

Malignant Lesions of the Larynx

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Incidence

- 10K new cases of laryngeal cancer in U.S. annually
 - 3,900 deaths annually
- Gender
 - Since 1950- M:F ratio 15:1 → 5:1 in 2004
 - women have equal place in the toxic work environment
 - cigarette smoking
- Risk factors:
 - Tobacco
 - 13-fold risk for laryngeal cancer for smokers
 - risk increases with increasing tobacco use
 - Alcohol
 - 34-fold risk for laryngeal cancer if consume >1.5 L wine/day
 - Tea time?
 - *mate* in Latin America and *chimarra* in Brazil

Decreasing Survival Among Patients with Laryngeal Cancer

- NCDB analysis:
 - mid-1980s to mid-1990s.
 - Increased chemo-radiation, decreased open surgery, increased endoscopic resection
- The most notable decline in the 5-year relative survival:
 - advanced-stage glottic cancer
 - early-stage supraglottic cancers
- *“The decreased survival recorded for patients with laryngeal cancer in the mid-1990s may be related to changes in patterns of management.”*

Genetics/ Risk factors

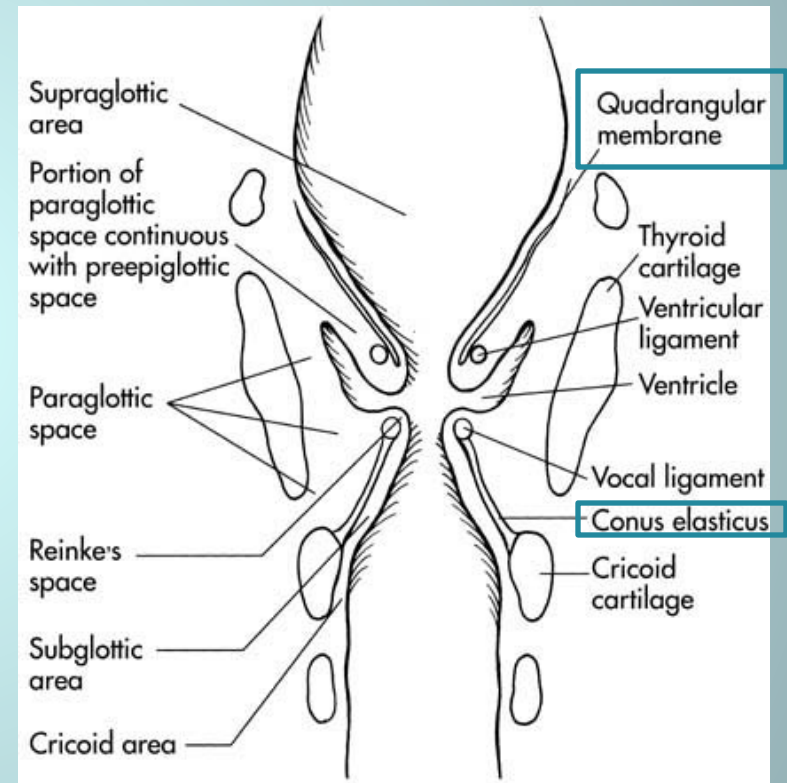
- Aneuploidy
- Tumor suppressor gene *inactivation*
 - Gene locus 17p13 : mutant *p53**DNA repair, apoptosis*
 - Gene locus 9p21 : mutant *p16* *Cell cycle regulation*
- Proto-oncogene *activation*
 - Proto-oncogene (11q13) amplifies cyclin D1..... *Cell cycle regulation*
- Mutagen-induced chromosome breaks
- HPV
 - Types 16 and 18: E6 and E7 viral protein-mediated degradation of *p53*
 - Oropharyngeal malignancy
- GERD
 - Koufman: n=31 with glottic SCC, GERD documented in 84%; only 58% were smokers

Embryology

- Frazer (1909)
 - supraglottis originates from the buccopharyngeal primordium
 - high risk of bilateral neck disease vs. glottic tumors - metastasize ipsilaterally
- Pressman (1956)
 - separate derivation from glottis- supraglottic tumors of substantial bulk do not spread across the laryngeal ventricle to the vocal cord
- Tucker and Smith (1982)
 - Dye studies anatomically based confirmation re: elastic tissue barriers
 - Formed basis of partial laryngeal surgery
 - Already advocated by Biller

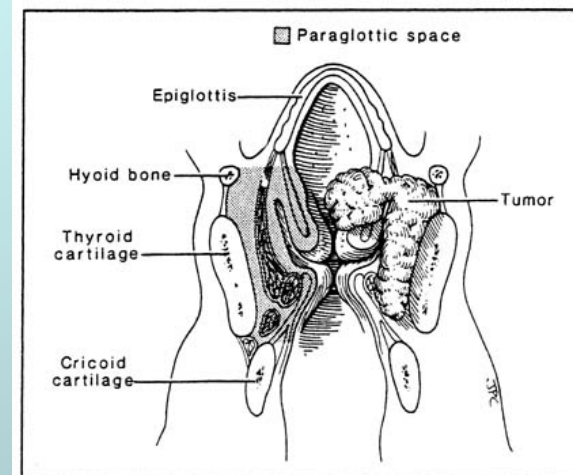
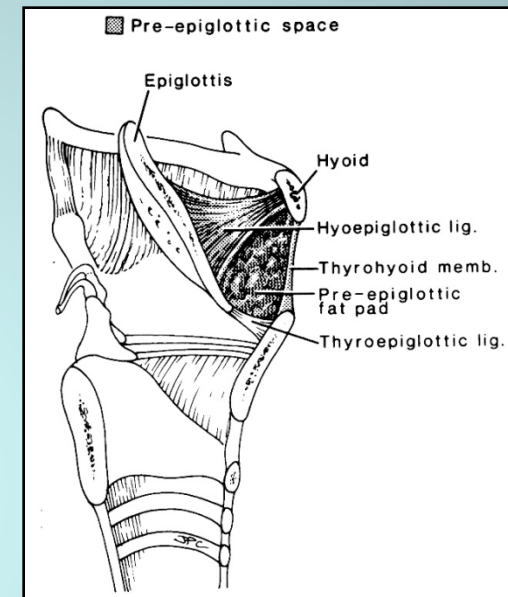
Anatomy

- Fibroelastic membranes
 - Barriers to carcinoma spread
- Quadrangular membrane
 - Superior free edge= AE fold
 - Inferior free edge= False cord
- Conus elasticus
 - Supports vocal fold
 - Lateral attachment at cricoid
 - Medial attachment at anterior thyroid cartilage
 - Free edge forms vocal ligament



Pre-epiglottic space & Para-glottic space

- Pre-epiglottic space
 - Anterior: thyrohyoid membrane & thyroid cartilage
 - Posterior: epiglottis elastic cartilage
 - Inferior: Petiole attachment to thyroid cartilage
 - Conduit :
 - elastic epiglottic cartilage has perforations -→direct extension of infrahyoid supraglottic cancer into this fascia-bound space
 - Bilateral neck drainage
- Paraglottic space
 - quadrangular membrane inferiorly
 - conus elasticus anteriorly and medially
 - thyroid cartilage laterally



Transglottic tumors

- Usually initiate as supraglottic or glottic cancers
- McGravan (1961)
 - must cross three regions: false cords, ventricle, true cord
 - alters prognosis
- Fail the compartmentalization hypothesis
 - direct mucosal extension
 - paraglottic space

Diagnosis

- Dysphagia
- Vocal changes
- Aspiration
- Otalgia
- Blood-tinged sputum
- Neck mass
- Cachexia
- Dyspnea
- Pain
- Halitosis

Natural History WITHOUT Treatment

- Hemoptysis> supraglottic tumors
- Dysphonia> TVC/glottic lesions
- Airway Obstruction> insidious subglottic tumors
- Aspiration> supraglottic (also with incompetent glottis)
- Otalgia> supraglottic (infiltration of musculature)
- Dysphagia: any location, muscle, sensory, motor, joint

Histology

- >95% SCC
 - Variations :
 - verrucous carcinoma, spindle cell carcinoma, basaloid SCC, and papillary SCC
- Other types of carcinoma:
 - neuroendocrine carcinoma
 - lymphoepitheliomatous carcinoma
 - adenocarcinoma
 - others (sarcomas, lymphomas)
 - adenoid cystic (trachea more than subglottis)
- Underlying:
 - hyperplasia, dysplasia, CIS
- Overlying:
 - surface keratinization may be present.

Histology

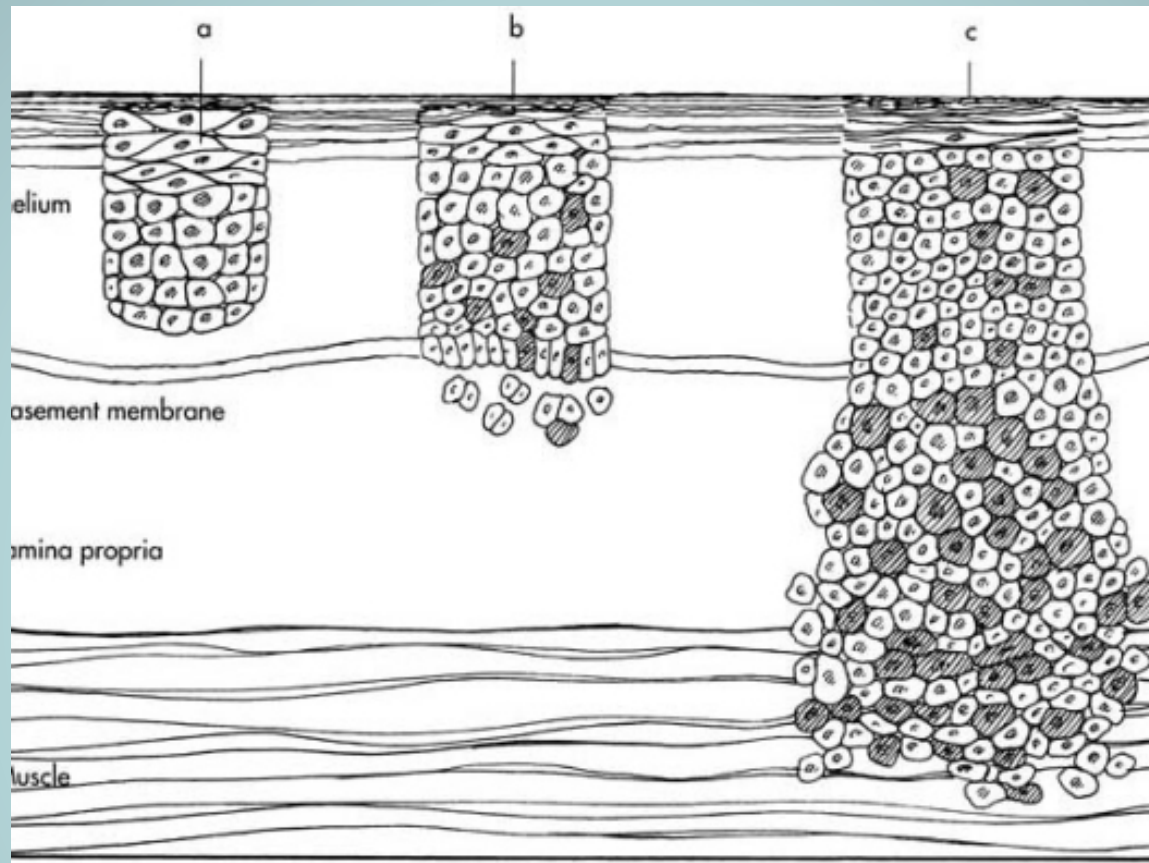
- Mucosa: 5-7 cell layers
 - stratified squamous epithelium, (eg, ventricle, false cord, and subglottis)
- Mitotic figures:
 - present in the basal layer
 - should be absent above this second layer
- CIS: full-thickness atypia of the squamous cells
- Atypia is characterized by the *cell architecture*:
 - mitoses count per hpf, high NC ratio, large nucleoli
- Differentiation is characterizes by the *tissue architecture*:
 - well, moderately, or poorly differentiated

Whatcha got???

- Patients with glottic tumors are seen early because of hoarseness....
 - Biopsy !!!!!
- Oops!
 - fungal laryngitis, sarcoidosis, tuberculosis, or Wegener's granulomatosis , pseudoepitheliomatous hyperplasia (granular cell myoblastoma)
- The five categories of laryngeal squamous cell *abnormality* (from benign to clearly malignant):
 - hyperkeratosis
 - hyperkeratosis with atypia
 - carcinoma in situ (CIS)
 - superficially invasive carcinoma
 - invasive carcinoma

H, H+A, CIS

- hyperkeratosis +/- atypia and CIS
 - conservative management: stripping of VC
 - 5%–30% with future invasive cancer
- follow-up and possible re-biopsy 6 - 12 weeks



Superficially invasive vs. Invasive SCC

Why care?

Superficial vs. Invasive Glottic SCC

- Superficial invasive carcinoma vs. CIS
 - It is all about the SLP!!!!!!
- “The central third”
 - early symptoms of voice change
- Sampling error:
 - Slaughter's hypothesis of field cancerization as described originally for the oral cavity (1946)

Management of precancerous lesions

- Radiotherapy *...not so much!!!*
 - failure (10%)
 - no future option for XRT T₁ / T₂
- Surgery
 - Generous stripping
 - Informed consent re: multiple treatments
 - Good compliance (years)
 - Supravital staining with toluidine blue
 - Rapid or frequent recurrence
- *Smoking cessation program must be part of management!!!!*

Peeps you know... things you should know...

- [Blackwell KE](#), [Calcaterra TC](#), [Fu YS](#). **Laryngeal dysplasia: epidemiology and treatment outcome.** Ann Otol Rhinol Laryngol. 1995 Aug;104(8):596-602.
- Retrospective (n=65) long-term follow-up for laryngeal squamous dysplasia
- Results:
 - 33 patients demonstrating moderate dysplasia, severe dysplasia, or carcinoma in situ
 - Invasive carcinoma developed in...
 - 10 of 21 patients (48%) treated endoscopically →all salvaged!!!!
 - 0 of 12 patients treated by more aggressive Tx (EBRT, partial laryngectomy, or TL)
 - Laryngeal preservation
 - 15 of 21 patients (71%) in the endoscopic treatment group
 - 11 of 12 patients (92%) in the aggressive treatment group(not statistically significant)
- *“We conclude that there is a moderately high rate of progression to invasive carcinoma.... However, with close, long-term follow-up, patients undergoing endoscopic therapy have an overall outcome similar to that in patients treated with partial laryngectomy or radiotherapy prior to developing invasive disease.”*

Radiology

- Tumor extent (limitations of endoscopy)
 - Pre-epiglottic space and paraglottic space involvement, cartilage erosion
- MRI:
 - high-density tumor vs fat in the preepiglottic space
 - Soft tissue invasion
 - Nodal disease
 - ECS
- CT: thyroid cartilage destruction
 - (presence mandates a total laryngectomy)
 - Still *undercalls* cartilage invasion

Early Glottic Cancer (T1/T2)

- Less biologically aggressive than supraglottic or hypopharyngeal
 - well to moderately differentiated
 - remains localized to the glottic compartment longer
 - without neck or distant metastases: sparse submucosal lymphatics
- Symptoms present early
 - most tumors originate on the free surface of the true vocal fold
 - anterior two-thirds - hoarseness invites medical evaluation
- Treatment
 - radiotherapy or conservation surgery
 - no need for elective ND
 - surgery offers 90% to 95% cure rates for T₁ lesions*****
 - surgical salvage → total laryngectomy
 - equal long-term cure but with different morbidities

***superstar status material

Early Glottic Cancer: Effect of anatomy on management

- Radiation failure site:
 - Sub-glottis , anterior commissure , and arytenoid involvement
- Middle third lesions
 - Easiest to cure:
 - respond well to XRT, endoscopic- laser resection, or open cordectomy
 - Cure rates approach 100%; 95% cure rate for radiotherapy
- Anterior commissure
 - Concerns regarding XRT: mixed reports for T1 lesions
 - Cure- 50-92%

Hemi-laryngectomy after XRT Failure

- Biller et al 1970:
 - Lesion limited to one VC
 - may involve the anterior commissure, but not contralateral VC
 - Body of arytenoid free of tumor
 - Sub-glottic extension <5 mm
 - Mobile VC
 - No cartilage invasion
 - Recurrence correlating with initial tumor

Sub-glottic SCC

- 1% of larynx cancers
- Clinical presentation:
 - airway obstruction
 - no response to management for COPD
 - airway insufficiency & immediate relief when intubated
- *Below* conus elasticus (1 cm below free edge of the TVC)
 - Local spread:
 - cricoid cartilage and thyroid gland
 - Lymphatic spread:
 - Level IV nodes, Delphian node, and paratracheal nodes

Management of Subglottic SCC

- Mandates TL
 - laryngeal framework invasion is frequent
- Adjunct procedures:
 1. Ipsilateral thyroidectomy
 2. paratracheal ND
- Adjuvant XRT
 - positive nodes
 - extensive invasion
 - ports must include the superior mediastinum
- *Monitor for stomal recurrence*

...Bad juju...

- VC hypomobility
 - reduces the cure rates
 - advantage of surgery over radiation
- Arytenoid invasion
 - High risk for post-op dysphagia in organ-sparing procedures

What Our Veterans Have Taught Us

- Department of Veterans Affairs (VA) Laryngeal Cancer Study
 - *NEJM*, 1991
 - Random assignment: Stage III & IV laryngeal SCC
 - TL and adjuvant XRT
 - Induction chemoTx with cisplatin and fluorouracil, followed by XRT
 - (if +response to induction chemotherapy)
 - Salvage TL
 - If no response to chemoTx
 - Residual/ recurrent disease after above 2
 - Results
 - 2 year survival rate in first 2 groups (non-salvage groups) was 68 %
 - laryngeal preservation: possible in 64 % of induction chemotherapy (41% overall)
- “The efficacy of chemotherapy followed by radiotherapy (with surgical salvage) was similar to that of surgery followed by radiotherapy and offered the added benefit of laryngeal preservation in two thirds of the patients treated by this approach.

RTOG (Radiation Therapy Oncology Group)

- *NEJM, 2003*
- Stage III & IV laryngeal SCC*
- Premise: XRT alone → survival and laryngeal preservation similar to those achieved in the VA study (*ie. We don't need no stinkin' chemo....)
 - Induction chemoTx followed by XRT
 - Concurrent chemoXRt
 - XRT alone
- *patients with large, T4 lesions (tumors extending through the thyroid cartilage or into the base of the tongue) were excluded
- Results:
 - 2 and 5 year survival rates were similar among the three groups
 - concurrent chemotherapy : higher rates of laryngeal preservation and local control
 - acute toxic effects were higher in both chemotherapy groups than in the XRT group
 - late toxic effects, including swallowing dysfunction, were similar in all three groups

RTOG (Radiation Therapy Oncology Group)

“These data confirm that initial treatment aimed at laryngeal preservation is a realistic and feasible option for most patients with intermediate- or late-stage laryngeal cancer. The outcome in patients able to tolerate chemotherapy will be best with concurrent chemotherapy and radiotherapy. The use of induction chemotherapy followed by radiotherapy is not supported by the results of this trial, and patients unable to tolerate concomitant chemotherapy and radiotherapy should receive radiotherapy alone.”

Ouch!!!!

“Often cancer seems to have limits, while the surgeon seems to have none... We should make efforts to force upon our knife the same limits as those which surrounding tissues or structures force upon cancer and its spread.”

...Partial laryngeal surgery...

Bocca et al. Extended supraglottic laryngectomy. Review of 84 cases. *Ann Otol Rhinol Laryngol* 1987; 96:384.

Supraglottic SCC

- Amenable to organ-sparing partial laryngectomy
- Endoscopic: Early supraglottic tumors (suprahyoid)
 - electrocautery or by carbon dioxide laser
 - best for suprahyoid lesions: no invasion of pre-epiglottic space
 - infrahyoid tumors – *not so much!*
- What hasn't changed...
 - Cervical metastasis
 - Bilateral

TLM (Transoral laser microsurgery)

- Prospective , multi-center
- TLM in 117 patients
 - T2 to T4 lesions, stage III or stage IV, glottic or supraglottic SCC
 - ND (91 patients), and adjuvant radiotherapy (45 patients)
- Outcomes- 5-year estimates:
 - local control (74%), locoregional control (68%), disease-free survival (58%), overall survival (55%), distant metastases (14%)
 - ...similar to other modalities...
- QOL?
 - 2 patients (3%) were tracheotomy dependent
 - 4 patients (7%) were feeding tube dependent

U wit me???

“Eligibility criteria for TLM are broad...

Contraindications: inadequate endoscopic access, extension of tumor to involve the great vessels of the neck, marked extension of the primary tumor and the nodal disease merged or encased around the great vessels, and tumor extension which would put the patient at risk for aspiration (ie, bilateral arytenoid invasion)...

Unlike chemo and XRT, select patients with large-volume T4 tumors are eligible for TLM... (***would you do this to your mother??***)

In addition, no rigid age-related, hematological, biochemical, or performance status criteria preclude patients from TLM surgery.”

No they diin't!!

RTOG trial:

Given comparable survival outcomes b/wn surgery and organ sparing Tx the logical preference must be for a nonsurgical organ-preserving approach.

Hinni et al:

“This view largely ignored the established role of current open partial laryngectomy techniques and a growing expertise with organ-preserving TLM in Europe and North America. In responding to this contention....The data presented herein can specifically compare the outcomes of TLM with or without adjuvant RT to the RTOG Trial data.”

Double-Edged Sword? Or Can't Go Wrong?

XRT worse than laryngeal preservation?
....But both are organ sparing.....

Conservation Laryngeal Surgery – *All Corners*

- Vertical Partial Laryngectomies
 - Vertical Hemilaryngectomy
 - Frontolateral vertical hemilaryngectomy.
 - Posterolateral vertical hemilaryngectomy
 - Extended vertical hemilaryngectomy
 - Epiglottic Laryngoplasty
- Horizontal Partial Laryngectomies
 - Supraglottic laryngectomy
- Supracricoid Partial Laryngectomy w/ Cricohyoido-Epiglottopexy

Supraglottic Laryngectomy

- Patient selection
 - younger
 - vigorous
 - strong motivation
 - good pulmonary reserve
 - Must tolerate the mild-to-moderate aspiration
 - COPD (*may nix the deal*)
 - Even with gastrostomy
 - -salivary aspiration may be over-whelming

Issues after Supraglottic Laryngectomy....

- Vocal quality
 - Better than TEP?
 - Predictors of success?
- Wound healing /stabilization
 - irradiation
- Prolonged NGT / PEG use
 - extent of removal of the arytenoid
 - asymmetric removal of the false cords
 - remember: at least one SLN is resected
 - resection of hyoid & BOT may *NOT* be related to swallowing outcome

Limitations to Supraglottic Laryngectomy

- Failed full-course radiation for supraglottic lesions
 - increased risk because of unrecognized submucosal tumor spread
 - original tumor configuration vs . recurrent tumor dimensions
- Thyroid cartilage invasion or anterior commissure involvement
 - tumor has broken the anterior inner perichondrial sheath
 - standard cartilage cuts for partial surgery are high risk
- Cricoid cartilage involvement
 - severe dysphagia- laryngeal preservation
 - bilateral arytenoid involvement: *absolute contraindication* (Biller)

Nodal Metastasis in Supraglottic SCC: Outcomes

- Snyderman et al:
 - decreased survival in patients with ECS within NM
- Myers et al:
 - Nodal metastasis
 - 84% of patients without NM survived at least 2 years
 - vs. 46% of patients with NM survived 2 years
 - Of patients w/ recurrence in the neck, 9 (64%) had ECS
 - 71% who developed distant metastasis had histologic evidence of ECS

Nodal Stage	Surgery/Xrt (%)	Surgery Only (%)	Total (%)
N0	12/22 (55)	35/41 (85)	47/63 (75)
N1	3/10 (30)	7/9 (78)	10/19 (53)
N2	4/11 (36)	4/4 (100)	8/15 (53)
N3	1/5 (20)	0/1 (0)	1/6 (17)
Totals (%)	20/48 (42)	46/55 (84)	66/103 (64)

Xrt = radiation therapy.

Myers et al. Management of carcinoma of the supraglottic larynx: evolution, current concepts and future trends. Laryngoscope 1996; 106:559

Supraglottic SCC and Survival

Two-Year Survival Rates of Supraglottic Carcinoma by Stage

Stage	Surgery/Xrt (%)	Surgery Only (%)	Total (%)
I	0/0	2/3 (67)	2/3 (67)
II	6/13 (46)	18/22 (82)	24/35 (69)
III	5/14 (36)	21/24 (88)	26/38 (68)
IV	9/21 (42)	5/6 (83)	14/27 (52)
Totals (%)	20/48 (42)	46/55 (84)	66/103 (64)

Xrt = radiation therapy.

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Conclusions

- Progress?
- HPV?
- Anatomy (period!)
- Multi-disciplinary approach
- Early glottic SCC: Slaughter's Hypothesis
- VA study
- RTOG
- TLM

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