Head & Neck Malignancies

Session Chair: Jonathan Riess MD/MS
Assistant to Session Chair: Brandon A. Dyer MD

1 - Department of Medical Oncology
2 - Department of Radiation Oncology
University of California Davis Comprehensive Cancer Center

Assistant to Session Chair
• Brandon A. Dyer, MD – Chief Resident, Dept. of Radiation Oncology, UC Davis Cancer Center

Panel Members
• Alain Algazi, MD - UCSF, Medical Oncology
• Arnaud Bewley, MD - UC Davis Cancer Center, Head & Neck Surgery, Dept. of Otolaryngology
• A. Dimitrios Colevas, MD - Stanford, Medical Oncology
• Vasu Divi, MD - Stanford, Head & Neck Surgery, Dept. of Otolaryngology
• Patrick Ha, MD - UCSF, Head & Neck Surgery, Dept. of Otolaryngology
• Jed Katz, MD - Kaiser Permanente, Medical Oncology
• Quynh Le, MD - Stanford, Dept. of Radiation Oncology
• Shyam S. Rao, MD/PhD - UC Davis Cancer Center, Dept. of Radiation Oncology

Topics Covered
1. Oropharynx
2. Management of metastatic HNSCC
3. Nasopharynx
4. Larynx

Learning Objectives
1. Understand the multidisciplinary treatment pathways that guide management of H&N cancer cases (oropharynx, nasopharynx, larynx).
2. Become (re)-familiar with the new AJCC8 staging system for HPV-associated oropharynx cancers
3. Improve understanding of the use of leading-edge H&N cancer treatments
Case 1

HPI: 50 year-old woman with persistent sore throat and L neck adenopathy despite several courses of antibiotic.

PMH: Remote 15 pack-year smoking history, otherwise healthy.

Normal renal function, audiometry normal.

Exam:
- Multiple left level II mobile LNs; right uninvolved
- Left tonsil ulcerated

Nasopharyngoscopy:
- Exophytic L tonsillar mass, free from tongue
  1-2 cm of soft palate involved

Biopsy: p16(+) moderately differentiated SCC

Question 1.1

The patient has HPV(+) squamous cell carcinoma (SCC) of the oropharynx (OPX). There is no evidence of distant metastases. TNM AJCC7: cT2N2bM0 (IVA); AJCC8: cT2N1M0 (I).

What would you recommend for initial treatment?

A. Surgery (TORS)
B. Radiation alone
C. Chemoradiation

RTOG 0129: Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

Ang NEJM 2010
Clinical Trials in Transoral Robotic Surgery (TORS)

• RTOG 1221: HPV(-) OPX surgical intensification
• ECOG 3311: HPV(+) OPX de-escalation
• ORATOR: HPV(+/−) OPX surgery vs RT
• ADEPT: HPV(+) OPX de-escalation in N(+) with extranodal extension

Question 1.2
This patient (cT2N1M0) is not interested in surgical options.

What is your non-surgical treatment recommendation?
A. RT alone (+ altered fractionation)
B. RT with cisplatin (CDDP) 40 mg/m² weekly during radiation
C. RT with cisplatin (CDDP) 100 mg/m² every 3 weeks for 3 cycles
D. RT with weekly concomitant cetuximab
E. RT with weekly concomitant carboplatin/paclitaxel

Bonner et al: RT vs cetux-RT

RTOG 1016: RT+CDDP vs Cetuximab in HPV(+) OPX SCC
Cisplatin dose: Definitive RT + CDDP (30 vs 100 mg/m²)

q3w cisplatin at 100 mg/m² results in superior LRC compared with weekly cisplatin at 30 mg/m², and is the preferred regimen for LAHNSCC.

NRG HN-002: Phase II trial in p16(+), non-smoking associated, locoregionally advanced oropharyngeal cancer

OPSCC p16+ IHC
≤ 10 pk-yr smoking hx
T1-2, N1-2b
or T3, N0-2b

44% of RTOG 1016 population eligible, closed to accrual

Case 1 continued

- The patient had a family emergency and deferred treatment for 6 months and now returns to clinic.
- Exam:
  - Trismus, L > R
  - Left middle ear effusion
  - Massive, firm, fixed left neck adenopathy appears to invade skin, fixed to the L SCM
  - Larynx mobile from pre-vertebral fascia

Nasopharyngoscopy:
- Exophytic L tonsillar mass, extends into BOT, involves posterior pharynx, extends cranially into posterior nasopharynx
Question 1.3
The patient now has HPV(+) squamous cell carcinoma (SCC) of the oropharynx (OPX), AJCC7: cT2N3M0 (IVB); AJCC8: cT2N3M0 (III).

What is your initial treatment recommendation?

A. Surgery  adjuvant chemoradiation
B. Induction chemotherapy → chemoradiation
C. Definitive chemoradiation

PET-NECK Trial: PET/CT surveillance vs neck dissection in advanced H&N malignancies

564 HNSCC patients with N2a-3 disease (79% N2a-b)
Randomized to planned neck dissection or PET-CT at 12 weeks post-CRT
The patient receives bolus cisplatin with concomitant radiation. 2 years later, patient is found to have metastatic disease to the lungs and mediastinal lymph nodes.

**Question 1.5:** Would you check the combined proportion score (CPS) for PD-L1 expression before considering next steps of therapy?

A. Yes  
B. No

**Question 1.6**  
The CPS score is 30%. What would you treat patient with for recurrent, metastatic HPV+ oropharynx cancer?

A. Nivolumab  
B. Pembrolizumab  
C. Carboplatin plus 5FU plus cetuximab (EXTREME Regimen)  
D. Carboplatin plus 5FU plus pembrolizumab  
E. Docetaxel
Question 1.7

In addition to CPS score, would you send tissue for additional molecular testing?

A. Yes, NGS panel of > 300 genes for broad molecular profiling
B. No
Case 2

HPI: A healthy 18 year old Chinese man with no past medical problems presents with a 2-month history of bilateral neck swelling and lymphadenopathy, nasal congestion, and epistaxis.

PMH: Healthy.

Exam:
  • Left middle ear effusion
  • Left level II 5 cm LN is mobile, right level II 4 cm LN is mobile

Nasopharyngoscopy:
  • Large left-sided nasopharynx tumor crosses midline, invades and obliterates the fossa of Rosenmüller and left eustachian tube

Biopsy: WHO type II, non-keratinizing SCC

Question 2.1

There is no evidence of distant metastases. The patient has TNM AJCC7/8: cT4N2M0 (IVA).

What is your initial treatment recommendation?

A. Radiation alone
B. Cisplatin-RT (100 mg/m^2 q3 weeks) x 3 cycles
C. Cisplatin-RT (100 mg/m^2 q3 weeks) → adjuvant cisplatin/5FU
D. Induction cisplatin/5FU → weekly cisplatin + RT
E. Induction cisplatin/5FU/docetaxel → weekly cisplatin+ RT
F. Cisplatin/cetuximab/paclitaxel → weekly cisplatin + RT

29% 24% 13%
**Is adjuvant chemotherapy necessary?**

Pts randomized to concomitant weekly cisplatin (40 mg/m²) + RT to 66 Gy ± adjuvant cisplatin (80 mg/m²) with SFU (800 mg/m²) x 3

- after concomitant chemoradiation, adjuvant cisplatin/SFU did not significantly improve failure free, overall survival
- only 40% were able to complete all therapy as initially prescribed
- performed in endemic population, may not be reflective of the US population

**Question 2.2**

The patient is preparing to receive therapy. Can EBV testing/levels assist with treatment decision making?

**Do you recommend plasma EBV DNA level testing?**

- A. No
- B. Yes, before treatment
- C. Yes, after treatment
- D. Yes, before and after treatment
- E. Yes, at recurrence

**Quantification of plasma Epstein-Barr Virus DNA in advanced nasopharynx cancer**

- 99 patients: neoadjuvant cisplatin/SFU then 70-74 Gy RT
- Pre-treatment: 94/99 patients with detectable plasma EBV DNA
- Post-treatment: 10/99 patients with detectable plasma EBV DNA

- post-treatment plasma EBV DNA levels are associated with treatment response/survival

**NRG HN-001: Randomized Phase II and Phase III Studies of Individualized Treatment for NPC Based on Biomarker EBV DNA**

- Stage II/III NPC
- Detectable pre-treatment plasma EBV DNA
- IMRT 70 Gy / 33 Fractions
- Cisplatin 40 mg/m²/week

- Post-CRT EBV DNA Detectable
- Gemcitabine/Paclitaxel x 4
- Control: Cisplatin/SFU x 3c

- Post-CRT EBV DNA Undetectable
- Observation

- RANDOMIZE
**Question 2.3**

This patient has locally advanced nasopharynx cancer [TNM AJCC7/8: cT4N2M0 (IVA)] with intracranial extension and cranial nerve involvement.

**Would you recommend induction chemotherapy?**

A. Yes, start cisplatin, 5FU, docetaxel (TPF)

B. No, start concurrent cisplatin plus RT

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**Question 2.4**

The patient continues on surveillance.

Two years later PET CT demonstrates metastatic NPC. EBV viral load, blood > 10,000. Biopsy of liver lesion shows EBV+ NPC.

**What is your recommendation for systemic treatment of metastatic nasopharynx cancer?**

A. Cisplatin/5FU

B. Cisplatin/gemcitabine

C. Pembrolizumab or Nivolumab (PD-1 antibody)
### KEYNOTE-028: Pembrolizumab in PD-L1(+) NPC

- **Phases**: Ib in 27 patients with recurrent/metastatic NPC and PD-L1 ≥ 1%
- **Drug**: Pembrolizumab 10 mg/kg Q2 weeks → 2 years or progression
- **Response**: Overall response rate (monotherapy) 26% with median follow-up of 20 months
- **Adverse Events**: iAE: rash/pruritus (26%), pain (22%), hypothyroidism (19%), and fatigue (19%)
- **Other**: G3 drug-related AE (8/27 patients) and one drug-related death due to sepsis

### NCI-9742: Nivolumab in recurrent/metastatic NPC

- **Phases**: II in 44 patients with recurrent/metastatic NPC
- **Drug**: Nivolumab 3 mg/kg Q2 weeks → progression (beyond initial 12 weeks)
- **Response**: Overall response rate (monotherapy) 21% at a median follow-up of 12.5 months
- **Survival**: 1-yr OS was 59% and PFS was 19%
- **Adverse Events**: G3+ in 22% (10/44) including colitis, diarrhea, fatigue, transaminitis, and cytopenia

### Adoptive T-cell transfer and chemotherapy in metastatic/recurrent NPC

- **Setting**: Phase II, 35 patients, first-line for metastatic disease
- **Treatment**: EBV-CTL, EBV-CTLs
- **Outcome**: *EBV-CTL production* → PMBC formation → EBV-CTLs
- **Response**: Overall response rate 71%, 2-yr OS 63%, 3-yr OS 37%
- **Survival**: LMP2 expression on CTL correlated with overall survival

### Case 3

**HPI**: 60 year-old man with 100 pack-year smoking history presents with hoarseness, globus sensation, weight loss.

**PMH**: Current smoker, COPD not on oxygen.

**Exam**:
- Normal tongue movement, 80% movement
- No cervical adenopathy bilaterally

**Nasopharyngoscopy**: Right TVF mass extends to the subglottis, sluggish right cord

**Biopsy**: p16(-) squamous carcinoma of larynx
Question 3.1

There are several right cervical lymph nodes in levels II/III < 3 cm on imaging. There is no evidence of metastatic disease. There is indeterminate cartilage invasion, and a sluggish right TVC. The patient has cT3N2bM0 (IVA).

What is your initial treatment recommendations?

A. Surgery followed by chemoradiation
B. Cisplatin + radiation
C. Cetuximab + radiation
D. Induction chemotherapy followed by radiation
E. Induction chemotherapy followed by platinum-radiation
F. Induction chemotherapy followed by cetuximab-radiation

Question 3.2

For which advanced-stage laryngeal cancer patients would you offer larynx-preserving approach (chemo-RT)?

A. Stage T3 and lower only
B. T1-3 and select T4 patients
C. Based on adequate laryngeal function regardless of stage
D. Based on induction chemotherapy response regardless of stage

Case 3 continued

Interval HPI: The patient initially refused any treatment (surgery or chemoradiation). He returns to clinic 6 months later for follow up. He has lost 10-15 pounds and has moderate obstructive airway symptoms.

Exam:
- Firm, fixed right cervical level II LN with +ENE and small, firm, mobile left neck LNs
- Tumor palpable along right lateral pharyngeal wall from soft palate to right BOT, extends past midline

Nasopharyngoscopy:
- Fungating right laryngeal mass involves the right soft palate, right lateral pharyngeal wall, obliterates vallecula, unable to visualize TVC or hypopharynx
Updated imaging shows no evidence of distant metastatic disease. The patient now has cT4aN3bM0 (IVB) larynx SCC.

What is your treatment recommendations?

A. Surgery followed by chemoradiation
B. Cisplatin (100 mg/m² x 3) + radiation
C. Cetuximab + radiation
D. Induction chemotherapy followed by radiation
E. Induction chemotherapy followed by platinum-radiation
F. Induction chemotherapy followed by cetuximab-radiation

Case 4

HPI: a 83 year old man initially presented with a right forehead SCC lesion s/p cryosurgery 2 years ago. He then developed local recurrence treated with Moh’s and subsequently had an enlarging right parotid gland/LN. The parotid was biopsied and demonstrated metastatic SCC.

PMH: HLD, HTN, CAD

Exam: Firm, fixed 3 cm LN in the tail of the right parotid, no skin changes
Question 4.1

The patient is discussed at multidisciplinary H&N tumor board and is felt to be a surgical candidate. He has recurrent cutaneous SCC of the H&N, rcT2N3M0 (IV).

What is your initial treatment recommendation?

A. Surgery alone
B. Radiotherapy
C. Concurrent Chemoradiation

Question 4.2

The patient completes oncologic resection consisting of scalp wide local excision, right parotidectomy, right MRND.

Pathology shows negative surgical margins. The primary tumor is 3.2 cm with 0.9 cm DOI. The right parotid shows a 3.1 cm metastatic deposit without evidence of a fibrous capsule. The temporal branch of the right temporal nerve was sacrificed due to tumor involvement (PNI).

Final pathologic stage rpT3N3bM0 (IV).

What is your recommendation for adjuvant therapy?

A. Radiotherapy
B. Chemotherapy
C. Concurrent chemoradiation
D. Observation

Prognostic factors for cutaneous SCC treated with surgery alone

Multivariate analysis of 615 patients with cutaneous SCC treated with surgery alone

Best predictors of locoregional recurrence:
- Desmoplastic growth (HR 16)
- Thickness > 6.0 mm (HR 6)

Best predictors of metastatic disease:
- Thickness > 6.0 mm (HR 4.8)
- Immunosuppression (HR 4.3)
- Tumor site = Ear (HR 3.6)
- Tumor width > 5 cm (HR 2.2)

Desmoplasia or > 6.0 mm
3-yr LRRFS: 99% vs. 86%

> 6.0 mm vs. < 2.0 mm
3-yr DMFS: 100% vs. 88%

Fla orescent head neck 2003

Florida perineural invasion series

Retrospective analysis of 135 patients with cutaneous SCC (80%) and BCC (20%); 15% cLN(+)

Clinical PNI
- 53% received postoperative RT
- 45% received definitive RT
- 69% recurrent
- 55% had +SM
- 12% local RT, 22% with extended RT fields, ~66% with large RT fields to base of skull
- 44% had elective nodal RT
- 5-yr LC 55%, LRC 50% \to regional failure 5%

Low rate of salvage surgery in cPNI group (12-30%)
High regional nodal failure with omission of elective RT consider elective nodal RT with any SCC with PNI
Post-Operative Skin Trial - TROG 05.01
Post-op concurrent CRT versus RT

High-risk post-op H&N SCC

Any of:
- T3-4 (no nose/EAC/lip)
- pN2b-3 cervical LN
- +ENE
- Intraparotid LN
- In-transit metastases

Primary endpoint: Locoregional failure

Randomize

Radiotherapy Alone

60-66 Gy in 2 Gy/frx

Radiotherapy + Carboplatin

60-66 Gy in 2 Gy/frx
Carboplatin AUC 2.0

Primary endpoint: Locoregional failure

S. Virgilio et al. JCO 2018

Question 4.3

If the prior patient was not a surgical candidate, what is the expected improvement in clinical outcome for definitive radiotherapy alone?

A. Local control
B. Overall survival
C. Toxicity

Florida definitive RT: T2-4 H&N cutaneous SCC

- 99 patients with T2-4 H&N SCC (55) and BCC (42) received 40-65 Gy
  - 56 lesions previously untreated
  - 44 lesions were recurrent

Mendenhall IJROBP 1987; Lee Head Neck 1993

definitive RT alone provides good local control and survival with low incidence of severe complications.

T4 lesions (bone, cartilage, nerve invasion) have poor outcomes

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ANCO
Case 4 continued
The patient does well for 9 months. Endorses increasing coughing at follow up.

This area is biopsied and confirms metastatic disease consistent with his skin primary.

Question 4.4
The patient subsequently develops metastatic cutaneous SCC from skin H&N primary. He has good performance status and interested in further treatment.

What is your initial systemic treatment recommendation for metastatic disease?

A. 1. Capecitabine
B. 2. Cemiplimab
C. 3. Carboplatin/paclitaxel

PD-1 blockade with cemiplimab in advanced cutaneous SCC
• Phase I→II in 26 patients with locally advanced or metastatic cutaneous SCC
• IV cemiplimab (3 mg/kg) q2wk for up to 96 wks, toxicity or progression

response rate was 47%, durable control in 61%
median time to response was 1.9 mo, lasting > 6 mo in 57%
of pts with response, 82% had ongoing response at data cutoff
median PFS and OS reached at data cutoff
The End!

Thank you for your attention