# Head and Neck Cancer - HNSCC

## UpToDate

1. Immuno check point inhibitor (Opdivo, keytruda) has been approved for 2nd line therapy for HNSCC cancers that have progressed on cisplatin-based therapy.

## Introduction

- Man:woman = 2.5:1
- Stage at diagnosis: regional (46%), localized (33%), distant (14%)
- Heterogeneity: 95% SCC
  * Oral cavity, Lip, Salivary gland
  * Pharynx → Nasopharynx, Oropharynx, Hypopharynx
  * Larynx → Supraglottis, Glottis, Subglottis

## Risk Factors

- Age (>50yrs)
- Tobacco
- Alcohol
- Viral (25-35% of pts with SCC)
  * HPV: > 50% oraphaphynx ca (Europe and North America)
  * EBV (nasophrynx): a/w WHO type II and III
- Hereditary: rare. 3.5 fold increased risk if positive family SCC history.
- Personal history of SCCHN: the single great risk
- Others: Plummer-Vinson Syndrom, Fanconi Anemi, HIV, all have increased risk

## Biology

1. HPV Pos SCCHN: mostly orophaphynx ca. HPV+/p16+ → good prognosis, ↑sensitivity to RT.
   - HPV 16, 18 → encode E6/E7 (viral protein) → inhibit p53 and Rb → pooly differentiated SCC.
   - Clinical: large cystic neck nodes, younger age at diagnosis, c/w sexual behavior, nonsmoker, nondrinker
2. HPV Neg SCCHN: a/w smoking, alcohol, oral hygiene. Poor prognosis

** Important: HPV status is currently used only as a prognostic factor NOT as a guide for tx. HPV-pos and HPV-neg SCCHN are treated the same way.

## Symptoms

- Sore throat, hoarsenses, difficulty swallowing, adult unilateral otitis media, double vision
- Spread to neck lymph node - reduce the cure rate for a given T-stage by 50%

## Diagnosis

- Triple endoscopy (EGD, Bronchoscopy, Laryngoscopy): → w/u for unknown primary neck mass
- CT or MRI of the neck. PET is NOT usually done.
- CXR, r/o lung cancer or metastasis (routine)
- CT chest: indicated for bulky N2 or N3 neck dz or hypopharynx tumor
- Biopsy: may require neck dissection if SCC is suspected.

## Pathology

A. Pre-cancerous lesions:

1) Leukoplakia - low risk.
   - Tx: observe only, but persistent leukoplakia should be biopsied.
2) Erythroplakia (Red, velvety patch) - high risk for malignant transformation.  
   - Tx: surgical removal (always resection upon discovery).

B. WHO Classifications of Head Neck Cancers
   - Type I: Squamous cell carcinoma (SCC)
   - Type II: Nonkeratinizing carcinoma
   - Type III: Undifferentiated carcinoma

C. Staging:
1) Common to lip, oral cavity, pharynx (oral, hypopharynx):
   - T1: <2cm
   - T2: 2-4 cm
   - T3: > 4 cm
   - T4 (not based on size): invade adjacent structures (T4a), or involve carotid artery, skull base, spaces (T4b)

2) Common to larynx (supraglottis, glottis): not based on size
   - T1: one side of supraglottis or vocal cord, → NORMAL vocal cord mobility
   - T2: invade adjacent membranes without fixation → Impaired vocal cord mobility
   - T3: invade adjacent structure with fixation, thyroid involvement → vocal cord paralysis
   - T4: invade deep structures (T4a) or prevertebral spaces/mediastinal structure/carotid artery (T4b)

3) N1: <3 cm, single ipsilateral
   - N2: 3-6 cm
      - N2a - single ipsilateral
      - N2b - multiple ipsilateral
      - N2c - bilateral or contralateral
   - N3: >6 cm

4) M0: no distant metastasis
   - M1: distant metastasis

5) Stage I:  T1, N0, M0
    - Stage II:  T2, N0, M0
    - Stage III: T3, N0, M0; T1-3, N1, M0
    - Stage IV:  IVA: T4a, N0-1, M0; T1-4a, N2, M0
      - IVB: T4b, anyN, M0; anyT, N3, M0
      - IVC: anyT, anyN, M1

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- Distant metastasis (stage IVC), Locally advanced resectable (IVA, bulky stage III) or unresectable (IVB).
- Early-stage: stage I and II and low-volume stage III (e.g T1 or T2 and N0 or N1)
- Early-stage: bulky stage III (T3, N1)

6) Unresectability: > N2 or T4b
   - base of skull involvement
   - fixation to the prevertebral fascia
   - carotid encasement
   - involvement of the pterygoid musculature
   - inability to perform an adequate reconstruction for a functional result
   - low likelihood to achieve negative margin
   - requirement total glossectomy.

**Prognosis:**
- Staging (most important!)
- Neck lymph node spread → bad
- Others:
  * HPV/p16 positivity → good prognosis
  * EBV → good prognosis
  * Overexpression of EGFR → poor prognosis.

- Salivary gland tumor: the site of the tumor predicts its malignant potential.
  * Parotid tumors → most benign
  * Minor salivary gland tumors (submandibular, sublingual) → most malignant

**Tx Principle:**
A. Limited or early-stage disease (33%): stage I and II, or low-volume stage III (T1-2, N1, M0)
   - Tx principle: SINGLE modality (surgery or RT alone), cure rate 52-100%, OS 90%
1) Oral cavity cancer:
   - Primary Tx: surgery (preferred), rather than RT (high morbidity)
   - Adj therapy (also used as a general rule):
     * Extracapcular spread and/or positive margin: → chemoRT (preferred - cat1) or re-resection
     * Other risk features (pT3,pT4, N2 or N3, perineural invasion, vascular embolism):
       → RT
   - Neck dissection after primary surgery depending on the tumor thickness:
     * Elective ipsilateral neck dissection: → for most pts with stage I oral tongue cancer and stage II oral cavity cancers at other sites.
     * Bilateral neck dissection: → for primary tumor close to or involving the midline.

2) Oropharynx cancer: T1-2, N0-1
   - Primary Tx: → RT (preferred) or surgery
   - If surgery is used as primary tx, following the same rule as above.
   - For T2, N1 only: → RT + systemic therapy

3) Hypopharynx cancer: → preserve voice, swallow, and airway
   - Primary Tx: Surgery ≈ RT (no head to head comparison, both have good local control)
   - If surgery (partial laryngectomy) is used as a primary tx → follow general rule as
above.
   - If RT is used as a primary tx → recommend elective RT to bilateral neck including retropharyngeal and supraclavicular nodes.

4) Larynx cancer:
   4.1 Supraglottic and glottic larynx cancer: → RT (better function preserve), rather than surgery
       If surgery (partial laryngectomy) is required, follow the same rule above
   4.2 Subglottic cancer: → total laryngectomy, in conjunction with thyroidectomy + bilateral paratracheal node dissection → adj RT rule as above.

B. Locally Advanced Head Neck SCC: stage III (bulky dz, T3, N1), and IV
1) Resectable Tumors:
   - Primary Tx → surgical resection
   - Adj RT or CRT (EORTC 22931, RTOG 95-01) depending post-op risk factors
     * Positive margins or extracapsular spread, → adj concurrent RT with cisplatin (cat 1).
     * Other risks (multiple LN, perineural/LVI, large tumor T3/T4), → adj RT only, with concurrent CRT as an optional.

2) Organ Preservation for Resectable Tumors:
   - Primary Tx: → concurrent chemoRT (standard), rather then surgery for organ preservation
     Induction chemo followed by chemoRT has additonal advantage (but NOT a standard yet)
     ** Pearl: Concurrent CRT may be preferred for pts less likely to have distant metastases (N0 and N1 presentations). Sequential CRT preferred for pts with high risk of distant metastases (more extensive lymph node disease). DO NOT use induction chemo alone for organ preservation.
       - Choice of concurrent chemoRT:
         * Concurrent CRT with Cisplatin (ECOG1392) or Carboplatin (TAX324) - first line
         * If NOT tolerate platinum, use concurrent CRT with Cetuximab.
       - Choice of induction chemotherapy: → TPF (Docetaxel, Cisplatin, 5-FU) → improved local control and OS (TAX 324 trial) - NOT a standard yet!
       - Neck dissection: indicated for clinically detectable residual diseases or a positive PET scan 12 wks after concurrent chemoRT.

3) Unresectable tumor: → concurrent chemoRT (similar to organ preservation)

C. Recurrent or metastatic SCCHN: incurable, poor prognosis, median OS 5-9 months
1). Locally recurrent disease: → salvage surgery and/or reirradiation.

2). Metastatic or distant recurrence:
   2.1 No prior chemo: → combination chemo for pts with good PS, or single agent (for poor PS)
     * 1st choice: "Platinum (cisplatin or carboplatin) + 5FU, + Cetuximab" - cat 1 for
non-nasopharyngeal SCC
or "Platinum + taxane" as an alternative
Note: Adding cetuximab to 1st line therapy \(\rightarrow\) OS compared with a platinum/5-FU alone, but no survival difference when cetuximab is started at the time of disease progression.

2.2 Had prior systemic chemo:
   - If long remission since last tx, good PS: \(\rightarrow\) re-treated with previous combination chemo.
   - If short remission since last tx, or poor PS: \(\rightarrow\) prefer single agent.
     * For platinum-refractory metastatic SCCHN, \(\rightarrow\) cetuximab (FDA approved 2nd line)
     * Other active agents: Taxane, Methotrexate, Gemcitabine (for nasopharyngeal), Cetuximab (non-nasopharyngeal).
   - If very poor PS, severe comobidities: \(\rightarrow\) Supportive care.

D. Principles of Neck management:
   - Neck dissection is part of primary surgery tx (not part of primary RT tx) in an attempt to eliminate potential risk for metastasis to the neck.
   - Ipsilateral neck dissection: \(\rightarrow\) for clinical positive neck nodes or large primary (>T3) or high-risk features on biopsy
   - Bilateral neck dissection: \(\rightarrow\) tumor with bilateral lymphatic drainage (base of tongue, palate, supraglottic larynx, deep space pre-epiglottic involvement) or tumors at or close the midline.
   - Tumors involving the anterior tongue or floor of mouth that approximate or close the midline \(\rightarrow\) should undergo contralateral submandibular dissection
   - Elective neck dissection: for early-stage cancer or clinical negative neck node.
   Indication is based on the risk of occult metastasis in most cases. e.g.
     * Oral cavity SCC: based on the depth of tumor invasion. If \(>4\)mm, \(\rightarrow\) go to elective dissection.
   - The type of neck dissection (selective or comprehensive) is determined by pre-op clinical staging as following:
     N0 \(\rightarrow\) Selective neck dissection (for most elective dissection)
     N1-N2a-c \(\rightarrow\) Selective or comprehensive neck dissection
     N3 \(\rightarrow\) comprehensive neck dissection

E. Radiation Therapy:
   - Hyperfractionation or accelrated fractionation: better local control and survival benefit.
     - IMRT \(\approx\) RT \(\rightarrow\) similar local control and survival (PARSPORT).
     - Post RT Follow-Up: TSH q 6-12 months

F. Site-specific organ presevation
   - Larynx preservation: chemoRT (VALCSG, Intergoup R91-11)
   - Hypopharynx/larynx: concurrent chemoRT or induction chemo with cisplatin/5-FU or cisplatin/5FU/docetaxel (better) (GORTEC 2000-01 trial, EORTC 2471/TAX 323)
Follow-Up:

A. Follow-up post RT/chemoRT:
   - H & P, q1-3 mos/1st yr, q2-6 mos/2nd yr, q4-8mos/3rd yr, q >5yrs/q12mos
   - Get post-tx imaging within 6 mos (such as PET). If PET (>12 wks after RT). If PET is negative, then further imaging is as clinically indicated. If PET positive (< CR with residual nodal mass of 1.5-2.5 cm), repeat PET/CT. If still positive, → neck dissection
   - CXR as needed. Speech/swallow as clinically indicated.
   - TSH q6-12 mos if neck irradiated.
   - Monitoring EBV for nasopharyngeal cancer

Pharmacology:

A. Ceruximab:
   - FDA approved for recurrent and metastatic SCCHN refractory to platinum → improve OS