Head and neck cancer

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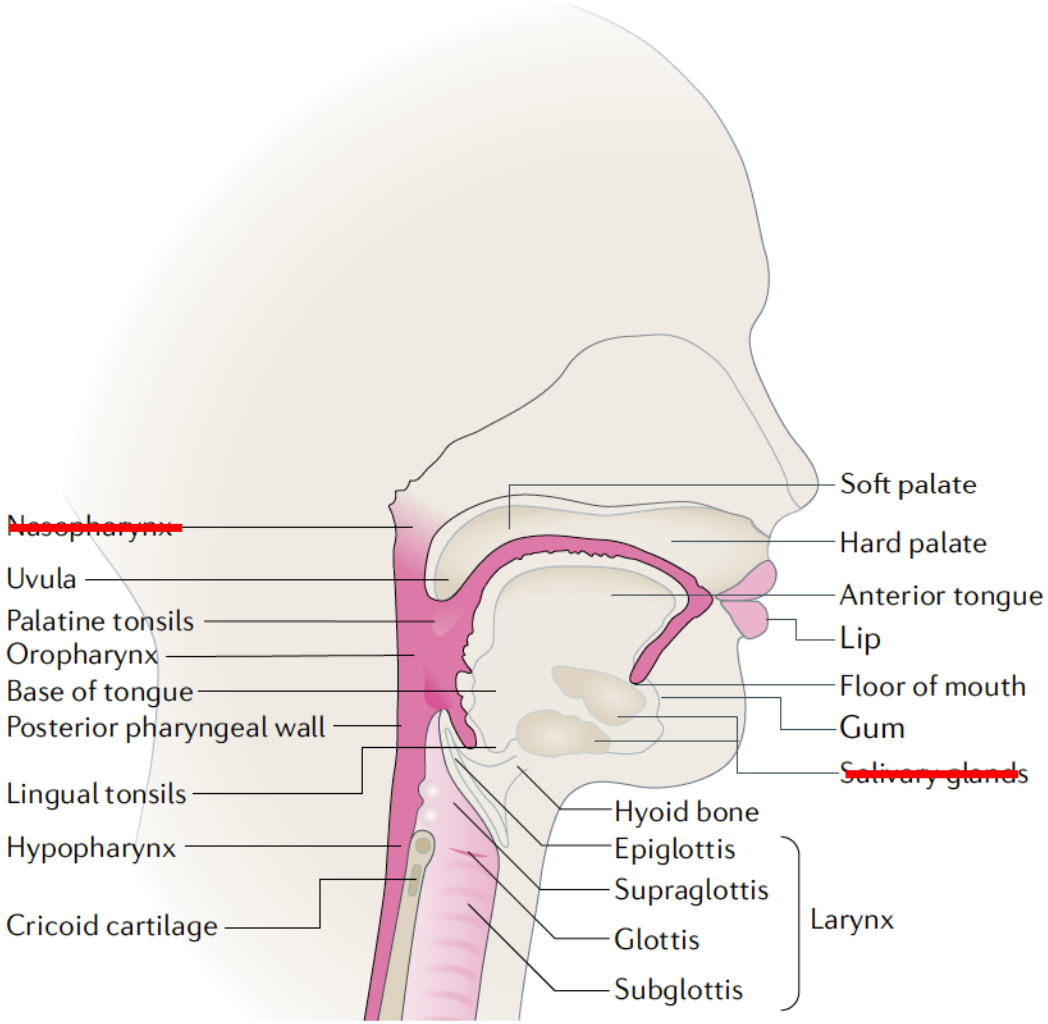
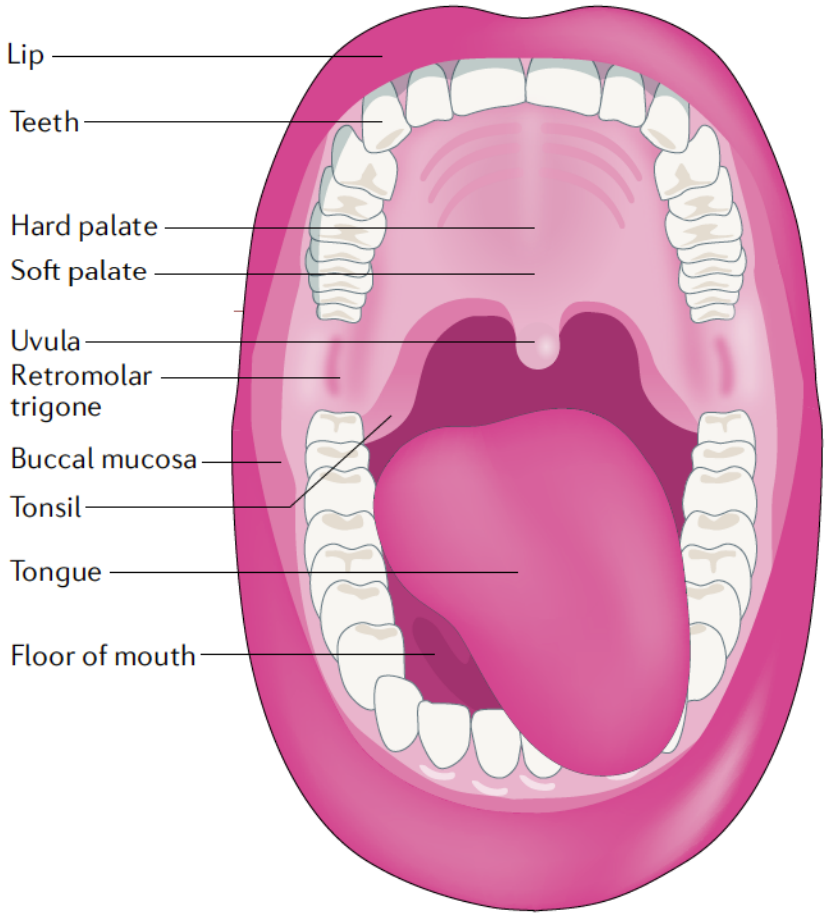
Head and neck cancer

Anatomical sites





Johnson et al. 2020

Incidence

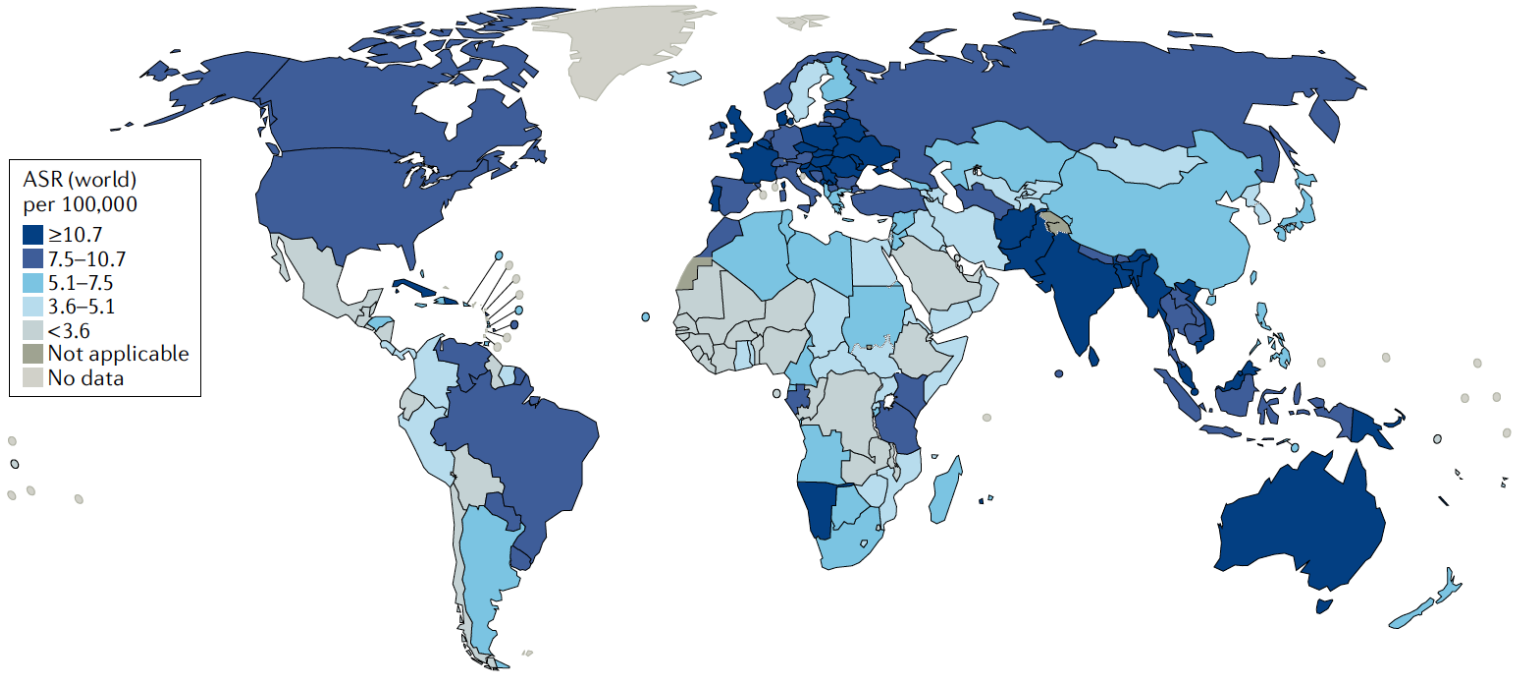
Sixth most common cancer: 4-6% of all cancers

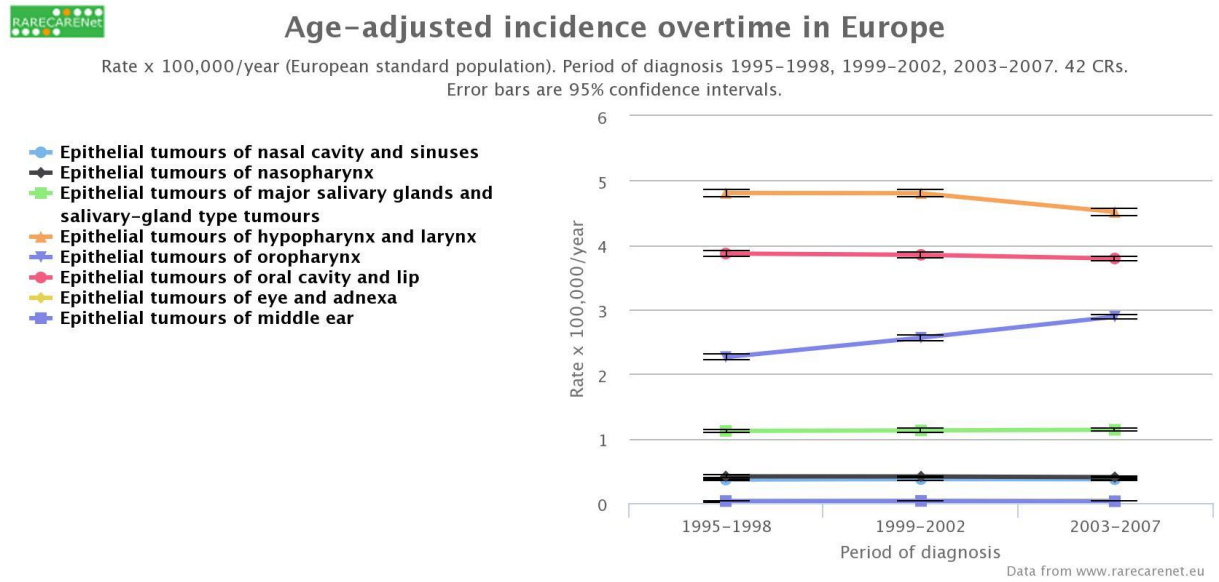
890,000 new cases and 450,000 deaths in 2018

Incidence is rising: > 1,000,000 new cases by 2030

M/F: 2-4

Median age: 66 years (HPV-)/53 years (HPV+)





Johnson et al. 2020; www.rarecancernet.eu

Risk factors

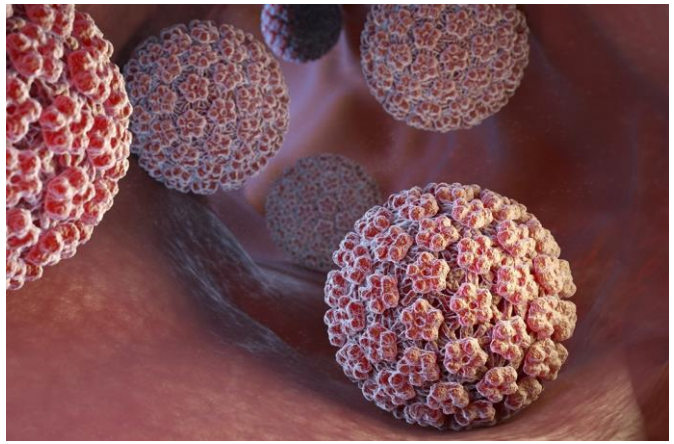
Tobacco

Excessive alcohol consumption

HPV, EBV (NPC)

Areca nut or “Betel quid” (India, Taiwan, China)

Genetic factors (Fanconi anemia)



Johnson et al. 2020

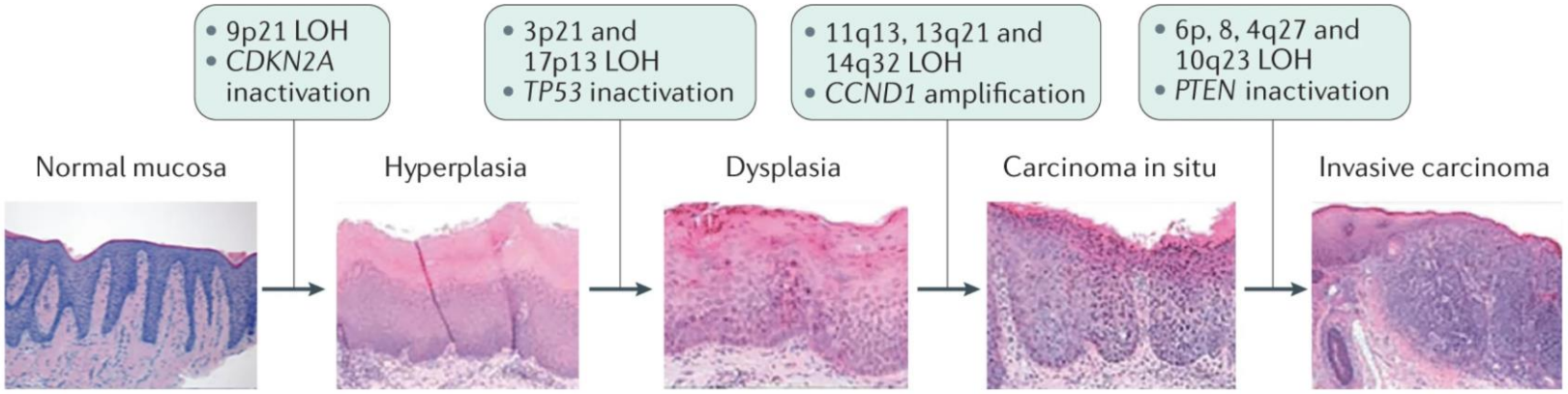
Carcinogenesis in HPV- disease

Originates from the mucosal epithelial cells that line the upper aerodigestive tract

Loss of tumor suppressor genes

Temporal sequence vs collective accumulation

“Field cancerization”: second primary tumors

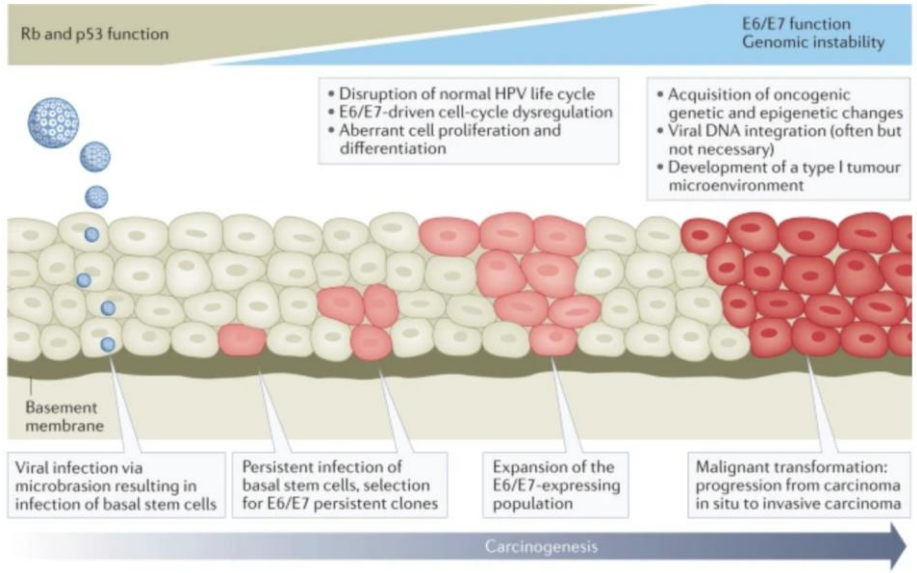


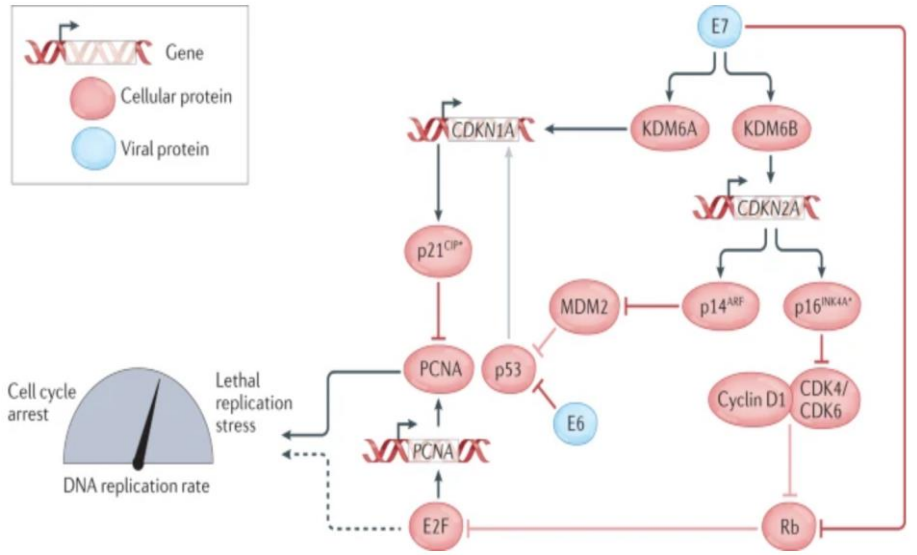
Johnson et al. 2020

HPV-driven carcinogenesis

APOBEC-mediated editing of the viral genome clears the infection

Oncogenic point mutations in *PIK3CA*: activation of the PI3K signaling pathway





Lechner et al. 2022

HPV+ oropharyngeal squamous cell carcinoma (OPSCC)

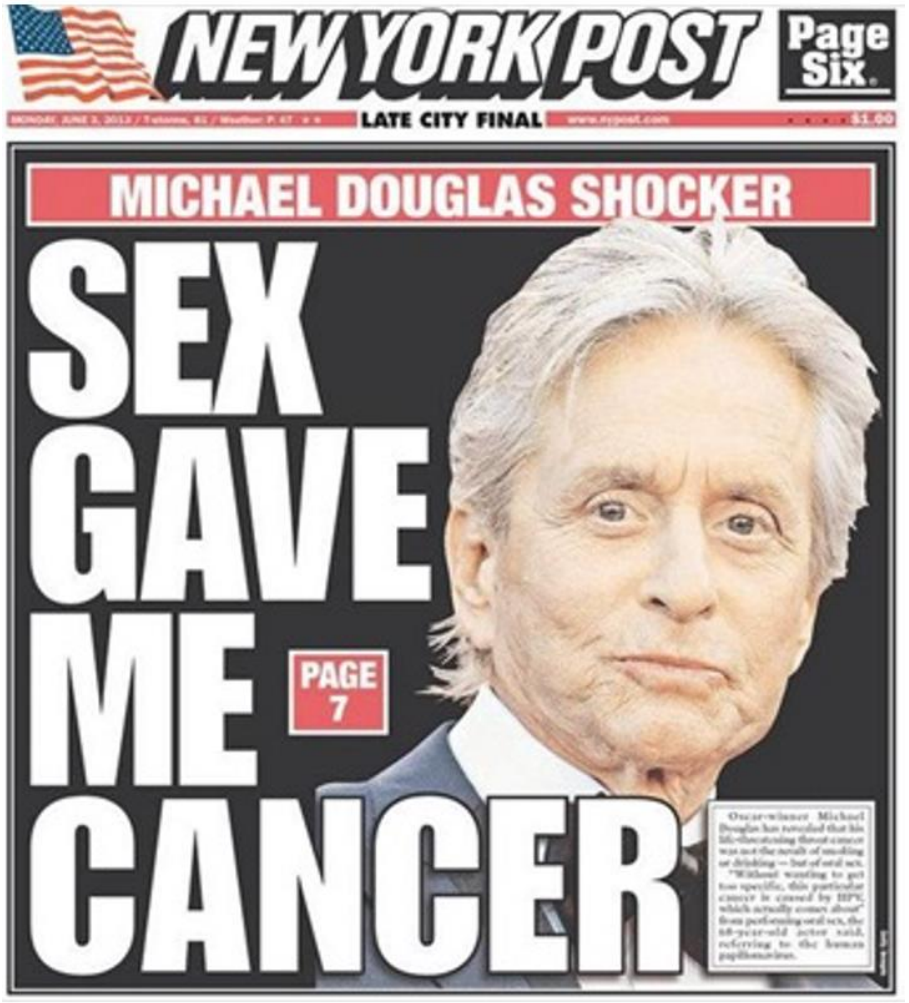
>70% of OPSCC positive for HPV

HPV-16 (85%) >> HPV-18, HPV-31, HPV-33, HPV-52

Sexually transmitted disease, strong association with the number of lifetime oral sex partners

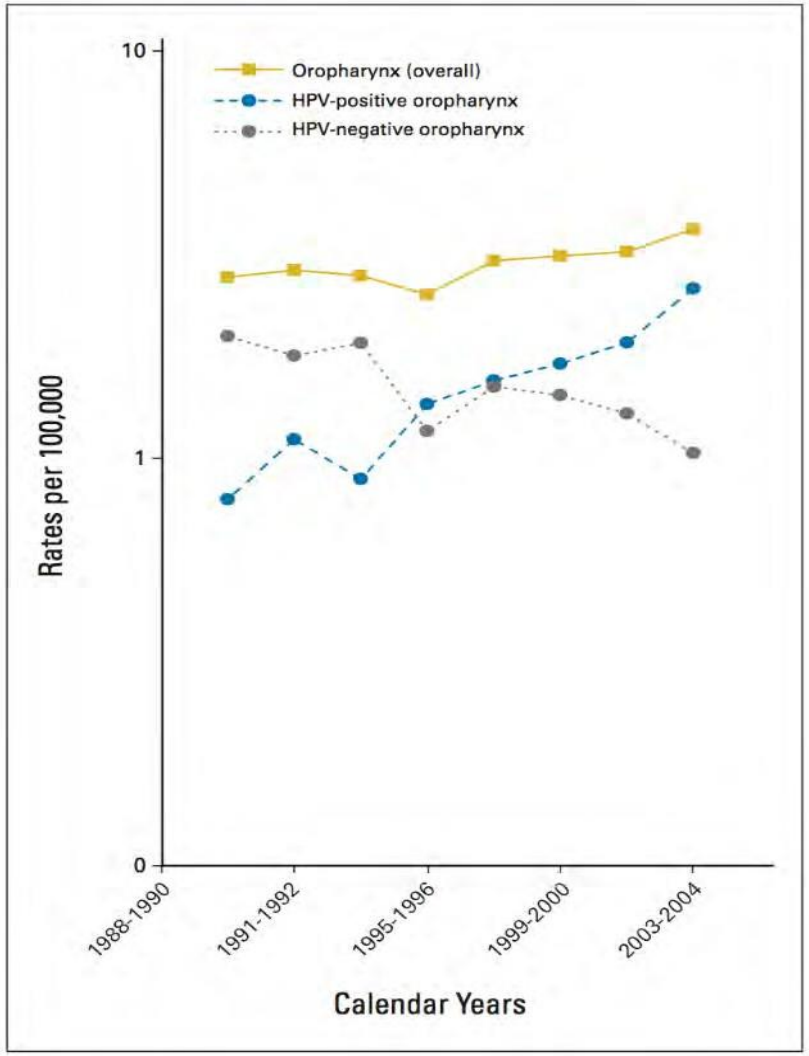
High-income countries, young, minimal to no smoking history

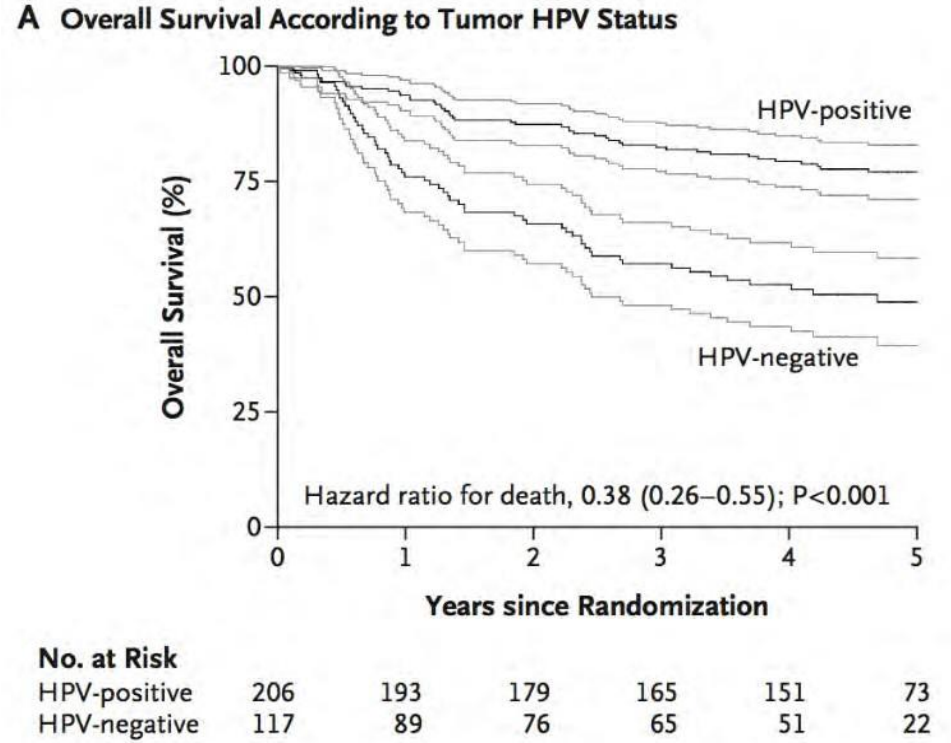
In the USA, the incidence of OPSCC in men has surpassed that of cervical cancer in women



D´Souza et al. 2007; Miller et al. 2012; Gillison et al. 2006

Increasing incidence and better prognosis of HPV+ OPSCC

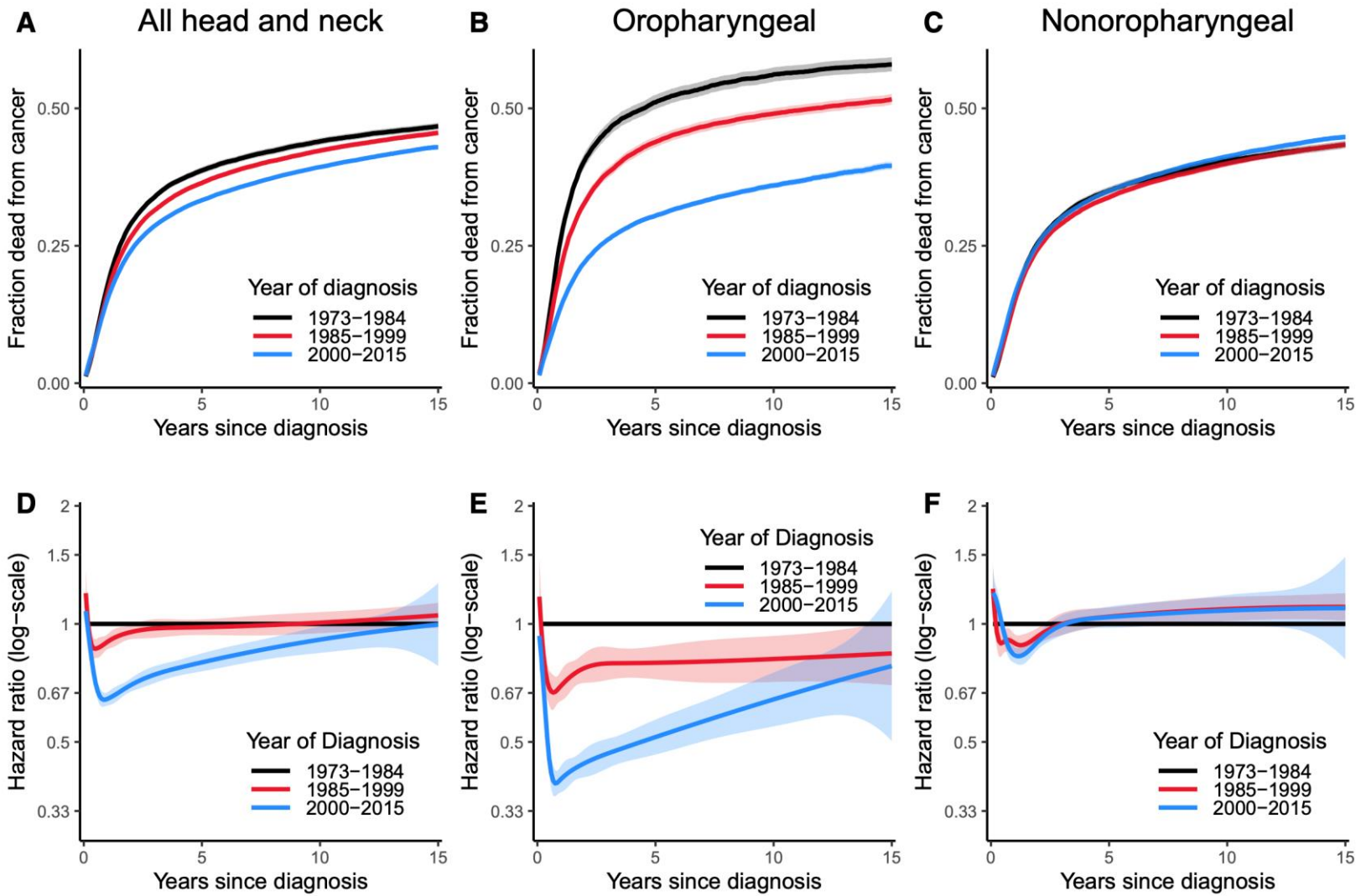




3-year OS with CRT: 82.4%, vs. 57.1%

Carvalho et al. 2005; Chaturvedi et al. 2011; Ang et al. 2010

Time-varying survival effects for HNSCC



5-year OS: 55% (1992–1996) > 66% (2002–2006)

Second highest rate of suicide among survivors (63.4/100,000 individuals): psychological distress and compromised QOL

Pulte et al. 2010; Brouwer et al. 2020

Clinical presentation depends on the anatomical site and etiology

Oral cavity: Non-healing mouth sore or ulcer – early stage

HPV- Oropharynx/hypopharynx: dysphagia, odynophagia, otalgia – late stage

HPV+ Oropharynx: neck mass

Larynx: hoarseness, dyspnea

Nasopharynx: neck mass, unilateral nasal obstruction, epistaxis

Johnson et al. 2020

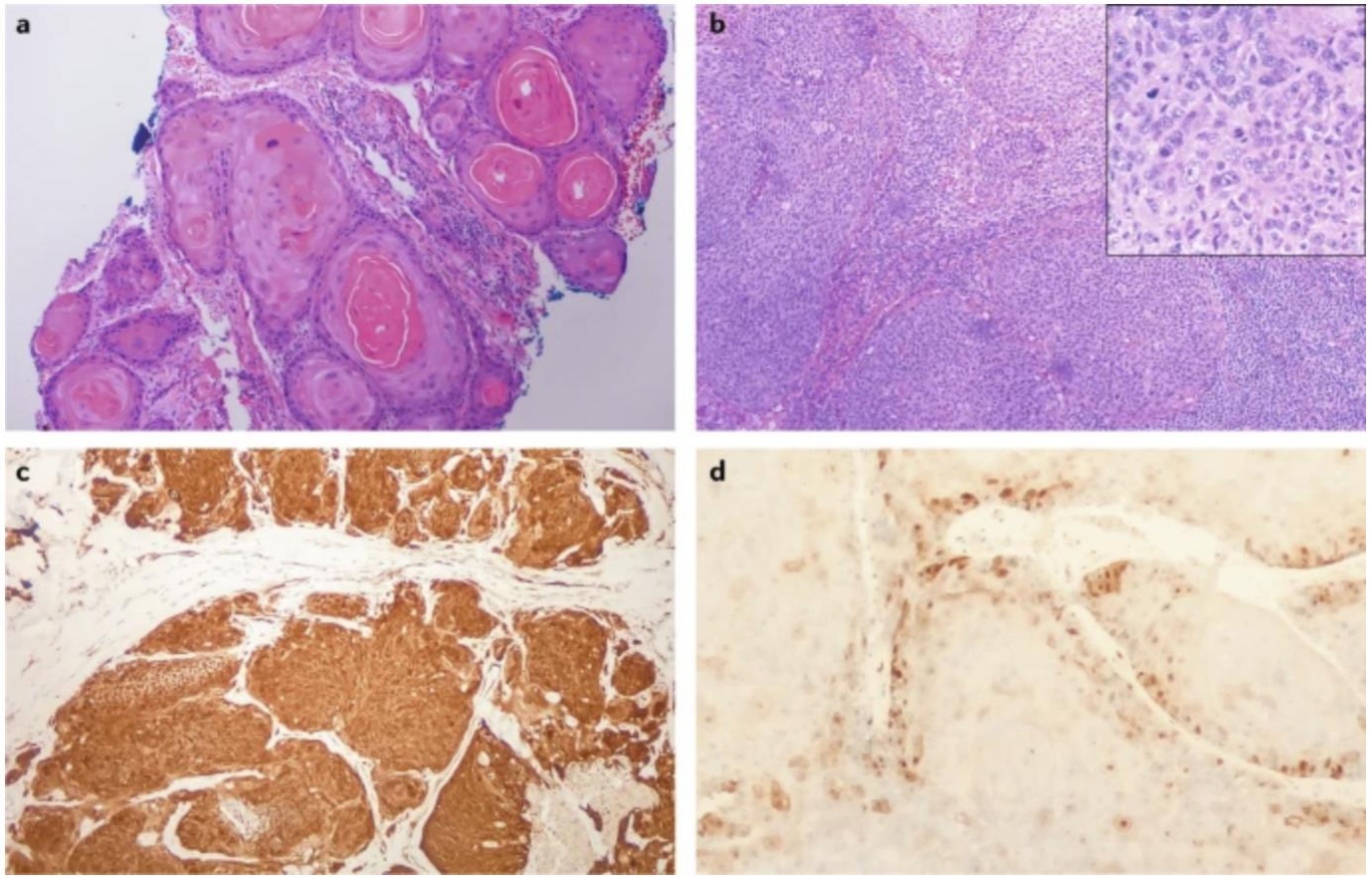
Diagnosis

Biopsy of the primary tumor and/or neck mass: FNA > excisional (non-diagnostic, unknown primary site, concurrent non-cervical lymphadenopathy)

Routine H&E is adequate for diagnosis: **>90% squamous cell carcinoma**

IHC for poorly differentiated/basaloid tumors: PanCK, CK5/6, p63

HPV testing for all oropharyngeal and unknown primary tumors: $p16^{INK4A}$ (diffuse nuclear and cytoplasmic staining in >70% of tumor cells) - is not a direct measure of HPV infection, *E6* and *E7* mRNA (rtPCR), HPV DNA (PCR, ISH)



Johnson et al. 2020; Taberna et al. 2017

Tumor microenvironment

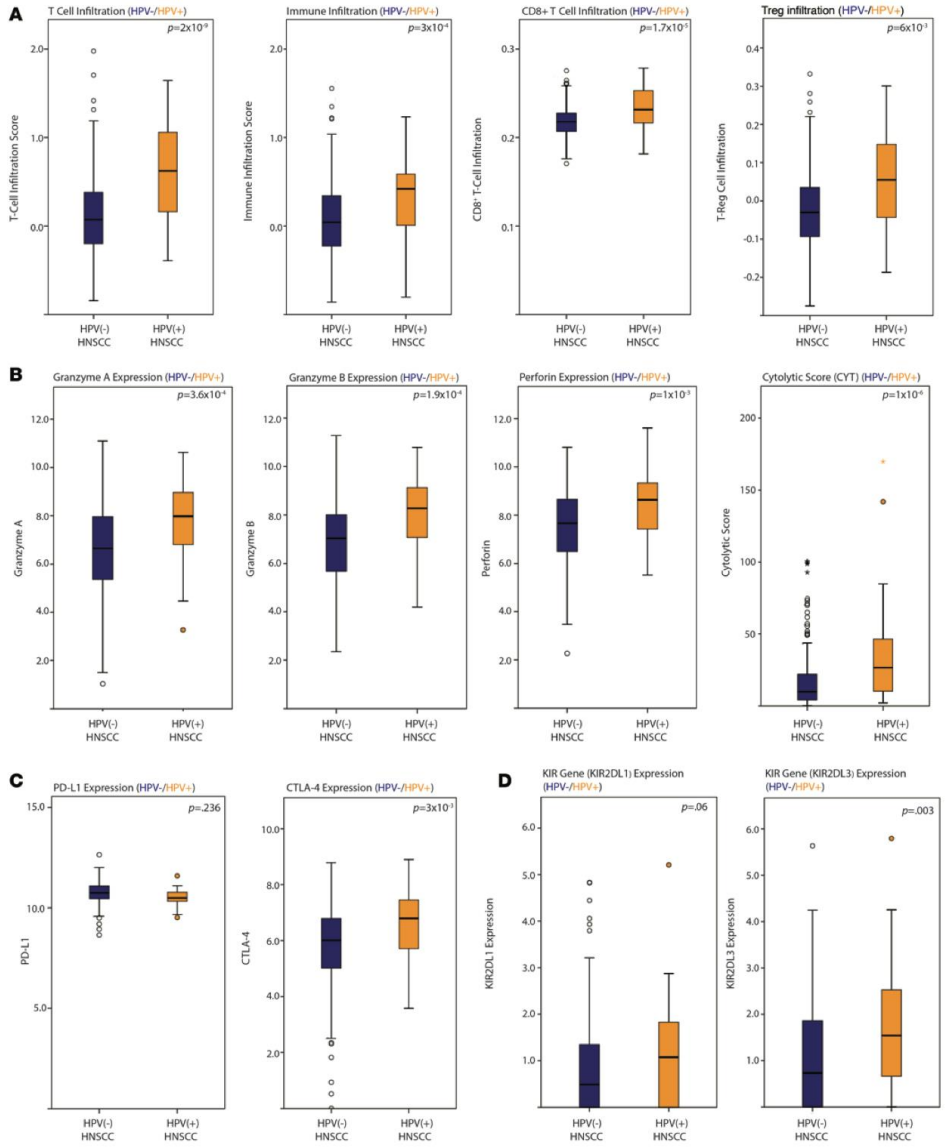
Highly immunosuppressive

- T_{eff}, NK cells vs T_{reg}, MDSCs and M2 macrophages
- Growth factors and cytokines (IL-10, TGFβ)
- Decreased HLA and defects in antigen processing
- Upregulation of PD-L1

Hypoxia

Oral microbiota?

Differences between HPV+ and HPV- disease



Mandal et al. 2016; Partlova et al. 2015; Ward et al. 2014

Stage and HPV status are major determinants of HNSCC prognosis

Classification of disease within each anatomical subsite

Complete head and neck examination with direct inspection of the oral cavity and fibre-optic nasopharyngolaryngoscopy, CT or MRI of the head and neck, CT chest or PET/CT

Panendoscopy (unknown primary site, second tobacco-related primary tumor)

Table 4
American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative (p16-) cancers of the oropharynx)

Primary Tumor (T)
T0 No primary identified
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*
Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)
Clinical N (cN)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6 cm
N2 Contralateral or bilateral lymph nodes, none larger than 6 cm
N3 Lymph node(s) larger than 6 cm

Pathological N (pN)
NX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 4 or fewer lymph nodes
pN2 Metastasis in more than 4 lymph nodes

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

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups

Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

Continued

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. (For complete information and data supporting the staging tables, visit www.springer.com.)

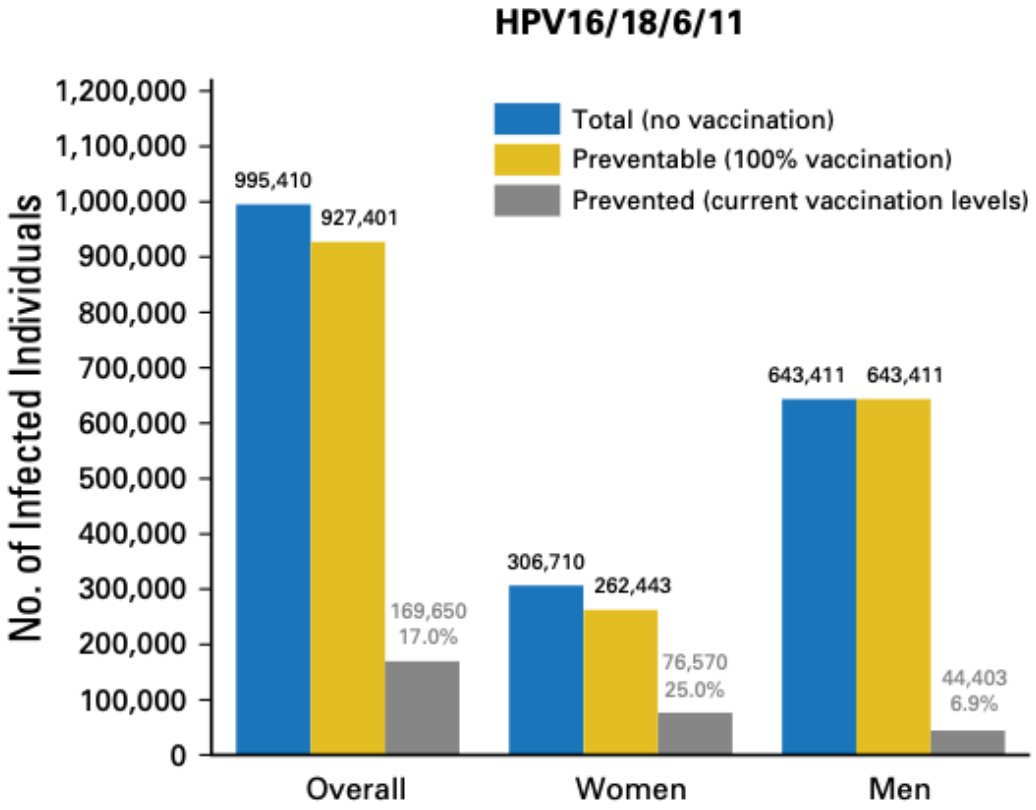
Primary prevention

Involves interventions to reduce the incidence of disease in the first place, by decreasing exposures, altering modifiable behaviours or increasing resistance in healthy people who are at risk

❖ **Tobacco cessation**

❖ **Vaccination against HPV**

- The US CDC recommends HPV vaccination for all children and adults aged 9–26 years
- The FDA approved HPV vaccination for adults aged 27–45 years who had not been adequately vaccinated earlier



Johnson et al. 2020; Chatuverdi et al. 2018

Secondary prevention

Refers to the early detection of latent, asymptomatic disease and subsequent interventions to halt disease progression to a harmful state; typically involves screening, such as mammography or Papanicolaou smears

HPV- HNSCC: chronic exposure to carcinogens > “field cancerization”: high risk of a second primary tumor of the upper aerodigestive tract, including in the head and neck, esophagus or lung; chemoprevention?

OPLs (leukoplakia, erythroplakia and dysplastic leukoplakia) are associated with an increased risk of HPV- HNSCC – most do not transform into invasive cancer

No validated tool exists for screening for HPV+ HNSCC

Johnson et al. 2020; Chan et al. 2017

Management

All patients with HNSCC should be treated in *high-volume* centers and by experienced *multidisciplinary* teams

The treatment approach to every individual patient is guided by anatomical subsite, stage, disease characteristics, local expertise, functional considerations and patient wishes

Locally/locoregionally advanced HNSCC: multimodality treatment (surgery, radiation and systemic therapy) with curative intent

Pathological features indicative of increased risk of recurrence include extra-nodal extension and positive (or close) surgical margins > concurrent chemoradiotherapy with cisplatin

In the event of treatment failure after single modality radiation or surgery, salvage with the alternative modality offers a high chance of cure

Johnson et al. 2020

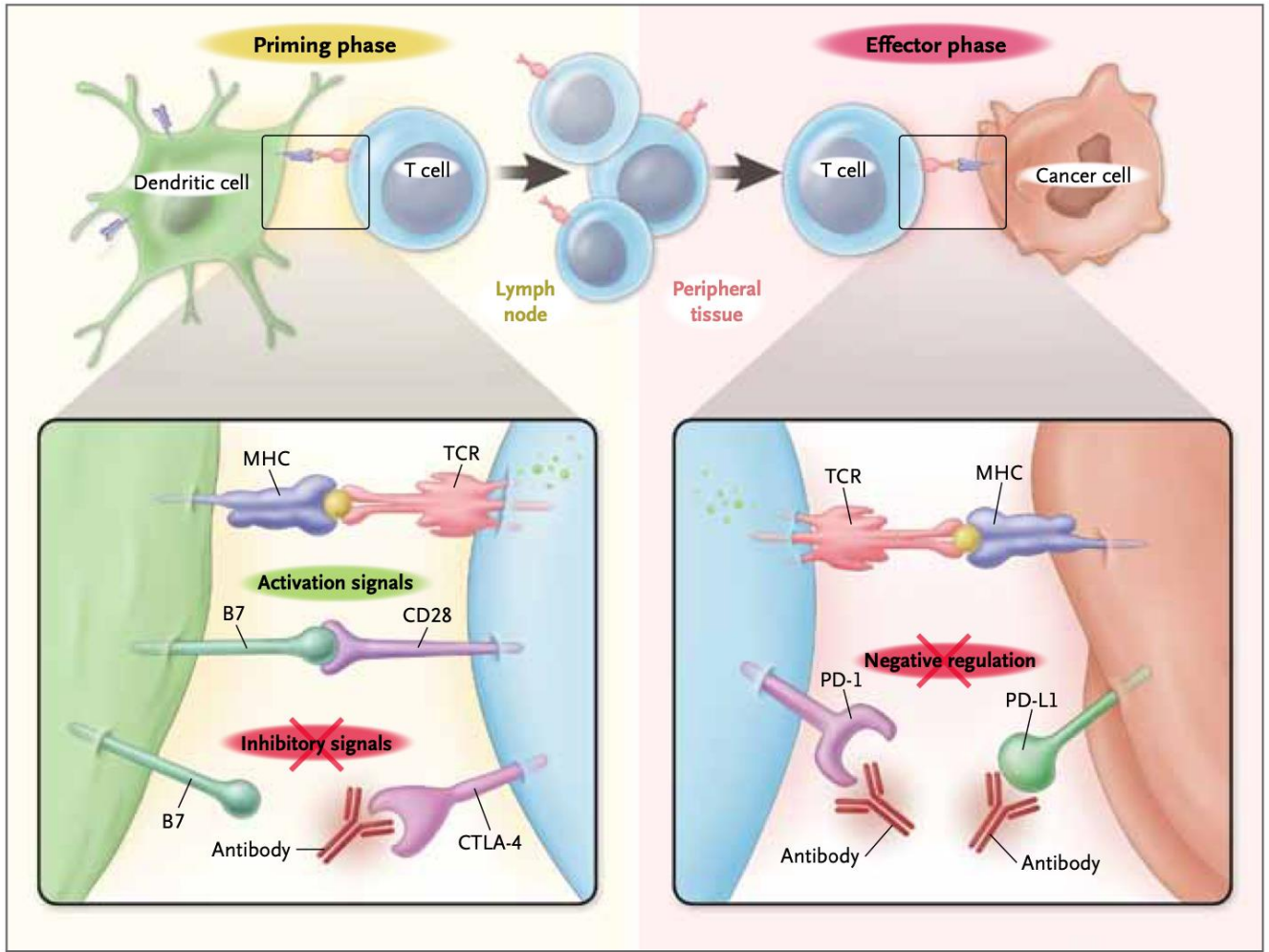
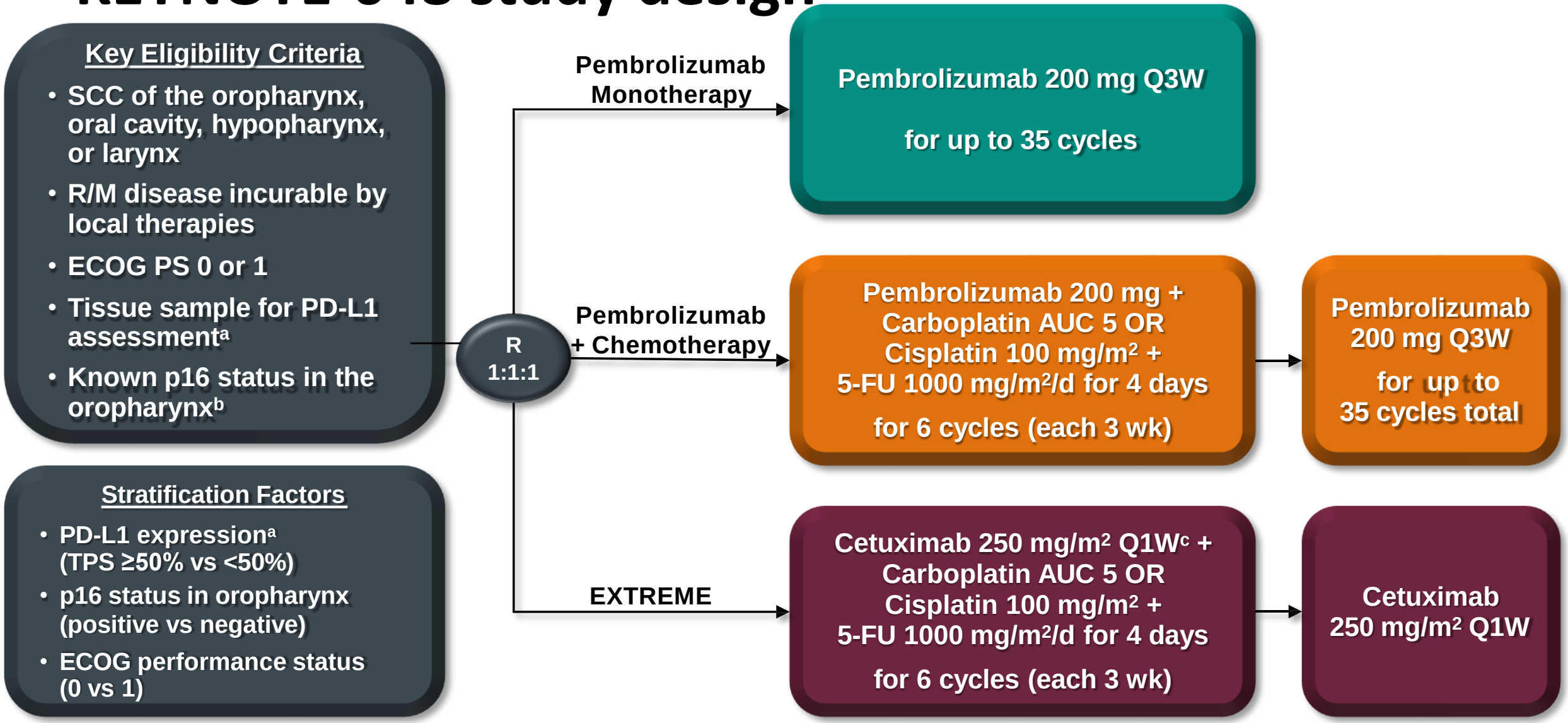


Figure 1. Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.

T cells recognize antigens presented by the major histocompatibility complex (MHC) on the surface of cancer cells through their T-cell receptor (TCR). This first signal is not enough to turn on a T-cell response, and a second signal delivered by the B7 costimulatory molecules B7-1 (or CD80) and B7-2 (or CD86) is required. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is up-regulated shortly after T-cell activation and initiates negative regulation signaling on T cells during ligation with the B7 costimulatory molecules expressed by antigen-presenting cells. When these molecules bind to CD28, they provide activation signals; when they bind to CTLA-4, they provide inhibitory signals. The interaction between CTLA-4 and the costimulatory molecules happens primarily in the priming phase of a T-cell response within lymph nodes. Programmed death 1 (PD-1) inhibitory receptor is expressed by T cells during long-term antigen exposure and results in negative regulation on T cells during ligation with PD-L1 and PD-L2, which are primarily expressed within inflamed tissues and the tumor microenvironment. The PD-1 interaction happens in the effector phase of a T-cell response in peripheral tissues. Its blockade with antibodies to PD-1 or PD-L1 results in the preferential activation of T cells with specificity for the cancer.

Ribas et al. 2012

KEYNOTE-048 study design



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Burtness et al. 2019

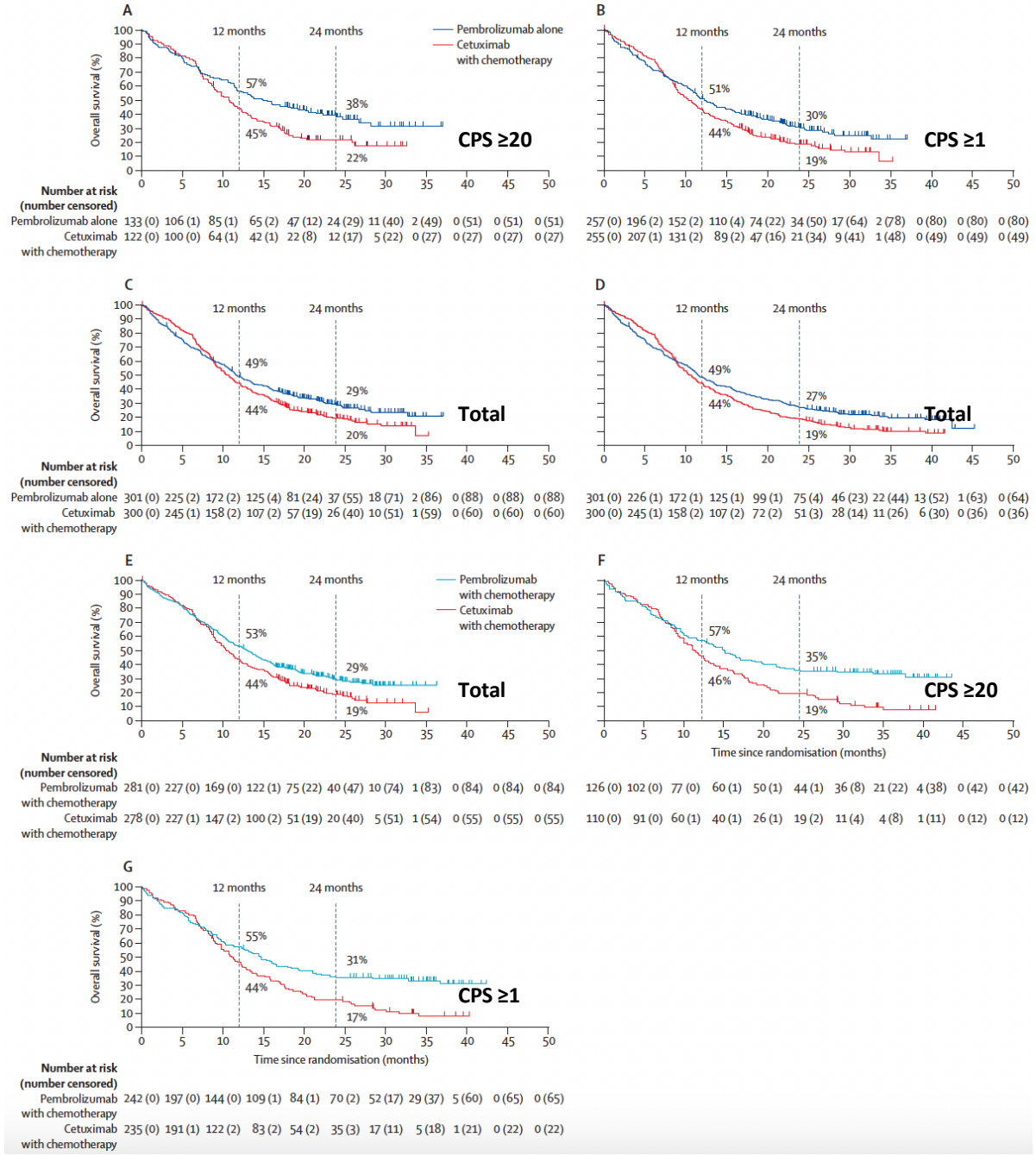
Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study

*Barbara Burtness, Kevin J Harrington, Richard Greil, Denis Soulières, Makoto Tahara, Gilberto de Castro Jr, Amanda Psyrri, Neus Basté, Prakash Neupane, Åse Bratland, Thorsten Fuereder, Brett G M Hughes, Ricard Mesía, Nuttapong Ngamphaiboon, Tamara Rordorf, Wan Zamaniah Wan Ishak, Ruey-Long Hong, René González Mendoza, Ananya Roy, Yayan Zhang, Burak Gumuscu, Jonathan D Cheng, Fan Jin, Danny Rischin, on behalf of the KEYNOTE-048 Investigators**

"Pembrolizumab combined with platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent or metastatic HNSCC and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1-positive recurrent or metastatic HNSCC".

Increased PD-L1 expression associated with benefit from pembrolizumab

Early exposure to pembrolizumab might induce durable alterations in the tumor microenvironment, altering the natural history of HNSCC and sensitizing it to subsequent therapy



Burtness et al. 2019

Survivorship: living with, through and beyond HNSCC

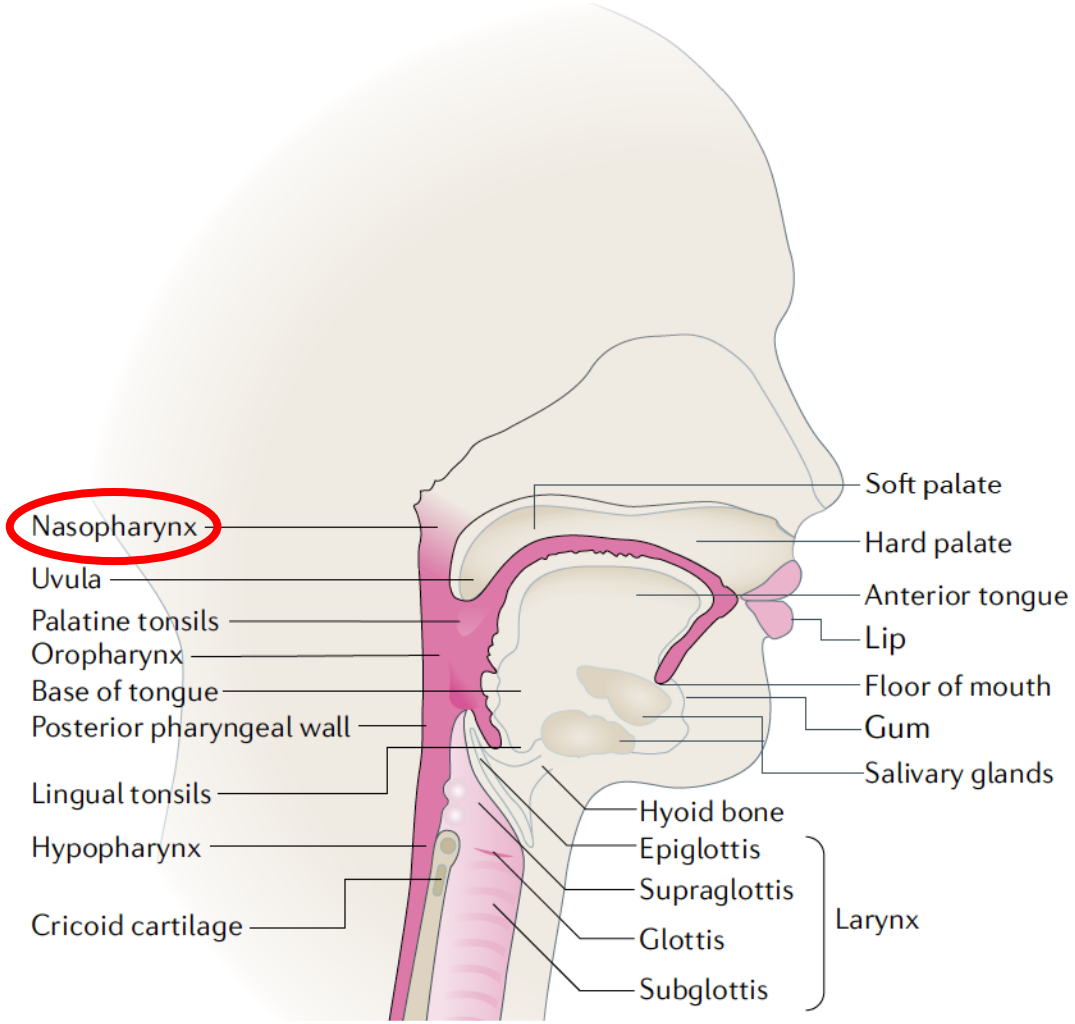
Different physical, emotional, functional and social sequelae, occupational dysfunction, as well as profound effect on the families

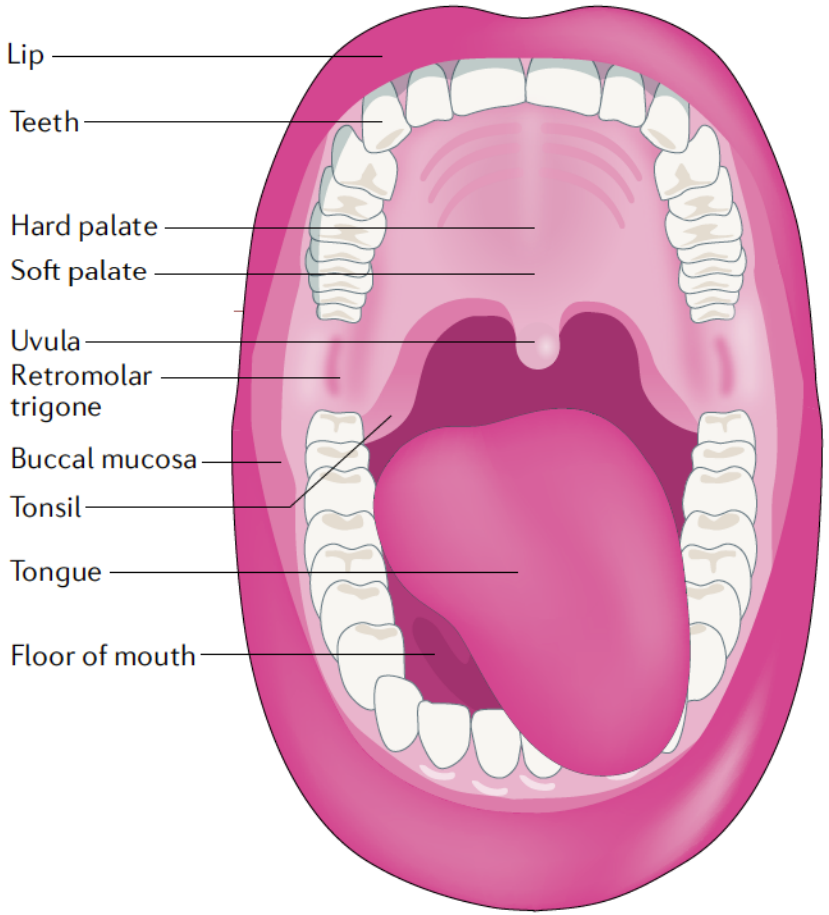
HRQOL is significantly associated with survival

Swallowing and speech impairments occur in most HNSCC survivors

Verdonck-de Leeuw et al. 2014; Quinten et al. 2009; Rettig et al. 2016

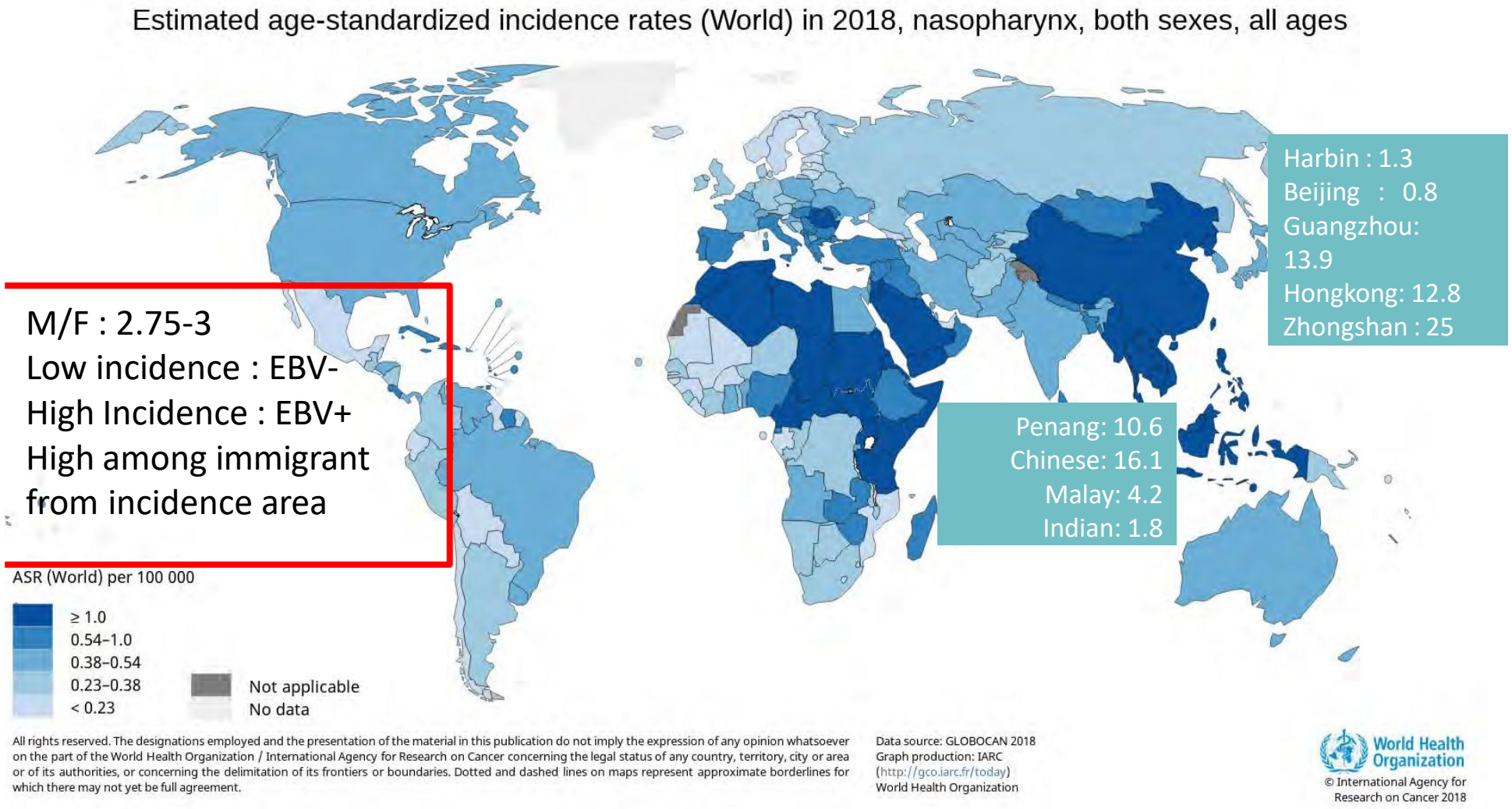
Anatomical sites





Johnson et al. 2020

Incidence


Estimated age-standardized incidence rates (World) in 2018, nasopharynx, both sexes, all ages
M/F : 2.75-3
Low incidence : EBV-
High Incidence : EBV+
High among immigrant from incidence area
Harbin : 1.3
Beijing : 0.8
Guangzhou: 13.9
Hongkong: 12.8
Zhongshan : 25
Penang: 10.6
Chinese: 16.1
Malay: 4.2
Indian: 1.8
ASR (World) per 100 000
≥ 1.0
0.54–1.0
0.38–0.54
0.23–0.38
< 0.23
Not applicable
No data
All rights reserved. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization / International Agency for Research on Cancer concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate borderlines for which there may not yet be full agreement.
Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization
World Health Organization
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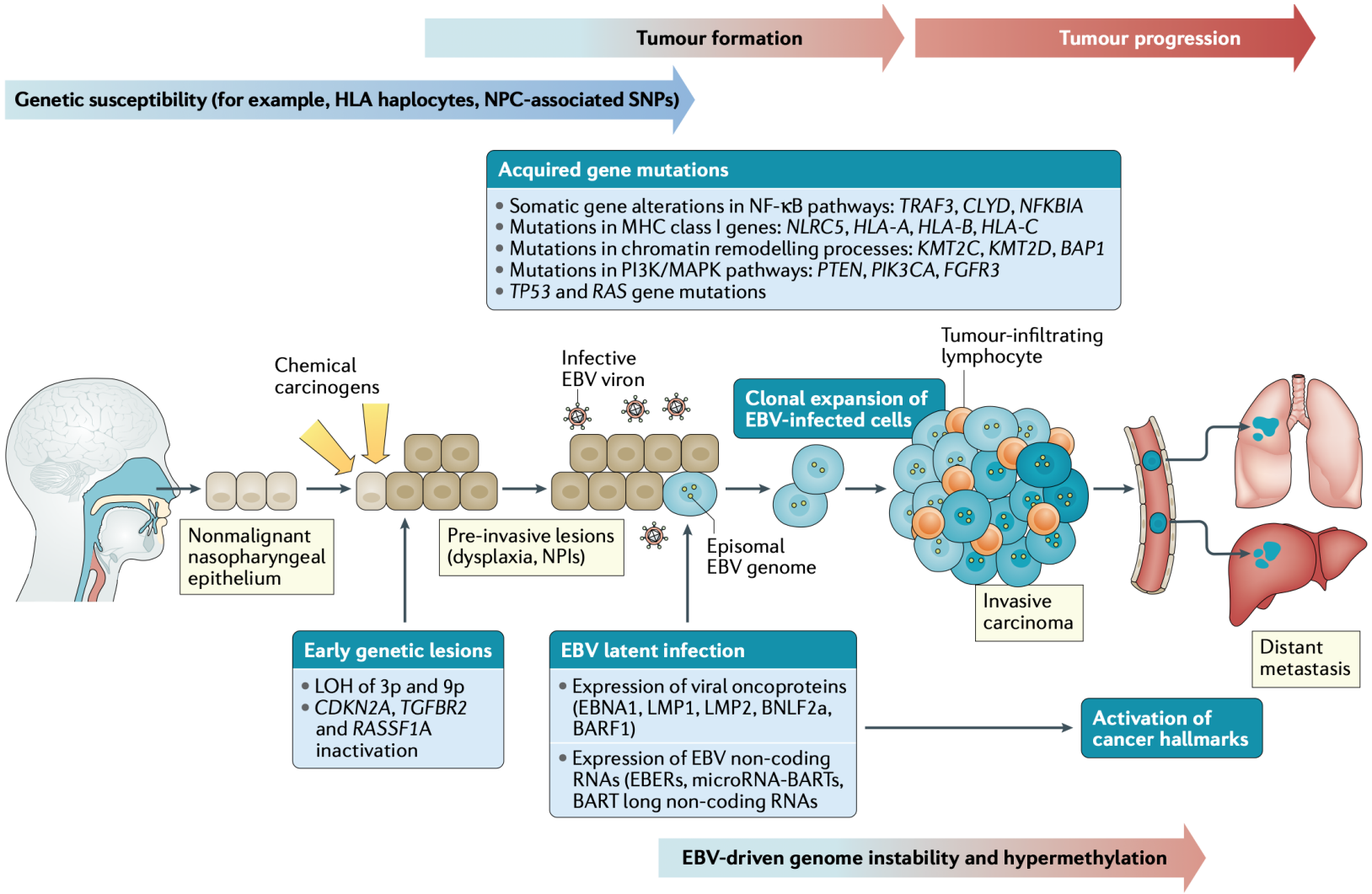
Hypothetical model of NPC carcinogenesis



Wong et al. 2021

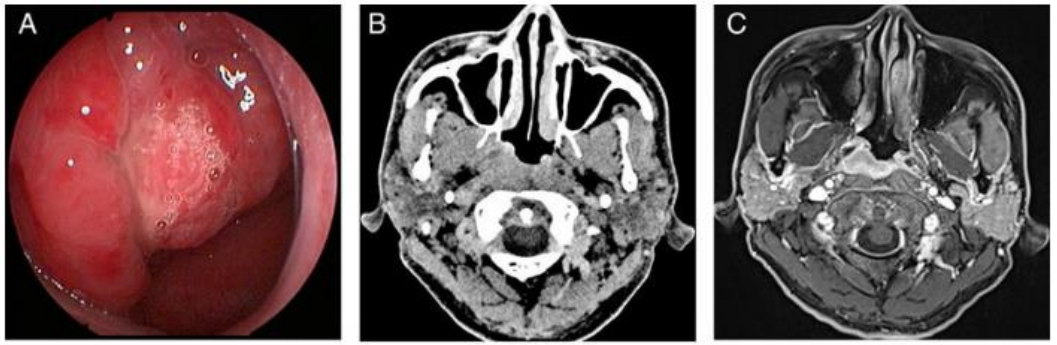
Nasopharyngeal cancer (NPC)

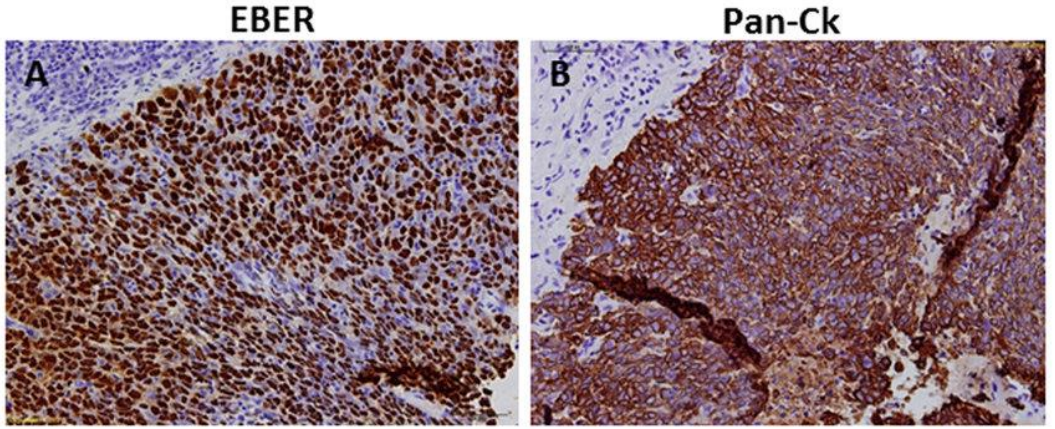
Diagnosis is standard H&E; EBER nearly confirmatory as > 95% are positive

Treatment is largely non-surgical based on staging

Surgical salvage is effective in locoregional recurrence

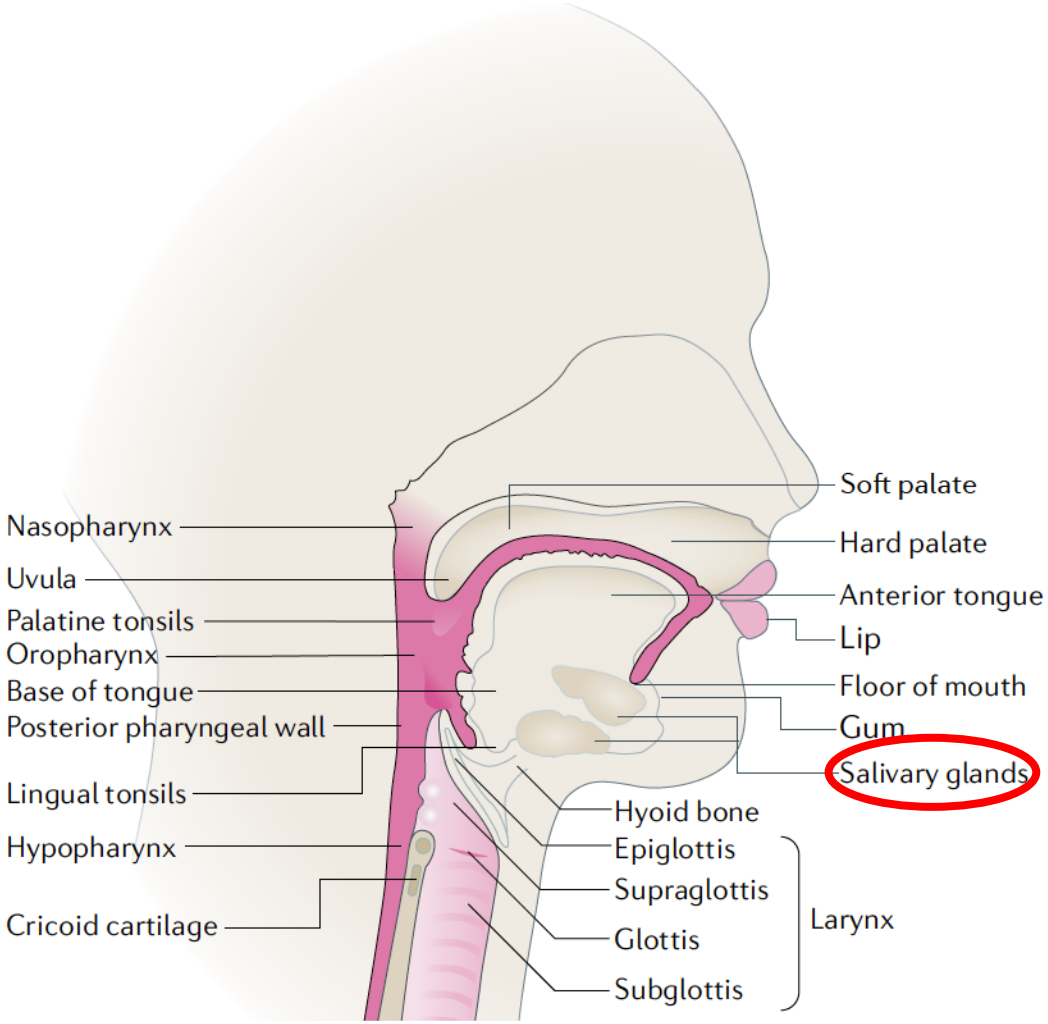
Plasma EBV DNA detection *may* be useful for prognostication and surveillance (97.1% sensitivity and 98.6% specificity)

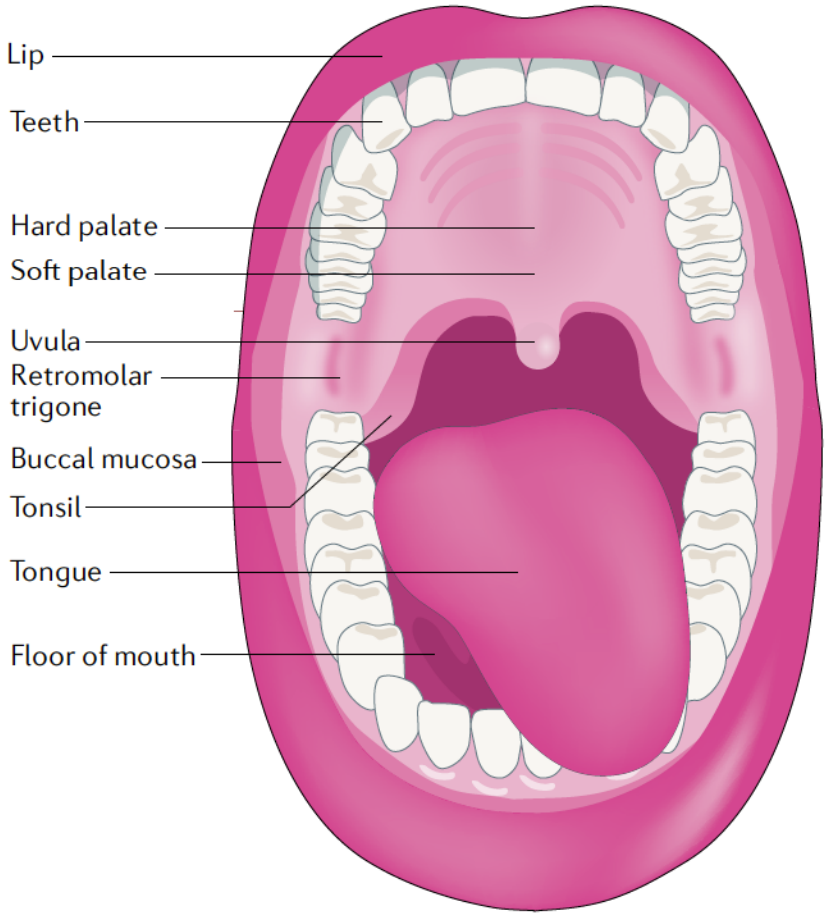




Chan et al. 2017

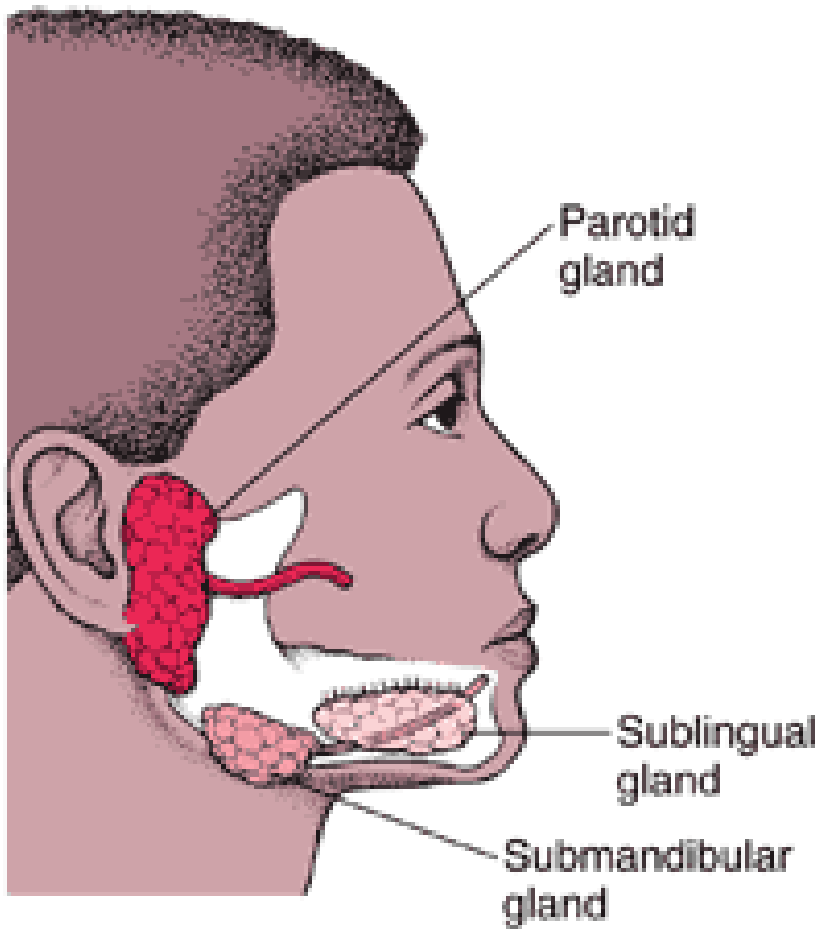
Anatomical sites





Johnson et al. 2020

Salivary gland cancer (SGC)



3 pairs of major salivary glands/minor salivary glands

Most common site – parotid

6-8% of head and neck cancers

Incidence: 1-3/100,000/year

WHO classification of head and neck tumors, 5th ed: **24 distinct histologic subtypes**

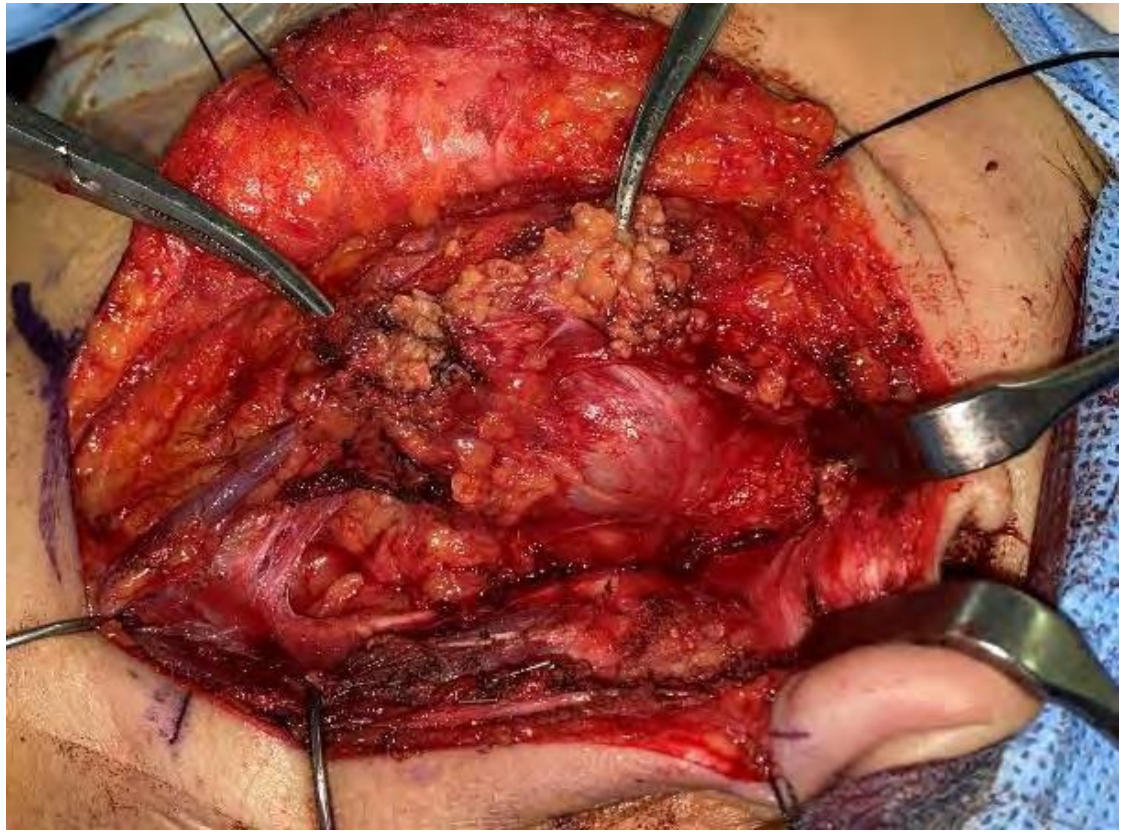
Management

Traditionally a surgical disease: surgery is both diagnostic and therapeutic

Adjuvant radiation therapy

Most subtypes not chemosensitive

Molecular characterization > histology-driven abnormalities: opportunities for targeted therapies



Thank you