Oropharynx
Malignant Neoplasm

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- Epidemiology
- Etiology
- Anatomy
- Histopathology
- Clinical presentation
- Diagnosis --- serology
- Imaging studies
- Staging
- Treatment
- Persistent / recurrent disease Rx (Re-irradiation)
Epidemiology

- Relatively uncommon
- Fewer than 1% of all new cancers
- Comprises 10-12% of head and neck malignancies
- Squamous cell carcinoma (SCCA) accounts for 90% of oropharyngeal malignancies
- Peak incidence in 6th or 7th decades of life
Etiology

- Genetic alterations
- Environmental factors
- Exposure to viruses
- Immune status (post SCT, HIV, transplantation)
- Dietary factors such as vitamin deficiency (Vitamin A)
- Poor oral hygiene
- Occupational exposure
- Previous irradiation
Alcohol & tobacco consumption

- Heavy tobacco users:
  - 5- to 25-fold higher risk of developing H&N CA than nonsmokers.

- Effect is dose related
  - The RR increases from (2.7) 10 cigarettes/day to (9) 1 pack per day.

- Concurrent exposure is synergetic
  - >40-pack-year + 5 alcoholic drinks per day → RR : 40

- HPV associated tumors in smokers with a greater than 10-packyear history & smoking have a worse prognosis than nonsmokers
Genetic factors

P53

- It is a tumor suppressors gene in human cancer.

- **Function**: P53 inhibits survival and proliferation and is an effector of DNA damage response.

- HPV(-) HNSCC inactivate p53 through mutation.

![Diagram](image)
Genetic factors
Retinoblastoma (Rb)

- It is a tumor suppressor in human cancer.

- **Function**: major regulator of cell cycle and proliferation.

- **HPV(−) HNSCC**: 
  - loss of CDKN2A (p16) or amplification of CCND1 (cyclin D1).

- **HPV(+) HNSCC**: 
  - inactivate Rb through expression of the viral oncoprotein E7.
Genetic factors
(Epidermal growth factor receptor) EGFR

- It is a tyrosine kinase receptor (TK).

- EGFR family members include HER2 that is amplified in a small percentage of HNSCC (3%).

- **Function**: Signaling through EGFR promotes survival and proliferation (over expression)
Genetic factors

P 16

- Aka: cyclin-dependent kinase inhibitor 2A, multiple tumor suppressor 1

- HPV(+)HNSCC
  - over expression of P 16 (surrogate Tissue marker biopsy from oropharynx).
    - 100% sensitive, 80% specific
## Epidemiology

<table>
<thead>
<tr>
<th>HPV negative SCC</th>
<th>HPV positive SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7th decades</td>
<td>4-5th decades</td>
</tr>
<tr>
<td>Male predominant</td>
<td>M=F</td>
</tr>
<tr>
<td>Alcohol &amp; tobacco exposure</td>
<td>Exposure to HPV</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>Poorly differentiated (Tonsil &amp; BOT)</td>
</tr>
<tr>
<td>Advanced T stage</td>
<td>Lower T stage</td>
</tr>
<tr>
<td>Less risk of LN involvement</td>
<td>Greater risk of LN involvement (Cystic)</td>
</tr>
<tr>
<td></td>
<td>Good response to Rx</td>
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<tr>
<td></td>
<td>Deescalating therapy</td>
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<tr>
<td></td>
<td>Better prognosis &amp; survival</td>
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</tbody>
</table>
Human papilloma virus

- DNA virus from the papilloma virus family
- Establish productive infections only in keratinocytes of the mucus membrane & skin
- Most HPV infections are subclinical.
- Subclinical infections will become clinical:
  - Benign lesions (such as RRP), squamous papilloma
  - Premalignant lesions
  - CA (45-70%) of oropharyngeal SCCA (Cohen 2011)
Human papilloma virus

Retrospective review of oropharyngeal SCCA (Ang 2010)
- HPV-positive in 206 out of 323 with stage III or IV disease (63.8%):
  - Improved 3-year overall survival (82.4% vs. 57.1%)
  - Improved 3-year progression-free survival (73.7% vs. 43.4%)
  - HPV-positive conveys 58% reduction in death
- One-percent increase in death or relapse for each pack-year of smoking regardless of HPV status

HPV-positivity is favorable prognostic factor (Ihloff 2010)
- Meta-analysis of 8 studies between 2000 and 2010
- HPV-positive tumors generally respond well to treatment

Advanced primary associated with recurrence and death (Sedaghat 2009).
Anatomy

- **Extension**: an imaginary horizontal plane through the hard palate to the hyoid bone.

- **Boundaries**:
  - Anterior: circumvallate papillae, anterior tonsillar pillars, and the junction of the hard and soft palates.
  - Posterior: posterior pharyngeal wall
  - Lateral: tonsillar fossae and pillars and the lateral pharyngeal walls.
Anatomy subsites

- Palatine tonsillar fossa and pillars
  - Most common site of OP SCC
- Soft palate
- Pharyngeal walls
- Base of tongue
Surgical anatomy

- small tumors: difficult to identify
  - The irregular surfaces of the tongue base and the tonsils
- Referred otalgia associated with tumors of this area.
  - The CN IX & X
- The retropharyngeal and parapharyngeal spaces also serve as potential routes for cancer spread.
- Surgical margins may be difficult to achieve in some patients
  - oropharyngeal structures lack natural boundaries.
- Tumors that involve the palate or tonsillar pillar:
  - Invasion or encasement bone of the mandible or maxilla.
- Involvement of the muscles of mastication
  - results in pain and trismus.
- Base of tongue tumors may spread in all directions
  - larynx, palatine tonsil, or oral tongue.
field cancerization
(condemned mucosa)

- Chronic exposure to carcinogenic agents:
  - alterations of the normal squamous mucosa of the entire upper aerodigestive tract resulting in dysplastic epithelial changes.

- Slaughter, 1953
Anatomy histology

- non-keratinized stratified squamous epithelium
  - SCC
- Lymphoid tissue
  - Lymphoma
- Minor salivary gland
  - Adenoid cystic, mucoepidermoid CA
- Muscles
Anatomy
lymphatic drainage

- Levels II, III, and IV
  - most common

- Retropharyngeal LN.
  - Posterior pharyngeal wall
  - Palatine tonsil

- Bilateral drainage
Anatomy
distant Metastasis

- 2% to 5%
- Base of tongue at higher risk
- Control of the disease above the clavicles,
  - Incidence of overt distant metastasis increases
- Most common affected site: lung, liver, and bones.
Physiology

- Essential for speech production, respiration, and deglutition.
- Intact motor & sensory innervation is mandatory to initiate the functions.
- Important role in the first three phases of swallowing.
- Soft palate: prevent nasopharyngeal premature spillage.
- Tongue base (bulk): major driving force of the bolus.
Clinical presentation

- Pain
- Neck mass
- Dysphagia
- Otalgia
- Foreign body sensation
- Hemoptysis
- Weight loss
- Voice changes
Clinical presentation

- Fiber optic nasopharyngolaryngoscopy is mandatory.
- Palpation of the primary tumor is always performed in order to judge the extent of submucosal spread.
- Dentition is also assessed because restoration or extraction may be required before initiation of treatment.
- The remainder of the physical exam is performed with emphasis on the cardiopulmonary and nutritional status of the patient
Imaging studies

- Chest radiograph—if not evaluated by CT or PET/CT
- CT scan with contrast
  - Bony erosions
  - Lymph nodes involvement (cystic Mets → HPV positive OPSCC)
- MRI with contrast
  - Soft tissue involvement
- PET/CT:
  - Stages III and IV
  - Occult primary
  - Synchronous lesions
Diagnosis

- FNA (occult primary):
  - Cell block for IHC (P16, HBV DNA)

- Biopsy of primary lesion under LA.

- Pan endoscopy:
  - Trismus
  - Tenuous airway
  - Lesions that are not accessible trans orally
  - Submucosal spread
Staging

AJCC (7th ed, 2010)

- Primary tumor (T)
- T0: no evidence of carcinoma
- TX: carcinoma in-situ
- T1: < 2cm in greatest dimension
- T2: 2-4cm in greatest dimension
- T3: > 4cm in greatest dimension
- T4:
STAGING
primary (T)

T4a
- Hard palate & Mandible invasion

T4b
- Skull base & carotid A invasion
Staging
lymph nodes (N) & distant Mets

- **Nx**: lymph nodes cannot be evaluated
- **N0**: no evidence of nodal metastasis
- **N1**: single node involved, < 3cm
- **N2**
  - **N2a**: single node involved, 3-6cm
  - **N2b**: multiple nodes involved unilaterally, < 6cm
  - **N2c**: bilateral nodal involvement, < 6cm
- **N3**: > 6cm

- **Mx**: distant metastasis cannot be evaluated
- **M0**: no distant metastasis
- **M1**: distant metastasis present
### Staging

<table>
<thead>
<tr>
<th>NO</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>I</td>
<td>III</td>
<td>IVA</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>III</td>
<td>IVA</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>III</td>
<td>IVA</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
</tr>
</tbody>
</table>

### 5 Years survival

- Stage I: **56.0%**
- Stage II: **58.3%**
- Stage III: **55.4%**
- Stage IV: **43.4%**
Management

- Multidisciplinary team approach (Oncologist, radiation oncologist, surgeon, maxillofacial)
- Dental evaluation
- Swallowing & speech assessment
- Status of nutrition & feeding
- Audiological assessment
- Psychosocial consultation
- Smoking cessation programs
Management

- Primary
- Neck
- Does management of HPV positive OP SCC differ from HPV negative ones?
- Prophylactic HPV vaccination
Management

Array of factors when deciding on the optimal treatment regimen for the individual patient:

- Treatment needed for the primary tumor and the neck
- The modality best suited for functional preservation or Restoration.
- General medical condition & patient’s preferences.
- Availability of facilities, expertise, and social support also play a role.
Management

T1, T2, N0 & N1

- Single modality (Surgery vs Radiation therapy).

T3, T4 & N>1

- Multimodality treatment (chemoradiation or surgery and postoperative radiation+/- chemotherapy).

** Treatment based on primary **
Management
primary tumor : Radiation therapy

- Radiation is typically delivered using IMRT
- Dose of 60 to 70 Gy
- Organ preservation strategies
- Similar tumor control when compared to surgery
- Midline structures mandate bilateral lymph nodes treatment.
Management
primary tumor: surgery

Oral
- Transoral resection
- Mandibular lingual release

Transpharyngeal
- Suprahyoid pharyngotomy
- Lateral pharyngotomy

Transmandibular
- Midline labiomandibular glosstomy
- Mandibular swing
- Mandibulectomy
Management: primary tumor open procedures

- The major open procedures were developed during a time when surgery was the primary mode of therapy.
- Largely obsoleted as primary therapy:
  - Success of CRT
  - Minimally invasive transoral surgical approaches.
- Indication:
  - HPV negative OP SCC (ongoing trials)
  - Advanced cancer with bone involvement.
  - Salvage of CRT failures.
Management: primary tumor

Transoral approach

- Resection of the tumor through the open mouth with no external incisions.

- Advantages:
  - Quick and have minimal morbidity,

- Disadvantages:
  - Limited exposure.

- Indications:
  - Small (T1), superficial & exophytic.
  - Sites: Upper or anterior sites of the oropharynx,
Management: primary tumor
Transoral approach

- **Technics:**
  - Co2 laser
  - Cautery

- **Limitation:**
  - Trismus
  - Height of the mandible
  - Presence of teeth

- **Laccourreye and colleagues (Tonsil CA):**
  - 5-year local control rate of 82%.
  - T1: 89% (5-year local control)
  - T2: 63% (5-year local control)
Management: primary tumor

TORS

- Advantages:
  - Improved optics
  - Three-dimensional tumor visualization
  - Tremor filtration

- Pre requisite:
  - Teeth/mandible
  - Trismus, tongue
  - Size, and flexibility of the neck
  - Tumor extent
Management: primary tumor
Transoral approach

- The oncologic benefit for TORS is still unclear.
- Many patients in the studies, required postoperative radiation therapy or chemo radiation therapy.
- Considering the fact that many patients with oropharyngeal tumors are treated successfully with primary radiation with or without chemotherapy, the additional benefit of surgery is unknown.
Management: primary tumor Mandibular lingual release (pull through)

- Indication: BOT
- Visor flap is mandatory
- Advantages:
  - Excellent direct visualization
  - No need for lip-splitting & mandibuolotomy
- Disadvantages:
  - Less access to the lateral pharynx and Para pharyngeal spaces
Management: primary tumor supra hyoid pharyngotomy

- **Indication:**
  - Small tumors of the base of the tongue and pharyngeal walls

- **Advantages:**
  - Excellent functional and cosmetic outcome,

- **Disadvantages:**
  - Limitation in visualization of the superior margin.
  - Risk of cutting into cancer if there is extensive involvement of the tongue base or vallecula.
  - Risk of damage CNXII & lingual A
Management: primary tumor lateral pharyngotomy

- **Indication:**
  - Small tumors of the base of the tongue and pharyngeal walls
  - Pharyngeal entrance on least affected side.

- **Advantages:**
  - Superior exposure: via lateral mandibulotomy
  - Excellent functional and cosmetic outcome,

- **Disadvantages:**
  - Limited superior, Para pharyngeal, lateral OP visualization
  - Risk of damage inferior alveolar, superior laryngeal, & CNXII, lingual A
Management: primary tumor
Midline labiomandibular glosstomy

- **Indication:**
  - BOT, Posterior pharyngeal wall

- **Advantages:**
  - Bleeding and neurologic deficits are minimal

- **Disadvantages:**
  - Limited access to Para pharyngeal space or lateral oropharyngeal sites.
Management of primary tumor: mandibular swing

- Advantages:
  - wide exposure to the entire oropharynx, lateral Op wall & Para pharyngeal space.

- Disadvantages:
  - Inferior functional & cosmetic result.
  - Lower lip anesthesia.
  - Hemi mandibulectomy if mandible is involved.
  - Require free flap reconstruction.
Management of primary tumor
Mandibulectomy

- **Indication:**
  - Overt bony invasion.
  - Mandibular invasion cannot be ruled out

- **Disadvantages:**
  - Functional and cosmetic deficits
  - Require free reconstruction
## Postoperative radiation therapy

### Tumor factors

- Close margin
- Involved resection margins
  (+ chemotherapy)
- Perineural or vascular invasion
- T3
- T4

### Neck factors

- Clinically N0 or N1 neck
  - Two or more histologically positive nodes
  - Histologically positive nodes at multiple sites
  - Perineural or vascular invasion
  - Extracapsular nodal spread
    (+ chemotherapy)
- N2
- N3
Management of neck

- Risk of occult Mets:
  - Almost always 20-30% (T1 or more) all subsites.
- Observation is not an option in management.
- Midline primaries require bilateral neck treatment.
- Retropharyngeal LN must be included in the radiation field.
The threshold of 20% is based on a decision analysis performed by Weiss et al. published in 1994 that compared survival outcomes for patients managed by END versus OBS.
Management of neck
N0,N1

- Single modality (IMRT VS Neck dissection)
- N0 ➔ II-IV +/- retropharyngeal LN
- N1 ➔ I-V +/- retropharyngeal LN
- Preferences favoring IMRT (66-70 Gy)
  - Retropharyngeal LN is addressed in comparison to neck dissection
- On the other hand, Neck dissection has the added benefits:
  - Pathologic staging.
  - Allow single modality surgery to be used for small primaries
Management of neck N2, N3

- Requires multimodality treatment.
- PET/CT post completion of CRRT (8 -12 weeks)
  - Persistent disease: salvage neck dissection
  - Complete response: observation vs salvage neck dissection
Management
HPV positive OP SCC

- Given favorable prognosis as well as good response to therapy, deascleriation of the treatment might be an option.
  - Radiation therapy alone
  - Surgery with or without adjuvant radiotherapy,
  - Combinations of radiation with chemotherapy (Induction or concurrent)

- ECOG phase II (protocol E1308) (ongoing trial)
  - Induction chemotherapy
  - Complete responder \(\rightarrow\) reduce dose radiation with concurrent cetuximab.

- RTOG phase III trial (protocol 1016)
  - 70 Gy of radiation with concurrent cisplatin or with concurrent cetuximab
Targeted therapy

HPV

- Therapies directly target E6 and E7 oncoproteins:
  - Direct therapeutic effects
  - Improving the sensitivity of tumors to radiation and chemotherapy.

- Cetuximab: improved survival in addition to radiotherapy in HPV-positive tumors.

- RTOG 1016
  - Concurrent cetuximab shows the same efficacy as concurrent cisplatin in enhancing the radiosensitivity HPV-associated oropharyngeal cancers.
HPV vaccine

- FDA-approved vaccine is presently available.
- HPV4 (Gardasil™), produced by Merck, provides protection against oncogenic HPV types 16 and 18.
- Large clinical trials have demonstrated that these vaccines are effective in preventing type-specific HPV-related premalignant lesions and cancers in women.
- The CDC recently recommended routine HPV vaccination of boys age 11 to 12 and for boys/men aged 13 to 21 who have not been previously vaccinated.
Prognosis

- TNM classification
- Location of the tumor
- Gender
- Age
- Performance status
- Impact of smoking and HPV/ p16 tumoral positivity on OPC oncologic and functional outcomes has evolved remarkably.
- Shoushtari et al.
  - P16 & EGFR, for OPC could provide prognostic information
Prognosis

Age

- Meta-analysis has shown that the effectiveness of chemo-RT and altered RT fractionation decreases with increasing age.
- Patient >70 years,
  - No difference in survival CRRT over RT alone.
- Michal et al. (>70 yrs. patient population)
  - Two cycles of concomitant cisplatin with RT.
  - Greater myelosuppression and required more supportive care.
  - Elderly patients (≥70) may not benefit from concomitant chemotherapy.
Prognosis

Chan and McBride et al.

- Active smoking during & after RT is predictive of
  - Decreased DSS, OS, PFS and DMFS
- Anemia around the time of RT
  - Higher rates of persistent/recurrent disease,
  - Correction may improve outcome
Prognosis

- A recent SEER analysis showed that the overall 5- and 10-year OS were approximately two times better for those patients with HPV-positive disease regardless of the treatment modality.
- This advantage disappears in the HIV-positive population and heavy smokers.
Prognosis
Soft palate SCC

- Loco regional control
  - Stage I-II = 75%-90%
  - Stage III = 75%
  - Stage IV = 35%

- 5-year overall survival:
  - Stage I-II = 70%-80%
  - Stage III = 64%
  - Stage IV = 20%-40%
Prognosis
Tonsil SCC

- Locoregional control:
  - Stage I-II = 75%-90%
  - Stage III = 50%
  - Stage IV = 20%

- 5-year overall survival:
  - Stage I-II = 80%
  - Stage III = 50%
  - Stage IV = 20%-50%
Prognosis
BOT SCC

- Locoregional control:
  - Stage I-II = 75%-90%
  - Stage III = 50%
  - Stage IV = 20%

- 5-year overall survival:
  - Stage I-II = 85%
  - Stage III-IV = 20%-50%
Post therapy follow up

<table>
<thead>
<tr>
<th>visit</th>
<th>Duration post treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1-3 months</td>
</tr>
<tr>
<td>2nd</td>
<td>2-4 months</td>
</tr>
<tr>
<td>3rd</td>
<td>3-6 months</td>
</tr>
<tr>
<td>4th &amp; 5th</td>
<td>4-6 months</td>
</tr>
<tr>
<td>After 5th</td>
<td>Every 12 months</td>
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- Clinical examination including flexible endoscopy
- TSH (6-12 months)
- Stage: T3,T4 imaging (PET/CT), 6 months after therapy completion
- Chest imaging as clinically indicated (smoking Hx)
- Speech, hearing, swallowing evaluation as indicated
- Dental rehabilitation
Conclusion

- The complete visualization and palpation of the tumor under general anesthesia greatly facilitate the assessment of submucosal spread, invasion of surrounding structures and identification of second primary tumors.

- Treatment of OPC SCC is complex, and a team including a head and neck surgeon, reconstructive surgeon, radiation oncologist, medical oncologist, prosthodontist, speech and language pathologist.

- Patients with early-stage cancer die of unrelated diseases or second primary tumors,

- Advanced disease die of loco regional recurrence or distal metastasis.
Conclusion

- HPV 16 is an independent risk factor for oropharyngeal carcinoma.
- HPV-positive tumors respond better to treatment and appear to have a survival benefit.
- Studies needed to investigate impact of HPV vaccinations
- Prognosis for OPC depends upon the location of the primary tumor and the stage at presentation
- Oropharyngeal cancer patients require close observation initially to detect recurrences and lifelong follow-up afterward to identify second primary tumors.
Case

- 45 years old male
- Cc : Left neck mass
- Approach & management ?
Case

- PET: SUV max: 7 @ BOT, left level II, III neck & no distant Mets.
- What is next step in management?
- Pan endoscopy
- Bilateral tonsillectomy
- Lingual tonsillectomy
BOT : SCC well differentiated.

What is extra information from pathology?

If primary tumor measure 3 cm, largest lymph node measure 2.5 cm, what is the stage & overall stage?
T1N2bM0 BOT, STAGE III

What is the proper treatment
- CRRT
- Bilateral ND, TOLS or TORS + Post op XRT
- Left neck dissection & XRT to base of tongue.
THANK YOU