

Chapter 9

Larynx and Hypopharynx Cancer

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PEARLS

LARYNX

- Larynx cancer is the most common cancer of the head and neck.
- Risk factors include tobacco, alcohol, betel and areca nuts, and deficiencies of iron, vitamin B12, and vitamin C.
- Larynx subsites:
 - Supraglottis: suprahoid and infrahyoid epiglottis, aryepiglottic folds, arytenoids, and false cords.
 - Glottis: true vocal cords (TVCs) including the anterior and posterior commissures.
 - Subglottis: extends from the lower boundary of the glottis to the inferior aspect of the cricoid cartilage.
- TVCs attach to the thyroid cartilage at the center of the “figure of 8” on a lateral X-ray.
- LN drainage is common from the supraglottis (to levels II–V) and subglottis [to pretracheal (Delphian), paratracheal, and inferior jugular nodes]. Glottic tumors rarely spread to LN when $\leq T1-2$ ($<3\%$), but more commonly spread to LN when T3–4 (~20–30%).
- Superior laryngeal nerve innervates the cricothyroid muscles that produce tension and elongation of the vocal cords. All other laryngeal muscles are innervated by the recurrent laryngeal nerve.

HYPOPHARYNX

- Portion of the pharynx extending from the plane of the superior border of the hyoid bone to the inferior border of the cricoid cartilage.
- Hypopharynx subsites:
 - Pyriform sinuses.

- Posterior and lateral hypopharyngeal walls.
- Postcricoid area.
- LN drainage from the hypopharynx is to levels II–V, the retropharyngeal LN, and to paratracheal and paraesophageal LN (when tumor involves the lowest portion of the hypopharynx and the postcricoid area).
- Ninety five percent of tumors of the larynx and hypopharynx are SCC.
- External auditory canal pain may be referred via the superior laryngeal nerve through the auricular nerve of Arnold (branch of CN X).
- A “hot potato” voice may be due to the involvement of the base of tongue.

WORKUP

- H&P, including hoarseness, pain, dysphagia, odynophagia, otalgia, trismus.
- All patients should have nasopharyngolaryngoscopy. Fixation of the true cord may be caused by invasion of the cricoarytenoid muscle or joint, or from recurrent laryngeal nerve injury.
- Esophagoscopy for hypopharnx tumors or if clinically indicated for laryngeal tumors.
- Bronchoscopy if clinically indicated.
- Biopsy tumor and/or lymph node(s).
- Labs include CBC, chemistries, BUN/Cr, LFTs, baseline TSH.
- Imaging includes thin-cut CT and/or MRI of the head and neck and a CXR. PET scans may be informative for stage III–IV.
- Preventive dental care and extractions should occur 10–14 days before RT.
- Baseline speech, swallowing, and nutrition evaluations. If locally-advanced, consider baseline audiometry too.

STAGING: LARYNX AND HYPOPHARYNX CANCER

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

(AJCC 6TH ED., 2002)**Primary tumor (T)***Larynx and hypopharynx*

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

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 the 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 tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)

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, and/or inner cortex of the thyroid cartilage

(AJCC 7TH ED., 2010)**Primary tumor (T)***Larynx*

TX: Primary tumor cannot be assessed

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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 the 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, and/ or inner cortex of the thyroid cartilage

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<p>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)</p> <p>T4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</p> <p><i>Subglottis</i></p> <p>T1: Tumor limited to the subglottis</p> <p>T2: Tumor extends to vocal cord(s) with normal or impaired mobility</p> <p>T3: Tumor limited to larynx with vocal cord fixation</p> <p>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)</p> <p>T4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</p> <p><i>Hypopharynx</i></p> <p>T1: Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension</p> <p>T2: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm, but not more than 4 cm in greatest dimension without fixation of hemilarynx</p> <p>T3: Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus</p> <p>T4a: Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue*</p> <p>T4b: Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures</p> <p><i>*Note:</i> Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.</p> <p>Regional lymph nodes (N)* <i>Larynx and hypopharynx</i></p> <p>NX: Regional lymph nodes cannot be assessed N0; no regional lymph node metastasis</p> <p>N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</p>	<p>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)</p> <p>T4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</p> <p><i>Subglottis</i></p> <p>T1: Tumor limited to subglottis</p> <p>T2: Tumor extends to vocal cord(s) with normal or impaired mobility</p> <p>T3: Tumor limited to larynx with vocal cord fixation</p> <p>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)</p> <p>T4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</p> <p><i>Hypopharynx</i></p> <p>T1: Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension</p> <p>T2: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm, but not more than 4 cm in greatest dimension, without fixation of hemilarynx</p> <p>T3: Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus</p> <p>T4a: Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue*</p> <p>T4b: Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.</p> <p><i>*Note:</i> Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.</p> <p>Regional lymph nodes (N) <i>Larynx and hypopharynx</i></p> <p>NX: Regional lymph nodes cannot be assessed</p> <p>N0: No regional lymph node metastasis</p>
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N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

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, not more than 6 cm in greatest dimension

N2c: Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension

N3: Metastasis in a lymph node more than 6 cm in greatest dimension

**Note:* Metastases at level VII are considered regional lymph node metastases.

Distant metastases (M)

Larynx and hypopharynx
M0: No distant metastasis
M1: Distant metastasis

Stage Grouping

	~2/5-Year OS	
	<i>Larynx</i>	<i>Hypopharynx</i>
0: TisN0M0	I: 65/35%	65/35%
I: T1N0M0	II: 80/60%	60/30%
II: T2N0M0	III: 70/50%	50/30%
III: T3N0M0, T1-3N1M0	IV: 60/35%	35/15%
IVA: T4aN0-1M0, T1-4aN2M0		
IVB: T4b any N, M0, any T, N3 M0		
IVC: Any T, any N, M1		

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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, not more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension

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, not more than 6 cm in greatest dimension

N2c: Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension

N3: Metastasis in a lymph node, more than 6 cm in greatest dimension

**Note:* Metastases at level VII are considered regional lymph node metastases.

Distant metastasis (M)

Larynx and hypopharynx
M0: No distant metastasis
M1: Distant metastasis

Anatomic stage/prognostic groups

Larynx and hypopharynx

0: Tis N0 M0

I: T1 N0 M0

II: T2 N0 M0

III: T3 N0 M0

IV: T1-T3 N1 M0

T4a N0 M0

T4a N1 M0

T1-T3 N2 M0

T4a N2 M0

IVB: T4b Any N M0

Any T N3 M0

IVC: Any T Any N M1

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SURGICAL OPTIONS

Operation	Indications	Removes	Contraindications/notes
Limited surgery (stripping or CO ₂ laser)	Carcinoma in situ	Mucosa of cord	Can lead to thickened or harsh voice. Difficult to determine if invasive CA present
Cordectomy	Early T1a lesions of middle 1/3 of one TVC	Transoral laser excision of part of one cord. Afterwards, pseudocord forms and patient has useful (but harsh) voice	
Vertical partial (hemi) laryngectomy	Voice preservation for TVC lesions involving one and <1/3 (<5 mm) of other TVC	Bisects larynx and removes 1/2 of thyroid cartilage, a portion or all of one TVC and up to 1/3 (5 mm) of other TVC	Contraindicated if TVC fixation, >5 mm posterior or >10 mm anterior subglottic extension (because must preserve cricoid), or supraglottic extension to false cord or interarytenoid area
Supraglottic (horizontal partial) laryngectomy (SGL)	Early supraglottic lesions for voice preservation	Removes epiglottis, aryepiglottic folds, false cords, upper 1/3–1/2 of thyroid cartilage, ± hyoid bone (if epiglottic space involvement). Preserves one or both arytenoids and both TVCs	Contraindicated if exolaryngeal spread, vocal cord fixation, involvement of arytenoids, <3 mm between tumor and anterior commissure, thyroid/cricoid cartilage invasion, and/or inadequate pulmonary function (due to high aspiration risk)

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Extended SGL	Supraglottic lesion with <1 cm base of tongue invasion	Same as SGL with removal of ipsilateral BOT up to circumvalate papillae	
Total laryngectomy	Indicated for advanced lesions with transglottic or extensive subglottic extension, most pyriform sinus lesions, and/or cartilage invasion	Removes hyoid, thyroid, and cricoid cartilages, epiglottis, strap muscles. Patient left with a permanent tracheostoma and pharynx reconstruction (by suturing to the base of tongue)	Most frequent sites of failure include tracheal stoma, base of tongue, and neck nodes. Rehabilitation options include tracheoesophageal speech, artificial electronic larynx, esophageal speech
Partial laryngopharyngectomy	Used for small medial and anterior pyriform sinus lesions	Removes false cords, epiglottis, aryepiglottic fold, and pyriform sinus, but TVCs are preserved	Contraindicated if transglottic extension, cartilage invasion, vocal fold paralysis, pyriform apex invasion (b/c below level of TVCs), postcricoid invasion, exolaryngeal spread, or poor pulmonary reserve
Total laryngopharyngectomy	For more advanced hypopharyngeal lesions	TL plus removal of varying amount of pharyngeal wall	Requires flap or gut graft if total pharyngectomy



TREATMENT RECOMMENDATIONS

2002 Stage	Larynx
Tis	<ul style="list-style-type: none"> Endoscopic removal (stripping/laser) or definitive RT
T1-2N0 glottic	<ul style="list-style-type: none"> Definitive RT. Advantage of RT is that failures can be salvaged with partial laryngectomy and still have third chance with salvage total laryngectomy. Alternative, cordectomy or partial laryngectomy ± selective neck dissection. Post-op RT for close/+ margin, PNI, LVSI
T1-2N0 supraglottic	<ul style="list-style-type: none"> Definitive RT. Or, partial supraglottic laryngectomy ± selective neck dissection. Post-op chemo-RT for + margin; post-op RT for close margin, PNI, LVSI
Resectable T1-2N+, T3N0/+ requiring total laryngectomy	<ul style="list-style-type: none"> Concurrent chemo-RT as in RTOG 91-11 (preferred). If < complete response, salvage surgery and neck dissection may be performed. If residual neck mass or initial N2-3, post-RT neck dissection considered Alternative is total laryngectomy, and ipsilateral or bilateral neck dissection (N0-1) or bilateral comprehensive neck dissection (N2-3). Post-op chemo-RT for + margin or nodal ECE. Post-op RT (or chemo-RT with multiple factors) for pT3-4, pN2-3, close margin, PNI, LVSI, ≥1 cm subglottic extension, and/or cartilage invasion Induction chemo × 3c may be considered. If CR or PR, proceed with concurrent chemo-RT as above. If < PR or progression, proceed to surgery and neck dissection as indicated
Resectable T4N0/+	<ul style="list-style-type: none"> Total laryngectomy and ipsilateral or bilateral neck dissection followed by post-op chemo-RT Alternative for selected patients is definitive concurrent chemo-RT as in RTOG 91-11. Induction chemotherapy may be considered
Unresectable T3-4 or N+	<ul style="list-style-type: none"> Concurrent chemo-RT. If unable to tolerate chemo, definitive RT with concomitant boost (CB) and consider concurrent cetuximab
2002 Stage	Hypopharynx
Early T1-2 not requiring total laryngectomy (T1N0-1, small T2N0, T1N2)	<ul style="list-style-type: none"> Definitive RT. If < complete response, salvage surgery and neck dissection as indicated. If complete response, neck dissection considered for N2-3

continued

T2-4N0/+ requiring total laryngectomy

- Alternatively, partial laryngopharyngectomy and ipsilateral or bilateral selective neck dissection (N0) or comprehensive neck dissection (N+). Post-op chemo-RT for + margin or nodal ECE. Post-op RT (or chemo-RT if multiple factors) for pN2-3, close margin, PNI, LVSI, cartilage invasion
- Concurrent chemo-RT as extrapolated from RTOG 91-11. Or, induction chemo ×2c (with a third cycle if PR). If CR at primary site, proceed with definitive RT (≥70 Gy). If primary site has only PR, proceed with concurrent chemo-RT. Nonresponders to induction chemo should undergo surgery → post-op RT or chemo-RT as indicated. If residual neck mass after definitive RT or initial N2-3, post-RT neck dissection considered
- Or, laryngopharyngectomy and selective (N0) or comprehensive neck dissection (N+ or T4). Post-op chemo-RT for + margin or nodal ECE. Post-op RT (or chemo-RT if multiple factors) for pT3-4, pN2-3, close margin, PNI, LVSI, cartilage invasion

Unresectable T3-4 or N+

- Concurrent chemo-RT. If unable to tolerate chemo, definitive RT with CB



STUDIES

RT DOSE FRACTIONATION

- Yamazaki et al. (2006): 180 patients with T1N0 glottic carcinoma randomized to 2 Gy/fx to 60 Gy (if ≤2/3 TVC involved) or 66 Gy (if >2/3 TVC involved) vs. 2.25 Gy/fx to 56.25–63 Gy. The 2.25 Gy/fx arm improved 5-year LC (77→92%), but not CSS (97 vs. 100%) or toxicity.
- RTOG 95-12 (Trotti et al. 2006, abstract): Randomized 250 patients with T2 glottic cancer to 70 Gy in 35 fx vs. 79.2 Gy at 1.2-Gy b.i.d. b.i.d. arm had nonsignificant trend for improved 5-year LC (70→79%, $p > 0.11$), DFS (37→51%, $p > 0.07$), and OS (62→73%, $p > 0.19$), but trial was underpowered.
- Le et al. (1997) reviewed 398 patients with T1-2 glottic cancer treated with RT alone. On multivariate analysis, overall treatment time ≤43 days, fraction size ≥2.25 Gy, and total dose ≥65 Gy improved LC for T2 lesions. Anterior commissure involvement decreased T1 LC, and impaired cord mobility and subglottic extension decreased T2 LC.

- Garden et al. (2003) reviewed 230 patients treated with RT alone for T2 glottic cancer. Treatment with ≤ 2 Gy/fraction had decreased 5-year LC (68%) compared to >2 Gy/fraction (82%) or b.i.d. RT (79%).
- *RTOG 90-03* (Fu et al. 2000; update ASTRO 2005): 268 patients with locally-advanced cancer of the oral cavity, oropharynx, supraglottic larynx, or hypopharynx randomized to 2/70 Gy (standard) vs. 1.2 b.i.d./81.6 Gy (HFX) vs. split-course 1.6 b.i.d./67.2 Gy (with 2 week break) vs. CB-RT to 72 Gy (1.8 Gy/fraction with a 1.5-Gy boost on the last 12 treatment days). On update, 5-year LRF and DFS improved w/ HFX and CB vs. standard fx and split-course. LRF: 60% standard, 58% split-course, 52% CB, 51% HFX. DFS: 21% standard, 27% split-course, 29% CB, 31% HFX. No difference in DM (27–29%), CSS (40–46%). Trend for improved OS with HFX (37 vs. 29–34%).

CHEMO-RT FOR LARYNX PRESERVATION

- Larynx preservation rates:
 - RT alone: ~60–70%.
 - Induction chemo \rightarrow RT: ~65–75%.
 - Concurrent chemo-RT: ~80–85%.
- *VA Larynx Trial* (Department of Veterans Affairs Laryngeal Cancer Study Group 1991): 332 patients with III/IV larynx (T1N1 excluded), randomized to surgery and post-op RT (50–74 Gy) vs. induction cisplatin/5-FU $\times 2c$ (with a third cycle if PR/CR) \rightarrow RT (66–76 Gy). No routine neck dissection for N+ patients. Chemo allowed 64% larynx preservation at 2 years. There was no difference in 2-year OS (68%). Chemo-RT decreased distant recurrences, but had higher LF (12 vs. 2%). Organ preservation improved quality of life. Salvage laryngectomy was required for 56% of T4 patients.
- *EORTC 24891* (Lefebvre et al. 1996; update ASCO 2004): 202 patients with operable pyriform sinus tumors randomized to surgery \rightarrow post-op RT (50–70 Gy) vs. induction cisplatin/5-FU $\times 2c$ (with a third cycle if PR/CR) \rightarrow RT (70 Gy). Nonresponders to chemo underwent surgery \rightarrow RT. Fifty-one to fifty-four percent of patients had a CR after chemo. There was no difference in LRF, and chemo decreased DM (36 \rightarrow 25%). The 3/5-year functional intact larynx rates were 42/35% with chemo. On update, no difference in 5- or 10-year OS and PFS.

- *RTOG 91-11* (Forastiere et al. 2003; update ASCO 2006): 547 patients with stage III/IV larynx (T2-3 or low-volume T4 without gross cartilage destruction or >1 cm base of tongue invasion, or LN+) randomized to one of three arms: RT alone, chemo → RT, or concurrent chemo-RT. RT was 2/70 Gy in all arms. Induction chemo was cisplatin/5-FU × 2c → reassessment. If progression or <PR, treated with laryngectomy and post-op RT. If PR/CR → third cycle chemo → RT. Concurrent chemo was cisplatin × 3c. All patients with cN2 had neck dissection within 8 weeks after RT. On update, concurrent chemo-RT improved 5-year larynx preservation (84%) vs. induction chemo (71%) and RT alone (66%), and LRC (69%) vs. induction chemo (55%) and RT alone (51%). Chemo reduced the rate of DM (13% concurrent, 14% induction vs. 22% RT alone) and improved DFS (39% with chemo vs. 27% with RT alone). No difference in OS (55% concurrent, 59% induction, 54% RT alone).
- *GORTEC 2000-01* (Pointreau et al. 2009): 220 patients with locally-advanced larynx or hypopharynx cancer that required total laryngectomy randomized to 3c of TPF (docetaxel, cisplatin, 5-FU) vs. PF (cisplatin, 5-FU) chemo. If CR, PR, and larynx mobility, patients received RT with or without additional chemo; if no response, patients had surgery and post-op RT with or without additional chemo. TPF improved overall response (80 vs. 59%) and 3-year larynx preservation rate (70 vs. 58%), but had more neutropenia.
- *TAX 324* (Posner et al. 2007): Randomized 501 patients with unresectable stage III/IV head and neck SCC (33% were larynx or hypopharynx) to induction TPF chemo (docetaxel, cisplatin, 5-FU) vs. PF (cisplatin, 5-FU) every 3 weeks for 3 cycles. Patients then had concurrent weekly carboplatin and RT to 70 Gy. TPF improved 3-year OS (48→62%) and LRC (62→70%), but not DM. TPF increased neutropenia (54→84%). Twenty-one percent of patients who got TPF induction were not able to receive subsequent concurrent chemo-RT.
- *EORTC 24954* (Lefebvre et al. 2009): 450 patients with resectable T3-T4 larynx or T2-T4 hypopharynx, N0-N2 randomized to sequential arm (2c cisplatin/5-FU → if >50% tumor reduction, 2 more cycles cisplatin/5-FU → 70 Gy) vs. alternating arm (4 c cisplatin/5-FU in weeks 1, 4, 7, and 10 alternating with 20 Gy RT during 2-week interval to 60 Gy total). No difference in larynx preservation, PFS, OS, or acute and late toxicity.



- *Cetuximab* (Bonner et al. 2006): 424 patients with locoregionally advanced resectable or unresectable stage III–IV SCC of oropharynx, larynx, or hypopharynx randomized to RT or RT + cetuximab given 1 week before RT and weekly during RT. RT options included 2/70 Gy, 1.2 b.i.d./72–76.8 Gy, or CB 72 Gy. Cetuximab increased 3-year LRC (34→47%) and OS (45→55%). With the exception of acneiform rash and infusion reactions with cetuximab, toxicity was similar.
- See Oropharynx chapter 7 for list of other key trials of chemo-RT, most of which included patients with larynx or hypopharynx cancer.

POST-OP RT AND POST-OP CHEMO-RT

- *RTOG 95-01* (Cooper et al. 2004): 459 patients with operable cancer of the oral cavity, oropharynx, larynx, or hypopharynx who had ≥ 2 involved lymph nodes, nodal extracapsular extension, or a + margin randomized to post-op RT (2/60–66 Gy) vs. post-op chemo-RT (2/60–66 Gy and cisplatin $\times 3$ c as in EORTC 22931). Chemo-RT improved 2-year DFS (43→54%), LRC (72→82%), and had a trend for improved OS (57→63%), but increased grade 3–4 toxicity (34→77%).
- *EORTC 22931* (Bernier et al. 2004): 334 patients with operable stage III/IV oral cavity, oropharynx, larynx, and hypopharynx cancer randomized to post-op RT (2/66 Gy) vs. post-op chemo-RT (2/66 Gy and cisplatin 100 mg/m² on days 1, 22, 43). All patients received 54 Gy to the low-risk neck. Eligible stages included pT3–4N0/+, T1–2N2–3, and T1–2N0–1 with ECE, +margin, or PNI. Chemo-RT improved 3/5-year DFS (41/36→59/47%), 3/5-year OS (49/40→65/53%), and 5-year LRC (69→82%), but increased grade 3–4 toxicity (21→41%).
- *Combined RTOG/EORTC analysis* (Bernier 2005): Chemo-RT improved OS, DFS, and LRC for ECE and/or + margins, but provided only trend for improvements ($p > 0.06$) for stage III–IV, PNI, LVSI, and/or enlarged LN in levels IV–V for OPX or oral cavity tumors based on EORTC data. Patients with ≥ 2 LN without ECE as their only factor did not benefit from chemo ($p > 0.73$).
- Ang et al. (2001): 213 patients with locally-advanced oral cavity, oropharynx, larynx, and hypopharynx cancers treated with surgery randomized by risk factors to post-op RT. Risk factors included > 1 node group, ≥ 2 nodes, nodes > 3 cm, microscopic +margins, PNI, oral cavity site, and nodal extracapsular extension.

Low-risk: no risk factors → no RT. Intermediate risk: 1 risk factor (but not ECE) → 1.8/57.6 Gy. High-risk: ECE or ≥2 risk factors → 1.8/63 Gy in 7 weeks or in 5 weeks with a CB. The 5-year LRC/OS for low-risk was 90/83%, for intermediate risk 94/66%, and for high-risk 68/42%. Overall treatment time <11 weeks increased LRC, and CB had a trend for improved OS.



META-ANALYSES

- *Altered fractionation* (Bourhis 2006): Meta-analysis of 15 trials with 6,515 patients, 74% with stage III–IV disease, mostly of oropharynx and larynx, treated with conventional RT (1.8–2/65–70 Gy), hyperfractionated RT (higher dose, same time), accelerated RT (same dose, shorter time), or accelerated RT with reduced total dose. Altered fractionation improved 5-year OS by 3.4%, with greatest benefit for hyperfractionated RT (8% benefit) vs. accelerated RT (1.7–2% benefit). Five-year LRC benefit 6.4% overall, mainly for local as opposed to regional failure. Benefit highest for youngest patients (<50–60 years). No effect of altered fractionation on DM.
- *MACH-NC meta-analysis* (Pignon et al. 2009): 93 phase III trials and 17,346 patients. OS benefit (4.5%) at 5 years when chemotherapy was added to RT, with greater benefit for concurrent chemo-RT vs. induction chemo followed by RT (6.5% OS benefit with concurrent chemo-RT). Similar results in trials with post-op RT, conventional, and altered fractionation. No difference between mono or polychemotherapy regimens, but increased benefit with platinum-based compounds. Decreasing benefit with increasing age, with no benefit observed if ≥71 years.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Simulate the patient supine with the head hyperextended. Wire neck scars and the tracheostoma (if present). Shoulders may be pulled down with straps. Immobilize with a thermoplastic head and shoulder mask. Bolus may be needed for anterior commissure tumors and over the tracheostoma (if present).
- A 3D conformal or IMRT plan should be used for any but simple opposed-lateral fields in order to spare normal tissues.
- Computed dosimetry should be used in all cases. Wedges and/or compensating filters may be required.

- Use fluoroscopy if available to evaluate superior motion of larynx with swallowing to ensure appropriate location of superior border.
- Glottic larynx traditional field design.
 - For T1N0, use a 5×5-cm field with the superior border at the top of the thyroid cartilage, the inferior border at the bottom of the cricoid, a 1-cm skin flash anteriorly, and a 2-cm margin posteriorly (or the anterior edge of the vertebral body) (Fig. 9.1).
 - For glottic T2N0, the field size is increased to 6×6 cm with the inferior border one tracheal ring below the cricoid.
 - For T3–4N0, extend the superior border to 2 cm above the angle of the mandible, the posterior border behind the spinous processes, and the inferior border to include 1.5–2 cm margin on the subglottic extent of the tumor. Match the lateral fields to the low-neck AP field. Treat the lateral fields to 42–45 Gy with a small cord block, then move the posterior border off-cord and use an electron boost to treat the elective posterior neck to 50 Gy. Boost the primary with a 1.5-cm margin to 70 Gy with chemo or to 72 Gy with a CB if chemo not used.

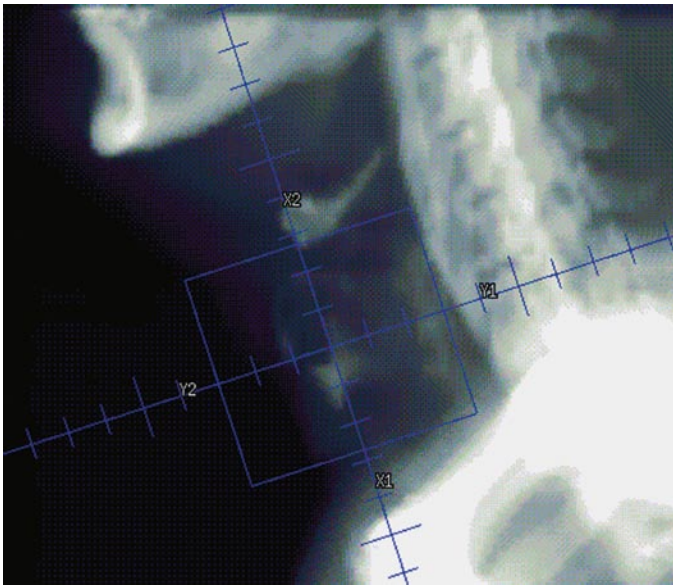


Fig. 9.1 Lateral DRR of a field used to treat a T1 glottic carcinoma

- Supraglottic larynx
 - For T1N0 treat the primary and levels II–III.
 - For T2–3, also treat low-neck because of increased risk of microscopic nodal disease.
 - For advanced cases, treat as described above for glottic.
- Hypopharynx
 - Treat primary and levels II–V and retropharyngeal nodes in all cases.
 - With traditional field design, the superior border is the skull base and mastoid. The inferior border is 1 cm below the inferior extent of disease (or 1 cm below cricoid) on the laterals and matched to the AP low-neck field. With posterior pharyngeal wall tumors, the anterior border does not need to flash the skin. A clothespin may be used to spare the skin anteriorly.
- Post-op
 - With traditional fields, use 3-field technique with stoma in low-neck AP field. Lateral fields cover neopharynx, adenopathy, and 1.5–2 cm margin on preoperative extent of disease.
 - With conventional three-field techniques, the spinal cord is shielded on the lateral fields at the matchline if no gross disease is present. If gross disease is present at the matchline, angling the lateral fields to match the divergence of the AP field may help. A small midline block on the AP field may be necessary.
 - Indications to boost tracheal stoma to 60–66 Gy: emergent tracheostomy, subglottic extension, tumor invasion to soft tissues of neck, extranodal extension in level VI, close/+ margin, scar crosses stoma.
- For low-lying high-risk areas in which matchline would go through the area, extended-field IMRT may be used.
 - Alternatively, may consider caudal tilt technique in which the lateral field gantry is moved 10° anterior and the couch is kicked 10° away from the beam and the SCV field is included in these lateral fields. At 42-Gy, posterior border is brought off-cord and this long strip is supplemented with electrons.
- IMRT
 - IMRT is not recommended for T1–2N0 glottic cancers, but may be considered for more advanced lesions.
 - GTV: clinical and/or radiographic gross disease.
 - CTV1: 0.5–2 cm margin on primary and/or nodal GTV (depending on the presence or absence of anatomic boundaries to microscopic spread).



- CTV2: elective neck.
- Individualized planning target volumes are used for the GTV, CTV1, and CTV2.

DOSE PRESCRIPTIONS

- T1–2N0 glottic larynx
 - >2 Gy/fx preferred. If 2 Gy/fx is used, total dose >66 Gy.
 - UCSF uses 2.25 Gy/fx.
 - Tis: 56.25–58.5 Gy.
 - T1N0: 63 Gy.
 - T2N0: 65.25 Gy.
- T3–4 and LN+ patients
 - Concurrent chemo-RT.
 - Total dose typically 70 Gy in daily fx with cisplatin 100 mg/m² q3 weeks ×3c.
 - Altered fractionation and multiagent chemo have been evaluated with no consensus on the optimal approach.
 - With definitive RT, use altered fractionation. Options:
 - Six fx/week during weeks 2–6: 70 Gy at 2 Gy/fx to primary and gross adenopathy.
 - CB: 72 Gy in 6 weeks (1.8 Gy/fx large field; 1.5 Gy boost as second daily fx during last 12 treatment days).
 - Hyperfractionation: 81.6 Gy in 7 weeks at 1.2 Gy b.i.d.
- Post-op RT
 - 60–66 Gy at 2 Gy/fx to high-risk areas and the postoperative bed.
 - Post-op chemo-RT indicated for nodal ECE and/or +margin(s) and considered for other risk features, including pT3–4, pN2–3, PNI, LVSI. Concurrent single agent cisplatin 100 mg/m² q3 weeks recommended.
- Elective neck
 - Uninvolved nodal stations: ≥50–56 Gy at 1.6–2 Gy/fx.
- IMRT
 - IMRT has been shown to reduce long-term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing dose to salivary glands, temporal lobes, auditory structures, and the optic apparatus. The use of IMRT for laryngeal and hypopharyngeal cancers is evolving and may be used at the discretion of the treating physician.
 - Simultaneous integrated boost (“dose-painting”) technique used at UCSF.

- 33 fx: GTV = 70 Gy at 2.12-Gy/fx, CTV1 = 59.4 Gy at 1.8-Gy/fx, CTV2 = 54 Gy at 1.64-Gy/fx.
- Alternative techniques.
 - Simultaneous integrated boost in 35 fx.
 - (a) GTV = 70 Gy at 2-Gy/fx, CTV1 = 63 Gy at 1.8-Gy/fx, CTV2 = 56 Gy at 1.6-Gy/fx.
 - Sequential technique.
 - (a) Initial lower-dose phase (weeks 1–5) followed by high-dose boost volume phase (weeks 6 and 7) using two to three separate dose plans.
 - CB schedule.
 - (a) Delivers dose to subclinical targets once daily for 6 weeks, and a separate boost plan as second daily treatment during last 12 treatment days.
- Typically, seven nonopposing beam angles are used.
- Extended whole field neck technique is typically preferred for larynx and hypopharynx as the glottic larynx is considered a target or when gross disease extends inferiorly and close to the glottic larynx. With this technique, lateral fields are typically not used because they would require treating through the shoulder, so these are replaced with anterior oblique fields.
- A split field technique with matched conventional low anterior neck field is sometimes used for nasopharynx and oropharynx lesions to reduce the dose to the glottic larynx. In this situation, the matchline is typically just above the arytenoids. A gradient match technique may be used as well.

DOSE LIMITATIONS

- Spinal cord maximum dose ≤ 45 –50 Gy. Brainstem maximum dose ≤ 54 Gy. Keep 50% of the volume of each parotid ≤ 20 Gy (if possible) and mean dose < 26 Gy. Mandible maximum dose ≤ 70 Gy. Brachial plexus dose < 60 Gy.
- Tracheostomas are limited to ≤ 50 Gy unless (1) significant subglottic extension, (2) emergent tracheostomy, (3) extranodal extension in neck level VI, or (4) close/+ margin, in which case it is boosted to 60–66 Gy.
- For other head and neck primary sites, the goal mean dose to the larynx is < 35 –45 Gy and 2/3 should be kept below 50 Gy.
- 70 Gy carries 5% risk of laryngeal cartilage necrosis.

COMPLICATIONS

- Complications of RT include mucositis, dermatitis, xerostomia, dysgeusia, soft-tissue fibrosis, hypothyroidism, and rarely radionecrosis, pharyngocutaneous fistula, or carotid rupture.
- Perioperative complications of surgery include bleeding, airway obstruction, infection, and wound complications. Post-op complications include webs, stenosis, chondritis, fistulas, and aspiration.
- Patients need $\geq 2,000$ calories/day to avoid malnutrition. Supplements (e.g., Boost or Ensure) and/or feeding tubes may be used.
- Amifostine may decrease xerostomia and mucositis, but it may be associated with significant side effects (e.g., hypotension, N/V).

FOLLOW-UP

- H&P every 1–3 month for year 1, every 2–4 month for year 2, every 4–6 month for years 3–5, and every 6–12 months thereafter. Posttreatment baseline imaging recommended, and thereafter, as clinically indicated. CXR annually. TSH every 6–12 month if neck irradiated. Speech, swallow, dental, and hearing evaluations and rehabilitation as indicated. Smoking cessation counseling.
- If recurrence is suspected but biopsy is negative, follow closely (at least monthly) until it resolves.

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