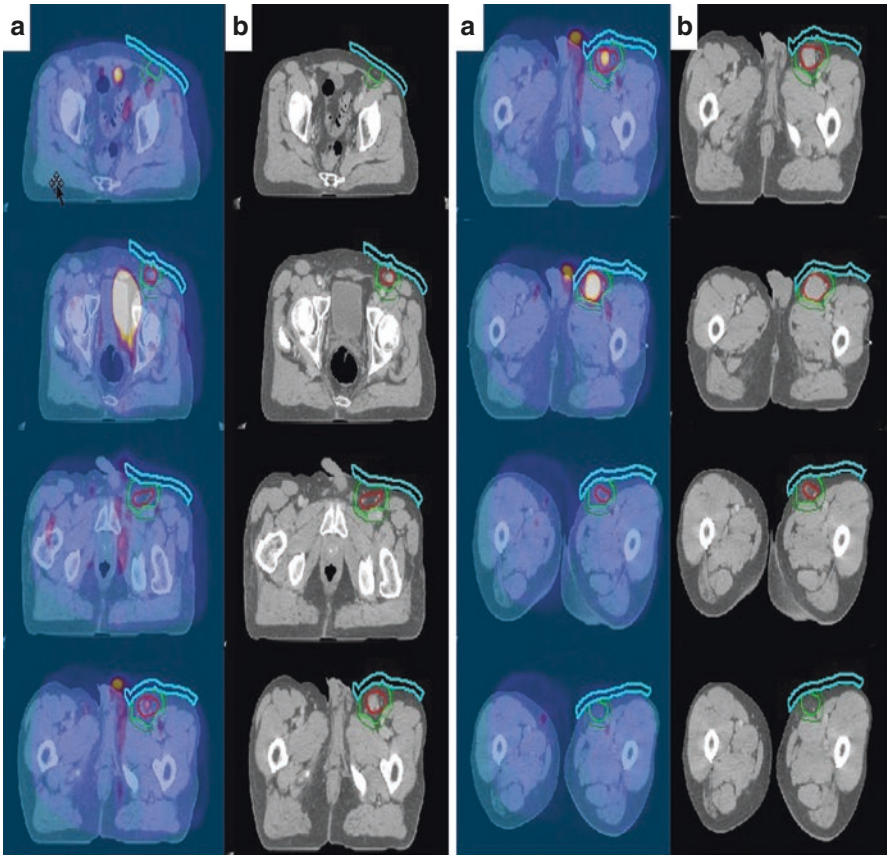

Fig. 31.5 A 70-year-old man with Stage IA non-bulky, grade I/II follicular lymphoma of the left inguinal/femoral region treated with definitive radiation therapy alone. For target delineation, the diagnostic PET/CT was registered to the simulation CT. (**a**) Axial slices from cranial to caudal extent of his disease on PET/CT (fused to the CT simulation) are shown (**b**) corresponding axial slices of his simulation CT alone. Gross disease is contoured in red and the ISRT CTV in light green. Radiation therapy was prescribed to the institutionally prescribed PTV margin (dark green). A bolus was used to increase superficial dose and improve dose coverage

31.4 Contouring for Select Sites Including Extranodal Sites

31.4.1 General Principles of Patient Setup and TV Delineation for Inguinal/Pelvic Region Lymphoma

- Patients should be simulated in the "frog-leg" position for coverage of the inguinal region in order to separate the leg from the external genitalia and flatten any inguinal skin folds to minimize potential skin reactions.
- Shield testicles with a clamshell and recommend sperm banking in men and consider the location of the ovaries for reproductive age women.
- Modern radiation techniques, including 3DCRT and IMRT, are recommended. One may also need to add bolus to increase superficial dose and improve coverage.

31.4.2 General Principles of Patient Setup and TV Delineation for Gastric Lymphoma

- Patients should fast 3–4 h prior to simulation and treatment in order to decrease gastric motility. Oral contrast should be used in all cases and IV contrast is recommended if there are involved lymph nodes.
- Patients should be simulated with arms up if using conformal radiation therapy and immobilized using a custom mold. Respiratory motion should be assessed using a 4D CT scan and treatment with deep inspiratory breath hold (DIBH) should be considered.
- Modern radiation techniques, including 3DCRT and IMRT, are recommended to spare dose to the kidney and liver. Suggested target volumes for gastric lymphoma radiation therapy are presented in Table 31.1.

The PTV margin should be adjusted accordingly based on the results of 4D assessment. In some cases, 2 cm may not be adequate given the degree of stomach motion.

Table 31.1 Suggested target volume delineation for gastric, orbital, and sinonasal lymphoma

Origin	Suggested target volume selection and delineation
Gastric (Fig. 31.6)	GTV = gross disease
	CTV = GTV + stomach from gastroesophageal to gastroduodenal junction
	PTV = CTV + 2 cm margin using 4D CT assessment of respiratory motion
Orbital (Fig. 31.7)	GTV = gross disease
	CTV = GTV + whole orbit
	PTV = CTV + 5-mm margin
Sinonasal (Fig. 31.8)	CTV = prechemo GTV + entire involved sinus(es)
	PTV = CTV + 4–5-mm margin depending upon setup technique

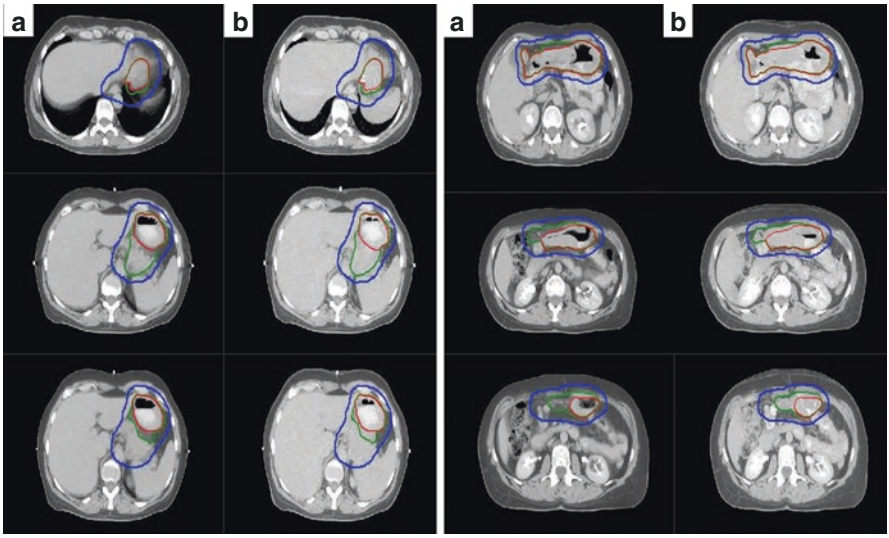

Fig. 31.6 A 63-year-old woman with a Stage IIAE MALT lymphoma with diffuse gastric involvement and perigastric lymphadenopathy was treated with definitive radiation therapy alone. For target delineation, axial slices from the cranial to caudal extent of her disease on the (**a**) CT simulation and (**b**) 4DCT MIP (maximum intensity projection). Since the patient had diffuse gastric involvement, GTV = CTV. ISRT CTV is shown in red and ITV is shown in green with corresponding images. Radiation therapy was prescribed to the PTV margin (blue)

31.4.3 General Principles of Patient Setup and TV Delineation for Orbital and Sinonasal Lymphoma

- The patient is simulated in the supine position with arms down and head immobilized using a thermoplastic mask.
- For orbital lymphoma, one may treat with a superior-inferior wedge pair technique, 3DCRT, or IMRT. Bolus may be added to increase superficial dose to localized soft tissue disease and consider a lacrimal gland shield if the prescribed dose is ≥30 Gy.
- For limited indolent disease of the conjunctivae, treat with anterior electron beam setup or may consider electron/photon mixed energy; consider lens shield if tumor located in the periphery.
- For sinonasal lymphomas, treatment with 3DCRT or IMRT is recommended given the higher doses delivered in the treatment of this disease depending on the histology and the number of surrounding critical structures.
- Suggested target volumes for orbital and sinonasal lymphoma radiation therapy are presented in Table 31.1. Case examples are presented in Figs. 31.7 and 31.8.

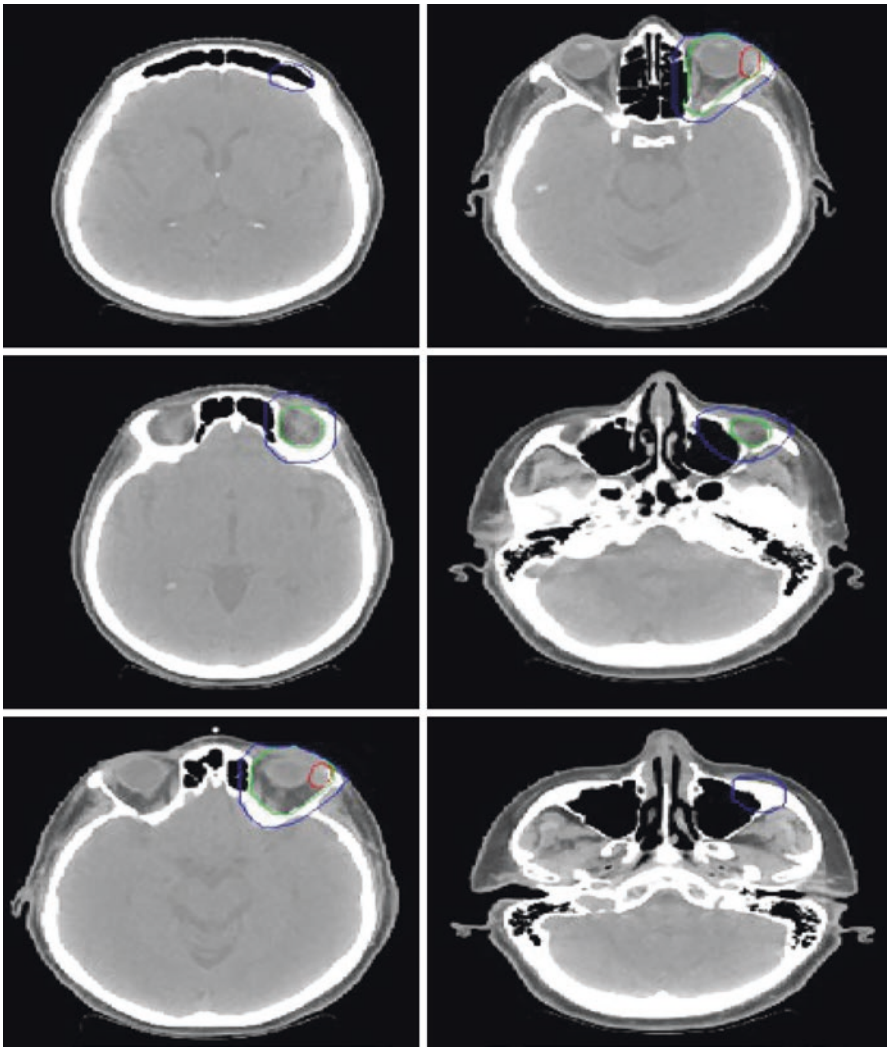

Fig. 31.7 A 69-year-old woman with Stage IAE MALT lymphoma of the left lacrimal gland treated with definitive radiation therapy alone. For target delineation, axial slices from the cranial to caudal extent of her disease on the simulation CT are shown. Gross disease is contoured in red and the ISRT CTV in light green covers the whole orbit. Radiation therapy was prescribed to the institutionally prescribed PTV margin (blue)

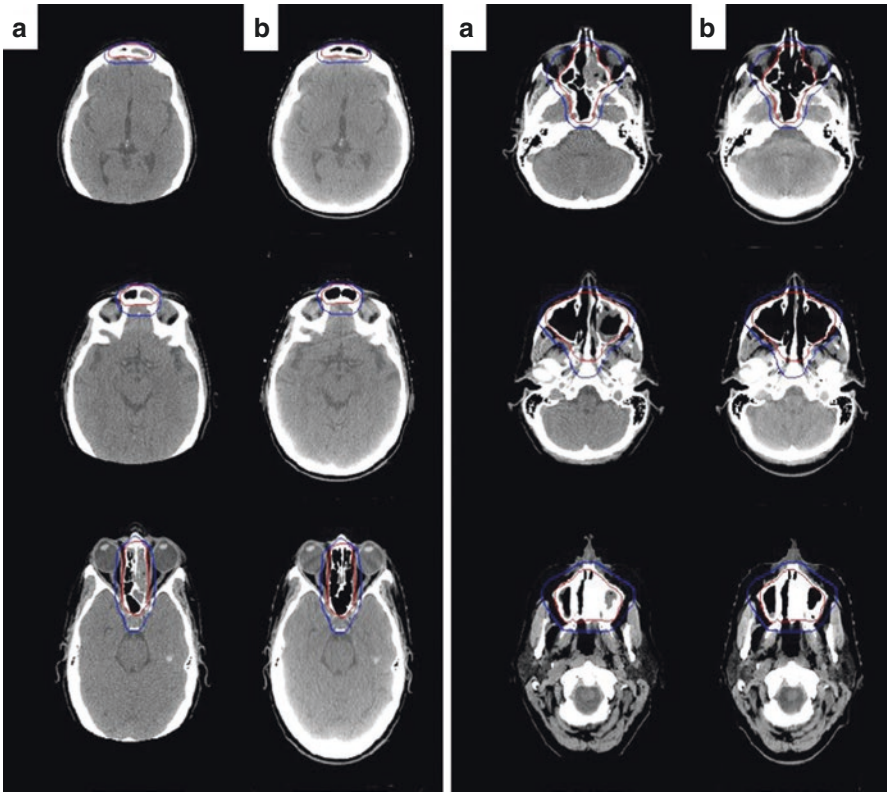

Fig. 31.8 A 56-year-old woman with Stage IAE diffuse large B-cell lymphoma of the left ethmoid/sphenoid sinus with extension across the nasal septum into the right nasal cavity. Superiorly, the mass is associated with erosive changes in the cribriform plate. Laterally, the mass erodes the left medial orbital wall and inferiorly, extends into the left maxillary sinus. The left frontal sinus was completely opacified. Patient was initially taken to surgery for resection of the mass for pathologic confirmation with a near total resection. She then received 3 cycles of R-CHOP and was treated with consolidative radiation therapy. (**a**) Preoperative (and pre-chemotherapy) axial slices from cranial to caudal extent of her disease are shown. (**b**) On corresponding axial slices of her simulation CT there is no gross disease and the ISRT CTV in red covers the entirety of the involved sinuses. Radiation therapy was prescribed to the institutionally prescribed PTV margin (blue)

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Soft Tissue Sarcoma

32

Charles Catton, Amy Parent, Colleen Dickie, and Brian O'Sullivan

Contents

32.1 General Principles of Planning and Target Delineation

- Anatomic location, size, depth (with respect to the superficial fascia), and pathological features dictate the management of soft tissue sarcoma (STS).
- Invasion is typically in the longitudinal direction within muscle and confined to the compartment of origin. Suspicious peritumoral changes, henceforth referred to as edema, may harbor microscopic disease. Edema is most often pronounced in the cranio-caudal dimension and should ordinarily be encompassed in the radiotherapy target volume.
- STS generally respect barriers to tumor spread such as bone, interosseous membrane, and major fascial planes, and this concept should be exploited in tissue/function preserving radiotherapy planning, especially in extremity lesions.
- Retroperitoneal tumors commonly grow to a large size and initially displace but eventually invade adjacent organs and tissues.
- In the event of an "unplanned" surgical resection with positive margins (surgical error), the RT target volume needs to generously include all disturbed muscle compartments in addition to any other tissues considered to be directly involved (see Figs. 32.1, 32.2, and 32.3).

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_32

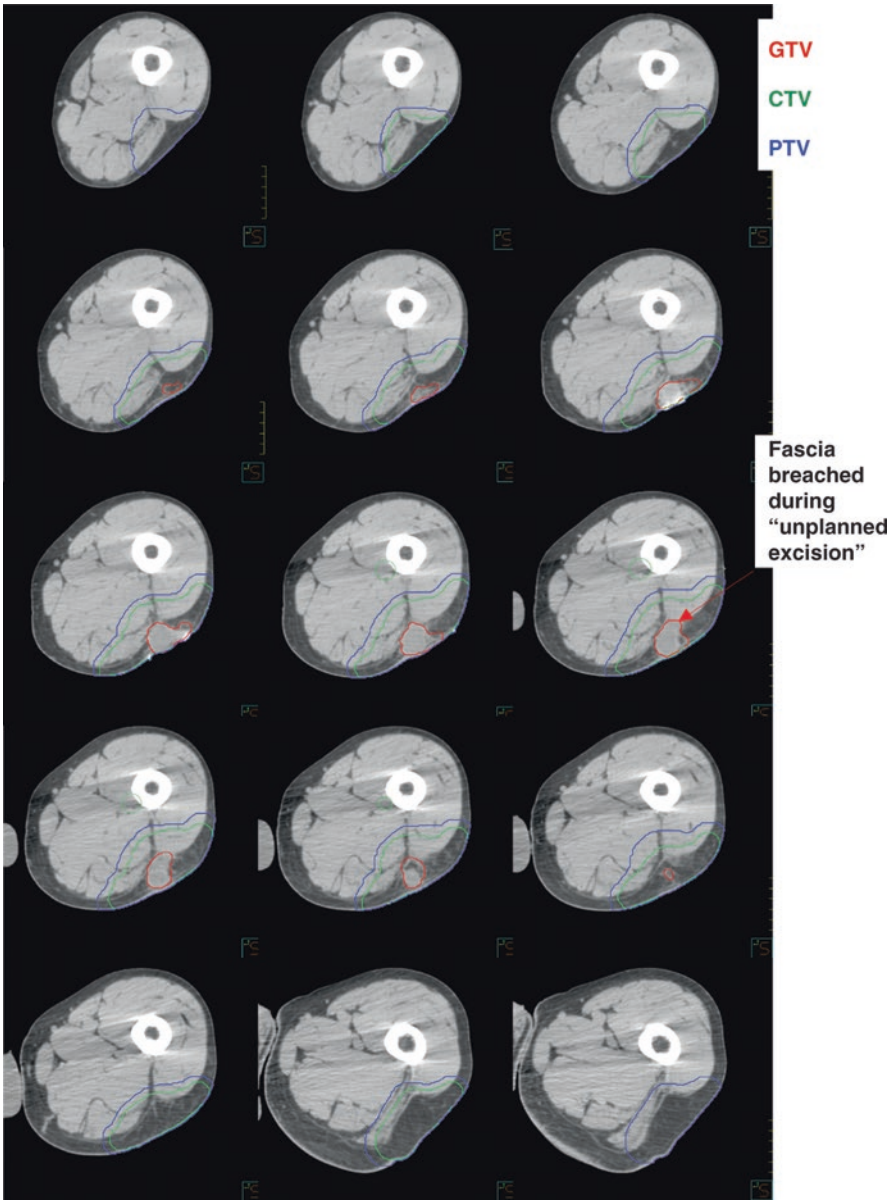

Fig. 32.1 A patient with a T1N0M0 Grade 3 dedifferentiated liposarcoma in the posterolateral thigh. This patient presented having had a previous unplanned excision of a superficial lesion where the fascia of the vastus lateralis was breached but did not involve the deeper compartment originally. CT simulation used 2.0-mm slice thickness. Notice the area of violated fascia due to previous surgical error. Shown are representative slices

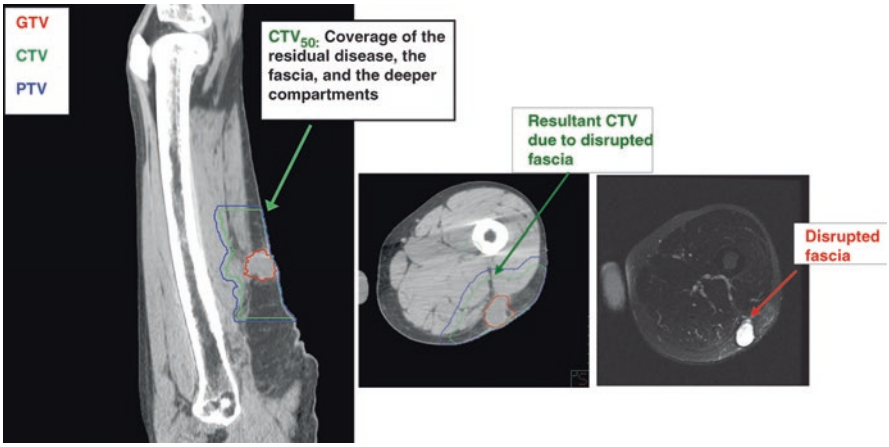

Fig. 32.2 Example of GTV, CTV, and PTV displayed in the sagittal view as well as an axial view of the disrupted fascia as a result of an unplanned excision with the corresponding planning CT target volumes

- For preoperative planning target volume definition, CT simulation imaging fused with MR imaging should be performed, ideally with the patient in the treatment position, to help guide delineation of the gross tumor volume (GTV) and clinical target volume (CTV) (see Figs. 32.1 and 32.2).
- For postoperative planning target volume definition after assumed complete surgical resection, there is no GTV to delineate. The location of the original GTV following the operation (GTV_{postop}) should be recreated in the planning CT dataset using preoperative CT/MRI imaging if available (see Figs. 32.4, 32.5, and 32.6).
- Note: The stage classification has changed in the recently published eighth edition of the TNM. Principle changes include different size thresholds for different anatomic sites and the elimination of depth in classification.

- For preoperative cases, 50 Gy is ordinarily used and target volumes include the GTV and the CTV_{50} and should be delineated on every slice on the planning CT (see Figs. 32.1, 32.2, 32.7, and 32.8).
- For postoperative RT delivery, 66 Gy is ordinarily used (60 Gy can be used in margin clear, low-grade cases) with an additional peripheral CTV volume for tissues with a lower risk of tumor infestation (see Figs. 32.4, 32.5, and 32.6).
- For unresectable residual gross disease, 70 Gy in 2 Gy/fraction or equivalent dose fractionation is ordinarily used depending on the tolerance of the anatomic region.
- Suggested GTV and CTV_{50} for preoperative IMRT of extremity STS are detailed in Table 32.1.

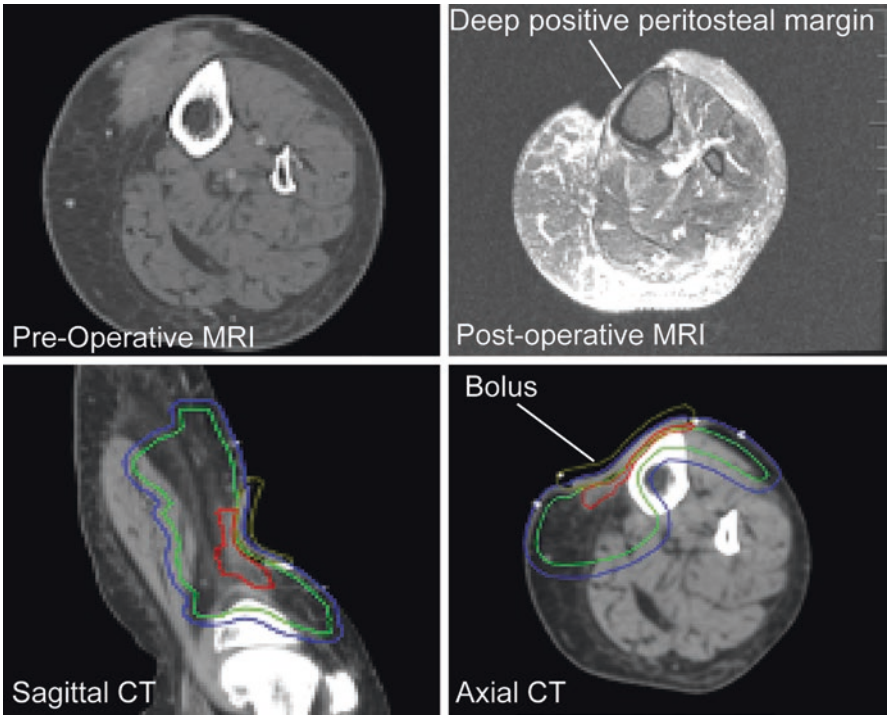

Fig. 32.3 A patient who presented following an unplanned excision of a right-sided 3 cm (T1N0M0) pre-tibial pleomorphic undifferentiated sarcoma. The defect was closed with a split-thickness graft and both radial and deep margins were positive. The recommendation was for 50 Gy preoperative radiotherapy followed by wide re-excision with free-flap closure. The post-op GTV for this case is as described in Chap. 30 Table 30.2. The CTV50 and PTV50 radiotherapy target volumes follow Table 30.1 as described for the preoperative setting. CT simulation used 2.0-mm slice thickness. Axial and sagittal CT simulation views of the radiotherapy target volumes are shown. Gross disease has been excised and the *postop* GTV identifies the position of the original tumor reconstructed from a preoperative CT scan. A representative axial T2-weighted MRI image demonstrates the soft tissue defect and the relationship of the skin graft and positive deep margin to the periosteum. The CTV_{50} comprises a 3–4 cm radial expansion beyond the site of the positive margins at the edge of the skin graft, and deeply, includes the involved periosteum. The radial margins more closely approximate postoperative margins to account for the lack of a GTV and the contamination from intralesional surgery. A 5 mm bolus plug has been placed to fill the soft tissue defect anterior to the skin graft to provide adequate build-up on the deep periosteal margin. An axial preoperative CT and postoperative MRI view is shown to demonstrate the defect

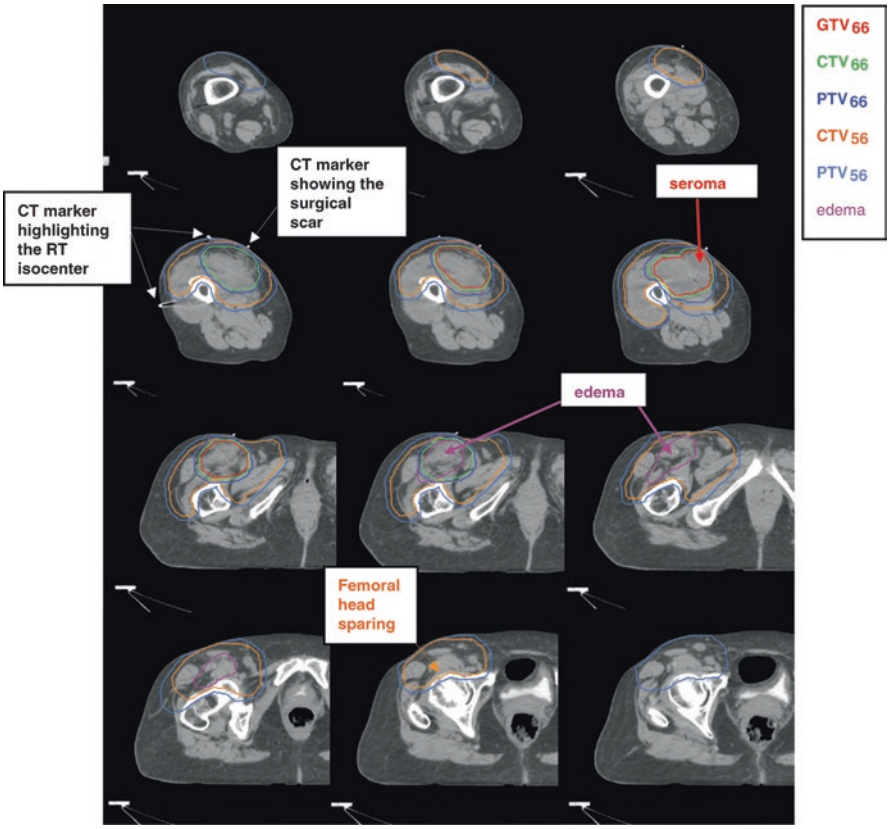

Fig. 32.4 A patient with a deep T3N0M0 Grade 3 pleomorphic rhabdomyosarcoma in the left thigh. This patient received postoperative RT for negative but close margins. CT simulation used 2.0-mm slice thickness. Edema was contoured at the superior aspect of the GTV_{postop} and included in the CTV_{56}. Shown are representative slices. CTV_{56} is limited by the femoral head and bone throughout the target. In some cases where the subcutaneous tissues have been contaminated, bolus may be applied to the surgical scar for a component of the treatment (e.g., 50 Gy)

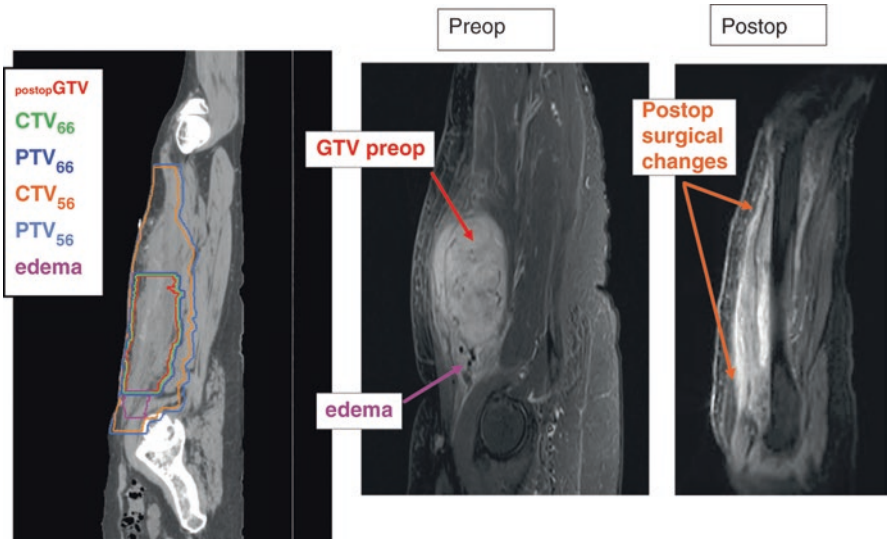

Fig. 32.5 Sagittal CT simulation view of the radiotherapy target volumes for this postoperative STS case and corresponding preoperative and postoperative MRI. Note the CTV_{56} is defined by edema and the postoperative surgical changes. Where the target may appear coincidental in this scaled anatomic illustration, the usual margins were applied (e.g., 0.5- to 1-cm PTV expansion). In addition, the preoperative imaging was imported and co-registered with the postoperative RT planning CT dataset in order to appreciate the original tumor extent for delineation of the GTV_{postop}

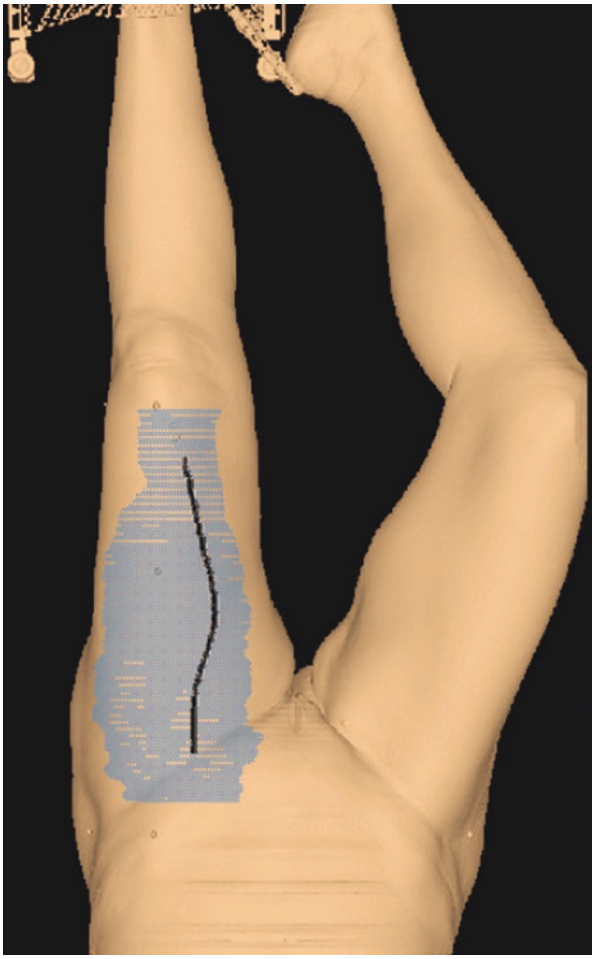

Fig. 32.6 The digitally reconstructed skin rendered image displaying the surgical scar and the planning target volume (PTV_{56}) shown in light blue that includes the surgical scar with a margin

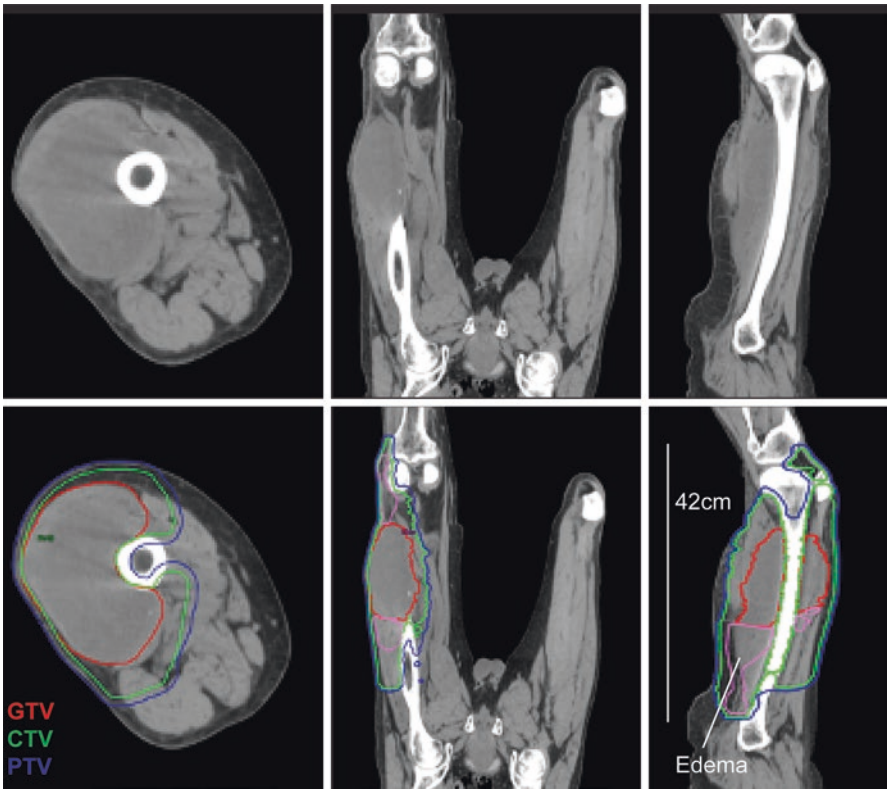

Fig. 32.7 A patient with a deep T3N0M0 grade 2 myxofibrosarcoma in the left lateral thigh. The patient received preoperative RT to minimize the necessary treatment volume. CT simulation used 2.0-mm slice thickness. The patient had extensive peritumoral edema extending superiorly and inferiorly that was included in the CTV_{50} and shown in representative slices. The CTV_{50} is limited by bone throughout the target. The PTV was 42 cm long exceeding the maximum machine capabilities for a single isocenter technique. Planning used a dual isocenter IMRT technique. The isocenters are strategically placed to approximate the center of both adjoining volumes and cooptimized to ensure uniform PTV coverage. Axial, coronal, and sagittal CT views are shown with corresponding target volumes delineated

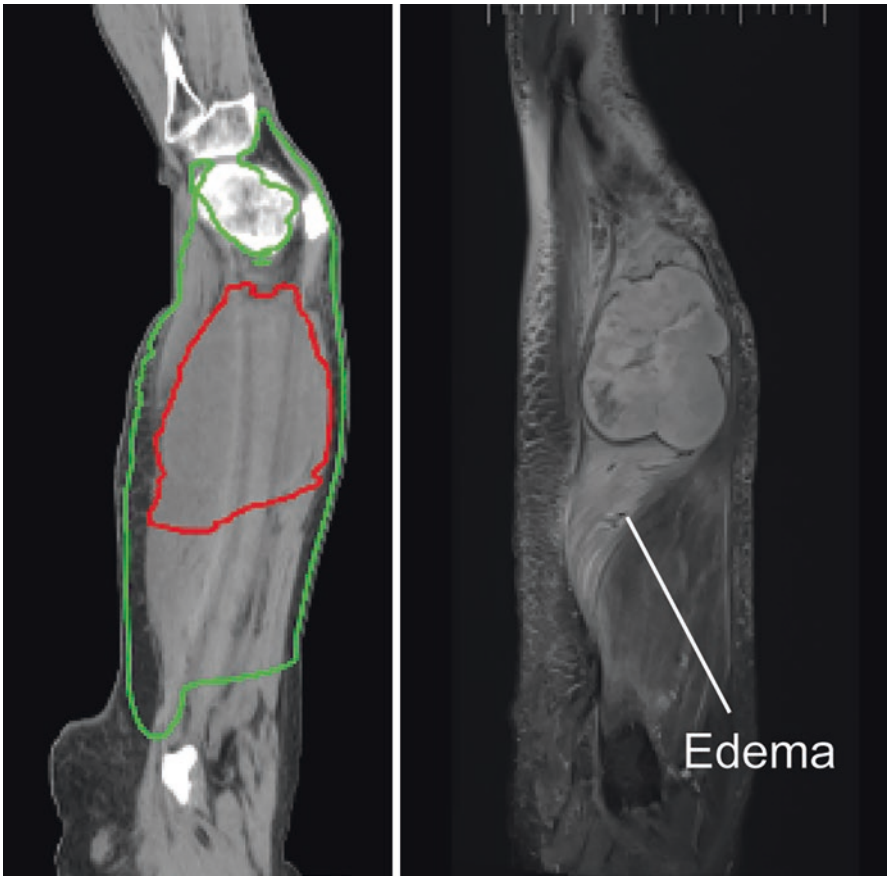

Fig. 32.8 Sagittal CT simulation view and corresponding sagittal T2-weighted preoperative MRI image that demonstrates extensive longitudinal peritumoural edema. Note that the CTV_{50} is defined by edema and usual margins were applied (e.g., 0.5- to 1.0-cm PTV expansion). The preoperative imaging was imported and co-registered with the planning CT dataset in order to appreciate the edema extent for delineation of the CTV_{50}

- Suggested GTV_{postop} and CTV_{66} for postoperative IMRT of extremity STS are detailed in Table 32.2.

- Suggested GTV and CTV (dose 50–50.4 Gy) for preoperative IMRT of retroperitoneal STS are detailed in Table 32.3 (Figs. 32.9 and 32.10).

Table 32.1 Suggested target volumes for preoperative extremity STS

Target volumes	Definition and description
GTV	Primary: All gross disease on physical examination and imaging. T1-weighted contrast-enhanced MRI preferable. Co-registration of the MRI and planning CT is facilitated by immobilizing the patient in the treatment position
CTV_{50*}	Includes all areas at risk of subclinical spread defined by the distance from the GTV or edema
	Includes the GTV + a 4-cm margin in the longitudinal dimensions and a 1.5-cm margin in the radial dimension limited to but including any anatomic barrier to tumor spread, such as bone or fascia
	Suspicious peritumoural edema, best demonstrated on T2-weighted MRI, may contain microscopic tumor cells and should be contoured separately with an adequate margin (usually 1–2 cm)
	For cases of "unplanned excision," margins should include $_{postop}$ GTV or any residual GTV + all surgically manipulated and disturbed tissues and violated fascia + 4 cm longitudinally and 1.5 cm radially limited to but including any barrier to tumor spread
PTV_{50*}	CTV_{50} + 0.5–1.0 cm, determined by individual institutional protocols and procedure

*Suggested gross tumor dose is 2.0 Gy/fraction to 50 Gy

Table 32.2 Suggested target volumes for postoperative extremity STS

Target volumes	Definition and description
GTV_{postop}	GTV_{postop} should identify the original site of the tumor
	Important to review and import presurgical imaging when contouring on the CT simulation scan for RT planning to ensure adequate coverage of the original tumor extent
CTV_{66*}	CTV_{66} should encompass the entire GTV_{postop} + immediate area of surgical change with a 1- to 2-cm margin in the longitudinal plane and a 1.5-cm margin in the transverse plane. This may, but not always, include all surgically disturbed tissues, scars, and drain sites
PTV_{66*}	CTV_{66} + 0.5–1.0 cm, determined by individual institutional protocols and procedure
CTV_{56*}	Includes all areas at risk of subclinical spread defined by the distance from the GTV_{postop} and additional disturbed tissues
	Includes the GTV_{postop} + a 4-cm margin in the longitudinal dimensions and a 1.5-cm margin in the radial dimension limited to but including any anatomic barrier to disease spread; additional disturbed surgical tissues and any scars or drain sites are ordinarily included with a 1- to 2-cm margin if they are not included in the CTV_{66}
	Suspicious peritumoural edema should be contoured separately and included with an adequate margin. Like surgically disrupted tissue, it is best identified from a recent postoperative MRI scan
	Discussion with the surgeon and review of surgical and pathology reports will facilitate the decision about whether or not a seroma, lymphocele, or hematoma should be included
PTV_{56*}	CTV_{56} + 0.5–1.0 cm, determined by individual institutional protocols and procedure

The table describes single-phase simultaneous boost technique. An alternative is the more traditional-phased shrinking field technique that delivers 50 Gy in 25 fractions to all areas of subclinical disease followed by a boost to deliver the final 16 Gy in 8 fractions using a second radiotherapy plan
*High-risk subclinical dose: 2.0 Gy/fraction to 66 Gy; for lower-risk subclinical regions 1.69 Gy/fraction to 56 Gy delivered to the CTV_{56}

Table 32.3 Suggested target volumes for retroperitoneal STS

Target volumes	Definition and description
GTV[a]	Primary: All gross disease on physical examination and imaging
CTV	Includes all areas at risk of subclinical spread defined by the distance from the GTV
	Includes the GTV + 2-cm margin in the longitudinal dimensions and a 0.5–2.0-cm margin in the radial dimension limited to but including any anatomic barrier to tumor spread and critical anatomy. For example, if the tumor is approximating an intact liver, 0.5 cm of the liver is included
	2-cm margins are usually used posteriorly to include fatty tissues and vessels
	Ipsilateral kidney may be sacrificed provided the contralateral kidney has acceptable function. In such a case, dose to the uninvolved opposite kidney should be kept as low as reasonably achievable
	Other organs at risk include the small bowel, liver, spinal cord, and lungs
PTV	CTV + 0.5 cm, determined by individual institutional protocols and procedure

[a]Suggested gross tumor dose range of 50 Gy/25 fractions to 50.4 Gy/28 fractions

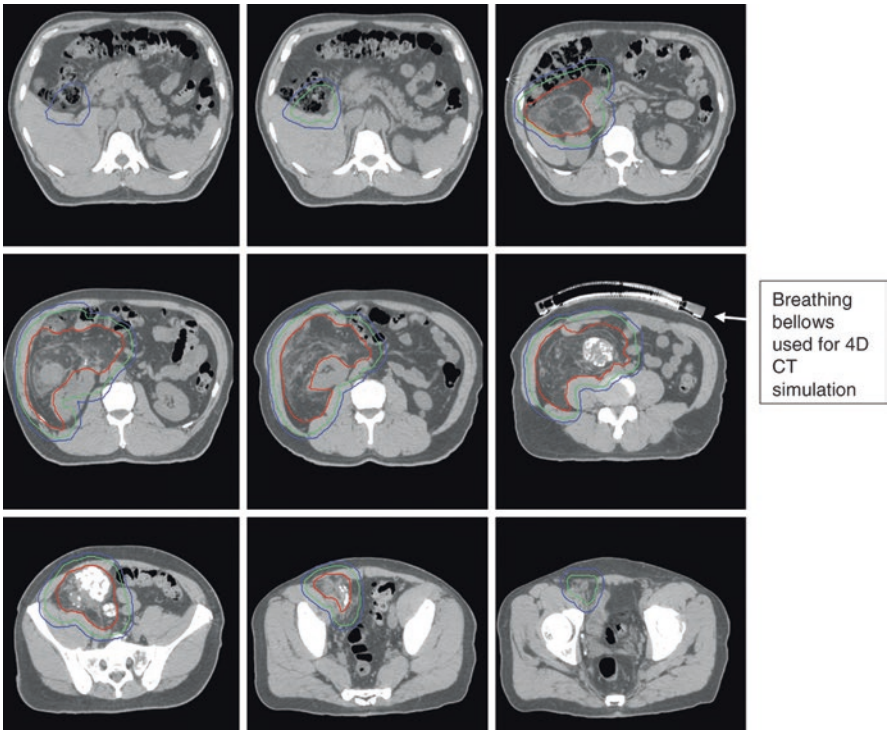

Fig. 32.9 An example of a right-sided T2bN0M0 Grade 3 undifferentiated pleomorphic retroperitoneal sarcoma juxtaposed to the duodenum, the right kidney, and the iliac vessels. CT simulation used a 2.0-mm slice thickness. Representative slices are shown. Note the small amount of liver included in the CTV and PTV in the first three axial slices. Multifocal areas of calcifications within the tumor aided in daily image guidance for targeted IMRT. 4D CT simulation is encouraged

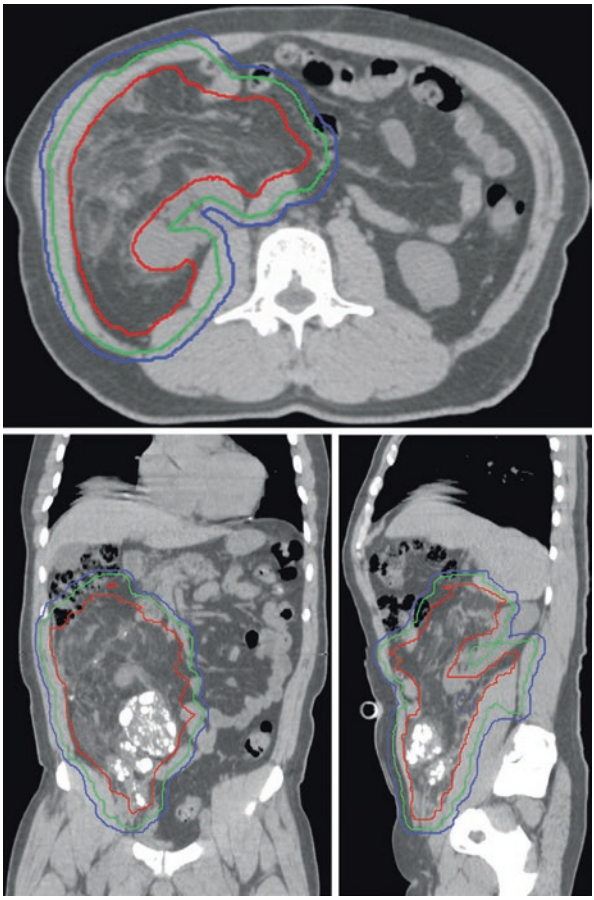

Fig. 32.10 An axial, coronal, and sagittal display of the right-sided retroperitoneal sarcoma. Note the bowel displacement by the tumor, one of the major advantages of preoperative radiotherapy in this setting

Pediatric Sarcoma

33

Ethan B. Ludmir, Benjamin T. Cooper, and Arnold C. Paulino

Contents

33.1 Background, Anatomy, and Patterns of Spread

- Pediatric sarcomas are a heterogeneous group of diseases, including both sarcomas of bone and soft tissue sarcomas (STS). Treatment algorithms for these diseases vary significantly by histology, stage and risk grouping, and even geographical site of practice (i.e., Europe versus the United States).
- Ewing sarcoma (EWS) is the second-most-common pediatric bone tumor (the most common being osteosarcoma, for which radiotherapy does not generally play as central a role in treatment). Rhabdomyosarcoma (RMS) is the most common pediatric STS.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_33

- In the treatment of both EWS and RMS, the conventional treatment algorithm includes a combination of systemic chemotherapy and local therapy. Local therapy can include surgical resection and/or radiotherapy.
- For unresectable EWS and RMS, radiotherapy alone is generally used for definitive local management, while radiotherapy can be delivered postoperatively in certain high-risk settings for both EWS and RMS.
- EWS and RMS, like many sarcomas, can occur in virtually any anatomic location in the body. This precludes in-depth discussion for the purposes of this chapter regarding nuances of each specific anatomic location where these sarcomas may arise.
- However, it is noteworthy that EWS most commonly occurs in the pelvis (25% of cases) followed by the femur (16% of cases). Patients with pelvic tumors are typically not amenable to resection and often dispositioned to definitive radiotherapy for local management of these tumors.
- RMS has a wide distribution across anatomic primary sites in the body, most commonly in the head-and-neck (35%), followed by genitourinary system (20%), and then extremity (20%). Primary tumor location of RMS is dichotomized into favorable and unfavorable sites, which directly impacts staging, risk stratification, and treatment algorithms for RMS patients. Within the head-and-neck lesions, tumors are classified as being parameningeal (15% of all RMS cases), orbital (10%), or other head-and-neck locations (10%). Parameningeal lesions, which occur in one of the eight specific sites (middle ear, mastoid, nasal cavity, nasopharynx, infratemporal fossa, pterygopalatine fossa, paranasal sinuses, and parapharyngeal space [commonly abbreviated with the mnemonic "MMNNOOPP"]), have increased risk of direct extension into the central nervous system and are classified as unfavorable primary site tumors.
- Generally, in considering local patterns of spread, uninvolved bone and intraosseous membranes provide anatomic boundaries for microscopic spread. That said, tumor erosion and invasion of bone are not uncommon and should be evaluated on imaging (primarily CT-based imaging for assessment of bone).
- As both EWS and RMS are often treated with chemotherapy before radiotherapy, post-chemotherapy volume reduction should be considered where pretreatment imaging demonstrates tumor "pushing" on nearby structures and displacing them (especially lung, bladder, and bowel); post-chemotherapy imaging in these settings generally shows that these anatomic structures return to a more normal position after response to induction chemotherapy. In contrast, direct invasion into surrounding structures (identified on pre-chemotherapy imaging) should warrant at least some coverage with post-induction radiotherapy fields.
- Nodal spread, while not commonly observed among most pediatric sarcomas, can be seen among select RMS cases, often by anatomic primary site. Extremity RMS has higher rates of nodal metastases and is often evaluated by sentinel node biopsy; certain genitourinary RMS (particularly paratesticular) patients may under surgical ipsilateral nerve-sparing retroperitoneal nodal dissection (generally reserved for patients >10 years old). While discussion regarding elective nodal coverage is ongoing in select contexts for RMS patients, elective nodal coverage is generally

not recommended for most RMS and EWS patients. However, when nodal metastases are observed, it is recommended to ensure at least some radiotherapy coverage of the entire nodal basin (not only the involved node/s).

33.2 Diagnostic Imaging for Target Volume Definition

- A combination of diagnostic imaging techniques is helpful for both target volume definition (gross tumor volume [GTV] and clinical tumor volume [CTV]) as well as staging.
- CT imaging is particularly helpful for outlining bony involvement/erosion, and MRI provides excellent soft tissue delineation to assess extent of disease including intracranial invasion. Both modalities are commonly utilized for both EWS and RMS.
- PET imaging has increasingly been utilized for both RMS and EWS at time of initial staging, with supporting literature for its adoption over other imaging techniques (such as bone scans). It may be helpful in identifying initially involved sites of disease pre-induction-chemotherapy.

33.3 Target Volume Delineation and Treatment Planning

- In the treatment of EWS, target volumes are generally split into two categories: a volume defined by extent of disease at initiation presentation (GTV1, CTV1) and a generally smaller volume defined by post-chemotherapy (and sometimes post-surgery) residual disease (GTV2, CTV2). Additional margins added to the CTVs for set-up uncertainty leads to resultant planning target volumes (PTVs). Table 33.1 outlines general target volume definitions for EWS, while Table 33.2 provides suggested doses based on the Children's Oncology Group (COG) AEWS1031 protocol.
- RMS radiotherapy can be delivered as a single volume (dose-level) or as two dose-levels similar to EWS; generally volume reductions for boost doses beyond 36 Gy in the treatment of RMS are recommended for "pushing" tumors into the thoracic or pelvis (see similar discussion regarding EWS above). Full details regarding this are presented in the ongoing COG ARST1431 protocol (for intermediate-risk RMS), but invasive RMS lesions may still require complete coverage of the pre-chemotherapy volume with the maximum dose (often 50.4 Gy for gross disease), irrespective of response to chemotherapy. This is particularly relevant for parameningeal head-and-neck RMS lesions, where the GTV2 volume should generally include pre-chemotherapy extent of disease regardless of induction chemotherapy response. For lesions "pushing" into surrounding structures, cone-down beyond 36 Gy can be performed. Table 33.3 provides general guidelines for target volume definitions for RMS; see the ongoing COG ARST1431 protocol for full details, which are beyond the scope of this chapter.

Table 33.1 Ewing sarcoma target volume definitions

Target volumes	Definition and description
Initial target volumes (pre-induction treatment)	
GTV1	Pre-chemotherapy extent of initial gross disease (including bone and soft tissue), including unresected enlarged/suspicious nodes. GTV1 may be modified if initial tumors extend into body cavities/spaces (pelvis, thorax) and subsequently regress with chemotherapy
CTV1	GTV1 + 1–1.5 cm. CTV1 includes involved nodal basins (clinical or pathologic involvement)
PTV1	CTV1 + set-up margin (institution- and image-guidance-specific, often 3–5 mm)
Reduced target volumes (post-induction treatment)	
GTV2	Residual tumor after induction chemotherapy; however, all pre-chemotherapy extent of bony involvement is typically included in GTV2. Postoperatively, GTV2 defined as residual disease (bone or soft tissue), and site(s) of positive margins
CTV2	GTV2 + 1–1.5 cm
PTV2	CTV2 + set-up margin (institution- and image-guidance-specific, often 3–5 mm)

GTV gross tumor volume; *CTV* clinical tumor volume; *PTV* planning tumor volume

Table 33.2 Ewing sarcoma doses (all in doses of 1.8 Gy per daily fraction)

Setting	PTV1 (Gy)	PTV2 (Gy)
Definitive radiotherapy (all sites except vertebral)	45	10.8
Definitive radiotherapy—Vertebral	45	5.4
Extraosseous EWS with complete response to chemotherapy	50.4	0
Postoperative with microscopic residual disease (R1 resection) with >90% tumor necrosis on pathology	0	50.4
Postoperative with microscopic residual disease (R1 resection) with <90% tumor necrosis on pathology	50.4	0
Postoperative with gross residual disease (R2 resection)	45	10.8

PTV planning target volume; *EWS* Ewing sarcoma

Table 33.3 Rhabdomyosarcoma target volume definitions

Target volumes	Definition and description
GTV1	Pre-chemotherapy extent of initial gross disease (including bone and soft tissue), including unresected enlarged/suspicious nodes
CTV1	GTV1 + 1 cm. CTV1 includes involved nodal basins (clinical or pathologic involvement)
PTV1	CTV1 + set-up margin (institution- and image-guidance-specific, often 3–5 mm)
GTV2	Residual tumor after induction chemotherapy, excluding areas where initial tumor "pushed" into surrounding structures such as the thorax or pelvis. However, pre-chemotherapy invasive disease (particularly in the context of parameningeal RMS of the head-and-neck) should generally be included in GTV2 irrespective of chemotherapy response
CTV2	GTV2 + 1 cm
PTV2	CTV2 + set-up margin (institution- and image-guidance-specific, often 3–5 mm)

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

- While the staging, grouping, and risk stratification of RMS are beyond the scope of this chapter, it is noteworthy that conventional definitions of RMS histology are shifting. Whereas previously RMS was broadly divided by the two most common histologic subtypes, embryonal (lower risk) and alveolar (higher risk), this is now shifting to a molecular definition of histologic risk. For ongoing COG RMS protocols, molecular fusion status is being used instead of embryonal/alveolar histology. Patients with translocations involving *FOX01* (chromosome 13) are associated with higher-risk alveolar-histology natural histories; these fusions typically include *PAX3-FOX01* and *PAX7-FOX01* translocations, represented by t(2;13) and t(1;13), respectively. Data support fusion-negative alveolar-histology RMS to behave similarly to embryonal-histology RMS. Table 33.4 outlines general guidelines for RMS RT dosing.

Table 33.4 Rhabdomyosarcoma doses (all in doses of 1.8 Gy per daily fraction)

Group	Fusion status (histology)	Dose (Gy)
I (R0 resection)	Negative (embryonal)	0
I (R0 resection)	Positive (alveolar)	36.0
II, node-negative (R1 [microscopic residual])	Either	36.0 (to pre-chemotherapy disease)
II, node-positive (involved node, resected)	Either	41.4 (to pre-chemotherapy site and nodal region)
III, non-orbital and orbital if incomplete response after induction chemotherapy	Either	50.4*
III, orbital if complete response after induction chemotherapy	Either	45.0**
Special considerations		
III, per ongoing ARST1431 for tumors >5 cm in size pre-chemotherapy who do not achieve complete response to induction chemotherapy (protocol only)	Either	59.4*
III, per ongoing ARST1431 if radiographic or biopsy-proven complete response at week 9 after induction chemotherapy	Either	36.0***
Extremity RMS, N0 (clinical and pathological), s/p amputation	Either (including alveolar/ fusion-positive)	0

RMS rhabdomyosarcoma; *N0* node-negative.*Per ongoing ARST1431, volume reduction can be performed after 36.0 Gy, such that PTV1 receives 36.0 Gy, and PTV2 receives the cone-down dose (either an additional 14.4 Gy or 23.4 Gy, depending on primary tumor size as above [5 cm cut-off]).**Per ongoing ARST1431, group III disease with complete response (either radiographic or biopsy-proven) at week 9 restaging (following induction chemotherapy) can be treated to a single dose-level to 36.0 Gy to the PTV1, without further boost or cone-down. Therefore, orbital primaries with week 9 complete response on ARST1431 may be treated to 36.0 Gy; see ARST1431 protocol for full details.***Per ongoing ARST1431, radiographic complete response by CT/MRI as well as complete metabolic response by FDG-PET or biopsy-proven absence of residual disease at week 9 restaging after induction chemotherapy allows for single dose-level treatment to 36.0 Gy to PTV1; see ARST1431 protocol for full details

- Example cases of target volume delineation are highlighted in the cases below. Figures 33.1 and 33.2 highlight cases of EWS in the pelvis and thorax, respectively, highlighting two-volume target volume delineation conventional for the treatment of EWS with RT. Figures 33.3, 33.4, and 33.5 highlight cases of RMS;

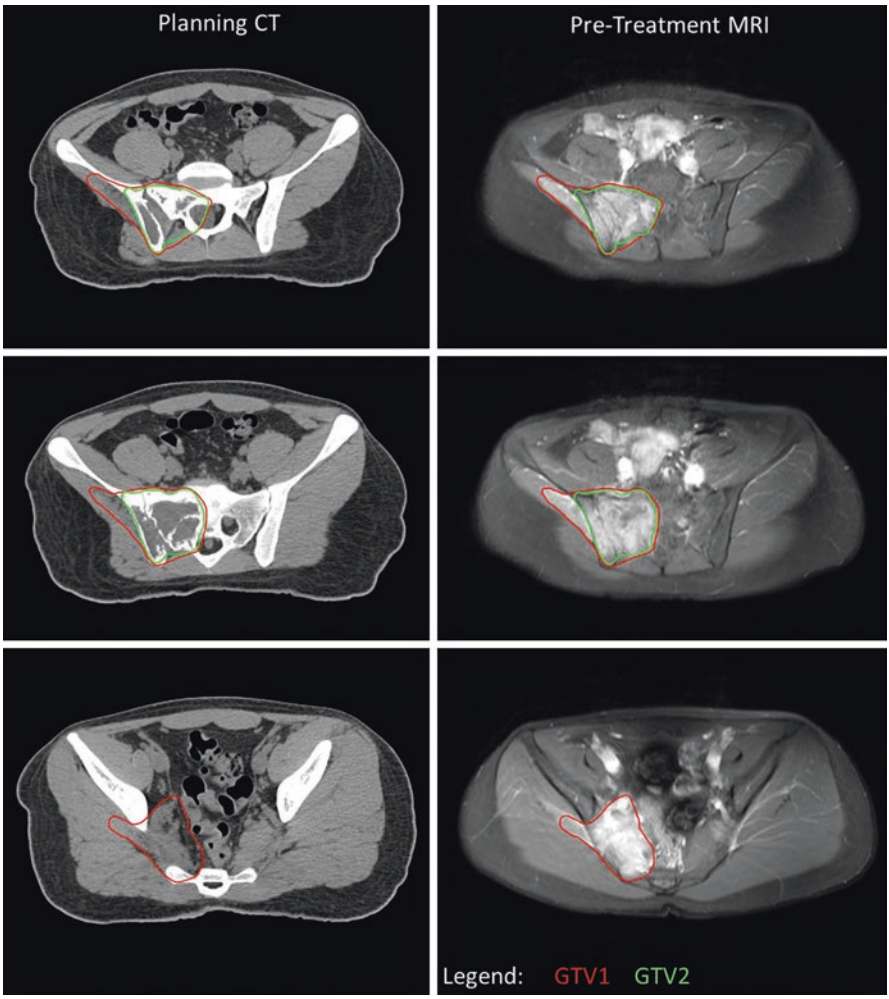

Fig. 33.1 A patient with Ewing sarcoma involving the pelvis. The post-induction-chemotherapy simulation CT is shown at left, and the pre-chemotherapy/pre-treatment MRI (T1 post-contrast sequence) is shown at right. Sample axial slices are shown at multiple axial levels. GTV1 (*red*) and GTV2 (*green*) are shown; CTVs are not shown but were contoured as GTV + 1.5 cm. Note that in the third row of images (inferior-most of the three axial slices shown), there was no residual disease at that level and therefore no GTV2 is seen. Similarly at this level, GTV1 extension into the pelvis was reduced to account for tumor "pushing" and interval response to induction chemotherapy. PTV1 was treated to 45.0 Gy, and PTV2 was treated to a further 10.8 Gy for a total dose of 55.8 Gy

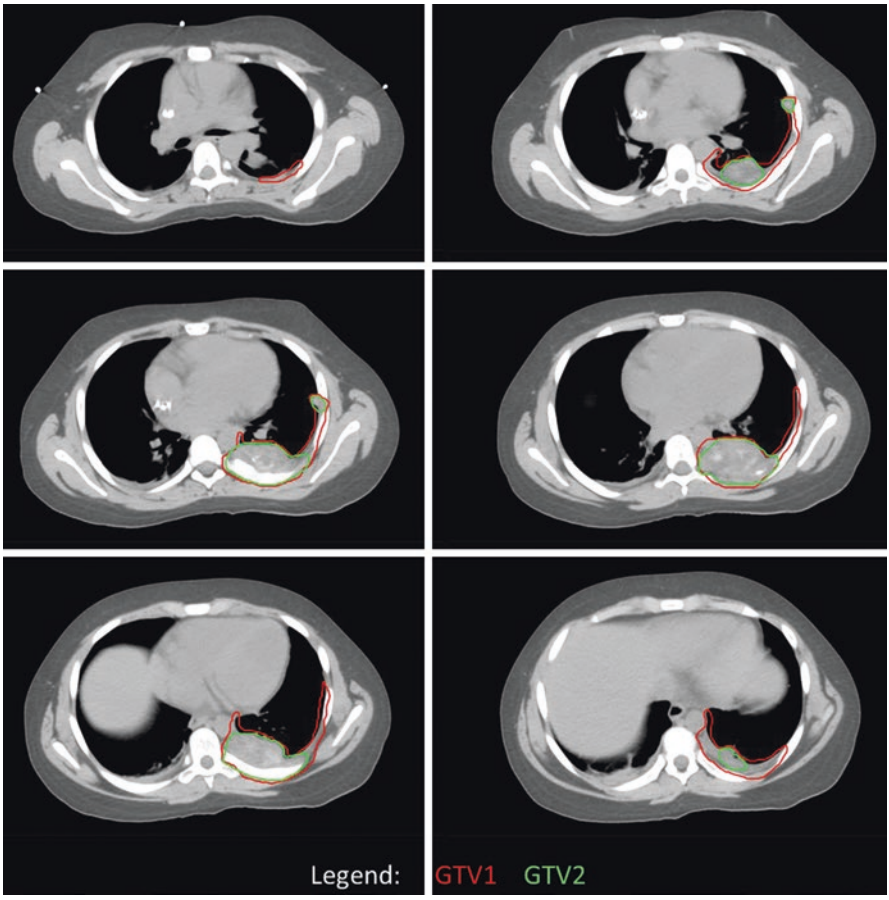

Fig. 33.2 A patient with left posterior chest wall Ewing sarcoma. Axial CT simulation slices are shown. Note that a four-dimensional CT simulation was performed to account for full respiratory excursion/motion of the target volumes. GTV1 (*red*) and GTV2 (*green*) are shown; CTVs are not shown but were contoured as GTV + 1 cm. Note as well that the initial primary tumor occupied the posterior half of the left hemithorax; however, the GTV1 (*red*) reflects adaption of the GTV contour to account for "pushing" of the tumor into space now occupied by normal lung tissue post-induction chemotherapy. The GTV1 (*red*) still covers all sites of contact/involvement of the original primary tumor in the left hemithorax. PTV1 was treated to 45.0 Gy, and PTV2 was treated to a further 10.8 Gy for a total dose of 55.8 Gy

Fig. 33.3 includes a case of parameningeal RMS with intracranial extension at diagnosis, often warranting early initiation of local therapy with a single high-dose volume. Figure 33.4 demonstrates principles and considerations of target volume delineation in the context of orbital RMS, and Fig. 33.5 highlights a case of extremity RMS with axillary (regional) adenopathy.

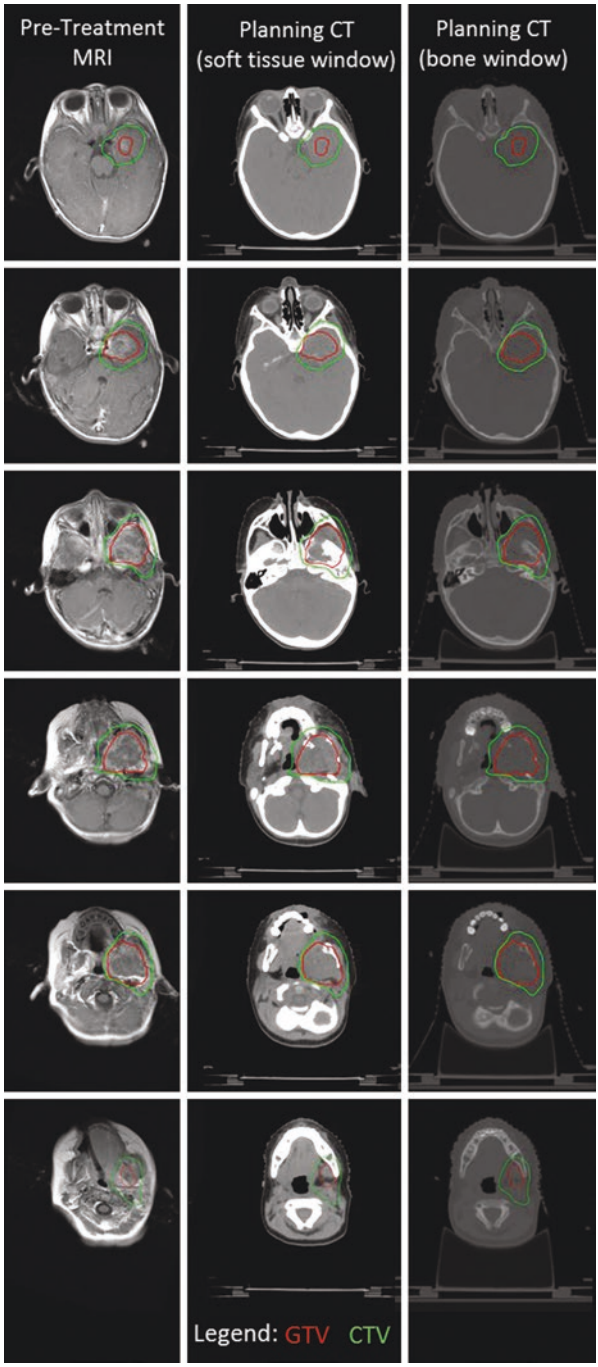

Fig. 33.3 A patient with infratemporal fossa embryonal (fusion-negative) rhabdomyosarcoma, with intracranial extension and evidence of bone erosion. Axial slices from pre-treatment MRI (T1 post-contrast sequence) and CT simulation (soft tissue and bone windows) are shown. GTV (*red*) and CTV (*green*) are shown. CTV reflects a 1 cm expansion from the GTV. Note that intracranial extension (observed in the top two rows of axial slices). Bony erosion and destruction of the left mandible and left pterygoid plate are noted as well. Single dose-level used as patient was treated concurrent with initiation of chemotherapy due to intracranial extension. With a thermoplastic mask and daily kV image guidance, a 3 mm PTV margin was utilized. PTV was treated to 50.4 Gy

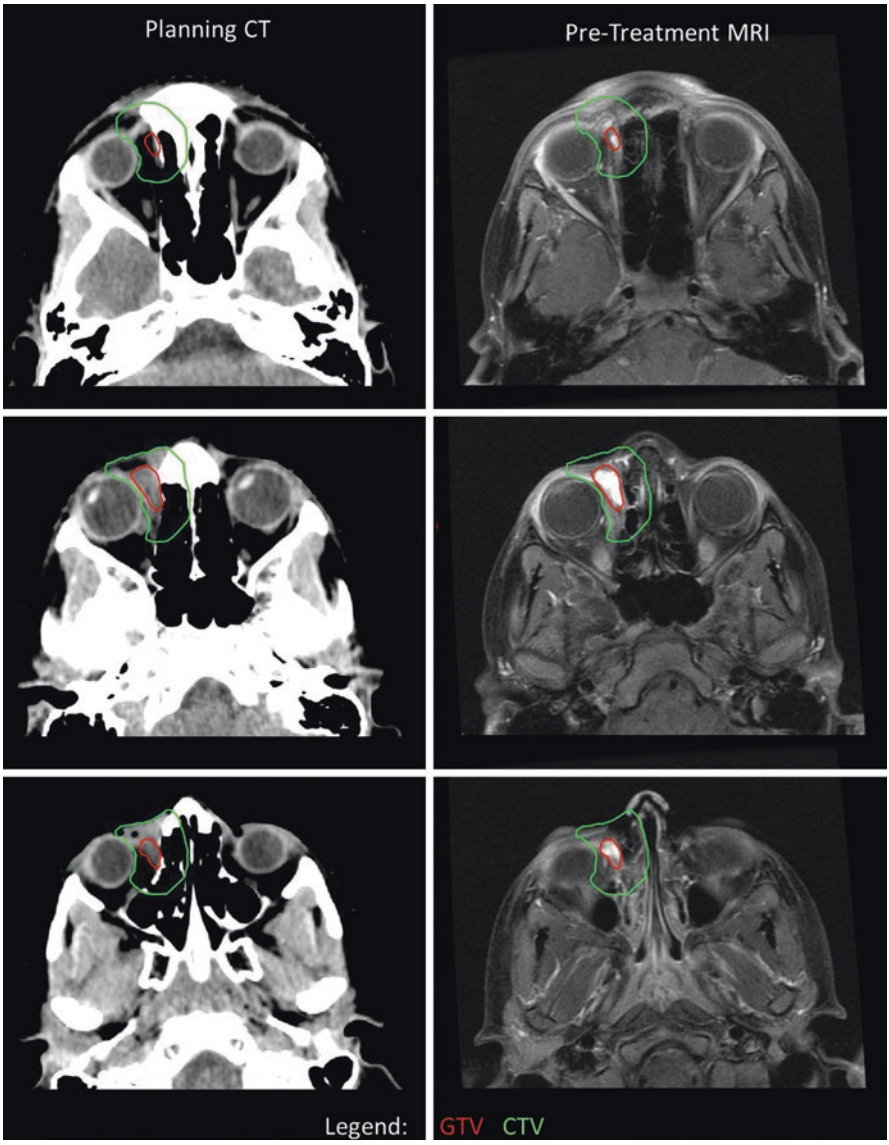

Fig. 33.4 A patient with orbital embryonal (fusion-negative) rhabdomyosarcoma, with incomplete response to induction chemotherapy. Axial slices from CT simulation and pre-treatment MRI (T1 post-contrast sequence) are shown. GTV (*red*) and CTV (*green*) are shown. CTV reflects a 1 cm expansion from the GTV; CTV extends beyond the bony orbit in certain slices due to potential concern for bony erosion on staging CT (generally orbital RMS CTVs should not extend outside the bony orbit absent bone erosion). Note that a rightward eye deviation is used to optimize sparing of both lens and optic nerve. Single dose-level used as GTV minimally responded to induction chemotherapy; had primary tumor responded to induction chemotherapy, two dose-levels to 36 Gy and cone-down to 50.4 Gy would have been utilized. Patient was treated with a thermoplastic mask and daily kV image guidance, and a 3 mm PTV margin was utilized. PTV was treated to 50.4 Gy

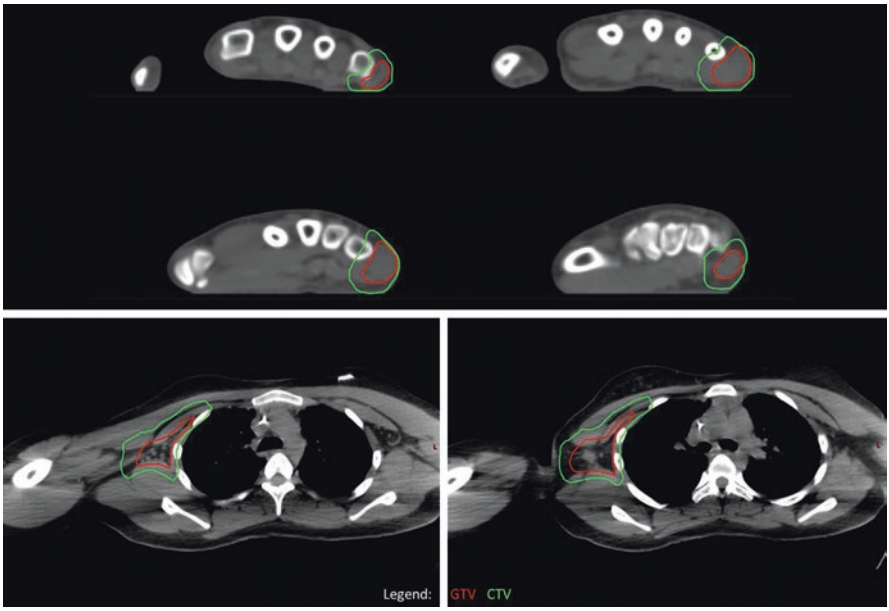

Fig. 33.5 A patient with right upper extremity alveolar (fusion-positive) rhabdomyosarcoma, with axillary nodal metastases. Axial slices from CT simulation in top panel show treatment to right hypothenar eminence primary site. Axial slices from CT simulation in bottom panels show treatment to the right axillary nodal basins where extensive FDG-avid adenopathy was identified on PET imaging; the complete nodal basin was contoured as the GTV (*red*) to ensure complete coverage of the nodal basin given multiple axillary nodes noted on staging PET imaging. For both the primary tumor site in the right hand and the right axillary nodal metastases, GTV (*red*) and CTV (*green*) are shown. Notably, the patient's extensive axillary adenopathy responded partially to induction chemotherapy, but the primary tumor site minimally responded to induction chemotherapy. The primary tumor site was therefore treated as a single dose-level to 50.4 Gy; had the primary site responded, two dose-levels to 36 Gy followed by a cone-down to 50.4 Gy would have been utilized. For the right axillary nodal disease, while the diffuse adenopathy in the right axillary basin achieved partial response to induction chemotherapy, the diffuse involvement of the basin resulted in the treating radiation oncologist to elect to cover the entire right axillary basin as a single dose-level as shown to 50.4 Gy. It is further noteworthy that no sites of disease in transit between the right hand and the right axillary were identified, and therefore no other parts of the right arm were treated in transit between the right hand and the right axilla

33.4 Simulation, Immobilization, Treatment Devices, and Daily Localization

- Immobilization during simulation is highly variable and dependent on anatomic sites to be treated. For head-and-neck lesions, immobilization of head and shoulder may be accomplished with thermoplastic mask. For thoracic lesions (including those involving thoracic vertebrae), arms are generally positioned up, with VacLok or similar cradle used in conjunction with wingboard. For pelvic lesions,

immobilization of pelvis and upper legs can be accomplished with VacLok or similar cradle. Extremity lesions may be simulated with custom VacLok cradles and other devices; extremity lesions may warrant feet-first positioning and non-supine positioning in select cases.

- If concern exists regarding respiratory motion of target volumes, four-dimensional simulation can be considered to assess the extent of target volume excursion with respiration.
- For pelvic lesions, particularly genitourinary lesions, bladder filling may also be a consideration; for prostate and bladder lesions, consistent bladder filling may be desirable and may be accomplished with daily ultrasound assessment of bladder filling. Depending on the child's age and ability to successfully fill (or empty) bladder, simulation with both full and empty bladder may provide a full extent of target volume excursion irrespective of bladder filling.
- For male patients with pelvic and proximal leg sarcomas, frog-leg positioning may be utilized if a testicular shield will be employed.
- Type and frequency of image guidance directly inform the CTV to PTV expansion. Many institutions utilize daily kV imaging for image guidance and consequently utilize 3–5 mm PTV expansions. Smaller PTVs can be considered depending on the type and frequency of image guidance, as well as proximity to critical structures (a common scenario among head-and-neck primary patients, where structures such as optic nerves, brainstem, and other structures are proximate to the target volumes).
- One additional consideration is that in addition to CT-based simulation, MR-based simulation may be used in conjunction with CT simulation to provide MRI data in the treatment position.
- Finally, simulation and radiotherapy treatments may require daily sedation/anesthesia for younger patients (typically patients younger than 8 years old).

33.5 Plan Assessment

- While there is variability across clinical scenarios regarding plan assessment and acceptability, generally at least 95% of the PTV (or PTVs) should be covered by the prescription dose, with minimization of hotspots greater than 110% (at most 10% of the PTV getting 110% or greater). Conventional dose constraints per COG protocols for EWS and RMS are shown in Table 33.5; however, as pediatric patients carry profound risks of long-term toxicities from radiotherapy, efforts to maximize organ-at-risk (OAR) sparing should be made. To that end, while not discussed in the context of this chapter, modalities such as proton beam therapy may be considered for pediatric patients. Special considerations for proton beam therapy techniques, range uncertainties, beam arrangements, and more are beyond the scope of this chapter and should be discussed with expert physicists as well as physicians experienced with the use of proton beam therapy for pediatric malignancies.

Table 33.5 Conventional normal tissue constraints

Organ/tissue	Volume (%)	Dose (Gy)
Brainstem	Point max	54
Optic chiasm/optic nerve	Point max	54
Spinal cord	Point max	45
Lens	Point max	6
Cochlea	Point max	35
Heart	100	30
Lungs (bilateral)	20	20
	100	15
Liver	100	23.4
	50	30
Kidney (bilateral)	50	24
	100	14.4
Small bowel	50	45
Bladder	100	45
Rectum	100	45

These represent general normal tissue constraints, including from COG protocols for EWS and RMS, as well as conventional institutional dose constraints; as per the text, given the long-term toxicities associated with pediatric RT, efforts should be made to optimize OAR sparing beyond these constraints. Certain clinical contexts may warrant exceeding these constraints, while others may warrant more rigorous sparing of the OAR than listed here

- In addition to considerations regarding the use of photon-based techniques (such as intensity-modulated radiotherapy) versus proton-based techniques, plan assessment should inform how patients and their parents are counseled regarding acute and late effects of each pediatric radiotherapy plan. Considerations regarding secondary malignancies should be made (particularly relevant for EWS, which carries a higher-than-expected rate of secondary malignancies relative to most other pediatric cancers), as well as site-specific risks including: for head-and-neck sarcoma patients—dentofacial abnormalities, xerostomia, xerophthalmia, decreased visual acuity, cataractogenesis, facial asymmetry, endocrinopathies, and neurocognitive dysfunction; for extremity patients—epiphyseal closure and decreased bone growth/skeletal asymmetry; for patients receiving vertebral RT—decreased height as well as risk of kyphosis, lordosis, and scoliosis (minimized with coverage of the complete vertebral body for pre-pubescent children); for patients receiving thoracic RT—pneumonitis, pulmonary fibrosis, cardiac radiotoxicity; for patients receiving pelvic RT—cystitis, urinary incontinence or stricture, and infertility (which should also be considered depending on specific chemotherapeutics utilized, in particular cyclophosphamide).

Further Reading

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Pediatric Brain Tumors

34

Benjamin T. Cooper, Ethan B. Ludmir,
and Arnold C. Paulino

Contents

34.1 Medulloblastoma

34.1.1 General Principles of Target Delineation and Radiation Treatment Planning

- Multiple different radiation delivery techniques can be used to successfully treat medulloblastoma including 3D conformal therapy, intensity modulated radiation therapy (IMRT), volumetric arc therapy (VMAT), and proton therapy. Regardless of treatment platform, careful volumetric target delineation is required.

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N. Y. Lee et al. (eds.), *Target Volume Delineation and Field Setup*, Practical Guides in Radiation Oncology, https://doi.org/10.1007/978-3-030-99590-4_34

- Comprehensive staging is critical in determining treatment dose and volume. All patients must undergo a comprehensive history and physical exam, a thin-cut (1–3 mm slice thickness) contrast-enhanced MRI of the brain both pre- and post-operatively, MRI of the spine with contrast, and CSF sampling to rule of dissemination. Patients with positive CSF cytology, gross metastasis, or ≥ 1.5 cm^2 of residual disease in the tumor bed on postoperative MRI are classified as having high risk disease while those with no tumor spread (M0 disease) and <1.5 cm^2 tumor bed residual are considered standard risk.
- CT simulation, with or without anesthesia depending on patient cooperativity, should be done in a reproducible manner. This often consists of a full body Vac-Lok or alpha cradle immobilization system in addition to a standard brain mask with multiple markings for both triangulation and longitudinal spinal alignment. Many CT software packages allow for variable CT slice thickness by region and this can be helpful to allow thinner slices through the brain to allow detailed contouring and thicker slices throughout the spine to limit the amount of contouring throughout the remainder of the body. The scan range should include all immobilization devices, include the top of the head cranially, and capture the gonads caudally.
- Careful discussion should take place between the radiation oncologist and the anesthesiologist regarding anesthesia needs when making the mask. For example, if a patient is intubated to start treatment but is anticipated to be treated with a laryngeal mask airway (LMA) or even nasal cannula later in the treatment an oral airway can be added to ensure reproducible chin position and avoid the need to resimulate due to a loose mask.
- Careful delineation of target and organ as risk (OAR) volumes should be done on every slice of the planning CT as seen in Figs. 34.1 and 34.2. The recommended target volumes for the craniospinal axis, tumor bed involved field boost, and whole posterior fossa boost are included in Tables 34.1 and 34.2.
- When using proton therapy to treat a growing child, some have recommended treating the entire vertebral body to a dose up to 30 Gy when 36 Gy CSI is given [1]. Many radiation oncologists include the bone in the PTV with no further expansion to avoid intentionally giving dose to the esophagus and lungs (Fig. 34.3). However, there is limited [2] and early data [3] that intentionally covering the whole vertebral body may not be necessary and is the subject of an ongoing clinical trials (ClinicalTrials.gov Identifier: NCT03281889).
- Care should be taken to identify the bottom of the thecal sac that is often, but not always, at the S2 vertebral level. Treating more inferiorly than necessary may increase exit dose to the gonads when using a single posterior photon field. This is not a concern with proton treatment.
- There were increased failures on the 18 Gy craniospinal dose arm of Children's Oncology Group (COG) ACNS0331 and 23.4 Gy craniospinal irradiation remains the standard of care for standard risk disease. This trial demonstrated the equivalence of an involved field boost to whole posterior fossa irradiation in patients with standard risk disease. Thus our recommendation is 23.4 Gy to the entire craniospinal axis followed by an involved field boost to 54 Gy for standard risk disease.

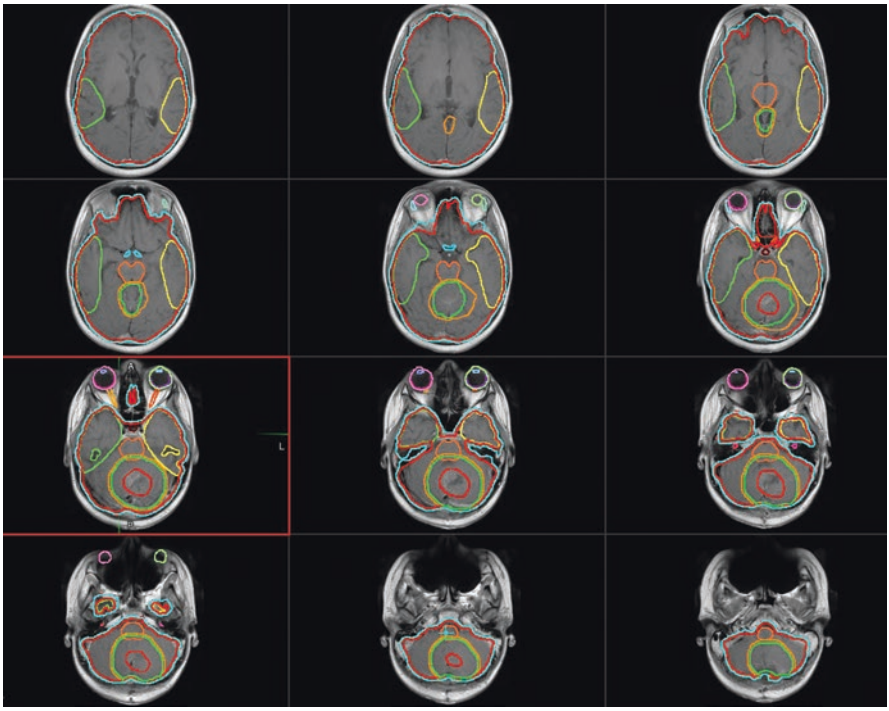

Fig. 34.1 A patient with standard-risk medulloblastoma. This patient was simulated using a 2.5 mm CT slice thickness. Note the coverage of the cribriform plate as part of the target volume (the *cyan line* is the PTV CSI, while the inner *red line* is the CTV_{CSI}). Also note the $PTV_{tbboost}$ (*orange line*), $CTV_{tbboost}$ (*green line*), and GTV (*red*) contours

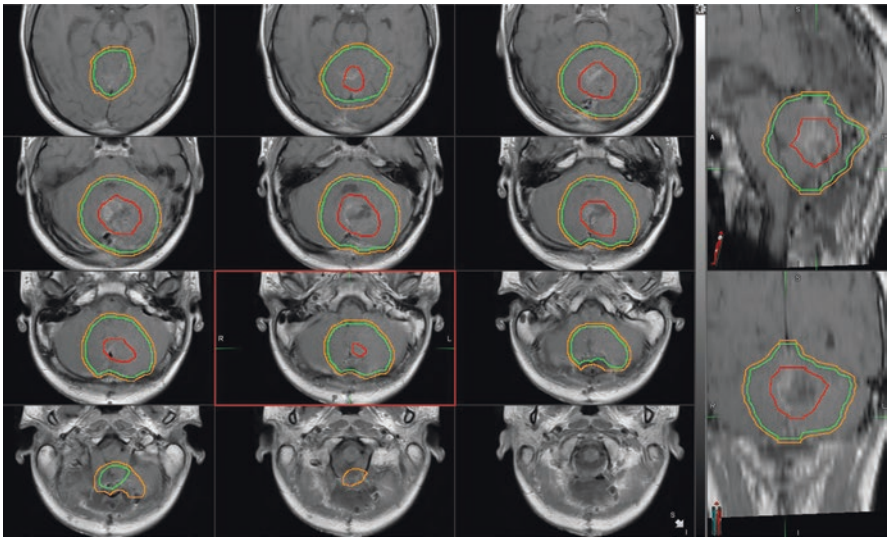

Fig. 34.2 MRI slices fused to CT simulation images from the same patient who had a gross total resection of a medulloblastoma. This is an example of a tumor bed boost. The GTV (resection cavity) is shown in *red*, $CTV_{tbboost}$ in *green*, and $PTV_{tbboost}$ in *orange*. Notice the CTV is cropped at the tentorium

Table 34.1 Recommended target volumes for the craniospinal (CSI) portion of treatment

Target volumes	Definition and description
GTV	Tumor bed including all residual gross disease and the walls of the resection cavity as noted on MRI and areas of concern outlined by the neurosurgeon. Surgical defects not initially involved with tumor and caused by the procedure (the route to and from the tumor bed) are not considered part of this cavity. Any areas of gross disease in the spine should be outlined as well for consideration of a boost
CTV_{CSI}	The entire volume contained by the dura matter and in contact with the cerebrospinal fluid is the CTV including any postoperative pseudomeningocele. The CTV is the entire vertebral body and canal (Fig. 34.3) in a growing child and the entire canal in a fully grown individual
PTV_{CSI}	CTV_{CSI} + 3–10 mm depending on comfort level of daily patient positioning and institutional experience

Table 34.2 Recommended target volumes for the tumor bed boost within the posterior fossa

Target volumes	Definition and description
GTV	Tumor bed including all residual gross disease and the walls of the resection cavity as noted on MRI and areas of concern outlined by the neurosurgeon. Surgical defects not initially involved with tumor and caused by the procedure (the route to and from the tumor bed) are not considered part of this cavity. Any areas of gross disease in the spine should be outlined as well for consideration of a boost
$CTV_{tbboost}$	$CTV_{tbboost}$ = GTV + a 1–1.5 cm anatomically confined margin. This should exclude barriers to spread such as the tentorium and limit the brainstem to a 2–3 mm margin in areas of tumor contact
$PTV_{tbboost}$	$CTV_{tbboost}$ + 3–5 mm depending on daily imaging and institutional experience

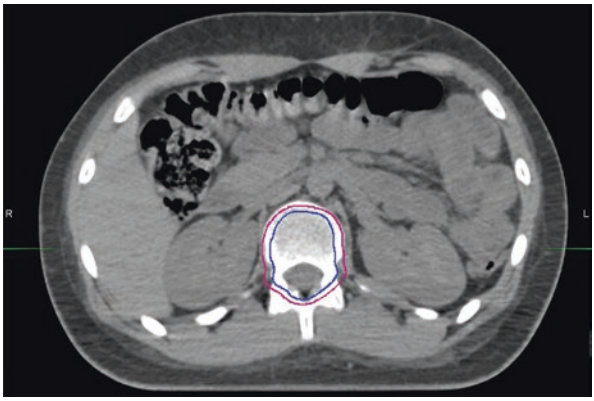

Fig. 34.3 Example of CTV_{spine} displayed on bone windows of the spine in a growing child. The CTV could cut across the vertebral body in a fully grown child or an adult

- We recommend a margin of 1–1.5 cm from the tumor bed delineated on the postoperative MRI and limited by anatomic boundaries such as the skull and tentorium cerebelli. Brainstem invasion can occur and we recommend including 2–3 mm of the brainstem in the CTV for tumors contacting the brainstem. However, if there was no contact on preoperative imaging or at surgery the brainstem can be excluded from the CTV. A PTV margin of 3–5 mm is recommended based on institutional setup data and frequency of imaging. The authors use 3 mm with daily image guided radiotherapy.
- Patients with M2 disease (intracranial subarachnoid disease) may receive boosts up to a total dose of 54 Gy to areas of supratentorial or posterior fossa metastatic disease.
- Patients with M3 disease (spinal deposits of disease) are subdivided into those with diffuse disease and those with focal disease. Diffuse spinal disease is defined as radiographically visible multiple sites of disease in each of at least 3 out of 4 spinal regions (i.e., cervical, thoracic, lumbar, or sacral).
- On the most recent COG high risk medulloblastoma protocol (ACNS 0332) diffuse spinal disease was prescribed 39.6 Gy, focal disease above the spinal cord 45 Gy, and focal disease below the spinal cord 50.4 Gy.
- For high risk disease or patients that will not be getting chemotherapy, such as some adult patients not fit to get chemotherapy, we recommend 36 Gy to the craniospinal axis with a boost to 54 Gy. There have been many retrospective series examining the use of tumor bed boost in high risk disease without excess non-tumor bed posterior fossa failures although there are no randomized trials.
- If the entire posterior fossa is to receive the boost, the CTV should include all structures below the tentorium cerebelli with the anterior border including the posterior clinoids (Table 34.3). The entire brainstem is included in the posterior fossa CTV. This is demonstrated at https://www.qarc.org/cog/ACNS0331Atlas.pdf as well as in Fig. 34.4.

Table 34.3 Recommended target volumes for the entire posterior fossa

Target volumes	Definition and description
GTV	Tumor bed including all residual gross disease and the walls of the resection cavity as noted on MRI and areas of concern outlined by the neurosurgeon. Surgical defects not initially involved with tumor and caused by the procedure (the route to and from the tumor bed) are not considered part of this cavity. Any areas of gross disease in the spine should be outlined as well for consideration of a boost
CTV_{pf}	CTV_{pf} should include the entire posterior fossa. The entire brainstem is included in this volume and the borders are the base of skull anteriorly, the tentorium superiorly, and the foramen magnum inferiorly. Posteriorly and laterally the bone of the skull constrains this volume as seen in Fig. 34.4
PTV_{pf}	CTV_{pf} + 3–5 mm depending on daily imaging and institutional experience

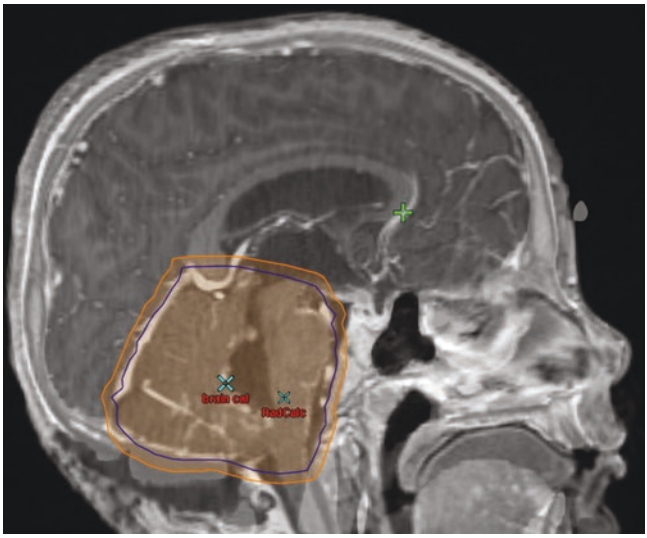

Fig. 34.4 A patient with high risk disease involving dissemination in the cerebellar folia requiring a whole posterior fossa boost. The CTV_{pf} in blue encompasses the entire posterior fossa with the PTV_{pf} in orange

34.2 Ependymoma

34.2.1 General Principles of Target Delineation and Radiation Treatment Planning

- Similar to medulloblastoma, CT-based volumetric target delineation and planning are required regardless of radiation therapy technique (3DCRT, IMRT, or proton therapy).
- All patients should undergo high quality (1–3 mm slice thickness) pre- and postoperative MRI of the brain and total spine in addition to a detailed history and physical.
- Unless medically contraindicated, MRI of the spine and CSF cytology should be obtained to rule out tumor dissemination though intracranial ependymoma is less likely (<10%) to disseminate at diagnosis when compared to medulloblastoma.
- Given that extent of resection is the most important prognostic factor for patients with intracranial ependymoma, re-resection should be entertained if possible with reasonable anticipated morbidity if residual disease is identified on postoperative MRI.
- CT simulation without contrast should be performed with 1–3 mm slice thickness to allow proper fusion, OAR delineation, and target delineation. The scan borders should include all immobilization devices and the entire cervical cord.
- As with medulloblastoma, many of these children will require daily anesthesia and careful planning with the anesthesiology will allow construction of a mask that can reproducibly accommodate the necessary respiratory assist devices.

- The GTV is the postoperative resection cavity with special attention to the foramen of Luschka and Magendie which are often involved in patients with intracranial ependymoma (Fig. 34.5). Speaking with the surgeon can be helpful to discuss any operative findings that are not readily apparent on MRI.
- GTV to CTV margins have decreased over the past decade with the most recent COG trial ACNS 0831 treating patients with a CTV = GTV + 0.5 cm to a total dose of 54 Gy in 30 fractions (Table 34.4).
- In order to minimize brainstem toxicity, the expansion of the CTV into the brainstem was limited to 3 mm. Additionally, a conedown was prescribed in this trial for children older than 18 months to a total dose of 59.4 Gy that excluded the entire brainstem, optic chiasm, and cervical cord from the boost volume (Fig. 34.5).

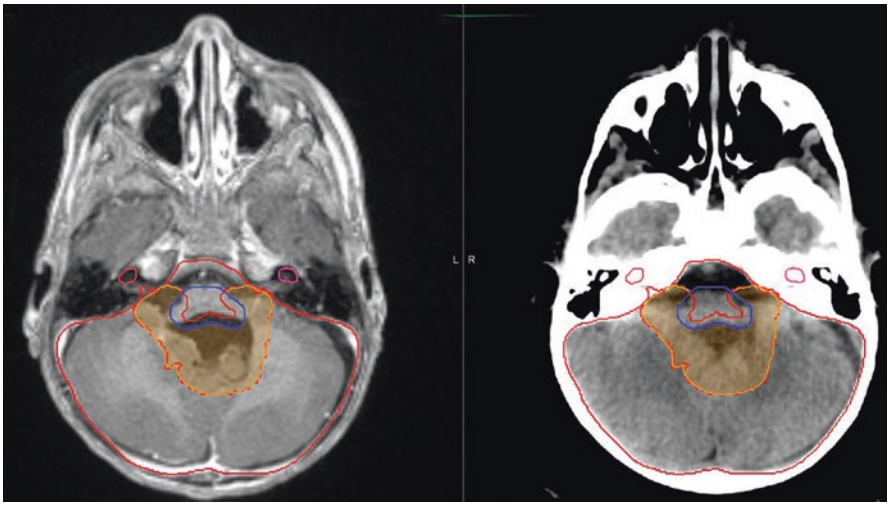

Fig. 34.5 This is a child with ependymoma and bilateral foramen of Luschka involvement showing the CTV_{54} (red) extending 3 mm into the brainstem (blue) but $CTV_{59.4}$ (orange) completely excluding the brainstem. $CTV_{59.4}$ would also exclude the cervical spinal cord and the optic chiasm

Table 34.4 Recommended target volumes for infratentorial ependymoma

Target volumes	Definition and description
GTV	Tumor bed including all residual gross disease and the walls of the resection cavity as noted on MRI and areas of concern outlined by the neurosurgeon. Special attention should be paid to the foramina of Magendie and Luschka (Fig. 34.7)
CTV_{54} and $CTV_{59.4}$	CTV_{54} = GTV + 5–10 mm constrained by bone and tentorium. The CTV_{54} should not extend into the brainstem more than 3 mm. $CTV_{59.4}$ as defined in ACSN 0831 was GTV + 5 mm excluding the entire brainstem, optic chiasm, and cervical cord
PTV_x	$PTV_{54,59.4}$ = $CTV_{54,59.4}$ + 3–5 mm depending on daily imaging and institutional experience. However, it is understood that PTV will be under-dosed in some locations to respect cervical spinal cord and optic chiasm tolerance

- It is important to note that many pediatric radiation oncologists still advocate for larger margins (CTV = GTV + 1 cm) and a total dose of 54 Gy when treating patients not enrolled on ACNS 0831 and this is considered acceptable.
- Given that extent of resection is the most important prognostic factor for patients with intracranial ependymoma, re-resection should be entertained if possible with reasonable anticipated morbidity if residual disease is identified on postoperative MRI.
- When treating to 59.4 Gy a two-phase treatment approach is suggested where a conedown at 54 Gy is employed to spare additional dose to the brainstem, optic chiasm, and cervical spinal cord. Essentially, regardless of inferior tumor extent, the PTV_{54} should not extend below the foramen magnum (Fig. 34.6).
- The most recently published COG Ependymoma Protocol, ACNS 0831, specified a goal cervical spinal cord D10% $\leq$ 57 Gy. They suggest during treatment of $PTV_{59.4}$ the entire spinal cord volume should receive no more than 70% or 126 cGy per fraction during each of the last three treatments to achieve the recommended maximum dose constraint.

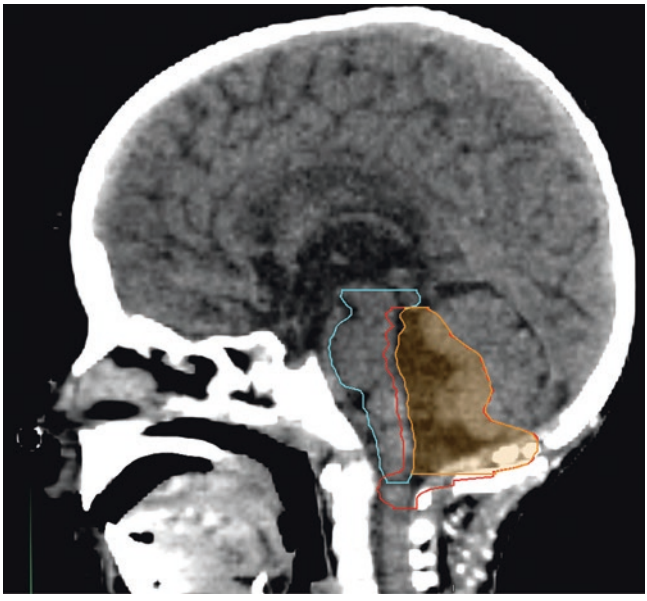

Fig. 34.6 Sagittal CT simulation scan demonstrating the $CTV_{59.4}$ cropped to avoid the brainstem (orange) and not extend past the foramen magnum. CTV_{54} (red) needed to extend into the brainstem and past the foramen magnum in this case due to tumor location

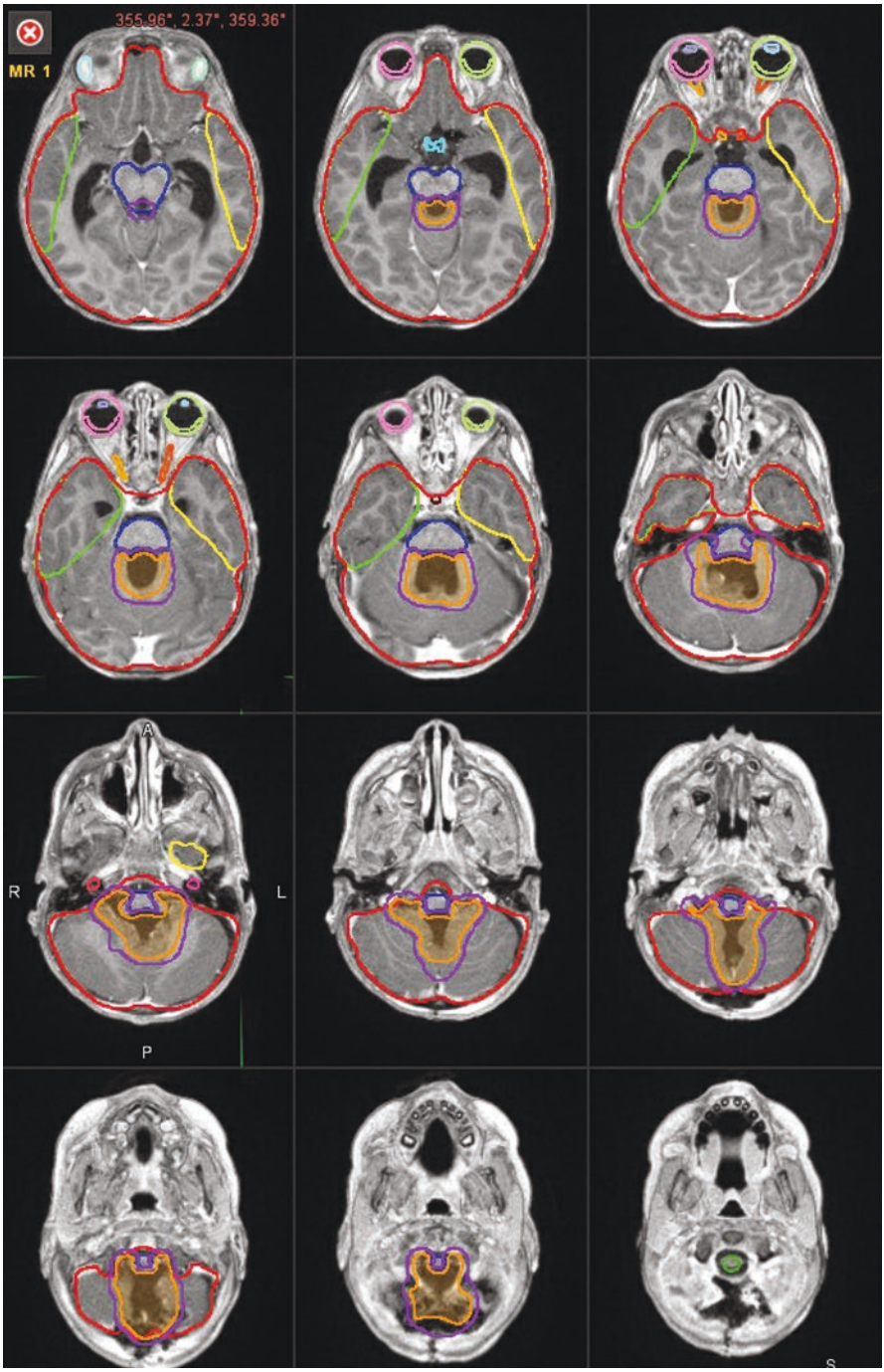

Fig. 34.7 Axial images for the same patient showing $CTV_{59.4}$ in orange expanded 3 mm per institutional standard to form $PTV_{59.4}$ in purple. The brainstem (blue), cochlea (red and magenta), cervical cord (green), temporal lobes (yellow and green), and the optic chiasm (light blue) are also outlined as organs at risk

34.3 Pure Germinoma

34.3.1 General Principles of Target Delineation and Radiation Treatment Planning

- CT-based volumetric target delineation and planning are required regardless of radiation therapy technique (3DCRT, IMRT, or proton therapy).
- All patients should undergo high quality (1–3 mm slice thickness) pre- and post-operative MRI of the brain and total spine in addition to a detailed history and physical.
- Unless medically contraindicated MRI of the spine and CSF cytology should be obtained to rule out tumor dissemination though germinoma is less likely to disseminate to the spinal axis at diagnosis when compared to medulloblastoma.
- Additionally, serum and CSF beta-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) levels are done to rule out a non-germinomatous germ cell tumor (NGGCT) component such as choriocarcinoma or endodermal sinus tumor.
- Off protocol in North America, NGGCT is currently treated with CSI though investigation into a more limited treatment field is ongoing [4].
- Patients with any elevation of AFP are treated as NGGCT.
- On ACNS 1123, the most recent COG trial for localized germ cell tumors, only patients with serum or CSF β-hCG $\leq$ 100 mIU/mL were treated as germinoma with patients with β-hCG > 100 treated as NGGCT.
- Construction of a face mask in the supine treatment position with standard brain triangulation marks is critical for setup reproducibility. If CSI is required for disseminated disease, the immobilization will be similar to patients with medulloblastoma above.
- Patients with involvement of only the suprasellar and pineal regions (bifocal germinoma) are treated as localized disease with the standard treatment approach of whole ventricular irradiation followed by an involved field boost to initial gross disease.
- The target volume includes the prechemotherapy tumor volume, any residual disease and the ventricles. It is critical to outline the prechemotherapy disease at initial treatment planning because this boost volume will often extend outside of the normal ventricular volume.
- The boost CTV is prechemotherapy GTV + 1–1.5 cm.
- Inclusion of the prepontine cistern is optional but should be considered for patients that have undergone a third ventriculostomy and for patients with large suprasellar tumors (Figs. 34.8 and 34.9).
- A whole ventricular contouring atlas was generated for ACNS 1123 and can be found at https://www.qarc.org/cog/ACNS1123_Atlas.pdf.
- If radiation is being used as the sole treatment modality the whole ventricular volume is treated to 21–24 Gy with a boost to bring the total dose to the prechemotherapy volume to 45 Gy. Given the good prognosis of this disease and the

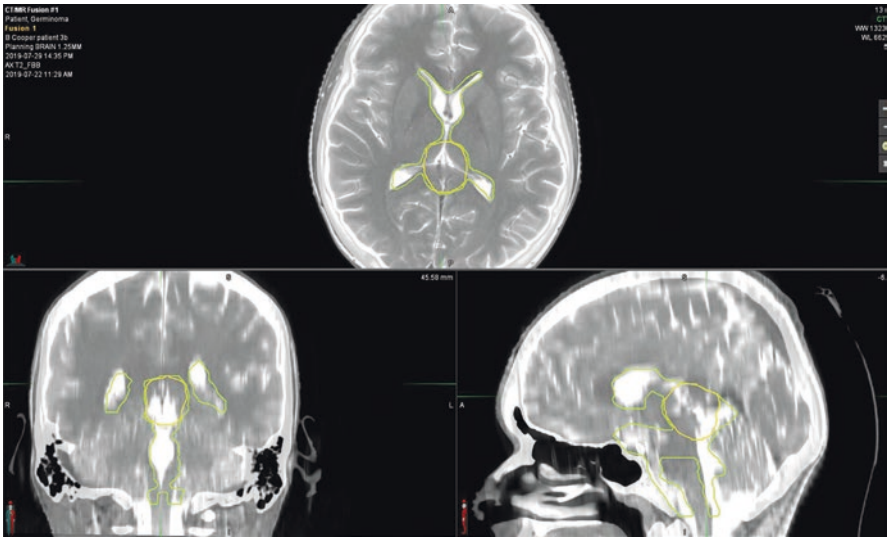

Fig. 34.8 T2 weighted MRI of patient with a germinoma illustrating the whole ventricle volume (lime green) and the boost volume (yellow). This patient underwent a third ventriculostomy so the prepontine cistern was electively covered

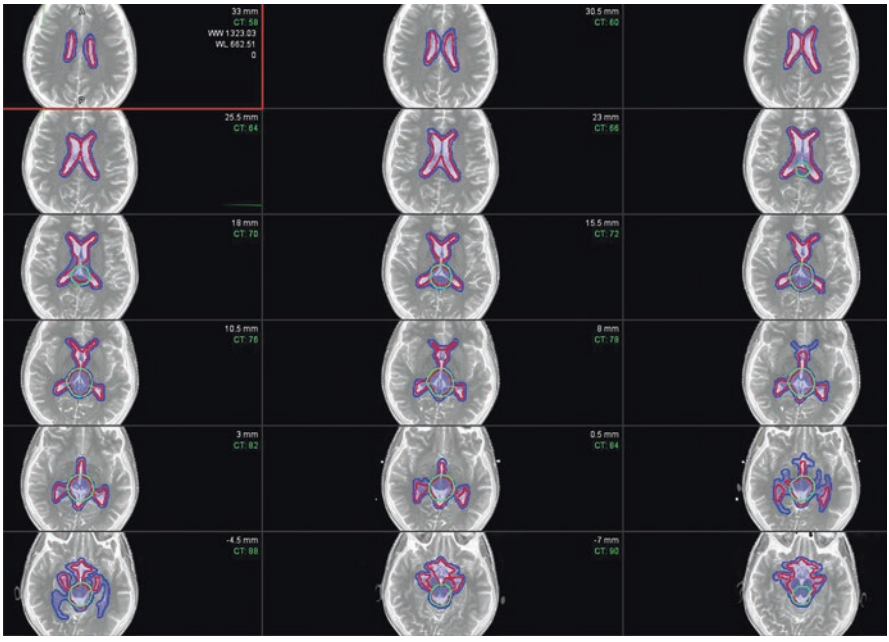

Fig. 34.9 Axial images showing the whole ventricular CTV (red), whole ventricular PTV (blue), and the boost PTV (green). It is important to contour the prechemotherapy GTV prior to the whole ventricular volume as the boost volume often extends outside of the whole ventricular volume and if the boost and initial plan are not planned upfront the boost volume will not receive sufficient dose

desire for long term neurocognitive toxicity a fraction size of 1.5 Gy is often used though 1.8 Gy a fraction is not unreasonable.

- When neoadjuvant chemotherapy is used, and the primary has a complete response, the dose to the whole ventricle is 21 Gy with a boost of 9 to 15 Gy to bring the total dose to the primary tumor to 30 to 36 Gy. Dose reduction of the whole ventricular volume to 18 Gy was studied in ACNS 1123. While there were no ventricular failures in the 74 evaluable patients treated with 18 Gy to the whole ventricular volume, the study failed to demonstrated noninferiority of this reduced dose compared to the design threshold of 95% 3-year progression free survival (https://doi.org/10.1093/neuonc/noab270).
- Patients with a partial response or progressive disease will require a boost such that the total dose to the primary tumor is 36–45 Gy.

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