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Laryngeal and Hypopharyngeal Cancers

Updated by Brian Deegan

BACKGROUND

What is the incidence of laryngeal cancer (LCX) in the United States?

Show Answer

~12,000 cases/yr of LCX (~20% of all H&N)

What are the risk factors for developing LCX?

Show Answer

Smoking, alcohol use, and voice abuse

What are the subsites of the larynx?

Show Answer

Supraglottic, glottic, and subglottic

What is the incidence/distribution of LCX according to subsite?

Show Answer

Glottic: 69%

Supraglottic: 30%

Subglottic: 1%

What % of premalignant lesions (leukoplakia/erythroplakia) progress to invasive laryngeal lesions?

Show Answer

20% of premalignant laryngeal lesions ultimately progress to invasive cancer (higher for erythroplakia than leukoplakia).
What is the most common LCX histology?

Show Answer

Squamous cell carcinoma (SCC) makes up >95% of LCX. Other histologies include verrucous carcinoma (1%–2%), adenocarcinoma, lymphoma, chondrosarcoma, melanoma, carcinoid tumor, and adenoid cystic carcinoma.
What are the subdivisions of the supraglottic larynx?

Show Answer

Supraglottic larynx: **Epiglottis (suprahyoid and infrahyoid), AE folds, arytenoids, ventricles, and false vocal cords** (FVCs)
What are the subdivisions of the glottic larynx?

Show Answer

Glottis: **Ant/Post commissures, true vocal cords** (TVCs)
What are the anatomic borders of the subglottic larynx?

Show Answer

Subglottis: **0.5 cm below the TVCs to the 1st tracheal ring**
What are the nodal drainage pathways of the various laryngeal subsites?

Show Answer

Supraglottic: levels II–IV
Glottic: virtually no drainage
Subglottic: pretracheal and Delphian (level VI)
What is the incidence of hypopharyngeal cancer (HPxC) in the United States?

Show Answer

There are **~2,500 cases/yr.**
What is the median age at Dx for HPxC?

Show Answer

The median age at Dx is **60–65 yrs** for HPxC.
What are the subsites of the hypopharynx (HPX)?

Show Answer

Pyriform sinus
Postcricoid area
Posterior pharyngeal wall

(Mnemonic: **“3 Ps”**)
What are the anatomic boundaries of the HPX?

Show Answer

The HPX spans from **C4–6 or from the hyoid bone to the inf edge of the cricoid cartilage.**
What is the sex predilection for HPxC based on the different subsites?

Show Answer

The sex predilection is **predominantly male for pyriform sinus and post pharynx primaries,** but **predominantly female for postcricoid area tumors.**
What are the classic risk factors for the development of HPxC?

Show Answer

Smoking, alcohol, betel nut consumption, nutritional deficiency (vitamin C, Fe [Fe deficiency is associated with 70% of postcricoid cancers in northern European women]), and prior Hx of H&N cancer
Is nodal involvement common with HPxC?

Show Answer

Yes. Nodal involvement is common due to abundant submucosal lymphatic plexus drainage to the retropharyngeal nodes, cervical LNs, paratracheal LNs, paraesophageal nodes, and SCV nodes.
What are the most commonly involved nodal stations in HPxC?

Show Answer

Levels II, III, and the retropharyngeal nodes are most commonly involved in HPxC. **Level VI** can also be involved and therefore should be covered when planning these cases for RT.
What is the name for the most sup of the lat retropharyngeal nodes?

Show Answer

The most sup of the lat retropharyngeal nodes is the **Node of Rouviere.**
What % of HPxC pts have nodal involvement at Dx?

Show Answer

~75% overall have nodal involvement at Dx (~60% for T1).
What is the typical histology seen in HPxC?

Show Answer

The predominant histology is **SCC** (>95%) → adenoid cystic, lymphoma, and sarcoma.
What are the most common subsites of origin for HPxC?

Show Answer

The **pyriform sinus (70%–80%), post pharyngeal wall (15%–20%), and postcricoid (5%)** are the most common subsites of origin.
At what cervical spine levels are the hyoid bone and the TVCs located?

Show Answer

The **hyoid bone is at C3,** whereas the **TVCs are located near C5–6.**

WORKUP/STAGING

How do pts with LCX typically present?

Show Answer

Hoarseness, odynophagia/sore throat, otalgia (via the Arnold nerve/CN X), aspiration/choking, and neck mass

What is the typical workup for pts presenting with a possible laryngeal mass?

Show Answer

Possible laryngeal mass workup: H&P (voice change, habits, indirect/direct laryngoscopy), CXR, CT/MRI, PET, basic labs, EUA + triple endoscopy, and Bx of the primary +/– FNA of the neck mass

What does the loss of the laryngeal click on palpation of the thyroid cartilage indicate?

Show Answer

Loss of the laryngeal click on exam indicates **postcricoid extension (or postcricoid tumor).**

What does pain in the thyroid cartilage indicate on exam?

Show Answer

Pain on palpation of the thyroid cartilage indicates **tumor invasion into the thyroid cartilage.**

What imaging modality is best to assess for bony or cartilage erosion in pts with LCX?

Show Answer

CT scan is best for assessing bony/cartilage erosion (bone window).

What is the incidence of nodal involvement for T1, T2, and T3–T4 glottic cancer?

Show Answer

T1: 0%–2%
T2: 2%–7%
T3–T4: 15%–30%
What is the incidence of nodal involvement for supraglottic lesions according to T stage?

Show Answer

T1–T2: 27%–40%
T3–T4: 55%–65% (Wang CC, Radiation therapy for head and neck neoplasms 1996)
What proportion of pts with supraglottic cancer present with unilat vs. bilat nodal Dz?

Show Answer

~55% of supraglottic cancer pts present with unilat nodal Dz, and **16%** present with bilat nodal involvement. (Lindberg R et al., Cancer 1972)
What % of pts with subglottic cancer present with nodal involvement?

Show Answer

20%–50% of subglottic pts present with nodal Dz (generally the prelaryngeal/Delphian, lower jugular, pretracheal or upper mediastinal nodes).
Describe the T staging for cancers of the supraglottic larynx (AJCC 8th edition, 2017).

Show Answer

T1: 1 subsite with normal VC mobility
T2: more than 1 adjacent subsite of supraglottis or glottis or region outside supraglottis (base of tongue, vallecula, medial wall of pyriform sinus) without fixation of larynx
T3: Larynx-confined with cord fixation and/or invasion of postcricoid area, pre-epiglottic space, paraglottic space and/or inner cortex thyroid cartilage

T4a (resectable): through outer cortex thyroid cartilage and/or beyond larynx (trachea, ST of neck, extrinsic muscles of tongue, strap muscles, thyroid, esophagus)

T4b: invasion of prevertebral space, encased carotid, mediastinum

Describe the T staging for cancers of the glottic larynx (AJCC 8th edition, 2017).

Show Answer

T1: limited to TVCs (+/– commissure involvement), normal mobility (T1a: 1 cord, T1b: both)

T2: extends to supra- or subglottis or impaired vocal cord mobility

T3: fixed vocal cords, confined to larynx and/or paraglottic space invasion and/or inner cortex thyroid cartilage

T4a–b: same as above/for supraglottic lesions

What is the T-staging breakdown for cancers of the subglottic larynx (AJCC 8th edition, 2017)?

Show Answer

T1: tumor limited to subglottis

T2: extension to vocal cords, with normal or impaired mobility

T3: limited to larynx with vocal cord fixation or paraglottic space extension, invasion of inner cortex thyroid cartilage

T4a–b: same as above

What is the clinical nodal staging for LCX (AJCC 8th edition, 2017)?

Show Answer

N1: single ipsi, ≤3 cm, ENE(–)

N2a: single ipsi >3 cm and ≤6 cm ENE(–)

N2b: multiple ipsi, ≤6 cm and ENE(–)

N2c: bilat or contralat, ≤6 cm and ENE(–)

N3a: >6 cm and ENE(–)

N3b: clinically overt ENE(+)

What is the pathologic nodal staging for LCX (AJCC 8th edition, 2017)?

Show Answer

N1: single ipsi, ≤3 cm, ENE(–)

N2a: single ipsi or contralat ≤3 cm and ENE(+) **or** single ipsi >3 cm and ≤ 6 cm ENE(–)

N2b: multiple ipsi, ≤6 cm and ENE(–)

N2c: bilat or contralat, ≤6 cm and ENE(–)

N3a: >6 cm and ENE(–)

N3b: single ipsi >3 cm ENE(+) **or** multiple ipsi/contralat/bilat nodes any with ENE(+)

Describe the overall stage groupings for LCX (AJCC 8th edition, 2017).

Show Answer

Stages I: T1N0

Stage II: T2N0

Stage III: T3N0 or N1

Stage IVA: T4a or N2

Stage IVB: T4b or N3

Stage IVC: M1

With what stage of Dz do most pts with HPxC present?

Show Answer

Most pts (>80%) present with **stage III or IV Dz** (lesions often remain asymptomatic until advanced Dz).

What % of pts with HPxC present with DMs?

Show Answer

~2%–4% of HPxC pts present with DMs. ~20%–30% develop DMs within 2 yrs despite Tx.

With what Sx do most HPxC pts present?

Show Answer

Neck mass, sore throat, dysphagia, hoarseness (**direct vocalis or cricoarytenoid joint invasion**), and otalgia (Arnold nerve/CN X involvement)

What is the typical workup for pts who present with hoarseness?

Show Answer

Hoarseness workup: H&P (check for thyroid click), labs, CT/MRI, PET, neck FNA, EUA + triple endoscopy, and Bx of the primary mass

Describe the T staging of HPxC (AJCC 8th edition, 2017).

Show Answer

T1: 1 site of HPX and/or ≤2 cm
T2: more than 1 subsite or 2–4 cm without hemilarynx fixation
T3: >4 cm or fixation of hemilarynx or esophageal extension
T4a: invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, central STs (prelaryngeal strap muscles and SQ fat)
T4b: invades prevertebral fascia, encases carotid artery, or mediastinal structures

What is the nodal staging breakdown for HPxC (AJCC 8th edition, 2017)?

Show Answer

Same system as used for p16 negative OPX

N1: single ipsi, ≤3 cm, ENE(–)
N2a: single ipsi, >3 cm, ≤6 cm, ENE(–)
N2b: multiple ipsi, ≤6 cm, ENE(–)
N2c: any bilat or contralat, ≤6 cm, ENE(–)
N3a: any >6 cm, ENE(–)
N3b: any clinically overt ENE(+)

Describe the overall stage groupings for HPxC.

Show Answer

Stage I: T1N0
Stage II: T2N0
Stage III: T3N0 or N1
Stage IVA: T4a or N2
Stage IVB: T4b or N3
Stage IVC: M1

TREATMENT/PROGNOSIS

What does total laryngectomy entail?

Show Answer

It entails the **removal of the hyoid, thyroid and cricoid cartilage, epiglottis, and strap muscle with reconstruction of the pharynx as well as a permanent tracheostomy.**
What structures are removed with a supraglottic laryngectomy?

Show Answer

A supraglottic laryngectomy sacrifices the **FVCs, epiglottis, and aryepiglottic folds.**
What is the preferred surgical option for dysplastic lesions on the glottic larynx?

Show Answer

Mucosal stripping is typically curative for dysplastic lesions. Close follow-up is needed.
What are the Tx options for Tis lesions of the glottic larynx?

Show Answer

1. **Cord stripping/laser excision** (need close follow-up; cannot r/o microinvasive Dz) **or definitive RT**

What are the ~5-yr LC rates for glottic CIS with the use of stripping vs. laser vs. RT?

Show Answer

Stripping: 72%
Laser: 83%
RT: 88%–92% (all >95% after salvage)
What are the Tx options for T1–T2 glottic cancer?

Show Answer

Cordectomy (CO2 laser)/partial laryngectomy, or definitive RT
What are the 5-yr control and survival rates after hemilaryngectomy for T1–T2 glottic cancer?

Show Answer

After hemilaryngectomy, the **~5-yr LC is 83%** and the **DFS is 88%** for T1–T2 glottic cancer. (Scola B et al., Laryngology 1999)
What is the salvage Tx of choice for glottic lesions after RT failure?

Show Answer

The salvage Tx of choice is **total laryngectomy +/- neck dissection.**
What is the ~5-yr CSS rate for T1 glottic cancers treated with definitive RT?

Show Answer

The 5-yr CSS rate with RT is **>90%** (95% with salvage; organ preservation rate is >90%).
What are the advantages and disadvantages of using RT for early glottic cancer?

Show Answer

Advantages: better voice quality, noninvasive, organ preservation

Disadvantages: long Tx duration, RT changes could obscure post-Tx surveillance

What is the voice quality preservation rate for early glottic tumors/pts treated with laser vs. RT?

Show Answer

The JHH data (Epstein BE et al., Radiology 1990) suggest **better voice quality after RT** (laser: 31%, RT: 74%, p = 0.012). More recent RCT from Finland (Aaltonen L et al., IJROBP 2014) also suggest better voice quality with RT.

What are the initial and ultimate (after salvage) LC rates for T2 glottic lesions?

Show Answer

Initial LC is 70%–90% and **50%–70% after salvage** for T2 glottic lesions.

What are the currently accepted dose fractionation and total dose Rx for CIS and T1 glottic lesions?

Show Answer

The currently accepted RT doses are **60.75 Gy for CIS** and **63 Gy for T1,** at **2.25 Gy/fx.**

What is the typical RT dose used for T2 glottic lesions?

Show Answer

The typical RT dose for T2 lesions is **70 Gy at 2 Gy/fx** or **65.25 Gy at 2.25 Gy/fx.**

What randomized data/trial highlighted the importance of hypofractionation for early glottic cancers?

Show Answer

Japanese data (Yamazaki H et al., IJROBP 2006): 180 pts, 2 fractionations: 2 Gy/fx (60–66 Gy) vs. 2.25 Gy/fx (56.25–63 Gy). 5-yr LC rate was better

with 2.25 Gy/fx (92% vs. 72%). The greater toxicity for the hypofractionation regimen was acute skin erythema (83% vs. 63%).
What RT field sizes/spans are employed for Tis/T1 glottic cancers?

Show Answer

5 × 5 cm opposed lat fields—from the upper thyroid notch to the lower border of the cricoid, post border at the ant edge of the vertebral body, and flash skin at the ant border.
What RT planning technique can be used when treating T1 glottic lesions with ant commissure involvement?

Show Answer

Generally, for T1 glottic lesions, **wedges** are used (heel ant, usually 15 degrees) to reduce ant hotspots due to curvature of the neck. However, if there is ant commissure Dz, the wedges can be removed, or wedge angle reduced, to add hotspots to this region. Bolus/beam spoiler can be added for additional coverage anteriorly.
What structures must be encompassed by the 95% IDL when irradiating T1 glottic cancer?

Show Answer

The 95% IDL must encompass the **TVCs, FVCs, and the sup subglottis.**
What RT fields are used for T2 glottic lesions?

Show Answer

This is **controversial** and may depend on the degree of supraglottic/subglottic extension. Most advocate using 6 × 6 cm opposed lat fields; others advocate covering levels II–III nodes (2 cm above the angle of the mandible, splitting vertebral body, down to the bottom of the cricoid) to **50–54 Gy,** with CD to the 5 × 5 cm box covering the larynx to **70 Gy.**
What are the Tx options for early-stage supraglottic LCX?

Show Answer

Supraglottic laryngectomy, transoral laser resection, or definitive RT
What are the 5-yr LC and OS rates for early supraglottic cancers treated with Sg and LND?

Show Answer

The **5-yr LC rate is ~85%,** whereas the **5-yr OS is ~100% for T1 and ~80% for T2** supraglottic lesions.
What are the LC rates for early-stage supraglottic cancers after definitive RT alone?

Show Answer

Retrospective series demonstrate LC rates of **73%–100% for T1 and 60%–89% for T2 lesions** (e.g., University of Florida and Italian data).
Describe the standard RT fields used in treating supraglottic cancers.

Show Answer

B/c 20%–50% of T1–T2 supraglottic cancers have +LNs (occult), necks need to be covered for all pts (levels II–IV). This required an off-cord CD after 45 Gy and a boost to the post neck to 50 Gy with electron fields. Most of these are currently treated with IMRT.
What definitive RT doses are typically recommended for early-stage supraglottic cancers?

Show Answer

T1 dose: **70 Gy** in 2 Gy/fx
T2–3 dose: hyperfractionated dosing to **79.2–81.6 Gy** in 1.2 Gy/fx bid or with concomitant boost techniques to **72 Gy** (1.8 Gy in AM × 30 fx to 54 Gy to areas of subclinical Dz, and 1.5 Gy in PM for the last 12 days of Tx to boost GTV + 1.5–2 cm to 72 Gy)
What early data showed feasibility/effectiveness of reirradiation for

previously treated early-stage LCX pts?

Show Answer

Massachusetts General Hospital data (Wang CC et al., IJROBP 1993): 20 pts treated with 1.6 Gy bid to 65 Gy. 5-yr OS was 93%, and LC was 61% after reirradiation.
What are the Tx options for pts with advanced LCX?

Show Answer

Total laryngectomy (with adj RT or CRT for +margin, +ECE) or organ preservation with definitive CRT **(RTOG 91–11)** or RT alone (altered fractionation)
What are the Tx options for pts with advanced HPxC?

Show Answer

Induction chemo → RT or Sg depending on response for T1–3N+ Dz; total laryngectomy/laryngoesophagectomy (with CRT for +margin, +ECE) for T4 Dz
What are the typical RT doses used to treat advanced LCX/HPxC?

Show Answer

Subclinical Dz (2^{nd}-echelon nodal regions) to **50–54 Gy; high-risk regions (1^{st}-echelon or involved nodal regions) to 60–63 Gy,** primary tumor to **70 Gy** (in 2 Gy/fx)
What are the 3 indications for boosting the stoma with PORT?

Show Answer

Indications for boosting the stoma with PORT:

- Emergency tracheostomy
- Subglottic extension
- Ant ST extension

What are some indications for performing an elective neck dissection after definitive RT?

Show Answer

This is controversial, but elective neck dissection should be done for persistent Dz and can be considered with >N2 Dz, although it is now common to observe if clinical and radiographic CR is obtained after RT.
What randomized data/study compared preop RT to PORT for (predominantly) HPxC?

Show Answer

RTOG 73–03 (Tupchong L et al., IJROBP 1991): 354 pts, 50 Gy preop vs. 60 Gy postop; 69% of pts had advanced supraglottic or HPxC. LC was better with PORT but not OS.
What are the 2 randomized phase III trials that demonstrated a benefit with postop CRT vs. PORT alone for high-risk H&N pts?

Show Answer

EORTC 22931 (Bernier J et al., NEJM 2004): 334 pts randomized to PORT 66 Gy vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: ECE, +margin, PNI, LVI, and levels 4–5 +N from oral cavity cancer/oropharyngeal cancer. There was better OS, DFS, and 5-yr LC with CRT but ↑ grades 3–4 toxicity.

RTOG 95–01 (Cooper JS et al., NEJM 2004): 459 pts randomized to 60–66 PORT vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: >2 LNs, ECE, +margin. There was better DFS (43% vs. 54%) and 2-yr LRC (72% vs. 82%) with CRT but only a trend to improvement in OS (57% vs. 63%).

What are the presumed reasons why EORTC 22931 showed an OS benefit while RTOG 9501 did not?

Show Answer

The EORTC trial included more margin+ pts (28% vs. 18%), pts with worse tumor differentiation (19% vs. 7%), more HPX cases (20% vs. 10%), and more pts who started RT 6 wks or later after Sg (32%).

Which randomized trials demonstrated a benefit with altered fractionation RT in advanced H&N cancer?

Show Answer

EORTC 22851 (Horiot JC et al., Radiother Oncol 1997): 512 pts (all H&N except the HPX) randomized to conventional RT to 70 Gy (7 wks) or 1.6 Gy tid to 72 Gy (5 wks). There was better 5-yr LRC with tid RT (59% vs. 46%) but not OS.

RTOG 9003 (Fu KK et al., IJROBP 2000): 1,073 pts (all H&N sites) randomized to (1) standard fx 70 Gy/2 qd; (2) 81.6 Gy/1.2 bid; (3) accelerated with split 67.2 Gy/1.6 bid; and (4) accelerated with concomitant boost 72 Gy/1.8 qd × 17 → 1.8 Gy AM + 1.5 Gy PM × 33 fx. All altered fx schemes were better than conventional RT in terms of LRC (54% vs. 46%) but not OS.

Which studies investigated induction CRT for organ preservation in pts with advanced LCX?

Show Answer

Department of Veterans Affairs (VA) larynx study (Wolf GT et al., NEJM 1991): stages III–IV resectable LCX; 332 pts randomized to 3 cycles induction PF f/b definitive RT (if Dz response, else TL) vs. upfront Sg + PORT. 2-yr larynx preservation rate was 64%. There was no OS difference (68%). There were more LRs with CRT and less mets.

GETTEC (Richard JM et al., Oral Oncol 1998): early closure due to poor accrual; only 68 pts, mostly T3N0, design similar to the VA study. There was poorer 2-yr survival for the chemo group (69% vs. 84%). 3-yr laryngectomy-free survival was 20%.

What is the only randomized study that investigated organ preservation for

advanced HPxC with induction CRT?

Show Answer

EORTC 24891 (Lefebvre JL et al., JNCI 1996 and Ann Oncol 2012): 194 pts randomized to Sg + PORT vs. induction chemo (5-FU/cisplatin) + RT; if NR to chemo → Sg + PORT. 5-yr larynx preservation rate was 35%. At 3 yrs, OS was better with induction therapy, but there was no difference at 5 and 10 yrs (DMs were less in the chemo arm; no difference in LRF).
Which study established concurrent CRT over both RT alone and induction approaches for larynx preservation?

Show Answer

RTOG 91–11 (Forastiere AA et al., NEJM 2003): 547 pts, T2–T4 (T4 with thyroid cartilage invasion or >1-cm base of tongue invasion excluded) randomized to (1) CRT (platinum 100 mg/m^2 q3wks), (2) induction PF chemo → RT (like the VA study), and (3) RT alone (all to 70 Gy). There was a better rate of laryngeal preservation at 3.8 yrs with concurrent CRT (84% vs. 72% vs. 67%); better 2-yr LRC (78% vs. 61% vs. 56%); and better DM rate with any chemo arm than with RT alone. There was no OS benefit. There was ↑ acute grades 3–4 toxicity but no ↑ late toxicity with concurrent CRT.
What are the survival/LC numbers based on the latest update of RTOG 91–11?

Show Answer

Long-term Results **RTOG 91–11** (Forastiere AA et al., JCO 2013) median follow-up 10.8 yrs. CRT improved larynx preservation over chemo → RT (HR, 0.58; $p = 0.005$) and over RT alone ($p < 0.001$), while chemo → RT and RT were equivalent (HR = 1.26; $p = 0.35$). Late effects were not different. The 10-yr OS was the same (27.5% CRT, 38.8% chemo → RT, and 31.5% RT). Deaths not attributed to larynx cancer or Tx were higher with CRT.
What is the only randomized study that compared Sg + RT to concurrent

CRT in advanced H&N SCC (Non-NPX)?

Show Answer

Singapore study (Soo KC et al., Br J Cancer 2005): 119 pts, most bulky T4 (56%) or stage IVA (78%) Dz; closed early d/t poor accrual; nonstandard PF chemo, nonstandard RT (66 Gy). 44% pts larynx/HPX (majority supraglottis). No difference in 3-yr DFS, primary larynx/HPX organ preservation 62% vs. nonlaryngeal sites 30%.
What study demonstrated an OS and DFS benefit with CRT over RT alone for unresectable H&N cancers?

Show Answer

Cleveland Clinic (Adelstein DJ et al., JCO 2003): 295 pts with unresectable stages III–IV H&N cancers (15% OC, 55% OPX, 20% HPX), RT alone vs. CRT with cisplatin 100 mg q3wks × 3. 3-yr OS (37% vs. 23%) and DFS (51% vs. 33%) were better with CRT.
What study demonstrated improvement in OS with the addition of cetuximab (C225) to RT in H&N cancers?

Show Answer

Bonner et al. (NEJM 2006): 424 pts with stages III–IV SCC of the OPX, larynx, or HPX randomized to RT vs. RT + C225; RT options were conventional to 70 Gy, 1.2 bid to 72–76.8 Gy, or concomitant boost to 72 Gy. There was better 3-yr LRC (47% vs. 34%) and OS (55% vs. 45%) with RT + C225. Subset analysis showed improvement mostly in OPC and in the altered fractionation RT arms (~50% with altered fractionation).
What 2 randomized studies demonstrated a benefit with induction taxane/platinum/5-FU (TPF) chemo over PF → in pts with unresectable H&N cancers?

Show Answer

TAX 324 study (induction chemo → CRT) (Posner MR et al., NEJM

2007): 501 pts, unresectable stages III–IV H&N cancers (52% OPX; 13%–18% OC, larynx, HPX) randomized to induction platinum + 5-FU or TPF → CRT with carboplatin. There was better 3-yr OS (62% vs. 48%), MS (71 mos vs. 30 mos), and LRC (70% vs. 62%) in the TPF arm. Pts in the TPF arm had fewer Tx delays than those who rcvd platinum/5-FU despite higher myelotoxicity in the TPF arm (98% rcvd planned Tx in TPF vs. 90% in the platinum/5-FU arm).

TAX 323 study (induction chemo → RT) (Vermorken JB et al., NEJM 2007): 358 pts, unresectable stages III–IV H&N cancers (46% OPX, 18% OC, 29% HPX, 7% larynx) randomized to induction platinum + 5-FU or TPF → RT alone. TPF resulted in better median PFS (11 mos vs. 8.2 mos), MS (18.8 mos vs. 14.5 mos), with an HR of 0.73. The rate of toxic deaths was greater in the platinum/5-FU group (5.5% vs. 2.3%). There was also more grades 3–4 thrombocytopenia, anemia, stomatitis, n/v, diarrhea, and hearing loss in the platinum/5-FU arm. Neutropenia, leukopenia, and alopecia were more common in the TPF arm.

Which studies compared induction chemo vs. upfront CRT?

Show Answer

1. **PARADIGM study (induction TPF → CRT vs. CRT)** (Haddad H et al., Lancet Oncology 2013): 145 pts, stages III–IV (25% larynx and HPX), randomized to induction TPF → CRT vs. CRT. At a median f/u of 49 mos, there was no difference in 3-yr OS (73% for induction vs. 78% for CRT), with a higher rate of febrile neutropenia observed in the induction arm.

2. **DeCIDE study (induction TPF(×2) → CRT vs. CRT)** (Cohen E et al., JCO 2014): 285 pts, N2–N3 Dz, docetaxel-based concurrent CRT regimen (Docetaxel, 5-FU, hydroxyurea “DFHX”). Randomized to induction TPF → CRT vs. CRT. At a min f/u of 30 mos, there was no difference in OS (median not reached), DFS, LRC or DMFS. HPV status did not impact findings, nor did OPX vs. Non-OPX primary. Toxicity higher with

induction (heme).

FOLLOW-UP/TOXICITY

What are some acute and late toxicities with RT in the Tx of LCX?

Show Answer

Acute: hoarseness, sore throat, odynophagia, skin irritation

Late: laryngeal edema, glottic stenosis, hypothyroidism, xerostomia, L'hermitte syndrome, myelitis, laryngeal necrosis

What are the main late toxicities after organ preservation with concurrent CRT for LCX?

Show Answer

Moderate speech impairment, dysphagia (25% of pts; <5% cannot swallow), and xerostomia (advanced/bilat cases)

What are some approximate RT dose constraints for laryngeal edema?

Show Answer

Some data suggest that the incidence of laryngeal edema ↑ significantly with mean doses **≥44 Gy.** (Sanguineti G et al., IJROBP 2007)

What is the QOL impact of larynx preservation when compared to laryngectomy in the Tx of LCX?

Show Answer

VA data demonstrated better social, emotional, and mental health function with larynx preservation (swallowing and speech function were similar), which suggests that better QOL is not d/t preservation of speech but d/t freedom from pain, emotional well-being, and less depression.

Hanna et al. demonstrated that pts had worse social functioning, greater sensory disturbance, more use of pain meds, and coughing after total laryngectomy than those treated with CRT. (Arch Otolaryngol H&N Surg 2004)

What is the follow-up paradigm for LCX pts?

Show Answer

LCX f/u paradigm: H&P + laryngoscopy (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, q12 mos if >5 yrs), imaging (for signs/Sx), TSH (if neck is irradiated), speech/hearing evaluation, and smoking cessation.