Laryngeal Cancer

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Erkan Topkan, Berna Akkus Yildirim, Cem Parlak, and Ugur Selek

Overview

Incidence, Etiology, and Epidemiology

Laryngeal carcinoma is the commonest head and neck carcinoma. Male to female ratio is around 1/5. Anatomically, larynx is situated anterior to the fourth and sixth cervical vertebrae and is divided into three regions for oncologic assessment and treatment purposes, namely, supraglottis, glottis, and subglottis. Majority of the laryngeal cancers arise from glottis followed by supra- and subglottic cancers, respectively. The strongest risk factor is the tobacco smoking, and the risk is directly associated with quantity and time of exposure. Alcohol is only second to tobacco use with its independent and synergistic actions on epithelium. Regardless of the tumor site, dysphonia and hoarseness are the commonest symptoms in laryngeal cancer patients with sore throat being the second commonest symptom in supraglottic tumors. However, besides other symptoms, a cervical mass may be the first presentation finding in some patients. Patients with hoarseness persisting longer than 3 weeks or with persisting sore throat, dysphagia, and odynophagia lasting for more than 6 weeks should be evaluated by an otolaryngologist for laryngeal carcinoma.

E. Topkan, MD (✉) • B.A. Yildirim, MD • C. Parlak, MD
Department of Radiation Oncology, Baskent University, Faculty of Medicine, Adana, Turkey
e-mail: drerkantopkan@yahoo.com

U. Selek, MD
Department of Radiation Oncology, Koc University, Faculty of Medicine, Nisantasi, Istanbul, Turkey

Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Pathological and Biological Features
More than 95 % of all laryngeal malignancies are of epithelial origin and histologically squamous cell carcinoma. Supraglottic cancers have high tendency for local invasion and uni-/bilateral cervical metastases. Depending on the tumor stage, 25–75 % of supraglottic cancers have cervical metastases at presentation, and 30 % of cN0 necks are pN+. Stage-dependent cervical metastases are rare in glottis (5–40 %) and subglottic (25–50 %). Thyroid and cricoid cartilages and associated perichondrium, conus elasticus, quadrangular membrane, and hyoepiglottic ligament are the natural barriers for laryngeal cancer spread until late stages. Two weak areas for cancer spread are anterior commissure, where thyroid membrane is deficient, and laryngeal ventricle, which is not reinforced by the quadrangular membrane.

Definitive Therapy
Age, performance, pulmonary function tests, tumor localization and extension, extent of lymphatic involvement, presence of distant metastasis, anticipated functional outcome, and patient's preference need to be considered in the management. Either surgical or nonsurgical treatment selection for laryngeal carcinoma should favor the laryngeal preservation without any anticipated decrease in locoregional control and survival outcomes. In early-stage disease, radiotherapy and conservative surgery are equally effective treatment options for medically fit patients. For patients with locoregionally advanced disease, induction chemotherapy followed by radiotherapy or concurrent chemoradiotherapy is the current standards for organ and function preservation. Doses per fraction >2 Gy should be preferred to achieve higher tumor control rates, especially in T2N0 cases.

Adjuvant Therapy
Adjuvant radiotherapy or chemoradiotherapy is indicated in patients with postsurgical risk factors such as close or positive margins, multiple lymph node involvement, and/or extracapsular extension. All medically fit patients without clinic or metabolic response must be managed with salvage surgery.

1 Case Presentation

A 67-year-old male, who has at least 150 pack year history of smoking, presented with a burning sensation in his throat and a 3-month history of right neck mass without any pain, dysphagia, odynophagia, otalgia, new voice changes, change in his cough or sputum, hemoptysis, dyspnea, aspiration, or weight loss. He had a true vocal cord benign nodule removed 20 years ago. His medical history is significant for diabetes and coronary heart disease.

His physical exam revealed normal external ear canals and tympanic membranes with appropriate light reflex. Clinical hearing acuity shows decreased to finger rub,

particularly on the right side. Nasal septum was midline without deviation and was clear to anterior rhinoscopy. He is edentulous with full dentures. There are no lesions, induration, tenderness, or friability of the gingiva, buccal mucosa, floor of mouth, oral tongue, base of tongue, hard palate, soft palate, tonsillar fossa, or posterior oropharyngeal wall by visualization or palpation. Palate elevates normally. Tongue protrudes normally.

There was a 5-cm poorly mobile right level 2 conglomerate nodal mass, but no other palpable neck mass, thyroid mass, or lymphadenopathy. Cranial nerves II–XII are grossly intact without any facial numbness.

The scope was introduced into the left nasal cavity. Clearly seen was normal appearing nasopharyngeal mucosa with clearly defined bilateral Rosenmuller fossa. There was no posterior pharyngeal/oropharyngeal wall, soft palate, tonsils, vallecula, or base of tongue bulging or lesions. The scope was advanced further. The mucosa was abnormal diffusely in the larynx with nodularity on the infrahyoid laryngeal surface of the epiglottis and submucosal fullness in the region of the left false vocal cord and ventricle. The entirety of almost both true vocal cords was showing hyperkeratotic changes. The arytenoids and vocal cords were moving normally, and the airway was intact with no supraglottic edema and no accumulated secretions. The pyriformis was open. The tongue base retracted symmetrically to phonation.

His PET-CT, CT, and MRI scans defined the obvious finding as a very large conglomerate of coalesced nodal metastases measuring $5 \times 2.9 \times 5$ cm at about the hyoid level without convincing contralateral nodal metastases (Fig. 9.1). PET-CT and CT scans were negative for a definite primary, while MRI was suspicious for mucosal thickening in supraglottic area. Incidental note was made of severe atherosclerotic disease at the bifurcation with obvious stenosis of the proximal right ICA. Neck ultrasound with fine needle aspiration revealed squamous cell cancer, as well as the surgical biopsy of infrahyoid epiglottis lesion as moderately differentiated invasive squamous carcinoma.

He was staged as T2N2bM0 (stage IVA) supraglottic laryngeal squamous cell cancer.

2 Evidence-Based Treatment Approaches

2.1 Glottic Larynx

Transoral laser excision is the currently recommended treatment for carcinoma in situ, and RT is the alternative option. For T1-2N0 and selected T3N0, cases amenable for larynx preservation can be treated with radiotherapy (RT) or partial laryngectomy/endoscopic or open surgery as indicated. Persistent residue after RT should be salvaged by appropriate surgery. Patients with residual disease after surgery should undergo re-resection and/or RT/CRT (chemoradiotherapy) depending on the existence of additional adverse factors.

Patients with T3N0-1 disease requiring total laryngectomy should undergo CRT (or RT if not candidate for systemic chemotherapy) or induction chemotherapy

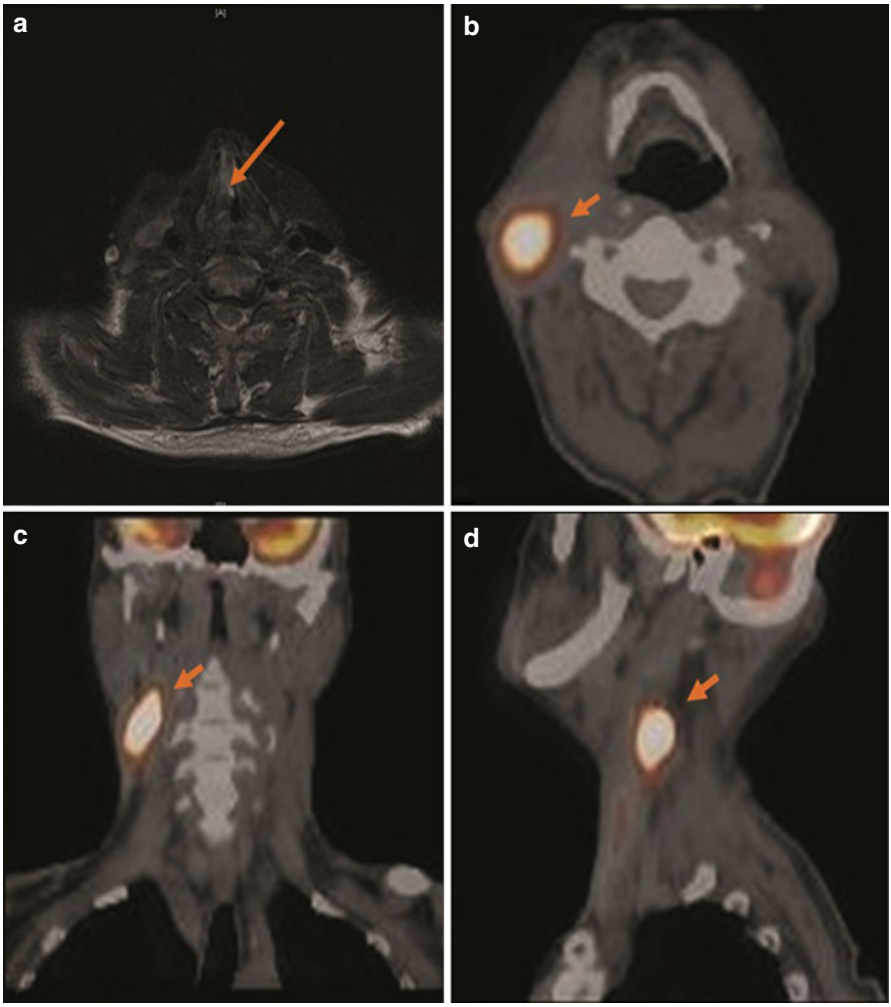


Fig. 9.1 (**a**) Suspicious mucosal thickening in supraglottic area on MRI. (**b**–**d**) Large conglomerate of coalesced nodal metastases measuring 5×2.9×5 cm at about the hyoid level on PET/CT images

(Category 2B) or laryngectomy with ipsilateral thyroidectomy in N0 and laryngectomy with ipsilateral thyroidectomy and ipsilateral/bilateral neck dissection (ND) in N1. Patients with complete response at primary site after RT/CRT should undergo salvage ND if residual neck disease persists. If residual disease persists at primary site, patients should undergo salvage laryngectomy and ND as indicated. In surgically treated patients with adverse features such as ECE (+) or positive margins, adjuvant CRT is indicated with category 1 evidence. RT or CRT should be considered for patients with other risk factors. Further treatment following induction chemotherapy is determined by the response at primary tumor site. Patients with complete response (CR) should receive definitive RT (Category 1). If residual neck

disease persists, salvage ND should be performed as indicated. Patients with partial response (PR) at primary site should receive RT (Category 1) or CRT (Category 2B). If residue persists following RT/CRT, salvage surgery is indicated. If primary site response is < PR, surgery is indicated. In such patients, if pathologically ECE (+) or surgical margins (+), CRT is indicated (Category 1). For patients with other risk factors, RT or CRT should be considered.

Patients with T3N2-3 disease requiring total laryngectomy should be treated with either CRT, laryngectomy with ipsilateral thyroidectomy and ipsilateral/bilateral ND, or induction chemotherapy followed by adjuvant treatment determined by response. Additional treatment should be performed similar to T3N1 disease as described above.

Patients with T4aN0-3 should undergo laryngectomy with total thyroidectomy and unilateral/bilateral ND as indicated. Such patients should receive postoperative RT or CRT, observation being reserved only for highly selected patients. For selected T4a patients refusing surgery, CRT or induction chemotherapy followed by RT/CRT is recommended. Any residual neck disease should be salvaged by ND, and residual disease at primary site should further be discussed with the patient for salvage surgery and ND.

2.2 Supraglottic Larynx

T1-2 N0 and selected T3N0 cases amenable for larynx preservation can either be treated with RT or open partial supraglottic laryngectomy/endoscopic resection with/without ND. Persistent residue after RT should be salvaged by appropriate surgery. Patients with residual disease after surgery should undergo re-resection or RT (Category 1) or CRT (Category 2B) depending on the existence of additional adverse features.

Patients with T3N0-1 disease requiring total laryngectomy should undergo CRT (or RT if not candidate for systemic chemotherapy) or induction chemotherapy (Category 2B) or laryngectomy with ipsilateral thyroidectomy and ipsilateral/bilateral ND. Patients with complete response at primary site after RT/CRT should undergo salvage ND if residual neck disease persists. If residual disease persists at primary site, patients should undergo salvage laryngectomy and ND as indicated. In surgically treated patients with pN0 or only single node involvement without other adverse factors, adjuvant RT should be considered. Patients with adverse features such as ECE (+) or positive margins should undergo CRT (Category 1). RT or CRT should be considered for patients with other risk factors. Following induction chemotherapy, further treatment is determined by the response at primary tumor site. Patients with complete response (CR) at primary site should receive definitive RT (Category 1). If residual neck disease persists, salvage ND should be performed. Patients with partial response (PR) at primary site should receive RT (Category 1) or CRT (Category 2B). If residue persists following RT/CRT, salvage surgery is indicated. If primary site response is < PR, surgery is indicated. In such patients, if pathologically ECE (+) or surgical margins (+), CRT is indicated (Category 1). For patients with other risk factors, RT or CRT should be considered.

Patients amenable for organ preserving surgery with T1-2 N1-3 and selected T3N1 disease should be treated with definitive RT or CRT or partial supraglottic laryngectomy and ND or induction chemotherapy. For patients treated with RT or CRT, any residual neck disease should be salvaged by ND, and if residue persists at primary disease site, salvage surgery and ND should be considered as indicated. For surgically treated patients with ECE (+) or margins (+), CRT (Category 1) and RT/CRT for other adverse factors should be considered. Salvage treatment after induction chemotherapy should be performed as described above.

T3N2-3 patients requiring total laryngectomy should be treated with CRT, laryngectomy with ipsilateral thyroidectomy and ND, or induction chemotherapy followed by adjuvant treatment determined by response type as detailed previously. Additional treatment should be performed for either modality similar with to their T3N1 disease as described above.

T4aN0-3 patients should undergo laryngectomy with total thyroidectomy and unilateral/bilateral ND as indicated. Such patients should receive postoperative RT or CRT, observation being reserved only for highly selected patients. For selected T4a patients refusing surgery, CRT or induction chemotherapy followed by RT/CRT is recommended. Any residual neck disease should be salvaged by ND, and residual disease at primary site should further be discussed with the patient for salvage surgery and ND.

2.3 Subglottic Larynx

Subglottic tumors are exceedingly rare, accounting for only 2 % of all laryngeal cancers. Most patients present with advanced disease (T3-4 N+). Definitive RT, CRT, and surgery are treatment options for such patients. If surgery is chosen, total laryngectomy should be performed regarding the tumor location and invasion of thyroid and/or cricoid cartilages. Postoperative RT/CRT should be considered to increase locoregional control rates. Salvage surgery is indicated in any patient with residual primary or neck disease.

Stage of disease is the strongest prognostic factor for laryngeal carcinoma (Table 9.1). Among staging parameters, M-stage determines the survival, while T- and N-stage are strong predictors of local control and distant metastasis, respectively. Female patients, in general, do better than male counterparts.

Functional larynx preservation without any decrease in local control and survival rates is the ultimate goal of any treatment directed to any stage of laryngeal carcinoma.

Although stripping and RT are options for carcinoma in situ, early RT should be preferred because recurrence is frequent and hoarsening of the voice may become evident due to cord thickening after repeated stripping. Additionally, many patients with carcinoma in situ have obvious lesions that probably contain invasive carcinoma, and early RT will spare many patients from repeat biopsy and many others from unavoidable RT.

Table 9.1 American Joint Committee on Cancer staging for laryngeal carcinoma (AJCC 7th edition)

Primary tumor (T)	
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease: Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease: Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease: Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

(continued)

Table 9.1 (continued)

Primary tumor (T)	
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

From Greene [14]

Transoral laser excision and RT are options for T1 and T2 glottic tumors. As the voice quality is inversely related with the quantity of tissue removed, RT is the first choice of treatment in many centers, surgery being reserved for RT failures. Five years local control rates following RT are in the range of 85–95 % for T1 and 60–89 % for T2 tumors [1].

There is a direct association between the overall treatment time and local control rates for laryngeal carcinoma patients treated with definitive RT. Longer treatment duration related with lower dose per fraction in the range of 1.8–1.9 Gy results in poorer local control rates compared to same total doses with >2 Gy per fraction. In a prospective randomized study reported by Yamazaki et al., authors compared 2 Gy/fr ($n=89$) and 2.25 Gy/fr ($n=91$) and reported significantly higher local control rates with 2.25 Gy/fr (94 % vs. 77 %; $p=0.004$) [2].

As respective 5-year isolated neck recurrence rates are 0, 3, and 8 % for T1, T2A, and T2B patients, neck treatment is not indicated [3]. Achievement of local control is of extreme importance as neck recurrences increase up to 20–25 % in primary disease site recurrences, which may be a sign of distant metastasis and poor survival [4].

Similar with glottic cancers, early supraglottic cancers can be treated with either of transoral laser excision, open surgery, or RT. As local control and voice quality outcomes are similar many centers prefer RT as the initial management option. In a series of 274 T1-2 supraglottic larynx cancer patients treated with RT demonstrated excellent 5-year local control (T1 = 100 % vs. T2 = 86 %) and cause specific survival (T1 = 100 % vs. T2 = 93 %) rates [5].

For locally advanced laryngeal carcinoma, total laryngectomy, induction chemotherapy followed by surgery or RT/CRT, and concurrent CRT are options for treatment.

The era of larynx preservation with CRT emerged with the publication of Veterans Affairs Laryngeal Cancer Study in 1991 [6]. In this study, 332 stage III or IV laryngeal cancer patients were randomized into induction chemotherapy with cisplatin and fluorouracil followed by RT or surgery followed by RT groups.

Although overall 2-year survival rates were 68 % for both groups, larynx was preserved in 64 % of patients in the induction chemotherapy arm. Significant differences between the two groups were seen with fewer local failures in the surgery group ($p = 0.0005$) and fewer distant metastases in the chemotherapy group ($p = 0.016$). These results led to a shift in advanced-stage laryngeal cancer treatment toward a primary nonsurgical approach, reserving total laryngectomy for salvage.

The RTOG 91–11 study randomly compared three nonoperative approaches in the treatment of 547 patients with stage III or IV laryngeal cancer: induction chemotherapy (cisplatin and fluorouracil) followed by RT, RT given concurrently with cisplatin, and RT alone [7]. Primary aim was to determine proper timing of chemotherapy (induction vs. concurrent). At 2 years, proportion of patients maintaining an intact larynx was greatest in the concurrent CRT group (88 %), compared to the induction chemotherapy (75 %; $p = 0.005$) and the RT alone groups (70 %; $p < 0.001$). Locoregional control was also significantly better in the concurrent CRT group than the induction chemotherapy and RT alone group (78 % vs. 61 % vs. 56 %, respectively). Both chemotherapy arms had longer disease-free survival compared to RT alone. Other randomized studies of larynx preservation are as summarized in Table 9.2.

Based on the results of these benchmark studies, induction chemotherapy followed by RT or upfront concurrent CRT (preferred) became the standards of care for locally advanced laryngeal carcinoma

For early-stage laryngeal carcinomas, 3D-conformal RT is preferred. If necessary, bolus material of appropriate thickness should be used to involve anterior commissure in the high-dose region. For locally advanced laryngeal carcinoma patients, IMRT is the preferred technique of RT with advantage of sparing surrounding normal tissues and structures of critical importance, allowing safer escalation of the dose beyond traditional limits. However, it is crucial to follow available guidelines during contouring process to prevent geographic misses and/or overtly large unnecessary radiation portals while using IMRT.

3 Target Volume Determination and Delineation Guidelines

In patients treated with induction chemotherapy target volumes should be determined on pre-chemotherapy images. In an effort to increase the accuracy of target volume determination and to prevent geographic misses, it is better to use co-registered pre- and post-chemotherapy images during delineation.

3.1 Gross Tumor Volume (GTV)

GTV can be divided into two parts; GTV-primary (GTV_P) and GTV-nodal (GTV_N). GTV_P should include all gross disease and its visible extensions on physical examination and/or imaging studies. All nodes, >1 cm on short axis, with necrotic center, and/

Table 9.2 Randomized larynx preservation trials

Reference	Patients (N)	Treatment arms	Overall survival	Larynx preservation
VALCS [6]	332	S + RT	68 % (2-y)	–
		ICT + RT	68 % (2-y)	64 % (2-y)
RTOG-91-11 [7]	547	ICT + RT	38.5 % (10-y)	67.5 % (10-y)
		CCRT	27.5 % (10-y)	81.7 % (10-y)
		RT alone	31.5 % (10-y)	63.8 % (10-y)
EORTC 24891 [8]	202	S + RT	32.6 % (5-y)	–
		ICT + RT	13.8 % (10-y)	–
			38 % (5-y)	21.9 (5-y)
			13.1 % (10-y)	8.7 % (10-y)
GETTEC [9]	68	S + RT	84 % (2-y)	–
		ICT + RT	69 % (2-y)	42 % (2-y)
GORTEC 2000–2001 [10]	213	ICT (PF) + RT	60 % (3-y)	57.5 % (3-y)
		ICT (TPF) + RT	60 % (3-y)	70.3 %) (3-y)
TAX 324 (Subgroup) [11]	166	ICT (PF) + CCRT	40 % (3-y)	32 % (3-y)
		ICT (TPF) + CCRT	57 % (3-y)	52 % (3-y)
EORTC 24954 [12]	450	Sequential PF + RT	62.2 % (3-y)	39.5 % (3-y)
		Alternating PF + RT	48.5 % (5-y)	30.5 % (5-y)
			64.8 % (3-y)	45.4 % (3-y)
			51.9 % (5-y)	36.2 % (5-y)
TREMPLIN [13]	153	ICT (TPF) + CCRT (Platin based)	92 % (18 mo)	87 % (18 mo)
		ICT (TPF) + CCRT (Cetixumab)	89 % (18 mo)	82 % (18 mo)

Abbreviations: CCRT concomitant chemoradiotherapy, *ICT* induction chemotherapy, *PF* cisplatin, flourouracil, *RT* radiotherapy, *TPF* docetaxel, cisplatin, fluorouracil, *S* surgery, *y* year, *mo* month

or positive on PET imaging, should be included in GTV_N. Combination of GTV_P and GTV_N can be subscripted with the prescribed dose as a single GTV such as $GTV_{70,}$ which is a commonly practiced dose for locally advanced laryngeal carcinoma.

3.2 Clinical Target Volume (CTV)

CTV is the entire larynx from the top of thyroid notch to the bottom of the thyroid cartilage for T1-2 N0 cancers. Based on risk definitions, there needs to be 3 CTV volumes for definitive RT/CRT of locally advanced laryngeal tumors (Table 9.3):

Table 9.3 Typical target volume definitions for postoperative IMRT and definitive RT/CRT

CTV	Postoperative IMRT (intermediate risk)	Postoperative IMRT (high risk)	Definitive IMRT (RT or CRT)
CTV1	Surgical bed[a] Residue tumor (−) Soft tissue involvement (−) ECE (−)	Surgical bed[a] Residue tumor (−) Soft tissue involvement (+) ECE (+)	Gross tumor + margins Primary tumor and local extensions Any enlarged node(s)
CTV2	Elective nodal regions	Elective nodal regions	Adjacent regions to CTV1 Soft tissue Nodal regions
CTV3	–	–	Elective nodal regions

Abbreviations: CRT chemoradiotherapy, *CTV* clinical target volume, *ECE* extracapsular extension, *IMRT* intensity modulated radiation therapy, *RT* radiotherapy

[a]In postoperative cases with residual tumor or nodal mass, residual mass(es) should be defined as GTV, and cases should be treated similar with definitive IMRT patients if no further surgery is planned or technically not possible

- *CTV_{70}:* Due to risk for microscopic disease spread, CTV_{70} should cover GTV_{70} with a margin of 5 mm at all directions but may be reduced to as low as 1 mm in close proximity of critical structures. For borderline nodes, such as ≤1 cm, a separate $CTV_{63–66}$ may be considered.
- *$CTV_{59.4}$:* It should encompass entire CTV_{70} with at least 1-cm margin. This volume should cover potential microscopic mucosal and submucosal routes of disease spread. For lymph node regions, the CTV_{70} should be covered with a 3–5 mm margin respecting the critical structures, which can be reduced to as low as 1 mm. High-risk nodal regions to be covered are levels II–IV on the involved N + neck. Level 1B should optionally be included if level 2 is positive. Level 5 is not included unless levels 2–4 are massively involved. As typical lymphatic drainage of larynx does not contain retropharyngeal nodes, they should not be included in the absence of bulky node, which may cause retrograde lymphatic flow to retropharyngeal nodes. Level 6 should be included in presence of subglottic extension or primary lesions originating from this region.
- *CTV_{54}:* Should include levels 2–4 of the uninvolved neck.

3.3 Planning Target Volume (PTV)

PTV is extra margin around the CTVs to compensate for the intra- and inter-fraction variabilities, uncertainties of treatment set-up, and internal organ motion. It is better for any institutions to define their own PTV margin. If the institution has not performed a study to define the appropriate magnitude of PTV, following recommendations can be followed:

- *PTV_{70}:* Although should be determined institutionally, as the laryngeal structures are highly mobile, it is appropriate to cover CTV_{70} (primary) with 1-cm margin or more (especially in craniocaudal direction. Nodal part of PTV_{70} should be contoured with a margin of 3–5 mm around nodal part of CTV_{70}.
- *$PTV_{59.4}$:* Should be contoured with a margin of 3–5 mm around $CTV_{59.4}$.
- *PTV_{54}:* Should be contoured with a margin of 3–5 mm around CTV_{54}.

3.4 Level definition tips are as follows

Submandibular gland and jugular vein interface separates levels 1B (submandibular) and 2a; level 2 (subdigastric-jugulodigastric) follows the jugular vein to the fossa; hyoid and cricoid define the borders of levels 2, 3 (midjugular), and 4 (low jugular and supraclavicular); and posterior edge of sternocleidomastoid defines level 5 (posterior cervical).

3.5 Case Contouring (Fig. 9.2)

- Check coverage whole larynx from the hyoid bone to lower border of cricoid cartilage.
- Check coverage prevertebral fascia.
- Check coverage of the paratracheal and prelaryngeal lymph nodes in locally advanced disease.

3.6 Guidelines for Normal Tissue Constraints

Normal tissue dose constraints detailed below should strictly be obeyed to prevent debilitating late toxicities. Dose-volume histogram of critical organ doses for the present representative patient is demonstrated in Figs. 9.3 and 9.4:

- Parotid glands: Mean dose (D_{mean}) of ≤26 Gy or less (should be achieved in at least one gland) or at least 20 cc of the combined volume of both glands should receive <20 Gy or at least 50 % of one parotid gland should receive <30 Gy).
- Brain stem: maximum dose (D_{max}) ≤54 Gy
- Spinal cord: D_{max} ≤45 Gy
- Oral cavity: D_{mean} <30–35 Gy
- Brain: D_{max} ≤50 Gy and any large volume of brain should receive <30 Gy
- Optic nerve, Optic Chiasm: D_{max} <54 Gy
- Lens: D_{max} is 10 Gy, and <5 Gy if achievable
- Mandible: D_{max} <69 Gy (hot spots >70 Gy should be kept out of the mandible).
- Cochlea: No more than 5 % receives ≥55 Gy
- Brachial plexus: 66 Gy max dose

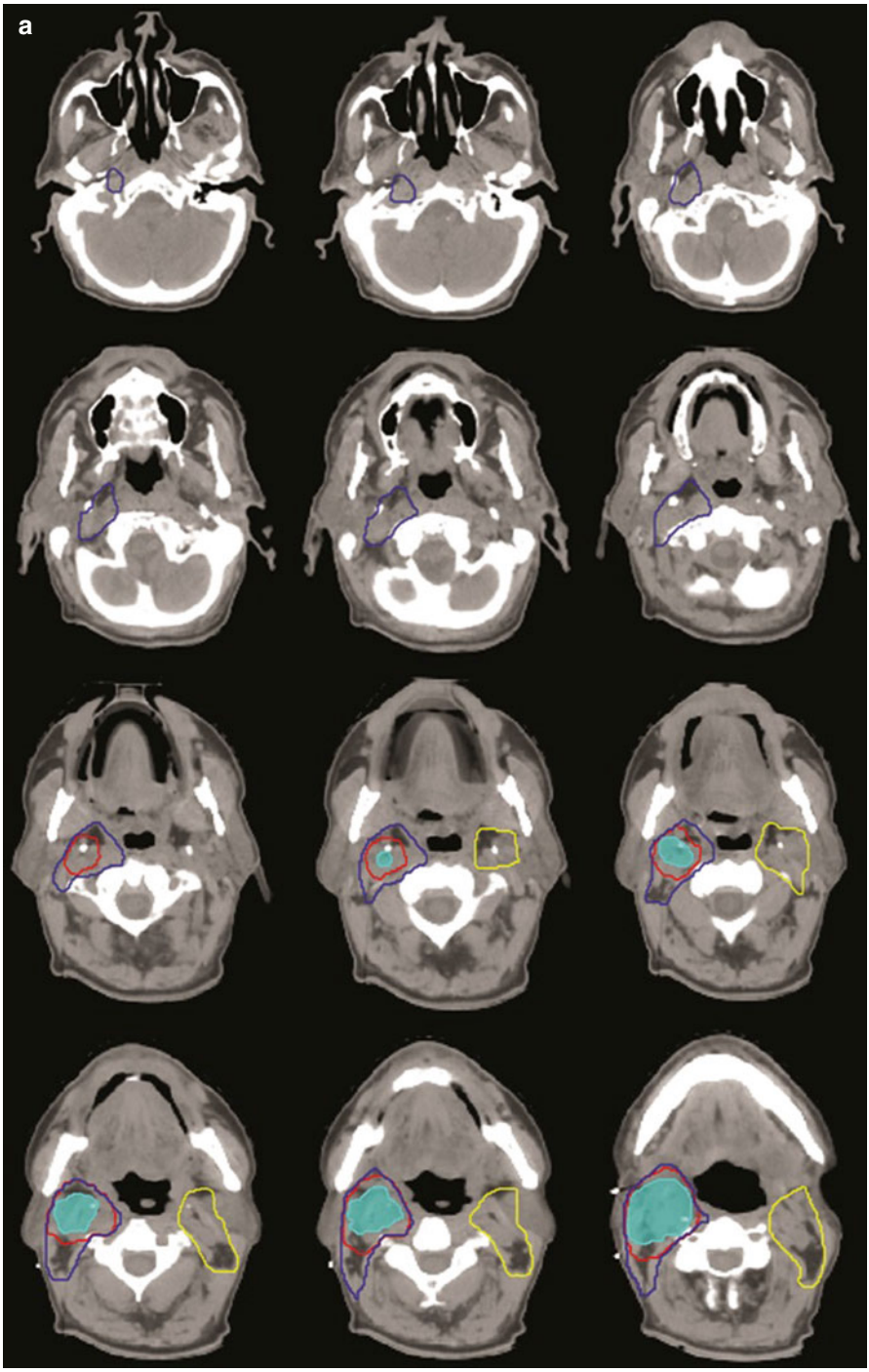


Fig. 9.2 (**a**, **b**) Representative target volumes for the laryngeal cancer case presented herein

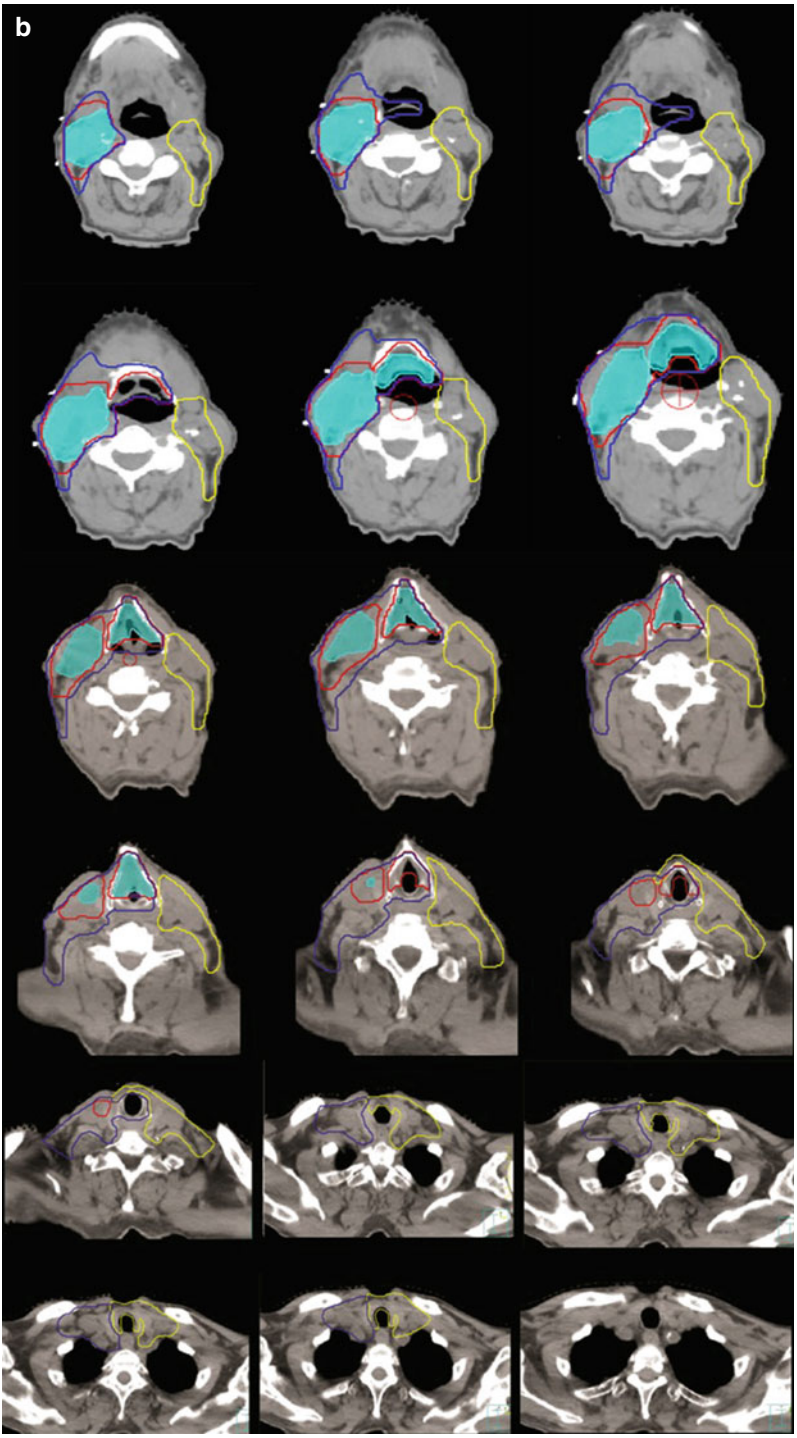


Fig. 9.2 (continued)

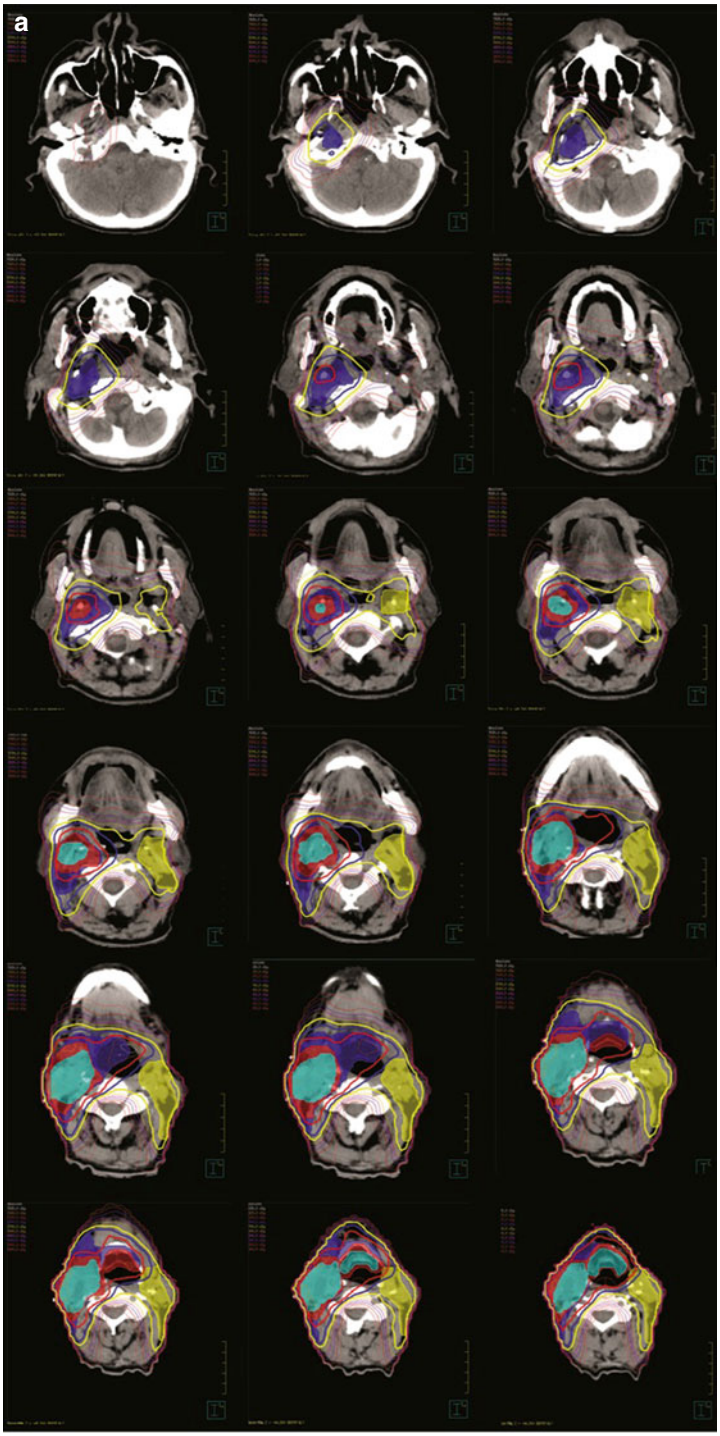


Fig. 9.3 (**a**, **b**) Dose distribution of PTV70, PTV59.4, and PTV 54 Gy for the case presented here

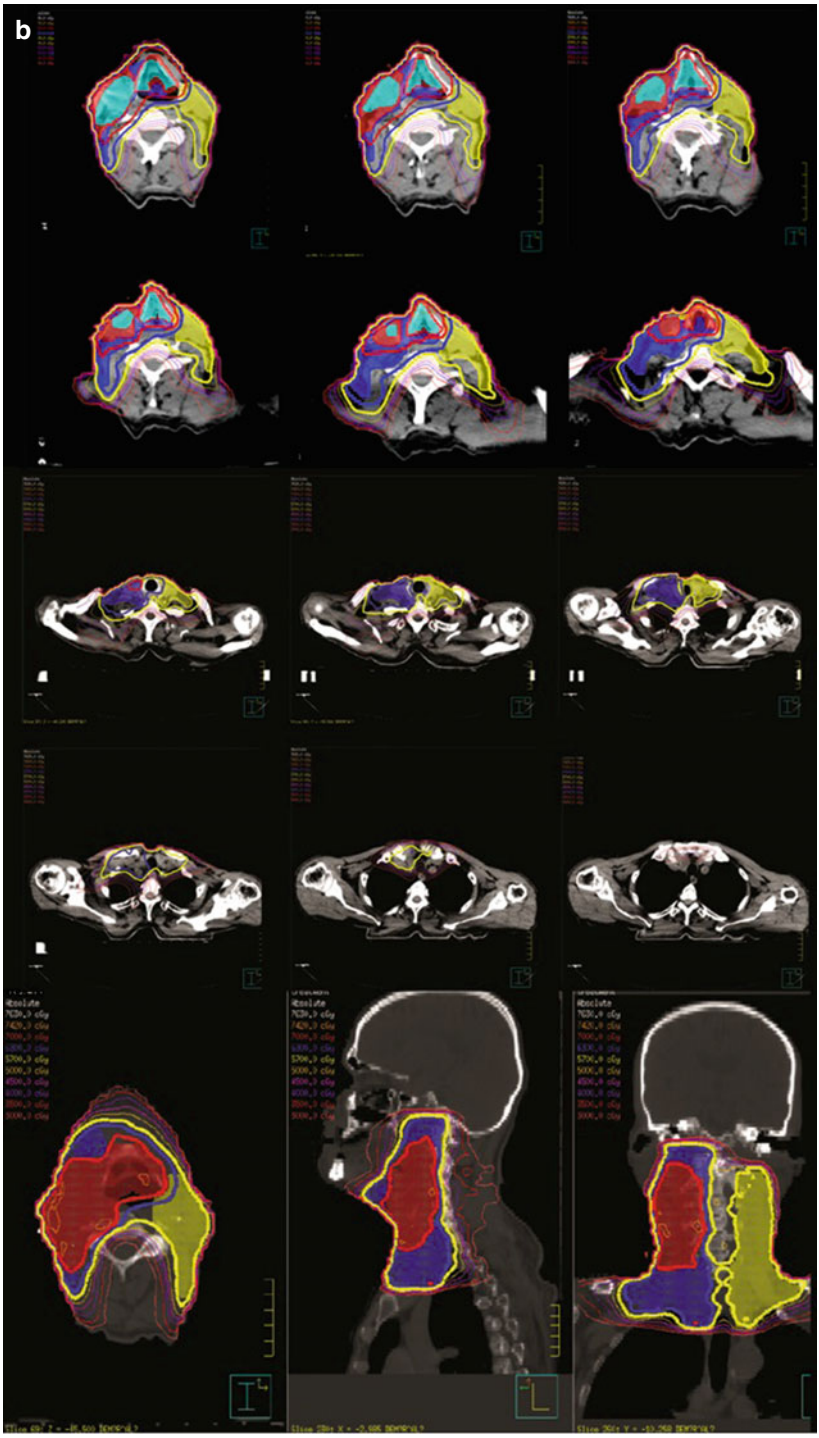
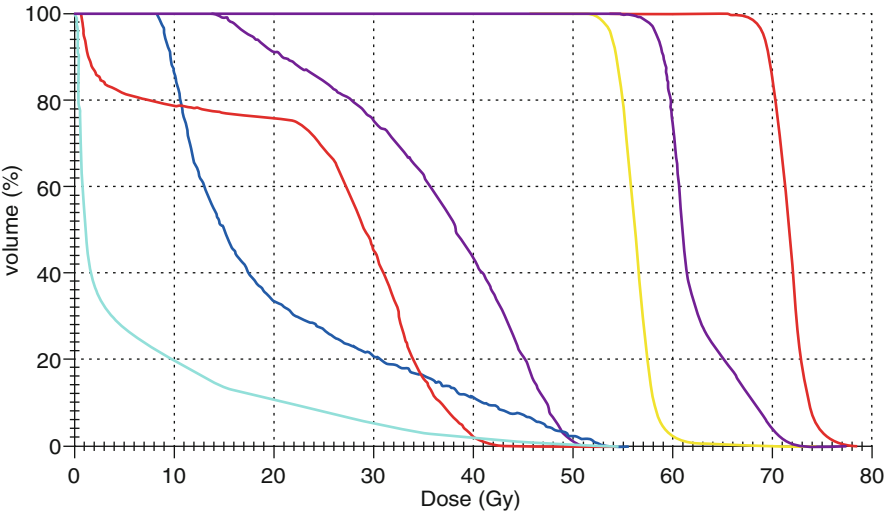


Fig. 9.3 (continued)



Structure	Min dose Gy	Max dose Gy	Mean dose Gy
PTV 70 Gv	64.145	79.349	71.648
PTV 59.4 Gy	53.428	74.882	62.241
PTV 54 Gy	48.205	72.922	56.311
Brain stem	13.942	51.552	36.408
Spinal cord	0.569	44.350	24.653
L parotid	0.096	67.423	5.988
R parotid	8.098	53.547	20.190

Fig. 9.4 Dose-volume histogram of prescribed target volume doses and critical organs at risk

4 Treatment Planning Assessment

- *Step 1:* Check whether the targets are adequately covered by prescribed dose for PTV1, 2, and 3 according to Table 9.4. As far as possible, every effort should be spent to achieve IMRT plans without any deviations. However, only for extensively large tumors and tumors in close proximity to critical structures, minor deviations can be accepted for necessary assessment parameters.
- *Step 2:* Presence of a large hot spot should be carefully checked and should not be permitted for more than 20 % of PTV1 (e.g., 70 Gy) to receive ≥110 % and no more than 5 % of PTV1 to receive ≥%115 of prescribed dose, respectively.
- *Step 3:* Normal tissue constraints should carefully be checked.
- *Step 4:* Check whether the hot/cold spots exist in the wrong place (slide by slide by looking at isodose distribution): The hot spots needs to be arranged in the GTV. It is necessary to make sure that the hot spot is not on a nerve in the CTV.

Table 9.4 Criteria for IMRT plan assessment

PTV	No variation	Minor variation
PTV70	1. 95 % of any PTV70 is at or above 70 Gy	1. 95 % of PTV70 is at or above 70 Gy
	2. 99 % of PTV70 is at or above 65.1 Gy	2. 97 % of PTV70 is at or above 65.1 Gy
	3. No more than 20 % of PTV70 is at or above 77 Gy	3. No more than 40 % of PTV70 is at or above 77 Gy
	4. No more than 5 % of PTV70 is at or above 80 Gy	4. No more than 20 % of PTV70 is at or above 80 Gy
	5. Mean dose ≤74 Gy	5. Mean dose ≤76 Gy
PTV63 (if applicable)	1. 95 % of any PTV63 is at or above 63 Gy	1. 95 % of any PTV63 is at or above 58.6 Gy
	2. 99 % of PTV63 is at or above 58.6 Gy	2. No more than 40 % of PTV63 is at or above 77 Gy
	3. No more than 20 % of PTV63 is at or above 77 Gy	3. No more than 20 % of PTV63 is at or above 80 Gy
	4. No more than 5 % of PTV63 is at or above 80 Gy	
PTV59.4	1. 95 % of any PTV59.4 is at or above 59.4 Gy	1. 95 % of PTV59.4 is at or above 55.2 Gy
	2. 99 % of PTV59.4 is at or above 55.2 Gy	2. No more than 40 % of PTV59.4 is at or above 77 Gy
	3. No more than 20 % of PTV59.4 is at or above 77 Gy	3. No more than 20 % of PTV59.4 is at or above 80 Gy
	4. No more than 5 % of PTV59.4 is at or above 80 Gy	
PTV54 (if applicable)	1. 95 % of any PTV54 is at or above 54 Gy	1. 95 % of PTV54 is at or above 50.2 Gy
	2. 99 % of PTV54 is at or above 50.2 Gy	2. No more than 40 % of PTV54 is at or above 65.3 Gy
	3. No more than 20 % of PTV54 is at or above 65.3 Gy	3. No more than 20 % of PTV54 is at or above 68.3 Gy
	4. No more than 5 % of PTV54 is at or above 68.3 Gy	

IMRT intensity modulated radiotherapy, *PTV* planning target volume

Case plan: The patient with locally advanced hypopharyngeal carcinoma presented here was treated with concurrent CRT (cisplatin 100 mg/m^2, every 21 days) utilizing SIB-IMRT technique. As demonstrated in Figs. 9.3 and 9.4, the prescribed doses for PTV1, PTV2, and PTV3 were 70, 59.4, and 54 Gy in 33 fractions, respectively.

Treatment algorithm and patient follow-up: Recommended-evidence based treatment options and patient follow-up after treatment for early and locally advanced-stage hypopharyngeal carcinoma patients are as depicted in Figs. 9.5, 9.6, 9.7, 9.8, 9.9, 9.10 and 9.11, respectively.

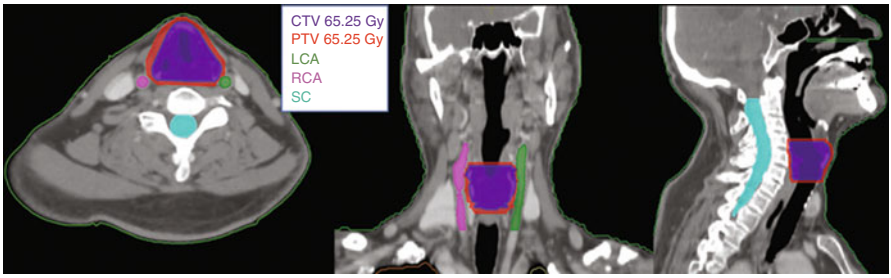


Fig. 9.5 Target volumes and critical organ contours for early-stage (T1-2 N0) laryngeal carcinoma on axial (**a**), coronal (**b**), and sagittal (**c**) planes (*CTV* clinical target volüme, *LCA* left carotid artery, *PTV* planning target volume, *RCA* right carotid artery, *SC* spinal cord)

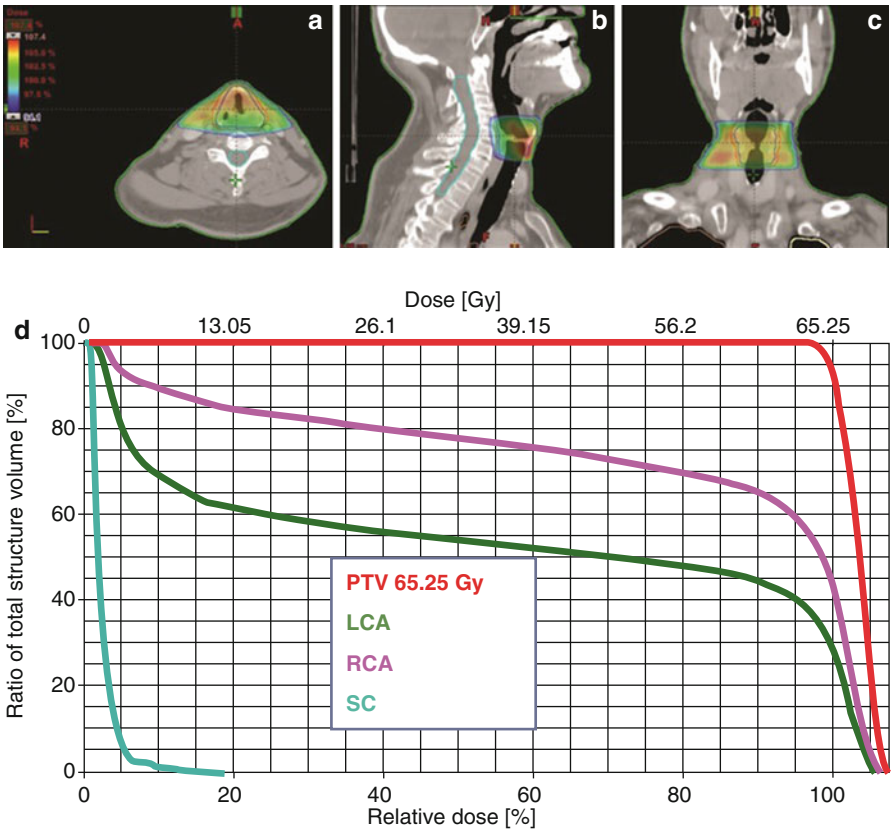


Fig. 9.6 Dose coverages (**a**–**c**) and dose-volume histogram (**d**) for 3D-conformal plans for early stage laryngeal cancer case

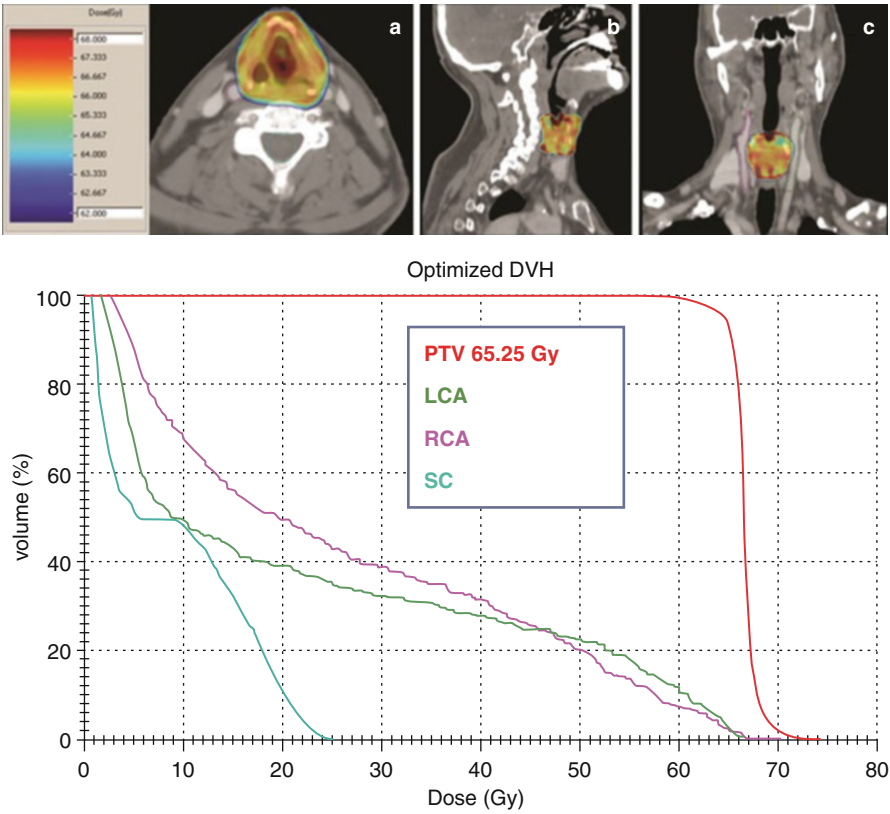


Fig. 9.7 Dose coverages (**a**–**c**) and dose-volume histogram (**d**) for carotid sparing IMRT plans for early-stage laryngeal cancer case

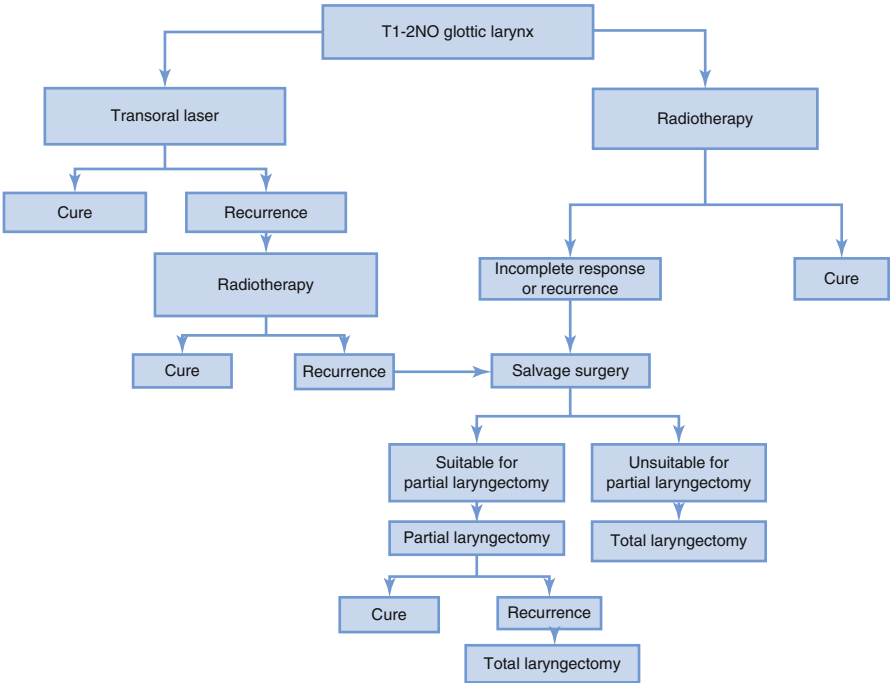


Fig. 9.8 Recommended algorithm for treatment of early glottic laryngeal cancer

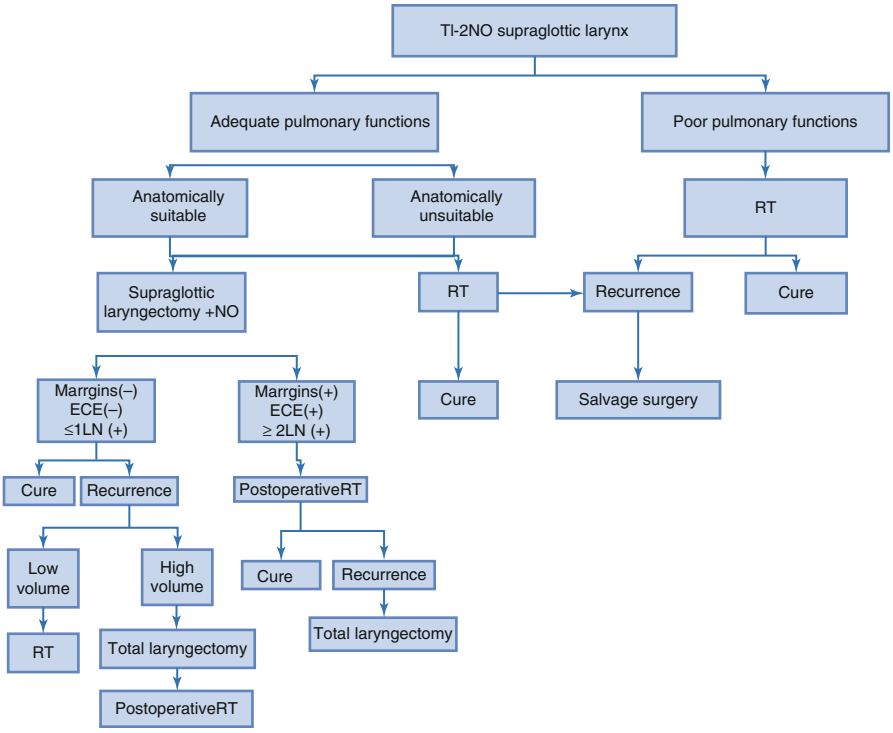


Fig. 9.9 Recommended algorithm for treatment of early supraglottic laryngeal cancer. *Abbreviations*: *ECE* extracapsular extension, *LN* lymph node, *ND* neck dissection, *RT* radiotherapy

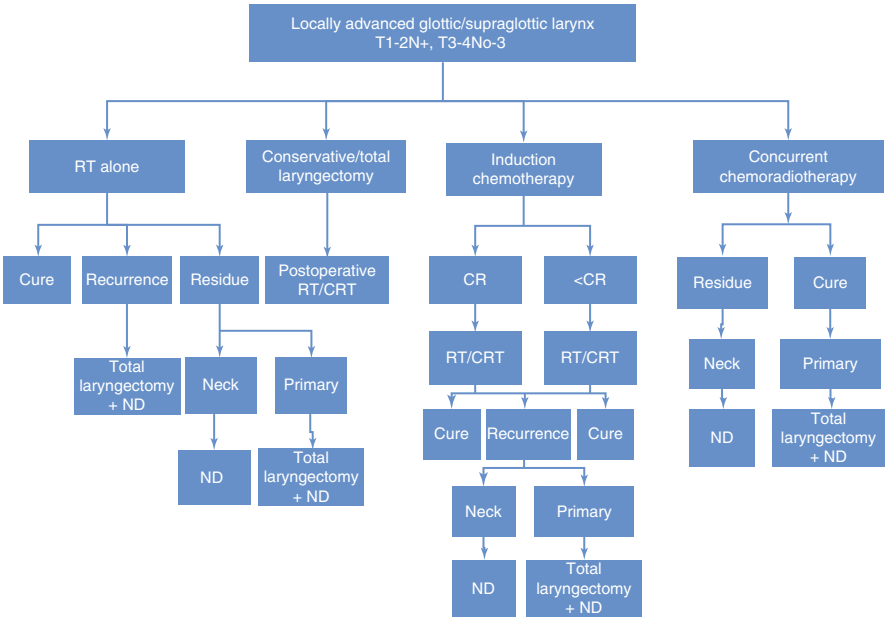


Fig. 9.10 Recommended algorithm for treatment of locally advanced laryngeal cancer. *Abbreviations*: *CR* complete response, *CRT* chemoradiotherap, *ECE* extracapsular extension, *LN* lymph node, *ND* neck dissection, *RT* radiotherapy

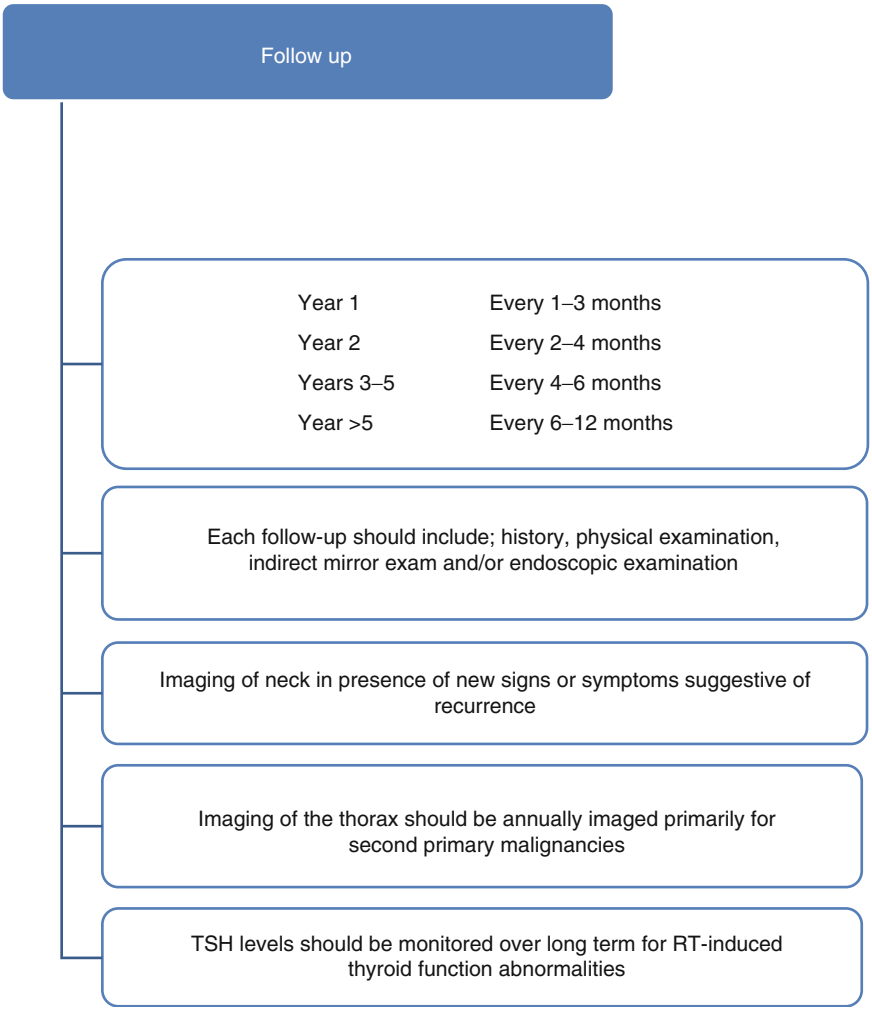


Fig. 9.11 Recommended algorithm for follow-up of laryngeal cancers

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