Oropharynx Malignant Neoplasm

MOHAMMED ALESSA MBBS , FRCSC
ASSISTANT PROFESSOR , CONSULTANT
OTOLARYNGOLOGY, HEAD & NECK SURGRY
KING SAUD UNIVERSITY

- 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

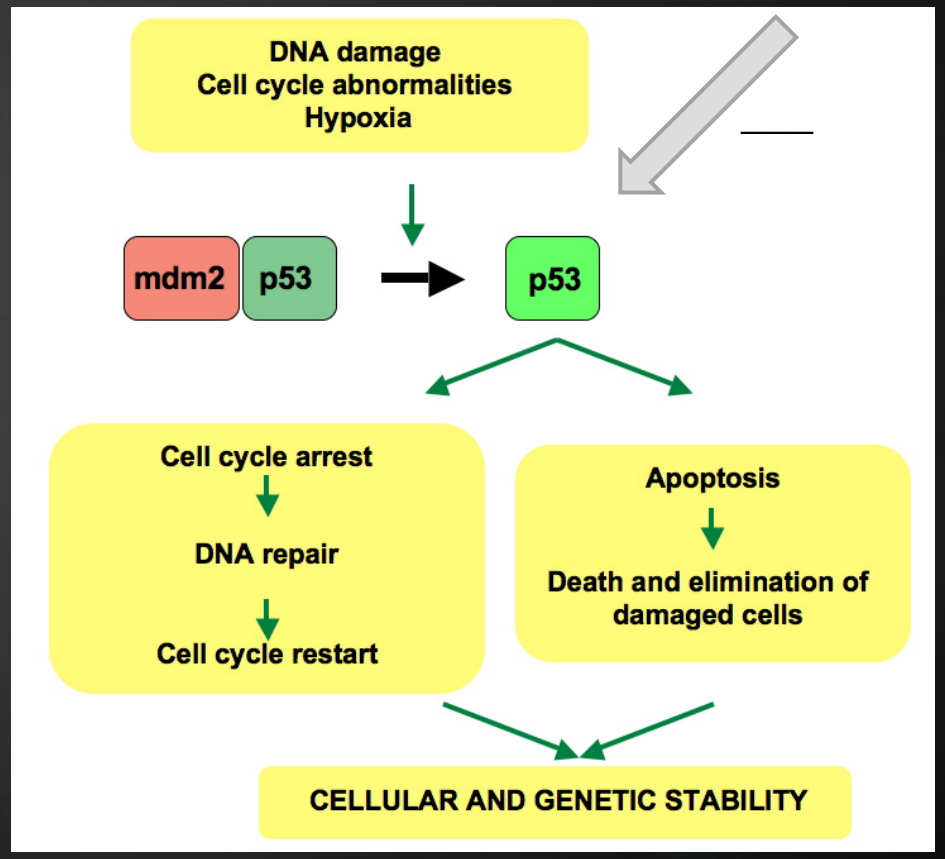
- Genetic alterations
- Environmental factors
- Exposure to viruses
- Immune status (post SCT , HIV , transplantation)
- Dietary factors such as vitamin deficiency (Vitamin A)
- Poor oral hygiene
- Occupational exposure
- Previous irradiation

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.



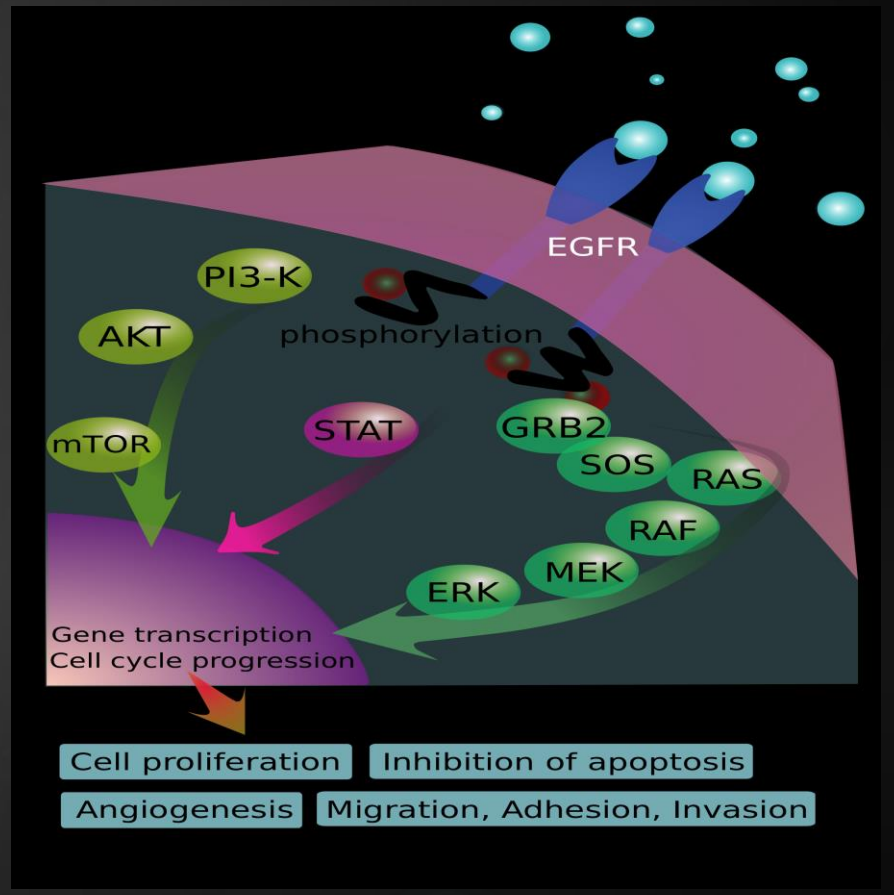
Genetic factors
Retinoblastoma (Rb)

- 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 vial 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

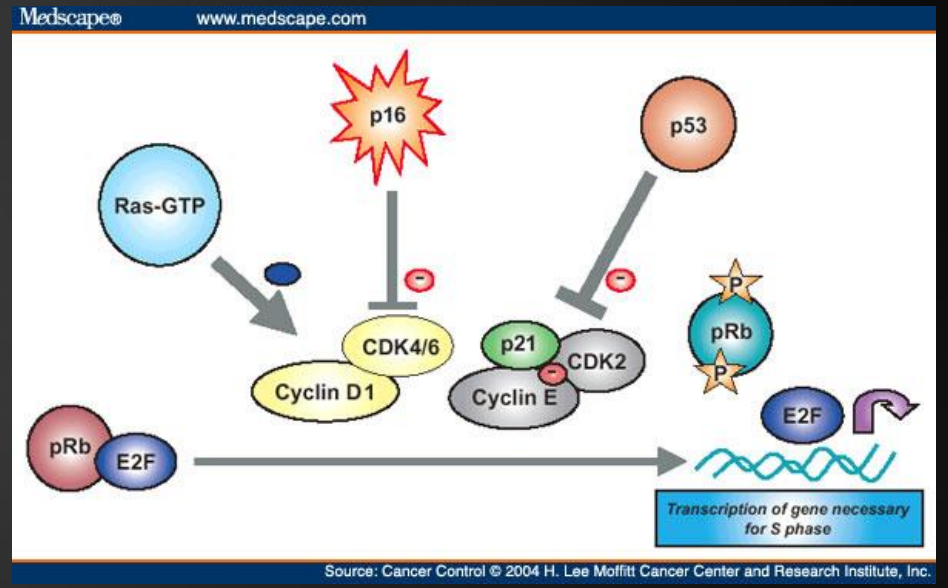
(over expression)



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

HPV negative SCC

- 6-7th decades
- Male predominant
- Alcohol & tobacco exposure
- Well differentiated
- Advanced T stage
- Less risk of LN involvement

HPV positive SCC

- 4-5th decades
- M=F
- Exposure to HPV
- Poorly differentiated (Tonsil & BOT)
- Lower T stage
- Greater risk of LN involvement (Cystic)
- Good response to Rx
- Deescalating therapy
- Better prognosis & survival

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 papllioma
  - 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

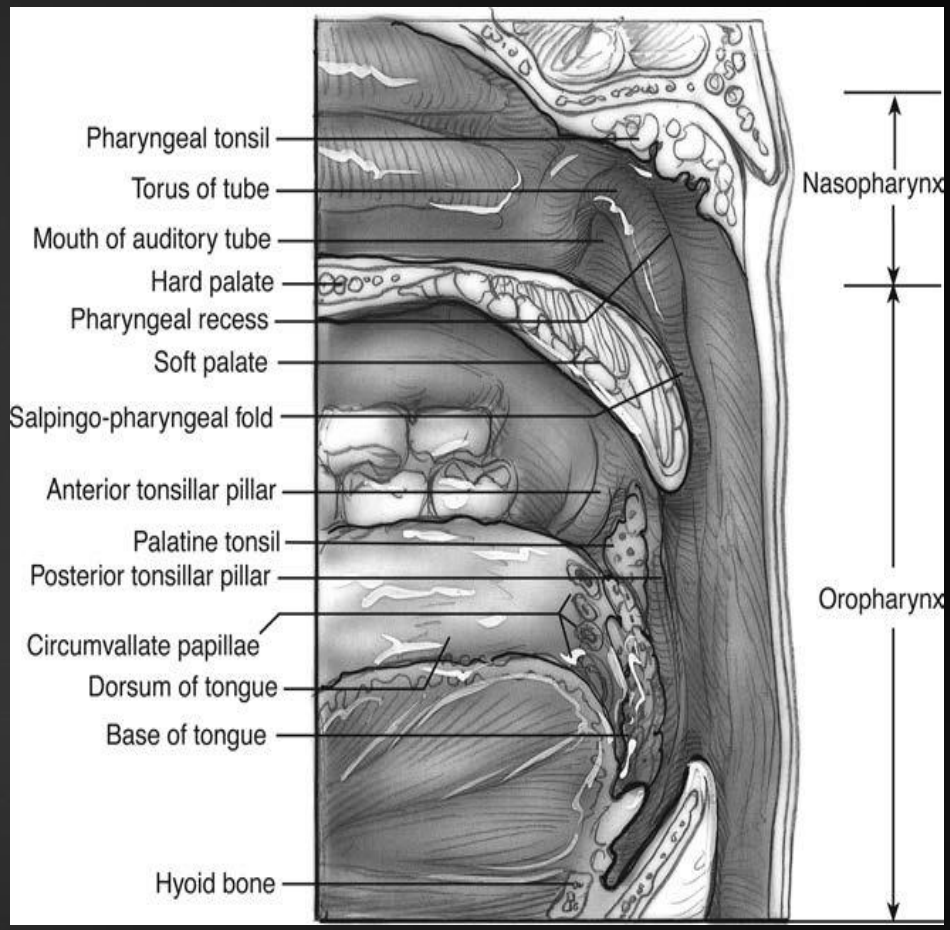
HPV-positivity is favorable prognostic factor (Ihloff 2010)

- 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).

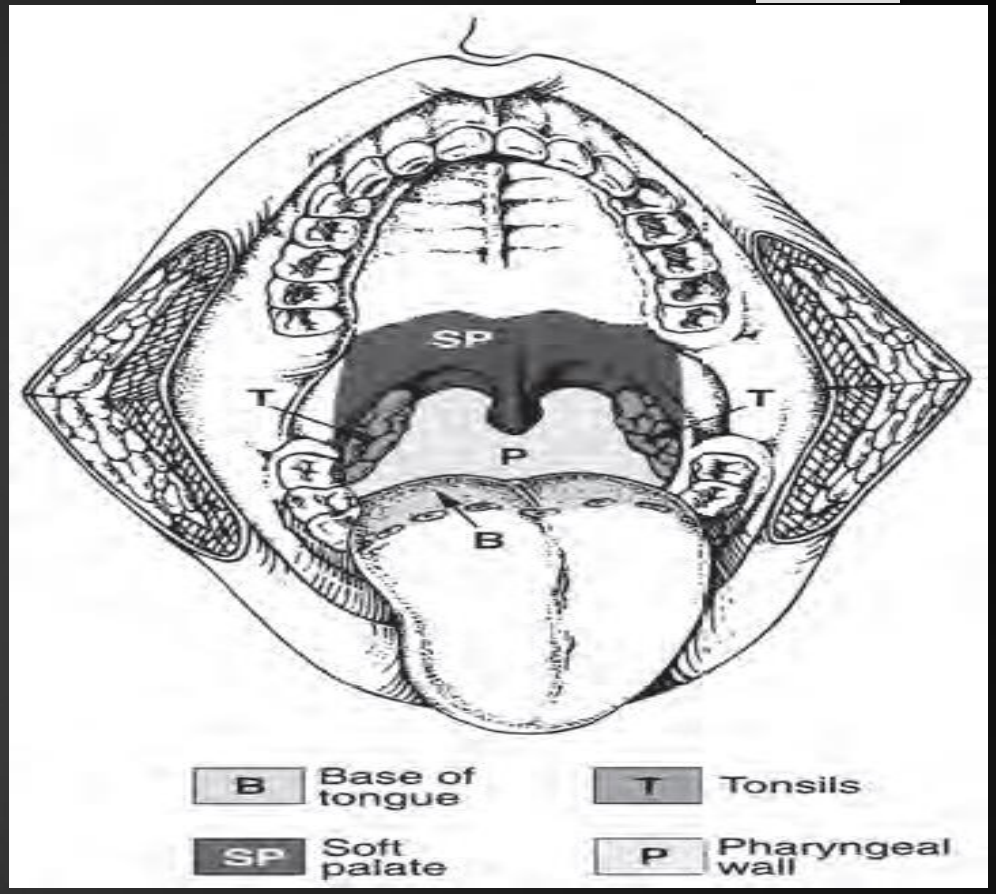
Anatomy

- **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



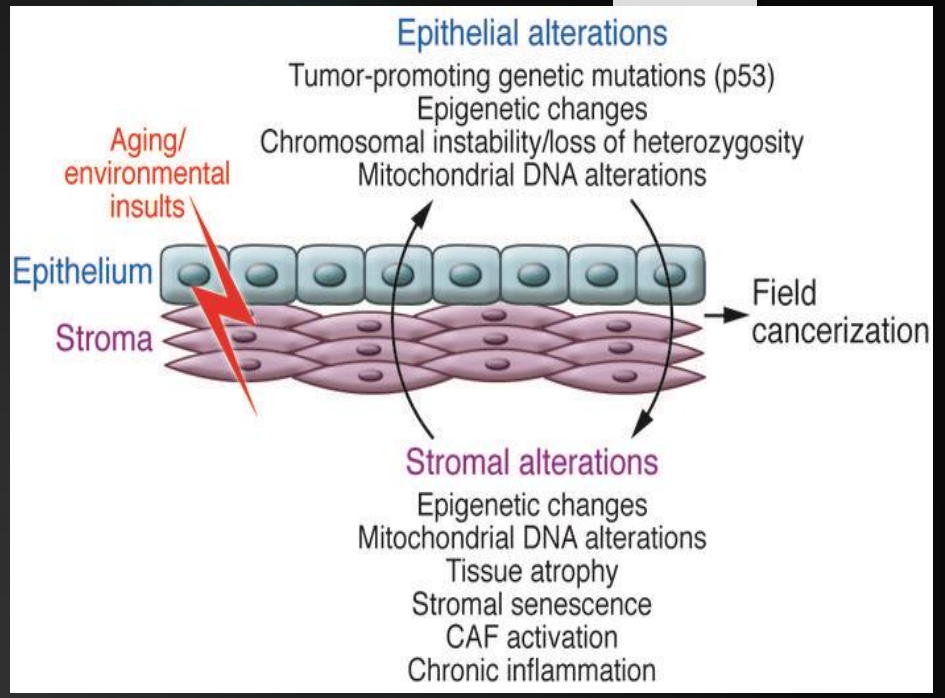
Surgical anatomy

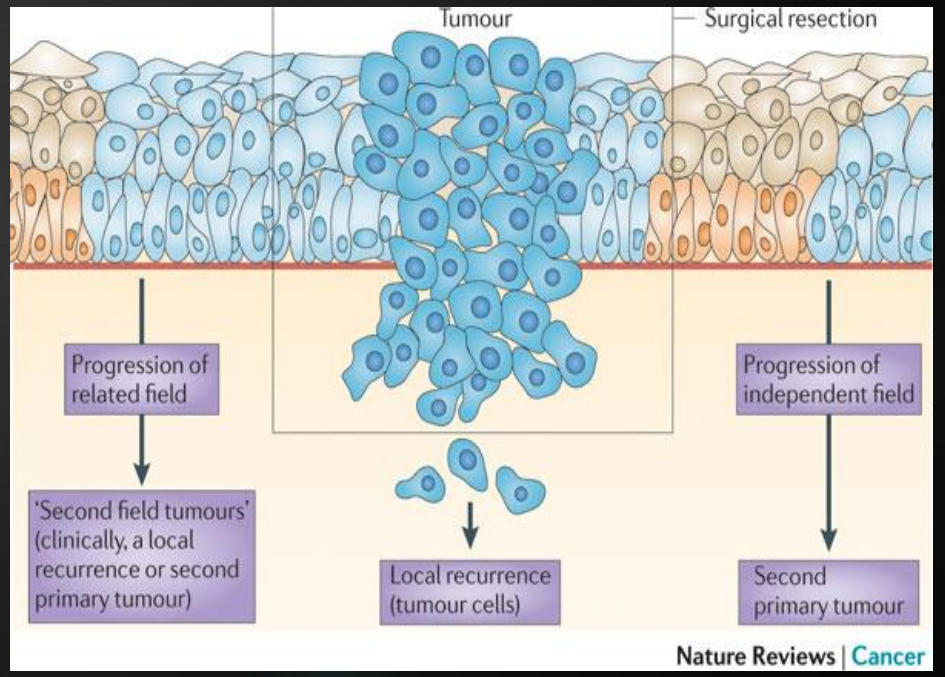
- small tumors : difficult to identify
  - The irregular surfaces of the tongue base and the tonsils
- Referred otalgia associated with tumors of this area.
  - The CN IX & X
- The retropharyngeal and parapharyngeal spaces also serve as potential routes for cancer spread.
- Surgical margins may be difficult 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.

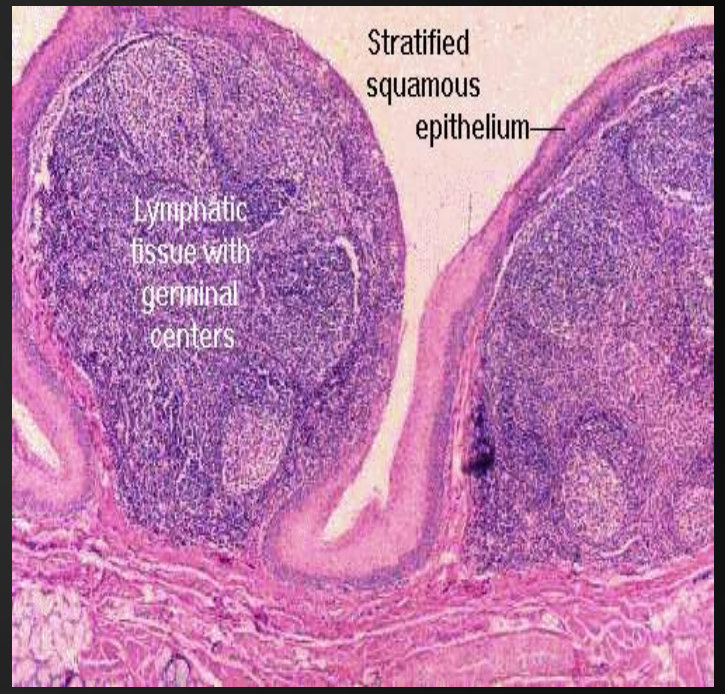
- **Slaughter , 1953**





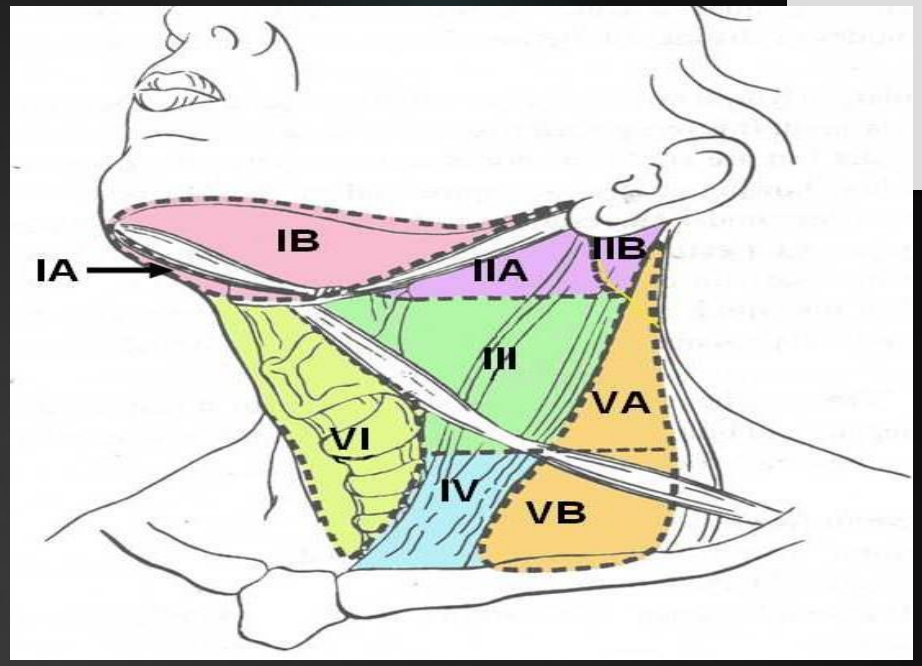
Anatomy histology

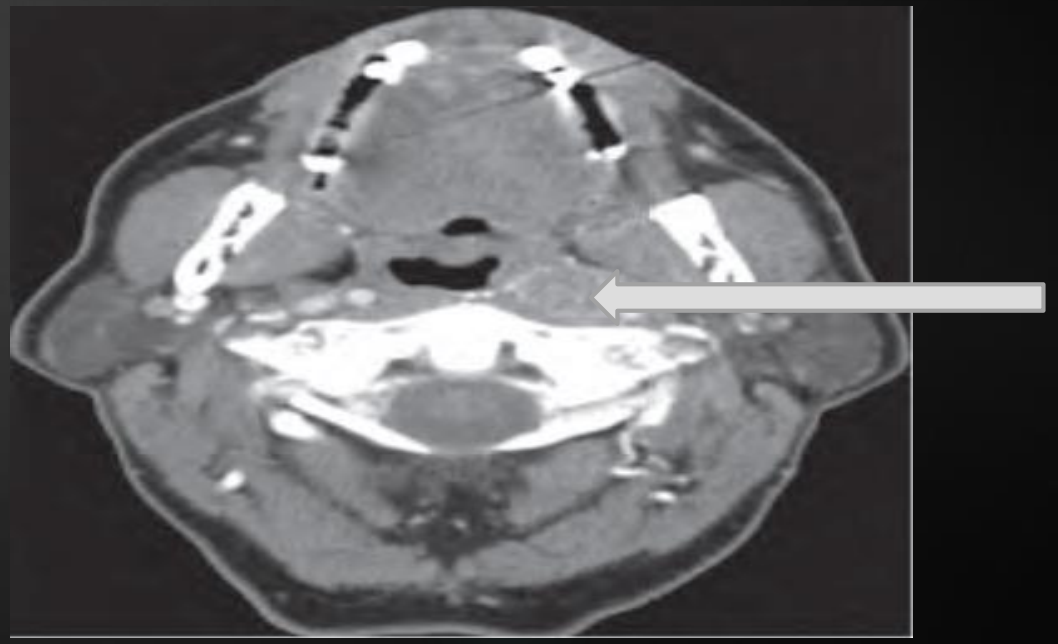
- non-keratinized stratified squamous epithelium
  - SCC
- Lymphoid tissue
  - Lymphoma
- Minor salivary gland
  - Adenoid cystic , mucoepidermoid CA
- Muscles



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)

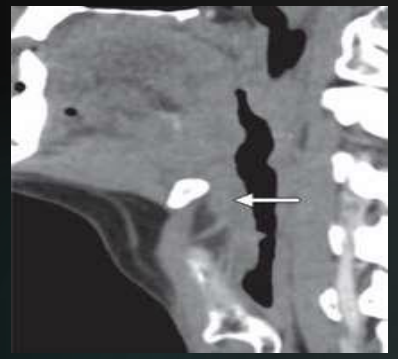
- Biopsy of primary lesion under LA .
- Pan endoscopy :
  - Trismus
  - Tenuous airway
  - Lesions that are not accessible trans orally
  - submucosal spread

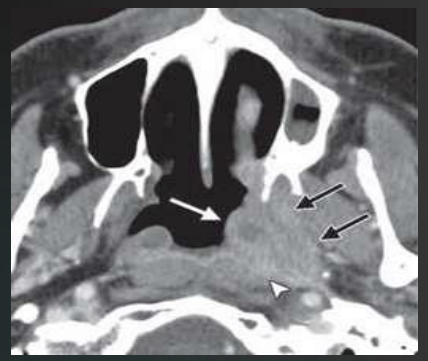
Staging
AJCC (7th ed , 2010)

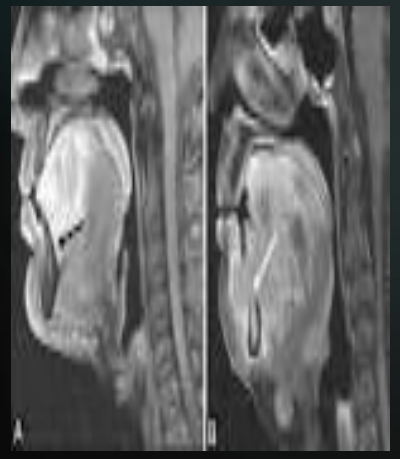
- Primary tumor (T)
- T0 : no evidence of carcinoma
- TX : carcinoma in-situ
- T1: < 2cm in greatest dimension
- T2 : 2-4cm in greatest dimension
- T3: > 4cm in greatest dimension
- T4:

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

	NO	N1	N2	N3
T1	I	III	IVA	IVB
T2	II	III	IVA	IVB
T3	III	III	IVA	IVB
T4	IVA	IVA	IVA	IVB

5 Years survival

- Stage I 56.0%
- Stage II 58.3%
- Stage III 55.4%
- Stage IV 43.4%

Management

- Multidiscblinary 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

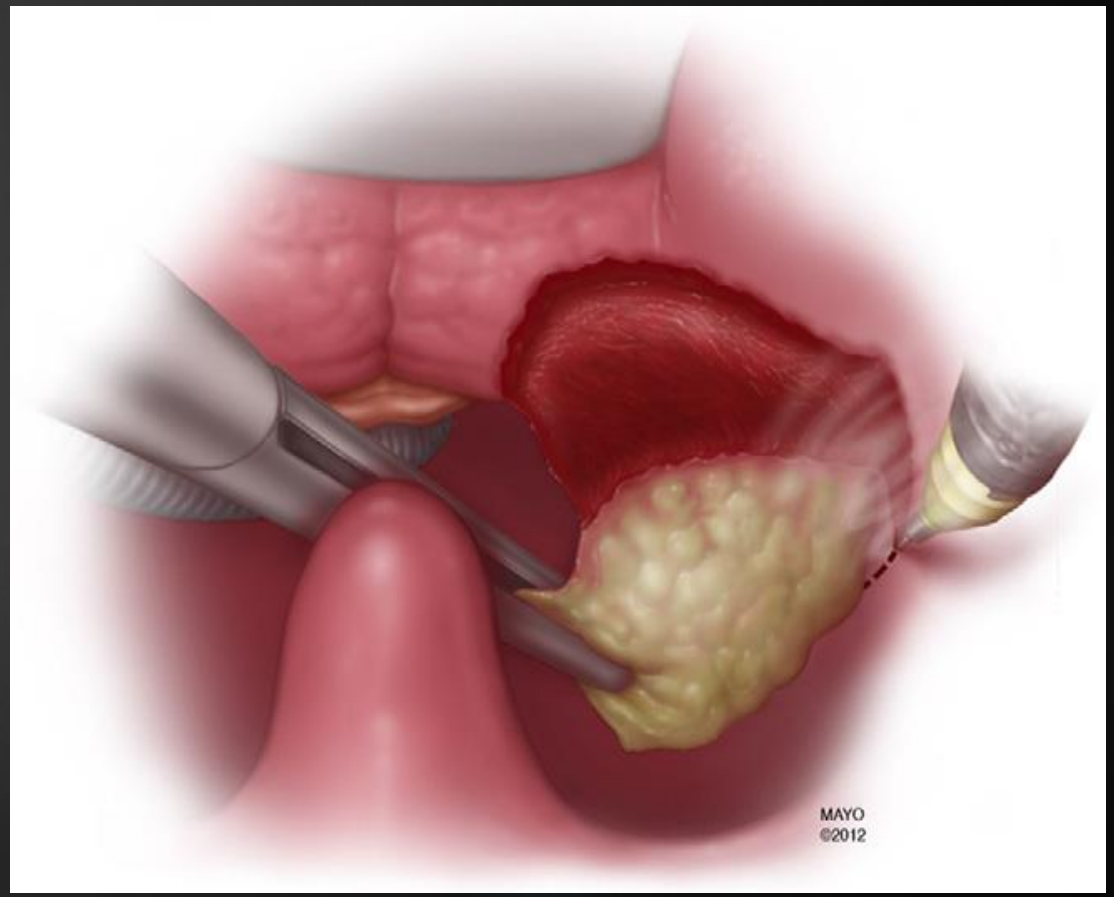
- The major open procedures were developed during a time when surgery was the primary mode of therapy.
- Largely obsoleted as primary therapy :
  - Success of CRT
  - Minimally invasive transoral surgical approaches.
- Indication :
  - HPV negative OP SCC (ongoing trials)
  - Advanced cancer with bone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

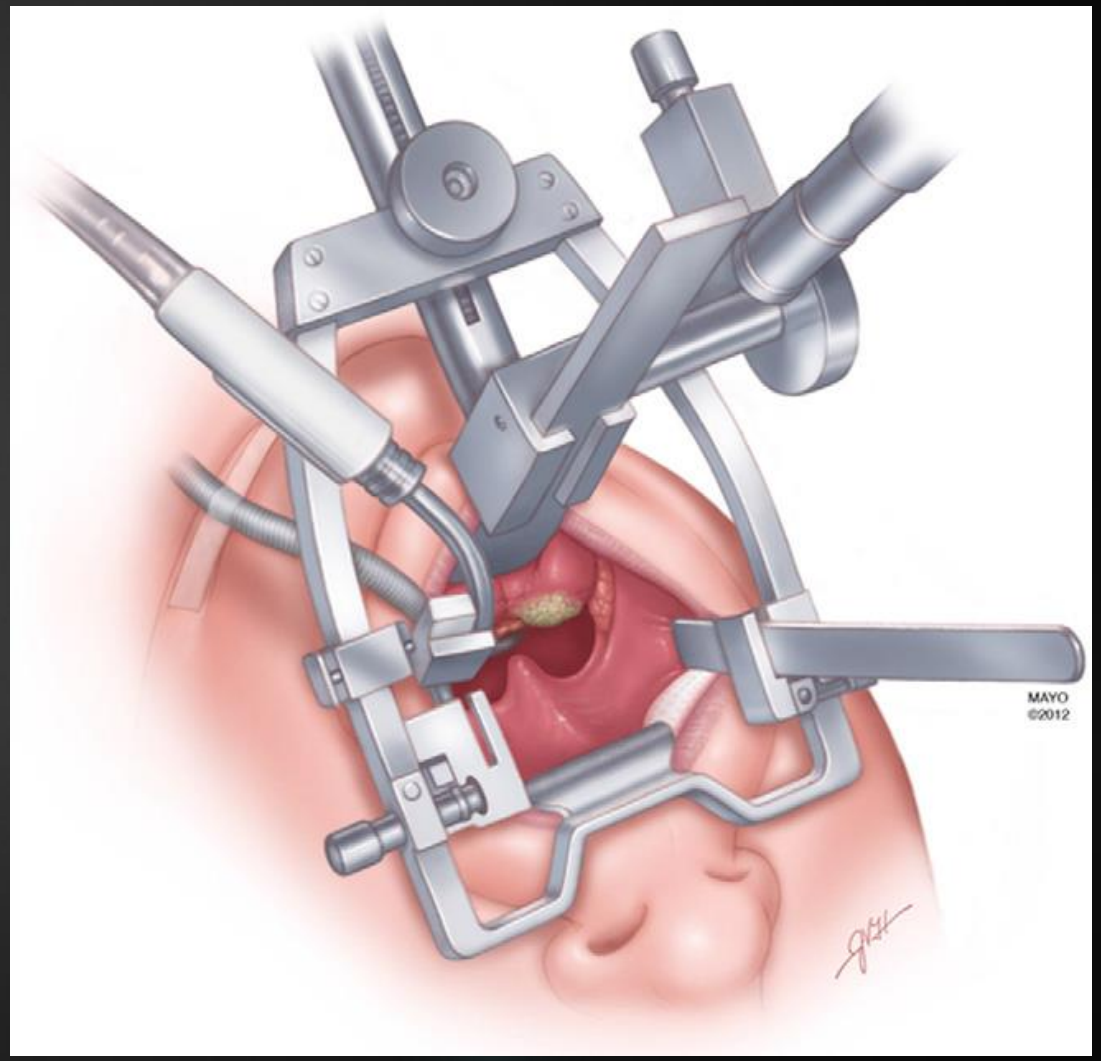
Management : primary tumor
Transoral approach

- 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

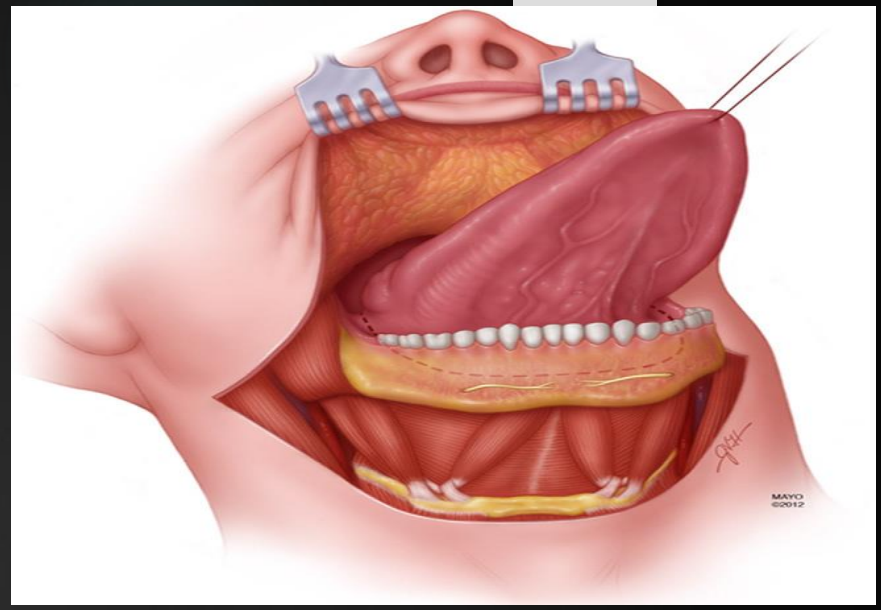


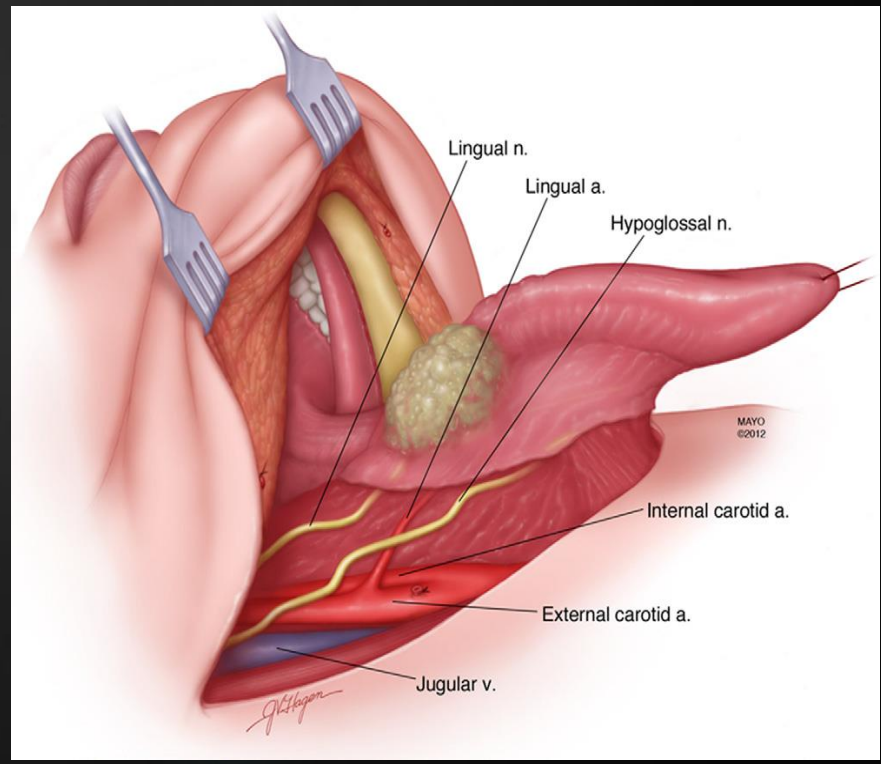
Management : primary tumor Transoral approach

- 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)

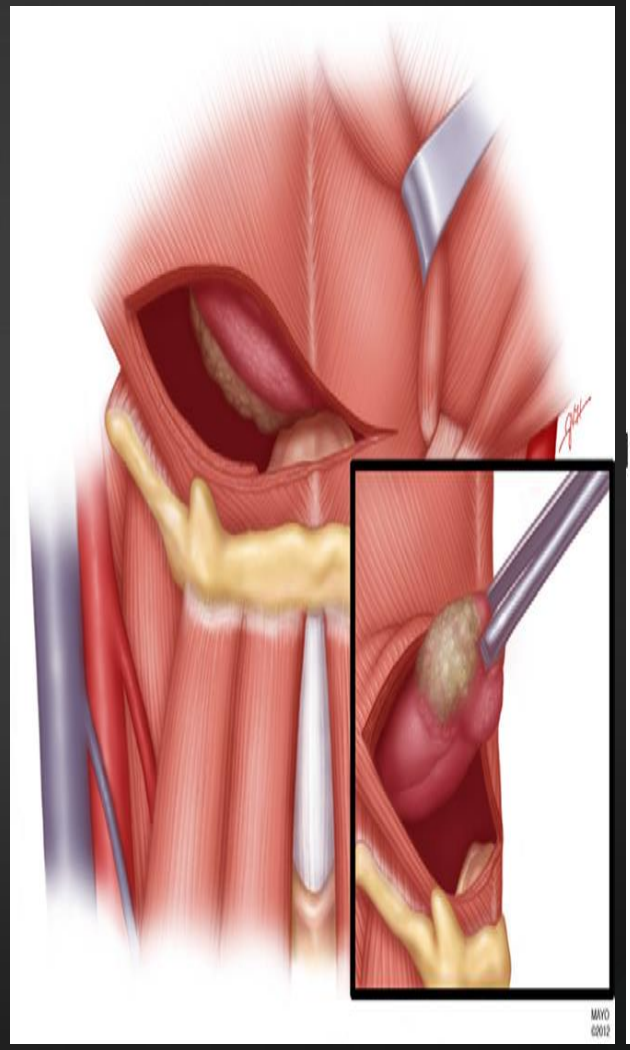
- Indication : BOT
- visor flap is mandatory
- Advantages :
  - Excellent direct visualization
  - No need for lip-splitting & mandibuolotomy
- Disadvantages :
  - Less access to the lateral pharynx and Para pharyngeal spaces

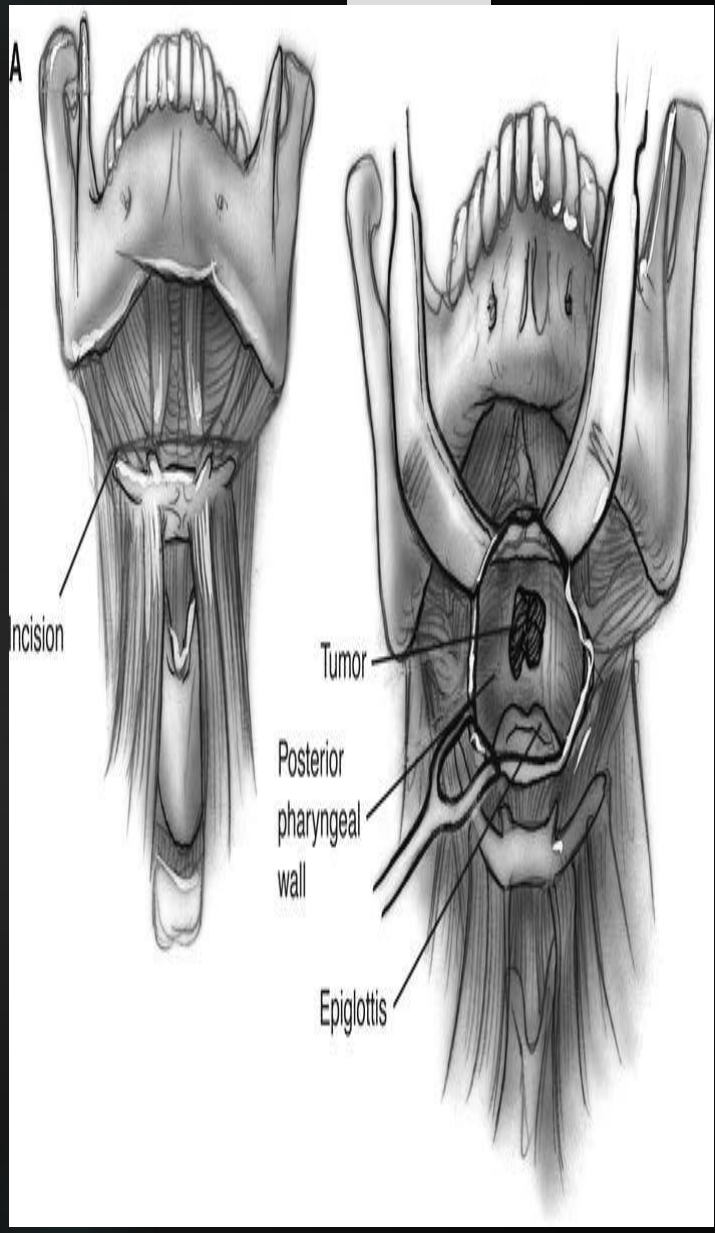




Management : primary tumor supra hyoid pharyngotomy

- 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

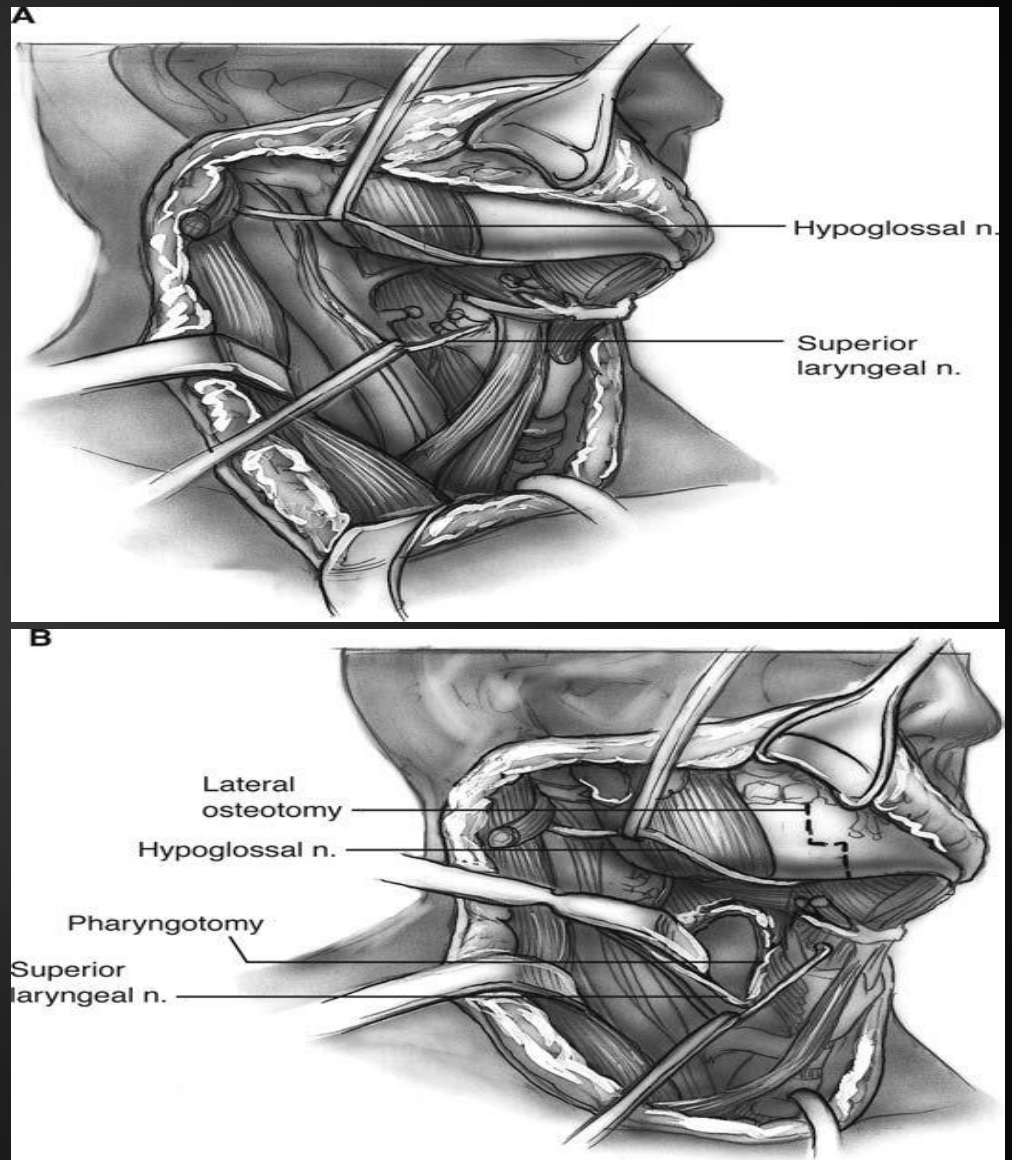




Management : primary tumor lateral pharyngotomy

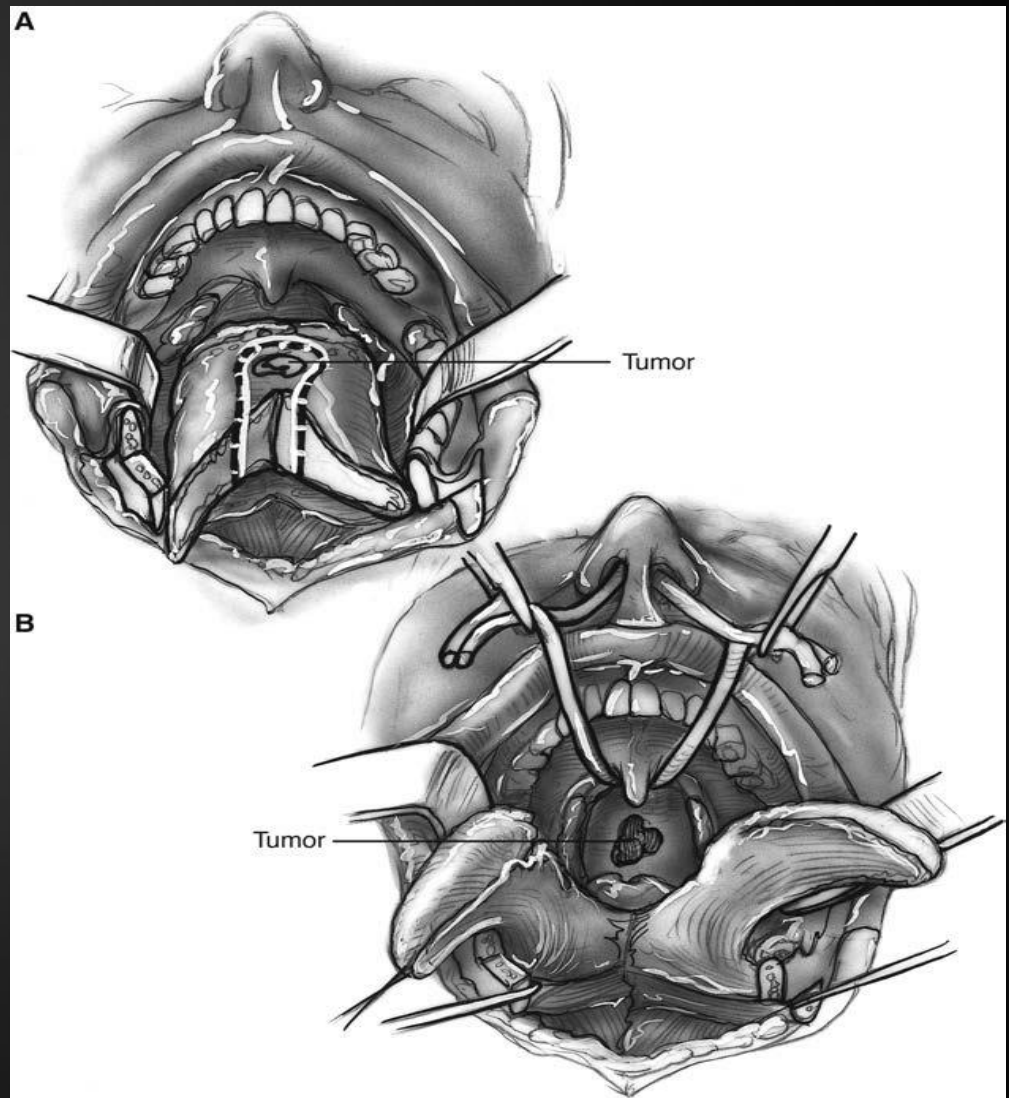
- Indication :
  - Small tumors of the base of the tongue and pharyngeal walls
- Pharyngeal entrance on least affected side .
- Advantages :
  - Superior exposure : via lateral mandibulotomy
  - Excellent functional and cosmetic outcome,
- Disadvantages :
  - Limited superior , Para pharyngeal , lateral OP visualization
  - Risk of damage inferior alveolar , superior laryngeal ,

  & CNXII , lingual A



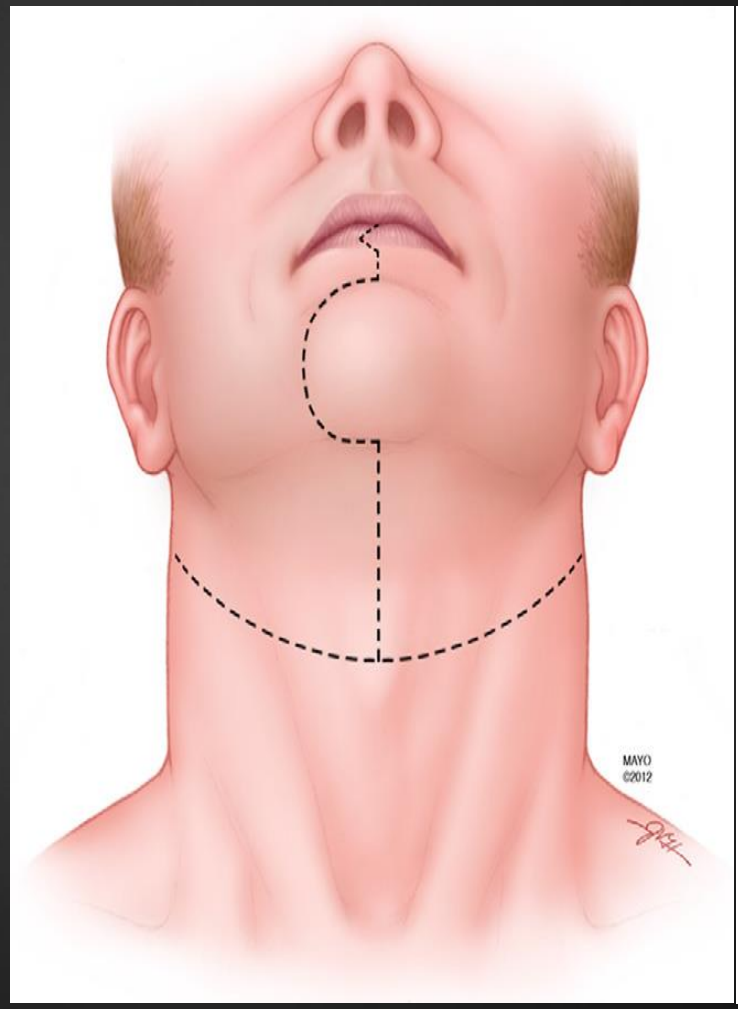
Management : primary tumor
Midline labiomandibular glosstomy

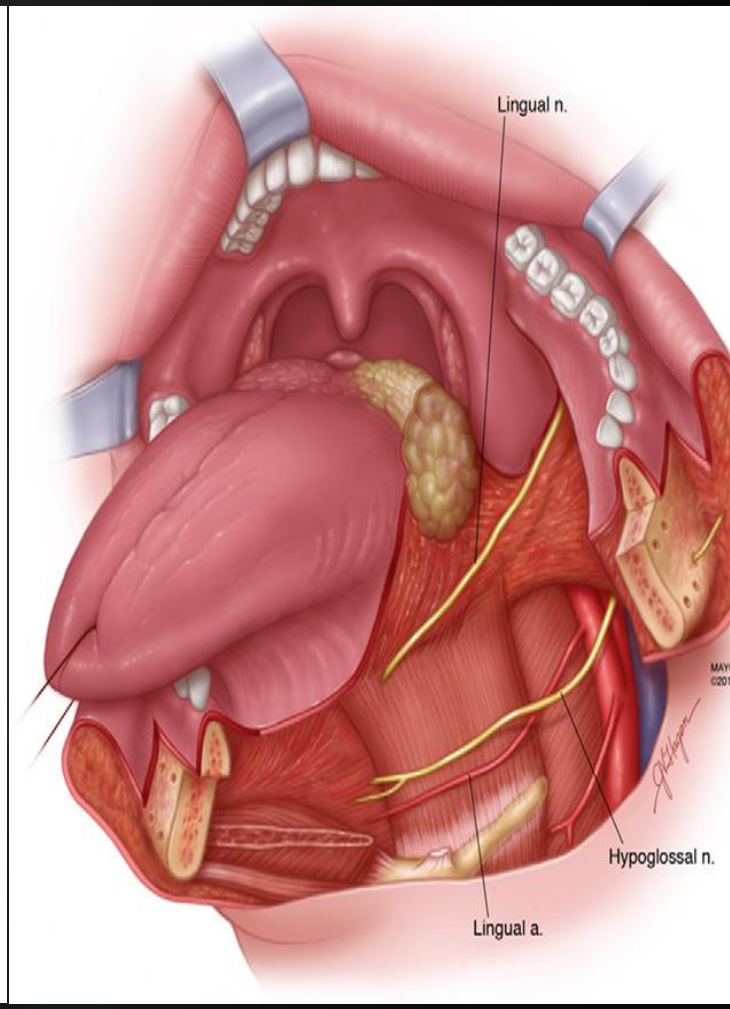
- Indication :
  - BOT , Posterior pharyngeal wall
- Advantages :
  - Bleeding and neurologic deficits are minimal
- Disadvantages :
  - Limited access to Para pharyngeal space or lateral oropharyngeal sites.



Management of primary tumor : mandibular swing

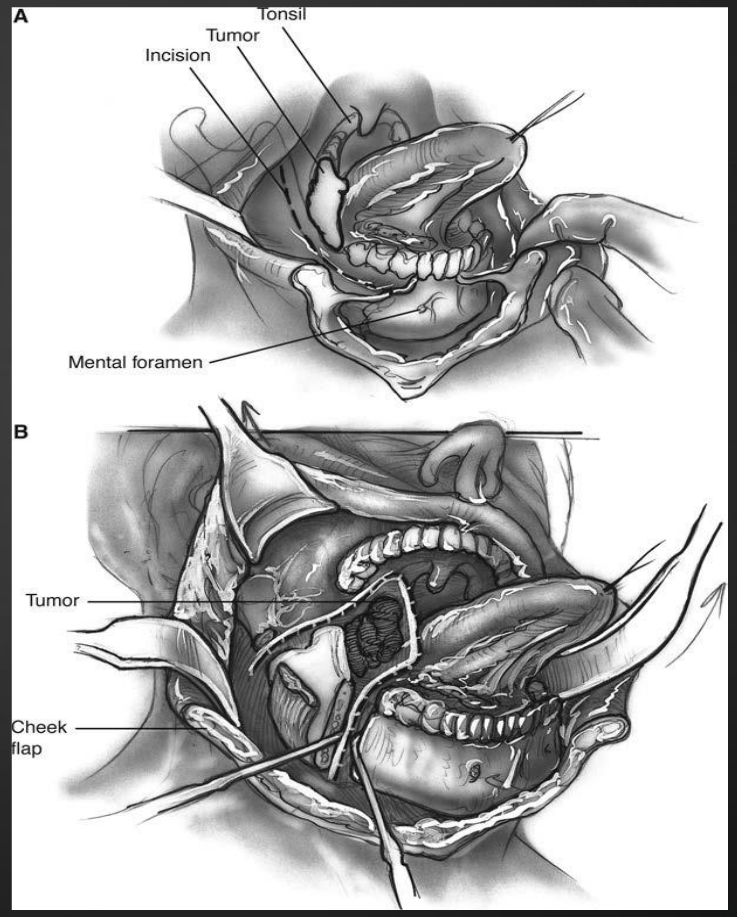
- Advantages :
  - wide exposure to the entire oropharynx , lateral Op wall & Para pharyngeal space .
- Disadvantages :
  - Inferior functional & cosmetic result .
  - Lower lip anesthesia .
  - Hemi mandibulectomy if mandible is involved.
  - Require free flap reconstruction.

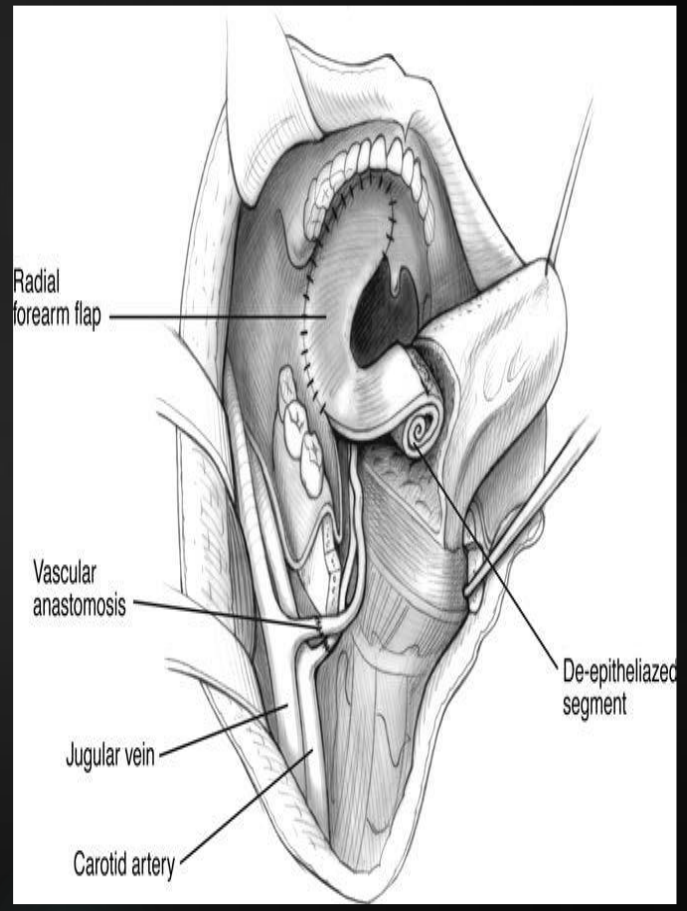




Management of primary tumor Mandibulectomy

- 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 .
- Method of Treatment : dictated by primary treatment .

Management of neck
No

- 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 , deascleation 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 ⟹ 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

visit	Duration post treatment
1st	1-3 months
2nd	2-4 months
3rd	3-6 months
4th& 5th	4- 6 months
After 5th	Every 12 months

- 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

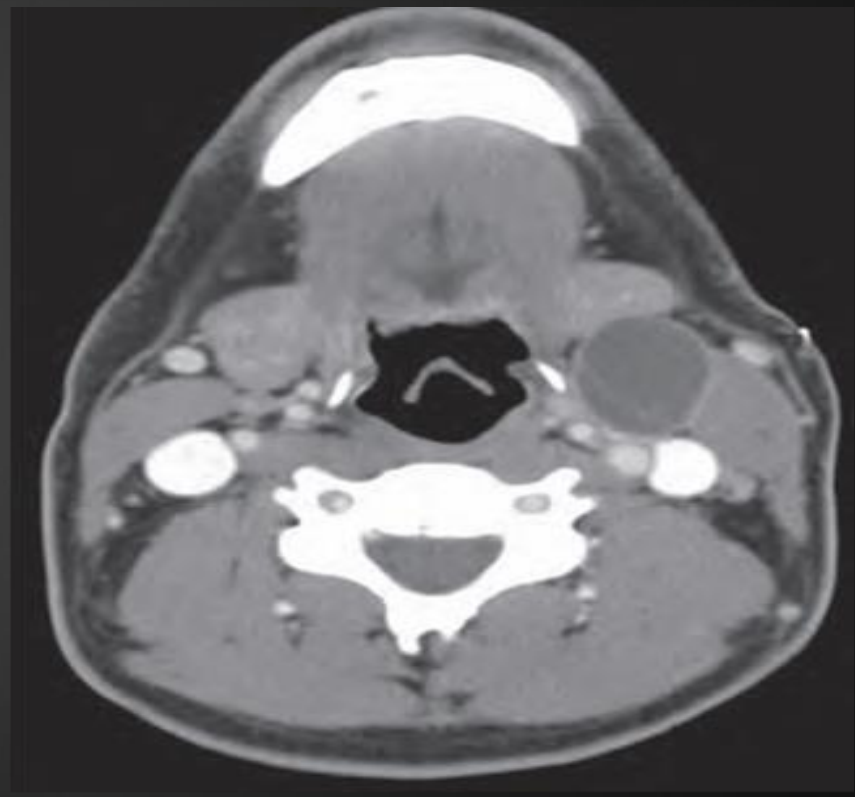
- The complete visualization and palpation of the tumor under general anesthesia greatly facilitate the assessment of submucosal spread, invasion of surrounding structures and identification of second primary tumors.
- Treatment of OPC SCC is complex, and a team including a head and neck surgeon, reconstructive 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.

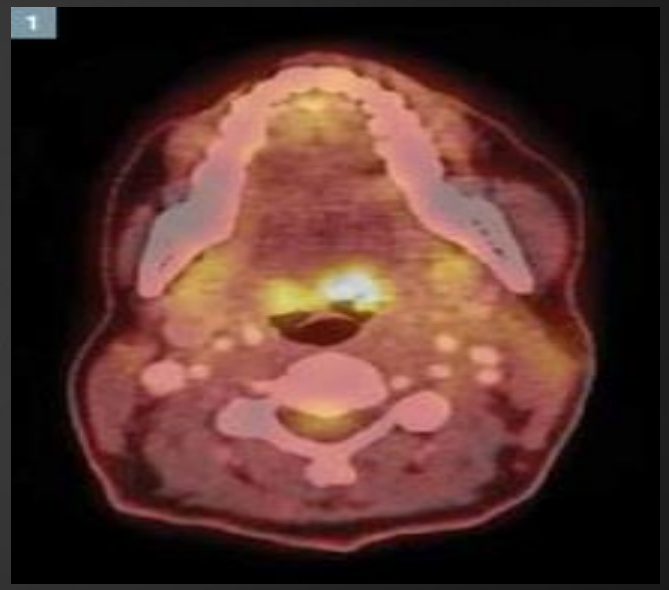
Case

- 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