EVIDENCE AND PRACTICE CHANGING TREATMENTS IN HEAD AND NECK TUMORS

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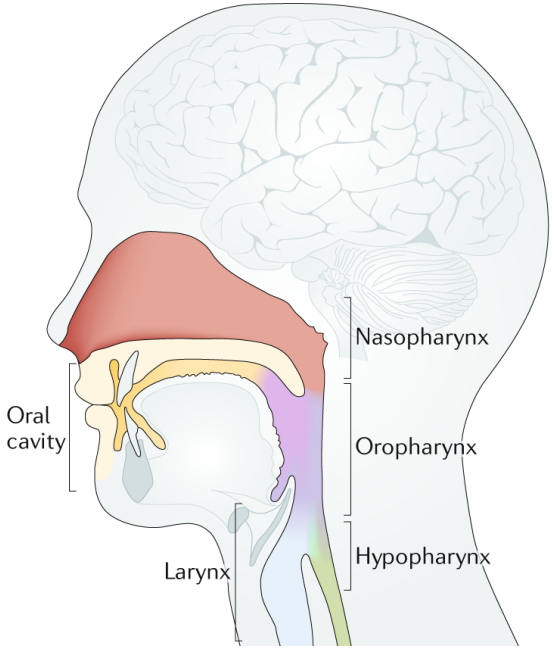
Agenda

-Head and Neck cancer – overview
-Oropharyneal cancer
-Nasopharyngeal cancer
-Oral cavity cancer
-Laryngeal Cancer
-Focus on Proton Therapy



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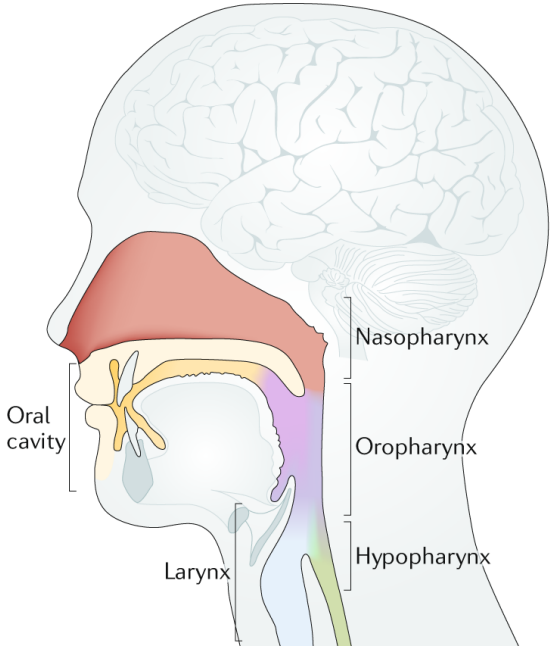

Head and Neck cancer - overview

Organs at Risk

Systemic therapies

SBRT

Palliative Treatment

Head and Neck cancer - overview

Organs at Risk

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Palliative Treatment

Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial

Christopher Nutting, Laura Finneran, Justin Roe, Mark A Sydenham, Matthew Beasley, Shree Bhide, Cheng Boon, Audrey Cook, Emma De Winton, Marie Emson, Bernadette Foran, Robert Frogley, Imran Petkar, Laura Pettit, Keith Rooney, Tom Roques, Devraj Srinivasan, Justine Tyler, Emma Hall, on behalf of the DARS Trialist Group

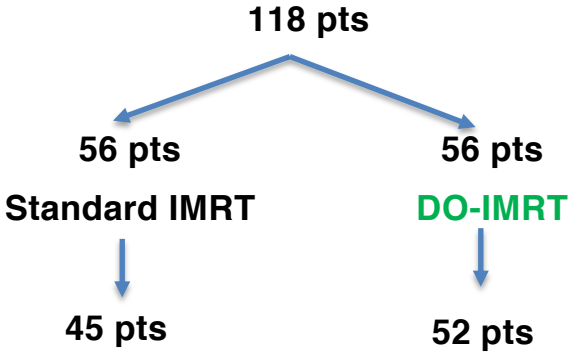
Disphagia-Aspiration Related Structures
DARS

Parallel-group, Phase III randomized controlled, Multicentric trial (22 centers UK-Ireland)

Standard IMRT vs DARS-OPTIMIZED (DO)-IMRT

Inclusion criteria: tumors of oropharynx and hypopharynx, bilateral RT

Exclusion criteria: post-operative RT



Primary end-point

MD Anderson Composit Score (MDADI) @ 12 months

(PRO-Patient reported Outcome)

Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial

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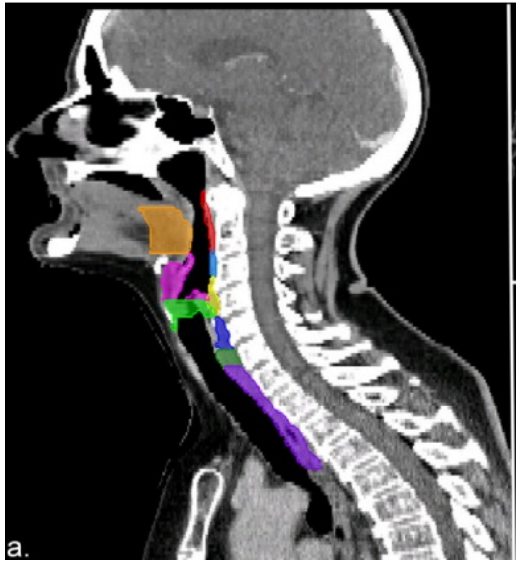
Dysphagia-Aspiration Related Structures

DARS



Constrictor Muscles

-Superior
-Middle } Mean Dose constraint < 50 Gy

-Inferior Mean Dose constraint < 20 Gy

Supr[illegible]c Larynx

Glott[illegible]nx

Dysphagia and aspiration after chemoradiotherapy for HN Cancer: which anatomic structures can affected and can be spared by IMRT? A. Eisbruch Int. J. Radiat Oncol Biol. Phys., Vol. 60, No. 5, pp. 1425–1439, 2004

Delineation of organs at risk involved in swallowing for radiotherapy treatment planning Miranda E.M.C. Christianen et al Radiother Oncol 101 (2011) 394–402

Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial

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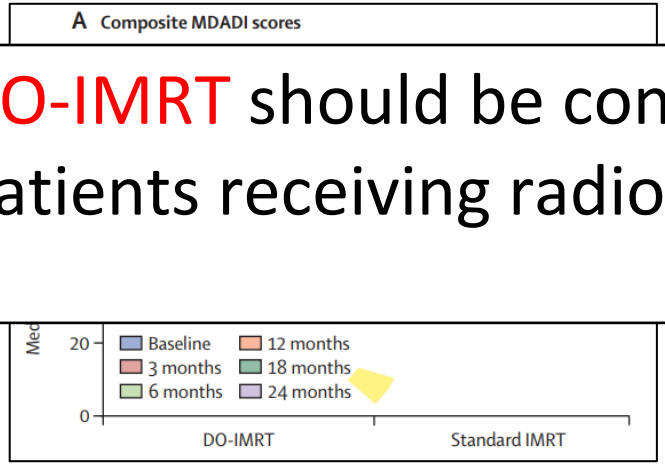
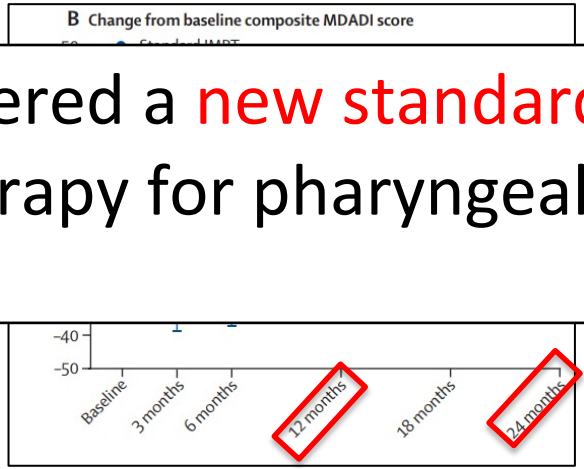
Dysphagia-Aspiration Related Structures

DARS





DO-IMRT should be considered a new standard of care for patients receiving radiotherapy for pharyngeal cancers.

-mean score **77·7** [SD 16·1] vs **70·6** [SD 17·3]

-mean difference **7·2** [95% CI 0·4–13·9]; p=0·037)

-after adjusting the mean difference was **9·8** (95% CI 3·5–16·0; p=0·0030)

-the difference persisted at 24 months

Das B, et al. Lancet Oncol. 2023. PMID: 37797635 McDowell L, et al. Lancet Oncol. 2023. PMID: 37797634

Practical Radiation Oncology® (2023) 13, 517–521

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Technical Report

Delineation of Lingual Artery as an Additional Organ-At-Risk for Stereotactic Body Radiation Therapy of Head and Neck Cancers

Indu Bansal, MD,[a,*] Roshni Singh, MD,[a] Kanika Bansal, DNB,[a] and Akash Bansal, MD[b]

[a]Department of Radiation Oncology; and [b]Department of Radiology, Narayana Superspecialty Hospital, Gurugram, Haryana, India

Received 7 March 2023; accepted 25 July 2023

SBRT RE-IRRADIATION

LINGUAL ARTERY

Contouring and Constraints

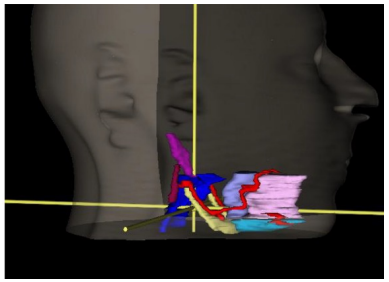


Table 1 Lingual artery dose constraints for lingual artery bleeding in reirradiation with stereotactic body radiation therapy in head and neck cancer

Author	No. of fractions	Dose constraints	Risk of bleeding
Diao et al[6]	5	D 0.5 cc: < 30 Gy 35 Gy 40 Gy	<3% 5% 10%
Bagley et al[7]	5	D 0.3 cc < 30 Gy <5 mm from target Dmax < 30 Gy no hot spot >5 mm from target Dmax < 20 Gy	

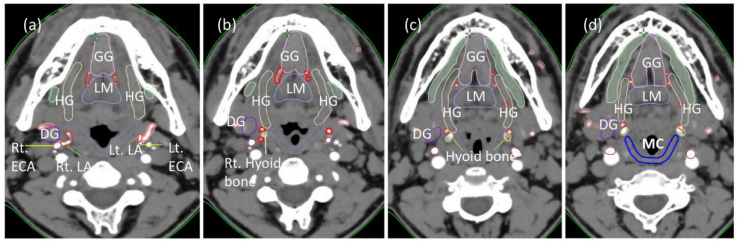


Figure 2 Axial sections of face and neck showing the course of the LA and its relations. (a) Right and left LAs (red) originating from respective ECAs (maroon); note right side LA forming a loop. (b, c) LA running medially along the body of the hyoid bone. (d) LA running between middle constrictor (blue) and HGs (peach); LA running between GG (pink) anteriorly and longitudinal muscles (mauve) posteriorly. *Abbreviations:* DG = digastric muscle; ECA = external carotid artery; GG = genioglossus; HG = hyoglossus muscle; LA = lingual artery; LM = longitudinal muscles; Lt. = left; Rt. = right.

Head and Neck cancer - overview

Organs at Risk

Systemic therapies

SBRT

Palliative Treatment

Head and Neck cancer - overview

Curative Setting
Standard of care

- **RT+ Cisplatin 100 mg/m²**
- **RT+ Cisplatin 40 mg/m²**
- **Carboplatin + 5 FU**
- **Cetuximab**

Organs at Risk

Systemic therapies

SBRT

Palliative Treatment

New practice changing treatment? NO

Curative Setting

- RT+ Cisplatin 100 mg/m² ✚ Cetuximab
- RT+ Cisplatin 40 mg/m²
- Carboplatin + 5 FU
- Cetuximab

Long-Term Update of NRG/RTOG 0522: A Randomized Phase 3 Trial of Concurrent Radiation and Cisplatin With or Without Cetuximab in Locoregionally Advanced Head and Neck Cancer

Jimmy J. Caudell, MD*, Pedro A. Torres-Saavedra, PhD†, David I. Rosenthal, MD‡, Rita S. Axelrod, MD§, Phuc Felix Nguyen-Tan, MD‖, Eric J. Sherman, MD¶, Randal S. Weber, MD‡, James M. Galvin, DSc#, Adel K. El-Naggar, MD‡, Andre A. Konski, MD**, Michelle I. Echevarria, MD*, Neal E. Dunlap, MD††, George Shenouda, MD‡‡, Anurag K. Singh, MD§§, Jonathan J. Beitler, MD, MBA‖‖, Adam Garsa, MD¶¶, James A. Bonner, MD##, Adam S. Garden, MD‡, Ozer Algan, MD***, Jonathan Harris, MS†, Quynh-Thu Le, MD†††

Update phase III randomized trial

No advantages in adding Cetuximab to Standard chemoradiation with Cisplatin

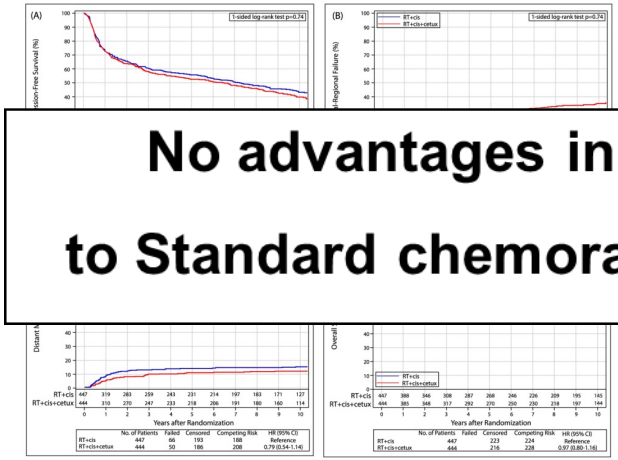


Fig. 1.
(A) Kaplan-Meier estimates of progression-free survival, (B) cumulative incidence estimates of locoregional failure, (C) cumulative incidence estimates of distant metastasis, and (D) Kaplan-Meier estimates of overall survival.

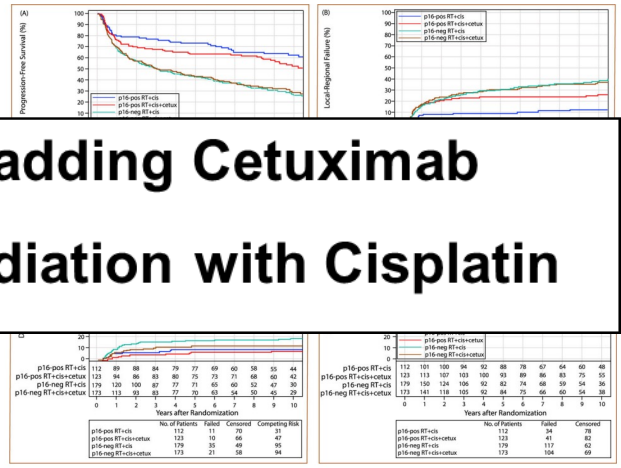


Fig. 2.
Kaplan-Meier estimates of (A) progression-free survival, (B) local-regional failure, (C) distant metastasis, and (D) overall survival by p16 status and assigned treatment including patients with nonoropharyngeal cancer in the p16-negative group.

Curative Setting

- RT+ Cisplatin 100 mg/m² **Cetuximab**
- RT+ Cisplatin 40 mg/m²
- Carboplatin + 5 FU
- Cetuximab

European Archives of Oto-Rhino-Laryngology (2023) 280:11–22
https://doi.org/10.1007/s00405-022-07572-8

REVIEW ARTICLE

Radiotherapy plus cetuximab or cisplatin in head and neck squamous cell carcinoma: an updated systematic review and meta-analysis of randomized controlled trials

Yuting Li[1] · Chensu Yang[1] · Yong Gan[2] · Furong Lu[3] · You Qin[1]

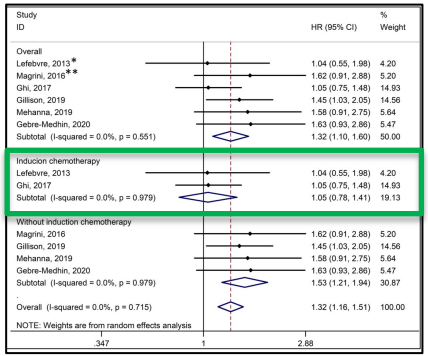
Received: 28 August 2021 / Accepted: 25 July 2022 / Published online: 20 August 2022

Updated Meta-analysis

7 Randomized Controlled Trials

2444 pts

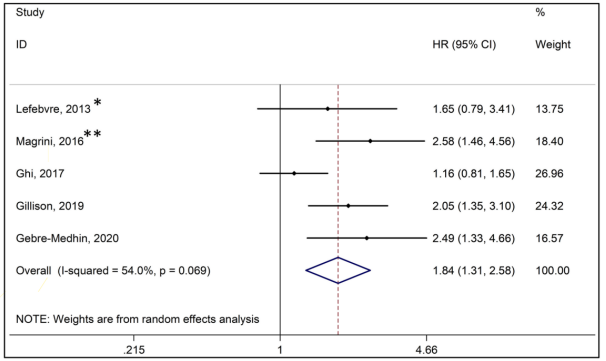
2013-2020



Overall Survival

Cisplatin > Cetuxiamb

No differences after induction CT



Locoregional Control

Cisplatin > Cetuxiamb

Curative Setting

- **RT+ Cisplatin 100 mg/m²**
- **RT+ Cisplatin 40 mg/m²**
- **Carboplatin + 5 FU**
- **Cetuximab** **Docetaxel**

Results of Phase III Randomized Trial for Use of Docetaxel as a Radiosensitizer in Patients With Head and Neck Cancer, Unsuitable for Cisplatin-Based Chemoradiation

Vijay Maruti Patil, MBBS, MD, DM[1]; Vanita Noronha, MBBS, MD, DM[1]; Nandini Menon, MBBS, MD, DNB[1]; Ajay Singh, MBBS, MD, DM[1]; Sarbani Ghosh-Laskar, MBBS, MD[2]; Ashwini Budrukkar, MBBS, MD[2]; Atanu Bhattacharjee, PhD[3]; Monali Swain, MBBS, MD[2]; Vijayalakshmi Mathrudev, BHMS, MBA[1]; Kavita Nawale, PGDCR[1]; Arun Balaji, MASLP[4]; Zoya Perday, MSc[1]; Mitali Alone, MSc[1]; Shruti Pathak, MSc[1]; Abhishek Mahajan, MBBS, MD[5]; Suman Kumar, MBBS, DNB[5]; Nilendu Purandare, MBBS, DNB[5]; Archi Agarwal, MBBS, DNB[5]; Ameya Puranik, MBBS, DNB[5]; Shantanu Pendse, MBBS, MD, DM[1]; Monica Reddy Yallala, MBBS, MD[1]; Harsh Sahu, MBBS, MD[1]; Venkatesh Kapu, MBBS, MD[1]; Sayak Dey, MBBS, MD[1]; Jatin Choudhary, MBBS, MD[1]; Madala Ravi Krishna, MBBS, MD[1]; Alok Shetty, MBBS, MD[1]; Naveen Kanvandan, MBBS, MD[1]; Rahul Ravind, MBBS, MD, DM[1]; Rahul Rai, MBBS, MD[1]; Kunal Jobanputra, MBBS, MD[1]; Pankaj Chaturvedi, MBBS, MS[1]; Prathamesh S. Pai, MBBS, MS[1]; Devendra Chaukar, MBBS, MS[1]; Sudhir Nair, MBBS, MS[1]; Shivakumar Thiagarajan, MBBS, MS[1]; and Kumar Prabhash, MBBS, MD, DM[1]

Single Center Phase II/III trial
2017-2021
Patients 356 pts unfit for CDDP

Primary end-point: 2y OS

A A

TABLE 3. Acute AEs

AE	RT Arm (n = 176), No. (%)		Docetaxel-RT Arm (n = 179), No. (%)		*P*	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Acute complications						
Mucositis	164 (93.2)	39 (22.2)	177 (98.9)	89 (49.7)	.006	< .001
Odynophagia	159 (90.3)	59 (33.5)	166 (92.7)	94 (52.5)	.450	< .001
Dysphagia	154 (87.5)	58 (33)	161 (89.9)	89 (49.7)	.505	.002

Curative Setting

- RT+ Cisplatin 100 mg/m² ✚ **Immunotherapy**
- RT+ Cisplatin 40 mg/m²
- Carboplatin + 5 FU
- Cetuximab

Pembrolizumab (Anti PD1) (Keynote 412)
Avelumab (Anti PDL1) (Javelin)

REVIEW ARTICLE

WILEY

Combinatorial approach of immuno-proton therapy in cancer: Rationale and potential impact

Utpal Gaikwad[1] | Jyoti Bajpai[2] | Rakesh Jalali[1]

IMRT (bath of dose)
-Lymphopenia

Proton therapy
-Less lymphopenia
-Higher immunogenic effect

Curative Setting

- RT+ Cisplatin 100 mg/m² ✚ **Immunotherapy** Pembrolizumab (Anti PD1) (Keynote 412)
  Avelumab (Anti PDL1) (Javelin)
- RT+ Cisplatin 40 mg/m²
- Carboplatin + 5 FU **Xevinapant** Inhibitor of IAPs (Inhibitor of Apoptosis Proteins)
- Cetuximab

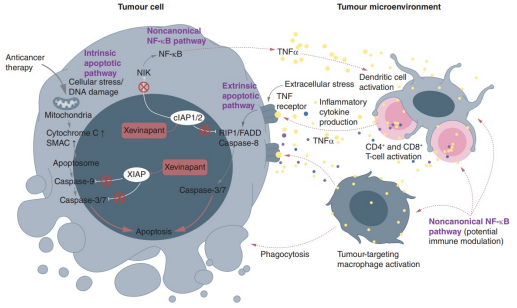
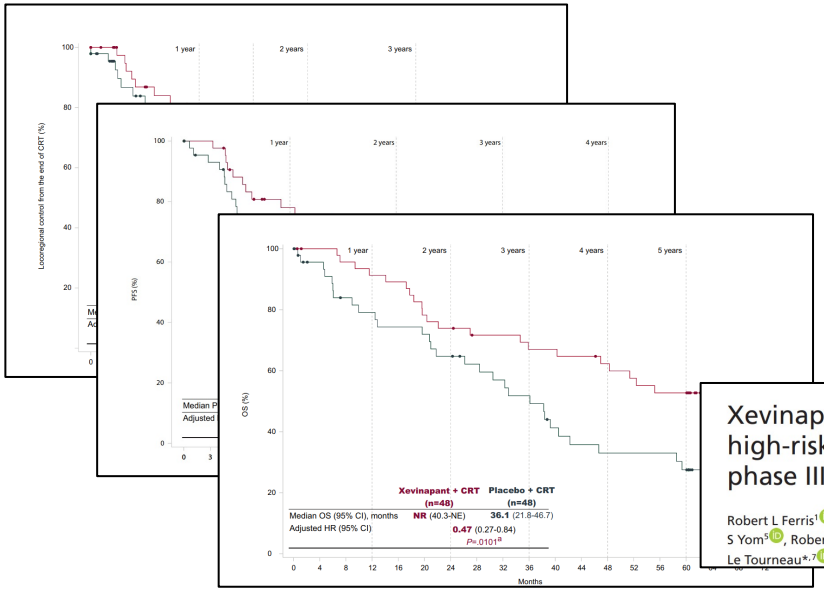


Figure 1. Xevinapant proposed mode of action. Xevinapant is a first-in-class, potent, oral, small-molecule IAP inhibitor. Xevinapant is thought to: 1) restore apoptosis in cancer cells by blocking XIAP and cIAP1/2, leading to activation of caspases downstream of the intrinsic mitochondrial and extrinsic TNF receptor signalling pathways, respectively, and 2) enhance the inflammatory antitumour response in immune cells of the tumour microenvironment by activating noncanonical NF-κB signalling through blocking of cIAP1/2 downstream of the TNF receptor.
Adapted from [47]. Copyright © 2022 Future Medicine Ltd.

Curative Setting

- RT+ Cisplatin 100 mg/m² ✚ Xevinapant
- RT+ Cisplatin 40 mg/m²
- Carboplatin + 5 FU
- Cetuximab

Phase II randomized trial
CT/RT+ Xev vs CT/RT+Placebo
Primary endpoint: LCR @18m




European Journal of Cancer 183 (2023) 24–37
Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER
EJC
Original Research
Extended follow-up of a phase 2 trial of xevinapant plus chemoradiotherapy in high-risk locally advanced squamous cell carcinoma of the head and neck: a randomised clinical trial

Phase III trial

Xevinapant plus radiotherapy in resected, high-risk, cisplatin-ineligible LA SCCHN: the phase III XRay Vision study design

Robert L Ferris[1], Hisham Mehanna[2], Jonathan D Schoenfeld[3], Makoto Tahara[4], Sue S Yom[5], Robert Haddad[3], André König[6], Pauline Witzler[6], Marcis Bajars[6] & Christophe Le Tourneau*,[7]

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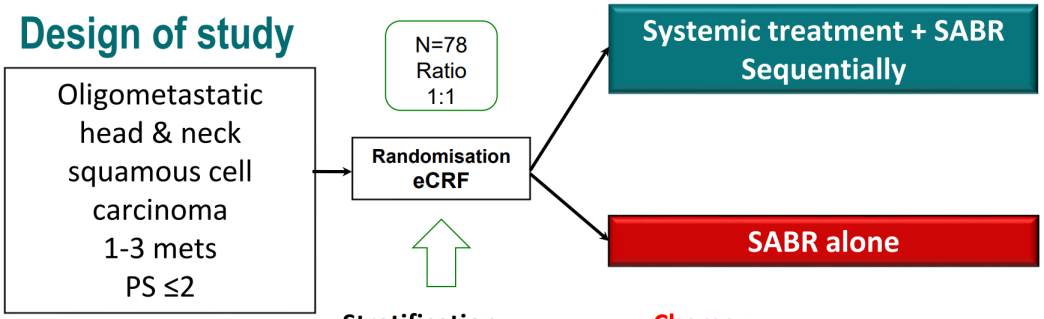
Aim of trial

The GORTEC 2014-04 (NCT03070366)

GORTEC

Randomized phase II study to assess the impact on Survival without Quality of Life (QoL) Deterioration score of **omitting upfront chemotherapy** in oligometastatic HNSCC patients by using **SABR alone**

Design of study



Stratification:

- Metastatic site (lung-only vs not)
- Centre
- Baseline QLQ-C30 score
- Extreme regimen or adapted

Chemo :
PS 0-1: **EXTREME**; maintenance
PS 2 ou CI 5FU : **platinum + cetuximab** + cetuximab maintenance
SABR : 3 ou 5 fractions up to 30 -50 Gy/3-21 days (≤ 6 weeks)

CT every 3mo

Courtesy Prof. P. Bossi

Aim of trial

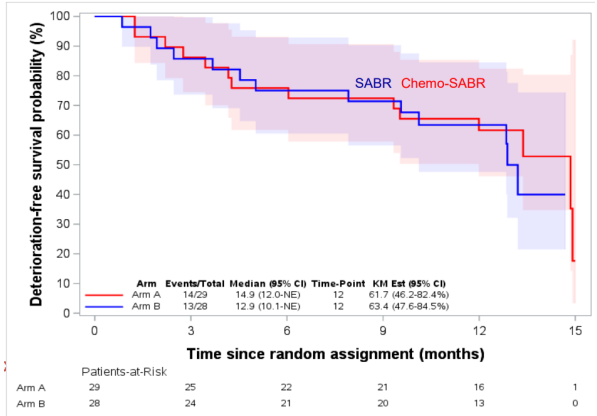
The GORTEC 2014-04 (NCT03070366)

GORTEC

Randomized phase II study to assess the impact on Survival without Quality of Life (QoL) Deterioration score of **omitting upfront chemotherapy** in oligometastatic HNSCC patients by using **SABR alone**

Results

- **69 pts** at 11 centers in 2016-2022
- **Lung-only mets 82.6%, HPV pos = 23%**
- Of 57 pts w/QoL miss, **1-year survival wo QoL deterioration = in both arms**
- Better physical functioning & cough deterioration-free survival w/ SABR-alone



Survival (median fup time 45 and 55 months)

In ITT for the 69 participants, one-year survival

63.4% (95%CI 47.6-84.5) with SABR-alone

61.7% (95%CI 46.2-82.4) with chemo-SABR

Toxicities

- Toxicities all grades

  10/34 (29.4%) with SABR alone

  33/35 (94.3%) with SABR-chemotherapy

- G3-4 toxicities

  2/34 (**5.9%**) with SABR-alone

  21/35 (**60.0%**) with SABR-chemotherapy

Courtesy Prof. P. Bossi

Head and Neck cancer – overview

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Head and Neck cancer - overview

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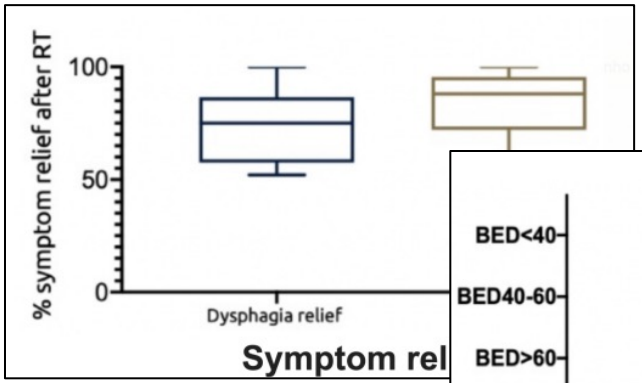
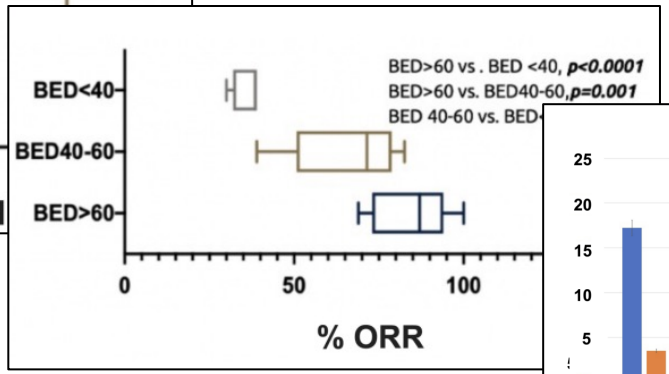
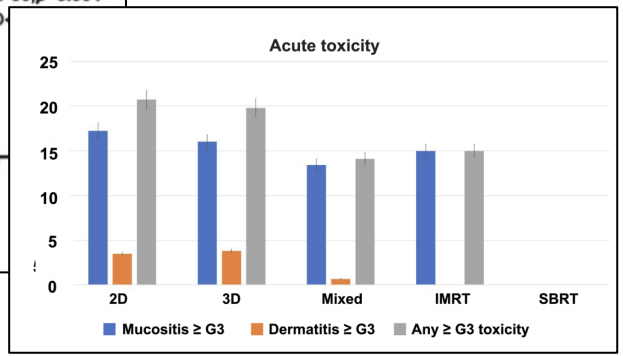
Assessing the efficacy of palliative radiation treatment schemes for locally advanced squamous cell carcinoma of the head and neck: a meta-analysis

Gustavo A. Viani[1,2], Andre G. Gouveia[2,3], Fernando K. Matsuura[1], Leonardo V.F. Neves[1], Gustavo N. Marta[2,4], Melvin L.K. Chua[5], Fabio Y, Moraes[2,6]







Take home messages

Constrictor Muscles should be contoured for all H/N cancer patients candidate to curative RT

RT + Platinum-based chemotherapy remains the standard of care.
Association with Xevinapant seems to be the most promising future approach

SBRT can ben considered as a personalized approach in oligometastatic patients

RT remains an effective approach in palliative setting. High precision techniques and BED >60 Gy shoudl be considered

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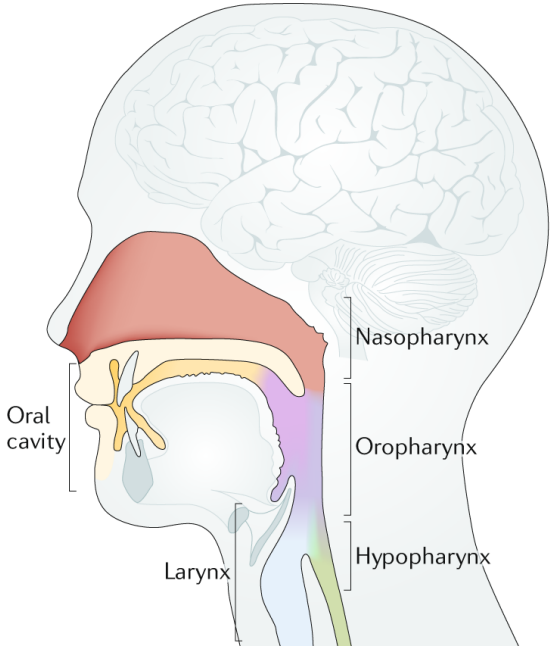

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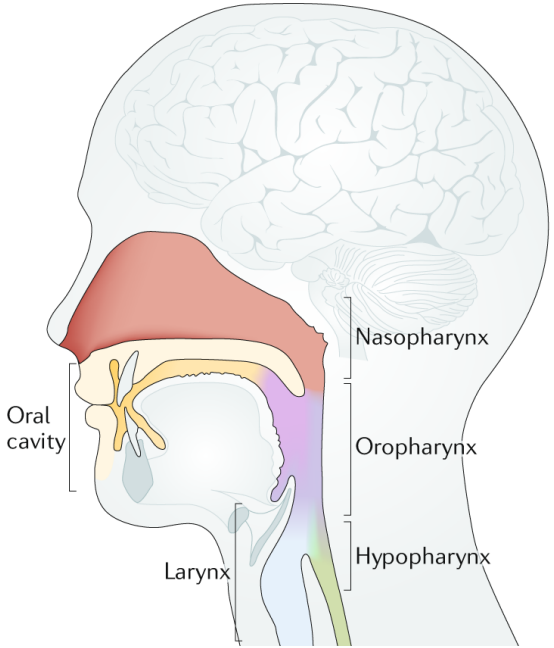

Oropharyngeal cancer

Deintensification strategies – where we are?

Biomarker

De-intensified treatments
-reduced **OS** in HPV+ OPCs (HR = 1.33, 95% CI 1.17–1.52; $p < 0.01$) ✗
-reduced **PFS** was also decreased (HR = 2.11, 95% CI 1.65–2.69; $p < 0.01$) ✗
-reduced **locoregional control** (HR = 2.51, 95% CI 1.75–3.59; $p < 0.01$) ✗
-reduced **distant disease control** (HR = 1.9, 95% CI 1.25–2.9; $p < 0.01$) ✗

Chemoradiation better than radiotherapy alone in curative setting (HR = 1.42, 95% CI 1.16–1.75; $p < 0.01$).
Adjuvant treatments were compared, standard and de-escalation strategies provided similar OS ✓

Fausto Petrelli **https://doi.org/10.1002/hed.27019**

Circulating Tumor DNA – HPV+ tumors

Predictive impact of human papillomavirus circulating tumor DNA in treatment response monitoring of HPV-associated cancers; a meta-analysis on recurrent event endpoints

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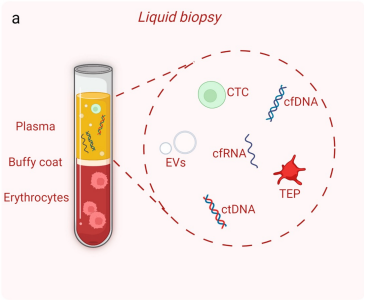

Received: 30 June 2023 | Revised: 30 August 2023 | Accepted: 31 August 2023
DOI: 10.1002/hed.27313

CLINICAL REVIEW

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It is time to improve the diagnostic workup of oropharyngeal cancer with circulating tumor HPV DNA: Systematic review and meta-analysis

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Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 Survival from baseline				
Chera et al. (2019)	2.12	0.87	6.5%	8.33 [1.51, 45.84]
Dahlstrom et al. (2015)	0.24	0.52	8.3%	1.27 [0.46, 3.52]
Jeannot et al. (Baseline) (2021)	0.46	0.36	9.0%	1.58 [0.78, 3.21]
Lefèvre et al. (2021)	1.4	0.8	6.9%	4.06 [0.85, 19.45]
Subtotal (95% CI)			**30.7%**	**2.17 [1.07, 4.41]**
Heterogeneity: Tau² = 0.18; Chi² = 4.63, df = 3 (P = 0.20); I² = 35%				
Test for overall effect: Z = 2.15 (P = 0.03)				
1.1.2 Survival from EoT				
Bernard-Tessier et al. (2018)	1.7	0.48	8.5%	5.47 [2.14, 14.02]
Cabel et al. (2018)	4.14	1.33	4.5%	62.80 [4.63, 851.29]
Cabel et al. (2021)	1.63	0.92	6.3%	5.10 [0.84, 30.97]
Chera et al. (2020)	4.04	0.42	8.8%	56.83 [24.95, 129.44]
Han et al. (2018)	2.33	1.12	5.4%	10.28 [1.14, 92.31]
Jeannot et al. (EoT) (2021)	2.39	0.67	7.5%	10.91 [2.94, 40.58]
Leung et al. (2021)	1.86	1.01	5.9%	6.42 [0.89, 46.51]
Routman et al. (2022)	2.67	0.66	7.6%	14.44 [3.96, 52.65]
Sivars et al. (2022)	1.635	0.678	7.5%	5.13 [1.36, 19.37]
Tanaka et al. (2020)	3.43	0.71	7.3%	30.88 [7.68, 124.16]
Subtotal (95% CI)			**69.3%**	**13.21 [6.62, 26.36]**
Heterogeneity: Tau² = 0.67; Chi² = 21.59, df = 9 (P = 0.01); I² = 58%				
Test for overall effect: Z = 7.32 (P < 0.00001)				
Total (95% CI)			**100.0%**	**7.97 [3.74, 17.01]**
Heterogeneity: Tau² = 1.53; Chi² = 62.54, df = 13 (P < 0.00001); I² = 79%				
Test for overall effect: Z = 5.37 (P < 0.00001)				
Test for subgroup differences: Chi² = 12.79, df = 1 (P = 0.0003), I² = 92.2%				

Hazard Ratio IV, Random, 95% CI

0.01 0.1 1 10 100

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Take home messages

De-intensification strategies should be proposed only in the contest of clinical trials

cfHPV DNA seems to be a promising marker in patients with HPV+ cancers

Thank you for your attention