Head and Neck Cancers

2

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2.1 Nasopharynx

Overview

Epidemiology

The distribution exhibits rare prevalence in United States and Europe while high incidence in Southern China, Southeast Asia, North Africa and the Middle East. Early infection with EBV results in developing NPC after EBV re-activation. EBV latent integral membrane proteins (EBNA-1, LMP-1 and LMP-2), and BamHI-A genome fragment are commonly expressed.

High incidence might be related with nitrosamines and/or potential EBV activators such as salt-cured foods, preserved or fermented foods, rancid butter and sheep's fat. Smoking is related with keratinizing NPC.

Pathological and Biological Features

WHO Type I: sporadic, keratinizing squamous cell carcinoma, high risk of local regional recurrence,

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WHO Type IIA/B: endemic, EBV related, non-keratinizing/undifferentiated carcinoma, high risk of distant metastasis

Lymphoepithelioma: High lymphoid component, high risk of distant metastasis, good local control.

Definitive Therapy

Radiation therapy is the backbone of treatment for all stages, sufficient alone in stage I, concurrent with chemotherapy for stages II–IVB. Neoadjuvant/Induction chemotherapy with platinum/5FU ± taxane followed by concurrent chemoradiotherapy is also an investigated option for stages II–IVB. Induction chemotherapy followed by response evaluation with definitive radiotherapy if complete response; if incomplete, then palliative radiotherapy to metastatic sites.

Adjuvant Therapy

Adjuvant chemotherapy is a standard approach following concurrent chemoradiotherapy.

Key Words: Nasopharynx cancer, Radiotherapy

2.1.1 Case Presentation

Forty years old female with no nonsmoking or significant past medical history admitted with a left neck swelling, a congested nose and epistaxis. She had no dysphagia, odynophagia, or swallowing, and chewing problems. Cranial nerves II–XII are grossly intact without any facial numbness. Her physical exam was normal for ears and nose. Exam with visualization or palpation showed no dental problems, no lesions of the gingiva, buccal mucosa, floor of mouth, oral tongue, base of tongue, hard palate, soft palate, tonsillar fossa or posterior oropharyngeal wall. Palate elevation and tongue protrusion were normal. There was approximately 1.5–2 cm hardly palpable, mobile nodes in bilateral level II. The fiberoptic scope through left nasal cavity revealed a left erythematous nasopharyngeal mass centered on the left fossa of Rosenmuller, superiorly to the roof of the nasopharynx, and inferiorly to the level of the soft palate, without any extention into the posterior aspect of the nasal cavity, oropharynx, larynx (mobile vocal cords), and hypopharynx. MRI defined a left nasopharyngeal lesion filling the Rosen Muller fossa with intact pharyngobasilar fascia and parapharyngeal space. (Figs. 2.1, 2.2, 2.3, and 2.4). The lesion was touching the carotid space posterolaterally without any invasion, as there was no invasion to clivus. The longus colli posterior to the lesion showed blurred enhancement with no direct invasion. No intracranial extension was defined. The imaging also revealed bilateral retropharyngeal nodal disease with central necrosis (one on right, two on left side), largest on left measuring 1.5 cm. Bilateral nodal disease was documented as left 13 × 12 mm and 7 × 4 mm at level IIA, 10 × 5 mm at level VA, right largest

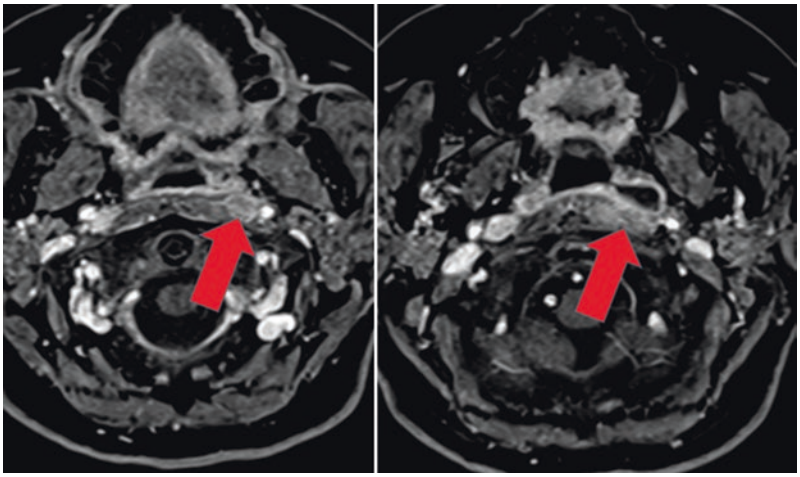


Fig. 2.1 Axial MRI images displaying retropharyngeal nodes

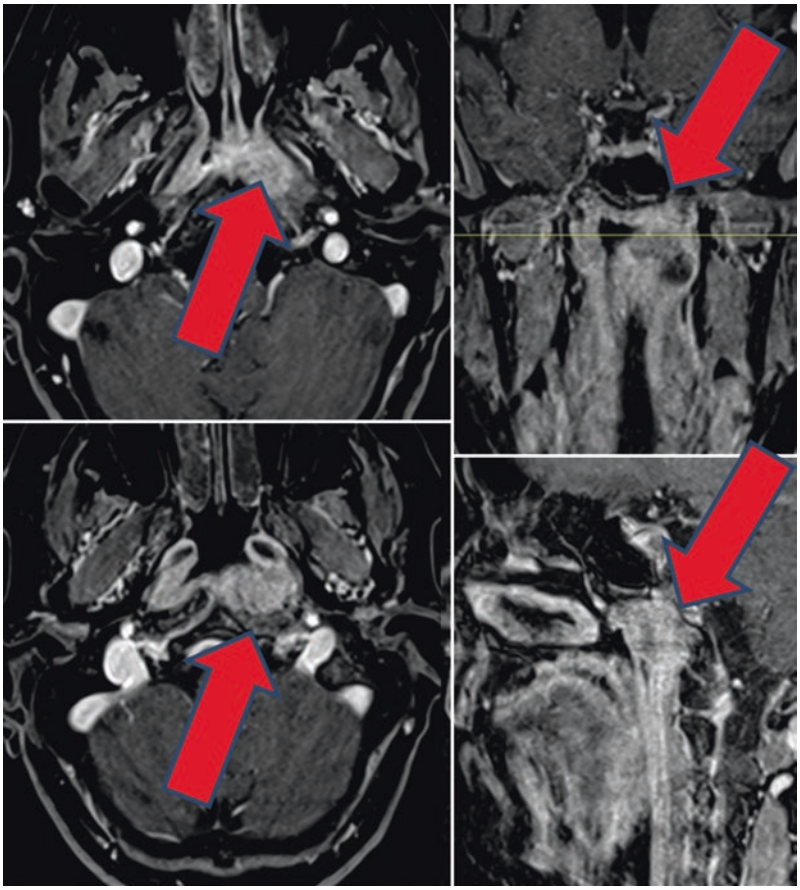


Fig. 2.2 Axial and coronal and sagittal MRI images showing left nasopharyngeal lesion filling the Rosen Muller fossa

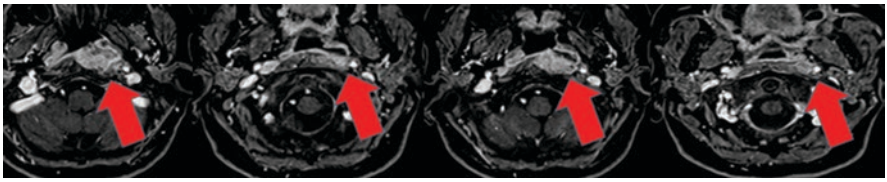


Fig. 2.3 Axial MRI images showing left nasopharyngeal lesion craniocaudally

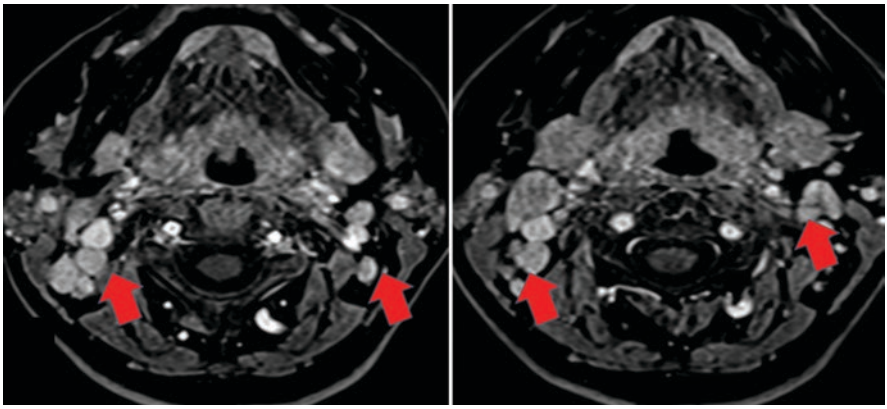


Fig. 2.4 Axial MRI images showing bilateral nodal involvement

20 × 13 mm at Level IIA, largest 12 × 6 mm at level VA in addition to multiple small levels II A, II B and VA nodes.

A biopsy from the left nasopharyngeal lesion confirmed the undifferentiated nonkeratinizing carcinoma (WHO Type IIB).

She was staged as T2N2M0, advanced stage nasopharyngeal cancer.

2.1.2 Staging

Physical examination ± fiberoptic examination is crucial. Head and neck MRI with contrast is encouraged for skull base invasion and soft tissue extension, while contrast enhanced CT might add cortical bone invasion details.

Systemic staging requires FDG PET/CT scan (preferred) or chest CT with upper abdomen. Pre-RT functional examination could require dental, speech and swallow, and audiology evaluation in addition to nutritional assesment.

The 8th Edition of AJCC Cancer Staging Manual Has Recent Changes (Tables 2.1 and 2.2)

T2 includes adjacent muscle involvement of medial, lateral pterygoid and prevertebral muscles.

T4 covers specific description of soft tissue involvement.

N3a and N3b are now in N3.

Table 2.1 AJCC Staging for Nasopharynx

Primary tumor (T)	
TX	Primary tumor cannot be assessed
	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Carcinoma in situ
T1	Tumor confined to the nasopharynx, or extenion to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle
Regional lymph nodes (N)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage
Distant metastasis (M)	
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Head and Neck. Used with permission of the American College of Surgeons, Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

Table 2.2 Prognostic stage groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T0–T1	N1	M0
	T2	N0–N1	M0
III	T0–T3	N2	M0
	T3	N1–N2	M0
IVA	T4	N0–N2	M0
	T Any	N3	M0
IVB	T Any	N Any	M1

2.1.3 Evidence Based Treatment Approaches

Stage T1N0M0 is recommended radiotherapy alone as the standard treatment. Concurrent chemoradiotherapy (CRT) has been the standard of care for non-metastatic advanced stage (stages T1, N1–3, M0 and T2–4, Any N, M0)

nasopharyngeal carcinoma, with adjuvant chemotherapy; induction chemotherapy followed by concurrent chemoradiotherapy has recently been considered an acceptable standard approach [1, 2].

RT alone was proved to be an effective treatment specifically for T1 disease in the MDACC series where RT alone succeeded a 5 year local control rates of 93%, 79%, 68%, and 53% for T1, T2, T3, and T4, respectively; defining poor prognostic factors for local control as T category, squamous histology, and cranial nerve deficits [3].

Concurrent chemoradiotherapy was encouraged with the phase III trial enrolling 230 stage II nasopharyngeal cancer patients for concurrent chemoradiotherapy with weekly cisplatin (30 mg/m^2) versus radiotherapy alone (Table 2.3) [4]. The concurrent arm demonstrated significantly improved overall survival of 94.5% at 5 years, in comparison to 85.8% for radiotherapy alone; along with improved distant metastasis free survival (94.8% vs. 83.9%) but no difference in locoregional relapse free survival (93.0% vs. 91.1%).

Intergroup 0099/RTOG 8817 phase 3 study concluded a significant disease free (69% vs. 24% at 5 years), and overall survival (78% vs. 47% at 5 years) benefit for concurrent cisplatin 100 mg/m^2 every 3 weeks and adjuvant 3 cycles chemotherapy of cisplatin 80 mg/m^2 and fluorouracil 1000 mg/m^2/day for stage III and IV nasopharyngeal cancer patients in comparison to RT alone (70 Gy, 35–39 fractions, 1.8–2.0 Gy/fraction/day, in both arms [5]. Concurrent chemoradiotherapy favored over radiotherapy alone at 5 years for disease free and overall survival in other trials as Taiwan, [6] Singapore, [7] China, [8] and Hong Kong [9, 10] randomized trials.

Though considered experimental, sequential therapy including induction chemotherapy followed by concurrent chemoradiotherapy has been in practical life for patients in case of high risk of distant metastasis of high nodal disease burden, supraclavicular disease, or in case of large T4 primary tumors, tumors compressing the critical organs at risk such as optic pathways, brainstem, temporal lobes increasing technical effort to deliver efficient and safe radiotherapy doses. Neoadjuvant/Induction chemotherapy approach followed by concurrent chemoradiotherapy has not demonstrated overall survival benefit overall concomitant chemoradiotherapy yet, but has concluded that a progression free survival and/or distant metastasis free survival could be provided with acceptable toxicity (Table 2.4) [18]. Phase II randomized trial comparing concomitant radiotherapy with weekly cisplatin and induction chemotherapy with docetaxel and cisplatin followed by concomitant radiotherapy with weekly cisplatin demonstrated with similar quality of life scores that there was a trend 3 year progression-free survival trend to improve with sequential therapy (88% vs. 60%, $p = 0.12$) in addition to significant increase in overall survival (94% vs. 68%) [16]. Recent phase III trials comparing sequential regimens with concurrent chemoradiotherapy alone have been published from Asia [1, 2]. Sun et al. documented their open-label, phase 3, multicenter, randomized controlled trial at 10 institutions in China with the primary endpoint of failure-free survival for induction chemotherapy (3 cycles of -TPF- docetaxel, 60 mg/m^2 on day 1, intravenous cisplatin, 60 mg/m^2 on day 1, and continuous intravenous fluorouracil, 600 mg/m^2 per day from day 1 to 5, every 3 weeks) plus concurrent chemoradiotherapy

Table 2.3 Randomized prospective trials of concurrent chemoradiotherapy for locally advanced nasopharyngeal cases

Study	#	Experimental arm	Standard arm	CRT	RT	*p*
				Disease free survival/overall survival		
Intergroup 0099; Al-Sarraf et al. [5, 11]	150	70 Gy with cisplatin + 3 cycles of cisplatin/5FU	70 Gy	58%/67%	29%/37%	<0.001/0.005
Singapore; Wee et al. [7]	221	70 Gy with cisplatin + 3 cycles of cisplatin/5FU	70 Gy	72% (3 years)/80% (3 years)	53% (3 years)/65%	0.01/0.01
Taiwan; Lin et al. [6]	284	70–74 Gy with cisplatin	70–74 Gy	72%/72%	53%/53%	0.0012/0.0022
Hong Kong; Lee et al. [9]	348	66 Gy with cisplatin + 3 cycles of cisplatin/5FU	66 Gy	72%/78%	62%/54%	0.027/0.97
China; Zhang et al. [8]	115	70–74 Gy + 10 Gy boost with oxaliplatin	70–74 Gy + 10 Gy boost	96% (2 years)/100%	83% (2 years)/77%	0.02/0.01
Hong Kong; Chan et al. [10]	350	66 Gy + 10–20 Gy boost with cisplatin	66 Gy + 10–20 Gy boost	60%/70%	52%/78%	NS/0.065
China; Chen et al. [12]	506	60–66 Gy with cisplatin + 3 cycles of cisplatin/5FU	60–66 Gy with cisplatin	86% (2 years)/NA	84% (2 years)/NA	0.13/NS

NS not significant, *CRT* chemoradiotherapy, *RT* radiotherapy

Table 2.4 Prospective randomized trials of neoadjuvant chemotherapy for locally advanced nasopharyngeal cases

Trials	*n*	Experimental arm	Standard arm	Experimental arm	Standard arm	*p*
				Disease free survival/overall survival		
International nasopharyngeal cancer study [13]	339	3 cycles of cisplatin + epirubicin + bleomycin, then 70 Gy	70 Gy	54% (2 years)/NA	40% (2 years)/NA	<0.001/ NS
China; Ma et al. [14]	456	2–3 cycles of cisplatin + bleomycin + 5FU, then 70 Gy	70 Gy	59%/63%	49%/56%	0.05/0.11
AOCOA; Chua et al. [15]	334	2–3 cycles of cisplatin + epirubicin, then 70 Gy	70 Gy	48% (3 years)/78% (3 years)	42% (3 years)/71% (3 years)	NS/NS
Hong Kong; Hui et al. [16]	65	2 cycles of docetaxel + cisplatin, then 70 Gy with cisplatin	70 Gy with cisplatin	59.5% (3 years)/94.1% (3 years)	88.2% (3 years)/67.7% (3 years)	0.12/0.012
China; Xu et al. [17]	338	2 cycles of cisplatin/5FU, then 70 Gy with cisplatin/5FU + 4 cycles of cisplatin/5FU	70 Gy with cisplatin/5FU + 4 cycles of cisplatin/5FU	82.5%/94.5% (3 years)	78.5%/95.9% (3 years)	0.16/0.54
China; Sun et al. [1]	477	3 cycles of docetaxel/cisplatin/5FU every 3 weeks, then ≥66 Gy IMRT with cisplatin every 3 weeks	≥66 Gy IMRT with cisplatin 100 mg/m^2 every 3 weeks	80% (3 years)/NA	72% (3 years)/NA	0.034/NA
China; Cao et al. [2]	476	2 cycles of cisplatin/5FU every 3 weeks, then ≥66 Gy with cisplatin every 3 weeks	≥66 Gy with cisplatin 80 mg/m^2 every 3 weeks	82% (3 years)/88.2% (3 years)	74.1% (3 years)/88.5% (3 years)	0.028/NS

NS not significant, *CRT* chemoradiotherapy, *RT* radiotherapy

(intensity-modulated radiotherapy with 3 cycles of 100 mg/m^2 cisplatin every 3 weeks) or concurrent chemoradiotherapy alone [1]. After a median follow-up of 45 months, 3-year failure-free survival was 80% in the sequential group and 72% in the concurrent chemoradiotherapy alone group (hazard ratio 0.68, p = 0.034); revealing most common grade 3 or 4 adverse events increased in sequential group as neutropenia (42% vs. 7%), leucopenia (41% vs. 41.17%), and stomatitis (41% vs. 35%). This Chinese trial in locoregionally advanced nasopharyngeal carcinoma showed that addition of TPF induction chemotherapy to concurrent chemoradiotherapy significantly improved failure-free survival with acceptable toxicity, awaiting long-term follow-up [1]. An other Chinese trial by Cao et al. published their phase III multicentre randomised controlled trial with the primary endpoint of disease-free survival (DFS) and distant metastasis-free survival (DMFS) for induction chemotherapy (2 cycles of -PF- intravenous cisplatin, 80 mg/m^2 on day 1, and continuous intravenous fluorouracil, 800 mg/m^2 per day from day 1 to 5, every 3 weeks) plus concurrent chemoradiotherapy (intensity-modulated or 3 dimensional conformal radiotherapy with 3 cycles of 80 mg/m^2 cisplatin every 3 weeks) or concurrent chemoradiotherapy alone [2]. The sequential arm with the 16.0% grade 3–4 neutropenia achieved higher 3-year DFS rate than the concurrent alone arm (82.0% vs. 74.1%, P = 0.028), while marginal statistical significance for 3-year DMFS rate (86.0% vs. 82.0%, P = 0.056), without any significant differences in OS or locoregional relapse-free survival (LRRFS) rates (OS: 88.2% vs. 88.5%, P = 0.815; LRRFS: 94.3% vs. 90.8%, P = 0.430). Induction arm was shown to improve tumor control, particularly at distant sites, in comparison to chemoradiotherapy alone without any early gain in OS [2].

2.1.4 Immobilization and Simulation

- Recommend the patient not to have any hair cut during the treatment weeks
- Position in supine with the neck extended and the head on headrest
- Wire surgical scars
- Use tongue depressors/displacers or jaw openers before thermoplastic mask if needed
- Use shoulder retractors for removing shoulders away to allow appropriate low-neck irradiation if required
- Use thermoplastic head and neck mask in possibly comfortable and reproducible position for the patient (Fig. 2.5)
- Check tightness of the mask for any space between the patient's skin and the mask, repeat this step for inter-fraction edema or weight loss to be proactive for adaptive approach
- Intravenous contrast is preferred during CT simulation to improve the visualization of the primary tumor and nodal disease as well as the parotids/submandibular glands to assist in contouring, if patient's renal functional status allows and if adequate measures for any possible anaphylactic reactions could be taken

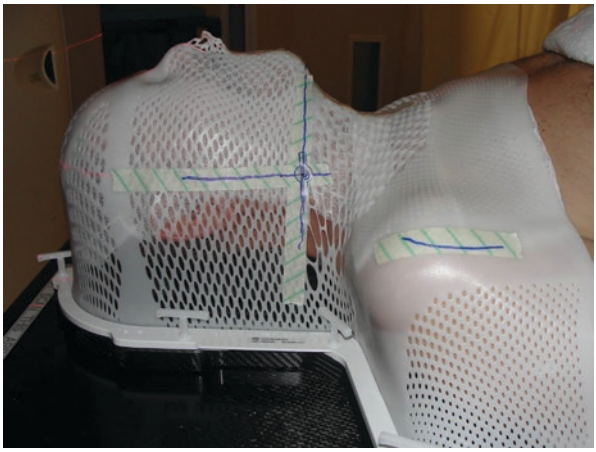


Fig. 2.5 Thermoplastic mask

- Generate CT topograms before the acquisition of the planning simulation scan to review and verify patient alignment and perform any relevant adjustments.
- Treatment planning CT is acquired using a slice-thickness of 1–3 mm covering cranium from top to the entire supra-clavicular region

2.1.5 Target Volume Delineation Guidelines

Case contouring was shown in Fig. 2.6.

Gross Tumor Volume (GTV): The gross disease at the primary disease site or any involved (>1 cm or with a necrotic center or PET positive) lymph nodes determined from physical/endoscopic examination, CT, MRI, PET-CT. The spreading pattern requires critical questioning for delineation [19, 20].

Check superiorly: skull base, foramen lacerum for VI nerve; foramen ovale; mandibular nerve in the parapharyngeal space; cavernous sinus for III, IV, ophthalmic division of V, and VI nerves.

Check anteriorly: nasal fossa or pterygopalatine fossa through sphenopalatine foramen; foramen rotundum to intracranial fossa; inferior orbital fissure into the orbital apex; superior orbital fissure to intracranium.

Check laterally: parapharyngeal space; medial or lateral pterygoid muscles (any trismus?); retrostyloid compartment related with the carotid space to cranial nerves IX, X, XI and XII; jugular foramen related with posterior cranial fossa and IX, X and XI cranial nerves.

Check inferiorly: submucosal plane into the oropharynx.

Check posteriorly: prevertebral muscles.

Clinical Target Volume (CTV):

Though the final tailoring of each case related with the treatment volumes should be based on full consideration of the individual factors and treatment facility abilities, target delineation should be consistent intra-departmentally based on

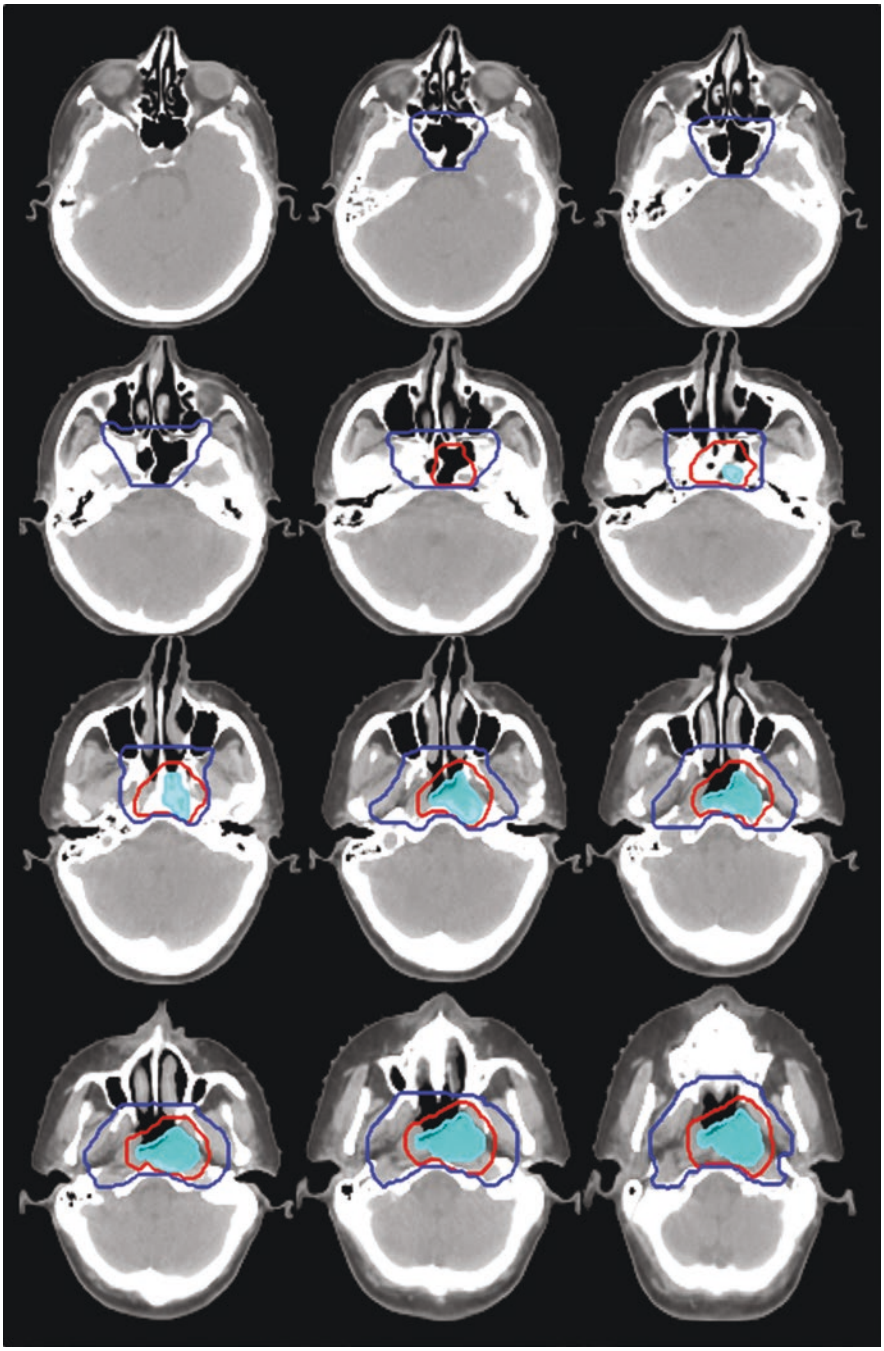
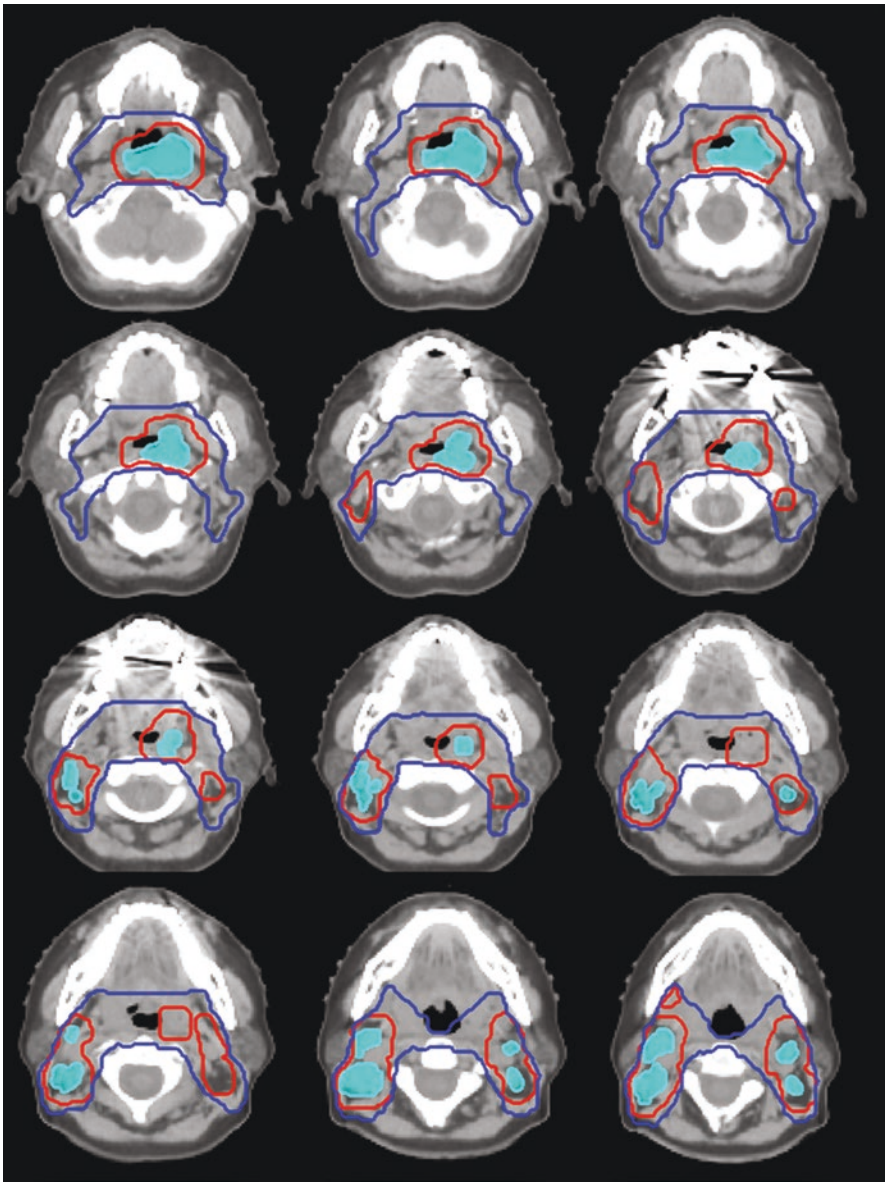


Fig. 2.6 Contouring the CTV1 (red), CTV2 (blue) and CTV3 (yellow)



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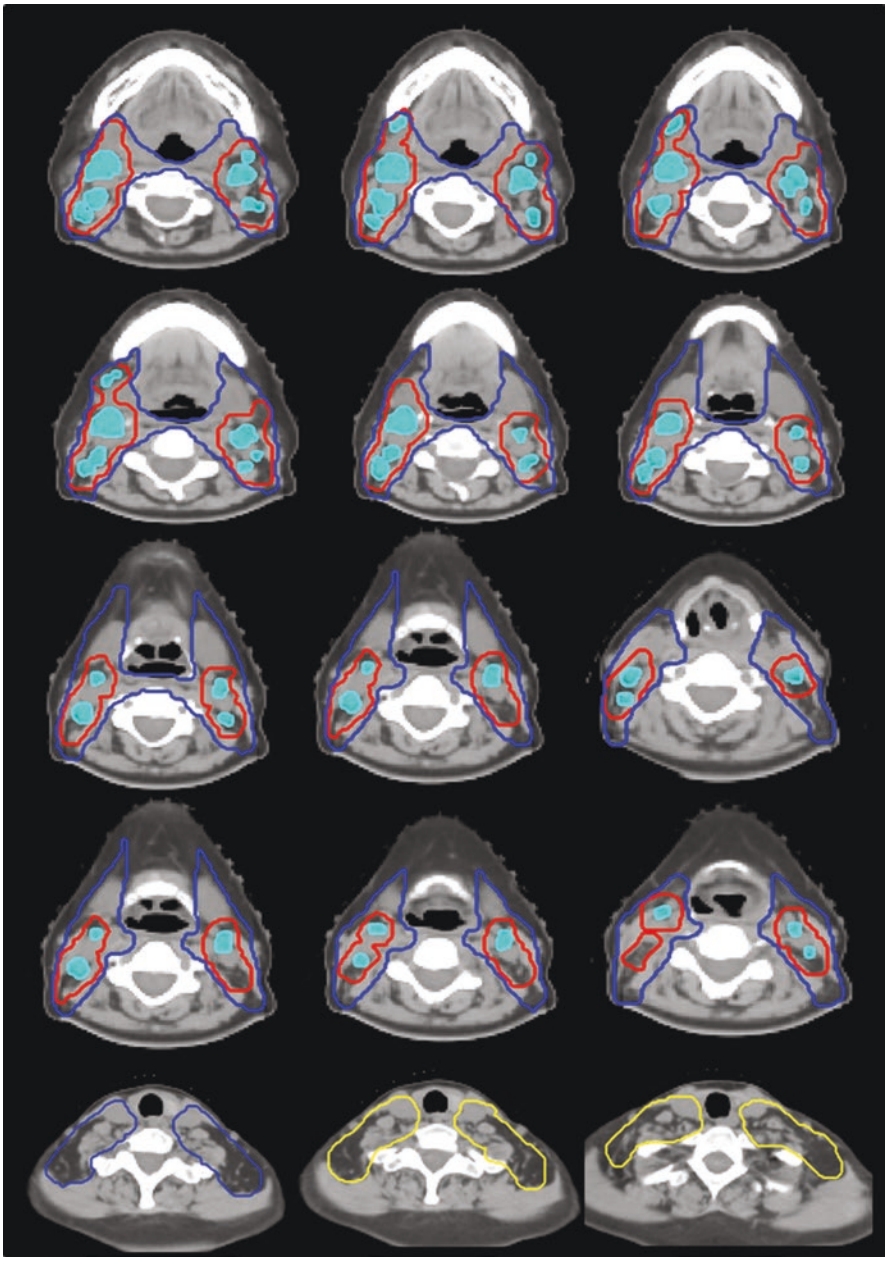


Fig. 2.6 (continued)

relevant literature; such as a recent international guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma [21].

We aim to define overall 3 CTV treatment volumes based on risk definitions;

CTV 1:GTV-Primary and GTV-Nodal with a margin of 5 mm given circumferentially around the GTV which is as low as 0–1 mm adjacent to critical organs at risk such as chiasm, brain stem.

The entire nasopharynx aside from the tumor being in whether CTV1 or CTV2 is not a common consensus, most nasopharyngeal cancer endemic Asian sites recommend whole nasopharynx to be in CTV1 while most non-Asian centers cover the rest of nasopharynx in CTV2.

CTV 2, high risk for microscopic subclinical disease including potential routes of spread for primary and nodal tumor. CTV 2 covers entire nasopharynx, anterior one third (entire if involved) of the clivus, skull base including bilateral foramen ovale and rotundum, pterygoid fossa, bilateral upper deep jugular and parapharyngeal space, inferior sphenoid sinus (all if T3-T4), posterior third of the nasal cavity and maxillary sinuses covering pterygopalatine fossa, cavernous sinus if T3, T4, bulky disease involving the roof of the nasopharynx.

CTV 2 covers nodal target bilaterally if both neck is involved, CTV 2 covers ipsilaterally if contralateral neck is free of gross nodal involvement. If bilateral neck is involved, CTV 2 includes bilateral retropharyngeal, level 1b, 2–5. If lower neck is uninvolved, CTV 2 omits level 4 and 5b to be covered in CTV 3.

CTV 3, the lower risk subclinical disease mainly low anterior neck, and contralateral neck if free of gross nodal involvement.

Planning Target Volume (PTV): Additional margin given around the CTV's to compensate for the treatment set up and possible internal organ motion. If the institution has not performed a study to define the appropriate magnitude of PTV such as 3 mm, a minimum geometric expansion in all directions of 5 mm is recommended.

2.1.6 Treatment Planning

The patient with locally-advanced nasopharyngeal carcinoma presented here was treated with concurrent CRT (cisplatin 100 mg/m^2, every 21 days) utilizing SIB-VMAT technique with CTV1 = 70 Gy, CTV2 = 63 Gy, and CTV3 = 57 Gy in 33 fractions, respectively (Fig. 2.7).

The recommended normal tissue constraints are detailed in Table 2.5.

The recommended target volume doses are detailed in Table 2.6.

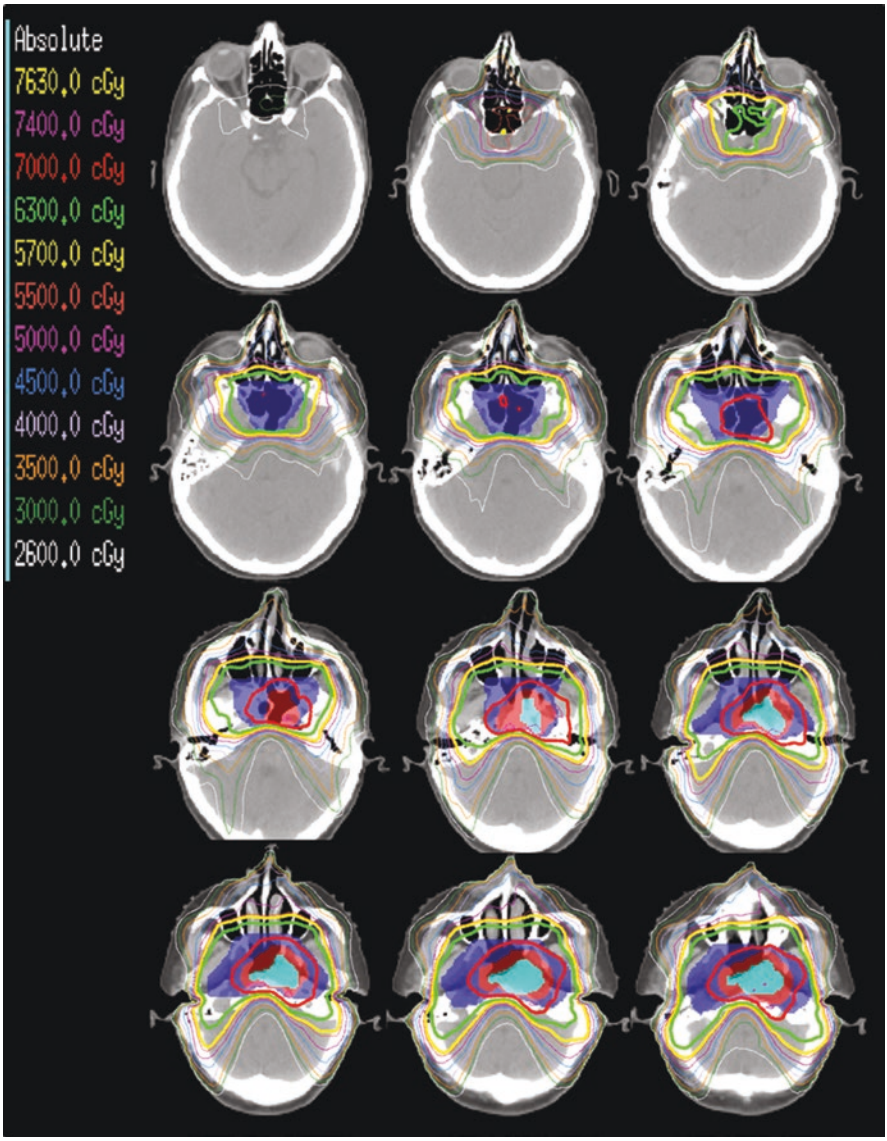
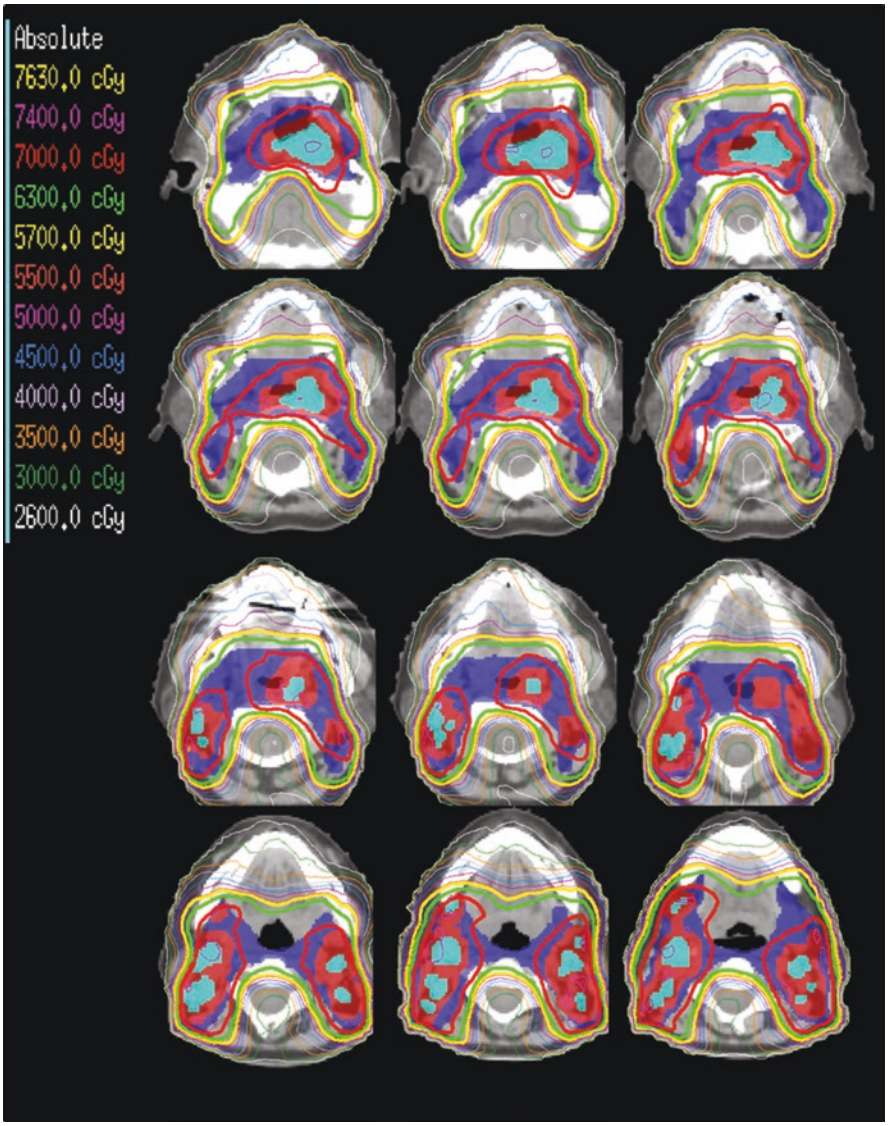


Fig. 2.7 Treatment plan for CTV70, CTV63 and CTV57



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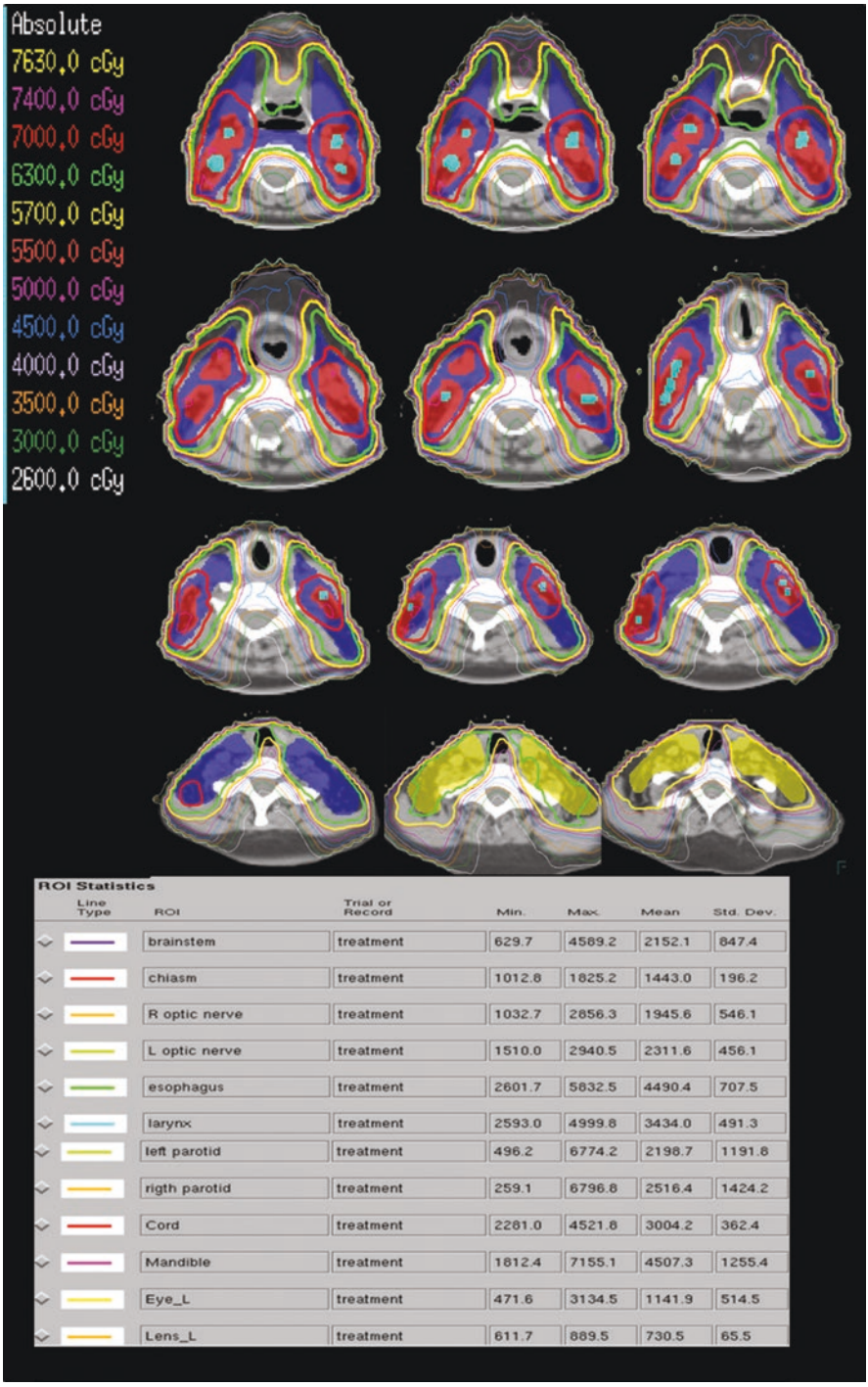


ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	brainstem	treatment	629.7	4589.2	2152.1	847.4
	chiasm	treatment	1012.8	1825.2	1443.0	196.2
	R optic nerve	treatment	1032.7	2856.3	1945.6	546.1
	L optic nerve	treatment	1510.0	2940.5	2311.6	456.1
	esophagus	treatment	2601.7	5832.5	4490.4	707.5
	larynx	treatment	2593.0	4999.8	3434.0	491.3
	left parotid	treatment	496.2	6774.2	2198.7	1191.8
	rigth parotid	treatment	259.1	6796.8	2516.4	1424.2
	Cord	treatment	2281.0	4521.8	3004.2	362.4
	Mandible	treatment	1812.4	7155.1	4507.3	1255.4
	Eye_L	treatment	471.6	3134.5	1141.9	514.5
	Lens_L	treatment	611.7	889.5	730.5	65.5

Fig. 2.7 (continued)

Table 2.5 Normal tissue constraints

Structure	Constraints
Brain	Dmax <54 Gy
Brainstem	Dmax <54 Gy (no more than 1% to exceed 60 Gy)
Spinal cord	Dmax <45 Gy (no more than 1% to exceed 50 Gy)
Optic nerves	Dmax <54 Gy
Chiasm	Dmax <54 Gy
Mandible (TM joint)	Dmax <70 Gy
Brachial plexus	Dmax <66 Gy
Oral cavity (excluding PTV's)	Mean dose <40 Gy
Submandibular/sublingual glands	As low as possible
Parotid glands	Mean dose <26 Gy
	At least 20 cc of the combined volume of both parotid glands <20 Gy
	At least 50% of one gland <30 Gy (in at least one gland)
Esophagus, postcricoid pharynx	Mean dose <45 Gy
Each cochlea	Dmax <35 Gy if possible, no more than 5% receives 55 Gy or more
Eyes	Dmax <50 Gy
Lens	Dmax <10 Gy, try to achieve <5 Gy (as low as possible)
Glottic larynx	Mean dose <36–45 Gy

Table 2.6 Target volume doses for nasopharyngeal cancer

TNM	CTV1 (70 Gy/33 fr)	CTV2 (59.4–63 Gy/33 fr)	CTV3 (54–57 Gy/33 fr)
T1–2 N0	GTVp + 1–5 mm	NA	Bilateral RP, Ipsilateral Ib, bilateral II-III-Va (lower neck- level IV and supraclavicular nodes can be omitted) [22]
T1–4 N1	GTVp + GTVn + 5 mm (1 mm)	Ipsilateral Ib–V, bilateral RP	Contralateral Ib, II–V
T1–4 N2	GTVp + GTVn + 5 mm (1 mm)	Ib–V, bilateral RPLN	Bilateral 4 and 5b if lower neck is uninvolved
T1–4 N3	GTVp + GTVn + 5 mm (1 mm)	Ib–V, bilateral RPLN	NA

2.1.7 Treatment Algorithm for Nasopharyngeal Cancer

Treatment Algorithm for nasopharyngeal cancer is summarized in Fig. 2.8.

2.1.8 Follow Up Algorithm for Nasopharyngeal Cancer

Follow-up Algorithm for nasopharyngeal cancer is summarized in Fig. 2.9.

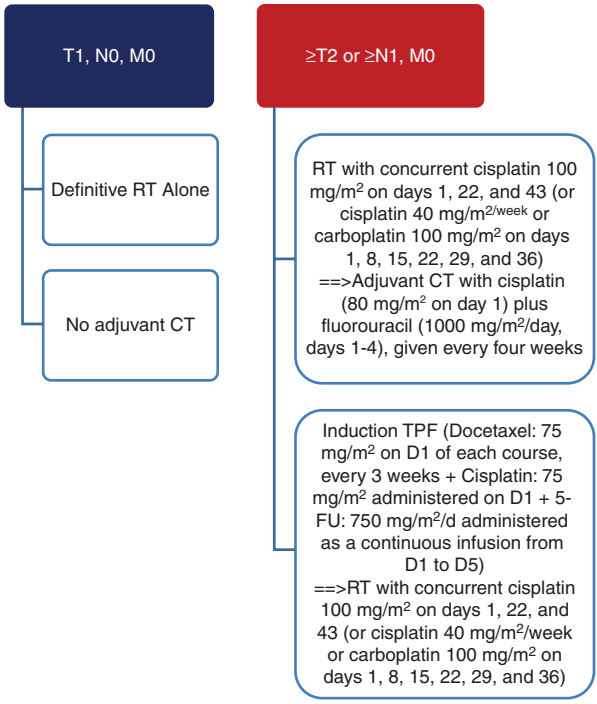


Fig. 2.8 Treatment Algorithm for nasopharyngeal cancer

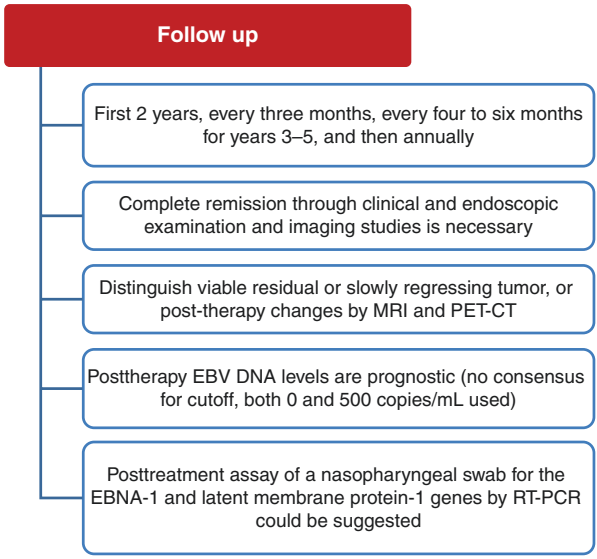


Fig. 2.9 Follow-up Algorithm for nasopharyngeal cancer

2.2 Oropharynx

Overview

Epidemiology

Tobacco and alcohol were historical major risk factors, while human papillomavirus (HPV) infection has become the current risk factor constituting approximately 70% of incidences, mainly in younger adults.

Pathological and Biological Features

Oropharyngeal subsites are soft palate, palatine tonsils, tonsillar pillars, base of tongue including lingual tonsils, posterior to circumvallate papillae, and pharyngeal wall. The most common locations are anterior tonsillar pillar and tonsil, as primary lymphatic drainage is to the retropharyngeal, level II and III nodes.

Oropharyngeal cancer is squamous cell (SCC) oriented in 95% of the cases defined as well-, moderately- or poorly-differentiated. HPV related SCC has a better prognosis. Others are adenocarcinoma, mucoepidermoid, adenoid cystic, melanoma, small cell carcinoma, non-Hodgkin's lymphoma.

Definitive Therapy

Early stage disease requires a single modality approach with surgery or radiotherapy, tailored individually per patient factors, leading to similar rates of local control and survival retrospectively. Bilateral neck needs elective treatment in almost all except for well lateralized tonsil primaries.

Locally advanced, without distant metastasis, stages III and IVA/B cancers need to be evaluated in a multidisciplinary approach to decide the initial modality to be surgery or not where radiotherapy and/or chemotherapy will also be on board; chemoradiotherapy with functional organ preservation approach or surgery and adjuvant chemoradiotherapy (for high-risk features: positive or close resection margins, nodal extracapsular extension, lymphovascular and perineural invasion).

Key Words: Oropharynx cancer, Radiotherapy

2.2.1 Case Presentation

Forty-five years old male who is an ex-smoker with 10 pack year history of smoking presented with a difficulty in swallowing with an obstruction feeling in his throat and 4 weeks old bilateral neck swelling which was prominent on the left. He denied any weight loss, trismus, odynophagia, otalgia, recent voice changes, hemoptysis, aspiration, cough, or dyspnea. He had no significant past medical history. The scope was introduced into the left nasal cavity. Nasopharyngeal mucosa and bilateral fossa of Rosenmuller were normal. As the scope was advanced, there was narrowed airway with a left sided oropharyngeal tumor localized in left vallecula. There were no lesions of the gingiva, buccal mucosa, floor of mouth, oral tongue by visualization. The scope was advanced further. There was no evidence of disease in the larynx, and hypopharynx. Vocal cords were mobile. In examination, base of tongue was soft

in palpation. Cranial nerves II–XII are grossly intact without any facial numbness. Palate elevates symmetrically. Tongue protrudes normally. The bilateral neck was also palpable for positive nodes. The MRI revealed a left sided 14 × 17 × 19 mm lesion filling the vallecular behind the base of tongue, possibly originating from lingual tonsil (Figs. 2.9 and 2.10). The tumor was not invading the base of tongue and not invading the hypopharyngeal wall, but pressing on the epiglottis medially, touching lateral pharyngeal wall laterally. The lesion was bordered by lingual tonsil superiorly and hyoid inferiorly. Multiple ipsilateral neck nodal disease was mainly at level IIA, IIB, III, IV, VA, the largest localized at left level IIA measuring 40 × 25 mm without any extranodal extension. Contralateral right nodal disease was mainly at anterior and posterior jugular chain, the largest localized at left level IIA posterior to submandibular gland measuring 16 × 7 mm without any extranodal extension. A biopsy was performed from the prominent tumor confirming moderately differentiated squamous cell carcinoma, with p16 overexpression. He was staged as T3N2M0, advanced stage oropharyngeal cancer (Fig. 2.11).

2.2.2 Staging

As the AJCC seventh edition staging of oropharyngeal cancers reflected the behavior of tobacco-related squamous cell cancer but not HPV+ disease, it had hazard discrimination with loss of the ability to differentiating between stages. Therefore AJCC 8th edition has been revised according to two distinct systems depending on whether or not they overexpress p16 to separate HPV+ or HPV− disease (Tables 2.7, 2.8, 2.9, 2.10, 2.11, and 2.12).

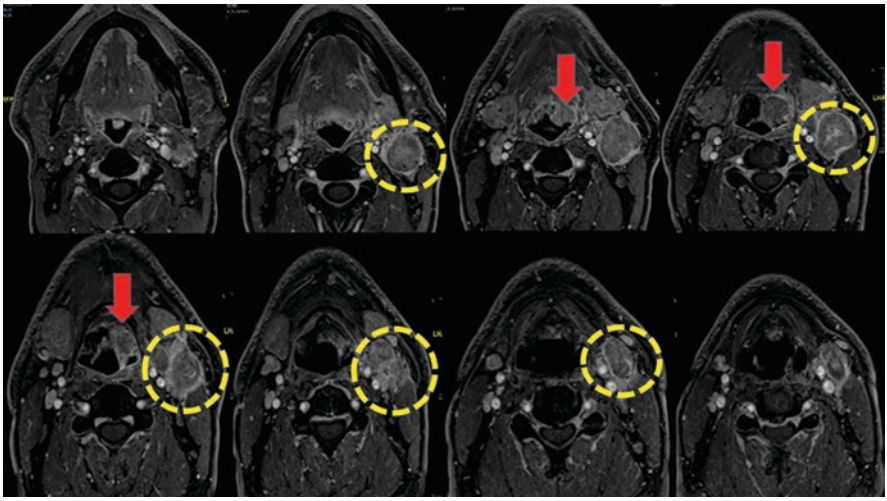


Fig. 2.10 Axial MRI images displaying left sided oropharyngeal tumor localized in left vallecula (red arrow) and large node on left neck (yellow circle)

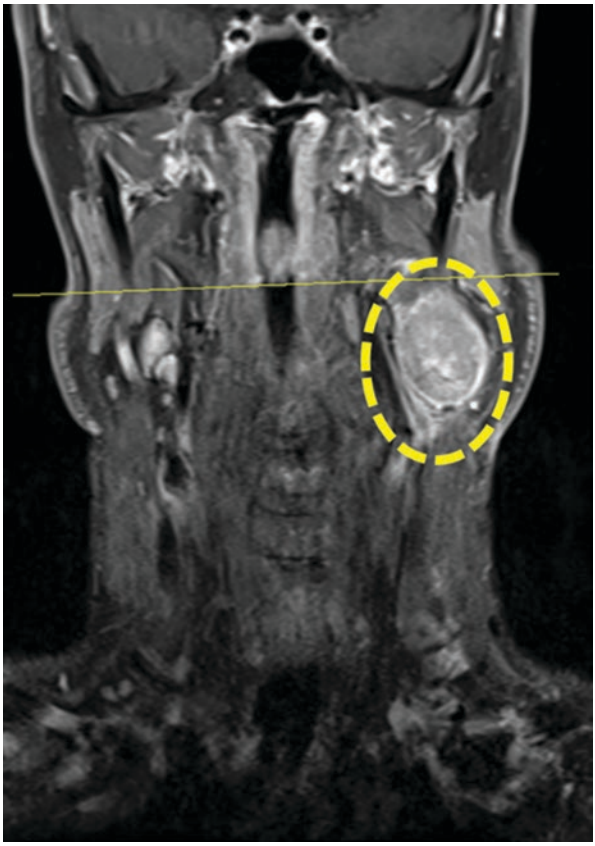


Fig. 2.11 Coronal MRI image displaying large node on left neck (yellow circle)

Table 2.7 TNM classification of HPV-mediated (p16+) oropharyngeal cancer

Primary tumor (T)	
T0	No primary tumor identified
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not more than 4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of the epiglottis
T4	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible or beyond[a]
Regional lymph nodes (N)	
Clinical N (cN)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none >6 cm
N2	Contralateral or bilateral lymph nodes, none >6 cm
N3	Lymph node(s) >6 cm

Table 2.7 (continued)

Pathological N (pN)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 4 or fewer lymph nodes
N2	Metastasis in more than 4 lymph nodes
Distant metastasis (M)	
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Head and Neck. Used with permission of the American College of Surgeons, Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

[a]Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx

Table 2.8 Clinical prognostic groups for HPV-mediated (p16+) oropharyngeal cancer (cTNM)

Stage	T	N	M
I	T0–T2	N0	M0
	T0–T2	N1	M0
II	T0–T2	N2	M0
	T3	N0–N2	M0
III	T0–T3	N3	M0
	T4	N0–N3	M0
IV	T Any	N Any	M1

Table 2.9 Pathological prognostic groups for HPV-mediated (p16+) oropharyngeal cancer (pTNM)

Stage	T	N	M
I	T0–T2	N0	M0
	T0–T2	N1	M0
II	T0–T2	N2	M0
	T3–T4	N0	M0
	T3–T4	N1	M0
III	T3–T4	N2	M0
IV	T Any	N Any	M1

Table 2.10 TNM classification of non–HPV-mediated (p16) oropharyngeal cancer

Primary tumor (T)aa	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not more than 4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of the epiglottis

(continued)

Table 2.10 (continued)

T4	Moderately advanced or very advanced local disease Tumor invades the larynx, extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible or beyond[a]
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible[a]
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Regional lymph nodes (N)	
Clinical N (cN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (−)
N2	Metastasis in a single ipsilateral lymph node >3 cm but not more than 6 cm in greatest dimension and ENE (−); or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE (−); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (−)
N2a	Metastasis in a single ipsilateral lymph node >3 cm but not more than 6 cm in greatest dimension and ENE (−)
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE (−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (−)
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE (−); or metastasis in any node(s) with clinically overt ENE (+)
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE (−)
N3b	Metastasis in any node(s) with clinically overt ENE (+)
Pathological N (pN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (+); or a single ipsilateral node >3 cm but not more than 6 cm in greatest dimension and ENE (−); or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE (−); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (−)
N2a	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (+); or a single ipsilateral node >3 cm but not more than 6 cm in greatest dimension and ENE (−)
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE (−)
N2c	Metastasis in bilateral or contralateral lymph node(s), none >6 cm in greatest dimension and ENE (−)
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE (−); or in a single ipsilateral node >3 cm in greatest dimension and ENE (+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+); or a single contralateral node of any size and ENE (+)

N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE (−)
N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE (+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+); or a single contralateral node of any size and ENE (+)
Distant metastasis (M)	
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

[a]Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Table 2.11 Prognostic stage groups for non–HPV-mediated (p16−) oropharyngeal cancer

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T Any	N3	M0
	T4b	N Any	M0
IVC	T Any	N Any	M1

Table 2.12 Histologic grade

Histologic grade (G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

The tumor suppressor protein p16 overexpression [diffuse ≥75% tumor expression, with at least moderate (+2/3) staining intensity] has been reliable inexpensive and widely available surrogate biomarker with immunohistochemistry which is easy to interpret, and an independent positive prognosticator for oropharyngeal cancer.

Changes for HPV Negative OPC Staging

T Classification: Unchanged except T0 removed.

N Classification: Unchanged with the exception of Extra Nodal Extension (ENE: Clinically evident as fixed, deep muscle or skin invasion) dividing N3 into N3a (lymph node >6 cm in dimension, no ENE) and N3b (any ENE+) M Classification: Unchanged.

Overall Stage: Unchanged except moving all ENE+ to N3b increased proportion of patients in stage IVb group Changes for HPV positive OPC Staging.

T Classification: Unchanged except removal of carcinoma in situ (Tis) and T4b (indistinguishable survival curves of T4a and T4b).

N Classification: ENE is not included in HPV positive tumors. Important difference is between clinical and pathologic staging as clinical staging is based on laterality and size of nodes whereas pathologic staging postoperatively is based on number of nodes (N1: 1–4 Nodes, N2: 5 or more nodes).

M Classification: Unchanged.

Overall Stage: Radical Change as stage IV is reserved for M1 disease.

NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. National Comprehensive Cancer Network. Available at http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Version 2. 2017—May 8, 2017; Accessed 5 Feb 2018.

2.2.3 Evidence Based Treatment Approaches

Although there is no prospective randomized comparison between surgery or radiotherapy for stage T1-2N0–1 disease, preferred approach is single modality as primary surgery (transoral or open resection) or radiotherapy alone with similar rates of local control and survival [23–25].

Concurrent chemoradiotherapy is typically the main choice of treatment for locally advanced stages III and IVA/B cancers without distant metastases (Table 2.13) [26–33]. Multidisciplinary evaluation is important to define the resectability of primary and neck nodal disease to decide whether proceed with initial surgery for primary and neck with adjuvant radiotherapy for close resection margins, lymphovascular and perineural invasion, pT3–T4, N2 or N3, nodal disease levels IV–V or adjuvant chemoradiotherapy for positive surgical margins and/or nodal extracapsular invasion (Table 2.14) [34–37].

Neoadjuvant/Induction chemotherapy followed by radiotherapy ± concurrent chemotherapy is becoming a more acceptable approach to be considered in heavy nodal volume with an increased risk of distant metastases [27, 28, 38–41]. In case of ineligibility for concurrent adequate dose of cisplatin, cetuximab as a single agent alternative could be concurrently used with radiotherapy for locoregionally advanced head and neck cancer, however cetuximab did not improve progression-free or overall survival when given additionally to the standard chemoradiotherapy with cisplatin [42].

Table 2.13 Definitive concurrent radiation plus chemotherapy trials

Study	#	Radiotherapy schedule		Concomitant chemotherapy	DFS or PFS	OS
		Standard	Experimental		RT/CRT	RT/CRT
GORTEC 94-01; Denis, Garaud et al. [26]	226	70 Gy; 2 Gy/fraction	70 Gy; 2 Gy/fraction	3 cycles of carboplatin +5FU	14.6%/26.6%	15.8/22.4
SAKK; Huguenin, Beer et al. [30]	224	74.4 Gy; 1.2 Gy/fraction twice daily	74.4 Gy; 1.2 Gy/fraction twice daily	2 cycles of Cisplatin	–/–	32%/46%
German 95–06; Budach, Stuschke et al. [31]	384	30 Gy; 2 Gy/fraction + 40.6 Gy; 1.4 Gy/fraction twice daily to a total of 70.6 Gy	14 Gy; 2 Gy/fraction + 63.6 Gy; 1.4 Gy/fraction twice daily to a total of 77.6 Gy	5FU + mitomycin	26.6%/29.3%	23.7%/28.6%
FNCLCC/GORTEC; Bensadoun, Benezery et al. [32]	163	80.4 Gy; 1.2 Gy/fraction twice daily, 5 days per week	80.4 Gy; 1.2 Gy/fraction twice daily, 5 days per week	3 cycles of Cisplatin + 5FU	25.2%(2 years) /48.2%(2 years)	20.1%(2 years)/37.8% (2 years)
RTOG 0129; Ang, Zhang et al. [33]	743	70 Gy; 2 Gy/fraction	72 Gy; 42 fractions over 6 weeks	2–3 cycles of Cisplatin	–/–	59%/56%

Table 2.14 Postoperative concurrent radiation plus chemotherapy trials

Study		RTOG 9501; (Cooper, Pajak et al., Cooper, Zhang et al. [36, 37]	EORTC 22931; Bernier, Domenge et al. [34]
#		416	334
Median follow up, months		45.9 (120)	60
% Oropharyngeal cancer		43	30
Radiotherapy alone (RT)		60 Gy in 6 weeks	66 Gy in 6.5 weeks
Concurrent radiotherapy and chemotherapy (CRT)		60 Gy in 6 weeks plus cisplatin 100 mg/m^2 on days 1, 22, and 43	66 Gy in 6.5 weeks plus cisplatin 100 mg/m^2 on days 1, 22, and 43
Inclusion criteria	Positive resection margin	+ (6% of patients)	+ (13% of patients)
	Extracapsular extension	+ (49% of patients)	+ (41% of patients)
	≥2 nodes involved	+	–
	Perineural involvement	–	+
	Vascular tumor embolism	–	+
	Oral cavity or oropharyngeal tumor with involvement of level IV or V lymph nodes	–	+
Overall survival	RT	47% (27%)	40%
	CRT	56% (29%)	53%
Local regional recurrence	RT	33% (28.8%)	31%
	CRT	22% (22.3%)	18%
Disease free survival	RT	36% (19.1%)	36%
	CRT	47% (20.1%)	47%
Conclusion by Bernier, Cooper et al. [35]		Concurrent chemoradiotherapy increased local-regional control and disease-free survival of subgroup of patients with either microscopically involved resection margins and/or extracapsular spread	

HPV-positive oropharyngeal cancer (HPVOPC) is considered as a different entity from HPV-negative cancers, based on the response to treatments and survival [43]. Patients with HPVOPC commonly admit with a smaller primary and large cervical lymph nodes [44–46]. Oropharyngeal cancer has initially been suggested to be classified on the basis of four factors defining increased mortality risk as low (HPV+, ≤10packyear smoking or >10packyear and N0–N2a), intermediate (HPV+, >10packyear smoking and N2b–N3 or HPV−, ≤10packyear smoking, T2–3), or high risk (HPV−, ≤10packyear smoking, T4 or HPV−, >10packyear smoking) of

death; [47, 48] now the staging system has completely been revised in AJCC 8th edition. As there are ongoing trials, current recommendation is treating regardless of the HPV status according to the stage (Table 2.15).

2.2.4 Target Volume Determination and Delineation Guidelines

Case contouring is given in Fig. 2.12.

Gross Tumor Volume (GTV): The gross disease at the primary disease site or any involved (>1 cm or with a necrotic center or PET positive) lymph nodes determined from physical/endoscopic examination, CT, MRI, PET-CT. Two major sites is covered below; base of tongue and tonsil:

Table 2.15 Ongoing phase 3 randomized trials in HPV-positive or HPV-negative oropharyngeal cancer patients

Trial	HPV status	Inclusion criteria	Exclusion criteria	Treatment
EORTC-1219	(−)	Oropharynx/larynx/hypopharynx primary tumor, stage III or IV (M0)	–	Accelerated 70 Gy in 6 weeks RT plus cisplatin vs. accelerated RT plus cisplatin plus nimorazole
RTOG-1016	(+)	T1–2,N2a–N3 or T3–4,any N	–	Accelerated 70 Gy IMRT plus high-dose cisplatin vs. accelerated IMRT plus cetuximab
TROG 12.01	(+)	Stage III (excluding T1–2 N1) or IV if ≤10 packyear smoking history. If >10 packyear smoking history, only N0–N2a	T4, N3 or M1	RT plus weekly cetuximab vs. RT plus weekly cisplatin
The Quarterback Trial	(+)	Oropharynx/unknown primary/nasopharynx, stage III or IV disease (M0)	Active smokers or smoking >20 packyear	Responders of 3 cycles of induction TPF randomized to 70 Gy RT plus weekly carboplatin vs RT (56 Gy) plus weekly carboplatin plus cetuximab
De-ESCALaTE	(+)	Stage III–IVa (T3N0–T4N0, and T1N1–T4N3) ≥N2b disease and smoking history	>10 packyear excluded	RT plus high-dose cisplatin vs RT plus cetuximab
ADEPT	(+)	Transoral resection (R0 margin) T1–4a, pN-positive with extracapsular spread	–	60 Gy IMRT in 6 weeks vs. IMRT plus cisplatin

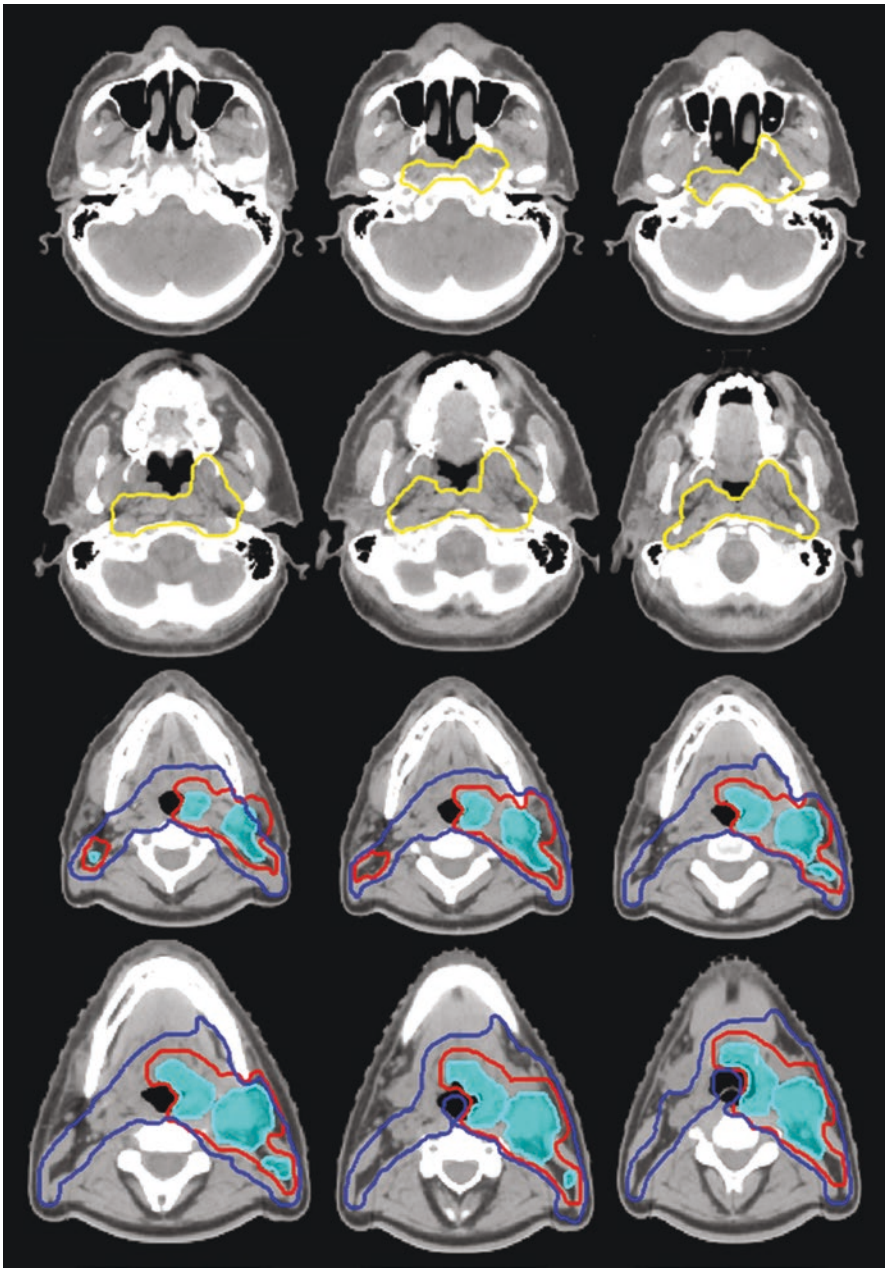


Fig. 2.12 Contouring the CTV1 (red), CTV2 (blue) and CTV3 (yellow)

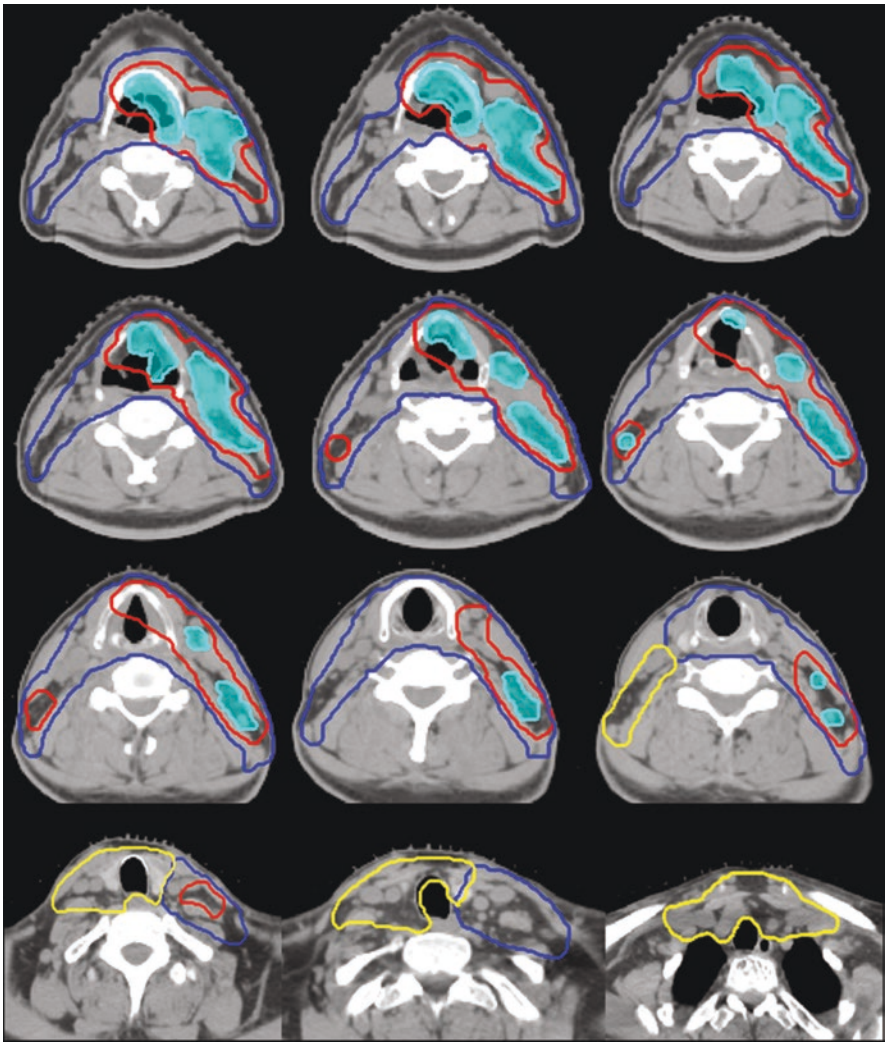


Fig. 2.12 (continued)

Check anteriorly: lingual surface of epiglottis, retromolar trigone, buccal mucosa, anterior tonsillar pillar, tonsillar fossa, oral tongue, mandible.

Check laterally: medial or lateral pterygoid muscles; retrostyloid compartment related with the carotid space to cranial nerves IX, X, XI and XII; jugular foramen related with posterior cranial fossa and IX, X and XI cranial nerves.

Check posteriorly: posterior tonsillar pillar, prevertebral fascia.

Check inferiorly: floor of the mouth, larynx, pyriform sinus, hypopharyngeal wall.

Check superiorly: soft palate, hard palate.

Clinical Target Volume (CTV): Though the final tailoring of each case related with the treatment volumes should be based on full consideration of the individual factors and treatment facility abilities, target delineation should be consistent intradepartmentally based on relevant literature; such as a recent international guideline for the delineation of the clinical target volumes (CTV) for oropharyngeal carcinoma [49].

2.2.4.1 Tonsil CTV1p

Expansion of GTV with 5–10 mm is recommended, while CTV1 of tonsil primary needs to be considered as a region/territory and a uniform expansion is not enough whereas a uniform expansion is suitable for a base of tongue primary.

Contours in air needs to be trimmed.

Anatomic landmarks which are necessary to be covered are maxillary tuberosity, minimal (≈3 mm) ipsilateral base of tongue, minimal (≈3 mm) ipsilateral glossopharyngeal sulcus, ipsilateral retromolar trigone, superior tip of hyoid inferiorly.

2.2.4.2 Tonsil CTV2

Anatomic landmarks which are necessary to be covered are ipsilateral soft and hard palate to midline, ipsilateral glossotonsillar sulcus, ipsilateral base of tongue, pterygoid plate (in CTV3 if N0), half of lateral pterygoid muscle (if trismus or radiological involvement, entire muscle), ipsilateral lateral pharyngeal wall at least to aryepiglottic fold inferiorly, ipsilateral parapharyngeal space, bilateral retrostyloid spaces if node positive.

Ipsilateral neck alone is sufficient for well-lateralized, small T1 tonsil primary without extension to soft palate or base of tongue, or node negative or low bulk Nl.

CTV2 needs to cover levels IB–V if node positive; IA needs coverage if there is extension to oral tongue or oral cavity; IB–IV or IB–V is based on location of nodal disease; ipsilateral level IB is in CTV2 if involved nodes are closer or might be in CTV3 if involved nodes are farther away. Contralateral level IB is spared if node negative, or level II is not involved.

Retropharyngeal nodal coverage starts cranially at jugular foramen if node positive, at tip of atlas or transverse process of C1 if node negative, ends inferiorly at bottom of hyoid or bottom of C2.

2.2.4.3 Base of Tongue CTV1

A uniform expansion of GTV with 8–10 mm for base of tongue.

Contours in air is trimmed.

Entire vallecula is in CTV1 if there is extension to vallecula.

2.2.4.4 Base of Tongue CTV2

Include circumferential 1 cm of remaining base of tongue for well lateralized T1 tumors, include remaining base of tongue for >T1.

Other than base of tongue, include circumferential 8–10 mm margin to all sites.

Include ipsilateral glossotonsillar sulcus anteriorly and inferiorly, minimum 1–1.5 cm pre-epiglottic space caudal to GTV, ipsilateral posterior pharyngeal wall with at least 1 cm circumferentially over CTV1.

Pterygoid plates and soft palate are covered if tonsil is involved.

Cover levels IB–V in CTV2 if node positive (tailoring between IB–IV or IB–V based on nodal disease location), level V is not necessary to be involved in low neck CTV3.

Cover ipsilateral level IB in CTV2 if involved node is closer, in CTV3 if involved node is farther away.

Spare contralateral level IB if node negative, or level II is not involved.

Cover IA if oral tongue or oral cavity is invaded.

Cover retropharyngeal nodes from jugular foramen if node positive, from tip of atlas or transverse process of C1 if node negative to inferiorly to bottom of hyoid or bottom of C2.

Cover bilateral retrostyloid spaces in CTV2 if node positive, can omit if node negative.

Planning Target Volume (PTV): Additional margin given around the CTV's to compensate for the treatment set up and possible internal organ motion. If the institution has not performed a study to define the appropriate magnitude of PTV such as 3 mm, a minimum geometric expansion in all directions of 5 mm is recommended.

2.2.5 Treatment Planning

The patient with locally-advanced tonsillar carcinoma presented here was treated with concurrent CRT (cisplatin 100 mg/m^2, every 21 days) utilizing SIB-VMAT technique with CTV1 = 70 Gy, CTV2 = 63 Gy, and CTV3 = 57 Gy in 33 fractions, respectively (Tables 2.16, 2.17 and Fig. 2.13).

2.2.6 Treatment Algorithm for Oropharyngeal Cancer

Treatment Algorithm for orophrayngeal cancer is summarized in Figs. 2.8 and 2.14.

2.2.7 Follow-Up Algorithm for Oropharyngeal Cancer

Follow-up Algorithm for oropharyngeal cancer is summarized in Figs. 2.9 and 2.15.

Table 2.16 Target volume doses for tonsil

TNM	CTV1 (70 Gy/33 fr)	CTV2 (59.4–63 Gy/33 fr) might be individualized as ≈2 cm below the lowest positive node to continue with CTV for the rest	CTV3 (54–57 Gy/33 fr)
N0, small Tl without extension to soft palate or base of tongue, well-lateralized	GTVp +5 mm + tonsillar territory	Ipsilateral Ib, II (might use CTV3 dose)	Ipsilateral III, IV and Va (individualized)
T1–2 N0	GTVp +5 mm + tonsillar territory	Ipsilateral Ib, II–III (might use CTV3 dose)	Contralateral II-III-IV-Va (individualized) bilateral RP (bilateral IV and Vb if lower neck is uninvolved)
T1–4N1–N2b (single node N3)	GTVp + GTVn + 5 mm + tonsillar territory	Ipsilateral Ib (Ia if oral tongue involved), Ipsilateral II-III-IV-Va, Ipsilateral RP	Contralateral II-III-IV-Va, contralateral RP (bilateral IV and Vb if lower neck is uninvolved)
T1–4N2c-3	GTVp + 5 mm + tonsillar territory + GTVn	Bilateral Ib–V, RPLN	Bilateral IV and V if lower neck is uninvolved

Tonsillar territory: region including maxillary tuberosity, ipsilateral minimal base of tongue, ipsilateral glossopharyngeal sulcus, ipsilateral retromolar trigone, superior tip of hyoid

Table 2.17 Target volume doses for base of tongue

TNM	CTV1 (70 Gy/33 fr)	CTV2 (59.4–63 Gy/33 fr) might be individualized as ≈2 cm below the lowest positive node to continue with CTV for the rest	CTV3 (54–57 Gy/33 fr)
T1–2 N0	GTVp + 5 mm	NA	Bilateral II-III-IV, bilateral RP
T1–4N1–N2b (single node N3)	GTVp + GTVn + 5 mm	Ipsilateral Ib (Ia if oral tongue involved), Ipsilateral II-III-IV-Va, Ipsilateral RP	Contralateral II-III-IV-Va, contralateral RP (bilateral IV and Vb if lower neck is uninvolved)
T1–4N2c-3	GTVp + GTVn + 5 mm	Ib–Va, bilateral RPLN	Bilateral IV and Vb if lower neck is uninvolved

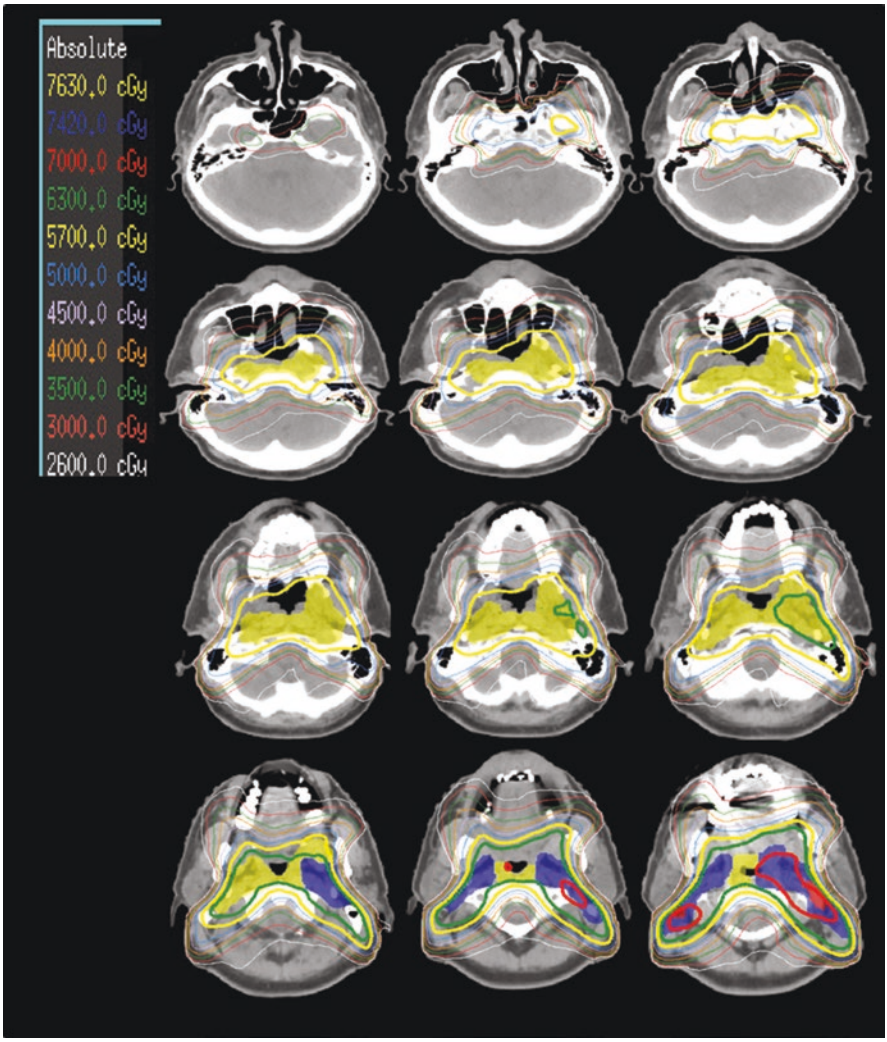
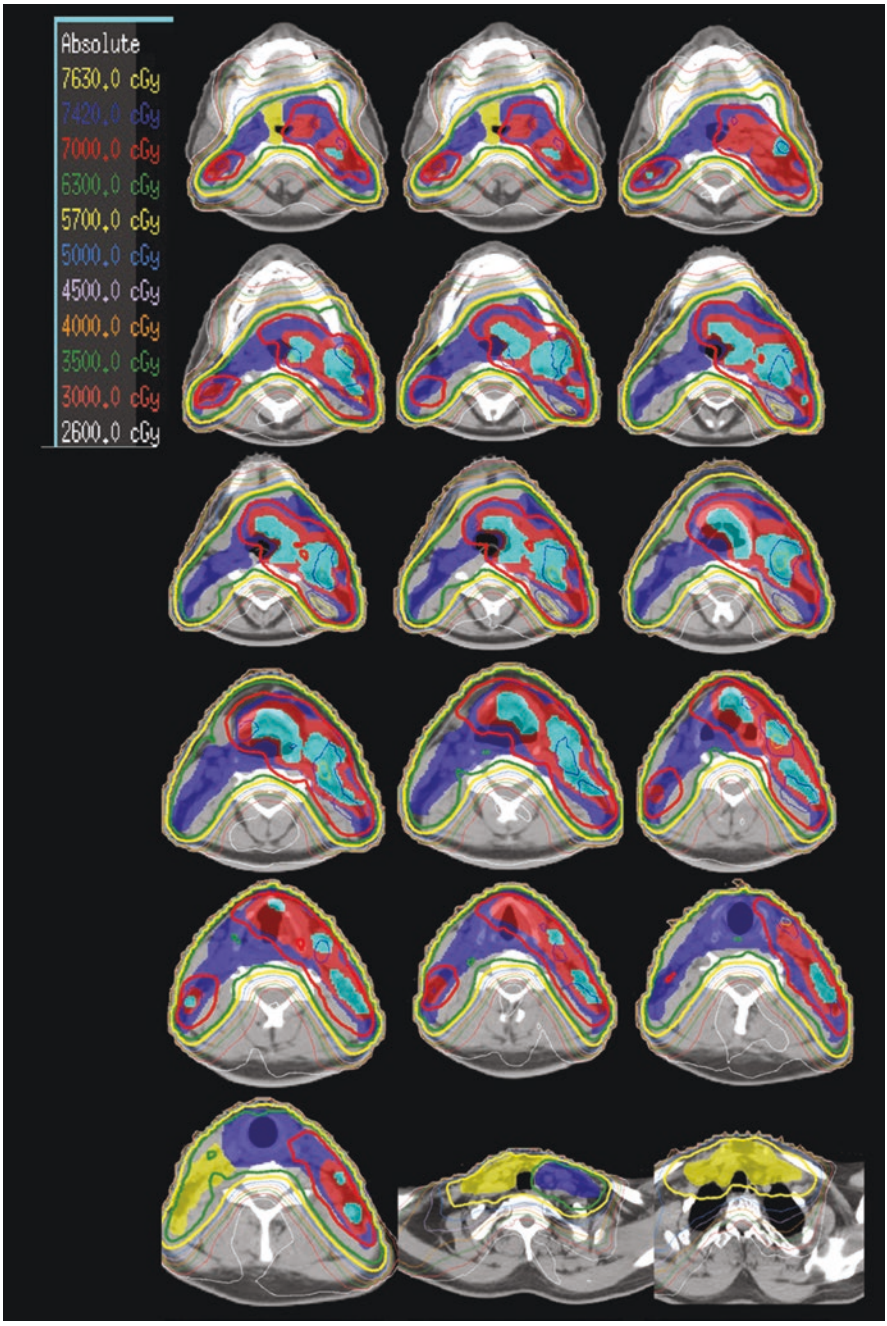


Fig. 2.13 Treatment plan



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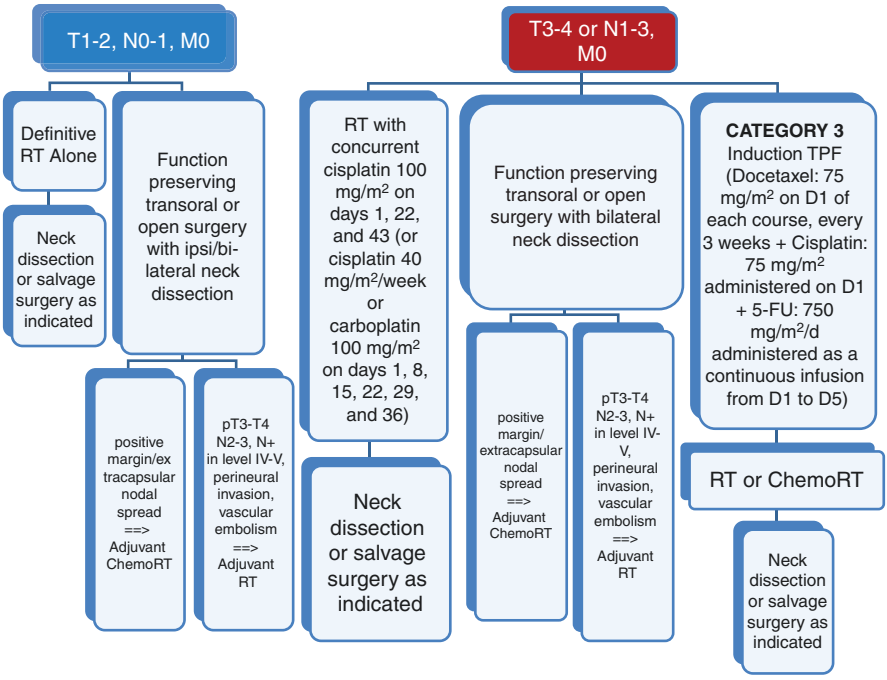
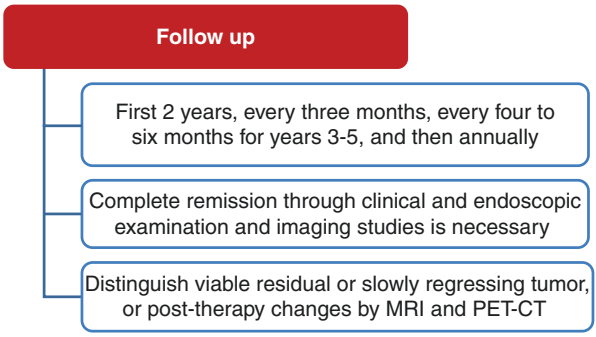


Fig. 2.14 Treatment Algorithm for oropharyngeal cancer

Fig. 2.15 Follow-up Algorithm for oropharyngeal cancer



2.3 Larynx

Overview

Incidence, Etiology, and Epidemiology

Larynx cancer is the most common head and neck carcinoma.

Larynx is divided into three subsites as supraglottis, glottis (most common cancer site), and subglottis. The natural barriers for laryngeal cancer are thyroid and cricoid cartilages bearing two weak sites as anterior commissure, and laryngeal ventricle.

The major risk factor is tobacco (packet per day x time of exposure in years), as alcohol is the second.

Pathological Features

>95% are squamous cell carcinoma.

Definitive Therapy

Admission and expected functional outcome, patient preference, age, tumor localization and extension, positive nodal disease and burden are on board for management. The goal with any selected single/multiple modality is to achieve maximal laryngeal preservation if possible without any predicted decrease in locoregional control and overall survival; radiotherapy or conservative surgery are similarly efficient in early stage disease, induction chemotherapy followed by radiotherapy or concurrent chemoradiotherapy are equally efficient for organ preservation, as well as surgery and postoperative radiotherapy (close or positive margins, multiple lymph node involvement, and/or extracapsular extension) ± chemotherapy in locoregionally advanced disease.

Key Words: Larynx cancer, Radiotherapy

2.3.1 Case Presentation

Fifty-eight years old female, admitted with a difficulty in swallowing and hoarseness accompanied by no major neck mass as well as no dyspnea, aspiration, pain, odynophagia, otalgia, dysphagia, hemoptysis, or weight loss. Her medical history is significant for 60 pack year history of smoking, and diabetes.

Her physical exam revealed small bilateral mobile non conglomerated subcentimeter nodes. The scope was introduced into the left nasal cavity. Nasopharyngeal mucosa was normal with well-defined bilateral Rosenmuller fossa, posterior pharyngeal/oropharyngeal wall, soft palate, tonsils, vallecula or base of tongue. The airway was narrow due to a supraglottic lesion measuring approximately 30 mm initiating at left aryepiglottic fold, extending to left vocal cord inferiorly while invading bilateral arytenoid cartilage. The vocal cords were moving normally.

His PET-CT, CT and MRI scans defined the supraglottic lesion measuring 30 × 25 mm extending from left aryepiglottic fold, to left vocal cord invading bilateral arytenoid cartilage and paralaryngeal blurred fatty planes. The inner part of the thyroid cartilage on left seemed minimally invaded (Figs. 2.16 and 2.17).

Bilateral neck nodal metastases were present in level 1B (measuring 6 mm on right, 8 mm on left) and level 2 (measuring 8 mm on right, 7 mm on left) Neck ultrasound guided bilateral level 2 nodal biopsy with fine needle aspiration revealed squamous cell cancer, as well as the surgical biopsy of supraglottic tumor as moderately differentiated invasive squamous carcinoma. She was staged as T3N2M0 (stage IVA) supraglottic laryngeal squamous cell cancer.

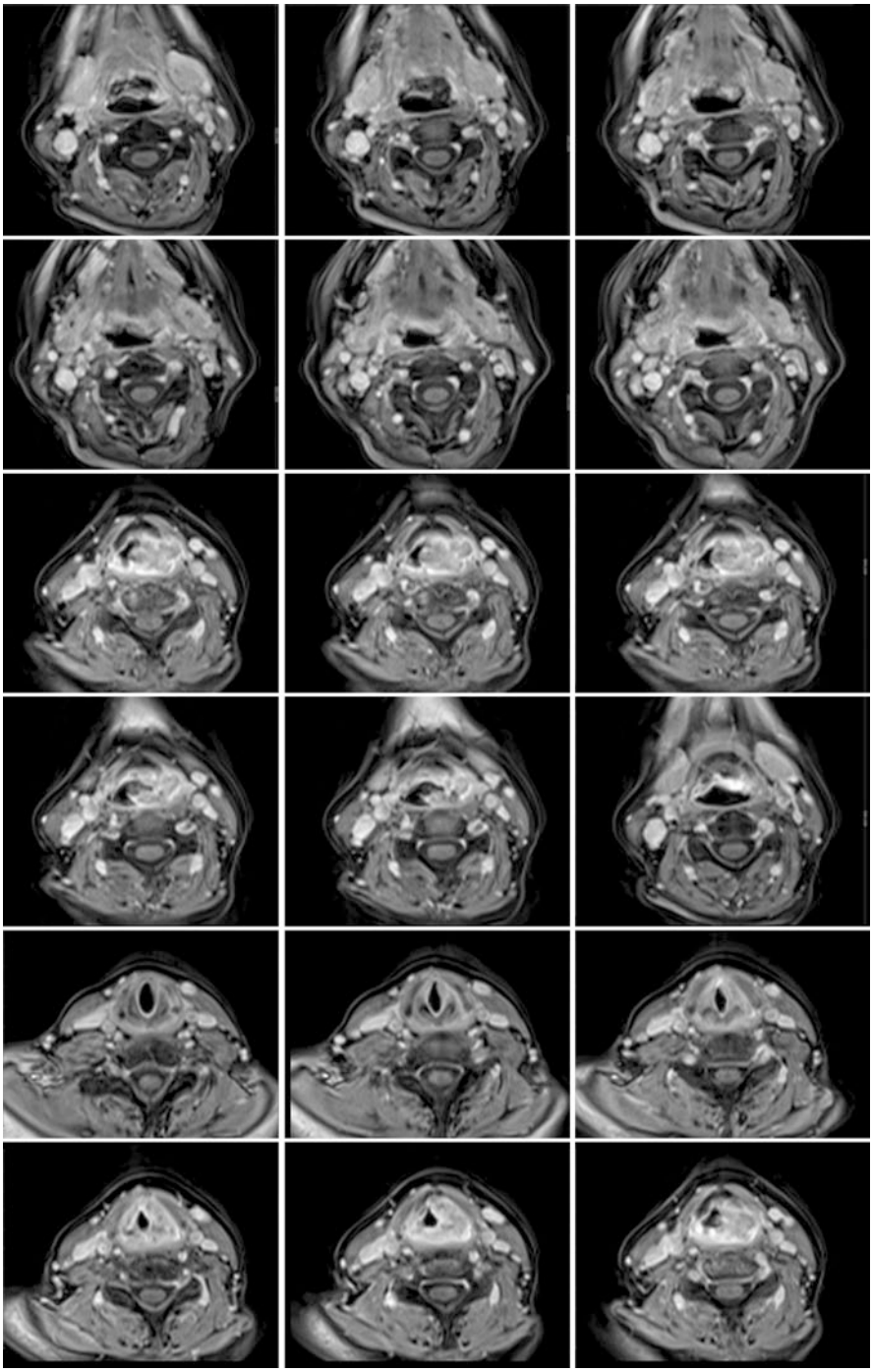


Fig. 2.16 Magnetic resonance imaging of the patient

2.3.2 Staging

American Joint Committee on Cancer staging for laryngeal carcinoma (AJCC 8th edition) was given Table 2.18. Only N staging was revised in new edition. N staging was given previously in Sect. 2.2.2 (Staging).

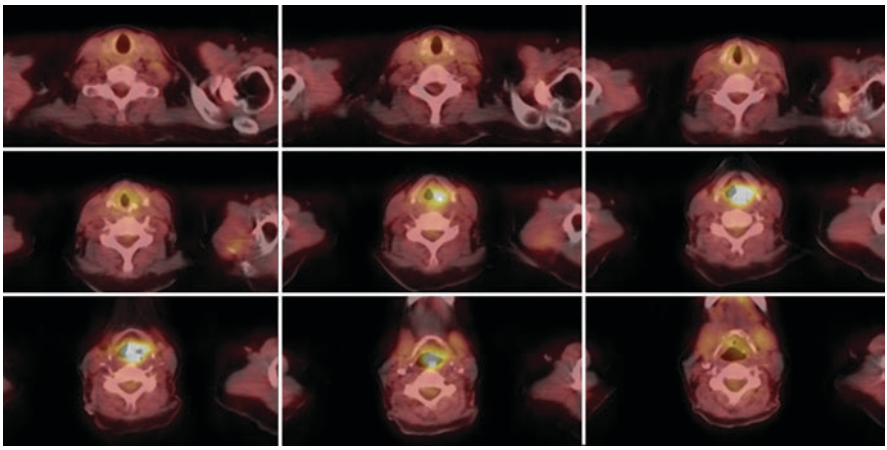


Fig. 2.17 Positron emission tomography imaging of the patient

Table 2.18 American Joint Committee on Cancer staging for laryngeal carcinoma (AJCC 8th 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

(continued)

Table 2.18 (continued)

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, and/or 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
Distant metastasis (M)	
M0	No distant metasttasis
M1	Distant metastasis
Stage groups	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1 N1 M0
	T2 N1 M0
	T3 N1 M0
Stage IVA	T4a N0 M0
	T4a N1 M0
	T1 N2 M0
	T2 N2 M0
	T3 N2 M0
	T4a N2 M0
Stage IVB	T4b Any N M0
	Any T N3 M0
Stage IVC	Any T Any N M1

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2.3.3 Evidence Based Treatment Approaches

The multidisciplinary effort is mainly on preserving functional larynx, if possible, without any detrimental decrease in local control and overall survival rates in any stage of laryngeal carcinoma.

2.3.3.1 Glottic/Supraglottic Larynx

Surgery with transoral laser excision is generally the first treatment option for carcinoma in situ, while RT is a good alternative. Larynx preservation with radiotherapy is recommended for T1–2N0M0 and selected T3N0M0 cases, with salvage surgery for any incomplete response, as definitive treatment with partial laryngectomy or endoscopic/open surgery is a good alternative to larynx preservation. Adjuvant radiotherapy ± chemotherapy is based on postoperative pathology. If total laryngectomy is indicated for T3N0–1M0 disease for definitive treatment, concurrent chemoradiotherapy or induction chemotherapy and consolidative radiotherapy are encouraged as the preferred option, while laryngectomy in N0 or laryngectomy and ipsilateral/bilateral neck dissection in N1. Salvage surgery is always on board if disease persists in primary or neck. Postoperative adverse features such as positive extracapsular extension or positive margins, adjuvant concurrent chemoradiotherapy is indicated, while radiotherapy alone for ≥2 nodes involved, perineural involvement, and vascular tumor embolism. If induction chemotherapy is the first step, definitive radiotherapy alone is recommended for complete responders, radiotherapy ± concurrent chemotherapy for incomplete responders. Incomplete response after definitive radiotherapy requires surgical salvage. Discussion with T4a should include laryngectomy and unilateral/bilateral lymph node dissection, on the other hand, selected T4a patients refusing surgery need to be treated with concurrent chemoradiotherapy or induction chemotherapy followed by radiotherapy/chemoradiotherapy.

2.3.3.2 Subglottic Larynx

Subglottic tumor alone which is very rare if not transglottic, mostly presenting with advanced T3–4N+ disease, requires definitive radiotherapy, chemoradiotherapy, or total laryngectomy ± adjuvant radiotherapy/chemoradiotherapy. Salvage surgery is inevitable if response is not complete following evaluation after first option radiotherapy/chemoradiotherapy.

T1 and T2 glottic/supraglottic tumors can be recommended transoral laser excision or RT are options, and, RT is generally the first choice of treatment with surgery being reserved for RT failures due to the fact that voice quality deteriorates with increasing resection; local control rates following RT at 5 years are 85–95% for T1 and 60–89% for T2 glottic tumors and supraglottic 100% for T1 and 86% for T2 supraglottic tumors [50, 51]. *Increasing treatment duration with less than 2 Gy per fraction decreases local control, therefore >2 Gy/fraction/day is general recommendation; such as the prospective randomized study by Yamazaki et al. emphasized that 2.25 Gy/fr (n = 91) versus 2 Gy/fr (n = 89) significantly increased local control*

rates (94% vs. 77%; p = 0.004) [52]. *Nodal radiotherapy is not recommended as nodal metastases is extremely rare for early stage glottis T1 (0%), T2a (3%) and T2b (8%);* [53] *whereas recurrences in primary should indicate considering nodal metastases up to 20–25% which might trigger distant metastases* [54].

In case of local-regionally advanced laryngeal (T1–2N+ disease or T3) carcinoma, total laryngectomy or induction chemotherapy followed by surgery or radiotherapy/chemoradiotherapy, or concurrent chemoradiotherapy are treatment options. Two benchmark studies cleared the path for larynx preservation standard approach as induction chemotherapy followed by radiotherapy or upfront concurrent chemoradiotherapy for locally advanced laryngeal carcinoma (Table 2.19) [55–57].

Larynx preservation era initiated with Veterans Affairs Laryngeal Cancer Study in 1991 leading to a shift in advanced-stage laryngeal cancer primary treatment with non-surgical approach reserving total laryngectomy for salvage, randomizing 332 stage III or IV laryngeal cancer patients into induction chemotherapy with cisplatin and fluorouracil followed by RT or surgery followed by RT groups; [55] larynx preservation was 64% in the induction chemotherapy arm with fewer local failures in the surgery group (P = 0.0005) and fewer distant metastases in the chemotherapy group (P = 0.016) [55]. RTOG 91-11 study randomized 547 patients with stage III or IV laryngeal cancer into three arms of induction chemotherapy (cisplatin and fluorouracil) followed by radiotherapy, radiotherapy given concurrently with cisplatin, and radiotherapy alone in order to define appropriate timing of chemotherapy (induction vs. concurrent), [56, 57] where both chemotherapy arms were shown to increase disease-free survival in comparison to radiotherapy alone. Larynx preservation with an intact larynx at 2 years was significantly higher with 88% in the concurrent schema versus 75% (P = 0.005) in induction and 70% in radiotherapy alone arms (P < 0.001); locoregional control rate was also similarly higher in the concurrent chemoradiotherapy arm than the chemotherapy and RT alone group (concurrent, 78% vs. induction, 61% vs. radiotherapy alone, 56%) [56, 57].

Three-dimensional conformal radiotherapy is a viable technique for early stage laryngeal carcinomas, while carotid sparing intensity modulated radiotherapy is also appealing [58–60].

Intensity modulated radiotherapy based techniques are preferred modalities for locally advanced laryngeal carcinoma patients due to better organ at risk sparing abilities [61, 62].

2.3.4 Target Volume Determination and Delineation Guidelines

Case contouring was shown in Fig. 2.18.

If there is induction chemotherapy, defining pre-chemotherapy target volumes carry importance to allow coverage of the regressed GTV to be delineated at least in CTV2 with co-registration of pre- and post-chemotherapy images.

Table 2.19 Randomized larynx preservation trials

Studies	#	Treatment arms			Overall survival	Larynx preservation
VA, Wolf et al. [55]	332	Surgery + radiotherapy	Induction chemotherapy + radiotherapy		68% (2 years)	–
					68% (2 years)	64% (2 years)
RTOG-91-11, Forastiere et al. [56, 57]	547	Induction chemotherapy + radiotherapy	Concurrent chemoradiotherapy	Radiotherapy	38.5% (10 years)	67.5% (10 years)
					27.5% (10 years)	81.7% (10 years)
					31.5% (10 years)	63.8% (10 years)
EORTC 24891, Lefebvre et al. [64]	202	Surgery + Radiotherapy	Induction chemotherapy + radiotherapy		32.6% (5 years)	–
					13.8% (10 years)	–
					38% (5 years)	21.9 (5 years)
					13.1% (10 years)	8.7% (10 years)
GETTEC, Richard et al. [65]	68	S + RT	Induction chemotherapy + radiotherapy		84% (2 years)	–
					69% (2 years)	42% (2 years)
GORTEC 2000–01, Janoray et al. [66, 67]	213	PF Induction chemotherapy + radiotherapy	TPF induction chemotherapy + radiotherapy		60% (3 years)	57.5% (3 years)
					60% (3-years)	70.3% (3-years)

TAX 324, Posner et al. (subgroup) [68]	166	PF Induction chemotherapy + chemoradiotherapy	TPF Induction chemotherapy + chemoradiotherapy		40% (3-years)	32% (3-years)
					57% (3 years)	52% (3 years)
EORTC 24954, Lefebvre et al. [69]	450	Sequential PF Induction chemotherapy + radiotherapy	Alternating PF Induction chemotherapy + radiotherapy		62.2% (3 years)	39.5% (3 years)
					48.5% (5 years)	30.5% (5 years)
					64.8% (3 years)	45.4% (3 years)
					51.9% (5 years)	36.2% (5 years)
TREMPLIN [70]	153	TPF induction chemotherapy + chemoradiotherapy (Platin based)	TPF induction chemotherapy + chemoradiotherapy (Cetixumab)		92% (18 months)	87% (18 months)
					89% (18 months)	82% (18 months)

Abbreviations: *TPF* docetaxel, cisplatin, fluorouracil

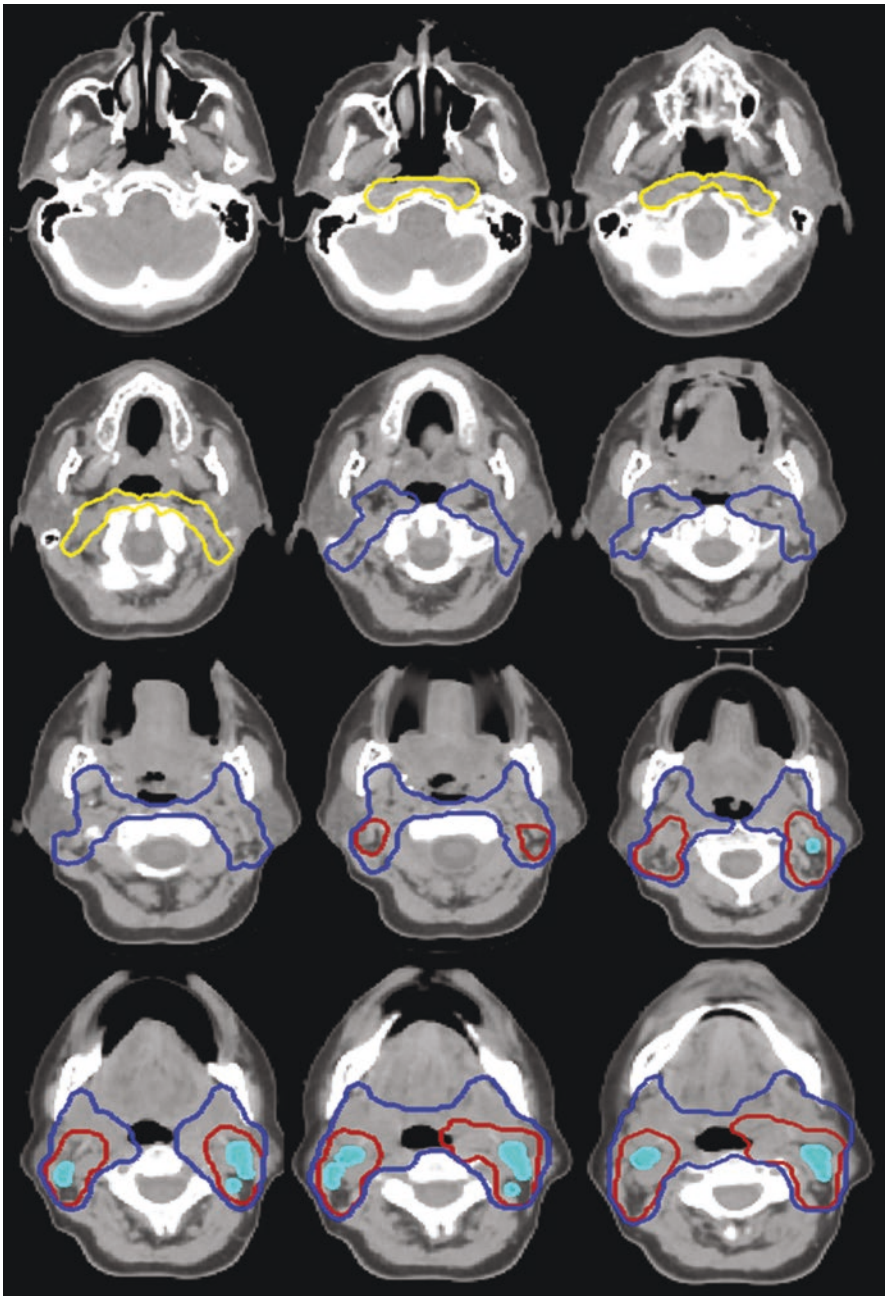
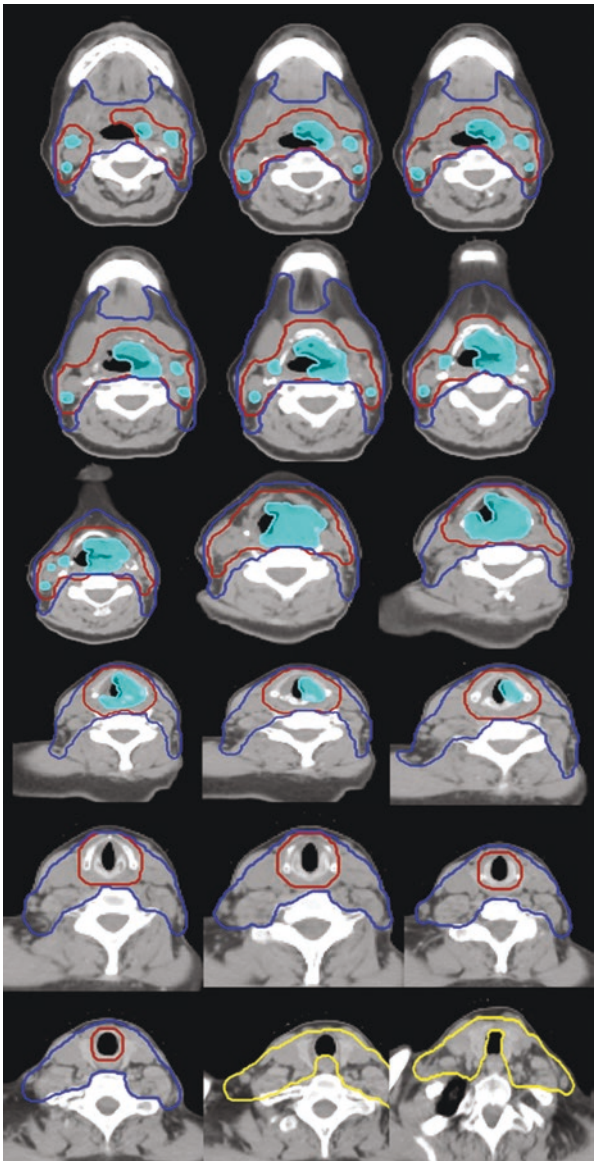


Fig. 2.18 Contouring the CTV1 (red), CTV2 (blue) and CTV3 (yellow)

Fig. 2.18 (continued)



Gross Tumor Volume (GTV): The gross disease at the primary disease site or any involved (>1 cm or with a necrotic center or PET positive) lymph nodes determined from physical/endoscopic examination, CT, MRI, PET-CT.

Clinical Target Volume (CTV): Though the final tailoring of each case related with the treatment volumes should be based on full consideration of the individual factors and treatment facility abilities, target delineation should be consistent

intra-departmentally based on relevant literature; such as a recent international guideline for the delineation of the clinical target volumes (CTV) for laryngeal carcinoma primary and nodal disease [49, 63].

CTV for T1–2N0 glottic cancer requires the entire larynx as an anatomic landmark to be covered, from top of thyroid notch to the bottom of the thyroid cartilage.

Risk definition implies three CTV for definitive radiotherapy in locally advanced laryngeal tumors.

CTV1: A uniform expansion of GTV with 5–8 mm at all directions, but may be reduced to as low as 1 mm in close proximity of critical structures.

CTV2: A uniform expansion of CTV1 with at least 10 mm at all directions, to cover potential microscopic mucosal and submucosal routes of disease spread.

CTV2 needs to cover levels II–IV if node positive; IB needs coverage if level 2 is positive.

Level 5 is covered if level II–IV are heavily involved. If bulky nodal volume present, tailoring retropharyngeal node coverage due to retrograde lymphatic flow might be an option which is not necessary in routine. Level VI requires to be covered in presence of subglottic extension or subglottic lesions.

CTV3: cover levels II–IV of the uninvolved neck.

Planning Target Volume (PTV): Additional margin given around the CTV's to compensate for the treatment set up and possible internal organ motion. If the institution has not performed a study to define the appropriate magnitude of PTV such as 3 mm, a minimum geometric expansion in all directions of 5 mm is recommended.

2.3.5 Treatment Planning

The patient with locally-advanced laryngeal carcinoma presented here was treated with concurrent CRT (cisplatin 100 mg/m^2, every 21 days) utilizing SIB-VMAT technique with CTV1 = 70 Gy, CTV2 = 63 Gy, and CTV3 = 57 Gy in 35 fractions, respectively (Fig. 2.19).

Guidelines for Target Volume Doses (Table 2.20).

Guidelines for Normal Tissue Constraints

As given in Table 2.5.

2.3.6 Treatment Algorithm for Larynx Cancer

Treatment Algorithm for larynx cancer is summarized in Figs. 2.20, 2.21, and 2.22.

2.3.7 Follow-Up Algorithm for Larynx Cancer

Please see Sect. 2.2.7.

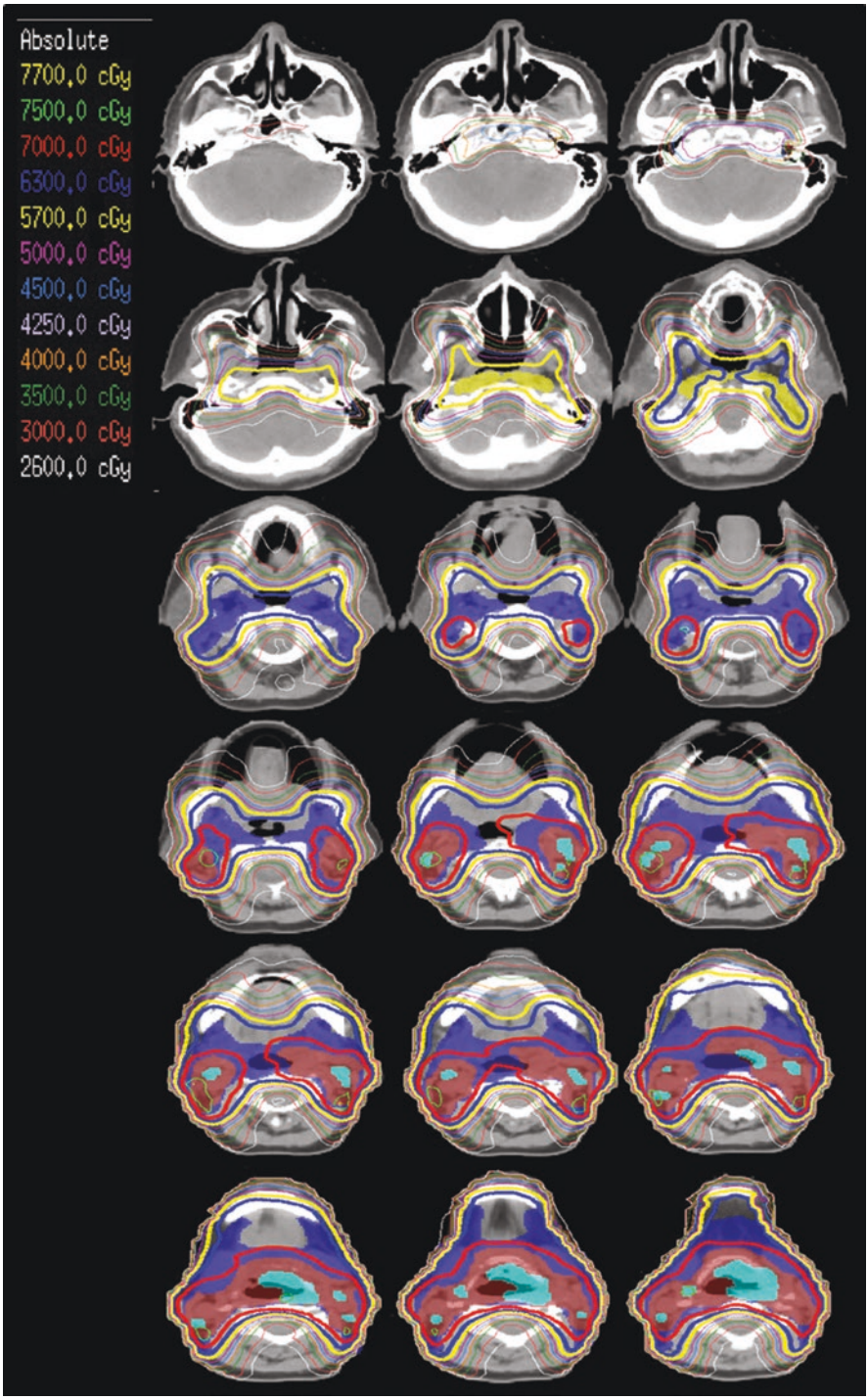


Fig. 2.19 Treatment plan

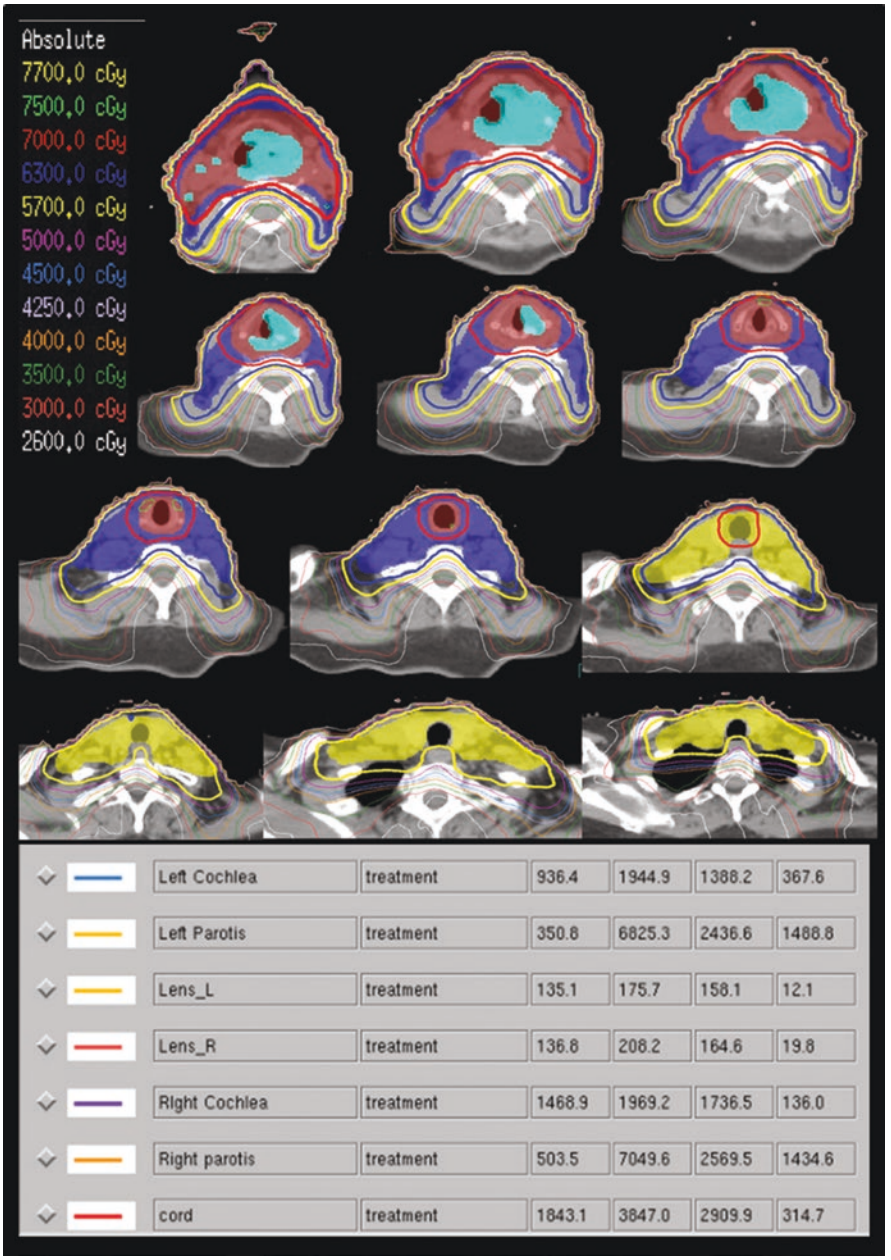


Fig. 2.19 (continued)

Table 2.20 Target volume doses for laryngeal cancer

TNM	CTV1 (70 Gy/33–35 fr) (T1–2N0, 65.25 Gy/2.25 fr)	CTV2 (59.4–63 Gy/33–35 fr) might be individualized as ≈2 cm below the lowest positive node to continue with CTV for the rest	CTV3 (54–57 Gy/33–35 fr)
T1–2 N0	GTVp + 5 mm + entire remaining larynx	NA	NA
T1–4N1–N3	GTVp + GTVn + 5 mm	Ipsilateral Ib (if level 2b involved), Ipsilateral II-III-IV	Contralateral II–III–IV

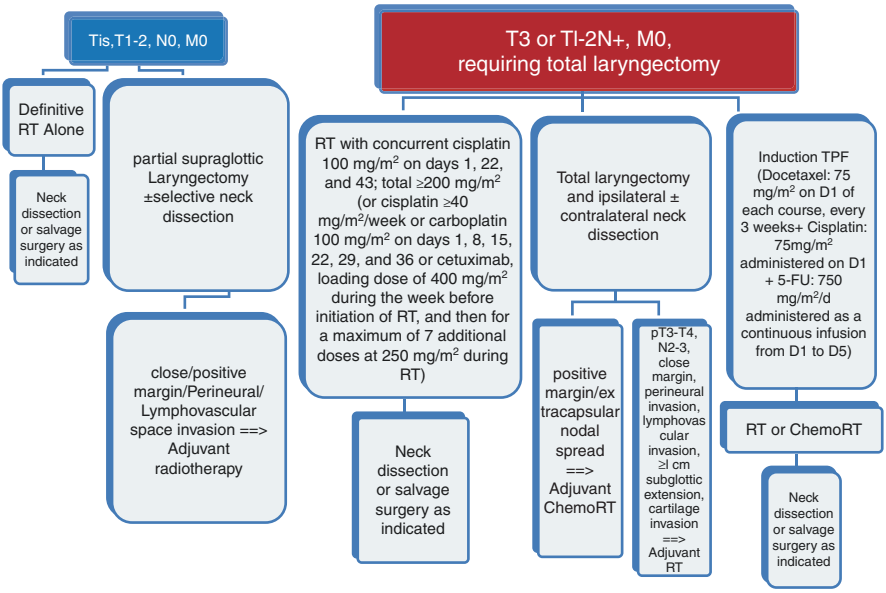


Fig. 2.20 Treatment Algorithm for supraglottic larynx cancer

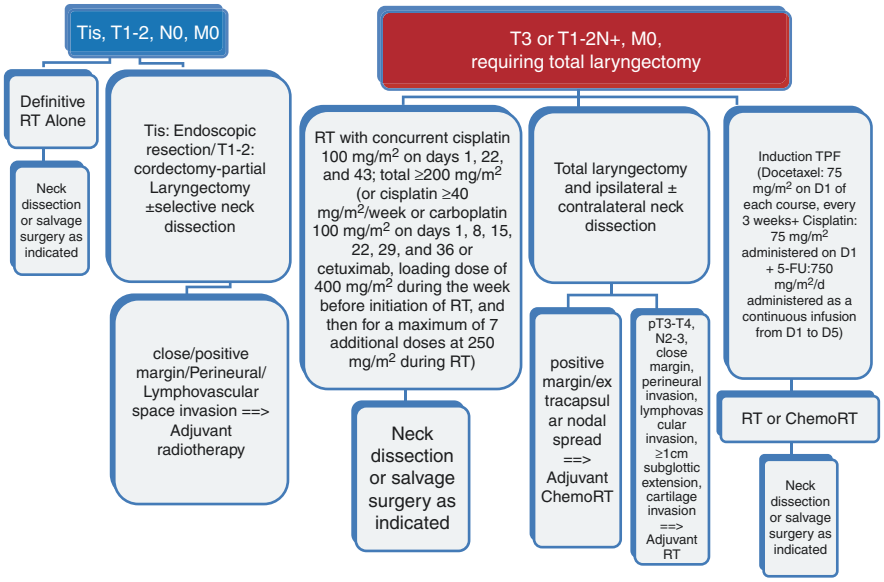


Fig. 2.21 Treatment Algorithm for glottis larynx cancer

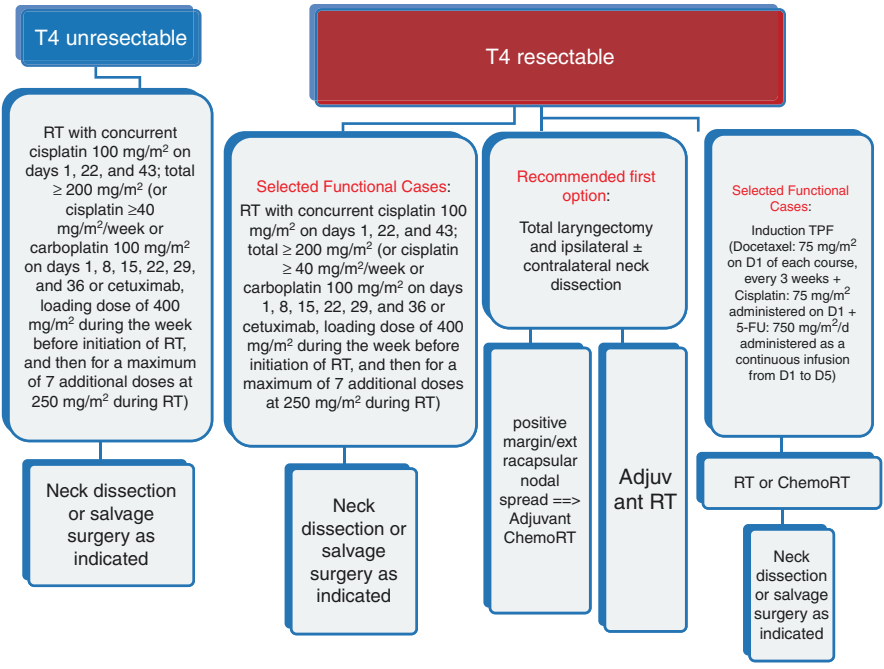


Fig. 2.22 Treatment Algorithm for T4 larynx cancer

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