13ème Biennale Monégasque de Cancérologie
31 Janvier - 3 Février 2018
GRIMALDI FORUM - MONACO

Session cancer des VADS

31 janvier 2018

Présidents : Y. Pointreau, J. Bourhis

Sous l'égide du GORTEC

Désescalade thérapeutique dans les cancers HPV

P. Boisselier

ICM Montpellier

Disclosures – Conflits d'intérêts

Consultant / Ad Board

AstraZeneca, Boehringer Ingelheim,
Lilly , Merck, MSD, Roche

DEFLATION THERAPEUTIQUE en ORL

Idée ancienne

But : **réduire le poids des traitements**

- en **chirurgie** :
  - curages sélectifs et plus récemment la technique du GS : limiter l'étendue des curages.
  - chirurgie laryngée au laser par voie endoscopique : volonté conservatrice.
- en **radiothérapie**:
  - RCMI / épargne des tissus sains
  - diminution de la dose
  - diminution (et adaptation …) des volumes
  - curiethérapie interstitielle
- en **chimiothérapie**:
  - protocoles ambulatoires: platine fractionné
  - soins oncologiques de support

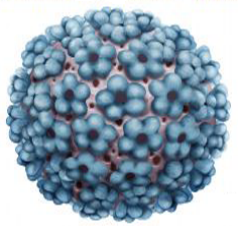
⇨ **Adénopathies primitives**

- hier: RT étendue
- aujourd'hui, après bilan exhaustif (TEP, IRM et biopsies): RT focalisée

⇨ **Stratégie de préservation laryngé**

HUMAN PAPILLOMAVIRUS INFECTION AS A RISK FACTOR FOR SQUAMOUS-CELL CARCINOMA OF THE HEAD AND NECK

JON MORK, M.D., A. KATHRINE LIE, M.D., EYSTEIN GLATTRE, M.D., GÖRAN HALLMANS, M.D., EGIL JELLUM, PH.D., PENTTI KOSKELA, PH.D., BJØRN MØLLER, M.SC., EERO PUKKALA, PH.D., JOHN T. SCHILLER, PH.D., LINDA YOUNGMAN, PH.D., MATTI LEHTINEN, M.D., AND JOAKIM DILLNER, M.D.



Matériel et méthode:

Sérums de 900.000 sujets prospectivement collectés puis conservés.

292 pts développent un cancer des VADS (26 COP) en moyenne 9.4 ans après le prlvt.

Sérologies comparées à 1568 témoins appariés.

Résultats:

Séropositivité HPV-16 augmente le risque de cancer

x 14.4	pour **COP**	(95% CI 3.6-58.1)
x 2.7	pour **base de langue**	(95% CI 2.7- 6.6)
x 2.2	pour VADS global	(95% CI 1.4-3.4)

Aucun risque accru observé / autres types de HPV.

ADN HPV-16 retrouvé en analyse en PCR dans :

50% des **COP**

14% des **cancers de langue**

Conclusion:

L'infection HPV-16 peut être un facteur de risque pour les carcinomes épidermoïdes des VADS.

La nature séquentielle de cette étude (exposition survenue des années avant le diagnostic de cancer) a permis d'établir un lien de causalité fort entre exposition à HPV16 et COP.

Mork NEJM 2001

TABLE 4. ODDS RATIOS FOR HEAD AND NECK CANCER ASSOCIATED WITH SEROPOSITIVITY FOR HUMAN PAPILLOMAVIRUS TYPE 16 (HPV-16), ACCORDING TO ANATOMICAL SITE, IN COMPARISON WITH THE PREVALENCE OF VIRAL DNA IN TUMOR TISSUE.*

SITE†	SEROPOSITIVE PATIENTS	SEROPOSITIVE CONTROLS	CRUDE ODDS RATIO (95% CI)	ADJUSTED ODDS RATIO (95% CI)‡	PATIENTS POSITIVE FOR HPV-16 DNA§
	no./total no. (%)				no./total no. (%)
Lips (code 140)	2/57 (4)	21/307 (7)	0.5 (0.1–2.4)	0.5 (0.1–2.1)	0/32 (0)
Tongue (code 141)	9/57 (16)	22/302 (7)	2.7 (1.2–6.4)	2.8 (1.2–6.6)	4/29 (14)
Floor of mouth (code 143)	0/23 (0)	15/125 (12)	—	—	0/15 (0)
Oral cavity, not otherwise specified (code 144)	2/19 (11)	2/104 (2)	5.4 (0.8–38.8)	3.6 (0.5–26.3)	0/15 (0)
Oropharynx (code 145)	10/26 (38)	14/137 (10)	8.6 (2.6–28.5)	14.4 (3.6–58.1)	9/18 (50)
Nasopharynx (code 146)	0/10 (0)	2/60 (3)	—	—	1/7 (14)
Hypopharynx (code 147)	0/16 (0)	3/81 (4)	—	—	0/8 (0)
Nose and paranasal sinuses (code 160)	2/7 (29)	3/36 (8)	3.5 (0.6–20.7)	3.4 (0.6–20.8)	0/4 (0)
Larynx (code 161)	9/76 (12)	20/411 (5)	2.5 (1.1–5.8)	2.4 (1.0–5.6)	1/32 (3)
All sites	35/292 (12)	102/1568 (7)	2.1 (1.4–3.2)	2.1 (1.4–3.2)¶	15/160 (9)

*CI denotes confidence interval.

†The numbers in parentheses refer to the codes of the *International Classification of Diseases, Seventh Revision*.[15] Site 148 (pharynx, not otherwise specified) was the location of only one cancer and is not listed.

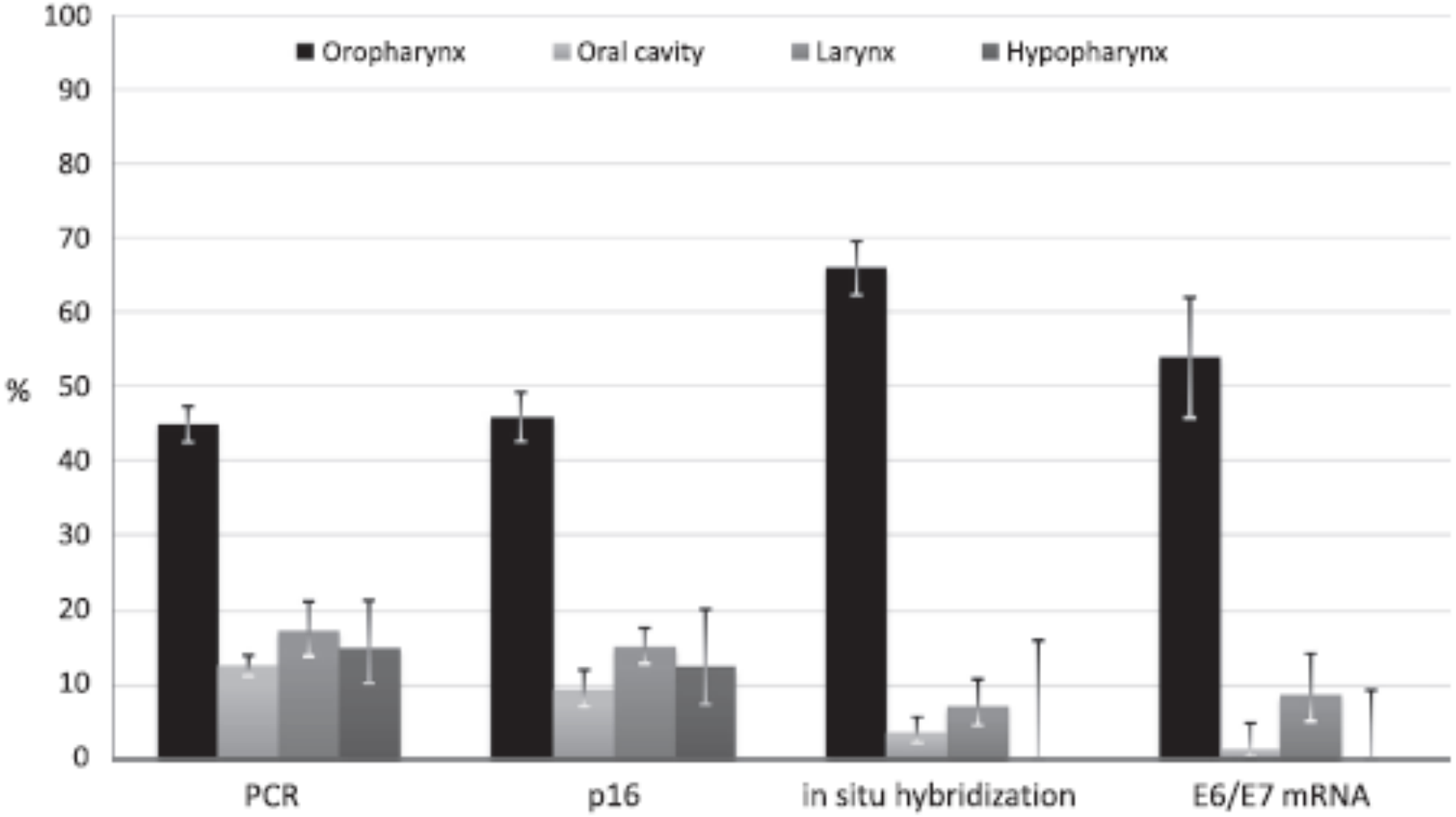
‡The odds ratios were adjusted for two levels of cotinine (nonsmoker, <20.00 ng per milliliter; smoker, ≥20.00 ng per milliliter).

§Tumor tissue was taken from 160 patients.

¶The difference between this estimate and the one given in Table 2 (2.1 vs. 2.2) is a consequence of the use of two as compared with three levels of cotinine in the adjustment procedure.

Mork NEJM 2001

HPV hors Oropharynx



Prevalence of HPV molecular markers and 95% confidence intervals by head and neck cancer site

Combes Oral Oncology 2014

- **Désescalade thérapeutique dans les cancers HPV**
- **Déflation thérapeutique dans les cancers oropharyngés HPV(+)**
- **Standards thérapeutiques dans les cancers oropharyngés HPV(+)?**

NCCN National Comprehensive Cancer Network®

Version 2.2017 — May 8, 2017

NCCN Guidelines Version 2.2017
Cancer of the Oropharynx

NCCN Guidelines Index
Table of Contents
Discussion

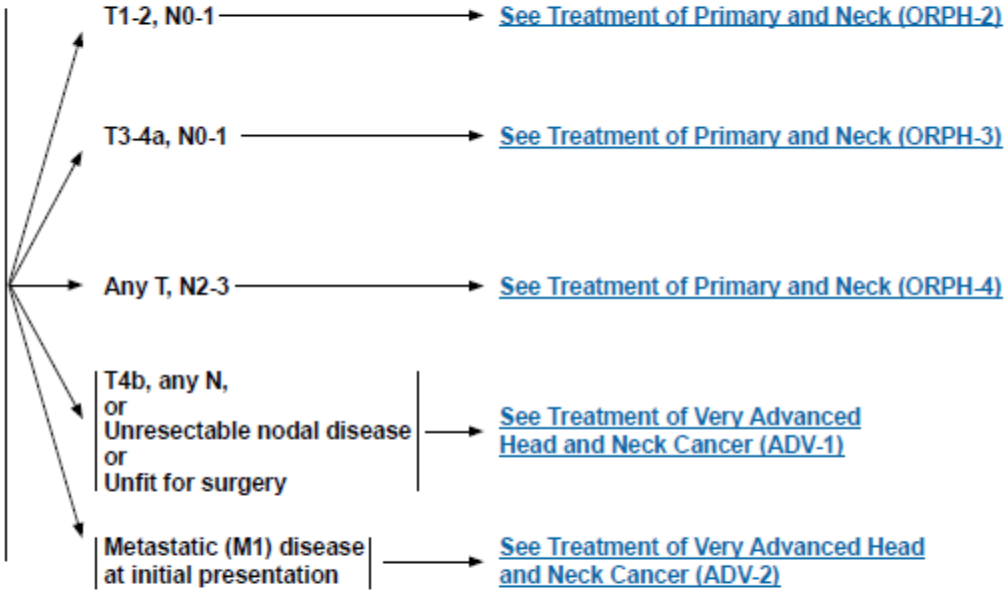
Base of tongue/tonsil/posterior pharyngeal wall/soft palate

WORKUP

- H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy of primary site or fine-needle aspiration (FNA) of the neck
- Tumor human papillomavirus (HPV) testing recommended[c]
- Chest CT[d] (with or without contrast) as clinically indicated
- CT with contrast and/or MRI with contrast of primary and neck
- Consider FDG-PET/CT for stage III-IV disease
- Dental evaluation,[e] including panorex as clinically indicated
- Nutrition, speech and swallowing evaluation/ therapy, and audiogram as clinically indicated[f]
- EUA with endoscopy as clinically indicated
- Pre-anesthesia studies

Multidisciplinary consultation as clinically indicated

CLINICAL STAGING



[a]H&P should include documentation and quantification (pack years smoked) of tobacco use history. Smoking cessation counseling as clinically indicated. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.

[b]Screen for depression (See NCCN Guidelines for Distress Management).

[c]P16 expression is highly correlated with HPV status and is widely available. HPV in situ hybridization or PCR-based assay is also available. Although not used to guide treatment, HPV testing is valuable prognostically. The results of HPV testing should not change management decisions except in the context of a clinical trial.

[d]Chest CT is recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer. See NCCN Guidelines for Lung Cancer Screening.

[e]See Principles of Dental Evaluation and Management (DENT-A).

[f]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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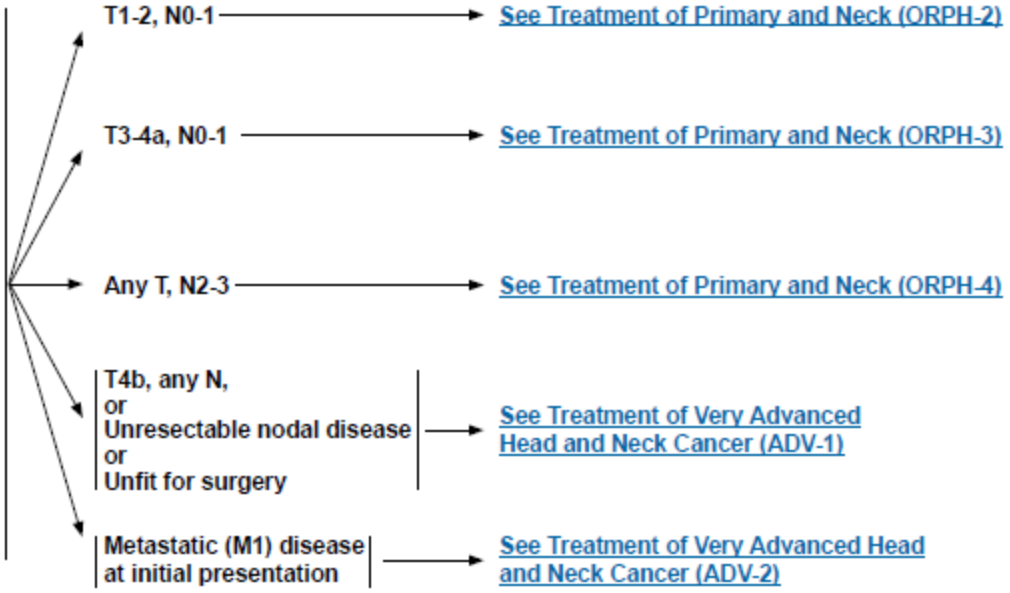

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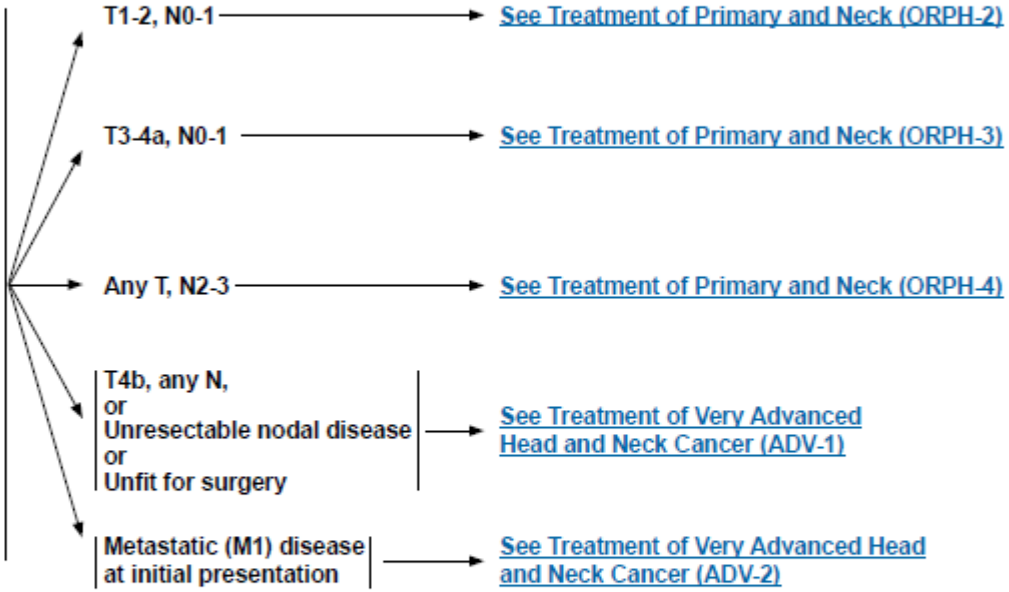

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Standards actuels en Radio Chimiothérapie

Radiothérapie (IMRT SIB):

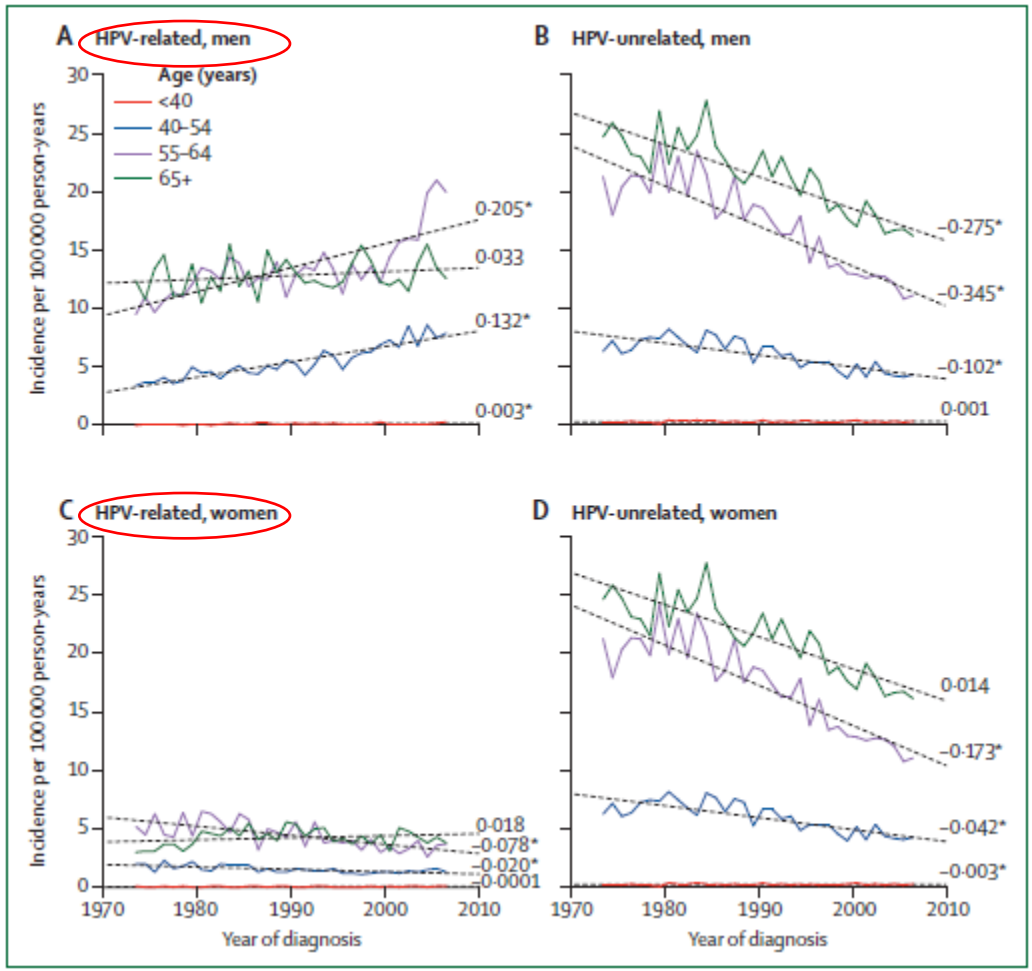
- Volume haut risque : 70 Gy en 35f
- Volume bas risque : 54-56 Gy en 35f (équivalent 50 Gy)

Chimiothérapie concomitante:

- Carboplatine & 5Fu S1 S4 S7 **(GORTEC 94-01)**
- Cisplatine 100 mg/m² J1 J22 J43 **(GORTEC 99-02)**
- Cetuximab 400 mg/m² puis 250 mg/m² en dose de charge J-7 hebdomadaire

Calais JNCI 1999
Denis JCO 2004
Adelstein, JCO 2003
Bernier NEJM 2005
Cooper NEJM 2005
Bonner NEJM 2006
Bourhis Lancet Oncol 2012

HPV-associated head and neck cancer: a virus-related cancer epidemic



Age-adjusted incidence of head and neck squamous cell cancers between 1973 and 2006, stratified by age at diagnosis

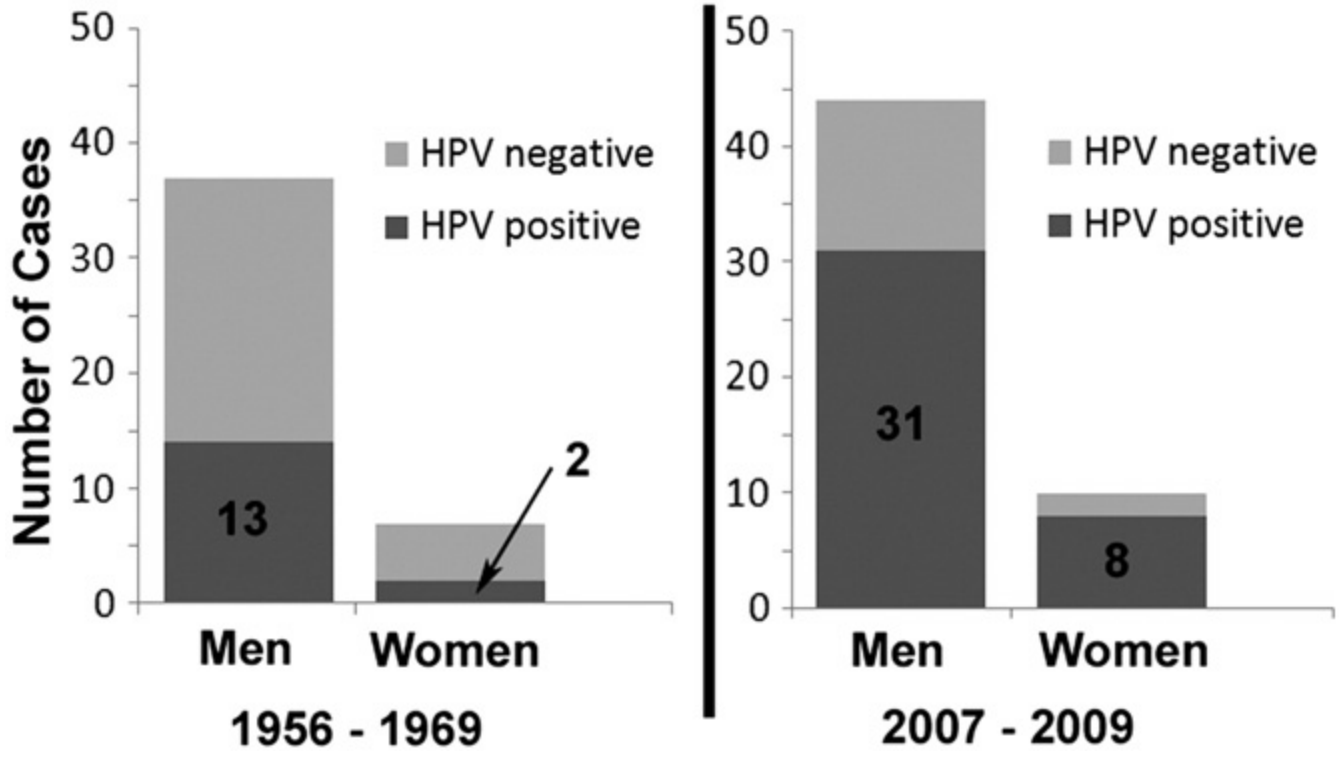
The annual percent change in incidence for every age category is shown next to every line. *Slope with $p<0{\cdot}05$.

HPV-related sites include base of tongue, lingual tonsil, tonsil, oropharynx, and Waldeyer ring.

HPV-unrelated sites include other and unspecifi ed areas of the tongue, gum, floor of mouth, palate, and other parts of the mouth

Marur Lancet Oncol 2010

Augmentation du nombre de cancers ORO HPV+ en 50 ans



x2 pour ♂
x4 pour ♀

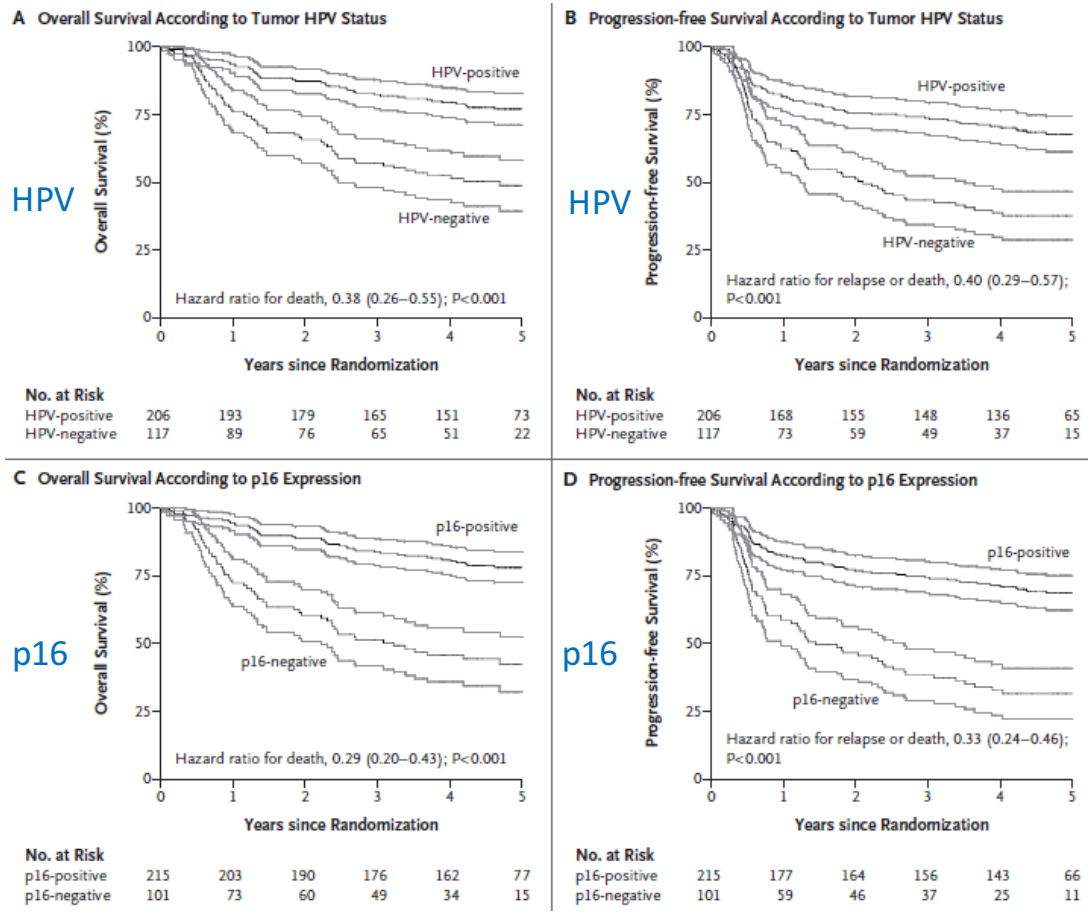
The increasing number of patients with HPV(+) OSCC, 1956 to 1969 versus 2007 to 2009. The increase is statistically significant in men (OR, 4.2; 95% CI, 1.65-10.79; P = .004).

Chevenert Human Pathology 2012

HPV (+) : Facteur de bon pronostic

Survie globale

Survie sans récidive



	hazard ratio (95% CI)	*P value*
Overall survival		
Treatment assignment (accelerated- vs. standard-fractionation radiotherapy)	1.24 (0.81–1.89)	0.32
Age (>50 yr vs. ≤50 yr)	1.62 (0.96–2.74)	0.07
Race (nonwhite vs. white)	1.57 (0.89–2.75)	0.12
Tumor stage (T4 vs. T2–T3)	2.15 (1.40–3.29)	<0.001
Nodal stage (N2b–N3 vs. N0–N2a)	1.99 (1.24–3.21)	0.005
Pack-years of smoking (per increase of 1 yr)	1.01 (1.00–1.02)	0.003
HPV status (positive vs. negative)	0.42 (0.27–0.66)	<0.001
HPV status (negative vs. positive)	2.38 (1.51–3.74)	<0.001

Hazard Ratios for Overall Survival.

Facteur pronostic indépendant

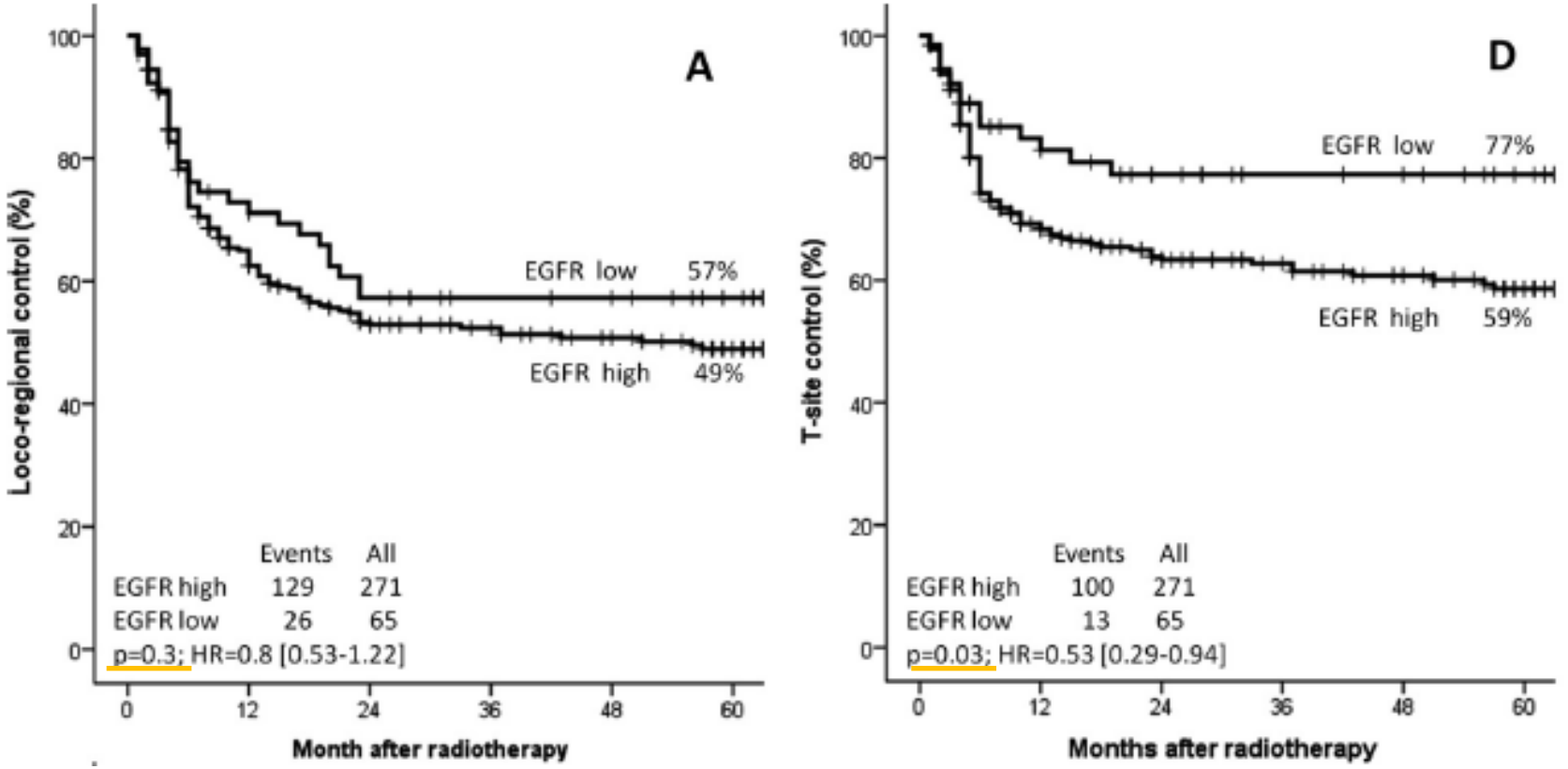
Kaplan–Meier Estimates of Survival among the Study Patients with Oropharyngeal Cancer, According to Tumor HPV Status or p16-Expression Status.

Analyse rétrospective du statut HPV RTOG 0129

Ang NEJM 2010

Expression of EGFR and HPV-associated p16 in oropharyngeal carcinoma: Correlation and influence on prognosis after radiotherapy in the randomized DAHANCA 5 and 7 trials

EGFR-expression

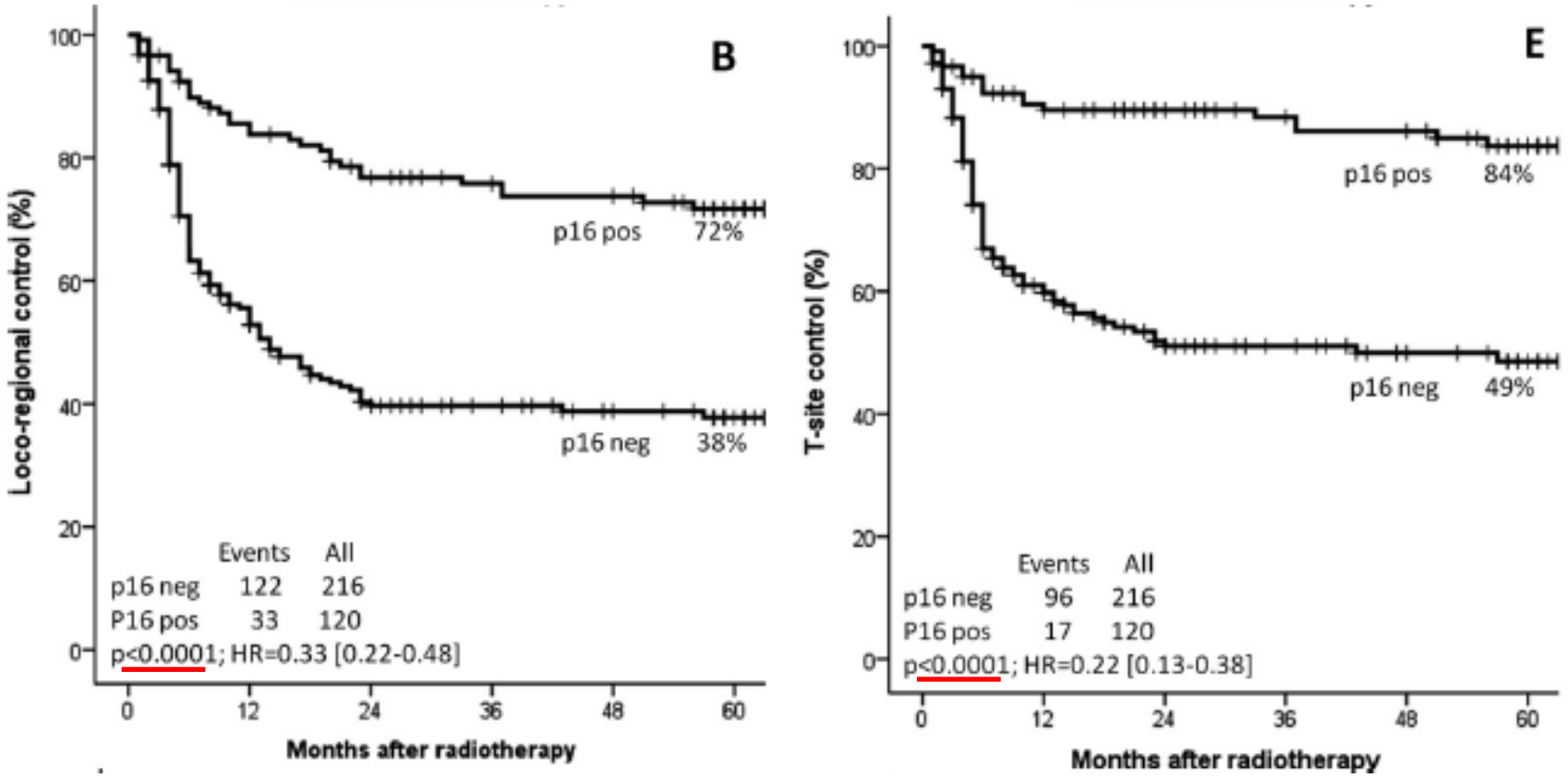


Loco-regional and T-site control by **EGFR-expression** (A and D), p16 status (B and E) and combined EGFR and p16 status (C and F). N = 336 oropharyngeal carcinoma.

Lassen Radiotherapy and Oncology 2013

Expression of EGFR and HPV-associated p16 in oropharyngeal carcinoma: Correlation and influence on prognosis after radiotherapy in the randomized DAHANCA 5 and 7 trials

16 status



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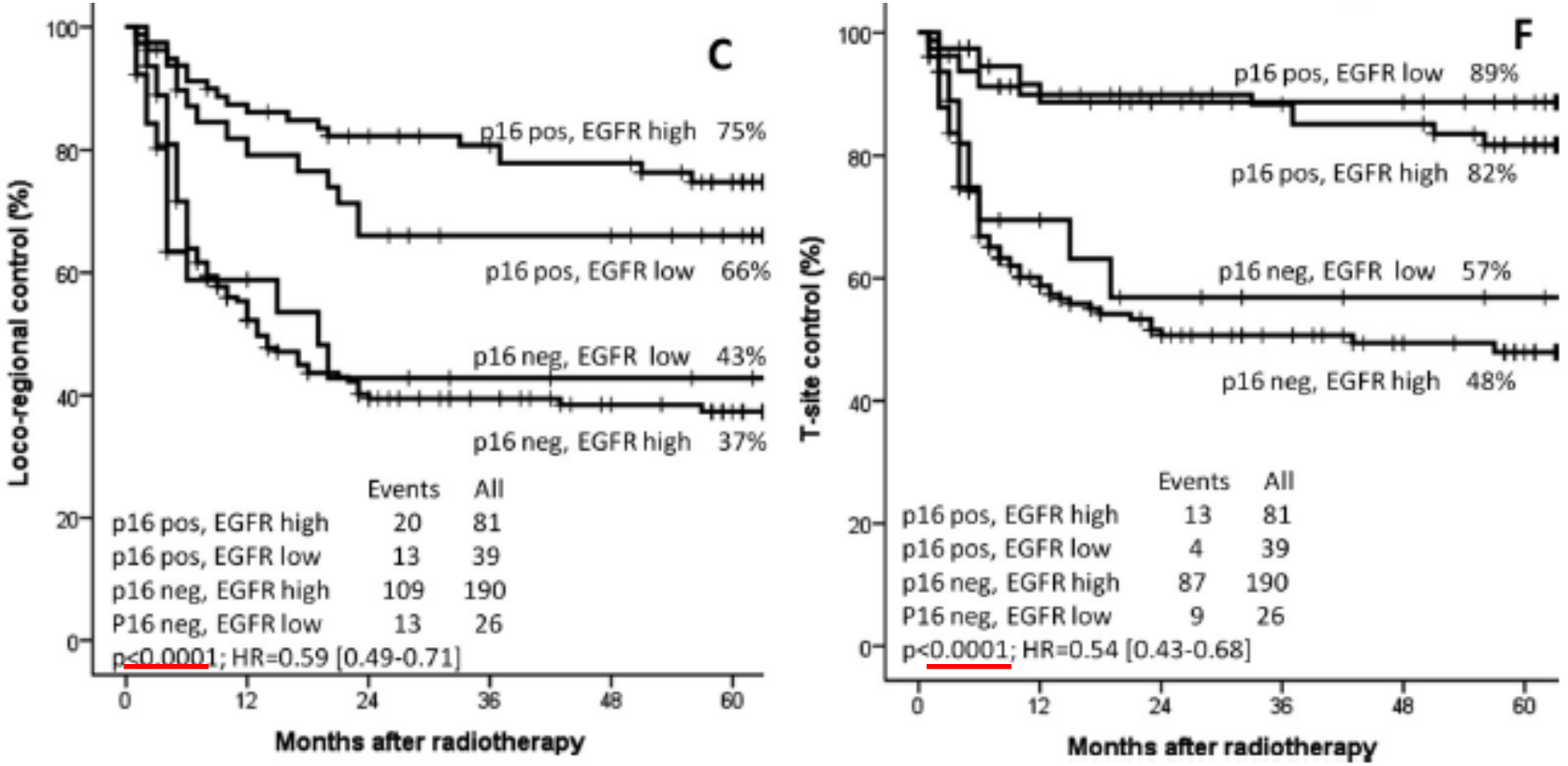
combined EGFR and p16 status



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Lassen Radiotherapy and Oncology 2013

Meta Analyse

Human papillomavirus related head and neck cancer survival: A systematic review and meta-analysis

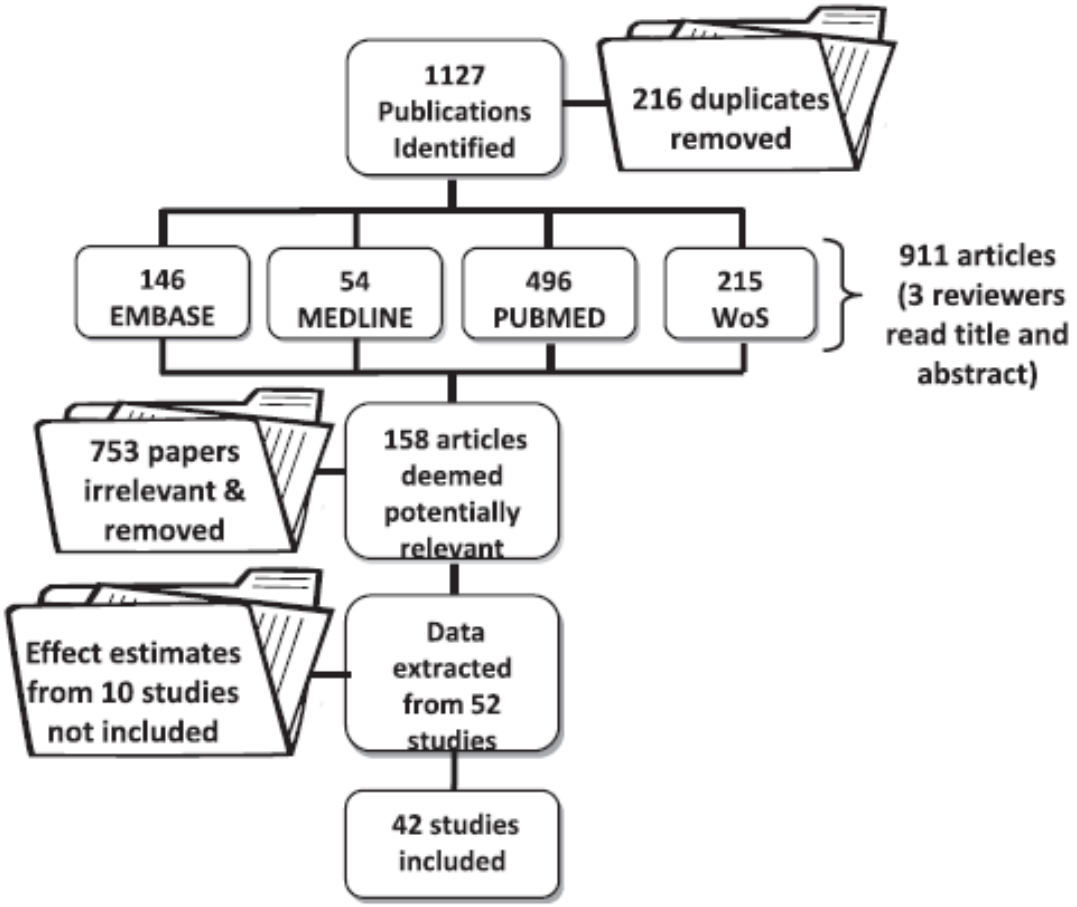
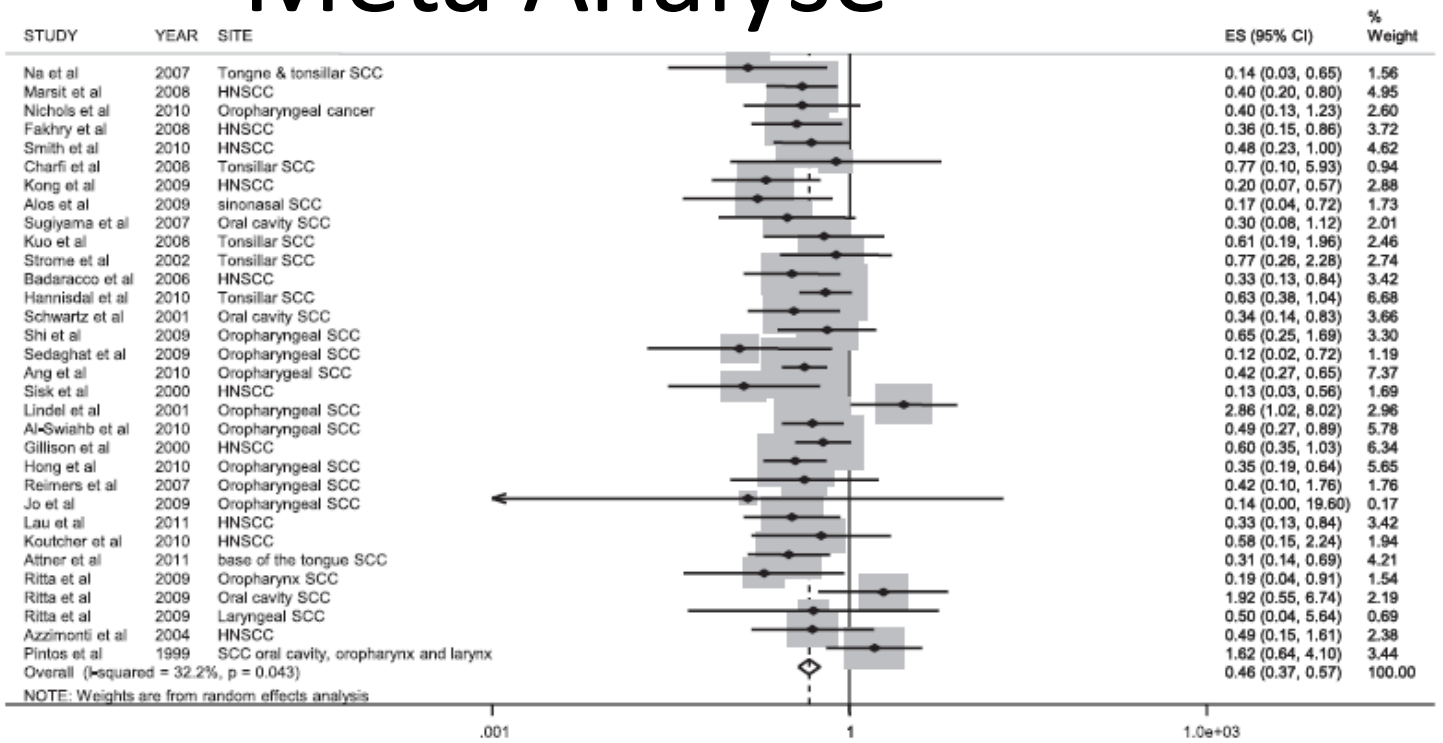


Figure 1 Flow diagram of the study selection process.

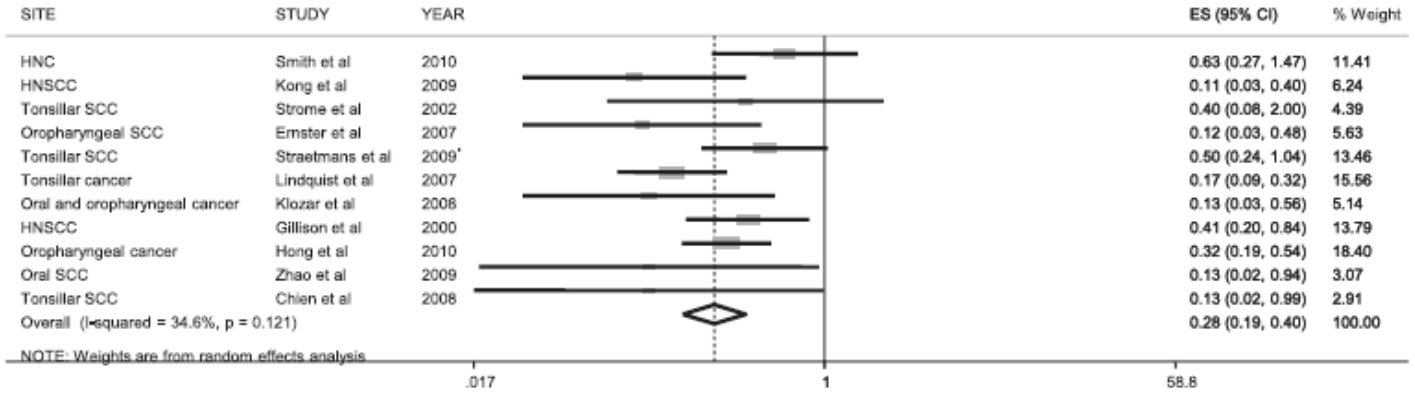
O'Rorke Oral Oncology 2012

Meta Analyse

overall survival



disease-specific survival

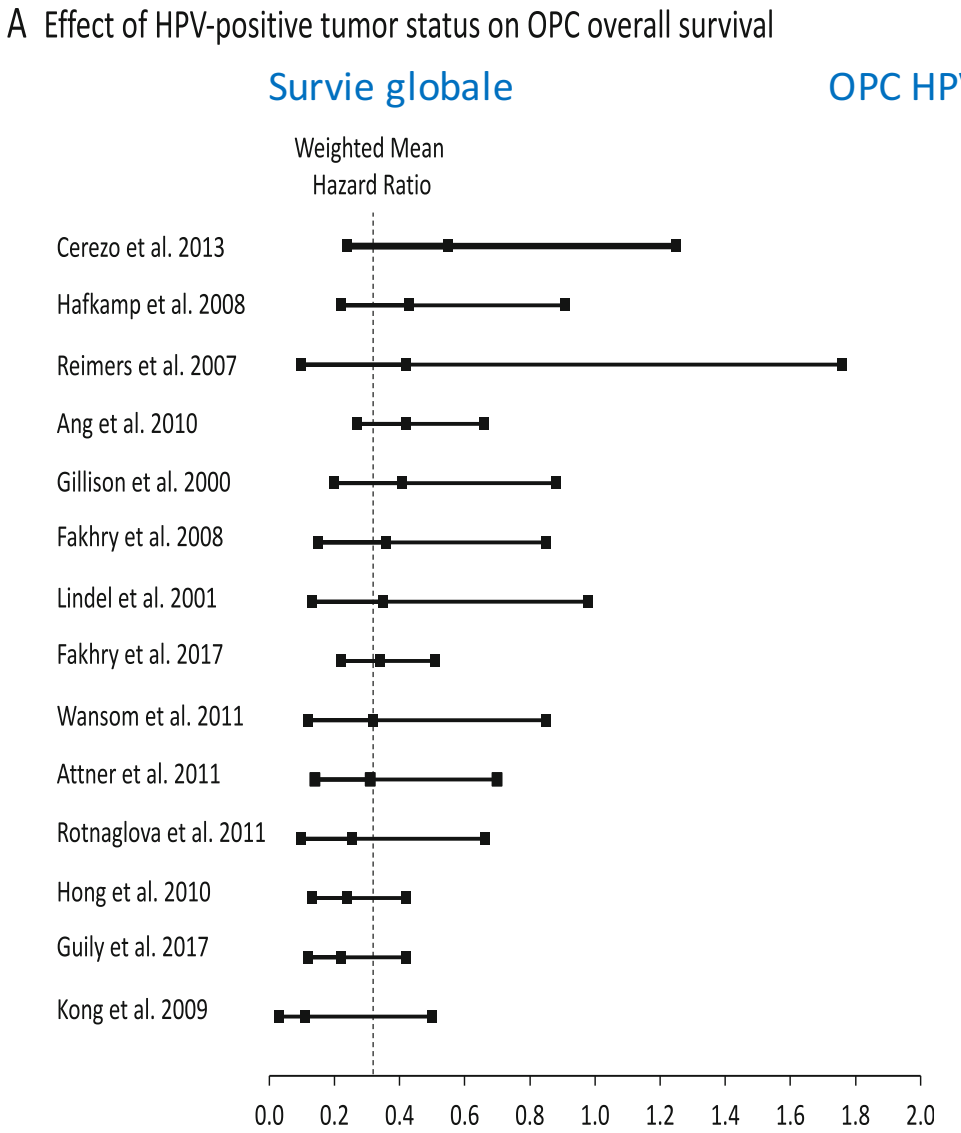


(A) Forest plot comparing HPV(+) to HPV(-) HNSCCs and overall survival (adjusted & unadjusted studies).

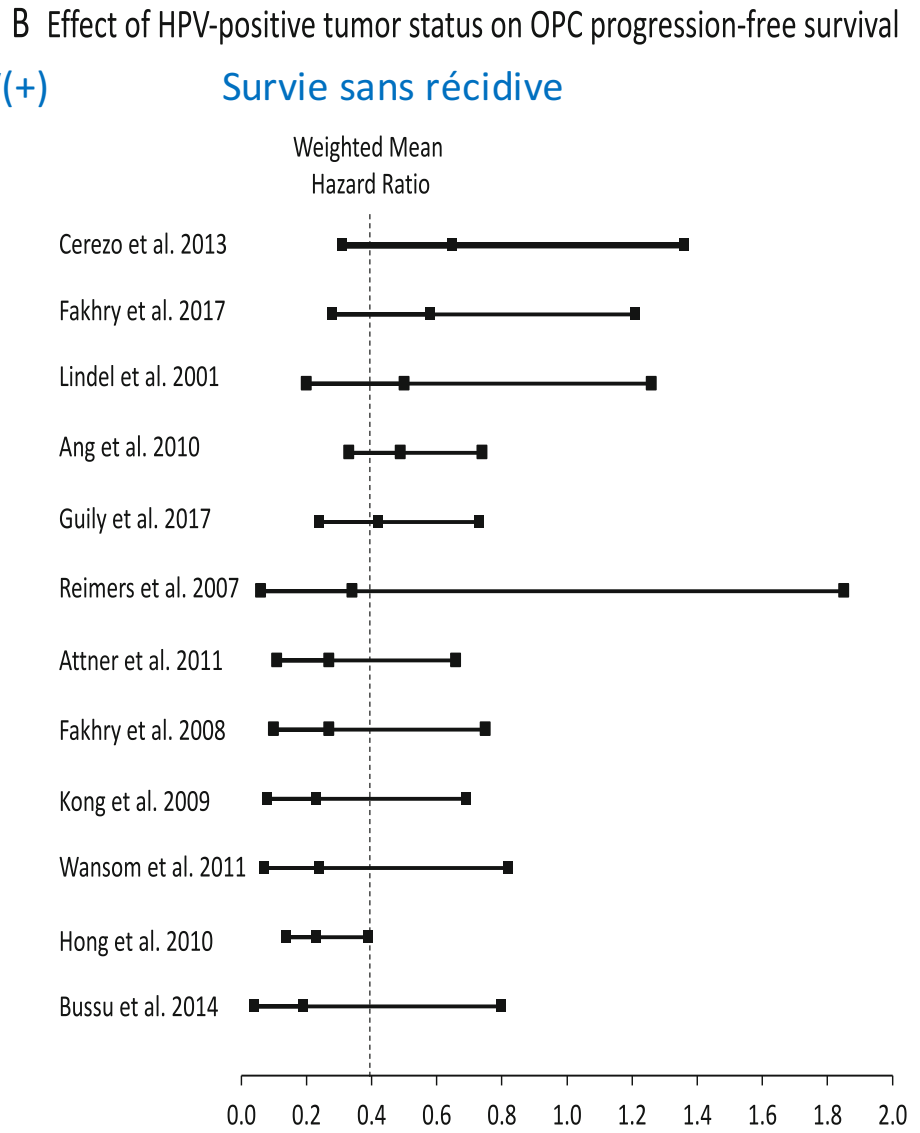
(B) Forest plot comparing HPV(+) to HPV(-) HNSCCs and disease-specific survival (all studies provided adjusted estimates).

O'Rorke Oral Oncology 2012

HPV (+) : Facteur de bon pronostic

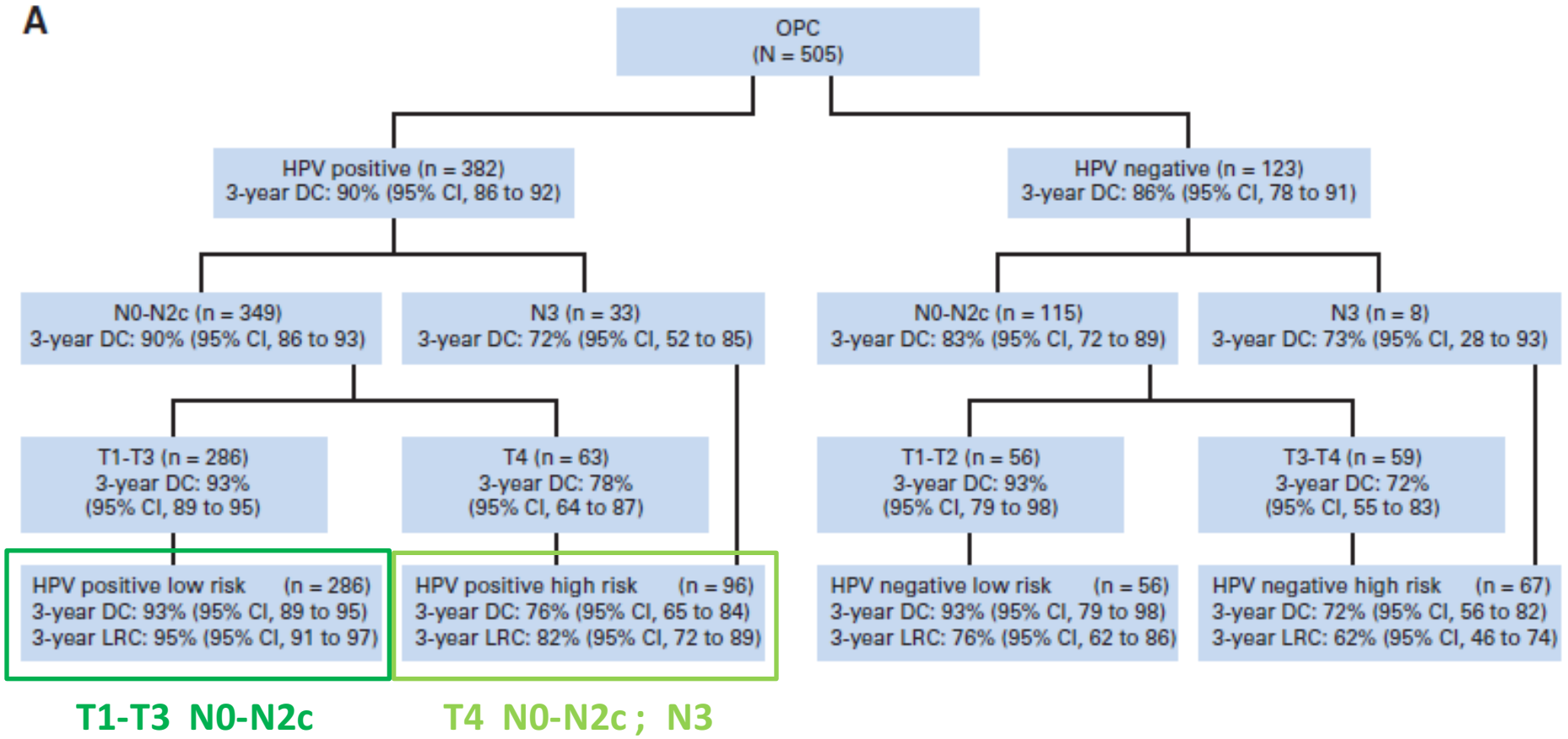


OPC HPV(+)



Fung Cancer Met Rev 2017

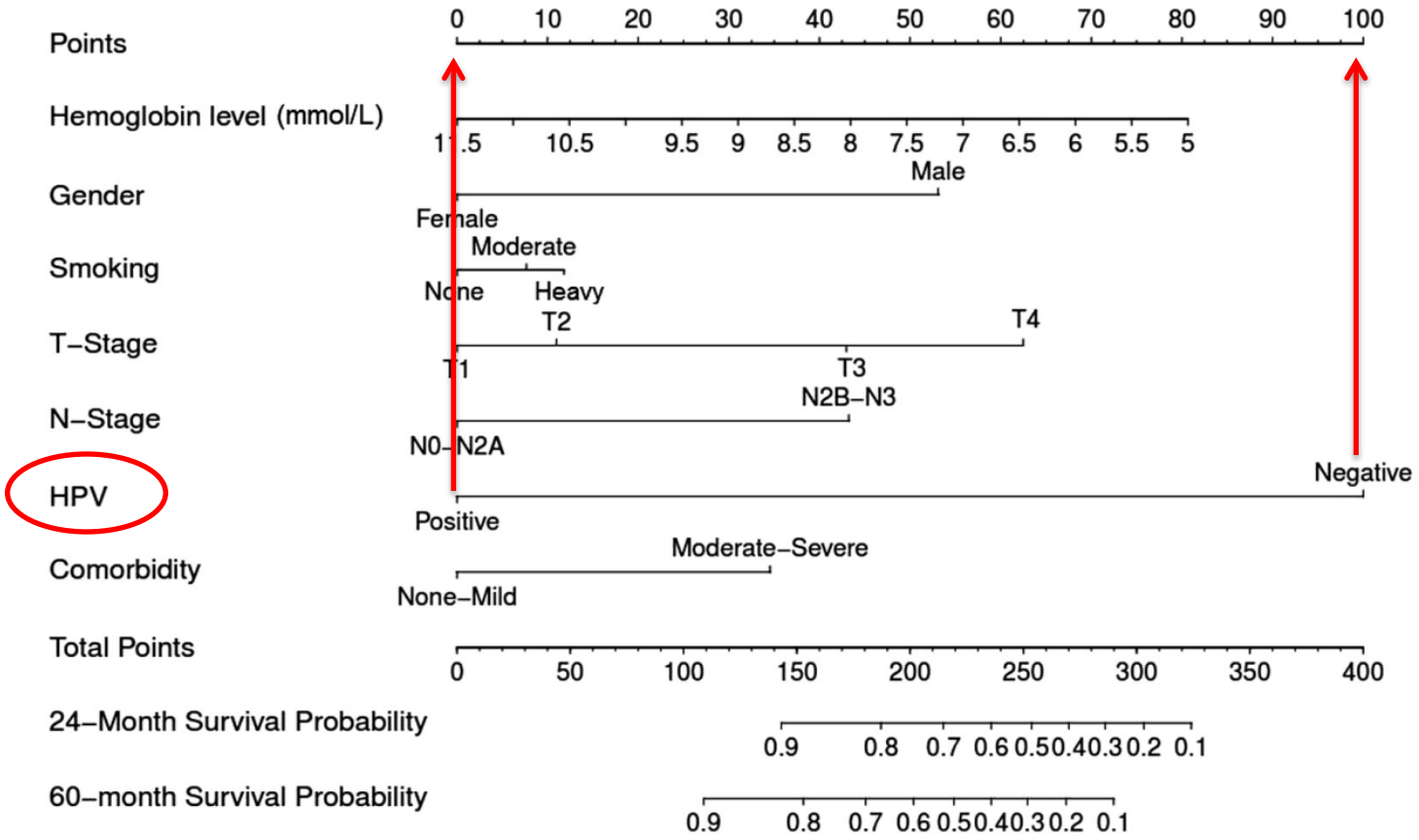
Deintensification Candidate Subgroups in Human Papillomavirus–Related Oropharyngeal Cancer According to Minimal Risk of Distant Metastasis



Distant control (DC) profile by STREE analyses. (A) Distant metastasis (DM) risk stratification based on STREE analyses of human papillomavirus (HPV) –positive and HPV-negative cohorts separately.

O'Sullivan JCO 2013

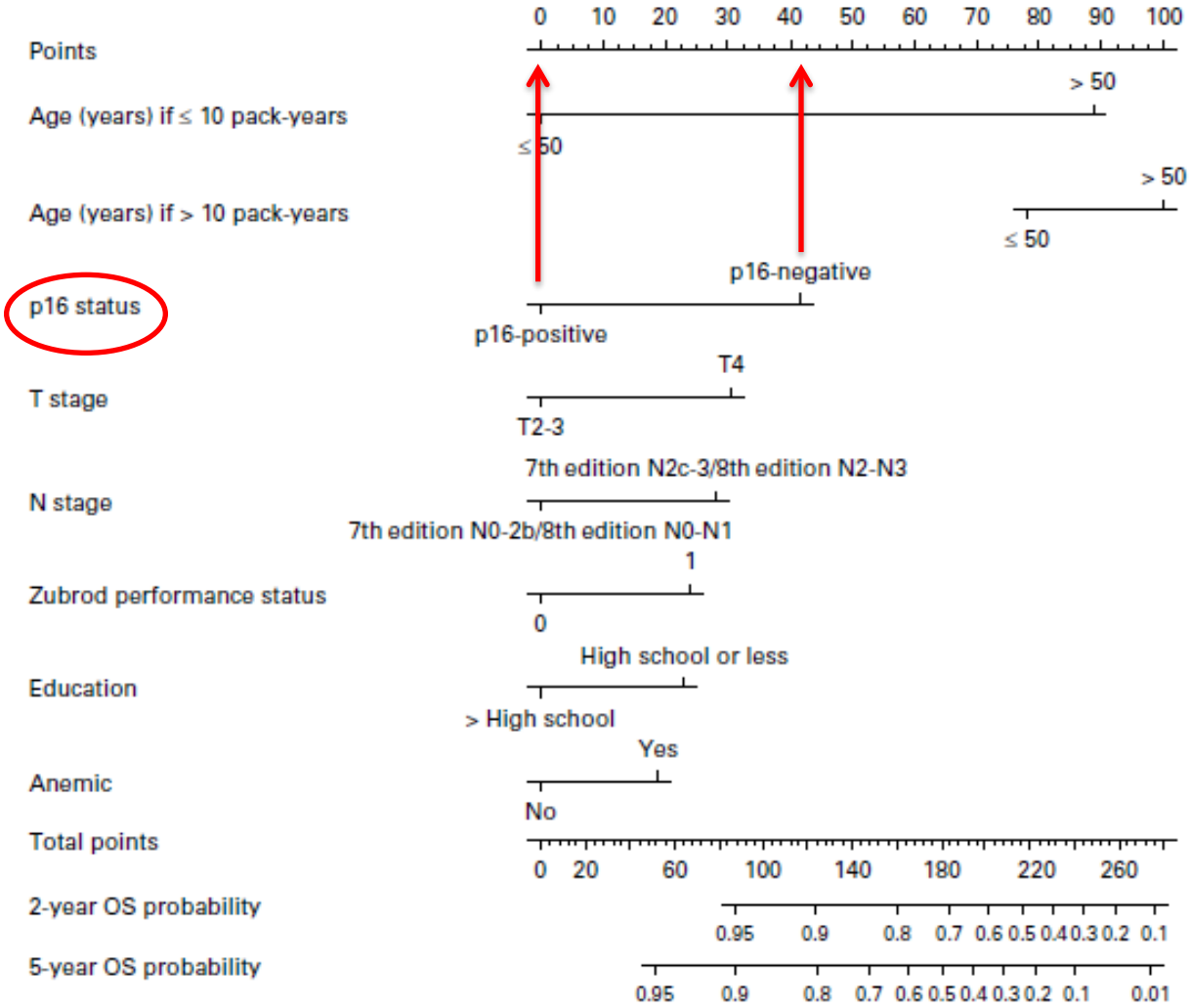
Externally validated HPV-based prognostic nomogram for oropharyngeal carcinoma patients yields more accurate predictions than TNM staging



Multivariate model converted to a graphic nomogram for prediction of overall survival.

Rios Velazquez Radiotherapy and Oncology 2014

Development and Validation of Nomograms Predictive of Overall and Progression-Free Survival in Patients With Oropharyngeal Cancer.



Nomogram for predicting probability of OS at 2 and 5 years.

Fakhry JCO 2017

CE OROPHARYNGE HPV (+)

STRATEGIES de DEFLATION

1. Modification de la chimiothérapie
   - substitution du CDDP
   - fractionnement du CDDP

2. Réduction de la dose de radiothérapie

3. Intégrer une chirurgie mini invasive

Tactique 1
Substitution du cisplatine par du cetuximab

- basée sur l'extrapolation de l'essai de Bonner en 2006:
  - patients < 65 ans, CE oropharyngés , petit T, gros N : *meilleur bénéfice du cetuximab*
  - pas de données initiales sur HPV ou p16, mais étude secondaire…
- stratégie principale évaluée dans plusieurs phase 3:

RTOG 1016 (NCT01302834) Start June 2011 – Expected June 2020	III	706 Active, not recruiting	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) Start November 2012 – Expected February 2019	III	304 Active, not recruiting	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) Start June 2013 – Expected June 2019	III	200 Recruiting	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

- mais …. quid cetuximab / HPV ?

EGFR & HPV ?

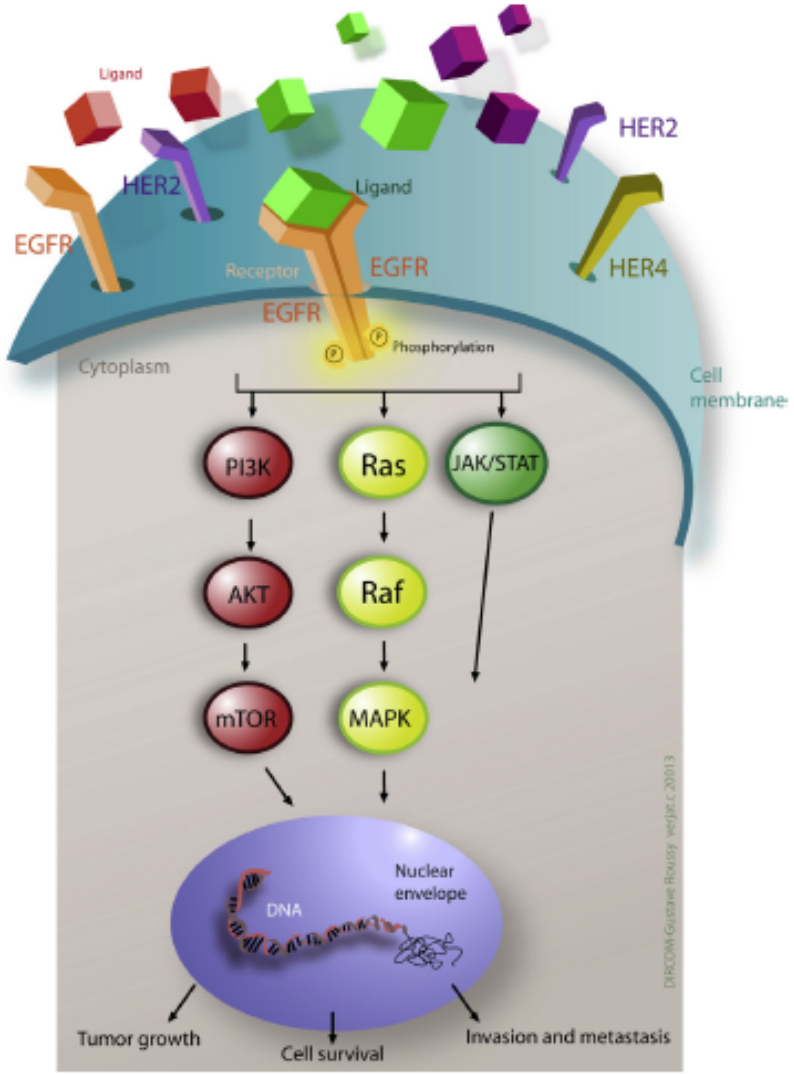


Fig. 1. Simplified model illustrating EGFR ligand interaction. Binding of ligand to epidermal growth factor receptor (EGFR) induces receptor dimerisation, autophosphorylation and activation of several intracellular downstream signalling pathways resulting in the transcription of genes involved in proliferation and survival. *Note*: MAPK: mitogen-activated protein kinase JAK: Janus-activated kinase STAT:signal transducer and activator of transcrip- tion PI3K: phosphatidylinositide 3-kinase mTOR: mamalian target of rapamycin.

Mirghani EJC 2014

EGFR & HPV ?

HPV status and EGFR alteration (gene copy number, protein over expression and tyrosin kinase domain mutation).

Author	Number of patients	Study analysing only OPSCC	No HPV+ (%)	EGFR expression assessment	Correlation between EGFR expression and HPV status	EGFR activating mutation	Combination of HPV status and EGFR as predictor of outcomes
Kumar [31] [a]	50	Yes	27/42 (64)	IHC	Inverse ($p = 0.007$)	–	Yes
Kong [33] [b]	99	No	36/82 (43)	IHC	Inverse ($p = 0.0002$)	–	Yes
Hong [32]	270	Yes	91 (33)	IHC	Inverse ($p = 0.0005$)	–	Yes
Perrone [34] [c]	90	Yes	17 (19)	FISH, IHC	No	No	–
Romanitan [35] [d]	83	Yes	52 (63)	IHC	Inverse ($p = 0.01$)		No
Kim [41]	52	Yes	34 (65)	FISH	Inverse ($p = 0.04$)	–	–
Reimers [30] [e]	106	Yes	30/96 (28)	IHC	Trend to inverse ($p = 0.083$)	–	Yes
Young [40] [f]	212	No	75/131 (57)	FISH,IHC	Inverse	–	–
Al-Swiahb [37]	220	Yes	33 (15)	IHC	Inverse ($p < 0.01$)	–	Yes
Won [82] [g]	121	No	21 (17)	IHC	Inverse ($p = 0.003$)	–	–
Hussain [83] [h]	101	No	29/87 (33)	IHC	Inverse ($p = 0.03$)	–	No

Inverse

IHC: immunohistochemistry, OPSCC: oropharyngeal squamous cell carcinoma, FISH: fluorescence in situ hybridisation, HPV: human papillomavirus, EGFR: epidermal growth factor receptor.

Definition of HPV status by:

Both p16 and DNA positivity: Hong, Romanitan (polymerase chain reaction (PCR)).

Both p16 and/or DNA positivity: Reimers (PCR), Al-Swiahb (PCR, in situ hybridisation).

p16 alone: Young, Hussain.

HPV DNA alone: Kong (PCR followed by pyrosequencing), Kumar (PCR followed by mass spectroscopy), Kim (PCR), Won (in situ hybridisation).

HPV DNA and E6/E7 mRNA positivity: Perrone.

[a] HPV status was assessed in 42/50 patients.

[b] HPV status was assessed in 82/99 patients. 33 of the 36 HPV positive (strong signal) patients were in the oropharynx.

[c] Expression of EGFR was not significantly different (IHC) but there was an inverse correlation between *EGFR* gene copy number and HPV status (6% versus 45%; $p < 0.01$). Only exon 19 was assessed.

[d] An inverse correlation was only found for phosphorylated EGFR (the activated form of EGFR).

[e] EGFR IHC was assessed in 96 patients, p16 (surrogate marker of HPV) was used to analyse the relationship with EGFR.

[f] 75 of 131 OPSCC were p16-positive, relationship between p16 and EGFR was limited to 126 OPSCC with available data for these two parameters.

[g] 19 of the 21 HPV-positive patients were in the oropharynx (61/121 patients).

[h] HPV status was assessed by p16 IHC in 87 patients. 20 of the 29 p16-positive patients were in the oropharynx (20/34 patients). EGFR was assessed in 80 of 101 patients.

Mirghani EJC 2014

EGFR & HPV ?

En théorie, tumeur avec un haut niveau d'EGFR devrait profiter plus de traitements visant l'EGFR…

CBNPC: un nombre accru de copie de gène de l'EGFR (FISH) = prédictif de meilleurs résultats avec des EGFR TKI ou cetuximab.

Tumeurs ORL HPV (+) , intérêt des anti-EGFR ? … *(/ moins d'expression d'EGFR…)*

Aucune étude utilisant des inhibiteur de l'EGFR dans les tumeurs des VADS n'a montré que le nombre de copie de gène EGFR ou le niveau d'expression sont prédictifs de réponse tumorale.

Les altérations de l'EGFR (nombres de copie de gène & surexpression) sont inversement corrélées au statut HPV dans OPSCC.

Le rôle de la voie de signalisation de l'EGFR est moins prépondérantes dans les OPSCC HPV(+) / HPV(-).

Le rationnel pour l'utilisation des traitement anti EGFR dans les OPSCC HPV(+) est… faible.

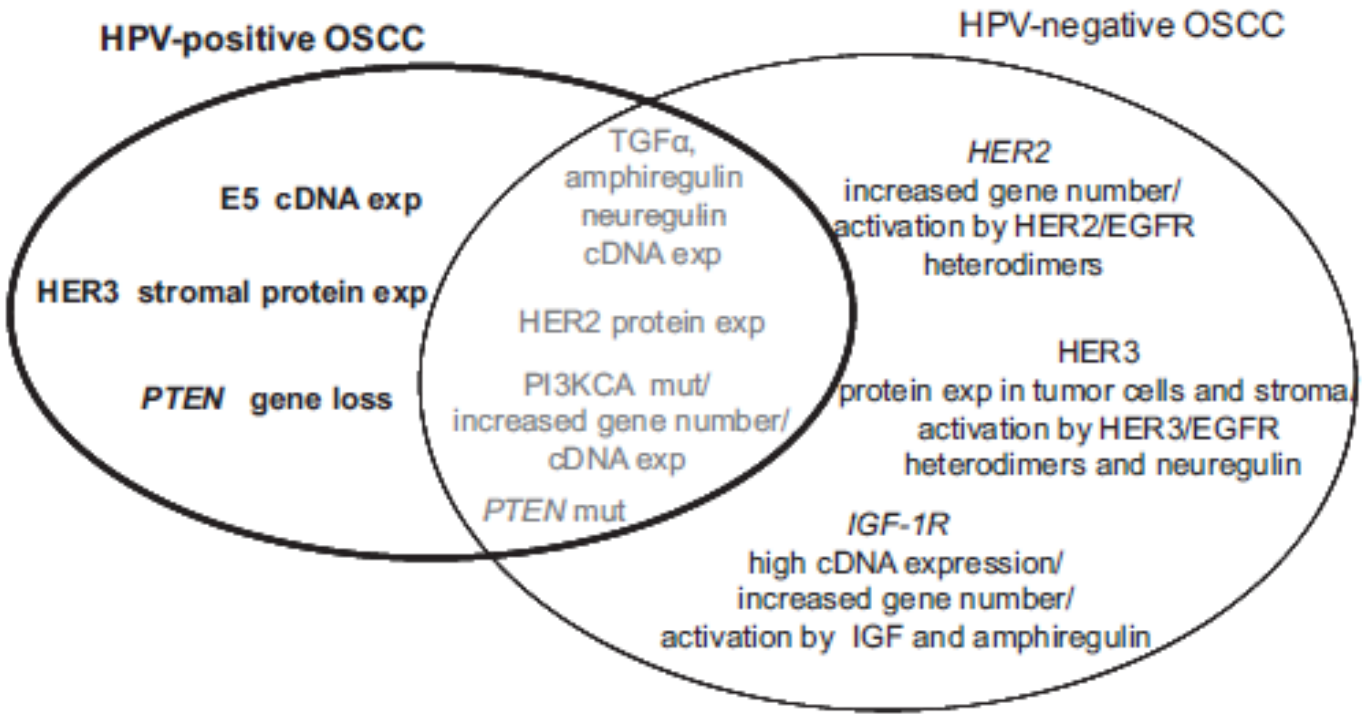
Les résultats des études en cours nous en diront plus…

Mirghani EJC 2014

Receptor tyrosine kinase profiles and human papillomavirus status in oropharyngeal squamous cell carcinoma

Barbara Cortelazzi[1], Paolo Verderio[2], Chiara Maura Ciniselli[2], Sara Pizzamiglio[2], Paolo Bossi[3], Annunziata Gloghini[1], Ambra V. Gualeni[1], Chiara C. Volpi[1], Laura Locati[3], Marco A. Pierotti[4], Lisa Licitra[3], Silvana Pilotti[1], Federica Perrone[1]

J Oral Pathol Med (2015) 44: 734–745

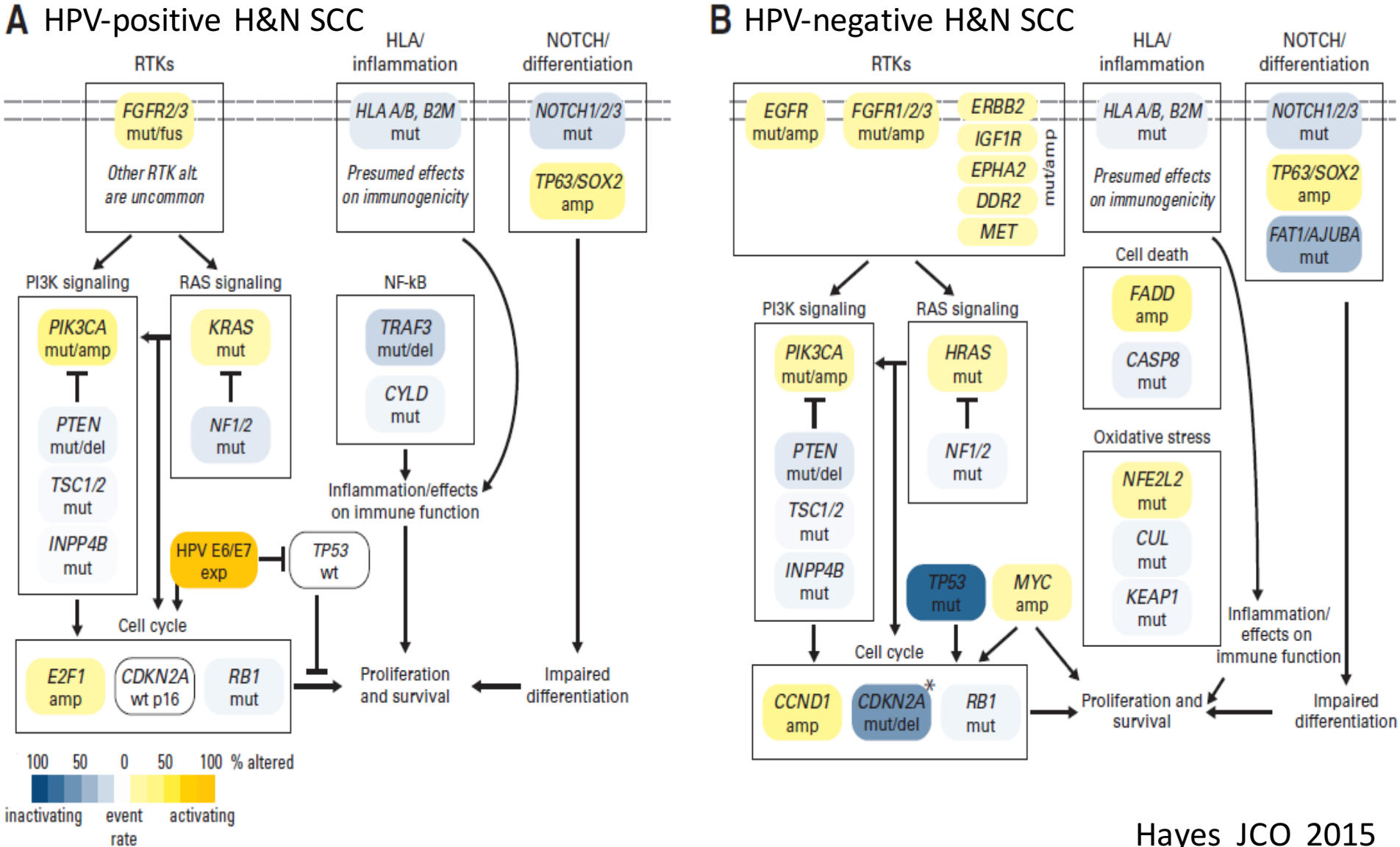


Immunophenotypic, cytogenetic, molecular and biochemical alterations or RTK and downstream effectors in HPV(+) and/or HPV (-) oropharyngeal squamous cell carcinomas (OSCCs). exp, expression; mut, mutation; RTK, receptor tyrosine kinases.

Cortelazzi J Oral Pathology & Medicine 2015

Genetic Landscape of Human Papillomavirus–Associated Head and Neck Cancer and Comparison to Tobacco-Related Tumors

D. Neil Hayes, Carter Van Waes, and Tanguy Y. Seiwert



Haves JCO 2015

Tactique 2
Réduction de la dose de radiothérapie

Pourquoi réduire la dose de RT ?

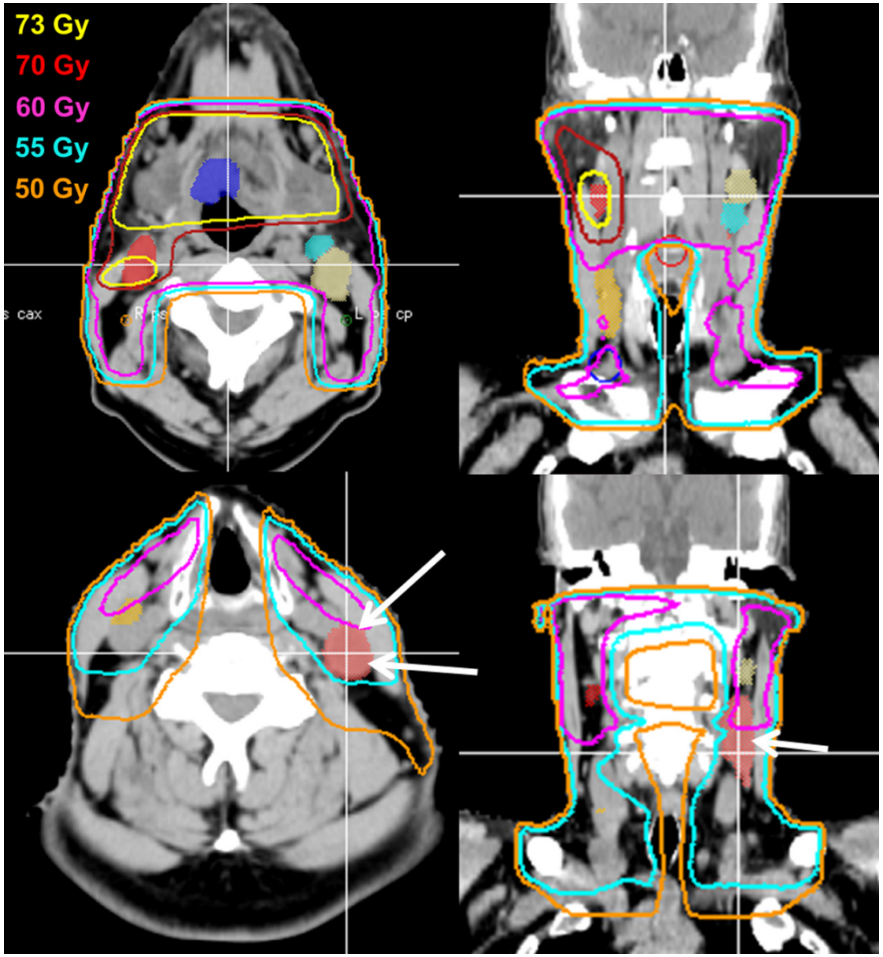
- Complications tardives impactant la qualité de vie
  - xérostomie
  - dysphagie

- Toxicités tardives liées aux doses reçues

- Morbidités liés à la radiothérapie en général

- *Déjà fait…*

Regional control is preserved after dose de-escalated radiotherapy to involved lymph nodes in HPV positive oropharyngeal cancer



HPV positive oropharyngeal cancer who underwent concurrent cisplatin based chemoradiotherapy to 70–76 Gy to the primary tumor and dose reduced radiotherapy to the involved nodes.

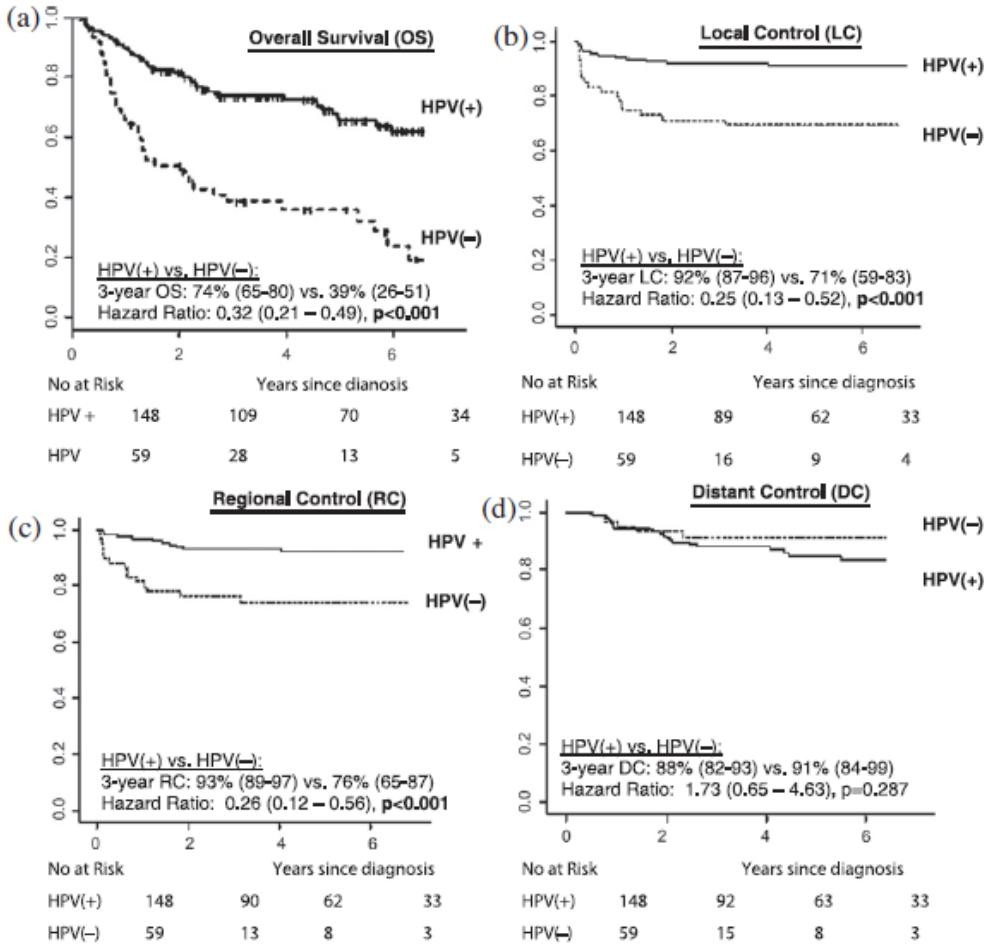
In this exploratory study, median D95 and D99 of 55.3 Gy and 52.2 Gy to nodes outside the primary boost portal did not decrease regional control relative to full dose radiotherapy.

No nodal failures were observed when D99 exceeded 55 Gy.

Woody Oral Oncology 2016

Outcomes of HPV-related oropharyngeal cancer patients treated by radiotherapy alone using altered fractionation

Overall survival



Local Control

Regional Control

Distant Control.

Outcomes of 207 pts treated with radiotherapy-alone: HPV(+) (n = 148) vs. HPV(-) (n = 59)

60 Gy/25 f/5 weeks, QD : 86 pts (42%)
64 Gy/40 f/4 weeks, BID : 68 pts (33%)
70 Gy/35 f/7 weeks, QD : 23 pts (11%)

O'Sullivan Radiotherapy and Oncology 2012

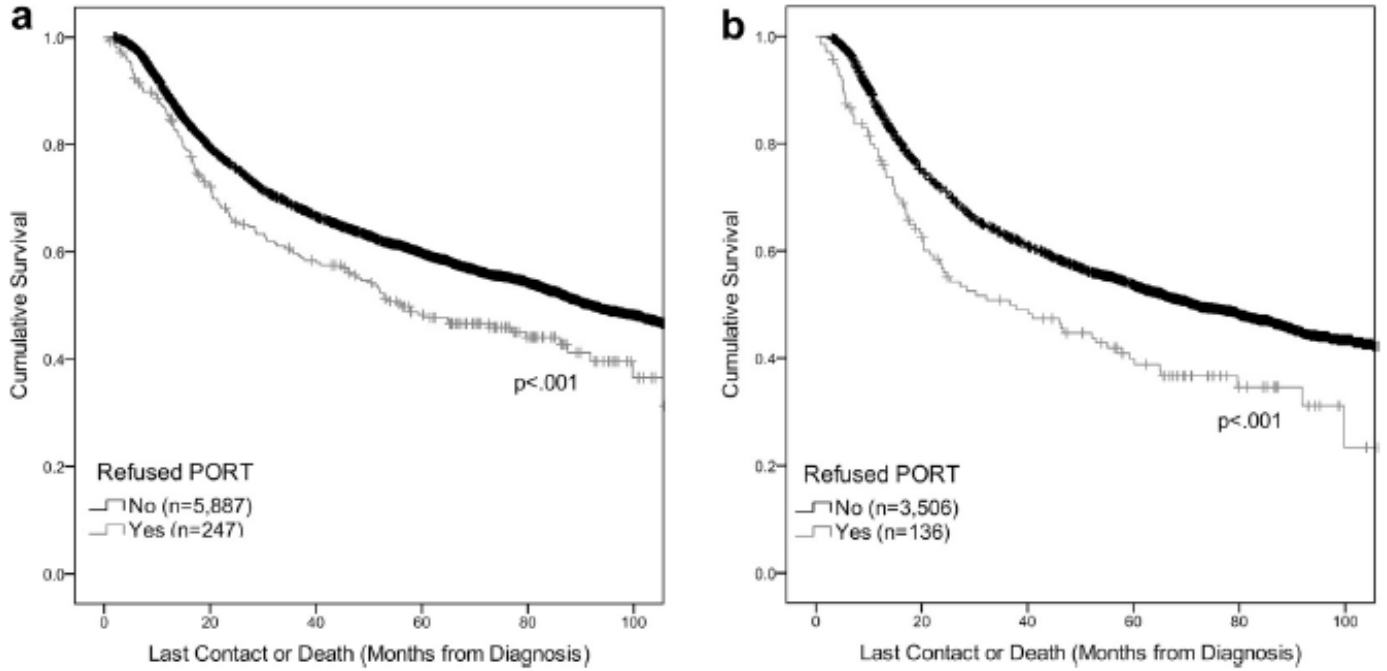
Pas de RT adjuvante?

Refusal of postoperative radiotherapy

Refusal of postoperative radiotherapy and its association with survival in head and neck cancer

Zachary G. Schwam [a,*], Zain Husain [b], Benjamin L. Judson [c]

[a] Yale University School of Medicine; [b] Department of Therapeutic Radiology; and [c] Department of Surgery, Section of Otolaryngology, Yale University School of Medicine, New Haven, USA



Kaplan–Meier curve depicting overall survival stratified by refusal of PORT for patients of all stages (a) and late stage disease (b).

Schwam Radiotherapy and Oncology 2015

Pas de RT adjuvante?

Clinical Investigation

Relapse Rates With Surgery Alone in Human Papillomavirus—Related Intermediate- and High-Risk Group Oropharynx Squamous Cell Cancer: A Multi-Institutional Review

Patients treated with TORS or TLM for OPSCC between 1998 and 2013 with HPV(+) tumors who had intermediate- or high-risk features and indications for adjuvant therapy but did not receive further treatment.

53 patients with HPV(+) OPSCC who **did not receive adjuvant therapy after TOS** despite indications for RT or CRT based on intermediate- or high-risk features.

25 from Mayo Clinic Rochester, 10 from Mayo Clinic Arizona, 10 from Mayo Clinic Florida, and 8 patients from the University of Pennsylvania Health System

Routman IJROBP 2017

Pas de RT adjuvante?

*[Retrospective analysis yielded estimated **5-year relapse rates of 15%** for patients with ECE receiving adjuvant therapy, with lower rates for intermediate-risk patients]*

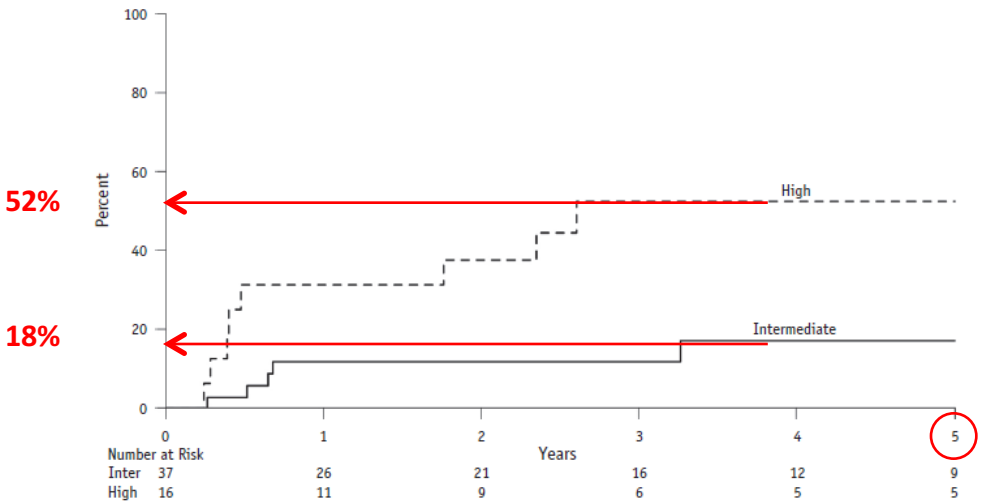


Fig. 2. Cumulative incidence of relapse by risk category (death as a competing risk). *Abbreviation:* Inter = intermediate

Conclusions: Risk category was associated with **clinically significant relapse rates** after TOS alone in HPV(+) oropharyngeal cancer, comparable to historical data and traditional indications for adjuvant therapy for all oropharyngeal cancer.

Extracapsular extension had the highest association with relapse.

Like HPV(-) patients, HPV(+) patients with traditional intermediate- and high-risk features should be offered adjuvant therapy.

However, given the potential for salvage therapy and relatively low risk for relapse in intermediate-risk patients, de-escalation of adjuvant treatment remains an open consideration best answered by a prospective, randomized trial.

Routman IJROBP 2017

Tactique 2
Réduction de la dose de radiothérapie

- morbidité associée à la dose totale de radiothérapie

NRG HN-002 (NCT02254278) Start October 2014 – Expected May 2019	II	296 Active, not recruiting	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 Start November 2011 – Results August 2017	II	40 Results	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) Start March 2010 – Results October 2015	II	80 Results	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) Start September 2012 – Expected December 2021	III	365 Active, not recruiting	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.
STR-DELPHI-2016 (NCT03396718) Start February 2018 – Expected January 2026	III	384 Open soon Not yet recruiting	Surgical removal OPSCC HPV(+) Lymph node dissection	De-escalation RT(CT) - L1: 54/ 59,4 Gy De-escalation RT(CT) – L2 : 48,8/ 55 Gy Standard RT(CT): 60/ 66 Gy

Phase 2 Trial of De-intensified Chemoradiation Therapy for Favorable-Risk Human PapillomaviruseAssociated Oropharyngeal Squamous Cell Carcinoma
NCT01530997

Single-arm, phase 2 study in a **favorable risk cohort of OPSCC**, 45 patients

Inclusion criteria :

- T0 to T3, N0 to N2c,M0 (**T1-2**: 80% ; **N2b** : 48% ; N2c : 16%)
- Human PapillomaVirus or p16 positive
- minimal/remote smoking history (**never smoker** : 82%)

Treatment : **IMRT** limited to **60 Gy**
with concurrent **weekly CDDP** (30 mg/m2) preferably on Mondays.

Primary study endpoint : pathologic complete response (pCR)

- **Surgical evaluation** was performed for 43 patients (1 patient refused surgery, 1 patient was taken off study due to cerebrovascular accident during CTRT) at a mean of **9 weeks** (range, 7-14 weeks).

Chera IJROBP 2015

Phase 2 Trial of De-intensified Chemoradiation Therapy for Favorable-Risk Human PapillomaviruseAssociated Oropharyngeal Squamous Cell Carcinoma NCT01530997

43 patients

pCR rate : **86%** (37 of 43)

pCR rate at the primary site : **98%** (40 of 41; 2 patients were T0)

pCR rate in the neck : **84%** (33 of 39; 4 patients were N0)

Incidence of CTCAE grade 3/4 toxicity and PRO-CTCAE severe/very severe symptoms

mucositis : 34%/45%, general pain : 5%/48%,

nausea : 18%/52%, vomiting : 5%/34%,

dysphagia : 39%/55%, xerostomia : 2%/75%.

Grade 3/4 hematologic toxicities : 11%.

39% of patients required a feeding tube for a median of 15 weeks [5-22 weeks].

No differences in modified barium swallow studies before and after CRT.

Chera IJROBP 2015

E1308: 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

Single-arm, phase 2 study in **OPSCC**, 90 patients

Inclusion criteria :

- resectable, stage III/IV OPSCC
- positive for p16 IHC and/or HPV16 in situ hybridization

Treatment :

IC : **cisplatin** 75 mg/m² on day 1;
paclitaxel 90 mg/m² on days 1, 8, and 15;
cetuximab 400 mg/m² on day 1 of cycle 1, followed by cetuximab 250 mg/m² weekly.
cycles were repeated every 21 days for **3 cycles.**

Tailored IMRT with **cetuximab** / evaluation of **response**

primary-site cCR :	54 Gy in 27 fractions to the primary site,
less than cCR :	69.3 Gy in 33 fractions to the primary site.
involved nodes with cCR :	54 Gy in 27 fractions to nodes,
less than cCR :	69.3 Gy in 33 fractions to nodes.
uninvolved cervical nodes :	51.3 Gy in 27 fractions (1.9 Gy per fraction) bilaterally

Primary study endpoint : 2-year PFS rate after primary-site cCR after IC and reduced-dose radiation.

Marur JCO 2017

E1308: 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

Table 3. Two-Year PFS and OS in Subsets Treated in the E1308 Trial

Cohort	2-Year PFS (95% CI)	2-Year OS (95% CI)
All patients (N = 80)	0.78 (0.67 to 0.86)	0.91(0.82 to 0.96)
cCR to IC, RRD 54 Gy (n = 51)	0.80 (0.65 to 0.89)	0.94 (0.84 to 0.99)
All cCR/PR/SD to IC, RRD ≤ 54 Gy (n = 62)	0.81 (0.69 to 0.89)	0.93 (0.83 to 0.97)
SRD (n = 15)	0.67 (0.38 to 0.85)	0.87 (0.56 to 0.96)
Subsets cCR to IC, treated on RRD (n = 51)		
Smoker ≤ 10 pk-yr (n = 30)	0.90 (0.71 to 0.97)	0.97 (0.79 to 0.995)
Smoker > 10 pk-yr (n = 21)	0.65 (0.41 to 0.82)	0.90 (0.66 to 0.97)
Smoker ≤ 10 pk-yr, and < T4N2c (n = 21)	0.95 (0.71 to 0.99)	0.95 (0.71 to 0.99)
Smoker > 10 pk-yr or T4 or N2c (n = 30)	0.69 (0.49 to 0.83)	0.93 (0.75 to 0.98)
Non-T4a (n = 45)	0.84 (0.69 to 0.92)	0.95 (0.83 to 0.99)
T4a (n = 6)	0.50 (0.11 to 0.80)	0.83 (0.27 to 0.97)
N2c (n = 15)	0.73 (0.44 to 0.89)	0.93 (0.61 to 0.99)
Non-N2c (n = 36)	0.82 (0.65 to 0.92)	0.94 (0.79 to 0.99)

Abbreviations: cCR, complete clinical response; IC, induction chemotherapy; pk-yr, pack-year; OS, overall survival; PFS, progression-free survival; PR, partial response; RRD, reduced radiation dose; SD, stable disease; SRD, standard radiation dose.

After three cycles of IC (cddp, paclitaxel, cetuximab) : excellent cCR of 70%

IC response would identify patients suitable for radiation dose reduction.

Among the 51 pts with primary site cCR treated with 54 Gy of radiation,

the 2-year PFS estimate was 80%

the 95% CI of 65% to 89% encompasses the target 2-year PFS of 85%.

All treatment failures were among patients with a > 10 pack-year smoking history,

and all occurred within the first 20 months of registration.

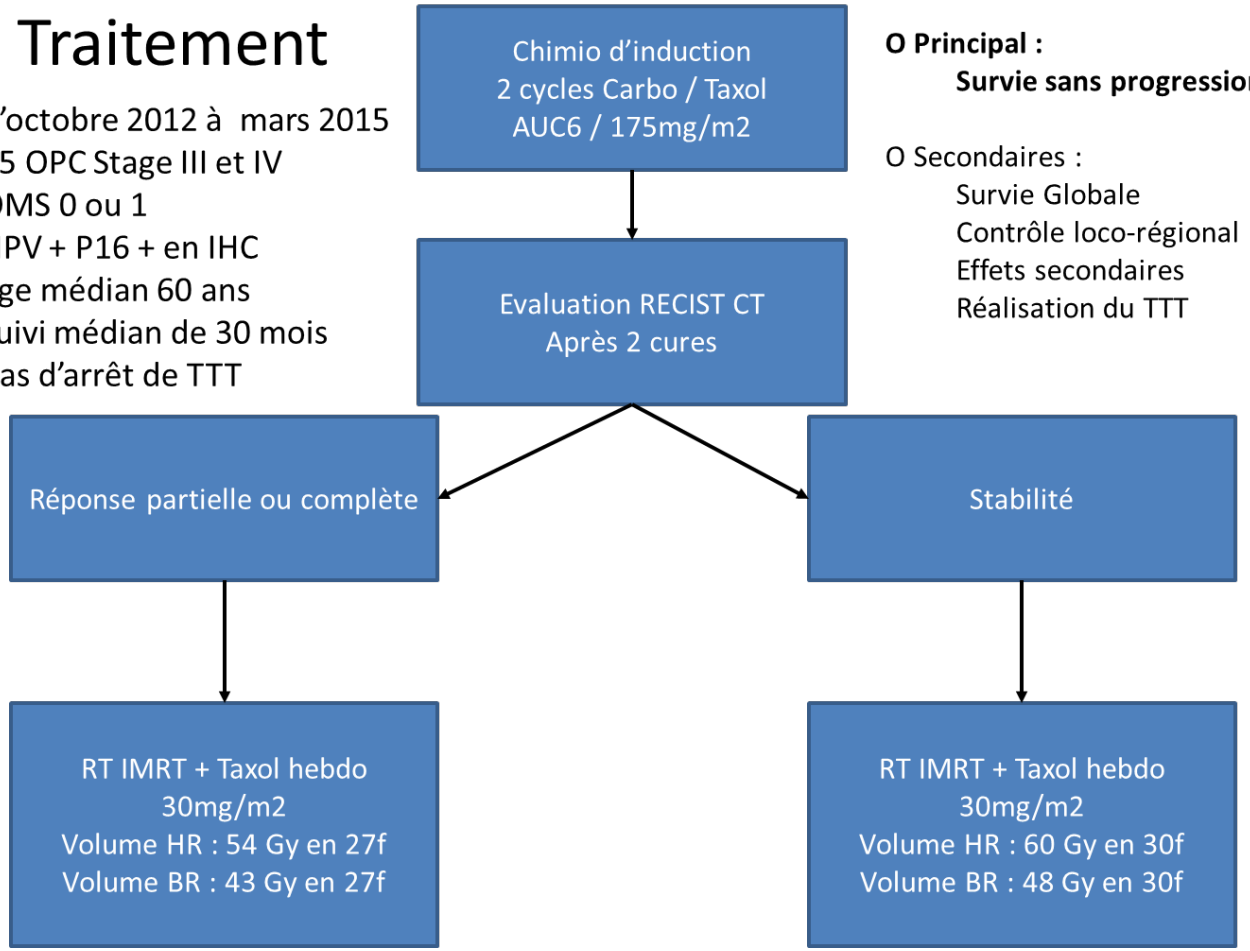
Marur JCO 2017

Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study

Allen M Chen, Carol Felix, Pin-Chieh Wang, Sophia Hsu, Vincent Basehart, Jordan Garst, Phillip Beron, Deborah Wong, Michael H Rosove, Shyam Rao, Heather Melanson, Edward Kim, Daphne Palmer, Lihong Qi, Karen Kelly, Michael L Steinberg, Patrick A Kupelian, Megan E Daly

Traitement

d'octobre 2012 à mars 2015
45 OPC Stage III et IV
OMS 0 ou 1
HPV + P16 + en IHC
âge médian 60 ans
suivi médian de 30 mois
pas d'arrêt de TTT



O Principal :
Survie sans progression à 2 ans

O Secondaires :
Survie Globale
Contrôle loco-régional
Effets secondaires
Réalisation du TTT

Chen LancetOncol 2017

Résultats

Réponse complète à 3 mois : 84%

SSP à 2 ans : **92%**

(IC95 : 77-97)

Contrôle LR à 2 ans : **95%**

(80-99)

Toxicité aigues

Toxicité tardives :

- 5% dysphagie G3 à 3 mois
- aucun patient avec NE à 6 mois

	Induction chemotherapy (n=44)		Chemoradiotherapy (n=44)	
	Grades 1–2	Grade 3	Grades 1–2	Grade 3
Anaemia	39 (87%)	1 (2%)	27 (61%)	1 (2%)
Anorexia	4 (9%)	1 (2%)	9 (20%)	2 (4%)
Anxiety	7 (16%)	0	4 (9%)	1 (2%)
Arthralgia	9 (20%)	1 (2%)	4 (9%)	0
Bone pain	6 (14%)	0	2 (5%)	0
Constipation	3 (7%)	0	17 (39%)	0
Cough	2 (5%)	0	16 (36%)	0
Dehydration	4 (9%)	1 (2%)	9 (20%)	1 (2%)
Dysphagia	20 (23%)	0	19 (43%)	4 (9%)
Hypokalaemia	8 (18%)	1 (2%)	4 (9%)	0
Hypomagnesaemia	5 (11%)	0	5 (11%)	0
Hyponatraemia	20 (23%)	2 (5%)	6 (14%)	2 (5%)
Increased creatinine	18 (41%)	0	4 (9%)	0
Leucopenia	23 (52%)	17 (39%)	37 (84%)	3 (7%)
Mucositis	16 (36%)	1 (2%)	34 (77%)	4 (9%)
Nausea	8 (18%)	1 (2%)	18 (41%)	1 (2%)
Neuropathy	9 (20%)	0	3 (7%)	0
Neutropenia	18 (41%)	5 (11%)	9 (20%)	0
Pneumonia	0	0	1 (2%)	1 (2%)
Dermatitis	0	0	33 (75%)	3 (7%)
Thrombocytopenia	20 (23%)	0	0	0
Voice alteration	0	0	6 (14%)	0
Vomiting	5 (11%)	0	0	0
Xerostomia	1 (2%)	0	42 (95%)	1 (2%)

Tactique 2
Réduction de la dose de radiothérapie

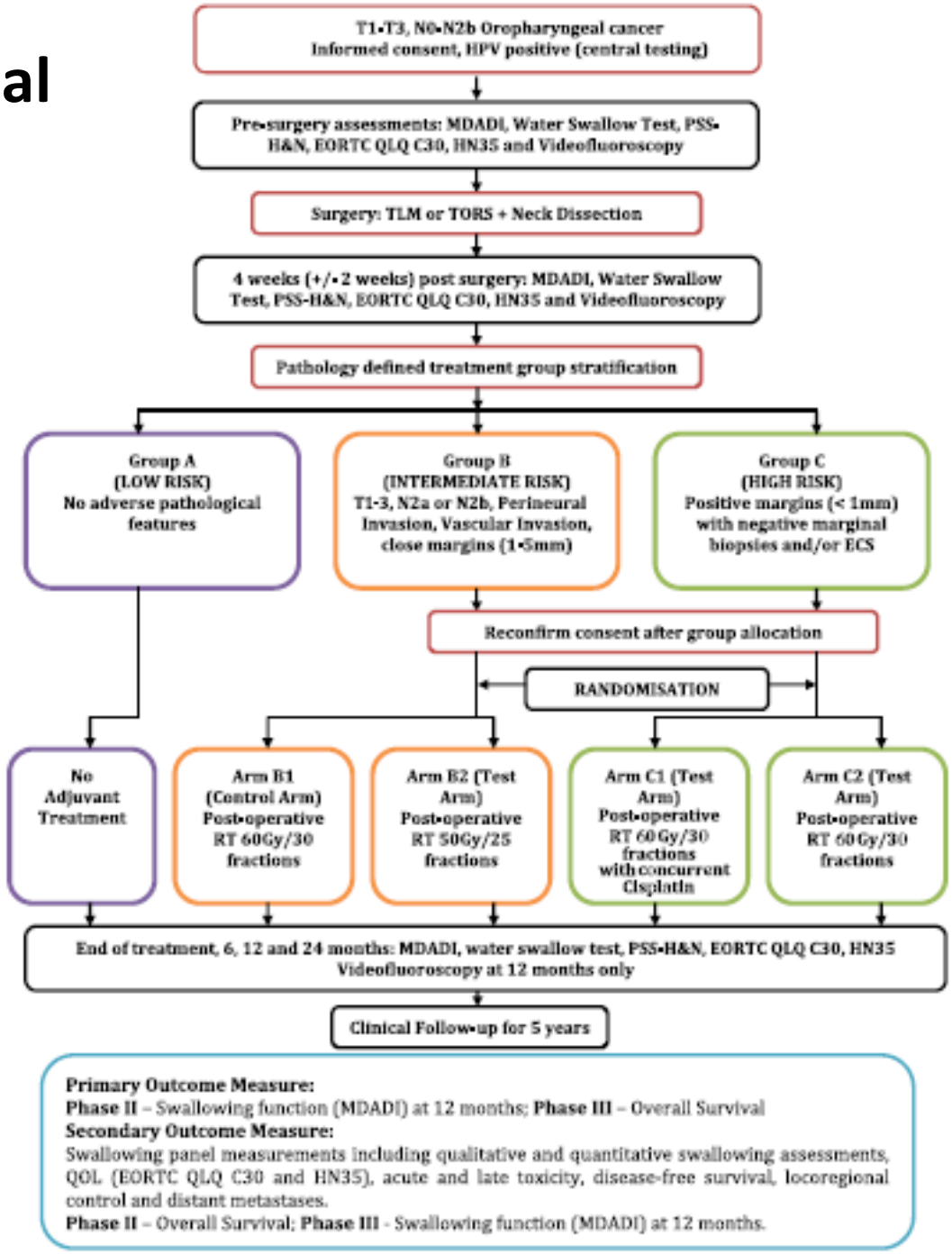
- 3 phases II à suivre

NRG-HN002 (NCT02254278) Start October 2014 – Expected May 2019	II	295 Active, not recruiting	Stage III - IV OPSCC HPV (+), Non-Smoking	IMRT, cisplatin weekly 60 Gy in 6 wks IMRT, cisplatin weekly 60 Gy in 5 wks
Adapative (NCT03215719) Adaptive Treatment De-escalation in Favorable Risk HPV+ OPSCC Start July 2017 – Expected July 2020	II	53 Recruiting	T1-T2, N1-N2b or T3, N1-N2b, HPV (+),	An interval scan at 4 weeks to assess R >40% shrinkage : deescalated RTCT ≤40% shrinkage: standard RTCT
MSCC (NCT03323463) Major Radiation Reduction for HPV+ Oropharyngeal Carcinoma Start October 2017 – Expected October 2020	II	76 Recruiting	HPV (+) and hypoxia (-) T1-2 N1-2b OPSCC Surgical resection	F-FMISO PET/CT Scan IMRT: 30 Gy over 3 weeks CT cisplatinum x2 cycles

Tactique 3
Intégrer une chirurgie mini invasive

ECOG 3311 (NCT01898494) Start August 2013 – Expected February 2020	II	377 Active, not recruiting	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) Start December 2014 – Expected December 2019	II/III	242 Not recruiting	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) Start January 2013 – Expected May 2018	III	500 Active, not recruiting	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 Start September 2013 – Expected October 2018	II	40 Active, not recruiting	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
ORATOR2 (NCT03210103) Start August 2017 – Expected August 2028	Open	120 Active, not recruiting	T1 or T2, N0-2 HPV (+),	Active Comparator: Arm 1, RT+/- CT Experimental: Arm 2, TOS + Neck Surg

PATHOS trial



KEY QUESTION

- La déflation thérapeutique est-elle vraiment **légitime** ?
  - / tolérance aiguë
  - / réduction des effets secondaires
  - / politique de santé

- Pour **quels patients** ?
  - Jeune (risque de seconde localisation)
  - Fragile
  - Systématique
  - Hyper sélectionné (T1-2 ; <N2b; non fumeur)

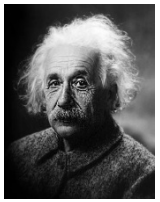
- Quel niveau de **risque** est acceptable ?
  - *Risque acceptable d'échec du traitement / information patient*

- Les test diagnostiques sont ils **fiables** ?
  - HPV
  - p16

KEY QUESTION

« Quelle réduction de taux de survie les patients sont-ils prêts à accepter pour réduire la morbidité associée au traitement standard ? »

« S'il n'y a pas de prix à payer, c'est que cela ne vaut rien.»



Le Pour/Contre de la déflation HPV(+)

Pour	Contre
Survies identiques?	Perte de chance de guérison ?
Diminution du profil de toxicité	Différence en toxicité minime (ou déplacée)
Diminution des couts individuel	Economie de soins au détriment des patients
Moins d'arrêt de travail	Barrière psychologique pour délivrer un traitement moindre
Couts collectifs en augmentation	
Absence de vaccination préventive	Vaccination efficace !

Kimple Oral Oncology 2014

Conclusions

- La déflation est **toujours à l'étude**, pour le traitement des carcinome épidermoïdes de l'oropharynx HPV induit.
- Emergence d'un **groupe de pronostic très favorable**:

  HPV(+) , non fumeur (< 10 PA) , < T4 N2c

- Aucune modification de prise en charge de ces patients ne devrait être faite en dehors d'essais cliniques.
- Idéalement, tous les patients avec un cancer oropharyngé HPV induit devraient être inscrits dans des essais cliniques.
- Pour ceux qui ne participent pas à un essai:
  - se rappeler que la prise en charge initiale, chirurgicale ou basée sur la radiothérapie, reste très efficace pour la grande majorité des cas.
  - aujourd'hui, ce sont surtout leurs préférences personnelles qui vont guider la thérapeutique plus que les résultats acquis des études évaluant la déflation.
- ***Des (nouvelles) données arrivent bientôt…***

  … mais leur interprétation sera (très) complexe !

Conclusion


Let's heve fun together
FALLING PRICES
THE DEFLATION IS NEAR!