Decennale di
HIGHLIGHTS in RADIOTERAPIA

Update degli Studi Practice Changing 2024

Undicesima Edizione

In memoria di Renzo Corvò

ROMA
30-31 gennaio 2025
Starhotels Metropole

NEW EVIDENCE AND PRACTICE CHANGING TREATMENTS IN HEAD AND NECK TUMORS

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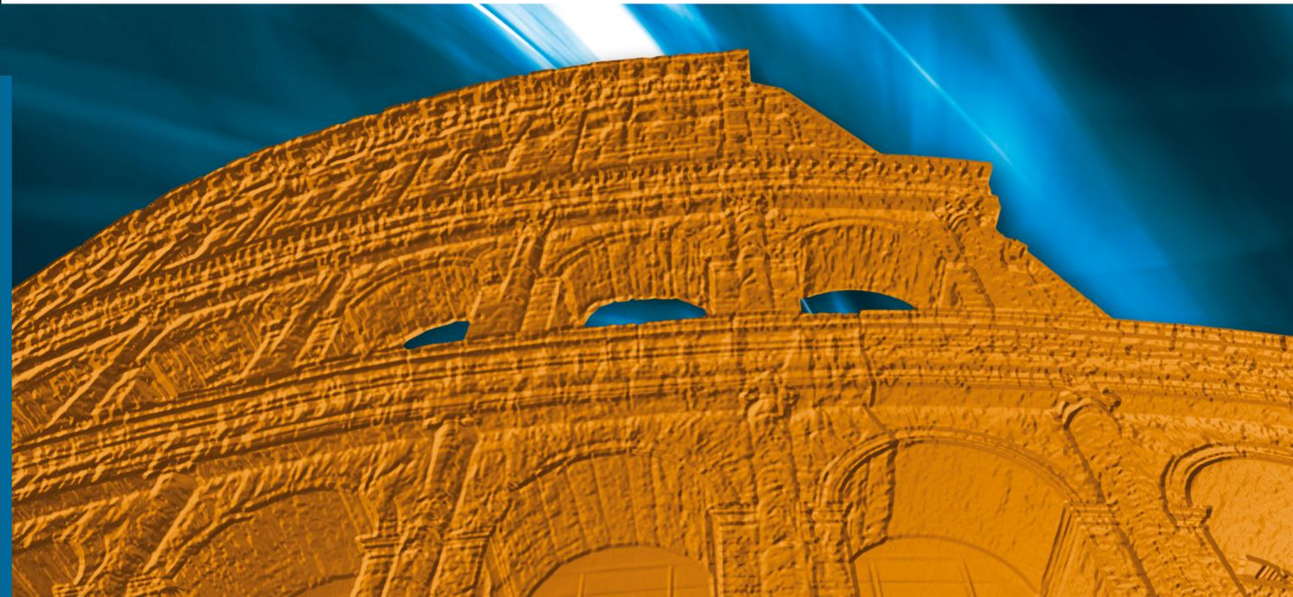
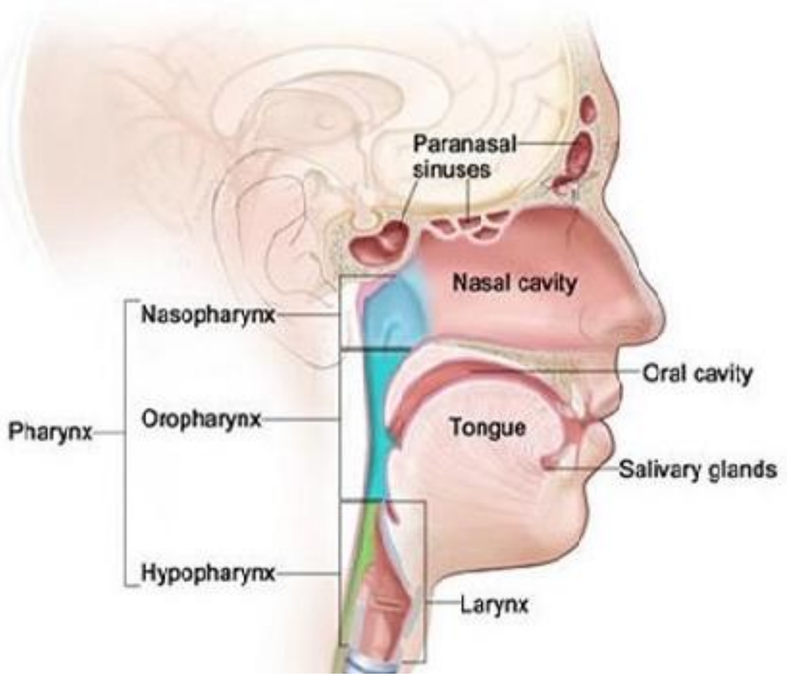


NO DISCLOSURE TO REPORT

AGENDA

- *Head and Neck cancer – overview*

- *Oropharyngeal cancer*
- *Nasopharyngeal cancer*
- *Oral cavity cancer*
- *Laryngeal Cancer*
- *Salivary Gland*



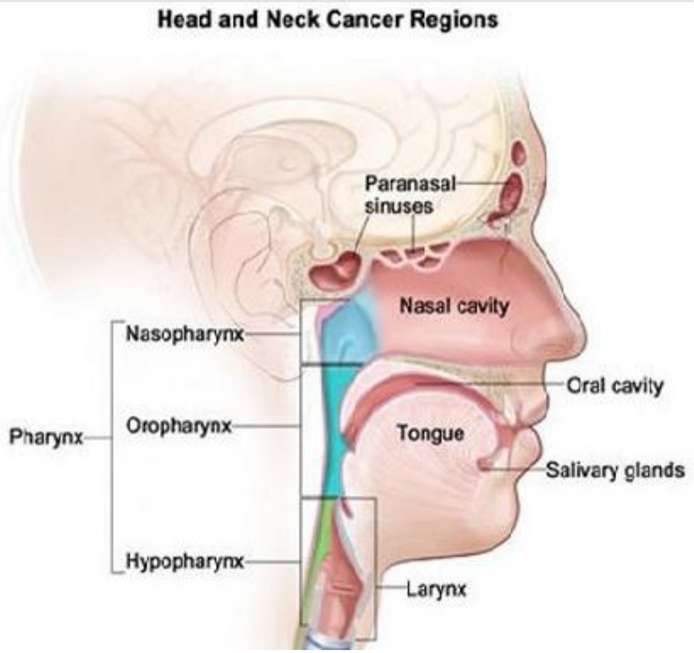
-Head and Neck cancer – overview

Systemic therapies

Toxicity

Proton therapy

Survivors



Standard versus fractionated high-dose cisplatin plus radiation for locally advanced head and neck cancer: Results of the CisFRad (GORTEC 2015-02) randomized phase II trial

Christian Borel [a,*,1], Xu-Shan Sun [b,c,1], Alexandre Coutte [d], Guillaume Bera [e], Christian Sire [e], Sylvie Zanetta [f], Marc Alfonsi [g], Guillaume Janoray [h], Thierry Chatellier [i], Muriel Garcia-Ramirez [j], Elisabeta Gherga [b], Yasser Hammoud [c], Mickaël Burgy [a,k], Nelly Etienne-Selloum [a,k], Adeline Pechery [l], Marie-Hélène Girard-Calais [l], Michel Velten [a,m], Jean-Pierre Pignon [n], Mathilde Wanneveich [l], Jean Bourhis [o]

CT

Primary endpoint : cumulative delivered CDDP dose

Aim: Cisplatin fractionation may allow, by decreasing the peak serum concentration, to decrease toxicity.

124 pts

Postoperative HR or definitive CTRT comparing
HD-Cis
to
FHD-Cis (25 mg/m2/d d1-4 q3w for 3 cycles)

Radiotherapy and Oncology 197 (2024)

RESULTS

Median cisplatin cumulative delivered dose was 291 mg/m2 in the FHD-Cis arm and 274 mg/m2 in the HD-Cis arm (*P* = 0.054)

However the proportion of patients receiving a third cycle of cisplatin was higher in the FHD-Cis arm: 81 % vs 64.1 % in the HD-Cis arm (*P* = *0*.04)
Fewer patients in the FHD-Cis arm required CDDP dose reductions

Lower proportion of grade 3–4 all acute toxicity in the FHD-Cis arm compared to the HD-Cis arm: 10 % vs 17 % (*P* = 0.002), respectively. (Hematological toxicity)

Median-FU of 48 months locoregional failure rate, PFS and OS **were similar** between the two arms.

…..for patients with borderline HD-Cis eligibility, but also for those at high risk who definitely need a third cycle of full-dose cisplatin.

an alternative worth

Oral Oncology 156 (2024) 106918

Contents lists available at ScienceDirect

Oral Oncology

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

Final analysis of a phase II trial of neoadjuvant chemoimmunotherapy for locoregionally advanced head and neck squamous cell carcinoma

Xueyan Zhao [a,1], Yan Zhou [a,1], Gang Peng [b,c,d,1], Lu Wen [b,c,d,1], Xiaohua Hong [b,c,d,1], Yuan Hu [a,1], Bian Wu [b,c,d,1], Xixi Liu [b,c,d], Zhanjie Zhang [b,c,d], Guixiang Xiao [e], JingHuang [b,c,d], Qian Ding [b,c,d], Chengzhang Yang [a], Xingao Xiong [a], Hui Ma [f], Liangliang Shi [b,c,d], Jinsong Yang [b,c,d], Jielin Wei [b,c,d], You Qin [b,c,d], Chao Wan [b,c,d], Yi Zhong [a], Yangming Leng [a], Tao Zhang [b,c,d], Gang Wu [b,c,d], MinYao [g], Yulin Jia [h], Xiaomeng Zhang [a,*], Kunyu Yang [b,c,d,**]

Neoadj CT + immuno

30 pts

- ❑ T3-4 73.3%
- ❑ N2-3 76.7%
- ❑ p16- 76.7%

3 cycles: docetaxel, CDDP, camrelizumab every 3 weeks

⇩

Surgery

⇩

RT postop was administered four weeks following surgery
Total dose 50-60 Gy

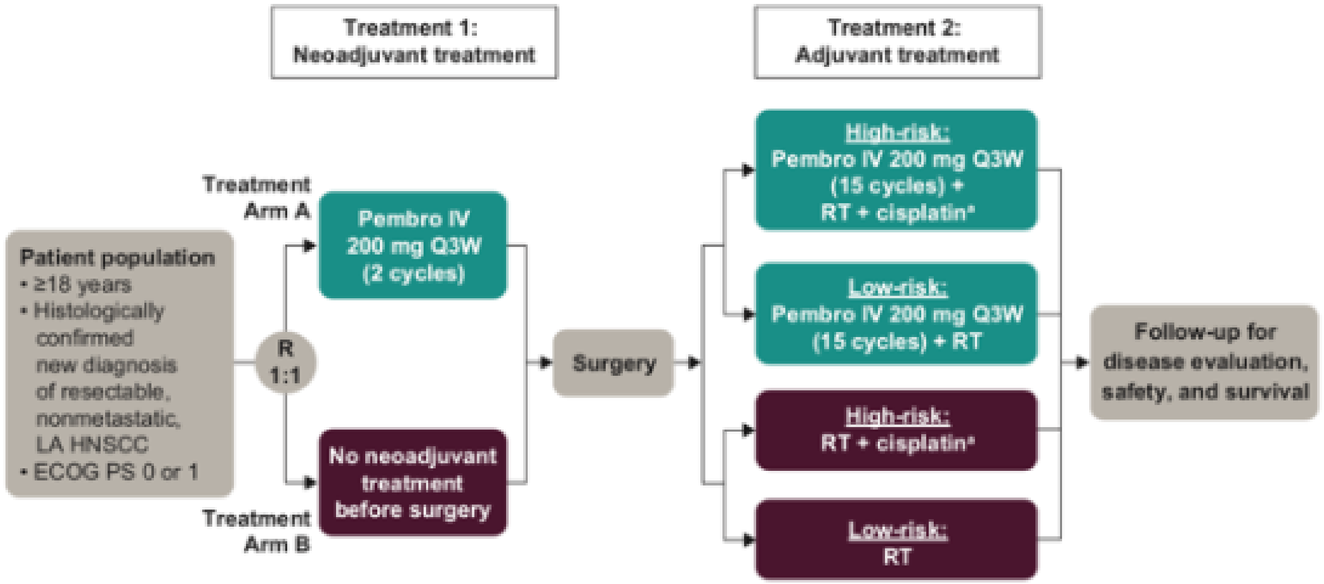
Median FU of 33.7 months, neither median DFS nor OS were reached for this trial
pCR and MPR rates of 37 % and 74 %
The probabilities of OS and DFS at 2 years were 100 % and 90 % respectively

Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)

Neoadjuvant immunotherapy

KEYNOTE-689 trial

Resectable SCC
-Stage III HPV positive oropharyngeal tumor size (T) 4, lymph node involvement (N) 0-2,
-Stage III or IVA oropharyngeal HPV negative;
-Stage III or IVA larynx/hypopharynx/oral cavity

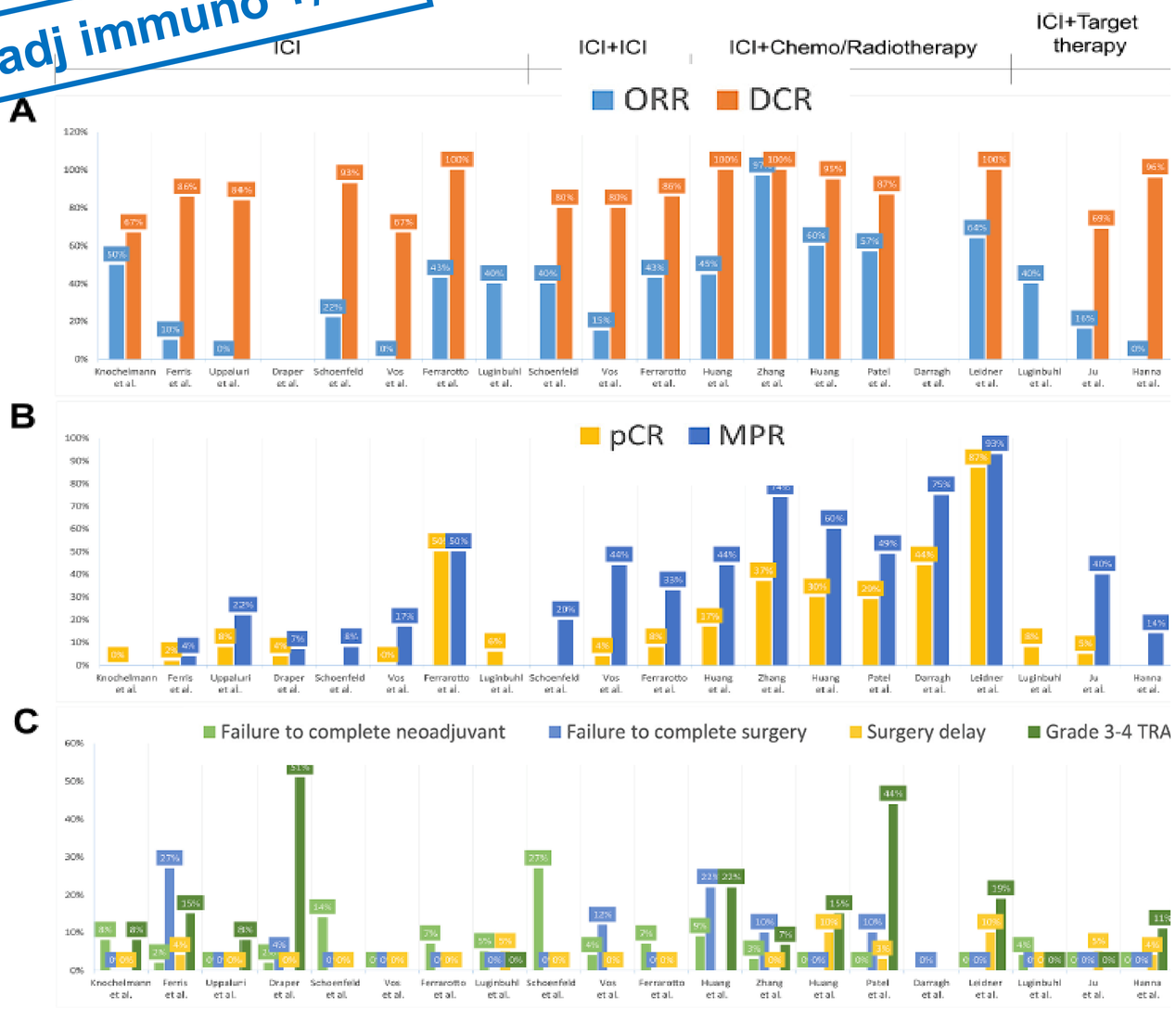


Primary Outcome Measures:

Event-free Survival

(ClinicalTrials.gov, NCT03765918)

Neoadj immuno +/-CT



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International Immunopharmacology
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Review

Advancements in neoadjuvant immune checkpoint inhibitor therapy for locally advanced head and neck squamous Carcinoma: A narrative review

Jin Li [a], Zhenqin Luo [a], Siqing Jiang [a,*], Junjun Li [b,*]

Radiological responses

15 trials: ORR 0 % - 97 %
DCR 64 % - 100 %
ICI + ICI or ICI+CT/ RT BETTER THEN ICI alone

Pathological responses

11 trials: R0 resection rates
ranged from 77 % - 100 %
pCR 0%-87% better ICI+CT/RT: 17%-87%

Safety

manageable profiles

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Review

Advancements in neoadjuvant immune checkpoint inhibitor therapy for locally advanced head and neck squamous Carcinoma: A narrative review

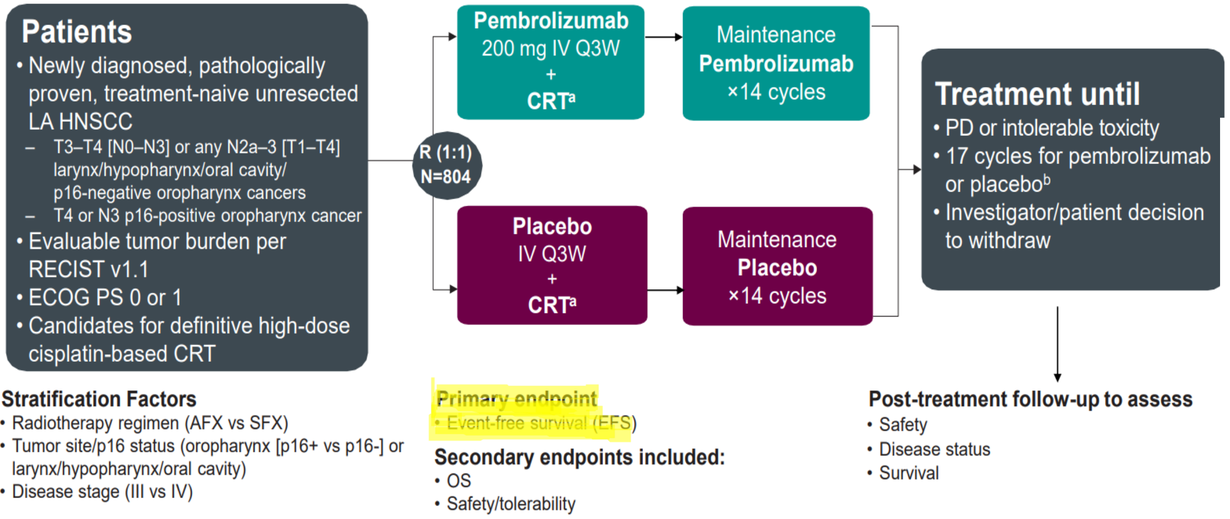
Jin Li [a], Zhenqin Luo [a], Siqing Jiang [a,*], Junjun Li [b,*]

Key challenges in neoadjuvant immune checkpoint inhibitor

KEYNOTE-412 Study Design (NCT03040999) **a randomised double-blind phase 3**

Lancet Oncol 2024 May;25(5):572-587

CT + immuno



[a]CRT included cisplatin (100 mg/m^2 Q3W) and accelerated fractionation (AFX) (70 Gy, 6 fractions/week for 5 weeks and then 5 fractions for the 6th week, 35 fractions in total) or standard fractionation (SFX) (70 Gy, 5 fractions/week for 7 weeks, 35 fractions in total). [b]A pembrolizumab/placebo priming dose was given 1 week before CRT, followed by 2 doses during CRT and 14 doses of maintenance therapy after CRT, for a total of 17 doses.

804 pts

No difference between the 2 gr in n.pts completed CTRT or maintenance phase

Summary and Conclusions

- Pembrolizumab plus CRT was associated with a favorable trend toward improved EFS vs placebo plus CRT in patients with LA HNSCC (HR, 0.83; *P* = 0.0429)
  - The difference did not reach statistical significance
  - 24-mo EFS rate: 63.2% vs 56.2%
- PD-L1 expression[a] may be an informative predictive biomarker
  - CPS ≥1: 24-mo EFS rate, 63.7% vs 56.3%; 36-mo OS rate, 71.4% vs 70.2%
  - CPS ≥20: 24-mo EFS rate, 71.2% vs 62.6%; 36-mo OS rate, 79.1% vs 73.0% (post hoc analysis)
- No new safety signals with the combination of pembrolizumab plus CRT
- LA HNSCC remains a challenging disease to treat

better sequential than concomitant?

- ❖ RT modifies the T microenvironment and blocks the antitumour immune reaction by depleting T cell or other immune cells thus impairing the immunoresponse by PD1 or PD L1 inhibition
- ❖ Prophylactic neck RT impair the immune function

2 ongoing phase3 studies (NTC03452137 and NCT03811015) for sequential treat (atezolizumab -nivolumab for oro)

IMMUNO for Pts unfit for CDDP
(age,comorbidity, PS)

Radiotherapy with cetuximab or durvalumab for locoregionally advanced head and neck cancer in patients with a contraindication to cisplatin (NRG-HN004): an open-label, multicentre, parallel-group, randomised, phase 2/3 trial

Loren K Mell, Pedro A Torres-Saavedra, Stuart J Wong, Julie A Kish, Steven S Chang, Richard C Jordan, Tian Liu, Minh Tam Truong, Eric W Winquist, Vinita Takiar, Trisha Wise-Draper, Jared R Robbins, Cristina P Rodriguez, Musaddiq J Awan, Beth M Beadle, Christina Henson, Samir Narayan, Sharon A Spencer, Steven Powell, Neal Dunlap, Assuntina G Sacco, Kenneth Shung Hu, Henry S Park, Julie E Bauman, Jonathan Harris, Sue S Yom, Quynh-Thu Le

89 academic and community medical centres in North America

190 pts

PRIMARY ENDPOINT: PFS

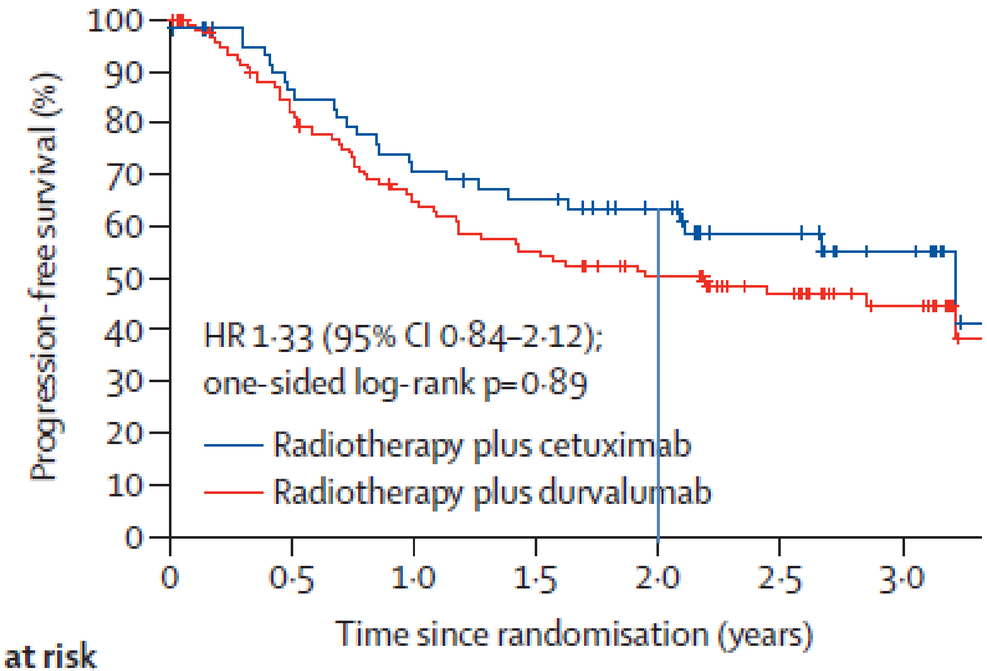
Durvalumab 1500 mg + IMRT starting 2 weeks before then every 4 weeks (seven cycles) *No adj infusion*

VS

CTX with IMRT 70 Gy

Phase 2 accrual was suspended

Lancet Oncol 2024; 25: 1576–88



Number at risk (number censored)							
Radiotherapy plus cetuximab	63 (0)	50 (5)	41 (5)	37 (6)	29 (13)	19 (21)	11 (28)
Radiotherapy plus durvalumab	123 (0)	96 (6)	74 (8)	63 (8)	52 (14)	34 (29)	19 (43)

2-year PFS was 50·6% (95% CI 41·5–59·8) in the durvalumab group versus 63·7% (51·3–76·1) in the CTX group p=0·89)

No improvement in efficacy with durvalumab

Lancet Oncol 2024; 25: 1576–88

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2024

CLINICAL INVESTIGATION

Randomized Phase 3 Trial of the Hypoxia Modifier Nimorazole Added to Radiation Therapy With Benefit Assessed in Hypoxic Head and Neck Cancers Determined Using a Gene Signature (NIMRAD)

David J. Thomson, FRCR, MD,*,†,‡ Nick J. Slevin, FRCR,* Helen Baines, MSc,§,‖ Guy Betts, FRCPath, PhD,¶ Steve Bolton, MSc,* Mererid Evans, FRCR, PhD,# Kate Garcez, FRCR,* Joely Irlam, BSc,† Lip Lee, FRCR,* Nicola Melillo, PhD,** Hitesh Mistry, MSc, PhD,†,** Elisabet More, PhD,‡ Christopher Nutting, MD, PhD,‖ James M. Price, FRCR,* Stefano Schipani, MD,†† Mehmet Sen, FRCR,‡‡ Huiqi Yang, FRCR, PhD,§,§§ and Catharine M. West, PhD† the NIMRAD Trial Group

Pts unfit for CDDP

BACKGROUND:DAHANCA-5 phase 3 study, showed that Nimo added to primary conventional RT improved 5-year locoregional tumor control (49%vs33%;P<.002)

338 pts 19 centers in UK
Median age 73 y (44-88)

IMRT 65 Gy in 30 fr plus nimorazole or placebo

Nimorazole mimic the effect of oxygen in rendering hypoxic cells radiosensitive

primary endpoint: freedom from locoregional progression (FFLRP)

Hypoxic tumors,defined as greater than or equal to the **median tumor hypoxia score**

of the first 50 pts analyzed (≥0.079), using a validated 26-gene signature

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The effect on locoregional tumor control favored nimorazole over placebo, not statistically significant

No difference in OS for intercurrent or treat –related competing mortality events ???

Addition of the hypoxia modifier nimorazole to IMRT for locally advanced HNSCC in older and less fit patients did not improve locoregional control or survival

Radiotherapy and Oncology 190 (2024) 110011

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Season of radiotherapy and outcomes of head & neck cancer patients in the MACH-NC & MARCH meta-analyses

Elaine Limkin [a], Pierre Blanchard [a, b, c, *], Benjamin Lacas [b, d], Jean Bourhis [c, e], Mahesh Parmar [f], Lisa Licitra [g], Quynh-Thu Le [h, i], Sue S. Yom [i], Catherine Fortpied [j], Johannes Langendijk [k], Jan B Vermorken [l], Jacques Bernier [m], Jens Overgaard [n], Jonathan Harris [i], Jean-Pierre Pignon [b, c, d], Anne Auperin [b, c, d], on behalf of the MACH-NC* and MARCH** collaborative groups [1]

BACKGROUND Elicin O, et al. The prognostic impact of daytime and seasonality of radiotherapy on head and neck cancer. Radiother Oncol 2021;158:293–9.

*Retrospective study in Switzerland on 655 patients showing that the effect of **seasonality of RT on loco-regional control** (5-year LRC, 73 % vs. 61 %; p = 0.0108)*
***progression-free survival** (5-year PFS, 51 % vs. 43 %; p = 0.0374)*
was superior when RT was administered during the darker half of the year than during the lighter half This period was likewise associated with increased acute toxicity

possible explanation is a variation in cell cycle progression in function of seasons, possibly related to vitamin D levels variations or for G2-M phase that occur in the late afternoon and evening

11.320 pts and 6276 pts

CONCLUSIONS: Season of RT had no impact on PFS or LRF

INTERNATIONAL JOURNAL of NURSING PRACTICE

Effect of nonpharmacological interventions on nutrition status, complications and quality of life in head and neck cancer patients undergoing radiotherapy: A systematic review and meta-analysis

Xiaolei Jin MSN, Registered nurse[1,2] | Yuying Fan BN, Head nurse[3] | Conghui Guo MSN, Registered nurse[2,4] | Jianrong Yang PhD, Professor[5] | Ying-chun Zeng PhD, Associate Professor[6] | Jun-e Zhang PhD, Professor[2]

27 RCT studies 2003-2023
2736 pts

5 categories of intervention:
- ✓ NUTRITIONAL SUPPORT
- ✓ EXERCISE
- ✓ SWALLOWING FUNCTION TRAINING
- ✓ PSYCHOLOGICAL INTERVENTION
- ✓ LOW-LEVEL LASER THERAPY

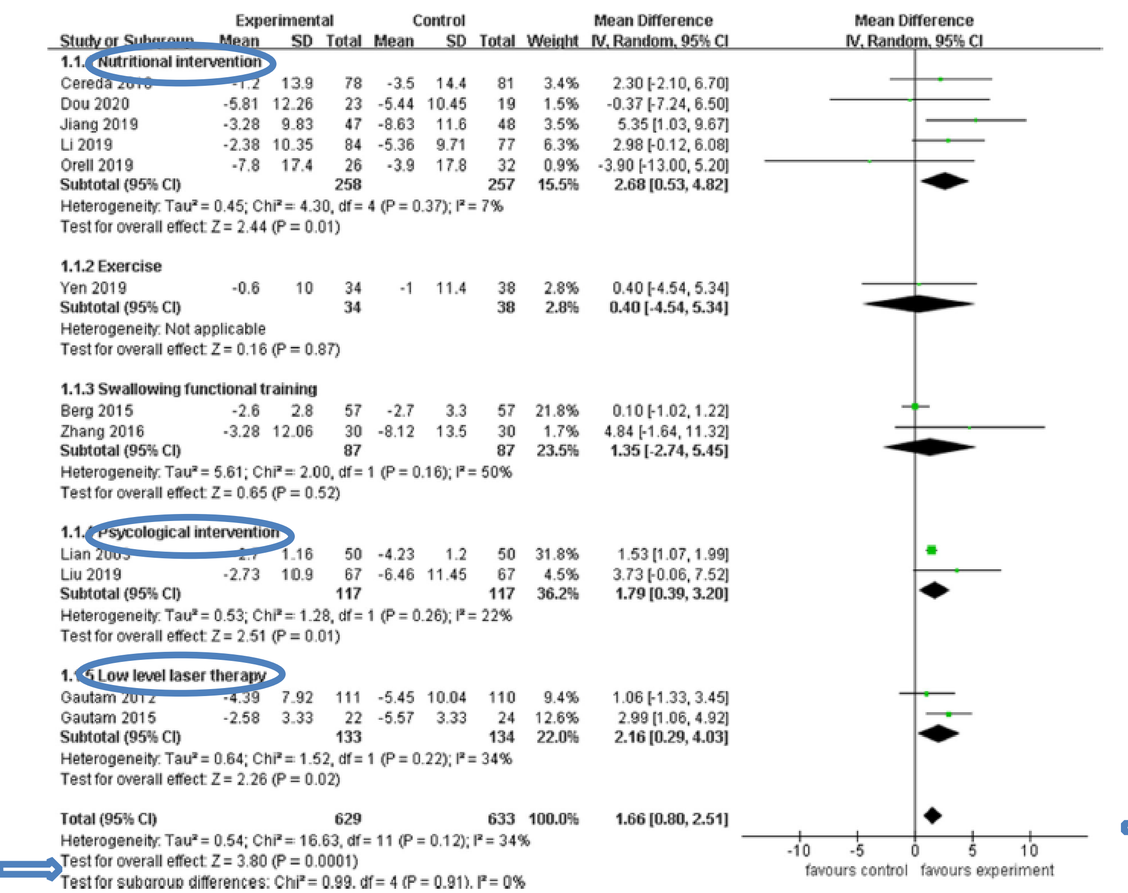
TOXICITY

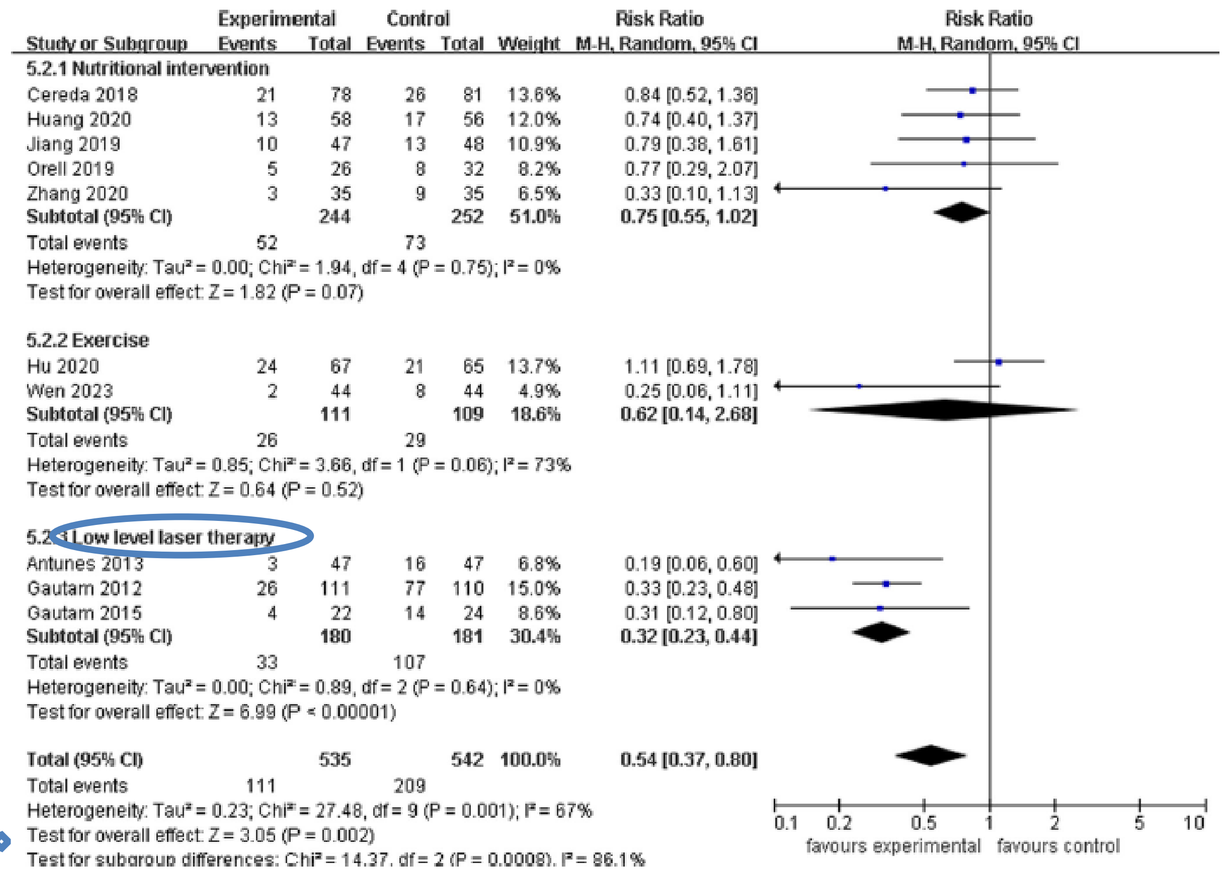
BACKGROUND:
At the time of diagnosis 35%–60% of HNC patients are undernourished

During RT 87% experience different degrees of weight loss

Low body weight has become an independent predictor of prognosis

Int J Nurs Pract. 2024





non-pharmacological interv were found to alleviate ***body weight loss*** *at the end of RT*

incidence of ***severe oral mucositis*** *was lower than in control group*

xerostomia and mouth opening ***were not improved*** *by nonpharmacological interventions*

Streptococcus salivarius K12 Alleviates Oral Mucositis in Patients Undergoing Radiotherapy for Malignant Head and Neck Tumors: A Randomized Controlled Trial

Xingchen Peng, MD[1]; Zixia Li, MDS[2]; Yiyan Pei, MM[1]; Shuhao Zheng, DDS[2]; Jinchi Liu, MDS[2]; Jingjing Wang, MD[1]; Ruidan Li, MD[1]; and Xin Xu, DDS[2]

DOI https://doi.org/10.1200/JCO.23.00837

TOXICITY

Microbiota plays a pivotal role in the development and progression of radiation-induced OM

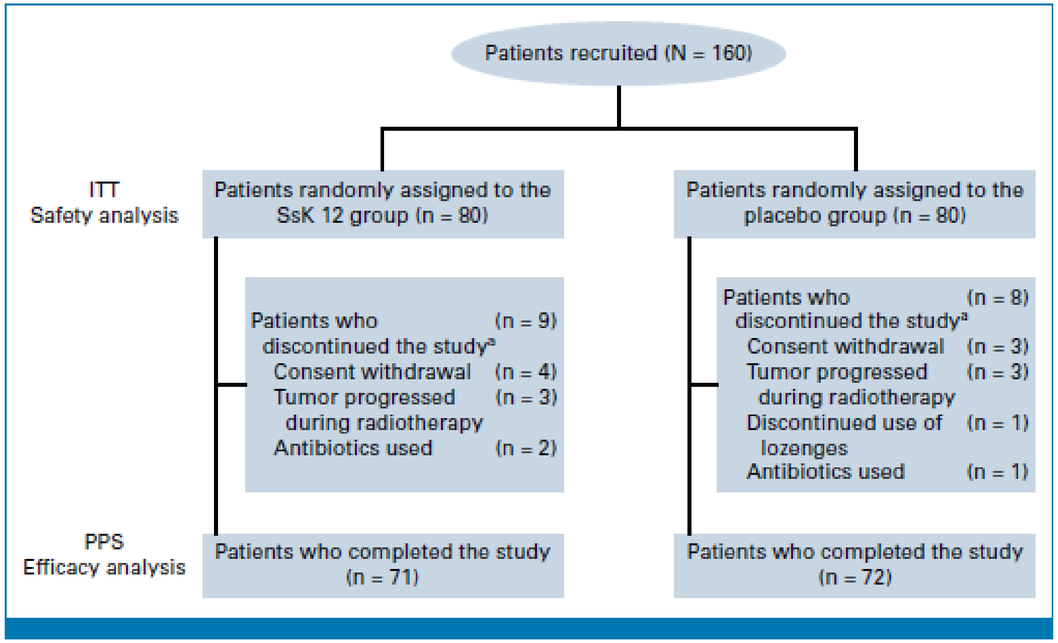
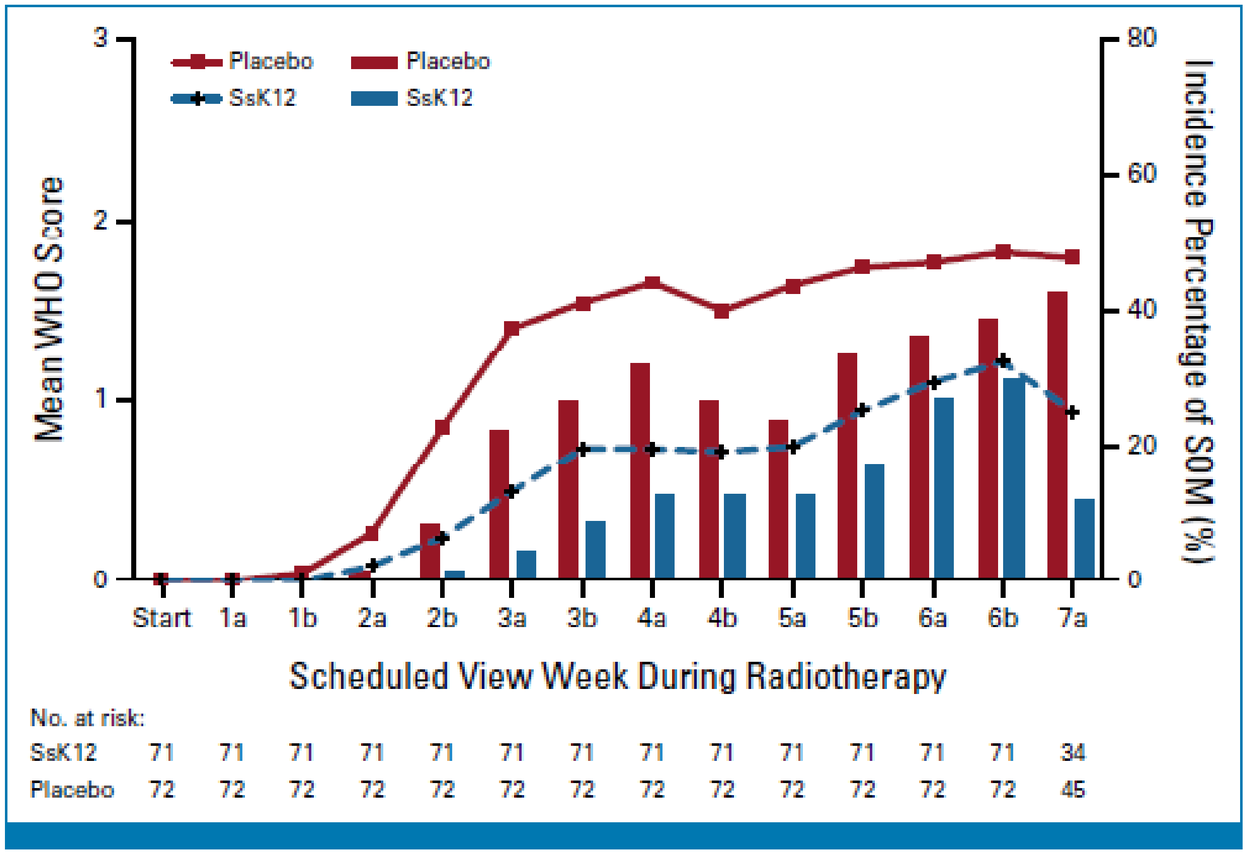


FIG 1. CONSORT diagram: patient random assignment. [a]Patients who discontinued the acute oral mucositis evaluation phase of the study. ITT, intent to treat; PPS, per-protocol set; SsK12, Streptococcus salivarius K12. probiot

J Clin Oncol 42:1426-1435



SOM =WHO grade 3-4

The incidence of SOM was significantly lower in the SsK12 group as compared with the placebo group (36.6% v 54.2%; P = .0351).

Duration mean, 8.9 days v 18.3 days; P = .0084

J Clin Oncol 42:1426-1435

TOXICITY

ASCO Special Articles

Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline

Douglas E. Peterson, DMD, PhD, FDS RCSEd, FASCO[1]; Shlomo A. Koyfman, MD[2]; Noam Yarom, DMD, MPH[3,4]; Charlotte Duch Lynggaard, MD, PhD[5]; Nofisat Ismaila, MD, MSc[6]; Lone E. Forner, DDS, PhD[7]; Clifton David Fuller, MD, PhD[8]; Yvonne M. Mowery, MD, PhD[9,10]; Barbara A. Murphy, MD[11]; Erin Watson, DMD, MHSc[12]; David H. Yang, DDS, FRCD(C)[13]; Ivan Alajbeg, DMD, MSc, PhD[14]; Paolo Bossi, MD[15,16]; Michael Fritz, MD[2]; Neal D. Futran, MD, DMD[17]; Daphna Y. Gelblum, MD[18]; Edward King, JD[19]; Salvatore Ruggiero, DMD, MD, FACS[20]; Derek K. Smith, DDS, PhD, MPH[21]; Alessandro Villa, DDS, MPH, PhD[22]; Jonn S. Wu, BMSc, MD, FRCPC[13]; and Deborah Saunders, DMD[23]

ORN about 3.1%.

PubMed, EMBASE, and Cochrane Library databases were searched for randomized controlled trials and observational studies, published between January 1, 2009, and December 1, 2023.
80 were identified

ASCO Journal of Clinical Oncology 2024

ASCO Guidelines MASCC WWW.MASCC.ORG SUPPORTIVE CARE IN CANCER ISOO INTERNATIONAL SOCIETY of ORAL ONCOLOGY

Prevention and Management of Osteoradionecrosis in Patients with Head and Neck Cancer Treated with Radiation Therapy: ISOO-MASCC-ASCO Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
How should ORN be characterized, graded, and reported? • Which patients should be considered at high risk for ORN? • What is the recommended workup to characterize ORN?	**1.1.** Osteoradionecrosis of the jaw (mandible, maxilla) should be characterized as a radiographic lytic or mixed sclerotic lesion of bone and/or visibly exposed bone and/or bone probed through a periodontal pocket or fistula, occurring within an anatomical site previously exposed to a therapeutic dose of head and neck RT.	IC	L	S
	1.2. A patient with radiation dose to the jaw of 50 Gy or higher should be considered at risk for development of ORN. Modifiable risk factors including poor oral hygiene, dentoalveolar surgeries, and/or tobacco use, should be considered as further increasing this lifelong risk.	EB	H	S
	1.3. Clinicians evaluating ORN should utilize the ClinRad staging system for ORN, as should clinical trials.	EB	M	S
	1.4. ORN assessment should have a defined formal characterization for disease evaluation at each visit which is usable across members of the clinical care or provider specialty spectrum. The panel recommends utilizing the ClinRad Classification system for ORN developed by Watson et al.[1]	EB	M	S
	1.5. ORN case reporting and diagnosis should include formal informatics, ontology, and lexical standards consistent with the characterization noted in Recommendation 1.1.	IC	L	S
	1.6. Recommended initial evaluation of ORN should include one or more of the following: (1) clinical intra-oral examination (including direct visual or endoscopic examination and/or formal periodontal assessment); and/or (2) formal radiographic examination (i.e., x-ray orthopanogram, cone-beam or fan-beam computed tomography, magnetic resonance imaging).	EB	M	S
	Qualifying statement: If either clinical or radiographic findings are initially detected, suspected or positive, subsequent confirmatory examination or imaging assessment is recommended.			

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Prevention and Management of Osteoradionecrosis in Patients with Head and Neck Cancer Treated with Radiation Therapy: ISOO-MASCC-ASCO Guideline

Clinical Question	Recommendation	Type	Evidence Quality	Strength
	1.7. Recommended serial characterization or surveillance of ORN should include clinical intra-oral examination (including direct visual, endoscopic examination, and/or comprehensive periodontal assessment) and comprehensive radiographic examination (i.e., x-ray orthopanogram, cone-beam or fan-beam computed tomography, magnetic resonance imaging).	EB	M	S
What are the recommended best practices for the prevention of ORN of the head and neck prior to RT?	**2.1.** Target coverage of tumor should not be compromised to avoid dose to bone.	EB	M	S
	2.2. Advanced radiation planning techniques (e.g., IMRT, IMPT) should be employed to deliberately reduce radiation dose to the jaw at risk as much as possible.	EB	M	S
	2.3. Focused effort should be made to reduce the mean dose to the jaw and the volume of bone receiving above 50 Gy, whenever possible.	EB	M	S
	Qualifying statement: While tumor site (e.g., oropharynx, oral cavity) and size impacts the specific dosimetric parameters that are achievable in each patient, the overall goal of reducing as much volume of bone receiving higher doses applies uniformly.			
	2.4.1. A dental assessment by a dentist (with a dental specialist if possible) is strongly advised prior to therapeutic-intent RT to identify and remove teeth which will place the patient at risk of ORN during the patient's lifespan, and to comprehensively educate the patient about lifelong risk of ORN.	EB	M	S
	2.4.2. Dental extraction, if clinically indicated, should occur at least 2 weeks prior to commencement of RT. In the setting of rapidly progressing tumor, extractions should be deferred and not cause a delay in the initiation of RT (see dental clearance, Table A3 in the guideline manuscript).	EB	M	S
	2.5.1. (general dentists and dental specialists) Teeth with poor prognosis including moderate-severe periodontal disease, within a field of therapeutic-intent RT should be removed prior to RT to reduce the risk of ORN. In addition, teeth with periapical disease, caries, and partially erupted third molars should be considered for treatment depending on tooth location, patient risk factors for ORN, and timing available for healing.	EB	M	S
	2.5.2. (radiation oncologists) Oral assessment, including a comprehensive dental, periodontal, and oral radiographic exam when feasible, should be performed by a dentist or dental specialist as early as possible prior to initiation of head and neck RT. Information about the planned volume to be irradiated, anticipated dose to the mandible and maxilla, and RT start date should be provided to the dentist or dental specialist.	EB	M	S

Prevention and Management of Osteoradionecrosis in Patients with Head and Neck Cancer Treated with Radiation Therapy: ISOO-MASCC-ASCO Guideline

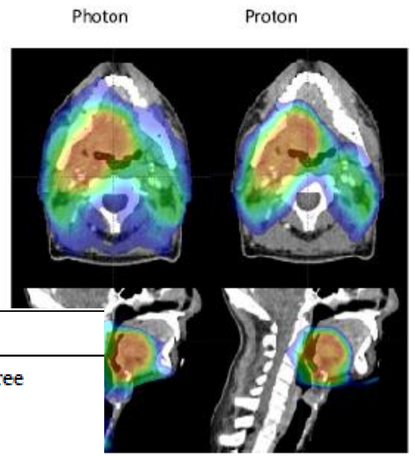
Clinical Question	Recommendation	Type	Evidence Quality	Strength
	2.6. A two week healing period between time of dental extraction and start of RT is advised only when this does not result in a delay to starting RT which may compromise oncologic control. If planned extractions will alter the vertical dimension of occlusion, they should be performed prior to fabrication of the immobilization mask that will be worn during RT.	EB	M	S
	2.7. Patients at risk of radiation-induced salivary hypofunction should be instructed to use prescription-strength topical fluoride applied to the teeth daily to reduce the risk of post-radiation caries, which in turn decreases risk of post-radiation extractions and ORN.	EB	H	S
	2.8. Modifiable risk factors that place patients at risk of ORN, like those listed in Recommendation 1.2, should be addressed prior to, during, and after RT.	EB	H	S
What are the recommended best practices for the prevention of ORN after RT?	**3.1.** Prior to finalizing dental treatment plans in patients with a history of head and neck RT, review of the RT plan should be performed with particular attention focused on dose to mandible and maxilla.	EB	M	S
	3.2. For teeth in areas at high risk for ORN, alternatives to dental extraction (e.g., root canal, crown, filling) should be offered unless the patient has recurrent infections, intractable pain, or other symptoms that cannot be alleviated without extraction. Similarly, dental implants in high-risk zones for ORN should be avoided unless alternatives to restoring oral function are not possible.	EB	M	S
	3.3. It is recommended that patients considered to be at higher risk for ORN due to prior RT encompassing the mandible and/or maxilla at site(s) of planned dental intervention receive oral antibiotics before and after invasive dental procedures, such as dental extraction and/or implant placement.	IC	L	W
	3.4. Patients at risk for ORN who have delayed healing after dental extraction may be prescribed antiseptic mouth rinses. Chlorhexidine gluconate (e.g., 0.12% or 0.2%) solution or povidone-iodine mouth rinses should be performed at least twice daily until sufficient healing has been achieved based on close follow-up evaluation with the treating dentist or oral surgeon.	IC	L	W

Prevention and Management of Osteoradionecrosis in Patients with Head and Neck Cancer Treated with Radiation Therapy: ISOO-MASCC-ASCO Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
	3.5. It is recommended that pentoxifylline (400 mg twice daily) and tocopherol (1000 IU once daily) be prescribed for at least one week before and four weeks after invasive dental procedures (preferably until the dental socket has healed) in cancer-free patients.	EB	L	W
	Qualifying statement: This should be considered for patients at elevated risk for ORN due to prior RT dose ≥50 Gy to the mandible or maxilla at site of the dental intervention unless the patient has contraindications to pentoxifylline and/or tocopherol such as increased bleeding risk.			
	3.6. Routine use of prophylactic hyperbaric oxygen (HBO) therapy prior to dental extractions in patients who received prior head and neck RT is not recommended.	EB	L	W
	Qualifying statement: Prophylactic HBO may be offered to patients undergoing invasive dental procedures at site(s) where a substantial volume of mandible and/or maxilla received >50 Gy.			
	No recommendation. Due to limited, low-quality available evidence, no recommendation can be made regarding utilization of leukocyte- and platelet-rich fibrin or photobiomodulation therapy to prevent ORN for patients undergoing dental procedures after head and neck RT.	N/A	N/A	N/A
How should ORN be managed non-surgically?	**4.1.** Pentoxifylline may be used in cancer-free patients with mild, moderate, and severe cases of ORN and is most likely to have a beneficial effect if the treatment is combined with tocopherol, antibiotics, and prednisolone.	EB	M	W
	4.2. HBO therapy in conjunction with surgical intervention may be used in cancer-free patients with mild, moderate, and severe cases of ORN. Potential benefit is most likely to be observed in mild cases.	IC	L	W
How should ORN be managed surgically?	**5.1.1.** In partial thickness ORN (ClinRad Stage I or II), surgical management can start with transoral minor intervention which can lead to resolution. This may include debridement, sequestrectomy, alveolectomy, soft tissue flap closure.	EB	H	S
	Qualifying statement: Partial thickness ORN is defined as disease extent whereby removal of all necrotic bone leaves native jaw with enough structural integrity such that oroantral or oronasal defect is unlikely in the maxilla, and pathological fracture in unlikely in the mandible.			
	5.1.2. Small defects <2.5cm in length may heal spontaneously with local measures. It is recommended that larger defects be covered with vascularized tissue.	EB	M	S
	5.2. In full thickness ORN (ClinRad selected Stage II and all Stage III), segmental maxillectomy or mandibulectomy with free flap reconstruction is recommended.	EB	H	S

Prevention and Management of Osteoradionecrosis in Patients with Head and Neck Cancer Treated with Radiation Therapy: ISOO-MASCC-ASCO Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
	Qualifying statement: Full thickness ORN is defined as disease extent whereby removal of all necrotic bone is likely to result in oroantral or oronasal defect in the maxilla or pathological fracture in the mandible.			
	5.3. In full thickness ORN or extensive partial thickness ORN where conservative therapy has not yielded appropriate disease control (ClinRad Stage II or III), segmental resection is recommended.	EB	H	S
	5.4.1. Maxillectomy defects that extend into the sinus (ClinRad Stage III) can be reconstructed with myocutaneous flaps or osteomyocutaneous flaps, whereby the latter has the additional benefit of allowing dental implantation where desired. Obturation of the defect with a prosthetic appliance may also be done for those patients who are poor candidates for microvascular surgery.	EB	H	S
	5.4.2. Osteomyocutaneous free flap reconstructions are recommended for mandibular continuity defects. A spanning reconstruction plate across a segmental defect covered by a myocutaneous flap may be an alternative in select settings where the medical status of the patient is compromised, or the treating institution has a limited scope of maxillofacial reconstruction.	EB	H	S
	5.5. Free flaps are recommended over pedicle flaps. Free flaps offer greater versatility and improved outcomes. Pedicle flaps can be used, especially in salvage procedures, with some limitations.	IC	L	S
	5.6. Pre-operative radiographic interpretation of extent of compromised bone, with intra-operative confirmation via bleeding bone endpoint, should be utilized in determination of resection borders. The potential for intra-operative findings to alter the resection margin should be a consideration in planning. If prefabricated cutting guides are used, contingency planning is recommended.	IC	L	S
	5.7.1. When patients are unfit to undergo definitive surgical treatment, the management should be focused on symptom control.	IC	M	S
	5.7.2. Removal of superficial bony sequestra should be performed if viewed as low risk by the clinician. Reduction of the disease burden and the biofilm environment can be synergistic with the ongoing systemic therapy.	IC	M	S

Proton therapy

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

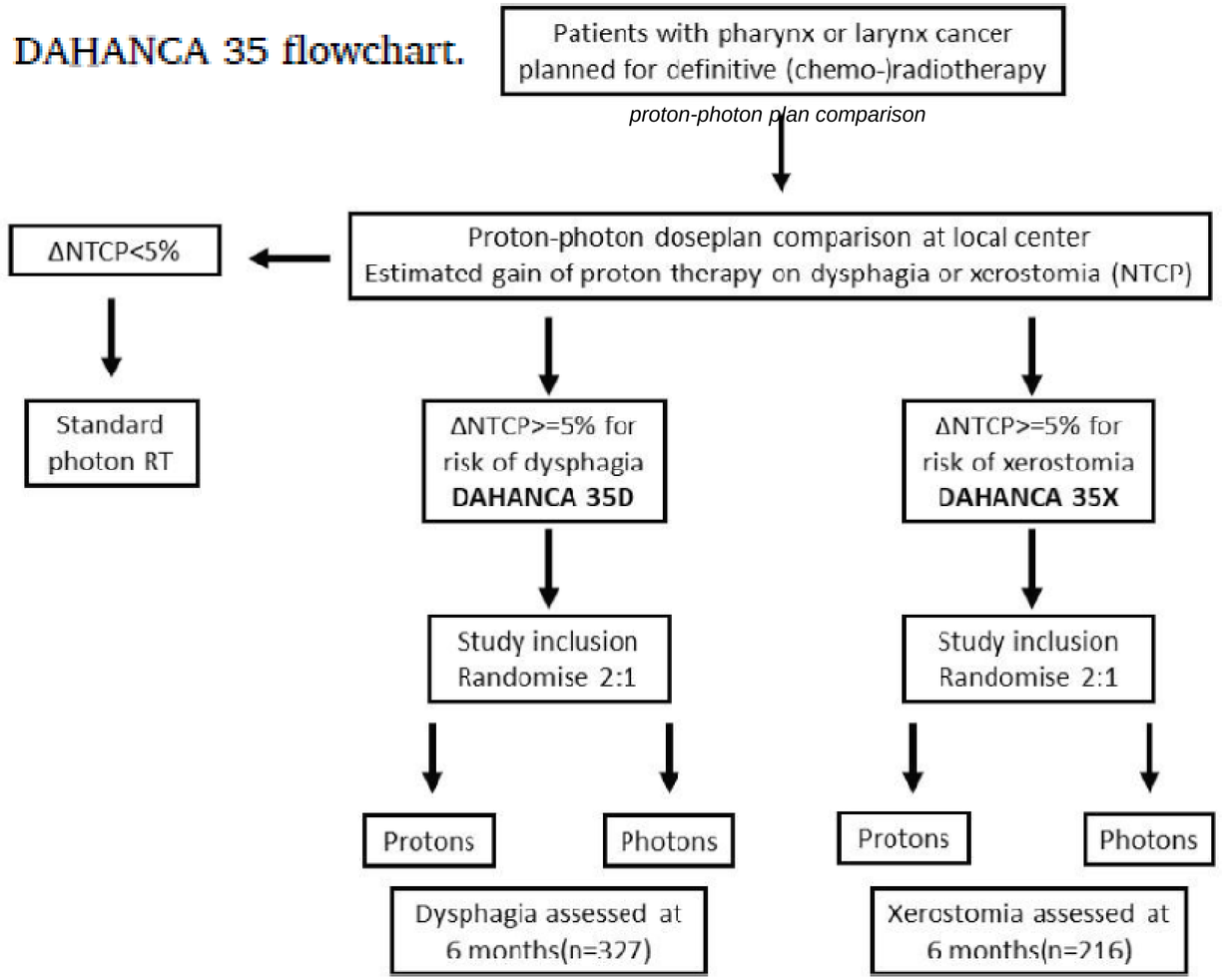


Considerations for study design in the DAHANCA 35 trial of protons versus photons for head and neck cancer

Trial number	Type	Institution	Trial name	Inclusion	Treatment	Primary endpoints
NCT01893307	RCT	MD Anderson (USA)	Intensity-Modulated Proton Beam Therapy or Intensity-Modulated Photon Therapy in Treating Patients With Stage III-IVB Oropharyngeal Cancer	St. III-IVb (AJCC 7th) HNSCC	IMPT: IMRT (1:1)	Overall survival/Progression-free survival (phase III)
NCT03829033	RCT	Lund (Sweden)	Photon Therapy Versus Proton Therapy in Early Tonsil Cancer. (ARTSCAN V)	Tonsil carcinoma (T1-2 N0-2b M0) – unilateral RT (non-chemotherapy)	IMPT: IMRT (1:1)	Locoregional side effects (acute and late)
ISRCTN: 16424014	RCT	Christie (UK)	Phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer (TORPEDO)	Locally advanced OPSCC, chemo-RT and bilateral neck treatment	IMPT: IMRT (2:1)	Co-primary endpoint 1) University of Washington physical toxicity composite score and 2) feeding tube dependence or severe weight loss 12-months post-RT.
NCT04607694	RCT	DAHANCA (Denmark)	Proton Versus Photon Therapy for Head-Neck Cancer (DAHANCA 35)	HNSCC, T1-4, N0-N3, M0 (excl. larynx T1-2N0M0)	IMPT: IMRT (2:1)	1) Observer-reported dysphagia (DAHANCA late toxicity score) 2) Patient-reported xerostomia (EORTC HN 35) at six-month post-RT
National protocol	NTCP-based	Netherlands	National Protocol for Model-Based Selection for Proton Therapy in Head and Neck Cancer in the Netherlands	Head-Neck Cancer	IMPT	Reduction in the risk of: 1) moderate-severe xerostomia, 2) dysphagia ≥ grade 2,3) tube feeding dependence

Secondary endpoints

loco-regional tumour control, disease-specific survival overall survival



NTCP model-based selection

Danish Center for Particle Therapy in Aarhus, Denmark

Dietary intervention for tertiary prevention in head and neck squamous cell carcinoma survivors: clinical and translational results of a randomized phase II trial

Stefano Cavalieri[1,2*†], Eleonora Bruno[3†], Mara Serena Serafini[4], Deborah Lenoci[4], Silvana Canevari[5], Laura Lopez-Perez[6], Liss Hernandez[6], Luigi Mariani[7], Rosalba Miceli[7], Cecilia Gavazzi[8], Patrizia Pasanisi[3], Elena Rosso[1,9], Francesca Cordero[9], Paolo Bossi[1], Wojciech Golusinski[10], Andreas Dietz[11], Primož Strojan[12], Thorsten Fuereder[13], Loris De Cecco[4*‡] and Lisa Licitra[1,2‡]

frontiers | Frontiers in Oncology

2024

SURVIVORS

open-label, randomized phase II multi-country trial

STAGE III IV

To explore the impact of a dietary approach in reducing recurrences and second tumors (10% to 20%)
in HNSCC survivors

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highly monitored dietary intervention plus the Word Cancer Research Fund/American Institute for Cancer Research recommendations for cancer prevention (intervention arm)

World Cancer Research Fund

Preventing cancer | Living well

CANCER PREVENTION
- What we know about preventing cancer
- Our Cancer Prevention Recommendations
- Cancer Health Check
- Influencing policy
- Leading research
- Order free guides & cookbooks

TOPICS
- Weight and obesity
- Physical activity
- Meat
- Alcohol
- Sugar
- Ultra-processed food
- More topics >

standard-of-care recommendations (control arm)

AN EXAMPLE OF DIETINT LUNCH

WINTER MENU
Miso soup with onions
Brown rice with pumpkins cream and leeks
Fried Tempeh
Marinated vegetables with humeboshi vinegar
Cereal coffee
Beverages: green tea
SUMMER MENU
Basmati rice with vegetables
Baked mackerel fillet
Fresh salad
Fruit Kanten
Beverages: water

	WINTER MENU	SUMMER MENU	*LARN
Kcal	649	642	
Protein	14%	15%	10-15%
Total fat	29%	28%	25-30%
Saturated	4%	5%	10 %
Monounsaturated	15%	14%	
Polyunsaturated	10%	11%	5-10%
Carbohydrate	57%	57%	45-60%
of which sugars	5%	8%	< 15%
Fiber	11 g	9 g	30 g
Cholesterol	0 mg	90 mg	< 300 mg

*LARN - Levels of reference intake of nutrients and energy for the Italian population

cooking classes (about specific nutrition topics), community meals, and dietary reinforcement meetings and individual counseling

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Primary endpoint

to assess the effectiveness of the dietary intervention in reducing tumor recurrences and second primary tumors

89 PTS

FU to 18 months as the final observation

Exploratory clinical endpoints:

- adherence to nutritional recommendations through nutritional questionnaires (24-h food frequency diaries)

- improvement of patients' QoL

Exploratory translational endpoints:

- blood-circulating food-derived miRNA(potential biomarkers of different dietetic styles)
- biological sample biobanking.

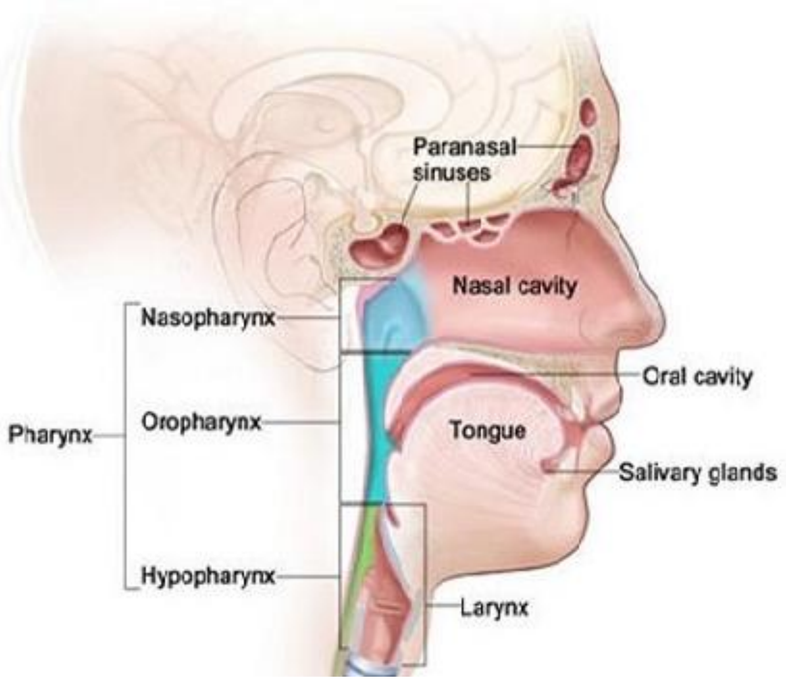
CONCLUSIONS:

- Subjects receiving specific counseling increased the consumption of the recommended foods indicating **feasibility of lifestyles interv**, but no relevant changes in QoL
- Food derived plasma miRNA might be considered promising circulating dietary biomarkers

NO DISCLOSURE TO REPORT

AGENDA

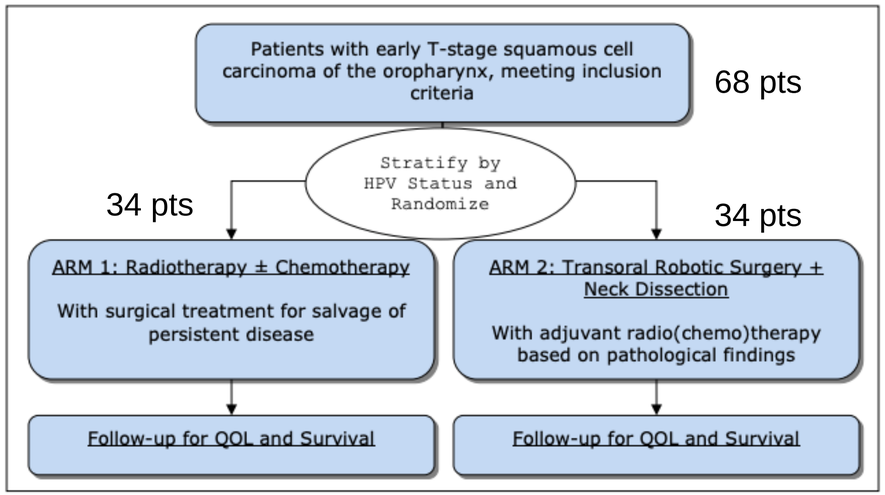
- *Head and Neck cancer – overview*
- *Oropharyngeal cancer* → Early stage; De-escalation
- *Nasopharyngeal cancer*
- *Oral cavity cancer*
- *Laryngeal Cancer*



Radiotherapy Versus Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma: Final Results of the ORATOR Randomized Trial

Anthony C. Nichols, MD[1]; Julie Theurer, PhD[2]; Eitan Prisman, MD[3]; Nancy Read, MD[4]; Eric Berthelet, MD[5]; Eric Tran, MD[5]; Kevin Fung, MD[1]; John R. de Almeida, MD[6]; Andrew Bayley, MD[7]; David P. Goldstein, MD[6]; Michael Hier, MD[8]; Khalil Sultanem, MD[9]; Keith Richardson, MD[8]; Alex Mlynarek, MD[8]; Suren Krishnan, MD[10]; Hien Le, MD[11]; John Yoo, MD[1]; S. Danielle MacNeil, MD, MSc[1]; Eric Winquist, MD, MSc[12]; J. Alex Hammond, MBBCh[4]; Varagur Venkatesan, MBBS[4]; Sara Kuruvilla, MD[12]; Andrew Warner, MSc[4]; Sylvia Mitchell, MRT[4]; Jeff Chen, PhD[4]; Stephanie Johnson-Obaseki, MD, MPH[13]; Michael Odell, MD[13]; Martin Corsten, MD[14]; Christina Parker, AuD[15]; Bret Wehrli, MD[16]; Keith Kwan, MD[16]; and David A. Palma, MD, PhD[4]

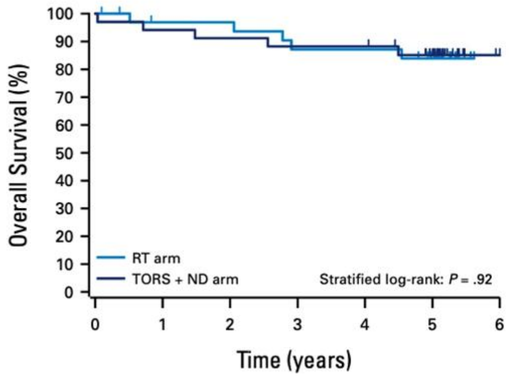
A PHASE II RANDOMIZED TRIAL FOR EARLY CARCINOMA OF THE OROPHARYNX: TRANS-ORAL ROBOTIC SURGERY VS. RADIOTHERAPY

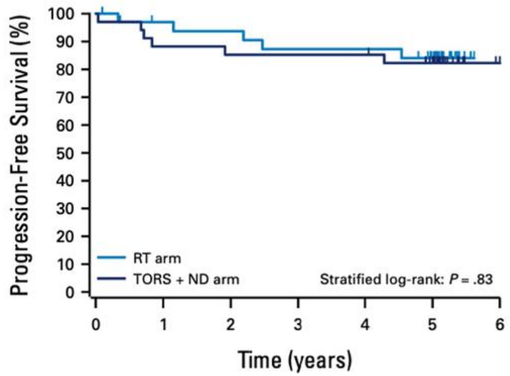


T1-2, N0-2 OPC
Tonsil/BOT
88% HPV pos

Primary end point: swallowing QOL assessed with the MD Anderson Dysphagia Inventory (MDADI)

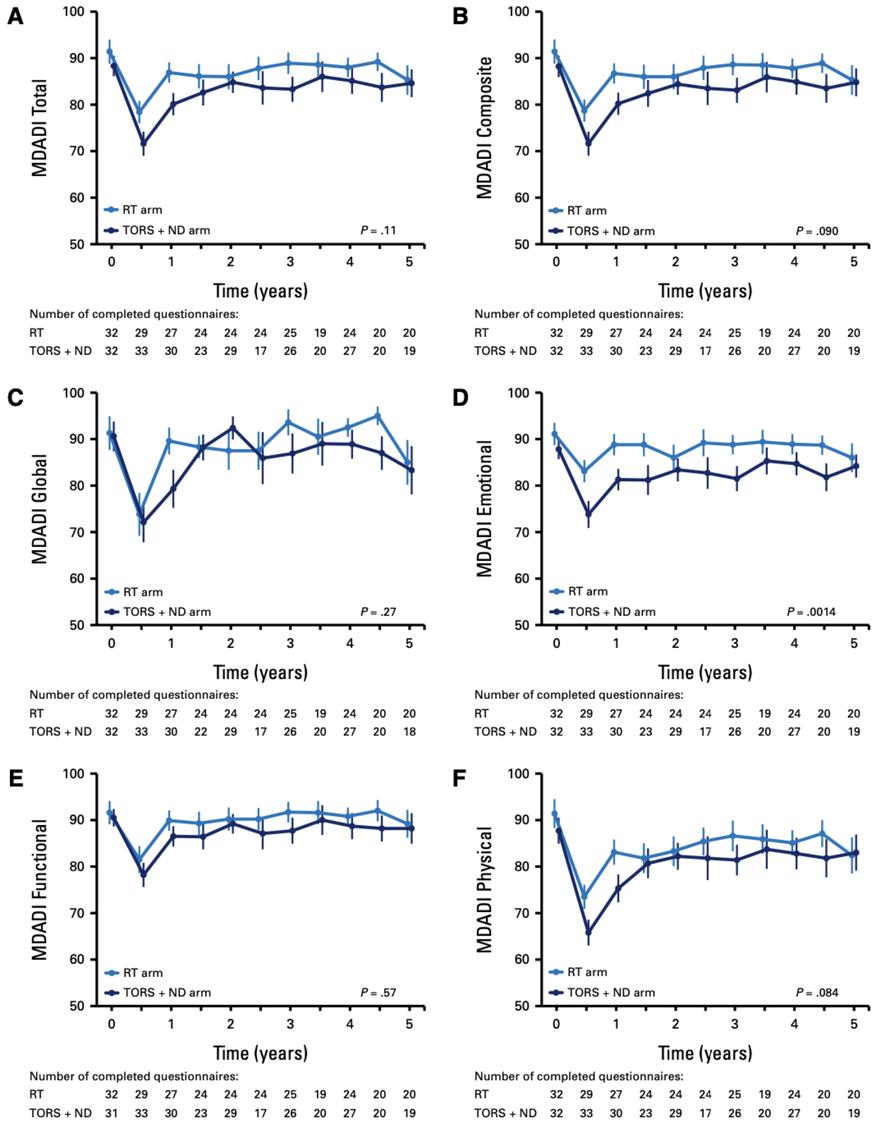
Secondary end points: OS, PFS, adverse events (AEs) and other QOL metrics





- No differences in 5-year functional oral intake score
- 95% receiving a total oral diet with no restrictions

J Clin Oncol 42:4023-4028, 2024



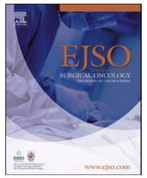
AEs	RT/CRT Arm (n°=34)	TORS Arm (n°=34)	P-value
G 2-5	31 (91.2%)	33 (97.1%)	0.61
G 3-5	19 (56%)	16 (47%)	0.47
G4	1 (2.9%)	2 (5.9%)	
G5	0(0%)	1 (2.9%)	

Specific toxicities (all p<0.05)

- RT Arm: neutropenia, hearing loss, and tinnitus
- TORS Arm: dysphagia and other pain

J Clin Oncol 42:4023-4028, 2024

Quality of life outcomes comparing primary Transoral Robotic Surgery (TORS) with primary radiotherapy for early-stage oropharyngeal squamous cell carcinoma: A systematic review and meta-analysis

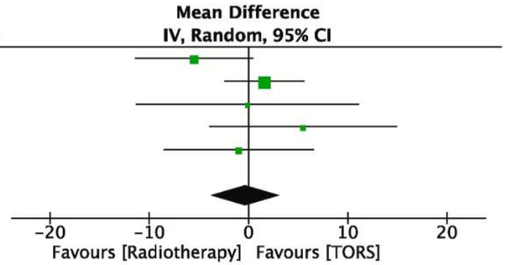


555 OPSCC pts:
236 pts TORS vs 319 pts RT
1° endpoints: swallowing and global QoL

MDADI at 12 months

Study or Subgroup	TORS Mean	TORS SD	TORS Total	RT Mean	RT SD	RT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Nichols (ORATOR), 2019	83.1	13.7	34	88.6	11.3	34	24.0%	-5.50 [-11.47, 0.47]	2019
Barbon, 2021	83	15.2	75	81.4	14.6	182	39.2%	1.60 [-2.44, 5.64]	2021
Charters, 2021	64.4	22.4	24	64.5	17	24	8.5%	-0.10 [-11.35, 11.15]	2021
Scott, 2021	90.5	15.2	31	85	13.8	12	11.5%	5.50 [-3.97, 14.97]	2021
Palma (ORATOR2), 2022	84.7	14.5	31	85.7	15.6	30	16.8%	-1.00 [-8.56, 6.56]	2022
Total (95% CI)			**195**			**282**	**100.0%**	**-0.24 [-3.70, 3.23]**	

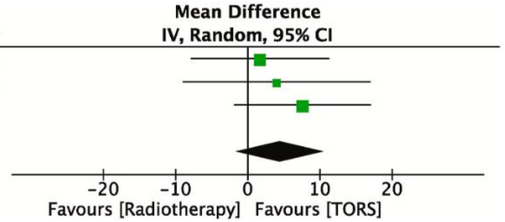
Heterogeneity: Tau² = 3.71; Chi² = 5.22, df = 4 (P = 0.27); I² = 23%
Test for overall effect: Z = 0.13 (P = 0.89)



EORTC QoLC30 at 12 months

Study or Subgroup	TORS Mean	TORS SD	TORS Total	Radiotherapy Mean	Radiotherapy SD	Radiotherapy Total	Weight	Mean Difference IV, Random, 95% CI	Year
Nichols (ORATOR), 2019	77.9	19.5	34	76.2	20.9	34	38.8%	1.70 [-7.91, 11.31]	2019
Scott, 2021	80.4	20.6	31	76.4	19.1	12	21.1%	4.00 [-9.01, 17.01]	2021
Palma (ORATOR2), 2022	87	17.2	31	79.4	20.3	30	40.1%	7.60 [-1.86, 17.06]	2022
Total (95% CI)			**96**			**76**	**100.0%**	**4.55 [-1.44, 10.53]**	

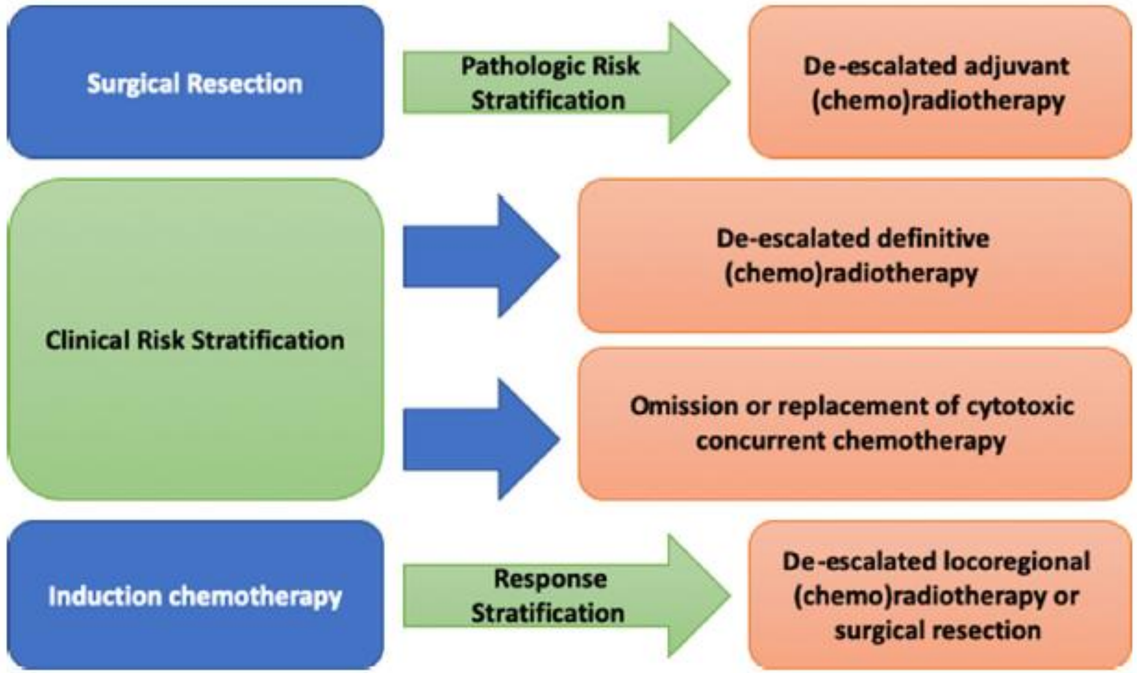
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



- 54.7% of pts in the TORS group receved multimodality therapy
- difficult to establish the 'true' QoL outcomes of surgery alone
- introduces bias against TORS:
post-op RT cause a synergistic effect with surgery leading to amplified damage at the surgical site

Gupta KK et al, European Journal of Surgical Oncology 50 (2024) 108434

Approaches to de-escalation



Review

Can we safely de-escalate HPV^{+} oropharyngeal cancers? – A review of current practices and novel approaches

Janis Morgenthaler [a,b,*], Maike Trommer [a,b], Richard Khor [a], Morikatsu Wada [a], Houda Bahig [c], Adam S. Garden [d], Alesha Thai [e], Hui Gan [e], Emmanouil Fokas [b], Sweet Ping Ng [a]

De-escalated radiation for human papillomavirus virus-related oropharyngeal cancer: Who, why, what, where, when, how, how much… and what next?

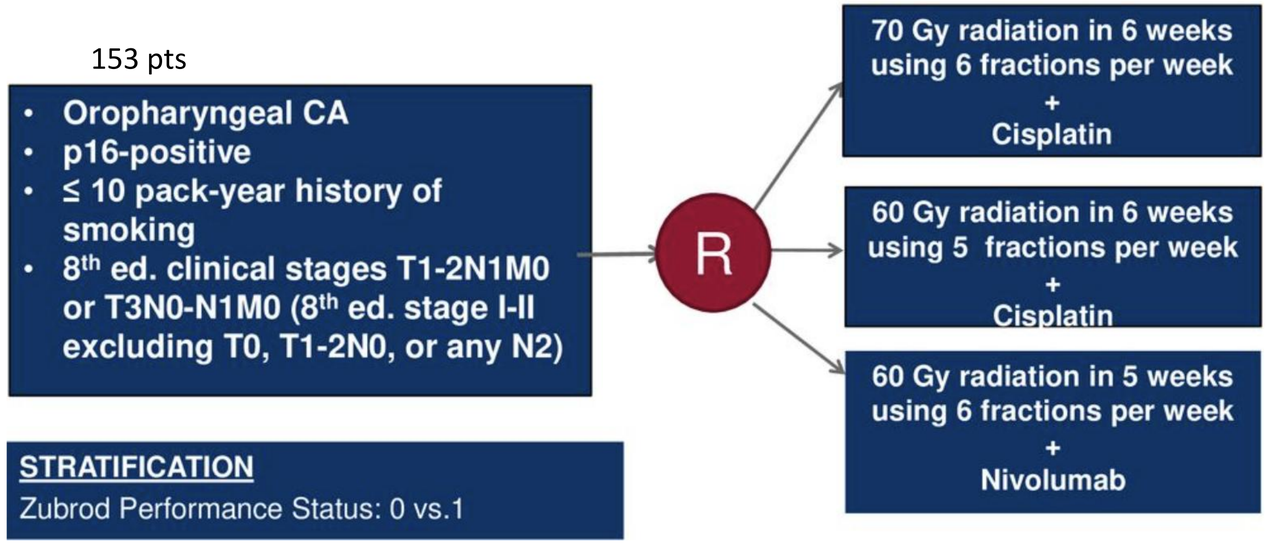
Allen M. Chen *

Review

De-Escalation Strategies in HPV-Associated Oropharynx Cancer: A Historical Perspective with Future Direction

Clinton Wu [1], Paulina Kuzmin [1] and Ricklie Julian [1,2,*]

Interim Futility Results of NRG-HN005, A Randomized, Phase II/III Non-Inferiority Trial for Non-Smoking p16+ Oropharyngeal Cancer Patients



- median follow-up 2.2 yy
- 2-year PFS: 98.1% vs 88.6% vs 90.3%
- 2-year OS: 99.0% vs 98.0% vs 96.1%

➔failed to show non-inferiority for both de-escalation arms

➔A phase III trial will not proceed

- For low-risk HPV-OPC standard of care has excellent results – 98%PFS
- Standard of care remains 70 Gy + CDDP

Yom SS et al, IJRBP Vol 120, 2, supplemet

Phase III randomized trial of intensity-modulated proton therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for the treatment of head and neck oropharyngeal carcinoma (OPC).

Steven J. Frank, Paul Busse, David Ira Rosenthal, Mike Hernandez, David Michael Swanson, Adam S. Garden, Erich M. Sturgis, Renata Ferrarotto, Gary Brandon Gunn, Samir H Patel, NANCY Y. LEE, Alexander Lin, James W Snider, Mark William McDonald, Christina Henson, Gopal Krishna Bajaj, Noah Kalman, Upendra Parvathaneni, Sanford R. Katz, Robert Leonard Foote, MD Anderson Clinical Trial Consortium; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital, Boston, MA; Baylor College of Medicine, Houston, TX; Mayo Hosp, Phoenix, AZ; Memorial Sloan Kettering Cancer Center, New York, NY; University of Pennsylvania, Philadelphia, PA; The South Florida Proton Therapy Institute, Delray Beach, FL; Emory University Winship Cancer Institute, Atlanta, GA; Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK; Inova Fairfax Hospital, Fairfax, VA; Miami Cancer Institute, Miami, FL; University of Washington, Seattle, WA; Willis-Knighton Medical Center, Shreveport, LA; Mayo Clinic Department of Pediatric and Adolescent Medicine, Rochester, MN

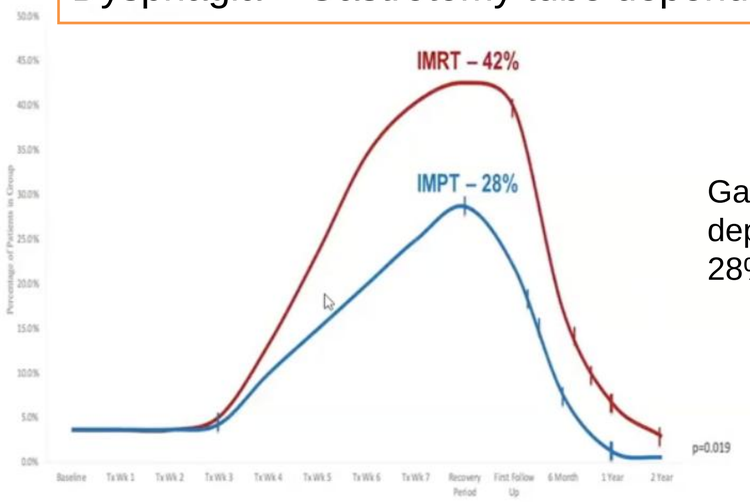
- 440 pts (219 IMRT vs 221 IMPT),
- RCT non inferiority
- 21 Institutions
- Primary endpoint: 3 yy PFS
- Secondary endpoints: OS, treatment-related malnutrition, gastrostomy-tube dependence

Median follow-up: 3.14 years

IMPT is non- inferior to IMRT

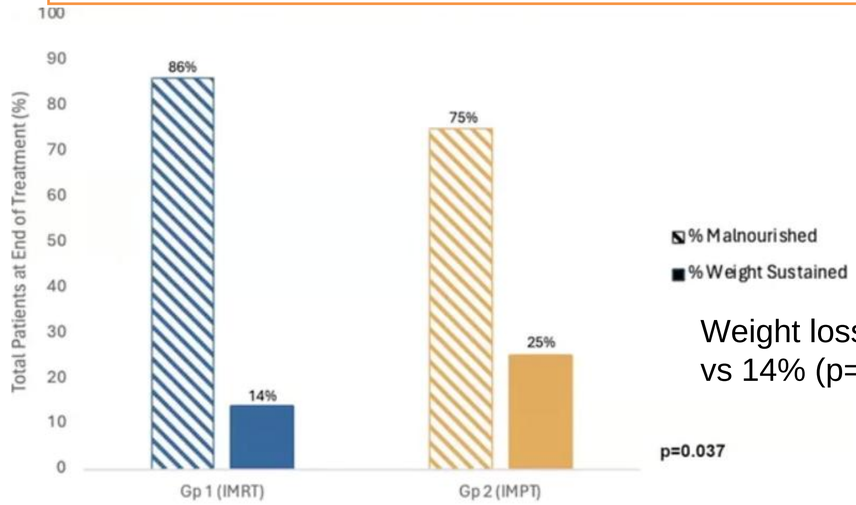
IMPT has emerged as a standard of care CRT approach for OPC that reduces malnutrition and gastrostomy-tube dependence

Dysphagia – Gastrotomy tube dependence



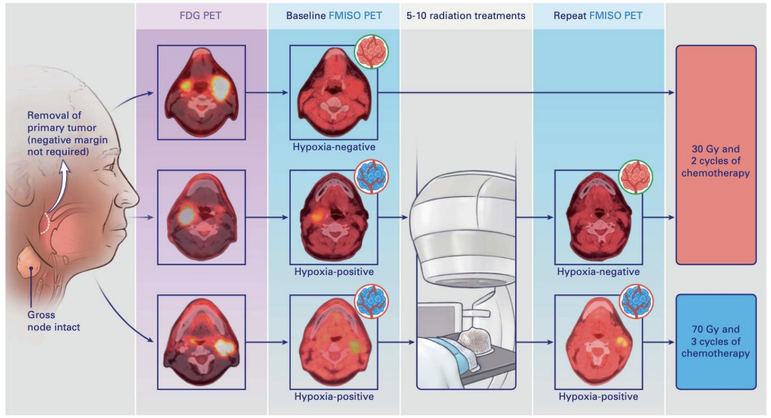
Gastrostomy tube dependence 42% vs 28% (p=0.019)

Malnutrition (weight loss/sustainability <5%)



Weight loss <5% 24% vs 14% (p=0.037)

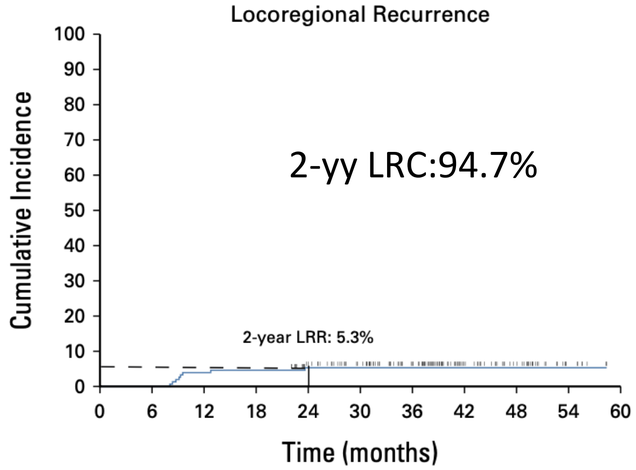
Hypoxia-Directed Treatment of Human Papillomavirus–Related Oropharyngeal Carcinoma

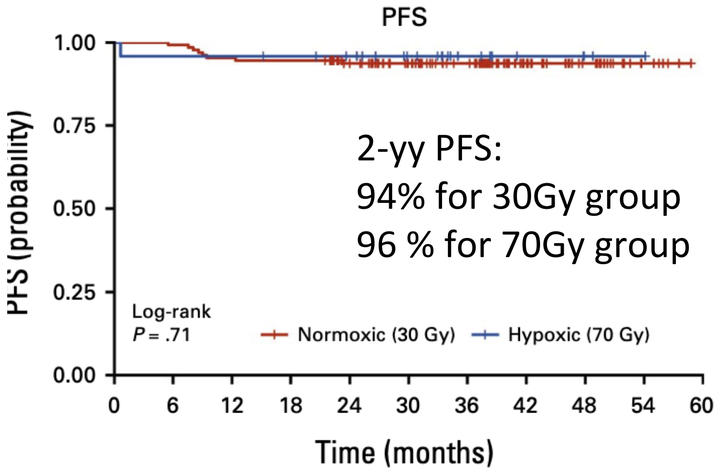


42 (28%) pts

86 (78%) pts

24 (22%)pts





- T0-2/N1-2c/M0 152 HPV pos OPC
- IMRT to the postoperative primary site, gross neck nodes, and potential areas of microscopic spread (typically bilateral necks)
- The primary objective: 2-year LRC of 95% (historical control) with a 7% noninferiority margin
- Median follow-up was 38.3 months

- 12 of 128 (9%) patients who received 30 Gy required neck dissections (vs 2%-8% in other series)
- No 70 Gy patients experienced a nodal failure

Lee A et al, J Clin Oncol 42:940-950, © 2024

TABLE 2. Most Common Investigator-Reported Adverse Events for the 30-Gy and 70-Gy Cohort

	30 Gy, %		70 Gy, %		
Acute Toxicity	Any	Grade 3-4	Any	Grade 3-4	*P*
RT-related					
Dermatitis	47.6	0.0	95.8	4.2	<.001
Dry mouth	89.1	0.0	100.0	0.0	.16
Dysphagia	57.0	0.7	95.8	8.3	<.001
Oral mucositis	78.9	0.0	95.8	4.2	<.001
Dysgeusia	93.8	0.0	100.0	0.0	<.001
Hypothyroidism	6.3	0.0	12.5	0.0	.38
Chemotherapy-related					
Neutropenia	57.0	29.7	79.2	45.8	.15
Anemia	85.9	0.7	95.8	4.2	.003
Thrombocytopenia	73.4	0.0	79.1	0.0	.01
Nausea	44.5	0.7	66.7	4.2	.08
Vomiting	9.4	1.5	12.5	0.0	.67
Neuropathy	3.9	0.0	8.3	0.0	.31
Acute kidney injury	42.9	0.7	62.5	4.2	.07
Hearing	8.6	0.0	8.3	0.0	1

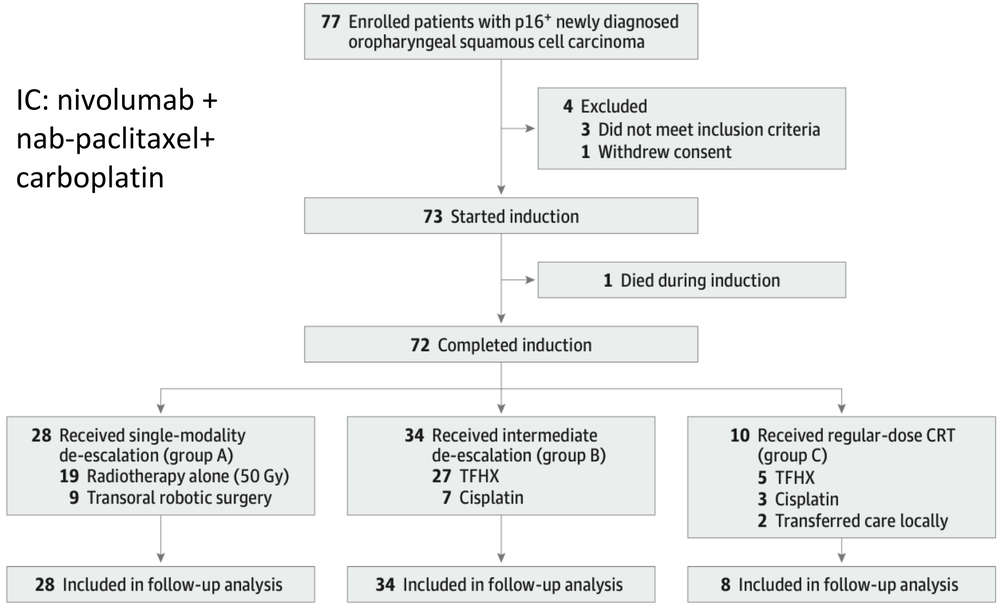
- First personalized phase II trial using functional PET imaging as an integral biomarker to markedly de-escalate definitive CTRT in HNC
  - ↓ decreased AEs, = oncologic outcomes to standard full-dose RT

JAMA Oncology | Original Investigation

Neoadjuvant Nivolumab Plus Chemotherapy Followed By Response-Adaptive Therapy for HPV+ Oropharyngeal Cancer
OPTIMA II Phase 2 Open-Label Nonrandomized Clinical Trial

Ari J. Rosenberg, MD; Nishant Agrawal, MD; Aditya Juloori, MD; John Cursio, PhD; Zhen Gooi, MD; Elizabeth Blair, MD; Jeffrey Chin, BS; Daniel Ginat, MD; Olga Pasternak-Wise, MD; Rifat Hasina, DDS, PhD; Anna Starus, PhD; Frederick S. Jones, PhD; Evgeny Izumchenko, PhD; Ellen MacCracken, MS; Rachelle Wolk, DDS; Nicole Cipriani, MD; Mark W. Lingen, DDS, PhD; Alexander T. Pearson, MD, PhD; Tanguy Y. Seiwert, MD; Daniel J. Haraf, MD; Everett E. Vokes, MD

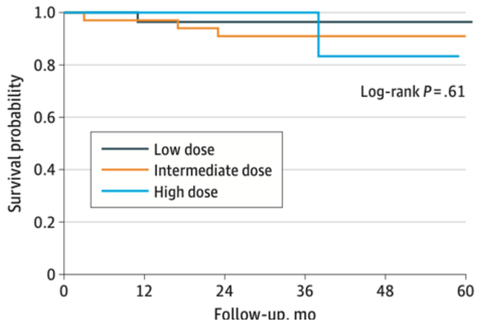
Figure 1. CONSORT Diagram of Study Participants



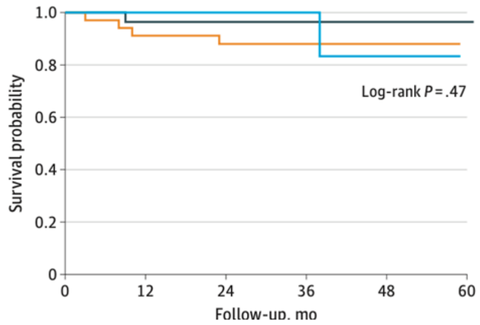
IC: nivolumab + nab-paclitaxel+ carboplatin

deep response rate (DRR)- proportion of tumors with >50% shrinkage per RECIST

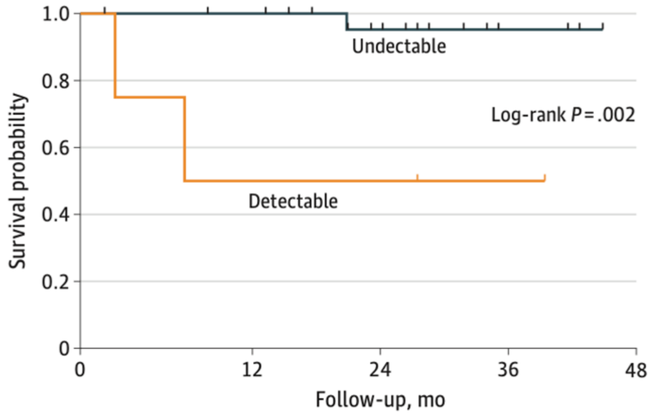
Overall survival by treatment group



Progression-free survival by treatment group



PFS for patients with detectable vs undetectable ctHPV-DNA



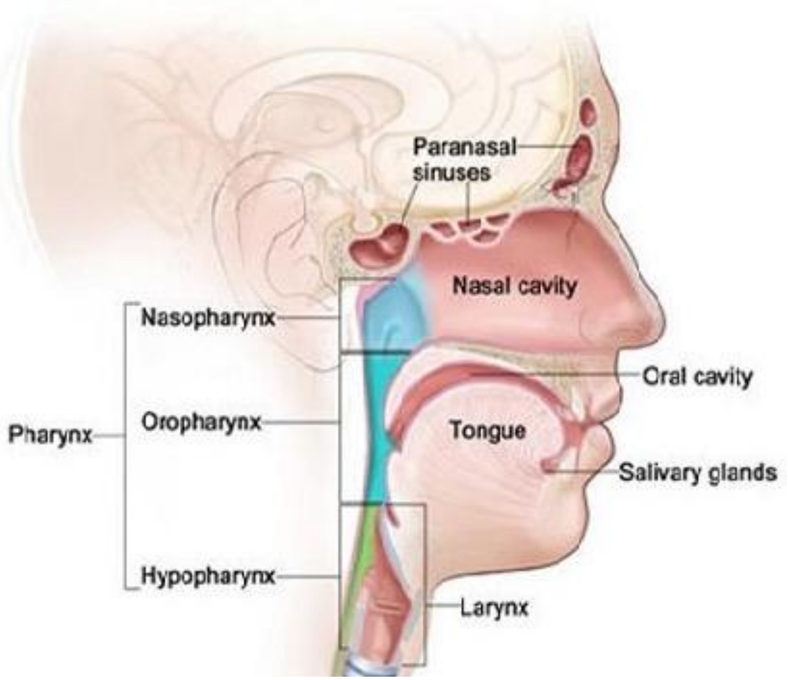
No. at risk

Undetectable	26	25	19	4	0
Detectable	5	2	2	1	0

AGENDA

- *Head and Neck cancer – overview*

- *Oropharyngeal cancer*
- *Nasopharyngeal cancer*
- *Oral cavity cancer*
- *Laryngeal Cancer*



Reduced-Volume Irradiation of Uninvolved Neck in Patients With Nasopharyngeal Cancer: Updated Results From an Open-Label, Noninferiority, Multicenter, Randomized Phase III Trial

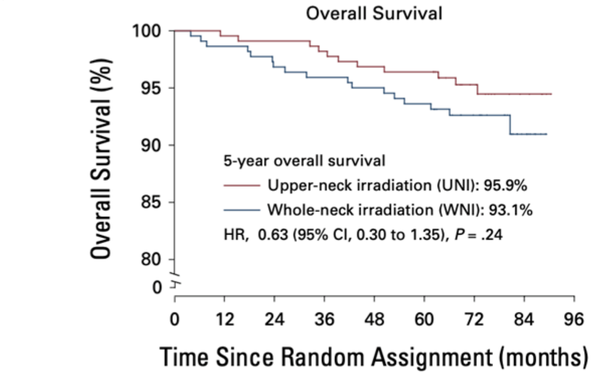
Cheng-Long Huang, MD[1]; Ning Zhang, MD[2]; Wei Jiang, MD[3]; Fang-Yun Xie, MD[1]; Xiao-Qing Pei, MD[4]; Shao Hui Huang, MD[5]; Xue-Yan Wang, MD[4]; Yan-Ping Mao, MD[1]; Kun-Peng Li, MD[1]; Qing Liu, PhD[6]; Ji-Bin Li, PhD[6]; Shao-Qiang Liang, MD[2]; Guan-Jie Qin, MD[1]; Wei-Han Hu, MD[1]; Guan-Qun Zhou, MD[1]; Jun Ma, MD[1]; Ying Sun, MD[1]; Lei Chen, MD[1]; and Ling-Long Tang, MD, PhD[1]

446 pts
Median f. up: 74 months

Toxicity:
5-year disease-free survivors significantly ↓:
- hypothyroidism (34% v 48%; P <0.004)
- dysphagia (14% v 27%; P 5 .002)
- neck tissue damage (29% v 46%; P < .001)

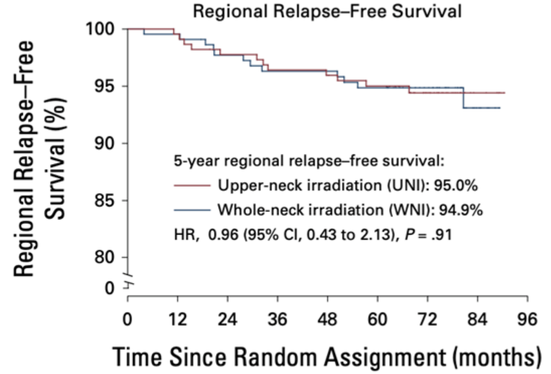
for UNI vs WNI group

- comparable 5-year survival outcomes
- Under this premise, the reduction in long-term toxicity burden and improvement of QoL outcomes are particularly valuable representing a definite step forward



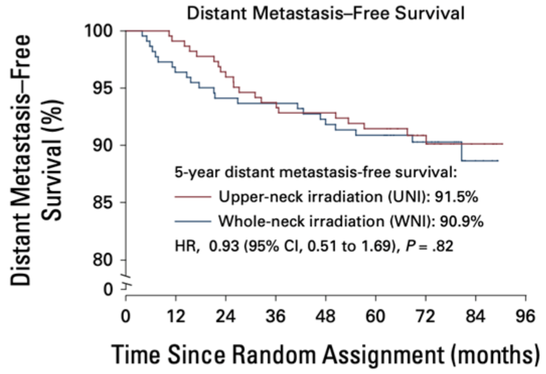
No. at risk (No. censored):

Whole-neck irradiation	222 (0)	218 (1)	214 (0)	210 (2)	204 (4)	201 (0)	128 (71)	29 (98)	0 (29)
Upper-neck irradiation	224 (0)	223 (0)	221 (1)	218 (1)	213 (2)	207 (5)	128 (77)	28 (99)	0 (28)



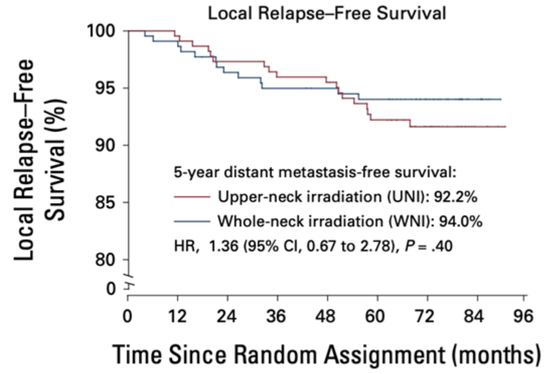
No. at risk (No. censored):

Whole-neck irradiation	222 (0)	218 (3)	211 (3)	204 (4)	199 (5)	196 (0)	126 (70)	28 (97)	0 (28)
Upper-neck irradiation	224 (0)	223 (0)	218 (1)	213 (2)	207 (5)	200 (5)	127 (72)	28 (99)	0 (28)



No. at risk (No. censored):

Whole-neck irradiation	222 (0)	213 (1)	207 (1)	204 (2)	197 (3)	194 (1)	123 (70)	28 (94)	0 (28)
Upper-neck irradiation	224 (0)	222 (0)	215 (1)	208 (1)	205 (1)	198 (4)	124 (73)	28 (95)	0 (28)



No. at risk (No. censored):

Whole-neck irradiation	222 (0)	217 (2)	210 (2)	204 (3)	198 (6)	195 (1)	125 (70)	29 (96)	0 (29)
Upper-neck irradiation	224 (0)	223 (0)	217 (1)	212 (2)	207 (4)	195 (5)	124 (70)	27 (97)	0 (27)

J Clin Oncol 42:2021-2025, 2024

Systematic Review

Dosimetric parameters predict radiation-induced temporal lobe necrosis in nasopharyngeal carcinoma patients: A systematic review and *meta*-analysis☆

Jun Dong [a], Wai Tong Ng [b,a,c,*], Charlene H.L. Wong [c], Ji-Shi Li [a], Heleen Bollen [d,e], James C.H. Chow [f], Avraham Eisbruch [g], Anne W.M. Lee [b,a,c], Victor H.F. Lee [c], Sweet Ping Ng [h], Sandra Nuyts [d,e], Robert Smee [i], Alfio Ferlito [j]

- 30,191 patients with NPC who underwent curative-intent RT
- 30 retrospective studies included
- IMRT was used in all studies
- RT dose: 66-76 Gy/ 30-38 fx
- MRI for TLN diagnosis

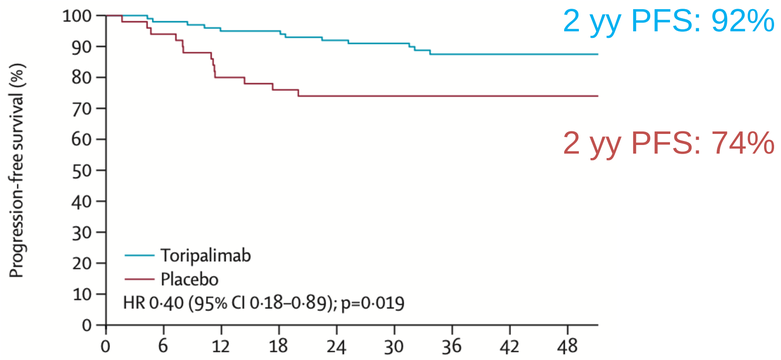
- Median latency period to TLN: 27-48 months
- Average crude incidence of TLN is approximately 14 % (2,3%-47,3%)

- Dmax ≤72 Gy and D1cc ≤62 Gy are potentially valuable in predicting TLN

Neoadjuvant and adjuvant toripalimab for locoregionally advanced nasopharyngeal carcinoma: a randomised, single-centre, double-blind, placebo-controlled, phase 2 trial

Sai-Lan Liu, Xiao-Yun Li*, Jin-Hao Yang*, Dong-Xiang Wen*, Shan-Shan Guo*, Li-Ting Liu*, Yi-Fu Li*, Mei-Juan Luo, Si-Yi Xie, Yu-Jing Liang, Xue-Song Sun, Zhen-Chong Yang, Xiao-Fei Lv, Dong-Hua Luo, Ji-Bin Li, Qing Liu, Pan Wang, Ling Guo, Hao-Yuan Mo, Rui Sun, Qi Yang, Kai-Qi Lan, Guo-Dong Jia, Ru Li, Chong Zhao, Rui-Hua Xu , Qiu-Yan Chen†, Lin-Quan Tang†, Hai-Qiang Mai†*

- 150 patients stages III–IVa NPC and pretreatment plasma EBV DNA ≥1500 copies per mL
- randomly assigned to the toripalimab group (n=100) or the placebo group (n=50)
- Chinese patients



Median f. up: 37,8 months
toripalimab group:
- ↑ any-grade xerostomia (88% vs 70%)
- ↑ alanine transaminase (39%*vs* 20%)

10% Immune relate AEs G3

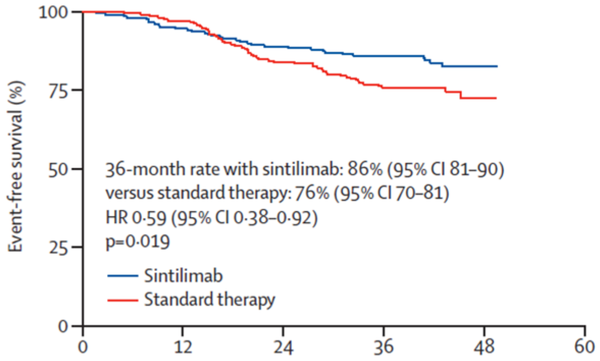
Lancet Oncol 2024; 25: 1563–75

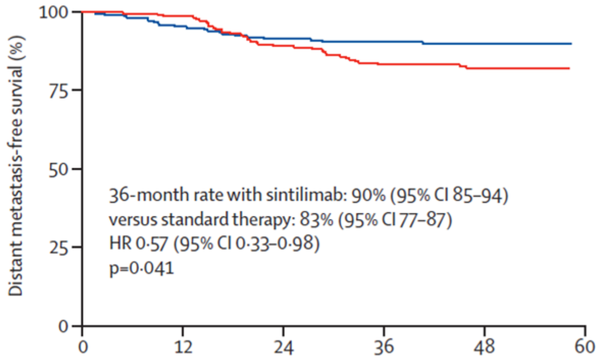
Induction-concurrent chemoradiotherapy with or without sintilimab in patients with locoregionally advanced nasopharyngeal carcinoma in China (CONTINUUM): a multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial

48% pts T4, 33% N3
70% stage 4°
median follow-up was 41·9 months

- 425 high-risk stage III–IVa NPC regardless of tumour PD-L1 status
- Sperimental arm (210 pts): Sintilimab+ICT(Gem+CDDP)->CTRT+Sintilimab->adj Sintilimab

vs standard arm (215 pts): ICT (Gem+CDDP) -> CTRT





Higher but manageable adverse events.
Immune-related AEs were mostly G1 -2, 10% pts G3–4 in the sintilimab group

Liu X et al, Lancet 2024; 403: 2720–31

JAMA Oncology | Original Investigation

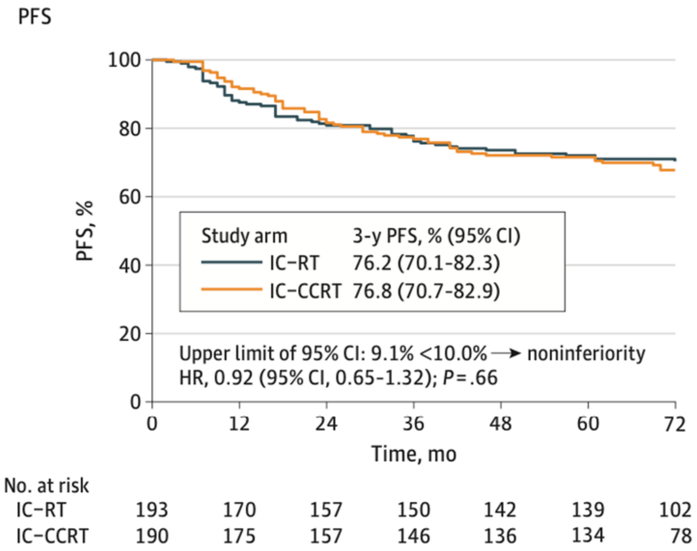
Induction Chemotherapy Followed by Radiotherapy vs Chemoradiotherapy in Nasopharyngeal Carcinoma
A Randomized Clinical Trial

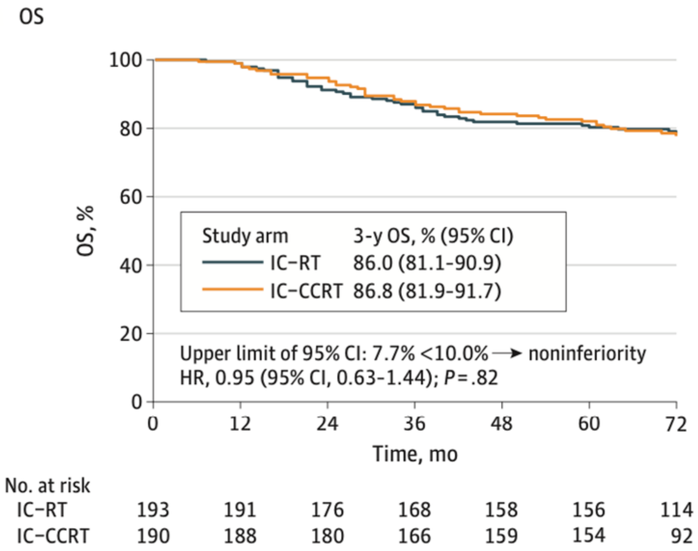
Jinxuan Dai, MD; Bin Zhang, MD; Yixin Su, MD; Yufei Pan, MD; Zhenkai Ye, MD; Rui Cai, MD; Guanjie Qin, MD; Xiangyun Kong, MD; Yunyan Mo, MD; Rongjun Zhang, MD; Zhengchun Liu, PhD; Yuan Xie, MD; Xiaolan Ruan, MD; Wei Jiang, PhD

April 2015- March 2018: 383 stage III-IVB NPC:

- IC-RT group 193 (50.4%) and to IC-CCRT group 190 (49.6%)
- IC: 3 cycles of fluorouracil, cisplatin, and docetaxel

3 yy PFS
the median follow-up time was 76





No data for plasma EBV DNA

No significant differences in 3 yy-OS,LRR, DMFS

- After IC, RT alone was non-inferior to CTRT in terms of the 3-year PFS for locoregionally advanced NPC
- G3-4 short-term toxic effects in the IC-RT group was less than that in the IC-CCRT group

JAMA Oncol. 2024;10(4):456-463

International Recommendations on Postoperative Management for Potentially Resectable Locally Recurrent Nasopharyngeal Carcinoma

1. Definition of resectability:
- Potentially resectable disease
- Unresectable diseases
2. Assessment of surgical margins
3. Definition of the surgical margin
4. Indications for post op re-RT
5. Method and dose for post op re-RT

4. Indications for postoperative re-RT	a. Postoperative re-RT should be offered for tumor cells seen on the surgical margin (Surgeons' agreement: 78% [7 of 9 voters]; oncologists' agreement: 95% [20 of 21 voters]; reached consensus in round 1) b. Postoperative re-RT should be considered for margins less than 1 mm after a thorough evaluation of the prior RT plan and dosimetric feasibility (surgeons' agreement: 100% [9 of 9 voters]; oncologists' agreement: 95% (19 of 20 voters); reached consensus in round 2)	a. Postoperative re-RT is not recommended if the margin is >1 mm but less than <3 mm. (surgeons' agreement: 67% [6 of 9 voters]; oncologists' agreement: 85% [17 of 20 voters]; reached consensus among oncologists only, but not surgeons after 2 rounds)
5. Method and dose for postoperative re-RT	a. CTV should include the postoperative tumor bed with a 5 mm margin (to account for microscopic disease extension) while respecting the adjacent critical organs at risk (oncologists' agreement: 100% [21 of 21 voters]; reached consensus in round 1) b. A dose of ≥60 Gy (in EQD2) should be given, but should not exceed 66 Gy (EQD2) (oncologists' agreement: 81% [17 of 21 voters]; reached consensus in round 1) c. Conventional fractionation is an acceptable treatment technique in the postoperative setting (oncologists' agreement: 76% [16 of 21 voters]; reached consensus in round 1) d. Doses>2 Gy per fraction should be avoided (oncologists' consensus: 76% [16 of 21 voters]; reached consensus in round 1)	a. Hyperfractionated IMRT should be the preferred treatment technique if resources allow (oncologists' agreement: 70% [14 of 20 voters]; did not reach consensus after 2 rounds)

- CTV: post op T bed+ 5mm
- Dose≥60Gy, not exceed 66Gy
- Avoid dose>2Gy/fx

Ji-Shi Li et al, Int J Radiation Oncol Biol Phys, Vol. 120, No. 5, pp. 1294–1306, 2024

AGENDA

- *Head and Neck cancer – overview*

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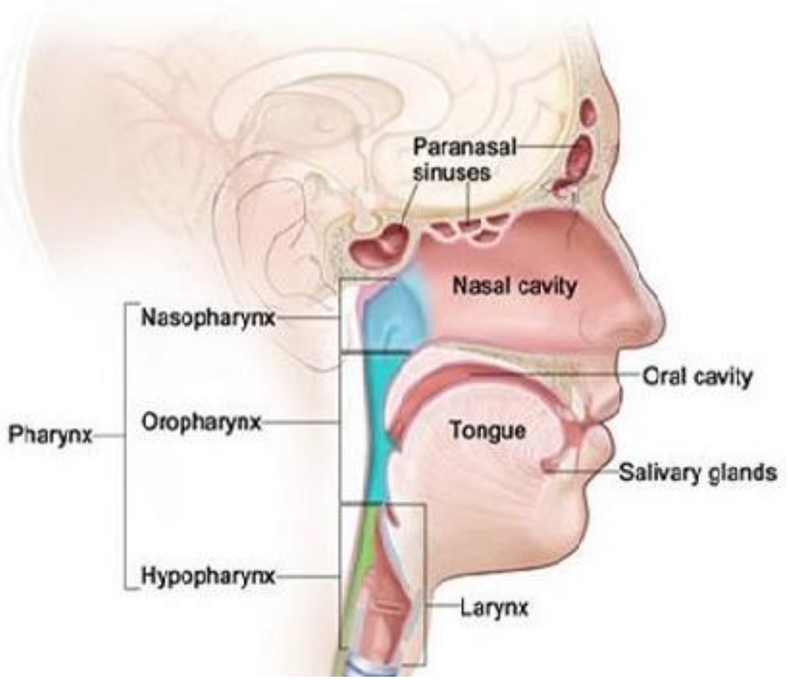
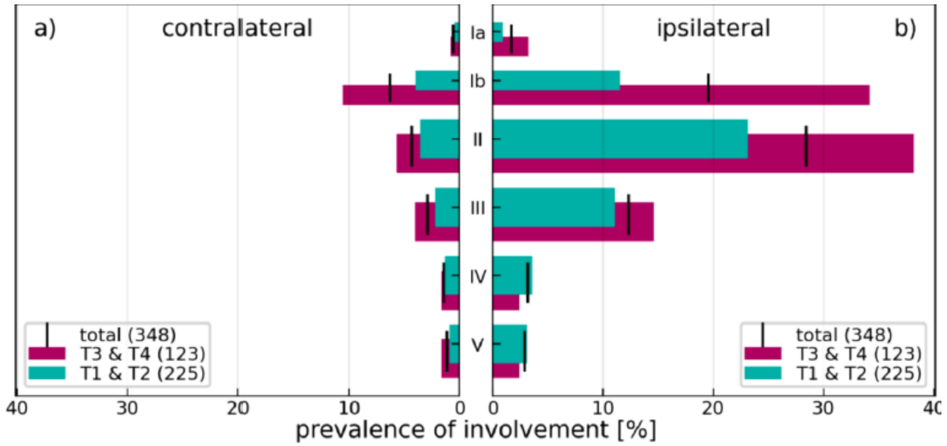
- *Nasopharyngeal cancer*
- *Oral cavity cancer*
- *Laryngeal Cancer*



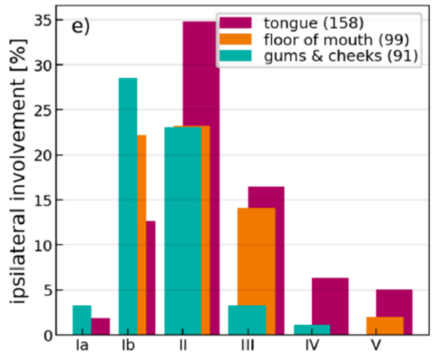
Patterns of lymph node involvement for oral cavity squamous cell carcinoma

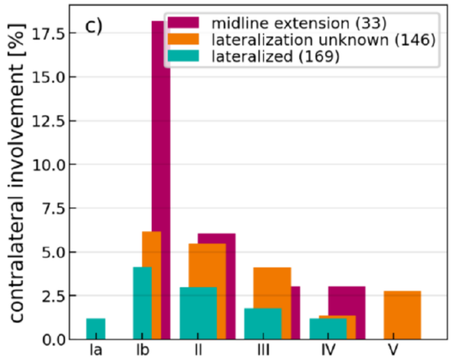
Roman Ludwig [a,1,*], Sandrine Werlen [b,c,1], Dorothea Barbatei [d,1], Lars Widmer [a], Bertrand Pouymayou [a], Panagiotis Balermpas [a], Olgun Elicin [e], Matthias Dettmer [f,g], Philippe Zrounba [h], Roland Giger [b,c], Vincent Grégoire [d,2], Adrian Schubert [2,b,c,i], Jan Unkelbach [a,2]

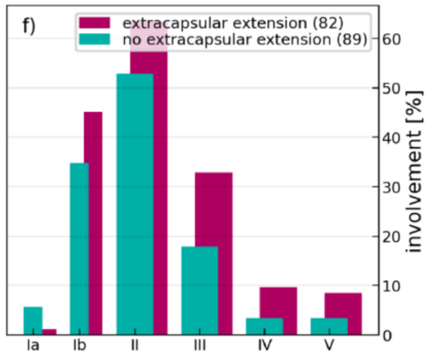
- 348 OCSCC pts
- Early T : T1-T2, advanced T: T3-T4
- to provide detailed per-level quantifications of neck node involvement for OCSCC



- Higher probability of N involvement in advanced T
- Ipsilateral involvement
- Liv I: 13 % (early) vs 35% (advanced)
- Liv II: 23 % (early) vs 38% (advanced)
- Liv III: 11 % (early) vs 15% (advanced)
- N metastases in one level increase the prevalence of metastases in an adjacent level
- Higher contralateral involvement was observed for tumors with midline extension







-> Potential implications for elective treatments

Radiotherapy and Oncology 200 (2024) 110474

GEC-ESTRO recommendations for head & neck cancer brachytherapy (interventional radiotherapy): 2nd update with focus on HDR and PDR

J.L. Guinot [a,*], W. Bacorro [b], A. Budrukkar [c], F. Bussu [d], V. Gonzalez-Perez [e], R. Jaberi [f], R. Martinez-Monge [g], A. Rembielak [h,i], A. Rovirosa [j], V. Strnad [k], Z. Takácsi-Nagy [l], L. Tagliaferri [m,n], on behalf of the Head & Neck and Skin Working Group of GEC-ESTRO

Recommended doses for brachytherapy of lip, buccal mucosa and hard palate

- **Lip:** 3 Gy × 18fx; 3.5 Gy × 14fx; 4 Gy × 13fx, 4.5 Gy × 9fx for small and postoperative cases, 5 Gy × 9fx for big tumors.
- PDR: 60–70 Gy at 0.4–0.6 Gy/h/24 h.
- **Buccal mucosa**: HDR: 3.5 Gy × 10–14fx; 4 Gy × 13fx. After 50–54 Gy EBRT 3–3.5 Gy × 6fx.
- PDR: 60–70 Gy at 0.4–0.6 Gy/h/24 h or 10–24 Gy as a boost.
- **Hard palate molds**: 3.5 Gy × 11–15fx. After EBRT 3 Gy × 5–10fx, at 5–7 mm from the source.

Recommended doses for brachytherapy of mobile tongue, floor of mouth and oropharynx

- **Mobile tongue, floor of mouth**: 4 Gy × 11–12fx; 5–6 Gy × 9–10fx (small volume one line).
- Postoperative: 3.4–3.5 Gy × 10–12fx; 4 Gy × 10–11fx; 3 Gy × 13–15–18fx; 6 Gy × 5fx.
- PDR: 50–64 Gy at 0.4–0.6 Gy/h/24 h.
- Boost after 50–60 Gy EBRT: HDR 4 Gy × 4–6fx; 3 Gy × 5–8fx; PDR: 10–24 Gy at 0.4–0.6 Gy/h/24 h.
- **Oropharynx**: 4 Gy × 10fx; 6 Gy × 8fx (small volumes tonsil, soft palate).
- Boost after 45–50 Gy EBRT: 3 Gy × 7–8fx; 4 Gy × 4–6fx.
- PDR: 0.4–0.6 Gy/h/24 h. 60–66 Gy or 10–24 Gy as a boost.

Radiotherapy and Oncology 201 (2024) 110533

AGENDA

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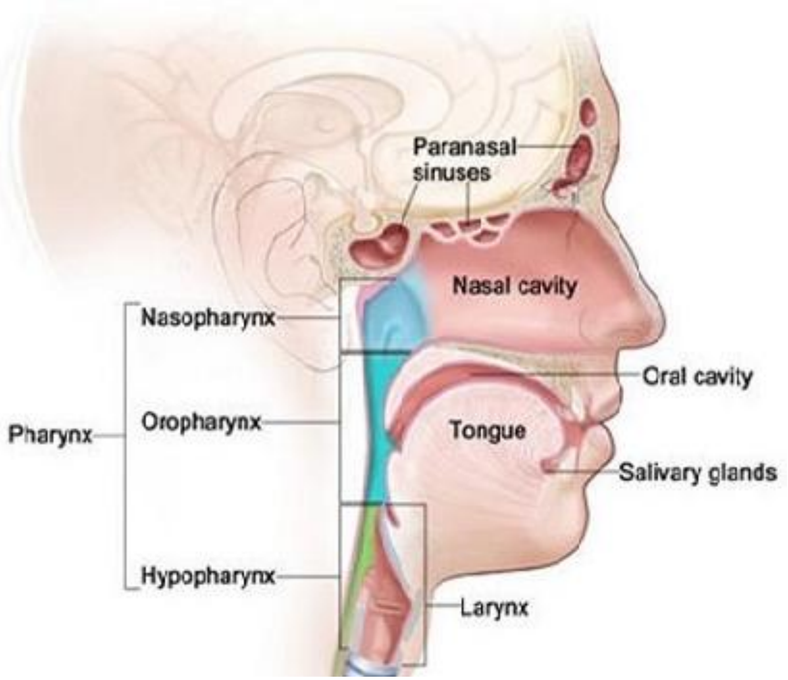

Stereotactic Ablative Radiotherapy for T1 to T2 Glottic Larynx Cancer: Mature Results From the Phase 2 GLoTtic Larynx-SABR Trial

David J. Sher, MD, MPH,* Vladimir Avkshtol, MD,* Dominic Moon, MD,* Dat Vo, MD, PhD,* Ted Mau, MD, PhD,† Lesley Childs, MD,† Mu-Han Lin, PhD,* Jeffrey Dubas, CMD,* Chul Ahn, PhD,‡ and Baran D. Sumer, MD†

Characteristic	25 pts	N (%)
Age (median, IQR)		72 y (65-81)
Gender (male)		24 (96%)
Stage		
Tis		1 (4%)
T1a		16 (64%)
T1b		5 (20%)
T2		3 (12%)
ECOG PS		
0		19 (76%)
1		5 (20%)
2		1 (4%)
Smoking		
None		8 (32%)
Previous		16 (74%)
Active		1 (4%)
Race		
White, non-Hispanic		19 (76%)
Other		6 (24%)
Treatment regimen		
42.5 Gy/5	8.5 Gy/fx	21 (84%)
58.08 Gy/16	3.63 Gy/fx	4 (6%)

Abbreviations: ECOG PS = Eastern Cooperative Group Performance Status.

Median follow up: 3,7 yy

- 1 and 2 yy LRR: 4% and 8%
- T1: 2 yy LRR: 4,5%

2 local recurrence (T1b and T2 at diagnosis)

	Grade 1 (N, %)	Grade 2 (N, %)	Grade 3 (N, %)
Acute			
Anorexia	1 (4%)	-	-
Cough	4 (16%)	-	-
Dermatitis	1 (4%)	-	-
Dry mouth	4 (16%)	-	-
Dysesthesia	1 (4%)	-	-
Dysgeusia	3 (12%)	-	-
Dysphagia	1 (4%)	-	1 (4%)*
Fatigue	4 (16%)	-	-
Hoarseness	4 (16%)	3 (12%)	-
Infection (thrush)	-	3 (12%)	-
Laryngeal edema/mucositis	7 (28%)	-	-
Neck edema	1 (4%)	-	-
Odynophagia	-	2 (6%)*	-
Sore throat	6 (24%)	1 (4%)	-
Productive cough	-	1(4%)*	-
Weight loss	1 (4%)*	-	-
Late			
Dermatitis	1 (4%)	-	-
Dry mouth	1 (4%)	-	-
Dysgeusia	1 (4%)	-	-
Dysphagia	2 (8%)	-	-
Hoarseness	5 (20%)	-	-
Sore throat	3 (12%)	-	-
Laryngeal edema	1 (4%)	-	-

16 fx

No acute or late soft tissue necrosis

Excellent tolerability and local control with SBRT
No unexpected late complications

Int JRadiationOncolBiolPhys,Vol.000,No.00,pp.1–8, 2024

Stereotactic Radiation Therapy in 3 Fractions for T1 Glottic Cancer

Giuseppe Sanguineti, MD,* Pasqualina D'Urso, MD,* Marta Bottero, MD,* Alessia Farneti, MD,* Lucia Goanta, MD,* Diana Giannarelli, PhD,† and Valeria Landoni, PhD‡

Characteristic	Stratification	Median (n)	IQR (%)
Age	Continuum	66	60-72
T stage	1a	23	69.7%
	1b	10	30.3%
Sex	Male	27	81.8%
	Female	6	18.2%
Smoking	Never	2	6.1%
	Quit	16	48.5%
	Current	15	45.5%
Alcohol	None	10	30.3%
	Social	18	54.5%
	Heavy	5	15.2%
Grading	Unknown	12	36.4%
	1	5	15.2%
	2	13	39.4%
	3	3	9.1%
Anterior commissure involvement	No	15	45.5%
	Yes	18	54.5%

33 pts
36Gy/3 fx
Primary endpoint: local failure

Median follow-up is 51.5 months
Local control: 100%

CTCAE Item	GR2	GR3	GR4	GR5	Overall
Laryngeal mucositis	0	4	2	0	6
Voice alteration	7	7	0	0	14
Laryngeal edema	6	0	1	0	7
Laryngeal pain	5	1	0	0	6
Dysphagia	4	0	1	0	5
Cough	1	0	0	0	1
Necrosis		5	1	0	6
Aspiration	0	0	1	0	1
Overall	22	18	6	0	46

Pt #	Age	Type	PTV36 volume (cc)	PTV30 volume (cc)	TC Dmax (0.1 cc) (cGy)	CC Dmax (0.1 cc) (cGy)	iAC Dmax (0.1 cc) (cGy)	Smoker at the time of the event	Onset after SBRT (y)	Resolution (duration-mo)	VHI at last FU	Notes
9	62	CNR	1.5	6.6	3230	3020	3100	Yes	1.4	Yes (4.5)	56	iAC
17	71	CNR	2.5	7.3	3630	2950	1960	Yes	1.7	No (23.6+)	64	TC, refusing TL
20	72	MRN	3.3	8.7	3450	2870	2870	No	0.8	Yes (3.0)	4	
24	72	MRN	2.9	6.5	3610	3080	2550	No	2.0	Yes (1.0)	21	Omicron
30	59	MRN	1.0	3.6	3290	2830	1100	Yes	1.1	Yes (2.0)	73	Omicron
32	59	MRN	5.2	8.6	3470	3080	3130	Yes	0.8	Yes (12.2)	19	

Concern on toxicity!

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Summary

- Oropharyngeal cancer
- *Early stage: RT = Surgery*
- *De-escalation*

- Nasopharyngeal cancer
- *Reduced N volume*
- *IT*
- *Adjuvant re-RT*

- Oral cavity cancer
- *BRT*

- Laryngeal cancer
- *SBRT*