Současný pohled na problematiku HVP-asociovaných karcinomů hlavy a krku

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CZECH HEAD AND NECK CANCER COOPERATIVE GROUP

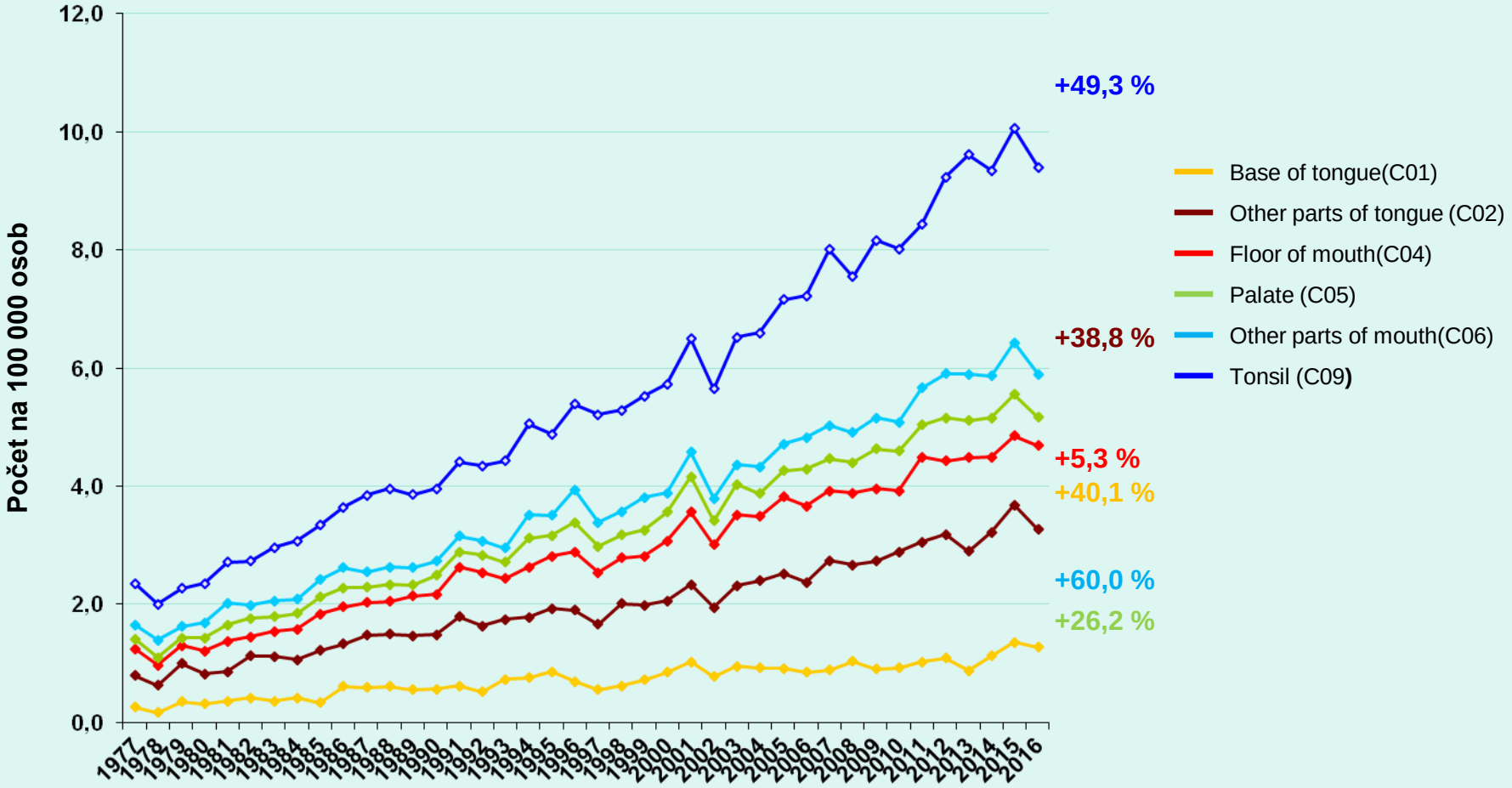
CLINICAL IMPLICATIONS OF HPV IN OROPHARYNGEAL CANCER

1. Epidemiology
2. New HNC patient
3. Prognosis, Classification
4. Markers of HPV infection
5. Deescalation of treatment
6. HPV outside of oropharynx

EPIDEMIOLOGY

- HR HPVs are responsible for the majority of oropharyneal (particularly tonsilar) cancers
- Spread of HPV changes the epidemiology of HNSCC
- Stagnation or decrease in the incidence of tobbacco related tumors
- Increase in the incidence of oropharyngeal cancer
- Rising proportion of HPV positive tumors within the group of oropharyngeal cancers

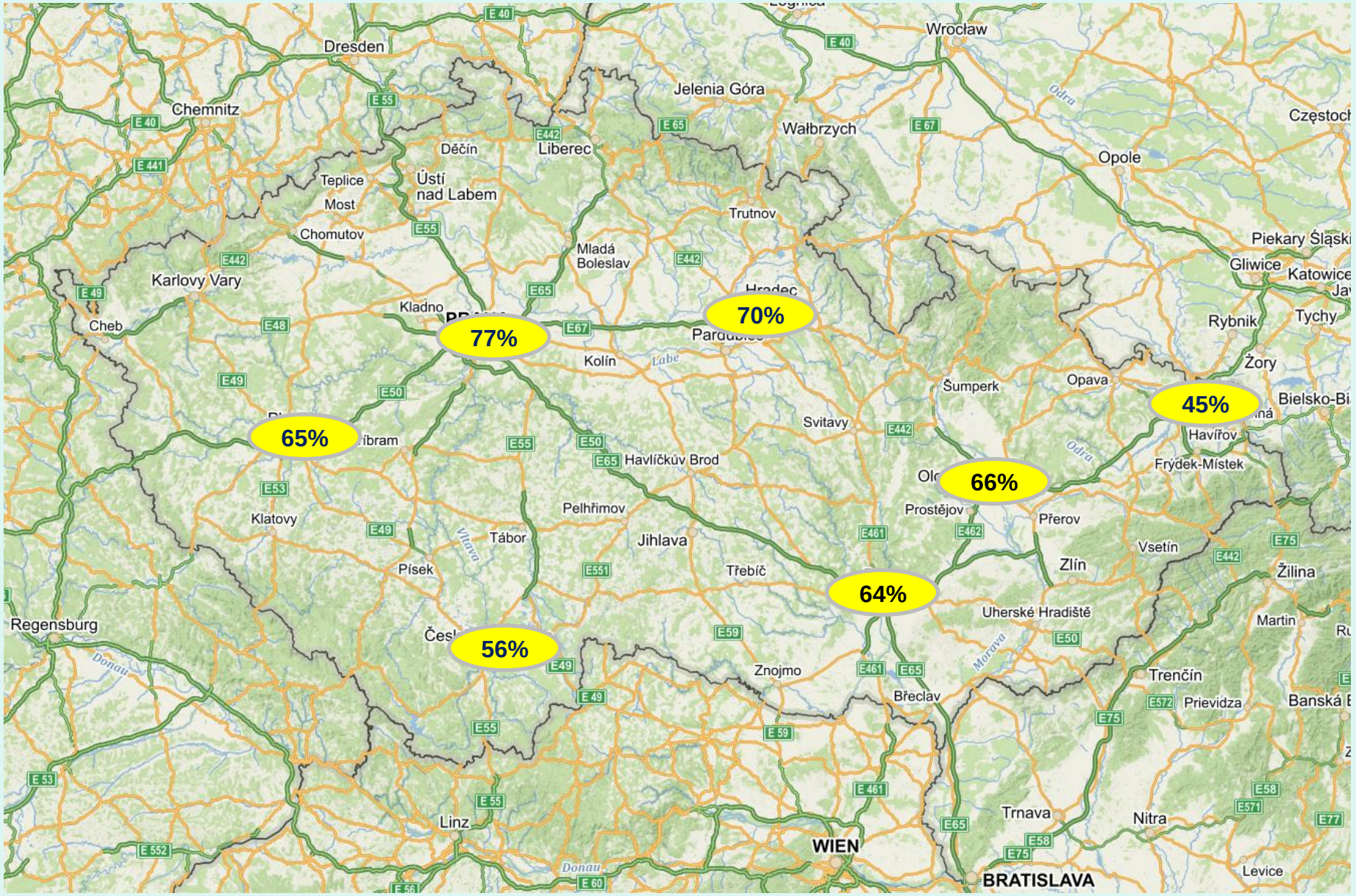
Trends of incidence of selected H+N cancers (C01, C02, C04–C06, C09) In the Czech Republic

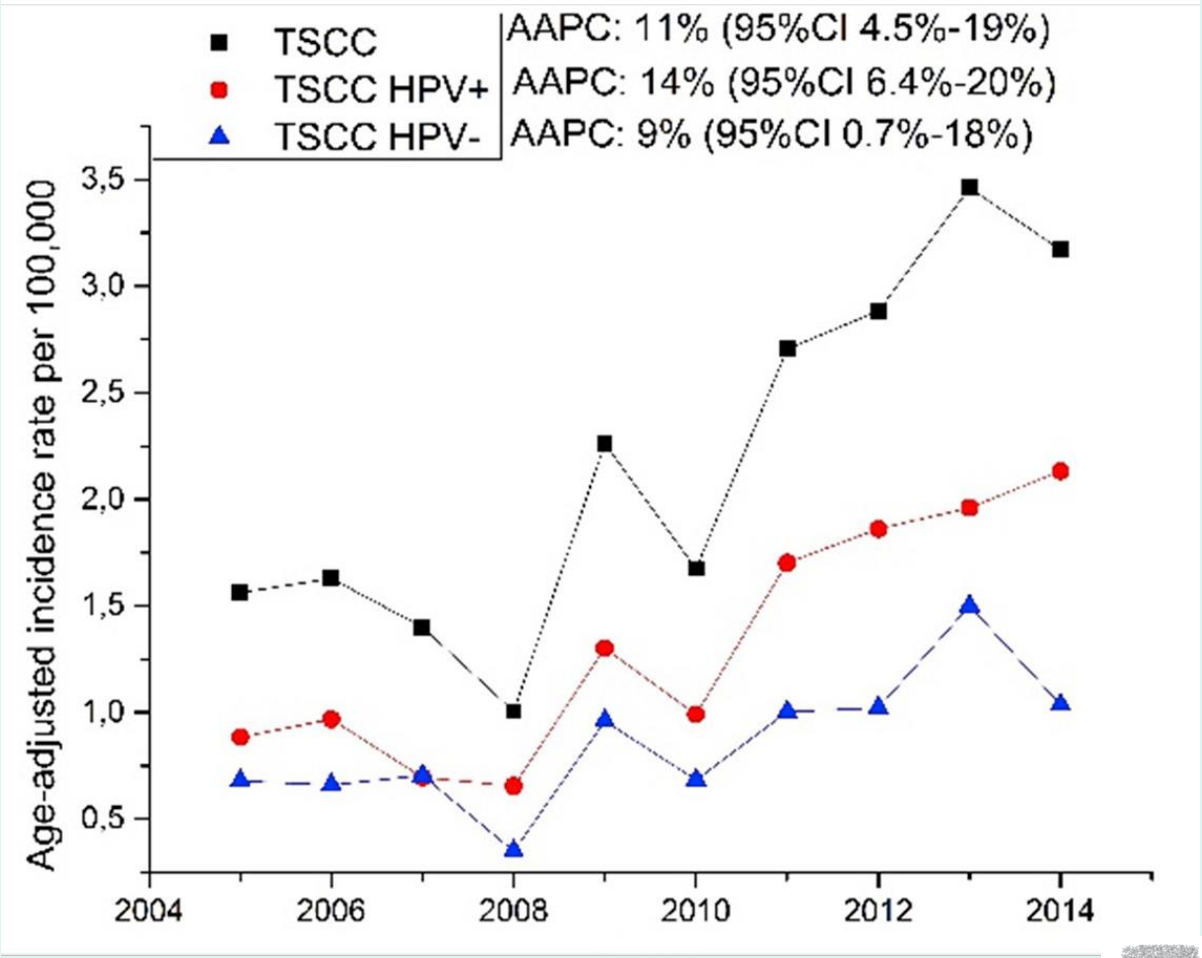


%: trend of increase between 2006–2016

Source: Národní onkologický registr ČR, ÚZIS ČR

HPV PREVALENCE IN OROPHARYNGEAL CANCER (2018)





ELSEVIER

European Journal of Cancer
Volume 70, January 2017, Pages 75-82

Original Research

Continuing rise in oropharyngeal cancer in a high HPV prevalence area: A Danish population-based study from 2011 to 2014

Amanda-Louise Fenger Carlander [a], Christian Grønhøj Larsen [a], David Hebbelstrup Jensen [a], Emilie Garnæs [a], Katalin Kiss [b], Luise Andersen [b], Caroline Holkmann Olsen [c], Maria Franzmann [d], Estrid Høgdall [e], Susanne K. Kjær [f, k], Bodil Norrild [g], Lena Specht [h], Elo Andersen [i], Thomas van Overeem Hansen [j], Finn Cilius Nielsen [j], Christian von Buchwald [a]

Relative number of new cases according to diagnosis (HPV related tumors) Time evolution

Source: Národní onkologický registr, ÚZIS ČR

Epidemiological summary of tumors related to HPV infection

Absolut numbers

	Incidence Average number of newly diagnosed cases per year 2012–2016			Prevalence Number of patients living with tumor or its history on 31. 12. 2016		
	Together	Men	Women	Together	Men	Women
Cervix Uteri (C53)	871	-	871	17 787	-	17 787
Vulva and vagina (C51, C52)	298	-	298	2 246	-	2 246
Anus and anal canal (C21)	162	56	106	1 068	308	760
Penis (C60)	106	106	-	829	829	-
Oropharynx and tongue (C01, C02, C04–C06, C09)	1 003	721	282	5 636	3 762	1 874
Total	2 440	883	1 557	27 566	4 899	22 667

Source: Národní onkologický registr, ÚZIS ČR

Global pan-gender HPV vaccination

Possibility to eliminate several high-risk HPV types in the younger generations and avoid more than 600 000 cancer cases annually worldwide

J Intern Med. 2019 Nov 16 [Epub ahead of print]

A global epidemic increase of an HPV-induced tonsil and tongue base cancer – potential benefit from a pan-gender use of HPV vaccine

A. Näsman[1,†], J. Du[2,†] & T. Dalianis[1]

From the [1]Department of Oncology-Pathology; and [2]Department of Microbiology, Tumor Biology and Cell Biology, Centre for Translational Microbiome Research (CTMR), Karolinska Institutet, Stockholm, Sweden

Social Science & Medicine 153 (2016) 193–200

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

"Saving lives": Adapting and adopting Human Papilloma Virus (HPV) vaccination in Austria

Katharina T. Paul

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OPEN QUESTIONS –EPIDEMIOLOGY
(some of them)

- Geographic disparities
- Racial – ethnic disparities
- The role of sexual behavior
  - the risk for partners of HPV + patients
- The natural history of oral/oropharyngeal HPV
  - prevalence in healthy population
  - clearence of HPV infection

GEOGRAPHIC HETEROGENEITY

Lifestyle differences
Differences in sexual behavior
Selection bias
Quality of diagnostic methods

533 OPHC cases	P16 + HPV DNA
US	60%
Europe	31%
Brasil	4%

Anantharaman et al. 2017

EUROPE: HPV PREVALENCE IN OPHC

Austria

60% (p16)

40% (HPV DNA) Heiduschka et al. 2015

Czechia

58% (p16, HPV DNA) Klozar et al. 2013

65% (p16, HPV DNA) tonsils only Rotnaglova et al. 2011

Italy

40% (p16, HPV DNA) Dona et al. 2015

Germany

34% (p16,HPV DNA, E6/7 RNA) Hauck et al. 2015

48% (p16,HPV DNA) Tinhofer et al. 2015

Denmark

62% (p16,HPV DNA) Carlander et al. 2017

Sweden

74% (HPV DNA) Nasman et al. 2015

ASIA: HPV PREVALENCE IN OPHC

	N	method	HPV+	
Thailand	110	P16 HPV DNA	14,5%	Nopmaneepaisarn 2019
Eastern China	188	P16 HPV DNA	11,7%	Wang et al. 2016
India	105	HPV DNA	22,8%	Bahl et al. 2017
New Zealand	161	p16	24% 94-99 76% 09-14	Kwon et al. 2016
Hong Kong	207	E6/7 mRNA	20.8%	Li et al. 2016
Japan	59	p16	29,5%	Toman et al. 2017
Kazakhstan	76	P16 HPV DNA	OPHC 25,7% OC 12,2%	Adilbay, 2018

„NEW TYPE“ of HNC patient

- More often non smoker
- More educated
- Higher SES
- Younger (?)
- Less Commorbidities
- More active sexual behavior (?)
- Better prognosis

„TYPICAL“ HPV positive tumor

- Lower T
- Higher N
- Regional metastasis frequently as the first symptom
- Frequent cystic metastasis
- nonkeratinizing morphology („basaloid“ appearence)

Otolaryngol Head Neck Surg. 2014 September ; 151(3): 375–380. doi:10.1177/0194599814538605.

The "New" Head and Neck Cancer Patient—Young, Nonsmoker, Nondrinker, and HPV Positive: Evaluation

Daniel G. Deschler, MD[1], **Jeremy D. Richmon, MD**[2], **Samir S. Khariwala, MD**[3], **Robert L. Ferris, MD, PhD**[4], and **Marilene B. Wang, MD**[5]

The dramatic rise in OPSSC related to HPV is characterized by a "new" cancer patient who is younger and lacks traditional risk factors.

Today's caregiver must be prepared to appropriately evaluate, counsel, and treat these patients with HPV-positive disease with the expectation that traditional treatment algorithms will evolve to maintain or improve current excellent cure rates while lessening treatment related side effects.

Laryngoscope. 2017 Oct; 127(10): 2270–2278. PMID: 28304083
Published online 2017 Mar 17. doi: 10.1002/lary.26566

Influence of Human Papillomavirus on the Clinical Presentation of Oropharyngeal Carcinoma in the United States

Matthew H. Stenmark, MD,[1] Dean Shumway, MD,[1] Cui Guo, MS,[2] Jeffrey Vainshtein, MD,[1] Michelle Mierzwa, MD,[1] Reshma Jagsi, MD, DPhil,[1] Jennifer J. Griggs, MD, MPH,[3] and Mousumi Banerjee, PhD[2]

„DISTINCT CLINICAL PROFILE“

HPV-related oropharyngeal carcinoma was associated with younger age, male sex, and white race (P<0.001).

Advanced primary tumor stage was associated with HPV-negative disease (P<0.001), while increasing nodal burden was associated with HPV-positive disease (P<0.001).

Despite less advanced nodal disease, HPV-negative tumors were associated with a higher likelihood of metastasis at presentation (P<0.001)

Demographic and SES characteristics of OPC patients by tumor HPV status determined by p16 expression and ISH with or without PCR and by smoking status (N=356)[a]

Characte	HPV-positive	HPV-negative		Crude OR	Adjusted OR	smokers	Smokers		Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Age, year										
≤55									1.0	1.0
>55									0.7 (0.4–1.2)	0.7 (0.4–1.2)
Median (										
Sex										
Male									1.0	1.0
Female	39 (12.4)	13 (31.7)		0.3 (0.1–0.6)	0.2 (0.1–0.6)	26 (14.9)	7 (6.9)		2.3 (1.0–5.6)	3.7 (1.3–11.1)
Ethnicity			.034					.525		
White	287 (91.1)	33 (80.5)		1.0	1.0	160 (91.4)	90 (89.1)		1.0	1.0
Other	28 (8.9)	8 (19.5)		0.4 (0.2–1.0)	0.5 (0.2–1.4)	15 (8.6)	11 (10.9)		0.8 (0.3–1.7)	0.8 (0.3–2.0)
Marital status			.043					.176		
Currently married	218 (79.6)	24 (64.9)		1.0	1.0	142 (82.1)	76 (75.3)		1.0	1.0
Never/formerly married	56 (20.4)	13 (35.1)		0.5 (0.2–1.0)	0.8 (0.3–2.0)	31 (17.9)	25 (24.8)		0.7 (0.4–1.2)	0.7 (0.3–1.5)
Missing	41	4								
Income/year			.052							
<$50,000	55 (21.4)	13 (38.2)								
$50,000–$99,999	79 (30.7)	11 (32.4)		1.7						
≥$100,000	123 (47.9)	10 (29.4)		2.9						
Missing	58	7								
Education level			.002							
High school or GED or less	65 (23.7)	19 (51.4)								
Technical or vocational school	85 (31.0)	6 (16.2)		4.1						
Bachelor's degree or greater	124 (45.3)	12 (32.4)		3.0						
Missing	41	4								
SES composite			.003							
Q1 (low)	65 (25.3)	18 (52.9)								
Q2 (mid)	104 (40.5)	7 (20.6)		4.1						
Q3 (high)	88 (34.2)	9 (26.5)		2.7 (1.1–6.4)	1.1 (0.4–3.0)	70 (42.7)	18 (19.4)		5.5 (2.7–11.2)	5.3 (2.5–11.3)

Oral Oncol. 2015 Sep; 51(9): 832–838. PMID: 26120093
Published online 2015 Jun 26. doi: 10.1016/j.oraloncology.2015.06.005

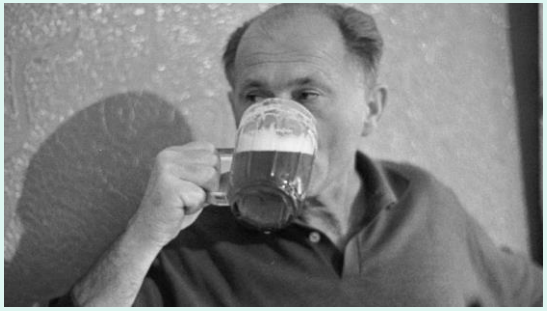
Socioeconomic characteristics of patients with oropharyngeal carcinoma according to tumor HPV status, patient smoking status, and sexual behavior

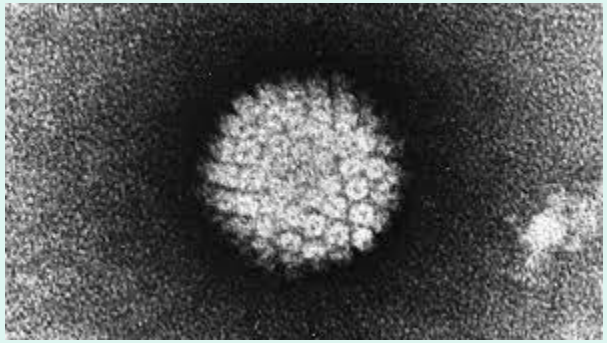
Kristina R. Dahlstrom,[1] Diana Bell,[2] Duncan Hanby,[1,4] Guojun Li,[1,3] Li-E Wang,[3] Qingyi Wei,[3,5] Michelle D. Williams,[2] and Erich M. Sturgis[1,3]

HPV positive patients
- more men
- more educated
- higher socioeconomic status
- more non smokers
- more tonsillar tumors
- lower T

Traditional risk factors
Corresponding patient type

HPV → pacient younger, healthier, more educated, non smoker,
Different sexual behavior??





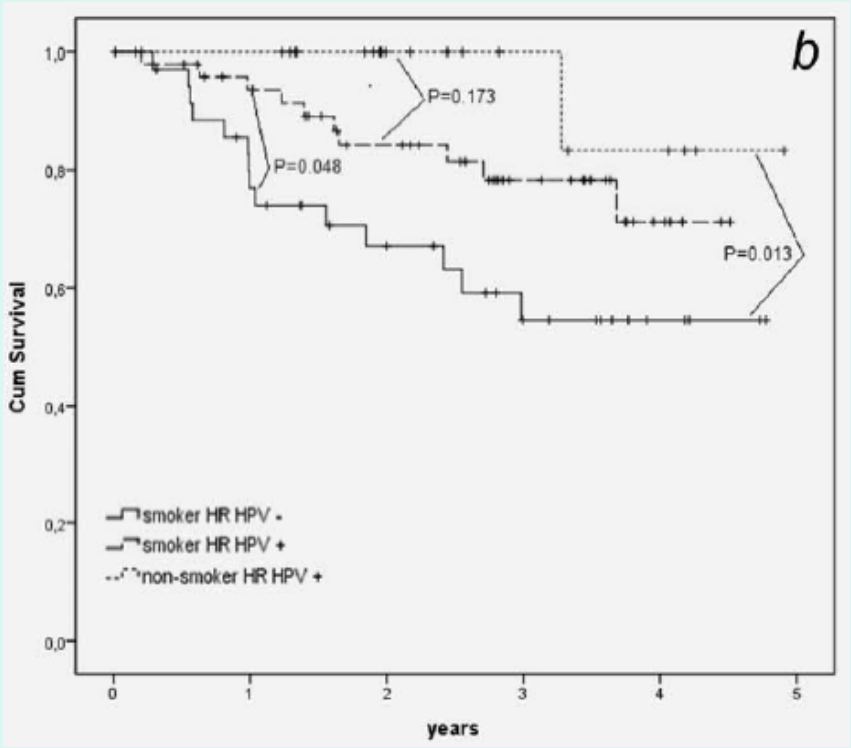
Other HN tumors > 90%
Orofarynx ~ 30%

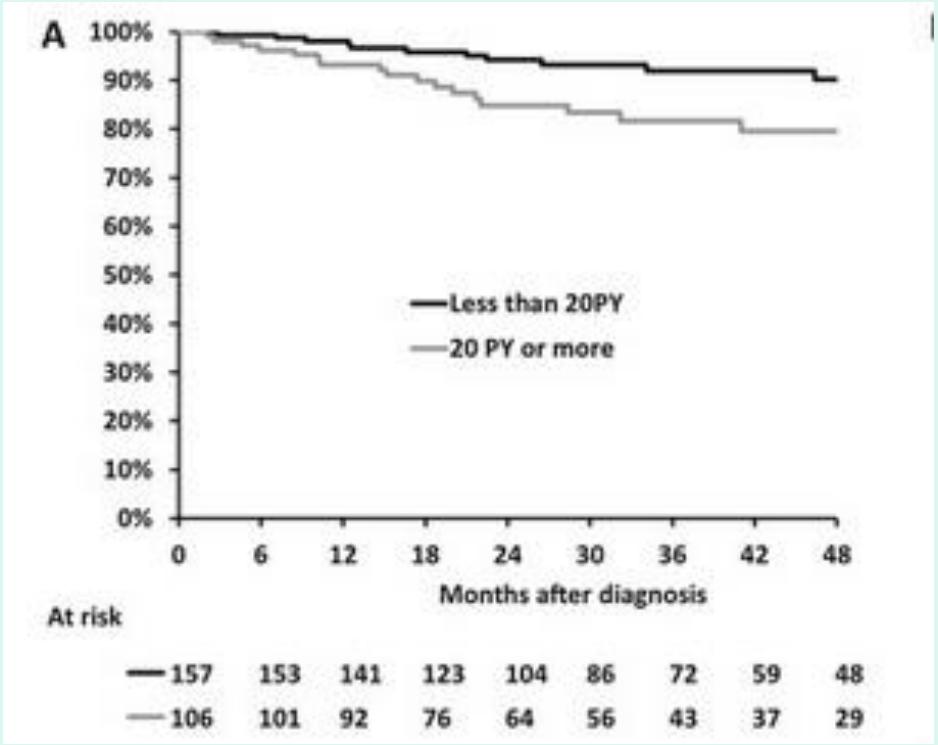
Other HN tumors ~ 1%
Orofarynx ~ 70%

PROGNOSTIC FACTORS

- Patients with HPV positive tumors have better prognosis
- HPV is the strongest prognostic factor
- Better prognosis is probably treatment independent
- Smoking status has a prognostic role within the group of patients with HPV+ cancers
- The role of other prognostic factors (N classification, ECS) may be weaker or absent in HPV positive tumors

PROGNOSTIC FACTORS
Smoking and HPV positive tumors

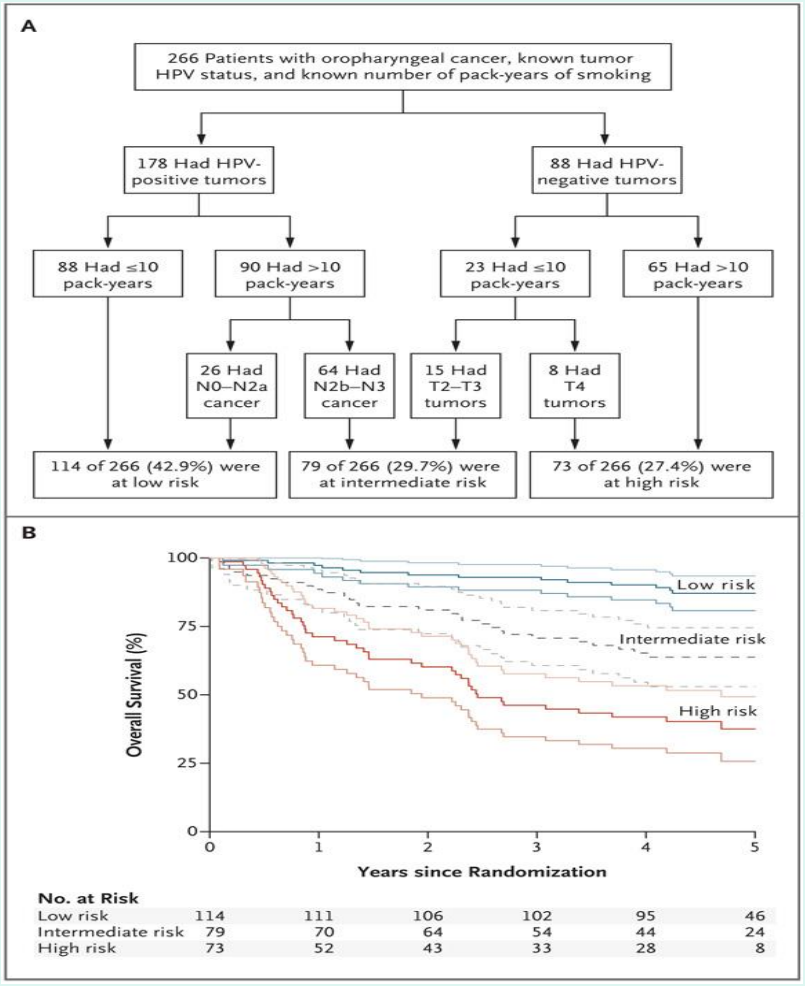




Rotnaglova et al. Int J Cancer, 2011

Mirghani et al. Oral Oncol, 2018

RISK MODELS



Using recursive-partitioning analysis, patients were classified as having a low, intermediate, or high risk of death on the basis of four factors: HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage

N Engl J Med. 2010 Jul 1;363(1):24-35. doi: 10.1056/NEJMoa0912217. Epub 2010 Jun 7.

Human papillomavirus and survival of patients with oropharyngeal cancer.

Ang KK[1], Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML.

N Engl J Med. 2010 Jul 1;363(1):24-35. doi: 10.1056/NEJMoa0912217. Epub 2010 Jun 7.

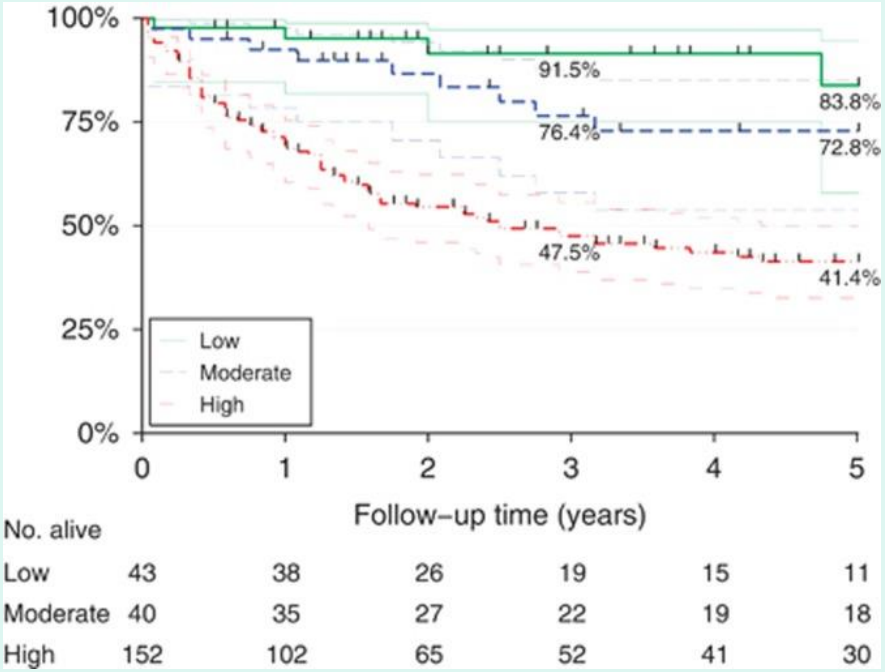
Human papillomavirus and survival of patients with oropharyngeal cancer.

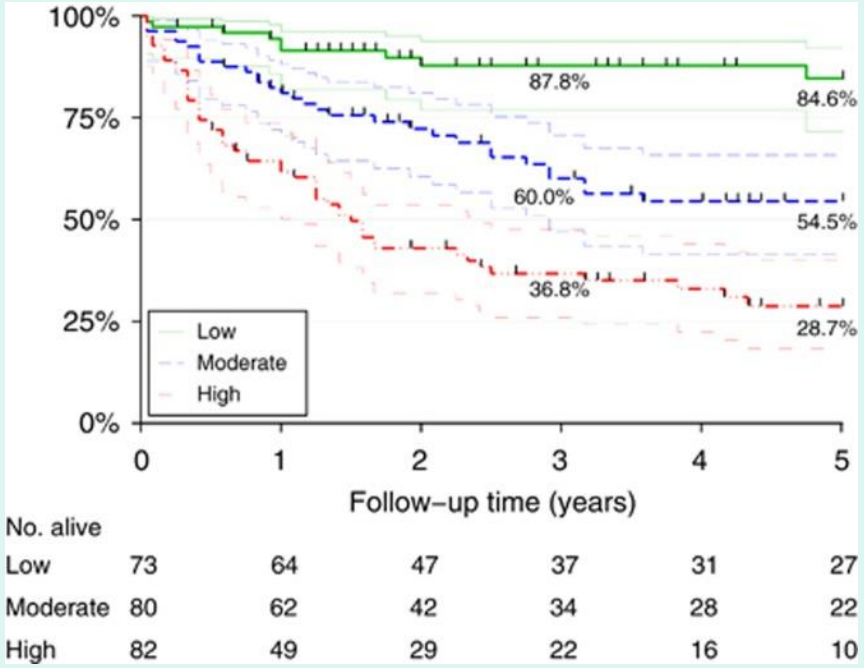
Ang KK[1], Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML.

Ann Oncol. 2013 Nov;24(11):2740-5. doi: 10.1093/annonc/mdt319. Epub 2013 Aug 14.

Human papillomavirus detection and comorbidity: critical issues in selection of patients with oropharyngeal cancer for treatment De-escalation trials.

Rietbergen MM[1], Brakenhoff RH, Bloemena E, Witte BI, Snijders PJ, Heideman DA, Boon D, Koljenovic S, Baatenburg-de Jong RJ, Leemans CR.





Straetmans JM1, Olthof N, Mooren JJ, de Jong J, Speel EJ, Kremer B
Human papillomavirus reduces the prognostic value of nodal involvement in tonsillar squamous cell carcinomas.
Laryngoscope. 2009 Oct;119(10):1951-7

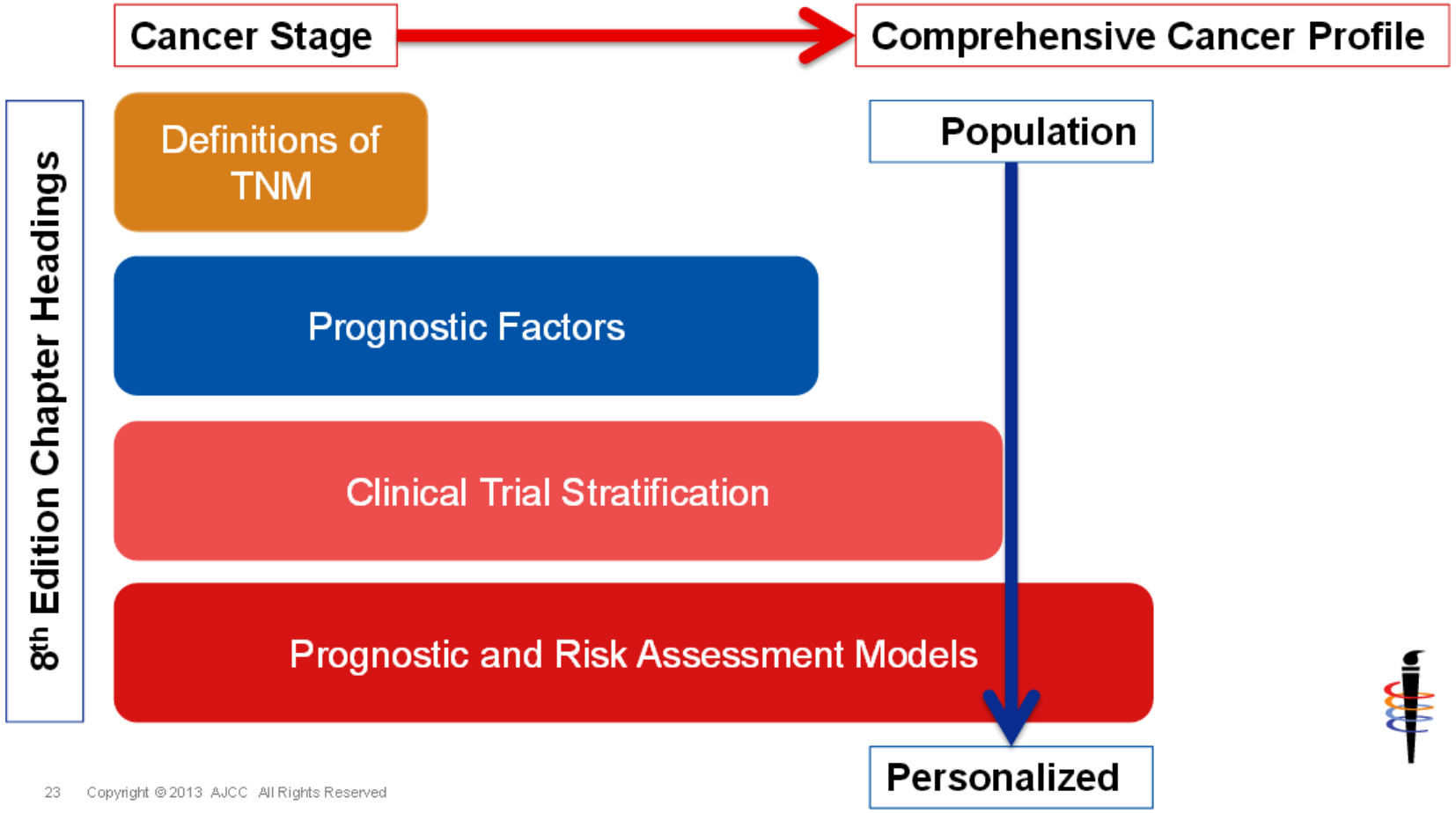
Sinha P1, Lewis JS Jr, Piccirillo JF, Kallogjeri D, Haughey BH.
Extracapsular spread and adjuvant therapy in human papillomavirus-related, p16-positive oropharyngeal carcinoma.
Cancer. 2012 Jul 15;118(14):3519-30

Dahlstrom KR1, Calzada G, Hanby JD, Garden AS, Glisson BS, Li G, Roberts DB, Weber RS, Sturgis EM.
An evolution in demographics, treatment, and outcomes of oropharyngeal cancer at a major cancer center: a staging system in need of repair. Cancer. 2013 Jan 1;119(1):81-9

Klozar J1, Koslabova E, Kratochvil V, Salakova M, Tachezy R.
Nodal status is not a prognostic factor in patients with HPV-positive oral/oropharyngeal tumors.
J Surg Oncol. 2013 May;107(6):625-33

AJCC Vision

…and Where It Fits in the 8th Edition:



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*

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

Pathological

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

MARKERS OF HPV INFECTION

Hazard of inaccurately assigning HPV-negative tumors to an HPV-positive category

Markers of HPV infection should:

- be adapted to clinical practice (invasiveness, difficulty to perform, cost)
- represent the best possible expression of viral involvement in cancerogenesis

RELEVANCE OF HPV INFECTION

The fact that HR HPV DNA is present in the tumor does not necessarily imply the etiological involvement of the virus in the cancerogenesis

The theoretical ‘gold standard’ test for oncogenic HPV infection is the demonstration of

transcriptionally active high-risk HPV

MARKERS OF HPV INFECTION

- Overexpresion of p16 (IHC)
- PCR HR HPV DNA detection
- DNA in situ hybridization
- Absence of detectable p53 (IHC)
- Presence of HR HPV E6, E7 mRNA
- Seropositivity for HPV 16 E6 /E7 specific antibodies

MARKERS OF HPV INFECTION
In clinical practice: p16

E7 inactivates the retinoblastoma tumor suppressor proteins pRb.
p16 is regulated by pRb protein by a negative feedback mechanism
Consequently the inactivation of pRb results in up-regulation of p16.
Protein p16 can be detected by immunohistochemistry

- Suboptimal analytical performance
- When used in isolation, increased p16 expression is highly sensitive (94–100%), but lacks specificity (79–82%)

Most frequently used combination of markers:

p16 and HPV DNA detection

p16 immunohistochemistry (IHC)

and

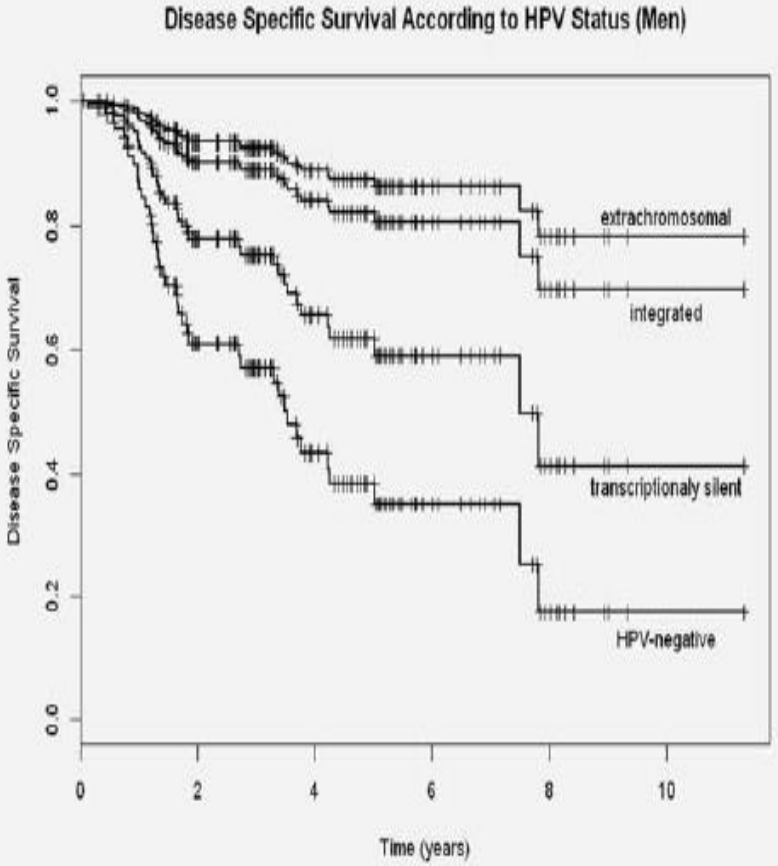
PCR for HPV DNA using consensus primers (GP5/GP6)
or
HPV16/18 fluorescent in situ hybridisation (ISH)

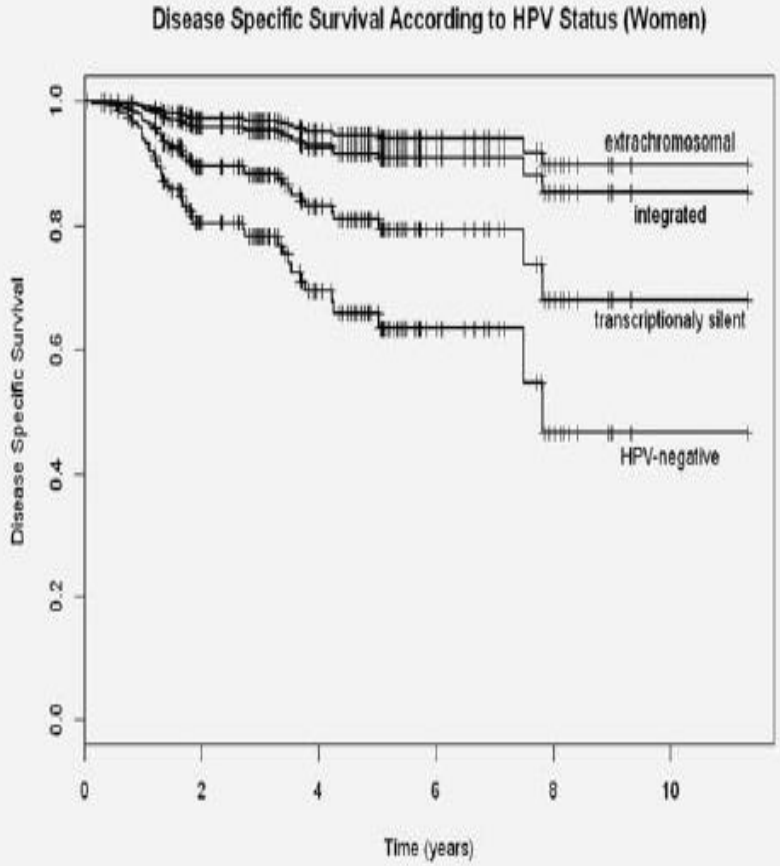
IJC
International Journal of Cancer

Analysis of the integration of human papillomaviruses in head and neck tumours in relation to patients' prognosis

Zuzana Vojtechova[1,2], Ivan Sabol[1], Martina Salakova[1], Lubomir Turek[3], Marek Grega[4], Jana Smahelova[1], Ondrej Vencalek[5], Eva Lukesova[1,6], Jan Klozar[6] and Ruth Tachezy[1,2]

[1] Department of Immunology, Institute of Hematology and Blood Transfusion, Prague, Czech Republic
[2] Department of Genetics an
[3] Veterans Affairs Healthcare
[4] Department of Pathology a
[5] Department of Mathematic
[6] Department of Otorhinolary
Czech Republic





MARKERS OF HPV INFECTION
E6/E7 mRNA

- Presence of E6/E7 mRNA testifies the transcription of oncogenes
- Reverse transcriptase polymerase chain reaction (qRT-PCR) amplifying high-risk HPV E6/E7 mRNA transcripts in fresh tissue or in FFPE material
- samples often contain degraded RNA molecules
- Developement of affordable methods of mRNA detection in the future. Depends also on quality of the FFPE material.

DEESCALATION OF THE TREATMENT

- Rationale for treatment de-intensification
- Choice of the appropriate patient
- Methods of de-intensification of therapy

DEESCALATION OF THE TREATMENT RATIONALE

- Acute and late toxicity of the non surgical treatment
- Mutilation induced by surgery
- Characteristics of the HPV+ patient
- Importance of QOL issues

DEESCALATION OF THE TREATMENT METHODS

Less aggressive surgical approaches

Reduction of chemotherapy-related toxicity

Reduction of radiotherapy dose

Novel anti - HPV approaches

De-intensification of chemotherapy

Trial	Phase	N	Inclusion criteria	Treatment
Chemotherapy de-intensification trials				
RTOG 1016 (NCT01302834)	III	706	T1–2, N2a–3, or T3–4, any N, HPV-positive OPSCC	Cetuximab versus high-dose cisplatin concurrent with accelerated IMRT (70 Gy in 6 weeks)
De-ESCALaTE HPV (NCT01874171)	III	304	Stage III–IVA HPV-positive OPSCC (T3N0–T4N0, T1N1–T4N3). Excludes > N2b, >10 PY	Cetuximab versus high-dose cisplatin concurrent with RT (70 Gy)
TROG 12.01 (NCT01855451)	III	200	Stage III (excluding T1–2, N1) or IV (excluding T4, N3, or M1) HPV-positive OPSCC if ≤10 PY. If >10 PY, only N0–2a	Cetuximab versus weekly cisplatin concurrent with RT (70 Gy) once per week

Lancet. 2019 Jan 5;393(10166):40-50. doi: 10.1016/S0140-6736(18)32779-X. Epub 2018 Nov 15.

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial.

Gillison ML[1], Trotti AM[2], Harris J[3], Eisbruch A[4], Harari PM[5], Adelstein DJ[6], Sturgis EM[7], Burtness B[8], Ridge JA[9], Ringash J[10], Galvin J[11], Yao M[12], Koyfman SA[13], Blakaj DM[14], Razaq MA[15], Colevas AD[16], Beitler JJ[17], Jones CU[18], Dunlap NE[19], Seaward SA[20], Spencer S[21], Galloway TJ[22], Phan J[23], Dignam JJ[24], Le QT[25].

Lancet. 2019 Jan 5;393(10166):51-60. doi: 10.1016/S0140-6736(18)32752-1. Epub 2018 Nov 15.

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial.

Mehanna H[1], Robinson M[2], Hartley A[3], Kong A[4], Foran B[5], Fulton-Lieuw T[4], Dalby M[6], Mistry P[6], Sen M[7], O'Toole L[8], Al Booz H[9], Dyker K[10], Moleron R[11], Whitaker S[12], Brennan S[13], Cook A[14], Griffin M[15], Aynsley E[16], Rolles M[17], De Winton E[18], Chan A[19], Srinivasan D[20], Nixon I[21], Grumett J[6], Leemans CR[22], Buter J[22], Henderson J[23], Harrington K[24], McConkey C[6], Gray A[25], Dunn J[6]; De-ESCALaTE HPV Trial Group.

Radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin

Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control

De-intensification of radiotherapy

Radiotherapy de-intensification trials				
NRG HN-002 (NCT02254278)	II	296	T1–2, N1–2b, or T3, N0–2b disease and <10 PY HPV-positive OPC	Reduced-dose IMRT (60 Gy) with/without weekly cisplatin
NCT01530997	II	40	T1–3, N0–2c HPV-positive OPSCC if <10 PY or >5 years of abstinence	IMRT (54–60 Gy) with weekly cisplatin (30 mg/m^2)
ECOG 1308 (NCT01084083)	II	80	Resectable stages IIIA/IIIB and IVA/IVB HPV-positive OPSCC (p16-high or HPV-16 ISH positive)	IC, then response-adapted RT (54 or 66–70 Gy) with cetuximab
The Quarterback Trial (NCT01706939)	III	365	Stage III/IV (M0) HPV-associated OPSCC/unknown primary/nasopharynx. Excludes active smokers/>20 PY	IC with TPF: patients with CR/PR randomly assigned 2:1 to carboplatin with RT (56 versus 70 Gy) per week. Non-responders receive standard RT.

ECOG 1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx- ECOG-ACRIN Cancer Research Group.

Patients registered
(N = 90)

Patients found eligible
(n = 80)

Patients started on IC per protocol
(n = 80)

cisplatin, paclitaxel, and cetuximab

Patients who received all three cycles of IC	(n = 77)
Infusion reaction to cetuximab	(n = 1)
Parathyroidectomy	(n = 1)
Received cycle 1, developed grade 4 infection, treated off protocol	(n = 1)

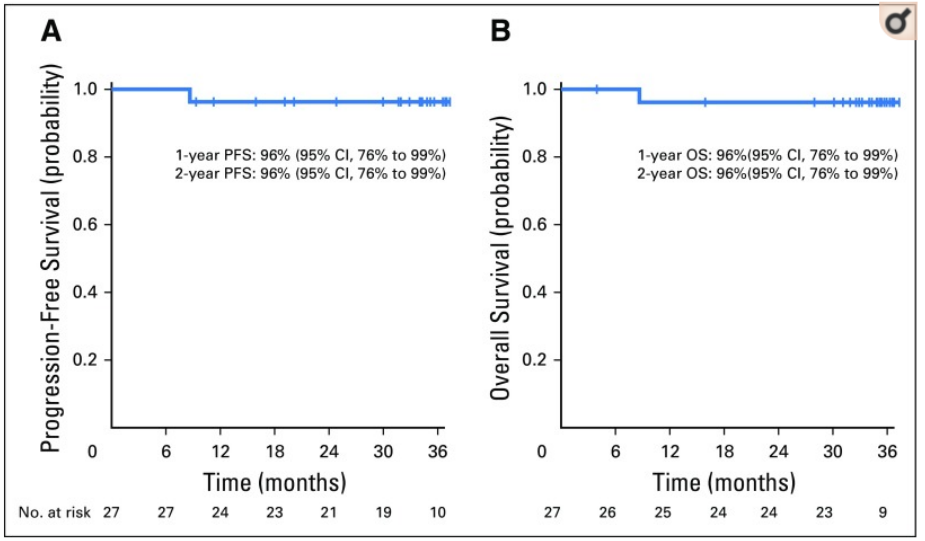
Clinical response at primary to IC:

cCR	(n = 56, including five patients with postbaseline biopsy and site-reported cCR)
PR	(n = 7)
SD	(n = 11)
UE	(n = 6)*

*Biopsy done after baseline measurements of primary, and site-reported non-cCR (n = 2)
Tonsillar primary had tonsillectomy after baseline measurement (n = 1)
Received D1 cycle 1 of IC, later off protocol received paclitaxel and carboplatin (n = 1)
No follow-up assessment (n = 1)
Postbaseline tonsillectomy (with positive deep margin) and no follow-up assessment (n = 1)

Radiation dose by primary site IC response:

cCR (n = 56)	54 Gy (n = 49), 52 Gy (n = 1), 40 Gy (n = 1), 69.3 Gy (n = 5)
PR (n = 7)	54 Gy (n = 2), 69.3 Gy (n = 5)
SD (n = 11)	40 Gy (n = 1), 54 Gy (n = 5), 65.1 Gy (n = 1), 69.3 Gy (n = 4)
UE (n = 6)	treated off protocol (n = 3), 54 Gy (n = 3)



PFS (A) and OS (B) in favorable cohort (non-T4, non-N2c, ≤ 10 pack-year smokers) with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 27). OS, overall survival; PFS, progression-free survival.

Marur S et al. J Clin Oncol. 2017;35(5):490-497.

[Intervention Review]

De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma

Liam Masterson[1], Daniel Moualed[2], Ajmal Masood[3], Raghav C Dwivedi[1], Richard Benson[4], Jane C Sterling[5], Kirsty M Rhodes[6], Holger Sudhoff[7], Piyush Jani[1], Peter Goon[8]

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Editorial group: Cochrane ENT Group.
Publication status and date: New, published in Issue 2, 2014.

There is currently insufficient high-quality evidence for, or against, de-escalation of treatment for human papillomavirus-associated oropharyngeal carcinoma

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Critical Review

Critical Review: Transoral Laser Microsurgery and Robotic-Assisted Surgery for Oropharynx Cancer Including Human Papillomavirus—Related Cancer

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T1T2, lesions can be adequately controlled locally with primary transoral surgery

Neck dissection can accurately stage the disease, and patients with N0 to N2a neck disease can be treated with surgery alone, whereas patients with N2b to N3 neck disease benefit from postoperative adjuvant RT and possibly chemoradiation therapy

Int J Radiat Oncol Biol Phys. 2013;85(5):1163-7

RESEARCH ARTICLE

Adjuvant Radiation Therapy Alone for HPV Related Oropharyngeal Cancers with High Risk Features

William Su[1], Jerry Liu[2], Brett A. Miles[3], Eric M. Genden[3], Krzysztof J. Misiukiewicz[4], Marshall Posner[4], Vishal Gupta[5], Richard L. Bakst[5]*

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Preliminary evidence suggesting that the omission of concurrent chemotherapy to adjuvant radiotherapy may offer comparative local control rates with a lower toxicity profile in the setting of HPV+ patients with traditional high risk features.

PLoS One. 2016 Dec 8;11(12)

De-intensification of surgery /adjuvant th

De-intensification of surgery/adjuvant therapy				
ECOG 3311 (NCT01898494)	II	377	Resectable stage III–IVB p16-positive OPSCC	TORS then risk-adapted post-operative treatment (observation/50 versus 60/66 Gy with weekly platinum)
PATHOS trial (NCT02215265)	II/III	242	Resectable T1–T3, N0–2b HPV-positive OPSCC. Excludes active smokers with N2b disease	TORS then re-adapted post-operative treatment (observation/50 versus 60Gy/60 Gy with or without weekly cisplatin)
ADEPT (NCT01687413)	III	500	Transoral resected p16-positive OPSCC (R0 margin), T1–4a, pN positive with ECE	Post-operative adjuvant 60-Gy RT with or without weekly cisplatin
NCT01932697	II	40	P16-positive OPSCC (R0 margin), stage I–IVB. Excludes ≥10 PY or smoking within 5 years	Surgery followed by hyperfractionated IMRT (36 Gy/20 fractions BID) + weekly docetaxel

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[Intervention Review]

De-intensified adjuvant (chemo)radiotherapy versus standard adjuvant chemoradiotherapy post transoral minimally invasive surgery for resectable HPV-positive oropharyngeal carcinoma

James Howard[1], Raghav C Dwivedi[1], Liam Masterson[1], Prasad Kothari[2], Harry Quon[3], F. Christopher Holsinger[4]

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Editorial group: Cochrane ENT Group.
Publication status and date: New, published in Issue 12, 2018.

Lack of high-quality randomised controlled trials studying treatment de-escalation after minimally invasive surgery in patients with HPV-positive OPSCC.
Trials are in progress with results expected between 2021 and 2023

HPV OUTSIDE OF OROPHARYNX

The presence of HPV DNA seems to be less frequent in non oropharyngeal locations.

There are insufficient data regarding the time trends in proportion of HPV containing tumors, but in contrast to oropharynx it probably did not increase in non oropharyngeal tumors in the last decades.

HPV 16 is most frequently encountered also in non-oropharyngeal tumors but the proportion of other HPV types is higher than in oropharynx.

Curr Opin Otolaryngol Head Neck Surg. 2019;27:80-84

HPV OUTSIDE OF OROPHARYNX

Presence of transcriptionally active HPV is very uncommon in oral cavity, laryngeal and hypopharyngeal squamous cell carcinomas.

In the small fraction of tumors which may be HPV driven the mechanism of viral involvement may be similar to that described in oropharyngeal tumors.

Due to the small number of cases and lack of studies reliably determining transcription of oncogenes there is up to date no clear evidence about the importance of HPV in non oropharyngeal tumors.

Curr Opin Otolaryngol Head Neck Surg. 2019;27:80-84

HPV OUTSIDE OF OROPHARYNX SURVIVAL

The impact of HPV on survival is not elucidated yet.

Further analyses especially studies using more specific markers of HPV involvement like E6/E7 mRNA are warranted.

Curr Opin Otolaryngol Head Neck Surg. 2019;27:80-84.

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