Chapter 18
Intensity-Modulated Radiation Therapy for Head and Neck Cancer

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Abstract Intensity-modulated radiation therapy (IMRT) has revolutionized the treatment of head and neck cancer. A general overview of IMRT in the treatment of head and neck cancer is provided, focusing on guidelines for target determination and delineation for the different subsites within the head and neck. General facts, general management, target delineation, and IMRT results of specific anatomic subsites are outlined, including the nasopharynx, the oropharynx, the hypopharynx, the larynx, the oral cavity, and the thyroid are discussed, along with cancer of unknown primary.

Keywords Intensity-modulated radiation therapy • Head and neck cancer • Target determination • Target delineation • Subsites

Introduction

Intensity-modulated radiation therapy (IMRT) has revolutionized the treatment of head and neck cancer. Compared with conventional opposed lateral fields that were used to treat these tumors, IMRT has provided comparable, if not better, local control with significantly improved long-term toxicities associated with high doses of radiation therapy. The ability to tightly conform to irregularly shaped tumors while limiting the dose delivered to the surrounding critical structures is the hallmark of IMRT. This advantage is especially seen when tumors are located near critical structures, i.e., the brainstem and optic structures, where there are great limitations in delivering effective therapeutic doses of radiation using conventional radiotherapy techniques. In addition, because there is minimal organ motion in the head and neck, with the use of proper immobilization the planned dose distribution can be delivered with great assurance. The theoretical dosimetric advantage of IMRT has translated clinically into improvement in patient quality of life. Several Phase III trials have now demonstrated the beneficial effects of IMRT when compared with conventional radiotherapy in terms of minimizing late toxicities, and in particular xerostomia. The purpose of this chapter is to provide a general overview of IMRT in the treatment of head and neck cancer, focusing on guidelines for target determination and delineation for the different subsites within the head and neck. Clinical updates will also be presented.

Target Determination and Delineation for Head and Neck Cancer

The complexity of the head and neck anatomy requires the treating radiation oncologist to carefully and accurately delineate the target volume prior to initiating IMRT. One must have an understanding of the relationship of the various structures to one another and the patterns of spread from the primary tumor site as well as the nodal drainage. To date, no consensus delineation guidelines other than the N0 nonsurgically violated neck have been published. A guideline regarding the different neck lymph node levels can be found in Table 18.1 [1]. It is important not to use the N0 guideline for node-positive or postoperative cases in which the nodal planes are not as well defined either due to the presence of nodes or surgical violation of tissue planes. A proposal, though not a consensus guideline, for the node-positive neck has been published by Gregoire et al. [2]. The probability of nodal drainage to a specific ipsilateral lymph node level is directly related to the location and stage of the primary tumor. Table 18.2 specifies the likelihood of pathologic lymph node involvement in both the clinically positive and negative neck, by anatomic subsites.

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Table 18.1 Lymph node levels

Robbins classification level	Terminology	Definition
Ia	Submental	Contains submental/submandibular triangles
Ib	Submandibular	Bounded by the posterior belly of digastric muscle, hyoid bone and the body of mandible
II	Upper jugular	Contains upper internal jugular lymph nodes. Extends from level of hyoid bone to skull base
III	Middle jugular	Contains middle internal jugular lymph nodes from hyoid bone to cricohyoid membrane
IV	Lower jugular	Contains lower internal jugular lymph nodes from cricohyoid membrane to clavicle
V	Spinal accessory	Posterior triangle lymph nodes bounded by trapezius, sternocleidomastoid, clavicle
VI	Anterior compartment	From hyoid bone to suprasternal notch bounded laterally by the carotid sheath
VII	Upper mediastinal	Lymph nodes inferior to suprasternal notch in the upper mediastinum

Table 18.2 Incidence and distribution of lymph nodes in N0 and N+ neck

	Radiologically enlarged retropharyngeal nodes (%)		Pathologic nodal metastasis(%)									
			Level I		Level II		Level III		Level IV		Level V	
Clinical presentation	N–	N+	N–	N+	N–	N+	N–	N+	N–	N+	N–	N+
Nasopharynx	40	86	–	–	–	–	–	–	–	–	–	–
Oral cavity												
Oral tongue	–	–	14	39	19	73	16	27	3	11	0	0
Floor of mouth	–	–	16	72	12	51	7	29	2	11	0	5
Aveolar ridge and RMT	–	–	25	38	19	84	6	25	5	10	1	4
Oropharynx												
Base of tongue	0	6	4	19	30	89	22	22	7	10	0	18
Tonsil	4	12	0	8	19	74	14	31	9	14	5	12
Hypopharynx												
Pharyngeal wall	16	21	0	11	9	84	18	72	0	40	0	20
Pyriform sinus	0	9	0	2	15	77	8	57	0	23	0	22
Larynx												
Supraglottic larynx	0	4	6	2	18	70	18	48	9	17	2	16
Glottic larynx	–	–	0	9	21	42	29	71	7	24	7	2

From Chao KSC, Wippold FJ, Ozyigit G, Tran BN, Dempsey JF. Determination and delineation of nodal target volumes for head and neck cancer based on patterns of failure in patients receiving definitive and postoperative IMRT. 2002;53:11. Reprinted with kind permission from Elsevier

General Delineation Guidelines

- An excellent reference in the delineation of nodal levels as visualized on computed tomography (CT) slices has been published by the Radiation Therapy Oncology Group (RTOG) (http://www.rtog.org/atlases/hnatlas/main.html) and the European Organization for Research and Treatment of Cancer (http://groups.eortc.be/radio/ATLAS.html).
- Gregoire et al. [2] has published recommendations for the treatment of the node-positive or postoperative neck. Selected recommendations are as follows:
  - Target delineation should include the retrostyloid space up to the skull base when level II is involved.
  - Supraclavicular fossa would be included when level IV or Vb is involved.
  - The entire muscle should be included in the target when there is clear extracapsular extension.
  - The entire surgical field ("surgical bed") should be included in the target in postoperative cases.
- Extracapsular extension is a significant independent risk factor for local recurrence and distant metastasis. The clinical target volume (CTV) should be extended to the skin to account for microscopic spread.
- An "all in one" IMRT technique where all treated regions are being included in the IMRT fields is preferred over "split-field" IMRT when the low neck contains involved lymph nodes, or if the primary tumor is located in the larynx, hypopharynx, and thyroid. A "split-field" technique is preferred in all other scenarios in an attempt to minimize the dose delivered to the normal larynx. A low anterior neck field is then matched to the IMRT fields. The common match point is just above the arytenoids cartilages, which

will ensure adequate dosimetric coverage to the level II lymph nodal regions.
- A "cheater" spinal cord block is placed at the match point, approximately 2×2 cm, to add an extra layer of protection over the spinal cord in the region of the match line.
- The size of the lymph node denotes whether it should be included in the gross target volume (GTV). Lymph nodes with a minimal axial diameter of more than 1.1 cm in the subdigastric region and more than 1.0 cm in other nodal regions is considered suspicious for metastasis. Lymph nodes with a necrotic center should also be considered within the GTV.
- Communication between the operating surgeon and the radiation oncologist is crucial to ensure adequate delineation of the postoperative case.
- Imaging studies that are helpful to accurately define the gross extent of disease include CT with contrast, magnetic imaging resonance (MRI) with gadolinium, and positron emission tomography (PET) scans. Nodes that are smaller than 1 cm but are PET avid should be included in the target volume as GTV.
- PET and MRI fusion treatment planning is being used at an increasing number of institutions. While the treating physician should exercise caution in strictly defining the GTV and CTV in correlation with areas of increased fluorodeoxyglucose (FDG) uptake, these more sensitive imaging studies can provide useful information in target delineation.
- Different CTVs are established for all targets within one plan along with suggested dosing.
  - CTV1: highest dose region, margin given to GTV or the postoperative surgical bed. Definitive cases: 70 Gy, postoperative dose: 60–66 Gy.
  - CTV2: intermediate dose region, which is at high-risk but clinically uninvolved regions. Definitive cases: 59.4–63 Gy; postoperative dose: 54–60 Gy.
  - CTV3: low-dose region including regions at a lower risk for microscopic disease. Definitive cases: 54–56 Gy; Postoperative dose: 54 Gy

Treatment of Specific Anatomic Subsites

Nasopharynx

General Facts

- Anterior border: posterior choanae
  Posterior border: at the level of the first two cervical vertebrae and clivus
  Superior border: basisphenoid, basiocciput
  Inferior border: soft palate
  Lateral border: pharyngeal fascia including the eustachian tube.
- Approximately 85–90% of patients with nasopharyngeal cancer have lymph node involvement and 50% have bilateral lymph node involvement. Nodal drainage can be direct to level V, through the lateral pharyngeal walls to the retropharyngeal and subdigastric nodes. Therefore, levels I–V are all at risk for involvement.
- Anatomic knowledge of the skull base is important as nasopharyngeal tumors can involve multiple cranial nerves including II–VI and IX–XII.
- The World Health Organization divides nasopharyngeal carcinoma (NPC) into the following: keratinizing squamous cell carcinoma; nonkeratinizing carcinoma, which subdivides into differentiated and undifferentiated; and basaloid squamous cell carcinoma. Lymphoepithelial carcinoma is a further subtype that represents nonkeratinizing and undifferentiated carcinomas with an abundance of lymphocytes.

General Management

- Treatment consists of definitive radiation therapy ± cisplatin followed by adjuvant chemotherapy, though there are debates regarding the added benefit of adjuvant chemotherapy.
- The 5-year overall survival rates range from 35 to 60%.
- In the Phase III trial (Al-Sarraf et al. [3]), patients with stage III–IV NPC were randomized to radiotherapy alone (70 Gy) or radiotherapy with concurrent cisplatin (100 mg/m^2) every 3 weeks during treatment, followed by cisplatin (80 mg/m^2) and fluorouracil (1,000 mg/m^2/day), 4 days every 4 weeks after the completion of radiation therapy. At 5 years, overall survival was 37% vs. 67% in the radiotherapy alone vs. chemoradiation arms, respectively, and progression-free survival was 29% vs. 58% in the radiotherapy alone vs. chemotherapy arms, respectively.
- A more recent Phase III study from Singapore [4] randomized 221 patients to radiation alone (70 Gy in 7 weeks) or concurrent cisplatin (weeks 1, 4, and 7 of radiation, 25 mg/m^2), followed by adjuvant cisplatin (20 mg/m^2) and fluorouracil (1,000 mg/m^2) every 4 weeks for three cycles after the completion of radiation therapy. This trial has a design nearly identical to the US Intergroup Trial. The 3-year overall survival rate was 80% vs. 65% for the chemoradiation vs. the radiation-alone arm, respectively, with a hazard ratio for overall survival of 0.51 ($p = 0.0061$). This trial confirmed the findings of the Intergroup Trial.

Table 18.3 Suggested target delineation guidelines for nasopharyngeal cancer

Stage	CTV1	CTV2
T1–T4N0	GTV + 5–10 mm	Entire nasopharynx, clivus, skull base, pterygoid fossae, parapharyngeal space, sphenoid sinus, posterior 1/4 to 1/3 of maxillary sinus and nasal cavity, bilateral retropharyngeal regions, bilateral levels II–V
T1–T4N1–3	GTV + 5–10 mm	As above and include bilateral level I

At the discretion of the treating physician, the CTV margin can be as small as 1 mm in regions near critical normal tissues, i.e., brain stem

- Several meta-analyses demonstrated that the addition of chemotherapy to radiation therapy increased both progression-free and overall survival.

Target Delineation for IMRT

- Table 18.3 contains the suggested guidelines for target delineation in NPC. The GTV includes the primary tumor and involved lymph nodes.
- Due to the high probability of lymph node metastases, levels IB-V and the retropharyngeal lymph nodes should be included in the CTV bilaterally. Level I can be omitted in N0 cases. CTV also includes areas where NPC is likely to spread: the entire nasopharynx, posterior 1/3 of the nasal cavity and maxillary sinuses, parapharyngeal fat, clivus, and skull base.
- Figure 18.1 depicts a sample target volume for a patient with locally advanced NPC. The planning target volume (PTV) represents the final treatment volume, and is the CTV with an "adequate" margin at the physician's discretion, to account for patient day to day set-up errors as well as organ motion.

IMRT Results

- Two randomized studies on early-stage NPC have demonstrated an advantage of IMRT over conventional techniques in terms of salivary preservation [5, 6].
- Lee et al. [7] reviewed 67 patients who underwent IMRT for NPC at the University of California-San Francisco between 1995 and 2000. At a median follow-up of 31 months, the 4-year locoregional progression-free rate was 98%. Sixteen patients experienced distant metastases. At 24 months, only one of the 41 evaluable patients had Grade 2 xerostomia, with the remaining having Grade 0 or 1 toxicity. Several other single institutions also published similar results.
- Due to the encouraging locoregional control as well as improved salivary function with IMRT for NPC, the RTOG conducted a Phase II multi-institution trial and the results reproduced the excellent locoregional control rates reported by single institutions, with control rates on the order of 90% [8].
- The predominant failure pattern in patients treated with IMRT for NPC is distant metastasis. Therefore, the RTOG is conducting a Phase II trial (RTOG 0615) in which patients with loco-regionally advanced NPC are being treated with the current standard chemotherapy and IMRT with the addition of the study drug, bevacizumab, a targeted agent directed against the vascular endothelial growth factor, to test whether this addition will further decrease the rate of distant metastasis with the ultimate goal of improving overall survival. The trial is closed to patient accrual and results are pending.

Oropharynx

General Facts

- The oropharynx consists of four subsites: soft palate, palatine tonsillar region (fossa and pillars), lingual tonsil or base of tongue, and posterior and lateral pharyngeal walls.
- The oropharynx has a rich lymphatic network, and primarily drains into the subdigastric, upper cervical (II and III), and parapharyngeal lymph nodes (in proximity to cranial nerves IX–XII). Progression of nodal metastases is usually orderly, starting at level II and proceeding inferiorly to levels III and IV. Skip nodal metastases are relatively rare.
- The vast majority of tumors of the oropharynx are squamous cell carcinomas.

General Management

- Surgery and adjuvant radiation ± chemotherapy was previously the treatment paradigm.
- The study RTOG 73-03 (Kramer et al. [9]) was the first to suggest that surgery was not necessary as a component of treatment. This study randomized patients to either surgery, preoperative or postoperative radiation therapy or to definitive radiation therapy, reserving surgery for salvage treatment. There was no difference in locoregional control or overall survival, and complications were higher in the surgical arms.
- Parsons et al. [10] compiled results from 11 institutions from 1970 to 2000 using a MEDLINE search, to determine

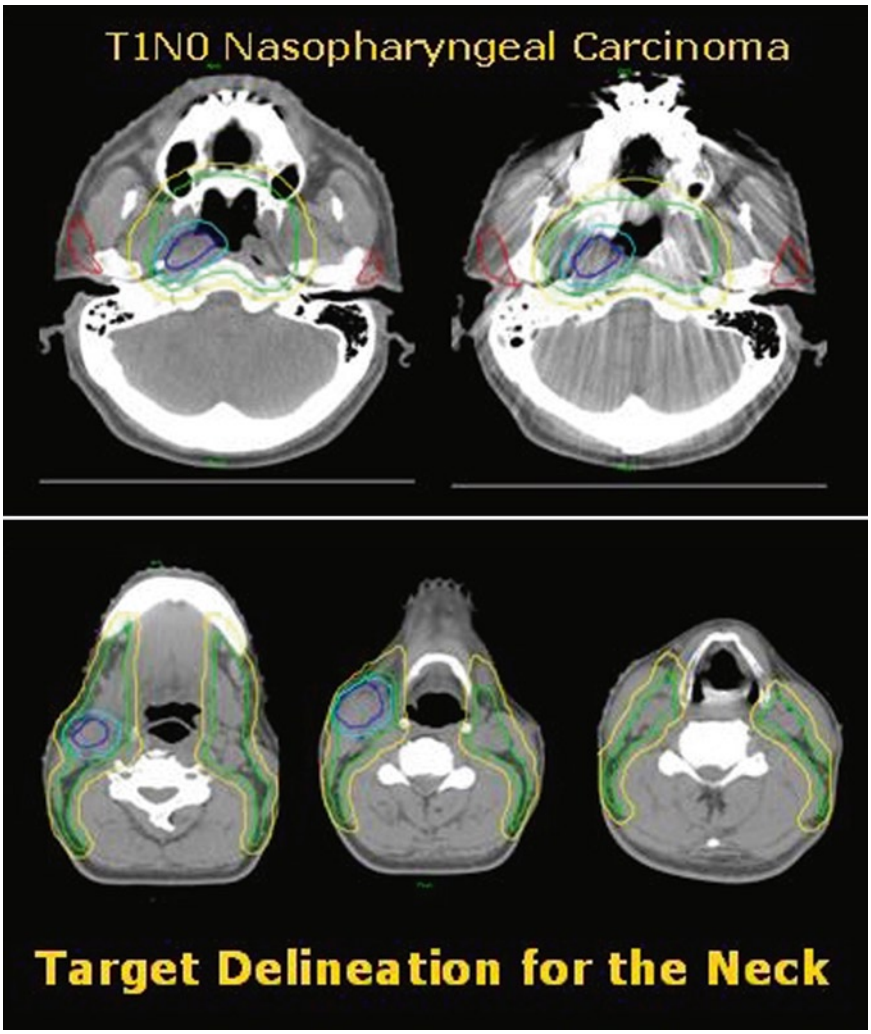

Fig. 18.1 Axial slices of representative slices of a nasopharyngeal carcinoma patient undergoing IMRT

if there was a difference in outcomes for patients treated with surgery ± adjuvant radiation vs. definitive radiation ± neck dissection. While rates of local-regional control, 5-year overall survival, and 5-year cause-specific survival were similar in the two groups, the rate of significant complications was higher in patients who underwent upfront surgery.

- Fu et al. [11] performed a randomized trial of over 1,000 patients with locally advanced head and neck cancer, randomizing them to (a) standard fractionation at 2 Gy once daily to 70 Gy, (b) accelerated fractionation, 1.2 Gy BID to 81.6 Gy, (c) accelerated fractionation with a split-course, 1.6 Gy BID to 38.4 Gy, 2-week break, then to 67.2 Gy, or (d) accelerated fractionation with a concomitant boost, 1.8 Gy daily to 72 Gy, with a boost of 1.5 Gy as a second daily treatment for the last 12 fractions. Arms (b) and (d) had better local-regional control than arms (a) and (c).
- Denis et al. [12], randomized 226 patients with stage III or IV oropharyngeal carcinoma to either (a) radiation alone (70 Gy in 2 Gy fractions) or (b) concomitant chemoradiation with the regimen above and carboplatin (70 mg/m^2) with fluorouracil (600 mg/m^2). Five-year overall survival (22% vs. 16%), disease-free survival (27% vs. 15%), and locoregional control (48% vs. 25%) all favored the chemoradiation arm.
- Pignon et al. [13] performed a meta-analysis that included trials between 1965 and 2000 of patients with carcinoma of the oropharynx, oral cavity, larynx, or hypopharynx; there was an overall survival benefit of approximately 6.5% in 5 years in favor of concomitant chemoradiotherapy.

Target Delineation

- Table 18.4 depicts suggested guidelines for target delineation in oropharyngeal carcinoma.
- Note that the bilateral neck is covered in all oropharyngeal lesions other than T1N0 and small well-lateralized

Table 18.4 Suggested target delineation guidelines for oropharyngeal cancer

Site/stage	CTV1	CTV2	CTV3
Tonsil/T1N0	GTV + 5–10 mm	Ipsilateral levels IB-V[a], RP	
Tonsil/T2–T4N0	GTV + 5–10 mm	Bilateral levels IB-V[a] RP	
Tonsil/T1–T4N+	GTV + 5–10 mm	Ipsilateral IB-V RP	Contralateral Ib-V, RP
Base of Tongue Soft Palate T1–T4N0	GTV + 5–10 mm	Bilateral IB-V[a], RP	
Base of Tongue Soft Palate T1–T4N+	GTV+ 5–10 mm	Ipsilateral Ib-V, RP	Contralateral Ib-V[a], RP

Note: For all dosing, the treating physician can also decide on whether the N0 nodal CTVs are treated with the CTV2 or CTV3 dose
RP retropharyngeal nodes
[a] At the discretion of the treating physician, can treat levels II–IV in N0 neck

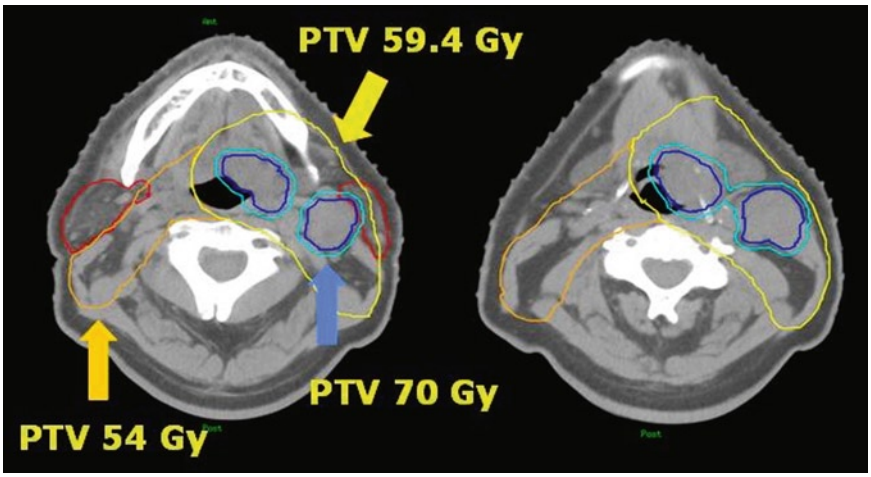

Fig. 18.2 Axial slices of representative slices of a oropharyngeal carcinoma patient undergoing IMRT

T2N0 tonsillar lesions without soft palate or base of tongue involvement.

- Figure 18.2 depicts the delineation of a representative patient from Memorial Sloan-Kettering Cancer Center (MSKCC).

IMRT Results

- Chao et al. [14] reviewed 74 patients with squamous cell carcinoma of the oropharynx (all stages) treated with IMRT. Thirty-one received definitive IMRT and the remaining were treated postoperatively. Four-year overall survival and disease-free survival were 87 and 81%, respectively. Fifteen patients experienced Grade 3 or higher skin toxicity, while 32 experienced Grade 3 or higher mucosal toxicity (28 with Grade 3). There were no Grade 3 or higher late toxicities. The most common late toxicity was xerostomia; there were 32 patients with Grade 1 and nine patients with Grade 2 late toxicity.
- In a study by de Arruda et al. [15] at MSKCC, 50 patients with oropharyngeal carcinoma treated with IMRT between 1998 and 2004 were analyzed (78% stage IV disease, 96% with definitive treatment). Two-year local control and overall survival were both 98%. Thirty-one patients had Grade 3 acute toxicities, none had Grade 4 acute toxicities. 67% had Grade 0–1 late toxicities, and the remainder had Grade 2 late toxicities. Of the 42 patients that had a percutaneous endoscopic gastrostomy (PEG) tube placed at the beginning of treatment, 36 had the PEG tube removed at the time of analysis.

Hypopharynx

General Facts

- The anatomical boundaries of the hypopharynx are as follows: superior, hyoid bone; inferior, inferior edge of cricoid cartilage. The pyriform sinuses are lateral to the vocal cords, but the apices of the pyriform sinuses extend inferiorly to the vocal cords.

- Superior to the hypopharynx is the oropharynx, and inferiorly lies the most superior portion of the esophagus (the cervical esophagus).
- There is significant lymphatic drainage to the hypopharynx. Three main pathways exist: (1) through the internal branch of the superior laryngeal artery to levels II and III, (2) through the paratracheal lymph nodes into level IV and the mediastinal lymph nodes, and (3) to the retropharyngeal lymph nodes.
- The most common site of lymph node metastasis is to level II.
- Almost all hypopharyngeal tumors are squamous cell carcinomas.

General Management

- T1–T2N0 disease can be treated with either definitive radiation or surgery.
- Conservative surgery for early-stage disease entails a partial laryngopharyngectomy with ipsilateral neck dissection. Patients with N2C disease undergo a bilateral neck dissection.
- The following are contraindications for conservation surgery: vocal cord paralysis, pyriform sinus apex invasion, cartilage invasion, extralaryngeal extension, and/or arytenoid involvement.
- For locally advanced disease, including T3–T4 or node-positive tumors, surgery with adjuvant radiation ± chemotherapy or concurrent chemoradiotherapy is the treatment of choice.
- The surgery for locally advanced disease is a total laryngectomy and partial pharyngectomy with neck dissection.
- Multiple retrospective studies have demonstrated the efficacy of postoperative radiation therapy for advanced tumors [16–18].
- Randomized studies have shown the added benefit of chemotherapy given concurrently with postoperative radiation therapy in patients with high-risk features, i.e., positive margins or extracapsular extension [19–21].
- In a Phase III trial by Lefebvre et al. [22], patients with T2–T4N0-N2b disease were assigned to either: (a) immediate laryngectomy with postoperative radiotherapy (50–70 Gy) or (b) induction chemotherapy with cisplatin (100 mg/m^2) and fluorouracil infusion (1,000 mg/m^2), followed by either radiation (70 Gy) in the responders or laryngectomy followed by postoperative radiation (50–70 Gy) in the nonresponders. While local failures were approximately the same in the two arms (12% vs. 17%), there were fewer distant failures in arm b (25% vs. 36%), and the median overall survival was also greater (44 months vs. 25 months). The authors concluded that laryngeal preservation is a feasible approach in patients with locally advanced hypopharyngeal cancer.
- Several randomized trials comparing chemoradiotherapy to radiotherapy alone included hypopharyngeal carcinoma and have shown improved locoregional control, disease-free survival, and overall survival in the combined-modality arm.

Target Delineation

- Table 18.5 depicts suggested target volumes for patients with hypopharyngeal tumors. GTV includes all gross disease and any clinically involved lymph nodes.
- Due to the high likelihood of lymphatic spread, levels II–V should be included in the field along with retropharyngeal nodal regions. Please see Table 18.5 for further details.
- Figure 18.3 depicts representative CT slices from a patient with locally advanced hypopharyngeal carcinoma.

IMRT Results

- Lee et al. [23] analyzed 20 patients with laryngeal cancer and 11 patients with hypopharyngeal cancer treated with IMRT and concurrent platinum-based chemotherapy at MSKCC, most of whom had stage IV disease. Two-year locoregional control for the patients with hypopharyngeal tumors was 73%, and 2-year overall survival was 53%. Four of the eleven pati-ents were PEG-tube dependent at the time of the analysis, and the 2-year PEG-tube dependency rate was 31%.

Larynx

General Facts

- The larynx is divided into three subsites: the supraglottis, the glottis, and the subglottis.
- The supraglottis contains the following: epiglottis, aryepiglottic folds, arytenoids, and false vocal cords.

Table 18.5 Suggested target delineation guidelines for hypopharyngeal cancer

Site/stage	CTV1	CTV2	CTV3
T1–T4N0	GTV + 5–10 mm	Bilateral levels II–V[a], RP	
T1–T4N+	GTV + 5–10 mm	Ipsilateral levels I–V, RP	Contralateral levels II–V, RP

RP retropharyngeal nodes
[a]At the discretion of the treating physician, can treat levels II–IV in N0 neck

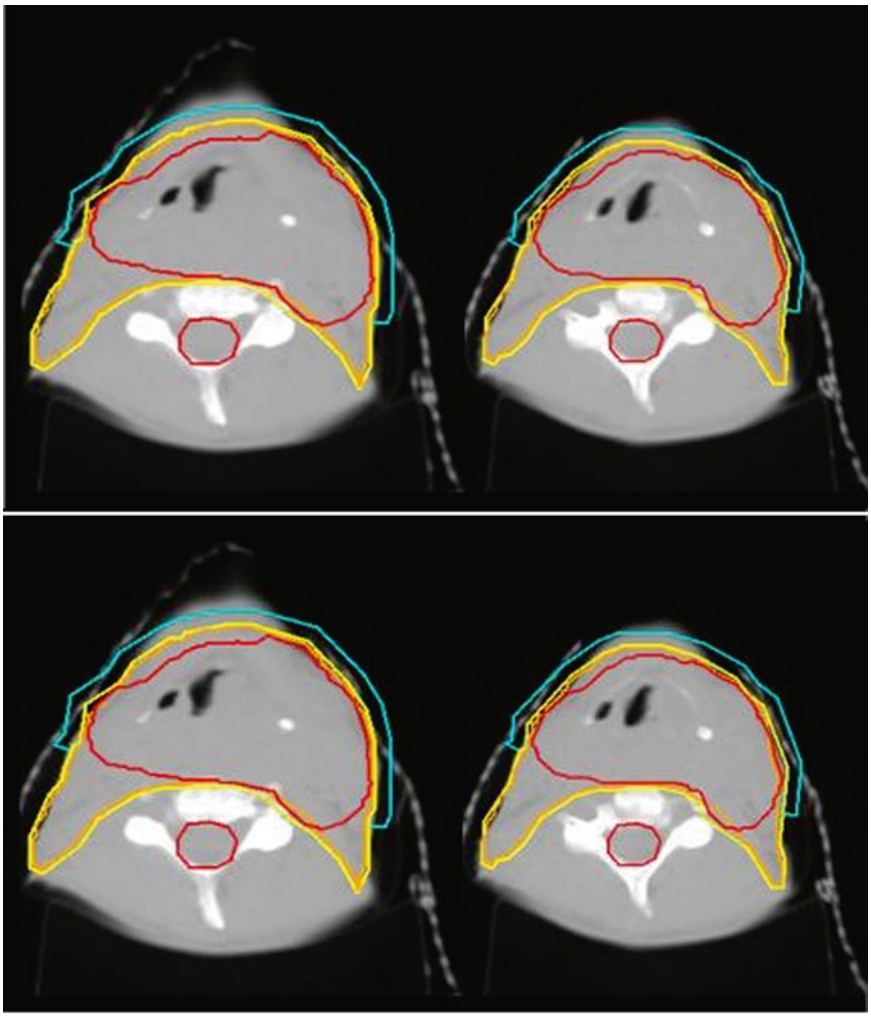

Fig. 18.3 Axial slices of representative slices of a hypopharyngeal carcinoma patient undergoing IMRT

The supraglottis has a significant amount of lymphatic drainage. Through the thyrohyoid membrane, the lymphatic drainage proceeds to levels II–IV.

- The glottis contains the true vocal cords and the anterior and posterior commissures. There are no lymph nodes that drain from the true vocal cords. Lymph node metastases from tumors of the true vocal cords occur with extension of the tumor to the subglottis or supraglottis.
- The subglottis extends from the lower boundary of the glottis to the inferior aspect of the cricoid cartilage. The subglottis drains to prelaryngeal, lower jugular, pretracheal, and upper mediastinal lymph nodes.
- Greater than 95% of laryngeal tumors are squamous cell carcinomas.
- One distinct entity of squamous cell carcinoma in laryngeal cancer is verrucous carcinoma, which is well differentiated and exophytic. It has been cited in the past that these tumors undergo transformation to an aggressive phenotype after radiation, but whether or not this truly occurs remains unclear.

General Management

- Carcinoma in situ of the vocal cord can be managed by either radiation therapy, local excision, or laser therapy. With vocal cord "stripping" or laser excision, tumors often recur, and such patients should be referred for radiation therapy. Control rates are above 95% with radiation.
- For early-stage carcinoma of the vocal cord (T1–T2N0M0), surgical excision and radiation therapy have been shown to have comparable results. However, voice quality is generally better preserved with radiation therapy. The typical dose is 2.25 Gy to a total dose of 63 Gy for T1 and 65.25 Gy for T2 lesions.
- To study locally advanced laryngeal cancer, RTOG 9111 [24] randomized 547 patients with stage III or IV laryngeal carcinoma (T1 tumors and large-volume stage IV excluded) to either (a) induction chemotherapy with cisplatin (100 mg/m^2) and fluorouracil (1,000 mg/m^2) followed by radiation therapy (70 Gy in 2 Gy fractions), (b) concurrent radiation (70 Gy in 2 Gy fractions) and

cisplatin (100 mg/m^2 on days 1, 22, and 43), or (c) radiation alone (70 Gy in 2 Gy fractions). The study found that concurrent chemoradiation provided an increased rate of larynx preservation at 2 years (88% vs. 75% and 70% in arms b vs. arms a and c, respectively), as well as improved disease-free survival.

- Early exophytic lesions of the supraglottis (T1N0) can be treated with either definitive radiation or hemilaryngectomy (supraglottic laryngectomy), which provides voice preservation.
- For intermediate disease (T2NX), definitive chemoradiation and supraglottic laryngectomy offer similar rates of local control. The following are contraindications to supraglottic laryngectomy: bilateral arytenoid involvement, arytenoid fixation, base of tongue involvement, invasion of the thyroid or cricoid cartilage, involvement of the postcricoid region, impaired vocal cord mobility, glottic extension, and/or patients at increased risk of aspiration (elderly, patients with lung disease).
- For extensive lesions (T3–T4), either voice preservation with chemoradiation or surgery and postoperative radiation ± chemotherapy are utilized. Note that patients with significant thyroid cartilage invasion are usually referred for surgery. Postoperative chemotherapy should be considered in patients with a positive margin or extracapsular extension.
- Subglottic tumors are rare and are usually diagnosed at an advanced stage. The treatment of choice is typically surgery followed by radiation ± chemotherapy. Alternative treatment consists of concurrent chemoradiotherapy.

Target Delineation

- Table 18.6 demonstrates the suggested target delineation for a patient with supraglottic cancer. As noted above, subglottic tumors are rare and treatment should be individualized depending on the clinical situation.
- Laryngeal cancer (other than T1–T2N0 glottic tumors) is generally treated using an "all-in-one" technique. No low anterior neck field is utilized.
- As noted above, in T1–T2N0 tumors the neck is generally not treated. However, in T2N0 tumors that are bulky, or with subglottic extension, the physician can consider treating the bilateral neck, as described for T3–T4N0 tumors.

IMRT Results

- In the Lee et al. [23] study cited above, 20 patients with laryngeal cancer (and mainly stage IV disease) were treated with IMRT and concurrent platinum-based chemotherapy. The 2-year rates of locoregional control and overall survival were 90 and 69%, respectively, for the patients with laryngeal cancer. One patient developed laryngeal necrosis and one patient had an unusual complication of necrotizing fasciitis. The 2-year PEG-tube dependency rate was 15%.

Table 18.6 Suggested target delineation guidelines for laryngeal cancer

Site/stage	CTV1	CTV2	CTV3
Supraglottic			
T1–T4N0	GTV + 5–10 mm	Bilateral levels II–V[a], RP	
T1–T4N+	GTV + 5–10 mm	Ipsilateral levels I–V, RP	Contralateral levels II–V, RP
Glottic			
T3–T4N0	GTV + 5–10 mm	Bilateral levels II–V[a]	
T1–T4N+	GTV + 5–10 mm	Ipsilateral levels I–V	Contralateral levels II–V[a], RP

Note: RP nodal regions should be covered if there is involvement of the hypopharynx or there are involved cervical lymph nodes
RP retropharyngeal nodes
[a] At the discretion of the treating physician, can treat levels II–IV in N0 neck

Oral Cavity

General Facts

- The oral cavity is made up of the lips, buccal mucosa, the floor of the mouth, the upper and lower gingiva, the anterior two-thirds of the oral tongue, the hard palate, and the retromolar trigone.
- The upper lips are drained primarily by level IB (submandibular) lymph nodes, and less commonly by the periauricular and parotid lymph nodes.
- The lymphatic drainage to the buccal mucosa is primarily to levels IB and II.
- The primary lymphatic drainage of the floor of mouth is to levels IA and II.
- The primary lymphatic drainage of the upper gingival is to levels IB and II.
- The muscles of the oral tongue are innervated by the hypoglossal nerve, and sensory innervation is through the lingual nerve, which is part of the mandibular branch of the trigeminal nerve (V). Taste sensation is provided by cranial nerve VII. The three most common routes of lymphatic drainage are to levels IB, II, and, less commonly, IA. However, there is also a direct route to level III, and occasionally isolated metastases are found in this region.
- The most common lymphatic metastases of the hard palate are to levels IB and II.

- The retromolar trigone primarily drains to levels IB and II.
- Squamous cell carcinoma accounts for the vast majority of cases.

General Management

- Definitive surgery is the preferred treatment of choice for all oral cavity cancers unless there is a contraindication. Postoperative radiation therapy is given to those at high risk for recurrence.
- Chemotherapy has been shown to benefit patients with positive margins or extracapsular extension, as detailed above in the Cooper et al. and Bernier et al. studies [19–21].

Target Delineation

- Due to the higher propensity for oral cavity tumors (and in particular floor of mouth and oral tongue cancer) to invade lymph node level I, these lymph nodes should be included in the neck volumes. Therefore, in the positive neck, levels I–V should be included. In the node negative contralateral neck, levels I–IV should be included.
- Coverage for the postoperative bed should be generous as this anatomic site has been surgically violated. This volume should at least include the preoperative GTV.
- One can consider sparing the contralateral neck in early-stage lesions of the buccal mucosa, retromolar trigone, and gingiva; for lesions that are not well lateralized the bilateral neck should be treated.
- The risk of metastasis to retropharyngeal lymph nodes is low, but these lymph nodes can be treated in locally advanced or midline lesions at the physician's discretion.
- Figure 18.4 demonstrates representative CT slices from a patient with oral tongue cancer treated at MSKCC.

IMRT Results

- Yao et al. [25] recently reported on 55 patients with squamous cell carcinoma of the oral cavity, 91% of whom had stage III or IV disease. At a median follow-up of 17 months, 2-year disease-free and overall survival rates were 82 and 68%, respectively. When examining prognostic factors for locoregional control, the study found that anatomic subsite was predictive, with 2-year rates of locoregional control being 69% in oral tongue cancer, 100% for floor of mouth cancer, and 83% for all other groups together. Extracapsular extension was also found to significantly affect locoregional control.
- Studer et al. [26] analyzed 58 patients with oral cavity cancer treated at the University of Zurich. Twenty-eight of these patients were referred for postoperative treatment, and the remainder for definitive treatment. Forty

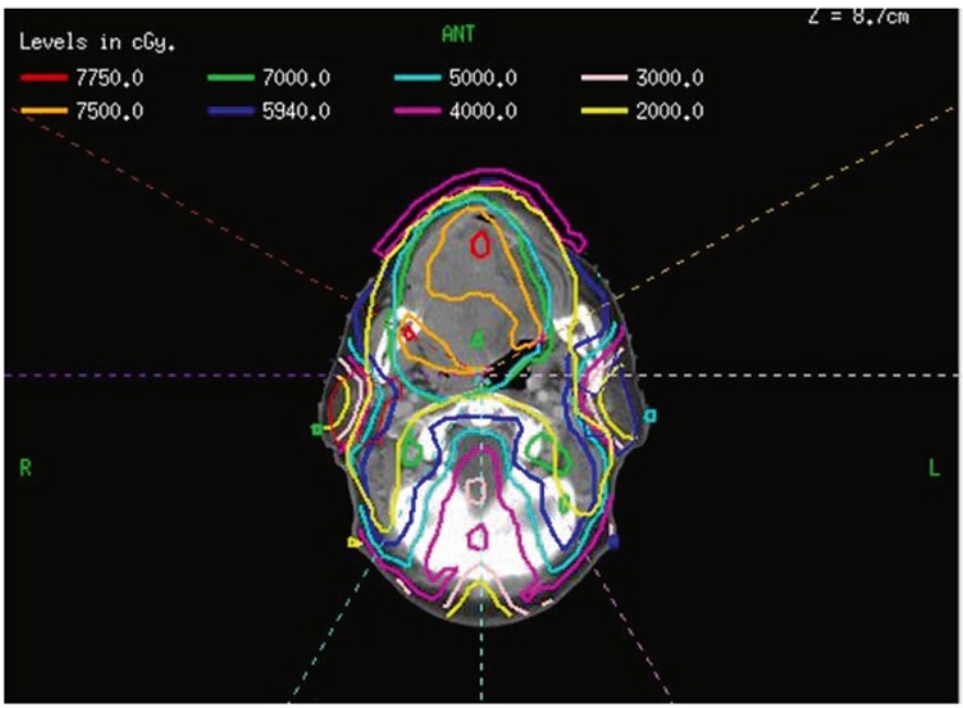

Fig. 18.4 Axial slices of representative slices of an oral cavity patient undergoing IMRT

patients had T3 or T4 lesions. Patients treated postoperatively had a 92% rate of local control at 2 years, while those treated with radiation alone had a local control rate of 30–40%.

- Gomez et al. [27] reported a series of 35 oral cavity patients treated with IMRT ± chemotherapy after definitive surgical resection. All patients had stage III–IV disease. With a median follow-up of 28.1 months, the 2 and 3 year estimates of locoregional progression-free survival were 84 and 77%, respectively. The overall survival was 74%. Late complications included trismus (17%) and osteoradionecrosis (5%).

Thyroid

General Facts

- The thyroid gland is made up of two lobes. They are joined by the thyroid isthmus. The gland lies posterior to the strap muscles and anterior to the prevertebral muscles, inferior to the thyroid cartilage and with the isthmus overlying the second and third tracheal rings.
- The thyroid gland has a rich vascular and lymphatic supply. The lymphatic drainage is primarily to the surrounding lymph nodes of the trachea and esophagus (level VI), with a secondary route being to the cervical lymph nodes, levels I–V. There is also lymphatic drainage to level VII.

General Management

- The mainstay of management for thyroid carcinoma is surgery. Depending on the extent of disease, this resection can entail a near-total thyroidectomy, total thyroidectomy, or wide composite resection to include the surrounding infiltrated tissue.
- External beam radiotherapy is given in select cases where patients are at high risk for local recurrence due to their locally aggressive nature, aggressive histology, or unsatisfactory surgery.

Target Delineation

- The CTV includes the thyroid bed, tracheo-esophageal groove, central compartment, levels II–VII, and the upper mediastinum to the level of the carina.
- Figure 18.5 demonstrates representative CT slices from a patient with thyroid cancer treated with IMRT.

IMRT Results

- Rosenbluth et al. [28] examined 20 patients with nonanaplastic thyroid carcinoma treated with IMRT. Seventeen of these patients had T4 disease and 16 patients had N1 disease. The median total radiation dose was 63 Gy

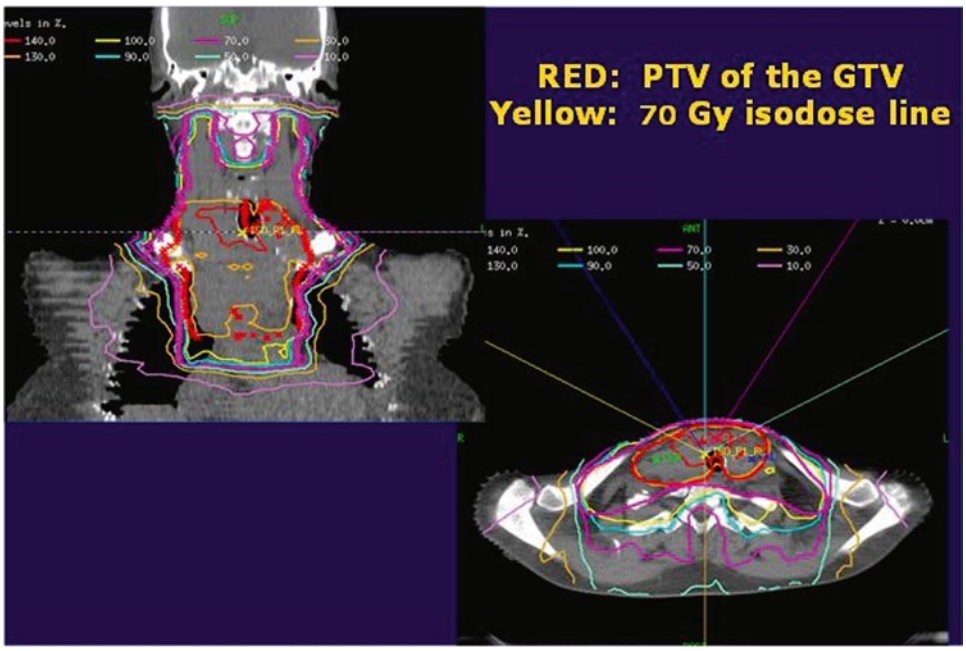

Fig. 18.5 Axial slices of representative slices of a thyroid cancer patient undergoing IMRT

("high-risk" PTV with a total dose of 59.4–63 Gy, positive margins treated to 63–66 Gy). The 2-year local control rate was 85% and the 2-year overall survival rate was 60%. Four of the six deaths were due to metastatic disease.
- In terms of toxicity, 7 of 20 patients had Grade 3 acute mucositis, 3 of 20 patients developed Grade 3 pharyngitis, and 2 of 20 patients had Grade 3 skin toxicity. There was no Grade 3 or higher xerostomia.

Cancer of Unknown Primary

General Facts

- The most commonly involved lymph nodes in cancer of unknown primary (CUP) of the head and neck are levels II and III. Levels I, IV, and V are less commonly involved.
- The most common primary site for CUP is the oropharynx, which accounts for approximately 80% of tumors.
- The most common histology of CUP is squamous cell carcinoma, with lymphoma, adenocarcinoma, and poorly differentiated tumors being less common.
- Multiple studies have examined the role of PET scan in detecting the primary tumor, particularly when conventional techniques have not elucidated the origin of disease.

General Management

- Patients with N1 disease can be treated with a neck dissection alone if there is no extracapsular extension. However, a review by the Danish Society for Head and Neck Oncology, showed that patients treated with surgery alone had an emerging primary rate of 54% at 5 years and a neck control rate of 58% [29].
- Radiation therapy alone is also an option for patients in lieu of neck dissection. In the same study by the Danish Society, the mucosal control rate was 84% in patients receiving radiation alone and the neck control rate was 50%.
- Surgery in combination with radiation therapy has appeared to produce the lowest rates of mucosal primary emergence and neck control. The emerging primary rate in the study above for patients receiving surgery with radiation therapy was 15%.
- Patients are usually treated with a field that encompasses the bilateral cervical lymph nodes, the retropharyngeal lymph nodes, and the comprehensive mucosal membranes. However, studies have also been done that utilized ipsilateral neck radiation, particularly for patients with poorer performance status.

Target Delineation

- In addition to lymph node coverage, the mucosal surfaces throughout the head and neck should also be targeted, including the nasopharynx, oropharynx, larynx, and hypopharynx, while the oral cavity is excluded.
- The dosing of the different mucosal sites can differ depending on the likelihood of emergence of primary in that site. For example, a patient with Asian descent should receive a higher total radiation dose to the nasopharynx while a Caucasian is more likely to have disease involving the oropharynx and hence a higher total dose should be delivered to that site.
- There are situations at the discretion of the treating physician where only the involved neck needs to be treated.

IMRT Results

- Klem et al. [30] examined 21 patients treated with IMRT. Fourteen were treated with chemoradiation, and five patients received radiation with definitive intent (rather than in the adjuvant setting). Two-year rates of locoregional survival, distant-metastasis-free survival, and overall survival were 90, 90, and 85%, respectively.
- In terms of toxicity, at 6 months posttreatment one patient had greater than Grade 1 xerostomia, and Grade 3 acute skin and mucosal toxicity were 5 and 14%, respectively. PEG tube placement was required in 13 patients, but at last follow-up only one patient was PEG-tube dependent. Three patients experienced esophageal strictures, and all had improvement with dilation.

Conclusions

IMRT has resulted in clinical improvement quality of life for patients with head and neck cancer. Yet target delineation remains a challenge, due to the complexity of the head and neck anatomy. Improved imaging promises to help improve the delineation of the extent gross disease, but understanding the patterns of spread of disease from the primary tumor site and the nodal drainage is required.

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