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# AIRO2022

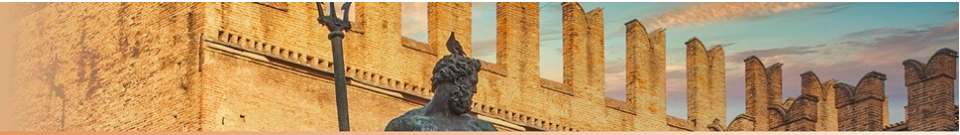
Radioterapia di precisione per un'oncologia innovativa e sostenibile

BOLOGNA, 25-27 NOVEMBRE  
PALAZZO DEI CONGRESSI

 Associazione Italiana  
Radioterapia e Oncologia clinica

 Società Italiana di Radiobiologia

 Associazione  
Italiana  
Radioterapia  
e Oncologia  
clinica  

## DICHIARAZIONE

Relatore: **Dott.ssa Silvana Parisi**

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro



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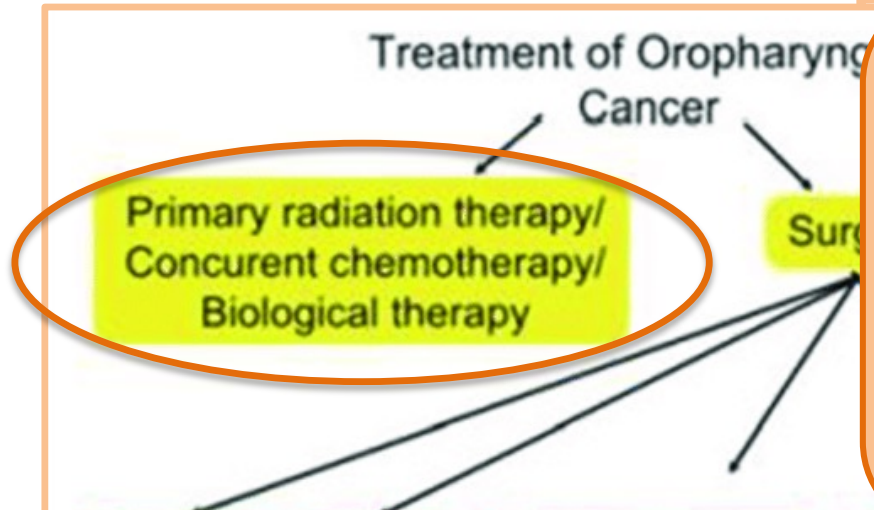
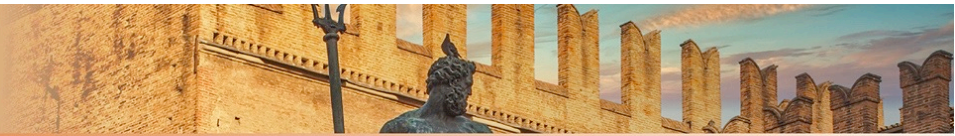
## ***De-escalation della chemio-radioterapia nel carcinoma orofaringeo HPV-positivo***

**Dott.ssa Silvana Parisi**

**Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini**

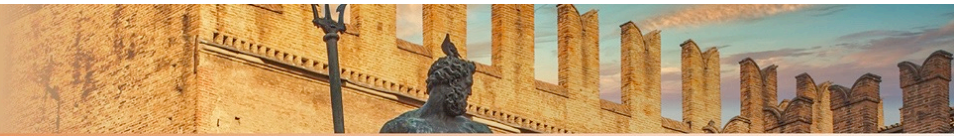
**Morfologiche e Funzionali**

**A.O.U. Policlinico "G. Martino" - Messina**



**OPCs HPV-related was associated with significantly improved outcomes, including overall survival (OS)**

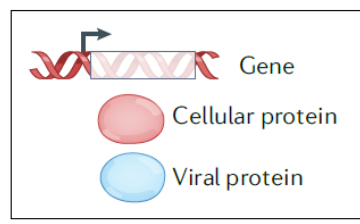
TNM stage	p16 <sup>-</sup>	p16 <sup>+</sup>
T staging	Same as AJCC 7th edn	Tis: not included T0: only for p16 <sup>+</sup> metastatic lymph nodes T4: formerly divided into T4a and T4b, now unified into a single category
Clinical N staging	N3: nodes >6cm in diameter further subdivided into N3a and N3b on the basis of the absence (former) or presence (latter) of extranodal extension	N1: ipsilateral lymph nodes ≤6 cm N2: bilateral or contralateral nodes ≤6 cm no N2 subcategories N3: nodes >6 cm
Pathological N staging	Same as AJCC 7th edn	N1: involvement of ≤4 metastatic lymph nodes N2: >4 metastatic nodes N3: removed
HPV status	p16 testing; tumours with at least moderate staining intensity and diffuse staining (≥75% of tumour cells) classified as probable HPV-associated aetiology on the basis of p16 positivity	



## Why, How and Why

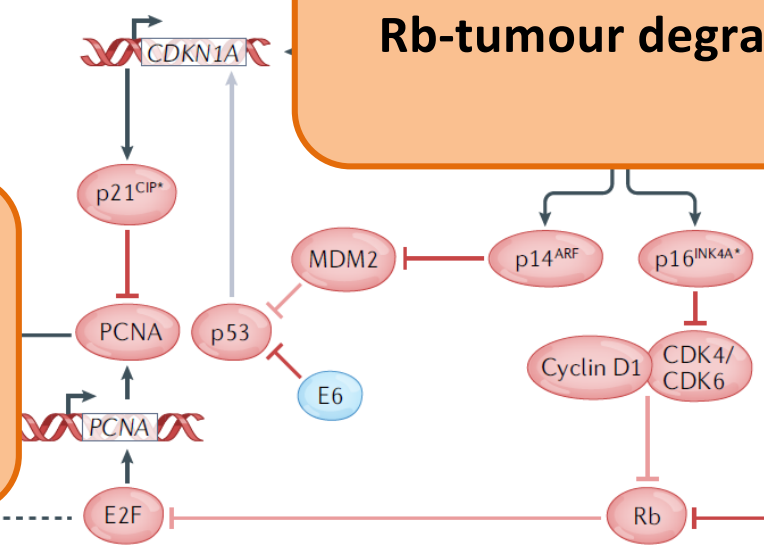
**a** Rb and p53 function E6/E7 function  
Genomic instability

- Biological characteristics
- Genetic alterations
- Other aberrations

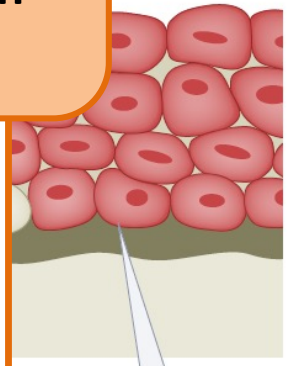


**E6 and E7 induce cell-cycle entry and DNA replication in basal stem cell**

**E6 and E7 induced p53 and Rb-tumour degradation**

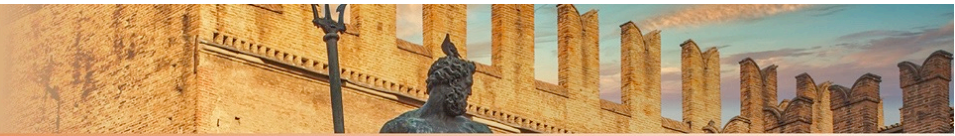


Genetic changes  
 (often but  
 type I tumour

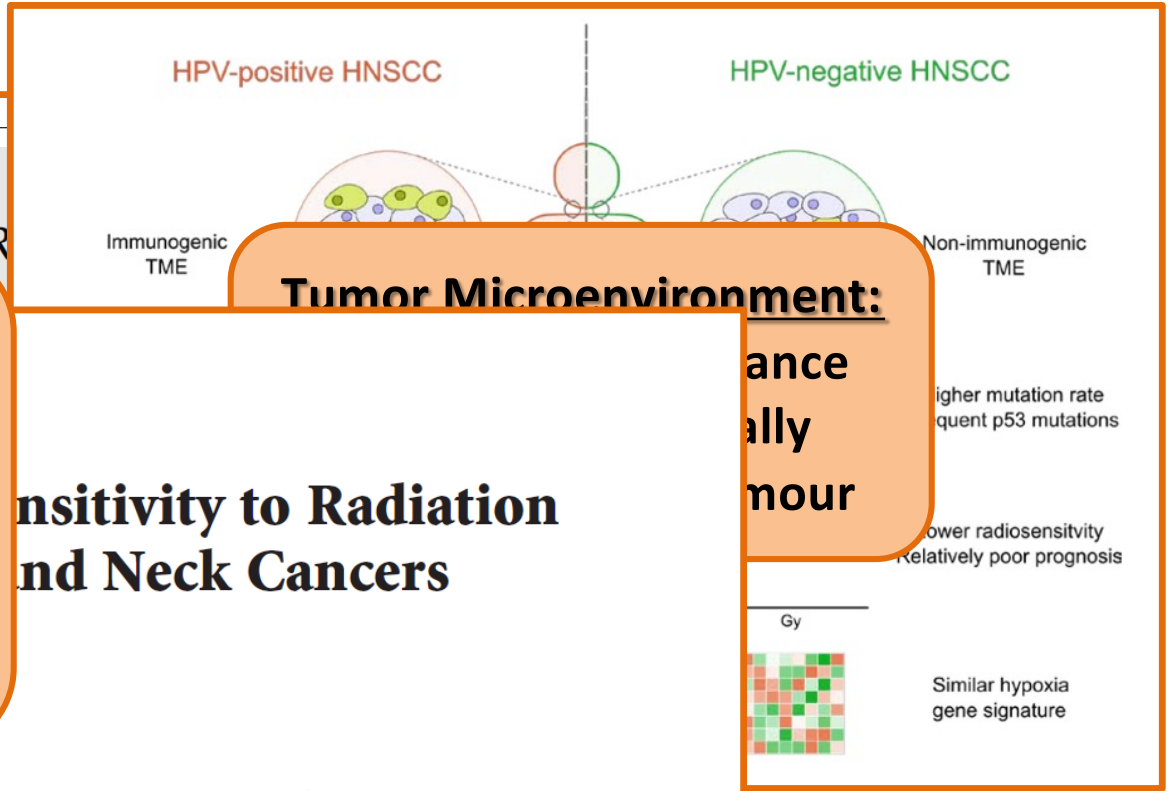


nant transformation:  
 ession from carcinoma  
 to invasive carcinoma

Carcinogenesis



## Why, How and When?



**Tumor Microenvironment:**  
 CD4+ and CD8+ type 1 cytokine producing T cells, reactive to E6- and E7-encoded antigens, have a positive impact on disease outcome

Center for Molecular Imaging, Radiotherapy and Oncology, Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain (UCL), B1.5407 Avenue Hippocrate, No. 54-55, 1200 Brussels, Belgium

EVA-LEONNE GOTTGENS,<sup>1,2,3</sup> CHRISTIAN OSTHEIMER,<sup>1</sup> PAUL N SPAN,<sup>1</sup> JAN BUSSINK and <sup>1</sup>ESTER M HAMMOND

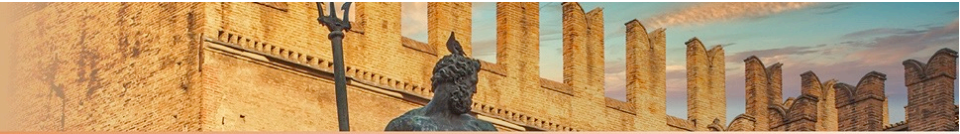
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# STANDARD COURSE VS DE-ESCALATION DOSE/VOLUME: CLINICAL OUTCOMES



**Table 1**  
 Results of reduced-dose concurrent chemoradiotherapy.

Reference	Sample size	Stage & smoking status	RT dose & volume	Concurrent therapy	Median	Tumor control	Clinical outcomes	Selected grade ≥3 toxicities
Chera et al. [9]	44	n = 7 (16%) > T2					100%, 3y	Acute xerostomia (n = 1, 2%)
		n = 7 (16%) > N2					100%, 3y OS	Acute dysphagia (n = 17, 39%)
		n = 2 (5%) > 10 pack years						Acute mucositis (n = 15, 35%) No late events
Chera et al. [10]	114	n = 13 (11%) > T2					77%, 2y DMFS	Feeding tube required by 17 patients (39%), median 15 weeks, 0% at 1 year
		n = 18 (16%) > N2					PFS 86%, 2y	Acute xerostomia (2%)
		n = 22 (19%) > 10 pack years					91%, 3y PFS OS 95%	Acute dysphagia (21%) Acute mucositis (33%) Acute dermatitis (2%) No late events

**Median FU: 32 – 36 months**  
**PFS 86%**  
**LC 95%**  
**DFS 91%**  
**OS 95%**

Abbreviations: RT, radiotherapy; Gy, Gray; fx, fractions; rd, retropharyngeal; pR, pathologic partial response; LRC, locoregional control; CSS, cause-specific survival; DMFS, distant metastasis-free survival; OS, overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival

Oral Oncology 103 (2020) 104608

First published: 26 March 2018 | <https://doi.org/10.1002/clin.51558> | Citations: 79





# Dose reduction of concurrent chemoradiotherapy

**Standard Course vs De-Escalation:**

**Overall-PFS 83-95%**  
**LRC ~90%**  
**Overall-OS 90%**

**Non-inferiority results of PFS, DFS, and OS**



ARTICLE

a phase II of human papillomavirus-positive oropharyngeal

Journal of Clinical Oncology 30: 297-302, 2019  
 doi:10.1200/JCO.2018.16.2222  
 Published online 27 November 2018



Standard  
 chemothe  
 Quarterback

K. Misiukiewicz<sup>a,b,h</sup>, V. Gupta<sup>e</sup>, B.A. Miles<sup>a,d</sup>, R. Bakst<sup>a,e</sup>, E.  
 H. Rainey<sup>a</sup>, N. Camille<sup>a</sup>, E. Roy<sup>a</sup>, D. Zhang<sup>c</sup>, F. Ye<sup>c</sup>, R. Jia<sup>a,g</sup>, E. Moshier<sup>a,g</sup>, M. Bonomi<sup>d,n</sup>,  
 M. Hwang<sup>h</sup>, P. Som<sup>f</sup>, M.R. Posner<sup>a,b,h,\*</sup>

R. J. Brisson<sup>2</sup>, A. Dekker<sup>1</sup>, S. Kochanny<sup>1</sup>, Z. Gooi<sup>3</sup>, M. W. Lingen<sup>6</sup>, V. M. Villafior<sup>7</sup>, D. T. Ginat<sup>8</sup>, D. J. Haraf<sup>2</sup> & E. E. Vokes<sup>1\*</sup>



## Dose and Field in Patients With Human Papillomavirus-Positive Oropharyngeal Carcinoma Treated With Intensity-Modulated Radiation Therapy

**276 Pz**

**Low-risk: 1b – IV → 30Gy**

**Intermediate-risk: II – V → 50Gy**

**GTV: 70Gy**

**GNV: 70Gy**

**plus**

**Platinum-based chemotherapy**

**Dose and Field in Patients With Human Papillomavirus-Positive Oropharyngeal Carcinoma Treated With Intensity-Modulated Radiation Therapy**

C. Jillian Tsai, MD, PhD; Sean M. McBride, MD, MPH; Nadeem Riaz, MD, MS; Jung H. Kim, MD; Daniel J. Spielsinger, BS; Todd Waldenberg, BS; Daphna Gelblum, MD; Yao Yu, MD; Kaveh Zakeri, MD; Richard J. Wong, MD, PhD; Lara Dunn, MD; David G. Pfister, MD

**Outcomes:**

**LRC**

**DFS**

**PFS**

**OS**

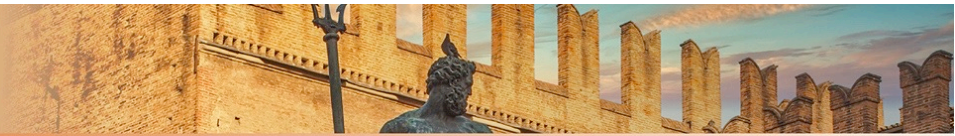


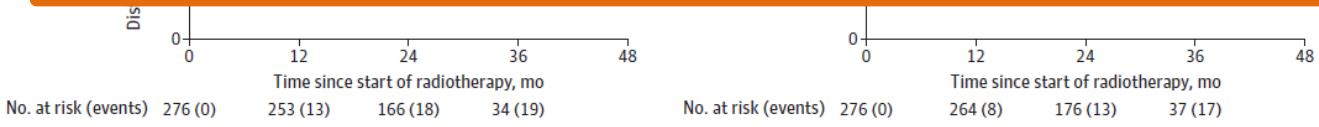
Figure 1. Survival Outcomes of the Study Cohort From Start of Radiotherapy

A

**Table 2. Radiation Doses to Gross Tumor and Subclinical Regions in Published Trials of Treatment Deintensification**

Source	Dose to gross tumor/tumor bed, Gy	Dose to subclinical regions, Gy	Outcome, % of patients		
			2-y LRC	2-y PFS	Use of feeding tube
Gillison et al, <sup>13</sup> 2019 (RTOG 10-16)	70	50-56	95	86	61.5
Yom et al, <sup>9</sup> 2021 (NRG HN 002)	60	48-54	96.7	90.5	21.7
Chera et al, <sup>14</sup> 2019 (University of North Carolina)	60	54	95	86	34
Sher et al, <sup>24</sup> 2021 (University of Texas Southwestern)	70	40	88	81	33
Deschuymer et al, <sup>25</sup> 2020 (Belgium)	70	40	76.4	61.3	NA
Ma et al, <sup>12</sup> 2019 (Mayo Clinic [postoperative])	30-36 (Twice daily)	30-36 (Twice daily)	96.2	91.15	0.9
Chen et al, <sup>15</sup> 2017 (University of California, Davis [induction chemotherapy])	54	43	93	92	7
Seiwert et al, <sup>10</sup> 2019 (OPTIMA [induction chemotherapy])	45-75	30-54	98	94.5	29
Marur et al, <sup>11</sup> 2017 (ECOG 13-08 [induction chemotherapy])	54	51.3	NA	80	NA

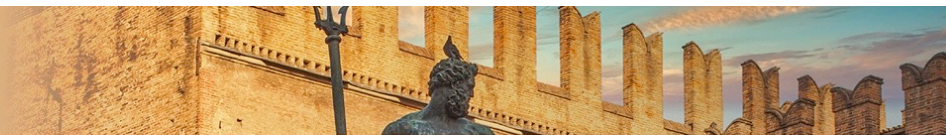
Abbreviations: ECOG, Eastern Cooperative Oncology Group; LCR, locoregional control; NA, not applicable; PFS, progression-free survival; RTOG, Radiation Therapy Oncology Group.



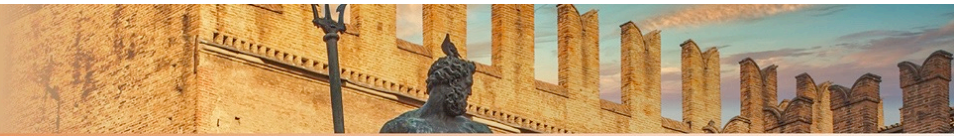
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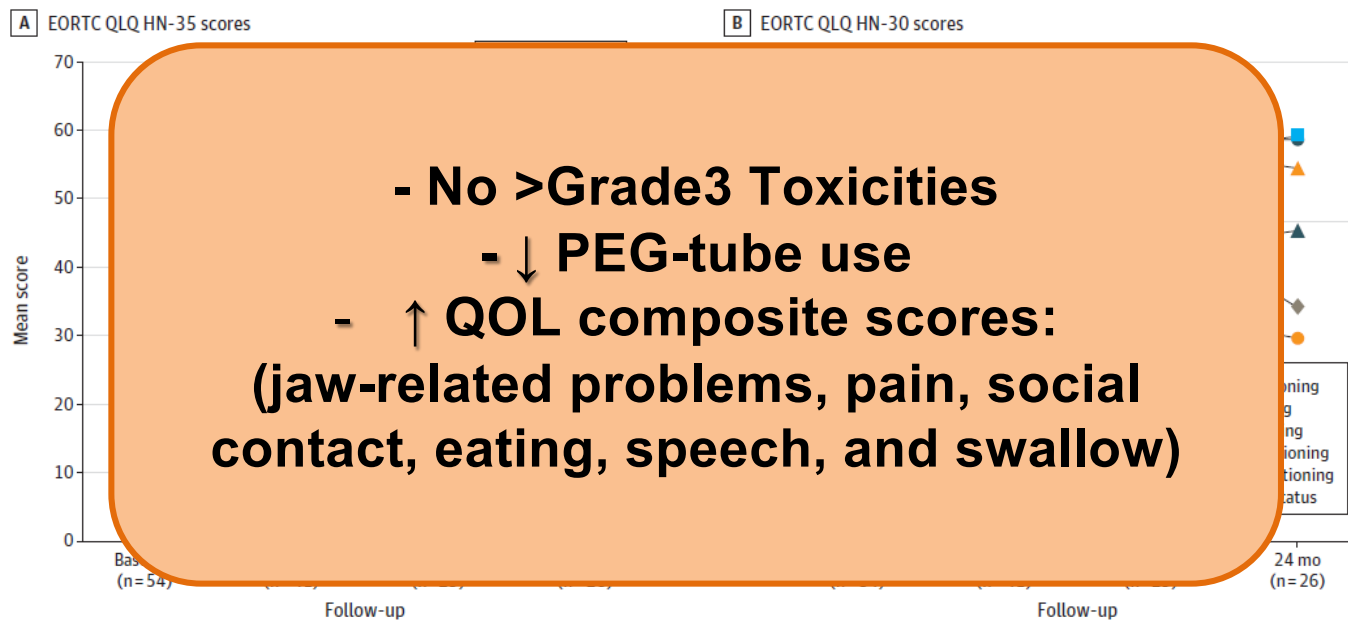


# STANDARD COURSE VS DE-ESCALATION DOSE/VOLUME: TOXICITIES



## Toxicities

Figure 3. Patient-Reported Outcomes Measured by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Scores



- No >Grade3 Toxicities  
 - ↓ PEG-tube use  
 - ↑ QOL composite scores:  
 (jaw-related problems, pain, social contact, eating, speech, and swallow)

↑ in Elective  
 patients With  
 With

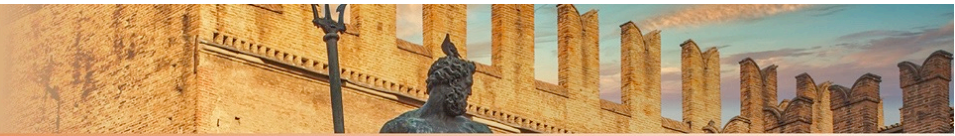


ORIGINAL ARTICLE

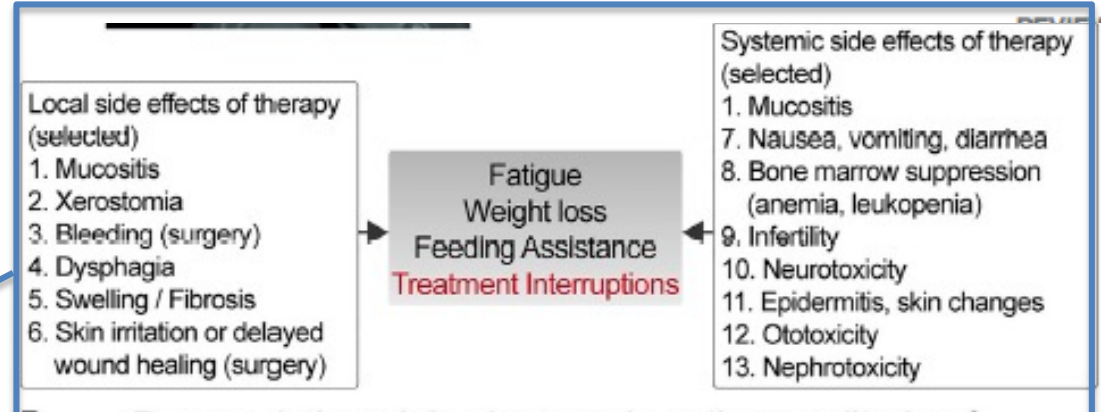
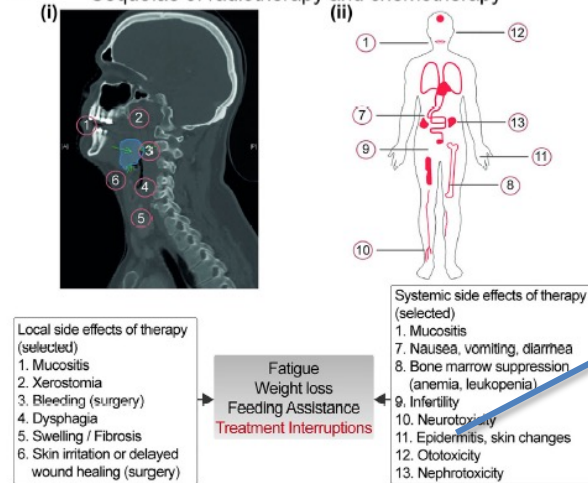
OPTIMA: a phase III clinical trial for human papillomavirus-positive oropharyngeal cancer

T. Y. Seiwert<sup>1†</sup>, C. C. Forster<sup>2</sup>, R. J. Brisson<sup>5</sup>, A. Dekker<sup>3</sup>, E. E. Vokes<sup>1\*</sup>

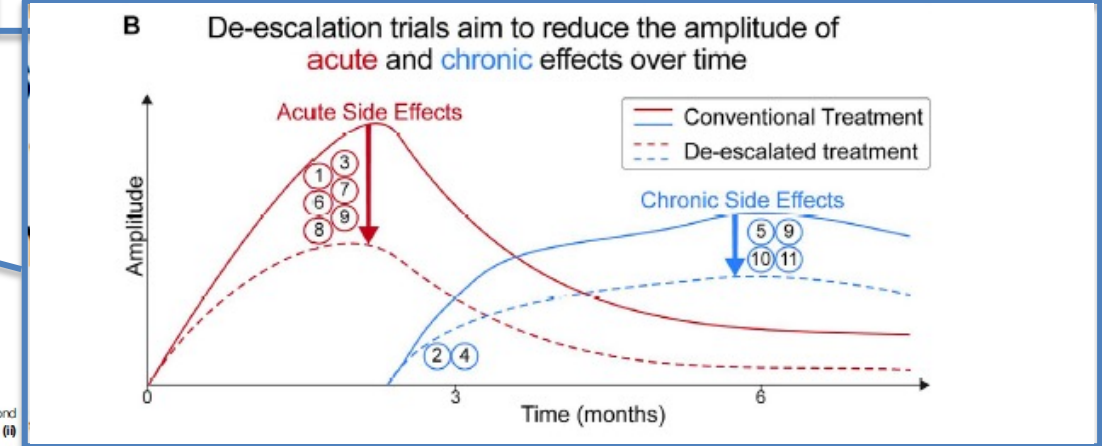
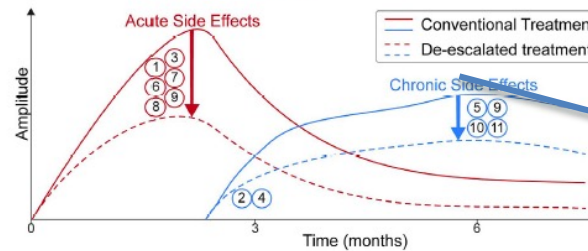
Higher scores indicate greater perceived dysfunction for EORTC QLQ HN-35 but better global functional status for EORTC QLQ-30. EORTC QLQ H&N35 indicates Head and Neck Module; EORTC QLQ-C30, Core Questionnaire 30.



### A Sequelae of radiotherapy and chemotherapy



### B De-escalation trials aim to reduce the amplitude of acute and chronic effects over time

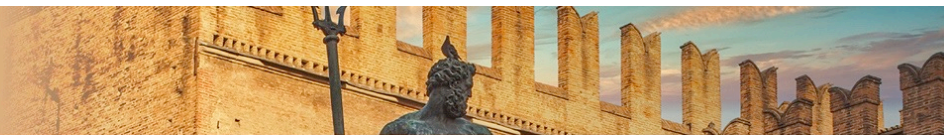


**FIGURE 1 | (A)** Acute and late toxicity profile of local and systemic chemotherapy. **(i)** Sagittal view of a CT-scan shows the patient's tumor (in blue). Local therapy (surgery and radiotherapy) and systemic treatment can result in acute side effects (occurring within the first 90 days of treatment) or chronic side effects (lasting beyond 90 days). Local side effects include dermatitis, mucositis, xerostomia (dry mouth), dysphagia (difficulty swallowing), bleeding, wound healing swelling, and fibrosis. **(ii)** Systemic side effects are related to the cytotoxic properties of chemotherapy. Increased rates of adverse events (occurring synergistically due to the combination of radiotherapy/chemotherapy) may lead to treatment interruptions, jeopardizing patient outcomes. **(B)** Kinetics of adverse events over time. The aim of de-escalation trials is to flatten the curve of adverse effects [whether acute (in red) or chronic (in blue)], thereby improving the quality of life of patients with HNSOC and cancer survivors.

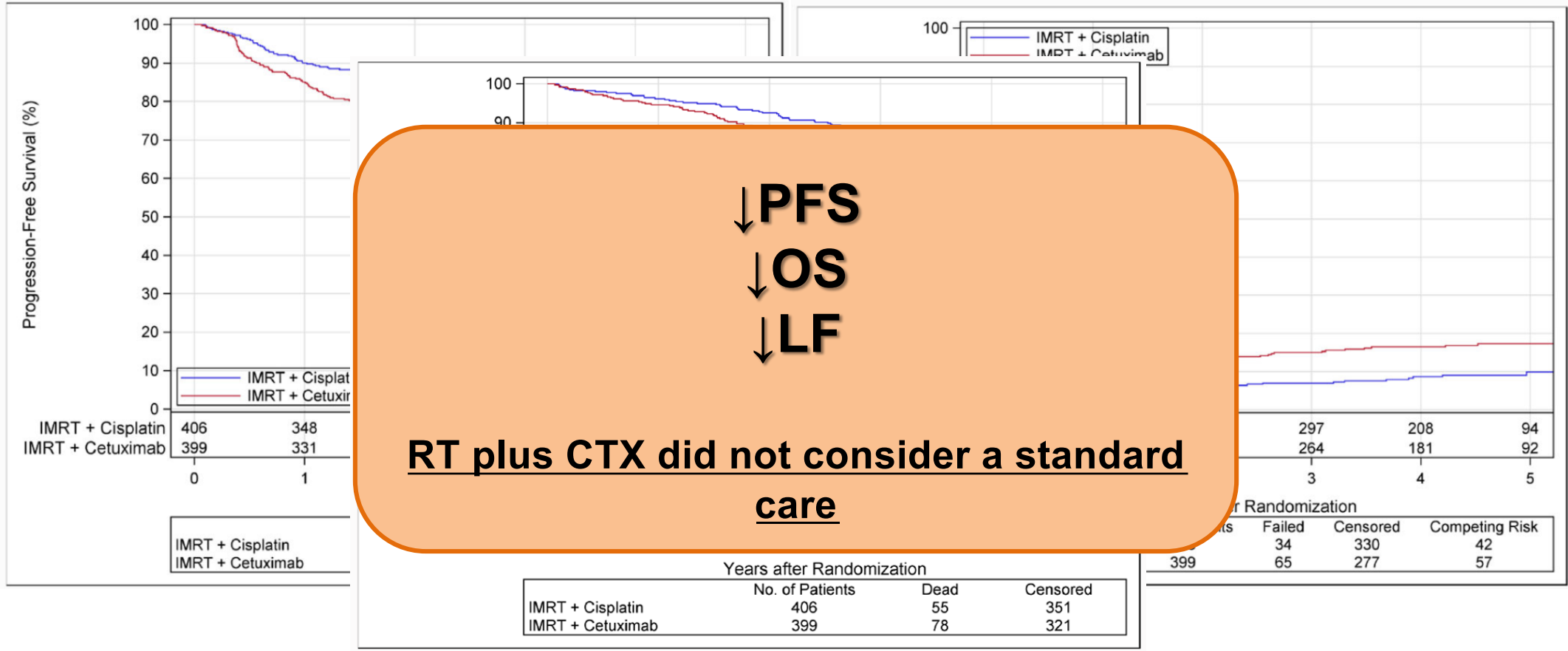
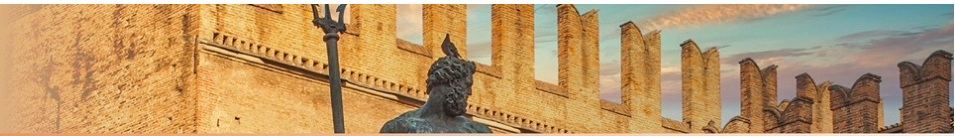
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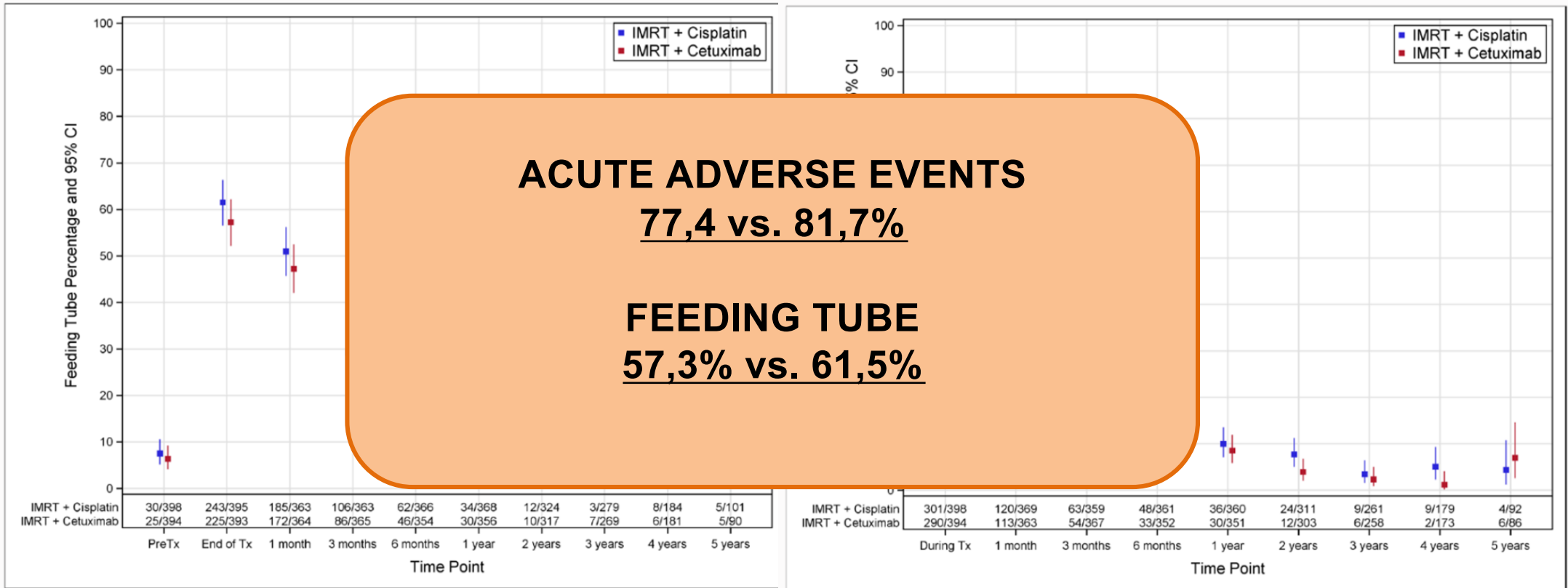
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# CHEMO-RADIOTHERAPY VS BIO-RADIOTHERAPY: CLINICAL OUTCOME AND TOXICITIES



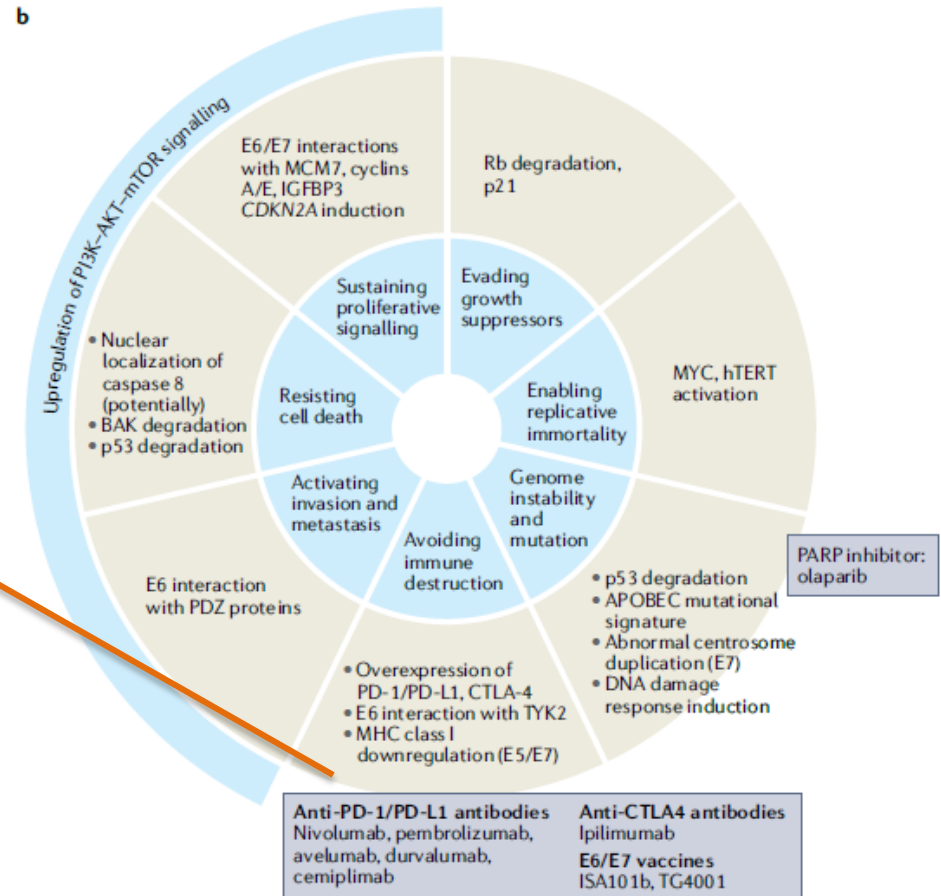


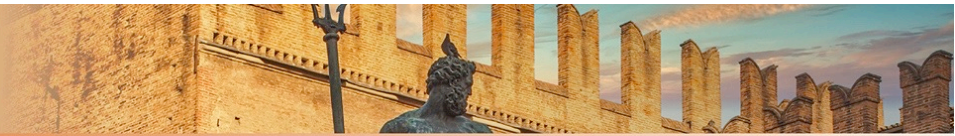




## Dose Reduction and Immunotherapy

Upregulation of the immune-checkpoint protein **PD-L1** has been observed at higher frequencies in patients with HPV+





Published in *Journal of Oral Oncology*

**Nivolumab for squamous survival in HPV-expressing**

Robert L. Ferraro, Liang Chen, Liang Even, Francis Tamara Rorick, and Maurizio

Table 7 | Ongoing immunotherapy clinical trials for HPV+ OPSCC

Study	Cohort	Treatment	Outcome measures	Current status
IMvoke010 (NCT03452137)	406 patients, with a CR/PR or stable disease following definitive local therapy	Atezolizumab or placebo as adjuvant therapy after definitive local therapy for patients with high-risk disease	EFS (primary outcome), OS and AEs included as secondary outcomes	Active
NCT03799445	180 patients with T1 N2a–N2 cM0, T2 N1–2c M0, T3 N0–2 cM0 (AJCC 7th ed) or stage I/II disease and T2 N0 (AJCC 7th ed)	IMRT (50–66 Gy) plus nivolumab and ipilimumab	Dose-limiting toxicities, CR rate, PFS (primary outcomes); grade 3 toxicity, clinical CR, acute toxicities, swallowing, treatment failure, OS	Recruiting
NCT03410615	180 patients with advanced, intermediate-stage, non-metastatic disease	IMRT (50–66 Gy) plus nivolumab and ipilimumab	PFS (primary outcome); clinical CR, local regional control, distant MFS, OS, toxicity, acute toxicities	Recruiting
NCT03669718	194 patients with recurrent and/or advanced disease	IMRT (50–66 Gy) plus nivolumab and ipilimumab	OS (primary outcome), PFS, toxicity, acute toxicities	Recruiting
NCT03952585	711 patients with early stage, p16 non-smoking-associated disease	image-guided RT or IMRT plus concurrent cisplatin vs reduced-dose image-guided RT or IMRT plus concurrent cisplatin vs reduced-dose image-guided RT or IMRT plus nivolumab	PFS, QOL (primary outcomes), locoregional failure, distant failure, OS, AEs	Recruiting
NCT03811015	744 patients with a ≥10 pack-year smoking history and stage T1–2 N2–3 or T3–4 N0–3 disease or <10 pack-years with stage T4 N0–3 or T1–2 N2–3	Cisplatin plus IMRT followed by nivolumab vs cisplatin plus IMRT followed by observation with potential crossover to nivolumab at 12 months	PFS, OS, negative FDG–PET at 12 weeks post-therapy	Recruiting

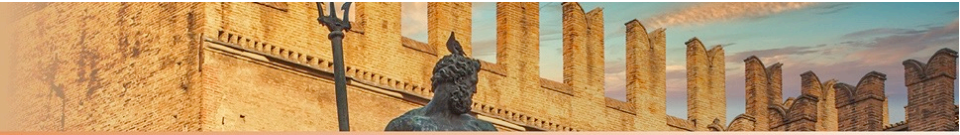
**Is the concomitant immuno-radiotherapy the feature??**



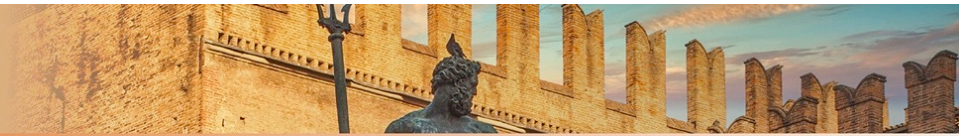
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# CONCLUSION



## CONCLUSION

### HNO

#### Leitthema

HNO  
<https://doi.org/10.1007/s00106-019-00766-3>

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S. Tribius<sup>1</sup> · N. Würdemann<sup>2</sup> · S. Laban<sup>3</sup> · T. K. Hoffmann<sup>3</sup> · S. J. Sharma<sup>2</sup> · J. P. Klussmann<sup>2</sup>

<sup>1</sup> Asklepios Tumorzentrum Hamburg, Asklepios Klinik St. Georg, Hermann-Holthusen-Institut für Strahlentherapie, Hamburg, Deutschland

<sup>2</sup> Medizinische Fakultät, Klinik für Hals-, Nasen-, Ohrenheilkunde, Kopf- und Halschirurgie, Universitätsklinik zu Köln, Köln, Deutschland

<sup>3</sup> Kopf-Hals-Tumorzentrum des Comprehensive Cancer Center Ulm, Klinik für Hals-Nasen-Ohrenheilkunde, Universitätsklinik Ulm, Ulm, Deutschland

Leitthema | [Published: 16 March 2022](#)

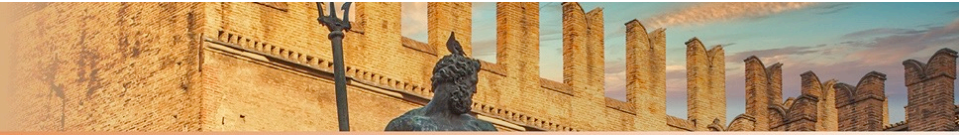
## Highlights der ASCO- und ESMO-Jahrestagungen 2021 zur Strahlentherapie von Kopf-Hals-Tumoren

Highlights from the 2021 ASCO and ESMO annual meetings on radiotherapy of head and neck cancer

[Markus Hecht](#) , [Jens von der Grün](#), [Sabine Semrau](#), [Sarina Müller](#), [Thomas Weissmann](#), [Udo S. Gaipl](#), [Heinrich Iro](#), [Rainer Fietkau](#) & [Antoniou-Oreste Gostian](#)

*HNO* **70**, 258–264 (2022) | [Cite this article](#)

## HPV-assoziierten Kopf- tumoren – Highlights Jahrestagung 2019



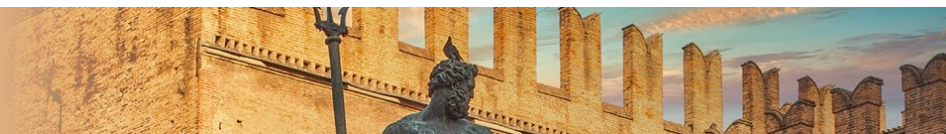
## TAKE HOME MESSAGE

- **De-escalation dose** could be considered a **valid approach** in **OPCs-HPV+** patients **remaining** the first therapeutic choice **over the Bio-Radiotherapy course**
- **Clinical Outcomes are comparable** between standard and de-escalation dose/volume
- De-intentification dose obtained better results in terms of **Toxicity, use of feeding tube** with positive impact on patients' QoL
- Could be the **immuno-radiotherapy** the future of concomitant approach?

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## *Grazie per l'attenzione*



 Associazione Italiana  
Radioterapia e Oncologia clinica

 Società Italiana di Radiobiologia



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