13. Prague ONCO
ONCOLOGY COOPERATION

HPV-asociované karcinomy hlavy a krku

Jan Klozar
Department of Otolaryngology,
Head and Neck Surgery,
First Medical Faculty, Charles University Prague

CZECH HEAD AND NECK CANCER COOPERATIVE GROUP

CLINICAL IMPLICATIONS OF HPV IN OROPHARYNGEAL CANCER

1. Epidemiology (New HNC patient)
2. Differences between HPV+ and HPV- tumors
3. Markers of HPV infection
4. Infuence on treatment strategy

EPIDEMIOLOGY

- HR HPVs are responsible for the majority of oropharyneal (tonsilar and base of tongue) 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

THE SAME LOCATION
TWO DISTINCT DISEASES

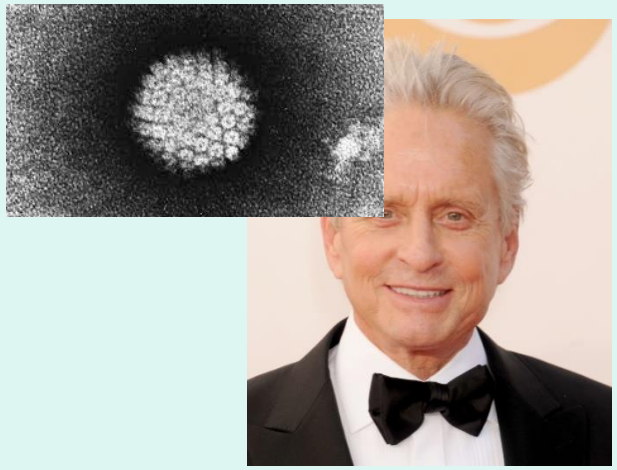
- Damage to p53 and pRb pathways by viral oncoproteins E6 and E7
- nonkeratinizing morphology („basaloid“ appearence)
- Small primary tumor, frequently CUP
- Important nodes, often cystic
- Rare second primary

- Tobbacco induced mutations (eg. p53 pathway, …)
- SCC of various differentiation (grade 1-3)
- Larger primary
- Nodal involvement moderately frequent
- Frequent second primary (H+N, lung, oesophagus)

Other HN tumors > 90%
Orofarynx ~ 30%

Traditional risk factors
Corresponding patient type
High comorbidity level
Lower socioeconomic status
Worse survival

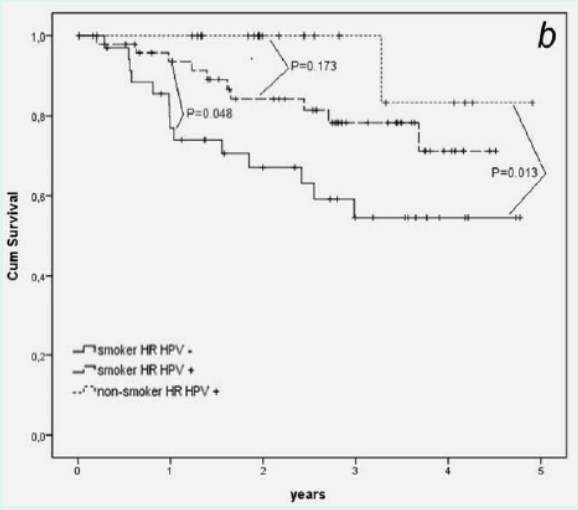
Orofarynx ~ 70%
Other HN tumors ~ 1%



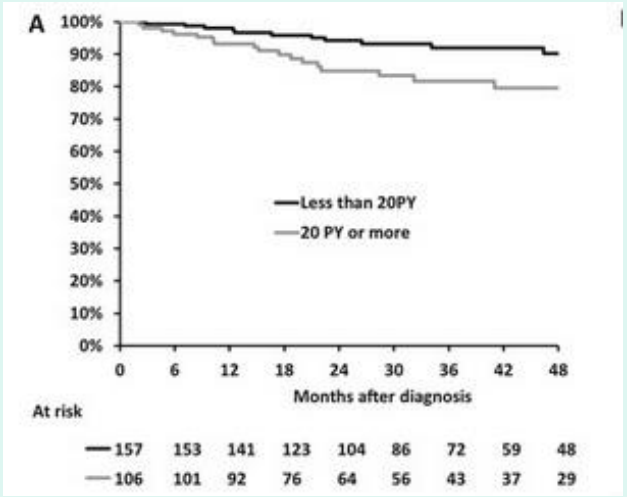
younger, healthier,
more educated, non smoker,
Different sexual behavior??
Higher socioeconomic status
Better prognosis

Orofaryngeal cancer: HPV positive Smoker

Intermediate prognosis



Rotnaglova et al. Int J Cancer, 2011

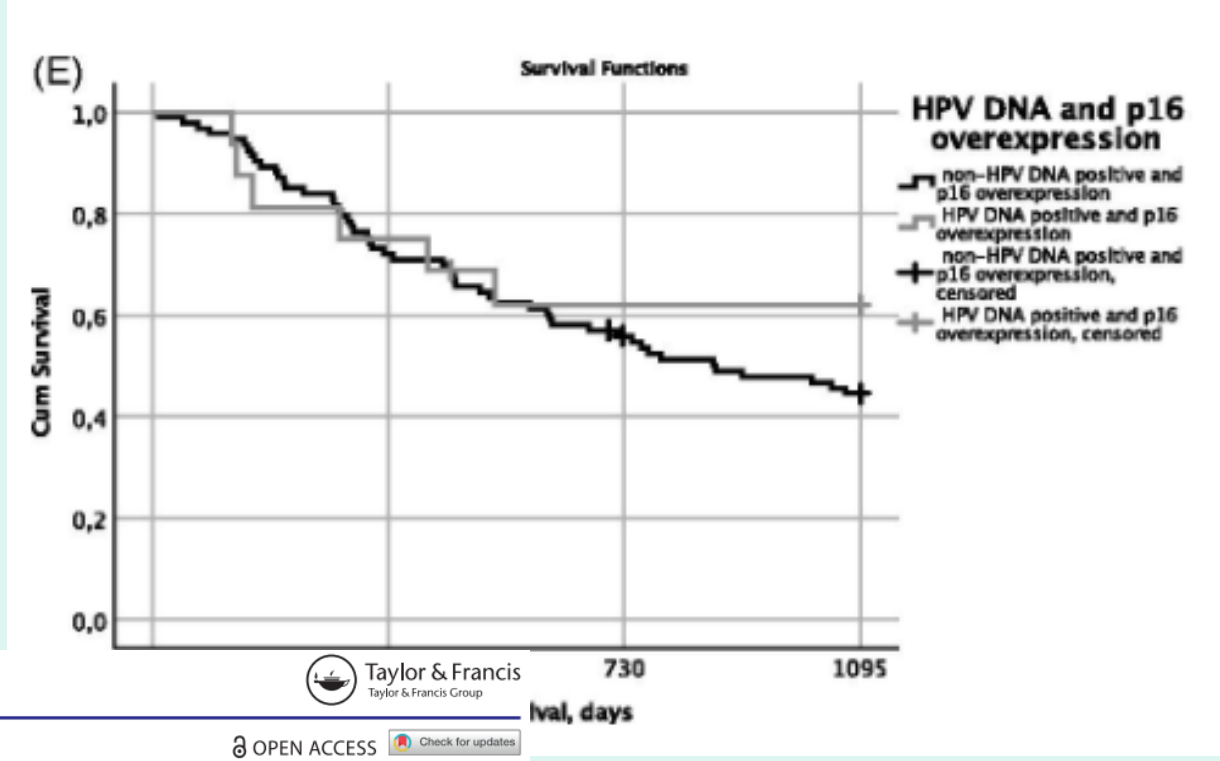


Mirghani et al. Oral Oncol, 2018

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

HPV positivity does not influence survival in non tonsilar and non base of tongue oropharyngeal cancers



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2021, VOL. 141, NO. 1, 89–94
https://doi.org/10.1080/00016489.2020.1813906

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ARTICLE

OPEN ACCESS Check for updates

The value of p16 and HPV DNA in non-tonsillar, non-base of tongue oropharyngeal cancer

Lalle Hammarstedt[a], Stefan Holzhauser[b], Mark Zupancic[b], Fani Kapoulitsa[b], Ramona G. Ursu[b,c], Torbjörn Ramqvist[b], Linnea Haeggblom[b], Anders Näsman[b,d], Tina Dalianis[b]* and Linda Marklund[a]*

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

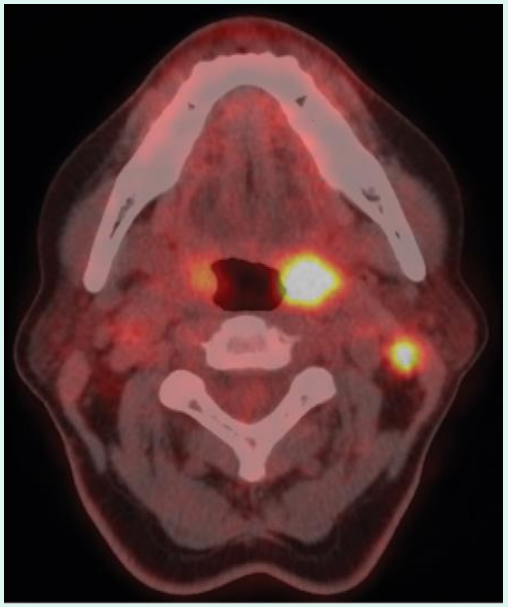
Prognostic Stage Groups

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



TONSILAR TUMOR 25 MM
2 IPSILATERAL LYMPHNODES

P16 negative
↓
T2 N2b M0

Stage IV A

P16 positive
↓
T2 N1 M0

Stage I

MARKERS OF HPV INFECTION

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

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%)

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

Impact of HPV status on therapeutic strategy

- Choice of treatment modality
- Deescalation of the treatment of HPV positive tumors
- (Escalation of the treatment of HPV negative tumors)

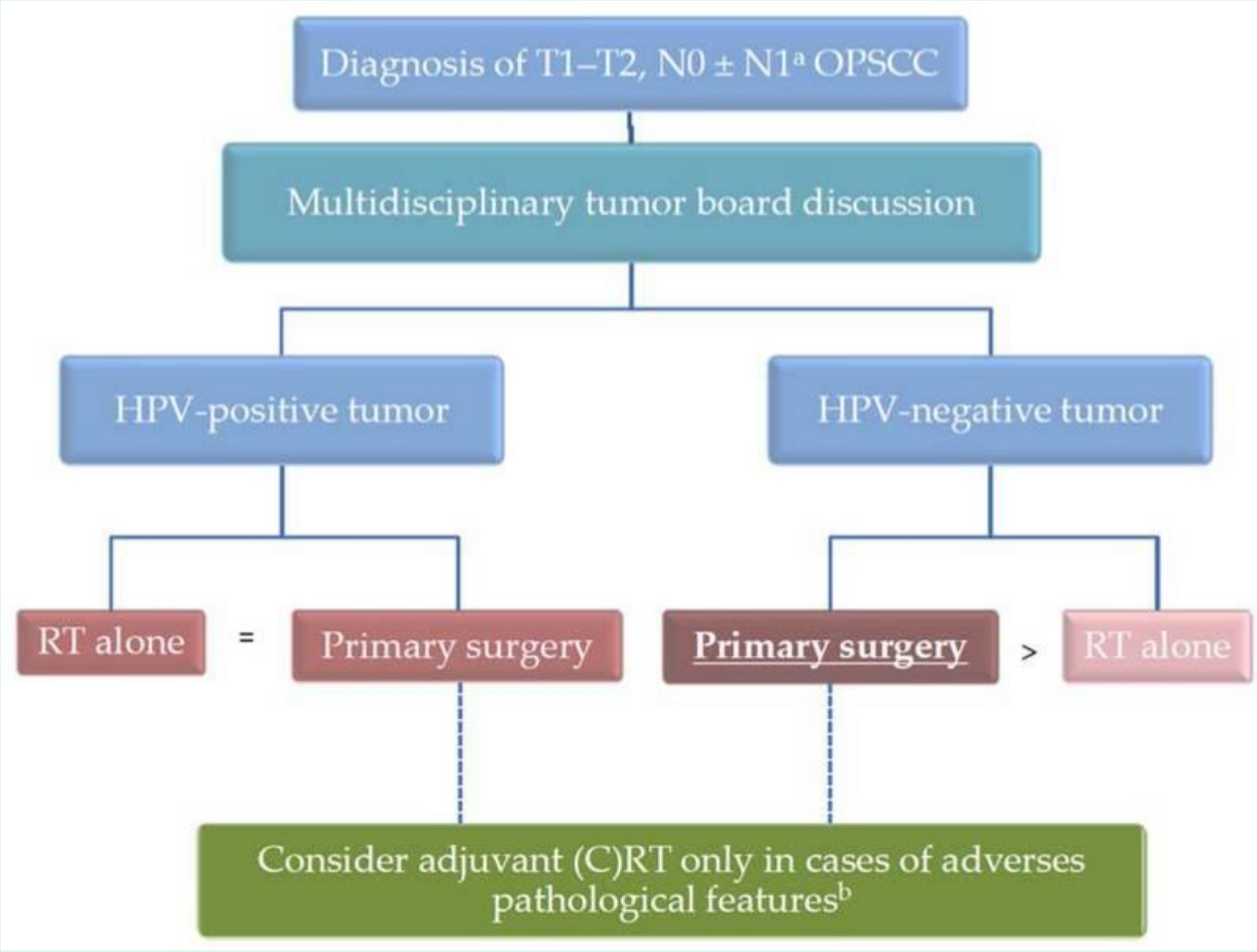
Impact of HPV status on the choice of treatment modality

- Results of surgery and RT (CRT) similar
- Importance of QoL
- Better oncologic results with upfront surgery in HPV negative cancers (?)

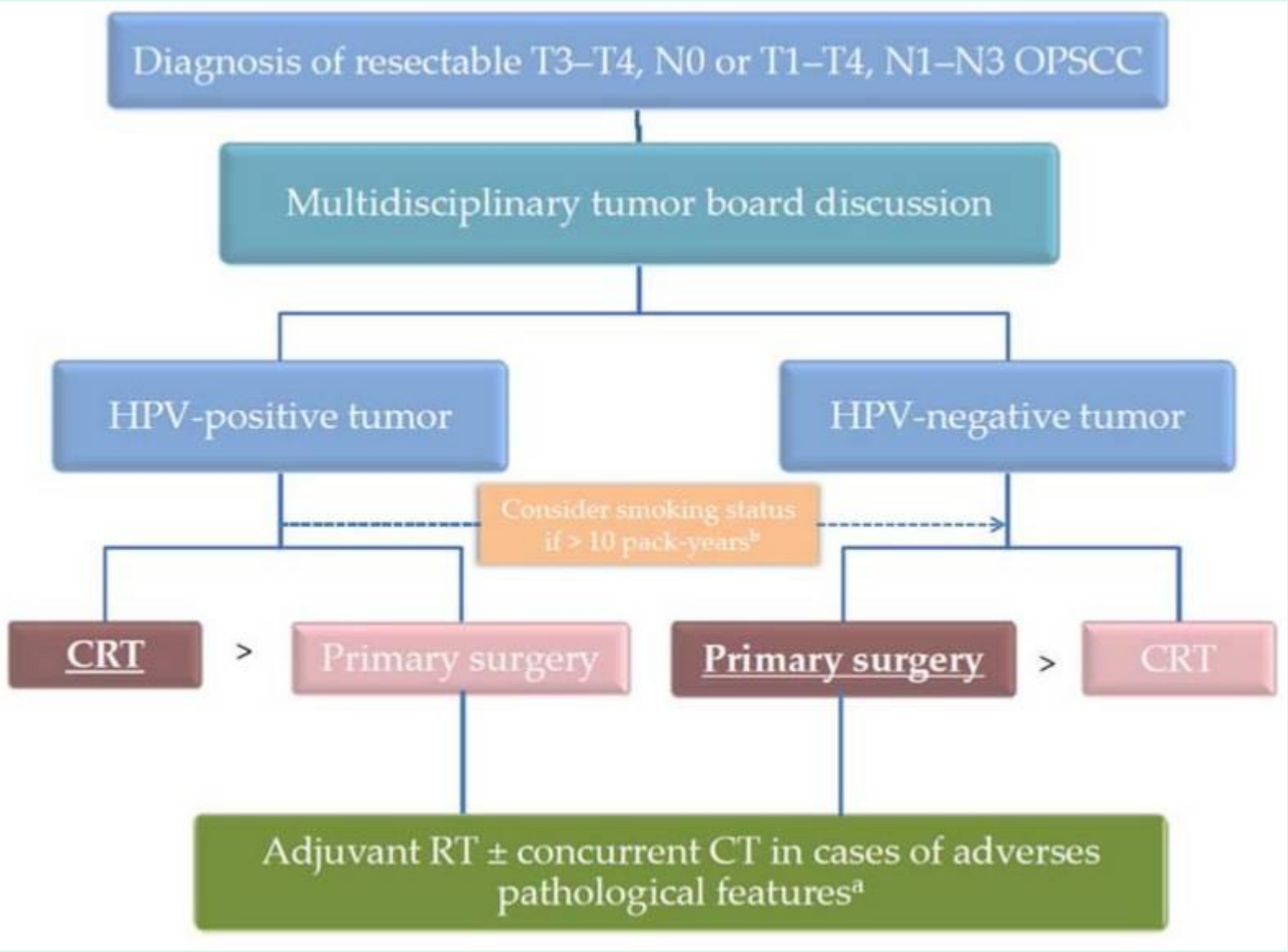
Guily, J.L.S. et al. Oropharyngeal cancer prognosis by tumour HPV status in France: The multicentric Papillophar study. Oral Oncol. 2017, 67**,** 29–36.

Culié, D. et al. Upfront surgery or definitive radiotherapy for patients with p16-negative oropharyngeal squamous cell carcinoma. AGETTEC multicentric study. Eur. J. Surg. Oncol. (EJSO) 2020, 47, 367–374.

Kamran, S.Cet al. Primary surgery versus primary radiation-based treatment for locally advanced oropharyngeal cancer. Laryngoscope 2017, 128, 1353–1364.



Bozec, A.; Culié, D.; Poissonnet, G.; Demard, F.; Dassonville, O. Current Therapeutic Strategies in Patients with Oropharyngeal Squamous Cell Carcinoma: Impact of the Tumor HPV Status. Cancers 2021, 13, 5456



Bozec, A.; Culié, D.; Poissonnet, G.; Demard, F.; Dassonville, O. Current Therapeutic Strategies in Patients with Oropharyngeal Squamous Cell Carcinoma: Impact of the Tumor HPV Status. Cancers 2021, 13, 5456

Early stage OPSCC
Choice of treatment TOS x RT

ORATOR Trial

Quality-of-life scores were statistically superior after radiation, although this difference did not meet the predefined threshold of a clinically meaningful change. Overall, transoral robotic surgery and RT had differing toxicity profiles, but similar long-term oncologic outcomes.

Nichols AC et al. Randomized Trial of Radiotherapy Versus Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma: Long-Term Results of the ORATOR Trial *Journal of Clinical Oncology* Published online January 07, 2022.

Early stage OPSCC
Choice of treatment TOS x RT

Ongoing trials (endpoint: OS, Dysphagia)

ORATOR II (NCT03210103)
HPV-positive T1-2,N0-2 (8th TNM edition) OSCC randomized between either de-escalated definitive radiotherapy with 60 Gy (plus concomitant chemotherapy depending on nodal status) or transoral surgery followed by de-escalated adjuvant radiotherapy with 50–60 Gy depending on pathological risk factors.

2017-A02253-50
IMRT and Primary Transoral Surgery in the Treatment of Squamous Cell Carcinomas (TORPHYNX)

EORTC-1420-HNCG-ROG
The "Best of" Radiotherapy vs the "Best of" Surgery in Patients With Oropharyngeal Carcinoma

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 STRATEGIES

Less aggressive surgical approaches

Deescalation of the radiation dose/volume

- in definitive RT (CRT)
- in adjuvant seting

Reduction of chemotherapy-related toxicity

Use of induction CT for selecting patients for deescalation

Reduction of adjuvant RT (omission of CT) in presence of risk factors (close R, ECS)

De-escalation trials in which the radiation dose/volume was de-escalated.

Study	# Patients	Phase	Study Arm(s)	Results
Chera et al. [8,9]	44	II	RT (60 Gy) + cisplatin (30 mg/m^2 weekly)	3-year LRC 100% 3-year DMFS 100% 3-year OS 95%
NRG-HN002 [6,10]	306	II	RT (60 Gy) + cisplatin vs. RT (60 Gy)	2-year PFS 90.5% (RT + cisplatin) vs. 87.6% (RT) 2-year OS 96.7% (RT + cisplatin) vs. 97.3% (RT)
MC1273 [11]	80	II	Adjuvant RT (30 Gy in 1,5 Gy twice per day or 36 Gy in 1,8 Gy twice per day)	2-year LRC 96.2% 2-year PFS 91.1% 2-year OS 98.7%
ECOG 3311 (ASCO abstract [12])	519	II	Depending on the risk profile after resection: Regular aftercare (low-risk, group A), randomization between adjuvant RT with 50 Gy (group B) or 60 Gy (group C) (intermediate-risk), additive cisplatin-based CRT (66 Gy) (high-risk, group D)	2-year PFS Group A: 93.9% Group B: 95.0% Group C: 95.9% Group D: 90.5%
AVOID [13]	60	II	Omission of the postoperative RT for the primary tumor site	2-year LRC 98.3% 2-year PFS 92.1% 2-year OS 100%

Rühle, A.; Grosu, A.-L.; Nicolay, N.H. De-Escalation Strategies of (Chemo)Radiation for Head-and-Neck Squamous Cell Cancers—HPV and Beyond. Cancers **2021, 13, 2204.**

De-escalation trials in which induction CT was used for selecting patients for deescalation

Study	# Patients	Phase	Study Arm(s)	Results
ECOG 1308 [22]	80	II	In case of cCR after IC: RT (54 Gy) + cetuximab	2-year PFS 80% 2-year OS 94% For patients with cCR and 54 Gy-deescalated RT: 2-year PFS 96% 2-year OS 96%
Chen et al. [23]	44	II	After IC: RT (54 Gy) + paclitaxel for cCR or pCR, RT (70 Gy) + paclitaxel for absent cCR/pCR	2-year LRC 95% 2-year PFS 92%
Quarterback [24]	20	II	After IC: RT (70 Gy) + carboplatin vs. RT (56 Gy) + carboplatin	3-year PFS 87.5% (70 Gy) vs. 83.3% (56 Gy) 3-year OS 87.5% (70 Gy) vs. 83.3% (56 Gy)
OPTIMA [25]	62	II	Complex study conception and treatment arm allocation in dependence of response to IC	Entire cohort: 2-year LRC 98% 2-year PFS 94.5% 2-year OS 98%

Rühle, A.; Grosu, A.-L.; Nicolay, N.H. De-Escalation Strategies of (Chemo)Radiation for Head-and-Neck Squamous Cell Cancers—HPV and Beyond. Cancers **2021, 13, 2204.**

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)

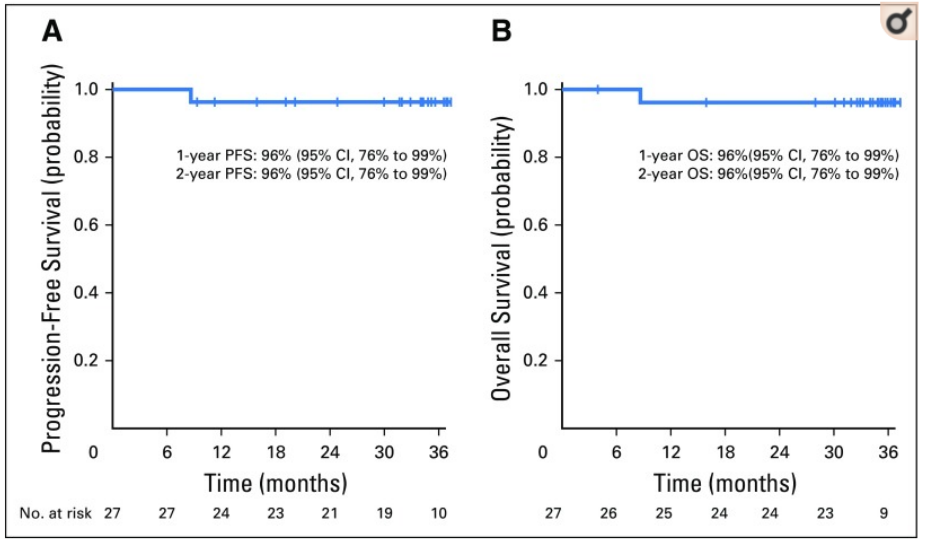
Clinical response at primary to IC:

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.

DEESCALATION OF CHEMOTHERAPY REPLACEMENT OF CISPLATIN

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

DEESCALATION OF CHEMOTHERAPY REPLACEMENT OF CISPLATIN

NCT03952585 **De-intensified Radiation Therapy With Chemotherapy (Cisplatin) or Immunotherapy (Nivolumab) in Treating Patients With Early-Stage, HPV-Positive, Non-Smoking Associated Oropharyngeal Cancer**

NCT03799445 **Phase 2 Study (With Safety Lead in) of the Safety, Tolerability and Efficacy of Anti-CTLA4 (Ipilimumab) and Anti-PD-1 (Nivolumab) in Combination With Radiation Therapy to 50-66 Gy in Low-Intermediate Volume, Local-Regionally Advanced HPV-Positive Oropharyngeal Squamous Cell Carcinoma (OPSCC)**

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Critical Review

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

Eric J. Moore, MD,* and Michael L. Hinni, MD†

*Otolaryngology/Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota; and †Otolaryngology/Head and Neck Surgery, Mayo Clinic, Scottsdale, Arizona

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]*

1 Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, **2** Department of Radiation Oncology, Mount Sinai Beth Israel, New York, New York, United States of America, **3** Department of Otolaryngology Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, **4** Department of Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, **5** Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America

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.

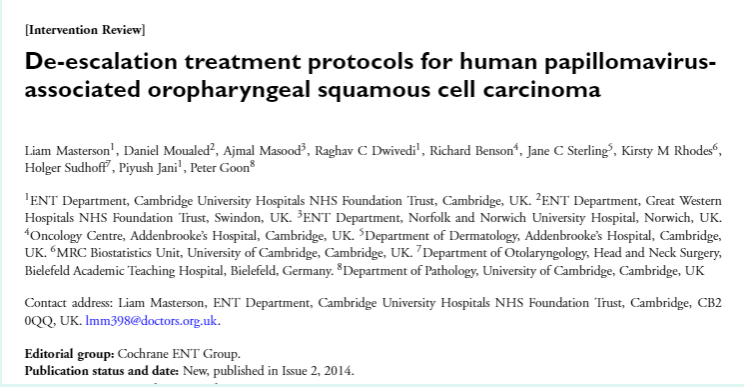
PLoS One. 2016 Dec 8;11(12)

Reduction of adjuvant RT (omission of CT) in presence of risk factors

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

(

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



[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]

[1]ENT Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. [2]ENT Department, Great Western Hospitals NHS Foundation Trust, Swindon, UK. [3]ENT Department, Norfolk and Norwich University Hospital, Norwich, UK. [4]Oncology Centre, Addenbrooke's Hospital, Cambridge, UK. [5]Department of Dermatology, Addenbrooke's Hospital, Cambridge, UK. [6]MRC Biostatistics Unit, University of Cambridge, Cambridge, UK. [7]Department of Otolaryngology, Head and Neck Surgery, Bielefeld Academic Teaching Hospital, Bielefeld, Germany. [8]Department of Pathology, University of Cambridge, Cambridge, UK

Contact address: Liam Masterson, ENT Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, UK. lmm398@doctors.org.uk.

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

CZECH HEAD AND NECK CANCER
COOPERATIVE GROUP

www.hnc-group.cz

Seminář České kooperativní skupiny pro nádory hlavy a krku, Kroměříž 28.-30.4.2022

International Conference of the Czech Head and Neck Cancer Cooperative Group, Znojmo, 30.9.-2.10.2022