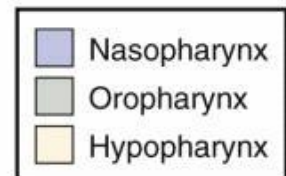
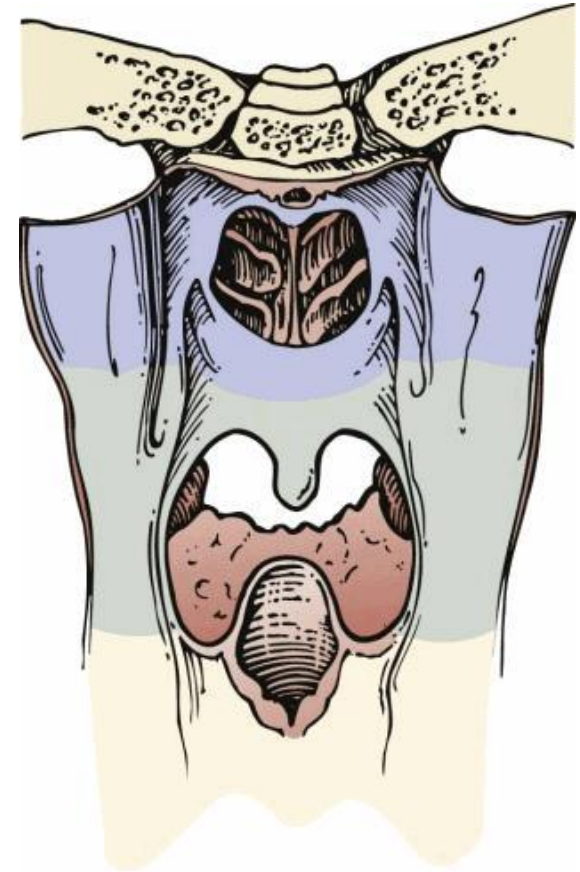


# CANCER OF THE PHARYNX

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HOPITAL UNIVERSITAIRE DE BERNE  
BERN UNIVERSITY HOSPITAL



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4. General Findings – Naso- / Oro- / Hypopharynx
5. Tumor-Management – Naso- / Oro- / Hypopharynx
6. Treatment-Complications

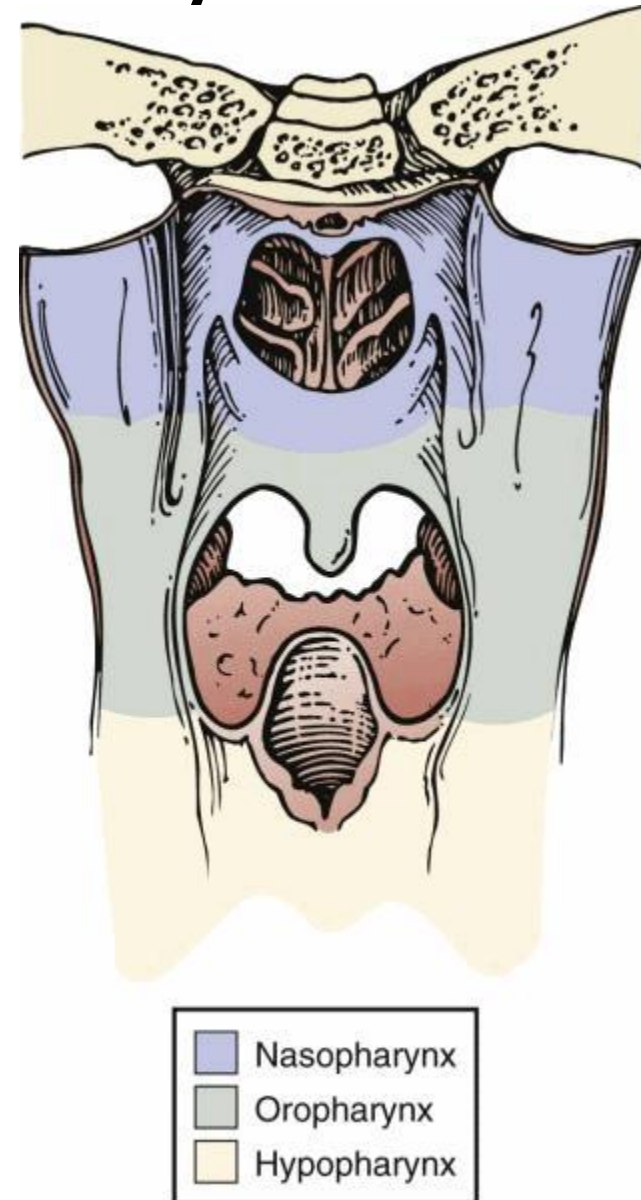
# Pharyngeal Cancer

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- 7. Follow-up
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- 9. Recurrence-Management – Naso- / Oro- / Hypopharynx
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# 1. Pharynx - Anatomy

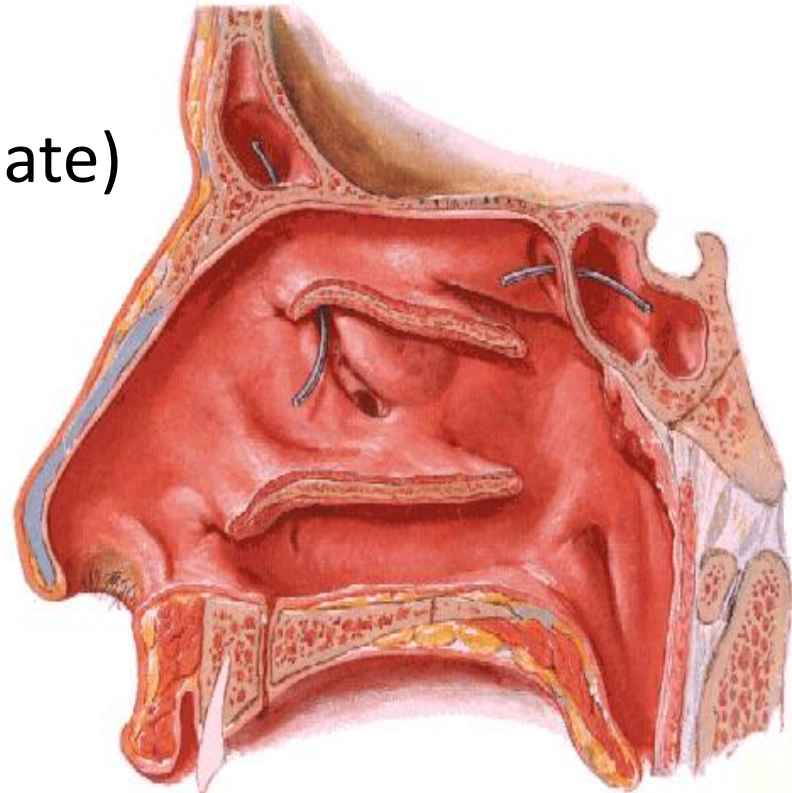
- Nasopharynx
- Oropharynx
- Hypopharynx



# Pharyngeal Cancer

## Nasopharynx – Subsites (UICC, TNM 2009)

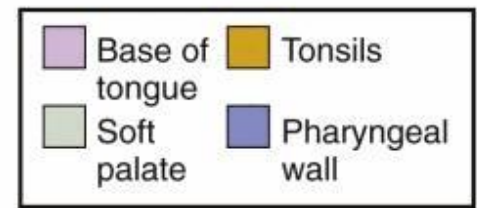
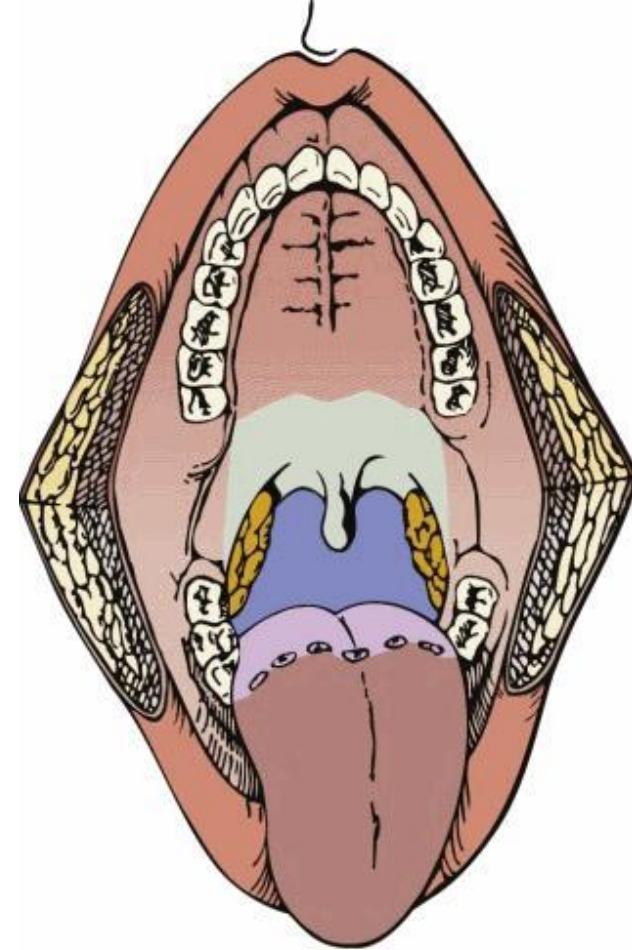
- Postero-superior wall
- Lateral wall (including the fossa of Rosenmüller)
- Inferior wall  
(=superior surface of the soft palate)



# Pharyngeal Cancer

## Oropharynx - Subsites (UICC, TNM 2009)

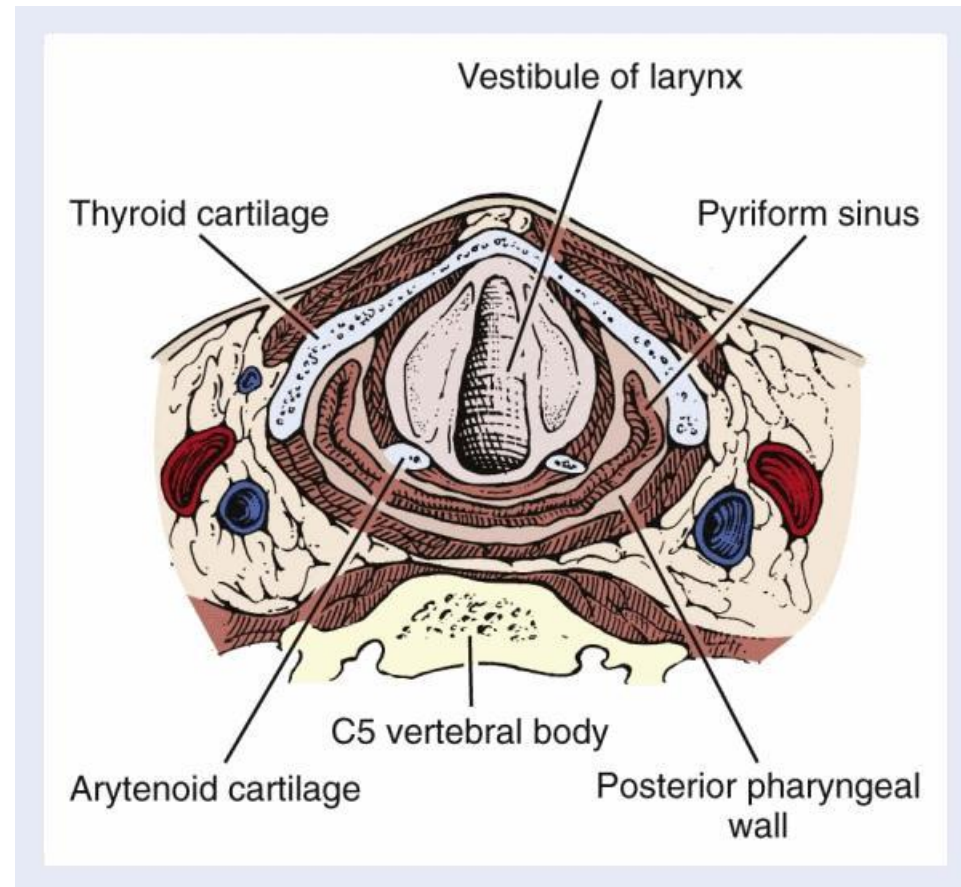
- Tonsils and tonsillar fossa, anterior and posterior faucial pillars
- Tongue base, vallecula
- Soft palate and uvula
- Posterior wall and adjacent lateral pharyngeal walls



# Pharyngeal Cancer

## Hypopharynx - Subsites (UICC, TNM 2009)

- Pyriform sinus (membraneous/cartilaginous part)
- Posterior cricoid
- Posterior wall

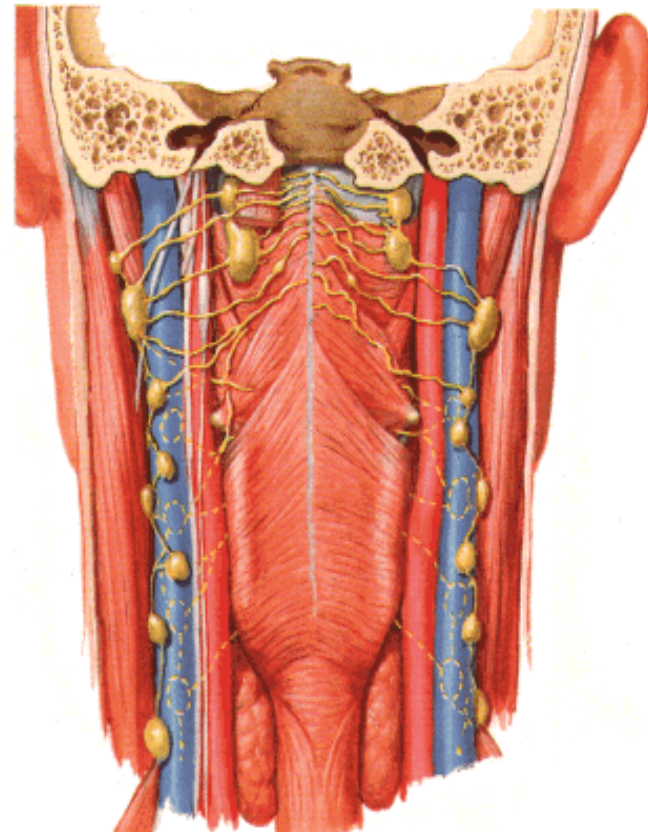




# Pharyngeal Cancer

## Lymphatics

- Very rich lymphatic network → ↗ lymph node metastases
- Bilateral lymphatic drainage:
  - » Posterior wall
  - » Tongue base
  - » Soft palate
- Retropharyngeal lymphatic drainage:
  - » Posterior wall
  - » Palatine tonsil





# Pharyngeal Cancer

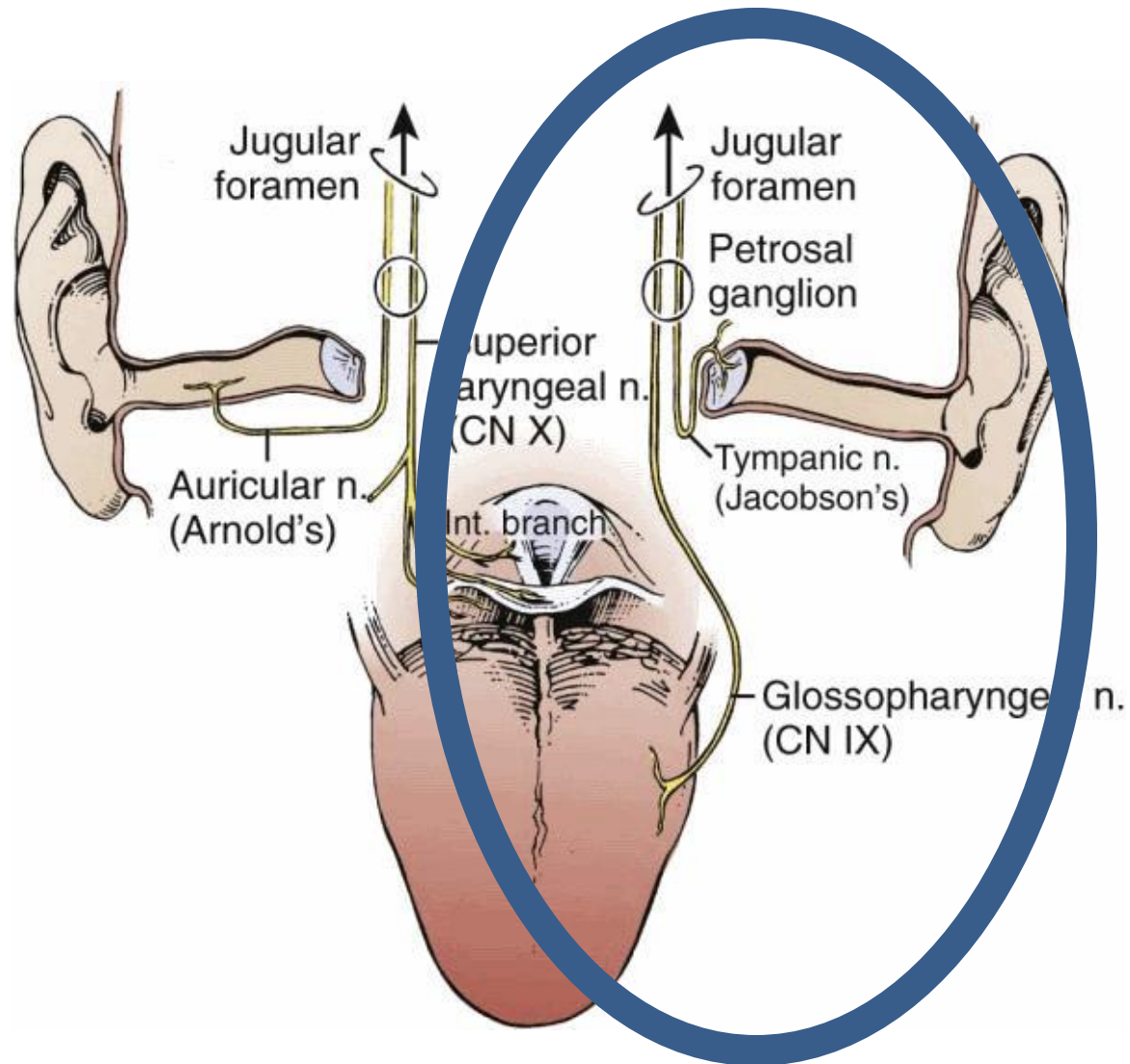
## Nasopharynx - Nerves

- Trigeminal (superior), glossopharyngeal and vagus nerve  
→ sensory

# Pharyngeal Cancer

## Oropharynx - Nerves

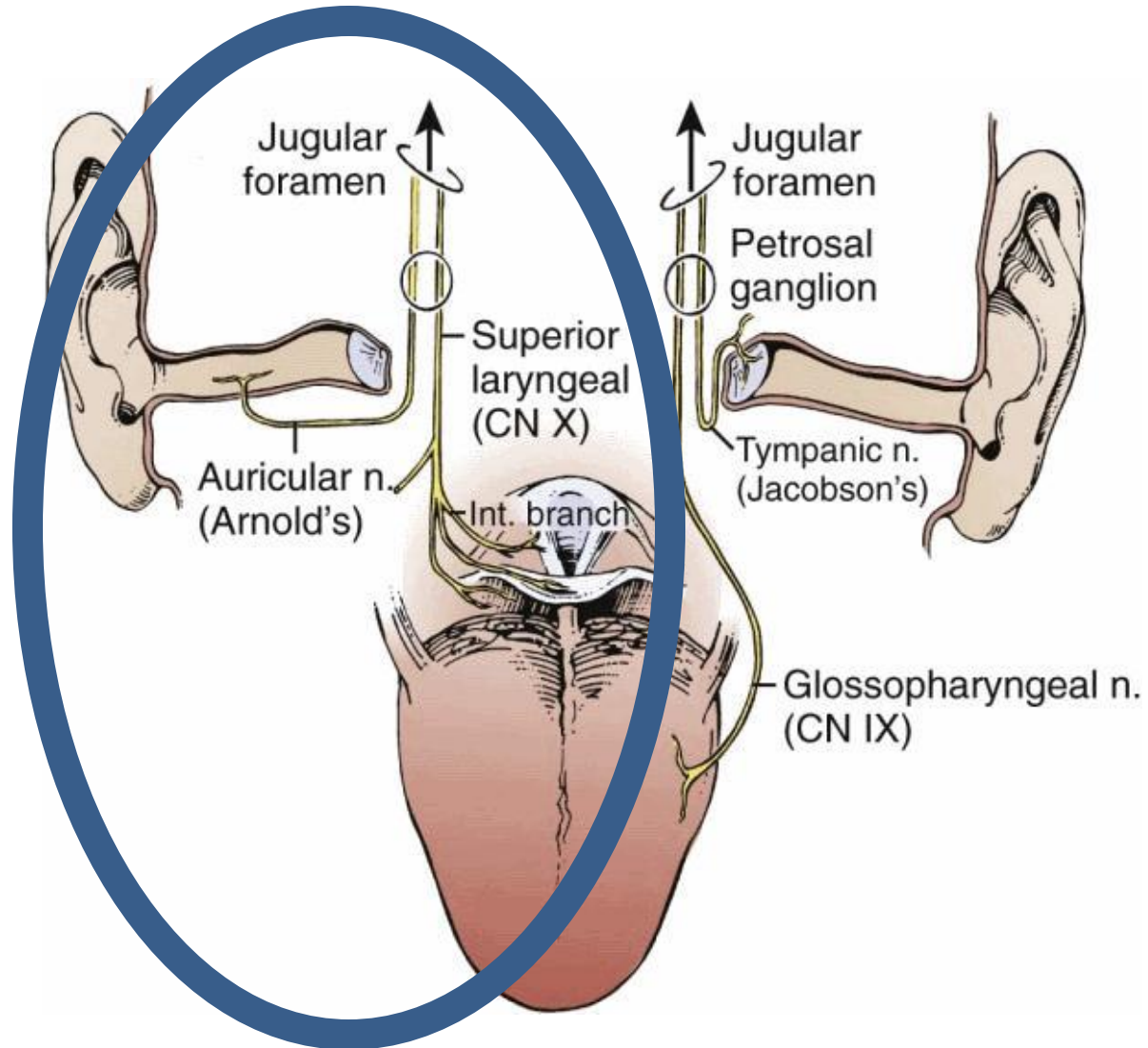
- Maxillary nerve / lesser palatine nerve
  - taste and secretomotoric
- Glossopharyngeal nerve
  - sensory
  - (referred otalgia from tympanic branch, Jacobson's nerve)**
  - and
  - parasympathetic secretomotoric
- Vagus nerve
  - sensory
- Postganglionic sympathetics from carotid plexus



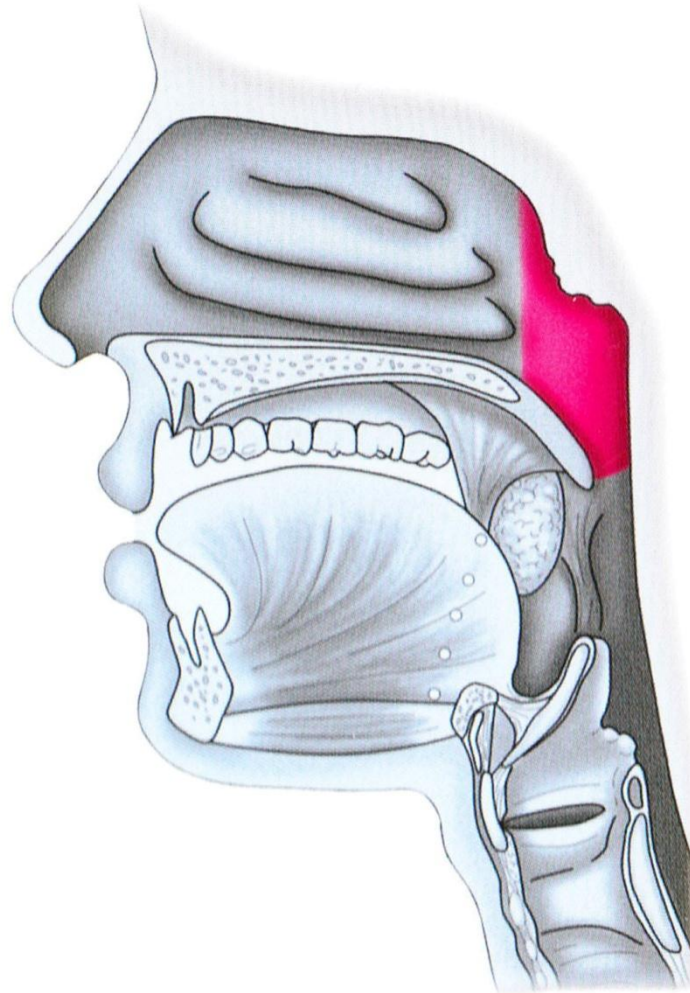
# Pharynx – Anatomy

## Hypopharynx - Nerves

- Vagus nerve → motoric
- Glossopharyngeal and superior laryngeal nerve (N. vagus) → sensory  
**(referred otalgia from ear canal branch, Arnold's nerve)**



## 2. CANCER OF THE NASOPHARYNX



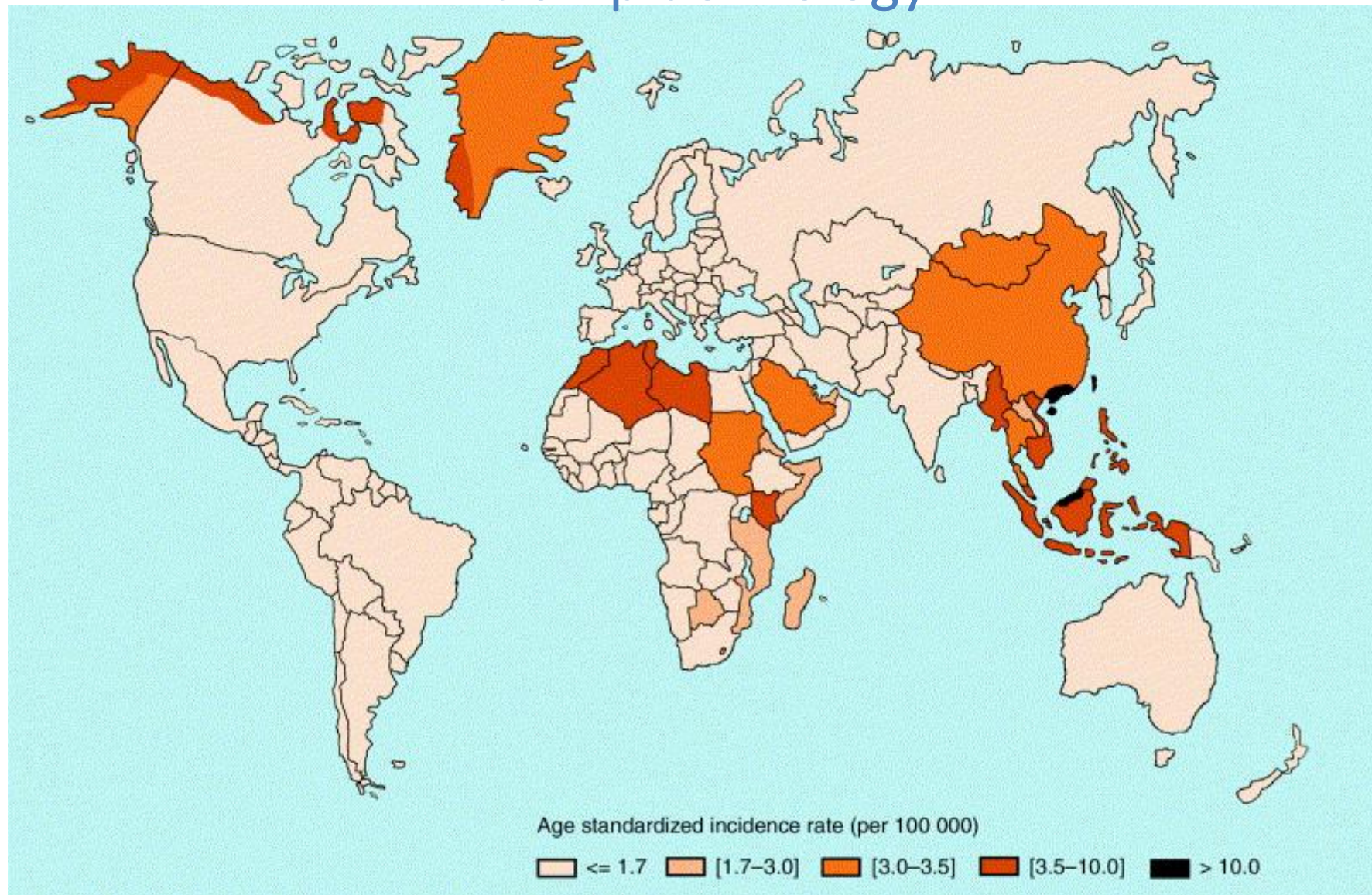


## 2.1. Etio-Epidemiology

- Frequency:
  - Incidence:
    - North-Europe and USA: 0.5-2 per 100'000 (rare!)
    - Mediterranean Bassin and Arctic: 5 per 100'000
    - **South-East Asia: 25-50 per 100'000**
- Sex:
  - M:F = 2-3:1
- Age:
  - Mean age = 50 years (20%: 15 – 30 years)

# Nasopharyngeal Cancer

## Etio-Epidemiology



# Nasopharyngeal Cancer

## Etio-Epidemiology

- Viral Factors
  - Epstein–Barr virus (**Tissue: viral-encoded RNA – not virus**)
    - EBV- well documented viral “fingerprints” in tumor cells and also anti-EBV serologies with nonkeratinizing carcinomas
    - All tumor cells are EBV + if EBV positivity proven
    - Multiple viral proteins (EBNA1, LMP1) have an *in vitro* mitotic activity
- Genetic factors
  - Chinese native > Chinese immigrant > North American native → both genetic and environmental factors
  - Presence of HLA-A2 and HLA-B sin-2 → HLA histocompatibility loci possible markers
  - Deletion of the short arm of chromosome 3 (96%) – RASSF1 (oncogen ras)
  - Deletion of the short arm of chromosome 9 (85%) – p16INK4 (inhibitor of the cellular cycle)

# Nasopharyngeal Cancer

## Etio-Epidemiology

- Environmental factors
  - Cooking of salted-cured food (fish) → volatile nitrosamine
  - Rancid butter and sheep's fat → butyric acid (= EBV activator (Tunisia, Algeria, Morocco))
  - Polycyclic hydrocarbons
  - Chronic nasal infection
  - Poor hygiene
  - Poor ventilation
  - Tobacco and alcohol??? → keratinizing SCC

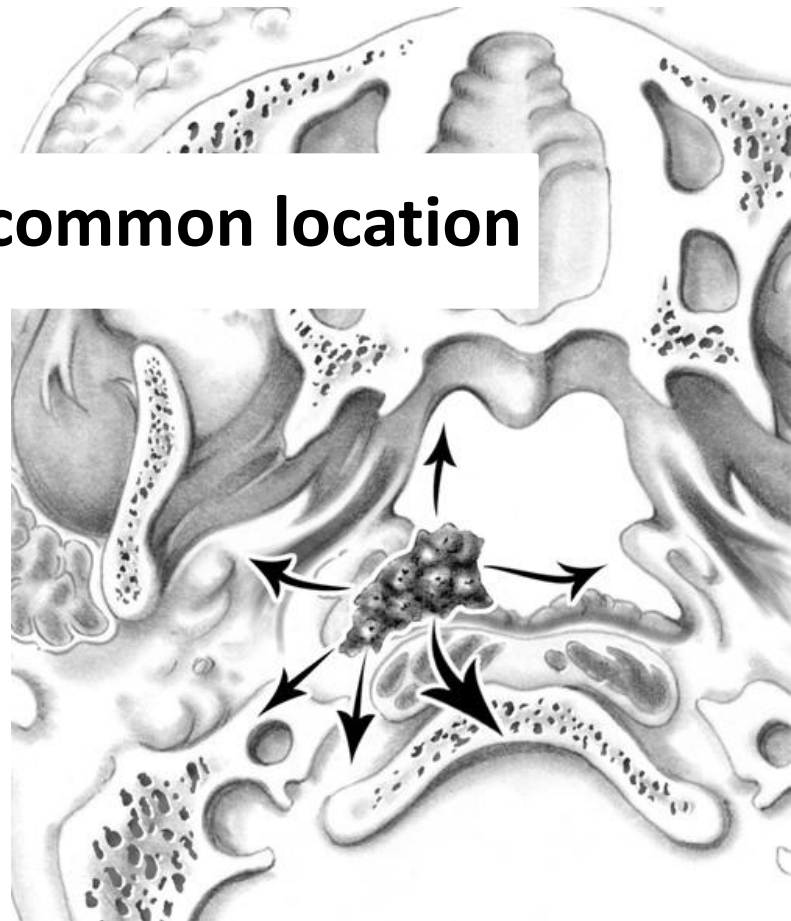




## 2.2. Macroscopic Aspects and Histology

- Submucosal spreading mass within normal NP
- Exophytic mass with teleangiectasis
- Ulcer

**Fossa of Rosenmüller = most common location**



# Nasopharyngeal Cancer

## Classification / Pathology / Histology

– 90% = Squamous cell carcinoma

- Actualized WHO classification

1. **(Keratinizing) squamous cell carcinomas**

- » < 0.3 - 2% Southeast Asia
- » 25% North America

} Not EBV-associated

2. **Nonkeratinizing carcinomas**

- Differentiated type

- » 3% Southeast Asia
- » 12% North America

} EBV-associated

-Undifferentiated type

- » 95% South-East Asia
- » 63% North America

} Highly EBV-associated

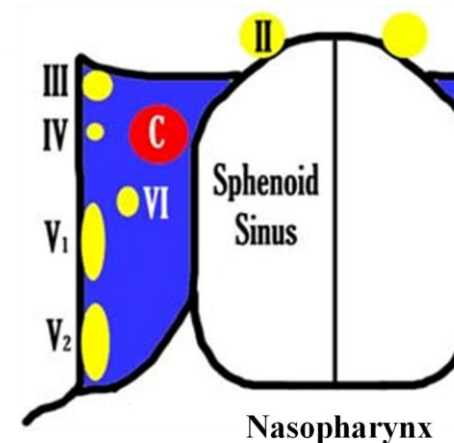
3. **Basaloid squamous cell carcinomas**

- » High-grade variant of SCC (rare!)

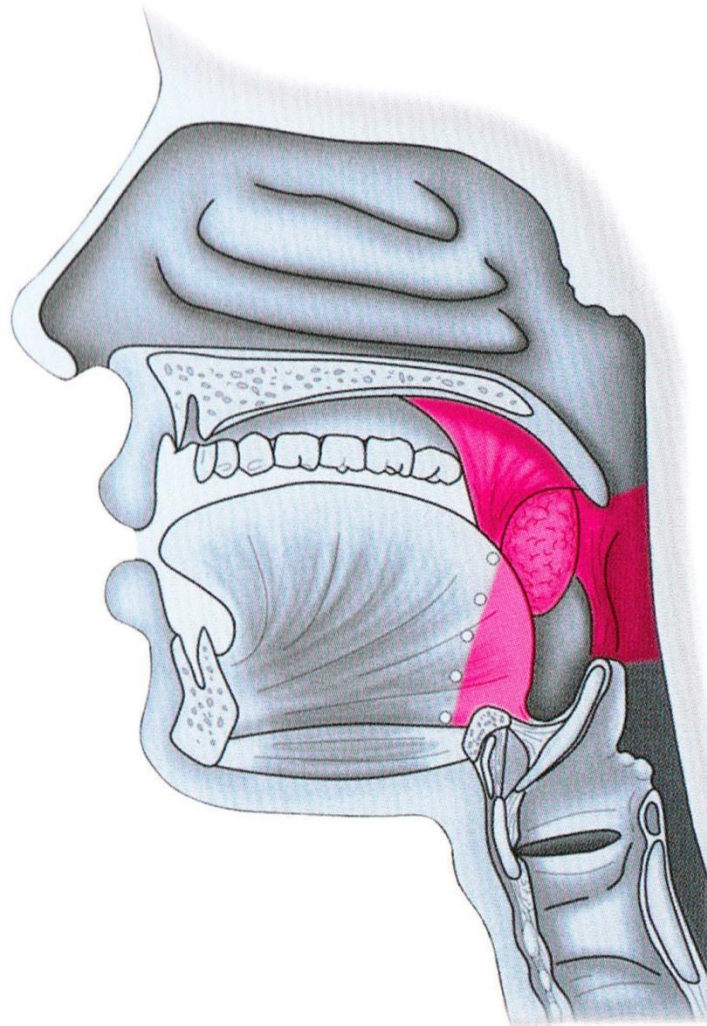


## 2.3. Symptoms and History

- Often subtle initial symptoms
  - **Early symptoms:**
    - » Unilateral hearing impairment → serous otitis
    - » Painless, slowly enlarging neck mass
  - **Late symptoms:**
    - » Nasal obstruction
    - » Nasal discharge
    - » Epistaxis
    - » Cranial nerve involvement:
      - CN V → facial pain and paresthesia
      - CN III, IV and VI → ophthalmoplegia and diplopia
    - » Xerophthalmia (greater sup. petrosal nerve)
    - » Proptosis (posterior orbit)
    - » Trismus (pterygoid muscle)
    - » Horner's syndrome (cervical sympathetics)
    - » CN's IX, X, XI, XII (extensive skull base invasion!)



## 2. CANCER OF THE OROPHARYNX



## 2.1. Etio-Epidemiology

- Frequency:
  - 0.5% (USA) – 1.5% (France) of all cancers
  - 15-20% of all malignancies of the H&N
- Race:
  - Very rare: Israel, Japan
- Sex:
  - M:F = 4:1 (USA) – 9:1 (France)
  - France: Male – Nord, Pas de Calais, Calvados (OH)
- Age:
  - Mean age = 60 years
  - Incidence ↗ in 4th and 5th decades of life

# Oropharyngeal Cancer

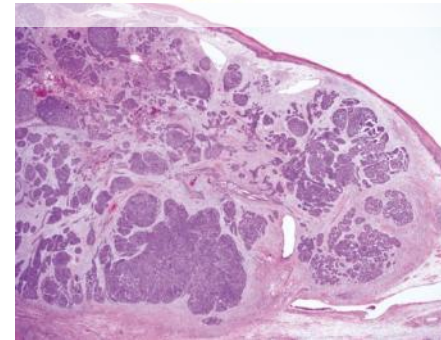
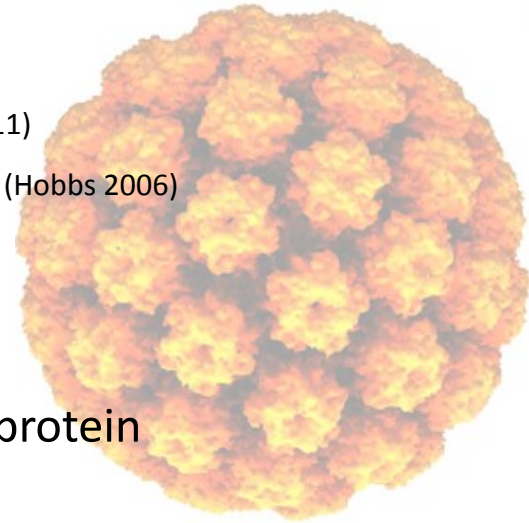
## Etio-Epidemiology

- Tobacco
  - Alcohol
- } **Synergistic effect!!! (80% of all oropharyngeal cancer)**
- Orogenital sexual practices (**HPV**)
  - Poor oral hygiene
  - Possible association with marijuana use ?
  - Genetic deficiencies (affection of the metabolism of tobacco-related and other carcinogens, malfunctions in DNA repair mechanisms and cell-cycle regulation, expl.: p53)

# Oropharyngeal Cancer

## Human Papilloma Virus (HPV)

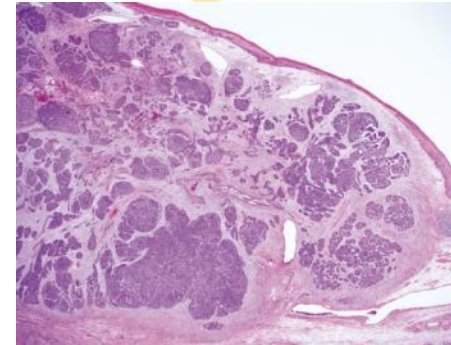
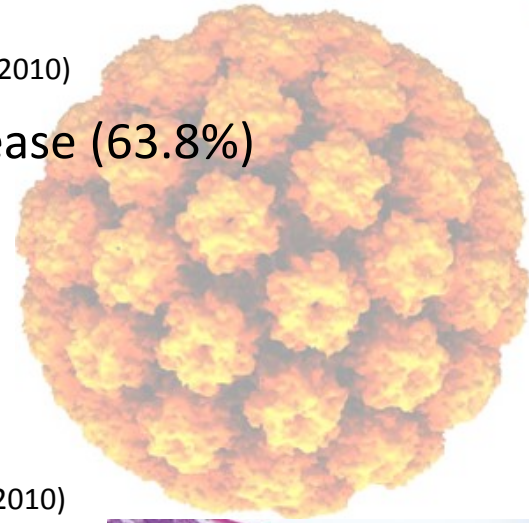
- High-risk HPV, type 16
  - Types 16 and 18 involved with cancer of genital tract
  - Associated with 45-70% of oropharyngeal SCCA (Cohen 2011)
  - Associated with: tonsil > oropharynx > oral and larynx (Hobbs 2006)
- Integration of genome into host cell nucleus
  - Express E6 and E7 oncoproteins
  - Inactivate tumor-suppressant p53 and retinoblastoma protein
  - Associated with p16-positivity
- Histology
  - Predominantly poorly differentiated SCC
  - Basaloid background
  - Correlated with HPV- and p16-positivity (Mendelsohn 2010)
    - No increase in lymphovascular or perineural invasion
    - Highly predictive of lymph node metastasis
- Transmission
  - Oro-sexually transmitted



# Oropharyngeal Cancer

## Human Papilloma Virus (HPV)

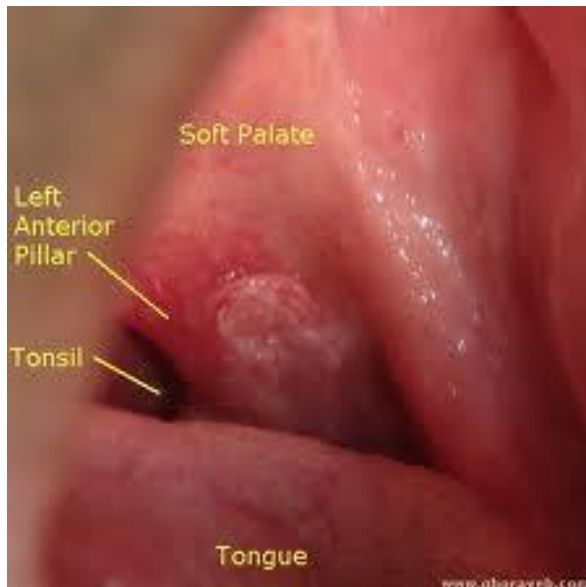
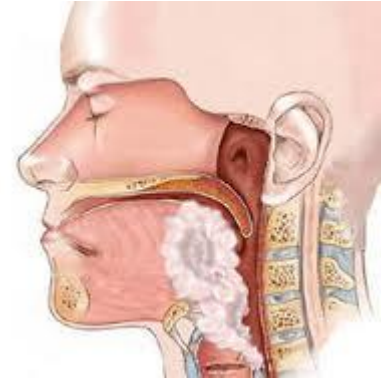
- Retrospective review of oropharyngeal SCCA (Ang 2010)
  - HPV-positive in 206 out of 323 with stage III or IV disease (63.8%)
    - Improved 3-year overall survival (82.4% vs. 57.1%)
    - Improved 3-year progression-free survival (73.7% vs. 43.4%)
    - HPV-positive conveys 58% reduction in death
- 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, they may be more radiosensitive (Mellin 2002, Lindel 2001)
  - HPV viral load ↗ → survival ↗ (Mellin 2002)





## 2.2. Macroscopic Aspects and Histology

- Macroscopy:
  - Submucosal (tongue base)
  - Ulcer and erosion (tonsills)
  - Superficial spreading ulcer (soft palate)



# Oropharyngeal Cancer

## Pathology / Histology

- 90-95%                      =                      Squamous cell carcinoma
- Well-differentiated                      16%
  - Moderately-diff.                      50%
  - Poorly-diff.                      34%

(Mehta, Laryngoscope 2010)

## 2.3. Symptoms and History

- Long-time silent and asymptomatic

- **Early symptoms:**

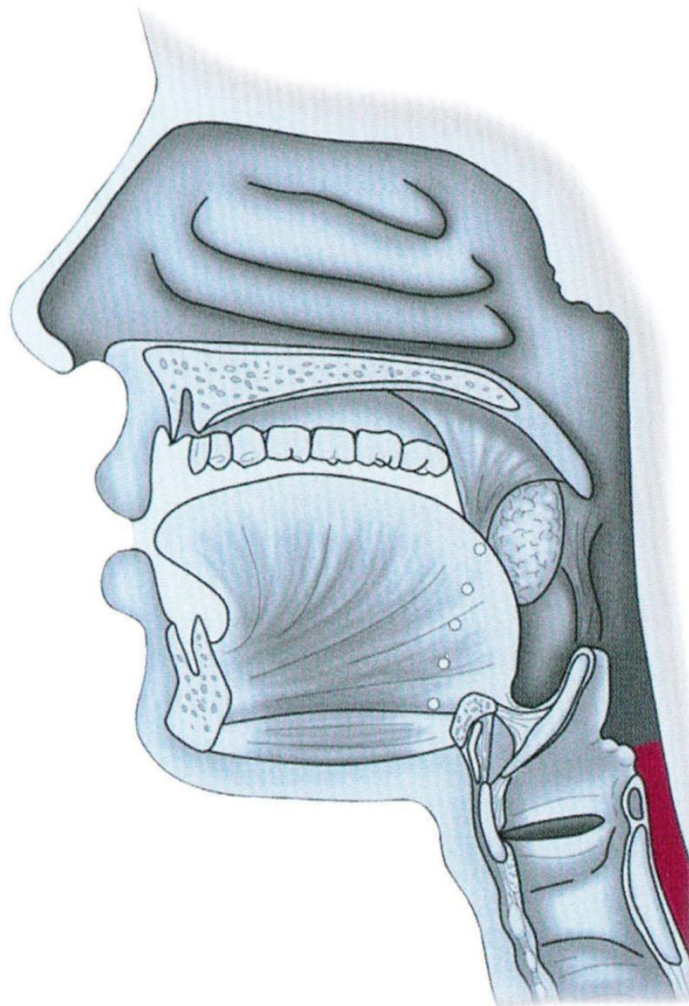
- » Pain
- » Dysphagia
- » Otalgia referred (Jacobson's nerve)
- » Metastatic, asymptomatic node in the neck (50-60%)
- » Foreign body sensation

- **Late symptoms:**

- » Trismus
- » Weight loss
- » Hemoptysis
- » Voice changes (Hot potato voice: tongue cancer  
Rhinolalia aperta: soft palate cancer)



## 2. CANCER OF THE HYPOPHARYNX



## 2.1. Etio-Epidemiology

- Frequency:
  - 0.4% of all cancers
  - 4% of all malignancies of the H&N
  - 7% of all malignancies of the upper aerodigestive tract (Calvados/France)
  - 2002: 124'000 cases worldwide
- Race:
  - African Americans ↗ since 1970s
- Sex:
  - M:F = 3:1
  - France/Switzerland: Male - pyriform sinus (**OH + tobacco**)
  - Ireland/Scandinavia/England: Female - postcricoid (Plummer-Vinson, hot drinks)
- Age:
  - Mean age = 65 years (> 40 years, rare < 30 years)

# Hypopharyngeal Cancer

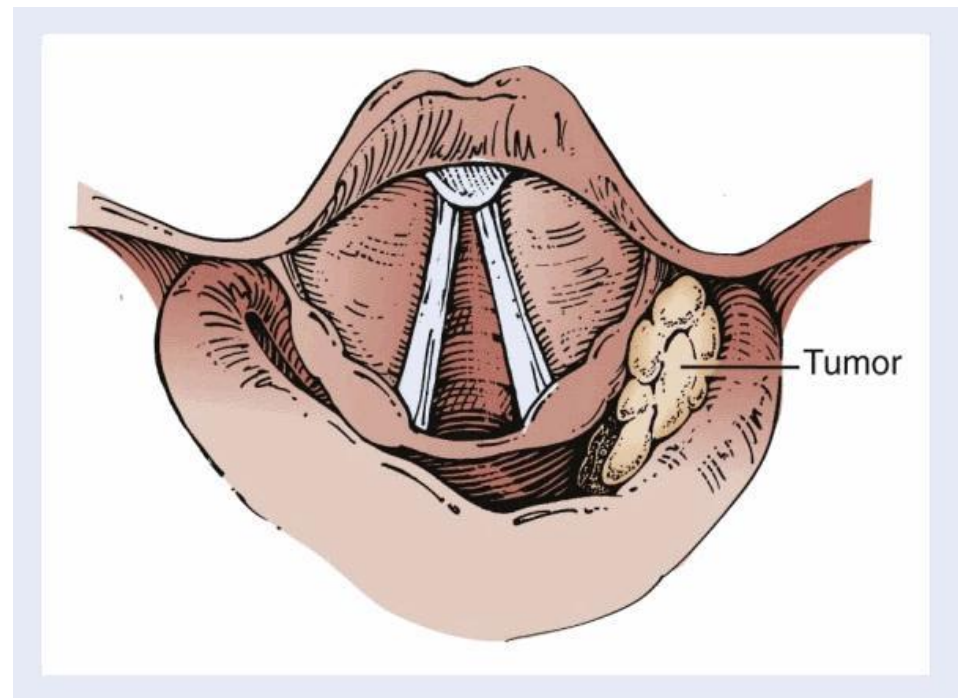
## Etio-Epidemiology

- Tobacco
  - Alcohol
- } **Synergistic effect!!!**
- Plummer-Vinson or Paterson-Kelly syndrome → postcricoid HPC in women (= dysphagia, oesophageal webs, weight loss, iron deficiency anemia)
  - Hot drinks → chronic burning lesions of the mucosa???
  - Nutrition (nitrosamines)???
  - Parasites???
  - GER ???
  - Asbestose ???
  - HPV ???
  - Genetic deficiencies (affection of the metabolism of tobacco-related and other carcinogens, malfunctions in DNA repair mechanisms and cell-cycle regulation)



## 2.2. Macroscopic Aspects and Histology

- Macroscopy:
  - Infiltrative (glands, muscles, cartilage, membranes)
  - Ulcer
  - Exophytic
  - Superficial spreading



# Hypopharyngeal Cancer

## Pathology / Histology

- 95% = Squamous cell carcinoma
  - 60% keratinizing
  - 33% nonkeratinizing
  - usually poorly differentiated

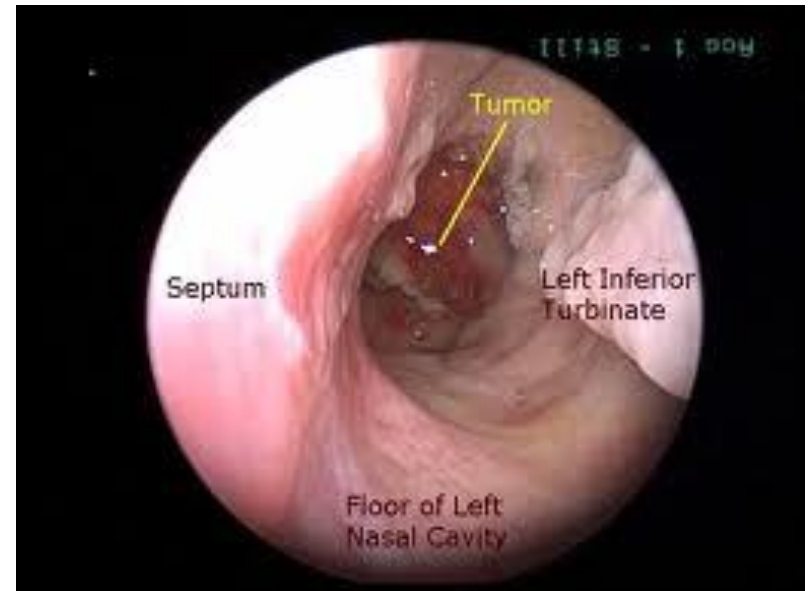
## 2.3. Symptoms and History

- Relatively silent and asymptomatic
- Symptoms delay: 3-4 months (3 – 12 months)
- **Symptoms = large lesions**
  - **Early symptoms:**
    - » Otolgia referred (Arnold nerve)
    - » Dysphagia
    - » Dysphonia/Hoarseness
    - » Chronic unilateral sore throat (> 1 course of AB)
    - » Foreign body sensation
    - » Metastatic, asymptomatic node in the neck (20%)
    - » Hypersalivation
  - **Late symptoms:**
    - » Weight loss
    - » Hemoptysis
    - » Laryngeal stridor
    - » Halithosis of necrosis



# 3. Work-up

- Complete H&N examination
  - Fiberoptic endoscopy
  - Bilateral neck examination
  - Head examination (CN function, jaw mobility → Trismus?)
  - Biopsy + Evaluation of tumor extension (Nasopharynx)
  - Panendoscopy (Oropharynx + Hypopharynx)
- Lab studies
- Full dental evaluation
  - extraction of non-restorable teeth, fluoride trays
- Imaging studies
  - Loco-regional: CT / MRI
  - Thoraco-abdominal: CT/PET-CT



# Pharyngeal Cancer

## Special diagnostic tests

- Nasopharyngeal cancer
  - EBV IgA viral capsid antigen (IgA VCA)
  - EBV early antigen (IgA EA)
- Plasma EBV DNA levels (pre-/post-tt.)
- Oropharyngeal cancer
  - HPV in the tissue

Screening and  
diagnostic  
markers, but  
lack of  
specificity

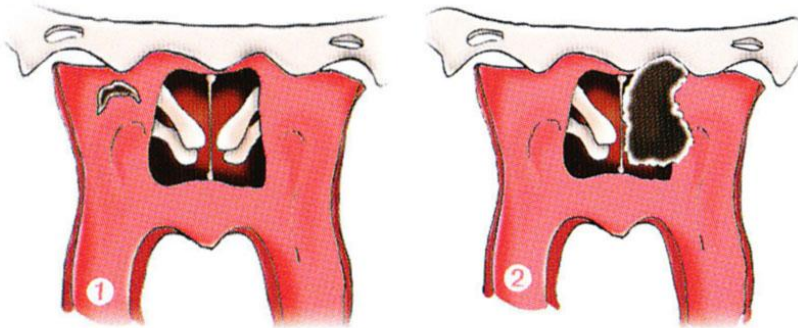
Monitoring of  
disease  
response and  
recurrence

# Pharyngeal Cancer

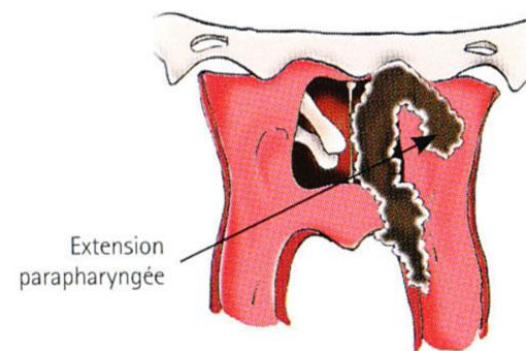
## Nasopharynx - UICC, TNM 2009



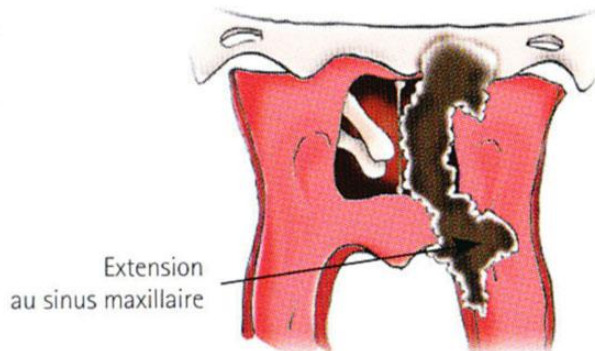
**T1**



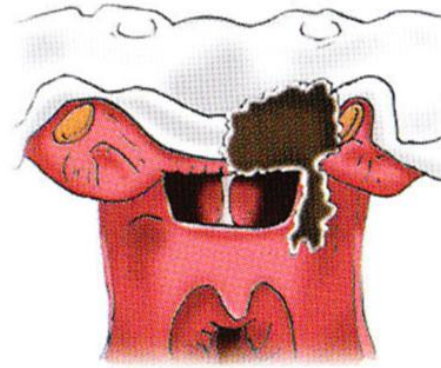
**T2**



**T3**



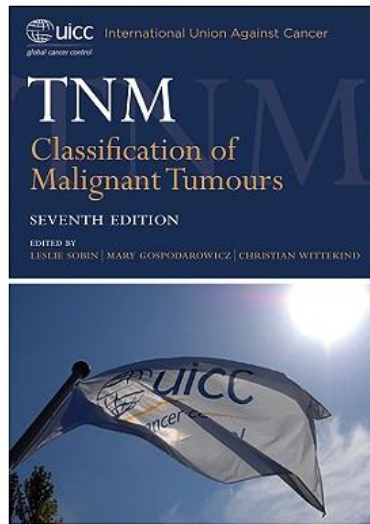
**T4**



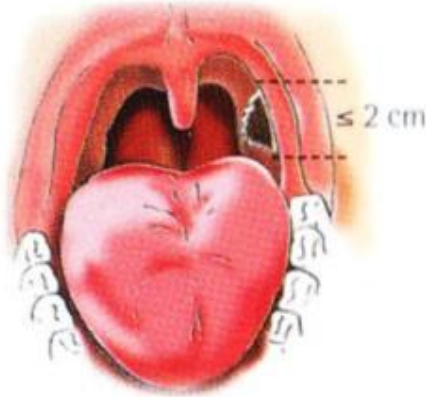


# Pharyngeal Cancer

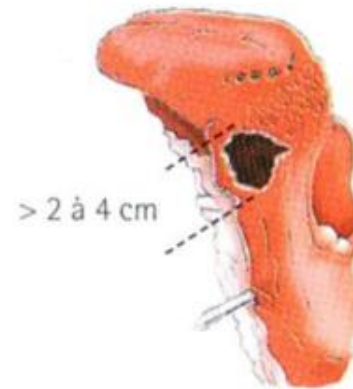
## Oropharynx - UICC, TNM 2009



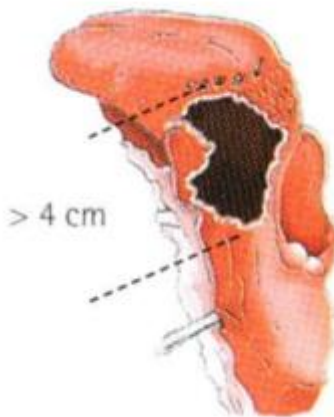
**T1**



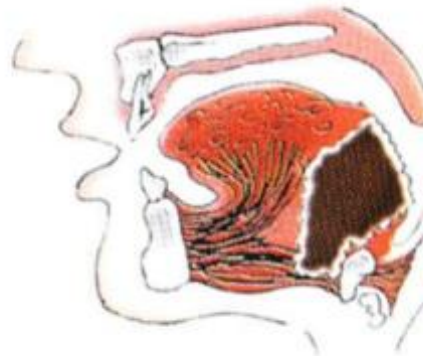
**T2**



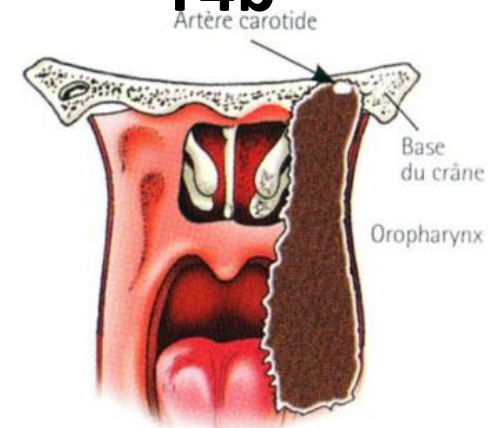
**T3**



**T4a**

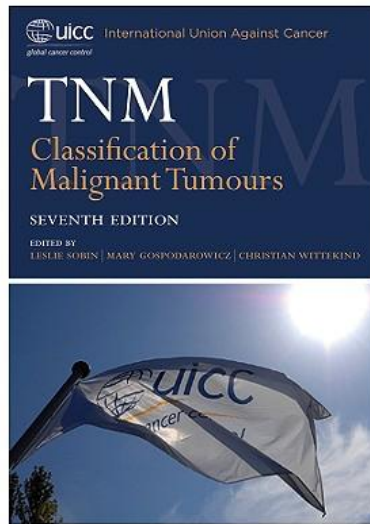


**T4b**

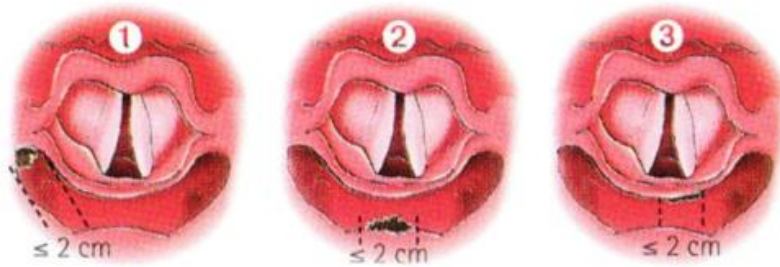


# Pharyngeal Cancer

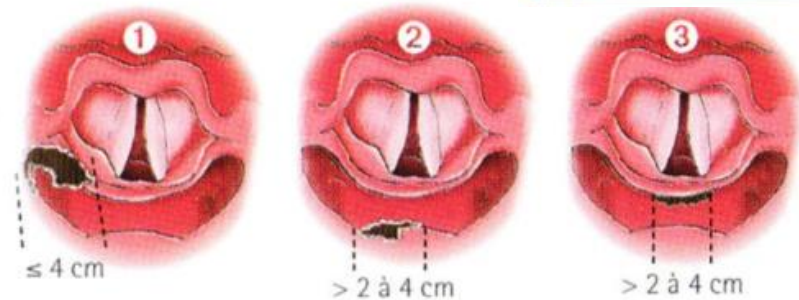
## Hypopharynx - UICC, TNM 2009



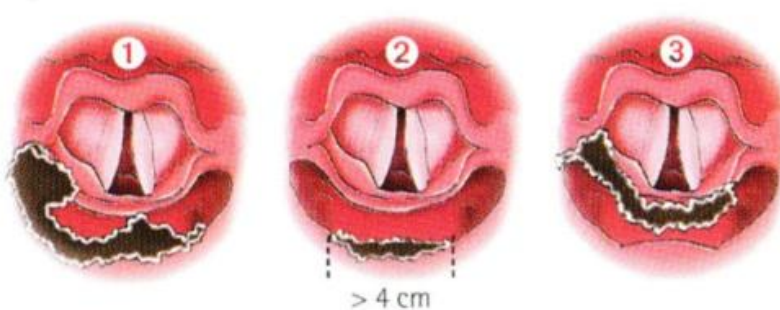
**T1**



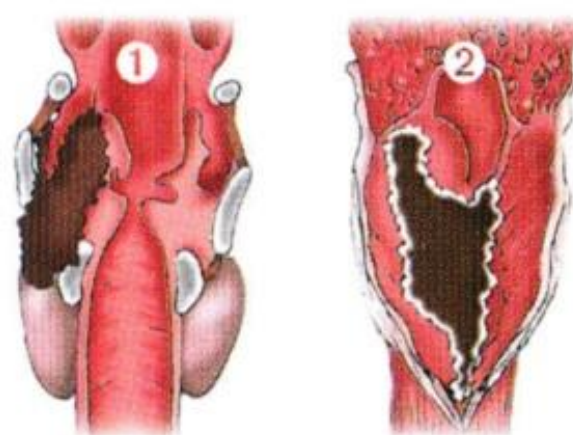
**T2**



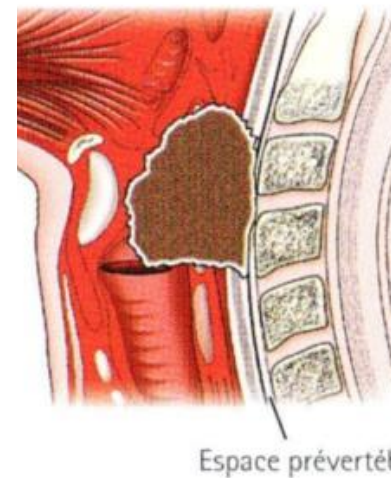
**T3**



**T4a**



**T4b**

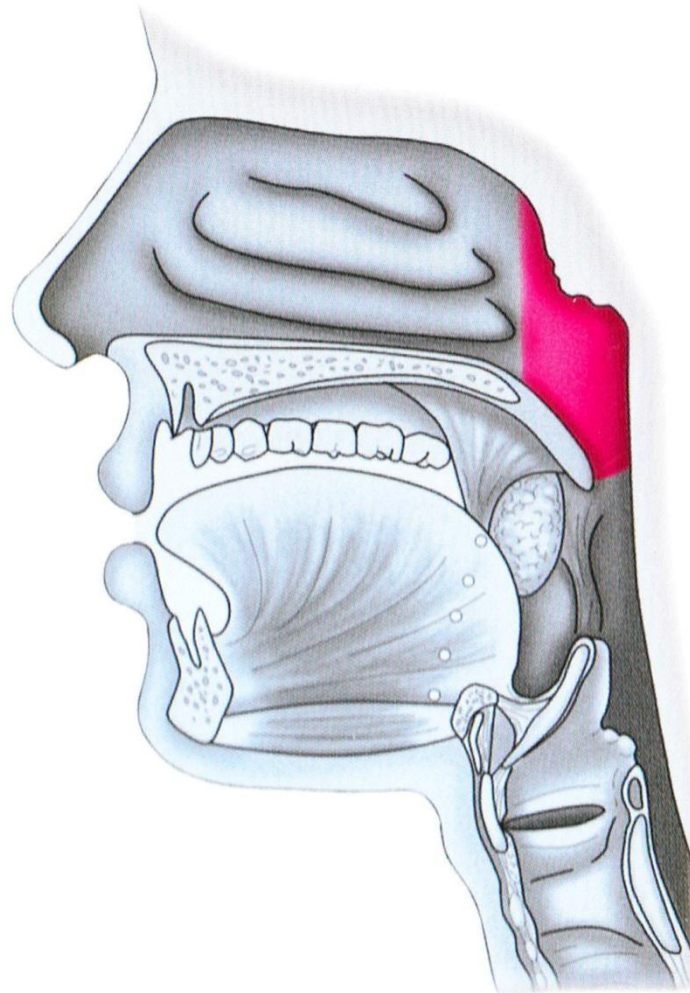


## 4. General Findings





# CANCER OF THE NASOPHARYNX



# Nasopharyngeal Cancer

## General Findings

- Natural History of NPC:
  - 10-15% = local disease
  - 85-90% = loco-regional disease  
**(50% = N3)**
  - 3% = distant metastases



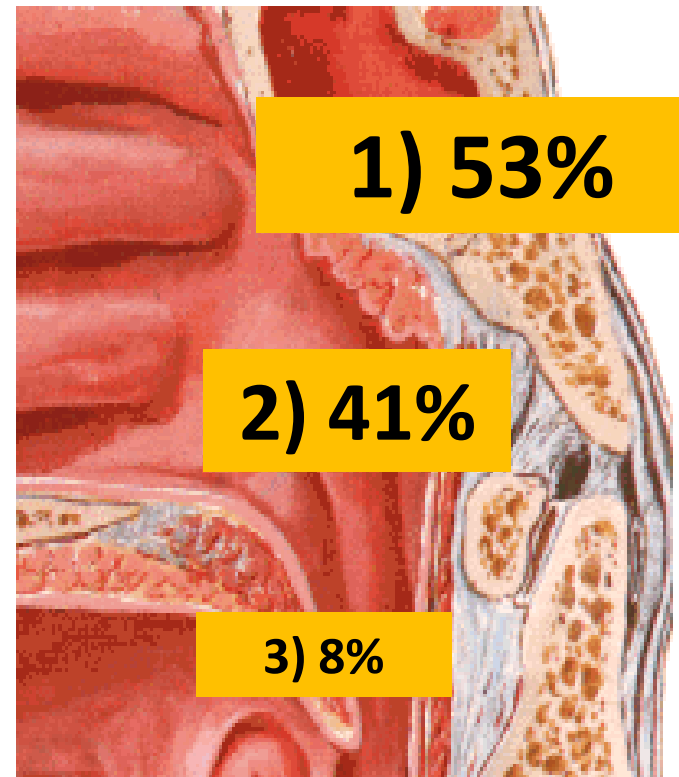
### CAVE:

M1 - 40%, if:  
undifferentiated  
T4  
N3  
supraclavicular fossa

# Nasopharyngeal Cancer

## General Findings

- Subsites:
  - 1. Postero-superior wall
  - 2. Lateral wall (including the fossa of Rosenmüller)
  - 3. Inferior wall





# Nasopharyngeal Cancer

## General Findings

TNM-Stages	Distribution of Nasopharynx Cancer
I	15%
II	32%
III	28%
IV	25%

# Nasopharyngeal Cancer

## Lymph node spreading – T stage

T stage	Risk of nodal disease	
T1	<b>85-90%</b>	
T2		
T3		
T4		
Any T	Palpation:	50-90%
	Bilateral:	50%
	Spinal level:	+++
	Retropharyngeal:	+++

# Nasopharyngeal Cancer

## Lymph node spreading - Levels



**Retropharyngeal  
lymph nodes**

**Level I  
7%**

**Level II  
82%**

**Level III  
31%**

**Level IV  
16%**

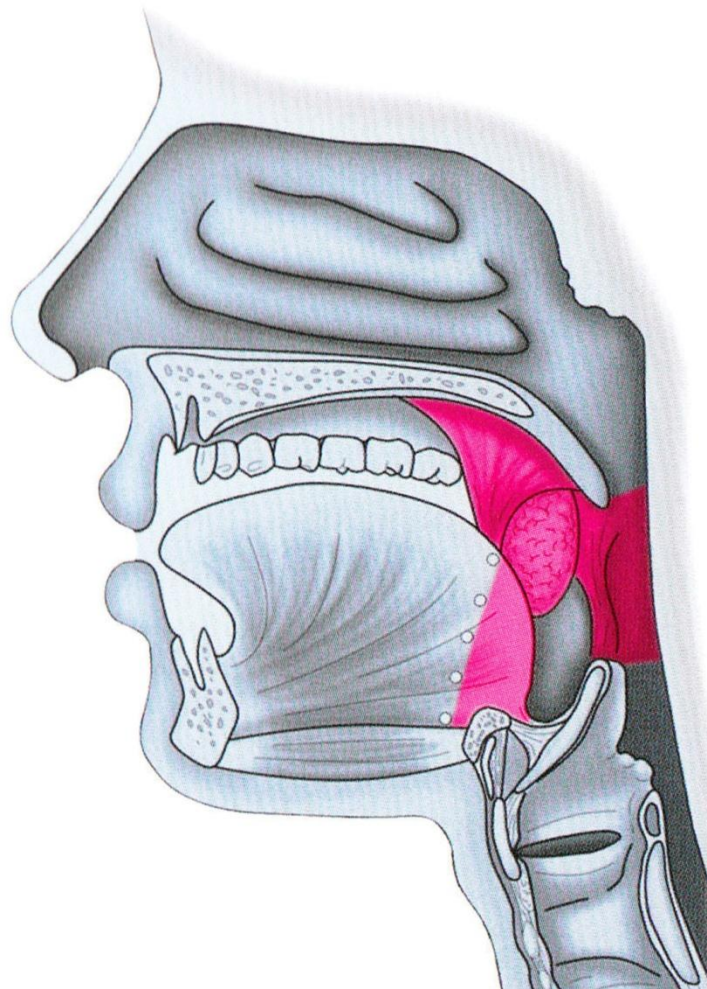
**Level V sup. 36%**

**Level V mid. 26%**

**Level V inf. 22%**

(Fletcher, 1980)

# CANCER OF THE OROPHARYNX



# Oropharyngeal Cancer

## General Findings

- Natural History of OPC:

- 35% = local disease
- 63% = loco-regional disease
- 2% = distant metastases



### **CAVE:**

concomitant primaries in UADT: 15%

soft palate cancer: metachronous  
2nd cancer in > 50%

# Oropharyngeal Cancer

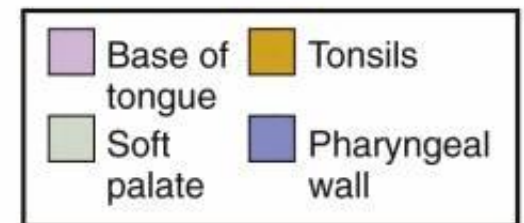
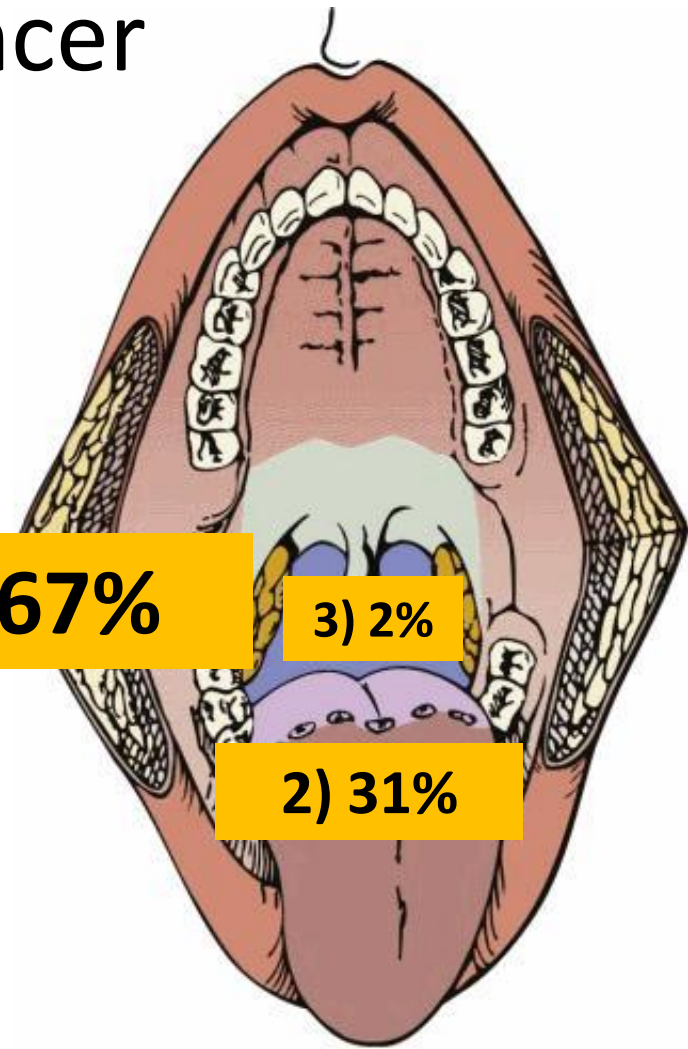
## General Findings

- Subsites:
  - 1. Latero-superior pharyngeal wall (tonsillar fossae)
  - 2. Glossoepiglottic area
  - 3. Posterior pharyngeal wall

**1) 67%**

**3) 2%**

**2) 31%**





# Oropharyngeal Cancer

## General Findings

TNM-Stages	Distribution of Oropharynx Cancer
I	34%
II	31%
III	25%
IV	10%

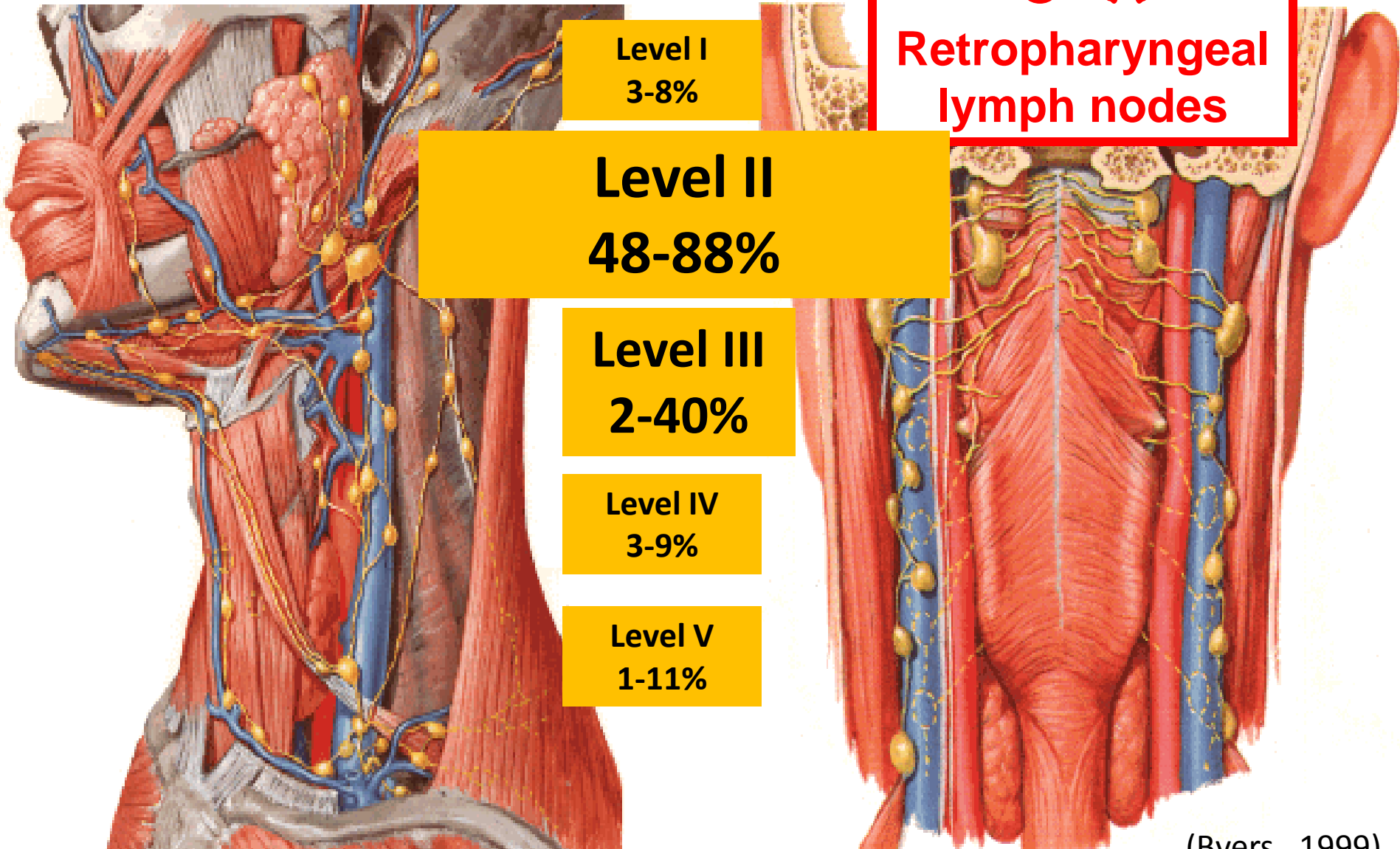
# Oropharyngeal Cancer

## Lymph node spreading – T stage

T stage		Risk of nodal disease	
T1		44%	
T2		52%	
T3		75%	
T4		80%	
Any T		Palpation:	63%
		Contralateral:	20%
		Bilateral:	40%
		(tongue base and soft palate)	
		Occult:	35%
Soft palate	45%		
Oropharyngeal posterior wall	49%		
Tonsillar fossa	75%		
Base of tongue	77%		

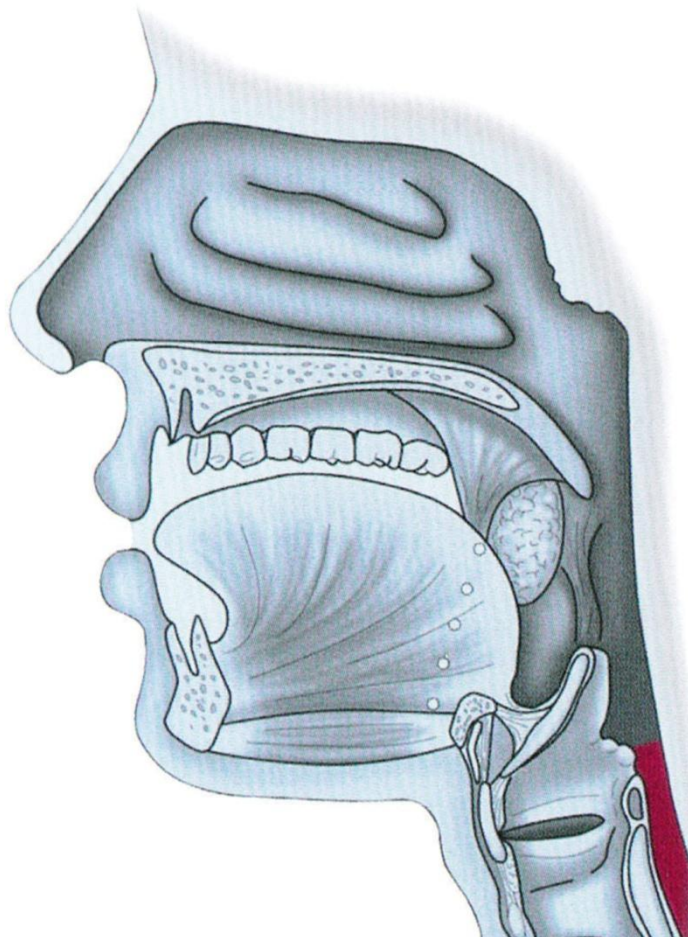
# Oropharyngeal Cancer

Lymph node spreading - Levels



(Byers , 1999)

# CANCER OF THE HYPOPHARYNX



# Hypopharyngeal Cancer

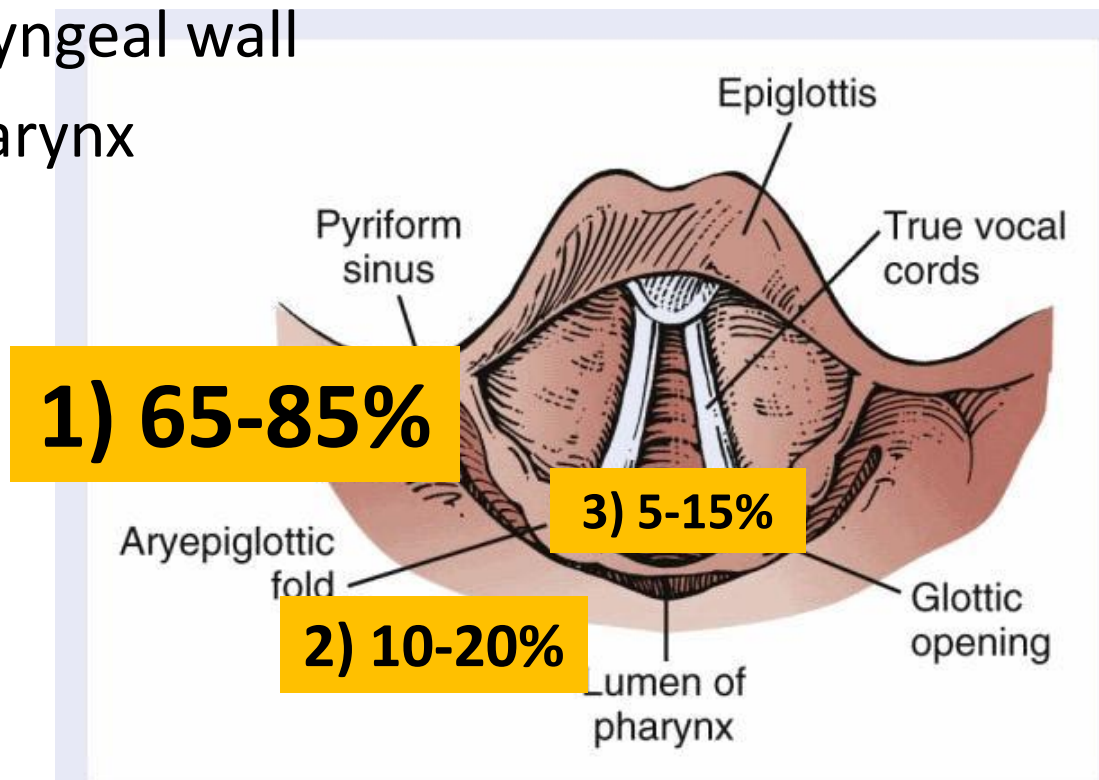
## General Findings

- Natural History of HPC:
    - 30% = local disease
    - 60% = loco-regional disease
    - 10% = distant metastases
    - Most patients = T3 / T4 tumors
- **CAVE:**
- |  |       |
|--|-------|
| synchronous pharyngeal tumors:         | 15%   |
| synchronous lung or esophageal tumors: | 5-10% |
- high risk tumors → often:
- Lymphovascular invasion
  - Perineural invasion
  - Poorly differentiated

# Hypopharyngeal Cancer

## General Findings

- Subsites:
  - 1. Pyriform sinus
  - 2. Posterior pharyngeal wall
  - 3. Postcricoid pharynx





# Hypopharyngeal Cancer

## General Findings

TNM-Stages	Distribution of Hypopharynx Cancer
I	10%
II	12%
III	23%
IV	55%

} **> 78%**

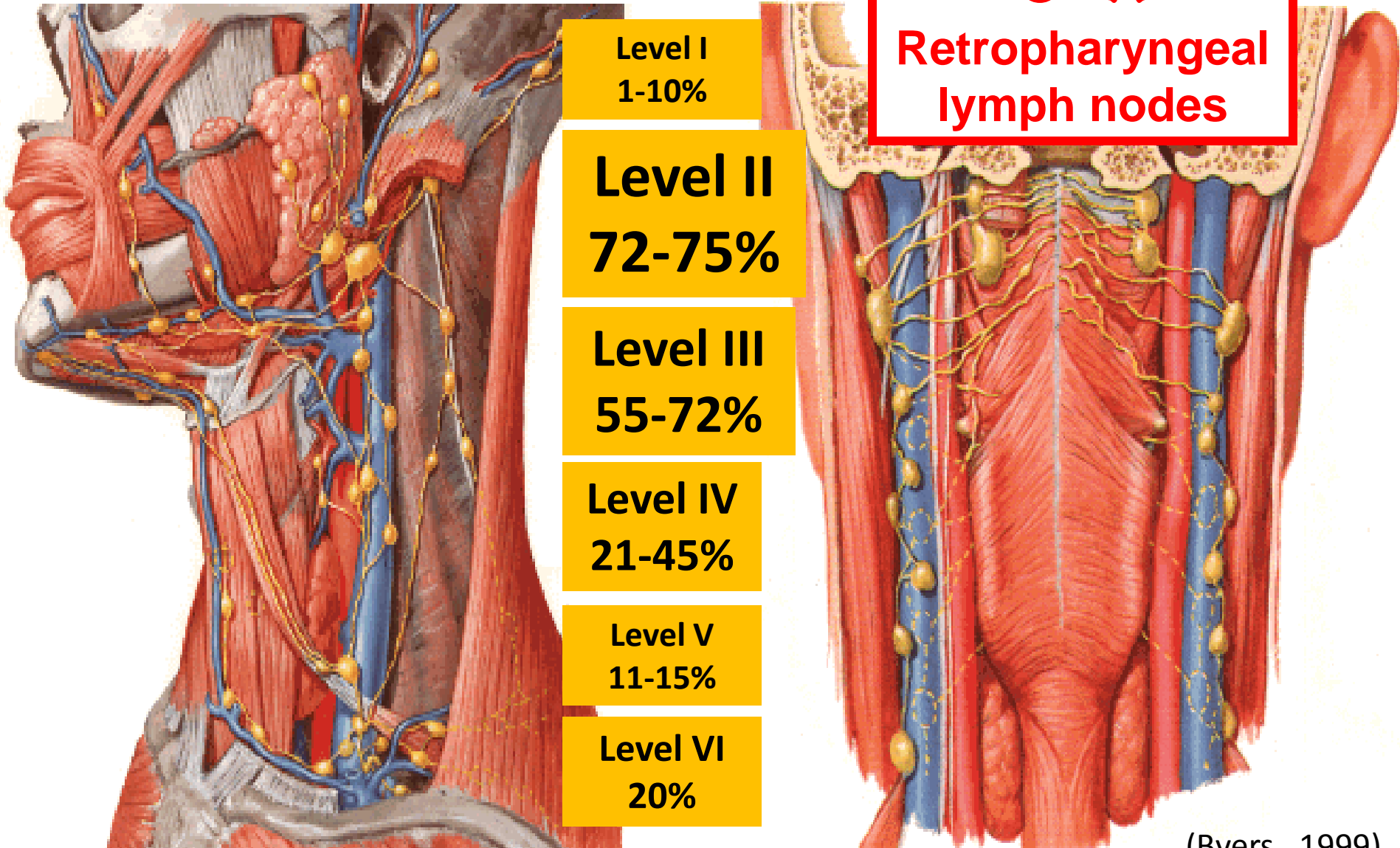
# Hypopharyngeal Cancer

## Lymph node spreading – T stage

T stage	Risk of nodal disease
T1	60%
T2	60-70%
T3	85%
T4	85%
Any T	Palpation: 70% Histol. N+/ECS: 85/50% Contralateral occult: 40% Bilateral: 10-20% Retropharyngeal, if N+: 90%

# Hypopharyngeal Cancer

Lymph node spreading - Levels



(Byers , 1999)

# 5. Tumor-Management

- **Pluridisciplinary  
Tumorboard!**



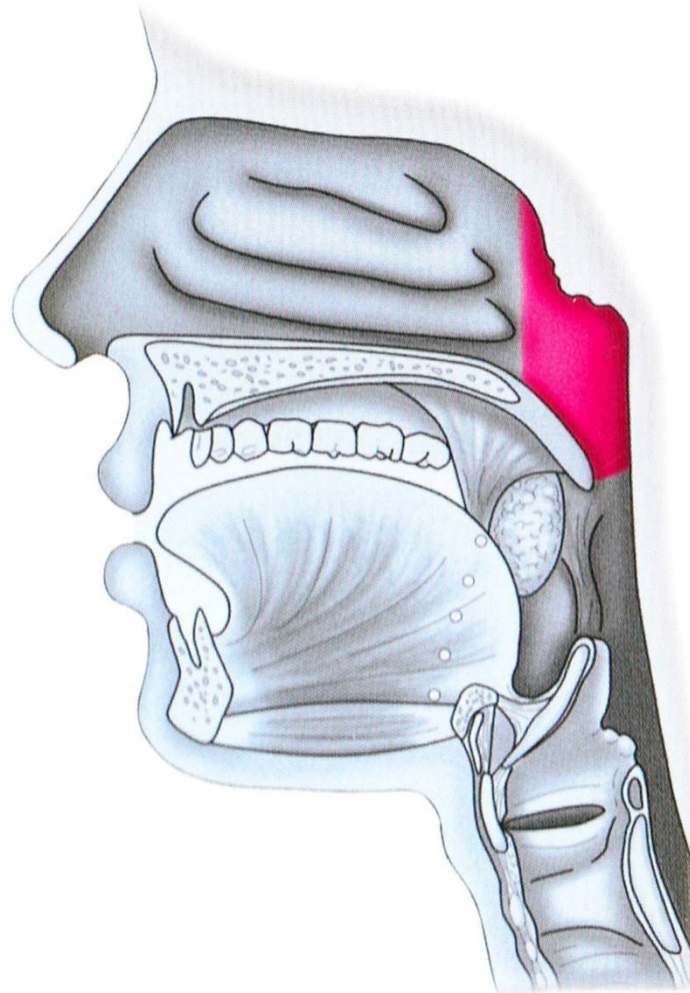
# Tumor-Management

## Pretreatment Care

- Dental care and prophylaxis with fluoride (osteoradionecrosis!)
- Nutritional evaluation (malnutrition!)
  - 75% with CXRT → feeding tube
  - Prophylactic placement often recommended, if laryngeal structures involved
- Speech/swallowing evaluation (**early evaluation for rehabilitation!**, maybe pretreatment barium swallow)
- Prophylactic tracheotomy?
  - Emergency tracheotomy in 5-15%

# Tumor-Management

## Cancer of the Nasopharynx

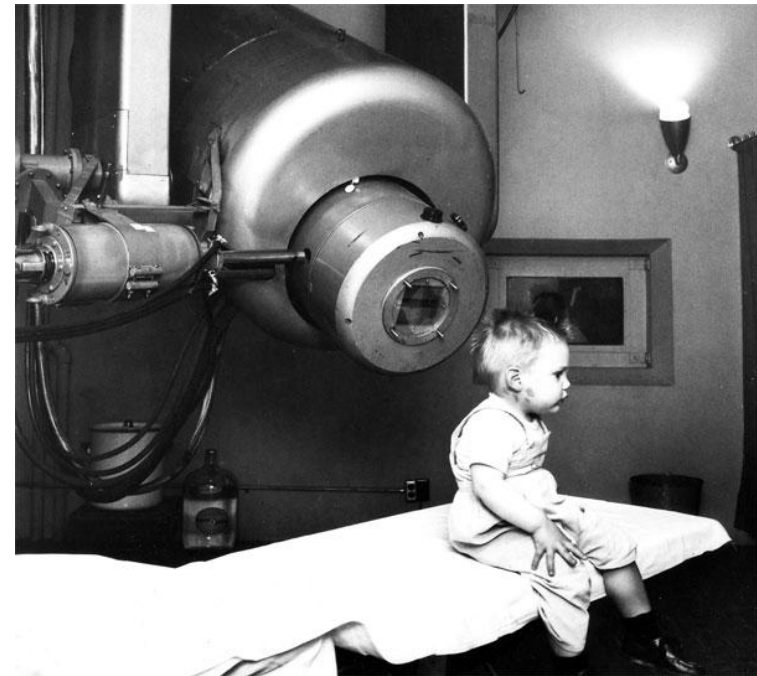


# Nasopharyngeal Cancer

## Treatment - Generalities

### Radiotherapy!

- RT as the mainstay
  - Difficult surgical approach
  - Sensitive to RT





# Nasopharyngeal Cancer

## Treatment - Generalities

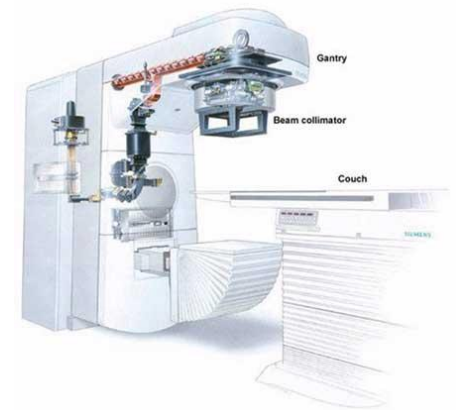


- ***Early-staged nasopharyngeal cancer (Stage I):***
  - **RT** (Lee, Int J Radiat Oncol Biol Phys 2005)
- ***Intermediate-staged nasopharyngeal cancer (Stage II):***
  - **RT vs CXRT?** (small number of patients in prospective studies)
  - **RT < CXRT** (11% better distant failure-free rate) (Cheng, J Clin Oncol 2000)
  - **Induction CX + RT > RT** (Chua, Int J Radiat Oncol Biol Phys 2006)
- ***Advanced-staged nasopharyngeal cancer (Stage III/IV):***
  - **RT = RT + adjuvant CX** (no benefit) (Chi, Int J Radiat Oncol Biol Phys 2002; Rossi, J Clin Oncol 1988)
  - **RT < CXRT** ( $\searrow$ 18% risk of death,  $\nearrow$ 4-6% 5-year overall survival (Meta-analysis, J Clin Oncol 2004; Meta-analysis, Int Radiat Oncol Biol Phys 2006; Levebvre (EORTC), J Natl Cancer Inst 1996)
  - **CXRT + adjuvant CX?** (optional, more randomized studies needed)
  - **Induction CX? + CXRT?** ( $\nearrow$  overall survival) (Hui, J Clin Oncol 2009)

# Nasopharyngeal Cancer

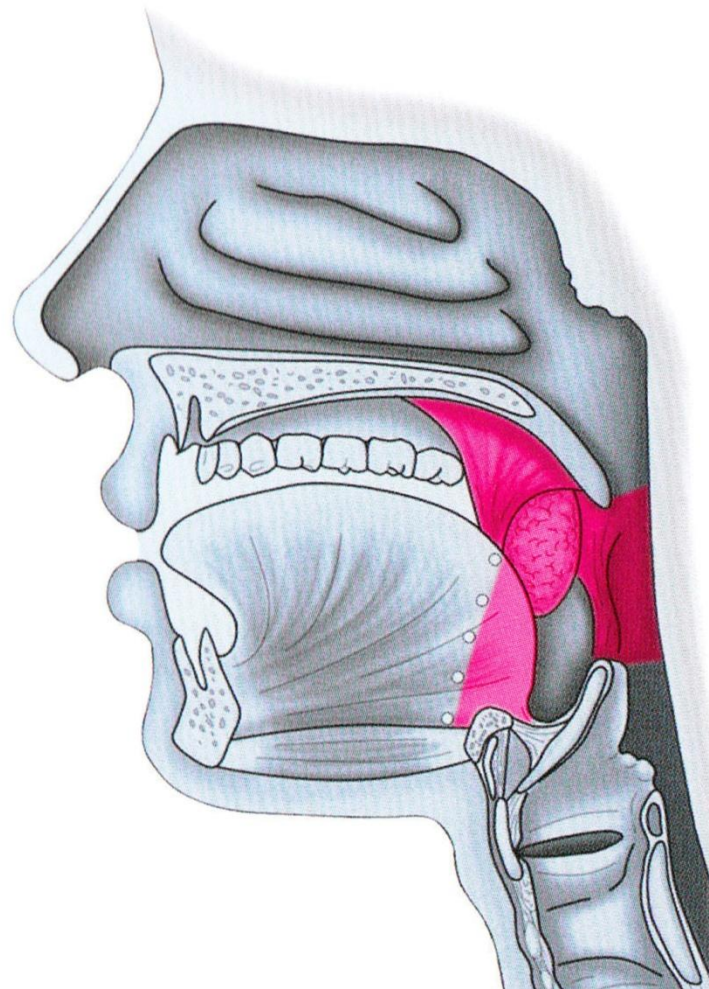
## Treatment

- **Early stage T1 N0**
  - External RT alone (primary / prophylactic RT of neck)
- **Intermediate and advanced stage > T1 and/or > N0**
  - External CXRT (evtl. + antibodies to EGFR) (primary / neck)
  - Adjuvant CX optional
  - ND for residual lymph nodes (survival ↗ compared with repeated RT)



# Tumor-Management

## Cancer of the Oropharynx



# Oropharyngeal Cancer

## Treatment - Generalities

- **Restriction of surgery to:**
  - **clinical situations in which probability of local control with RT is low**
  - and/or**
  - **RT would be associated with a high risk of severe complications**

# Oropharyngeal Cancer

## Treatment - Generalities

- ***Early-staged oropharyngeal cancer:***
  - **RT = Surgery** (Hinerman, Laryngoscope 1994, Mendenhall, J Clin Oncol 2000)
- ***Advanced-staged oropharyngeal cancer:***
  - **Surgery > RT** (Hicks, Laryngoscope 1998)
  - **Surgery + postop. RT(CX) > RT(CX)**  
(Foote, Cancer 1994)
- ***All-staged oropharyngeal cancer:***
  - **CX + RT > RT (loco-regional control and survival)**  
**(concomitant CX > adjuvant and neoadjuvant CX)**  
(Blanchard, Metaanalysis, Radiother Oncol 2011)



# Oropharyngeal Cancer

## Treatment of the Base of Tongue / Vallecula

- **T1 T2**
  - CXRT
  - If N+: ND prior to RT or planned post-RT
  - Treat both necks for central lesions
- **T3 T4 (lesions with epiglottic destruction or invasion of pre-epiglottic space)**
  - CXRT / Surgery and postop. RT(CX) may be discussed (patients with reasonable good general conditions!)
  - If N+: ND prior to RT or planned post-RT



# Oropharyngeal Cancer

## Treatment of the Tonsillar Fossa

- **T1 T2 T3**
  - CXRT
  - If N+: ND prior to RT or planned post-RT
  - Address retropharyngeal nodes
- **T4 (Lesions with deep extension to the mandible with trismus and/or destruction of the bony table)**
  - Surgery and ND with reconstruction and postop. RT(CX)





# Oropharyngeal Cancer

## Treatment of the Soft Palate

- **T1 < 10 mm:** transoral surgery and ND
- **>T2 (surgery will provide problems of speech and swallowing)**
  - CXRT
  - If N+: ND prior to RT or planned post-RT
  - Treat both necks for central lesions
  - Address retropharyngeal nodes

# Oropharyngeal Cancer

## Type of Surgery

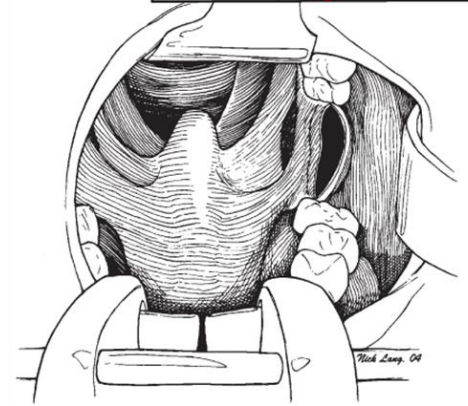
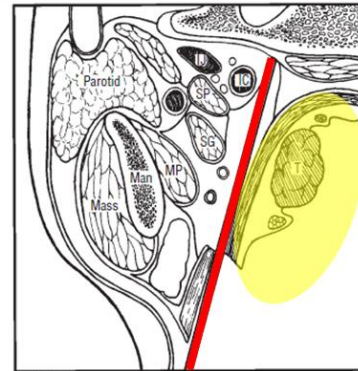
- Oral
  - Transoral resection
  - Mandibular lingual release
- Transpharyngeal
  - Suprahyoid pharyngotomy
  - Lateral pharyngotomy
- Transmandibular
  - Midline labiomandibular glossotomy
  - Mandibular swing
  - Mandibulectomy



# Oropharyngeal Cancer

## Transoral - Generalities

- For small, superficial, or exophytic lesions
  - Soft palate, anterior tonsillar pillar, posterior pharyngeal wall
  - Requires 1-2cm margin
- Positives
  - Quick
  - Minimal morbidity
  - Satisfactory functional outcomes, may avoid XRT/CXRT
  - Transoral laser microsurgery (TLM)
- Negatives
  - Affected by mandibular height, dentition, trismus
  - Limited visualization of posterior and deep margins
  - Bone invasion and advanced lesions = Contraindication



# Oropharyngeal Cancer

## Transoral – CO2-Laser (single modality)

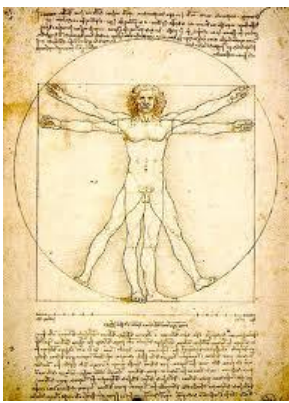
- Two-center retrospective series from 1996-2008 (Grant 2009)
  - No XRT indicated in 44 or refused in 25 patients
  - Mostly tonsil (41%) or tongue base (41%)

T1	T2	T3	T4
36%	43%	17%	3%

N0	N1	N2a	N2b	N2c	N3
45%	16%	23%	9%	1%	3%

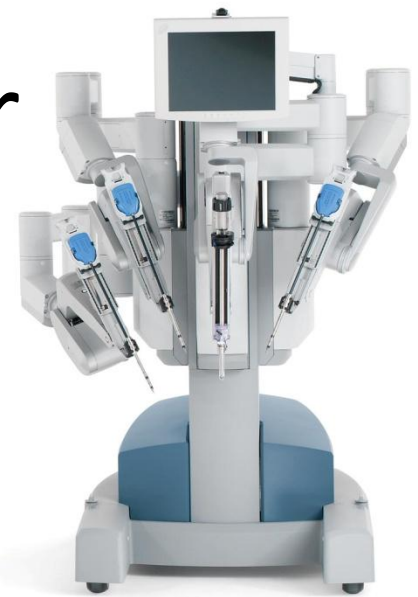
- Five-year results
  - 90-94% Local control
  - 74-82% Locoregional control
    - XRT not indicated: (73%), III (70%)
    - No difference between XRT or refusal groups

XRT Status	Not Indicated	Refused
Overall Survival	86%	49%
Disease-Free Survival	86-88%	72%



# Oropharyngeal Cancer

## Transoral Robotic Surgery



- Single-center retrospective series from 2005-2007
  - 50 patients with stage III or IV oropharyngeal SCCA
  - Transoral robotic surgery with ND
  - Adjuvant XRT/CXRT for large nodal disease or extracapsular spread, lymphovascular invasion, or positive margins
- Two-year results
  - HPV status: 37 positive, 13 negative
  - No difference in local, locoregional, recurrences

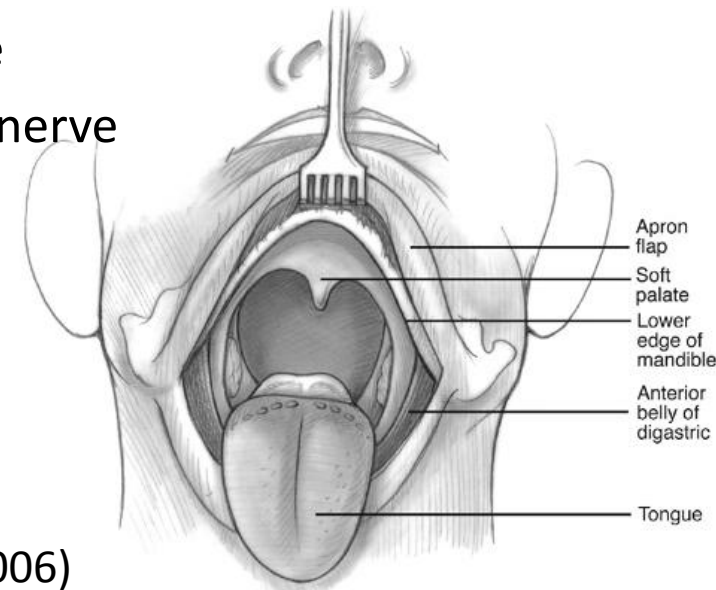
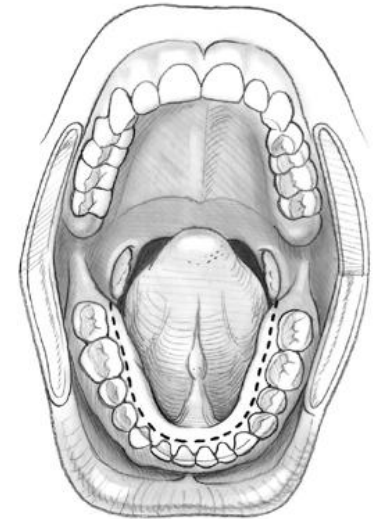
Classification	T3 or T4	Stage III or IV
HPV Positive	24.3%	89.2%
HPV Negative	15.4%	76.9%

Overall Survival	1 Year	2 Year
HPV Positive	97.2%	81.0%
HPV Negative	90.9%	80.0%
Disease-Free Survival	1 Year	2 Year
HPV Positive	97.2%	89.5%
HPV Negative	100%	100%

# Oropharyngeal Cancer

## Open Surgery - Mandibular Lingual Release

- Deliver tongue and floor of mouth into neck
- Positives
  - Good for base of tongue lesions
  - Does not require lip split or mandibulotomy
- Negatives
  - Less access laterally to parapharyngeal space
  - Risk to lingual artery and nerve, hypoglossal nerve



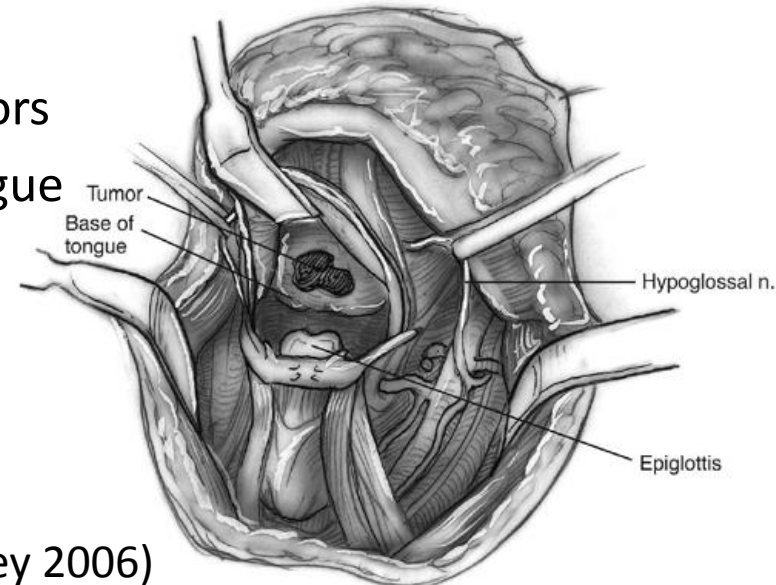
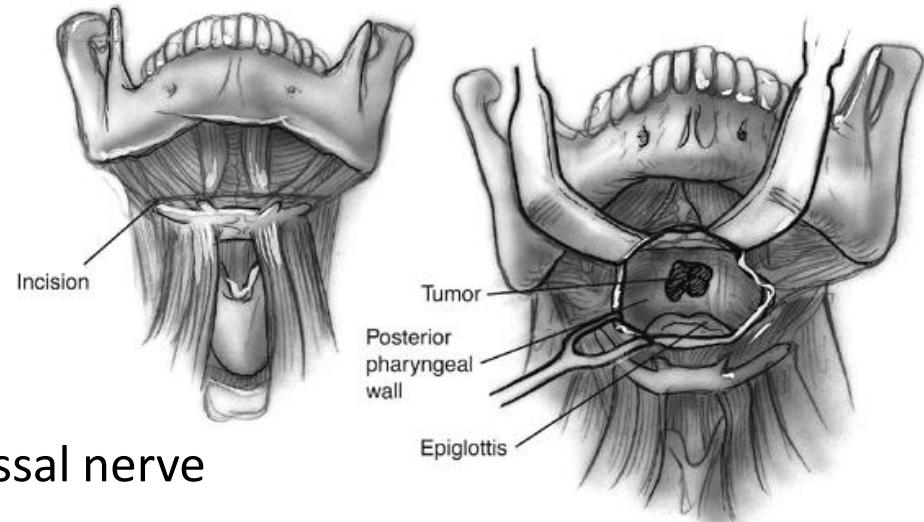
(Bailey 2006)



# Oropharyngeal Cancer

## Open Surgery - Suprahyoid Pharyngotomy

- Enter pharynx at vallecula
- Positives
  - Small tumors on base of tongue and pharyngeal walls
  - Preserves lingual artery and hypoglossal nerve
- Negatives
  - Inadequate superior margin with large tumors
  - Risk cutting into tumor if in vallecula or tongue base



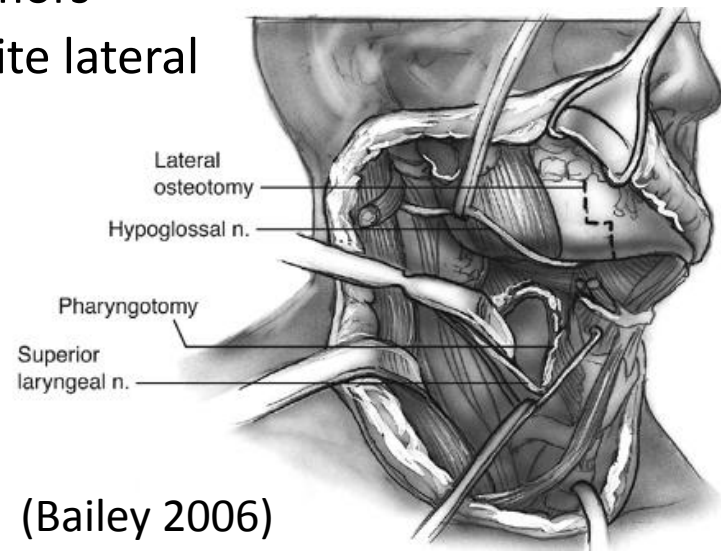
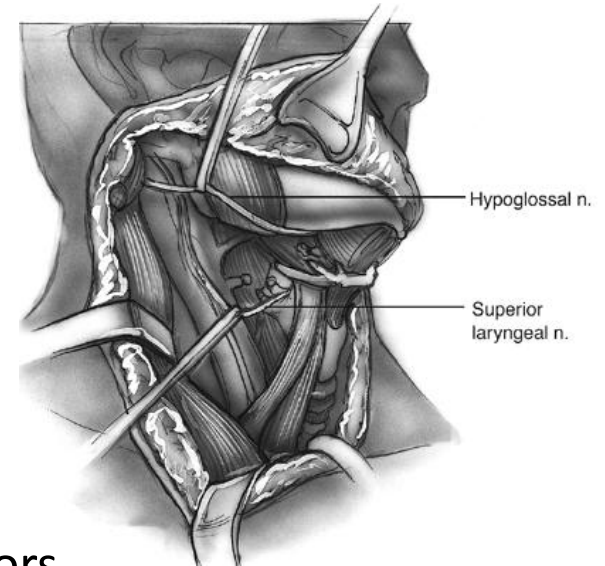
(Bailey 2006)



# Oropharyngeal Cancer

## Open Surgery - Lateral Pharyngotomy

- Enter pharynx posterior to thyroid ala
  - Retract hypoglossal and superior laryngeal nerves
  - Increase superior exposure across vallecula or lateral mandibulotomy
- Positives
  - Small base of tongue and pharyngeal wall tumors
  - View entire posterior pharyngeal wall, opposite lateral wall, and tongue base
- Negatives
  - Limited superior margin
  - Risk damaging hypoglossal and superior laryngeal nerves



(Bailey 2006)

# Oropharyngeal Cancer Ope

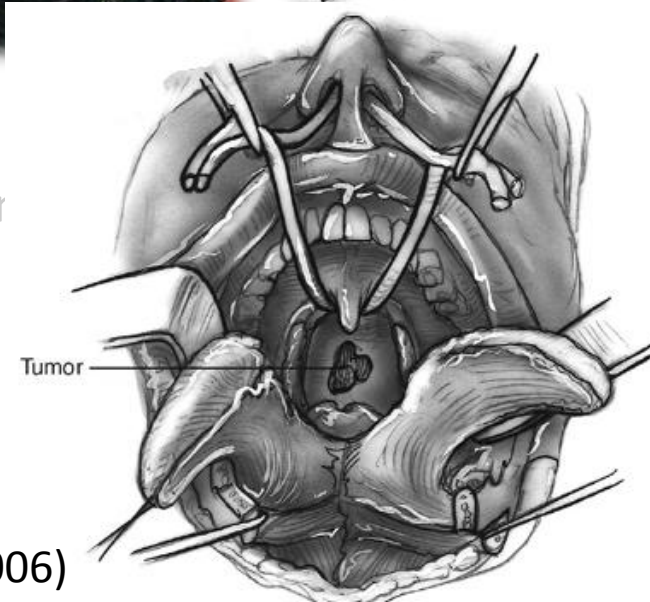
## Open Surgery - Midline Labiomandibular Glossotomy

- Trotter Procedure
- Split lip, gingiva, mandible, and tongue
- Positives

Get to da ~~chopper!!!~~  
**TROTTER**



lateral oropharynx

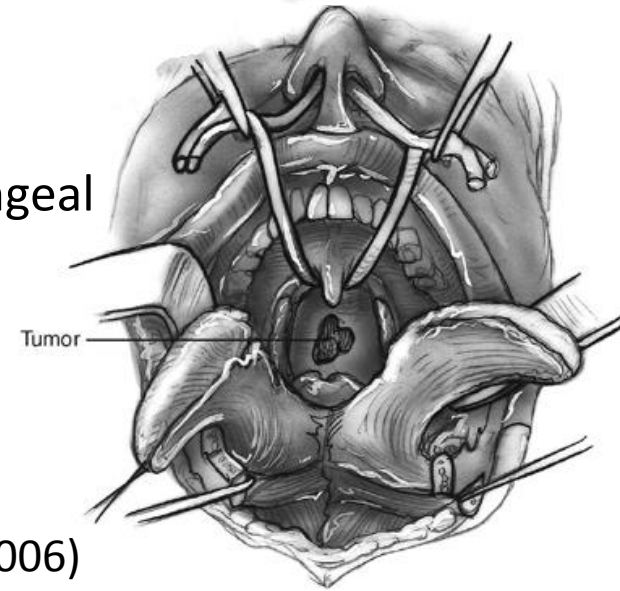
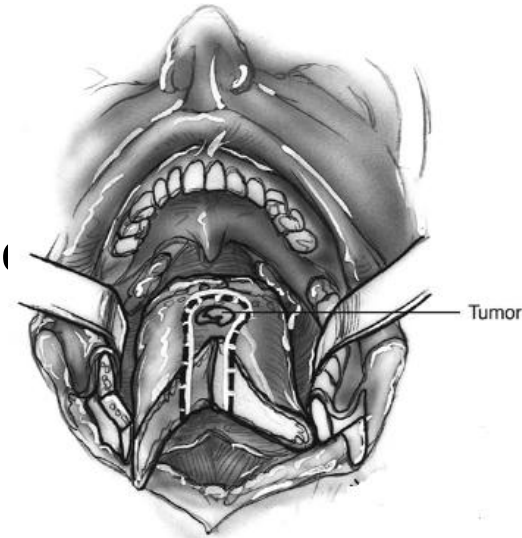


(Bailey 2006)

# Oropharyngeal Cancer

## Open Surgery - Midline Labiomandibular Glossotomy

- Trotter Procedure
- Split lip, gingiva, mandible, and tongue at midline
- Positives
  - Midline posterior pharynx or tongue base too low for transoral approach
  - Spares hypoglossal nerve and lingual artery
- Negatives
  - No access to parapharyngeal or lateral oropharyngeal sites



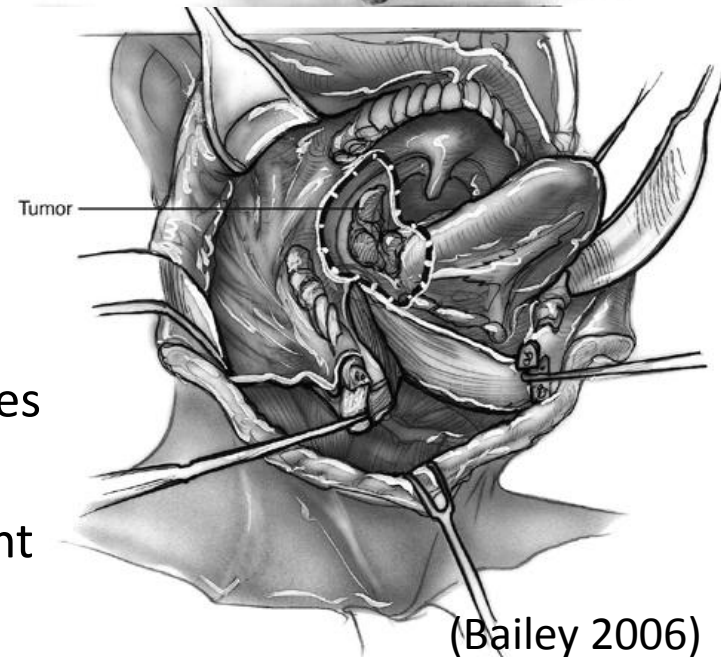
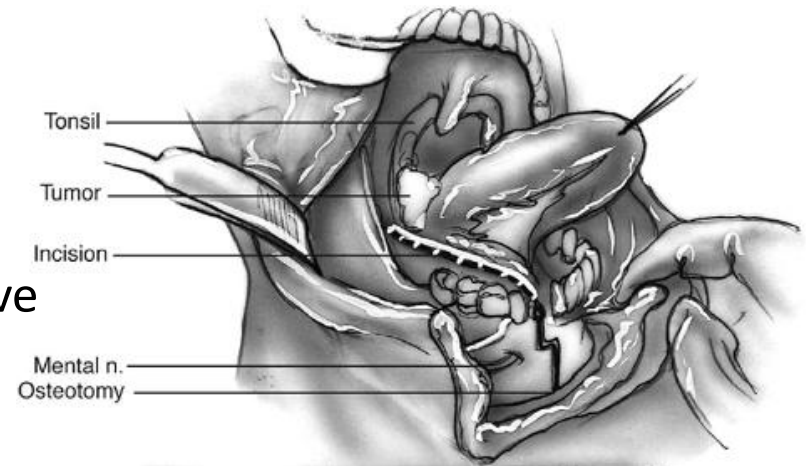
(Bailey 2006)



# Oropharyngeal Cancer

## Open Surgery - Mandibular Swing

- Wide local excision
  - Incise lip and floor of mouth
  - Mandibulotomy anterior to mental nerve
  - Dissect carotid and lingual and hypoglossal nerves
- Positives
  - Wide exposure of entire oropharynx
  - En bloc resection with lymphadenectomy possible
- Negatives
  - Neck dissection to identify arteries and nerves
  - Usually requires free flap reconstruction
  - Contraindicated with mandibular involvement

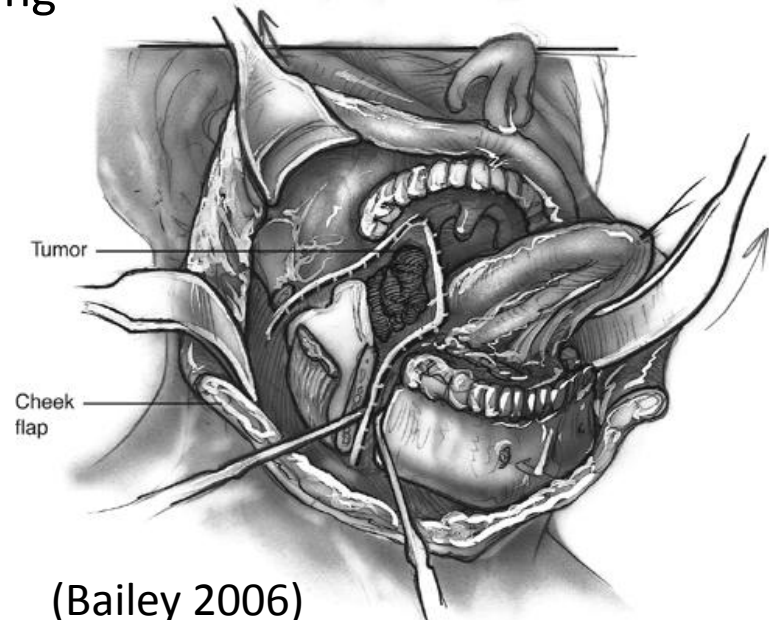
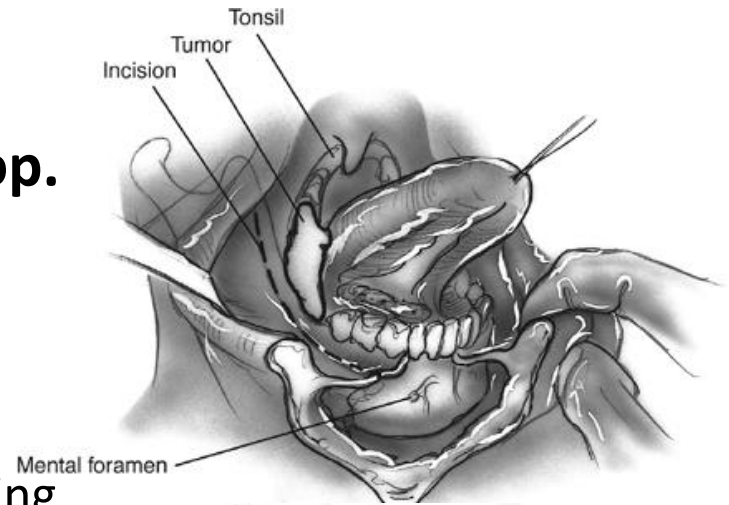


(Bailey 2006)

# Oropharyngeal Cancer

## Open Surgery - Mandibulectomy

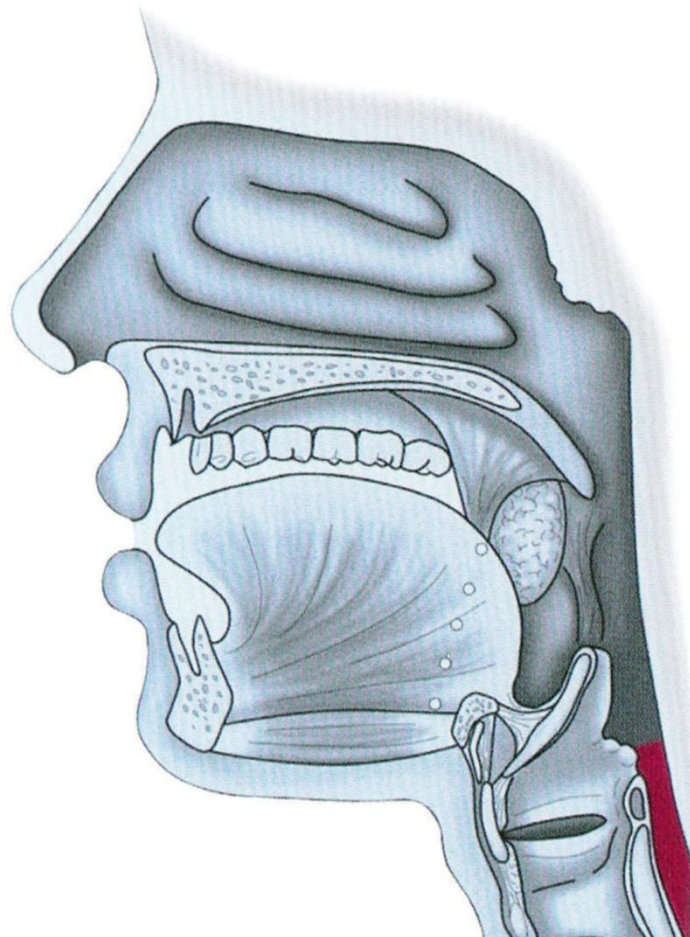
- Composite resection = **“Commando” op.**
  - Incise lip and gingivobuccal sulcus
  - Usually preceding neck dissection
- Positives
  - Comparable approach with mandibular swing
  - Addresses mandibular invasion
- Negatives
  - Functional and cosmetic deficits
  - Mental canal transected
  - Usually requires free flap reconstruction



(Bailey 2006)

# Tumor-Management

## Cancer of the Hypopharynx



# Hypopharyngeal Cancer

## Treatment - Generalities

**Preservation of the larynx!**



# Hypopharyngeal Cancer

## Treatment - Generalities

- **Early-staged hypopharyngeal cancer:**
  - **RT = Surgery + RT** (Rabani, Int J Radiat Oncol Biol Phys 2008)
- **Advanced-staged hypopharyngeal cancer:**
  - **RT (+ salvage surgery) < Surgery + RT** (Godballe, Laryngoscope 2002)
  - **RT < RT + cetuximab** (Bonner, Lancet Oncol 2010)
- **All-staged hypopharyngeal cancer:**
  - **Surgery + RT = Induction CX + RT in responders** (35% functional larynx,  $\searrow$  distant metastases) (Levebvre (EORTC), J Natl Cancer Inst 1996)
  - **Hyperfractionated RT > RT** ( $\nearrow$  10-15% in local control, = survival) (Garden, Head Neck 1996)
  - **CXRT > RT** (survival benefit of 4% at 2 and 5 years) (Lancet, Metaanalysis 2000)
  - **Surgery + RT = Concurrent CXRT** (=survival, =loco-regional control,  $\nearrow$  organ- preservation 68% vs 30%) (Soo, Br J Cancer 2005)



# Hypopharyngeal Cancer

## Treatment – Early Stage

- **T1/T2 N0 N1**

- CXRT alone
- Surgery (partial pharyngectomy + bilateral ND)  
± postop. (CX)RT

**Larynx  
Preserv.**



- **T1/T2 N2-3**

- CXRT alone
- Surgery (partial pharyngectomy + bilateral ND)  
+ postop. (CX)RT
- Bilateral ND + CXRT

**Larynx  
Preserv.**

# Hypopharyngeal Cancer

## Treatment – Advanced Stage: resectable

- **T3/T4a anyN**

- Surgery (Partial or Total Laryngopharyngectomy + bil. ND I-VI + ipsilateral Hemithyroidectomy) + postop. (CX)RT
- CXRT (cisplatin + 5-FU/cetuximab?)
- Induction CX → organ-preservation if 80% response  
→ CXRT otherwise radical surgery



(Yoon, Acta Otolaryngol 2008)

# Hypopharyngeal Cancer

Treatment – Advanced Stage: unresectable / unstable

- **T4b / medical problems**

- CXRT (cisplatin + 5-FU/cetuximab?)
- Induction CX → CXRT (cisplatin + 5-FU/cetuximab?)  
if response, otherwise palliation

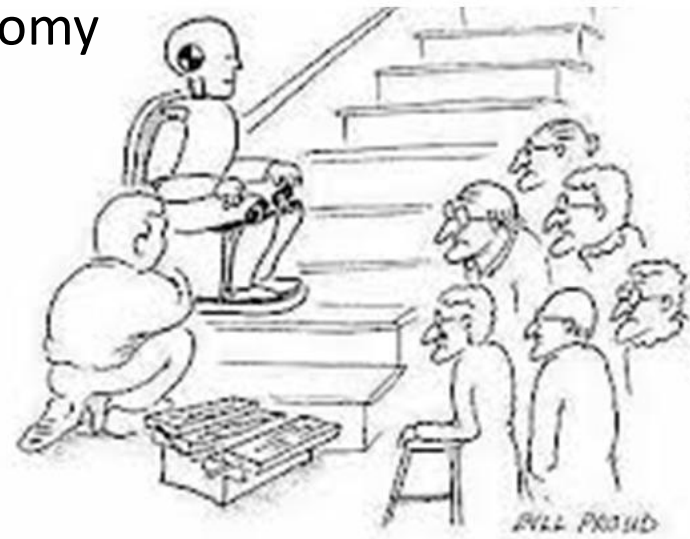


# Hypopharyngeal Cancer

## Type of Surgery

- **Conservative procedures**
  - Oral
    - Transoral CO2 laser / robotic surgery
  - Transpharyngeal
    - Partial lateral pharyngectomy
    - Extended supraglottic hemipharyngolaryngectomy
    - Supracricoid hemipharyngolaryngectomy
    - Posterior partial pharyngectomy

**CAVE: „Ogura stair test“**  
(=climb 2 flights of stairs)



# Hypopharyngeal Cancer

## Type of Surgery

- **Radical procedures → + total laryngectomy (TLT)**
    - Extended laryngectomy
    - Total circumferential pharyngolaryngectomy
- Vocal restoration with phonatory implant  
PROVOX or BLOM-SINGER

# Hypopharyngeal Cancer

## Transoral - CO2-Laser / Robotic Surgery

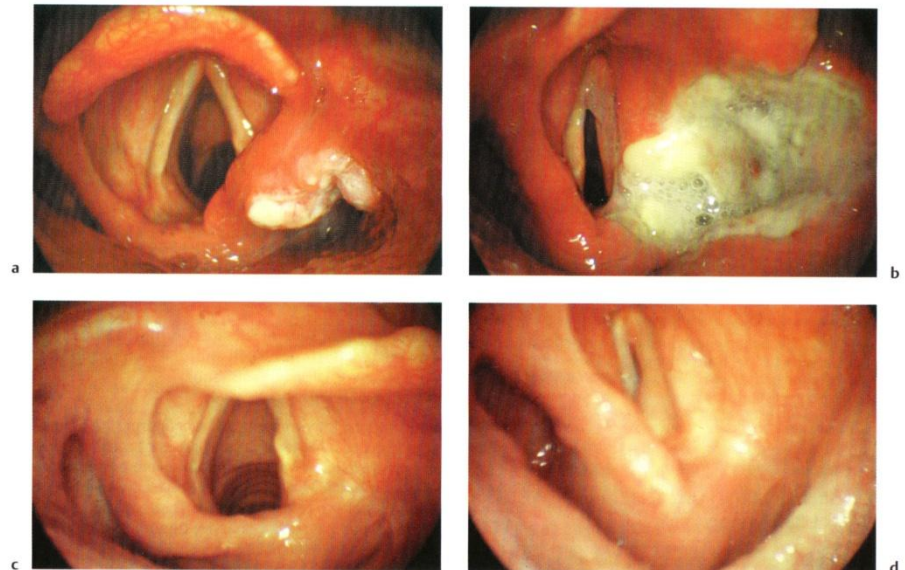
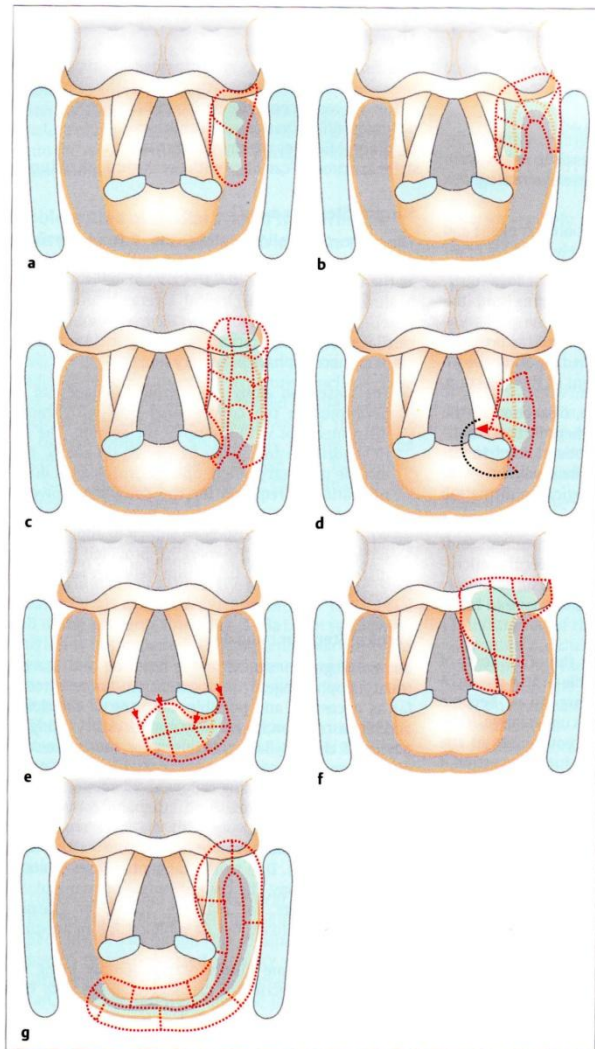
- For small, superficial, or exophytic lesions
  - Lateral pyriform sinus wall, posterior pharyngeal wall
  - Requires 1-2cm margin
- Positives
  - Quick
  - Minimal morbidity
  - Satisfactory functional outcomes, may avoid XRT/CXRT ???
  - Transoral laser microsurgery (TLM)
- Negatives
  - Exposition!
  - Limited visualization of inferior and deep margins





# Hypopharyngeal Cancer

## Transoral – Types of CO2-Laser Hypopharyngectomy



(Steiner)

# Hypopharyngeal Cancer

## Transoral – CO2-Laser / Robotic Surgery

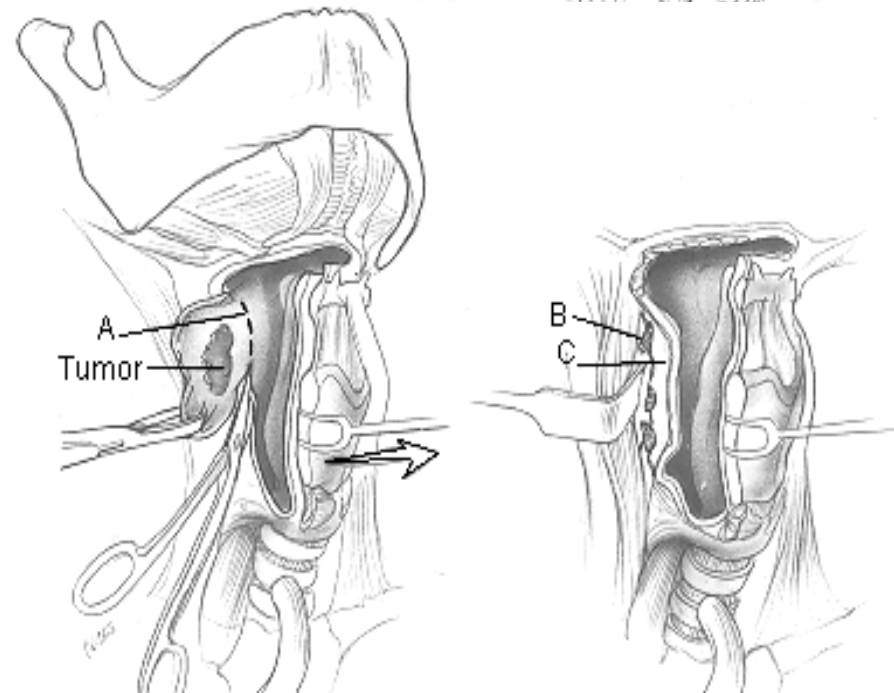
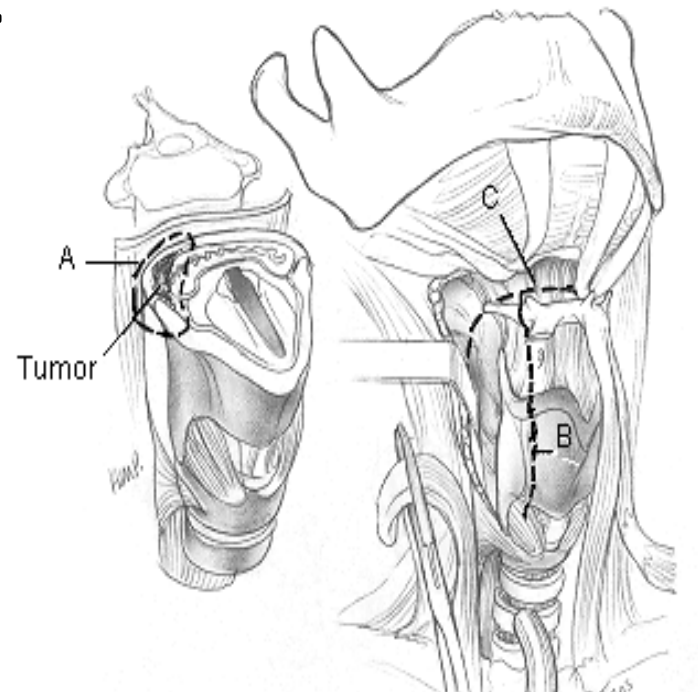
- Promising results with good functional outcome in early stage disease → use as single modality?
- Three-year results
  - 69-84% Disease-free survival
  - 89% Overall survival

Iro , Laryngorhinootologie 2011  
Park, Oral Oncol 2012

# Hypopharyngeal Cancer

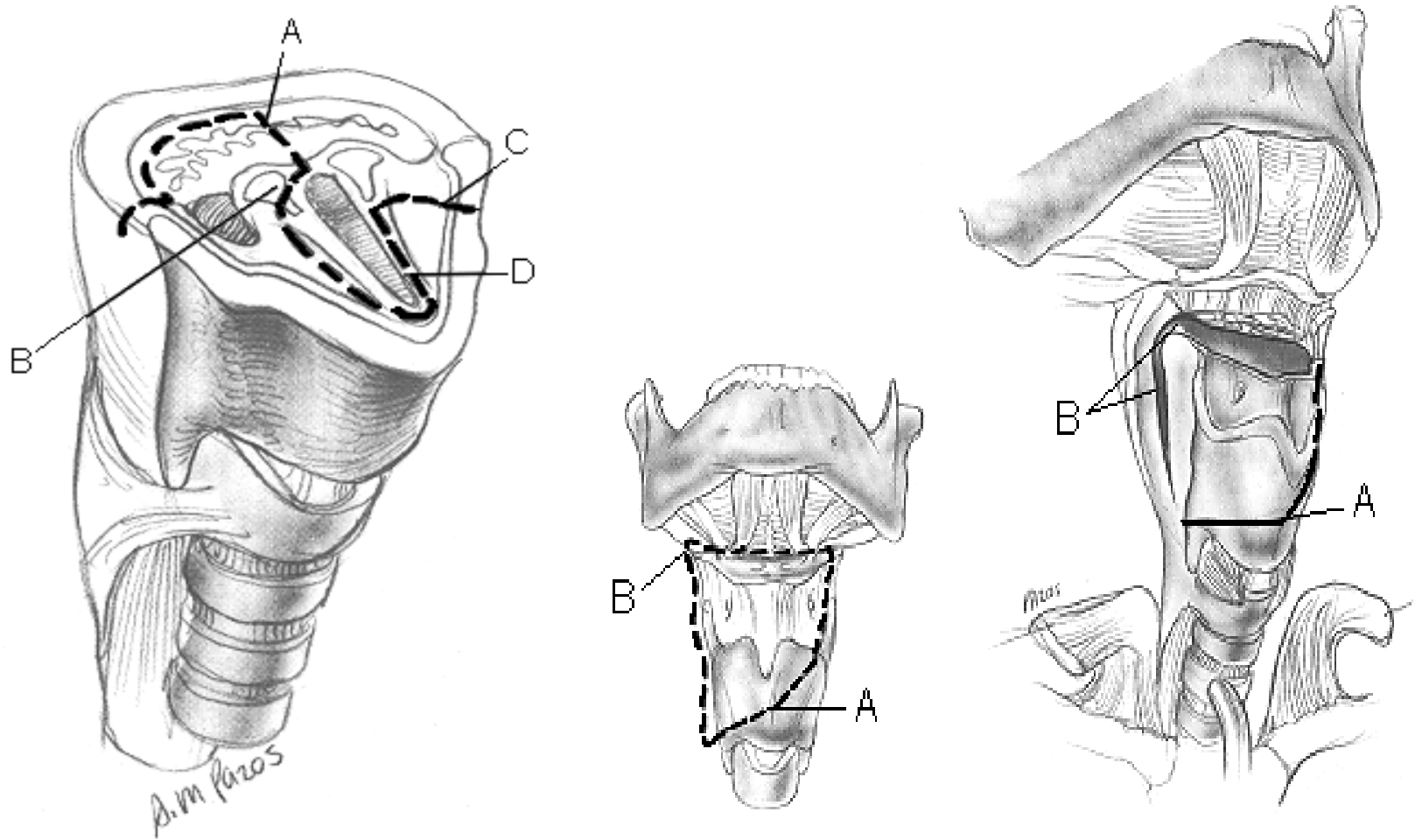
## Transpharyngeal – Partial lateral Pharyngectomy

- Enter hypopharynx at vallecula
- Positives
  - Small tumors on lateral pharyngeal wall
  - Larynx preservation
  - Good functional outcome
- Negatives
  - Tracheotomy needed!
  - Inadequate anterior margin with large tumors
  - Contraindication: transcartilagenous tumor extension



# Hypopharyngeal Cancer

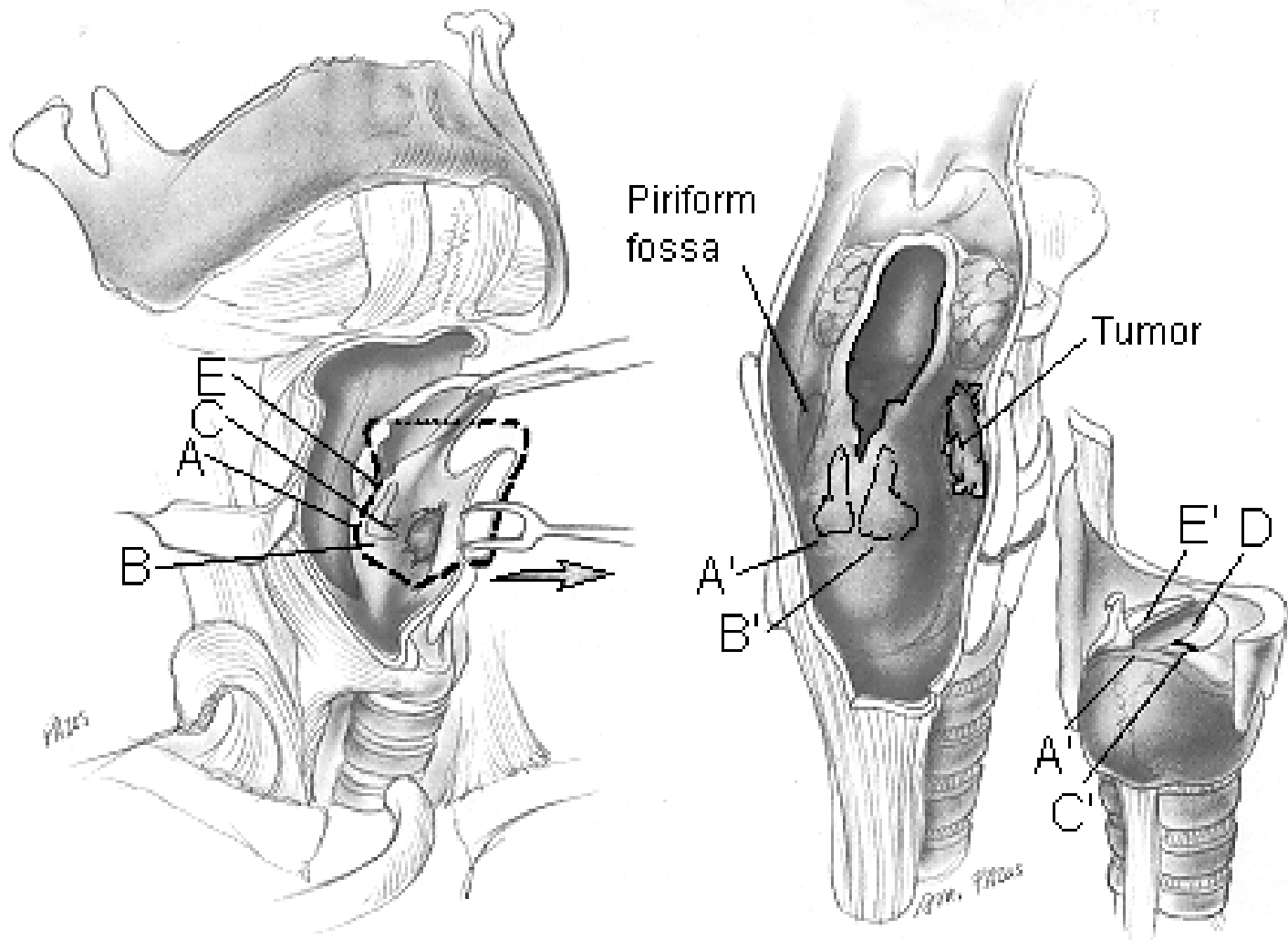
## Transpharyngeal – Extended supraglottic Hemipharyngolaryngectomy



# Hypopharyngeal Cancer

Transpharyngeal –

Extended supraglottic Hemipharyngolaryngectomy

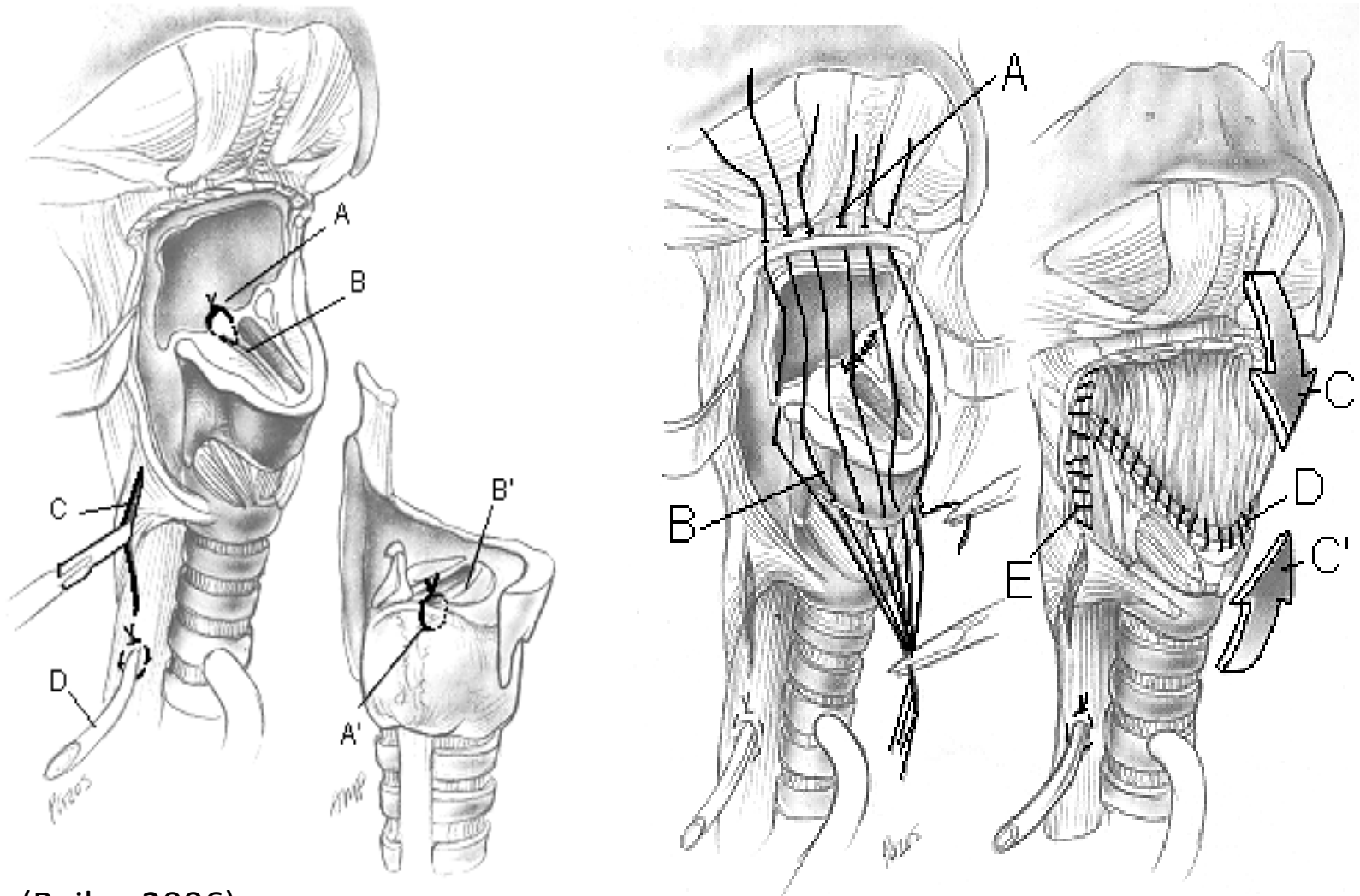


(Bailey 2006)

# Hypopharyngeal Cancer

Transpharyngeal –

Extended supraglottic Hemipharyngolaryngectomy



(Bailey 2006)

# Hypopharyngeal Cancer

## Transpharyngeal –

## Extended supraglottic Hemipharyngolaryngectomy

- Enter pharynx posterior to thyroid ala
  - Entrance through the involved pyriform sinus
- Positives
  - T1 cancer of the piriform sinus of the upper 1/3
  - View entire pyriform sinus
- Negatives
  - Aspiration and pneumonia +++
  - Arytenoid cartilage is often included in the resection →  
↗compromise swallowing and vocal functions
  - Fistula formation
  - Tracheotomy needed!



# Hypopharyngeal Cancer

## Transpharyngeal – Supracricoid Hemipharyngolaryngectomy

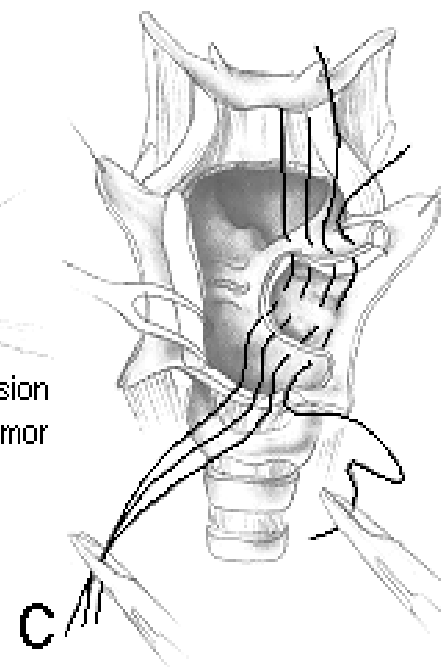
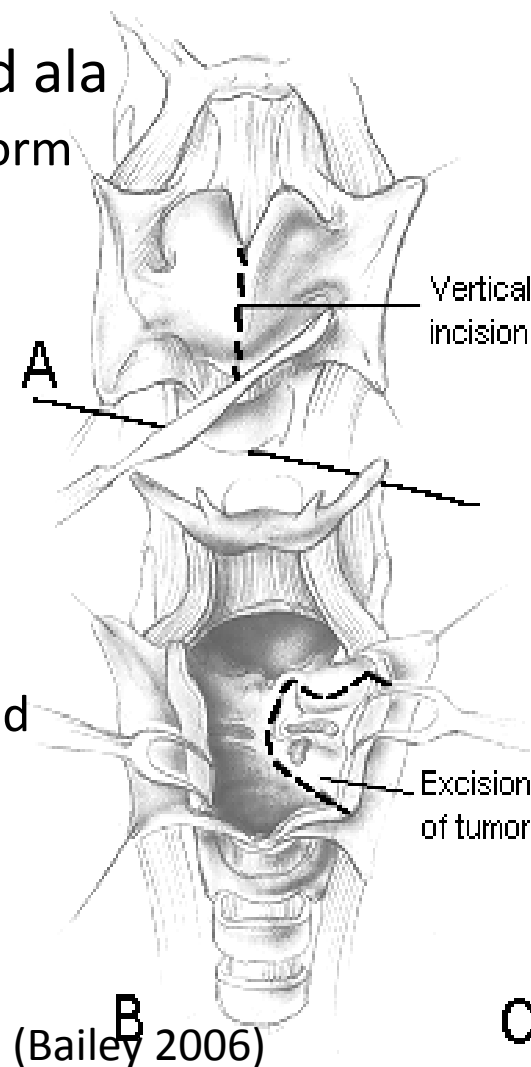
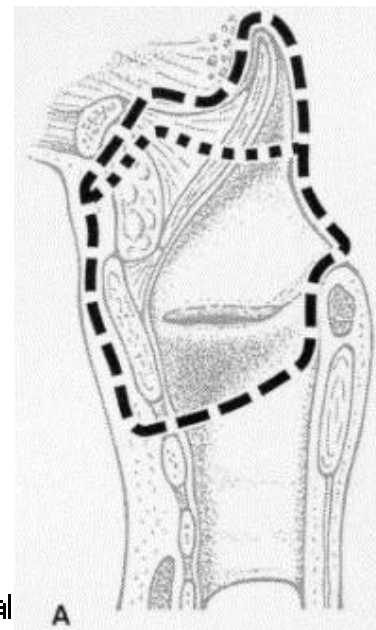
- Enter pharynx posterior to thyroid ala
  - Entrance through the involved piriform sinus

- Positives

- T1-2 cancer of the piriform sinus of medial wall of piriform sinus
- View entire piriform sinus

- Negatives

- Aspiration and pneumonia +++
- Arytenoid cartilage is always included in the resection → ↗ ↗ compromise swallowing and vocal functions
- Fistula formation
- Tracheotomy needed!

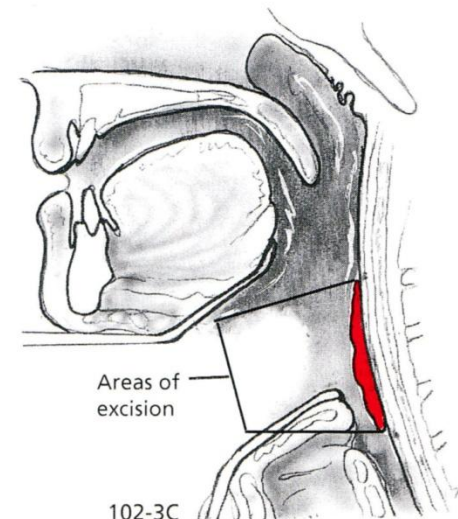
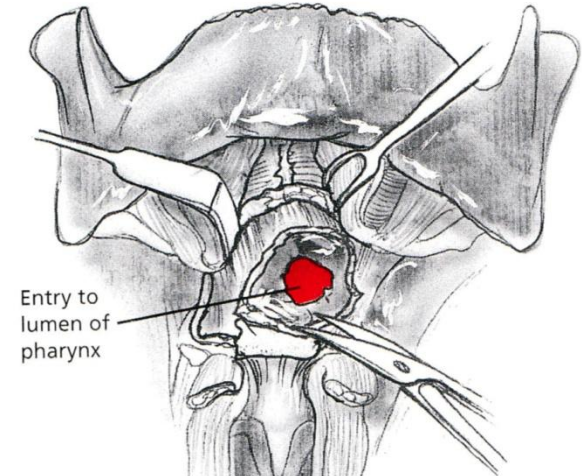
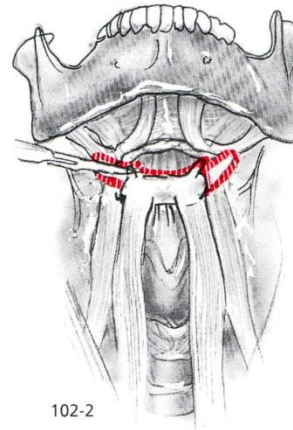


(Bailey 2006)

# Hypopharyngeal Cancer

## Transpharyngeal – Posterior partial Pharyngectomy

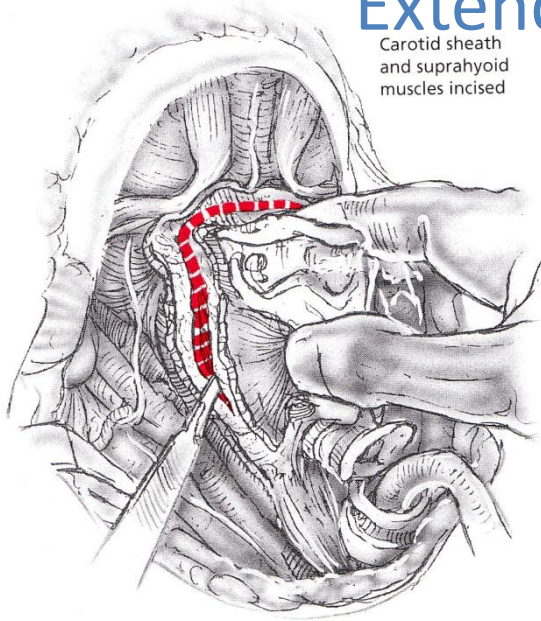
- Enter hypopharynx at vallecula
- Positives
  - Small tumors on posterior pharyngeal wall
  - View entire posterior pharyngeal wall
  - Larynx preservation
  - Good functional outcome
- Negatives
  - Tracheotomy needed!
  - Inadequate inferior margin with large tumors
  - Risk damaging hypoglossal and superior laryngeal nerves



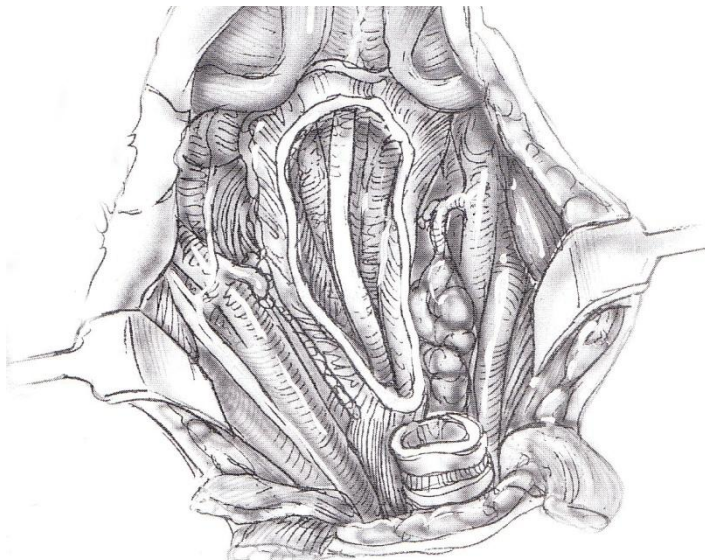
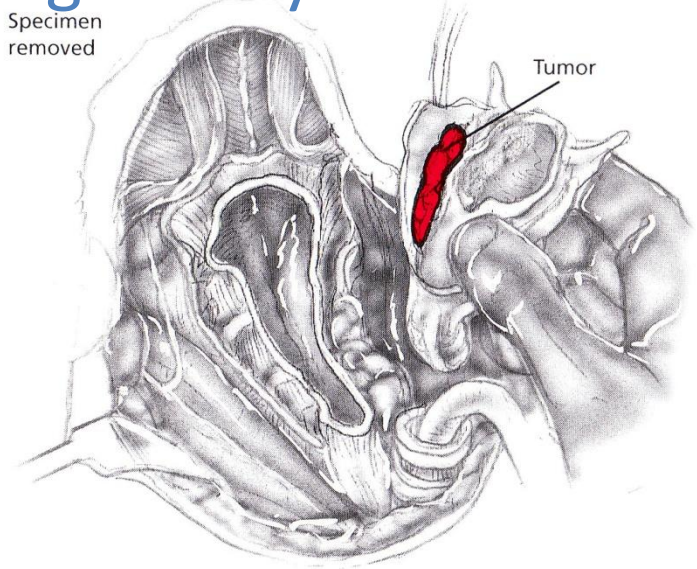
(Bailey 2001)

# Hypopharyngeal Cancer

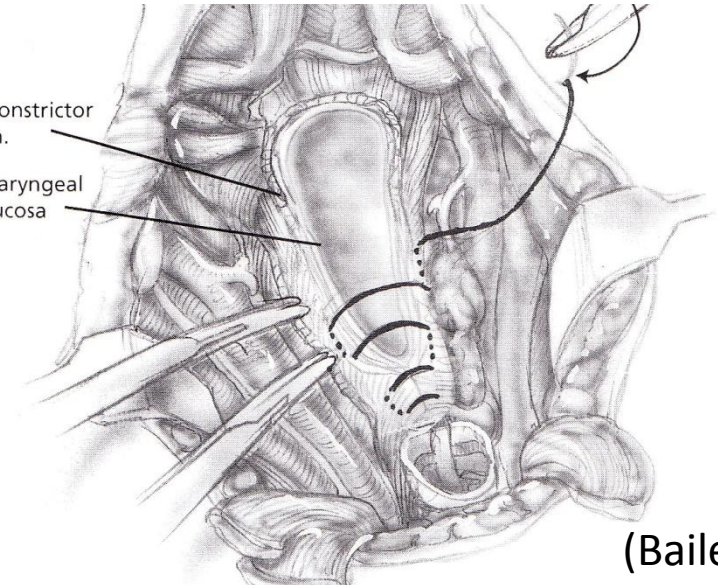
## Extended Laryngectomy



Specimen removed



Constrictor m.  
Pharyngeal mucosa





# Hypopharyngeal Cancer

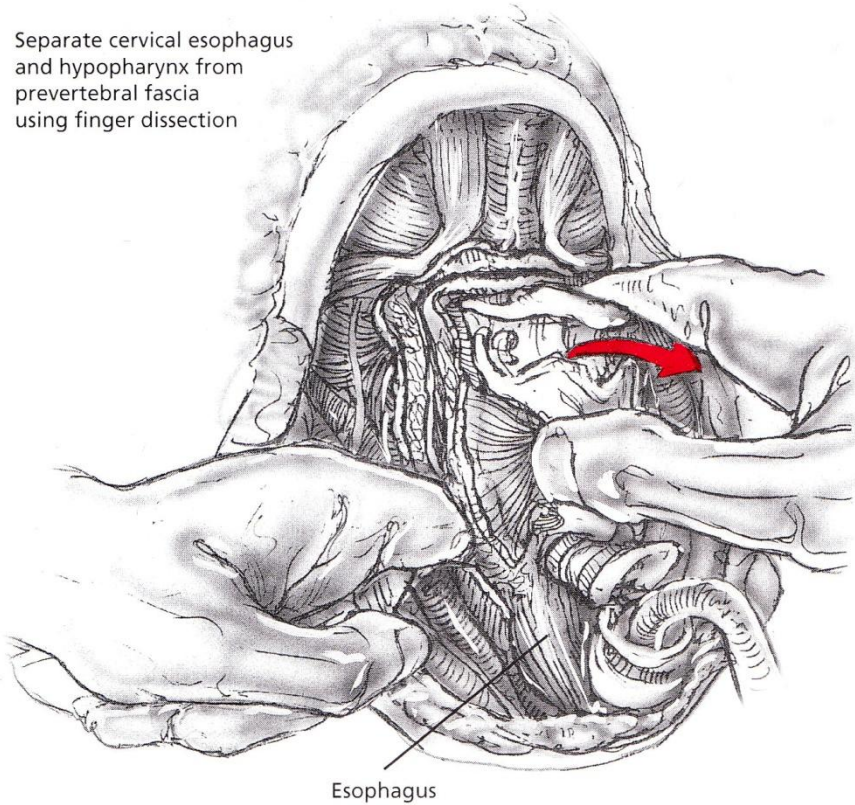
## Extended Laryngectomy

- Excision of the larynx with up to  $\frac{1}{2}$  the circumference of the hypopharynx
- Positives
  - Piriform sinus cancer involving the lateral and medial wall or apex
  - Primary closure / evtl. pedicled-(free-) tissue transfer
- Negatives
  - Possible mucosal tumor spread
  - Stricture formation
  - Fistula formation

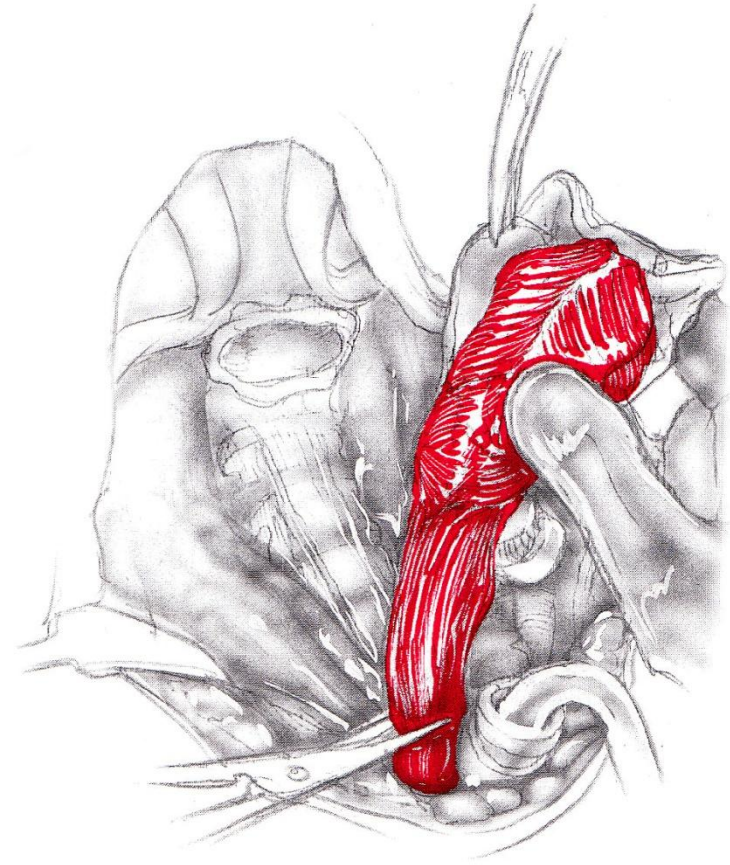
# Hypopharyngeal Cancer

## Total circumferential Pharyngolaryngectomy

Separate cervical esophagus  
and hypopharynx from  
prevertebral fascia  
using finger dissection



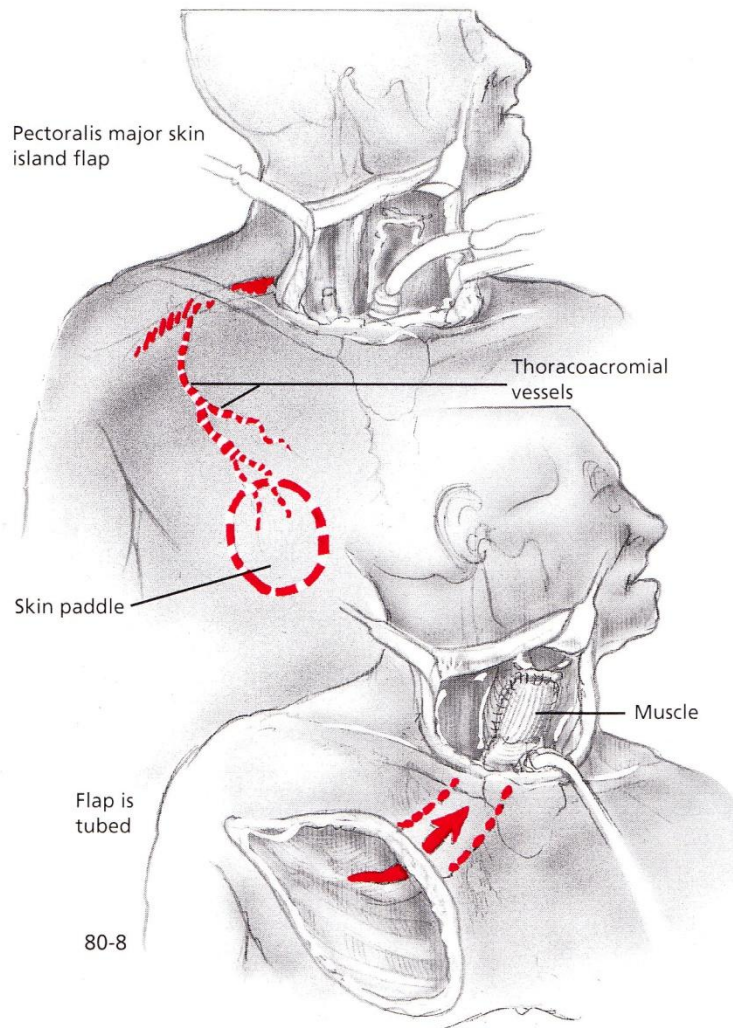
Amputate cervical  
esophagus



(Bailey 2001)

# Hypopharyngeal Cancer

## Total circumferential Pharyngolaryngectomy



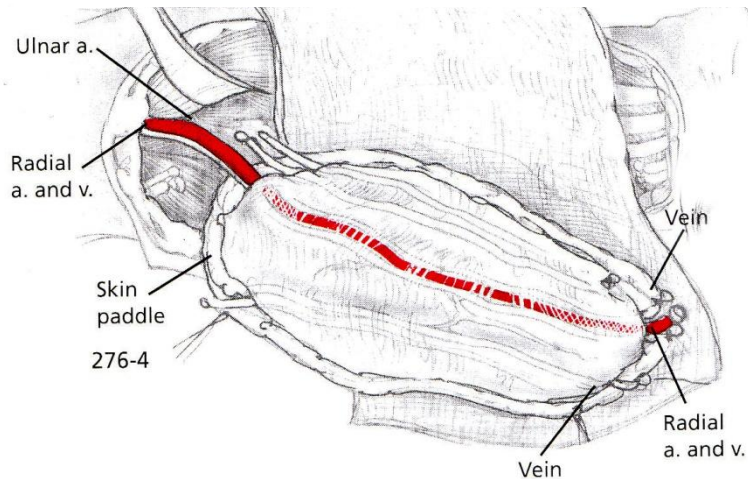
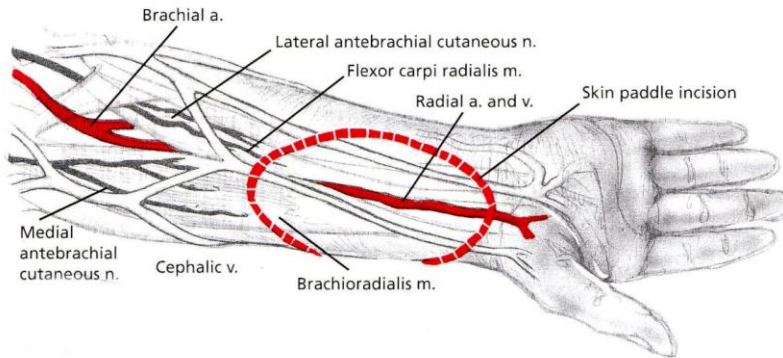
Reconstruction with pedicled flap:

- musculo-cutaneous pectoralis major-flap

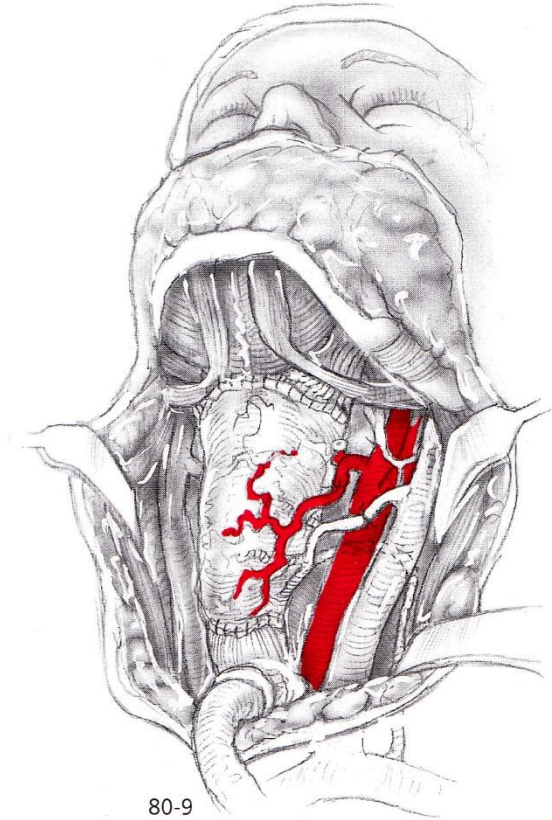


# Hypopharyngeal Cancer

## Total circumferential Pharyngolaryngectomy



Jejunum microvascular  
free flap reconstruction



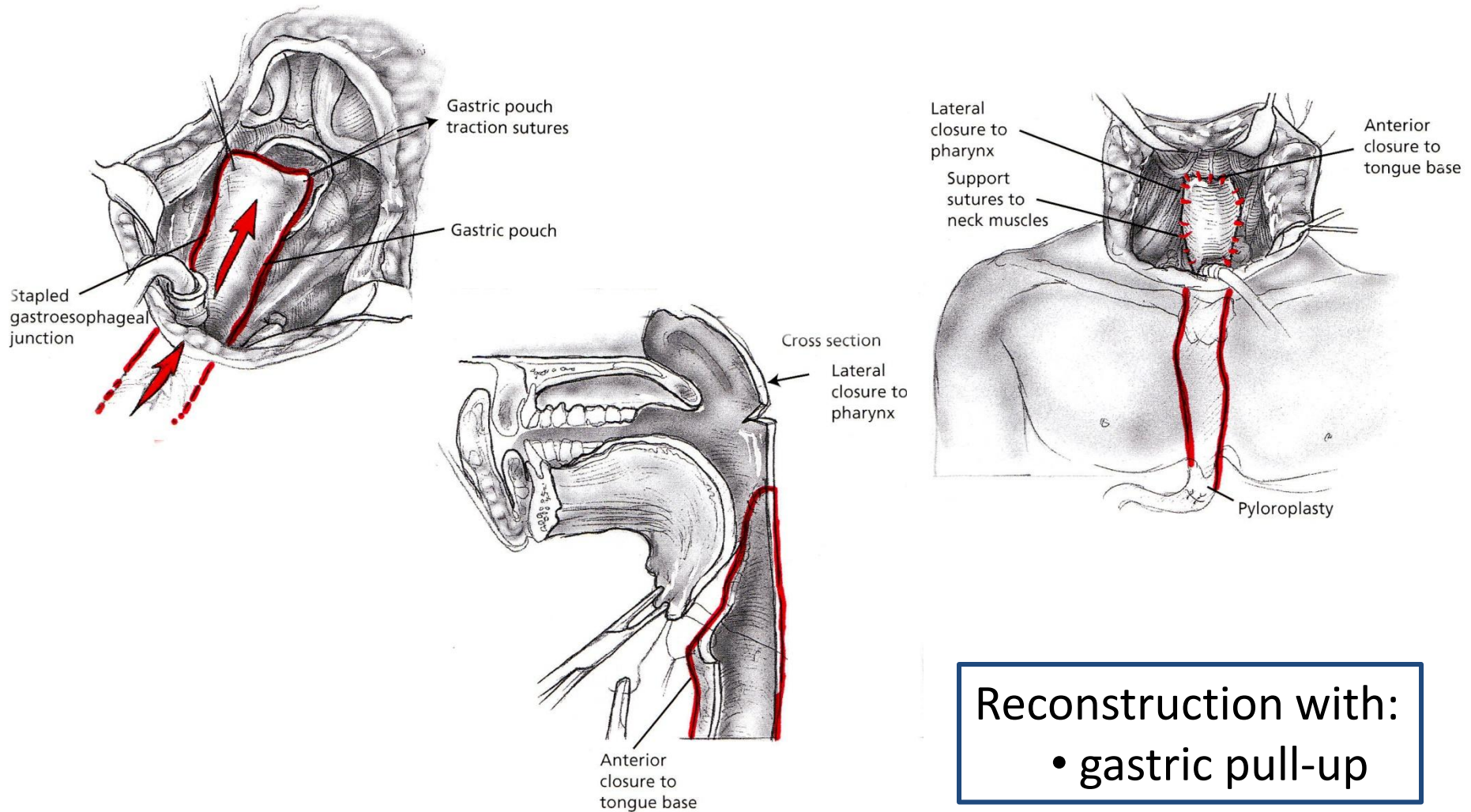
Reconstruction with free flap:

- forearm / jejunum



# Hypopharyngeal Cancer

## Total circumferential Pharyngolaryngectomy



Reconstruction with:

- gastric pull-up

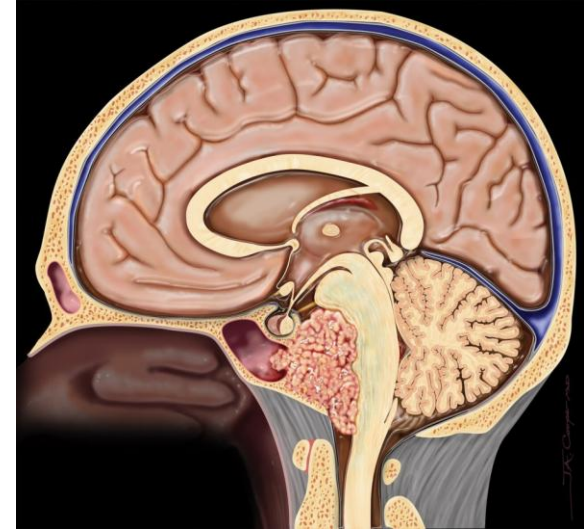
# Hypopharyngeal Cancer

## Total circumferential Pharyngolaryngectomy

- Excision of the larynx, hypopharynx (and upper cervical esophagus)
- Positives
  - Piriform sinus cancer involving more than  $\frac{1}{2}$  of the hypopharyngeal circumference or extending into the upper esophagus sphincter
- Negatives
  - Primary closure not possible → Reconstruction needed!  
(Gastric pull-up: periop. Complications / Mortality 50% / 5-10%)
  - Stricture formation
  - Fistula formation

# 6. Complications

- **Radiotherapy**
  - Early / late toxicities
- **Surgery**
  - Pulmonary embolism
  - Gastric ulceration
  - Hemorrhage (carotid rupture < 1% without RT)
  - Aspiration pneumonia
  - Infection
  - Damage of nerves
  - Fistula formation
  - Death (1-2%)
  - -77% no normal feeding habits
  - -40% tracheotomy tube necessary



# 7. Follow-up

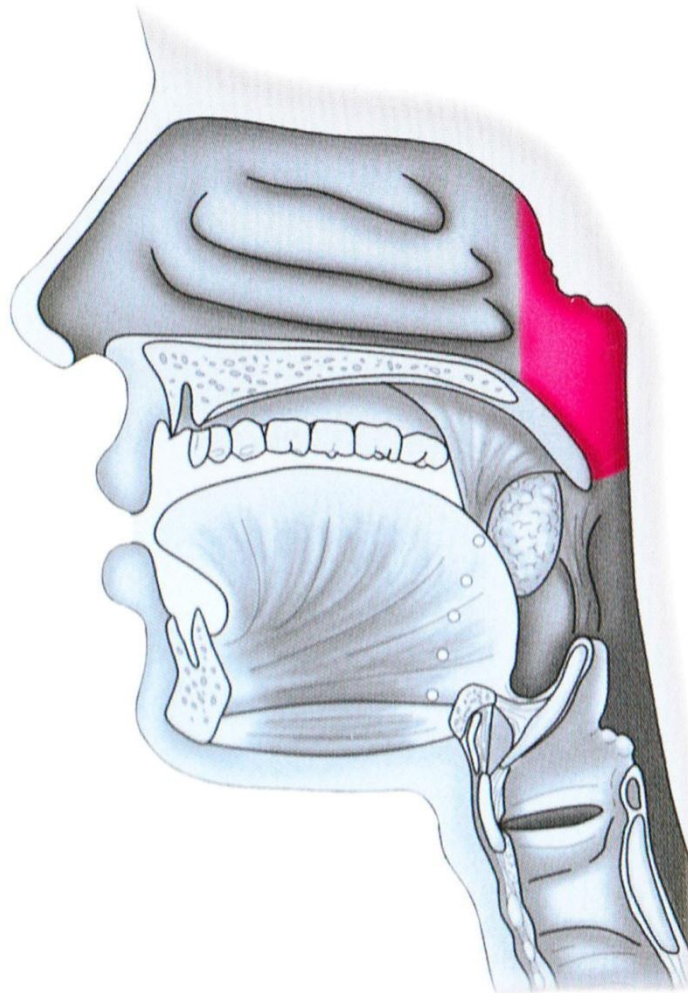
Follow-up						
	1 y	2 y	3 y	4 y	5 y	> 5 y
ENT-examination	2 mth.	3 mth.	6 mth.	6 mth.	6 mth.	1 y.
Rx examination -loco-regional	4 mths/1 y: MRI/CT	2 y: MRI/CT	1x/y. Chest x-ray (CT – 5 y.)			
-systemic	1 y: CT	2 y: CT				
Panendoscopy Biopsy / FNA	if signs and symptoms of recurrence					
Dental monitoring	lifelong with topical fluoride treatment					
Thyroid hormone (if RT on neck)	2 x TSH	2 x TSH	1 x TSH			

## 8. Outcome and Prognosis



# Outcome and Prognosis

## Cancer of the Nasopharynx





# Nasopharyngeal Cancer

## Outcome and Prognosis

- Local control (**CXRT!!!**)
  - T1/T2 75-90%
  - T3/T4 50-75%
- Regional control (**CXRT!!!**)
  - N0/N1 90%
  - N2/N3 70%
- Distant metastases 18-50%
  - Bone > lungs, liver



# Nasopharyngeal Cancer

## Outcome and Prognosis

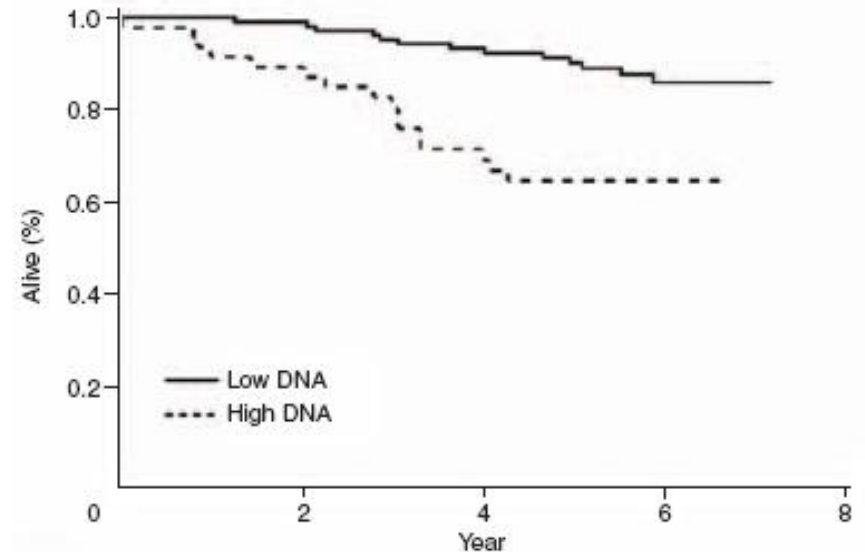
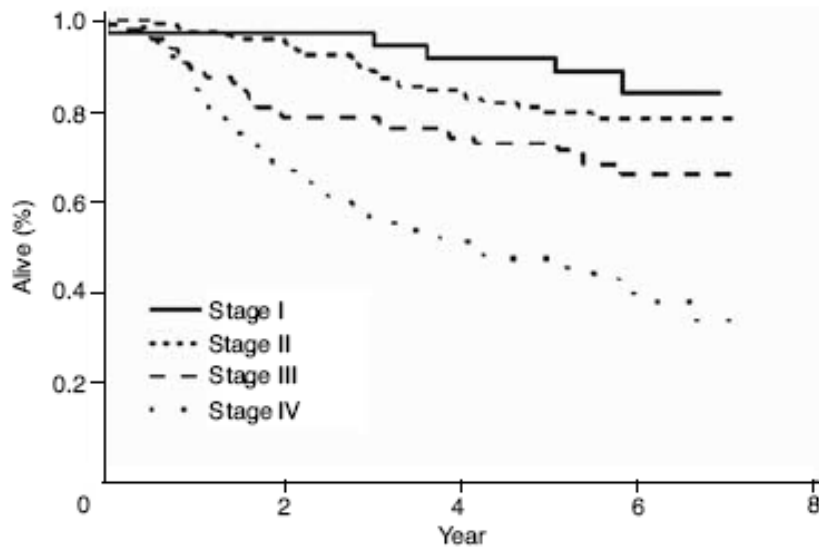
- 90% of recurrences within 5 years
- Second primary initially (low incidence!) 3%
- 5-year disease-specific survival 70-73%
- Overall 5-year survival (**CXRT!!!**) 63-86%

Prognostic groups	Outcome
T1-2 N0-1	Good
T3-4 N0-1	Local failure dominant
T1-2 N2-3	Distant failure dominant
T3-4 N2-3	Both

- More favorable outcome in:
  - Early stage tumors
  - Female gender
  - Nonkeratinizing histology
  - Younger age

# Nasopharyngeal Cancer

## Outcome and Prognosis: plasma EBV DNA



**Table 2.** Actuarial Survival of Patient Groups With Different UICC Stages and With Different EBV DNA Levels Within UICC Stages

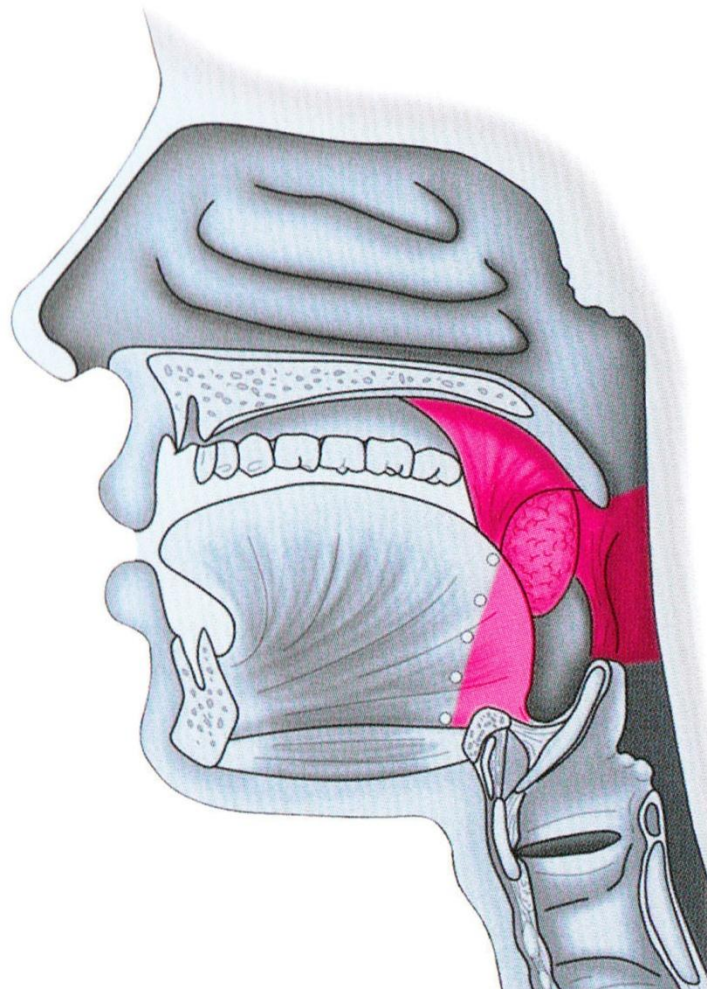
Stage	No. of Patients	5-Year Survival (%)	95% CI (%)
I	36	92	83 to 100
II	119	80	73 to 88
III	95	73	64 to 82
IV	126	47	38 to 56
I + II, low DNA*	108	91	85 to 97
I + II, high DNA*	47	64	53 to 75
III + IV, low DNA	73	66	50 to 81
III + IV, high DNA	148	54	44 to 65

## Predicting factors for relapse

posttreatment plasma EBV DNA  
>  
pretreatment plasma EBV DNA

# Outcome and Prognosis

## Cancer of the Oropharynx



# Oropharyngeal Cancer

## Outcome and Prognosis

- Local control 73%
  - T1 / T2 80-90%
  - T3 / T4 < 60%
- Regional control 85%
  - N0 (RT alone) 96%
  - N1 (RT and ND) 90%
  - N2 (RT and ND) 73-86%
  - N3 (RT and ND) 62-86%
- Distant metastases 20%
  - Lungs, liver, bones

# Oropharyngeal Cancer

## Outcome and Prognosis

- Second primary initially 15%
- Metachronous second primary **> 50% in soft palate cancer**

Stage	5-year disease-specific survival
Mean	53%
I	56%
II	58%
III	55%
IV	44%

# Oropharyngeal Cancer

## Outcome and Prognosis

- After RT and salvage surgery

5-Year Results	Locoregional control	Disease-Free Survival	Overall Survival
Soft Palate	82%	NS	33-37%
Tonsillar	65-69%	57-59%	43-47%
Base of Tongue	60-69%	62-63%	49-52%

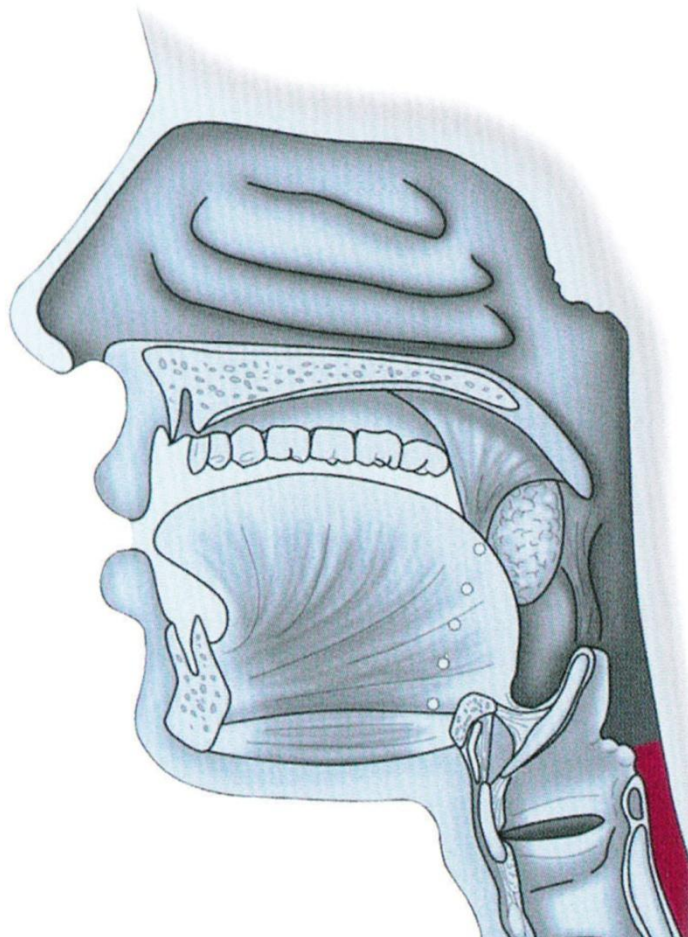
} > 50%  
metachron  
cancer

- Comparing RT and CXRT

5-Year Results	Locoregional control	Progression-Free Survival	Overall Survival
XRT	69%	36%	40%
CXRT	82%	47%	53%

# Outcome and Prognosis

## Cancer of the Hypopharynx





# Hypopharyngeal Cancer

## Outcome and Prognosis

- Local control
  - After surgery + RT 82-96%
  - After RT (+ CX) 60-70%
- Regional control
  - After surgery + RT 53-83%
- Distant metastases
  - Lungs, liver, bones 20-30%

# Hypopharyngeal Cancer

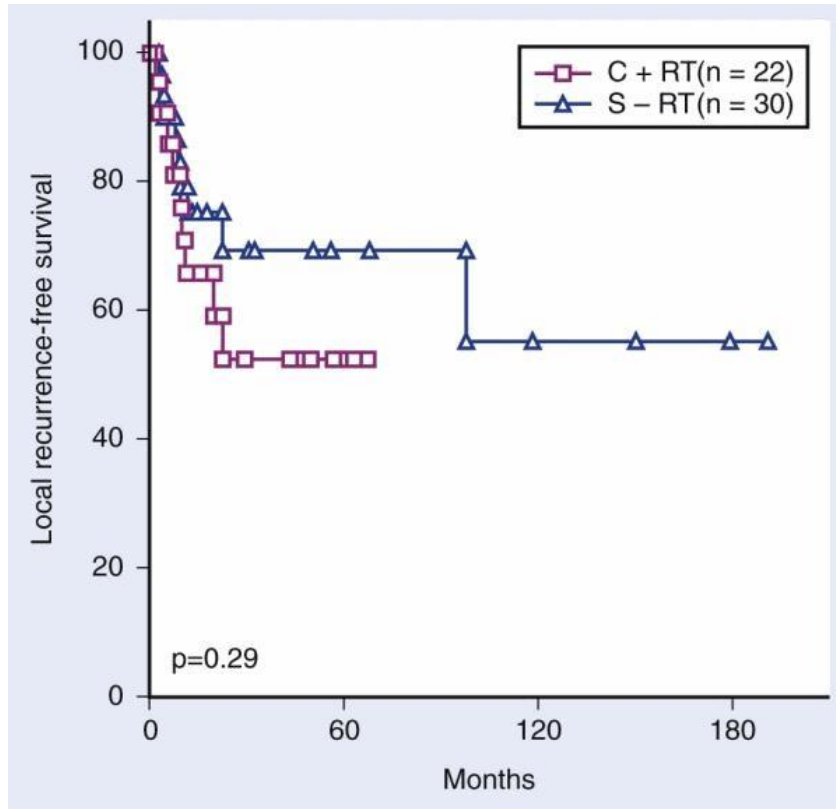
## Outcome and Prognosis

- Second primary initially 7%
  - Soft palate, buccal cavity, esophagus
- Metachronous second primary 10-17%

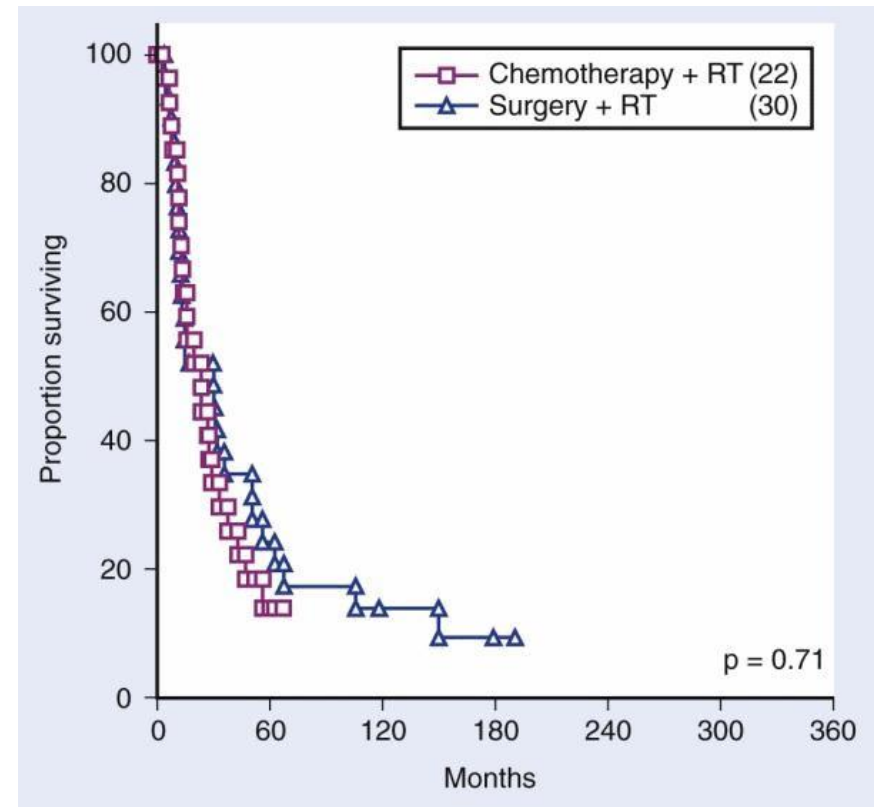
Stage	5-year disease-specific survival
Mean	33%
I	63%
II	58%
III	42%
IV	22%

# Hypopharyngeal Cancer

## Outcome – Larynx-preservation therapy



Local control using larynx-preserving therapy (chemotherapy + RT) compared with surgery and postoperative radiotherapy (surgery + RT), Memorial Sloan-Kettering Cancer Center



Survival using larynx-preserving therapy (chemotherapy + RT) compared with surgery and postoperative radiotherapy (surgery + RT), Memorial Sloan-Kettering Cancer Center

# 9. Recurrence-Management

- **Salvage treatment**

- **Surgery (NP, OP, HP)**

- **CO2-Laser**

- **Open surgery with reconstruction (free-/pedicled flap)**

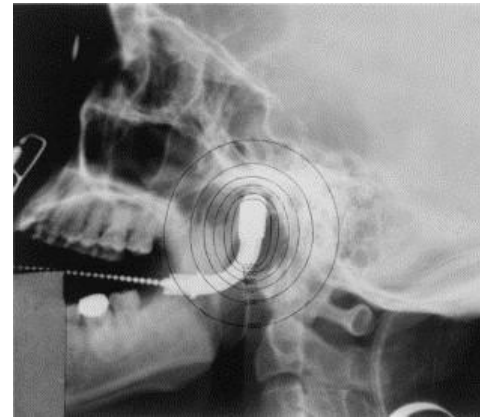
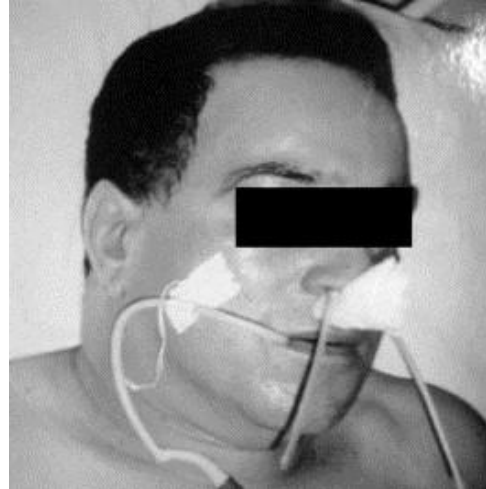
- **Re-irradiation**

- Brachytherapy (NP, OP)

- External RT with or without CX (NP)

- Stereotactic Radiosurgery (NP)

- **Systemic chemotherapy: palliation**



# Nasopharyngeal Cancer

## Recurrence-Management

- Outcome after Salvage-Treatment
  - 5-year-local control rate 15-60%
  - 5-year-survival
    - rT1 40-70%
    - rT2 20-40%
    - rT3/rT4 0-14%
  - Treatment complications and late toxicity 24-54%
  - Treatment mortality 1.8-5%

# Nasopharyngeal Cancer

## Salvage-Surgery

- **Approaches**

- Transnasal endoscopic
- Transpalatal
- Transmaxillary
- Infratemporal fossa
- Transparotid temporal bone
- Transmandibular



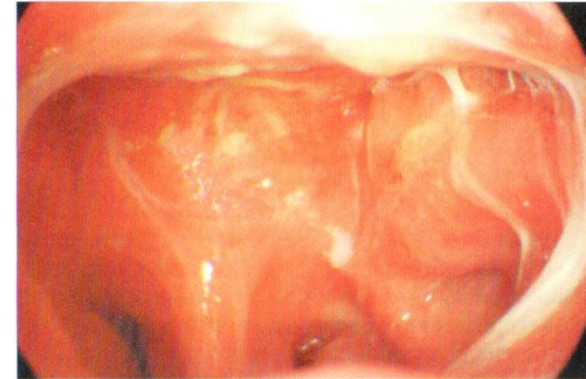
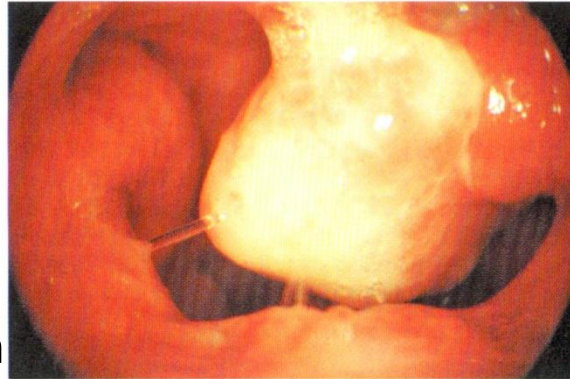


# Nasopharyngeal Cancer

## Transnasal endoscopic approach

### CO2-Laser resection

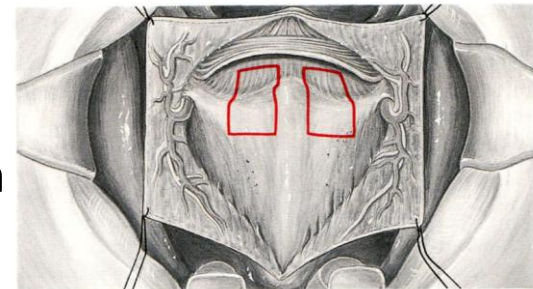
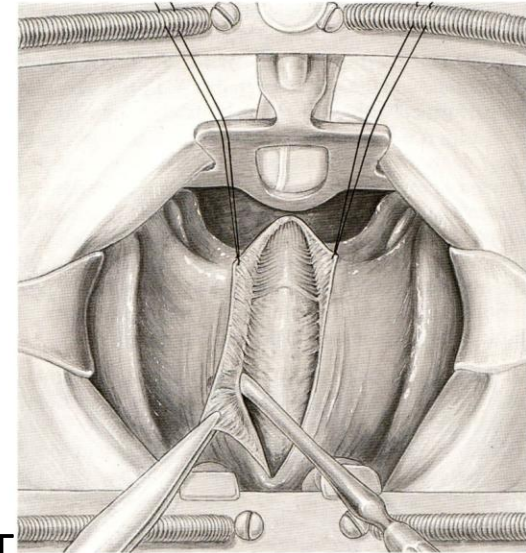
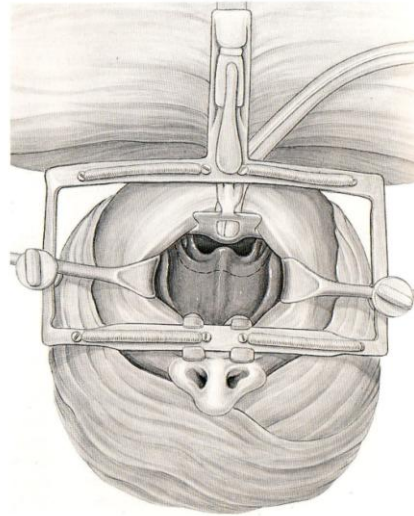
- For small, superficial, or exophytic lesions
  - Posterior pharyngeal wall
  - Requires 1-2cm margin
- Positives
  - Quick
  - Minimal morbidity
  - Satisfactory functional outcomes, may avoid XRT/CXRT
- Negatives
  - Limited visualization of inferior and deep margins



# Nasopharyngeal Cancer

## Transpalatal Approach

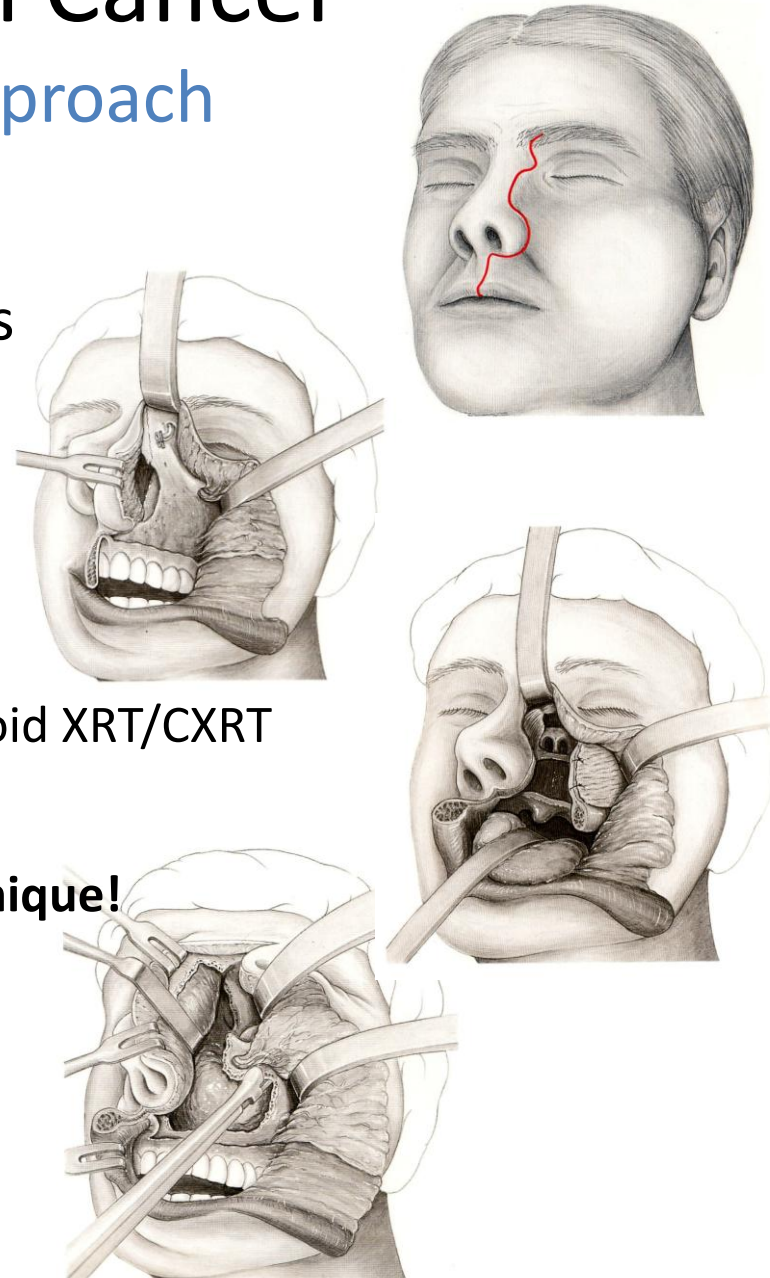
- For intermediate lesions
  - Posterior pharyngeal wall
  - Requires 1-2cm margin
- Positives
  - Minimal morbidity
  - Satisfactory functional outcomes, may avoid XRT/CXRT
  - Use of transoral laser microsurgery (TLM)
- Negatives
  - Affected by trismus, mandibular height, and dentition
  - Limited visualization of superior and deep margins



# Nasopharyngeal Cancer

## Transmaxillary Approach

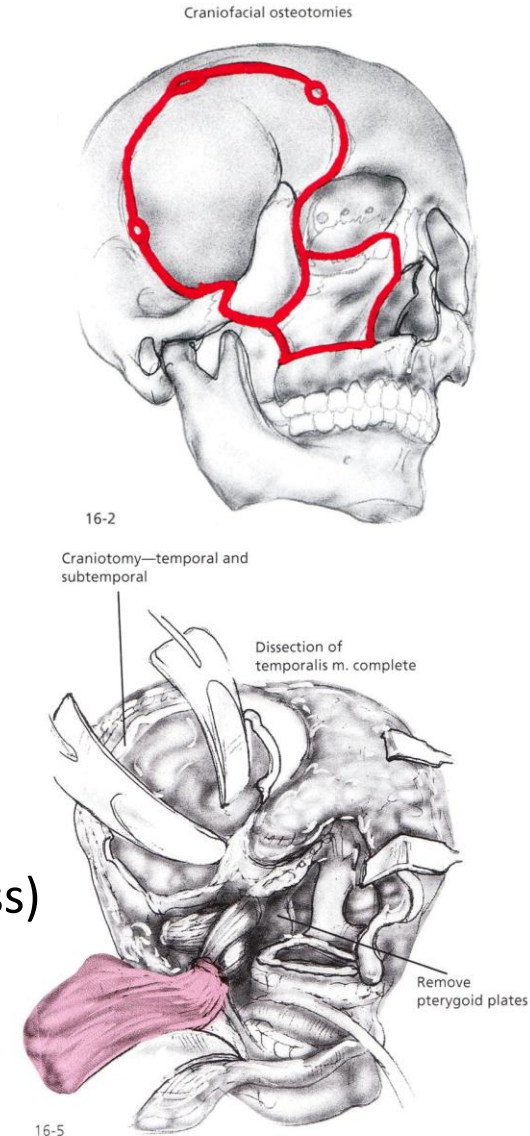
- For intermediate and advanced lesions
  - Posterior and lateral pharyngeal wall
  - Requires 1-2cm margin
- Positives
  - Minimal morbidity
  - Satisfactory functional outcomes, may avoid XRT/CXRT
- Negatives
  - Esthetic problems → use **Degloving Technique!**
  - Trigeminus neuropathy



# Nasopharyngeal Cancer

## Transparotid temporal bone Approach

- For advanced lesions with extension into skull base and parapharyngeal space
  - Posterior , superior and lateral pharyngeal wall
  - Requires 1-2cm margin
- Positives
  - En monobloc-resection possible
  - Satisfactory functional outcomes, often combined with postoperative XRT/CXRT
- Negatives
  - High morbidity (hemorrhage, meningitis, brain abscess)
  - Esthetic problems



# Oropharyngeal Cancer

## Recurrence-Management

- Outcome after Salvage-Treatment
  - Complications 42%
  - Mortality 8%
  - 5-year-survival 20-30%

# Hypopharyngeal Cancer

## Recurrence-Management

- Outcome after Salvage-Treatment
  - Complications 40% (with flap: 20%)  
(without fl.: 77%)
  - Mortality 7%
  - 2-year-control rate 15-40%
  - 5-year-survival 7-26%

**→ Organpreservation (larynx) almost not possible!**

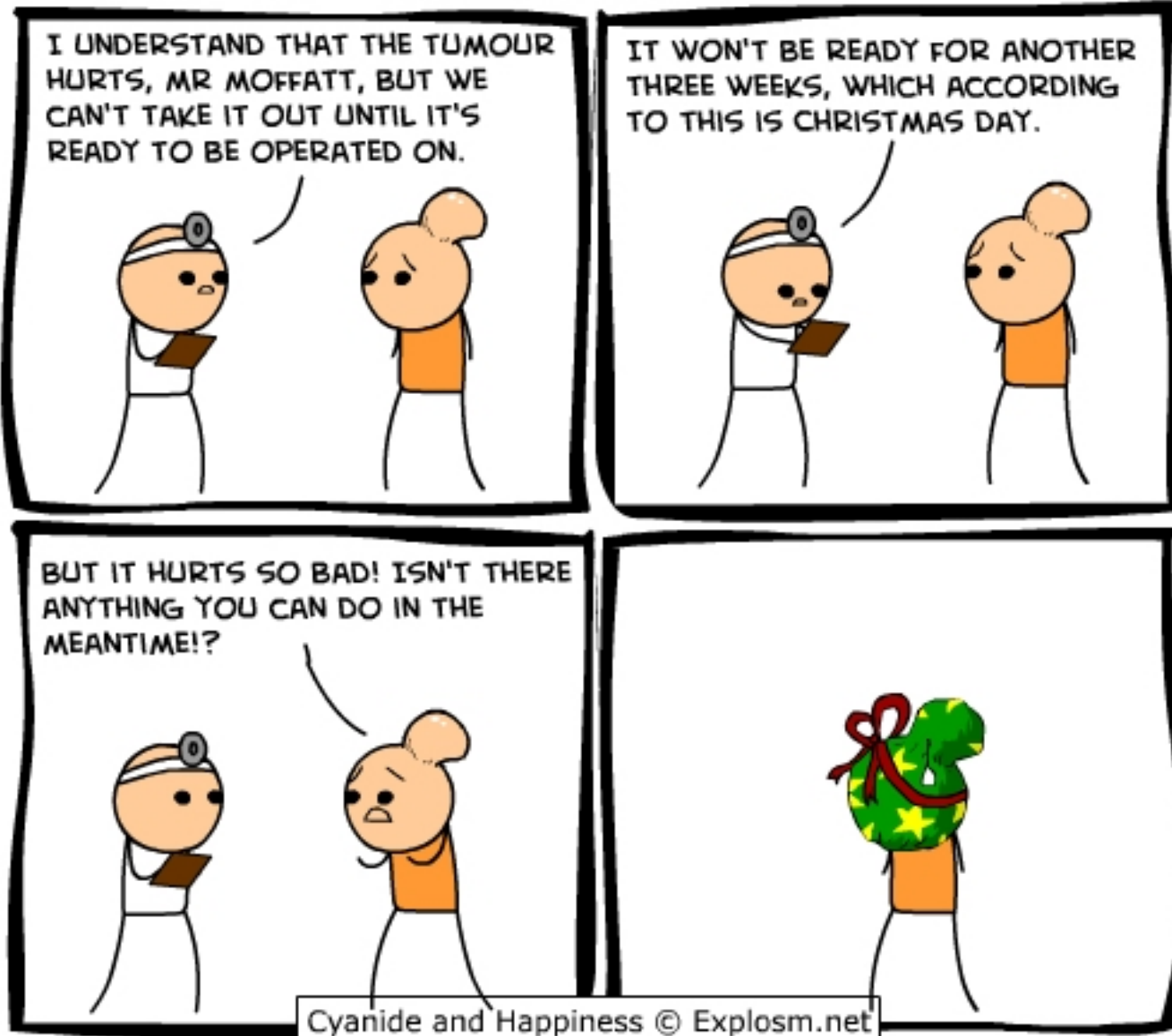


# 10. Future Directions

- Induction chemotherapy
- Monoclonal antibody against EGFR (cetuximab)
- Monoclonal antibody against VEGFR (bevacizumab)
- Proton radiation
- Improvement of imaging techniques (precising tumor extension?)
- Improvements of surgery techniques for recurrences (robotic assistance)
- Development of agents that bind to areas of tumor hypoxia (EF5)
- Epigenetic therapies (DNA methyltransferase inhibitors (azacitidine))
- Immunotherapy against viral antigens expressed by NPC cells (cytotoxic T cells)
- EBV and HPV vaccination



# 11. Summary



# Nasopharyngeal Cancer

## Summary

- Rare in occidental Europe and North America, more common in China
- Etiology: EBV, nitrosamine
- 3 WHO-types
  - Keratinizing SCC
  - Nonkeratinizing C
  - Basaloid SCC
- Treatment is primarily CXRT
- WHO-type 2 (nonkeratinizing carcinoma) → better prognosis
- 70-73% overall 5-year survival



# Oropharyngeal Cancer

## Summary

- Oropharyngeal cancer often treated with a multimodality approach (CXRT, Surgery + (CX)RT)
- Two distinct pathways
  - Carcinogen exposure from tobacco and alcohol
  - Genomic instability from HPV
- HPV plays significant prognostic role
- Transoral surgery affords favorable outcome in appropriately selected patients
- 53% overall 5-year survival



# Hypopharyngeal Cancer

## Summary

- Early hypopharyngeal cancer often treated with organpreservation therapy (CXRT)
- Advanced hypopharyngeal cancer treated with surgery (laryngopharyngectomy) and postop CXRT
- One distinct pathways
  - Carcinogen exposure from tobacco and alcohol
- 35% overall 5-year survival

A Bad Prognosis



## 12. References





# Nasopharyngeal Cancer

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