Role of human papillomavirus infection in oropharyngeal cancer – update and clinical perspectives

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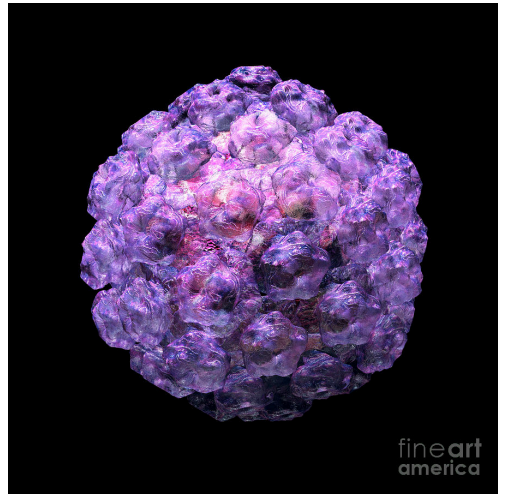
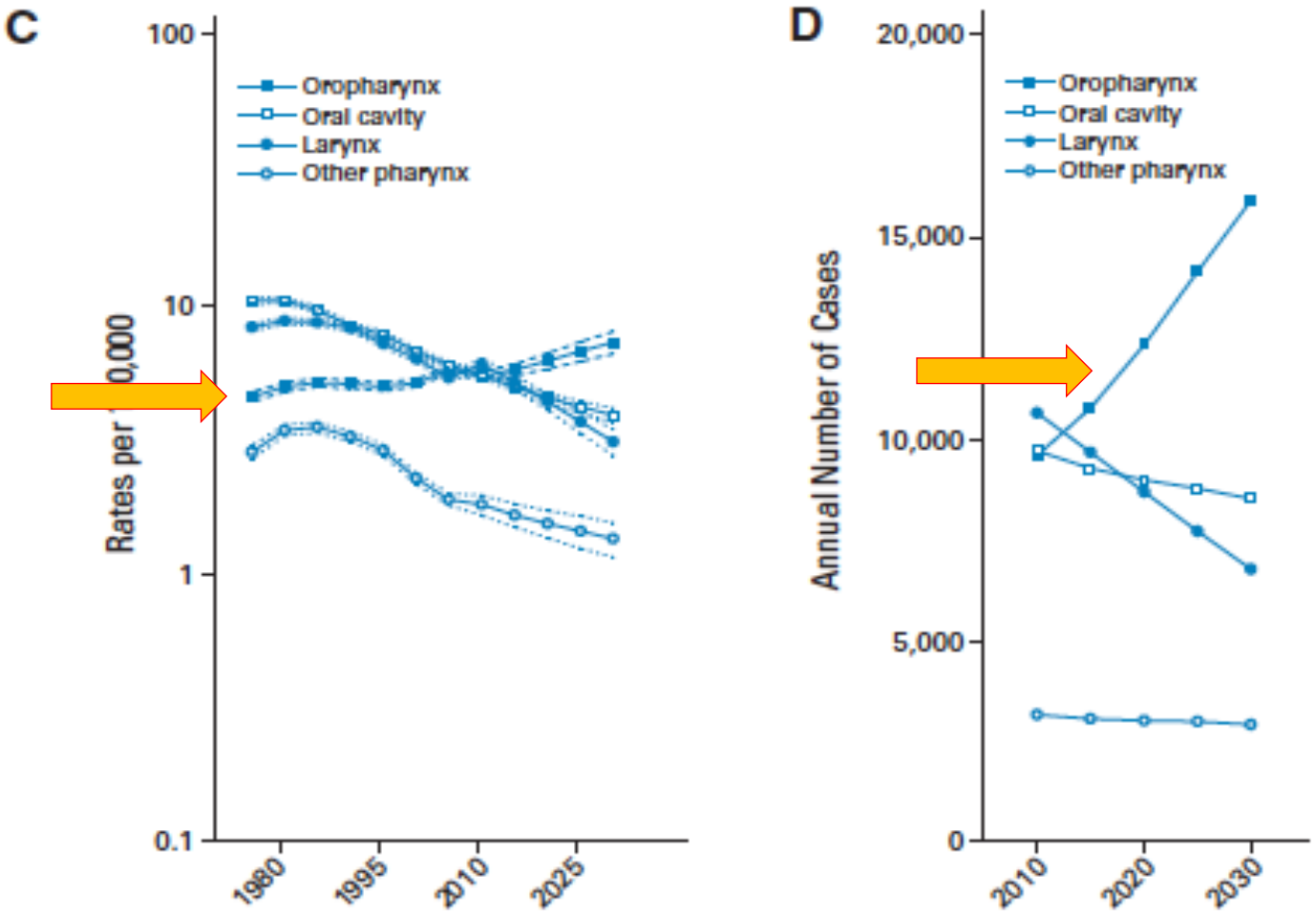
HUMAN PAPILLOMA VIRUS

- DNA virus
- Ca. 150-200 different types
- Human are the only host
- Transmission: skin and mucosal contact
- Mainly harmless: skin warts
- “Low-risk” & “high-risk”
- **The most frequent sexually transmitted virus**



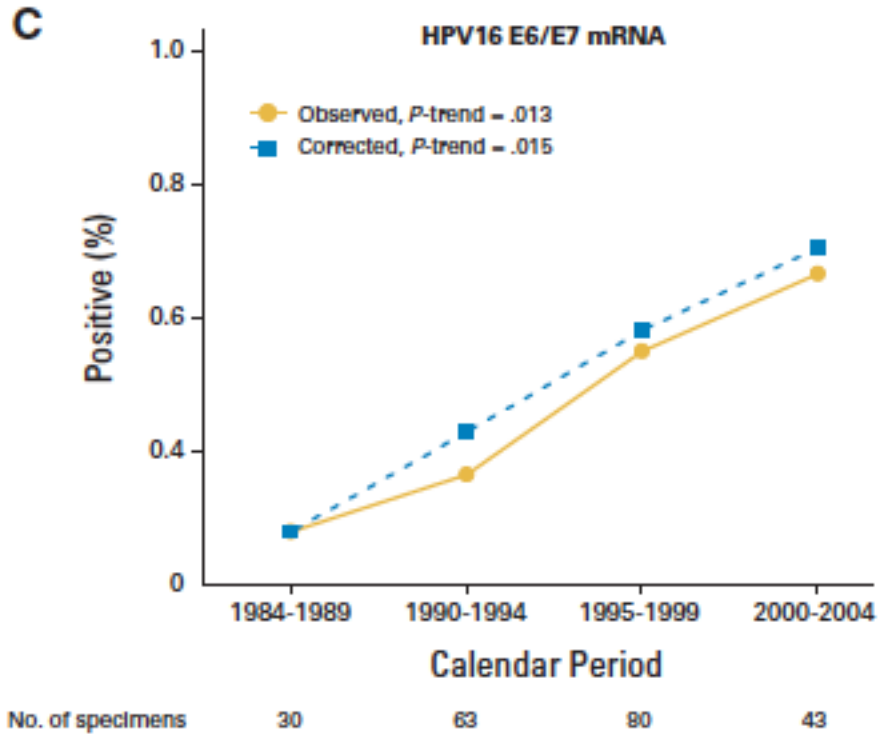
Incidence head and neck cancer 1980 - 2025



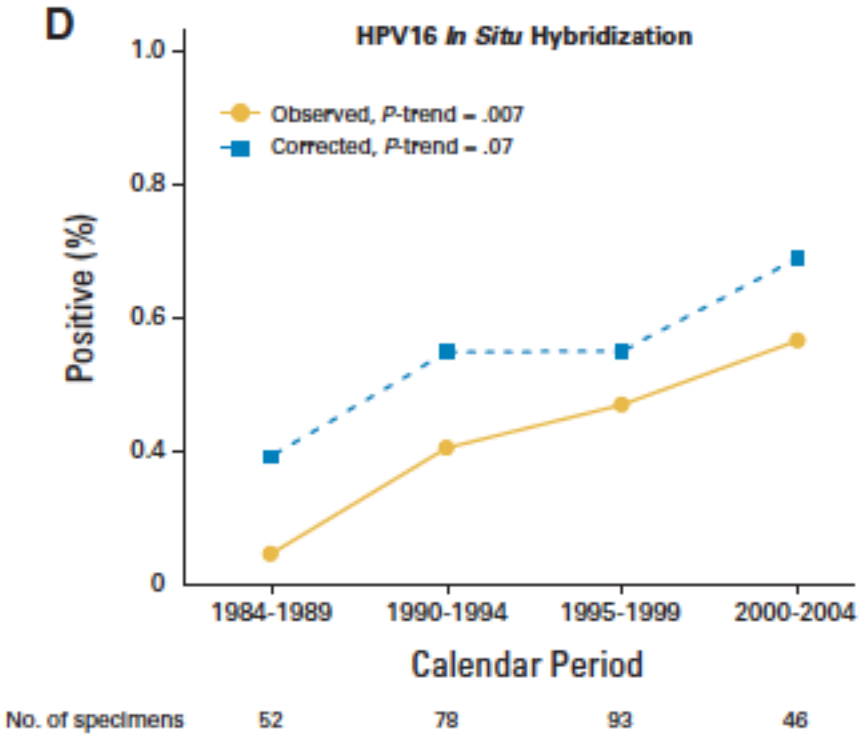
Chaturvedi et al JCO 2011

Increase of OPSCC is dependent on HPV

E6/E7



HPV 16 ISH



Chaturvedi et al JCO 2011

Oropharyngeal cancer (OPSCC) with 2 faces

Table 1. The two distinct subtypes of oropharyngeal squamous cell carcinoma

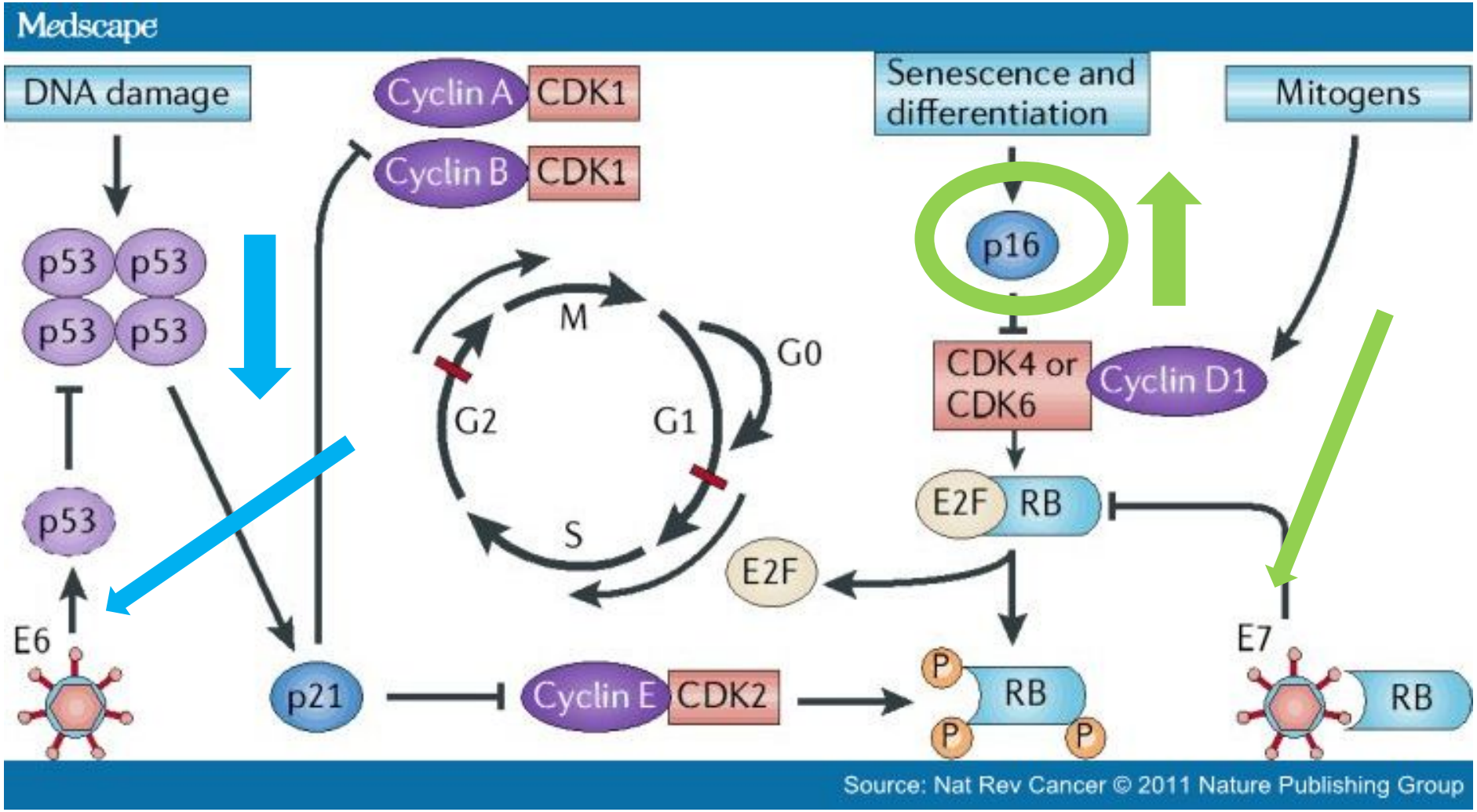
	HPV-associated OPSCC	HPV-negative OPSCC
Epidemiology/risk factors		
1. Race	White > Black	White > Black
2. Age	Between 4th and 6th decade	Usually 7th decade
3. Sex	M:F 8:1	M:F 3:1
4. Socioeconomic status	Middle to higher	Lower to middle
5. Smoking/alcohol history	Never or minimal exposure	Significant exposure
6. Marijuana use	Strong association	Not known
7. Early sexual debut	Strong association	Not known
8. Multiple lifetime sexual partners	Strong association	Not known
Clinical features		
9. Tumor (T) stage	Early tumor stage	More advanced tumor stage
10. Nodal (N) stage	More advanced nodal stage	Early nodal stage
Outcomes in stage III /IVa, b		
11. Distant metastasis risk	Distant control rate: 70–90%	Distant control rate: 70–90%
12. Second primary (SP) risk	Rate of SP: 11%	Rate of SP: 4.6%
13. Overall response to treatment	>80% respond	>50% respond
14. 2-year OS	95% (95% CI 87–100)	62% (95% CI 49–74)

Challenges with HPV+ OPSCC

- „white healthy young man with lump at neck“
- No suspicion as NON-SMOKERs
- Difficult pharyngeal examination
- Difficult detection: SMALL PRIMARY TUMOR, CYSTIC NECK MASS
  - **Often misdiagnosed as Cancer of unknown primary or lateral neck cyst**

Detection methods

- HPV DNA PCR
- HPV DNA ISH (in situ hybridization)
- P16 immunohistochemistry
- Combination of markers?



E6/E7: oncoprotein promote cell cycle progression by inactivation of

- tumorsuppressor gene p53 : low levels of wtp53
- Inhibition of pRb: induction of cyclin-dependent kinase inhibitor p16

HPV DNA

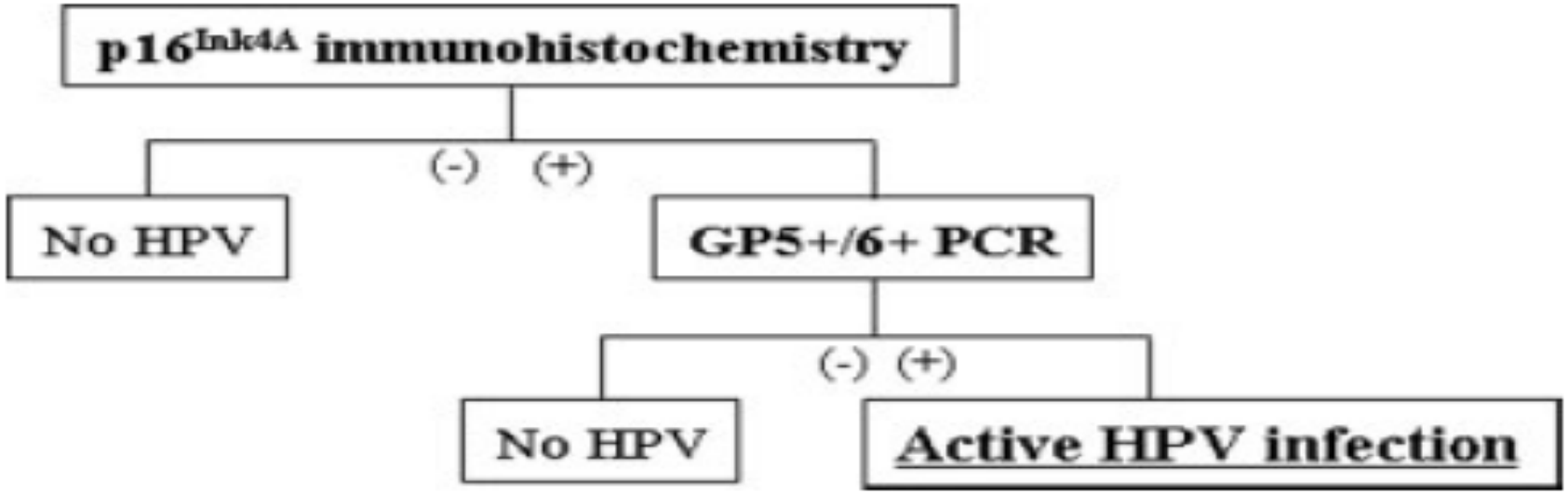
- PCR: easy to perform, type specific
  - High sensitivity
  - Low specificity due to high rates of false positive results
- ISH
  - standard in many US-insitutions
  - Lower sensitivity due to high rate of false negative results

P16 immunohistochemistry

- Surrogate marker for HPV-driven tumors
- Not specific
  - Detection of p16 positive cells also in healthy tonsils

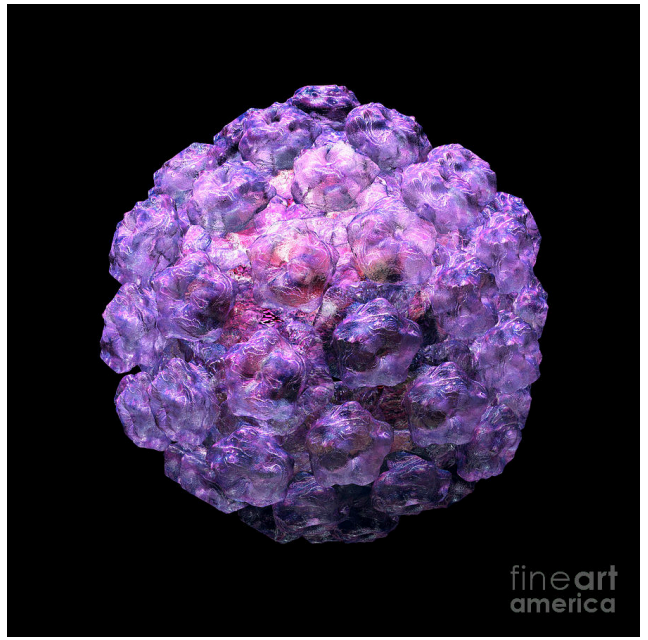
Combination of markers

- Enhances the reliability
- Accuracy 98% compared to RNA serving as the goldstandard



Therapeutic approach?

- Surgery?
- Salvage?
- Histopathological workup?



Clinical implications?

Staging?

Optimal therapeutic approach

- Dependent on HPV-status?

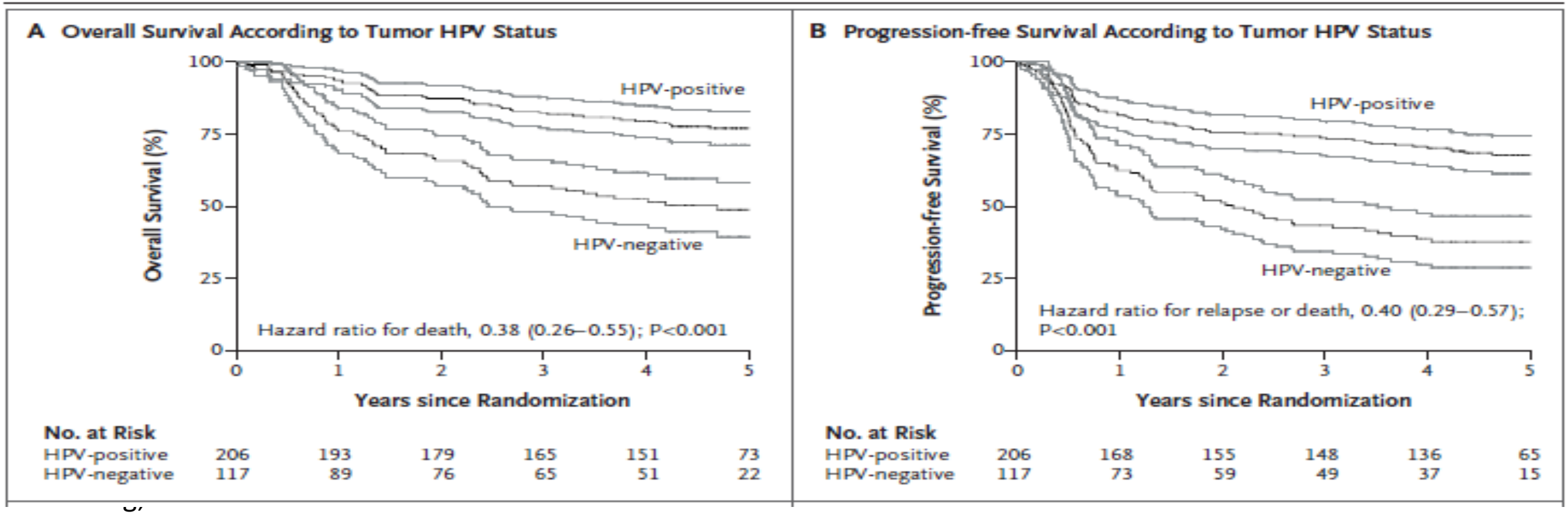
Possible therapeutic options

- Primary chemoradiation / primary radiotherapy
- Primary surgery
- Combined approach
  - Surgery
  - Adjuvant chemoradiation / radiotherapy

- **What is best in HPV-associated tumors?**

Primary Chemoradiation

- Clear survival benefit of HPV-associated tumors



Combined approach

- Clear survival benefit HPV-associated tumors

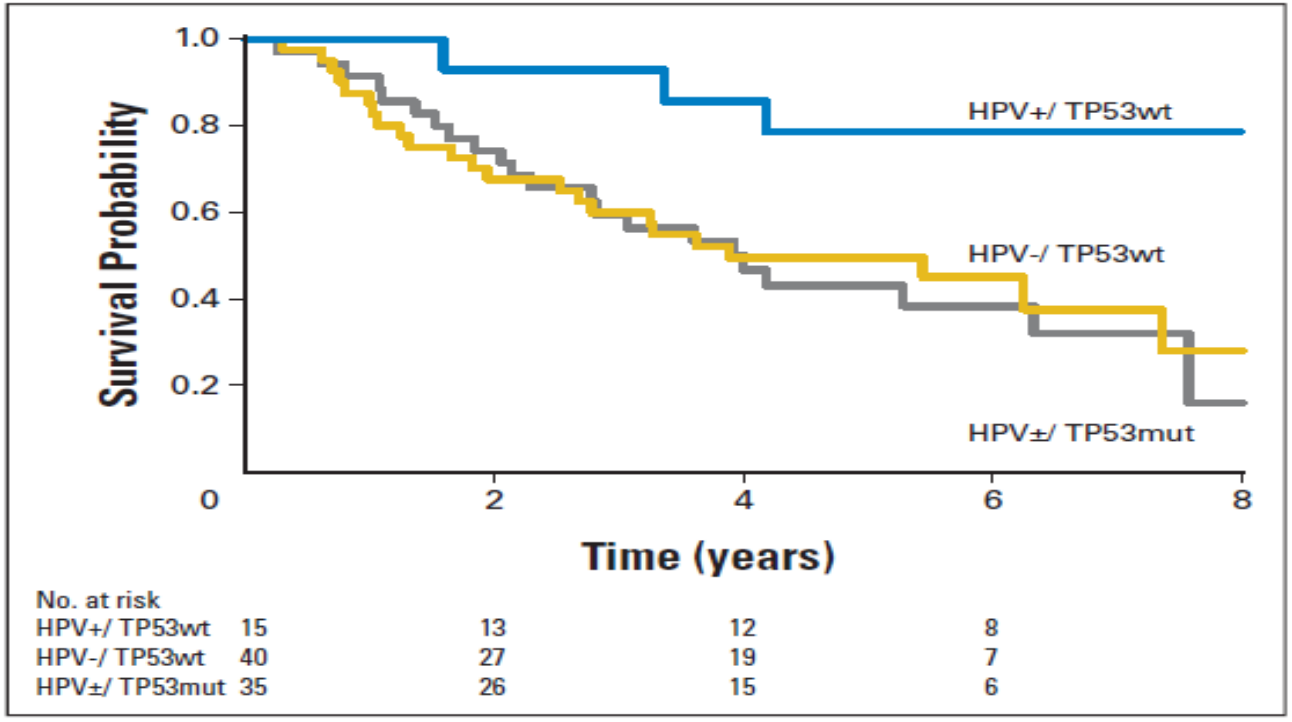
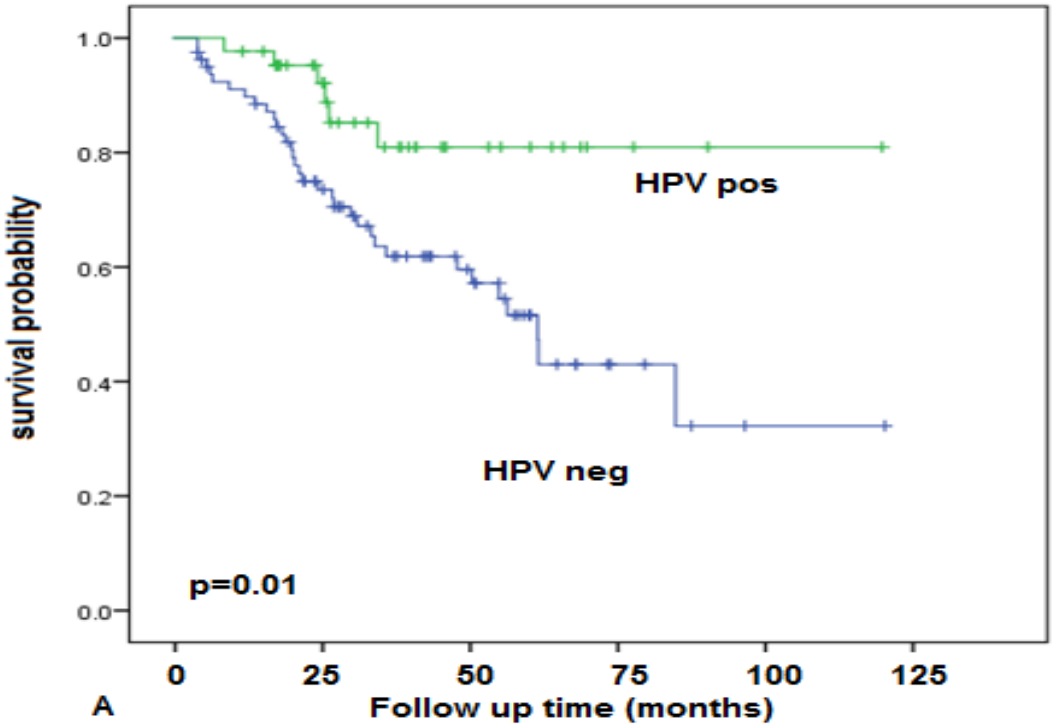
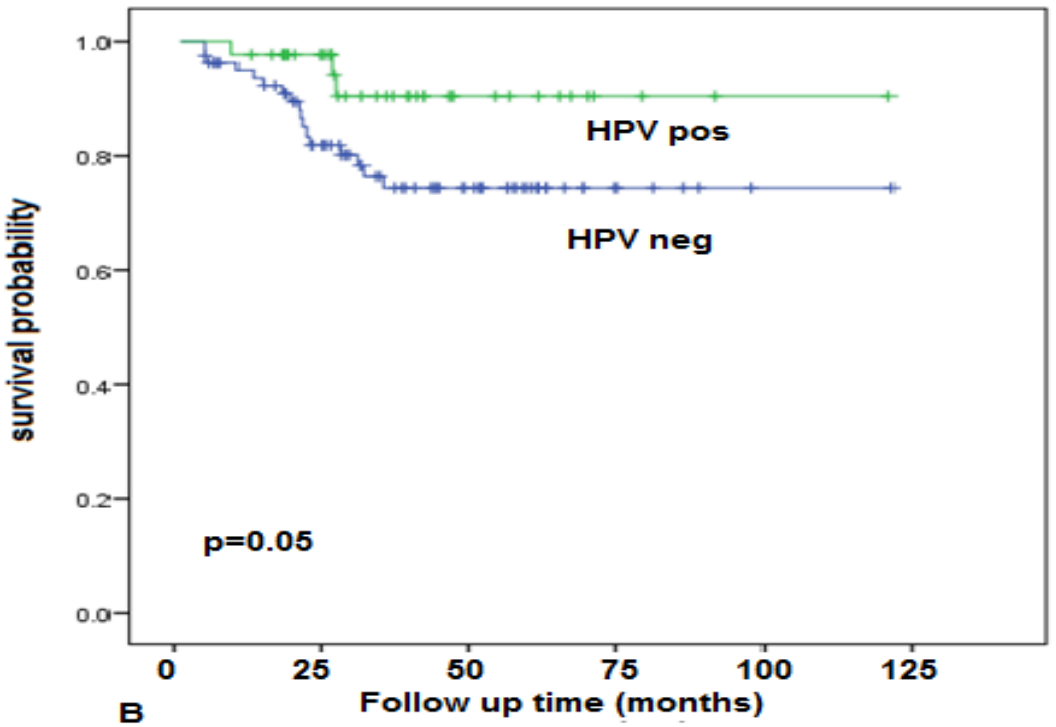


Fig 1. Overall survival according to human papillomavirus (HPV)/*TP53* status. mut, mutated; wt, wild type.

Licitra et al, JCO 2006

Surgery alone?





Broglie at al. Head and Neck 2017

Further risk factors?

- Smoking
  - HPV positive smokers do have a significant reduction in survival probability
- Performance status
- TNM
  - Nodal stage no longer a signficant prognosticator in HPV-driven cancer
- Extracaspular spread?
  - Some studies suggest an inferior prognostic role of ECS in HPV-driven cancer

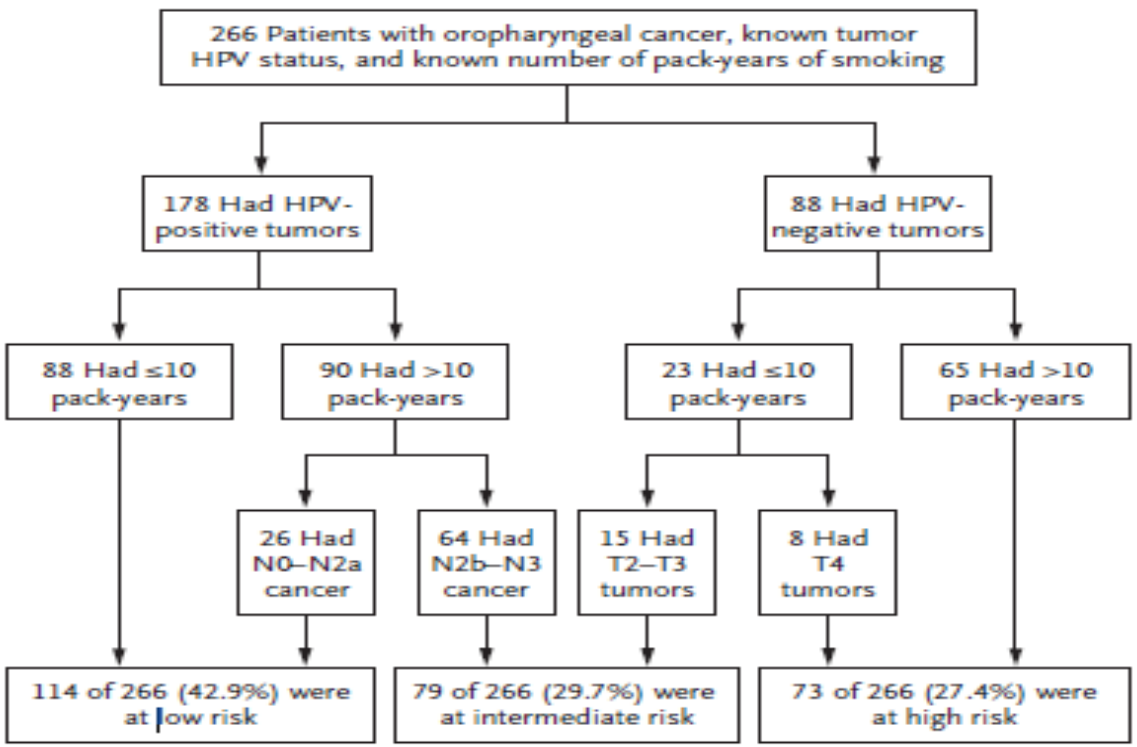
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

A



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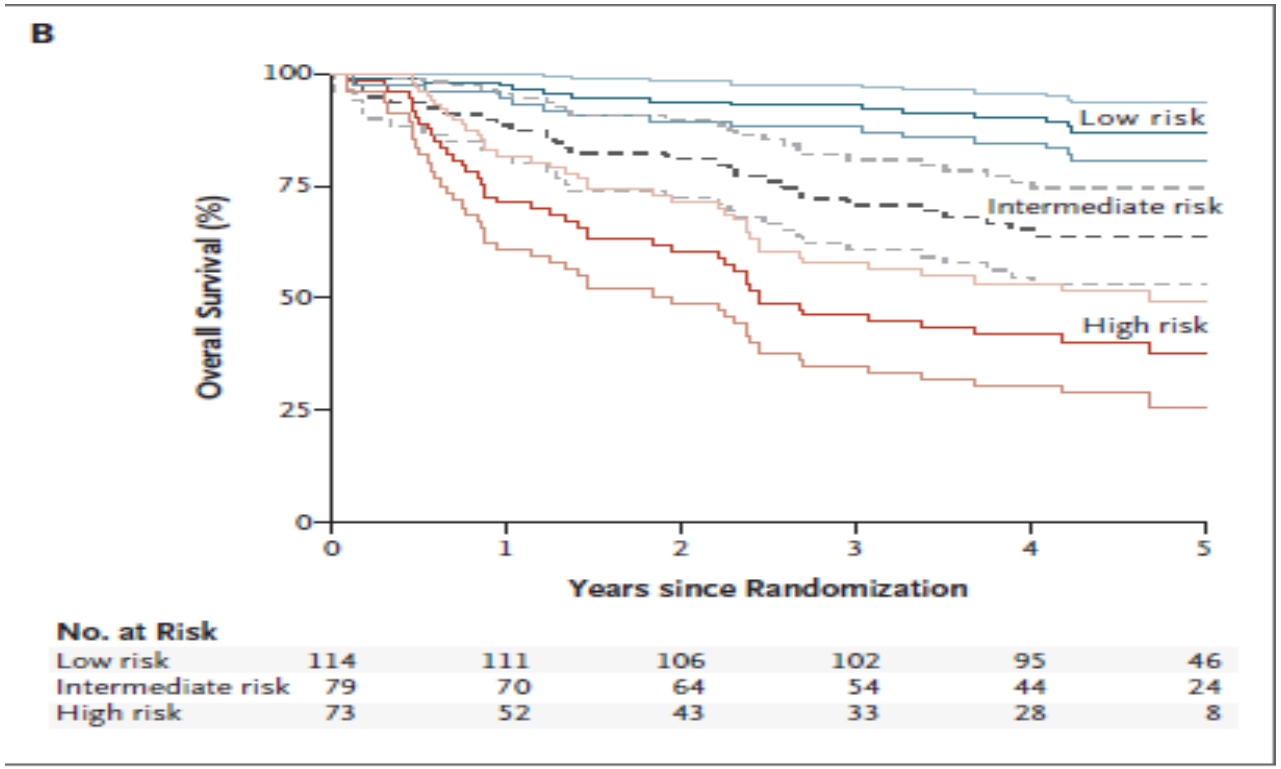


Combined approach

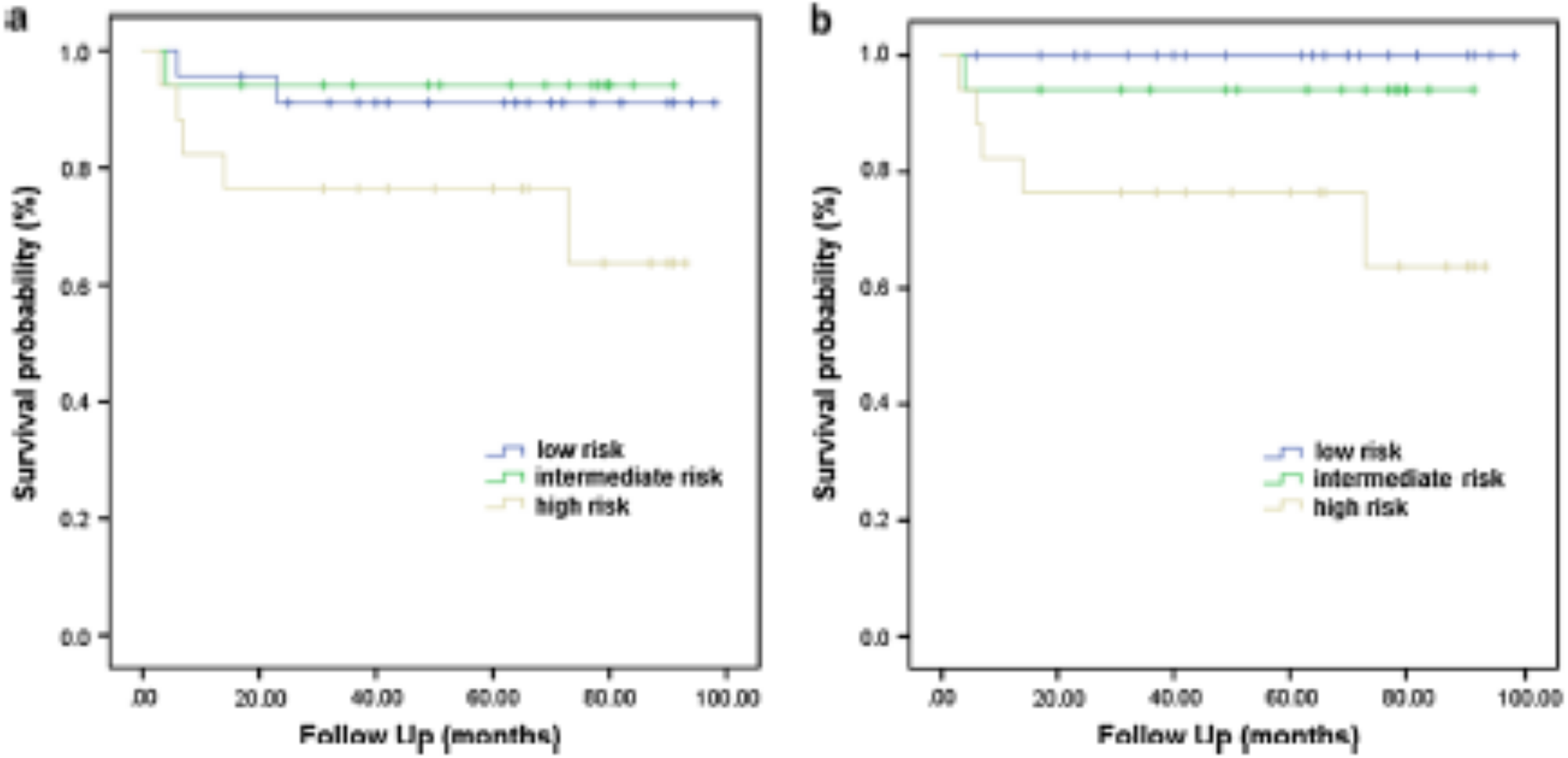
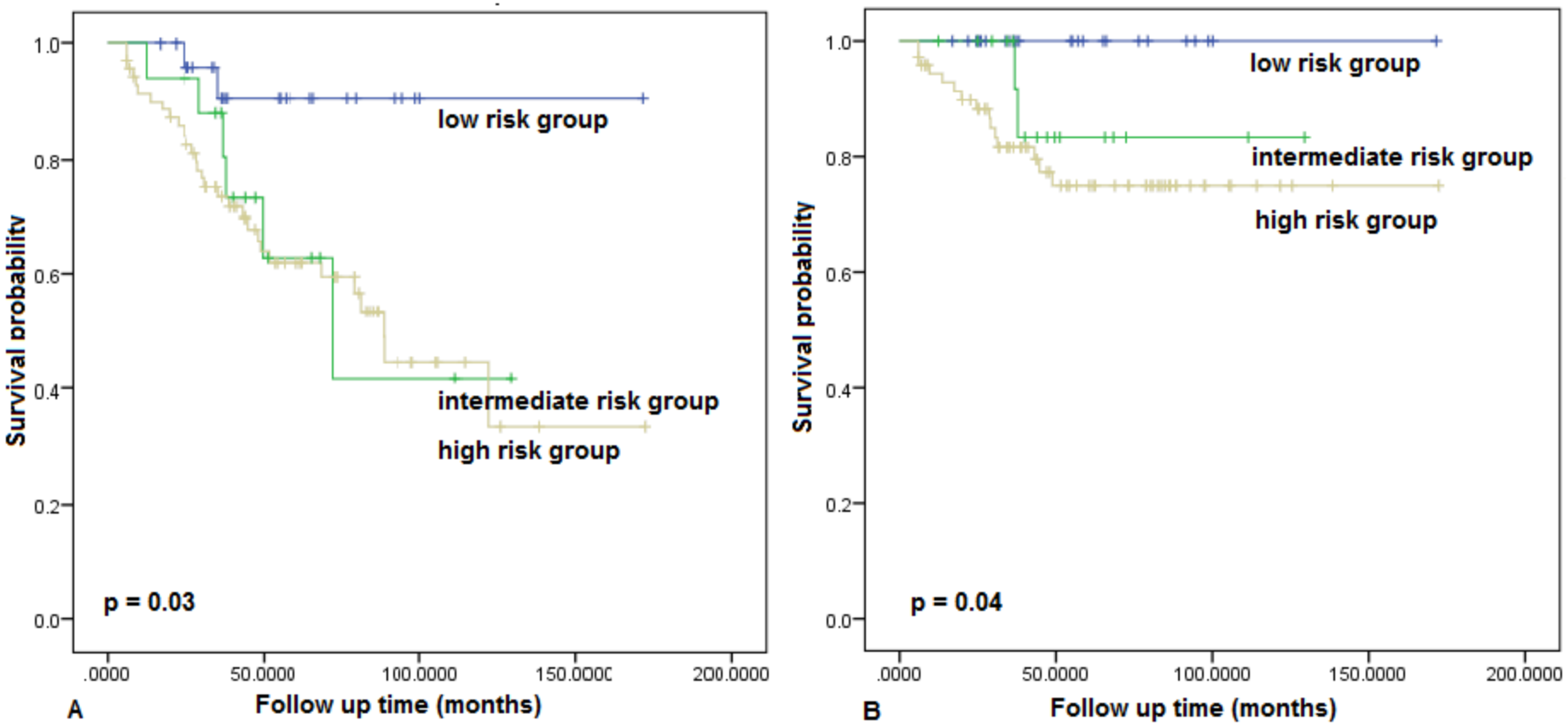


Fig. 3 a Overall survival according to Ang's [7] risk stratification. b Disease-specific survival according to Ang's [7] risk stratification

- Broglie et al, EAOR 2015

Surgery alone



- Broglie et al, Head and Neck 2017

ICON-S staging system

- The current TNM-staging system is no longer valid for HPV-driven OPSCC

TABLE 6. Anatomic Stage and Prognostic Groups for *Clinical* TNM Grouping of Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

	N CATEGORY			
T CATEGORY	N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

[a]Any M1 is stage IV.

BUT STILL

- Treatment of OPSCC is a challenge
- Still a considerable risk for disease associated death and long term mordity with influence on quality of life and difficult reintegration in working processes

- Therefore the aim should be
- PREVENTION AND SCREENING

Vaccination

- Since 2007 prophylactic HPV-avccination recommended for girls , since 2015 also for boys in Switzerland
- Since 1.7.2016 costs are covered by the health insurance
- Age 11-26 years
- Quadrivalent: Gardasil (HPV 16, 18, 6, 11), Bivalent: Cervarix (16, 18)
- Two doses age 11-14, later 3 doses

Screening

- HPV-driven precursor lesions have not been detected so far
- Evaluation of an oropharyngeal Pap-test equivalent for HPV-positive cancers not feasible (Fakhry et al. 2011)
- Limitations in sampling the relevant tonsillar crypt epithelium
- Other possible marker for cancer screening?

Role of Antibodies?

Table 2: Sensitivity and specificity of serum antibodies to HPV proteins to diagnose a HPV-attributable tumor

HPV protein		Molecular HPV status of the tumor		Sensitivity % (CI)	Specificity % (CI)
		Positive	Negative		
E6	Seropositive	26	1	100 (85-100)	96 (80-99)
	Seronegative	0	23		
E7	Seropositive	18	3	70 (52-87)	88 (69-96)
	Seronegative	8	21		
E1*	Seropositive	17	1	77 (57-90)	96 (80-99)
	Seronegative	5	23		
E2*	Seropositive	18	0	82 (62-93)	100 (86-100)
	Seronegative	4	24		
E4*	Seropositive	16	5	73 (52-87)	79 (60-91)
	Seronegative	6	19		
L1	Seropositive	13	1	50 (31-69)	96 (80-99)
	Seronegative	13	23		

*only available for HPV16 attributable tumors

Broglie et al, 2017

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

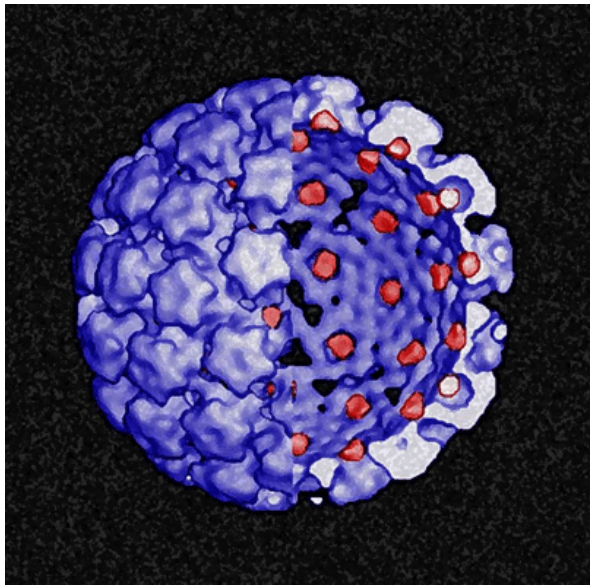
Evaluation of Human Papillomavirus Antibodies and Risk of Subsequent Head and Neck Cancer

Aimée R. Kreimer, Mattias Johansson, Tim Waterboer, Rudolf Kaaks, Jenny Chang-Claude, Dagmar Drogen, Anne Tjønneland, Kim Overvad, J. Ramón Quirós, Carlos A. González, Maria José Sánchez, Nerea Larrañaga, Carmen Navarro, Aurelio Barricarte, Ruth C. Travis, Kay-Tee Khaw, Nick Wareham, Antonia Trichopoulou, Pagona Lagiou, Dimitrios Trichopoulos, Petra H.M. Peeters, Salvatore Panico, Giovanna Masala, Sara Grioni, Rosario Tumino, Paolo Vineis, H. Bas Bueno-de-Mesquita, Göran Laurell, Göran Hallmans, Jonas Manjer, Johanna Ekström, Guri Skeie, Eiliv Lund, Elisabete Weiderpass, Pietro Ferrari, Graham Byrnes, Isabelle Romieu, Elio Riboli, Allan Hildesheim, Heiner Boeing, Michael Pawlita, and Paul Brennan

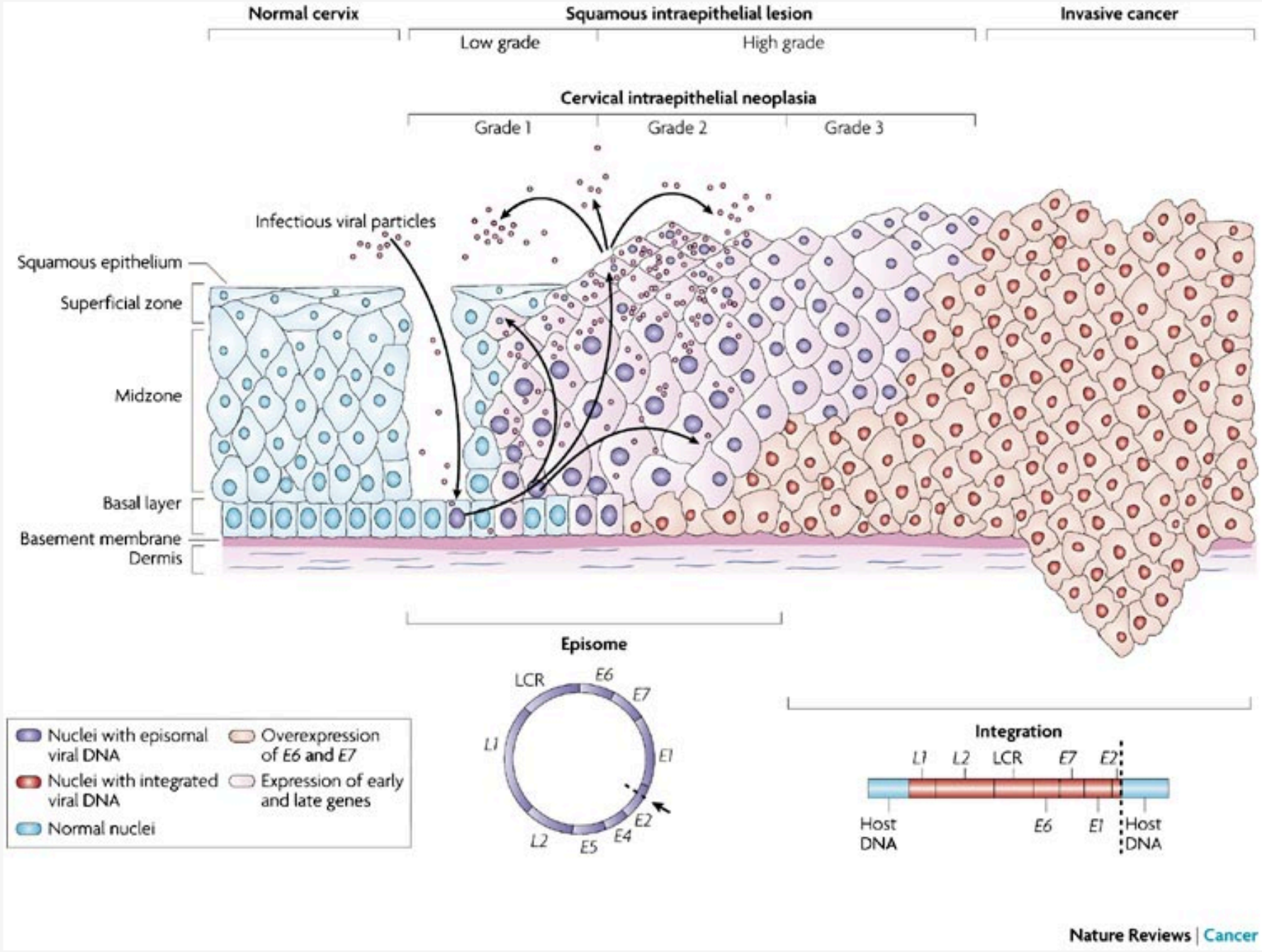
„The increased risk of OPSCC among seropositive participants was independent of time between blood collection and diagnosis and was observed more than 10 years before diagnosis“

…from infection to cancer…

- Infection:
  - Expression of the capsidproteins L1 & L2
  - Leads to proliferation of virus intracellularly



- Cancer:
  - Integration of viral DNA
  - Expression of E6 & E7
  - Induction of dedifferentiation of epithelial cells


Normal cervix
Squamous intraepithelial lesion
Low grade
High grade
Invasive cancer
Cervical intraepithelial neoplasia
Grade 1
Grade 2
Grade 3
Infectious viral particles
Squamous epithelium
Superficial zone
Midzone
Basal layer
Basement membrane
Dermis
Episome
LCR
E6
E7
L1
E1
E2
L2
E5
E4
Integration
L1
L2
LCR
E7
E2
Host DNA
E6
E1
Host DNA
Nuclei with episomal viral DNA
Nuclei with integrated viral DNA
Normal nuclei
Overexpression of E6 and E7
Expression of early and late genes

Take home messages

- Incidence and prevalence of HPV-associated tumors rising
- Affects younger patients with no other risk factors
- Difficult to detect (small primary tumor)
- Prognosis and optimal therapeutic approach
  - Irrespective of treatment outcome significantly improved
- Prevantion by vaccination / Screening difficult (no precurso r lesions)
  - Possible marker: HPV serum antibodies

TNM-Staging system

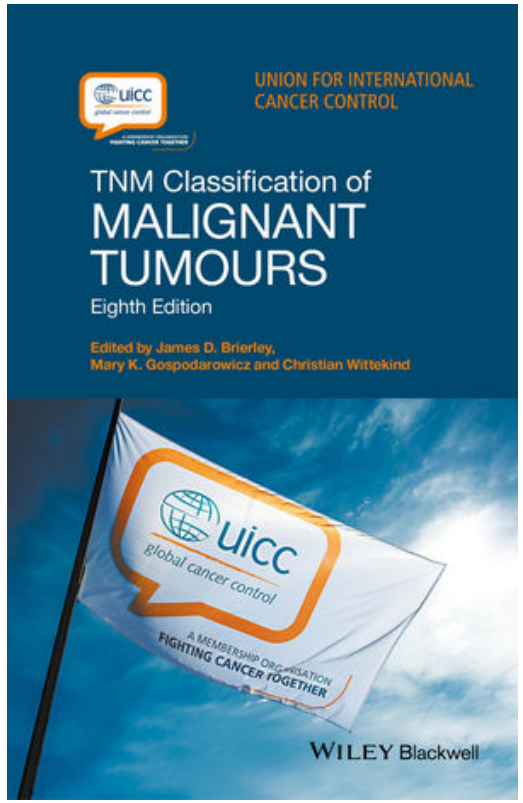
- The first TNM system was published 1946 (Denoix PF. Bull Inst Nat Hyg 1946)
- Refined by the Union for International Cancer Control (UICC) to achieve an internationally accepted standard for staging of solid cancer.
- In 1987, the UICC and American Joint Committee on Cancer (AJCC) staging systems have been combined
- Active participation of internationally renowned experts (TNM Core Committee)
- Supported by sub-committees, the evaluation Committee, the prognostic Factors Committee and 21 national or regional TNM Committees

Objectives

- Aid treatment planning
- Provide an indication of prognosis
- Assist in the evaluation of treatment results
- Facilitate the exchange of information between treatment centres and disciplines
- Standardized system for research
- Support cancer control activities, including cancer registries

2017: Significant Changes in Head and Neck Cancer

- New classification for p16 positive oropharyngeal cancers
- Modified classification for nasopharyngeal cancers, oral cancer and thyroid cancers
- New classification for cervical nodal involvement with unknown primary depending on p16 IHC and EBV
- Modified N-classification with separate classifications for clinical and pathological neck nodes for all sites



Cervical Nodes – 8th edition

Clinical

N1, N2a, N2b and N2c unchanged other than specify without extranodal extension

- N3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
- N3b Metastasis in a single or multiple lymph nodes with clinical extranodal extension*
- * The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extra nodal extension

Pathological

N1, N2a, N2b and N2c unchanged other than specify without extranodal extension

- pN3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
- pN3b Metastasis in a lymph node more than 3 cm in greatest dimension with extranodal extension or, multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension
- extra nodal extension (ENE)
  - ENE_{mi} → < 2mm
  - ENE_{ma} → > 2mm

Oropharynx-Carcinom T-Stadium

P16 pos

- **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

    - no Carcinoma in situ (Tis)
    - No differentiation between T4a und T4b

P16 neg

- **Tx** Primary tumor cannot be assessed
- **Tis** Carcinoma in situ
- **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
- **T4a** Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate,or mandible
- **T4b** Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates,

Oropharynx-Carcinom HPV+

Clinical N categories

N0	No regional lymph node metastasis
N1	Unilateral metastasis, in lymph node(s), all 6 cm or less
N2	Contralateral or bilateral metastasis in lymph node(s), all 6 cm or less in greatest dimension
N3	Metastasis in lymph node(s) greater than 6 cm in dimension

Pathological N categories

pN0	No regional lymph node metastasis
pN1	Metastasis in 1 to 4 lymph node(s)
pN2	Metastasis in 5 or more lymph node(s)

Cervical Node CUP

- If EBV positive stage as per nasopharyngeal carcinomas
- If p16 positive stage as per p16 positive oropharynx carcinomas

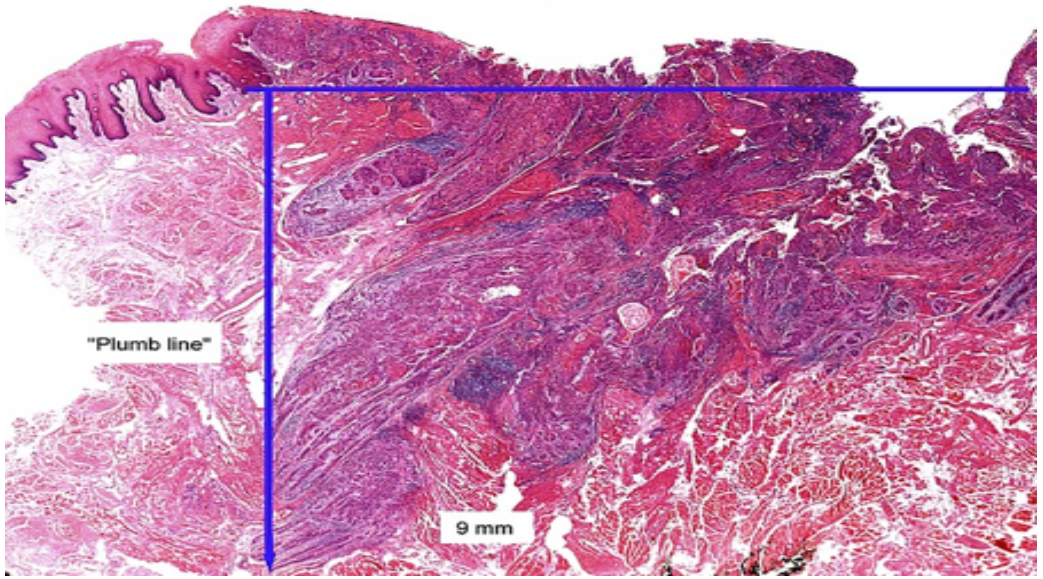
- If EBV and p16 negative clinical and pathological node definitions are as above

Stage III	T0	N1	M0
Stage IVA	T0	N2	M0
Stage IVB	T0	N3	M0
Stage IVC	T0	N1, N2, N3	M1

Oral cancer

TABLE 9. T Category for Oral Cavity Cancer, 8th Edition Staging Manual[a]

T CATEGORY	T CRITERIA
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm, ≤5 mm depth of invasion (DOI) (DOI is depth of invasion and not tumor thickness)
T2	Tumor ≤2 cm, DOI >5 mm and ≤10 mm *or* tumor >2 cm but ≤4 cm, and ≤10 mm DOI
T3	Tumor >4 cm *or* any tumor >10 mm DOI
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease: (lip) tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose); (oral cavity) tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery



Papillary and Follicular Thyroid Carcinoma

The definition of T3 has been revised

T3a Tumor more than 4 cm in greatest dimension, limited to the thyroid

T3b Tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, or omohyoid muscles)

The age for a poor prognosis has changed from 45 years to 55 years

Stage < 55 years old

Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1

Stage ≥55 years old

Stage I	T1a,T1b,T2	N0	M0
Stage II	T3	N0	M0
	T1, T2, T3	N1	M0
Stage III	T4a	Any N	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1