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

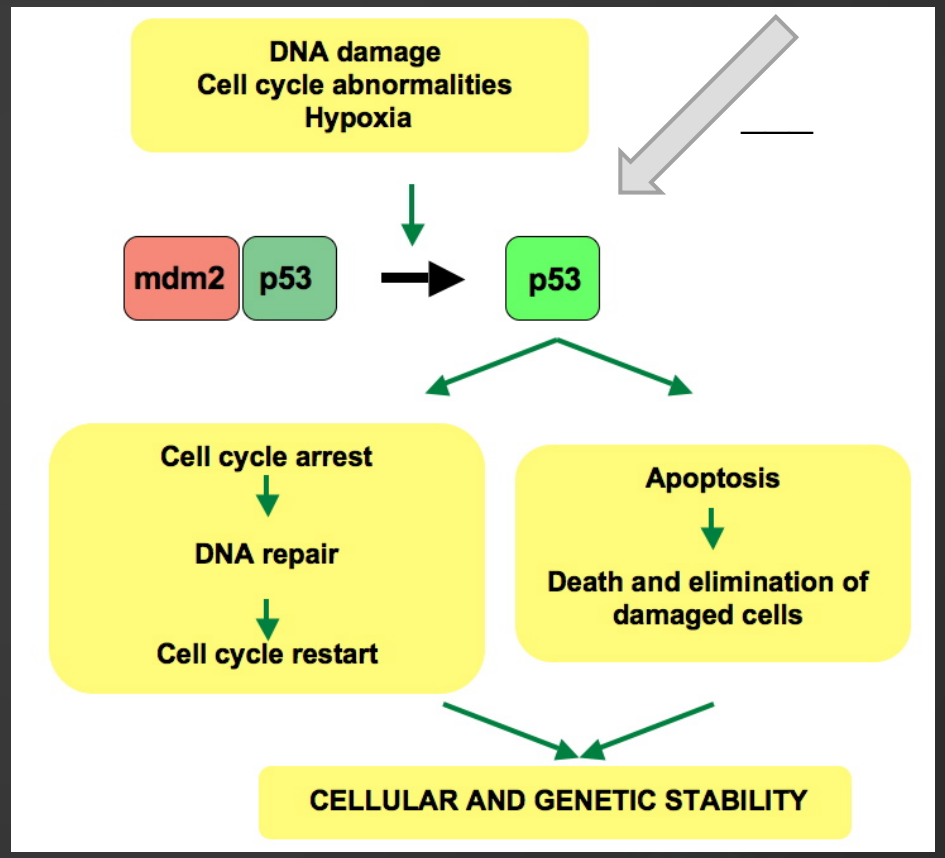
- Genetic alterations
- Environmental factors
- Exposure to viruses
- Immune status (post SCT , HIV , transplantation)
- Dietary factors such as vitamin deficiency (Vitamin A)
- Poor oral hygiene
- Occupational exposure
- Previous irradiation

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.



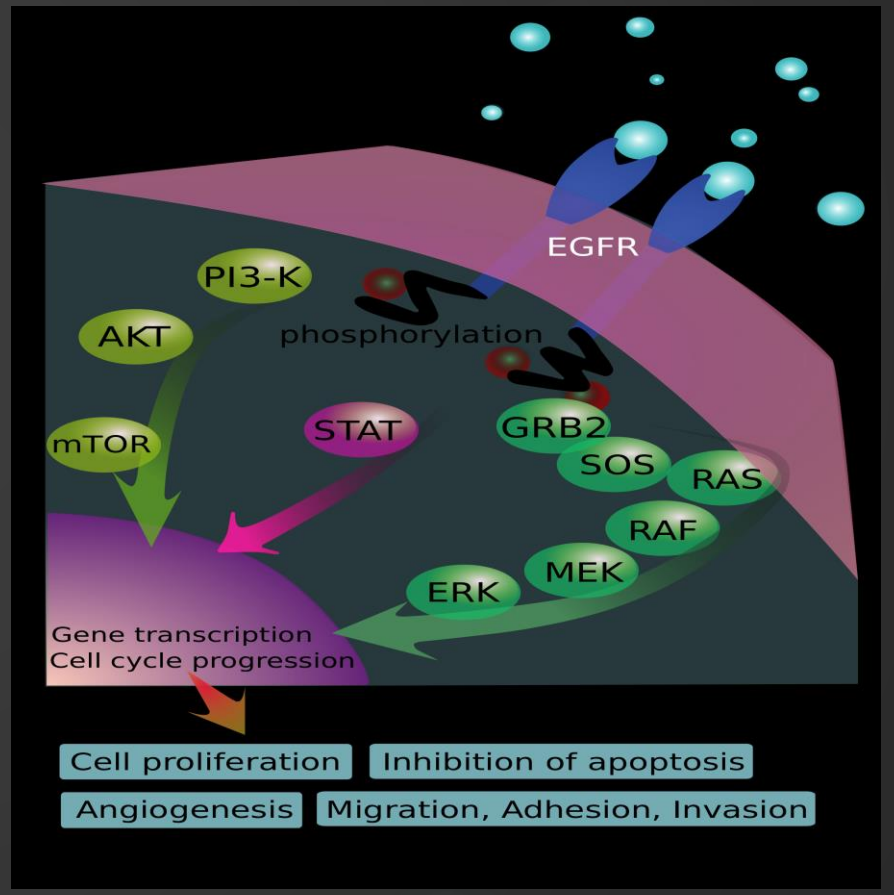
Genetic factors
Retinoblastoma (Rb)

- 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

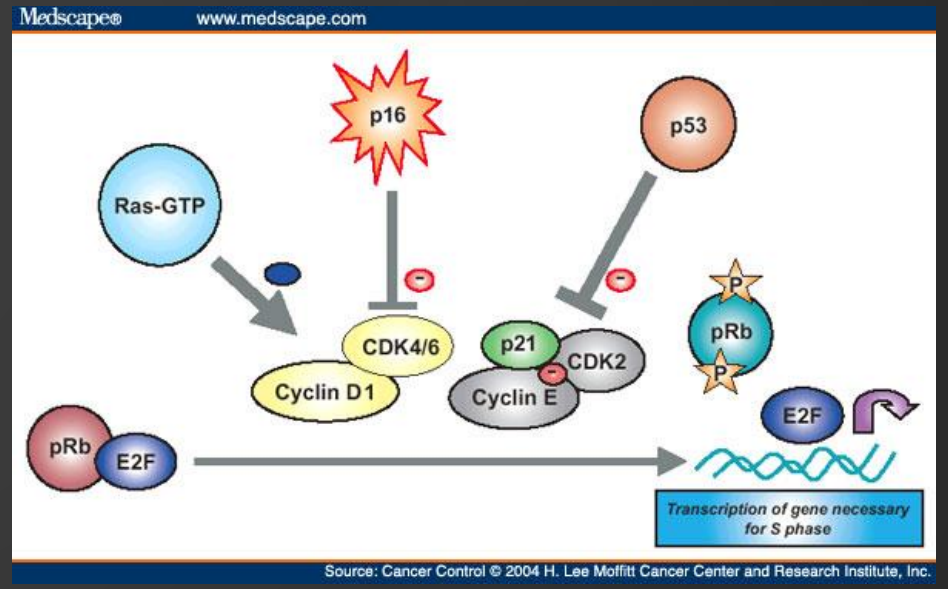
(over expression)



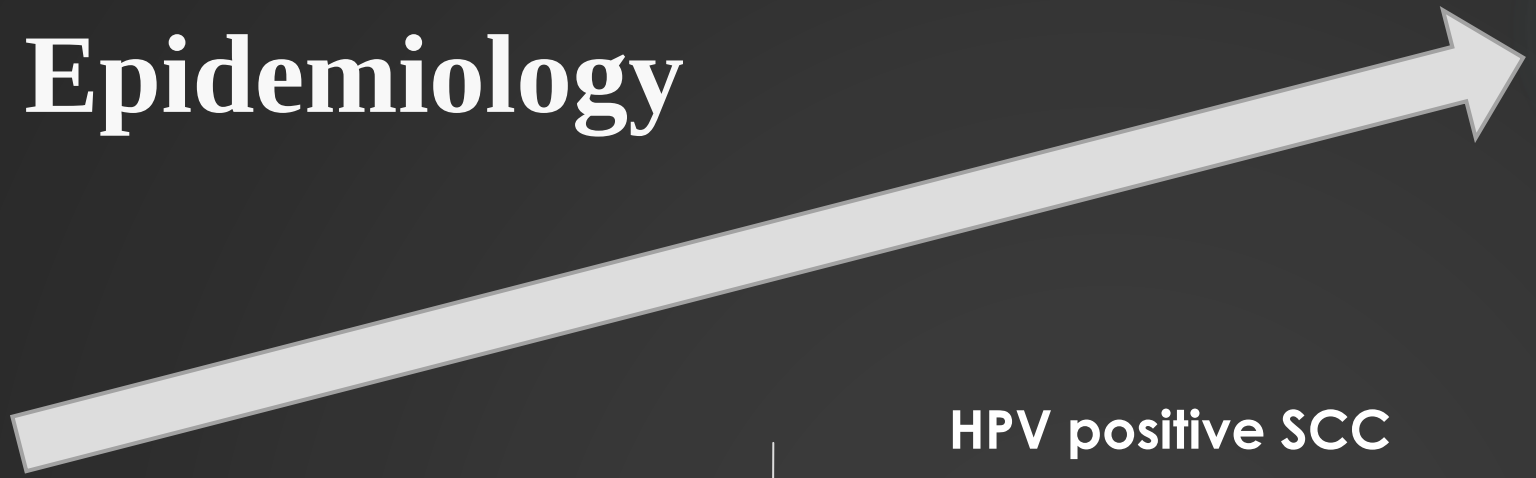
Genetic factors
P 16

- 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

poor socioeconomic

Male predominant

Alcohol & tobacco exposure

Well differentiated

Advanced T stage

Less risk of LN involvement

HPV positive SCC

4-5th decades

M=F

Healthier

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

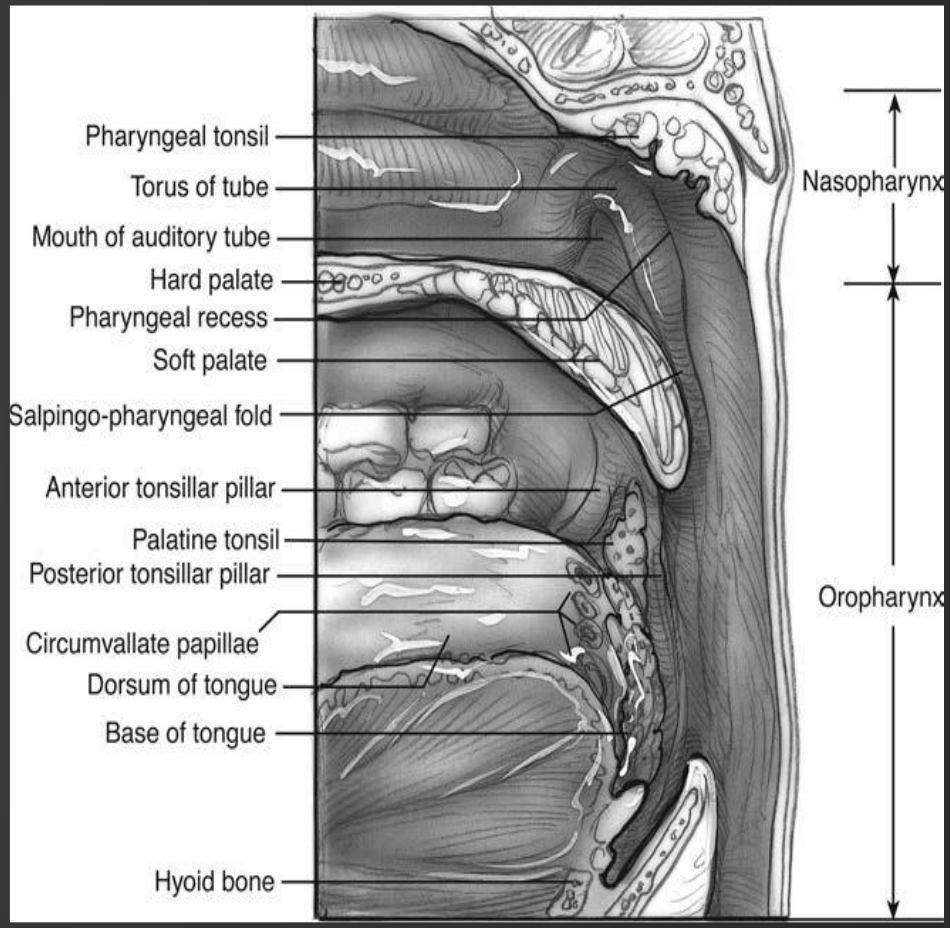
HPV-positivity is favorable prognostic factor (Ihloff 2010)

- 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).

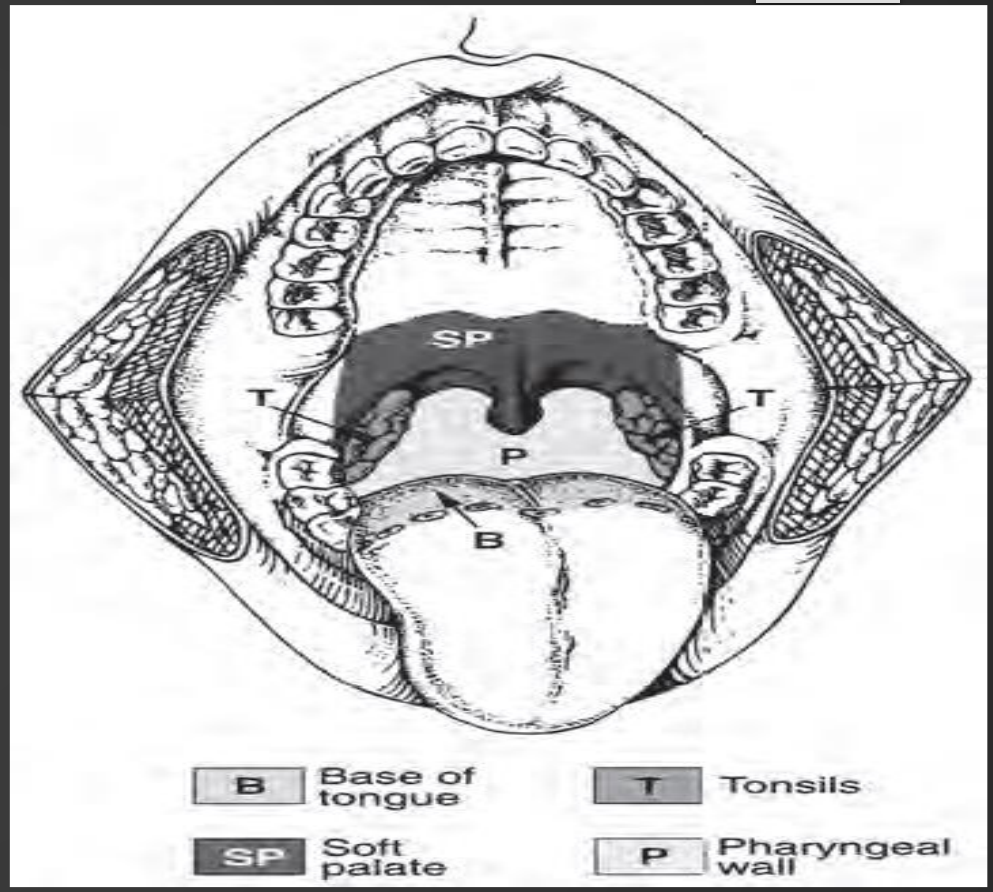
Anatomy

- **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



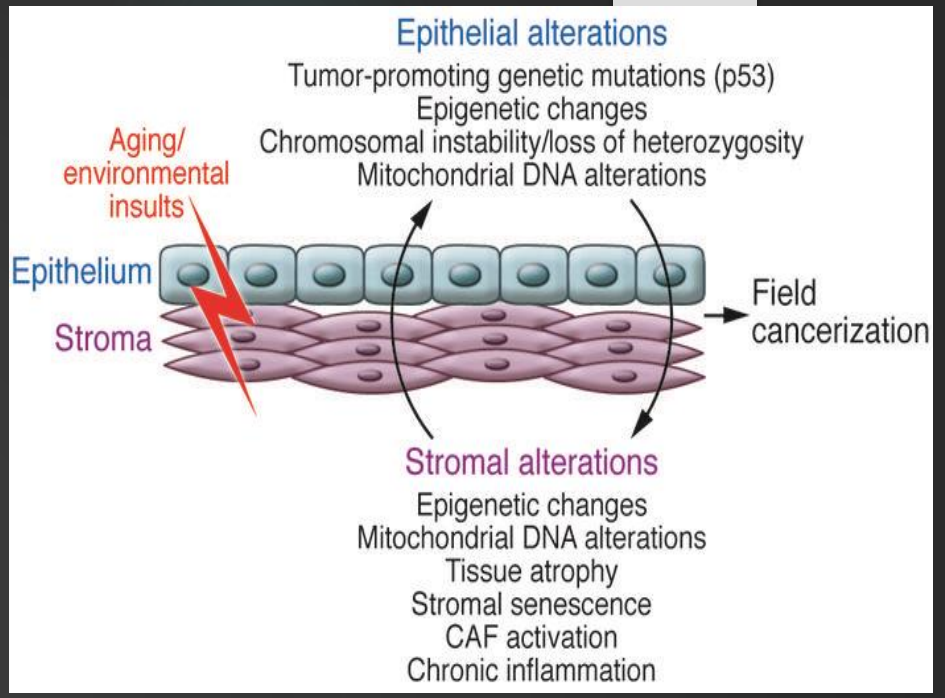
Surgical anatomy

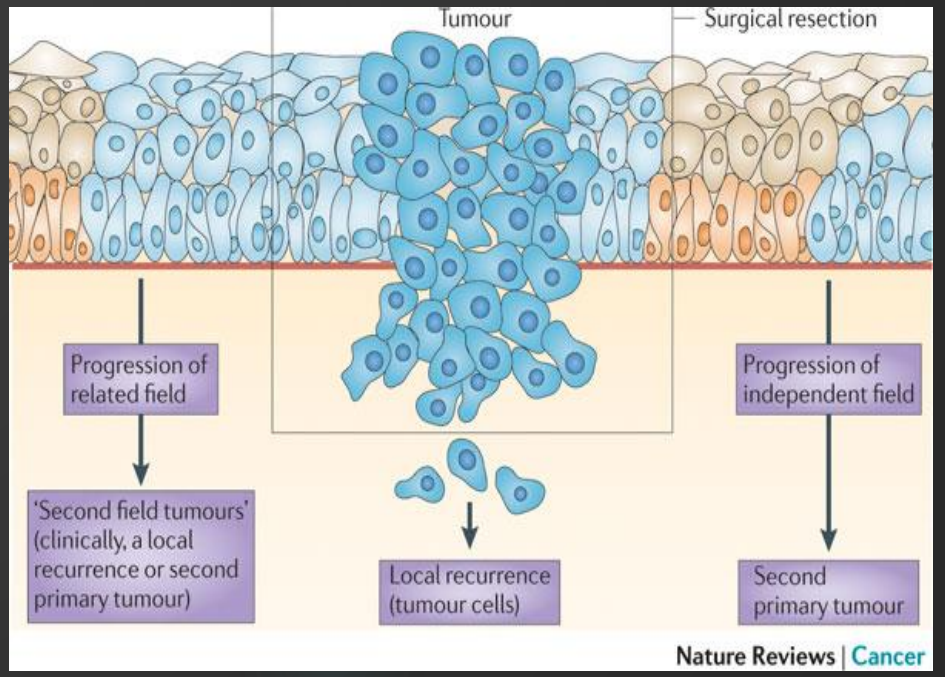
- small tumors : difficult to identify
  - The irregular surfaces of the tongue base and the tonsils
- Referred otalgia associated with tumors of this area.
  - The CN IX & X
- The retropharyngeal and parapharyngeal spaces also serve as potential routes for cancer spread.
- Surgical margins may be difficult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

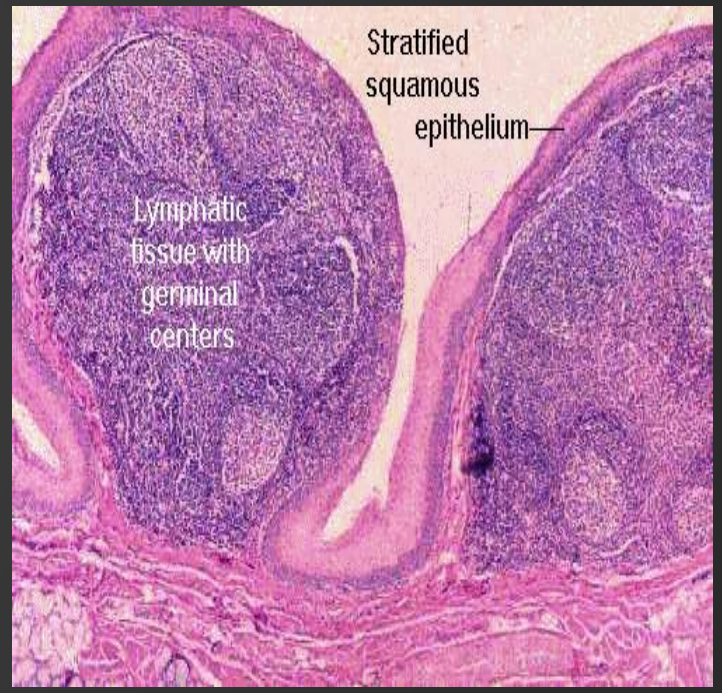
- **Slaughter , 1953**





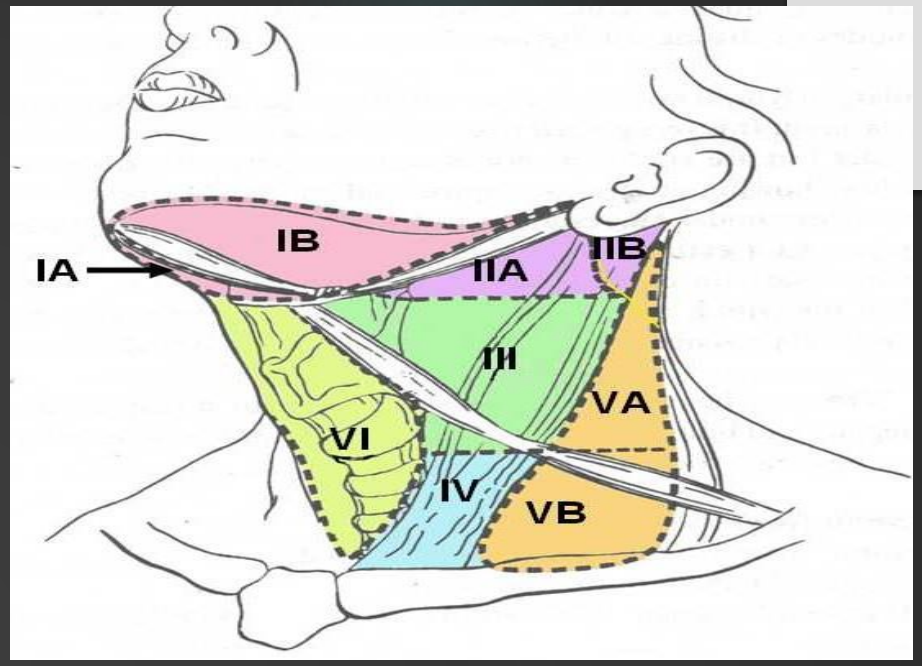
Anatomy histology

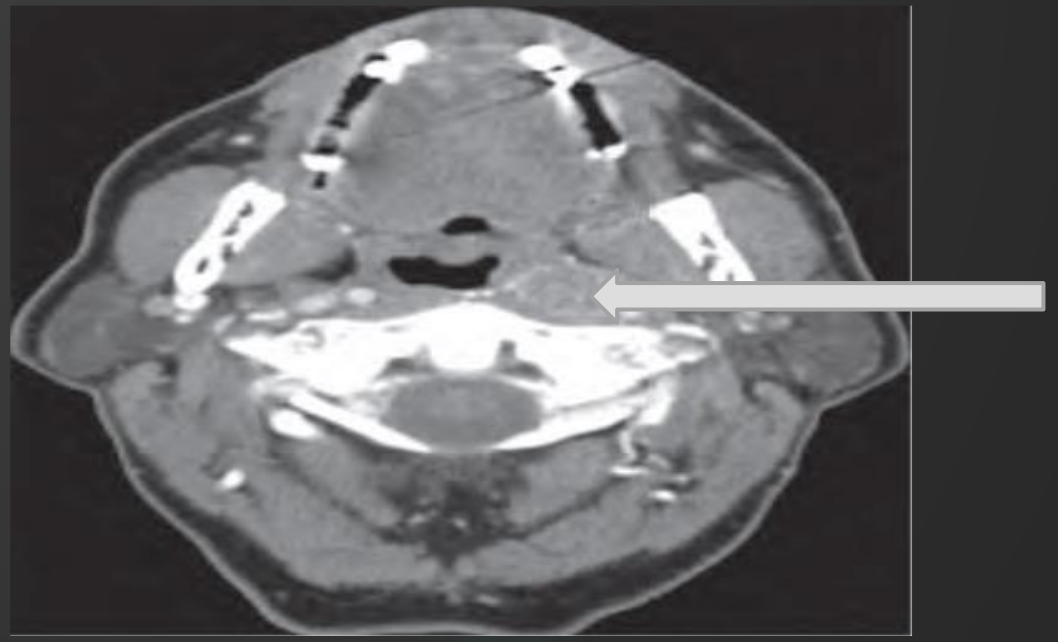
- non-keratinized stratified squamous epithelium
  - SCC
- Lymphoid tissue
  - Lymphoma
- Minor salivary gland
  - Adenoid cystic , mucoepidermoid CA
- Muscles



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 neck with contrast**
  - Bony erosions
  - Lymph nodes involvement (cystic Mets ⟹ HPV positive OPSCC)
- **MRI neck with contrast**
  - Soft tissue involvement
- **CT scan chest**
  - Advanced nodal disease
  - Distant metastasis
  - Smokers
- **PET/CT**:
  - Stages III and IV .
  - Occult primary
  - Synchronous lesions

Diagnosis

- FNA (occult primary):
  - **Cell block for IHC (P16 , HBV DNA)**
  - Direct HR-HPV (ISH) Vs tumor suppressor protein p16

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

HPV tissue detection

	ISH	**P 16 overexpression**
	Expensive	Inexpensive
	Not universally available	available

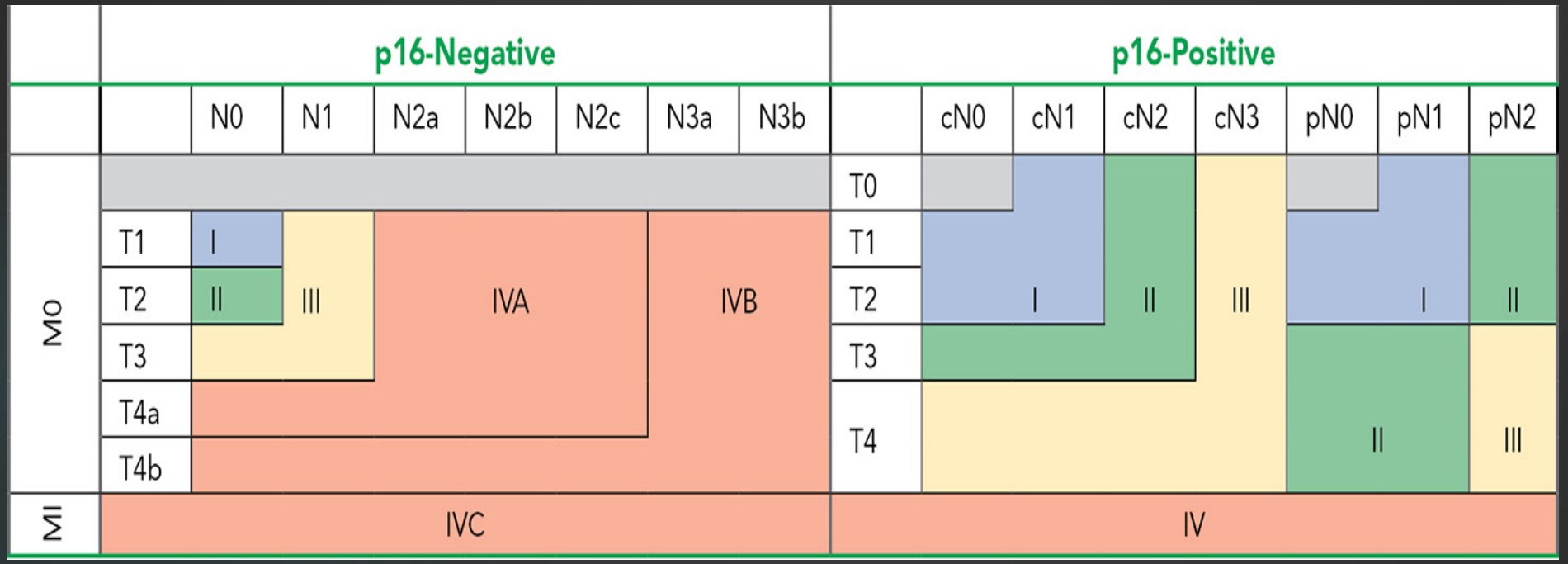
AJCC staging 8th edition

Tumor Staging (T)	Category	p16-Negative	p16-Positive
	T0		Unknown primary
	Tis	Carcinoma in situ	
	T1	≤2 cm	≤2 cm
	T2	>2 cm but ≤4 cm	>2 cm but ≤4 cm
	T3	>2 cm or involving lingual epiglottis	>2 cm or involving lingual epiglottis
	T4		Invades the larynx, extrinsic musculature of tongue, medial pterygoid, hard palate, or mandible
	T4a	Invades the larynx, extrinsic musculature of tongue, medial pterygoid, hard palate, or mandible	
	T4b	Invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or displays carotid encasement	

Nodal Staging (N)	Category	p16-Negative	p16-Positive (Clinical)	p16-Positive (Pathologic)
	N0	No regional LN	No regional LN	No regional LN
	N1	Single ipsilateral LN, ≤3 cm without ENE	≥1 ipsilateral LN, all ≤6 cm	≤4 LN
	N2		Contralateral or bilateral LN, all ≤6 cm	>4 LN
	N2a	Single ipsilateral LN >3 cm but ≤6 cm without ENE		
	N2b	Multiple ipsilateral LN, all ≤6 cm without ENE		
	N2c	Bilateral or contralateral LN, 6 cm or less without ENE		
	N3		At least one LN >6 cm	
	N3a	At least one LN >6 cm without ENE		
	N3b	Any LN with ENE		

Distant Metastasis Staging (M)		
	M0	No distant metastasis
	M1	Distant metastasis

Prognostic group staging



Management

- Multidiscblinary team approach (Oncologist , radiation oncologist , surgeon)
- 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

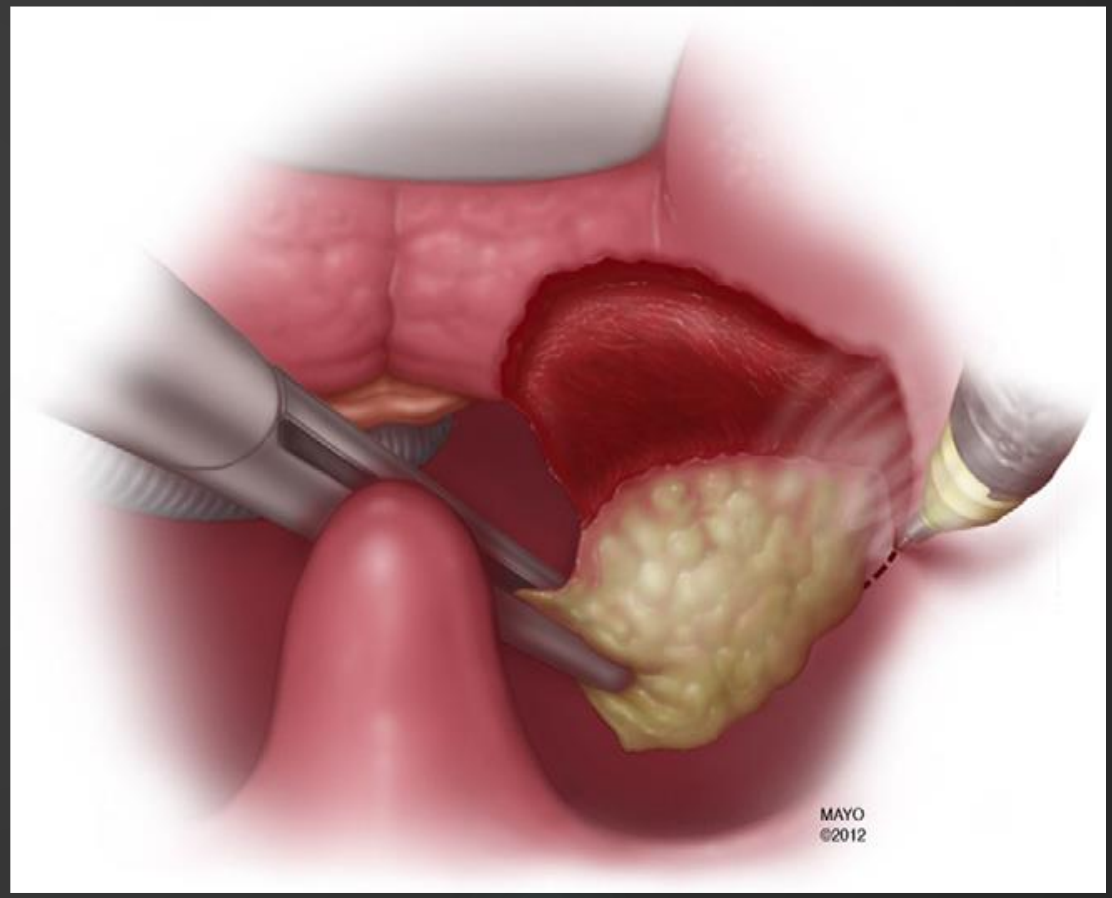
- The major open procedures were developed during a time when surgery was the primary mode of therapy.
- Largely obsoleted as primary therapy :
  - Success of CRT
  - Minimally invasive transoral surgical approaches.
- Indication :
  - HPV negative OP SCC (ongoing trials)
  - Advanced cancer with bone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

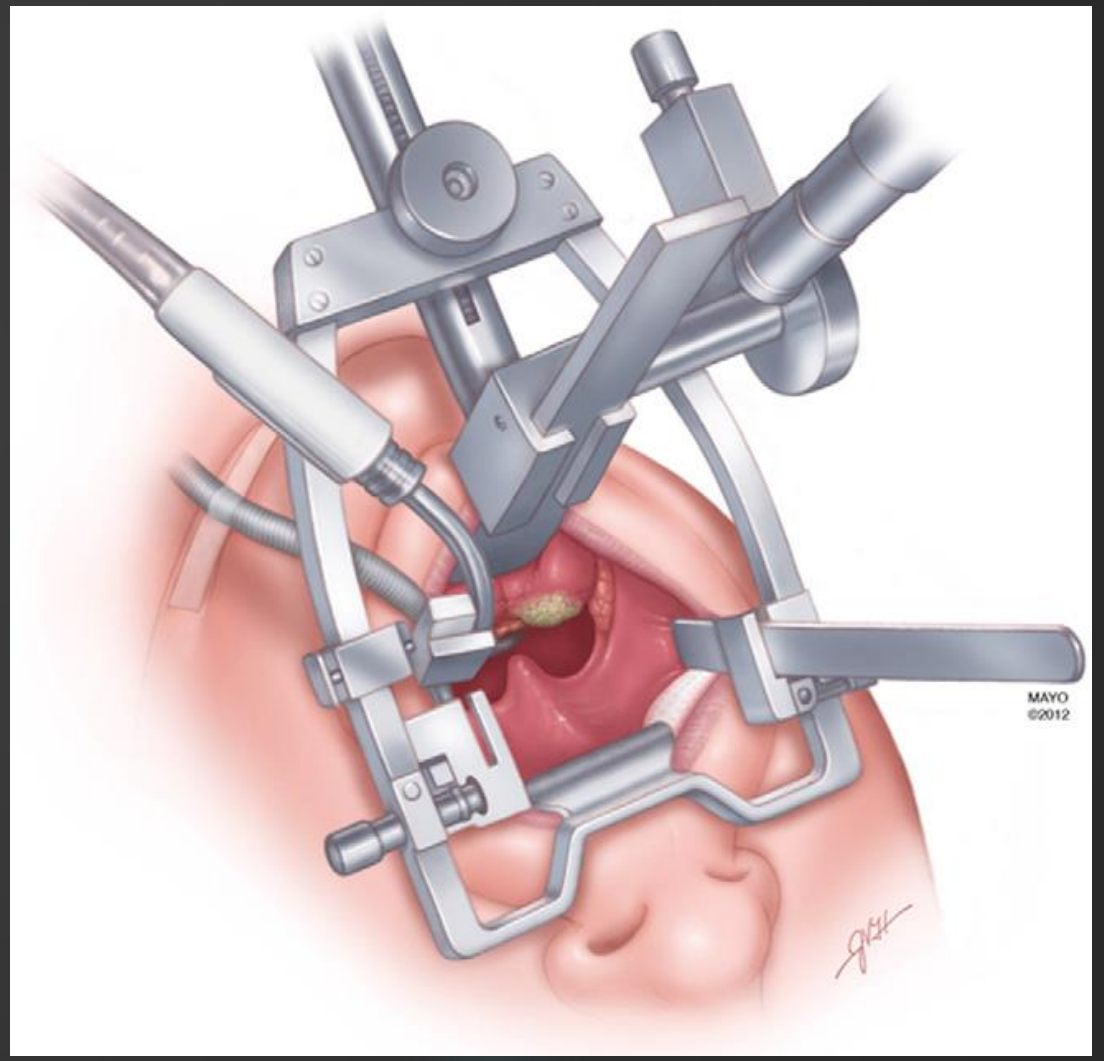
Management : primary tumor Transoral approach

- 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

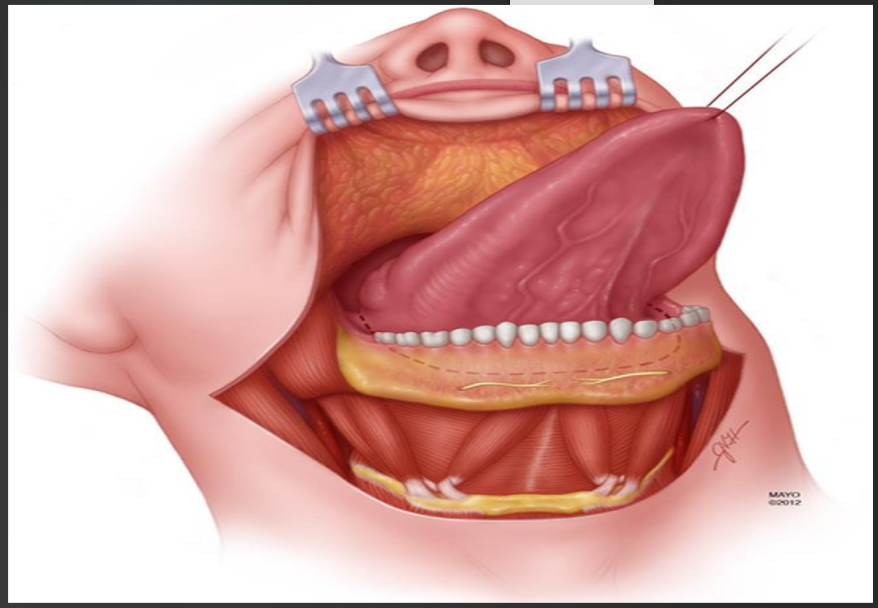


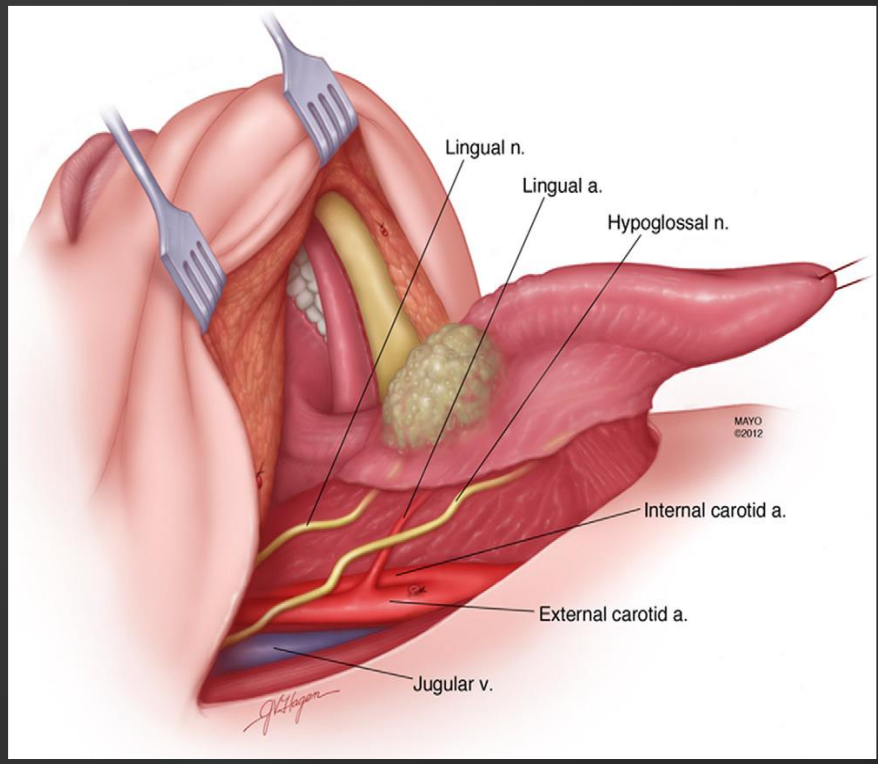
Management : primary tumor Transoral approach

- 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)

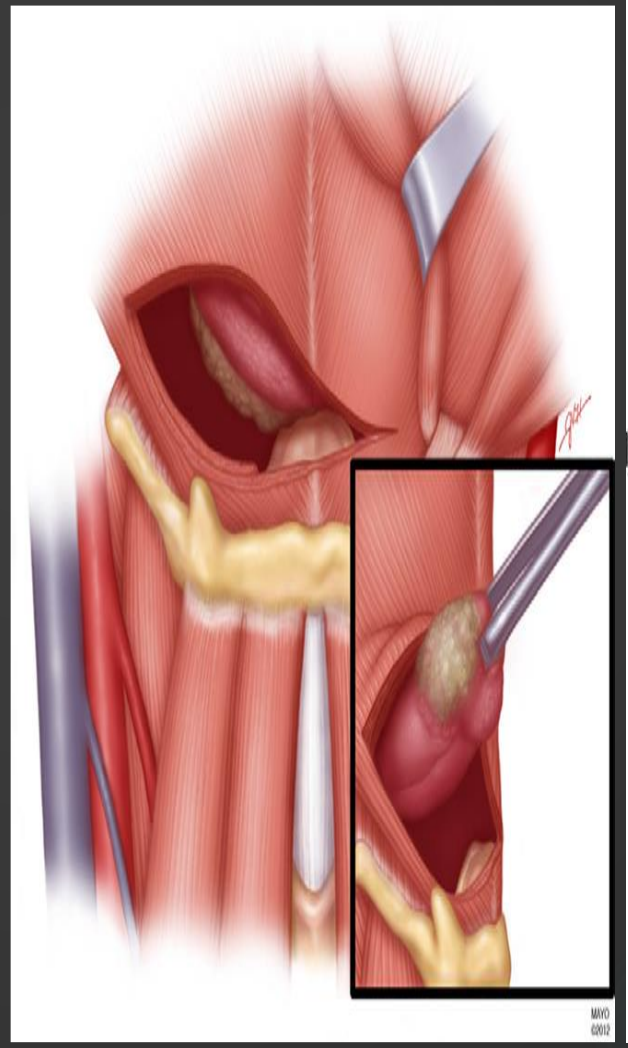
- Indication : BOT
- visor flap is mandatory
- Advantages :
  - Excellent direct visualization
  - No need for lip-splitting & mandibuolotomy
- Disadvantages :
  - Less access to the lateral pharynx and Para pharyngeal spaces

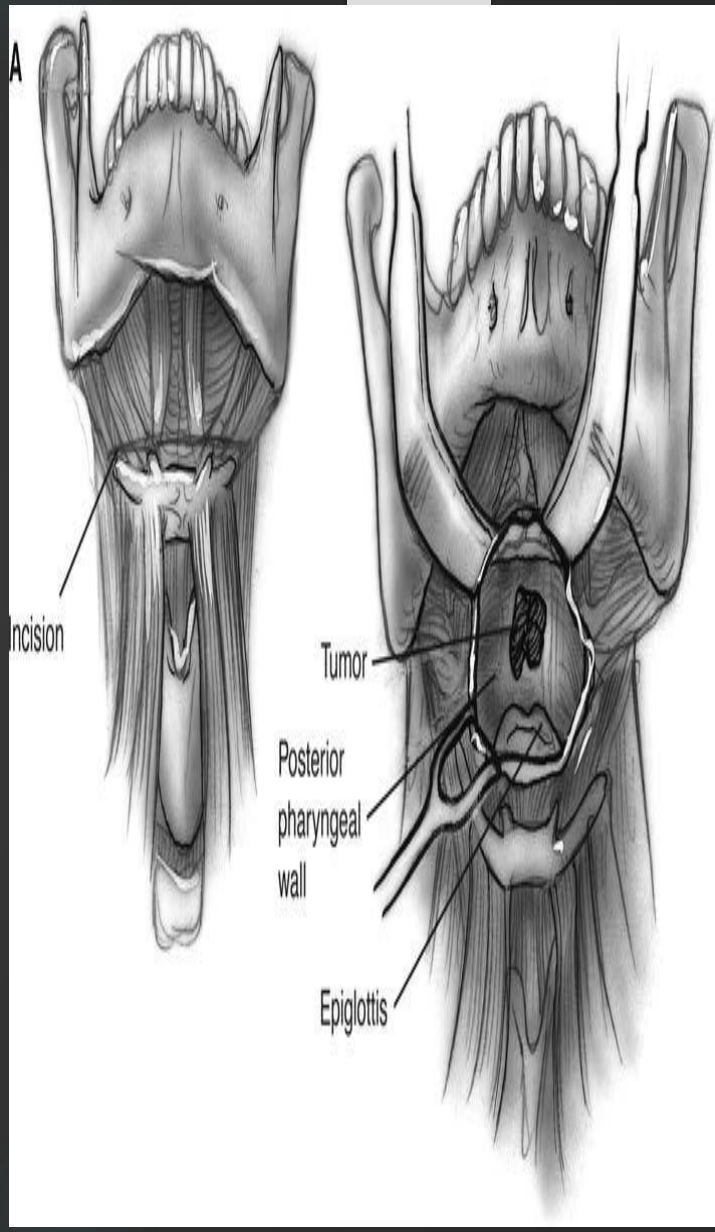




Management : primary tumor supra hyoid pharyngotomy

- 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

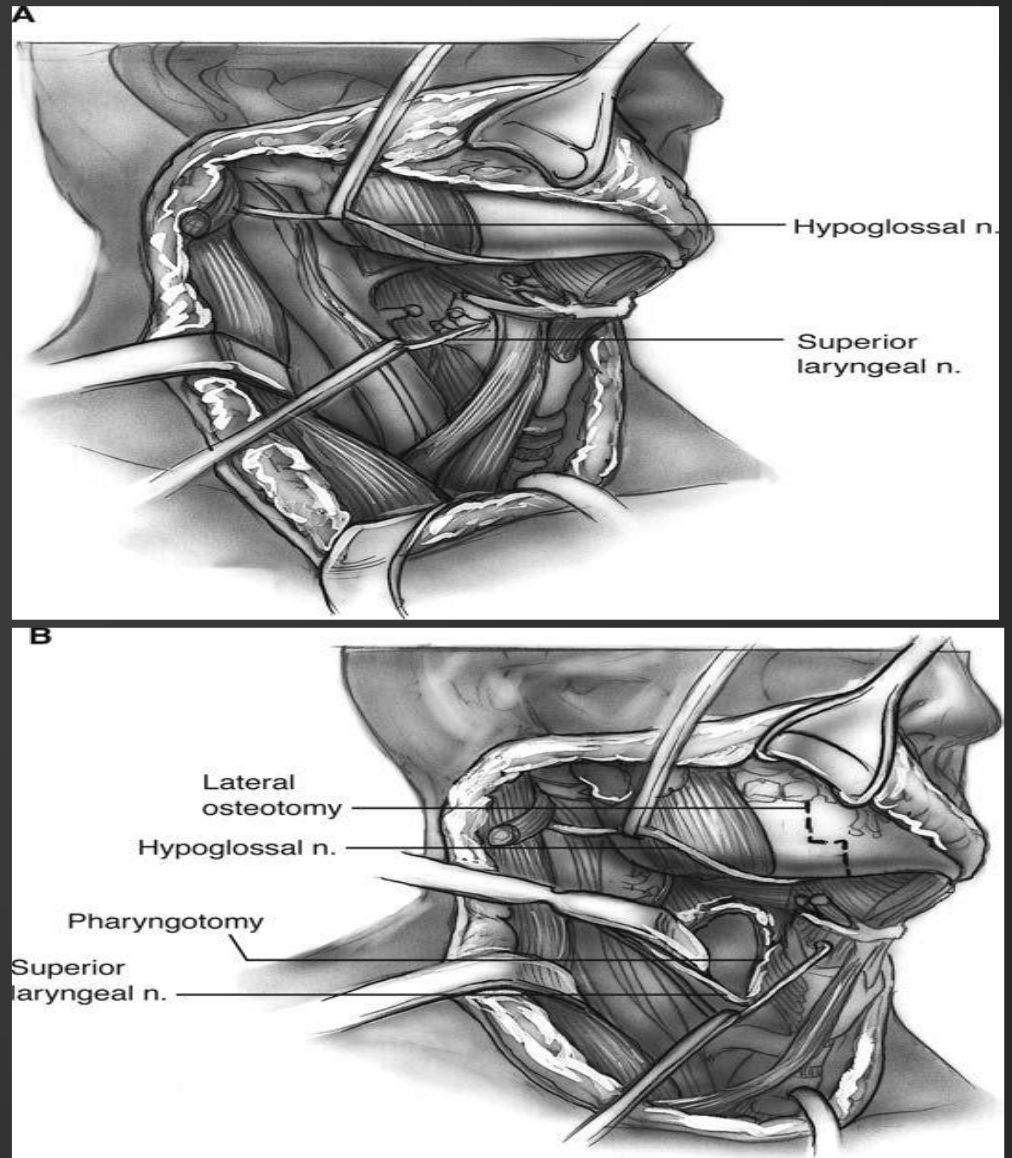




Management : primary tumor lateral pharyngotomy

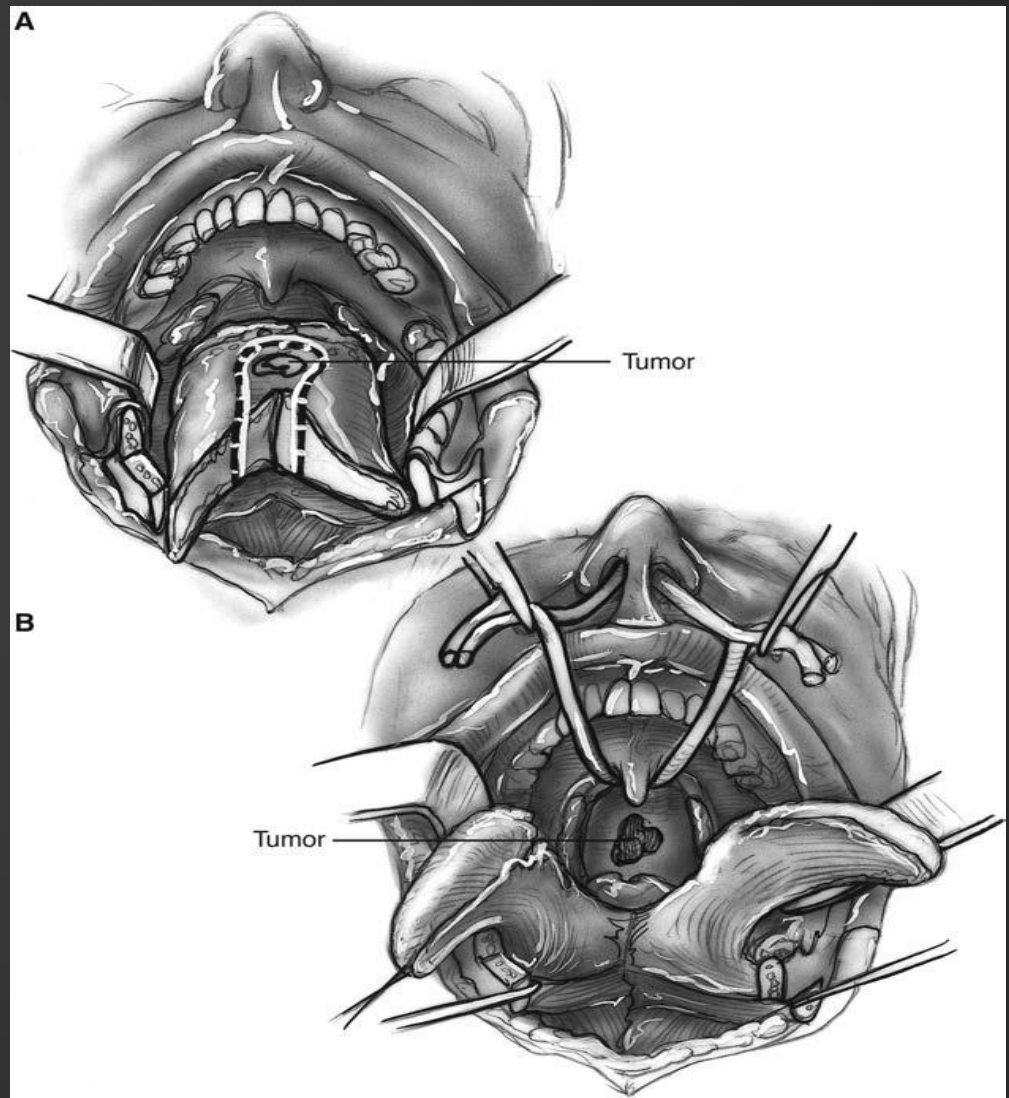
- Indication :
  - Small tumors of the base of the tongue and pharyngeal walls
- Pharyngeal entrance on least affected side .
- Advantages :
  - Superior exposure : via lateral mandibulotomy
  - Excellent functional and cosmetic outcome,
- Disadvantages :
  - Limited superior , Para pharyngeal , lateral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

  & CNXII , lingual A



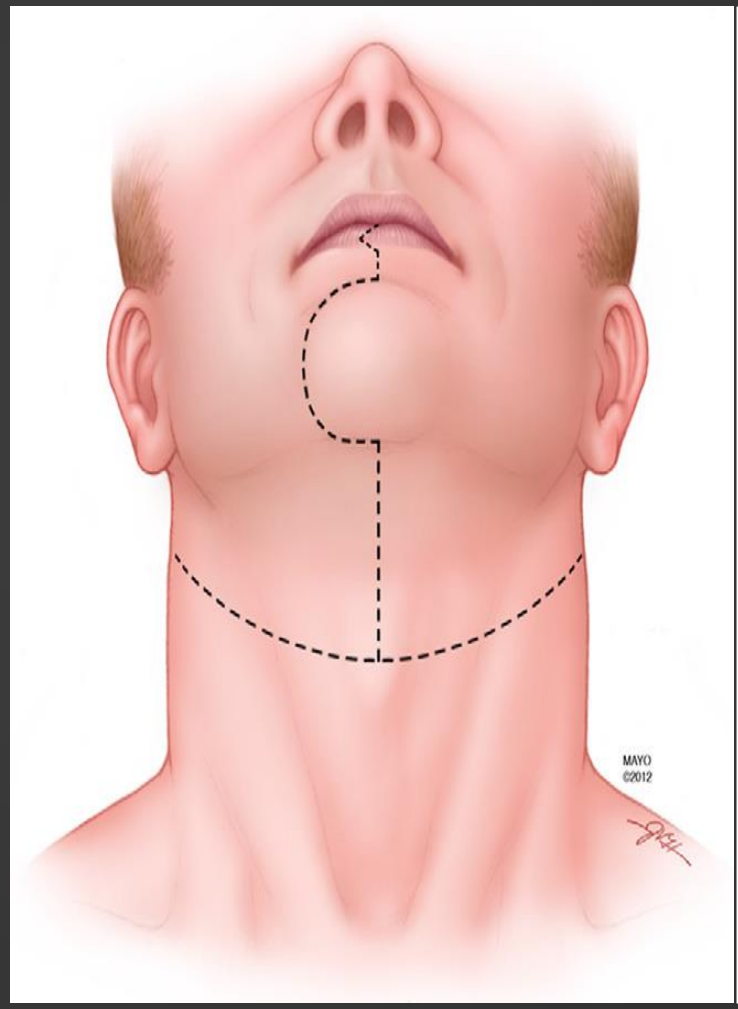
Management : primary tumor
Midline labiomandibular glosstomy

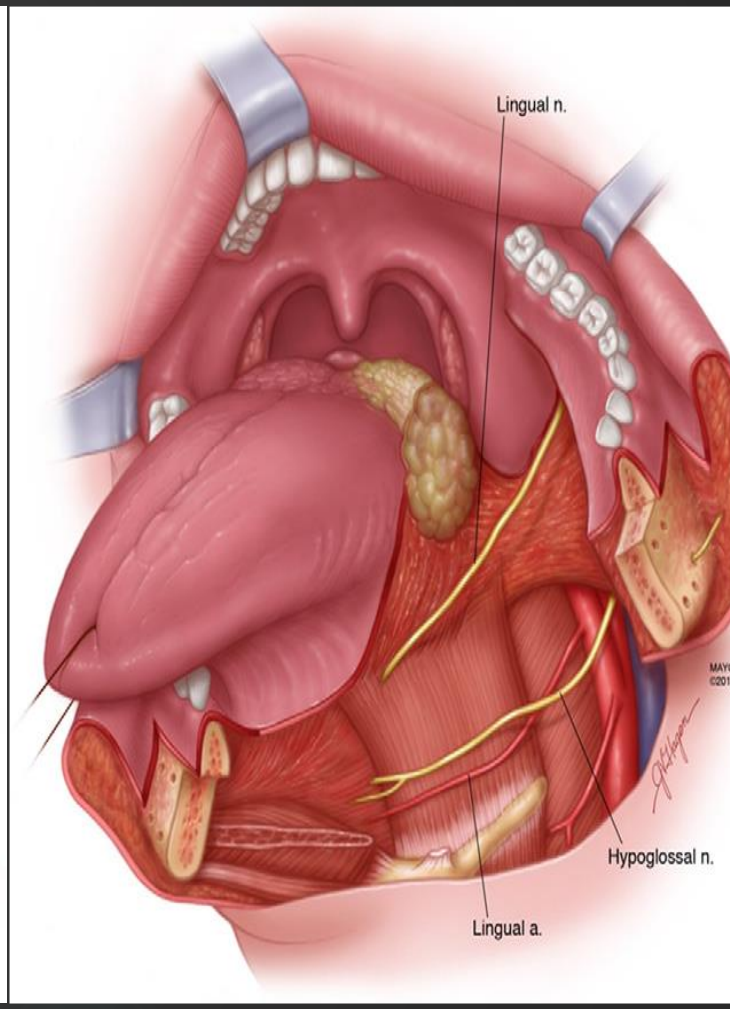
- Indication :
  - BOT , Posterior pharyngeal wall
- Advantages :
  - Bleeding and neurologic deficits are minimal
- Disadvantages :
  - Limited access to Para pharyngeal space or lateral oropharyngeal sites.



Management of primary tumor : mandibular swing

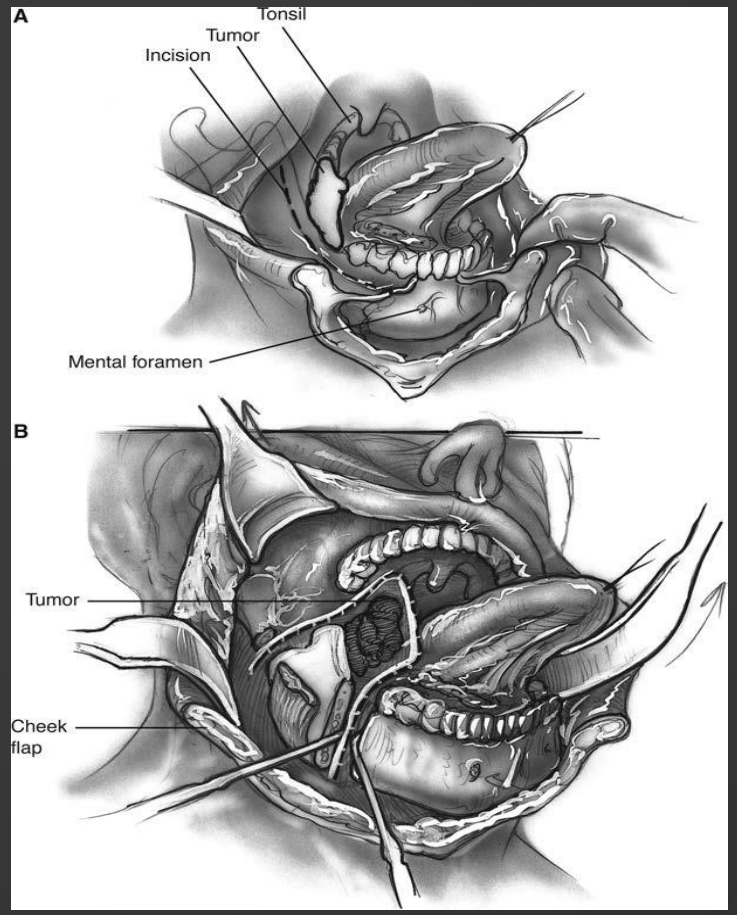
- Advantages :
  - wide exposure to the entire oropharynx , lateral Op wall & Para pharyngeal space .
- Disadvantages :
  - Inferior functional & cosmetic result .
  - Lower lip anesthesia .
  - Hemi mandibulectomy if mandible is involved.
  - Require free flap reconstruction.

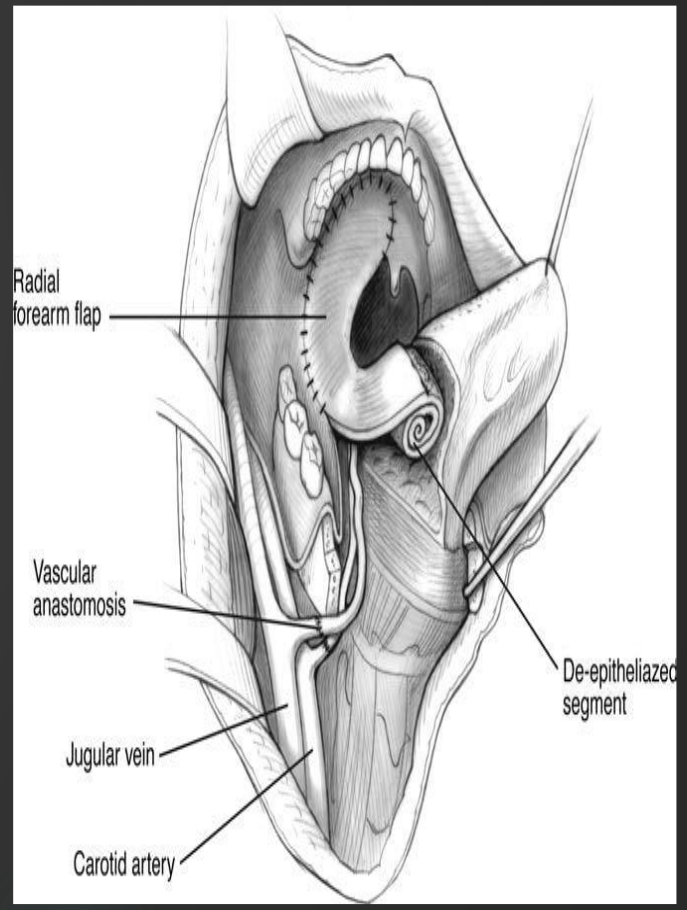




Management of primary tumor Mandibulectomy

- 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.

THANK YOU