ARRO *Case*:
SUPRAGLOTTIC LARYNX CARCINOMA (POST TRACHEOSTOMY)

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CASE CAPSULE

- 67 F, 40 PY Smoker, Past heavy alcohol consumer, h/o COPD, Congestive heart failure.
- Presentation:
  - Lump left upper neck x 1 year, non-tender, no overlying skin changes, gradually increasing in size.
  - Recent swallowing discomfort (solids), gradually worsening.
  - Chronic cough, shortness of breath, throat irritation, thickened voice since many years, restricted physical activities, 2-3 L O2 required during activity but poor compliance. SoB increased in last year.
  - No hemoptysis, choking spells, or ear pains.
  - Admitted as in-patient due to increased breathing difficulty in last month.

PHYSICAL EXAMINATION

- KPS 60, Obese, SpO2 93 @ 5 L continuous oxygen. No obvious stridor.
- Neck: 2x2 cm, mobile, hard, non-tender lymph node in left level II.
- OC/ Ophx: Poor dental hygiene, adequate tongue protrusion, asymmetric fullness over left posterior pharyngeal wall. Pt. not co-operative to digital examination or IDL.
- Flexible endoscopy: Ulcero-infiltrative mass arising from left supraglottis, involving left AE fold, left edge of epiglottis, thickening of complete epiglottis, bilateral vallecula, lateral pharyngeal wall, just reaching base tongue. Pooling of saliva making it difficult to visualize left true vocal cord (TVC). Right TVC appears mobile. Concern for moderate airway compromise
- Bilateral wheezing on auscultation, trachea central in position.

WORK-UP

- Labs: Elevated random glucose.
- PFT: findings are consistent w/ COPD
  - FVC 1.2 L (41% pred), FEV1 (0.85 L (42% pred), DLCO SB 21% pred (19% corrected).
  - Severe reduction in both FEV1 and FVC with a very severe reduction in terminal flows, significant improvement following inhaled bronchodilator.
  - Diffusion capacity is severely reduced even when corrected for alveolar volume.
  - Patient at increased risk for peri-operative pulmonary complications.
- ECHO: LVEF 75%
- Swallowing study: Aspiration with thin and nectar thick liquids. None with honey thick liquids, pudding or solids.
- Pathology: Examination under anesthesia not feasible due to risks. Hence, only FNA left neck performed: confirms metastatic squamous cell carcinoma.

IMAGING ASSESSMENT

- CT NECK (W & W/O CONTRAST):
  - Mass centered within the epiglottis, extends to the level of the left false vocal cord, left aryepiglottic fold, contralateral suprahyoid epiglottis, left vallecula, glossoepiglottic fold and base of tongue. Potential involvement of the intrinsic muscles of the tongue.
  - Abnormal, enhancing left level IIA LN, 2.1 cm in maximal diameter, with irregular margins, suggestive of extracapsular spread. Additional abnormal, 1.2 cm LN superiorly within left level IIA and 0.9 cm in left level III. There is a normal 0.9 cm node in the right level 2 A region.
- CT CHEST (W & W/O CONTRAST): No concern for metastatic disease. Main pulmonary artery enlargement and right ventricular hypertrophy, highly suggestive of pulmonary hypertension.
- PET-CT: Demonstrates abnormal hypermetabolism in the supraglottic mass with SUVmax of 12.4 and in ipsilateral level II and III LN with SUV max of 8.9. No other metastatic disease.

Final staging: Squamous cell carcinoma, Supraglottic larynx, cT4aN2bM0, Stg IV A


T: 5.0
P: 134.8
31f
P
27
(B:-2%,T:26%) 2: HU(B:-160,T:230)
A
P R
L
CT and PET findings as described earlier

TREATMENT DECISION POINT

- Surgical oncology, Radiation oncology, Medical oncology, Pulmonary medicine, Internal medicine consults done.
- Potential treatment options:
  - Total laryngectomy with possible partial pharyngectomy with bilateral neck dissection and pectoralis major myocutaneous flap followed by vocal rehabilitation. Adjuvant chemo-radiotherapy.
  - Definitive chemoradiation/ Altered fractionation.
- Patient considered a very high anesthesia risk based on PFTs, imaging concern for severe pulmonary hypertension, recent history of congestive heart failure, requirement of 5-6 L continuous oxygen.

Primary surgical approach

- **Pros:**
  - **Higher likelihood of local control for advanced disease if resectable.**
  - **Potential for vocal rehabilitation for usable communication**
- **Cons:**
  - **Very high risk of intra-/ post-operative pulmonary complications**
  - **Non-organ preserving approach/ QoL.**

Definitive chemoradiation approach

- **Pros:**
  - **Organ preservation/ QoL**
  - **Avoids operative complications.**
- **Cons:**
  - **Concern of effective function preservation post-therapy**
  - **Aspiration risk in setting of low pulmonary reserve**

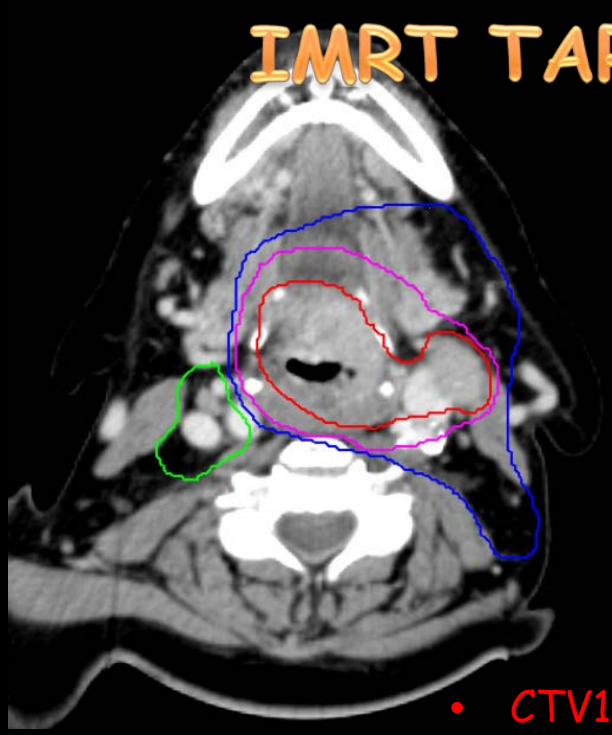
TREATMENT DECISION POINT

- Decision made to proceed with definitive chemo-radiotherapy.
- Issues with chemotherapy:
  - Doubtful tolerance/ compliance for concurrent Cisplatin based chemotherapy.
  - Other options: Concurrent Cetuximab vs. Altered fractionation.
  - Decision to proceed with Cetuximab (400 mg/m2 loading, then 250 mg/m2)
- Concern for complete obstruction of already compromised airway. Hence, planned tracheotomy done. RT planning one week after tracheotomy to allow edema to subside.
- Swallowing function: G-tube insertion done because of concern of aspiration as revealed on swallowing studies and due to potential for acute worsening of function with planned chemoradiotherapy.
- Pre-RT dental prophylaxis arranged.

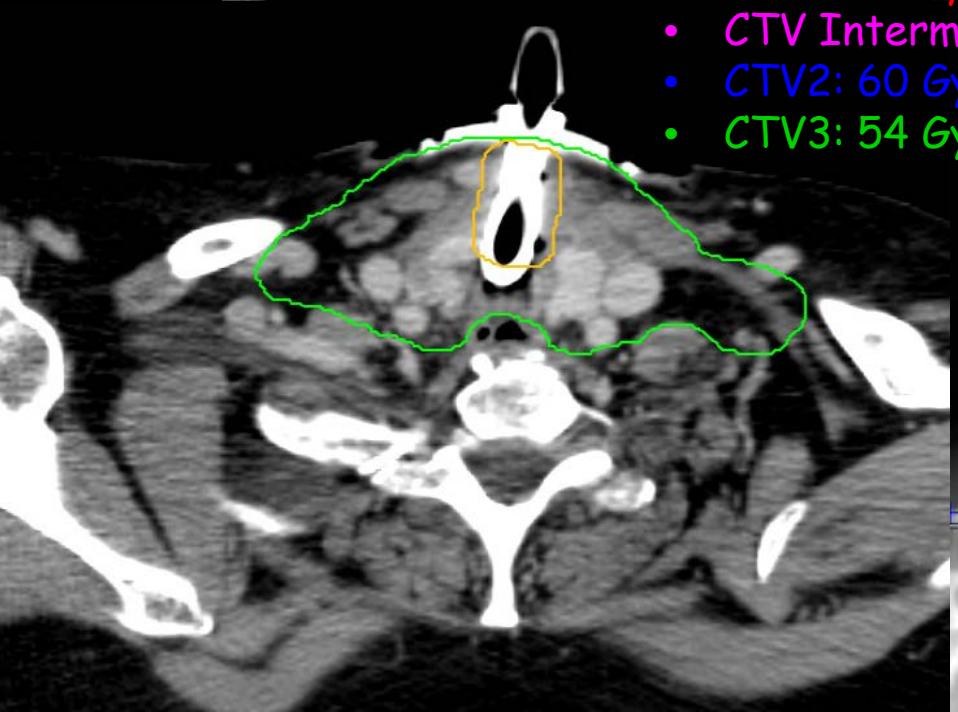
RADIATION PLANNING: IMRT

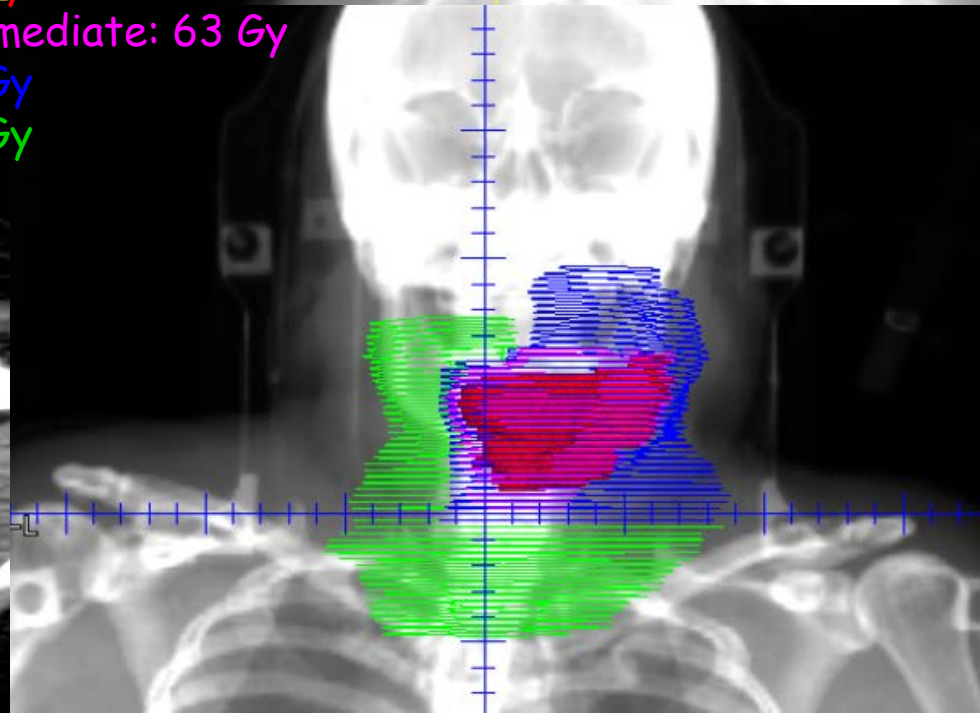
- SIMULATION:
  - Planning CT with i.v. contrast, Head and Neck protocol.
  - Head position: Neutral. Shoulders pulled inferiorly as much as possible.
  - Thermoplastic mold
  - Region to be included in CT: From above base skull to upper mediastinum
- CONTOURS: (PRIMARY) TARGET VOLUME-
  - GTV Primary: Outlined on contrast-enhanced planning CT co-registered with diagnostic CT and PET scan.
  - CTV2 (High-risk): Includes entire larynx, extra-laryngeal and parapharyngeal tissues, bilateral hypopharynx, vallecula and base tongue with a margin of at least 0.5 cm around GTV. Stoma contoured as a region and included to the point of entry into trachea.
  - CTV3 (Low-risk): Remaining contralateral base tongue, posterior third tongue.
- CONTOURS: (NODAL) TARGET VOLUME-
  - GTV-Nodal
  - CTV2-Nodal: Ipsilateral retropharyngeal, level II-IV and VI
  - CTV3-Nodal: Ipsilateral level V, Contralateral low level IIA/ RP (lower edge of C1), III, IV
- PTV MARGINS: 5 mm per institutional protocol. Trimmed off of skin to prevent desquamation.
- OAR: Brain stem, spinal cord, bilateral parotids, oral cavity avoidance, mandible.

IMRT TARGET VOLUMES



- CTV1: 70 Gy
- CTV Intermediate: 63 Gy
- CTV2: 60 Gy
- CTV3: 54 Gy





RADIATION PLANNING

- PRESCRIPTION:
  - PTV1 = PTV primary + PTV nodal = 70 Gy/ 33 fraction @ 2.12 Gy/ fraction [Univ. Wisconsin dose scheme, Std. RTOG prescription is 70 Gy/ 35 fr]
  - PTV Intermediate primary = 63 Gy/ 33 fr @ 1.91 Gy/fraction Uncertainty of tumor delineation in this case, hence slightly higher dose chosen.
  - PTV2 = PTV2 primary + PTV2 nodal = 60 Gy/ 33 fr @ 1.82 Gy/fraction
  - PTV3 = 54 Gy/ 33 fr @ 1.64 Gy/fraction

- PTV COVERAGE GOALS:
  - V70 = 95% of PTV1.
  - At 1 cc PTV1 volume on the DVH curve, the dose should not be > 110% of the prescribed dose.
  - At a volume of 0.03 cc within the PTV1 volume on the DVH curve, the dose should not be < 95% of the prescribed dose.
  - For any volume of tissue outside the PTVs that has a size of 1 cc, the dose should not be > 74 Gy.

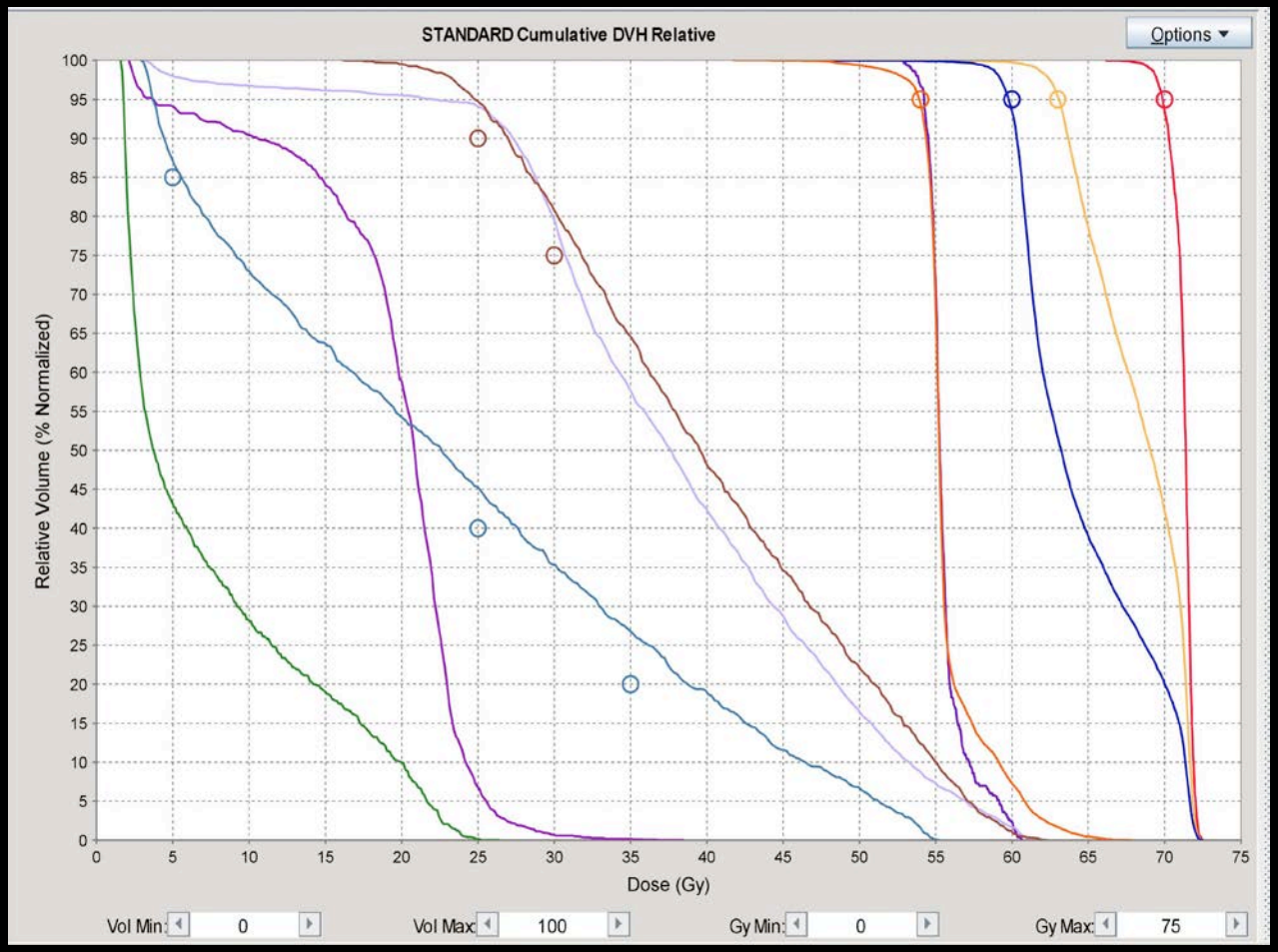
RADIATION PLANNING

- OAR CONSTRAINTS:
  - Spinal Cord PRV: Dmax not more than 48 Gy to 0.03cc and 50 Gy to any point. Given highest priority.
  - Brain stem PRV: not more than 52 Gy to 0.03 cc
  - Oral cavity avoidance: Mean dose 30 Gy, Avoid hot spot > 60 Gy
  - Parotid: No constraint for ipsilateral parotid. Contralateral parotid mean at least 26 Gy, Aim: ALARA
  - Contralateral submandibular gland: Mean ≤ 26 Gy (39 Gy per RTOG 1016)
  - Mandible: Dmax ≤ 70 Gy

- Prioritization for IMRT Planning: Spinal Cord > Brainstem > PTV1 > PTV2 > PTV3 > contralateral parotid > Mandible > Oral Cavity > contralateral submandibular gland.

- Ongoing protocol for IMRT planning details:
  - RTOG 1016: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1016

RADIATION PLANNING



DVH Right to Left

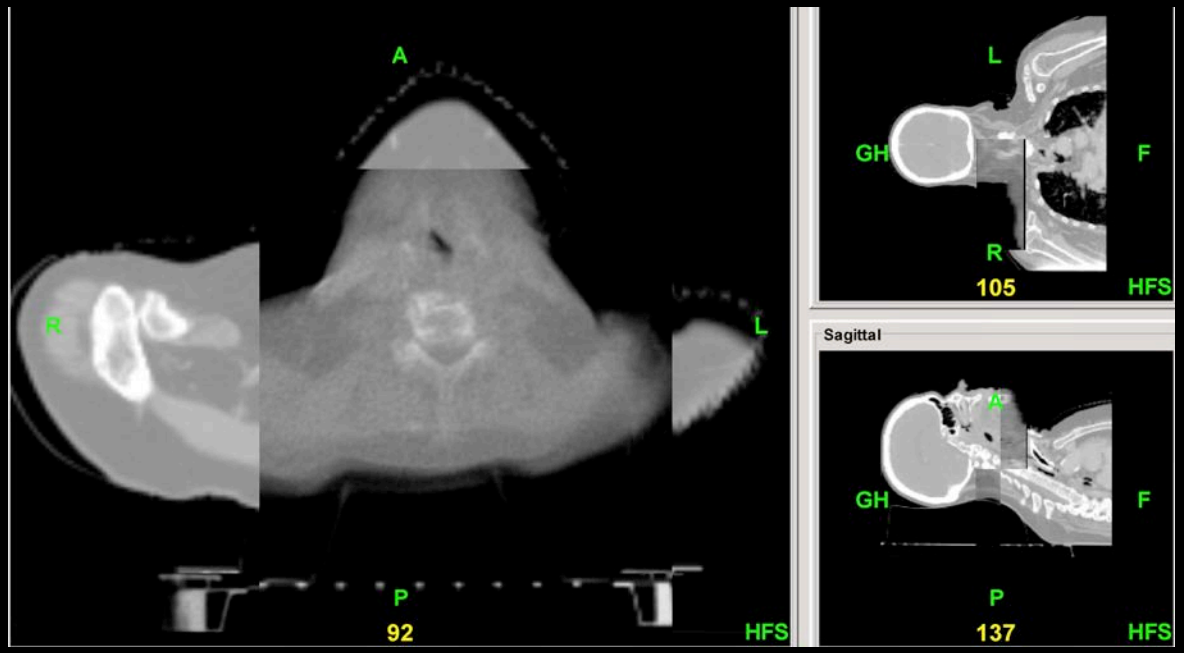
- PTV1: 70 Gy
- PTV Intermediate: 63 Gy
- PTV2: 60 Gy
- PTV3: 54 Gy
- Stoma
- Ipsilat. Parotid
- Mandible
- Contralat. Parotid
- Cord
- Brain stem

ON TREATMENT ISSUES/ MANAGEMENT

- G-tube and Tracheotomy-tube management.
- Mucositis: Topical numbing mouthwashes, oral hygiene, opioid based analgesics, baking soda and salt solution
- Changes in saliva: Oral hygiene
- Dermatitis: Non-alcoholic, water-based creams (avoid immediately before RT)
- Maintain diet/ hydration.
- Lung physiotherapy, be alert for aspiration.
- Cetuximab skin rash: Topical OTC hydrocortisone, 2.5% Hydrocortisone, Oral Doxycycline 50-100 mg BID.
- Monitor labs.

CASE-SPECIFIC TEACHING POINTS

- This case highlights the importance of multi-disciplinary health care in such complicated presentations.
- Interesting discussion between primary surgical approach (risk of pulmonary complications in peri-operative period) Vs. RT approach (delayed pulmonary complications from swallowing dysfunction) in setting of poor pulmonary reserve at baseline.
- Decision regarding arranging tracheotomy prior to start of RT in view of already compromised airway and measures to include it in low-risk CTV.
- In view of significant weight loss, obvious mis-match noted in daily MVCT and planning CT (figure below). Decision to re-plan taken at 18th fr. and started on new plan for last 11 fractions.



AJCC STAGING 7th Ed.

Supraglottis		Glottis		Subglottis	
T1	Limited to one subsite with normal VC mobility	T1a	Limited to one VC, may involve AC/ PC	T1	Limited to subglottis
		T1b	Involves both VC		
T2	Invades mucosa of >1 adjacent subsite of supraglottis or glottis or region outside supraglottis (mucosa of BOT, vallecula, medial wall of PS) without fixation of larynx.	T2	Extends to supraglottis and/or subglottis and/or impaired VC mobility	T2	Extends to VC with normal or impaired mobility
T3	Limited to larynx w/ VC fixation and/or invades: postcricoid area, pre-epiglottic space, paraglottic space, and/or minor thyroid cartilage erosion (inner cortex)	T3	Limited to larynx with VC fixation and /or inv paraglottic space, and/or minor thyroid cartilage erosion (inner cortex)	T3	Tumor limited to larynx with vocal cord fixation
T4a	Invades through cricoid or thyroid cartilage, and/or invades tissues beyond larynx (trachea, soft tissue of neck including extrinsic tongue muscle, strap muscles, thyroid gland, or esophagus)				
T4b	Invades prevertebral space, encases carotid artery, invades mediastinal structures				

Nodal and Overall staging is the same as most other H&N sites.

N1	single ipsilateral node ! 3 cm
N2a	single ipsilateral node > 3 cm and ! 6 cm
N2b	multiple ipsilateral nodes ! 6 cm
N2c	bilateral or contralateral nodes, ! 6 cm
N3	> 6 cm
M0	no distant metastases
M1	distant metastases (includes mediastinum)

I	T1
II	T2
III	T3 N0, T1-3 N1
IVA	T4a N0-1 or N2
IVB	T4b or N3
IVC	M1

NCCN Guidelines (2012)

T1-2 N0: Definitive RT -OR- open partial supraglottic laryngectomy ± SND -OR- endoscopic resection ± SND.
Post-op ChemoRT if adverse features on path (consider post-op RT alone if 1 LN+ only)

T3-4a, N0: ChemoRT preferred -OR- Total Laryngectomy (preferred if cartilage, skin, high volume BOT involved) + SND + PORT.
Post-op ChemoRT if one or both major RF or ! 2 minor RF. Post-op RT alone if only 1 minor RF.

T1-2 N+: ChemoRT (preferred) or Definitive RT; add adjuvant ND if residual neck mass or initial N2-3
-OR- Partial supraglottic laryngectomy with comprehensive ND; Post-op ChemoRT if one or both major RF or ! 2 minor RF. Post-op RT alone if only 1 minor RF.

T3-4 N+: ChemoRT preferred (unless cartilage, skin, high volume BOT involved); add adjuvant ND if residual neck mass or initial N2-3
-OR- laryngectomy + comprehensive ND. Post-op ChemoRT if adverse features on path, all other patients get adjuvant RT.
-OR- induction chemo followed by chemoRT in selected N2/3 patients.

Major Adverse Features on surgical pathology: + margins or LN ECE
Minor Adverse Features on surgical pathology: pT4, N2/3, perineural invasion, vascular embolism.

NCCN RT Principles:

Definitive RT: T1/2: ! 66 Gy (2 Gy/ fr). T2-4: ! 70Gy (2Gy/day) to primary and gross adenopathy, 44-64 Gy (1.6- 2 Gy / fr) to low risk nodal stations
Post-op RT: 60-66 Gy (2Gy/fr) to primary and gross adenopathy, 44-64 Gy (2Gy/fr) to low risk nodal stations
ChemoRT: Concurrent single agent cisplatin 100mg/m^2 q3W recommended. Most of the experience is with 70Gy in 35fx.
Altered fractionation:
6 fractions/week accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease.
Concomitant boost accelerated RT: 72 Gy/ 6 weeks (1.8 Gy/fr; 1.5 Gy boost as second daily fraction during last 12 treatment days)
Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fr twice daily)

CLINICAL PEARLS/ HIGH-YIELD POINTS

- VA Laryngeal Cancer study group Organ preservation study, NEJM 1991:
  - Reduced local recurrences with Surgery (2% Vs 12%) but no difference in 2 yr-OS 68%. 64% laryngeal preservation in RT arm.
- RTOG 9111 (Forastiere et al, NEJM 2003): Concomitant CT-RT vs. Induction CT-RT vs. RT alone

Arm	2y Larynx preservation	LRC	5y-Laryngectomy FS	5y OS	5y DFS	5y DM	All High Grade Toxicity
Induction	75% p=0.005	61% p=0.003	43%	55%	38 %	15%	81%
Concomitant	88%	78%	45%	54%	36 %	12%	82%
RT alone	70% p<0.001	56% p<0.001	38% p=0.01	56%	27 %	22% p=0.03	61%

- Updated MACH-NC Meta-analysis (Pignon et al, Radiother. Oncol. 2009):
  - The hazard ratio for death was 0.81 (95%CI: 0.78–0.86; p < 0.0001) in favor of concomitant chemotherapy with an absolute benefit of 6.5% at 5 years.
- Cetuximab (Bonner et al, NEJM 2006)

	2y LRC	Median LRC	2y PFS	Median PFS	3y OS	Median OS	2y DM
RT alone	41%	14.9m	37%	12.4m	45%	29.3	17%
RT+cetuximab	50%	24.4m	46%	17.1m	55%	49.0	16%
p-value	0.005		0.006		0.03		

  - Cetuximab concomitantly with RT may be recommended in Stage III-IV H&N cancer patients with a contraindication to cisplatin (poor renal function, baseline hearing deficits, low blood counts) and no contraindication to cetuximab.

Useful references

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