EVIDENCE AND PRACTICE CHANGING TREATMENTS IN HEAD AND NECK TUMORS

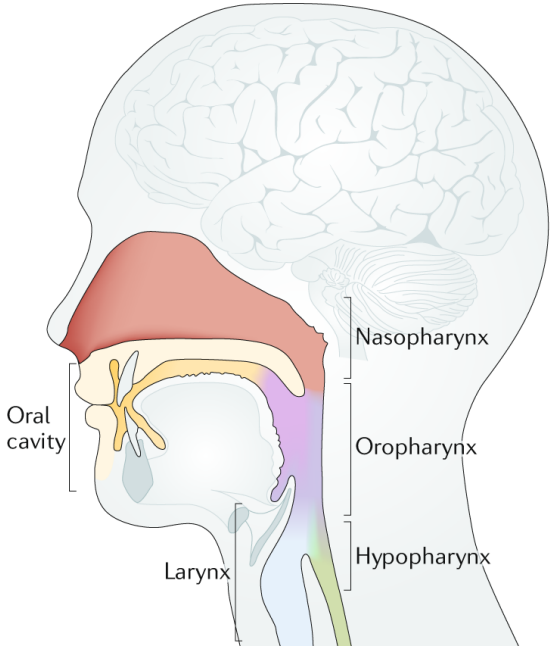
D. Alterio[1] and L. Belgioia[2]

1 Istituto Europeo di Oncologia, Milano

2 Università degli Studi di Genova, IRCCS Ospedale Policlinico San Martino

Agenda

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



Role of chemotherapy in patients with nasopharynx carcinoma treated with radiotherapy (MAC-NPC): an updated individual patient data network meta-analysis

- 28 trials
- 8214 patients
- 1988-2016

	Overall survival (primary endpoint)	Progression-free survival	Locoregional progression	Distant progression	Nasopharynx cancer death	Non-nasopharynx cancer death
Treatment data	28 trials; 36 comparisons; 8214 patients; 3073 events	28 trials; 36 comparisons; 8214 patients; 3694 events	24 trials; 32 comparisons; 7239 patients; 1170 events	24 trials; 32 comparisons; 7239 patients; 1481 events	25 trials; 33 comparisons; 7498 patients; 2217 events	25 trials; 33 comparisons; 7498 patients; 457 events
Concomitant chemoradiotherapy	1 (ref); 46%	1 (ref); 33%	1 (ref); 28%	1 (ref); 39%	1 (ref); 47%	1 (ref); 38%
Induction chemotherapy with taxanes followed by chemoradiotherapy	0·75 (0·59–0·96); 92%	0·72 (0·58–0·89); 89%	0·82 (0·55–1·24); 58%	0·66 (0·47–0·93); 87%	0·70 (0·53–0·91); 94%	1·11 (0·53–2·34); 33%
Induction chemotherapy without taxanes followed by chemoradiotherapy	0·81 (0·69–0·95); 87%	0·72 (0·63–0·83); 92%	0·79 (0·62–1·00); 67%	0·65 (0·53–0·80); 91%	0·77 (0·64–0·92); 87%	0·80 (0·44–1·47); 62%
Chemoradiotherapy followed by adjuvant chemotherapy	0·88 (0·75–1·04); 72%	0·84 (0·72–0·98); 68%	0·80 (0·61–1·06); 63%	0·85 (0·68–1·06); 60%	0·87 (0·72–1·05); 71%	0·90 (0·53–1·51); 49%
Induction chemotherapy followed by radiotherapy	1·01 (0·83–1·22); 45·7%	0·89 (0·75–1·06); 55%	0·96 (0·73–1·27); 24%	0·78 (0·57–1·07); 70%	1·04 (0·82–1·31); 41%	1·14 (0·49–2·63); 30%
Induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy	1·15 (0·76–1·75); 28%	1·10 (0·77–1·57); 24%	0·62 (0·35–1·10); 80%	1·54 (0·92–2·56); 7%	1·15 (0·74–1·78); 30%	0·94 (0·16–5·67); 48%
Radiotherapy followed by adjuvant chemotherapy	1·22 (0·88–1·68); 18%	1·01 (0·73–1·39); 36%	0·75 (0·43–1·32); 75%	1·09 (0·67–1·76); 33%	1·22 (0·84–1·77); 22%	0·75 (0·34–1·64); 66%
Radiotherapy	1·26 (1·08–1·47); 11%	1·25 (1·09–1·44); 4%	1·13 (0·88–1·44); 5%	1·29 (1·03–1·61); 14%	1·34 (1·11–1·60); 8%	0·72 (0·43–1·22); 75%

Petit C et al, Lancet Oncol 2023; 24: 611–23

Summary

1- treatment modalities containing concomitant CTRT ranked better OS than methods without concomitant chemoradiotherapy

2- concomitant chemotherapy: ICH better than adjuvant chemotherapy or concomitant chemotherapy alone

3- ICH the greatest benefit for distant progression

4- adjuvant chemotherapy greatest benefit for locoregional progression

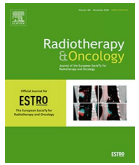
5- adverse events: the schedules containing more than one timing of chemotherapy generally resulted in more toxicity than the use of only one timing.

Petit C et al, Lancet Oncol 2023; 24: 611–23

Systematic Review

Efficacy and toxicities of elective upper-neck irradiation versus whole-neck irradiation of the uninvolved neck in patients with nasopharyngeal carcinoma: A meta-analysis

Xiaoxu Ding [a,1], Xiangguo Cui [a,1], Xiao Cui [b,*], Sai Wang [b,*]

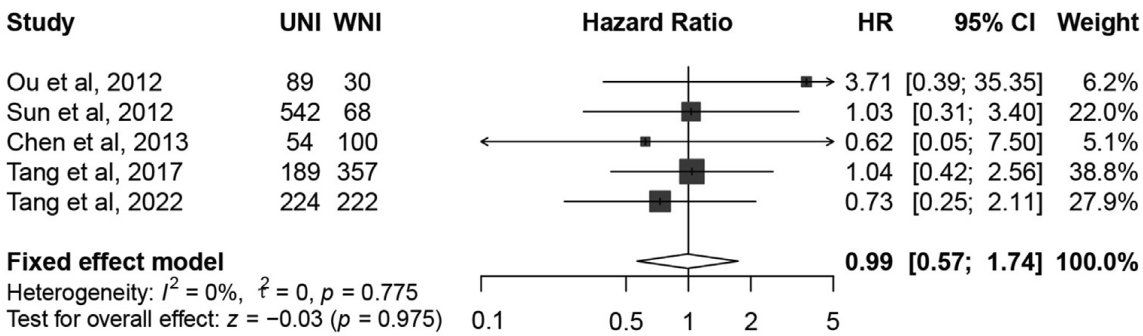


- 2 RCTs + 6 retrospective cohort studies (2005-2022)
- 2568 pts: 55,6% (1427) UNI vs 44,4% (1141) WNI

UNI:

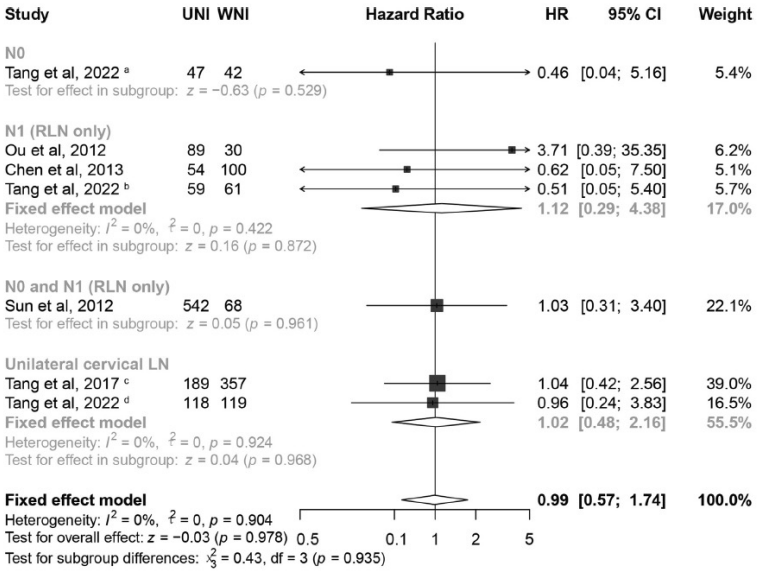
- N0 (except RLN)-> elective irradiation to bilateral II, III, Va
- RLN positive , and unilateral cervical lymph node positive -> RT to whole neck on the involved side and to upper neck on the contralateral uninvolved side for patients with unilateral cervical LN involvement.

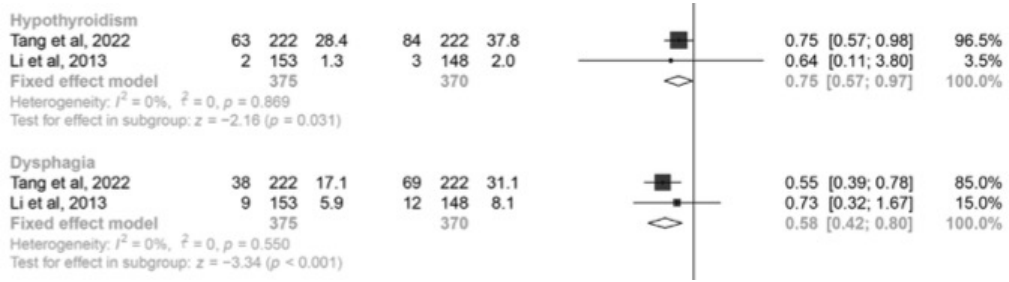
Regional relapse-free survival



similar LC, DM and PFS between UNI and WNI

Ding et al, Radiotherapy and Oncology 188 (2023) 109860



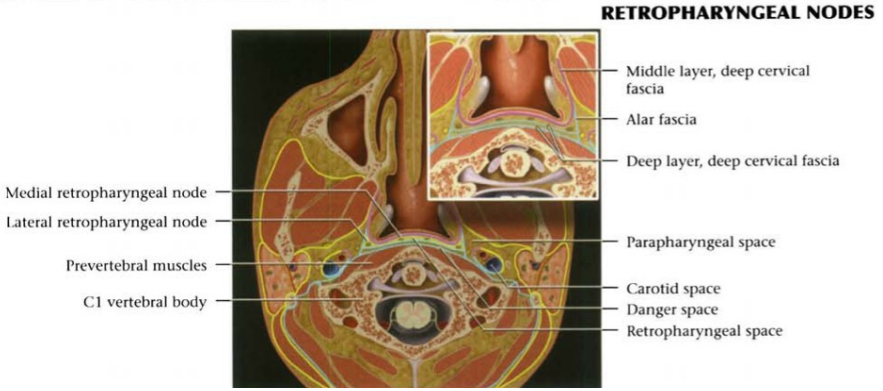


lower incidences: G1-2 hypothyroidism and G1-2 dysphagia for UNI vs WNI

UNI had similar efficacy and fewer toxicities compared with WNI for patients with unilateral or bilateral node-negative NPC

European Archives of Oto-Rhino-Laryngology (2023) 280:3097–3106

Medial retropharyngeal nodal region sparing radiotherapy versus standard radiotherapy in patients with nasopharyngeal carcinoma: open label, non-inferiority, multicentre, randomised, phase 3 trial



The MRLN lies between the pharyngeal constrictors and the prevertebral fascia near the midline

Inclusion criteria:

- non-keratinising NPC
- T1-4 N0-3 M0
- 18-65 years
- KPS>70

1 outcome: LRFS

2 outcomes: OS, DMFS, RRFS, acute and late toxic effects, and quality of life.

Low risk CTV:

- Standard RT group (283 pts): LRLN+MRLN regions from a base of the base of skull to the caudal border of hyoid bone or caudal border of C3
- MRLN sparing RT group (285 pts) : only the LRLN region

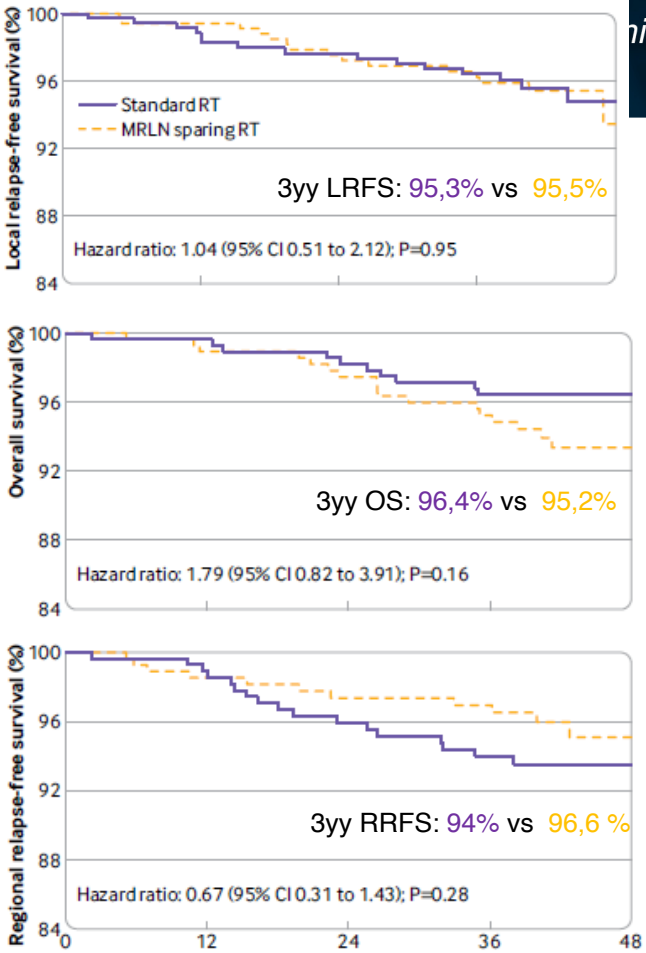
Mao YP et al, BMJ 2023;380:e072133 I

Table 1 | Baseline characteristics. Data are number (percentage) unless otherwise stated

	MRLN sparing RT (n=285)	Standard RT (n=283)
Sex		
Male	215 (75.4)	209 (73.9)
Female	70 (24.6)	74 (26.1)
Median age (range), years	46 (19-64)	49 (23-65)
Karnofsky performance score		
70-80	9 (3.2)	8 (2.8)
90-100	276 (96.8)	275 (97.2)
Histology		
WHO II	0	3 (1.1)
WHO III	285 (100)	280 (98.9)
Tumour category*		
T1	26 (9.1)	26 (9.2)
T2	47 (16.5)	51 (18.0)
T3	129 (45.3)	133 (47.0)
T4	83 (29.1)	73 (25.8)
Nodal category*		
N0	23 (8.1)	25 (8.8)
N1	109 (38.2)	106 (37.5)
N2	106 (37.2)	96 (33.9)
N3	47 (16.5)	56 (19.8)
Stage*		
I	7 (2.5)	8 (2.8)
II	38 (13.3)	25 (8.8)
III	123 (43.2)	126 (44.5)
IVA	117 (41.1)	124 (43.8)
Treatment modality†		
RT	18 (6.3)	21 (7.4)
Concurrent chemoradiotherapy	96 (33.7)	90 (31.8)
IC+concurrent chemoradiotherapy	165 (57.9)	167 (59.0)
IC+RT	5 (1.8)	4 (1.4)
Pre-treatment Epstein-Barr virus DNA test‡	250 (87.7)	251 (88.7)
DNA<2000 copies per mL	147 (51.6)	154 (54.4)
DNA ≥2000 copies per mL	103 (36.1)	97 (34.3)
DNA (copies per mL), median (IQR)	1190 (271-7853)	1030 (388-6030)

CCRT=concurrent chemoradiotherapy; EBV=Epstein-Barr virus; IC=induction chemotherapy; IQR=interquartile

wide ranging eligibility criteria



Mao YP et al, BMJ 2023;380:e072133 I

Table 2 | Acute and late toxicities related to radiation. Data are number (percentage), unless otherwise specified

	MRLN sparing RT (n=282)				Standard RT (n=282)				P value for events grade ≥1	P value for events grade ≥3
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4		
Any acute toxicities										
Dermatitis	106 (37.6)	41 (14.5)	3 (1.1)	0	127 (45.0)	30 (10.6)	3 (1.1)	1 (0.4)	0.35*	>0.99*
Mucositis	55 (19.5)	106 (37.6)	28 (9.9)	2 (0.7)	34 (12.1)	144 (51.1)	43 (15.2)	4 (1.4)	0.001*	0.04*
Dry mouth	88 (31.2)	98 (34.8)	2 (0.7)	0	88 (31.2)	106 (37.6)	4 (1.4)	0	0.36*	0.68*
Dysphagia	34 (12.1)	34 (12.1)	4 (1.4)	0	51 (18.1)	39 (13.8)	9 (3.2)	0	0.01*	0.16*
Weight loss	100 (35.5)	31 (11.0)	1 (0.4)	0	63 (22.3)	95 (33.7)	5 (1.8)	0	0.009*	0.22*
Trismus	0	0	0	0	0	1 (0.4)	0	0	>0.99†	—
Subcutaneous soft tissue	0	0	0	0	0	0	0	0	—	—
Any late toxicities‡										
Skin	63 (22.6)	8 (2.9)	0	0	56 (20.0)	22 (7.9)	0	0	0.52*	—
Neck tissue damage	48 (17.2)	22 (7.9)	0	0	52 (18.6)	20 (7.1)	4 (1.4)	0	0.58*	0.13*
Dysphagia	51 (18.3)	15 (5.4)	1 (0.4)	0	71 (25.4)	24 (8.6)	1 (0.4)	0	0.008*	>0.99*
Hoarseness	2 (0.7)	0	0	0	4 (1.4)	0	0	0	0.68*	—
Dry mouth	116 (41.6)	66 (23.7)	8 (2.9)	0	112 (40.0)	72 (25.7)	16 (5.7)	0	0.39*	0.10*
Trismus	11 (3.9)	3 (1.1)	0	0	13 (4.6)	6 (2.1)	0	0	0.38*	—
Auditory/hearing	108 (38.7)	21 (7.5)	4 (1.4)	0	107 (38.2)	40 (14.3)	8 (2.9)	0	0.07*	0.25*
Temporal lobe injury	18 (6.5)	1 (0.4)	0	0	24 (8.6)	0	0	0	0.43*	—

MRLN sparing region from elective RT volumes is a safe way for local control and effectively preserves swallowing function, which could benefit almost all patients with non-keratinising, nonmetastatic nasopharyngeal carcinoma.

Hyperfractionation compared with standard fractionation in intensity-modulated radiotherapy for patients with locally advanced recurrent nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial

SF: 60-60-54 Gy in 27 fx once a day vs
Hyperfx: 65-65-54 Gy in 54 fx twice daily

Primary endpoints: severe (>=G3) late complications and OS

144 pts enrolled

	Hyperfractionation group (n=72)	Standard fractionation group (n=72)
(Continued from previous column)		
Recurrent T classification		
T2	5 (7%)	8 (11%)
T3	49 (68%)	47 (65%)
T4	18 (25%)	17 (24%)
Recurrent N classification		
N0	45 (63%)	42 (58%)
N1	20 (28%)	25 (35%)
N2	7 (10%)	5 (7%)
Recurrent stage		
II	5 (7%)	8 (11%)
III	49 (68%)	47 (65%)
IV	18 (25%)	17 (24%)
Median time from primary diagnosis to local recurrence, years	3·0 (1·9–5·2)	2·8 (1·6–4·9)
Radiotherapy technique in first treatment		
Two dimensional radiotherapy	14 (19%)	10 (14%)
Three dimensional radiotherapy	10 (14%)	14 (19%)
Intensity-modulated radiotherapy	43 (60%)	41 (57%)
Unknown	5 (7%)	7 (10%)

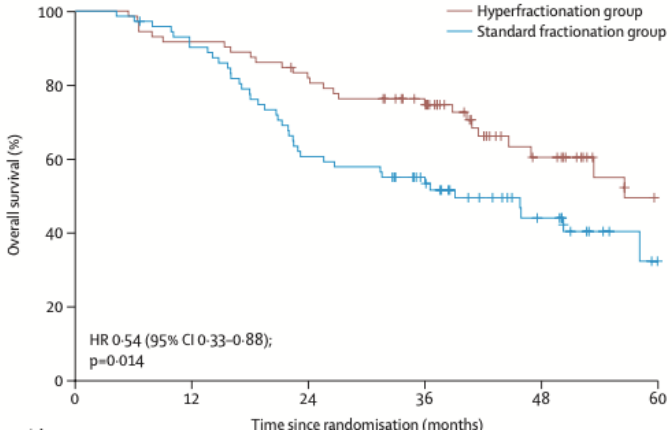
You R et al, Lancet 2023; 401: 917–27

	Hyperfractionation group (n=68)				Standard fractionation group (n=68)			
	Grade ≥3	Grade 1–2	Grade 3–4	Grade 5	Grade ≥3	Grade 1–2	Grade 3–4	Grade 5
Any late adverse events	23 (34%)	45 (66%)	18 (26%)	5 (7%)	39 (57%)	29 (43%)	23 (34%)	16 (24%)
Nasopharyngeal mucosal necrosis	13 (19%)	10 (15%)	13 (19%)	0	22 (32%)	13 (19%)	20 (29%)	2 (3%)
Nasal haemorrhage	5 (7%)	12 (18%)	0	5 (7%)	14 (21%)	14 (21%)	3 (4%)	11 (16%)
Eye disorders	4 (6%)	15 (22%)	4 (6%)	0	5 (7%)	23 (34%)	5 (7%)	0
Hearing impairment	15 (22%)	23 (34%)	15 (22%)	0	17 (25%)	30 (44%)	17 (25%)	0
Trismus	7 (10%)	27 (40%)	7 (10%)	0	10 (15%)	32 (47%)	10 (15%)	0
Dry mouth	1 (1%)	34 (50%)	1 (1%)	0	2 (3%)	28 (41%)	2 (3%)	0
Dysphagia	5 (7%)	23 (34%)	5 (7%)	0	8 (12%)	15 (22%)	8 (12%)	0
Skin reaction	0	18 (26%)	0	0	0	15 (22%)	0	0
Neck tissue damage	8 (12%)	11(16%)	8 (12%)	0	9 (13%)	10 (15%)	9 (13%)	0
Temporal lobe necrosis	7 (10%)	21 (31%)	7 (10%)	0	18 (26%)	21 (31%)	15 (22%)	3 (4%)

-23% G3 AEs

21% pts in the hyperfractionation group and 44%pts in the standard fractionation group died from late complications.

Overall Survival:



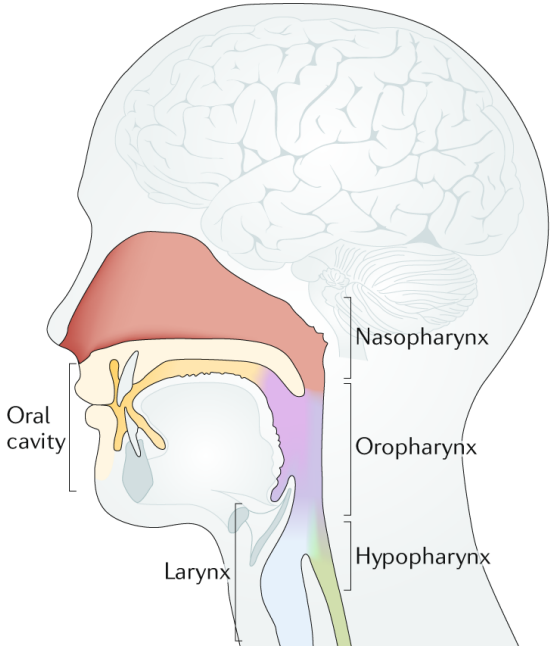
You R et al, Lancet 2023; 401: 917–27

Take Home message: Nasopharyngeal cancer

- Role of chemotherapy
- Contouring: Medial RNF Nodes and Upper neck RT
- Recurrence: Hyperfractionation re-RT

Agenda

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



JAMA Otolaryngology–Head & Neck Surgery | Original Investigation | FROM THE AMERICAN HEAD AND NECK SOCIETY

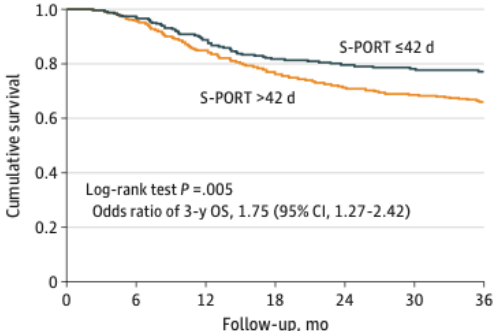
Oncologic Significance of Therapeutic Delays in Patients With Oral Cavity Cancer

- Retrospective analysis: multicenter cohort of **1368** OCSCC pts
- 2005-2019
- Primary curative surgery
- Adjuvant RT or CTRT

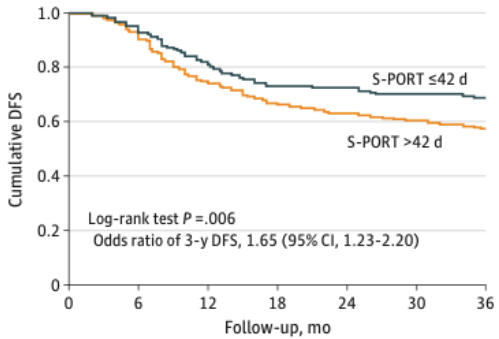
1 Endpoint: OS
2 Endpoint: DFS

- Median overall S-PORT interval: 56 days
- 80% of patients initiated RT > 42 days after surgery
- Median RTI: 43 days
- 26% of pts had a prolonged RTI

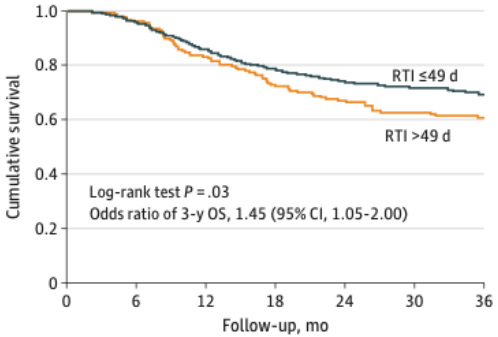
Dayan GS et al, *JAMA Otolaryngol Head Neck Surg.* 2023;149(11):961-969



3yy OS: 66% vs 77% (S-PORT>42 d)



3 yy DFS: 57% vs 67% (S-PORT> 42d)



3yy OS: 57% vs 67% (RTI >49 d)

10% difference in 3-year OS between patients who completed S-PORT by 42 days and those who did not

- Retrospective nature
- Not pts restage to 8th ed TNM (DOI, ENE?)
- Not explore reasons for prolonged treatment times- > Critical importance of the postoperative period (postoperative complications and prolonged wound healing, delays in pathology reports…)

Dayan GS et al, *JAMA Otolaryngol Head Neck Surg.* 2023;149(11):961-969

Long-term outcomes of neo-adjuvant chemotherapy on borderline resectable oral cavity cancers: Real-world data of 3266 patients and implications for clinical practice

Vanita Noronha [a,1], Aditya Dhanawat [a,1], Vijay Maruti Patil [a,1], Nandini Menon [a], Ajay Kumar Singh [a], Pankaj Chaturvedi [b], Prathamesh Pai [b], Devendra Chaukar [b], Sarbani Ghosh Laskar [c], Kumar Prabhash [a,*]

- prospectively collected dataset of 3266 OCSCC
- 2008-2020
- Bordeline resectable
- 1 Endpoint: OS

NACT x 2-3 cycles (TF or TPF) → Radiologically re-evaluation →
- Surgery + PORT
- CTRT
- Palliative CT

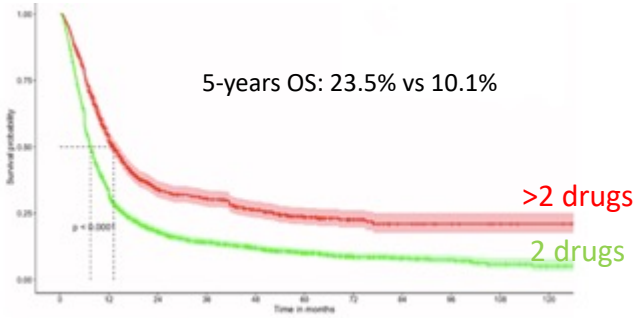
Treatment received after completion of NACT.

Treatment received	Number of patients (n = 2905)
Surgery + Adjuvant CTRT	873 (30.1%)
Surgery + Adjuvant RT	41 (1.4%)
Surgery alone	15 (0.5%)
Definitive CTRT	429 (14.8%)
Palliative Chemotherapy	1168 (40.2%)
Palliative Radiotherapy	242 (8.3%)
Best supportive care	87 (3%)
Defaulted	21 (0.7%)
Death	29 (1%)

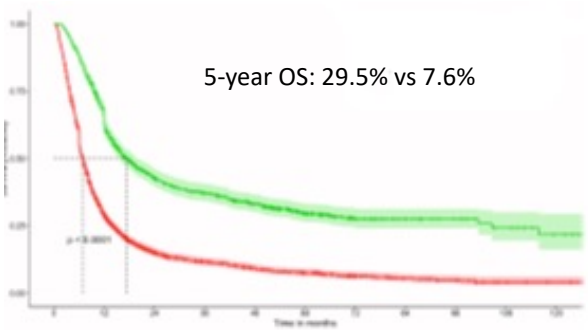
- Median f up: 52,6 months
- > 2 drugs NACT : 32,9%
- Response rate to NACT: 32,5%
- 46,8% pts received a curative treatment after NACT (32% Surgery – 14,8% CTRT)
- Surgery: 98,4% R0
- 8,2% pts pCR

Oral Oncology 148 (2024) 106633

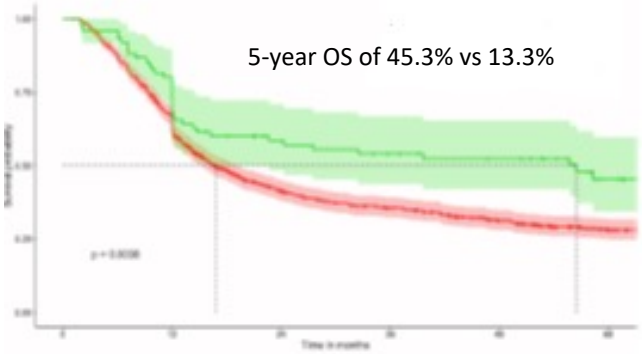
2 drugs vs > 2 drugs



Surgery vs non surgery



pCR vs no pCR



NACT

- improves resectability in upfront technically unresectable tumours
- leads to long term survival benefit (>2-drug regimen better then 2-drug regimen)
- Patients who achieve a CR/PR and undergo surgical resection post NACT have a significantly longer survival

Take Home message: Oral Cavity

- Timing:

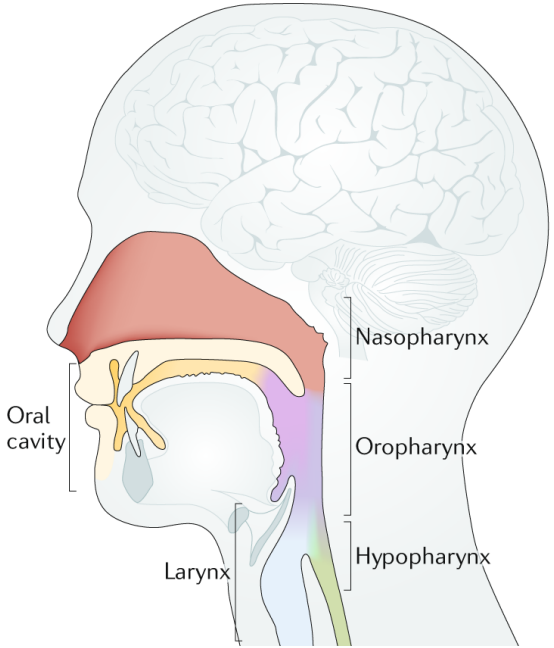
- S-PORT interval impact on OS e DFS and RTI

- Intensification of treatment:

- NACT in borderline resectable disease

Agenda

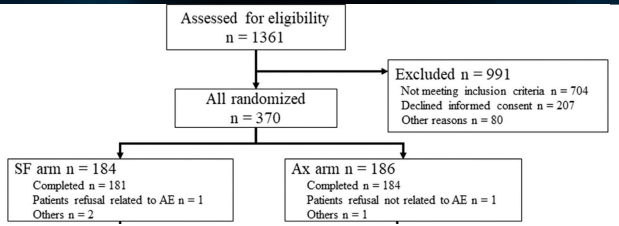
-Head and Neck cancer – overview
-Oropharyneal cancer
-Nasopharyngeal cancer
-Oral cavity cancer
-Laryngeal Cancer (early vs advanced)
-Focus on Protontherapy



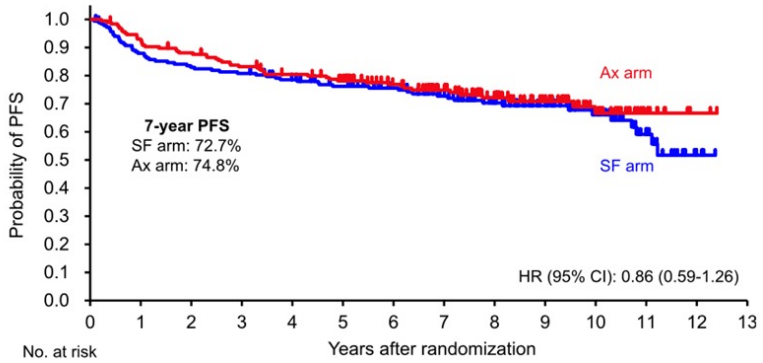
Long-Term Follow-up of a Randomized Controlled Trial on Accelerated Radiation Therapy Versus Standard Fractionated Radiation Therapy for Early Glottic Cancer (JCOG0701A3)

T1/T2 lesions, N0, M0 disease
2007- 2013

1 endpoint: PFS



SF: 66/70 Gy for T1/T2 60/64.8 Gy in 2.4 Gy/fraction



	SF					Ax				
Toxicity	**G1**	**G2**	**G3**	**G4**	**G2-4**	**G1**	**G2**	**G3**	**G4**	**G2-4**
Bleeding: larynx	0.6	0	0	0	0	0.5	0	0	0	0
Laryngeal edema	22.2	1.1	0	0.6	1.7	22.3	0.5	0	0	0.5
Pain: pharynx/larynx	5.5	2.2	0.6	0	2.7	8.7	0	0.5	0	0.5
Soft tissue necrosis: cervix	-	0	0	0.6	0.6	-	0.5	0	0	0.5
Lymphedema: skin	8.3	0.0	-	-	0	5.4	0	-	-	0
Induration	3.0	0.6	0	-	0.6	1.6	0.5	0	-	0.5
Voice change	45.1	9.3	0	0.0	9.3	45.9	4.9	0.5	0	5.4
CNSI	-	1.8	0.6	1.8	4.1	-	0.6	0.6	0	1.1
Any				2.7	14.3				0	7.6

≥ G2 Late Aes: 14,3% SF vs 7,6% Ax (p=0,045)

AX Arm show comparable efficacy to SF and a tendency for better safety

Kodaira T et al, Int J Radiat Oncol Biol Phys. 2023 Dec 1;117(5):1118-1124.

European Archives of Oto-Rhino-Laryngology (2023) 280:2911–2926
https://doi.org/10.1007/s00405-023-07871-8

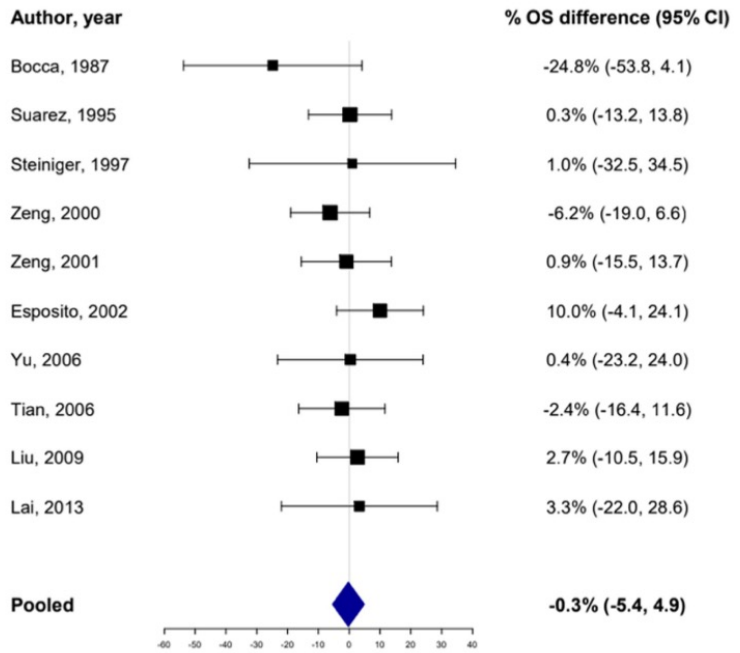
HEAD AND NECK

Check for updates

Oncological and functional impact of adjuvant treatments after open partial laryngeal surgery: a systematic review of the literature and a meta-analysis

Luca Giovanni Locatello[1,2,3] · Serena Jiang[1] · Lixiao Chen[3] · Saverio Caini[4] · Giandomenico Maggiore[1] · Pin Dong[3] · Oreste Gallo[1,5]

1969-2010:
10 articles for a total of 1198 patients
- 40.9% (491) PORT
- 59.1% (707) without PORT



No OS difference for patients receiving or not PORT, but PORT group show a more advanced disease (worse prognosis) compared to those treated with surgery alone.

Table 2 Complications related to PORT after OPLS (14)

Reference (year, country)	Sufficient oral intake (%)	Need of NGT/PEG (%)	Time of NGT (months)	Comparison between surgery alone vs. surgery + PORT
Costa et al. (2016, Italy) [16]	92	NA	NA	NA
Buglione et al. (2015, Italy) [17]	100	NA	NA	NA
Oksuz et al. (2008, Turkey) [20]	91.1	1.3	NA	NA
Bron et al. (2005, Switzerland) [12]	79	10.3	< 3	NA
Sessions et al. (2005, USA) [34]	78.2	7.9	NA	Overall 37.8% of complications in surgery + PORT and 38 in surgery alone (p = NS)
Laccourreye et al. (2000, France) [26]	94.5	2.2	NA	NA
Spriano et al. (2000, Italy) [11]	81	NA	NA	NA
Steiniger et al. (1997, USA) [27]	65	35	34.8	All surgery-alone patients were able to gain an adequate oral intake between 2 and 30 weeks, and none required permanent feeding gastrostomies Time to decannulation: PORT group 62.5% delayed decannulation (> 3 week), 43.7% delayed decannulation (> 3 months) VS surgery-alone group 33% delayed decannulation (> 3 week), 16.6% (> 3 months) (p = 0.32 for 3 weeks and .13 for 3 months) Adequate oral intake (mean): PORT group after 34.8 weeks and surgery-alone group after 7.5 weeks (p = 0.20) Delayed development of full oral intake > 3 weeks/ > 3 months: PORT group 56.2%/31.2% VERSUS surgery-alone group 41.6%/25.0% (p = 0.18/0.52)
Naudo et al. (1997, France) [35]	91	2.5	NA	Time of decannulation between the irradiated and non irradiated groups
Gregor et al. (1996, South Africa) [36]	100	0	NA	PORT with or without bilateral neck dissection did not show an increase in postoperative morbidity
Wang et al. (1990, USA) [31]	91.7	20.8	NA	NA
Spaulding et al. (1989, USA) [37]	93.9	NA	NA	NA
Robbins et al. (1988, USA) [38]	32	8	NA	OPL versus OPL + PORT: aspiration in 33% VS 44%; weight loss (> 10% of body weight) in 0% VS 12%; NGT 0% VS 8%; pneumonia 0% VS 16%; tracheostomy 0% vs. 8%

Low level of evidence regarding the oncological role of PORT

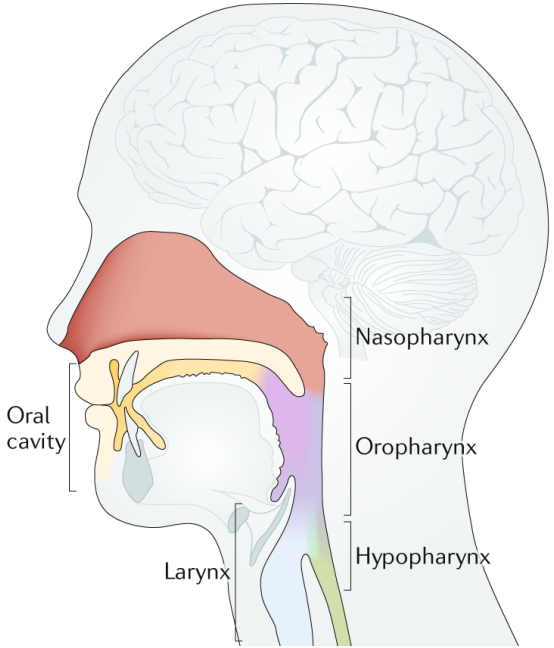
this holds also true for the functional complications of RT

Take Home message: Laryngeal cancer

- Early stage: Ax schedule
- PORT

Agenda

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



Original Investigation | Oncology

Evaluation of Proton Therapy Reirradiation for Patients With Recurrent Head and Neck Squamous Cell Carcinoma

242 pts PT-ReRT for recurrent/2 T HNSCC in a previously irradiated field (2013- 2020)

Subsequent treatment site, No. (%)	
Pharyngeal mucosa	150 (62.0)
Oropharynx	54 (22.3)
Lip and oral cavity	53 (21.9)
Larynx or hypopharynx	21 (8.7)
Nasal cavity or paranasal sinus	17 (7.0)
Nasopharynx	5 (2.1)
Neck	51 (21.1)
Auricular region	20 (8.3)
Skull base	11 (4.5)
Orbit	6 (2.5)
Cheek	2 (0.8)
Scalp	2 (0.8)
Salvage surgery, No. (%)	
No	144 (59.5)
Yes	98 (40.5)
Concurrent systemic treatment with reirradiation, No. (%)	
No	104 (43.0)
Yes	138 (57.0)

Characteristic	Finding (N = 242)
Reirradiation fractionation, No. (%)	
Fractionated	154 (63.6)
Quad shot	88 (36.4)
Proton therapy treatment year, No. (%)	
2013	4 (1.7)
2014	27 (11.2)
2015	28 (11.6)
2016	49 (20.2)
2017	38 (15.7)
2018	43 (17.8)
2019	44 (18.2)
2020	9 (3.7)
Age at reirradiation, median (IQR), y	63 (55-71)
Prior irradiation dose, median (IQR), cGy	6996 (6214-7020)
Proton reirradiation dose, median (IQR), CGE	66.0 (44.4-70.0)
Fractionated reirradiation dose, median (IQR), CGE	70 (66-70)
Quad shot reirradiation dose, median (IQR), CGE	44.4 (18.5-44.4)
No. of cycles, median (IQR)	3 (1-3)
Interval between irradiation courses, median (IQR), mo	22 (11-69)
Follow-up, median (IQR), mo	12.0 (5.8-26.0)
Follow-up of living patients, median (IQR), mo	24.5 (13.8-37.8)

- Early toxicity: 73 were G3 toxic effects (2 G4 dysphagia and 4 G4 dermatitis)
- Late toxicity79 were potential grade 3 toxic effects
- 5 potentially re Rt related G5 bleeding events.

Lee A et al, JAMA Network Open. 2023;6(1):e2250607

Table 3. Cox Proportional Hazards Model for Local Control of Head and Neck Squamous Cell Carcinoma

	Univariate		Multivariate	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Prior irradiation dose, cGy	1.00 (1.00-1.00)	.03	1.00 (1.00-1.00)	.12
Proton reirradiation dose, CGE	0.98 (0.96-0.99)	.004	0.97 (0.95-1.00)	.01
Interval between irradiation courses	1.00 (0.99-1.00)	.21	NA	NA
Smoking or tobacco use				
Never	1 [Reference]	NA	NA	NA
<10 pack-years	0.92 (0.42-2.02)	.82	NA	NA
≥10 pack-years	0.73 (0.44-1.21)	.22	NA	NA
Disease status at the time of irradiation				
Locoregional	1 [Reference]	NA	NA	NA
Distant metastases	1.59 (0.39-6.50)	.52	NA	NA
Salvage surgery				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	0.42 (0.25-0.71)	.001	0.40 (0.22-0.74)	.003
Concurrent systemic treatment with reirradiation				
No	1 [Reference]	NA	NA	NA
Yes	0.79 (0.49-1.27)	.34	NA	NA
Reirradiation fractionation				
Fractionated	1 [Reference]	NA	1 [Reference]	NA
Quad shot	1.66 (1.01-2.73)	.046	0.56 (0.26-1.22)	.14

The 1-year LC:68.4%,
1 year LC for fractionated reRT: 71.8%
1-year OS for fractionated reRT: 66.6%

Single-institution, nonrandomized cohort, including challenges with medical record review and the availability of data

Difficult assessment of toxic effects -> many patients present with adverse effects from their first course of treatmen


Thank you