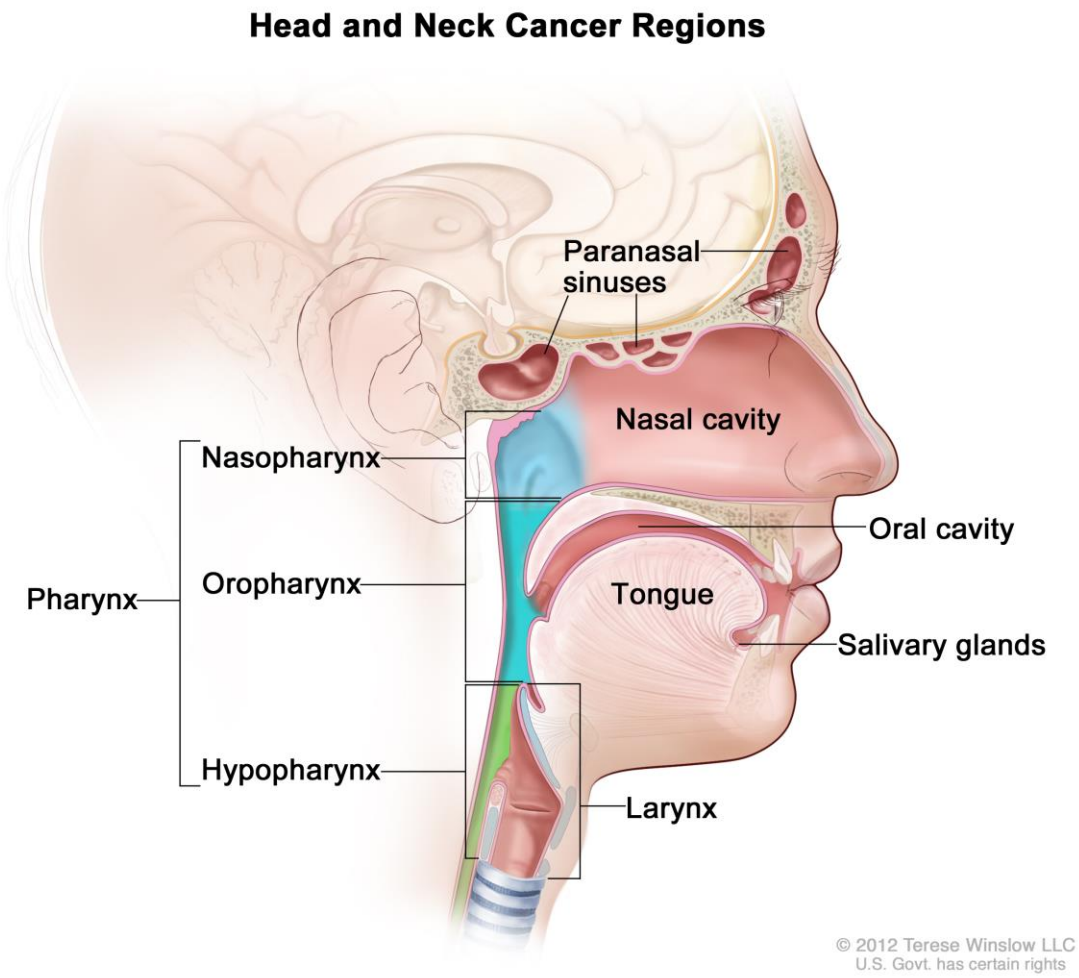
HPV positive Kopf-Hals Tumore

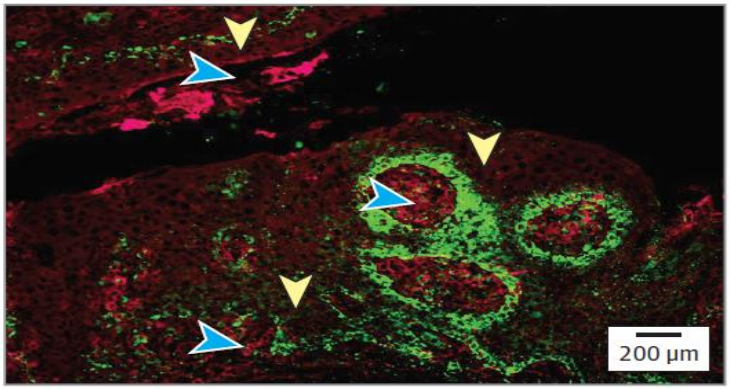
Assoc.Prof.Priv.Doz.Dr.Thorsten Füreder

Kopf Hals Tumore



https://www.ohsu.edu/xd/health/services/cancer/getting-treatment/services/head-and-neck-cancer/about.cfm

HPV Infektion bei gesunden Probanden (Tonsille)

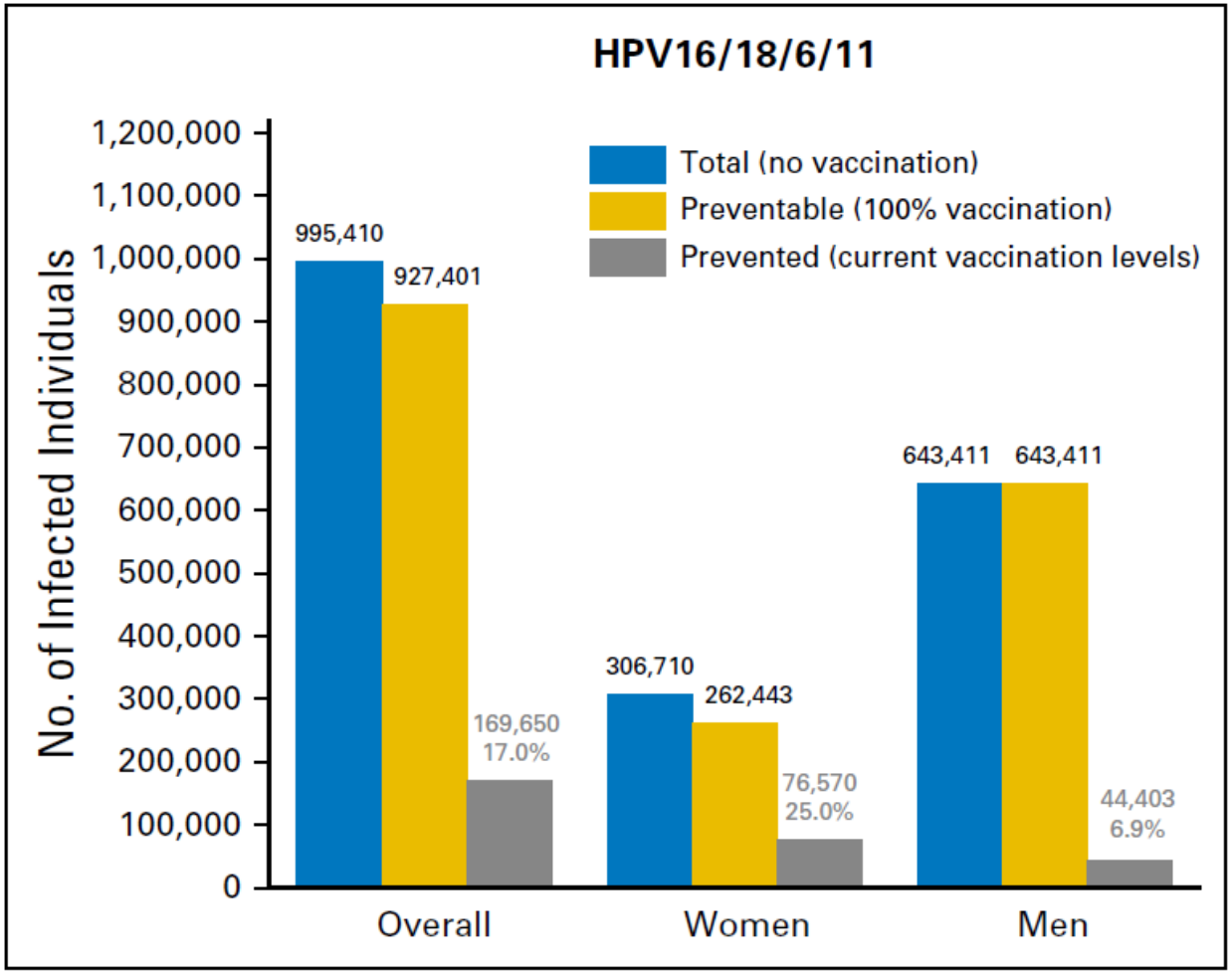


Characteristic	Sex (M/F)	Total, No. (%)	With HPV Infection, No.	HPV Prevalence, %	HPV16 E6/E7	HPV18 E6/E7	High-Risk HPV Prevalence, %
Age, y							
18-19	M	2 (1.9)	1	50	0	1	50
	F	1 (1.0)	0	0	0	0	0
20-29	M	34 (33.3)	2	5.9	2	0	5.9
	F	45 (44.1)	2	4.4	0	1	2.2
30-39	M	11 (10.8)	0	0	0	0	0
	F	9 (8.8)	0	0	0	0	0
Categorical total	M	47 (46.1)	3	2.9	2	1	3.0
	F	55 (53.9)	2	2.0	0	1	1.0
Total, % (95% CI)		102	5	4.9 (0.7-9.1)	2.0	2.0	4.0 (0.2-7.8)

Abbreviation: HPV, human papillomavirus.

Rieth et al.; JAMA Otolaryngology 2018

Prävalenz orale HPV Infektion und Impfung



Chatuverdi et al. JCO 2017

Prävalenz orale HPV Infektion und Impfung

Table 2. Effect of HPV Vaccination on Oral HPV Prevalence in the US Population, Ages 18 to 33 Years at Participation in the National Health and Nutrition Examination Survey 2011 to 2014

	Overall			Women			Men		
HPV Type	Vaccinated	Unvaccinated	*P* (model adjusted */ propensity adjusted†)	Vaccinated	Unvaccinated	*P* (model adjusted */ propensity adjusted†)	Vaccinated	Unvaccinated	*P* (model adjusted */ propensity adjusted†)
No. of individuals	496‡/11,310,006§	2,131‡/50,516,709§		394‡/9,225,357§	905‡/22,394,263§		102‡/2,084,649§	1,226‡/28,122,446§	
Vaccine type						.087/.14			.007/.003
HPV16/18/6/11							0		
No. of infections‡	1	32	.008	1	9		0.0	23	
Prevalence, % (95% CI)§	0.11 (0.0 to 0.96)	1.61 (1.00 to 2.47)	.054	0.14 (0.00 to 1.21)	0.97 (0.40 to 1.95)		—	2.13 (1.12 to 3.65)	
HPV16			.063/.14			.19/.21	0		.081/.071
No. of infections‡	1	19		1	6		0.0	13	
Prevalence, % (95% CI)§	0.11 (0.0 to 0.96)	0.94 (0.47 to 1.67)		0.14 (0.0 to 1.21)	0.71 (0.23 to 1.64)		—	1.12 (0.40 to 2.46)	
Nonvaccine types‖			.24/.52			.42/.58			.93/.83
No. of infections‡	24	116		16	23		8	93	
Prevalence, % (95% CI)§	3.98 (2.42 to 6.13)	4.74 (3.52 to 6.35)		3.70 (1.76 to 6.77)	2.29 (1.36 to 3.60)		5.19 (1.78 to 11.46)	6.69 (4.92 to 9.05)	

Abbreviation: HPV, human papilloma virus.

*Binary logistic regression modeling was initially conducted with oral HPV infection as the outcome and age, sex, and race as predictors to account for the imbalance in confounders between vaccinated and unvaccinated individuals, after which the score test *P* value was computed for the comparison of oral HPV prevalence between vaccinated and unvaccinated individuals. The binary logistic regression models were adjusted for age (linear), sex, and race (Hispanic, non-Hispanic white, non-Hispanic black, and other races). Models in women and men were adjusted for age (linear) and race (Hispanic, non-Hispanic white, non-Hispanic black, and other races). Models for HPV16 in men were adjusted for age (linear) and race (non-Hispanic white, non-Hispanic black, and other races) to avoid zero cells.

†The logistic propensity model had vaccination as the outcome and age (linear), sex, and race (Hispanic, non-Hispanic white, non-Hispanic black, and other races) as the predictors. Predicted odds from the propensity model were used to modify the poststratified National Health and Nutrition Examination Survey Mobile Exam Center weights of the unvaccinated individuals, which were then used as weights for the comparison of oral HPV prevalence between vaccinated and unvaccinated individuals using a quasi-score test. Sex-specific propensity models included age (linear) and race (Hispanic, non-Hispanic white, non-Hispanic black, and other races).

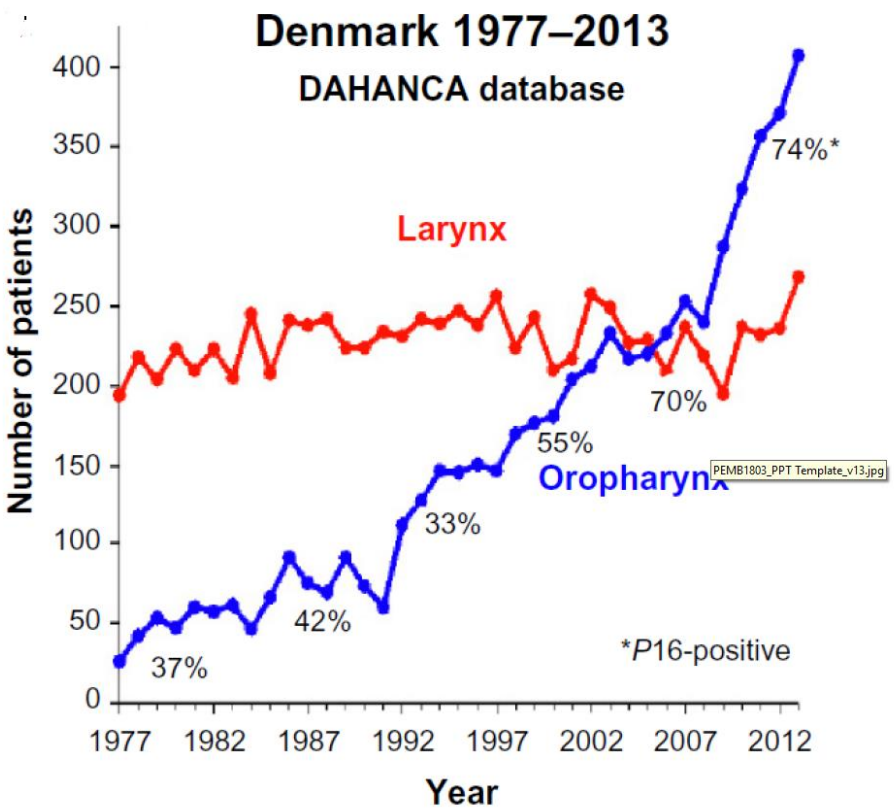
‡Unweighted totals.

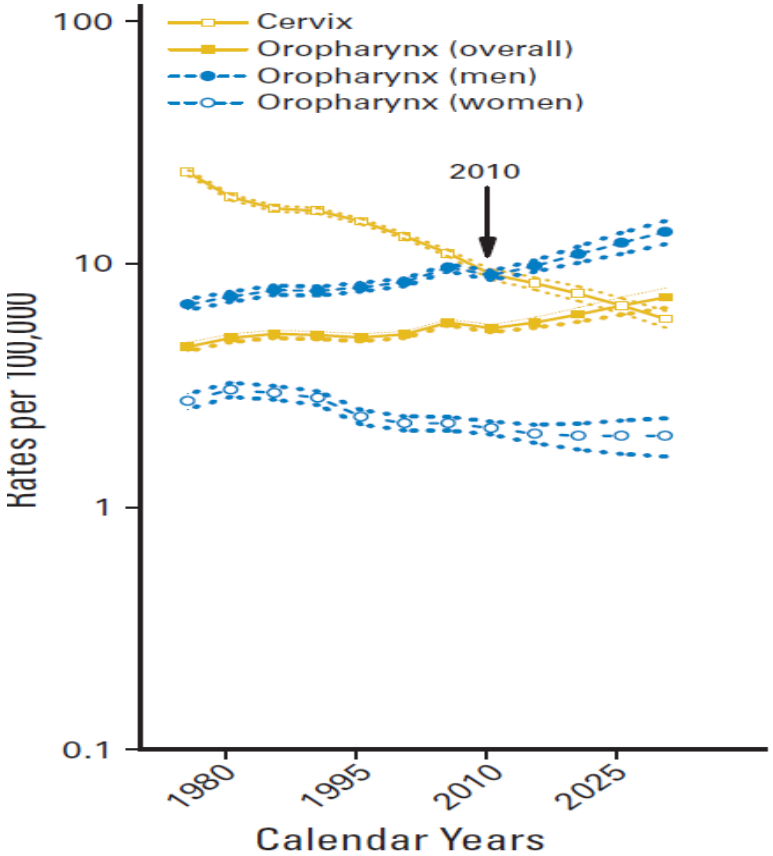
§Weighted estimates.

‖Category includes 33 HPV types: HPV 26, 31, 34, 33, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 82 subtype IS39, 83, 84, and 89.

Chatuverdi et al. JCO 2017

Epidemiologie HPV positive OPC





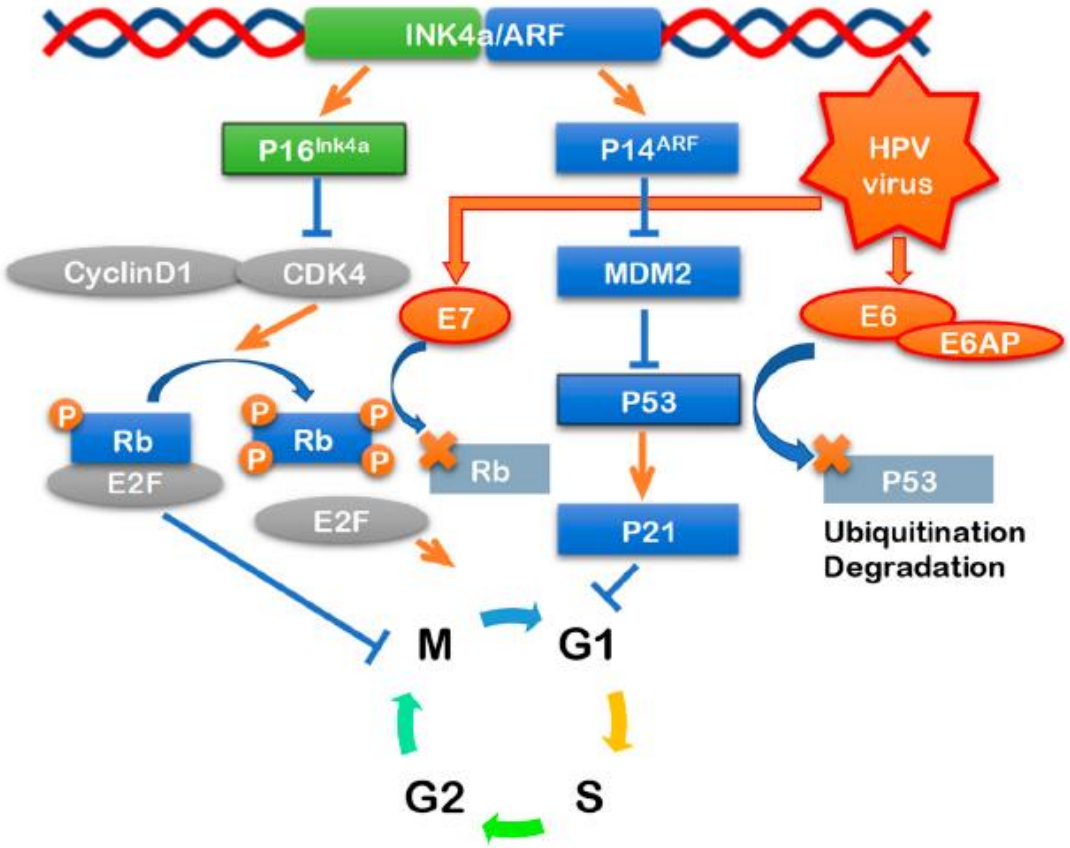
Overgaard et al.; Clinical Epidemiology 2016; Chatuverdi et al. JCO 2011

Epidemiologie HPV positive OPC

Variable	HPV-16–positive case subjects, % (n = 92)	Control subjects, % (n = 184)	Adjusted OR (95% CI)	P_{trend}	HPV-16–negative case subjects, % (n = 148)	Control subjects, % (n = 296)	Adjusted OR (95% CI)	P_{trend}
Total lifetime number of vaginal sex partners								
0–1	8	19	1.0 (referent)	<.001	20	24	1.0 (referent)	.58
2–10	38	53	2.5 (0.75 to 8.2)		46	50	0.61 (0.31 to 1.2)	
≥11	54	28	6.4 (1.9 to 22)		34	26	0.74 (0.32 to 1.7)	
Total lifetime number of oral sex partners								
0	8	20	1.0 (referent)	.004	30	26	1.0 (referent)	.47
1–5	47	54	2.1 (0.66 to 6.7)		51	52	0.93 (0.48 to 1.8)	
≥6	46	26	4.3 (1.4 to 14)		20	22	0.70 (0.28 to 1.8)	
History of casual sex								
No	40	61	1.0 (referent)		55	63	1.0 (referent)	
Yes	60	39	2.9 (1.5 to 5.6)		45	37	0.71 (0.39 to 1.3)	

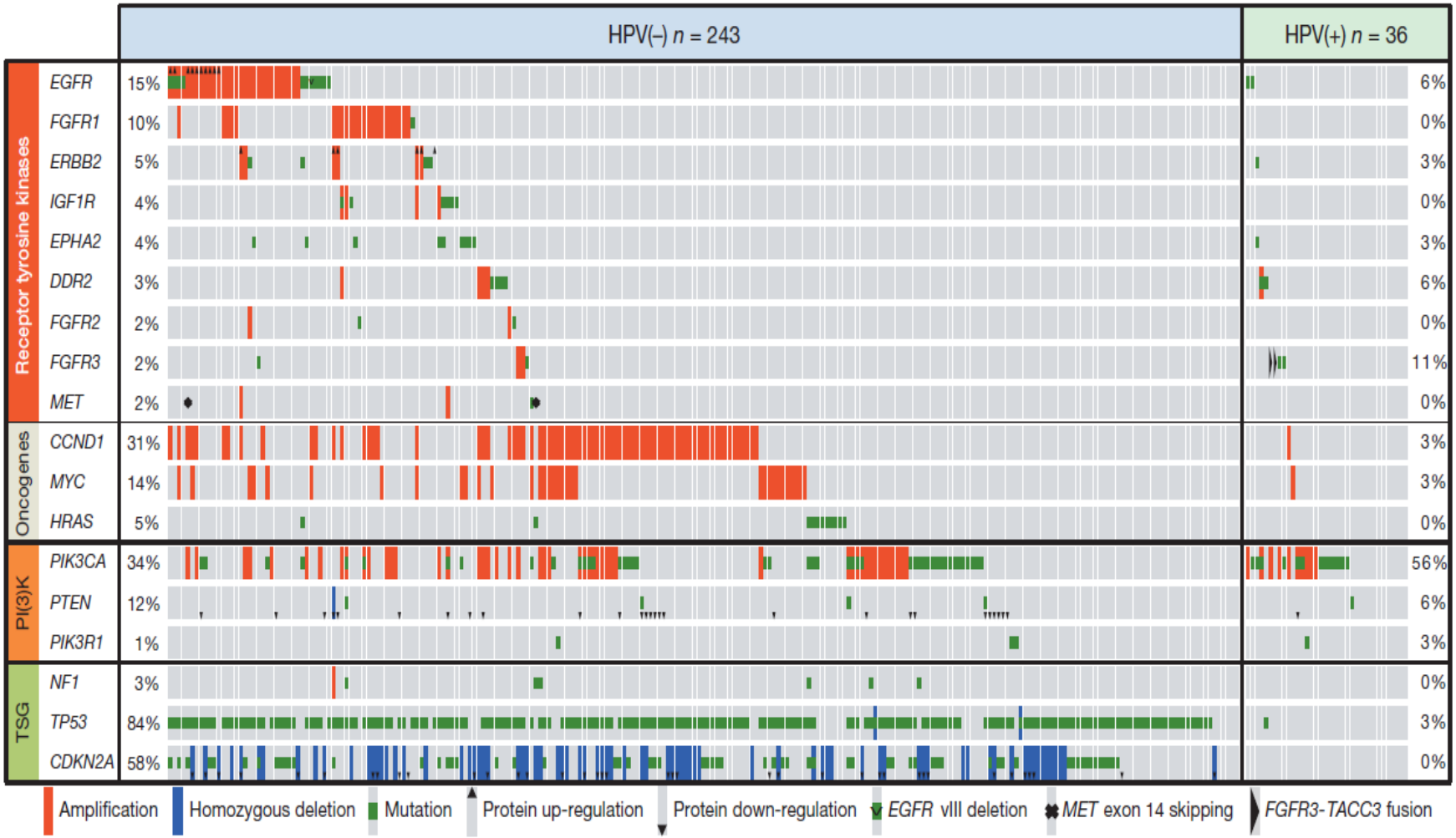
Gillision et al.; JNCI 2008

HPV und Tumorigenese



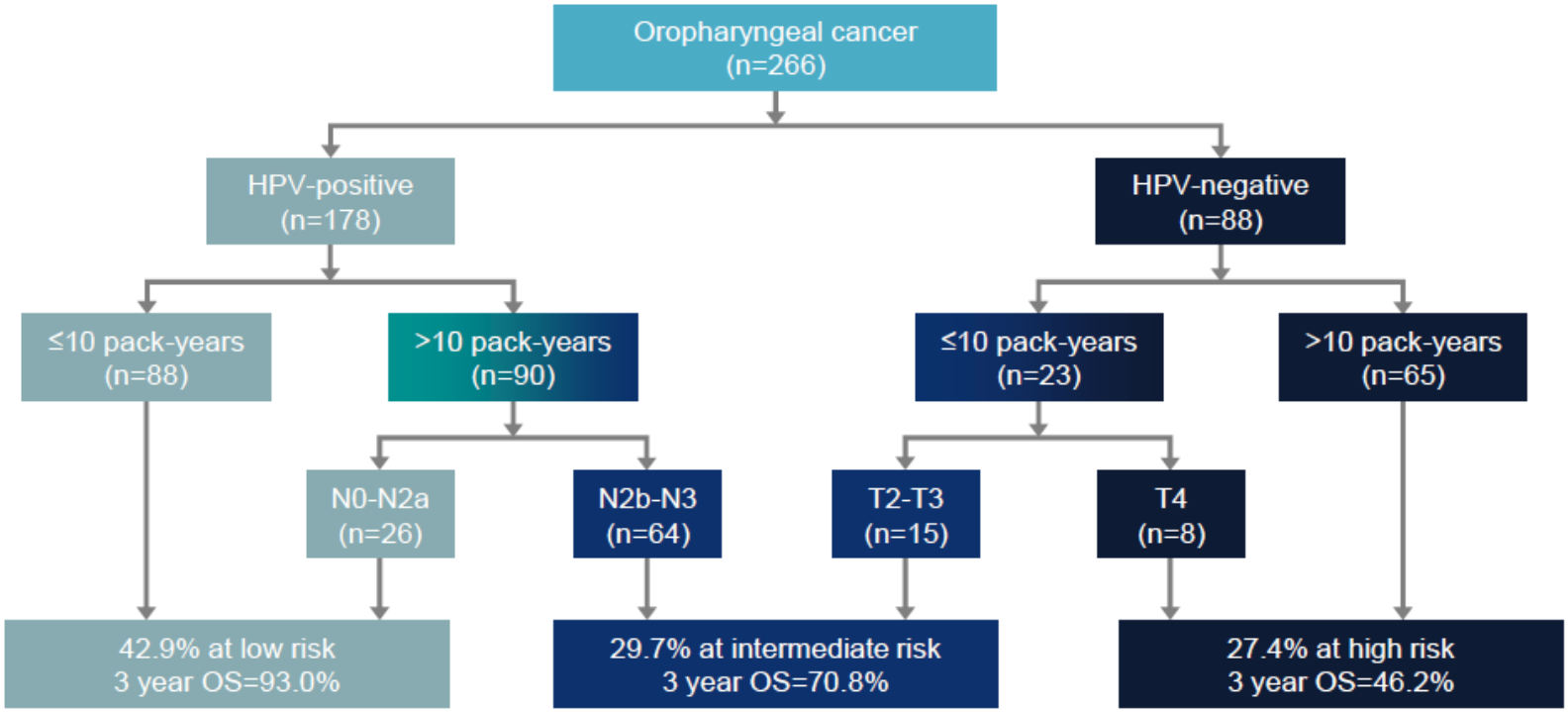
Kobayashi et al.; Journal of Clinical Medicine 2018

HPV und molekulares Profil



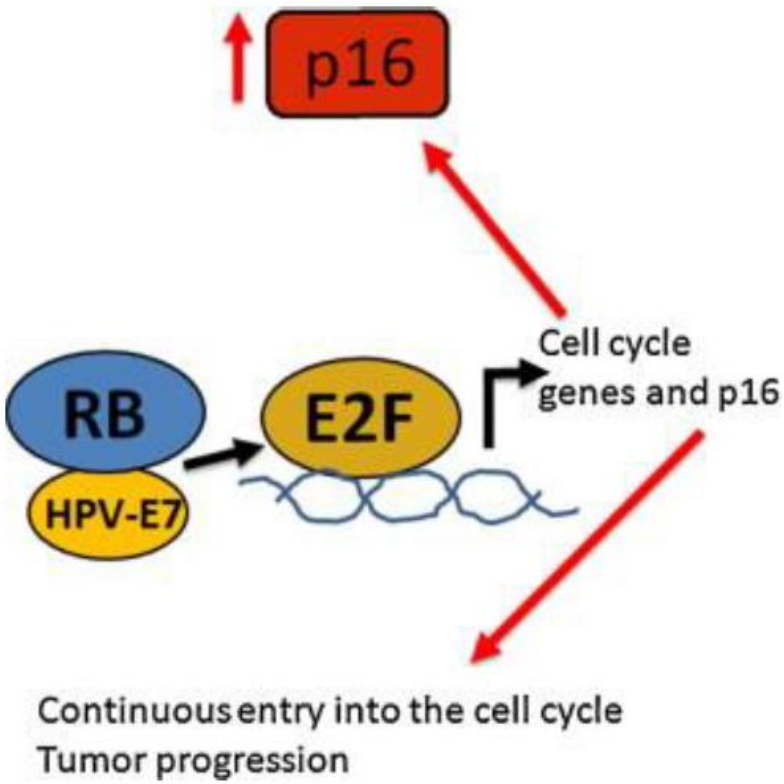
Cancer Genome Atlas Network, Nature 2015

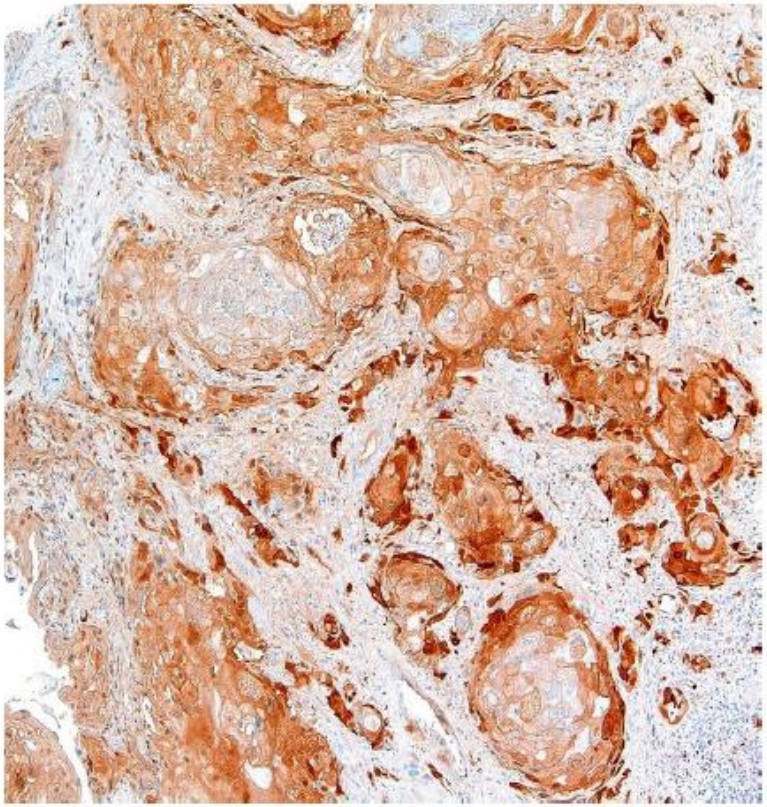
HPV und Prognose



Ang et al.; NEJM 2010

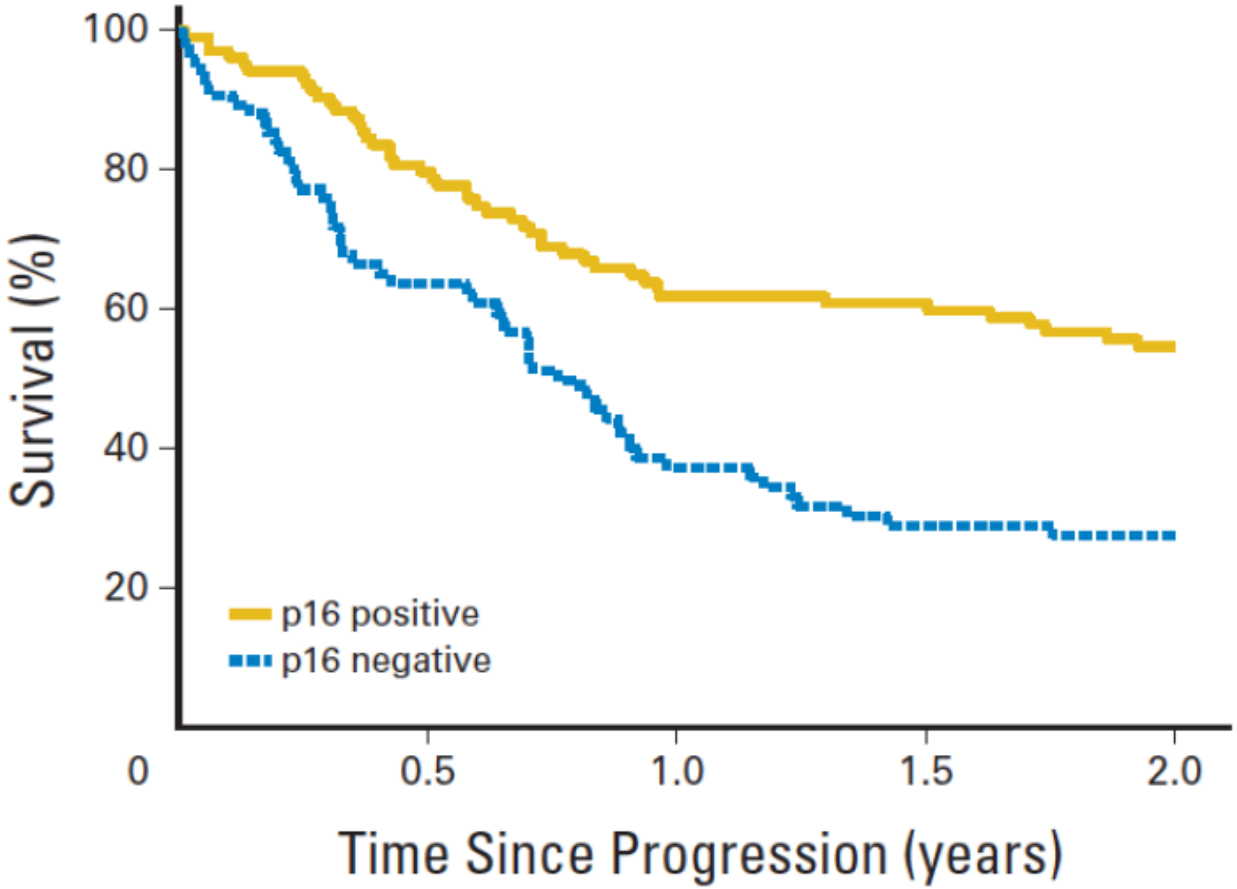
HPV und p16





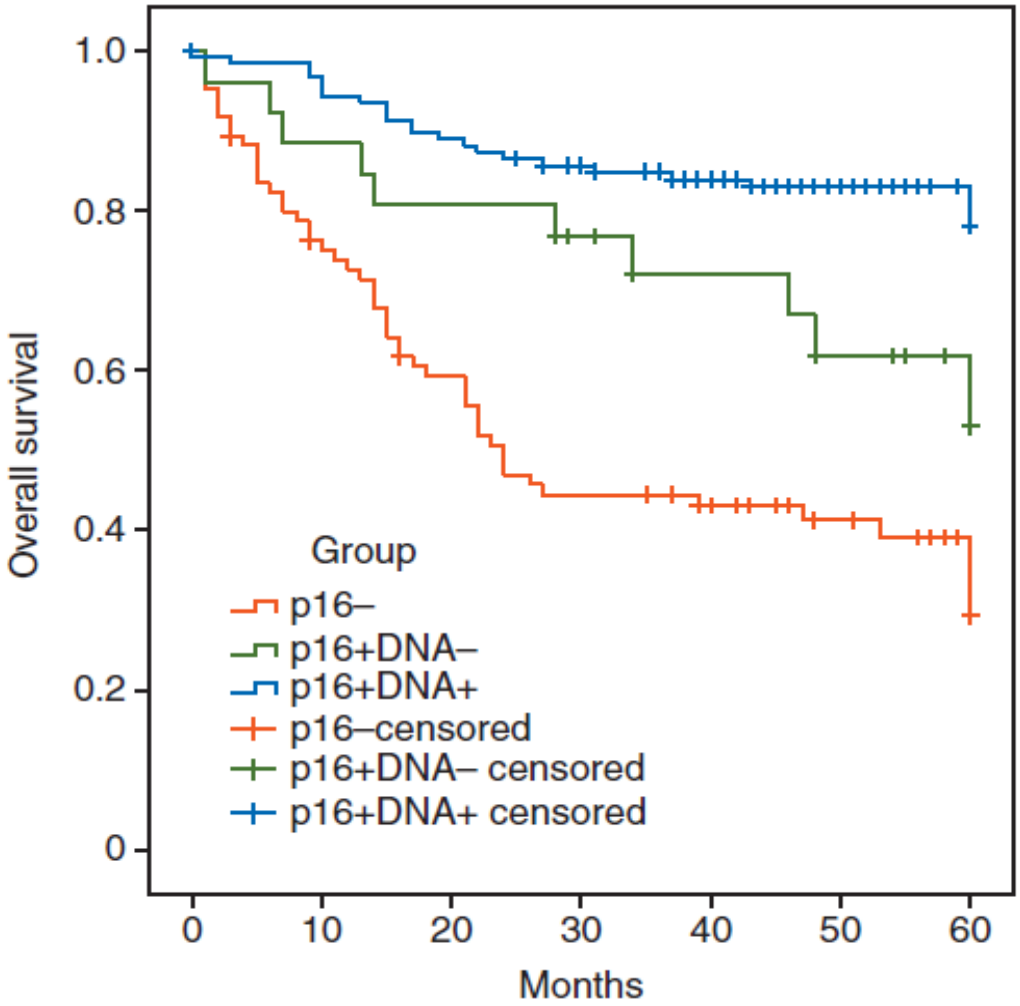
Amir et al.; Seminars in Cancer Biology 2015

p16 und Prognose



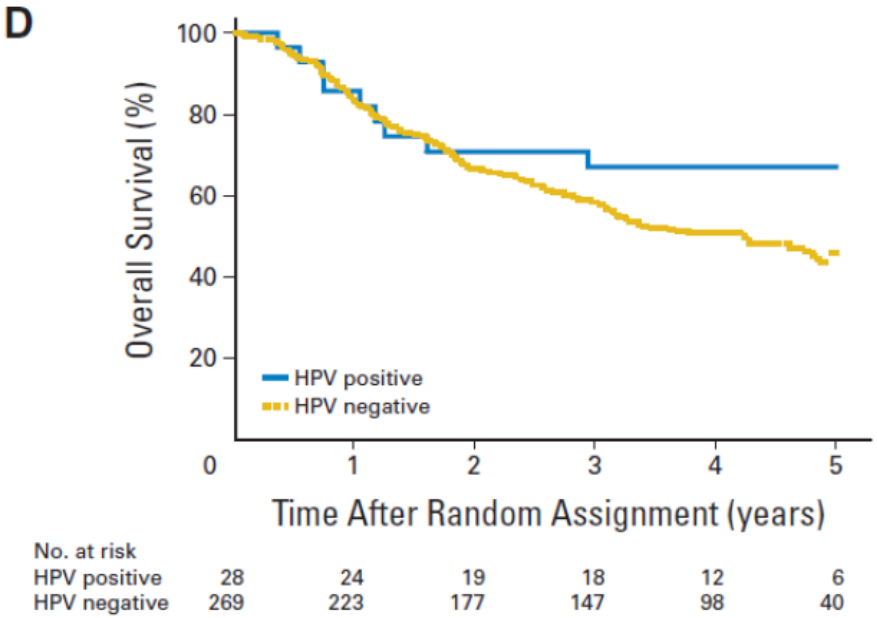
Fakhry et al.; JCO 2015

HPV und p16 Diskonkordanz



Sathasivam et al.; Annals of Oncology 2018

Prognose in HPV+ non-OPC



NA *in situ* hybridization (%)	
Negative	71 (97.3)
Positive	2 (2.8)
HPV type 16	2
Other HPV types	0
NA *in situ* hybridization (%)	
Negative	70 (97.2)
Positive	2 (2.8)

Chung et al.; JCO 2016; Lewis et al.; Histopahtology 2011

P16 Testung in allen OPC

JOURNAL OF CLINICAL ONCOLOGY

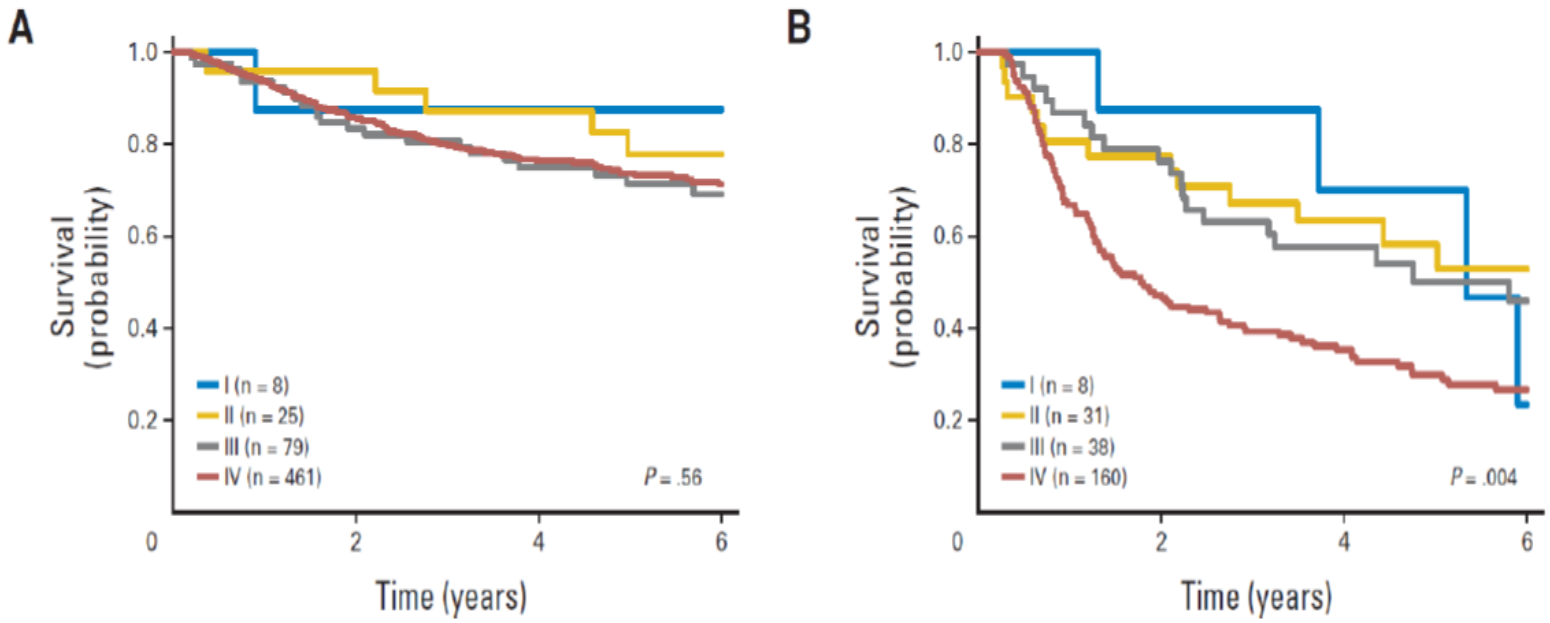
ASCO SPECIAL ARTICLE

Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists Guideline

Carole Fakhry, Christina Lacchetti, Lisa M. Rooper, Richard C. Jordan, Danny Rischin, Erich M. Sturgis, Diana Bell, Mark W. Lingen, Seema Harichand-Herdt, John Thibo, Jose Zevallos, and Bayardo Perez-Ordonez

Should patients with newly diagnosed OPSCC be routinely tested for HR-HPV?	**Recommendation 1**: Pathologists should perform HR-HPV testing on all patients with newly diagnosed OPSCC, including all histologic subtypes. This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary.	The ASCO Endorsement Panel reinforces the need to determine HPV tumor status in newly diagnosed OPSCC.	Convincing

Altes Staging System



Huang et al.; JCO 2015

Neues Staging System

Prognostic stage groups – Clinical

P16 positive OPC

When T is…	And N is…	And M is…	Then the stage group is…
T0, T1 or T2	N0 or N1	M0	I
T0, T1 or T2	N2	M0	II
T3	N0, N1 or N2	M0	II
T0, T1, T2, T3 or T4	N3	M0	III
T4	N0, N1, N2 or N3	M0	III
Any T	Any N	M1	IV

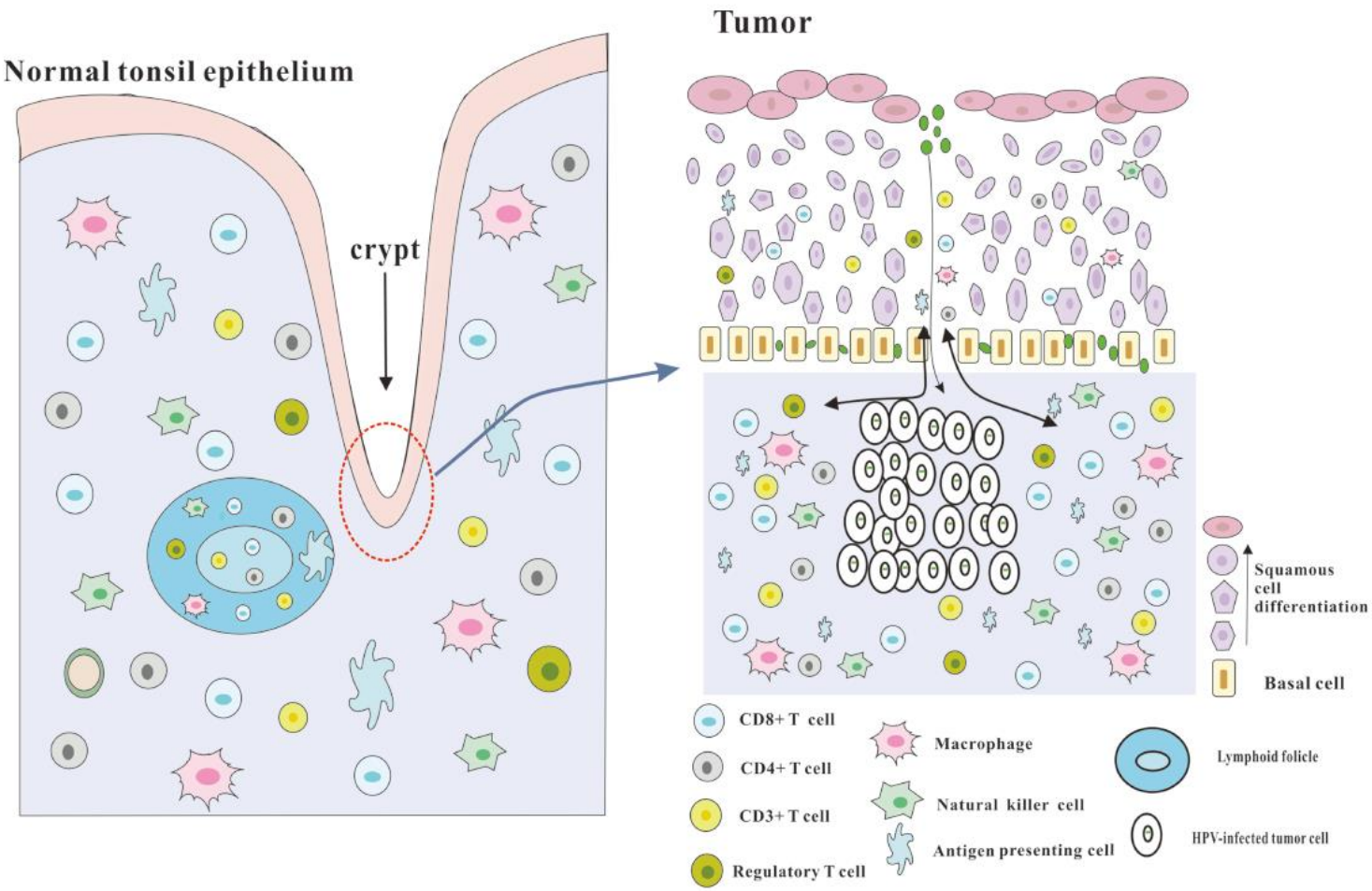
Prognostic stage groups – Clinical

P16 negative HNC

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	No	M0	II
T3	No	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

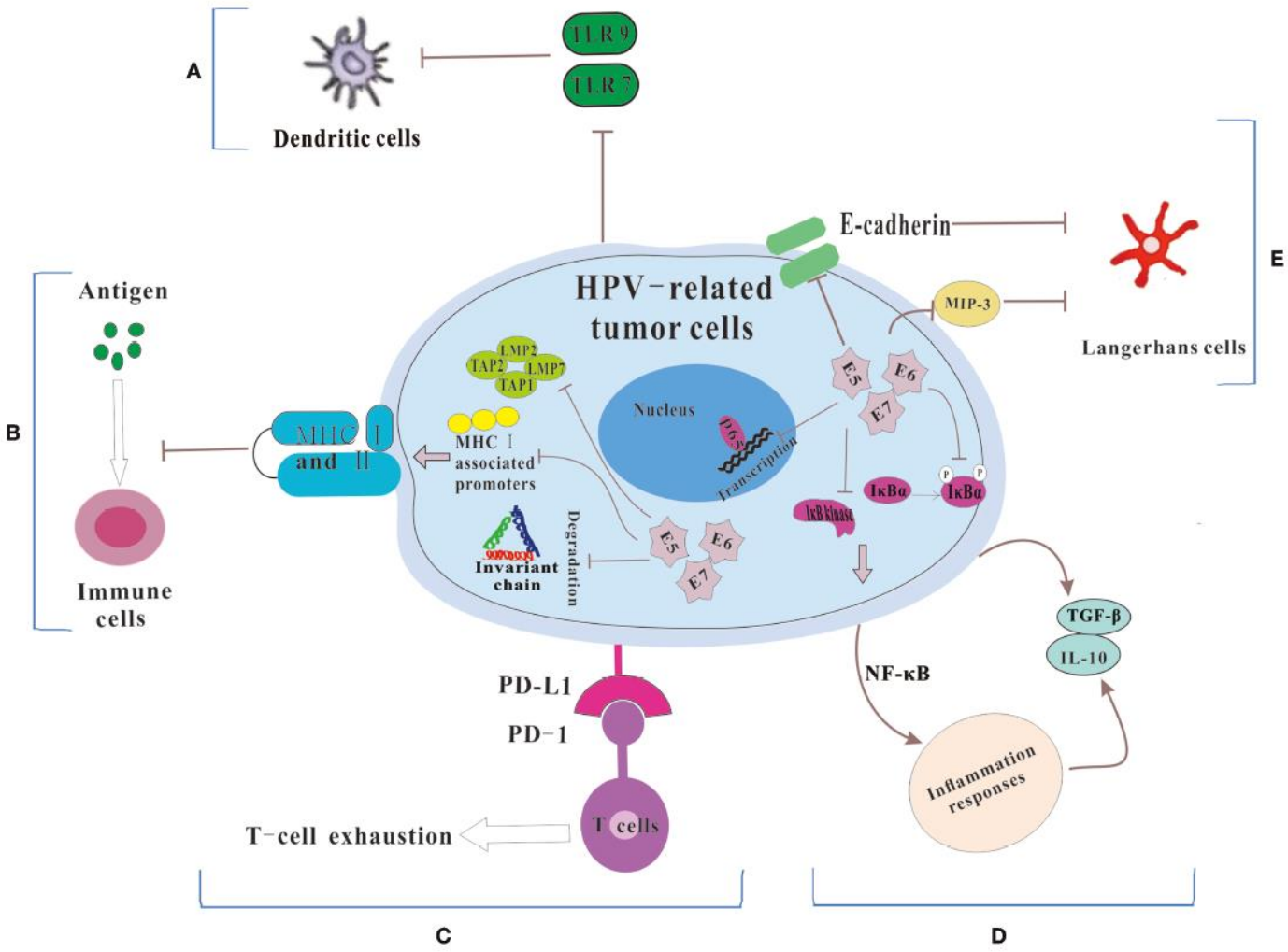
TNM Staging UICC 2017

HPV und Immunsystem



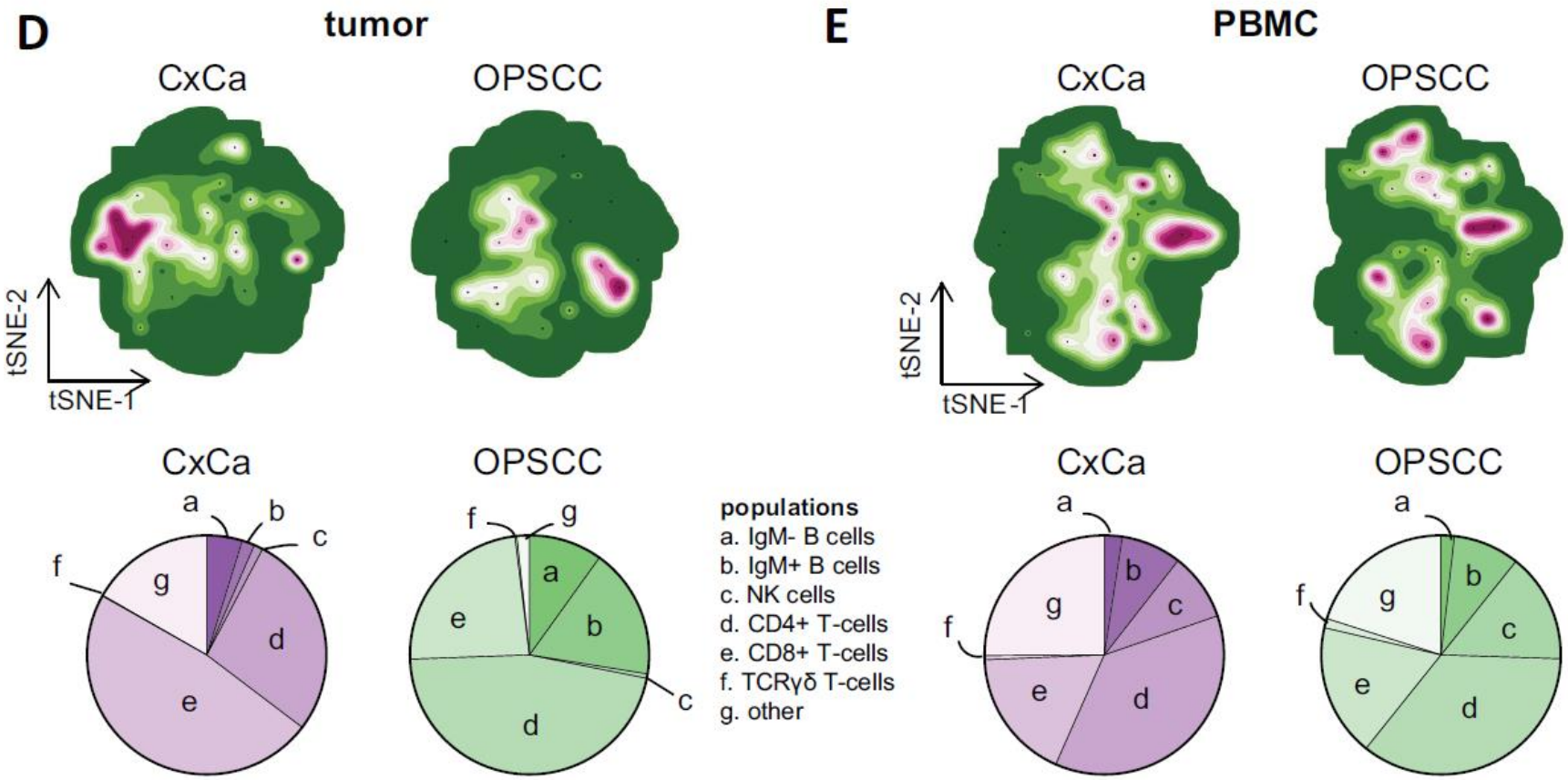
Wang et al.; Frontiers in Immunology 2019

HPV und Immunsystem



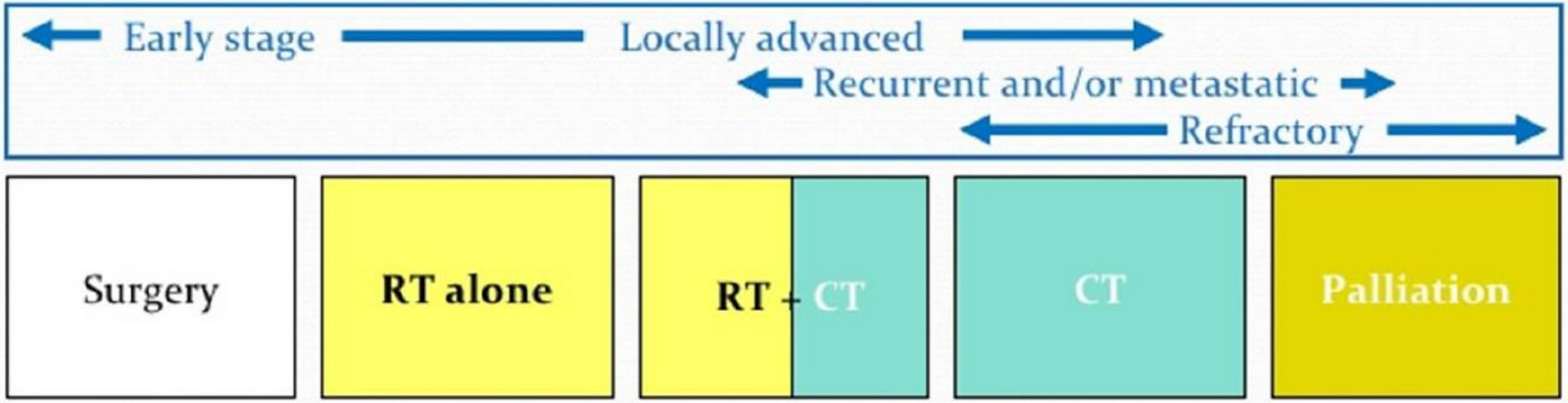
Wang et al.; Frontiers in Immunology 2019

HPV und Immunsystem: KHT vs. Zervixkarzinom



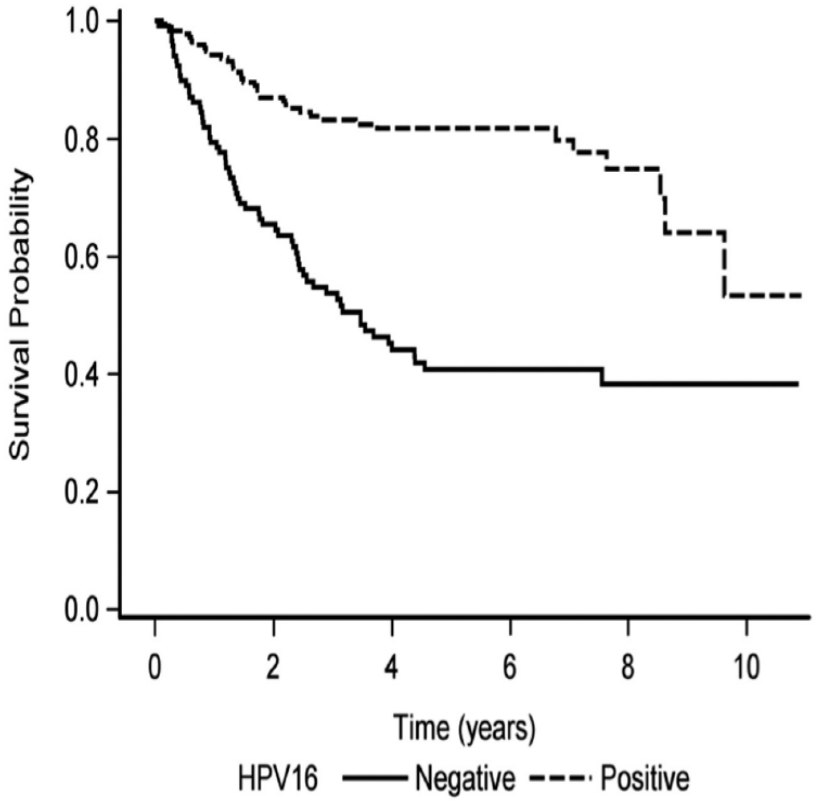
Santegoets et al.; CCR 2018

Therapie HPV positive OPC



Vermorken et al.; Annals of Oncology 2010

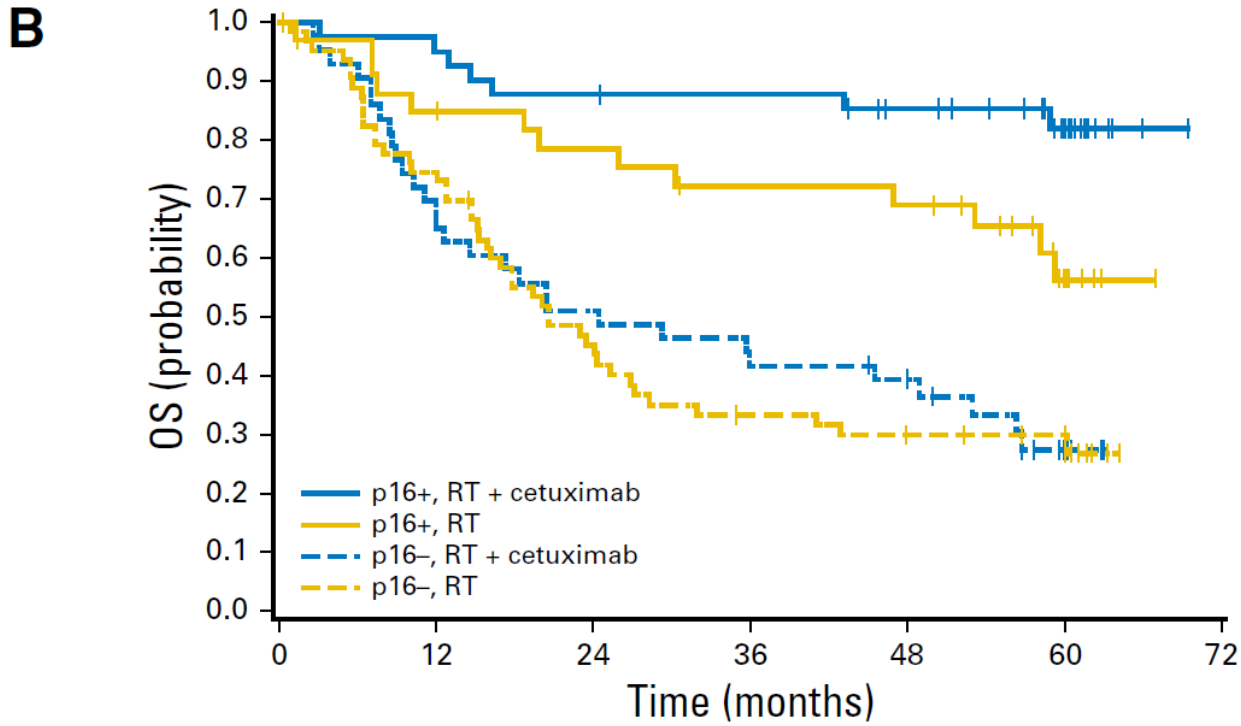
Therapie HPV positive OPC: OP



	Survival Rates			
	1 year (%)	3 year (%)	5 year (%)	10 year (%)
Overall	88.5	71.3	65.1	52.2
HPV Negative	79.5	53.3	40.3	37.9
HPV Positive	94.2	83.3	81.8	58.3

Kumar et al.; Head and Neck 2015

Therapie HPV positive OPC: RT v. RIT

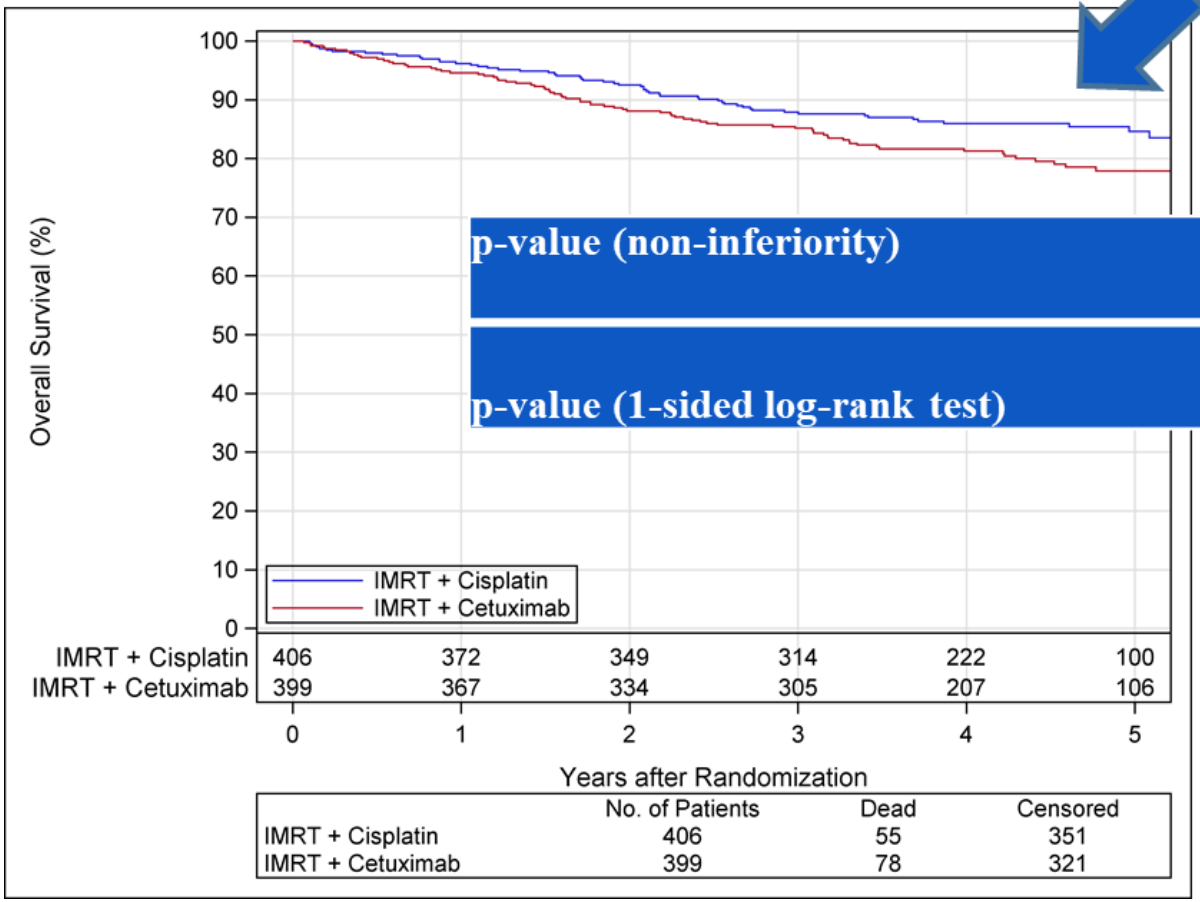


No. of patients at risk

p16+, RT + cetuximab	41	39	36	35	31	17	0
p16+, RT	34	28	25	22	21	10	0
p16–, RT + cetuximab	43	29	22	18	15	6	0
p16–, RT	64	47	27	19	16	13	0

Bonner et al.; JCO 2016

Deeskalation möglich?



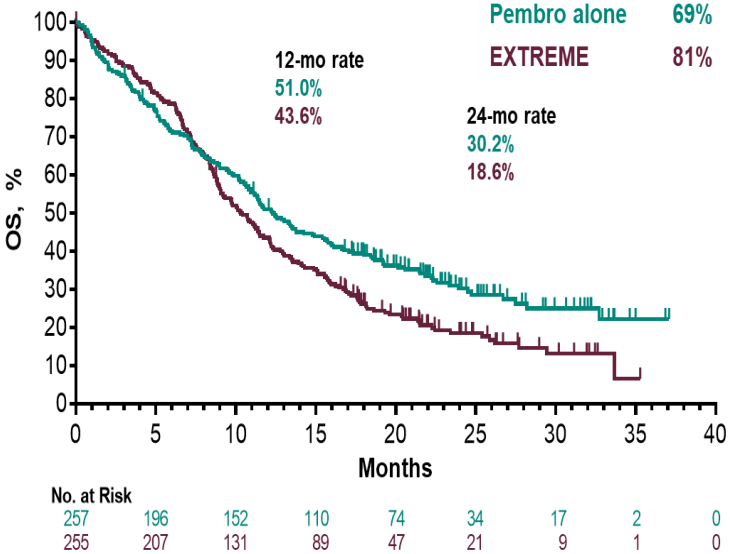
Cisplatin

85 vs 78% 5-yr

p-value (non-inferiority)	0.51
p-value (1-sided log-rank test)	0.02

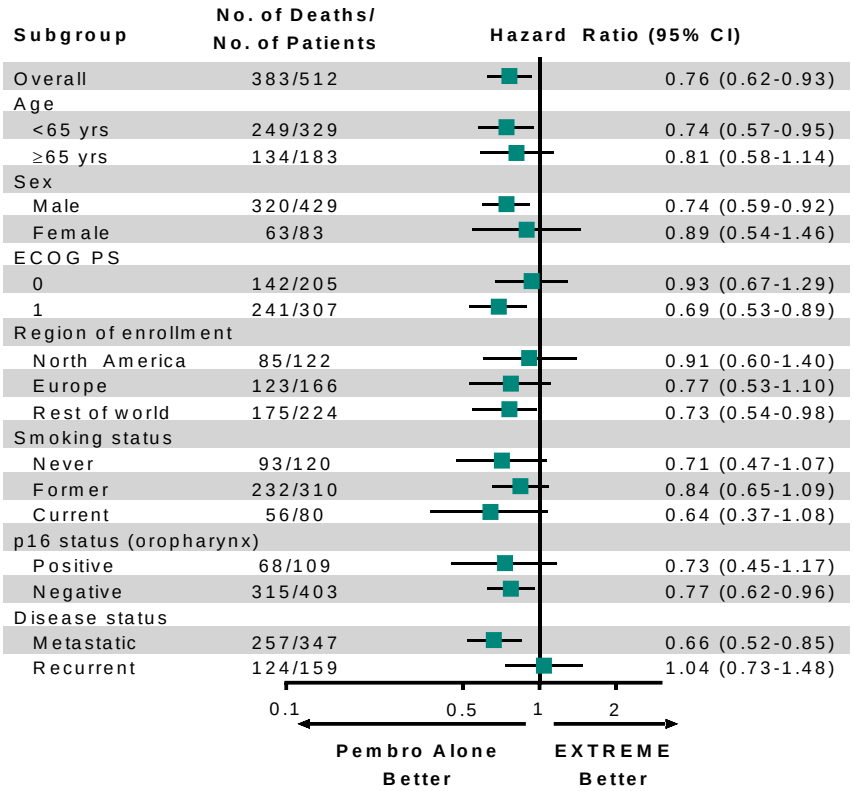
Trotti et al.; ASTRO 2018

Rezidivierte/metastasierte KHT: Keynote 048



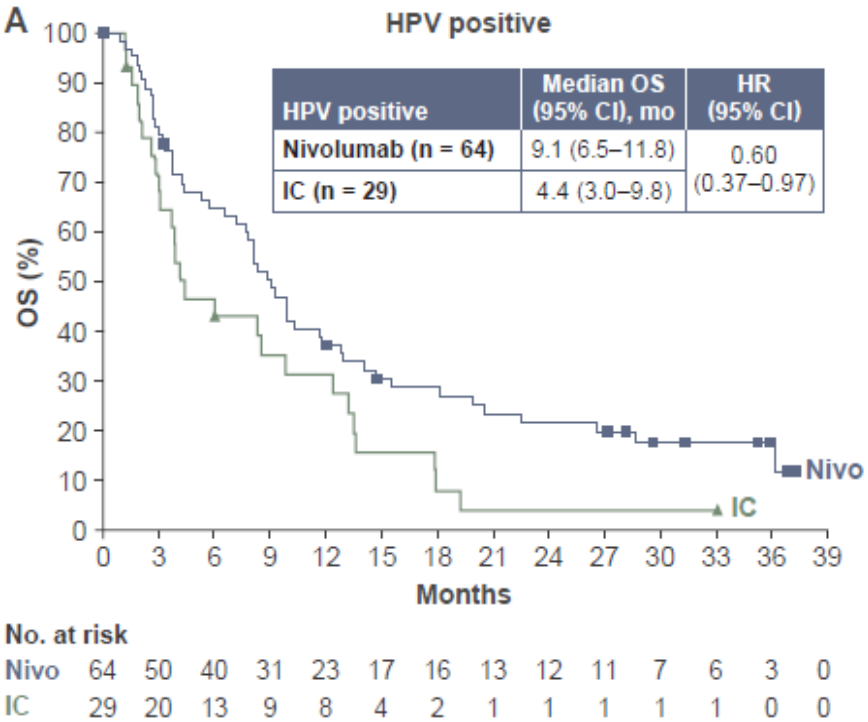
	Events	HR (95% CI)	*P*
Pembro alone	69%	0.78 (0.64-0.96)	0.0086
EXTREME	81%		

Median (95% CI)
12.3 mo (10.8-14.9)
10.3 mo (9.0-11.5)

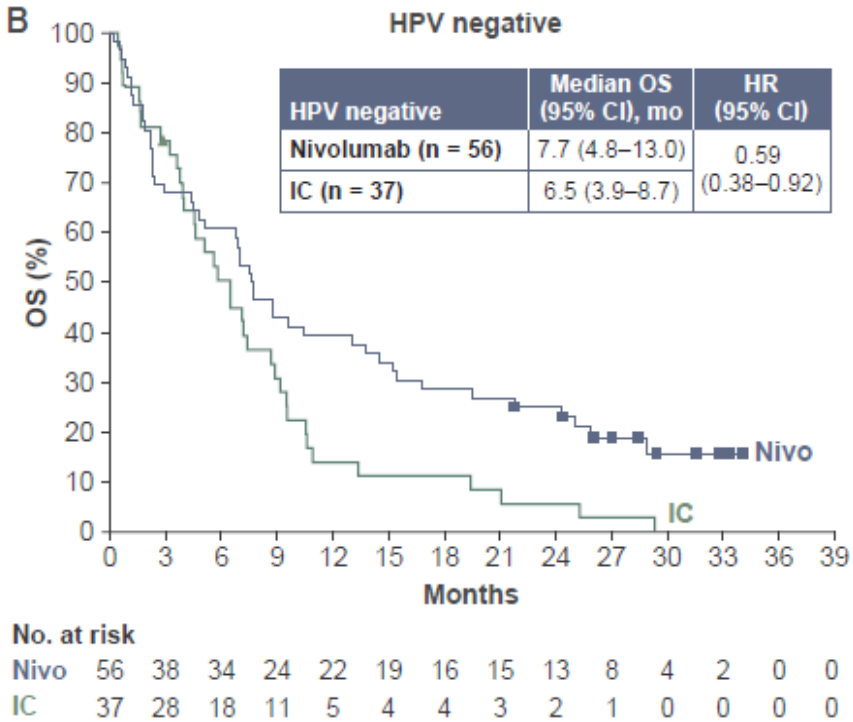


Burtness et al; ICHNO 2019

Rezidivierte/metastasierte KHT: Checkmate 141



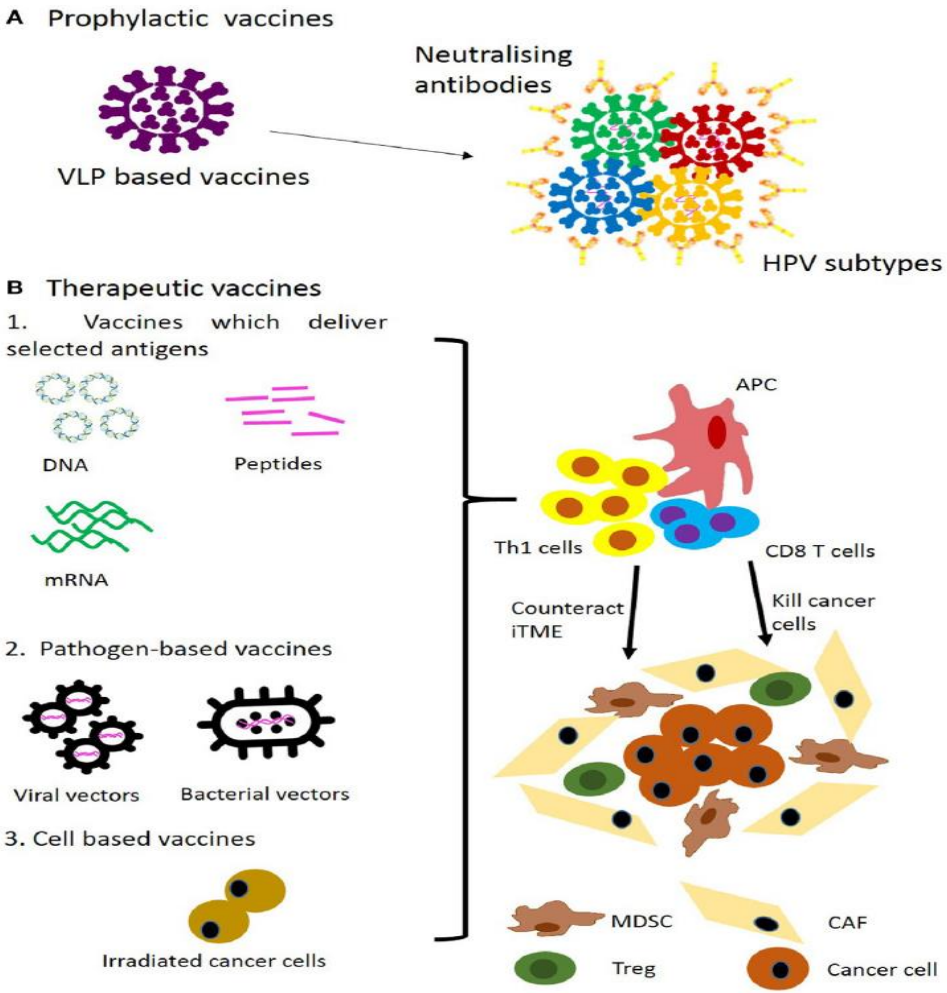
HPV positive	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 64)	9.1 (6.5–11.8)	0.60 (0.37–0.97)
IC (n = 29)	4.4 (3.0–9.8)	



HPV negative	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 56)	7.7 (4.8–13.0)	0.59 (0.38–0.92)
IC (n = 37)	6.5 (3.9–8.7)	

Ferris et al.; Oral Oncology 2018

Impfungen: Die Zukunft?



Wang et al.; Frontiers in Immunology 2018

Kein PAP Abstrich bei OPC

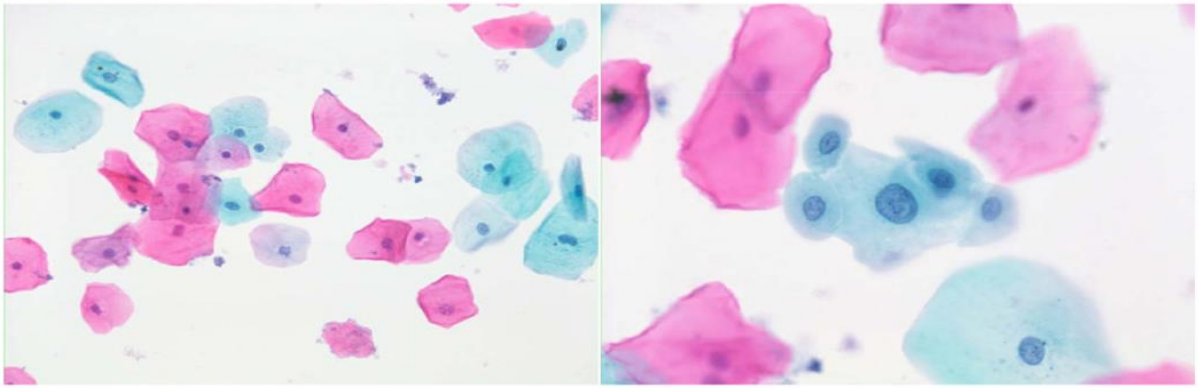
Associations between oral HPV16 infection and cytopathology: evaluation of an oropharyngeal "Pap-test equivalent" in high-risk populations

Carole Fakhry, MD, MPH[1], **Barbara T. Rosenthal, BA, CT**[2], **Douglas P. Clark, MD**[2], and **Maura L. Gillison, MD, PhD**[3,*]

[1]Johns Hopkins Medicine Department of Otolaryngology-Head and Neck Surgery

[2]Johns Hopkins Medicine Department of Pathology

[3]Ohio State University, James Comprehensive Cancer Center



Fakhry et al.; Cancer Prevention Research 2011

HPV im Speichel

HPV Type	No. (%) of Specimens		Agreement (n = 171)[a]	
	Oral Gargle Sample (n = 203)	Tumor Specimen (n = 172)	No.	% (95% CI)
HPV HR types[b]				
HPV 16	128 (63.1)	143 (83.1)	126	73.7 (66.4-80.1)
HPV 18	8 (3.9)	8 (4.7)	161	94.2 (89.5-97.2)
HPV 31	1 (0.5)	1 (0.6)	169	98.8 (95.8-99.9)
HPV 33	9 (4.4)	12 (7.0)	165	96.5 (92.5-98.7)
HPV 35	5 (2.5)	7 (4.1)	165	96.5 (92.5-98.7)
HPV 39	1 (0.5)	0	170	99.4 (96.8-100)
HPV 45	1 (0.5)	1 (0.6)	169	98.8 (95.8-99.9)
HPV 51	3 (1.5)	1 (0.6)	168	98.2 (95.0-99.6)
HPV 52	1 (0.5)	3 (1.7)	167	97.7 (94.1-99.4)
HPV 56	1 (0.5)	0	170	99.4 (96.8-100)
HPV 58	1 (0.5)	1 (0.6)	171	100
HPV 68	1 (0.5)	0	170	99.4 (96.8-100)

Gomez et al.; Jama Otolaryngology Head and Neck Surgery 2019

Übertragung durch Küssen?

Factor	Prevalance of HPV,[b] total no. (%)[c]	Univariate analysis OR (95% CI)[d]	Univariate analysis P[e]	Multivariate analysis[a] OR (95% CI)[d]	Multivariate analysis P[e]
People open-mouthed kissed, no.					
In lifetime			.083		.067
0–9	129 (0.8)	1.0		1.0	
≥10	81 (6.2)	8.4 (0.97–73.0)		9.5 (0.76–118.0)	
In past year			.037		.023
0–5	144 (0.7)	1.0		1.0	
≥6	66 (7.6)	11.7 (1.3–102.0)		17.4 (1.5–198.0)	
Vaginal sex partners, no.					

To further evaluate the independent effect of open-mouthed kissing, a subset analysis was performed for the 59 college-aged men who reported no history of performing oral sex. Among these men, oral HPV infection was significantly more common among those with ≥10 lifetime (25% vs. 0%; $P = .0002$) and those with ≥5 recent (17% vs. 0%; $P = .003$) open-mouthed kissing partners.

HSV-2 antibodies					
No	199 (3.0)	1.00		1.00	
Yes	11 (0.0)	…		…	

D'Souza et al.; J.Infectious Dis. 2009

HPV Infektion beim Partner?

Oral HPV-infection in partners of patients with cervical, oropharyngeal or anal dysplasia/carcinoma.

Reference	No. partners	Sampling method	HPV testing method	Oral HR-HPV infection rate
Partners of cervical dysplasia/carcinoma patients				
Uken et al. [53]	60	Brushing	PCR	3/60 (5%)
Tatar et al. [54]	34	Oral rinse	PCR	6/34 (17%)[a]
Marques et al. [55]	22	Brushing	PCR	3/22 (13.6%)
Partners of oropharyngeal cancer patients				
D'Souza et al. [57]	93	Oral rinse	PCR	2/93 (2.1%)
Tsao et al. [56]	128	Brushing	PCR	17/128 (13.3%)
Partners of anal dysplasia/carcinoma patients				
Prendes et al. [72][b]	66	Oral rinse	PCR	7 (11%)

[a] 3 infections were related to HR-HPV, 1 to LR-HPV and 2 were not genotyped.
[b] The study cohort included 49 HIV-positive patients.

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Zusammenfassung

- **Inzidenz von HPV pos. Oropharynxkarzinomen steigend**
- **OPC Tumore haben bessere Prognose**
- **Studien zur Optimierung der Therapie laufen (Vakzinierung?)**