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Nasopharyngeal Cancer

Updated by Brian Deegan

BACKGROUND

What is the incidence of nasopharyngeal cancer (NPC) in the United States vs. in Asian countries?

Show Answer

NPC is rare in the United States (0.2–0.5 in 100,000) but endemic in Asia (25–50 in 100,000).

What are the environmental risk factors associated with NPC?

Show Answer

Consumption of salted fish and preserved meats, EBV infection, and smoking for keratinizing squamous cell type (no alcohol association)

What is the median age at Dx for NPC?

Show Answer

~50 yrs

Is there a sex predilection for NPC?

Show Answer

Yes. **Males > Females** (3:1)

What are the anatomic boundaries that make up the nasopharynx (NPX)?

Show Answer

Superior: sphenoid bone
Inferior: soft palate
Posterior: clivus/C1–2
Anterior: post edge of choanae
From what anatomic location do most NPCs arise?

Show Answer

Fossa of Rosenmuller (pharyngeal recess)
What is the local pattern of spread for NPC superiorly, inferiorly, posteriorly, laterally, and anteriorly?

Show Answer

Superiorly: invades (via the **foramen lacerum**) the cavernous sinus with initial CN VI involvement
Inferiorly/posteriorly: OPX
Laterally: parapharyngeal space
Anteriorly: nasal cavity
What 2 CN syndromes are commonly associated with NPC, and what CNs are involved in each?

Show Answer

Petrosphenoidal syndrome: CNs III–IV and VI involvement (oculomotor signs/Sx)
Retroparotidian syndrome: CN IX–XII involvement
What CNs or structures traverse through the base of skull sinuses/foramina (e.g., cavernous sinus, foramen rotundum, ovale, lacerum, jugular, hypoglossal)?

Show Answer

Cavernous sinus: CNs III–IV, V1 and V2, and VI
Foramen rotundum: V2
Foramen ovale: V3

Foramen lacerum: cartilage of the eustachian tube
Jugular foramen: CNs IX–XI
Hypoglossal canal: CN XII
What are the histologic subtypes of NPC and corresponding WHO classifications?

Show Answer

Keratinizing SCC (WHO type I, 25%). Sporadic form
Nonkeratinizing carcinoma: Differentiated (WHO type II, 12%).
Undifferentiated (WHO type III 63% vs. 95% in Asia)
Which type of NPC is endemic and prone to distant recurrence?

Show Answer

Nonkeratinizing undifferentiated (WHO type III) is endemic (better LC but higher metastatic risk).
Which type of NPC is associated with smoking and has poor LC but a lower propensity for DM?

Show Answer

Keratinizing SCC (WHO type I) is associated with smoking, poorer LC, and less distant spread.
Which type of NPC is most strongly associated with EBV exposure?

Show Answer

Nonkeratinizing undifferentiated (WHO type III)
With what autoimmune condition can NPC be associated?

Show Answer

Dermatomyositis
What histologic feature of NPC is an adverse prognostic factor in terms of LC and OS?

Show Answer

Presence of keratin (WHO type I)
What role does p53 play in the pathogenesis of NPC?

Show Answer

Little. p53 alteration is seen in the minority of cases (unlike other H&N cancers).
What is a commonality b/t NPX and OPX cancers?

Show Answer

Viral-associated tumors (EBV-NPX: HPV-OPX) have better LC but higher propensity for distant spread compared to nonviral-associated tumors in these regions.

WORKUP/STAGING

What are some common presenting Sx in pts with NPC?

Show Answer

Neck mass (>60%); epistaxis, headache, diplopia, facial numbness, otalgia, and nasal congestion. Trismus and/or CN deficits are seen with more advanced Dz.
What is the workup for a pt who presents with a neck node and a suspicious mass in the NPX according to the NCCN guidelines?

Show Answer

H&P, nasopharyngolaryngoscopy and Bx of the lesion, MRI with gadolinium of base of skull, NPX, and neck to clavicles, CT of skull base/neck with contrast as indicated; dental, speech and swallow, and audiology evaluations as indicated, and PET scan or other imaging to evaluate for DM
What is the DDx for a pt with a nasopharyngeal mass?

Show Answer

Carcinoma, lymphoma, melanoma, plasmacytoma, angiofibroma, RMS (children), and mets
What % of NPC pts present with palpable LAD?

Show Answer

60%–90%
What % of NPC pts present with bilat LAD?

Show Answer

Up to **50%**
Adenopathy near the mastoid tip is indicative of involvement of which nodal group?

Show Answer

Retropharyngeal nodes (node of Rouviere)
Pts with upper-level V LAD are most likely to have what kind of H&N primary?

Show Answer

NPC
What factors predict for DM in pts with NPC?

Show Answer

Lower neck nodal involvement, advanced nodal stage, and nonkeratinizing undifferentiated (WHO type III) **histology**
What are the common DM sites for NPC?

Show Answer

Bones, lungs, and liver
What correlates better with DM spread in NPC: N stage or T stage?

Show Answer

N stage

How does the latest AJCC 8th edition staging of NPC differ from the previous version?

Show Answer

T Stage	Description
T0	No primary identified with EBV+ cervical node(s)
T1	NPX ± OPX ± nasal cavity without parapharyngeal involvement
T2	Parapharyngeal extension ± adjacent ST involvement (medial or lat pterygoid, prevertebral muscles)
T3	Base of skull bones ± PNS ± cervical vertebra, pterygoid structures
T4	intracranial extension, CNs, hypopharynx, orbit, parotid, beyond lat pterygoid muscle
N Stage	**Description**
N1	Unilat cervical ≤6 cm ± retropharyngeal LN ≤6 cm (unilat or bilat), above caudal border of cricoid
N2	Bilat cervical ≤6 cm above the caudal border of the cricoid
N3	>6 cm and/or extension or involvement below the caudal border of the cricoid

Masticator space extension (to the lat pterygoid) is now T2 vs. T4 previously.

SCV involvement is no longer formally recognized (previously N3b) and is consolidated with any Dz present below the cricoid as N3.

Stage grouping:

	N0	N1	N2	N3
T1	I	II	III	IVA
T2	II	II	III	IVA
T3	III	III	III	IVA
T4	IVA	IVA	IVA	IVA

M1: stage group IVB

TREATMENT/PROGNOSIS

What is the typical Tx paradigm for pts with NPC?

Show Answer

RT alone for stage I, CRT for stages II–IVA, chemo (with RT reserved for focal palliation) for stage IVB

What must be done before planning the NPC pt for RT?

Show Answer

Nutrition consult, dental evaluation are recommended before RT.

When is Sg indicated in the management of NPC?

Show Answer

To Bx the lesion and in cases of selective neck dissection for persistent Dz after CRT.

For early-stage NPC, what are the typical survival and control rates with RT alone?

Show Answer

With RT alone, the 3-yr OS is **70%–100% for stage I–II NPC** and LC rates are **70%–80% for T1–T2 lesions.**

What stages of NPC should be treated with concurrent chemoradiotherapy (CRT)?

Show Answer

Per the **Intergroup 0099 study** (Al Sarraf M et al., JCO 1998), all T3–T4 or N+ pts should be considered for CRT. Per **RTOG 0225** (Lee N et al., JCO 2009), pts with T2 and N+ Dz should be considered (AJCC 8th edition staging).

What was the CRT regimen used for locally advanced NPC in the Intergroup 0099 (Al-Sarraf et al.) study?

Show Answer

Concurrent chemo with **cisplatin (100 mg/m^2) q3 wks** and **RT to 70 Gy** → adj chemo with cisplatin/5-FU × 3 cycles

What were the PFS and OS outcomes in the Intergroup 0099 (Al-Sarraf et al.) trial?

Show Answer

In **Intergroup 0099,** 3-yr PFS was 24% vs. 69%, and **3-yr OS was 46% vs. 76%** in favor of CRT over RT alone. B/c of this striking difference, the study was closed early. This was 1 of the 1st studies to demonstrate a survival benefit with CRT.

What are the main criticisms of the Intergroup 0099 (Al-Sarraf et al.) study?

Show Answer

Major criticisms of **Intergroup 0099** include the large number of pts (25%) with WHO type I NPC (not typically seen in endemic areas) and the poor results of the RT-alone arm. Single-institution studies with RT alone (PMH: Chow E et al., Radiother Oncol 2002) for locally advanced NPC had better **5-yr** DFS (48%) and OS (62%). Other groups (NYU: Cooper JS et al., IJROBP 2000) also demonstrated better outcomes with RT alone (3-yr DFS was 43%, and 3-yr OS was 61%).

What are the 3 key confirmatory randomized trials from Asia that

demonstrated a benefit with CRT vs. RT alone for locoregionally advanced NPC?

Show Answer

- **Hong Kong** (**NPC-9901:** Lee AWM et al., Cancer 2017): 348 pts, RCT, median f/u 10.7 yrs; concurrent cisplatin + RT + adj chemo vs. RT alone, no adj chemo; CRT improved PFS (56% vs. 42%), LRC (87% vs. 74%), and OS (62% vs. 49%, p = .047) but not DM rate; toxicities similar @10 yrs (52% vs. 47%)
- **Singapore** (**SQNP01:** Wee J et al., JCO 2005): 221 pts, RCT, median f/u 3.2 yrs; used Al-Sarraf regimen: better DFS (72% vs. 53%), OS (80% vs. 65%), and DM rate (13% vs. 30%); greater toxicity with CRT; **confirmed results** of Intergroup 0099 for endemic NPC
- **Taiwan** (Lin JC et al., JCO 2003): 284 pts, median f/u 5.4 yrs; cisplatin/5-FU + RT vs. RT alone: better PFS (72% vs. 53%) and OS (72% vs. 54%). The subgroup reanalysis (Lin JC et al., IJROBP 2004) showed that CRT benefited low-risk "advanced" NPC (LN <6 cm, no SCV) but not high-risk "advanced" pts

Is there a benefit to the addition of induction chemo followed CRT in locally advanced NPC?

Show Answer

Yes. Sun Trial (Sun et al., Lancet Oncol 2016). 480 pts. RCT of **induction TPF** f/b CRT vs. CRT alone. Median follow-up 3.75 yrs. Improved 3-yr: FFS (80% vs. 72%), OS (92% vs. 86%), DMFS (90% vs. 83%). No significant difference in LRF.

Is there a benefit with the use of adj chemo after definitive CRT in locally advanced NPC?

Show Answer

Maybe. Network Meta-analysis (Ribassin-Majed et al., JCO 2017) found the

addition of adj chemo ranked sup to CRT alone for PFS, LRC and OS. However, only PFS was statistically significant.
Estimate the LC of NPC treated with IMRT to 70 Gy in standard fx.

Show Answer

UCSF data (Lee N, IJROBP 2004) suggests LC rates as high as 97% for NPC pts treated with IMRT.
What is the typical IMRT dose painting technique, and what are the corresponding IMRT doses used in the Tx of NPC?

Show Answer

Many institutions (MSKCC/RTOG) employ the SIB technique: **2.12 Gy × 33 = 69.96 Gy** to GTV, **1.8 Gy × 33 = 59.4 Gy** to intermediate-risk areas, and **1.64 Gy × 33 = 54 Gy** to low-risk areas.
How would you support the use of IMRT in NPC?

Show Answer

Better salivary outcomes with IMRT were demonstrated in data from Queen Mary Hospital (Pow EH et al., IJROBP 2006): 51 pts, stage II NPC, 2D vs. IMRT. At 2 mos, there was no difference in xerostomia; however, over time, QOL and objective salivary function improved for the IMRT group.

FOLLOW-UP/TOXICITY

What are the RTOG 0225 dose constraints for the chiasm/optic nerves when using IMRT for NPC?

Show Answer

Per **RTOG 0225,** the dose constraints for the chiasm/optic nerves are **54 Gy** or 1% of the PTV not >60 Gy.
What are the accepted RTOG 0225 dose constraints for the parotids?

Show Answer

Per **RTOG 0225,** the dose constraints for the parotids are as follows: mean dose <**26 Gy** (should be achieved in at least 1 gland) or at least 20 cc of the combined volume of both parotid glands <20 Gy or at least 50% of 1 gland <30 Gy.

Why might sparing of the parotid glands not be sufficient to prevent xerostomia?

Show Answer

Sparing of the parotids alone may not be sufficient b/c **mucus production by minor salivary glands may be necessary for subjective improvement,** according to data from Prince of Wales Hospital (Kam MK et al., JCO 2007): 60 pts randomized to IMRT or 2D-RT. Objective improvement in both stimulated and unstimulated salivary flow was found, but not in the subjective improvement of xerostomia.

What is the NCCN-recommended f/u schedule for NPC pts?

Show Answer

H&P with nasopharyngolaryngoscopy (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, and q12 mos if >5 yrs), imaging (for signs/Sx or smoking Hx/surveillance), TSH q6–12 mos (if neck irradiated), speech/hearing/dental evaluation, and smoking cessation