

Changes to the AJCC Staging of Head & Neck Cancer: Implications for the Surgical Pathologist



**Mount
Sinai**

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Disclosures: Special advisor to Merck, AstraZeneca, Champions Oncology, and the National Cancer Institute



Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

LIP AND ORAL CAVITY:**Select a single response unless otherwise indicated.****Procedure (select all that apply)**

- Excision
 Glossectomy (specify): _____
 Buccal mucosal resection (specify): _____
 Mandibulectomy (specify): _____
 Maxillectomy (specify): _____
 Palatectomy
 Neck (lymph node) dissection (specify): _____
 Other (specify): _____
 Not specified

Tumor Site (Note A)

- Lip
 - + External upper lip (exclude vermilion border)
 - + External lower lip (exclude vermilion border)
 - + Mucosa of upper lip
 - + Mucosa of lower lip
 - + Commissure of lip
- Oral
 - + Lateral border of tongue
 - + Ventral surface of tongue
 - + Dorsal surface of tongue
 - + Anterior two-thirds of tongue
 - + Upper gingiva
 - + Lower gingiva
 - + Anterior floor of mouth
 - + Floor of mouth
 - + Hard palate
 - + Buccal mucosa
 - + Vestibule of mouth, maxillary
 - + Vestibule of mouth, mandibular
 - + Alveolar process, maxillary
 - + Alveolar process, mandibular
 - + Retromolar area
 - + Mandible
 - + Maxilla
- Other (specify): _____
 Not specified

Tumor Laterality (select all that apply)

- Right
 Left
 Midline
 Not specified

Tumor Focality

- Unifocal

AJCC Changes for 8th Edition

New chapters/staging systems

Cervical Lymph Nodes and Unknown 1° Tumors of the Head & Neck

Pharynx: HPV-Mediated Oropharynx Cancer (p16+)

Cutaneous Squamous Cell Carcinoma of the Head and Neck

Thymus

Bone: Appendicular Skeleton/Trunk/Skull/Face, Pelvis, and Spine

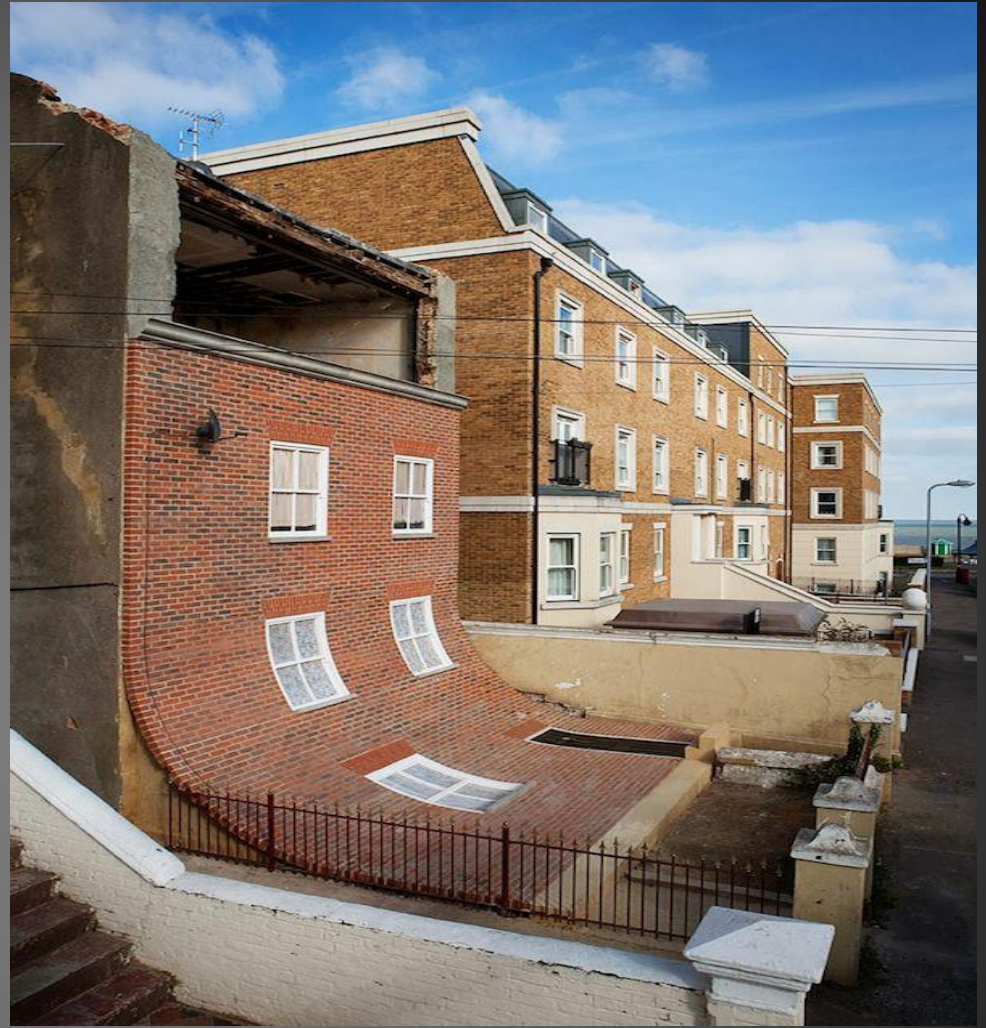
Soft Tissue Sarcoma of the Head and Neck

Soft Tissue Sarcoma of the Trunk and Extremities

Split chapters

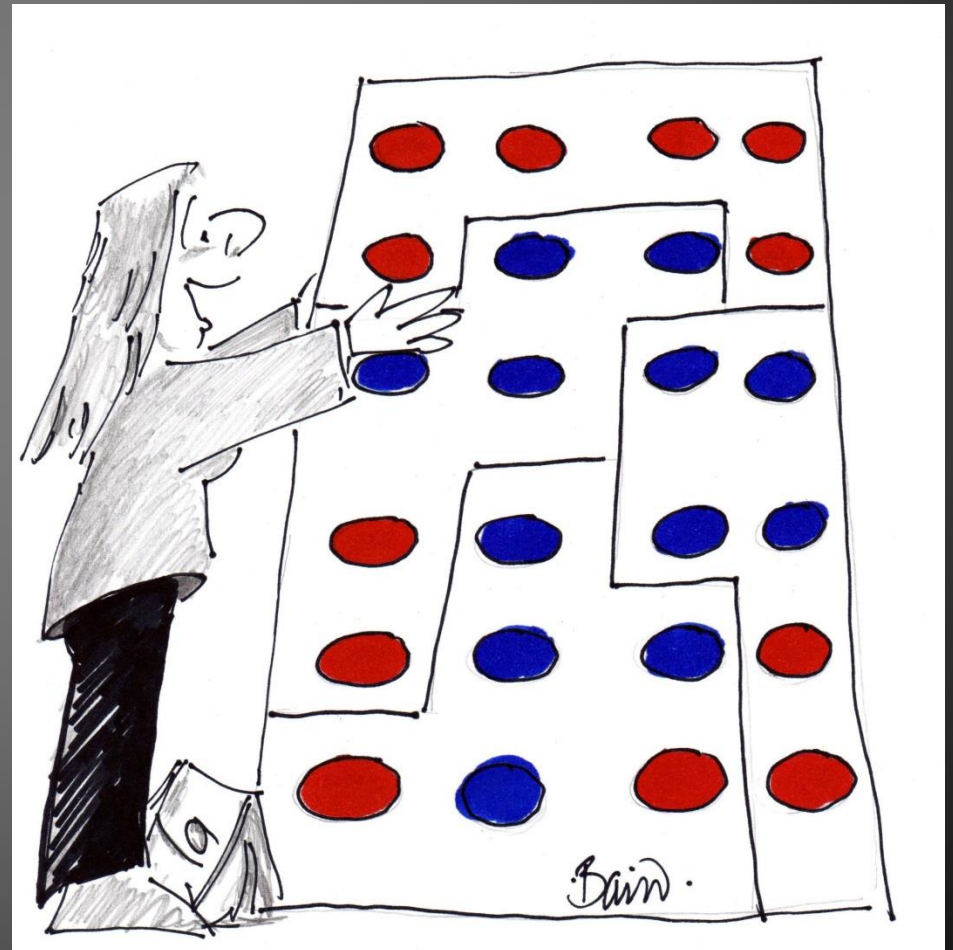
P16 negative oropharynx and hypopharynx (previously pharynx)

Nasopharynx (previously pharynx)



Change 1.

Repositioning of Anatomic Boundaries of the Head and Neck from an Oncologic HPV Perspective



WHO Classification of Head and Neck Tumours

Edited by

Adel K. El-Naggar, John K.C. Chan, Jennifer R. Grandis, Takashi Takata, Pieter J. Slootweg



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5 Tumours of the oropharynx (base of tongue, tonsils, adenoids)

WHO and TNM classifications

Introduction

2017 edition

Squamous cell carcinoma

- Squamous cell carcinoma, HPV-positive
- Squamous cell carcinoma, HPV-negative

Salivary gland tumours

Pleomorphic adenoma

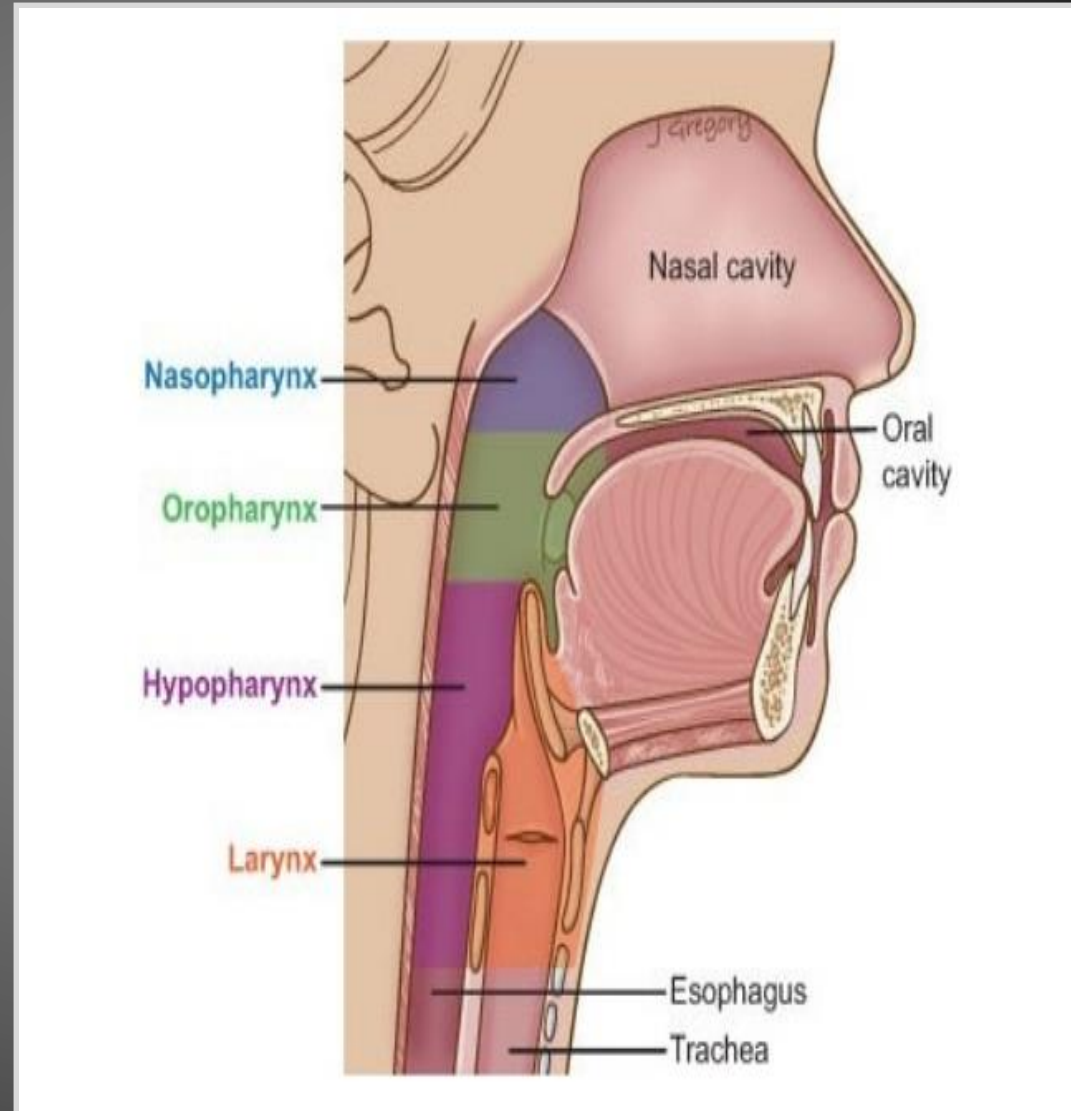
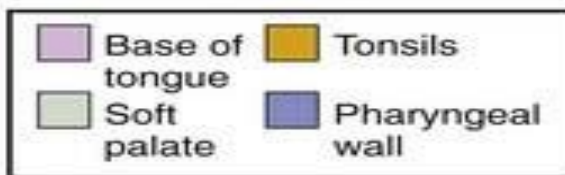
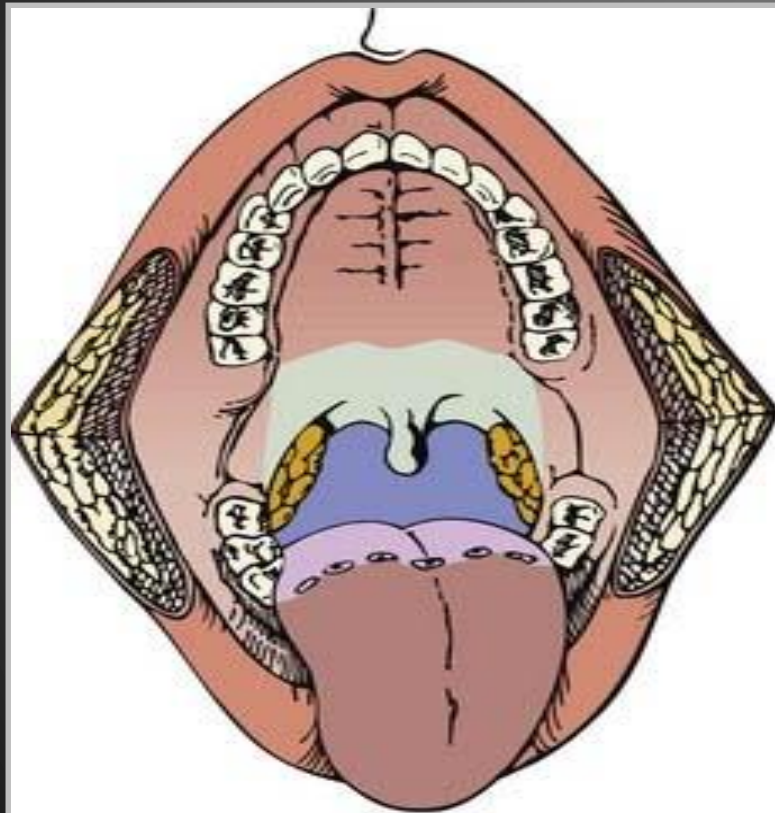
Adenoid cystic carcinoma

Polymorphous adenocarcinoma

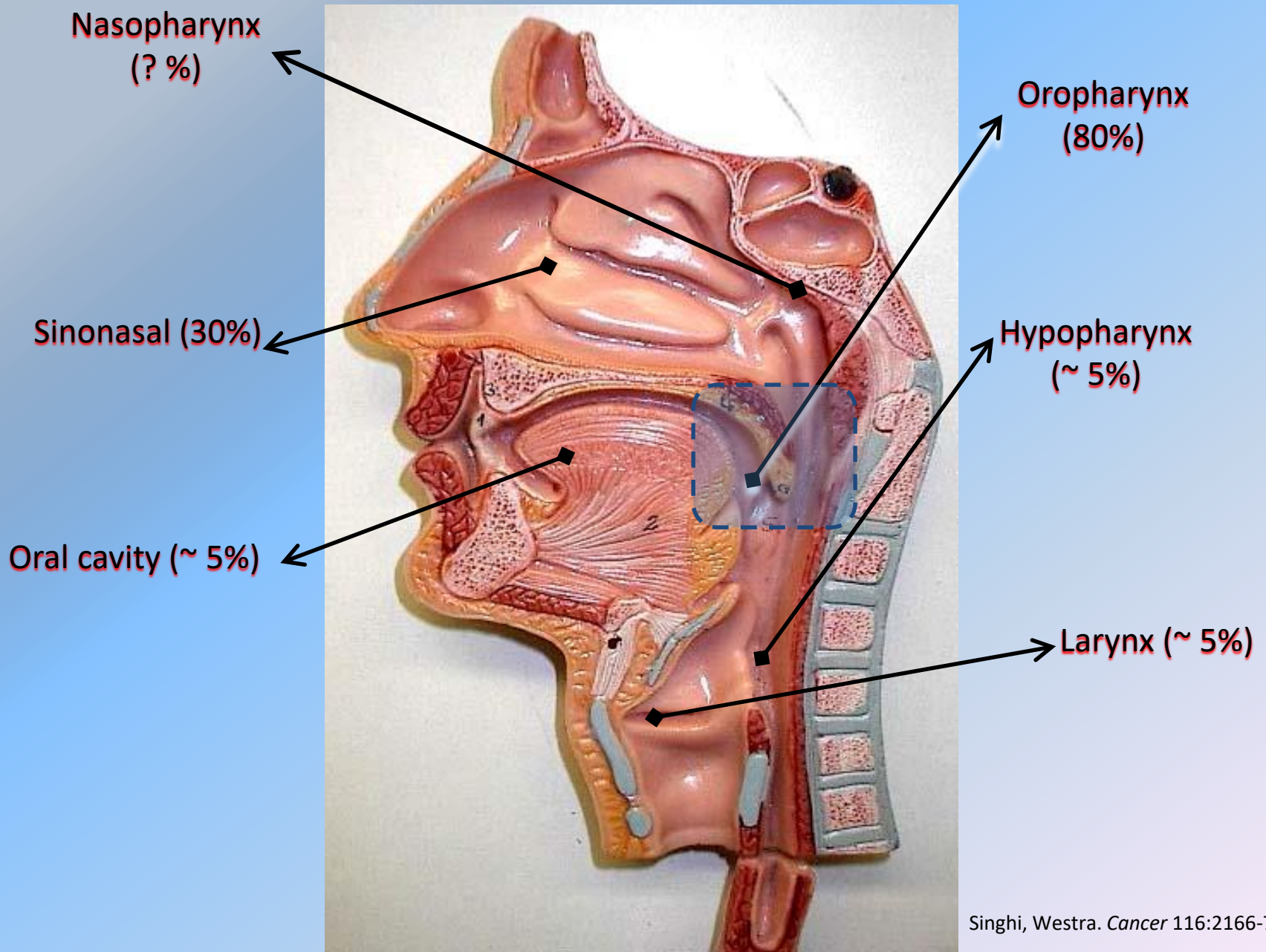
Haematolymphoid tumours

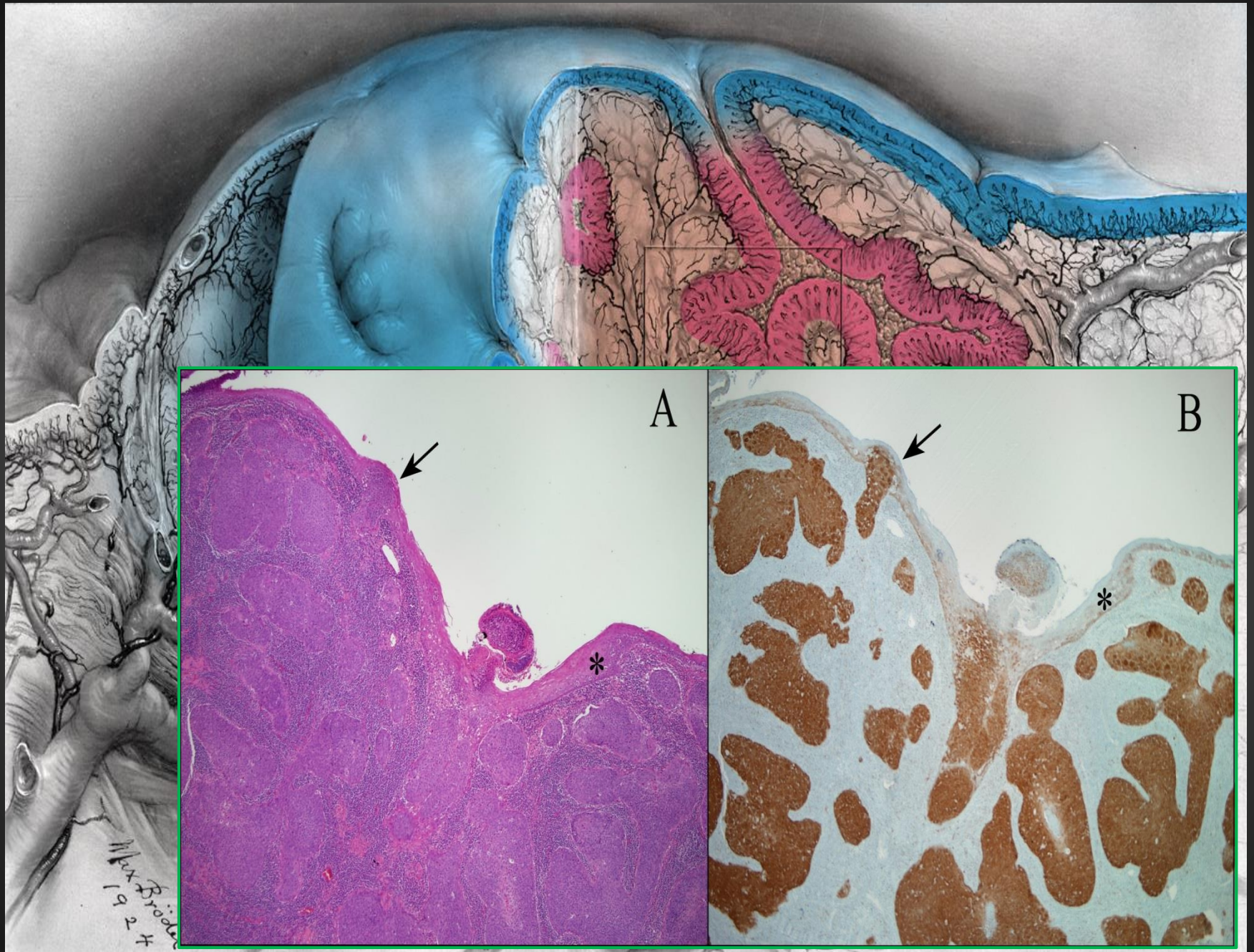
“To reflect the very different biological and etiological differences between nasopharyngeal carcinoma, HPV-associated OPC, non-HPV-associated OPC, and hypopharyngeal cancer, the 8th edition of the staging manual has been divided into 3 separate chapters – nasopharynx, HPV-associated OPC, and Hypopharyngeal / non-HPV associated OPC.”

Lydiatt et al. CA A Cancer J Clin, 67:122, 2017

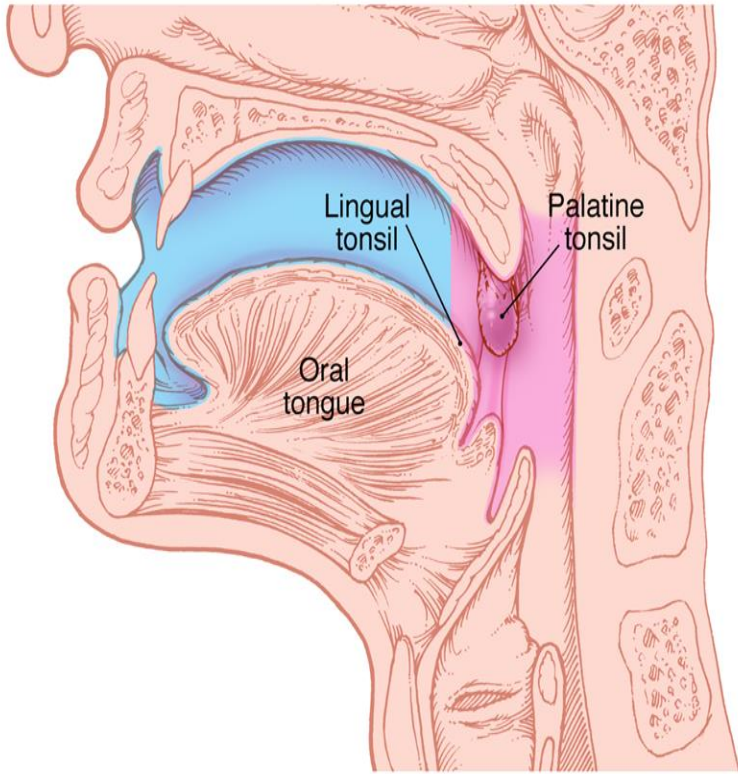


Anatomic distribution of HPV-related HNSCC

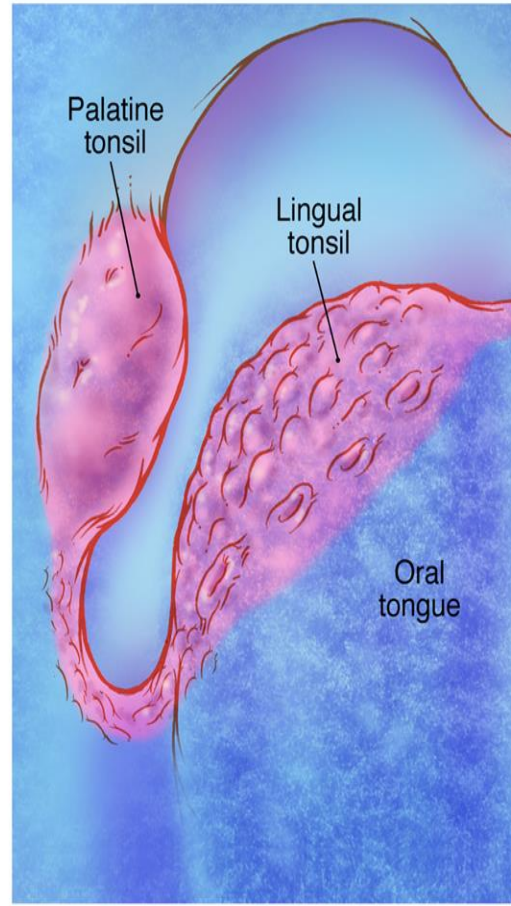




HPV detection in oropharyngeal squamous cell carcinomas Of non-tonsillar sites



Lateral View



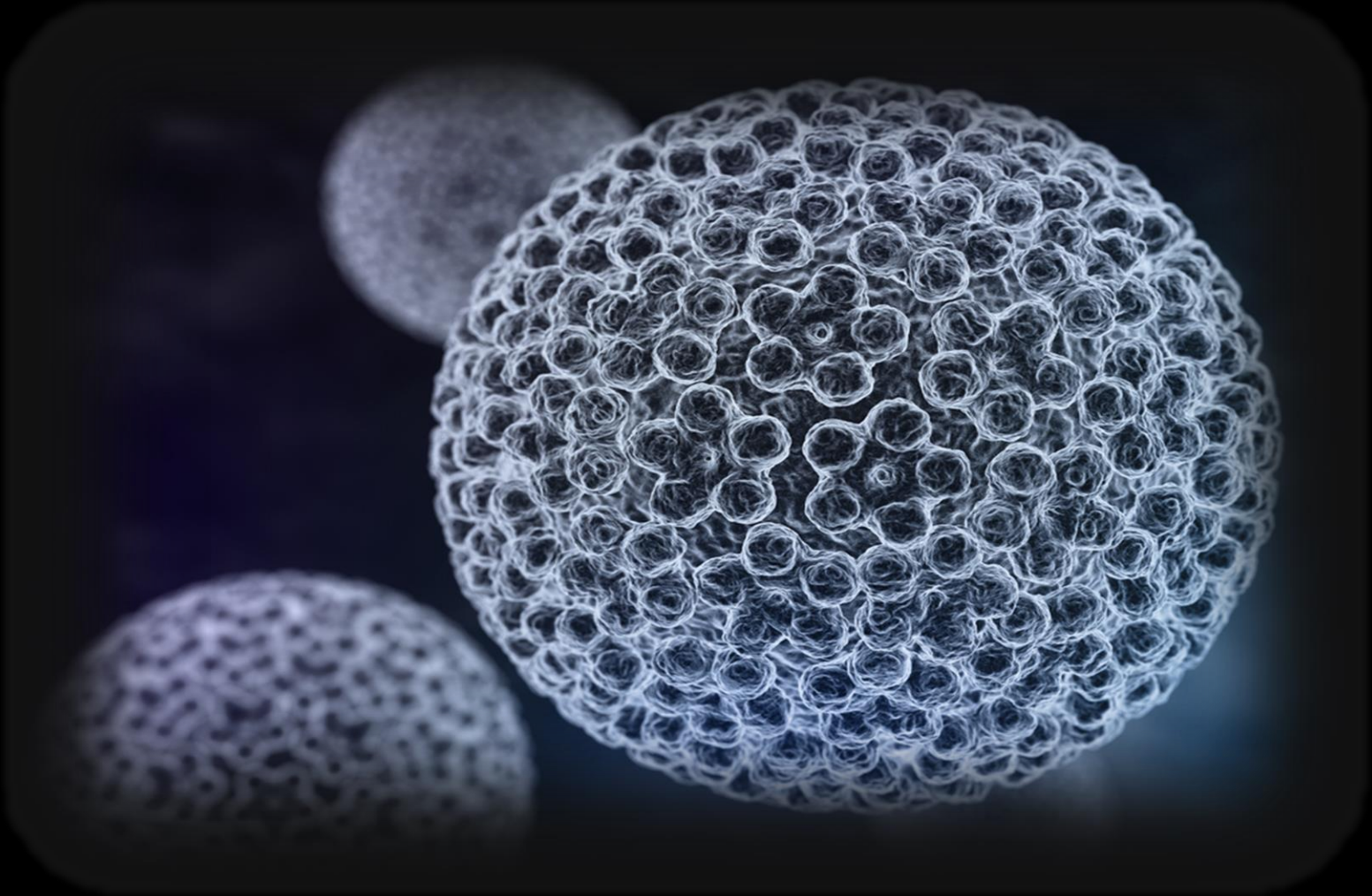
Oral View

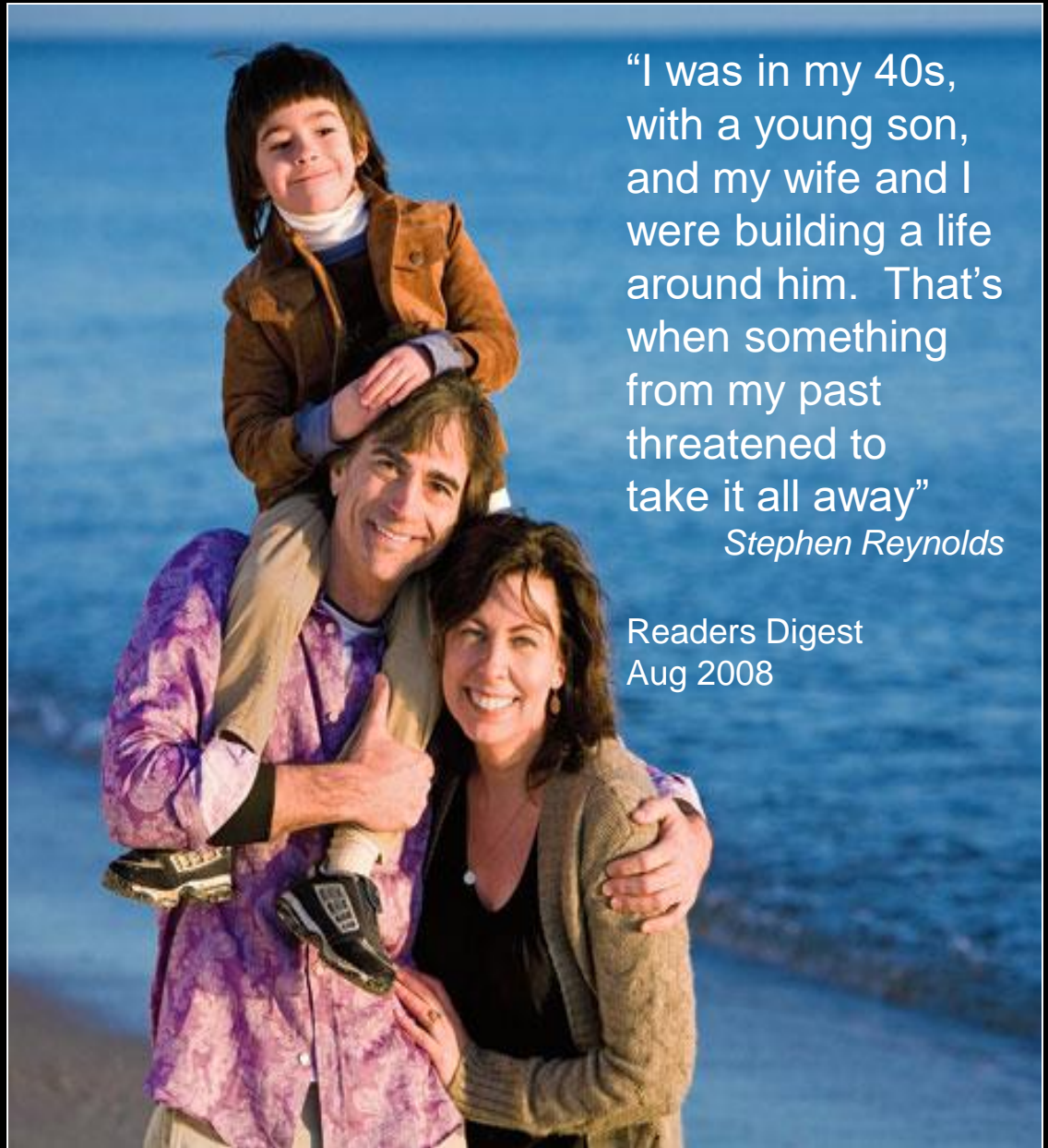
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thelium of
surface of
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ng on the

Change 2.

Molecular staging of oropharyngeal squamous cell carcinomas





“I was in my 40s,
with a young son,
and my wife and I
were building a life
around him. That’s
when something
from my past
threatened to
take it all away”

Stephen Reynolds

Readers Digest
Aug 2008

Two distinct HNSCCs

HPV +

HPV -

Age younger older

Gender 3:1 men 3:1 men

SE status high

Molecular

p16

↑

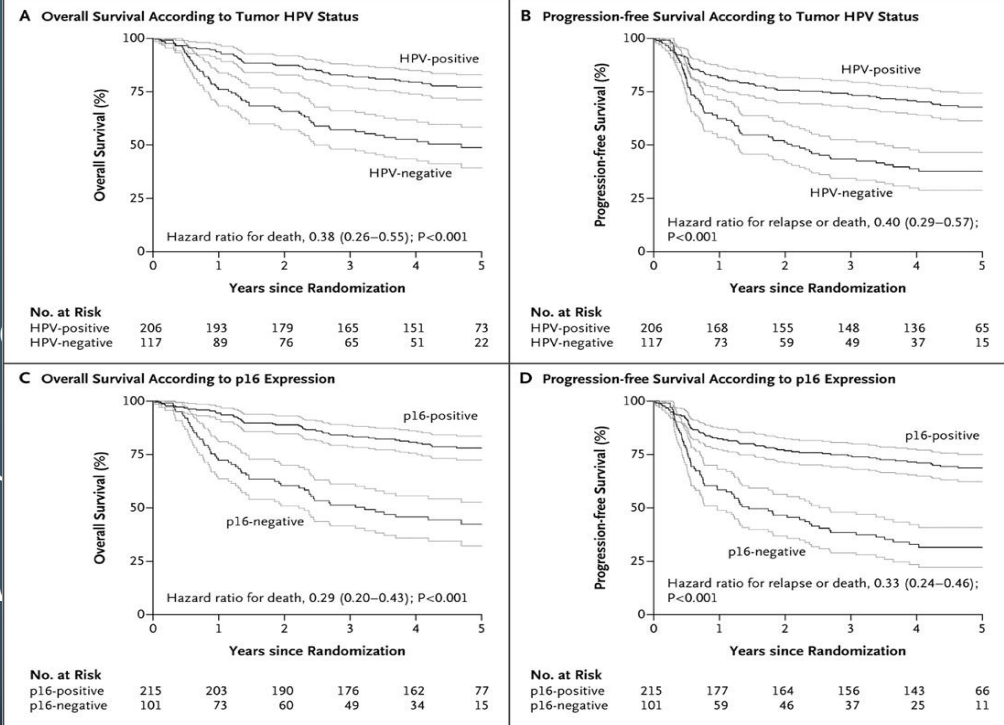
Rb

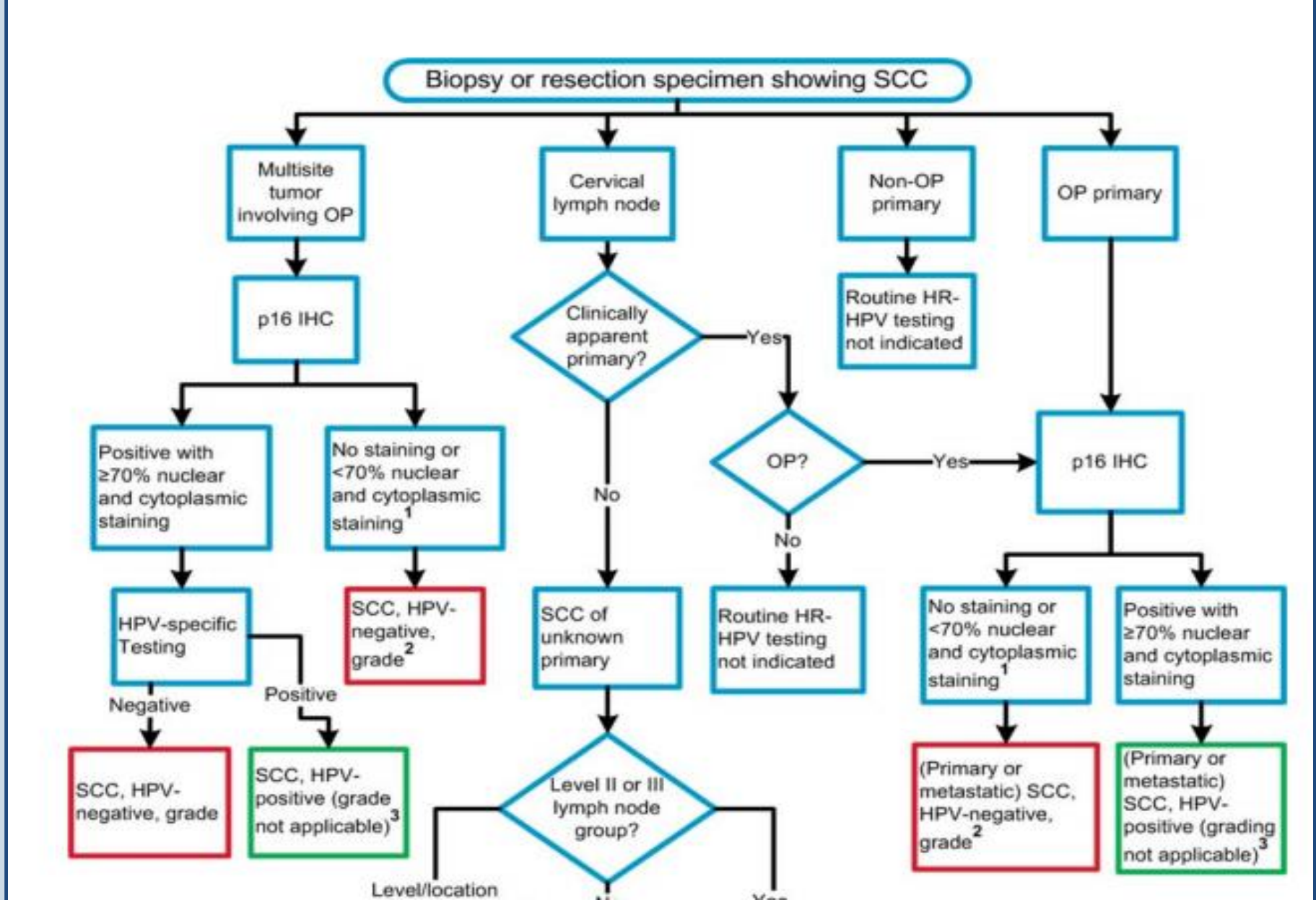
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P53

wt

Survival better





Human Papillomavirus Testing in Head and Neck Carcinomas

Guidelines from the **College of American Pathologists** (Arch Pathol. 2017, Epub ahead of press)

Guideline 1:

Pathologists should perform high risk human papillomavirus (HR-HPV) testing on **all patients** with newly diagnosed **oropharyngeal squamous cell carcinoma (OPSCC)**...

Guideline 2:

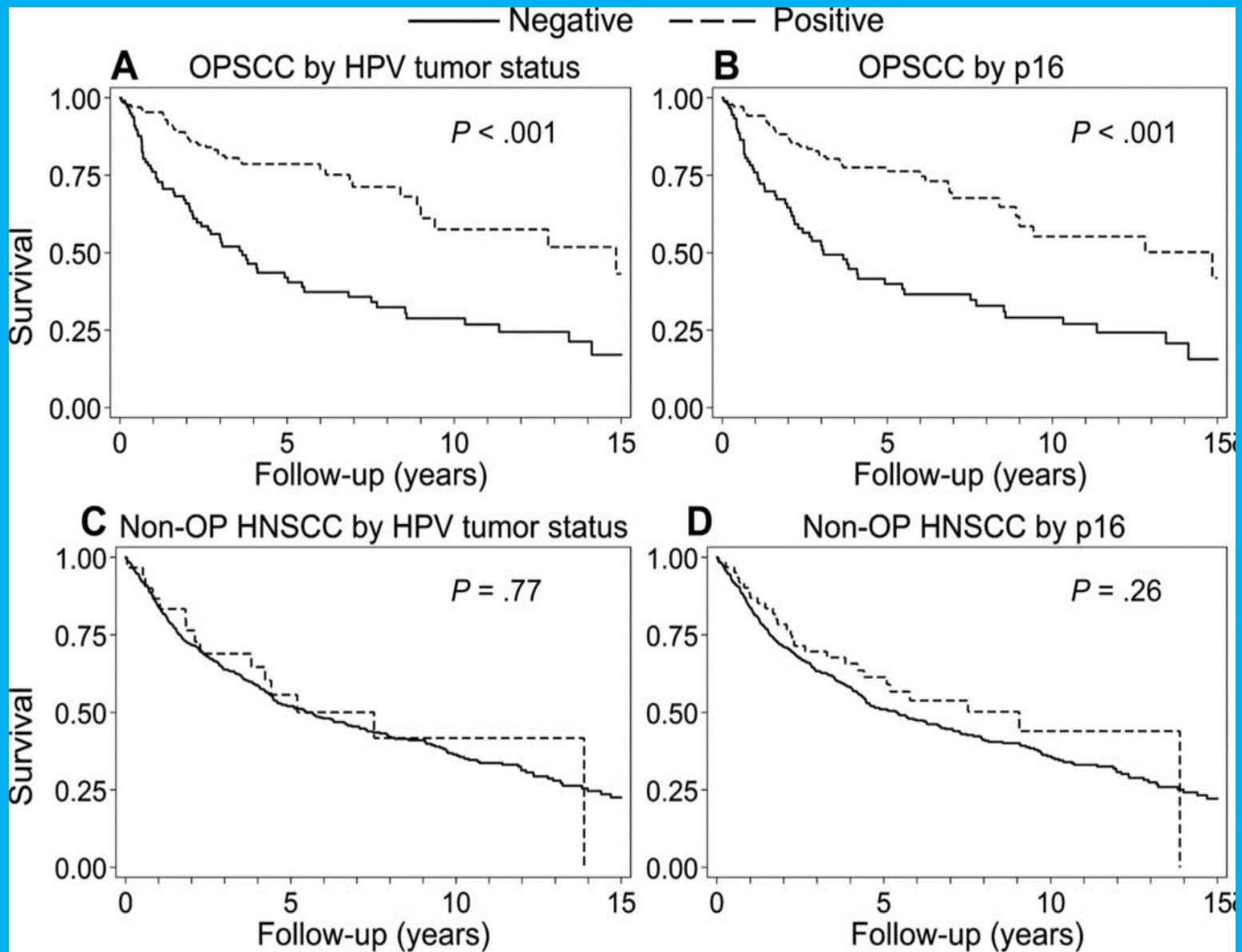
For oropharyngeal tissue specimens (i.e., non-cytology), pathologists should perform HR-HPV testing by **surrogate marker p16 IHC**. Additional HPV-specific testing may be done at the discretion of the pathologist and/or treating clinician, or in the context of a clinical trial.

Guideline 4:

Pathologists should **not routinely perform HR-HPV testing** on patients with **non-oropharyngeal** primary tumors of the head and neck

Why not routinely test non-oropharyngeal sites?

- ✓ HPV positive tumors map to the oropharynx
- ✓ It remains to be proved that the presence of HPV in non-oropharyngeal HNSCCs is prognostically or clinically relevant
 - Low positive predictive value for p16 IHC alone (22%-50%)
 - Only 7 of 29 (24%) clinical outcomes studies showed statistically different survival between HPV+ and HPV- tumors
 - Highly variable in anatomic subsites and HPV detection methods
 - 5 improved prognosis and 2 worse prognosis for HPV+ tumors

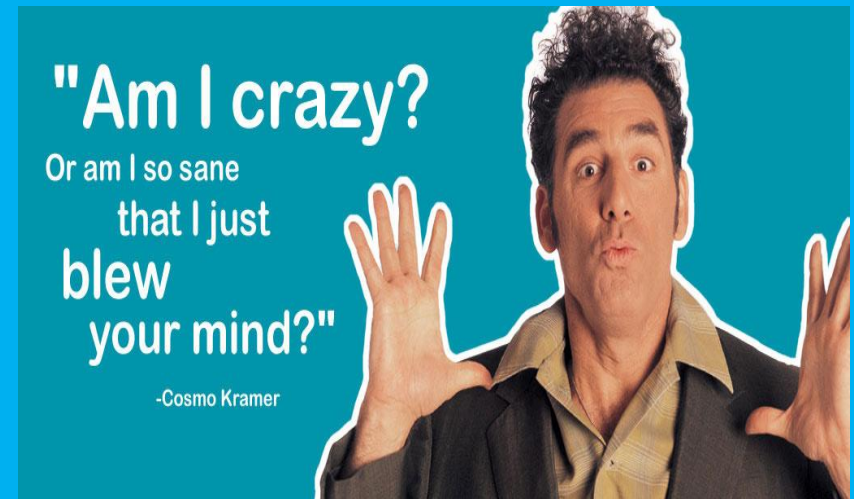


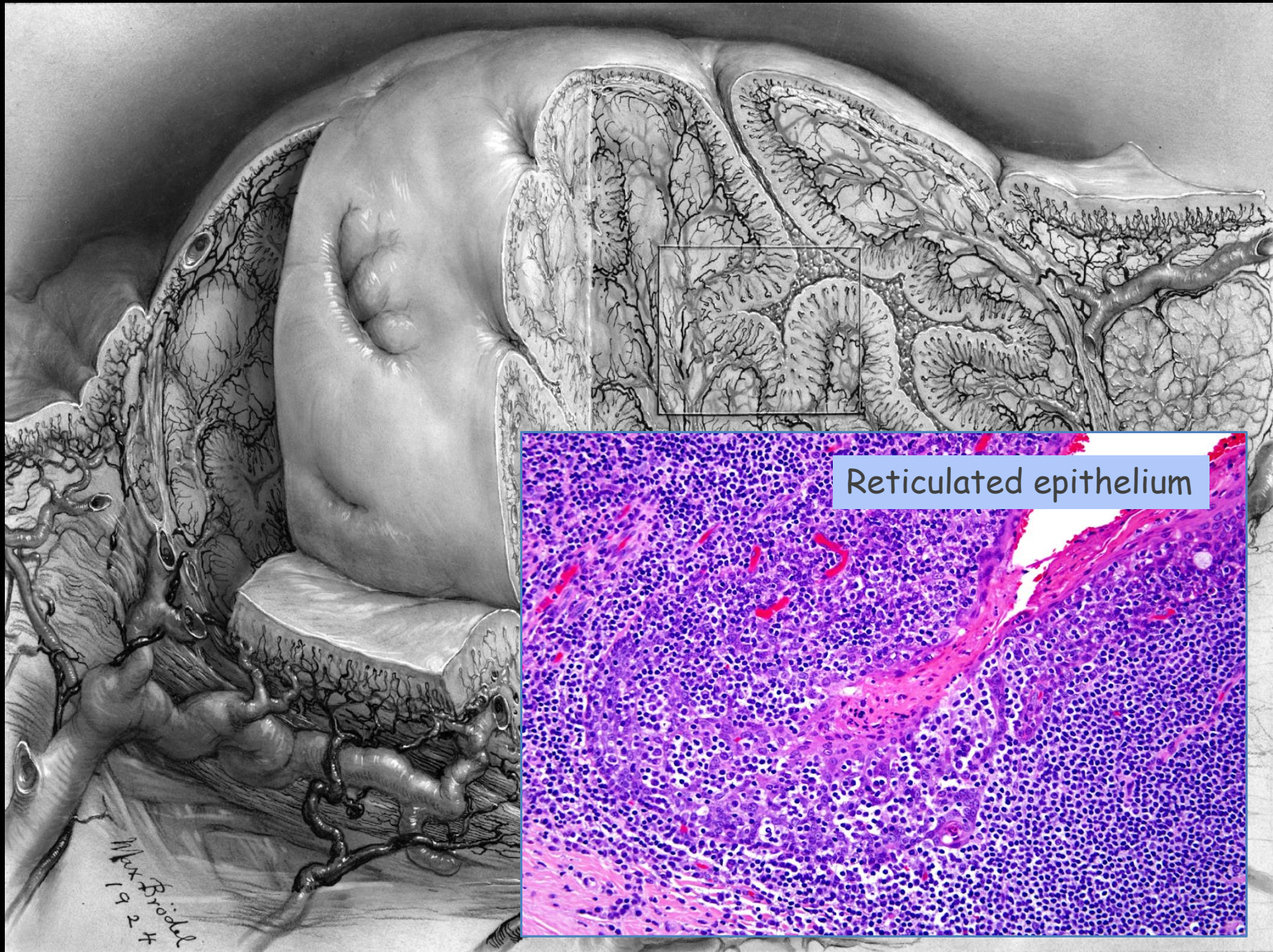
Change 3.

Modification of T-stage for Oropharyngeal Carcinomas based on HPV status: elimination of Tis category

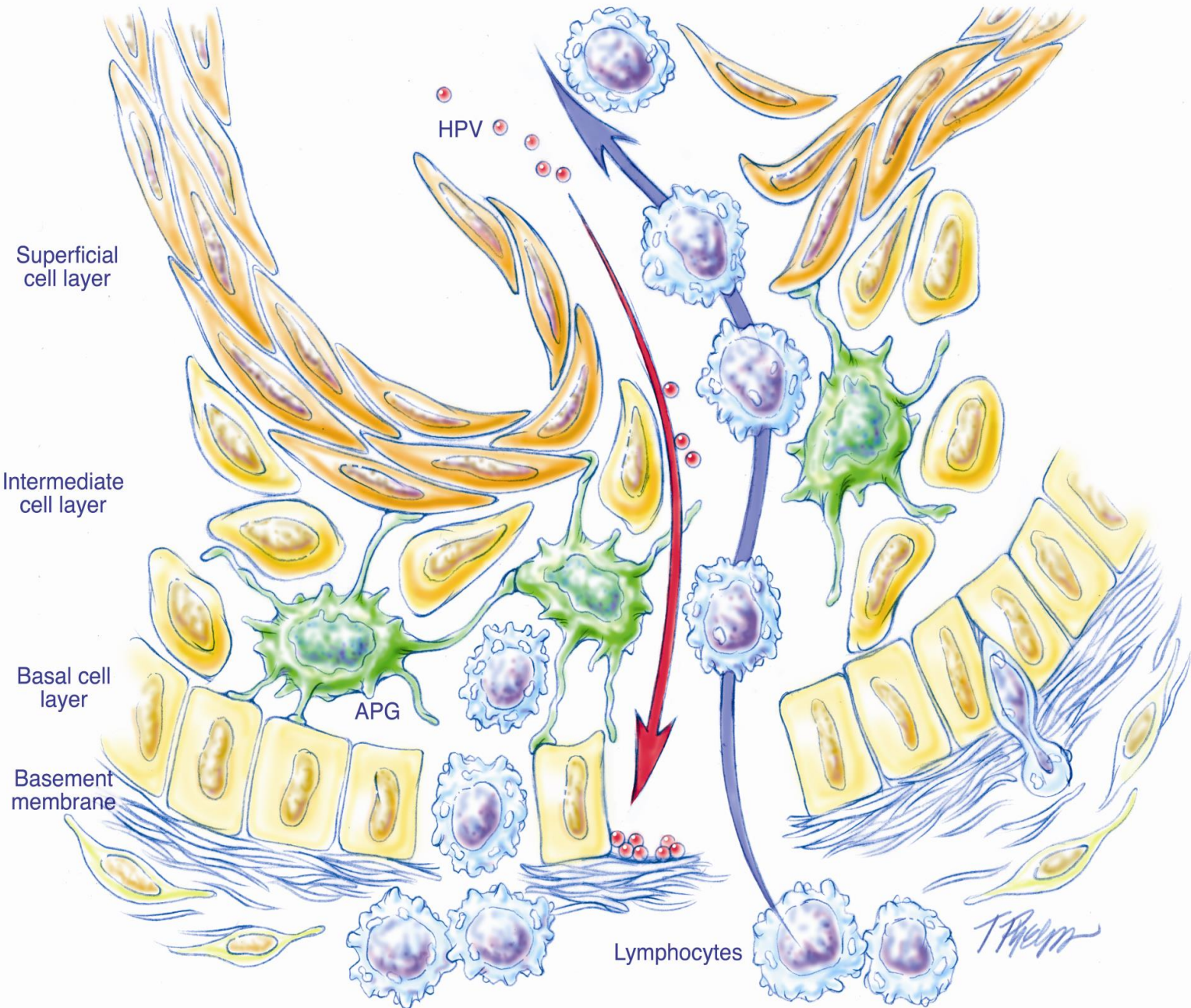
1. Carcinoma *in-situ* vs. invasive carcinoma

2. Histologic grading





Reticulated epithelium



Superficial cell layer

Intermediate cell layer

Basal cell layer

Basement membrane

HPV

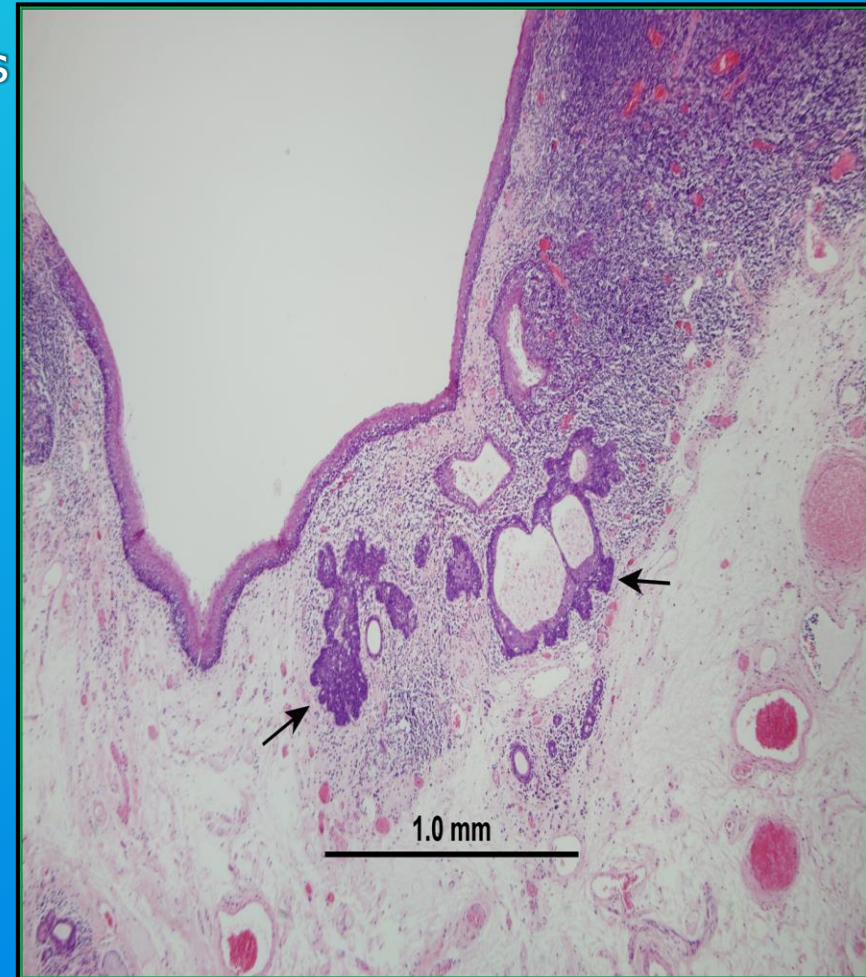
APG

Lymphocytes

T. Palm

The traditional microscopic approach to the recognition of invasion is invalid for HPV-related tonsillar carcinoma

- subsurface origin from tonsillar crypts
- absence of stromal desmoplasia
- blurred epithelial/lymphoid junction
- porous nature of the B.M.
- propensity for small (even occult) carcinomas to metastasize in the absence of clear cut stromal invasion



Change 3.

Modification of T-stage for Oropharyngeal Carcinomas based on HPV status: elimination of Tis category

HPV-Associated Oropharyngeal Cancer	
T category	T criteria
T0	No primary tumor identified
T1	Tumor 2 cm or smaller
T2	Tumor larger than 2 cm but smaller than 4 cm
T3	Tumor larger than 4 cm or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond

Non-HPV-Associated Oropharyngeal Cancer	
T category	T criteria
Tx	Primary tumor cannot be accessed
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller
T2	Tumor larger than 2 cm but smaller than 4 cm
T3	Tumor larger than 4 cm or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond
T4b	Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Change 4.

Eliminate tumor grading of HPV-positive oropharyngeal squamous cell carcinoma

1. Carcinoma *in-situ* vs. invasive carcinoma

2. Histologic grading

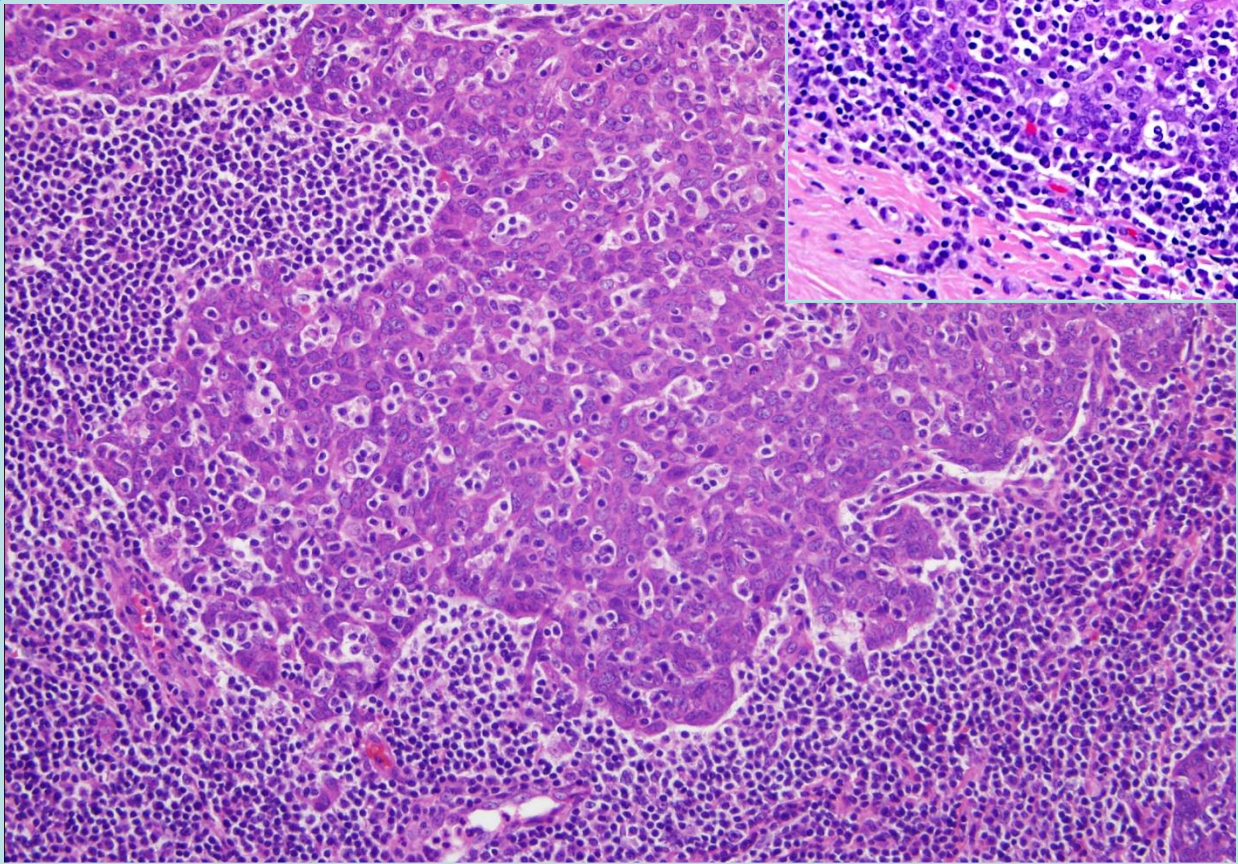
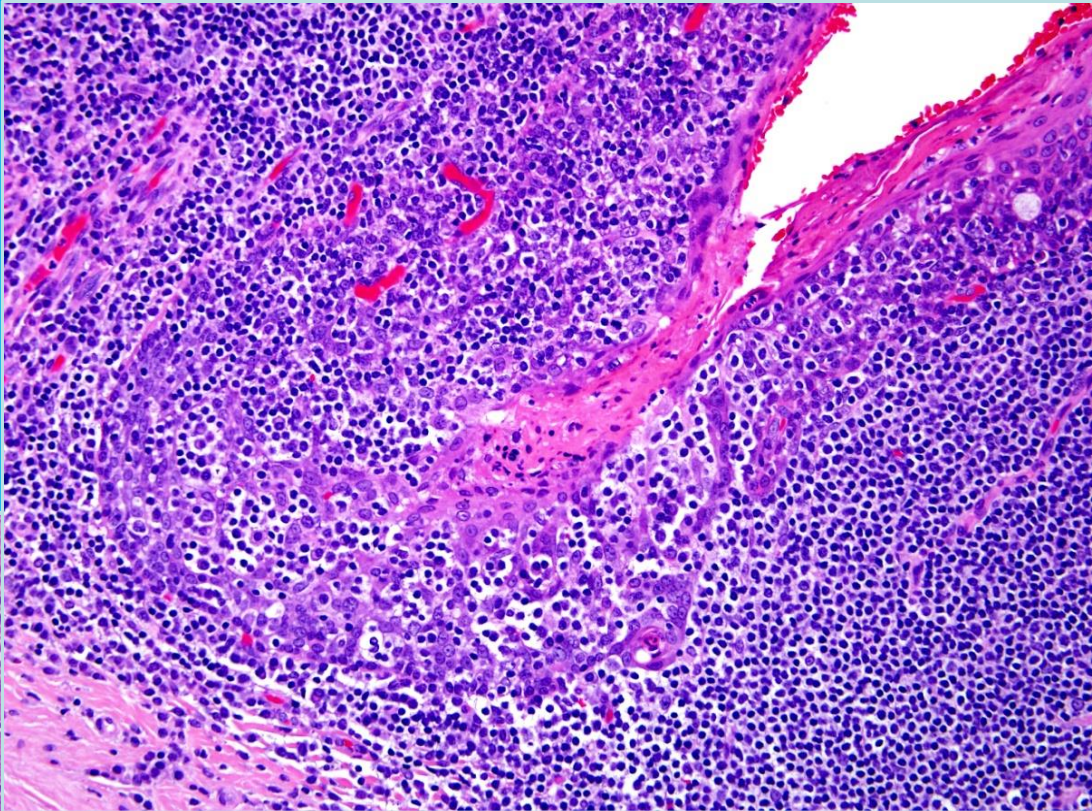
Well differentiated – a carcinoma with histological and cellular features that closely resemble normal epithelium of similar type.

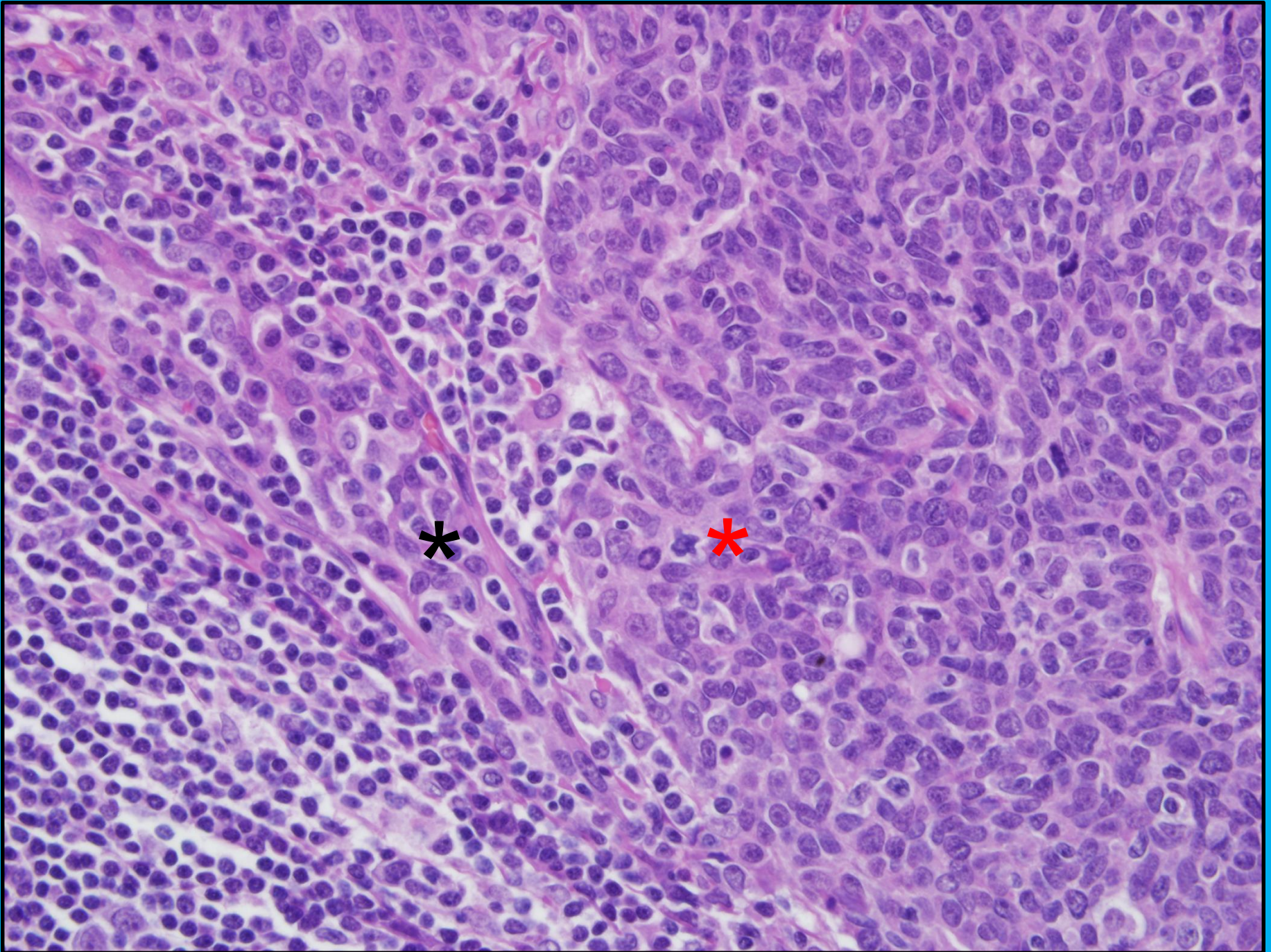
Moderately differentiated – a carcinoma with histological features Intermediate between well differentiated and poorly differentiated.

Poorly differentiated – a carcinoma with histological and cellular features which only barely resemble normal epithelium of similar type.

Histological typing of upper respiratory tract tumors
World Health Organization, 1978

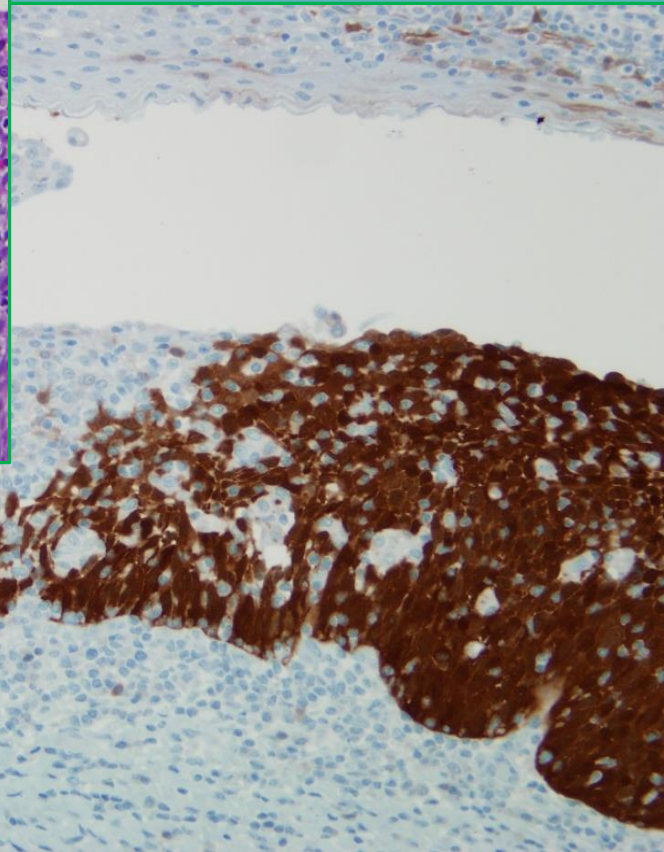
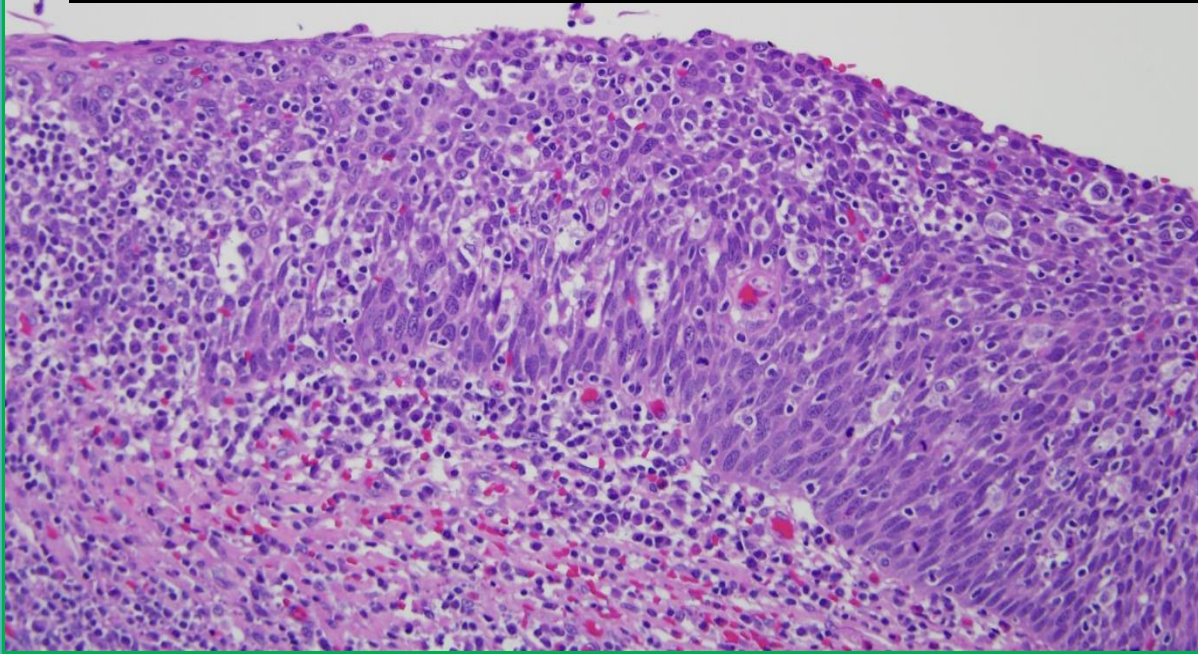
Histologic grading of HPV-related HNSCC





Change 4.

Eliminate tumor grading of HPV-positive oropharyngeal squamous cell carcinoma (AJCC, W.H.O., C.A.P.)



Change 5.

Refinement of nodal staging for more effect stratification of survival outcomes as a function of HPV status

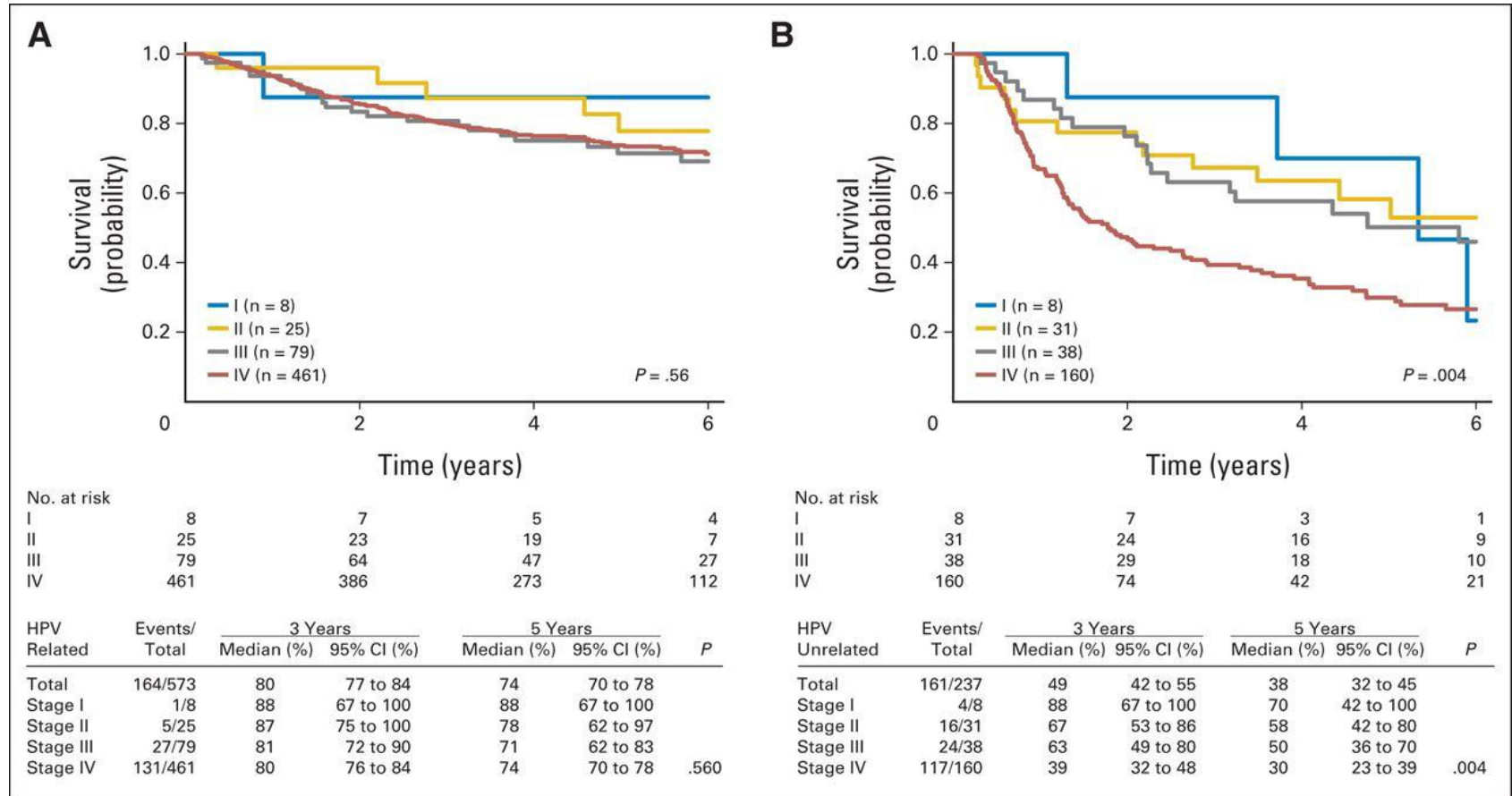


Fig 1. Overall survival by current American Joint Committee on Cancer/Union for International Cancer Control TNM stage in (A) human papillomavirus (HPV)–related and (B) HPV-unrelated oropharyngeal carcinomas.

Shao Hui Huang; Wei Xu; John Waldron; Lillian Siu; Xiaowei Shen; Li Tong; Jolie Ringash; Andrew Bayley; John Kim; Andrew Hope; John Cho; Meredith Giuliani; Aaron Hansen; Jonathan Irish; Ralph Gilbert; Patrick Gullane; Bayardo Perez-Ordonez; Ilan Weinreb; Fei-Fei Liu; Brian O'Sullivan; *JCO* 2015, 33, 836-845.

DOI: 10.1200/JCO.2014.58.6412

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Change 5.

Refinement of nodal staging for more effect stratification of survival outcomes as a function of HPV status

Pathologic N category for HPV-negative oropharyngeal cancer	
N category	N criteria
Nx	Regional lymph nodes cannot be addressed
N0	No regional lymph node metastasis
N1	Single ipsilateral lymph nodes, 3 cm or less, and ECE negative
N2a	Single ipsilateral or contralateral node 3 cm or less and ECE (+); or single ipsilateral node > 3 and < 6 cm and ECE (-)
N2b	Multiple ipsilateral lymph nodes, none larger than 6 cm and ECE (-)
N2c	Bilateral lymph nodes, none larger than 6 cm and ECE (-)
N3a	Lymph node > 6 cm and ECE (-)
N3b	Single ipsilateral node > 3 cm and ENE (+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE (+)

* Pathologic N category for HPV-positive oropharyngeal cancer	
N category	N criteria
NX	Regional lymph nodes cannot be accessed
N0	No regional metastases
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

*nodal staging is not impacted by size, location or extranodal extension (ENE)!

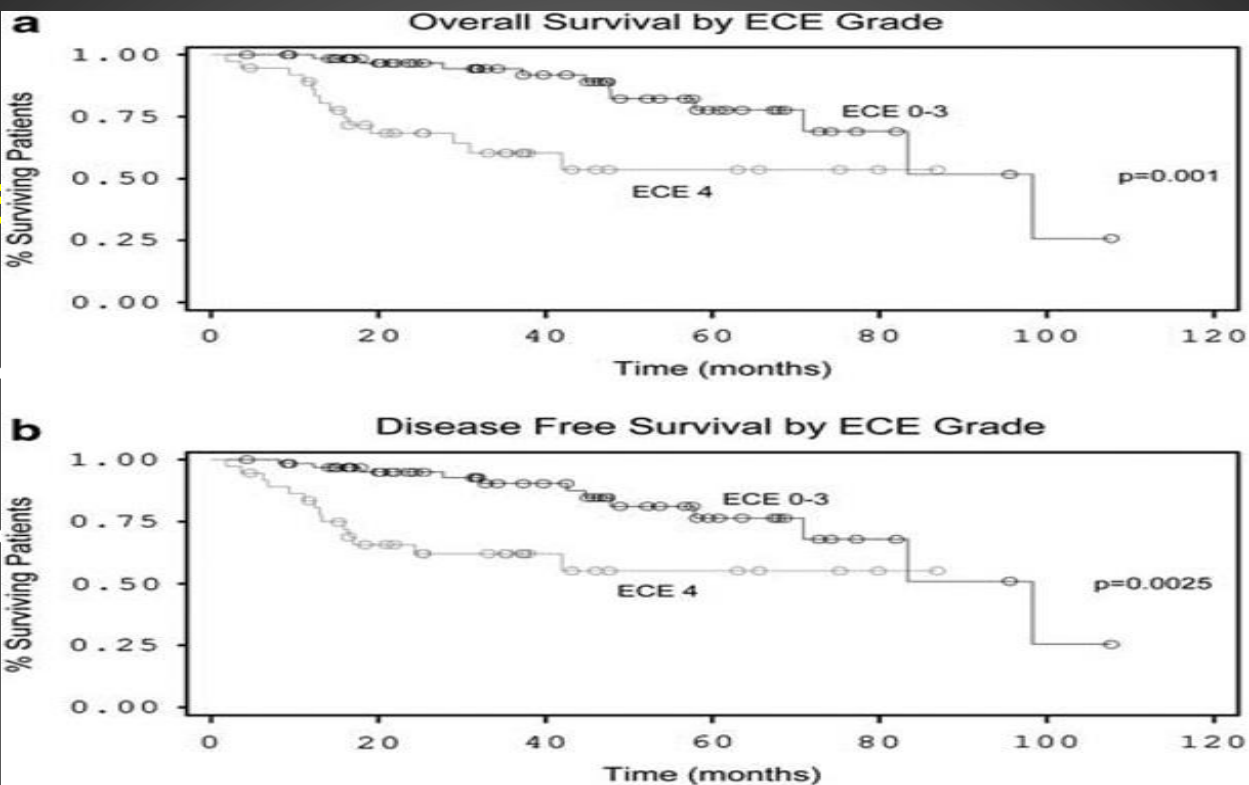
What is extranodal extension (ENE)?






- ✓ Extension of metastatic carcinoma through the fibrous node capsule and into perinodal soft tissues
- ✓ Minor ENE: ≤ 2 mm beyond node capsule
- ✓ Major ENE: > 2 mm beyond node capsule
- ✓ Major ENE includes soft tissue implants
- ✓ Major and minor subcategories are for data collection purposes only (both ENE positive for staging purposes)

Why
parameter

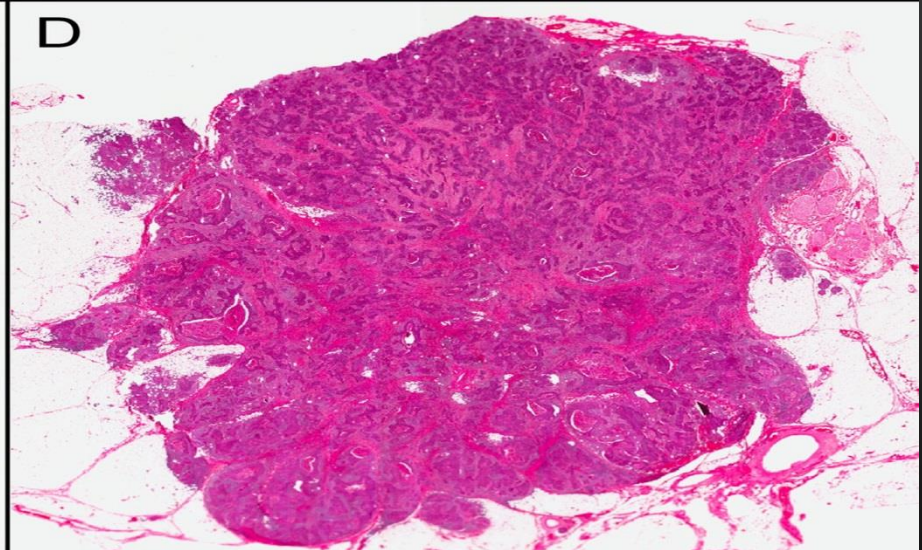
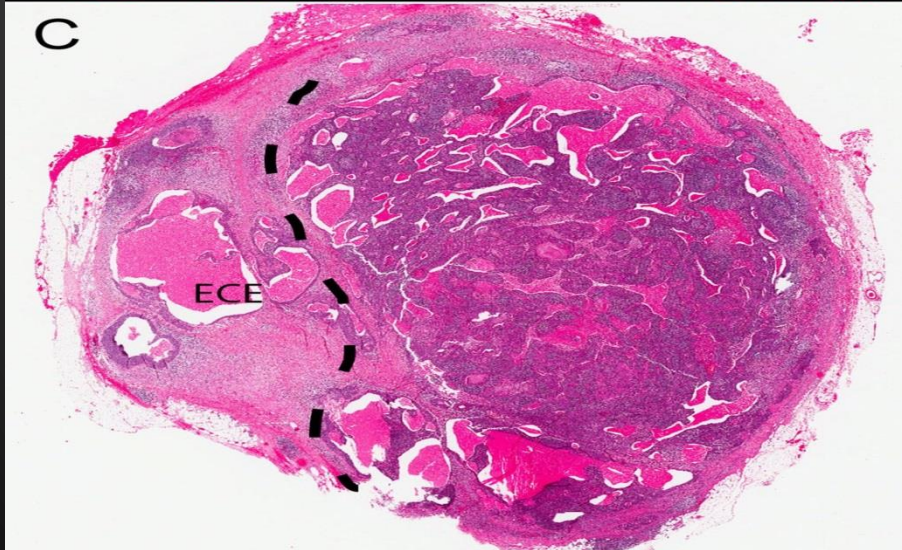
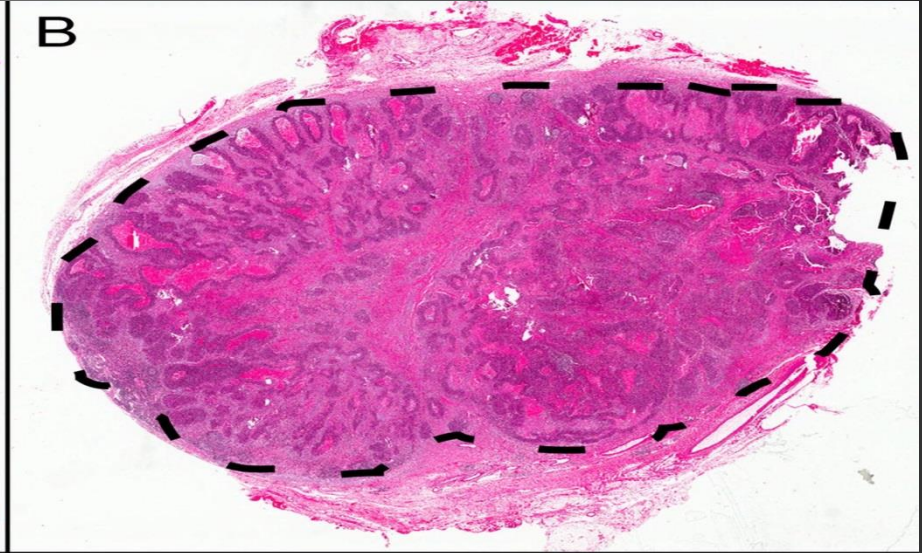
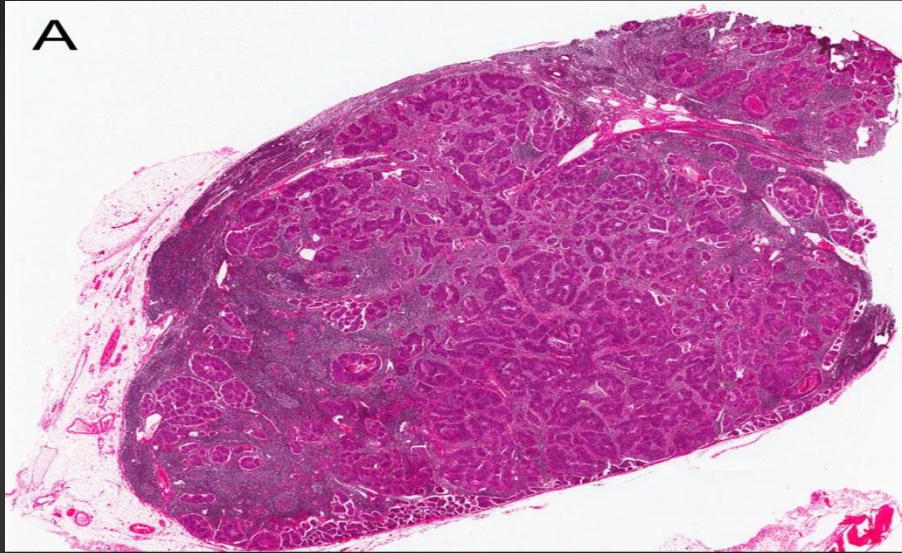
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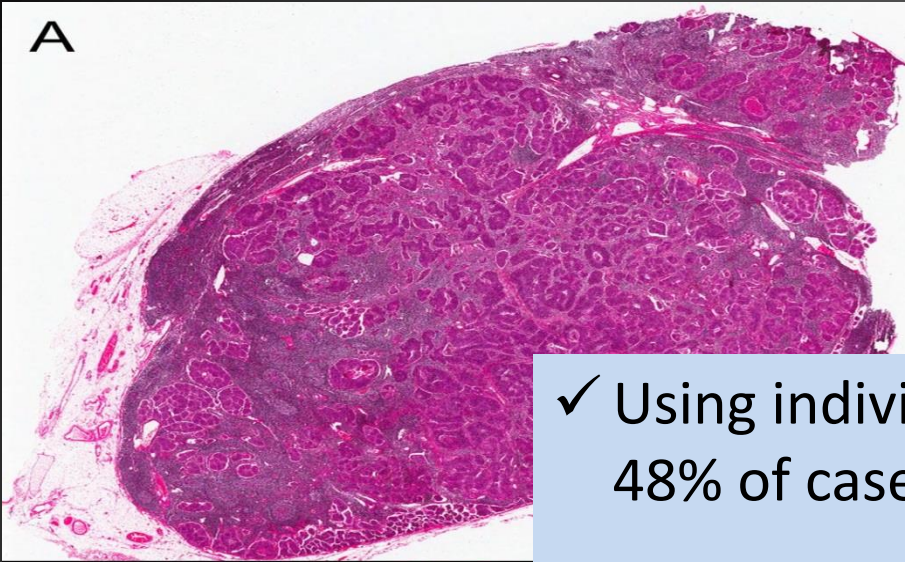
aging
l cancer?



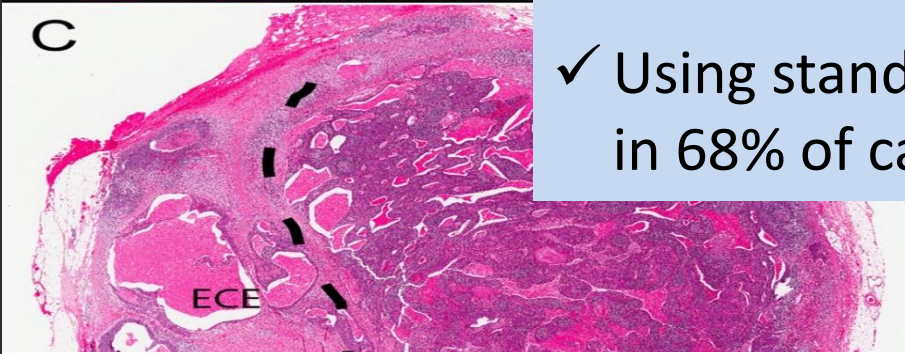
ECE grade	0	1	2	3	4
Illustration					
Description	Tumor confined to the substance of the lymph node (surrounded by lymphoid tissue)	Tumor reaching the capsule of the lymph node (no intervening lymphoid tissue) and with thickening of overlying capsule.	Tumor in perinodal tissue but extending ≤1mm beyond the lymph node capsule.	Tumor in perinodal tissue and extending >1 mm beyond the lymph node capsule.	Soft tissue metastasis. Tumor mass without residual nodal tissue or architecture (no germinal centers or subcapsular sinus).

Why is extracapsular extension not a staging parameter for HPV-associated oropharyngeal cancer? Not reproducible

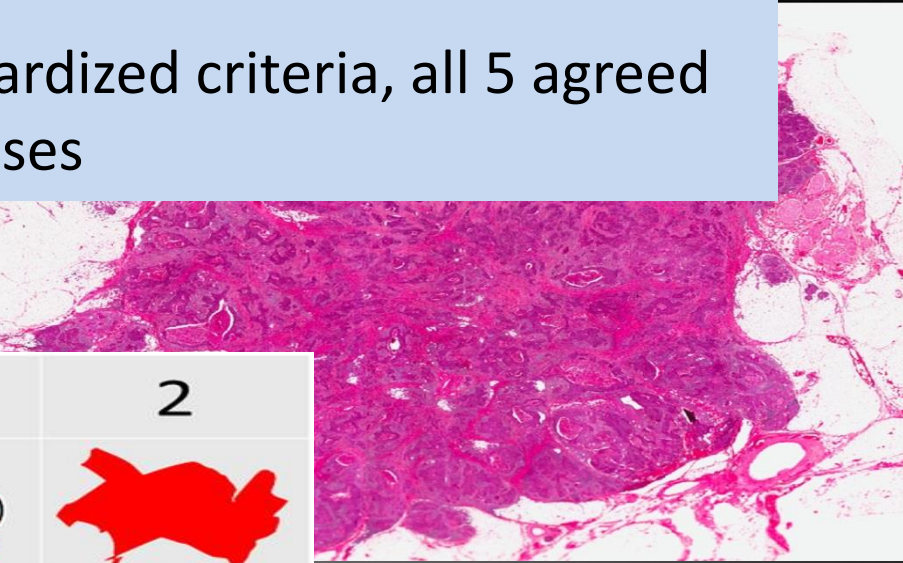


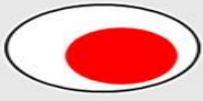





✓ Using individual criteria, all 5 agreed in 48% of cases



✓ Using standardized criteria, all 5 agreed in 68% of cases

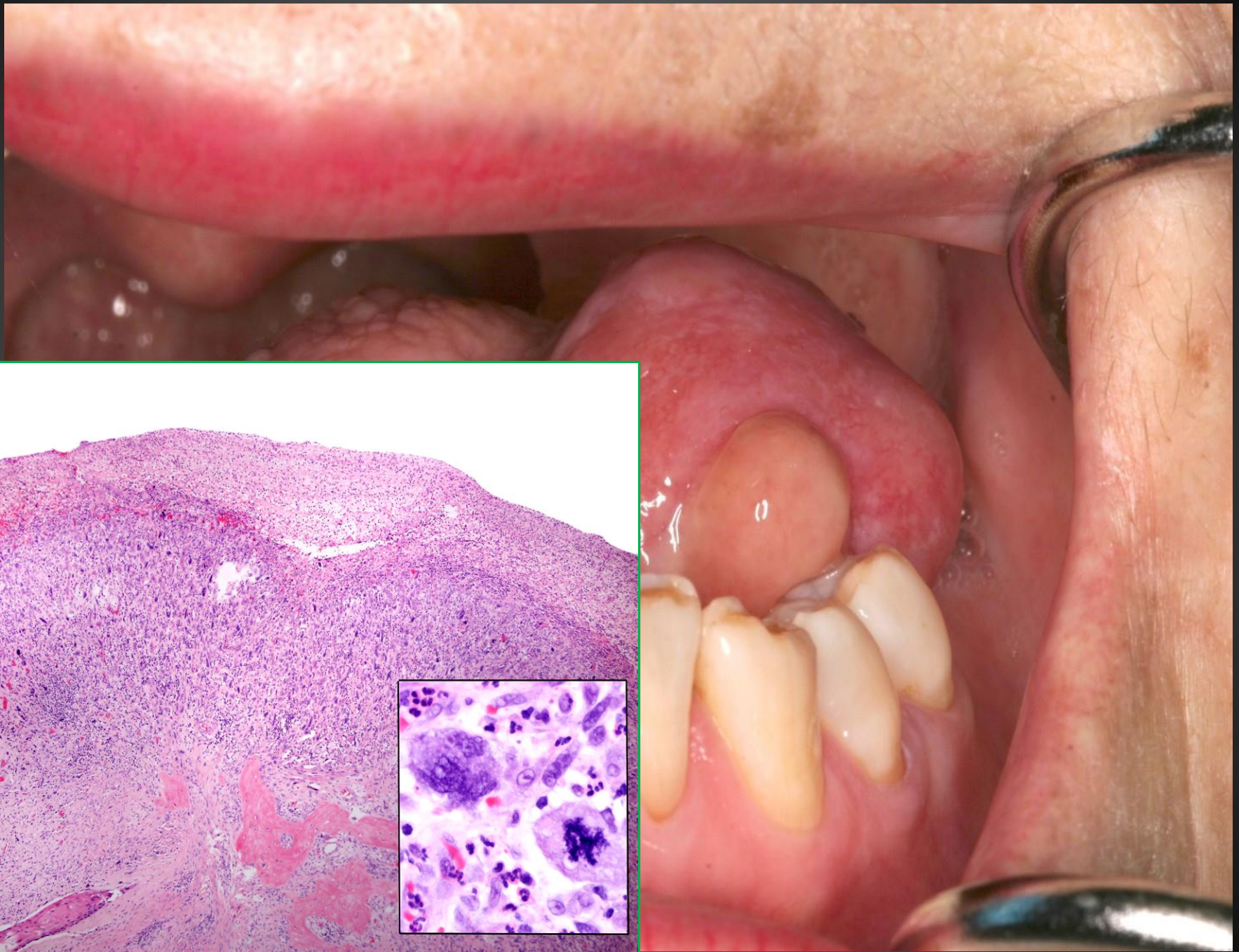


ECE grade	0	0(c)	1	2
Image				
	Tumor confined to the substance of the lymph node (surrounded by lymphoid tissue)	Tumor expanding to the capsule of the lymph node (no intervening lymphoid tissue) with thickening of overlying capsule.	Tumor invading beyond lymph node capsule into perinodal tissue.	Soft tissue metastasis. Tumor mass without residual nodal tissue or architecture (no remaining LN germinal centers or subcapsular sinus).

Lewis et al. Oral Oncol 51:985,2015

The dirty little secret of Head & Neck Tumor Boards





Change 6.

For oral cavity squamous cell carcinoma, T stage now incorporates depth of invasion (DOI)

- For every 5 mm increase in DOI, pT category increasing by one level ($\leq 5\text{mm}$, $> 5\text{mm}$ but $\leq 10\text{ mm}$, $> 10\text{ mm}$).
- DOI supersedes tumor thickness as a staging parameter

Horizon from adjacent mucosal basement membrane

