Locally Advanced Larynx Cancer

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Outline

- Case
  - Clinical Presentation
  - Workup/Diagnosis
  - Management
    - Definitive chemoRT
      - CT simulation
      - Target delineation
      - Plan Evaluation
  - Follow-up

- Background
- Workup
- Management
  - Surgery vs ChemoRT
  - Radiation
    - Definitive
    - Adjuvant

Case: Clinical Presentation

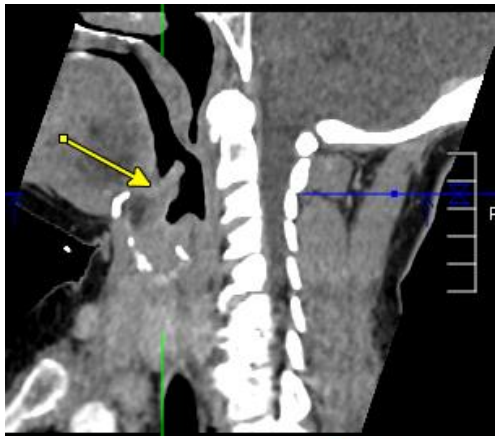
- **HPI:** 56 yo female referred to ENT for throat pain, dysphagia and inability to catch her breath
- **ROS:** Positive for dysphonia, otalgia and fatigue. No weight loss, fevers, or neck masses
- **SH:** Current every day smoker, 1 pack every 3 days for 20 years. Quit after diagnosis. No alcohol use.
- **PMH:** Asthma
- **PSH, meds/allergies, FH** otherwise non-contributory
- **Physical exam:** No lesions of the oral cavity, base of tongue or posterior pharynx. No palpable cervical lymphadenopathy

Case: Diagnostic Workup

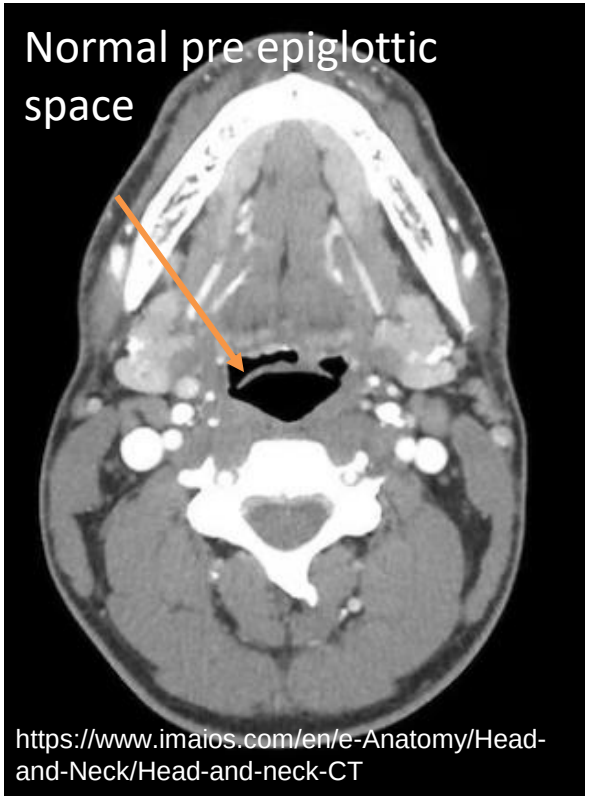
- ENT performed **flexible nasopharyngolaryngoscopy**
  - Mass present on laryngeal surface of the epiglottis
  - Swallowing function intact, able to clear secretions
  - Mobile vocal cords
- Biopsy of epiglottic mass: + Invasive Poorly Differentiated SCCa, p16 negative

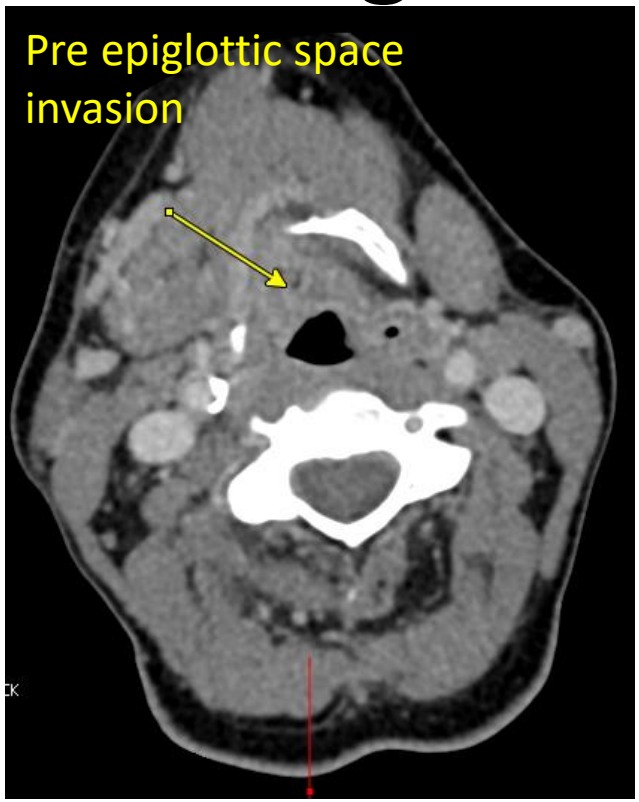
Case: Diagnostic Workup

- **CT neck with IV contrast**
  - Abnormal appearance of the right vallecula with contiguous thickening of the suprahyoid epiglottis
  - Gap of relatively normal appearing supraglottic larynx then with a possible abnormal finding involving the left false vocal fold
  - Both inferior aryepiglottic folds appear thicker than usual
  - No extralaryngeal or cartilage involvement
  - Slightly prominent lymph nodes in right level 3 but not positive per imaging size/morphology criteria
- **CT chest**
  - No distant mets



Case: Management





cT3: T2 by extent but T3 by minimal pre epiglottic space invasion
cN0: CT neck negative for adenopathy
cM0: CT chest negative for metastatic disease

- **Head and Neck Multidisciplinary Tumor Conference** recommended **definitive chemoradiation**

Case: Definitive ChemoRT

- CT simulation:
  - **Position:** Supine, arms at side, shoulders down, head extended
  - **Immobilization:** Thermoplastic Aquaplast head mask, accufix board with shoulder depression mechanism and hand bars
  - **Bolus:** None
  - **Additional instructions:** IV contrast

Case: Definitive ChemoRT

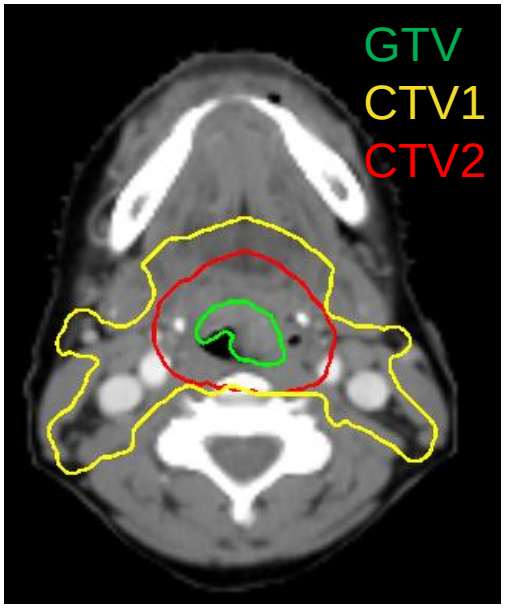
RT volumes:

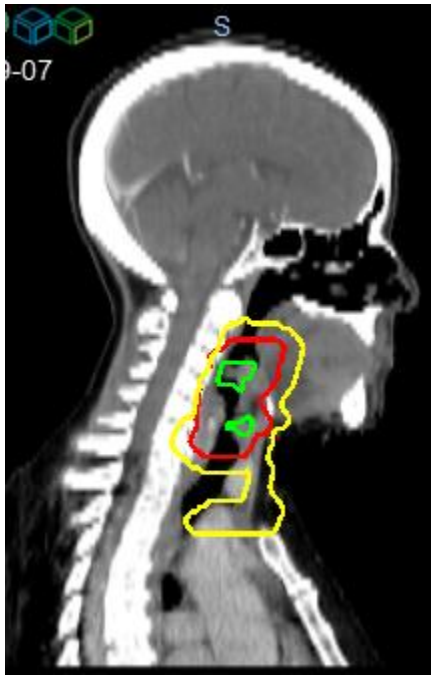
CTV1 = CTV2 + bilateral levels 2-4 and 6 (elective nodal irradiation)

CTV2 = GTV + 1 cm

PTV1 = CTV1 + 3 mm

PTV2 = CTV2 + 3 mm





RT Prescription:

PTV1: 56 Gy at 1.6 Gy per fraction, QD

PTV2: 70 Gy at 2 Gy per fraction, QD

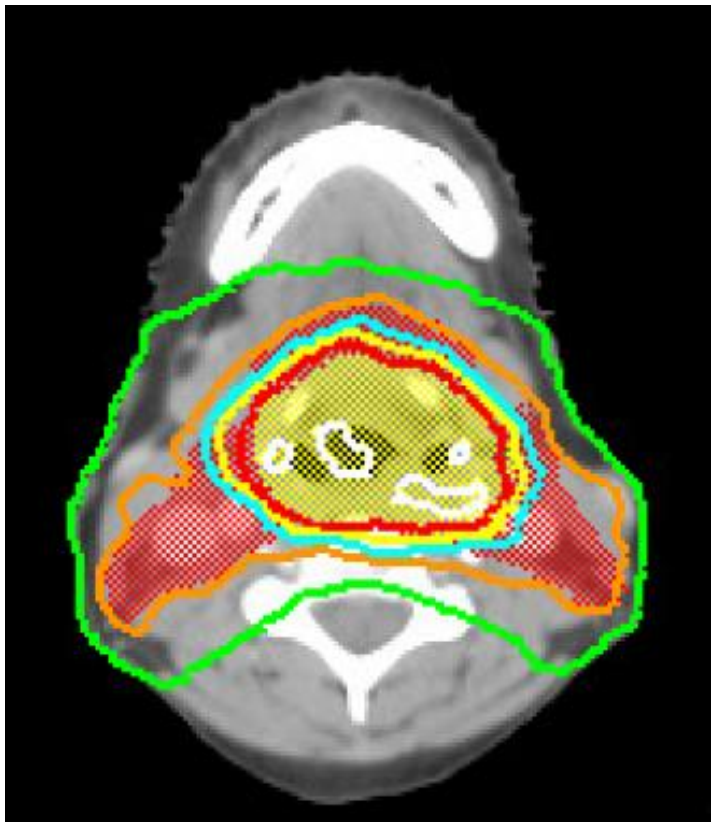
Total fractions: 35

Total treatment days: 35

Concurrent chemo: Yes, weekly cisplatin
Technique: IMRT SIB
Beam Energy: 6 MV photons
IGRT: CBCT prior to each fx

Case: Definitive ChemoRT

IMRT Isodose Plan (6MV photons)



Shaded Volumes
(colors opposite of previous slide)
PTV1 (56 Gy)
PTV2 (70 Gy)

Isodose lines (IDL)
Blue IDL: 110% rx (77 Gy)
White IDL: 105% rx (73.5 Gy)
Red IDL: 100% rx (70 Gy)
Yellow IDL: 95% rx (66.5 Gy)
Cyan IDL: 90% rx (63 Gy)
Orange IDL: 80% rx (56 Gy)
Green IDL: 50% rx (35 Gy)

Case: Definitive ChemoRT

Target Coverage Goals/Heterogeneity Constraints			Major OAR Constraints			
Structure	**DVH Point**	**Objective**	**Structure**	**DVH Point**	**Objective**	**Dose (Gy)**
PTV	D95%	≥ 100% Rx	Brainstem	D0.1cc	≤55 Gy	7.4
PTV	D99%	≥ 93% Rx	Spinal Canal	D0.1cc	≤50 Gy	36
PTV	Dmax	<110% Rx	Brach_Plex_LT	D0.1cc	≤66 Gy	55.1
PTV	V110% Rx	< 20%	Brach_Plex_RT	D0.1cc	≤66 Gy	52.5
Met primary objective Met secondary objective Did not meet objective			SMG_LT	Mean dose	≤40 Gy	59.8
			SMG_RT	Mean dose	≤40 Gy	59
			Cervical esophagus	Mean dose D0.1cc	≤35 Gy 60 Gy	54.9 61.9
			Thoracic esophagus	Mean dose D0.1cc	≤35 Gy 60 Gy	18.4 55.5
			Parotid_LT	Mean dose	≤26 Gy	23.1
			Parotid_RT	Mean dose	≤26 Gy	23.1

Case: Follow-up

- Treatment course:
  - Treated for oral thrush
    - Fluconazole PO (200 mg loading dose, followed by 100 to 200 mg daily for 7 to 14 days)
  - Hospitalized during RT for mucositis and G tube place for malnutrition
    - Pain treated with opiates
- Now 4 years since RT: **NED** (flexible nasopharyngolaryngoscopy and CT neck)
  - No G tube
    - Removed 2 months after completing treatment
  - Chronic left ear pain and throat pain

Follow up

- **PE/scope exam:**
  - Year 1: q1-3 mos (q 3 mos)
  - Year 2: q2-6 mos (q 4 mos)
  - Years 3-5: q4-8 mos (q 6 mos)
  - >5 years: q 12 mos

NCCN Guidelines Version 2.2022
Head and Neck Cancers

- **Imaging: (low quality conflicting evidence)**
  - PET/CT at 3 months
  - CT neck can be done less frequently than PE/scope exam but beneficial in advanced larynx cancer due to high chance of nodal involvement/recurrence
  - CT chest once a year
    - Smoking prevalent in larynx cancer, refer for LDCT chest for lung cancer screening as indicated
- **TSH** every 6-12 months if neck irradiated
- **Supportive care and rehabilitation as clinical indicated:**
  - Speech/hearing and swallowing evaluation and rehabilitation
  - Nutritional evaluation and rehabilitation
  - Ongoing surveillance of depression
  - Smoking cessation and alcohol counseling
  - Lymphedema evaluation and rehabilitation

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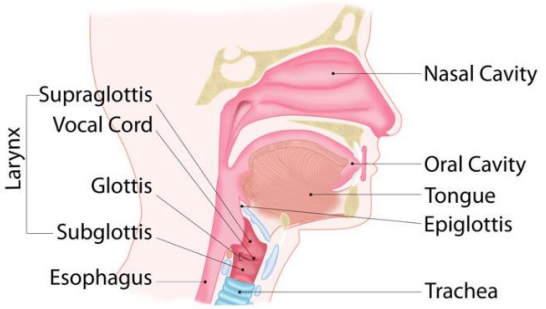
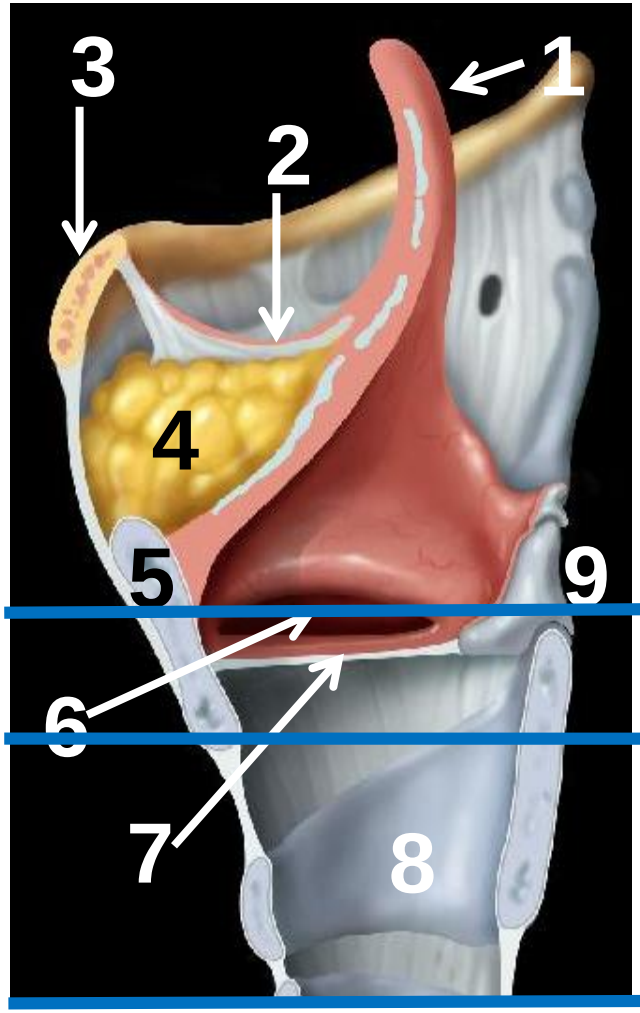
Larynx Cancer: The Basics



https://www.kennedy-center.org/education/resources-for-educators/classroom-resources/media-and-interactives/media/music/so-you-want-to-be-a-singer/so-you-want-to-be-a-singer/taking-care-of-your-voice/

1. Epiglottis
2. Vallecula
3. Hyoid bone
4. Pre-epiglottic space (fat)
5. Thyroid cartilage
6. Laryngeal ventricle
7. TVC
8. Cricoid cartilage
9. Arytenoid cartilage



3 subdivisions and subsites of the Larynx

Supraglottis: epiglottis, AE fold, arytenoid mucosa, false VC

Glottis: TVC, anterior commissure

Subglottis

https://quizlet.com/389397020/sagittal-view-of-the-larynx-diagram/

Larynx Cancer: The Basics

- Epidemiology:
  - 12,400 new cases each year in US
  - M>F
  - Incidence increases with age
- Risk Factors:
  - Smoking, alcohol, environmental exposures (asbestos, cement, wood dust, perchlorethylene)
- Pathology:
  - Majority are SCCa
    - Carcinoma in situ occurs in vocal cords, rare in supraglottis
  - Role of HPV is controversial
  - Rare: malignant minor salivary gland, small cell, lymphoma, plasmacytoma, carcinoid, soft tissue sarcoma, chondrosarcoma, osteosarcoma, malignant melanoma

Clinical Presentation

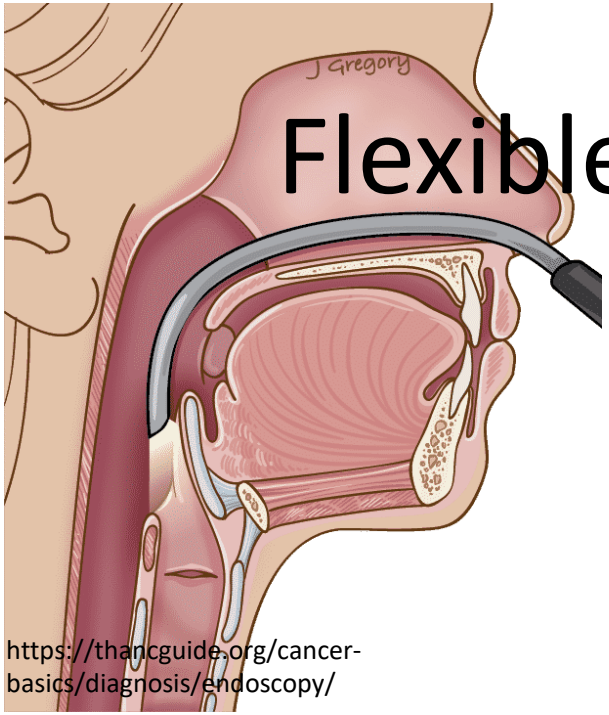
- Presenting symptoms related to site of origin
  - Glottis
    - Early stage: hoarseness
    - Late stage: otalgia (referred pain to auricular branch of Arnold, vagus nerve), dysphagia, cough hemoptysis, stridor
  - Supraglottis
    - Detected later: dysphagia, globus sensation, airway obstruction and lymphadenopathy

Diagnostic Workup

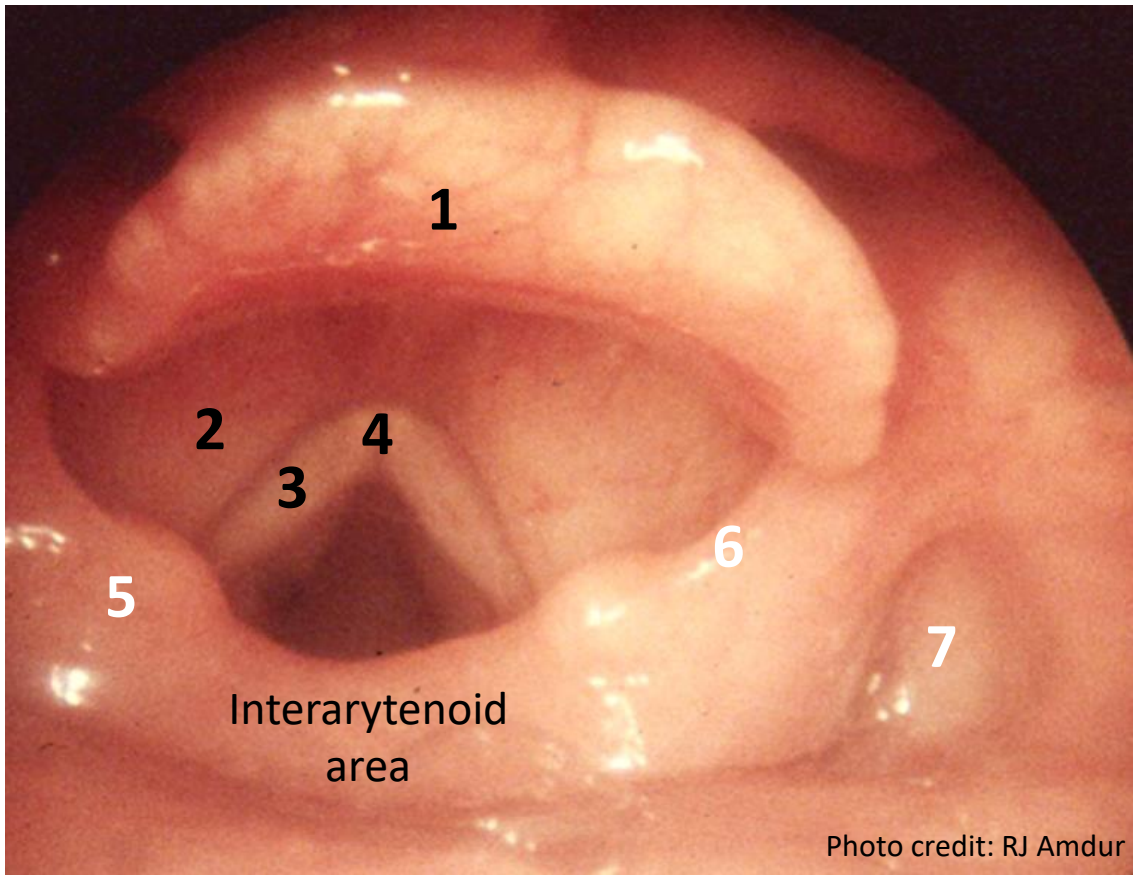
- Complete head and neck exam (+ fiberoptic examination)
- FNA or core needle biopsy
- CT with contrast (thin angle cuts through larynx) and/or MRI with contrast of primary and neck
- EUA with endoscopy
- As clinically indicated:
  - CT chest (with or without contrast)
  - Consider FDG PET/CT (Stage III/IV)
  - Preanesthesia studies (preop assessment)
  - Consider videostrobe for select patients
  - Dental evaluation
  - Nutrition, speech and swallowing evaluation/therapy
  - Audiogram
  - Smoking cessation counseling

NCCN Guidelines Version 2.2022
Cancer of the Glottic Larynx

Flexible Nasopharyngoscopy



https://thancguide.org/cancer-basics/diagnosis/endoscopy/



1. Epiglottis
2. FVC
3. TVC
4. Anterior commissure
5. Mucosal surface of arytenoid cartilage
6. Aryepiglottic (AE) fold
7. Pyriform sinus

How to Stage (General Concepts)

	Supraglottis	Glottis	Subglottis
T stage (T1*, T2, T3, T4a, T4b)	• # subsites involved • Involvement beyond supraglottis	• *T1a and T1b: one TVC vs two involved • Involvement beyond vocal cords • Vocal cord mobility	• Involvement beyond subglottis • Vocal cord mobility
N stage (N0, N1, N2abc, N3ab)	Number, size, ENE		
M stage (M0, M1)	Y/N distant mets		

AJCC 8th Edition Staging

T stage	Supraglottis	Glottis	Subglottis
T1	1 subsite of supraglottis, normal VC mobility	Limited to vocal cords T1a: one T1b: both	Limited to subglottis
T2	>1 adjacent subsite of supraglottis or glottis or region outside of supraglottis (base of tongue, vallecular, medial wall of pyriform sinus) without fixation of larynx	Extends to supraglottis and/or subglottis and/or with impaired VC mobility Old staging system split T2 glottis into T2a and T2b (impaired TVC mobility)	Extends to the VCs with normal or impaired mobility
T3	Limited to larynx with VC fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space and/or inner cortex of thyroid cartilage	Limited to larynx with VC fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage	Limited to larynx with VC fixation and/or inner cortex of the thyroid cartilage
T4a	Invades through outer cortex of thyroid cartilage, cricoid and/or invades tissues beyond larynx (trachea, soft tissues of neck, deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus		
T4b	Invades prevertebral space, encases carotid artery or mediastinal structures		

AJCC 8th Edition Staging

	cN	pN
N1	Single, ipsilateral, ≤ 3 cm, ENE -	
N2a	Single, ipsilateral, > 3 cm but ≤ 6 cm, ENE -	Single, ipsilateral, > 3 cm but ≤ 6 cm, ENE - OR Single, ipsilateral, ≤ 3 cm, ENE +
N2b	Multiple, ipsilateral, ≤ 6 cm, ENE-	
N2c	Bilateral or contralateral, ≤ 6 cm, ENE -	
N3a	> 6 cm and ENE -	
N3b	ENE +	ENE + (except Single, ipsilateral, ≤ 3 cm, ENE +)

	M Stage
M0	No distant metastasis
M1	Distant metastasis

General Management Overview

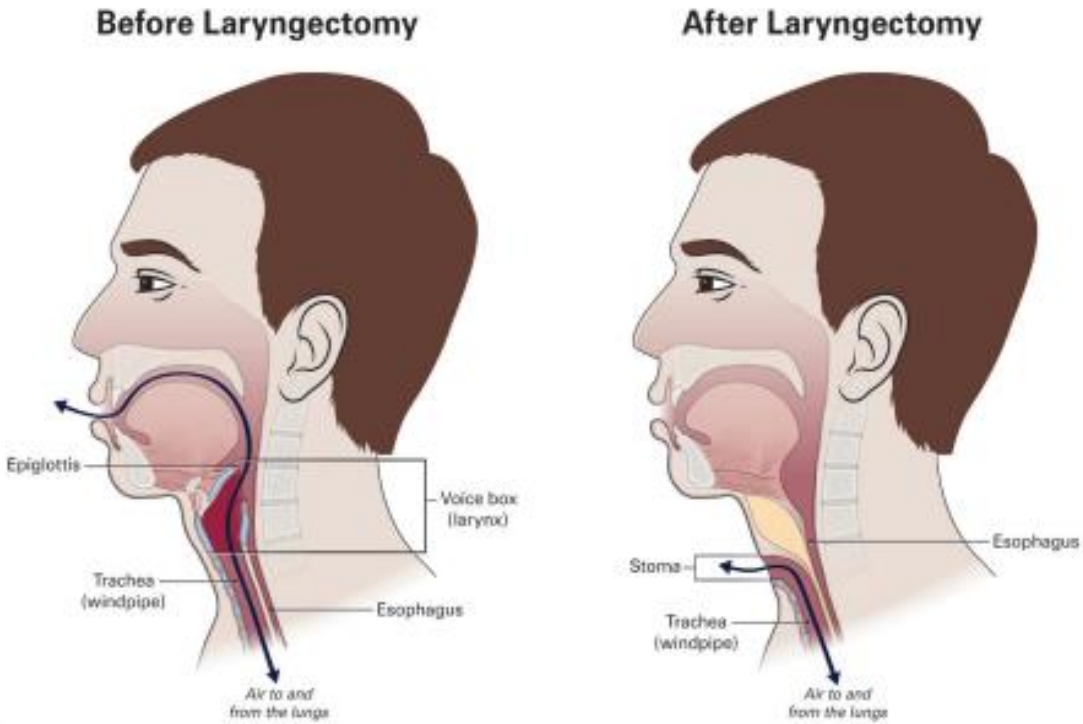
- Early stage (T1-2N0)
  - RT alone or microsurgery
- Advanced (T3-4 or node positive)
  - ChemoRT vs total laryngectomy +/- PORT

Concurrent Chemotherapy

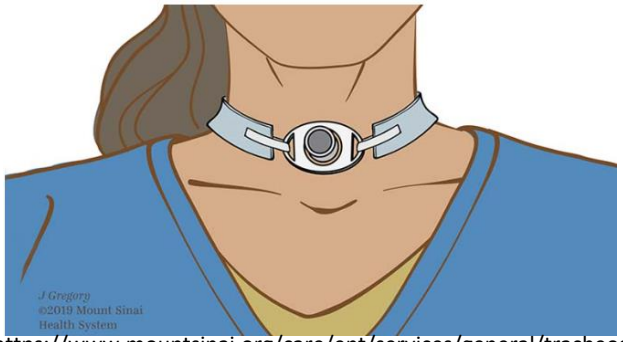
- Early stage (T1-2N0):
  - Not routinely given but can consider for T2 with impaired mobility (T2b per old staging)
- Locally Advanced (T3-4 or node positive)
  - Concurrent cisplatin
    - 100 mg/m^2 bolus weeks 1, 4, 7 (NCCN category 1) or 40 mg/m^2 weekly (NCCN category 2B)
- Other considerations:
  - Induction chemotherapy is controversial

Surgical Management

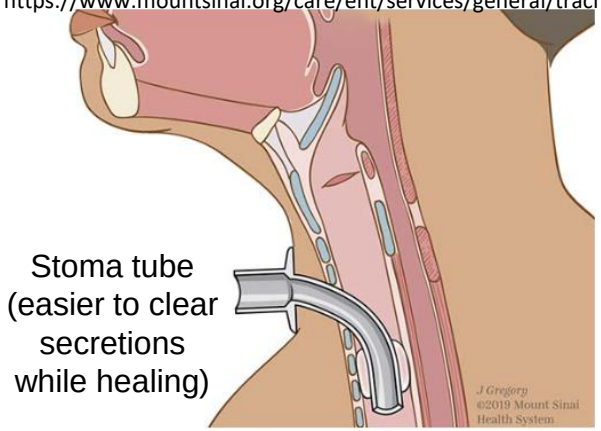
- Total laryngectomy + bilateral neck dissection



https://www.uhn.ca/PatientsFamilies/Health_Information/Health_Topics/Documents/Laryngectomy.pdf



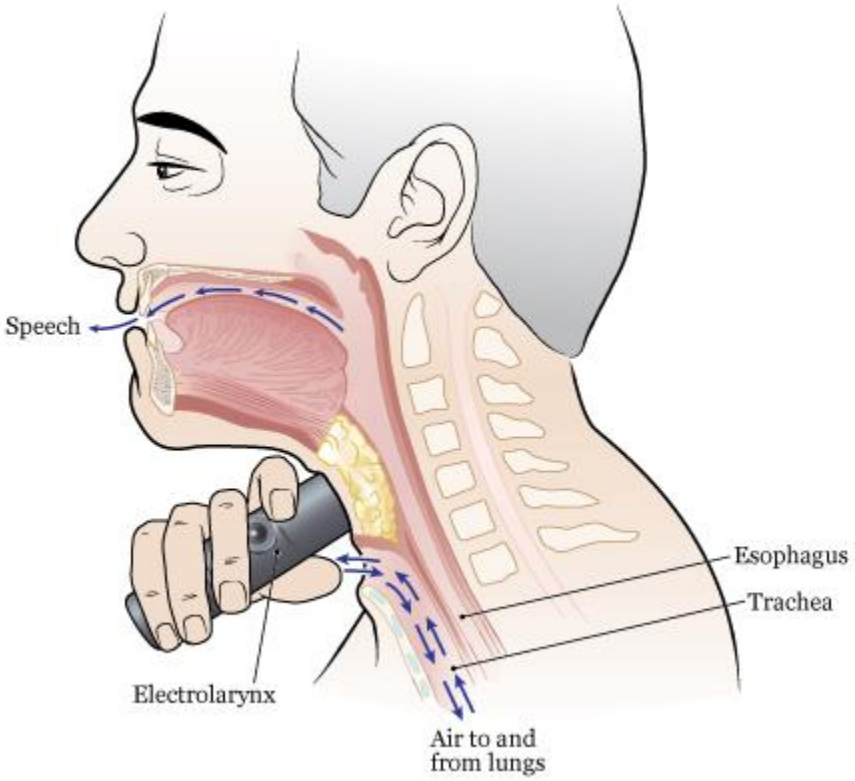
https://www.mountsinai.org/care/ent/services/general/tracheostomy



Stoma tube (easier to clear secretions while healing)

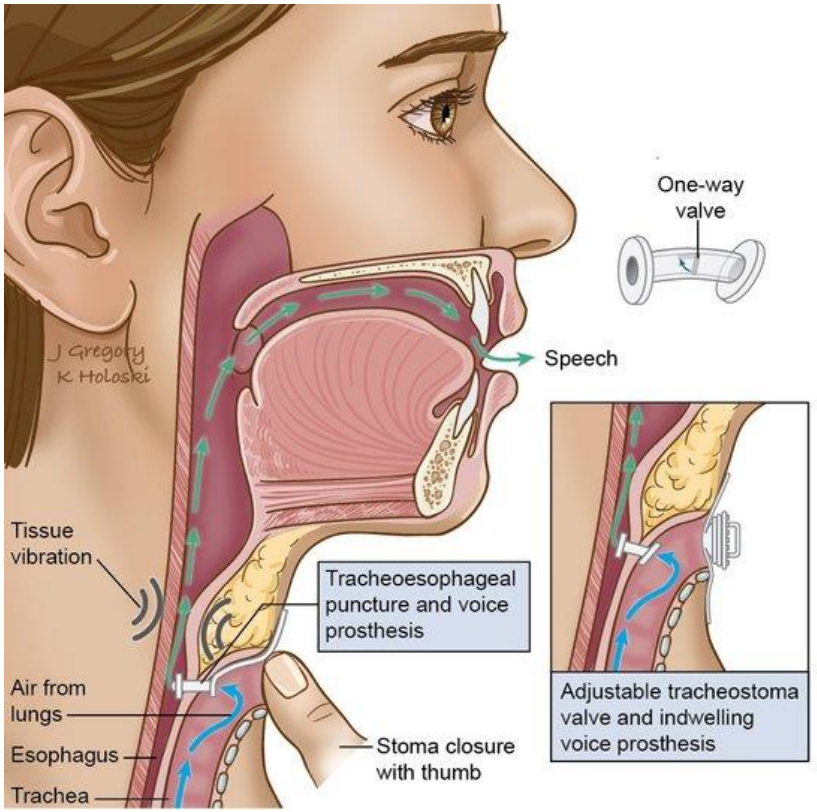
Speech After Total Laryngectomy

Electrolarynx



https://www.mskcc.org/cancer-care/patient-education/total-laryngectomy-01

Tracheo-esophageal
Voice Prosthesis



https://www.e4ent.com/articles/tracheoesophageal-prosthesis-tep-speech/

Surgical Vs ChemoRT

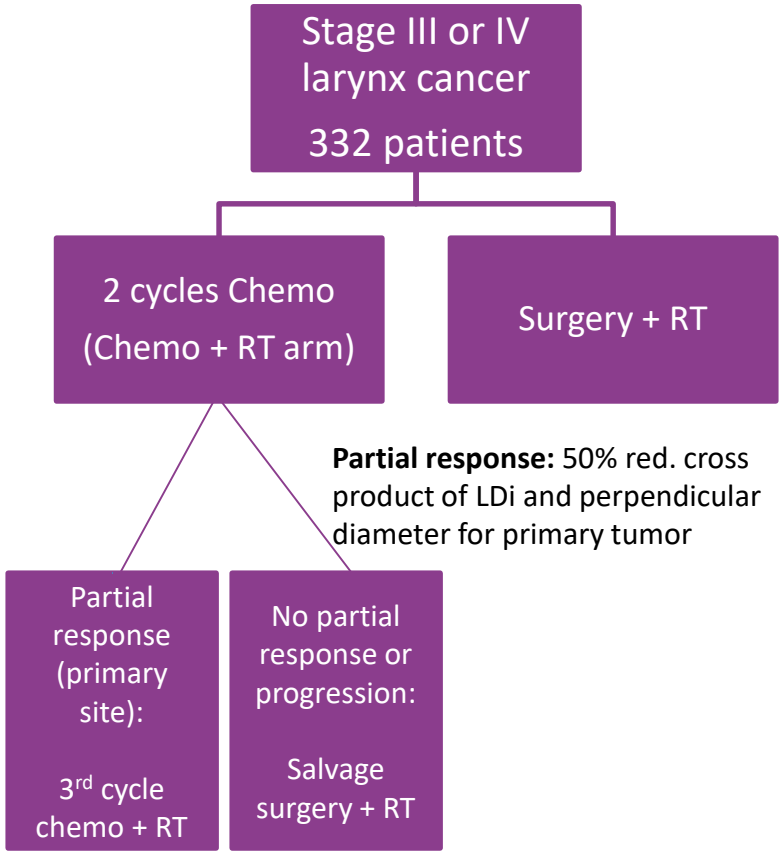
- Discussion only applies if:
  - Larynx is functional (swallowing, not speech)
  - Medically operable and patient agreeable to surgery
  - Partial laryngectomy is not an option
- Larynx preservation studies
  - VA larynx preservation study
  - RTOG 91-11

INDUCTION CHEMOTHERAPY PLUS RADIATION COMPARED WITH SURGERY PLUS RADIATION IN PATIENTS WITH ADVANCED LARYNGEAL CANCER

THE DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY GROUP*

NEJM 1991

VA Larynx Study



Chemotherapy: Cisplatin and fluorouracil
After 2 cycles chemo: CR 31%, PR 54%
After 3 cycles chemo: CR 49%, PR 49%

Question: Is induction chemo and definitive RT, with laryngectomy reserved for salvage safe and will people die more often without surgery?

Outcomes: OS, Disease free survival, Larynx preservation

Randomization: Chemo + RT vs Surgery + RT

Inclusion: Advanced (stage III or IV), glottic and supraglottic laryngeal SCCa, Node positive

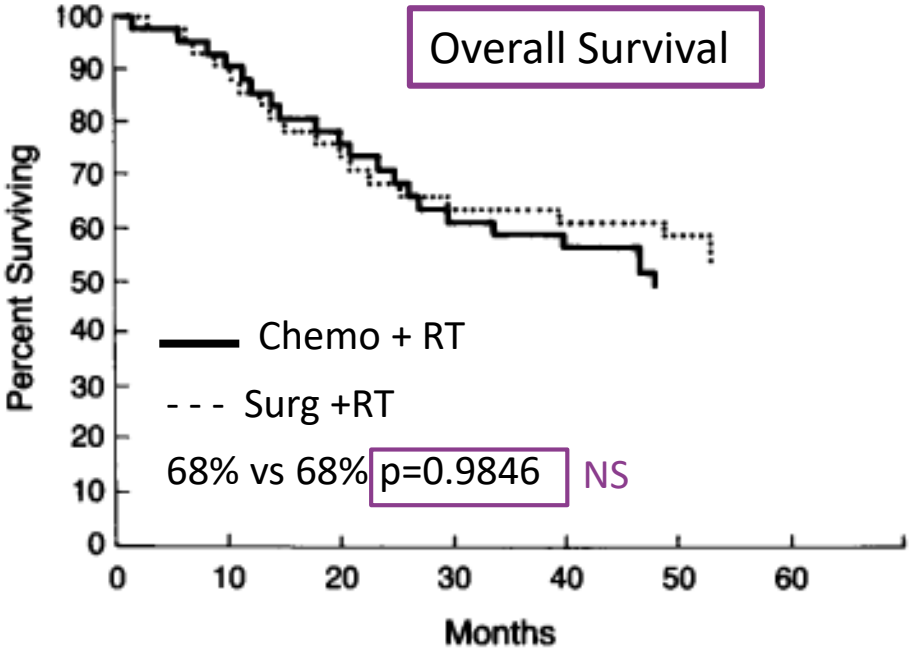
RT:

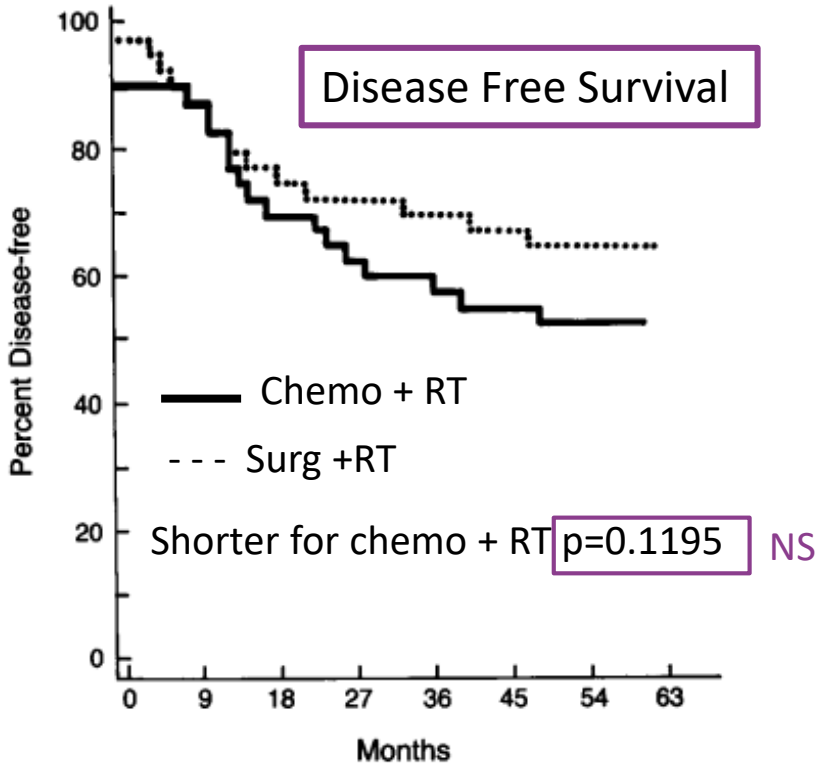
- Definitive RT: 66-76 Gy to primary, 50-75 Gy to nodes, 50-50.4 Gy to areas at risk of microscopic disease
- Post op RT: 50-50.4 Gy to normal risk, 10 Gy boost to high risk, 15-23.8 Gy boost for residual disease

VA Larynx Study Results

No difference in overall recurrence rates. Primary site recurrences more likely in chemo arm but distant mets less frequent.

64% of surviving pts treated with chemoRT retained a functioning larynx





Conclusion: Induction chemotherapy and definitive RT can be effective in preserving the larynx in a high percentage of patients without compromising overall survival

RTOG 91-11

Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

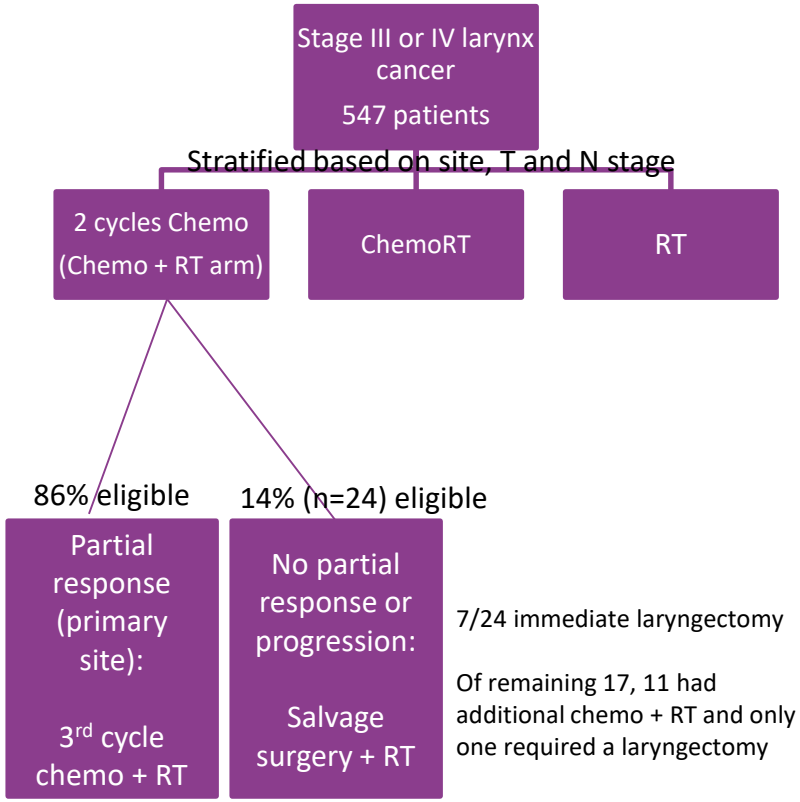
NEJM 2003

Arlene A. Forastiere, M.D., Helmuth Goepfert, M.D., Moshe Maor, M.D., Thomas F. Pajak, Ph.D., Randal Weber, M.D.,

Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer

JCO 2013

Arlene A. Forastiere, Qiang Zhang, Randal S. Weber, Moshe H. Maor, Helmuth Goepfert, Thomas F. Pajak,



Induction Chemotherapy: Cisplatin and fluorouracil
Concurrent Chemotherapy: Cisplatin

Question: What is the value of adding chemotherapy to RT and what is the optimal timing of chemotherapy?

Primary Outcome: Larynx preservation

Secondary Outcome: OS, DFS, local control, locoregional control, time to distant metastasis, laryngectomy free survival (LFS)

Randomization: Induction chemo + RT, chemoRT, RT

Inclusion: Stage III/IV SCCa of the glottic or supraglottic larynx

Exclusion: Large volume T4 (tumor penetrating through the cartilage or extending > 1cm into base of tongue

RT:

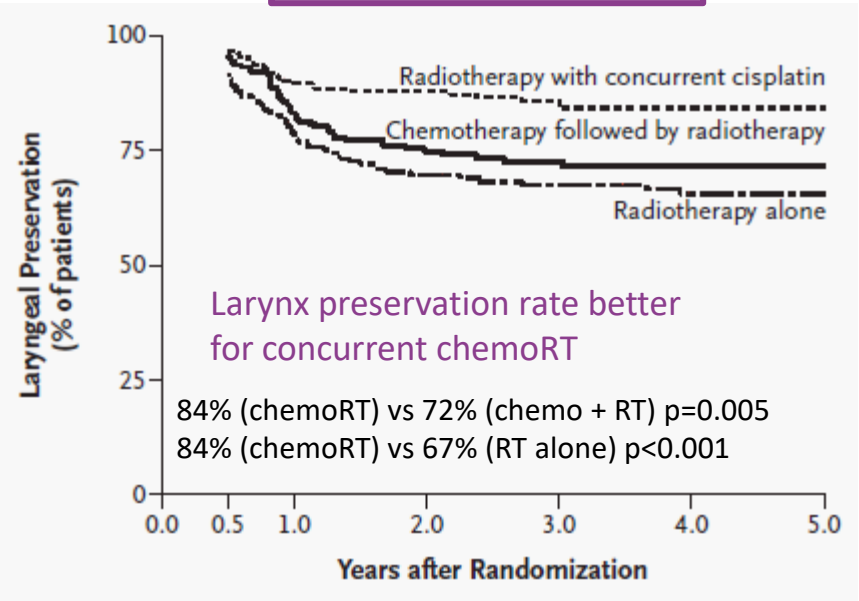
- Definitive: 70 Gy @ 2 Gy to primary and positive nodes, entire neck (including SCV and posterior neck) 50 Gy
- Adjuvant: 50-70 Gy depending on margin status

Median follow up: 3.8 years

No difference in OS (75% @ 2 yrs)
Chemotherapy improved disease free survival and reduced rate of distant metastasis

RTOG 91-11 Results

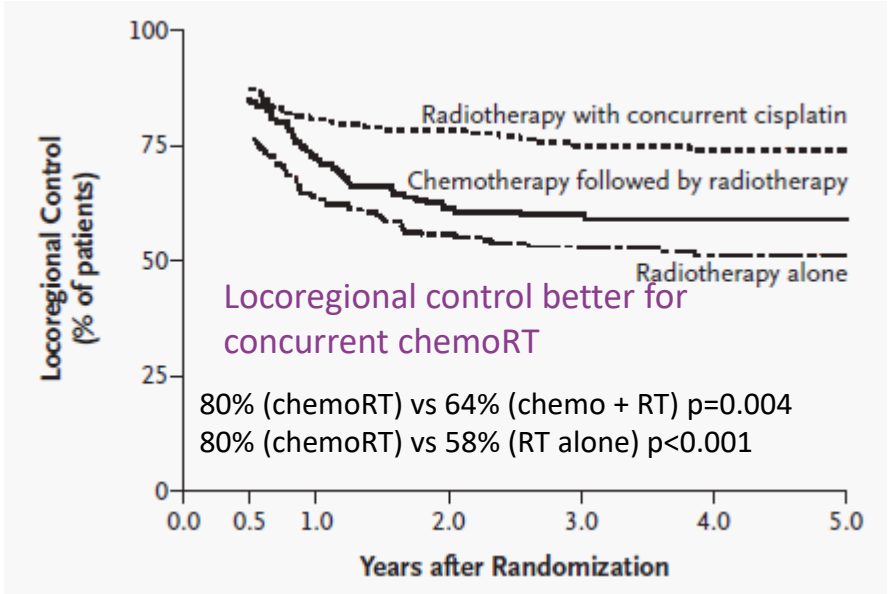
Larynx Preservation



Larynx preservation rate better for concurrent chemoRT

84% (chemoRT) vs 72% (chemo + RT) p=0.005
84% (chemoRT) vs 67% (RT alone) p<0.001

Locoregional Control



Locoregional control better for concurrent chemoRT

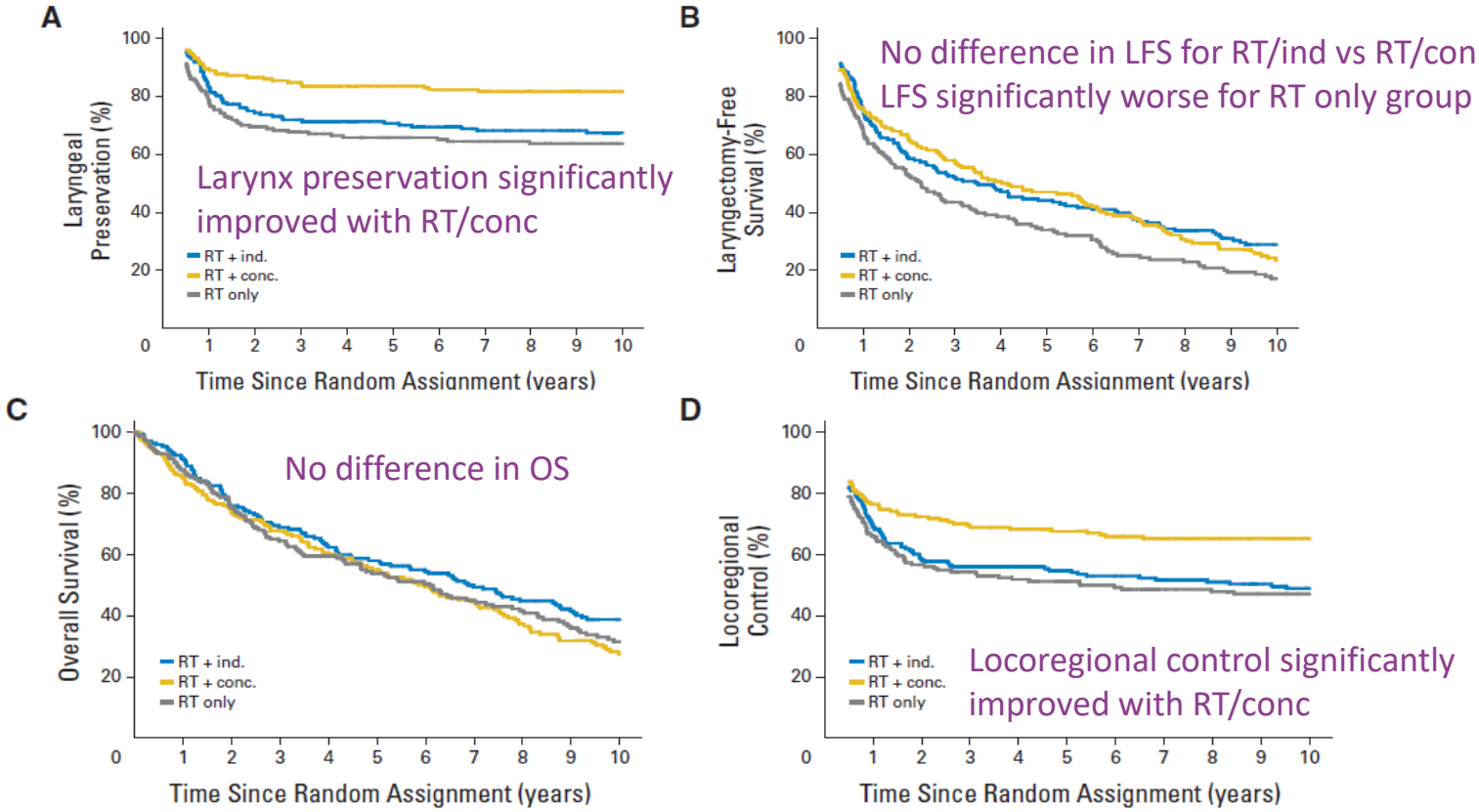
80% (chemoRT) vs 64% (chemo + RT) p=0.004
80% (chemoRT) vs 58% (RT alone) p<0.001

Conclusion: Concurrent chemoRT is superior to induction chemotherapy followed by RT or RT alone for laryngeal preservation and locoregional control for stage III/IV (T2, T3, or low volume T4 primary) larynx cancer

Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer JCO 2013

Arlene A. Forastiere, Qilong Zhang, Randal S. Weber, Moshe H. Maor, Helmuth Goepfert, Thomas F. Pajak,

RTOG 91-11 Long-term Results



Conclusion: 10 year results show that RT/ind and RT/conc show similar efficacy for the composite endpoint of LFS (Laryngectomy Free Survival). Locoregional control and larynx preservation were significantly improved with RT/conc

Larynx preservation is going UP during the period that survival is going DOWN

NATIONAL CANCER DATABASE REPORT ON CANCER OF THE HEAD AND NECK: 10-YEAR UPDATE

Head and Neck 2009

Jay S. Cooper, MD,[1] Kim Porter, MPH,[2] Katherine Mallin, PhD,[2] Henry T. Hoffman, MD,[3] Randal S. Weber, MD,[4] Kian K. Ang, MD, PhD,[5] E. Greer Gay, RN, PhD, MPH,[2] Corey J. Langer, MD[6]

Table 9. Percent distribution of treatment by diagnosis year, laryngeal tumors only.

Treatment	1990–1994	1995–1999	2000–2004	*N*
Surgery only	21.4	19.2	17.5	29,378
Radiation only	32.5	33.6	32.0	49,444
Chemotherapy only	1.1	1.5	1.5	2049
Surgery and radiation	28.9	25.9	20.2	38,100
Surgery and chemotherapy	0.4	0.5	0.4	663
Radiation and chemotherapy	4.4	8.1	15.0	13,442
Surgery, radiation, chemotherapy[1]	1.5	2.2	3.3	3426

Larynx preservation 4.4 ↑8.1 ↑15

TABLE 6. Trends in 5-Year Relative Survival Rates* (%) by Race and Year of Diagnosis, United States, 1975 to 2011

Siegel, CA Statistics, 2016

Survival for all other sites increasing

	ALL RACES			WHITE			BLACK		
	1975 TO 1977	1987 TO 1989	2005 TO 2011	1975 TO 1977	1987 TO 1989	2005 TO 2011	1975 TO 1977	1987 TO 1989	2005 TO 2011
All sites	49	55	69†	50	57	70†	39	43	62†
Brain & other nervous system	22	29	35†	22	28	33†	25	32	40†
Breast (female)	75	84	91†	76	85	92†	62	71	81†
Colorectum	50	60	66†	50	60	67†	45	52	59†
Esophagus	5	10	20†	6	11	21†	4	7	14†
Hodgkin lymphoma	72	79	88†	72	80	89†	70	72	86†
Kidney & renal pelvis	50	57	74†	50	57	74†	49	55	74†
Larynx	66	66	63†	67	67	65	58	56	51

66 ↓63 67 ↓65 56 ↓51

REEXAMINING THE TREATMENT OF ADVANCED LARYNGEAL CANCER

Kerry D. Olsen, MD Head and Neck 2010

Determining the standard of care for a cancer with a diverse set of treatment variables is difficult. Advanced laryngeal cancer is one such case. The treatment for advanced laryngeal cancer is now at a point where the current standard of care—concurrent chemotherapy and radiotherapy with surgical salvage (ie, laryngectomy)—must be reexamined. Why? Because published studies—identified as evidence-based medicine—have set a standard of care that has resulted in major unintended consequences.

The survival of patients with laryngeal cancer should not be decreasing. Unfortunately, this is happening today. The focal points of this

Conclusions

conclusions. The studies have been conducted with good intentions. Many patients have a preserved larynx, good function, and no signs of recurrence or complications today after receiving chemotherapy and RT. However, we need to better identify who these patients are and why their therapy was effective—we cannot continue on the present course. Survival after laryngeal cancer should be improving, not decreasing.

REEXAMINING THE TREATMENT OF ADVANCED LARYNGEAL CANCER: THE VA LARYNGEAL CANCER STUDY REVISITED

Gregory T. Wolf, MD

Head and Neck 2010

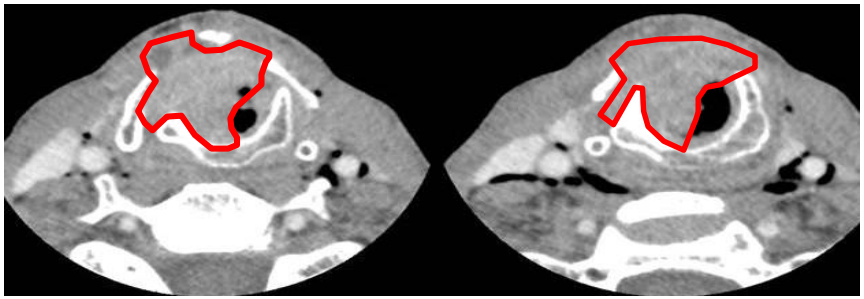
The reasons for the modest decreases in NCDB survival are not fully understood but appear across all stages of disease and seem more closely related to the use of radiation alone or local surgical resection as treatment modalities.

It may be equally likely that the increasing use of endoscopic techniques by unskilled surgeons may also be a contributing reason for these results.

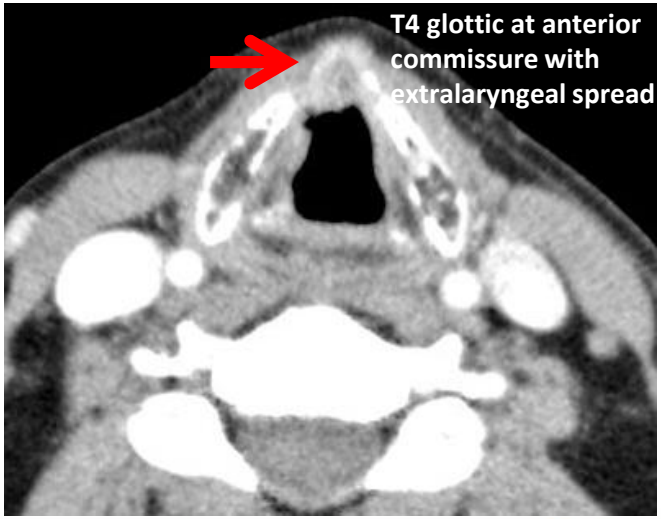
Decreasing larynx cancer survival results are multifactorial. We will hurt patients if we extrapolate the results of larynx preservation trials to poor prognosis cases where the trial results do not apply.

Indications for Laryngectomy: T stage alone?

T4 based on full thickness Thyroid-Cartilage destruction is a good indication for Laryngectomy because all are high volume and have low chance of larynx conservation



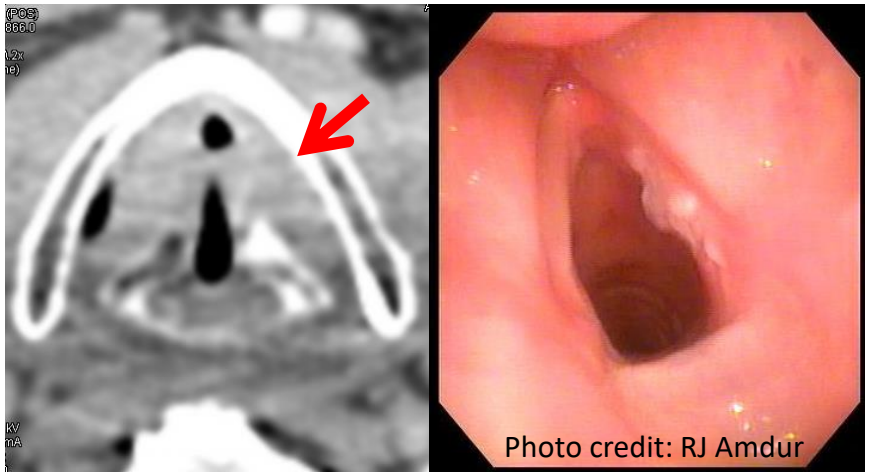
Limitation of T stage alone: T4 by extralaryngeal spread WITHOUT thyroid cartilage invasion may be low volume (good prognosis for larynx preservation)



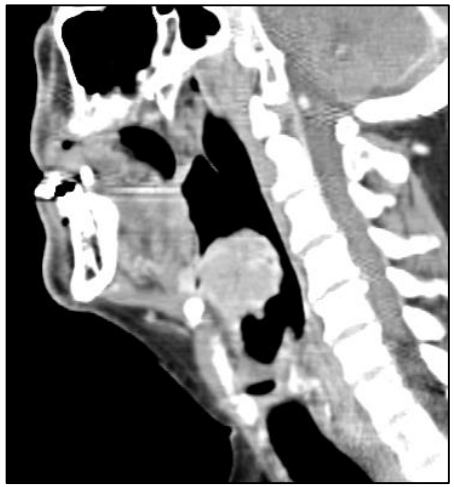
Indications for Laryngectomy: T stage alone?

T3 definition: fixed cord, invasion limited to the inner cortex of the thyroid cartilage or pre or para glottis space invasion

T3: small lesion with good cord movement but **paraglottic space invasion**



T3: large lesion with **fixed cord**



Both are T3, but the patient on the left would do well with RT +/- chemo and the patient on the right would benefit from a laryngectomy (poor prognosis with larynx preservation)

T stage alone is not enough information to make the decision or larynx preservation vs laryngectomy

Larynx Preservation Selection: Primary Tumor Volume

Institution	Author	Journal	Year	Journal details
U Florida	Pamiejer	IJROBP	1999	No. 2, pp 359-366
U Michigan	Mukherji	Head and Neck	2000	22: 282-287
U Florida	Mendenhall	Head and Neck	2003	25: 535-542
RTOG	Mukherji	Cancer	2005	103: 2616-22
U Florida	Bryant	Hong Kong J Radiol	2013	16;198-202
U Florida	Nurkic	Am J Clin Onc	2018	41(11): 1089-1093

Some institutions have published on the utility of primary tumor volume to help identify candidates for larynx preservation

Fixed cord = Bad
Small volume = Good
(≤3.5 cc glottis and ≤6 cc supraglottic)

Indications for Postoperative RT

Primary Site Indications for post op RT	
Margin	Other
Positive invasive	PNI
Close invasive <2-5 mm	pT4
Positive carcinoma in situ	LVSI
	Subglottic > 5mm

Nodal Indications for post op RT
ENE
≥ 2 positive nodes

Post op RT: Target Volumes and Prescription

Risk	Path Finding	RT dose (Gy)	CTV (According to most guidelines)
High	Positive invasive margin ENE	66 @ 2 Gy (33 fxs)	CTV66 = Preop GTV + 1 cm, edited (Primary GTV if margin problem, Node GTV if ENE)
Standard	Any other	60 @ 2 Gy (30 fxs)	CTV60 = Primary site resection area* and Node positive stations, + 1 cm, edited * When nodes are the only indication for postop RT, historic standard has been to treat primary site to 60 Gy, but emerging controversy is no RT to primary site if no indications at primary
Elective	pN0 or cN0 stations	54 @ 1.8 Gy (30 fxs) 54 @ 1.6 Gy (33 fxs)	CTV54 = stations at risk for subclinical disease (Biau and Evans)

Concurrent chemotherapy: positive invasive margin or ENE. Relative indications: close margin, pT4, ≥ 2 positive nodes

Conclusions

- Historically, advanced larynx cancer (T3-4N0, node positive) was treated with laryngectomy
- However, in certain clinical scenarios, larynx preserving treatment consisting of definitive chemoRT can be employed
- Good candidates for larynx preservation include those with a low volume primary and functional larynx
- When a laryngectomy is performed, post operative RT is recommended for a positive invasive margin, close invasive margin (<2-5 mm), positive CIS margin, PNI, pT4, LVSI, subglottic > 5mm, ENE, ≥ 2 positive nodes

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