14 ■ LARYNGEAL CANCER

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QUICK HIT ■ Laryngeal cancer includes squamous carcinoma originating from the supraglottis, glottis, or rarely the subglottis. Goal of treatment is to achieve disease control while maintaining organ function, defined as functional voice with intact swallowing. Early-stage glottic cancers can be managed with RT alone or microsurgery. Locoregionally advanced disease, defined as T3–4 or node-positive, frequently requires either total laryngectomy (with adjuvant RT as indicated) or definitive chemoRT to attempt voice preservation. For patients with T4a disease with extralaryngeal spread, total laryngectomy with PORT is preferred over definitive chemoRT (Table 14.1).

Table 14.1 General Treatment Paradigm for Larynx Cancer

	Supraglottic	Glottic
Tis	Endoscopic Surgery	
T1N0	Larynx-sparing surgery OR Definitive RT (66–70 Gy) to primary tumor + elective LN levels II to IV	Definitive RT (63 Gy/28 fx at 2.25 Gy/fx) OR larynx-sparing surgery
T2N0		Definitive RT (65.25 Gy/29 fx at 2.25 Gy/fx) OR larynx-sparing surgery
T3 or node-positive	Larynx-sparing surgery w/ PORT OR definitive chemoRT (70 Gy/35 fx) to tumor + elective LN II to IV (V if LN +) w/ cisplatin	
T4a	Total laryngectomy (preferred for thyroid cartilage penetration or significant soft-tissue extension) with adjuvant RT ± concurrent cisplatin as indicated OR Larynx preservation with concurrent chemoRT to 70 Gy/35 fx with cisplatin	

EPIDEMIOLOGY: A total of 12,400 new diagnoses of laryngeal cancer in the United States with estimated 3,750 deaths in 2020. More common in men than women; incidence increases with age.[1]

RISK FACTORS: Smoking, alcohol, environmental exposures (asbestos, cement, wood dust, perchlorethylene).

ANATOMY: Major functions of larynx are voice production, airway patency during breathing, and airway occlusion during swallowing. It spans from C3 to C6 vertebral bodies and is bordered superiorly by hyoepiglottic ligament, inferiorly by cricoid, anteriorly by thyrohyoid membrane/thyroid cartilage, and posteriorly by arytenoid cartilage. Preepiglottic and paraglottic spaces are one continuous space anterosuperiorly. Laryngeal muscles (with exception of cricothyroid) are innervated by recurrent laryngeal nerve (branch of vagus nerve). Damage to this nerve results in a fixed, midline cord. Cricothyroid muscle is innervated by superior laryngeal nerve. Damage to this nerve results in mobile, "bowed" cords.

The larynx is divided into three segments:

1. *Supraglottis* (one third of all laryngeal cancers,[1] mnemonic FAVEA: false vocal cords, arytenoids, ventricles, epiglottis, aryepiglottic folds): Bordered superiorly by epiglottis, posteriorly by arytenoids, anteriorly by posterior edge of vallecula and anterior false cord, and inferiorly by epithelium of true vocal cord as it turns upward to form apex of ventricle. More than 50% of patients with supraglottic primaries present with node-positive disease due to presence of extensive lymphatics in this part of larynx. Levels II to IV are primary drainage sites for supraglottis.
2. *Glottis* (two thirds of all laryngeal cancers[2]): Consists of true vocal cords and anterior and posterior commissures. Due to sparse lymphatics, early-stage disease rarely involves regional nodes. True

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vocal cord is made up of the following layers: epithelial mucosa, basement membrane, superficial layer of lamina propria, and thyroarytenoid muscle.
3. *Subglottis* (1%–2% of all laryngeal cancers[3]): Starts 5 mm inferior to margin of vocal cords to inferior aspect of cricoid cartilage. Subglottic tumors can drain to pretracheal (Delphian) nodes.

PATHOLOGY: Ninety-five percent of tumors are SCC. Carcinoma in situ occurs in vocal cords but is rare in supraglottis. Rare malignancies: malignant minor salivary gland, small cell, lymphoma, plasmacytoma, carcinoid, soft-tissue sarcoma, chondrosarcoma, osteosarcoma, malignant melanoma. HPV positivity has not been shown to be prognostic or predictive in laryngeal cancer.

CLINICAL PRESENTATION: Presenting clinical symptoms are classically related to site of origin. Glottic cancers often present at early stage with hoarseness but as disease progresses, patients develop otalgia, dysphagia, cough, hemoptysis, stridor. In supraglottis, cancers are often detected later and commonly present with dysphagia, globus sensation, airway obstruction, and lymphadenopathy. Otalgia is due to referred pain to auricular branch of Arnold (from vagus nerve).

WORKUP: H&P including flexible nasopharyngolaryngoscopy. Videostroboscopy can be used to evaluate mucosal wave of true cords. Pain with palpation of thyroid cartilage can be reflective of cartilage invasion.

Labs: Routine CBC and CMP. Pre-CHT audiology exam.

Imaging: CT neck with contrast and PET/CT for stage III/IV disease. CT scan has high positive-predictive value for thyroid cartilage penetration (74%) and extralaryngeal spread (81%).[4]

Procedure: EUA with triple endoscopy (~4% incidence of second primary) and biopsy. Dental, nutrition, speech and swallow evaluation as indicated.

STAGING

Table 14.2 AJCC 8th ed. (2017): Staging for Larynx Cancer

SUPRAGLOTTIS

T/M \ N		cN0	cN1	cN2a	cN2b	cN2c	cN3a	cN3b
T1	Limited to 1 subsite of supraglottis with normal vocal cord mobility	**I**	**III**	**IVA**			**IVB**	
T2	Invades mucosa of >1 adjacent subsite of supraglottis or glottis, or region outside supraglottis without fixation of larynx[1]	**II**						
T3	• Limited to larynx with vocal cord fixation • Invasion[2]							
T4	a. Moderately advanced local disease[3]							
	b. Very advanced local disease[4]							
M1	Distant metastasis	**IVC**						

Notes: Larynx[1] = Regions include mucosa of BOT, vallecula, medial wall of pyriform sinus. Invades[2] = Postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage. Disease[3] = invades through thyroid cartilage outer cortex, trachea, soft tissues of neck, deep extrinsic muscles of tongue, strap muscles, thyroid, or esophagus. Disease[4] = Invades prevertebral space, encases carotid artery, or invades mediastinal structures.
cN1, single ipsilateral LN (≤3 cm) and ENE; cN2a, single ipsilateral LN (3.1–6 cm) and –ENE; cN2b, multiple ipsilateral LN (≤6 cm) and –ENE; cN2c, bilateral or contralateral LN (≤6 cm) and –ENE; cN3a, LN (>6 cm) and –ENE; cN3b, clinically overt ENE.
pN1, single LN (≤3 cm) and –ENE; pN2a, single ipsilateral or contralateral LN (≤3 cm) and +ENE or single ipsilateral LN (3.1–6 cm) and –ENE; pN2b, multiple ipsilateral LN (≤6 cm) and –ENE; pN2c, bilateral or contralateral LN (≤6 cm) and –ENE; pN3a, LN (>6 cm) and –ENE; pN3b, LN (>3 cm) and +ENE.

<table>
<tr><th colspan="9">GLOTTIS</th></tr>
<tr><th colspan="2">N / T/M</th><th>cN0</th><th>cN1</th><th>cN2a</th><th>cN2b</th><th>cN2c</th><th>cN3a</th><th>cN3b</th></tr>
<tr><td rowspan="2">T1</td><td>a. Limited to 1 vocal cord with normal mobility</td><td>I</td><td rowspan="4">III</td><td rowspan="5" colspan="3">IVA</td><td rowspan="5" colspan="2">IVB</td></tr>
<tr><td>b. Involves 2 vocal cords with normal mobility</td><td rowspan="3">II</td></tr>
<tr><td>T2</td><td>Extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility[1]</td></tr>
<tr><td>T3</td><td>• Limited to larynx with vocal cord fixation
• Invades[2]</td><td colspan="2"></td></tr>
<tr><td rowspan="2">T4</td><td>a. Moderately advanced local disease[3]</td><td colspan="5"></td></tr>
<tr><td>b. Very advanced local disease[4]</td><td colspan="6"></td></tr>
<tr><td>M1</td><td>Distant metastasis</td><td colspan="7">IVC</td></tr>
</table>

Notes: Mobility[1] = Unofficially, T2 can be divided into T2a (mobile cord) and T2b (impaired cord mobility). Invades[2] = Paraglottic space and/or inner cortex of thyroid cartilage. Disease[3] = invades through thyroid cartilage outer cortex, trachea, soft tissues of neck, deep extrinsic muscles of tongue, strap muscles, thyroid, or esophagus. Disease[4] = Invades prevertebral space, encases carotid artery, or invades mediastinal structures.
Refer to supraglottic larynx for nodal staging.

<table>
<tr><th colspan="9">SUBGLOTTIS</th></tr>
<tr><th colspan="2">N / T/M</th><th>cN0</th><th>cN1</th><th>cN2a</th><th>cN2b</th><th>cN2c</th><th>cN3a</th><th>cN3b</th></tr>
<tr><td>T1</td><td>Limited to subglottis</td><td>I</td><td rowspan="3">III</td><td rowspan="4" colspan="3">IVA</td><td rowspan="4" colspan="2">IVB</td></tr>
<tr><td>T2</td><td>Extends to vocal cords with normal or impaired mobility</td><td>II</td></tr>
<tr><td>T3</td><td>• Limited to larynx with vocal cord fixation
• Invades[1]</td><td colspan="2"></td></tr>
<tr><td rowspan="2">T4</td><td>a. Moderately advanced local disease[2]</td><td colspan="5"></td></tr>
<tr><td>b. Very advanced local disease[3]</td><td colspan="6"></td></tr>
<tr><td>M1</td><td>Distant metastasis</td><td colspan="7">IVC</td></tr>
</table>

Notes: Invades[1] = Invasion of paraglottic space and/or inner cortex of thyroid cartilage. Disease[2] = invades through thyroid cartilage outer cortex, trachea, soft tissues of neck, deep extrinsic muscles of tongue, strap muscles, thyroid, or esophagus. Disease[3] = Invades prevertebral space, encases carotid artery, or invades mediastinal structures.

TREATMENT PARADIGM

Surgery

Glottis: Modern surgical options for early glottic tumors focus on endoscopic resection with aim of preserving laryngeal function and have largely replaced external approaches. Note that at least one mobile arytenoid complex must be preserved to maintain adequate function of larynx. Endoscopic techniques can include mucosal stripping (for in situ disease), microdissection (including TORS), electrocautery, CO_2 laser (TLM or TOLM), among others. Other voice-conserving options are as follows:

Vertical hemilaryngectomy: Removes up to one true vocal cord as well as one-third of contralateral true cord. Appropriate for lesions with up to 1 cm anterior subglottic extension and 5 mm posterior subglottic extension.[5]

SCPL–CHEP: Resection of true and false cords, paraglottic spaces, and entire thyroid cartilage. Arytenoids and cricoid cartilage are preserved. CHEP is performed, which involves reconstruction by suturing cricoid to hyoid and epiglottis.

Supraglottis: Voice-preserving options include the following:

SGL: Swallow- and voice-preserving surgery that may be used for tumors of epiglottis, single arytenoid, aryepiglottic fold, or false cord. Included in resection are hyoid bone, epiglottis, superior half of thyroid cartilage, AE folds, and false cords to arytenoids.

SCPL–CHEP: Resection of both true and false cords, paraglottic space, preepiglottic space, epiglottis, and thyroid cartilage. Reconstruction includes suturing of cricoid to hyoid, cricohyoidopexy. Total laryngectomy includes removal of larynx, pharynx is reconstructed (often with free flap), and permanent tracheostomy is required. For patients treated with primary surgical approach, elective neck dissection of bilateral levels II to IV is warranted for most patients with supraglottic cancer and for locally advanced glottic disease.

Chemotherapy: Concurrent CHT is not routinely given for early-stage disease, but is considered by some for unfavorable T2 disease (impaired mobility). In definitive chemoRT for T2b or stage III to stage IVB disease, concurrent cisplatin is the standard of care, given as 100 mg/m^2 bolus weeks 1, 4, 7 (NCCN Category 1) OR 40 mg/m^2 weekly (NCCN category 2B). Cetuximab can be used for nonplatinum candidates, with loading dose of 400 mg/m^2 1 week prior to RT followed by 250 mg/m^2 weekly during RT. Use of induction CHT is controversial but has been used to select patients for laryngectomy versus preservation and consists of docetaxel, cisplatin, 5-fluorouracil (TPF) q3 weeks × 4 cycles completed 4 to 7 weeks prior to RT.

Radiation

Indications: Early-stage disease (cT1–T2N0) is typically treated with RT alone. Locally advanced disease is treated definitively (larynx preservation) or postoperatively (see Chapter 17). Nodal basins are typically not electively included in RT volumes in early-stage glottic patients unless supraglottic involvement is suspected, making risk of occult nodal metastasis higher. Cervical LN levels II to IV are targeted bilaterally and level V is included for node-positive hemineck or with primary tumor extension to base of tongue. Consider inclusion of level VIa for anterior soft-tissue extension or emergency tracheostomy with tumor cut-through. Consider level VIb with subglottic extension of primary tumor.

Dose: For T1N0 glottic cancers, accelerated hypofractionation has been shown to improve LC compared to standard fractionation. Recommended dose is 63 Gy/28 fx (2.25 Gy/fx). For T2aN0 disease, common dose is 65.25 Gy/29 fx. For patients with T2bN0 disease, LC is inferior with RT alone and thus alternative approaches including addition of concurrent CHT or hyperfractionation are considered. For locally advanced disease, 70 Gy/35 fx with CHT is common.

Toxicity: Acute: Fatigue, dysphagia, mucositis, hoarseness, xerostomia, odynophagia, RT dermatitis, dysgeusia, aspiration. Late: Dysphagia, esophageal stricture, aspiration, hoarseness, hearing loss, renal insufficiency, neck fibrosis, stroke, hypothyroidism.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 4.[6]

■ EVIDENCE-BASED Q&A

EARLY-STAGE DISEASE

■ What is the general treatment paradigm for early-stage disease?

Both RT and laryngeal preservation surgery provide excellent outcomes for early-stage disease.

Retrospective evidence demonstrates 5-year DFS above 90% for stage I disease and around 80% for stage II disease with either definitive RT or surgery.[7] *Randomized data are sparse, however. Small randomized trial published in 2014*[8] *did show less patient-reported hoarseness in those treated with RT compared to those treated*

with transoral laser surgery, but overall voice quality was similar. In general, voice quality is related to amount of vocal cord resected.

What is the impact of larger fraction size for early-stage disease?

Mild hypofractionation and acceleration has shown consistent improvement in local control for early disease.

Le, UCSF (*IJROBP* 1997, PMID 9300746): RR of 398 patients with T1 to T2 glottic cancer (315 T1, 83 T2) treated with definitive RT to median dose of 63 Gy. Overall, 5-yr LC was 85% for T1 patients and 70% for T2 patients. Anterior commissure involvement and earlier treatment era predicted for worse LC in T1 patients. In T2 patients (but NOT T1), poor prognostic factors for LC included overall treatment time (>43 days), smaller fraction size (<1.8 Gy/fx), lower total dose (≤65 Gy) impaired VC mobility, and subglottic extension.

Table 14.3 UCSF Experience in Early Larynx Cancer (cT2 patients)

	5-Yr LC		5-Yr LC		5-Yr LC
Treatment time ≤43 days	100%	**Fx ≥ 2.25 Gy/day**	100%	**>65 Gy**	78%
Treatment time >43 days	84%	**Fx < 1.8 Gy/day**	44%	**≤65 Gy**	60%
p value	.003	*p* value	.003	*p* value	.01
No VC mobility impaired	79%	**No subglottic extension**	77%		
VC mobility impaired	45%	**Subglottic extension**	58%		
p value	.02	*p* value	.04		

Yamazaki, Japan (*IJROBP* 2006, PMID 16169681): PRT of 180 patients with T1N0 SCC of glottis (80% T1a) treated with definitive RT and randomized to 2 Gy/fx or 2.25 Gy/fx. For standard fractionation arm, patients treated to 60 Gy for tumor length <⅔ of glottis and to 66 Gy for ≥⅔ of glottis. In 2.25 Gy/fx arm, total dose was 56.25 and 63 Gy respectively for tumor length <⅔ and ≥⅔ of glottis respectively; 5-yr LC was 92% in hypofractionation arm compared to 77% in standard fractionation arm. Fraction size was independent predictor for LC. Acute and late toxicities were equivalent. **Conclusion: Decreasing overall treatment time with larger fraction sizes improved LC without causing increased acute or late toxicity in patients with T1N0 glottic cancer.**

What is impact of hyperfractionation for early-stage disease?

RTOG 95-12 demonstrated modest, but not statistically significant, benefit in local control with use of hyperfractionated RT in patients with T2N0 glottic cancer. T2b was a negative prognostic factor.

Trotti, RTOG 9512 (*IJROBP* 2014 PMID 25035199): PRT of 250 patients with T2N0 SCC of glottis treated with definitive RT randomized to hyperfractionation (79.2 Gy/66 fx at 1.2 Gy BID) or standard fractionation (70 Gy/35 fx). Primary end point was LC. While there were trends toward improved outcomes with HFRT, there were no significant differences in 5-yr LC (78% vs. 70%, $p = .14$), 5-yr DFS (49% vs. 40%, $p = .13$), or 5-yr OS (72% vs. 63%, $p = .29$). LC in T2b patients was relatively lower (70% T2b vs. 76% T2a, $p = .1$). No difference in rates of grade 3 to grade 4 late toxicity between treatment arms. Of note, the trial was powered to detect 15% absolute difference in 5-yr LC. **Conclusion: Hyperfractionation modestly improves LC, as seen in other disease sites of head and neck, though not statistically significant in this study.**

How should T2B patients be treated?

T2b glottic cancer has not been adopted by the AJCC but has been described as presence of hypomobile cord. Patients with T2b disease had worse control in RTOG 9512 (LC 70 vs. 76% p = .10 and LRC 63% vs. 74%, p = .03) and in other large retrospective series[9,10] and thus may benefit from alteration from standard treatment. Options to improve local control in this unfavorable subset include hyperfractionation, hypofractionation (e.g., 65.25 Gy/29 fx), or addition of concurrent CHT.[11]

■ **Is there any role for IMRT in early-stage population?**

There is no routine role, and IMRT should be considered investigational. Proposed rationale is late toxicity avoidance, particularly vascular toxicity with carotid sparing. Early series have shown that carotid sparing is feasible without detriment in local control,[12,13] *but results are still immature at this time.*

LOCALLY ADVANCED DISEASE

■ **What is the basis for larynx preservation for locally advanced disease?**

While definitive surgery followed by PORT had been the traditional paradigm, the VA Larynx Study prospectively demonstrated equivalent survival rates with nonoperative approach and RTOG 91-11 demonstrated superior rates of larynx preservation with concurrent chemoRT compared to patients treated with either induction CHT or RT, or RT alone. T4 patients had higher rate of needing salvage laryngectomy in VA Larynx study and thus a large volume of T4 patients were excluded in RTOG 91-11. However, an NCDB analysis demonstrated that majority of patients with T4a disease still undergo organ preservation paradigm in clinical practice, despite general guidelines, with inferior overall survival compared to those who had TL (median survival 61 mos vs. 39 mos).[14] *Multiple individual retrospective series have also identified tumor volume as prognostic for outcomes in addition to T stage.*

Wolf, VA Larynx Study (*NEJM* 1991, PMID 2034244): PRT of 332 patients with stage III to stage IV locally advanced SCC of larynx (63% supraglottis, 57% vocal cord fixation) randomized to induction CHT followed by RT or total laryngectomy followed by post-op RT. Patients in larynx preservation arm received cisplatin 100 mg/m^2 and 5-FU 1,000 mg/m^2/d × 5 days on days 1 and 22. Tumor response was assessed by exam and indirect laryngoscopy 18 to 21 days after 2nd cycle. Patients w/o at least PR in larynx and those w/ any evidence of disease progression (including neck disease) underwent salvage laryngectomy. Patients w/ at least PR at primary tumor site and no progression of any neck lymphadenopathy received 3rd cycle of CHT on day 43. This was followed by definitive RT consisting of 66 to 76 Gy delivered at 1.8 to 2 Gy/fx to primary tumor site and 50 to 75 Gy to LNs. Twelve weeks after completion of RT, tumor response was reassessed; patients w/ persistent disease in larynx underwent salvage laryngectomy. Patients w/ persistent neck disease alone underwent neck dissection only. All laryngectomy patients underwent post-op RT consisting of 50 to 50.4 Gy for microscopic disease, 60 to 60.4 Gy for areas felt to be at high risk for local recurrence and 65 to 74.2 Gy for areas of residual disease. MFU 33 mos. Thirty-one percent had CR and 54% had PR after 2 cycles of CHT. Lack of response to induction CHT, however, was not associated with reduced OS. Rate of laryngeal preservation was 64%. Fifty-six percent of patients with T4 primary tumors required salvage laryngectomy (vs. 29% in remainder of study population). Rate of DM was lower in CHT arm, but LC was inferior. **Conclusion: Induction CHT followed by definitive RT can be effective in preserving larynx in high percentage of patients, w/o compromising OS.**

Table 14.4 Results of VA Larynx Study

	2-Yr OS	2-Yr LC	Recurrence at Site of Primary	DM
Induction CHT + Definitive RT	68%	80%	12%	11%
TL + PORT	68%	93%	2%	17%
***p* value**	.9846	.001	.001	.001

Forastiere, RTOG 91-11 (*NEJM* 2003, PMID 14645636; Update *JCO* 2013, PMID 23182993): PRT of 518 patients with SCC of supraglottic/glottic larynx, stage III to stage IV (T1 or T4 with tumor extending through thyroid cartilage into neck of soft tissue or >1 cm of BOT involvement were excluded) randomized to 1 of 3 arms: Arm 1 (Induction, from VA Larynx): cisplatin 100 mg/m^2 day 1 + 5-FU 1,000 mg/m^2/day for 5 days for 2 cycles on day 1 and day 22 followed by response evaluation. Those with less than PR or progression proceeded to laryngectomy with PORT. Those with CR or PR continued to additional cycle of cisplatin/5-FU followed by 70 Gy/35 fx RT alone. Arm 2 (chemoRT): cisplatin 100 mg/m^2 days 1, 22, 43 concurrent with 70 Gy/35 fx. Arm 3 (RT alone): 70 Gy/35 fx. Patients with single LN >3 cm or multiple LNs underwent neck dissection 8 weeks after completion of therapy. Seven end points were reported but primary end point was LFS. Standard arm was induction. Update published with MFU of 10.8 yrs. In an update, compared to induction, chemoRT improved

larynx preservation, LC, and LRC but not LFS (primary end point) and trended to worse OS ($P = .08$) potentially suggestive of unexplained late effects. See Table 14.5. **Conclusion: Concurrent chemoRT declared "winner" due to LRC and LP benefit although LFS was similar.**

Table 14.5 Ten-Year Results of the RTOG 9111 Larynx Preservation Trial

Arm	LFS (1°)	LP	LC	LRC	DC	DFS	OS
1. Induction	28.9%*	67.5%	53.7%	48.9%	83.4%	20.4%	38.8%
2. ChemoRT	23.5%*	81.7%*†	69.2%*†	65.3%*†	83.9%	21.6%*	27.5%
3. RT alone	17.2%†	63.8%	50.1%	47.2%	76.0%	14.8%	31.5%

*Significant relative to RT alone.
†Significant relative to induction (standard arm).

What is role of cetuximab for locally advanced laryngeal cancer?

The Bonner trial[14] *established survival benefit with addition of cetuximab to RT in patients with locally advanced SCCHN.*

Bonner, Cetuximab Secondary Analysis (*JAMA Otolaryngol Head Neck Surg* 2016, PMID 27389475): Secondary analysis of original Bonner trial investigating role of cetuximab in larynx preservation. Arms included RT alone vs. RT with concurrent cetuximab; 168 patients with larynx or hypopharynx cancers were included in this subset (90 in cetuximab, 78 in RT alone). Two-year rates of larynx preservation were 87.9% for cetuximab and 85.7% for RT alone (HR: 0.57, 95% CI: 0.23–1.42, $p = .22$). HR for laryngectomy-free survival was 0.78 ($p = .17$). No difference in OS. **Conclusion: There was statistically nonsignificant benefit to cetuximab with regard to larynx preservation and laryngectomy-free survival.** *Comment: Conclusions are limited by lack of power and retrospective nature of subset analysis.*

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