31

Oropharyngeal Cancer

Updated by Hubert Pan and Gopal K. Bajaj

BACKGROUND

What is the incidence of oropharyngeal cancer (OPC) in the United States?

Show Answer

~36,000 cases/yr of OPC in the United States with 6,850 deaths (2013 data)

How does the incidence of OPC compare to that of other H&N sites?

Show Answer

The incidence of **OPC is increasing,** whereas **cancer of other H&N sites is decreasing.**

Is there a sex predilection for OPC?

Show Answer

Yes. Males are more commonly affected than females (3:1).

What are the 4 subsites of the OPX?

Show Answer

Soft palate, tonsils, base of tongue (BOT), and pharyngeal wall

From which subsite do most OPCs arise?

Show Answer

The **tonsil** (ant tonsil pillar and fossa) is the most common primary site.

What are the borders of the OPX?

Show Answer

Anterior: oral tongue/circumvallate papillae
Superior: hard palate/soft palate junction
Inferior: valleculae
Posterior: pharyngeal wall
Lateral: tonsil

What 3 structures make up the walls of the tonsillar fossa?

Show Answer

Walls of the tonsillar fossa:

- Ant tonsillar pillar (palatoglossus muscle)
- Post tonsillar pillar (palatopharyngeus muscle)
- Inf glossotonsillar sulcus

What are the 4 most important risk factors for the development of OPC?

Show Answer

Risk factors for developing OPC:

- Smoking
- Alcohol
- HPV infection (up to 80% of cases now)
- Betel nut consumption

What is the 1st-echelon drainage region for most OPCs?

Show Answer

The 1st-echelon drainage site for most OPCs is the **level II (upper jugulodigastric) nodes.**

Are skip mets common for OPC?

Show Answer

No. Skip mets are **extremely rare** in OPC (<1%).
What are the 2 most common histologies encountered in the OPX? Rare histologies?

Show Answer

Most common histologies: squamous cell carcinoma (SCC) (90%), non-Hodgkin lymphoma (10% tonsil, 2% BOT)
Rare histologies: lymphoepithelioma, adenoid cystic carcinoma, plasmacytoma, melanoma, small cell carcinoma, mets
What proportion of pts with OPC fail locoregionally vs. distantly?

Show Answer

1:1 proportion of locoregional:distant failures
How prevalent is HPV infection in OPC?

Show Answer

Depending on the series, **40%–80%** of OPCs are associated with HPV infection.
Which HPV serotype is most commonly associated with OPC?

Show Answer

HPV 16 is the most common serotype in OPC (80%–90%).
What is a surrogate marker of HPV infection in OPC that can be used as an indirect indication of HPV seropositivity?

Show Answer

The surrogate marker for HPV infection is **p16 staining;** E7 protein inactivates Rb, which upregulates p16.
Which pt population is most likely to present with HPV-related OPC?

Show Answer

Nonsmokers and nondrinkers are most likely to have HPV+ SCC of the

OPX.
Do HPV+ or HPV– OPC pts have a better prognosis?

Show Answer

HPV+ OPC pts have a better prognosis. Data from **RTOG 0129** (Ang KK et al., NEJM 2010) showed better 3-yr OS (82.4% vs. 57.1%) and risk of death (HR 0.42) for HPV+ pts. Smoking was an independent poor prognostic factor.
What is the hypothesis behind why HPV+ OPC pts have a better prognosis?

Show Answer

HPV+ H&N cancers are **usually in nonsmokers and nondrinkers, so p53 status is usually nonmutated;** p53 mutation (which is common in non–HPV-related H&N cancers) predicts for a poor response to Tx.

WORKUP/STAGING

What nerves are responsible for otalgia in cancers of the oral tongue, BOT, and larynx/hypopharynx (HPX)?

Show Answer

Oral tongue: CN V (auriculotemporal) → preauricular area
BOT: CN IX (Jacobson nerve) → tympanic cavity
Larynx/HPX: CN X (Arnold nerve) → postauricular area
What are the 4 extrinsic tongue muscles, and what are their anatomic spans?

Show Answer

Extrinsic tongue muscles (-glossus) and anatomic spans:

- Genioglossus (ant mandible to tongue)
- Styloglossus (styloid process to tongue)
- Palatoglossus (palate to tongue; also forms ant tonsillar pillar)

. Hyoglossus (hyoid bone to tongue)

What is the most common presentation of OPC?

Show Answer

The most common presentation is a **neck mass,** especially with HPV+ OPC.
What are additional common presenting Sx by OPX subsite?

Show Answer

Base of tongue: sore throat, dysphagia, otalgia, neck mass
Tonsils: sore throat, trismus (T4b), otalgia, neck mass
Soft palate: leukoplakia, sore throat with swallowing, trismus/perforation, phonation defect with advanced lesions
Pharyngeal wall: pain/odynophagia, bleeding
Describe the workup for a pt with an OPX mass (per NCCN 2018).

Show Answer

OPX mass workup: H&P (bimanual exam of the floor of mouth), labs, laryngoscopy, CT/MRI with contrast H&N, tissue Bx with HPV testing (EUA if necessary), CT chest, consider PET/CT for stages III–IV Dz, nutrition, speech/swallow, audiogram
If the neck mass Bx is positive, is an additional Bx of the primary lesion necessary?

Show Answer

Yes. A Bx of the primary (or suspected primary) should also be done.
What % of OPC pts have clinically +nodes? Clinically occult nodes? Bilat nodes?

Show Answer

~75% of OPC pts have clinically+ nodes at presentation, **30%–50%** have clinically occult nodes, and **~30%** have bilat nodes (especially BOT/midline).

What is the T staging of p16(-) OPC? How is it different for p16(+) OPC?

Show Answer

T staging of p16(–) OPC is as follows:

T1: ≤2 cm
T2: >2 cm, ≤4 cm
T3: >4 cm or extension to lingual surface of epiglottis
T4a (moderately advanced): invades larynx, deep/extrinsic tongue muscles, medial pterygoid, hard palate, mandible
T4b (very advanced): invades lat pterygoid muscle, pterygoid plate, lat NPX, skull base, carotid encasement

For p16+ OPC, T4a and T4b are combined into a single T4 designation.

What are the N and summary staging of p16(-) OPC?

Show Answer

N and summary staging for p16(–) OPC are the same as other H&N sites (except for NPX).

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(+)
Stage I: T1N0
Stage II: T2N0
Stage III: T3N0 or T1–3N1
Stage IVA: T4aN0–1 or T1–4aN2
Stage IVB: T4b any N or any T N3
Stage IVC: any T any N M1

What is the N staging of p16(+) OPC?

Show Answer

Clinical

N1: any ipsi, ≤6 cm
N2: any contra or bilat LNs, ≤6 cm
N3: any >6 cm

Pathologic

N1: ≤4 LN positive
N2: >4 LN positive
What is the overall stage grouping for p16(+) OPC?

Show Answer

Clinical

Stage I: T1–2 N0–1
Stage II: T1–2 N2 or T3 N0–2
Stage III: any T N3 or T4 any N
Stage IV: M1

Pathologic

Stage I: T1–2 N0–1
Stage II: T1–2 N2 or T3–T4 N0–1
Stage III: T3–4 N2
Stage IV: M1

TREATMENT/PROGNOSIS

Broadly speaking, what OPC pts/stage groups are deemed early, intermediate, and advanced?

Show Answer

Based on RTOG 0129 and AJCC 8th edition staging:
Early: stages I–II (cT1–2N0) and select III (T2N1)

Intermediate/favorable: HPV(+) stages III–IV (without T2N1) in nonsmokers/drinkers, T3N0 (exophytic) regardless of HPV/smoking status
Advanced/unfavorable: HPV(–) smokers with stages III–IV Dz, T4 Dz regardless of HPV/smoking status
What are the Tx paradigms for early oropharyngeal tumors?

Show Answer

Early oropharyngeal tumor Tx paradigm: **surgical resection with selective neck dissection +/- PORT or definitive RT alone**
What are the Tx paradigms for intermediate oropharyngeal tumors?

Show Answer

Intermediate-group oropharyngeal tumor Tx paradigms: **Sg +/- postop CRT, altered fractionation RT, and CRT** (conventional fractionation)
What are the Tx paradigms for advanced/unfavorable oropharyngeal tumors?

Show Answer

Advanced/unfavorable oropharyngeal tumor Tx paradigm: **CRT (conventional)**
When is WLE alone appropriate for OPC?

Show Answer

Rarely. WLE may suffice in the rare instance of a small (<1 cm), ant tonsillar pillar lesion.
Is tonsillectomy ever adequate as a definitive Tx for tonsillar cancers?

Show Answer

Generally, **no.** Simple tonsillectomy is considered an excisional Bx and thus needs further definitive Tx. Radical tonsillectomy may be adequate in select cases but results in worse functional outcomes than RT.
What type of Sg is required for the surgical management of OPC?

Show Answer

Historically, labiotomy and mandibulotomy were required to gain access to the OPX, but there is growing experience with transoral approaches with transoral laser microsurgery (TLM) and **transoral robotic surgery (TORS).**
When is PORT indicated for OPC? When is postop CRT indicated for OPC?

Show Answer

Similar to other H&N sites, PORT is generally for intermediate-risk factors such as **T3–T4, LN+, LVSI, and PNI,** while postop CRT is indicated for **+margin or +ENE.**
When can unilat neck Tx be considered for OPC pts?

Show Answer

Unilat neck Tx can be considered **if the lesion is well lateralized** (T1–T2, <1 cm soft palate extension, no BOT involvement) **and 1 or few regional ipsi nodes <6 cm** based on multiple retrospective reviews showing a very low contralat failure rate (<3%).
Which LN regions/levels should be irradiated in pts with an early T stage but N+ OPC?

Show Answer

Levels II–IV should always be included/irradiated; however, some data (Sanguineti G et al., IJROBP 2009) suggest that levels I and V may be omitted d/t a significantly lower incidence of nodal spread.
What is the main indication for a neck dissection after definitive CRT for OPC?

Show Answer

The main indication for a neck dissection after CRT is **persistent nodal Dz** that can be documented by fine-needle sampling, CT (at 4–6 wks), or

PET/CT (at 10–12 wks).
What is the recommended timing for a neck dissection after CRT?

Show Answer

Neck dissection should typically occur at **6–8 wks** (**12–15 wks** if evaluated by PET/CT).
How should OPC pts be set up for simulation?

Show Answer

OPC pts should be simulated **supine, with arms pulled inferiorly and the head extended with a bite block or stent.** Contrast is recommended with CT.
What type of custom stent can be used?

Show Answer

Mouth opening, tongue depressing stent
What should the pre-RT evaluation/preparation include?

Show Answer

Dental evaluation/fluoride prophylaxis, speech and swallow evaluation/exercises, and nutrition evaluation with a PEG tube if the pre-Tx weight loss is >10% over 3 mos
What are the typical CTVs for IMRT planning?

Show Answer

CTV high dose (CTVHD): primary tumor and nodal GTV with 0.5–1-cm margin
CTV intermediate dose (CTVID): soft palate, adjacent parapharyngeal space, sup tonsillar pillars for lat tumors, and nodal levels adjoining involved nodes
CTV elective dose (CTVED): levels II–IV, RP nodes. If node+, most include ipsi IB and V.

What are the typical RT doses and volumes used for OPC?

Show Answer

T1 and superficial T2N0: **66–70 Gy to CTVHD, 60 Gy to CTVID, and 54 Gy to CTVED, given in 30–35 fx over 6–7 wks**

>T2+ without chemo: (1) 70 Gy to CTVHD, 63 Gy to CTVID, and 56 Gy to CTVED given in 35 fx over 6 wks (per Danish Head and Neck Cancer Group [DAHANCA]); (2) 70 Gy to CTVHD, 60 Gy to CTVID, and 57 Gy to CTVED given in 33 fx

>T3 or >N2 with chemo: 70 Gy to CTVHD, 63 Gy to CTVID, and 59.5 Gy to CTVED in 35 fx

What is the 2-yr LF rate after IMRT alone for early (T1–2N0–1) OPC?

Show Answer

RTOG 00–22 (Eisbruch A et al., IJROBP 2010) demonstrated excellent results with accelerated hypofractionated IMRT for early OPC: **2-yr LF rate was 9%** (if major deviations, 50%; otherwise, 6%, SS).

What were the RT techniques and doses employed in RTOG 00–22? How was the N stage established?

Show Answer

In **RTOG 00–22** (Eisbruch A et al., IJROBP 2010), RT was delivered with **accelerated hypofractionated IMRT** as follows: 66 Gy in 30 fx (2.2 Gy/fx) to the primary PTV and 54–60 Gy in 30 fx (1.8–2 Gy/fx) to the secondary PTV. **Neck staging was clinical** (not from CT); however, pts "upstaged" by CT (e.g., cN1 but N2 after CT) were also eligible.

What did the RTOG 90–03 study demonstrate about the use of altered fractionation in H&N cancers?

Show Answer

RTOG 90–03 (Fu KK et al., IJROBP 2000): 1,073 pts with H&N cancers (10% OC, 60% OPX, 13% HPX) with stage III (28%) or stage IV (68%) Dz

randomized to (a) conventional 70 Gy qd, (b) 81.6 Gy in 1.2 Gy/fx bid, (c) accelerated with split, and (d) concomitant boost (1.8 Gy/fx qd × 17, with last 12 fx bid with 1.8 Gy AM, 1.5 Gy PM to 72 Gy). There was better LC with altered fx (54% vs. 46%) but no OS/DFS benefit. There was worse acute toxicity but no difference in late toxicity.

What randomized studies demonstrated better outcomes with hyperfractionated RT over conventional RT for OPC?

Show Answer

RTOG 90–03 (Fu KK et al., IJROBP 2000): see above.

EORTC 22791 (Horiot JC et al., Radiother Oncol 1992): 325 pts (all OPX, but no BOT): 70 Gy vs. 80.5 Gy at 1.15 Gy bid. There was better LC (60% vs. 40%) but no OS benefit. LC was best for T3 Dz.

What data showed good LC rates with RT alone for select advanced (stages III–IV) OPCs?

Show Answer

MDACC data (Garden AS et al., Cancer 2004): pts with small primaries but stages III–IV Dz by virtue of +LNs; treated with RT alone. There were acceptable 5-yr LF (15%), DM (19%), and OS (64%) rates.

What are 2 important randomized trials that demonstrated the importance of adding chemo to conventionally fractionated RT in OPC?

Show Answer

GORTEC 94–01 (Calais G et al., JNCI 1999): 222 pts with stages III–IV OPC randomized to conventional RT alone vs. conventional RT + carboplatin/5-FU, no planned neck dissection for N2–3 Dz. The CRT arm had better 3-yr OS (51% vs. 31%), DFS (30% vs. 15%), and LC (66% vs. 42%); however, there was significantly worse grades 3–4 mucositis and weight loss/feeding tube use in the CRT arm.

Head and Neck Intergroup Study (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 q3 wks × 3. 3-yr OS was better in the CRT arm (37% vs. 23%). There also was improved DFS (51% vs. 33%) in the CRT arm.

Pooled analysis from which 2 important RCTs support adding chemo to PORT in H&N cancers for +margin and ECE?

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 OCC/OPC. 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 Gy PORT vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: >2 LN, ECE, +margin. There was better DFS (43% vs. 54%) and 2-yr LRC (72% vs. 82%) but only a trend to improvement in OS (57% vs. 63%).

What study demonstrated improvement in OS with the addition of cetuximab (C225) to RT in H&N cancers?

Show Answer

Bonner JA et al. (NEJM 2006): 424 pts with stages III–IV SCC of the OPX, laryngeal cancer, 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 C225 + RT. Subset analysis showed improvement mostly in OPC and in the altered fractionation RT arms (~50% treated with altered fractionation).

What studies are looking at Tx deintensification for HPV+ OPX?

Show Answer

1. **E1308:** Phase II, stages III/IV, induction chemo (paclitaxel, cisplatin,

cetuximab) f/b 54 Gy in 27 fx if CR or 69.3 Gy in 33 fx if PR, both with concurrent cetuximab. Although the study (Marur S et al., J Clin Oncol 2017) met its 2-yr PFS target based on historical control, other phase III trials indicate induction chemo adds toxicity without survival benefit (PARADIGM, DeCIDE).

2. **RTOG 1016:** Phase III, stages III/IV, treated with accelerated IMRT to 70 Gy/6 wks randomized to concurrent cisplatin vs. cetuximab.
3. **NRG HN002:** Phase II, stages III/IV, randomized to dose-reduced cisplatin CRT (60 Gy in 6 wks) vs. accelerated RT alone (60 Gy in 5 wks).

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 in the platinum/5-FU arm despite higher myelotoxicity in the TPF arm (98% rcvd planned Tx in the TPF arm vs. 90% in the PF 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), and HR 0.73. The rate of toxic deaths was greater in the platinum/5-FU group (5.5% vs. 2.3%). Also, there was 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.

What study compared induction chemo vs. upfront CRT?

Show Answer

PARADIGM study (induction TPF → CRT vs. CRT) (Haddad H et al., Lancet Oncol 2013): 145 pts, stages III–IV (55% OPX), randomized to induction TPF → CRT vs. CRT. At a median follow-up 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.

What are some advantages and disadvantages of split-field IMRT (vs. whole-field IMRT) in the Tx of H&N cancers?

Show Answer

There is potentially **better laryngeal sparing with split-field IMRT techniques;** however, the drawback is that the **practitioner may have to junction the RT dose through involved nodes.**

What are the advantages and disadvantages of IMRT "dose painting" (vs. sequential plans) in the Tx of H&N cancers?

Show Answer

The main advantage of IMRT dose painting is that **better conformality can be achieved** in a single plan. The drawback, however, is that **nonstandard doses/fx are required.**

How do unplanned RT interruptions in H&N cancer affect LC rates and why?

Show Answer

Each wk of Tx-time prolongation **reduces the LC rate by ~10%–12%** in H&N cancer pts b/c of **accelerated repopulation.**

What is the best way to compensate for several/few missed RT sessions and avoid Tx-time prolongation in H&N cancer pts?

Show Answer

According to Bese NS et al. the best way to compensate is by preserving total time, dose, and dose/fx (i.e., can treat bid on Fridays or extra fx on Saturdays). Alternatively, dose/fx can be increased (e.g., by 0.5–0.7 Gy/day). (IJROBP 2007)

FOLLOW-UP/TOXICITY

What is the approximate long-term PEG tube dependency rate after CRT for OPC?

Show Answer

The long-term PEG tube dependency rate after CRT can be as high as **15%–20%,** which is reduced with efforts on sparing swallowing structures (pharyngeal constrictors, larynx) with swallowing exercises and the use of PEG on demand.

What are some typical RT dose constraints for the parotid glands?

Show Answer

Typical RT dose constraints for the parotid glands are (a) mean dose to either parotid **<26 Gy** or (b) at least 50% of either parotid gland **<30 Gy.**

What is the typical RT dose constraint for the inner ears?

Show Answer

The mean dose to the inner ears should be **≤35 Gy.**

Appx what % of pts receiving cisplatin-based chemo will experience hearing loss as a result of ototoxicity?

Show Answer

~30% of pts will experience hearing loss.

What were the xerostomia rates for OPC pts treated with IMRT in RTOG 00–22?

Show Answer

Xerostomia rates in **RTOG 00–22** (Eisbruch A et al., IJROBP 2010) were **55% at 6 mos, 25% at 1 yr, and 16% at 2 yrs.** Salivary output did not recover over time.

What was the observed rate of osteoradionecrosis with accelerated hypofractionated IMRT in RTOG 00–22?

Show Answer

The observed rate of osteoradionecrosis was **6%** in **RTOG 00–22** (Eisbruch A et al., IJROBP 2010), which is higher than expected for IMRT (potentially b/c of the accelerated hypofractionated approach). Other toxicities were acceptable (grade 2+ for mucosa [24%], salivary [67%], esophagus [19%]).

What oral care do all pts need to be instructed on?

Show Answer

Fluoride trays. Consult a dental oncologist before any dental procedures.

What is the follow-up paradigm for OPC pts?

Show Answer

OPC follow-up paradigm: H&P + pharyngolaryngoscopy (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), annual TSH, speech/hearing/dental evaluation, and smoking cessation.