Dichiarazione di Assenza di conflitto di interessi

In qualità di Relatore dell'evento formativo Highlights in Radioterapia del 23 Gennaio 2020 organizzato a Roma dal Dott. V. Donato e sotto la mia responsabilità, consapevole che chiunque rilasci dichiarazioni mendaci è punito ai sensi del codice penale e delle leggi speciali in materia (DPR 445/2000)
DICHIARO ai sensi e per gli effetti dell'art. 76, comma 4 sul Conflitto di interessi, dell'accordo Stato - Regione del 2 Febbraio 2017 e ai sensi e per gli effetti dell'art. 48, comma 25, deL d.l. 269/2003, convertito in legge 25 novembre 2003 nr. 326
che, nell'esercizio delle funzioni su indicate e per l'evento indicato nel titolo, **NON SONO** in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio;

HIGHLIGHTS in RADIOTERAPIA

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERO-UNIVERSITARIA POLICLINICO UMBERTO I
SAPIENZA UNIVERSITÀ DI ROMA

Gli studi del 2019 che modificano la pratica clinica in radioterapia esclusiva ed associazione farmacologica

Tumori testa-collo

D. Musio

ROMA
23 gennaio 2020

Associazione Italiana Radioterapia e Oncologia clinica

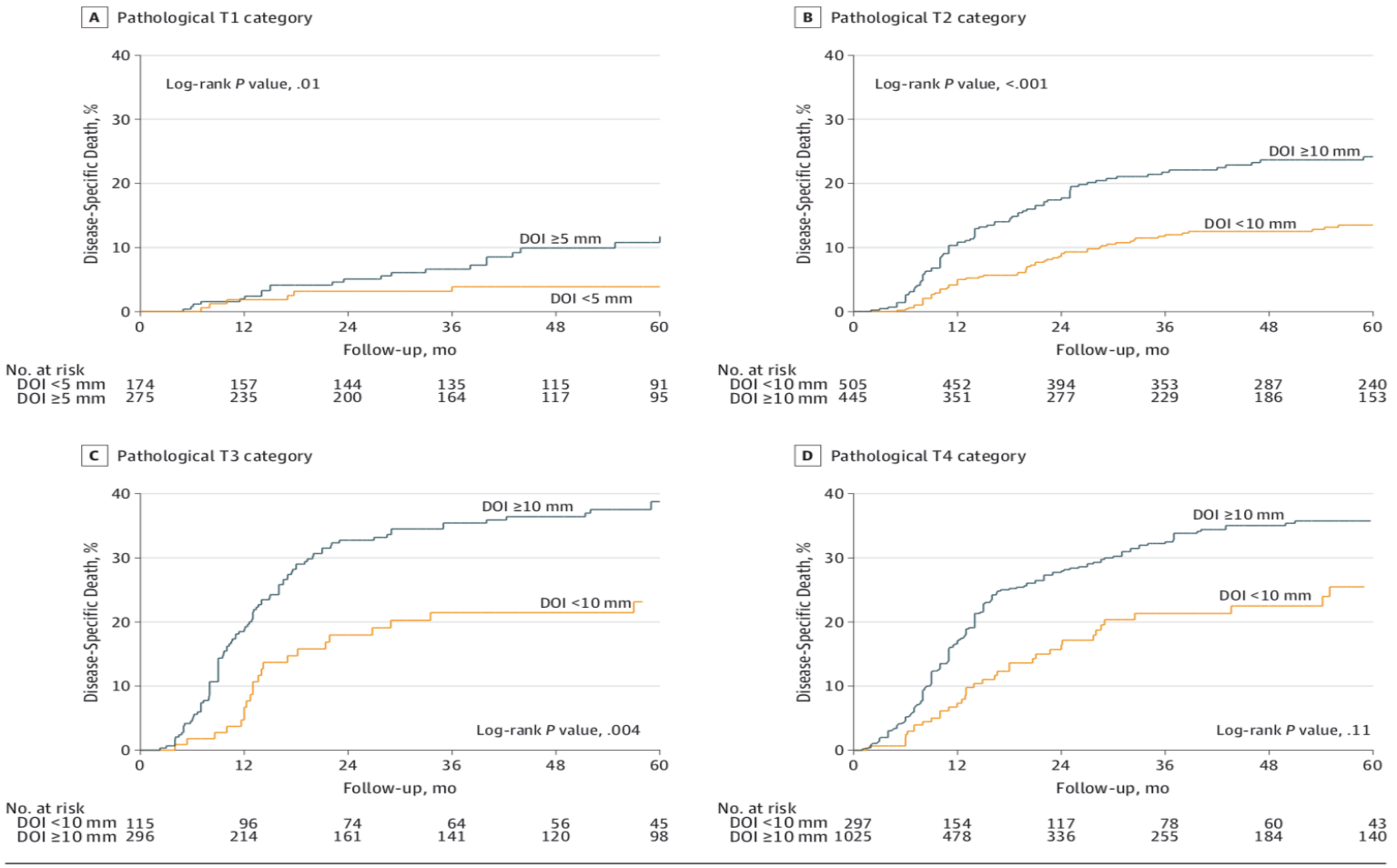
Studi del 2019 neoplasie del testa-collo

- Linee guida
- De-intensificazione di terapia
- Associazione con i farmaci
- Contornazione

Linee guida

JAMA Otolaryngology–Head & Neck Surgery

La profondità di infiltrazione (DOI) è stato dimostrato essere un importante fattore prognostico per il carcinoma squamoso del cavo orale (OCSCC) in ogni categoria T dell' AJCC

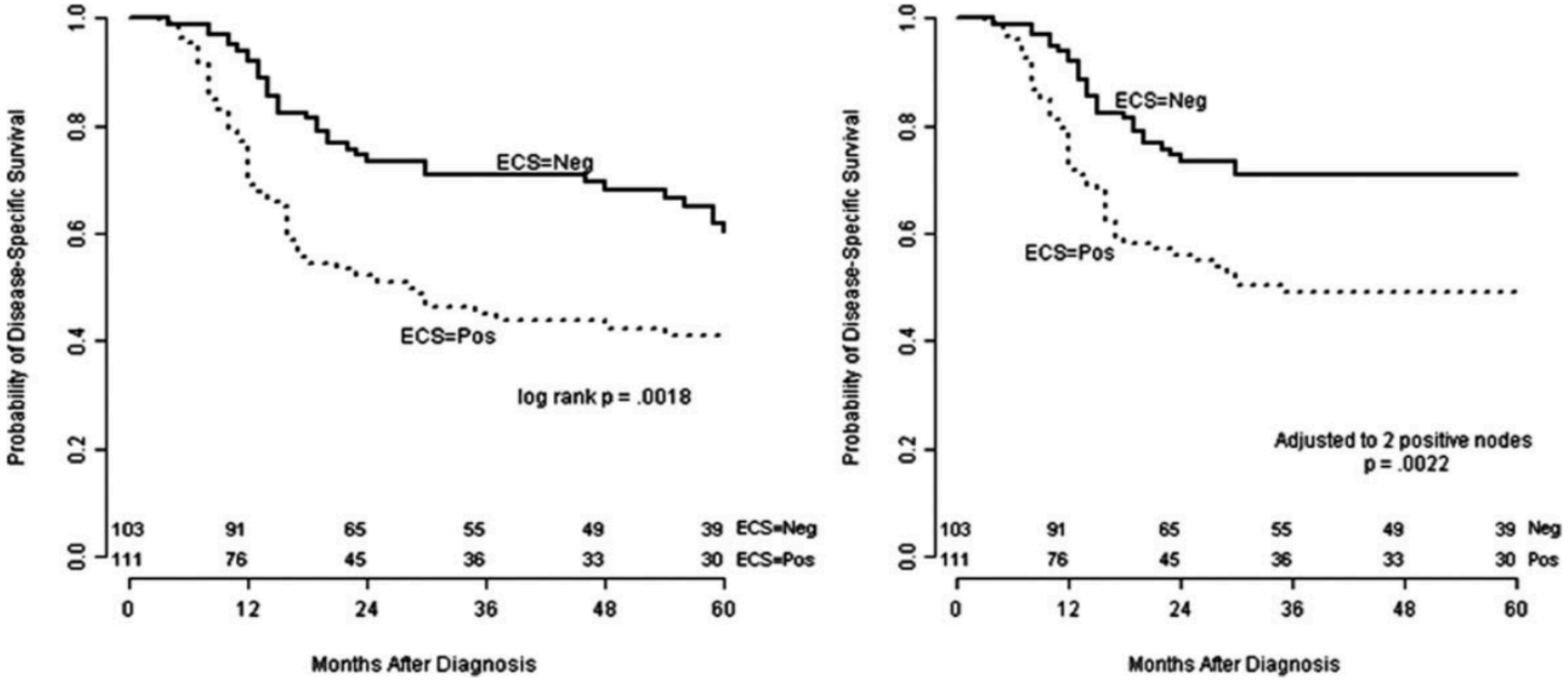


Ebrahimi A 2014.

Linee guida

Cancer

L'estensione extracapsulare linfonodale di malattia (ECS) è un fattore indipendente predittivo negativo nel OCSCC



Maxwell J.H. 2013

Linee guida

2017

UICC/AJCC 7a Edizione → UICC/AJCC 8a Edizione

AJCC
American Joint Committee on Cancer
Validating science. Improving patient care.

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Oral Cavity (including mucosa of lip) (8th ed., 2017)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor ≤2 cm with depth of invasion (DOI)* ≤5 mm
T2	Tumor ≤2 cm, with DOI* >5 mm and ≤10 mm *or* tumor >2 cm and ≤4 cm, with DOI* ≤10 mm
T3	Tumor >2 cm and ≤4 cm, with DOI* >10 mm *or* tumor >4 cm, with DOI* ≤10 mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor > 4 cm, with DOI* > 10 mm *or* tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

*DOI is depth of invasion and *not* tumor thickness.

Regional Lymph Nodes (N)

Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Regional Lymph Nodes (N)

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(–)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension, and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral node(s), none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)

Linee guida

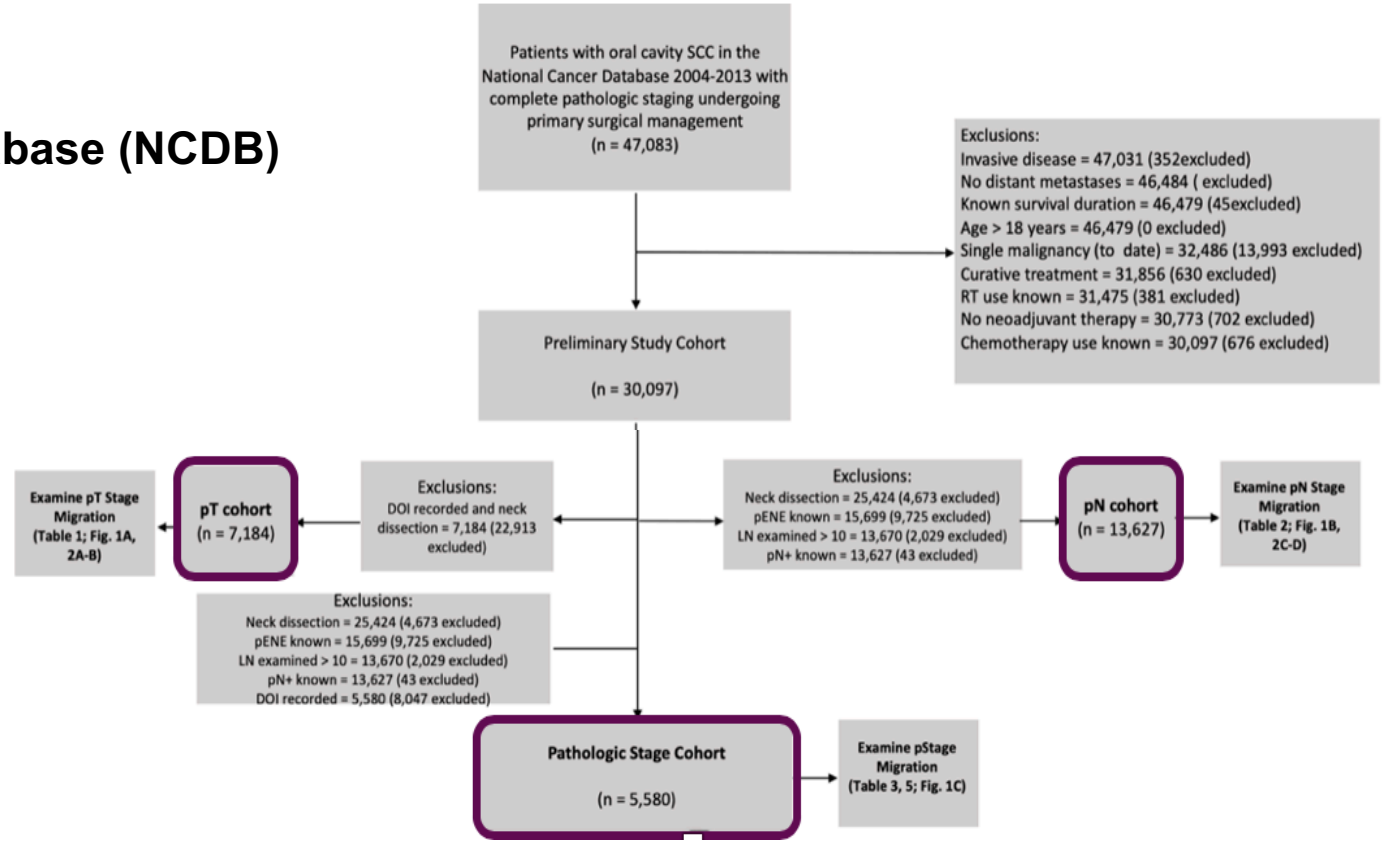
Pathologic Staging Changes in Oral Cavity Squamous Cell Carcinoma: Stage Migration and Implications for Adjuvant Treatment

Cancer

The National Cancer Database (NCDB)

Endpoint primario:

- OS a 5 anni



Nicholas C. J. 2019

Linee guida

Cancer

A AJCC 7	Stage Migration (AJCC 8)	AJCC 8	ΔOS (% Change)*
pT1: 76.2%	pT1: 76.7% pT2: 74.4% pT3: 71.7%	pT1: 76.7%	+0.5 (0.7%)
pT2: 59.7%	pT2: 60.8% pT3: 54.5%	pT2: 63.4%	+3.7 (6.2%)
pT3: 43.7%	pT3: 43.7%	pT3: 49.4%	+5.7 (13.0%)
pT4a: 45.8%	pT3: 44.4% pT4a: 45.9%	pT4a: 45.9%	+0.1 (0.2%)
pT4b: 41.9%	None	pT4b: 41.9%	None

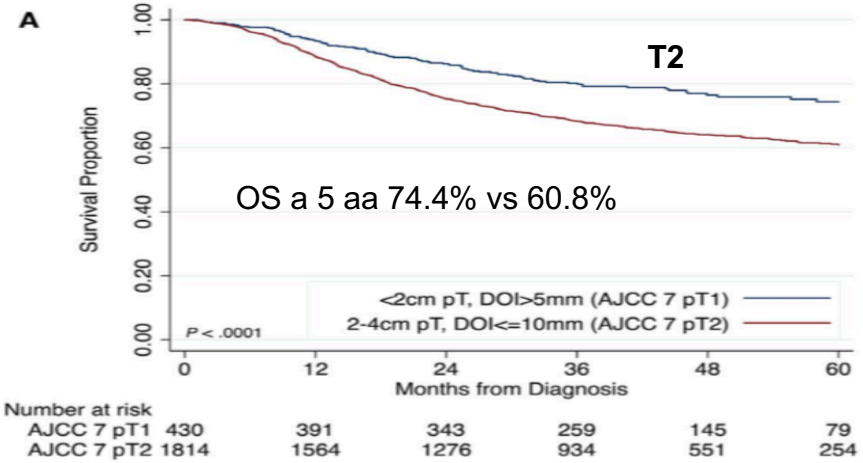
B AJCC 7	Stage Migration (AJCC 8)	AJCC 8	ΔOS (% Change)*
pN0: 68.4%	None	pN0: 68.4%	None
pN1: 55.4%	pN1: 56.8% pN2a: 50.3%	pN1: 56.8%	+1.4 (2.5%)
pN2a: 43.5%	pN2a: 48.2% pN3b: 38.3%	pN2a: 49.7%	+6.2 (14.3%)
pN2b: 40.9%	pN2b: 45.7% pN3b: 46.0%	pN2b: 45.7%	+4.8 (11.7%)
pN2c: 26.8%	pN2c: 30.6% pN3b: 24.9%	pN2c: 30.6%	+3.8 (14.2%)
pN3: 28.6%	pN3a: 40.0% pN3b: 25.0%	pN3a: 40.0% pN3b: 33.0%	+11.4 (39.9% +4.4 (15.4%)

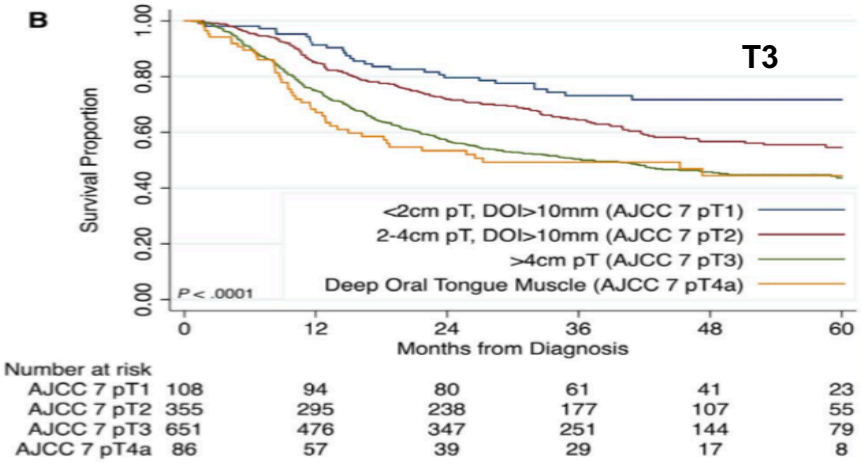
ΔOS è espresso in % ed esprime la percentuale di cambiamento tra OS/AJCC 7 e OS AJCC8

C AJCC 7	Stage Migration (AJCC 8)	AJCC 8	ΔOS (% Change)*
I: 81.7%	I: 82.1% II: 79.2% III: 83.7%	I: 82.1%	+0.4 (0.5%)
II: 71.7%	II: 72.3% III: 67.7%	II: 73.8%	+2.1 (2.9%)
III: 64.4%	III: 65.8% IVA: 58.5%	III: 66.7%	+2.3 (3.6%)
IVA: 44.8%	III: 60.1% IVA: 50.7% IVB: 34.3%	IVA: 51.5%	+6.7 (15.0%
IVB: 41.4%	None	IVB: 34.7%	-6.7 (-16.2%

Nicholas C. J. 2019

Linee guida

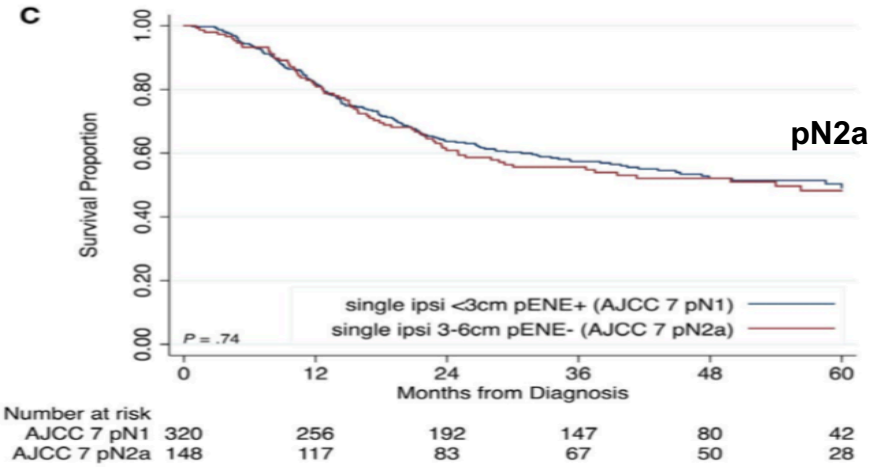


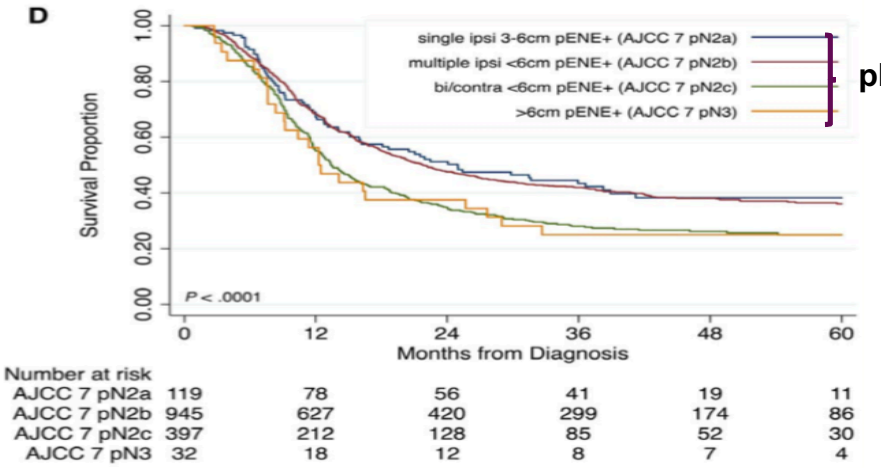


T3

T3

Sopravvivenza dei pz "up-stadiati" più alta





pN3b

Nicholas C. J. 2019

Linee guida

Cancer

- In tutti i casi la sopravvivenza dei pazienti “up-stadiati” per T è significativamente più alta rispetto a quella del gruppo nel quale confluiscono.
- Quando l’analisi è ristretta ai pz. stadiati secondo l’AJCC 7 pT1N0 e upgradati secondo l’AJCC 8 a pT3N0 solo per DOI la SO a 5 anni è 81.1%, vs 64.0% rispetto ai pz. AJCC 8 pT3N0.
- La positività pENE non è un indicatore omogeneo di cattiva prognosi pertanto la categoria pN3b dovrebbe essere rivista nelle prossime edizione dell’AJCC.

Nicholas C. J. 2019

Linee guida

Cancer

L' International Consortium on Outcomes Research ha codificato che sia usato il DOI e non il tumor thickness per la stadiazione. Usando il tumor thickness… **"we assumed heterogeneity between centers was unavoidable".**

- Gli autori non possono escludere che possa essere stato riportato in alcuni casi lo spessore e non la profondità di infiltrazione (DOI).
- Studio retrospettivo. Generatore di ipotesi……

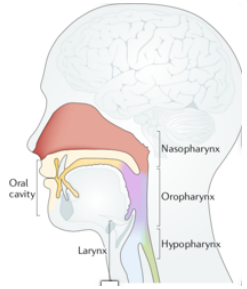
……**fenomeno di Will Rogers non per miglioramento delle metodiche diagnostiche ma per cambi di Stadiazione. Necessari dati provenienti da studi che stadiano con AJCC 8th**

Nicholas C. J. 2019

Linee guida

Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline

Journal of Clinical Oncology®



Panel di esperti ASCO che ha formulato delle "evidence-based recommendations"

Cavo Orale

1) *What are the indications for and the hallmarks of a high-quality neck dissection in oral cavity squamous cell carcinoma (SCCOC)?*

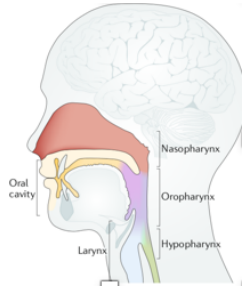
2) *Under what circumstances should a dissected neck receive adjuvant radiotherapy or chemoradiotherapy in patients with SCCOC?*

3) *Is neck radiotherapy to an undissected clinically node-negative (cN0) neck an adequate replacement for high-quality elective neck dissection in SCCOC?*

Linee guida

Journal of Clinical Oncology®

Cavo Orale



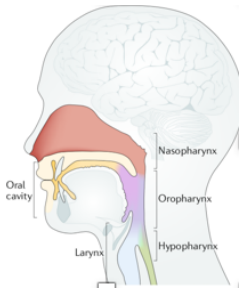
- Dissezione linfonodale adeguata se sono rimossi almeno **18** linfonodi. (Positività forte)
- Svuotamento elettivo ipsilaterale per cN0 livelli Ia, Ib, II, III. (Positività forte)
- Svuotamento terapeutico ipsilaterale per cN+ livelli Ia, Ib, IIa, IIb, III, and IV. (Positività moderata)
- Nei pz.con malattia ben lateralizzata cT2-cT4, cN0, senza evidenza radiologica di malattia linfonodale, deve essere effettuato solo lo svuotamento omolaterale. (Positività forte)

Koyfman S.A. 2019

Linee guida

Journal of Clinical Oncology®

Cavo Orale



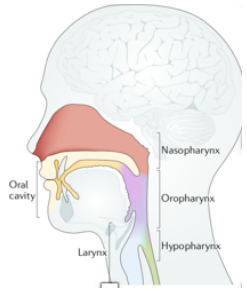
- La radioterapia elettiva potrebbe sostituire la chirurgia in pazienti non candidabili a dissezione linfonodale o nei casi in cui la dissezione non è stata corretta.
- La radioterapia adiuvante potrebbe essere effettuata nei pz. pN1 senza adeguata dissezione linfonodale.
- La radioterapia adiuvante non devrebbe essere effettuata nei pz. pN0 e pN1 senza fattori di rischio e con una adeguata dissezione linfonodale.

National Comprehensive Cancer Network®
NCCN Guidelines Version 2.2019
Cancer of the Oral Cavity

Koyfman S.A. 2019

Linee guida

Journal of Clinical Oncology®



Orofaringe

1) *What are the hallmarks of a high-quality neck dissection in oropharynx squamous cell carcinoma (SCCOP)?*

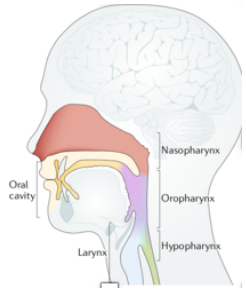
2) *For patients with SCCOP, what features of clinical/radiographic nodal involvement would sway management away from surgery in favor of a nonoperative approach?*

3) *Under what circumstances should a patient with SCCOP undergo a neck dissection after definitive radiotherapy or chemoradiotherapy?*

Linee guida

Journal of Clinical Oncology®

Orofaringe



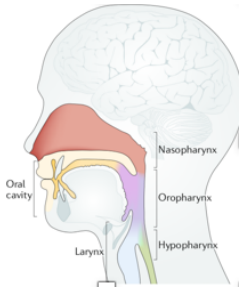
- Per i pz. con tumore che si estende oltre la meta di base lingua e palato molle o che coinvolge la parete posteriore dell'ipofaringe sarebbe preferibile la radiochemioterapia.
- La radioterapia dovrebbe essere la prima scelta terapeutica nel caso di linfoadenopatie che infiltrano i tessuti molli o in caso di infiltrazione delle carotidi o dei nervi crenici.
- Per pazienti con metastasi a distanza l'intervento chirurgico sul tumore primitivo e collo non ha indicazione.

Shlomo A. 2019

Linee guida

Journal of Clinical Oncology®

Orofaringe



- Se la PET/CT 12 settimane dal completamento della radioterapia/radiochemioterapia mostra una captazione intensa del tracciante (FDG) a livello linfonodale, il pz deve essere avviato a dissezione del collo cosa da evitare se, al contrario, non c'è captazione. (Positività forte)

- Se la TC o la RM mostrano a 12 settimane dal termine della radioterapia/radiochemioterapia la scomparsa di linfonodi precedentemente ritenuti patologici il pz. non deve essere avviato alla dissezione linfonodale. (Positività forte)

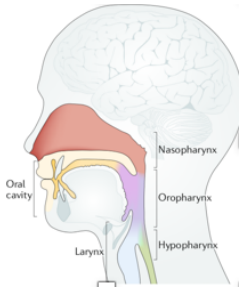
- Se la PET/CT a 12 settimane mostra una lieve captazione del tracciante in un linfonodo di un centimetro o meno di diametro o persiste un linfonodo do 1 cm di diametro non captante il pz. andrebbe osservato eseguendo PET/TAC riservando la dissezione linfonodale a progressione di malattia. (Positività moderata)

Shlomo A. 2019

Linee guida

Orofaringe

Journal of Clinical Oncology®



- Non una linea guida ma una **“evidence-based recommendations”**

- Trattazione organica di un argomento sul quale ancora ci sono numerose controversie che può fornire punti di riflessione per studi futuri

Shlomo A. 2019

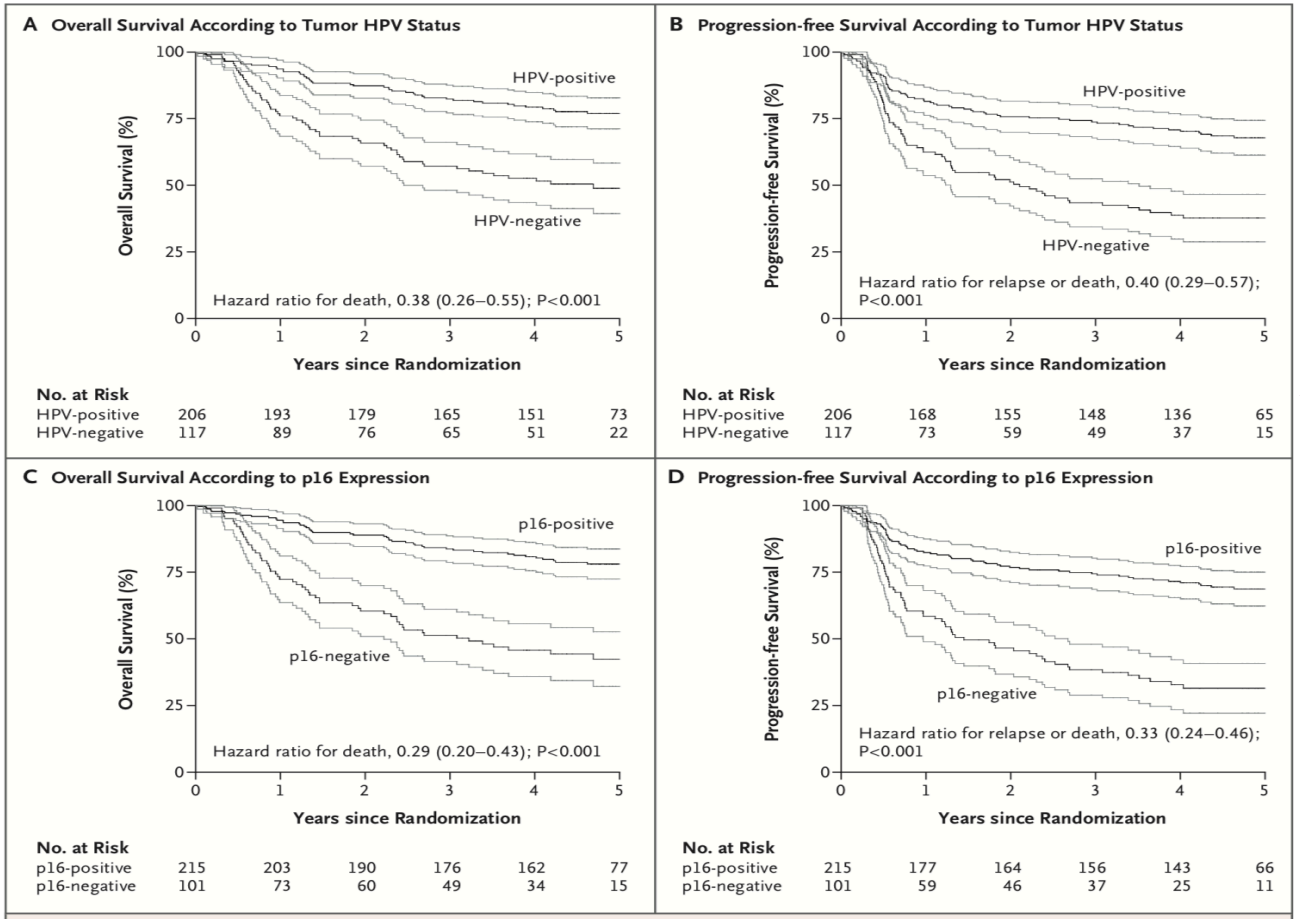
De- intensificazione della terapia

The NEW ENGLAND JOURNAL of MEDICINE

Os a 3 anni 82.4% HPV +
(95% CI, 77.2 to 87.6)
57.1% HPV –
(95% CI, 48.1 to 66.1)

PFS 3 anni 73.7% HPV +
(95% CI, 67.7 to 79.8)
43,4% HPV –
(95% CI, 34.4 to 52.4)

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer



10

Ang K.K. 2010

De-intensificazione della terapia

Tipi di approccio

- Diminuire la dose di radioterapia
  ma aumentare la dose di chemioterapia (CHT di induzione)

- Diminuire la dose di radioterapia
  ma introdurre la chirurgia trans-orale robotica (TORS)

- Sostituire il Cisplatino con il cetuximab

De-intensificazione di terapia

THE LANCET Oncology

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

Primary endpoint:

- overall survival

Secondary endpoints:

- progression free survival
- Locoregional failure
- Distant metastasis

805 pz

Cetuximab +RT(399pz)
400mg/mq 5-7 gg prima della radioterapie
poi 250 mg/mq una volta a settimana per 7 settimane

Cispaltino +RT (406Pz)
100 mg/mq gg 1-22

Radioterapia accellerata
IMRT 70 Gy in 35 fr/6W Bid

Gillison M.L 2019

De-intensificazione di terapia

THE LANCET Oncology

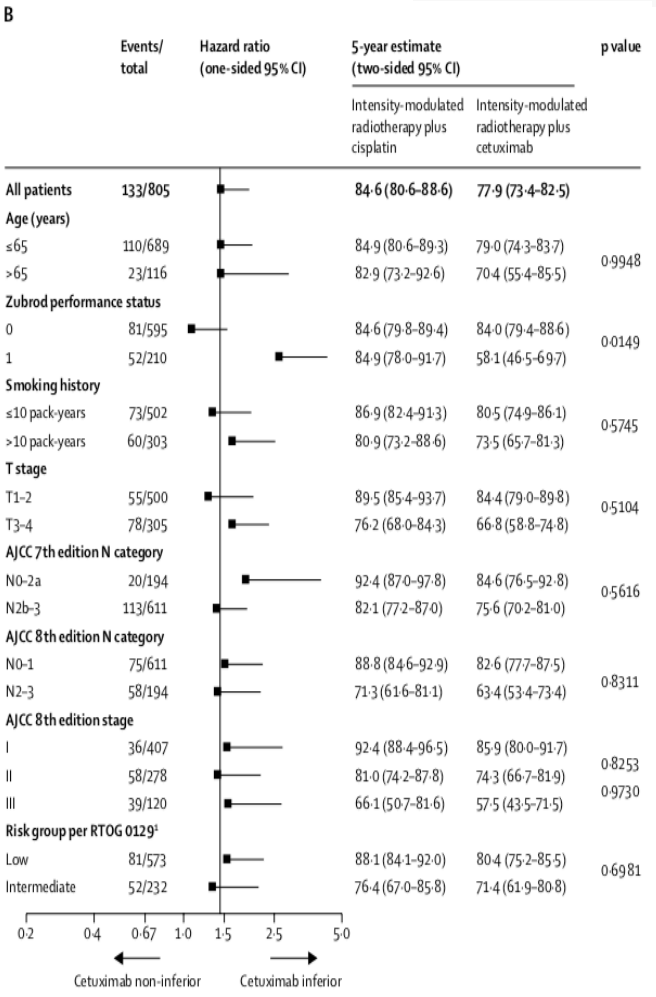
	Intensity-modulated radiotherapy plus cisplatin (n=406)	Intensity-modulated radiotherapy plus cetuximab (n=399)	Total (n=805)
Age (years)			
≤65	344 (85%)	345 (86%)	689 (86%)
>65	62 (15%)	54 (14%)	116 (14%)
Mean (SD)	57·7 (8·1)	57·4 (7·8)	57·6 (8·0)
Median (IQR)	58 (52–63)	58 (52–63)	58 (52–63)
Range	33–83	33–80	33–83
Sex			
Men	373 (92%)	355 (89%)	728 (90%)
Women	33 (8%)	44 (11%)	77 (10%)
Race			
White	380 (94%)	367 (92%)	747 (93%)
Black	17 (4%)	19 (5%)	36 (4%)
Other	2 (<1%)	8 (2%)	10 (1%)
Unknown	7 (2%)	5 (1%)	12 (1%)
Ethnicity			
Hispanic or Latino	11 (3%)	15 (4%)	26 (3%)
Not Hispanic or Latino	383 (94%)	369 (92%)	752 (93%)
Unknown	12 (3%)	15 (4%)	27 (3%)
Zubrod performance status			
0	295 (73%)	300 (75%)	595 (74%)
1	111 (27%)	99 (25%)	210 (26%)
Smoking history			
0 pack-years	194 (48%)	181 (45%)	375 (47%)
>0 to ≤10 pack-years	59 (15%)	68 (17%)	127 (16%)
>10 pack-years	153 (38%)	150 (38%)	303 (38%)
Mean (SD)	15·0 (23·5)	14·8 (23·9)	14·9 (23·7)
Median (IQR)	2 (0–22)	3 (0–24)	2 (0–23)
Range	0–147	0–202	0–202
Primary site			
Tonsillar fossa, tonsil	202 (50%)	199 (50%)	401 (50%)
Base of tongue	174 (43%)	179 (45%)	353 (44%)
Oropharynx, not otherwise specified	16 (4%)	15 (4%)	31 (4%)
Pharyngeal oropharynx	8 (2%)	5 (1%)	13 (2%)
Soft palate	4 (1%)	0	4 (<1%)
Vallecula	2 (<1%)	1 (<1%)	3 (<1%)

(Table 1 continues in next column)

	Intensity-modulated radiotherapy plus cisplatin (n=406)	Intensity-modulated radiotherapy plus cetuximab (n=399)	Total (n=805)
(Continued from previous column)			
Tumour stage*			
T1	89 (22%)	86 (22%)	175 (22%)
T2	162 (40%)	163 (41%)	325 (40%)
T3	108 (27%)	100 (25%)	208 (26%)
T4	47 (12%)	50 (13%)	97 (12%)
Node category*			
N0	20 (5%)	14 (4%)	34 (4%)
N1	20 (5%)	25 (6%)	45 (6%)
N2a	59 (15%)	56 (14%)	115 (14%)
N2b	209 (51%)	208 (52%)	417 (52%)
N2c	82 (20%)	83 (21%)	165 (20%)
N3	16 (4%)	13 (3%)	29 (4%)
Overall stage*			
III	29 (7%)	31 (8%)	60 (7%)
IV	377 (93%)	368 (92%)	745 (93%)
Risk group per RTOG 0129[1]			
Low risk	289 (71%)	284 (71%)	573 (71%)
Intermediate risk	117 (29%)	115 (29%)	232 (29%)
Consented to patient-reported outcome or quality of life collection			
No	17 (8%)†	21 (10%)‡	38 (9%)§
Yes	196 (92%)†	185 (90%)‡	381 (91%)§

Data are n (%) unless otherwise indicated. *According to American Joint Committee on Cancer 7th edition. †n=213. ‡n=206. §n=419.

Table 1: Patient and tumour baseline characteristics



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De-intensificazione di terapia

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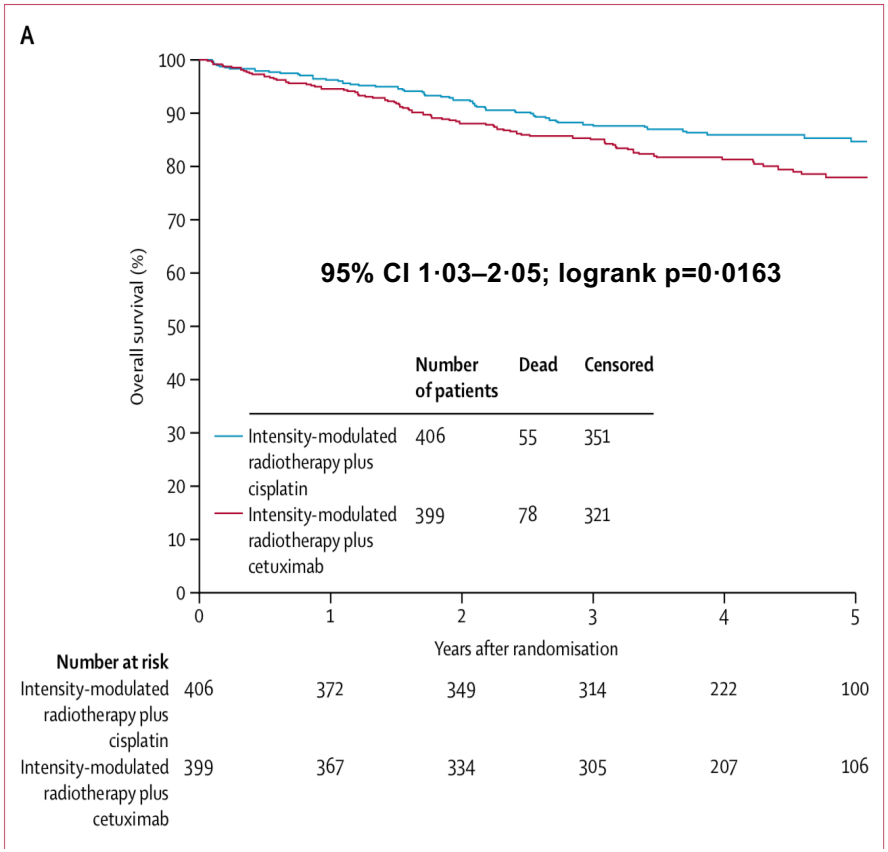
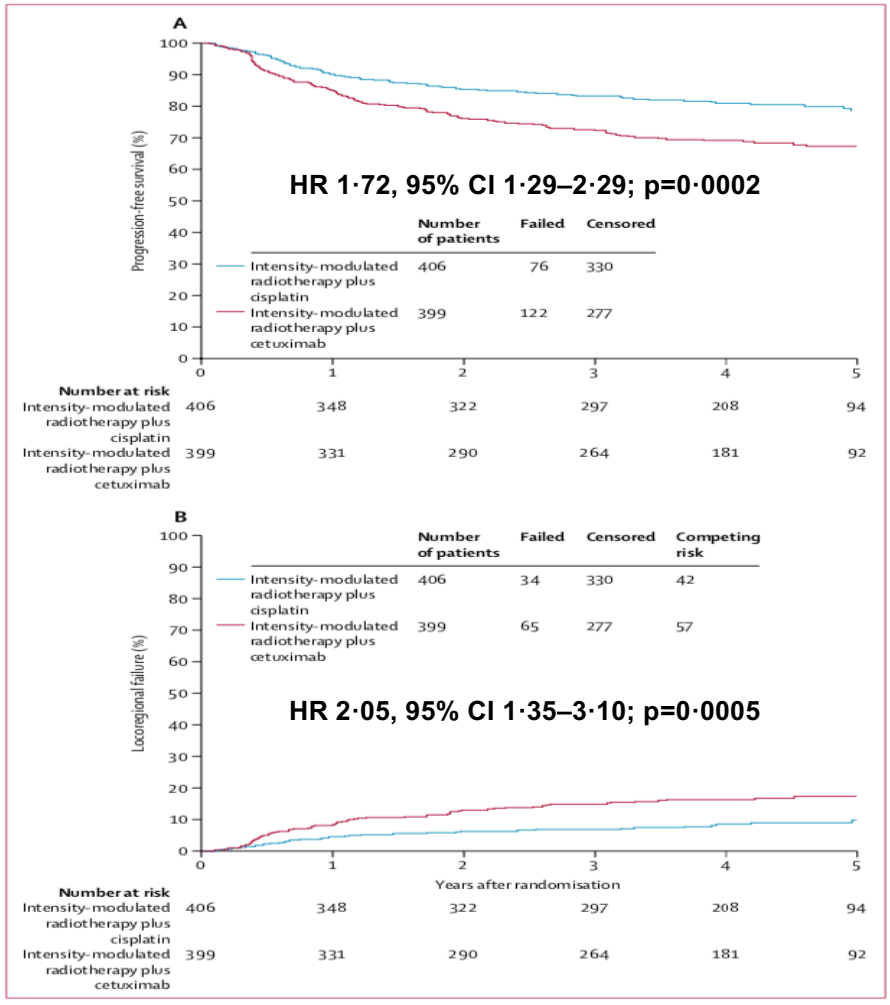


OS a 5 anni

Cetuximab 77% (95% CI 73·4–82·5%)

Cisplatino 84·6% (80·6–88·6)



PFS a 5 aa

Cetuximab 67,3%

(95% CI 62·4–72·2)

Cisplatino 78.4%

(73·8–83·0)

LRF a 5 aa

Cetuximab 9,9%

(CI 6·9–13·6)

Cisplatino 17,3%

(CI 13·7–21·4)

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Il numero di uno o più eventi avversi acuti di grado 3-4 è simile nei due gruppi:

- Cetuximab+ RT= 305 su 394 pazienti (77·4%, 95% CI 73·0–81·5)
- *Cisplatino + RT* = 325 su 398 pazienti (81·7%, 77·5–85·3;)

	Intensity-modulated radiotherapy plus cisplatin	Intensity-modulated radiotherapy plus cetuximab	p value
Acute period patient total	398	394	..
Early death	6 (1·5%)	6 (1·5%)	1·0000
Grade 3–4 overall	325 (81·7%)	305 (77·4%)	0·1586
Grade 3–4 anaemia	11 (2·8%)	0	0·0009*
Grade 3–4 hearing impaired	12 (3·0%)	1 (0·3%)	0·0032*
Grade 2–3 dry mouth	198 (49·7%)	211 (53·6%)	0·2872
Grade 3–4 dysphagia	149 (37·4%)	126 (32·0%)	0·1171
Grade 3–4 mucositis oral	165 (41·5%)	182 (46·2%)	0·1974
Grade 3 nausea	76 (19·1%)	32 (8·1%)	<0·0001*
Grade 3–4 vomiting	48 (12·1%)	16 (4·1%)	<0·0001*
Grade 3 fatigue	23 (5·8%)	17 (4·3%)	0·4178
Grade 3–4 dermatitis radiation	32 (8·0%)	49 (12·4%)	0·0462
Grade 3–4 lymphocyte count decreased	68 (17·1%)	69 (17·5%)	0·9252
Grade 3–4 neutrophil count decreased	61 (15·3%)	2 (0·5%)	<0·0001*
Grade 3 weight loss	31 (7·8%)	23 (5·8%)	0·3241
Grade 3–4 white blood cells decreased	48 (12·1%)	0	<0·0001*
Grade 3–4 anorexia	89 (22·4%)	61 (15·5%)	0·0144*
Grade 3–4 dehydration	61 (15·3%)	24 (6·1%)	<0·0001*
Grade 3–4 hyponatremia	21 (5·3%)	4 (1·0%)	0·0008*
Grade 3–4 acute kidney injury	13 (3·3%)	1 (0·3%)	0·0017*
Grade 3–4 pharyngeal mucositis	54 (13·6%)	40 (10·2%)	0·1535
Grade 3–4 rash acneiform	1 (0·3%)	37 (9·4%)	<0·0001*
Grade 3–4 pain (all terms)	58 (14·6%)	50 (12·7%)	0·4694
Mean raw T-score	3·19	2·35	<0·0001*
Late period patient total	383	375	..
Grade 3–4 overall	78 (20·4%)	62 (16·5%)	0·1904
Grade 3–4 hearing impaired	24 (6·3%)	8 (2·1%)	0·0060*
Grade 2–3 dry mouth	123 (32·1%)	126 (33·6%)	0·6991
Grade 3–4 dysphagia	17 (4·4%)	23 (6·1%)	0·3318
Grade 3 weight loss	17 (4·4%)	11 (2·9%)	0·3366
Grade 3–4 osteonecrosis of jaw	8 (2·1%)	3 (0·8%)	0·2234
Grade 3–4 pain (all terms)	5 (1·3%)	8 (2·1%)	0·4154
Mean raw A-score	0·38	0·27	0·1189

Data are n or n (%). *Significant after adjustment for multiple comparisons.

Table 2: **Prespecified treatment-related adverse events of interest or occurring in at least 5% of patients**

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De-intensificazione di terapia

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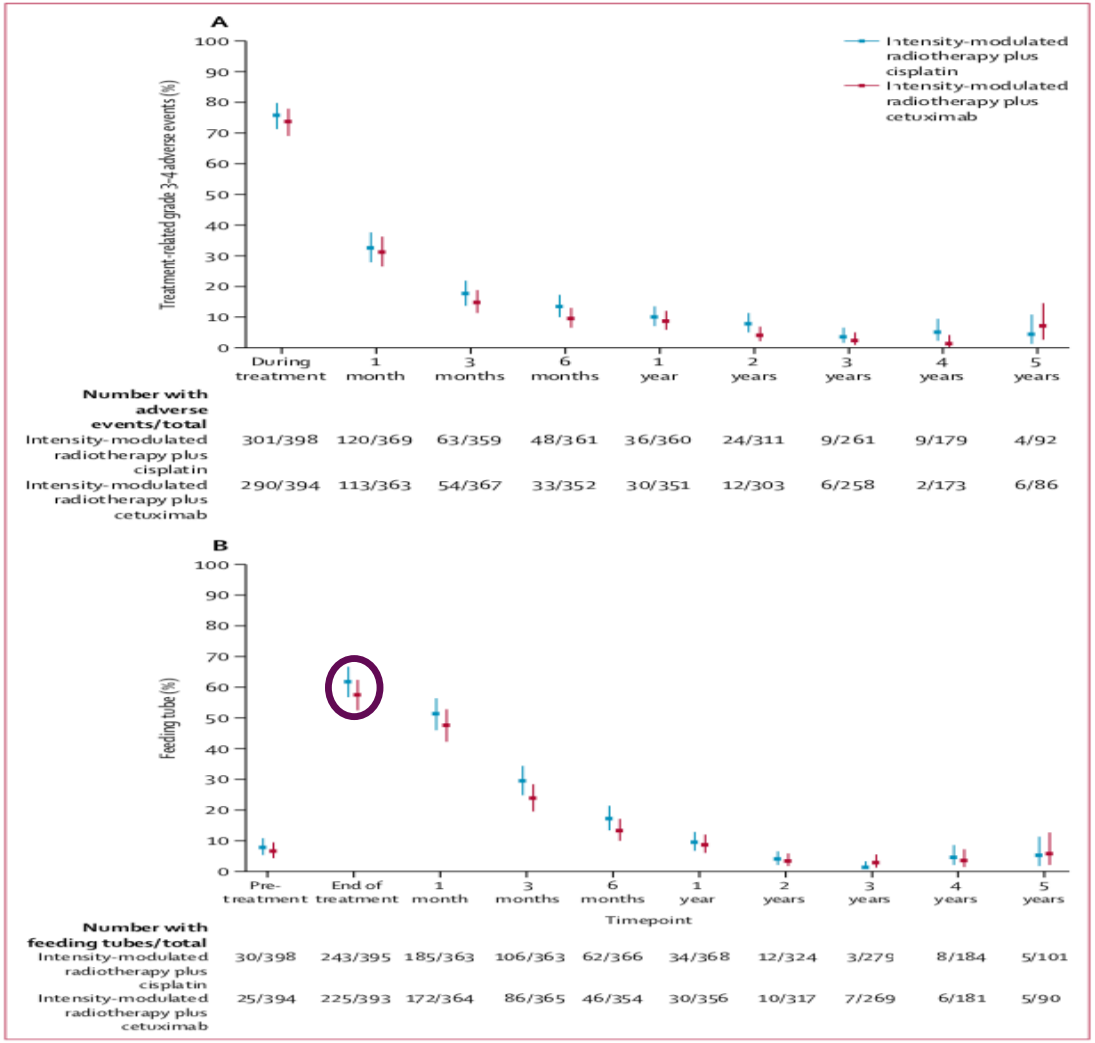

Il numero di uno o più eventi avversi tardivi di grado 3-4 è simile nei due gruppi nel tempo. A 1 anno dal trattamento:

- Cetuximab+ RT= 30 (8·5%, 95% CI 5·8–12·0) su 351
- Cisplatino + RT = 36 (10·0%, 7·1–13·6) su 360

Pz. con SNG al termine del trattamento (valore simile tra i due gruppi)

- Cetuximab+RT= 225 (57·3%, 95% CI 52·2–62·2) su 393
- Cisplatino+RT = 243 (61·5%, 56·5–66·3) su 395

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	Cisplatin group (n=166)	Cetuximab group (n=168)	All patients (n=334)
Age, years			
Mean	57·0 (7·8)	57·0 (8·3)	57·0 (8·0)
Median	56·5 (52·0–62·0)	57·0 (51·0–64·0)	57·0 (52·0–63·0)
Sex			
Men	132 (80%)	134 (80%)	266 (80%)
Women	34 (20%)	34 (20%)	68 (20%)
HPV testing results (n=324)			
p16-positive, HPV-ISH positive	151 (94%)	153 (94%)	304 (94%)
p16-positive, HPV-ISH negative	10 (6%)	10 (6%)	20 (6%)
Tumour stage (TNM 7)			
T1–T2	109 (66%)	107 (64%)	216 (65%)
T3–T4	57 (34%)	61 (36%)	118 (35%)
T4 only	32 (19%)	24 (14%)	56 (17%)
Nodal stage (TNM 7)			
N0–N1	40 (24%)	41 (24%)	81 (24%)
N2–N3	126 (76%)	127 (76%)	253 (76%)
N3 only	1 (1%)	1 (1%)	2 (1%)
Primary tumour laterality (n=328)			
Left only	80 (49%)	86 (52%)	166 (51%)
Right only	75 (46%)	67 (41%)	142 (43%)
Midline or any combination	8 (5%)	12 (7%)	20 (6%)
Primary subsite (n=329)			
Base of tongue	54 (33%)	58 (35%)	112 (34%)
Tonsil	107 (65%)	104 (63%)	211 (64%)
Other	3 (2%)	3 (2%)	6 (2%)
ECOG performance status (n=328)			
0	142 (87%)	149 (91%)	291 (89%)
1	22 (13%)	15 (9%)	37 (11%)
Current alcohol consumption (n=329)			
No	44 (27%)	37 (22%)	81 (25%)
Yes	120 (73%)	128 (78%)	248 (75%)
Median reported units per week	10·0 (4·0–20·0)	10·0 (4·0–20·0)	10·0 (4·0–20·0)
Ever smoked?			
No	94 (57%)	86 (51%)	180 (54%)
Yes	72 (43%)	82 (49%)	154 (46%)
Median pack years	6·5 (3·0–13·0)	8·0 (3·0–15·0)	8·0 (3·0–15·0)
Radiotherapy			
Unilateral	34 (20%)	34 (20%)	68 (20%)
Bilateral	132 (80%)	134 (80%)	266 (80%)
Planned PEG use before treatment			
No	57 (34%)	58 (34%)	115 (34%)
Yes	109 (66%)	110 (66%)	219 (66%)

Data are n (%), mean (SD), or median (IQR). There were no significant differences between the two treatment groups for any of the factors. Continuous variables were compared with *t* tests or Mann-Whitney U tests, and categorical variables compared with χ^2 test. HPV=human papillomavirus. ISH=in-situ hybridisation. TNM=tumour, node, and metastasis. ECOG=Eastern Cooperative Oncology Group. PEG=percutaneous endoscopic gastrostomy.

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

334 pz

Cetuximab +RT(168pz)
400mg/mq 5-7 gg prima della radioterapie
poi 250 mg/mq una volta a settimana per 7 settimane

Cispaltino +RT(166pz)
100 mg/mq gg 1-22-43

Radioterapia
IMRT 70 Gy in 35 fr/5W

Primary endpoint:
- tossicità acuta e tardiva (Grado 3-4)

Secondary endpoints:
- OS
- time to recurrence
- QoL

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De-intensificazione di terapia

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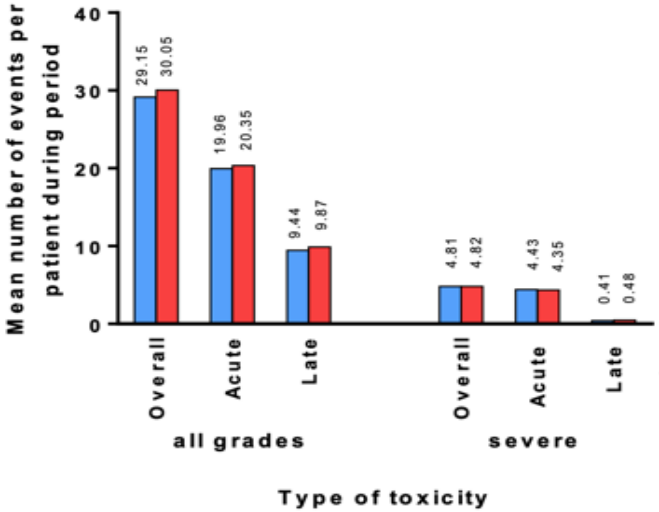
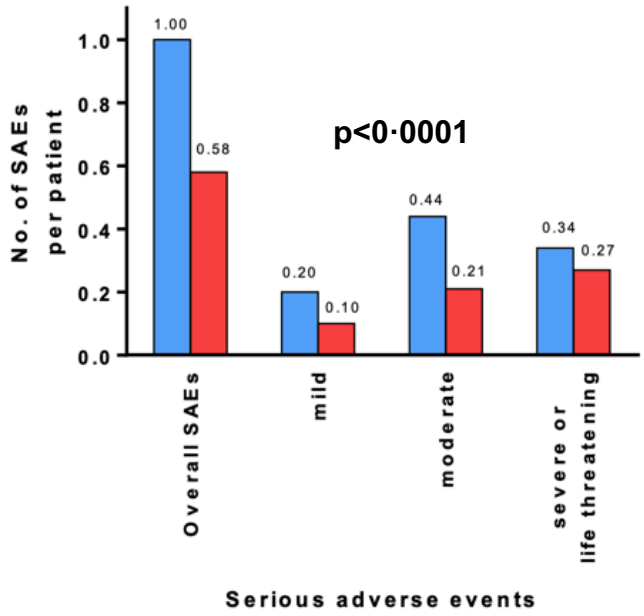
	Cisplatin plus radiotherapy (95% CI)	Cetuximab plus radiotherapy (95% CI)	p value
Primary outcome			
Overall			
Grade 3–5	4·81 (4·23–5·40)	4·82 (4·22–5·43)	0·98
All grades	29·15 (27·33–30·97)	30·05 (28·26–31·85)	0·49
Secondary outcomes			
Acute short-term toxicities			
Grade 3–5	4·43 (3·88–4·97)	4·35 (3·84–4·86)	0·84
All grades	19·96 (18·81–21·12)	20·35 (19·18–21·52)	0·64
Severe late toxicities			
Grade 3–5	0·41 (0·29–0·54)	0·48 (0·30–0·67)	0·53
All grades	9·44 (8·53–10·34)	9·87 (9·02–10·72)	0·49

t test used to compare treatment groups. No adjustments have been made for multiple testing. Toxicity assessed with Common Toxicity Criteria for Adverse Events, version 4.0.

Table 2: Mean number of acute, late, and overall toxicity events per patient, by treatment group



Supplementary Figure S1B: Serious adverse events by severity , by group



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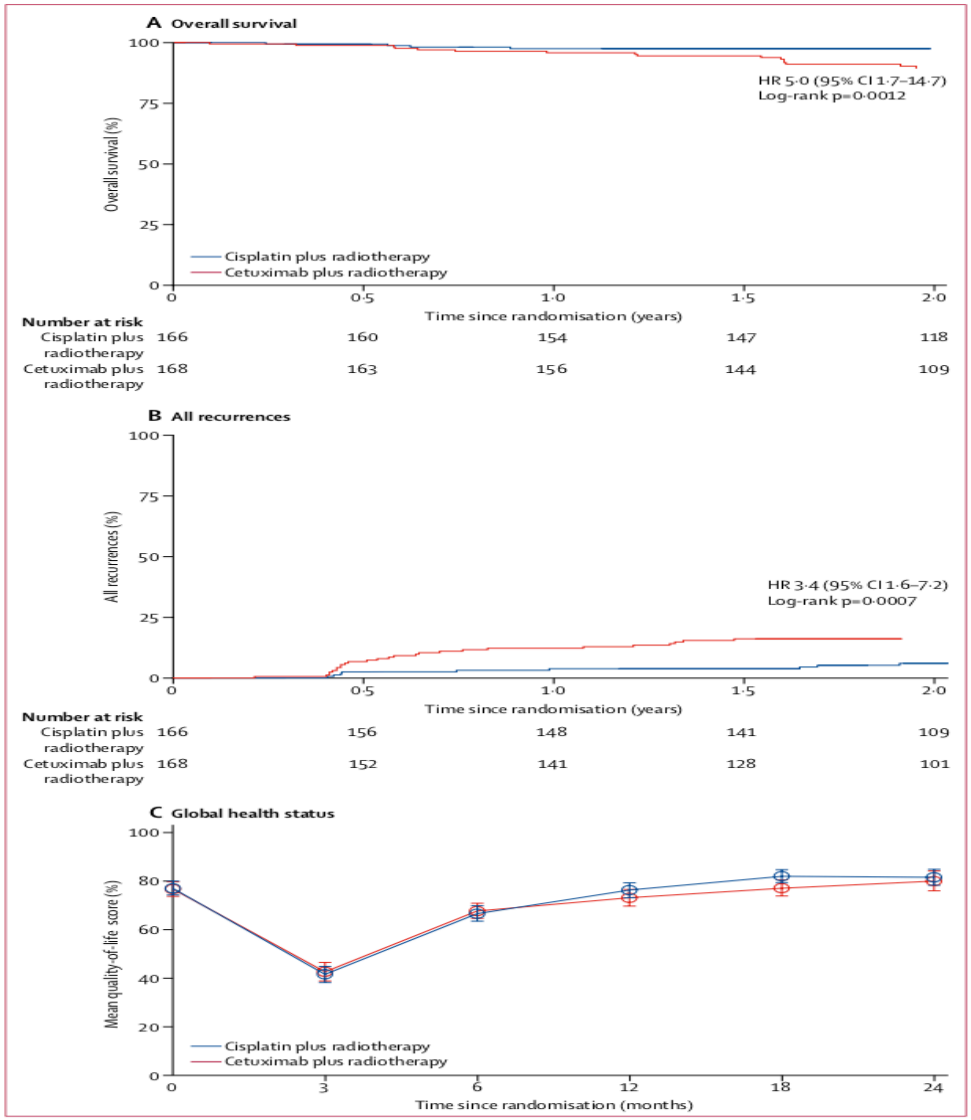

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OS a 2 aa
Cisplatino 97·5%
Cetuximab 89·4%,
All recurrence a 2 aa
Cisplatino 6·0%
Cetuximab 16·1%,

Nel gruppo del cisplatino
62 (38%) ha ricevuto tutti e 3 i cicli
83 (51%) ne ha ricevuti 2
16 (10%) ne ha ricevuti 1

Nel gruppo del cetuximab
130 (79%) ha ricevuto tutti gli 8 cicli
23 (14%) ha ricevuto 7 cicli

Il risultato del questionario **EORTC QLQ-C30** non differisce tra i 2 gruppi.
p=0·9976;

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De-intensificazione di terapiaa

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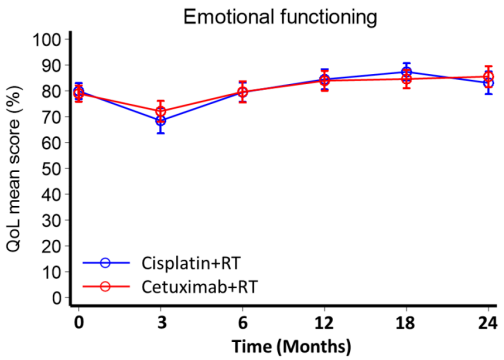
EORTC C30

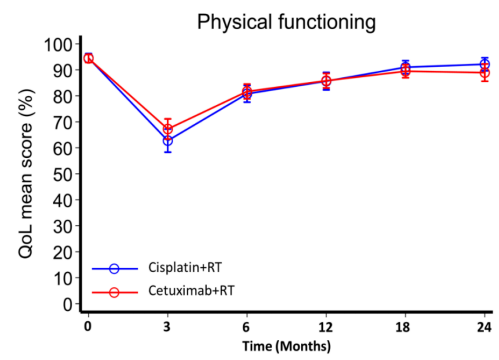
C. EORTC Emotional functioning

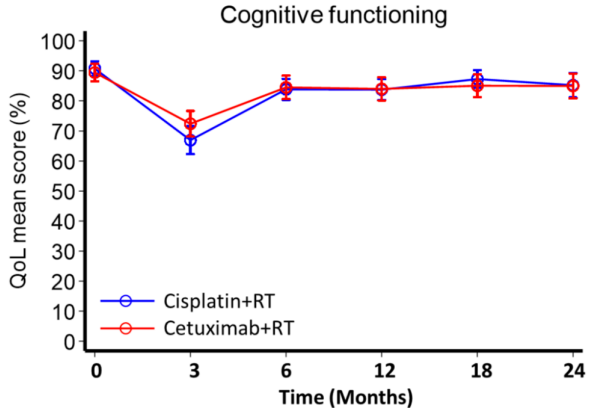
P-value = 0.851



A. EORTC Physical functioning

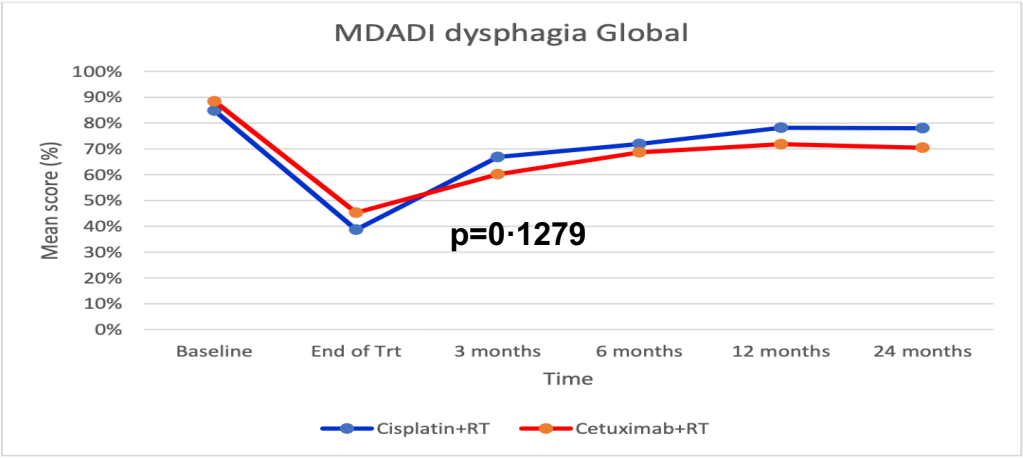
P-value = 0.122





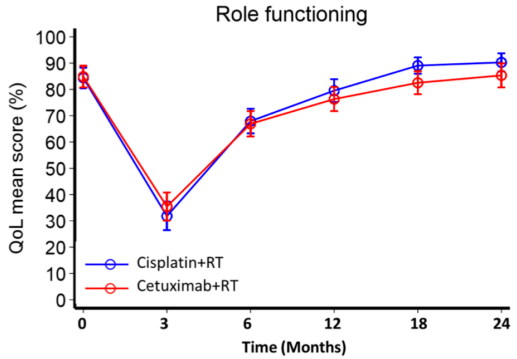
F. MDADI dysphagia global

P-value = 0.0948



B. EORTC Role functioning

P-value = 0.121



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De-intensificazione di terapiaa

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Cisplatino + RT vs Cetuximab + RT:

- migliori outcomes di trattamento
- profili di tossicità paragonabili

N.B. Alto numero di tossicità severe con ricorso all'ospedalizzazione per CCDP.

Nei pz. affetti da carcinoma dell' orofaringe HPV correlato la Radioterapia con cisplatino è lo standard di trattamento.

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Deintensificazione di terapia

TABLE 1. Patient Characteristics (N = 114)

Characteristic	Patients
Age, years, mean (range)	62 (37-87)
Sex	
Male	96 (84)
Female	18 (16)
Ethnicity	
African American	7 (6)
White	104 (91)
Other	1 (1)
Unknown	2 (2)
Marital status	
Married	90 (79)
Unmarried	23 (20)
Unknown	1 (1)
Tobacco use	
Never smoked	54 (47)
≤ 10 pack-years	38 (33)
> 10 pack-years	22 (19)
Primary tumor location	
Tonsil	52 (46)
Base of tongue	57 (50)
Unknown primary	5 (4)
T stage*	
T0	5 (4)
T1	35 (31)
T2	61 (54)
T3	13 (11)
N stage (AJCC 7th edition)	
N0	18 (16)
N1	16 (14)
N2a	5 (4)
N2b	57 (50)
N2c	18 (16)
N stage (AJCC 8th edition)	
N0	18 (16)
N1	78 (68)
N2	18 (16)
HPV/p16 status	
HPV+/p16+	46 (40)
HPV−/p16+	12 (11)
HPV unknown/p16+	56 (49)

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

Journal of Clinical Oncology®

114 pz

Radioterapia IMRT

CTV high risk 60 Gy 30 fr/5w

CTV low risk 54 Gy 30 fr/5w

Ib-V ipsilaterale+ retrofaringei

II-IV controlaterale

Primary end point a 2 aa:

- progression free survival (PFS).

Secondary end points a 2 aa:

- local-regional control (LRC)
- overall survival (OS)
- distant metastasis-free survival (DMFS)
- patient- reported QOL.

Patient-reported outcomes:

- EORTC Qol
- PRO-CTCAE

Follow-up 31.8 months (range, 1.1 to 51.4 months)

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Deintensificazione di terapia

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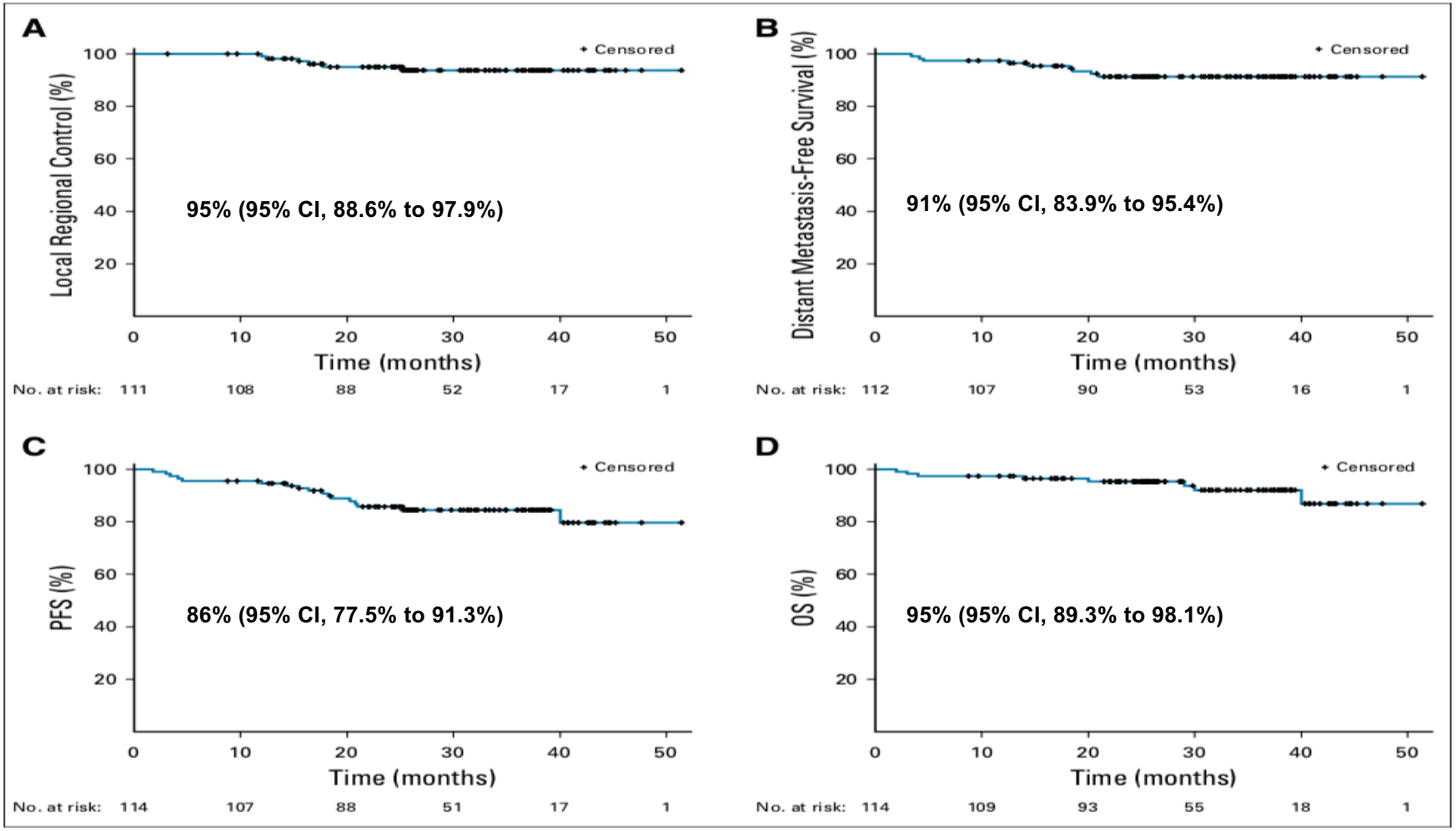

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Deintensificazione di terapia

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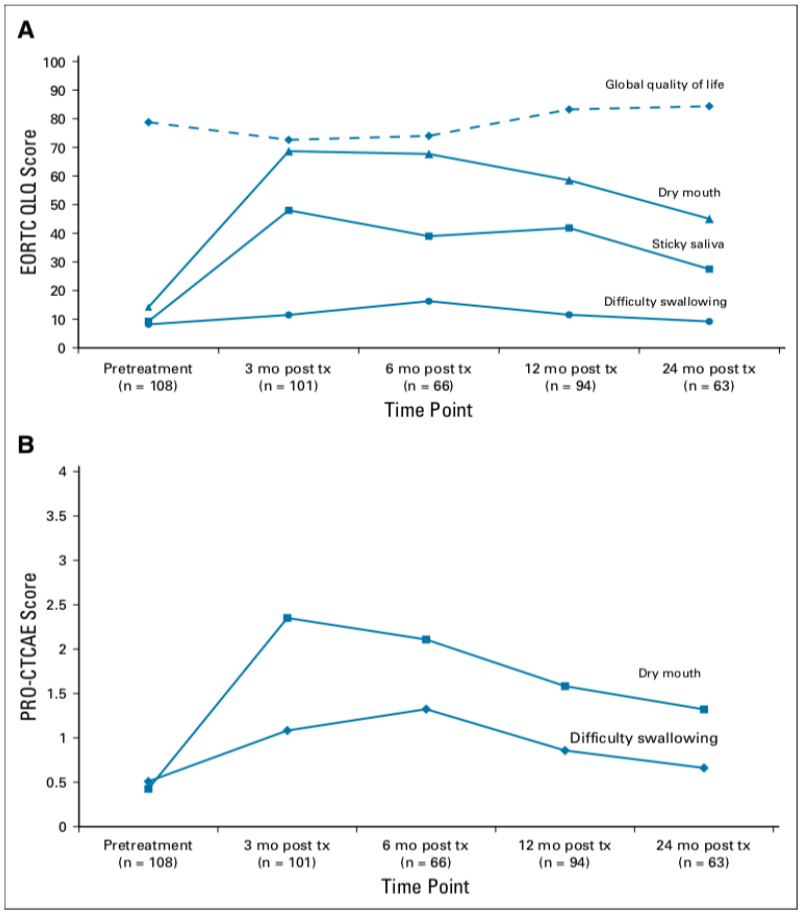
Toxicity	CTCAE Version 4.0 Grade 3 or Higher (%)	PRO-CTCAE Severe or Very Severe (%)
Hematologic		
Anemia	1	N/A
Neutropenia	2	N/A
Renal		
Acute kidney injury	1	N/A
Nonhematologic		
Xerostomia	2	60
Dysphagia	21	50
Mucositis (oral and/or pharyngeal)	33	37
Nausea	8	22
Vomiting	2	14
Dermatitis radiation	2	30
Pain	12	45
Hoarseness	0	21
Fatigue	3	39
Anxiety	3	11
Depression	0	10
Appetite	25	59
Tinnitus	0	17

34% dei pz.(38 di 113) ha richiesto il posizionamento di SNG per un tempo medio di 10.5 settimane (range, 3-66)



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- **Clinical outcomes favorevoli:**
  2-3-anni PFS del 86% e OS 95% vs RTOG 1016 (70 Gy+ cisplatin) che mostra a 5 anni PFS del 78% 2 OS del 85%.

- **Non ricorso a chirurgia né a CHT di induzione**

- **Buon profilo di tossicità.**

Deintensificazione di terapia

Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma

Journal of Clinical Oncology®

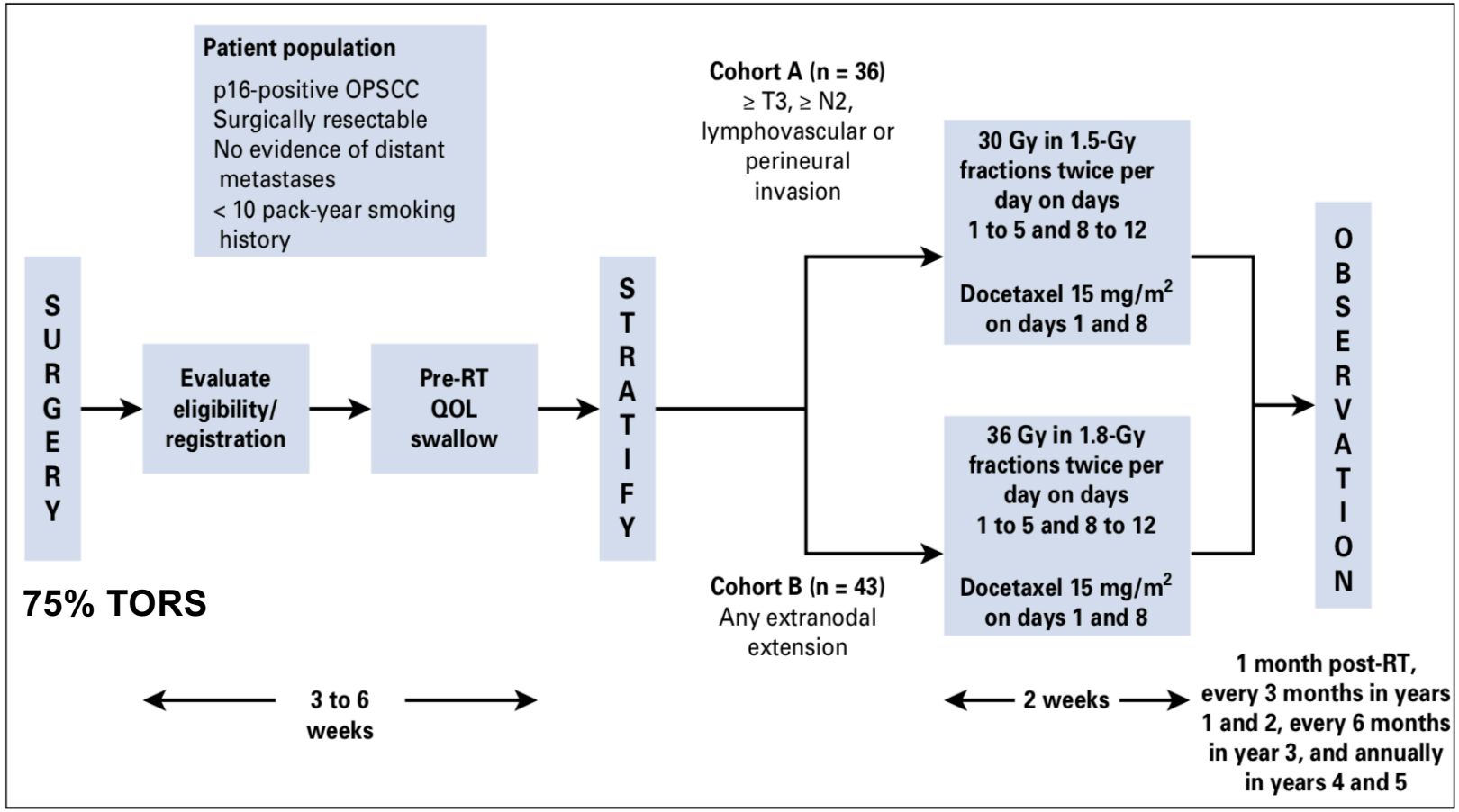
MC1273

Primary end point:

- locoregional tumor control (LRC) a 2 anni.

Secondary end points:

- 2-year progression free survival (PFS)
- overall survival (OS)
- locoregional recurrence (LRR)
- Toxicity
- swallow function
- patient- reported QOL.



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Deintensificazione di terapia

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Radioterapia VMAT

CTV: tumor bed, livelli omolaterali dissezionati (II - IV, +/- IB, V, and retro-pharyngeal), se sottosede base lingua, tonsillao palato molle, livelli linfonodali controlaterali (II to IV)

Characteristic	No. (%) Cohort A (n = 36)	Cohort B (n = 43)	Total (N = 79)
Age, years			
Mean	58.4	58.9	58.7
SD	6.7	10.2	8.8
Median	60.0	61.0	61.0
Sex			
Female	3 (8.3)	5 (11.6)	8 (10.1)
Male	33 (91.7)	38 (88.4)	71 (89.9)
ECOG PS			
0	34 (94.4)	41 (95.3)	75 (94.9)
1	2 (5.6)	2 (4.7)	4 (5.1)
Primary tumor site			
Base of tongue	16 (44.4)	21 (48.8)	37 (46.8)
Tonsil	15 (41.7)	18 (41.9)	33 (41.8)
Tonsil and tongue	5 (13.9)	4 (9.3)	9 (11.4)
Pathologic T stage			
pT1	18 (50.0)	19 (44.2)	37 (46.8)
pT2	14 (38.9)	13 (30.2)	27 (34.2)
pT3	4 (11.1)	4 (9.3)	8 (10.1)
pT4a	0 (0.0)	7 (16.3)	7 (8.9)
Pathologic N stage			
pN0	2 (5.6)	0 (0.0)	2 (2.5)
pN1	6 (16.7)	4 (9.3)	10 (12.7)
pN2a	13 (36.1)	9 (20.9)	22 (27.8)
pN2b	12 (33.3)	17 (39.5)	29 (36.7)
pN2c	3 (8.3)	5 (11.6)	8 (10.1)
pN3	0 (0.0)	8 (18.6)	8 (10.1)
Total No. of involved lymph nodes			
0	2 (5.6)	0 (0.0)	2 (2.5)
< 5	32 (88.9)	36 (83.7)	68 (86.1)
≥ 5	2 (5.6)	7 (16.3)	9 (11.4)

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Deintensificazione di terapia

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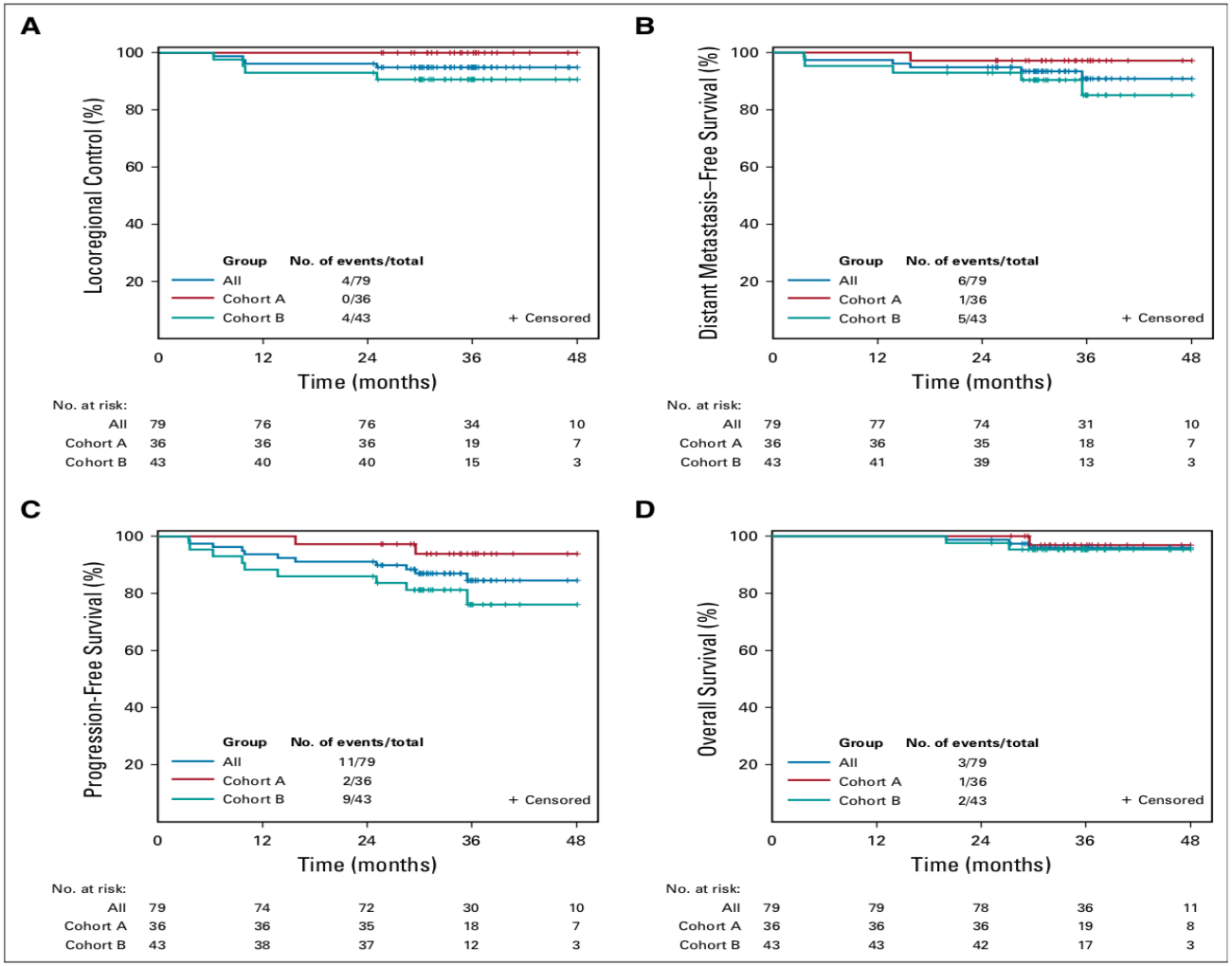

Median follow-up:
35.7 mesi (range, 25.2 -61.8).

***A 2 anni**:*

- **LRC** 96.2%
- **DMFS** 94.9%
- **PFS** 91.1%
- **OS** rate of 98.7%

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Deintensificazione di terapia

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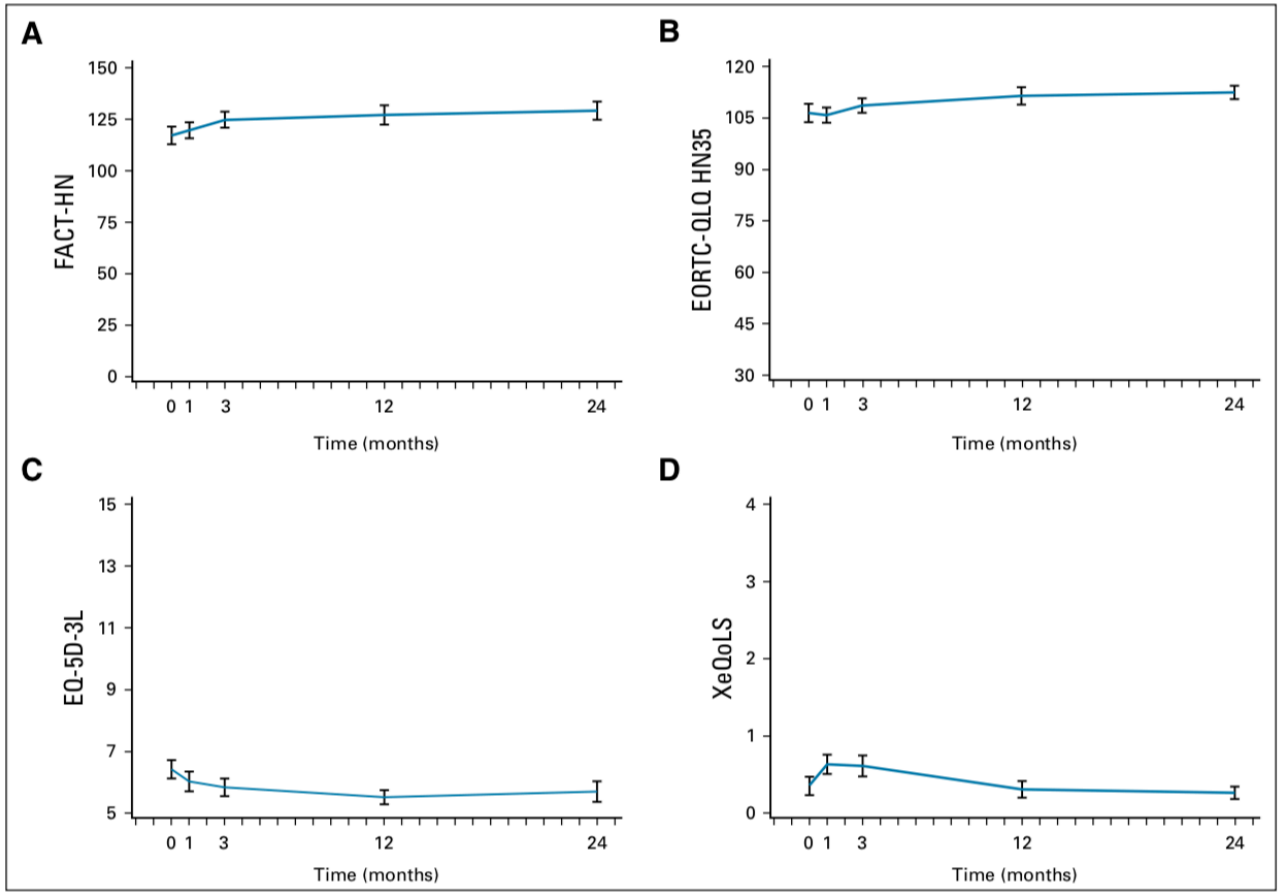
	Grade							
	1		2		3		4	
Adverse Event by Cohort	No.	%	No.	%	No.	%	No.	%
Dry mouth								
A	27	75	8	22.2				
B	31	72.1	11	25.6				
Fatigue								
A	27	75	5	13.9	1	2.8		
B	30	69.8	8	18.6				
Dysphagia								
A	15	41.7	10	27.8	2	5.6		
B	23	53.5	10	23.3	1	2.3		
Superficial soft tissue fibrosis								
A	20	55.6	3	8.3				
B	28	65.1	2	4.7				
Mucositis oral								
A	14	38.9	4	11.1	3	8.3		
B	18	41.9	8	18.6	2	4.7		
Oral pain								
A	13	36.1	6	16.7	1	2.8		
B	24	55.8	5	11.6				
Lymphedema								
A	15	41.7	2	5.6	1	2.8		
B	23	53.5	3	7				
Nausea								
A	13	36.1	3	8.3				
B	10	23.3	3	7				
Pharyngitis								
A	10	27.8	3	8.3				
B	15	34.9						
Lymphocyte count decreased								
A			2	5.6	1	2.8		
B			1	2.3				
Radiation dermatitis								
A					1	2.8		
Osteonecrosis of jaw								
A			1	2.8				
Vasovagal reaction								
B							1	2.3



Ma D.J. 2019

Deintensificazione di terapia

Journal of Clinical Oncology®

- MC1273 è attualmente lo studio con una riduzione di dose più spinta (30-36 Gy al posto di 60-66 Gy)
- LRC, PFS, e OS a 2 anni del 96.2%, 91.1%, and 98.7%, sono paragonabili ad outcome di studi con schema di trattamento classico (PFS nel RTOG 0234 è 86.4%).
- Profilo di tossicità favorevole. Solo un pz. ha posizionato PEG (18% in altri studi)
- Riduzione dei costi ($17,791 vs $26,603)

Visto i risultati ottenuti è in corso uno studio di fase III randomizzato

Ma D.J. 2019

Deintensificazione di terapia

A Phase 2 Trial of Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID): Omission of the Resected Primary Tumor Bed After Transoral Robotic Surgery for Human Papilloma Virus—Related Squamous Cell Carcinoma of the Oropharynx

Studio di fase 2 a singolo braccio

End-poin primario:

- Primary site local control a 2aa

End-poins secondari:

- Regional control a 2 anni
- Local recurrencee free survival
- distant metastasis free survival
- Progression free survival
- Overal survival

60 pz.

↓

TORS

↓

Radioterapia

Solo su Collo risparmiando la sede dell'intervento

Radioterapia

IMRT/PBT

50-60 Gy in 30 Fr

63/66 Gy in 33 Fr

su ENE

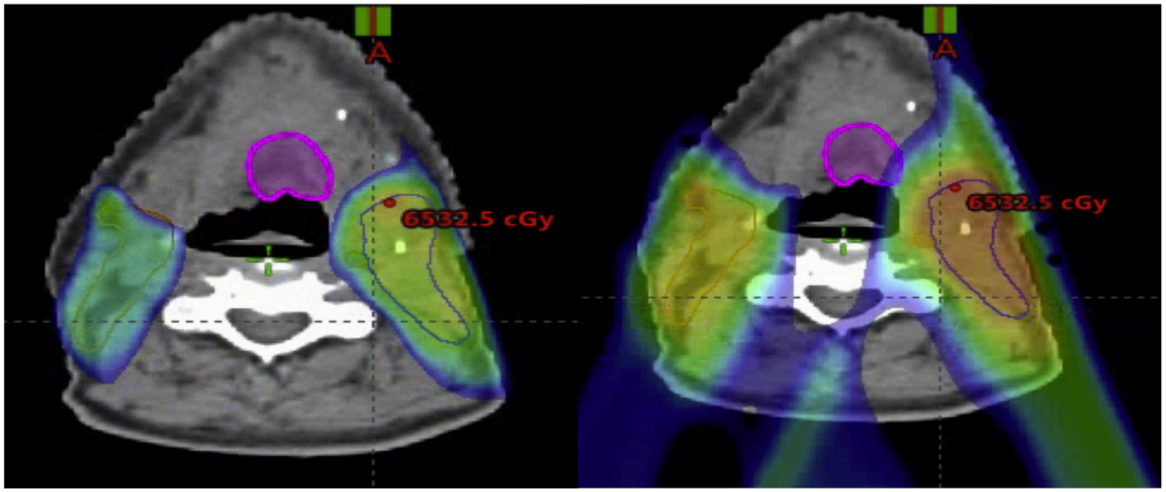
Swisher-McClure S. 2019

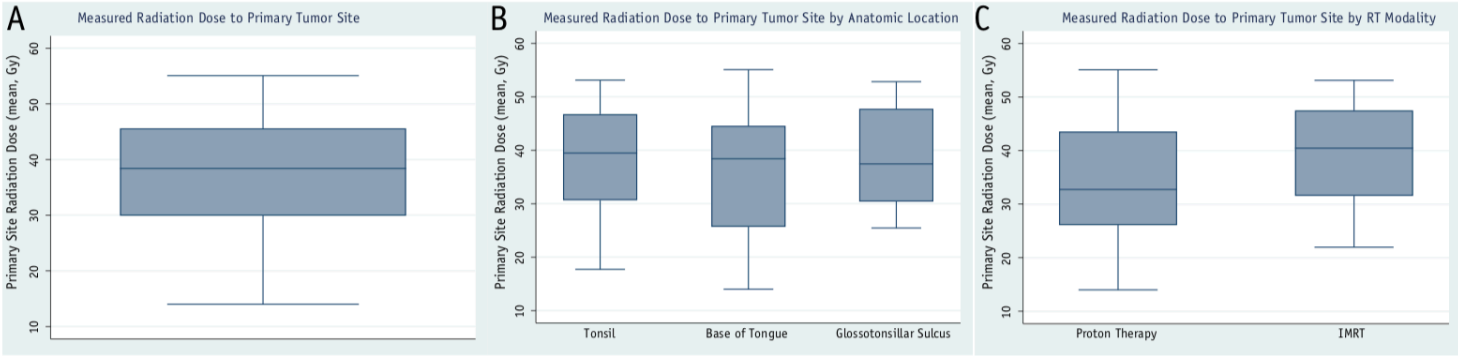
Deintensificazione di terapia

Table 1 Patient characteristics of the study cohort

	All patients (n = 60)
	Percent (n) or median (range), %*
Age at diagnosis (y)	57 (34-84)
Sex	
Male	83.3% (50)
Female	16.7% (10)
Primary tumor location	
Tonsil	48.3% (29)
Base of tongue	40% (24)
Overlapping/ glossotonsillar sulcus	11.7% (7)
Pathologic AJCC tumor stage (7th ed.)	
pT1	73.3% (44)
pT2	26.7% (16)
Pathologic AJCC nodal stage (7th ed.)	
pN2a	41.7% (25)
pN2b	55% (33)
pN2c*	1.7% (1)
pN3	1.7% (1)
Primary tumor diameter (mm)	12 (2-37)
Presence of ENE	
Yes	21.7%
No	78.3%
No. of lymph nodes involved	2 (1-23)
Maximum diameter of involved lymph nodes (mm)	38 (13-62)
Tobacco use history	
No. of pack years	2 (0-100)
Reported never smokers	53% (32)
Receipt of concurrent chemotherapy	
Yes	21.7% (13)
No	78.3% (47)
Adjuvant RT technique	
Proton beam therapy (PBT)	45% (27)
IMRT	53.3% (32)
Combination (IMRT/PBT)	1.7% (1)
Management of the neck	
Unilateral selective neck dissection	100% (60)
Bilateral selective neck RT	100% (60)

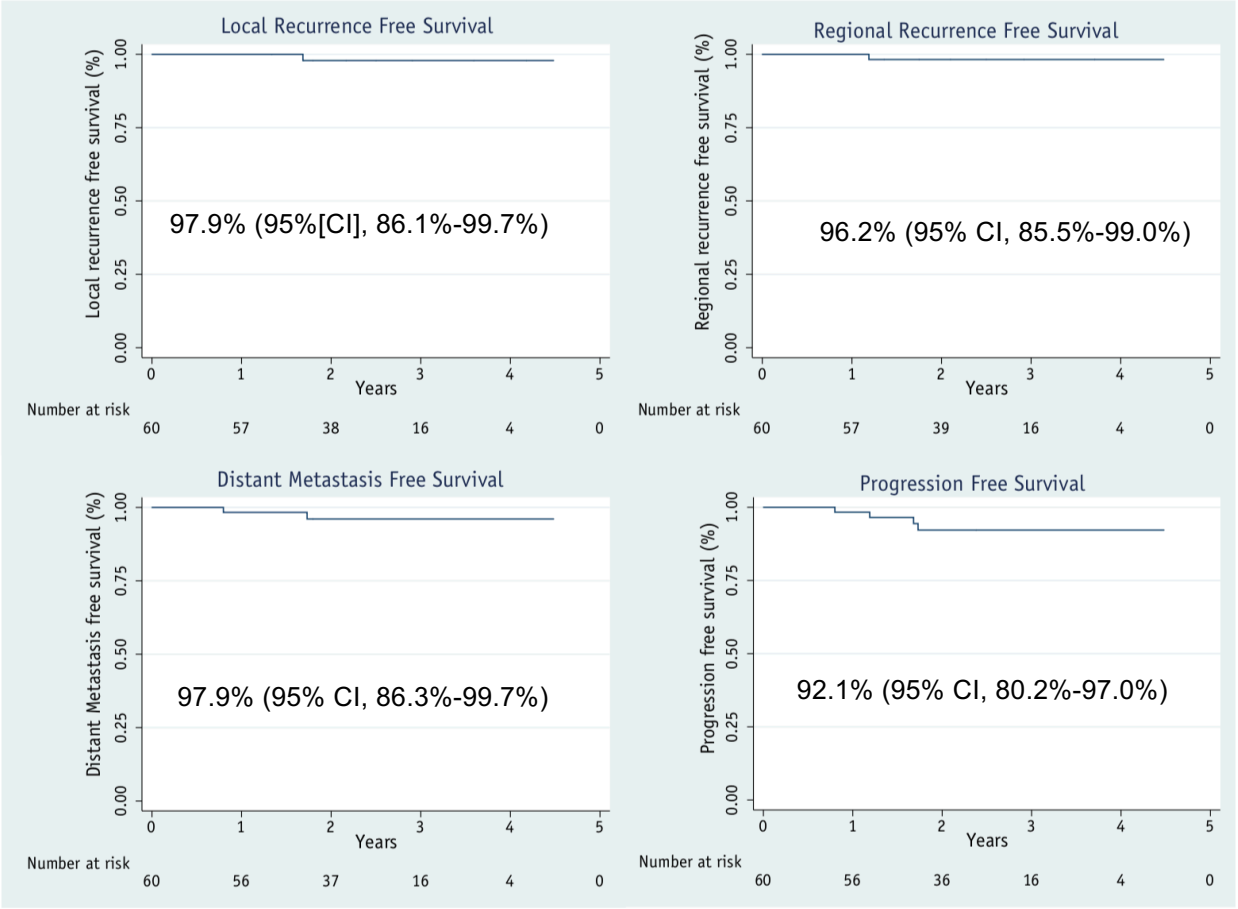
Tutti i pz. R0 senza infiltrazione perineurale e linfovascolare





Swisher-McClure S. 2019

Deintensificazione di terapia



- Nessun pz. ha avuto necessità di sondino naso-gastrico durante la RT.
- Due pz. necrosi dei tessuti molli (sede TORS) a 3 mesi da RT.
- Un pz. con ripresa locale a 20 mesi da RT
- Un pz. ripresa N in field

Swisher-McClure S. 2019

Deintensificazione di terapia

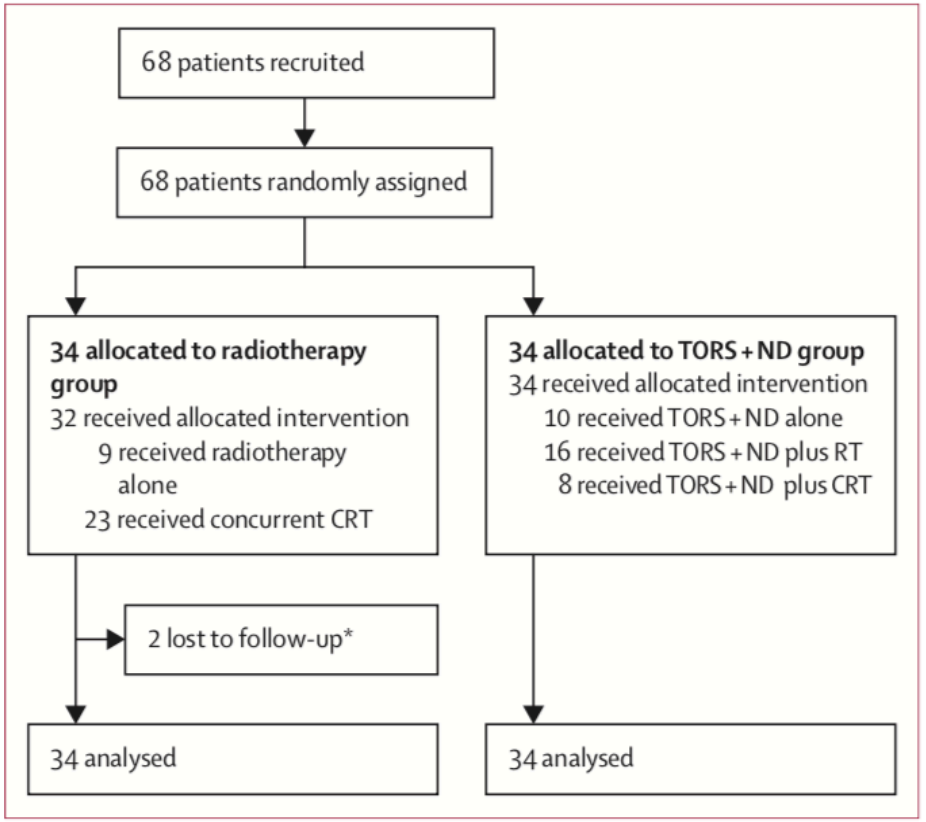
Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial

THE LANCET Oncology

	All patients (n=68)	RT group (n=34)	TORS + ND group (n=34)
Age, median (IQR)	58·5 (52·9–65·2)	60·0 (53·2–65·2)	58·1 (52·6–64·5)
Sex			
Male	59 (87%)	31 (91%)	28 (82%)
Female	9 (13%)	3 (9%)	6 (18%)
Smoking history	49 (72%)	28 (82%)	21 (62%)
>21 drinks per week	7/40 (18%)	1/18 (6%)	6/22 (27%)
Primary site			
Tonsil or tonsillar foss	50 (74%)	26 (76%)	24 (71%)
Base of tongue	18 (26%)	8 (24%)	10 (29%)
Clinical T stage			
T1	30 (44%)	13 (38%)	17 (50%)
T2	38 (56%)	21 (62%)	17 (50%)
Clinical N stage			
N0	21 (31%)	12 (35%)	9 (26%)
N1	12 (18%)	5 (15%)	7 (21%)
N2	35 (51%)	17 (50%)	18 (53%)
Baseline ECOG			
0	60 (88%)	30 (88%)	30 (88%)
1	8 (12%)	4 (12%)	4 (12%)
Baseline scan			
CT head, neck, and chest	40 (59%)	22 (65%)	18 (53%)
CT chest and MRI head and neck	6 (9%)	2 (6%)	4 (12%)
CT neck and chest	9 (13%)	4 (12%)	5 (15%)
PET and CT neck and chest	13 (19%)	6 (18%)	7 (21%)
p16 positive	60 (88%)	30 (88%)	30 (88%)
Radiotherapy	56 (82%)	32 (94%)	24 (71%)
Chemotherapy	31 (46%)	23 (68%)	8 (24%)
Chemotherapy regimen			
Cisplatin	24/31 (77%)	19/23 (83%)	5/8 (63%)
Carboplatin	6/31 (19%)	3/23 (13%)	3/8 (38%)
Cetuximab	1/31 (3%)	1/23 (4%)	0
Chemotherapy cycles, median (IQR)	3 (3–6)	3 (2–6)	6 (4·5–6)

Data are presented as number (%) unless otherwise stated. RT=radiotherapy. TORS + ND=transoral robotic surgery and neck dissection. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline and treatment characteristics**



End-poin primario:

- QoL correlata alla capacità deglutitoria a 1 anno

End-points secondari

- OS
- PFS

Nichols A.J. 2019

TORS plus neck dissection was not associated with better QOL.

Deintensificazione di terapia

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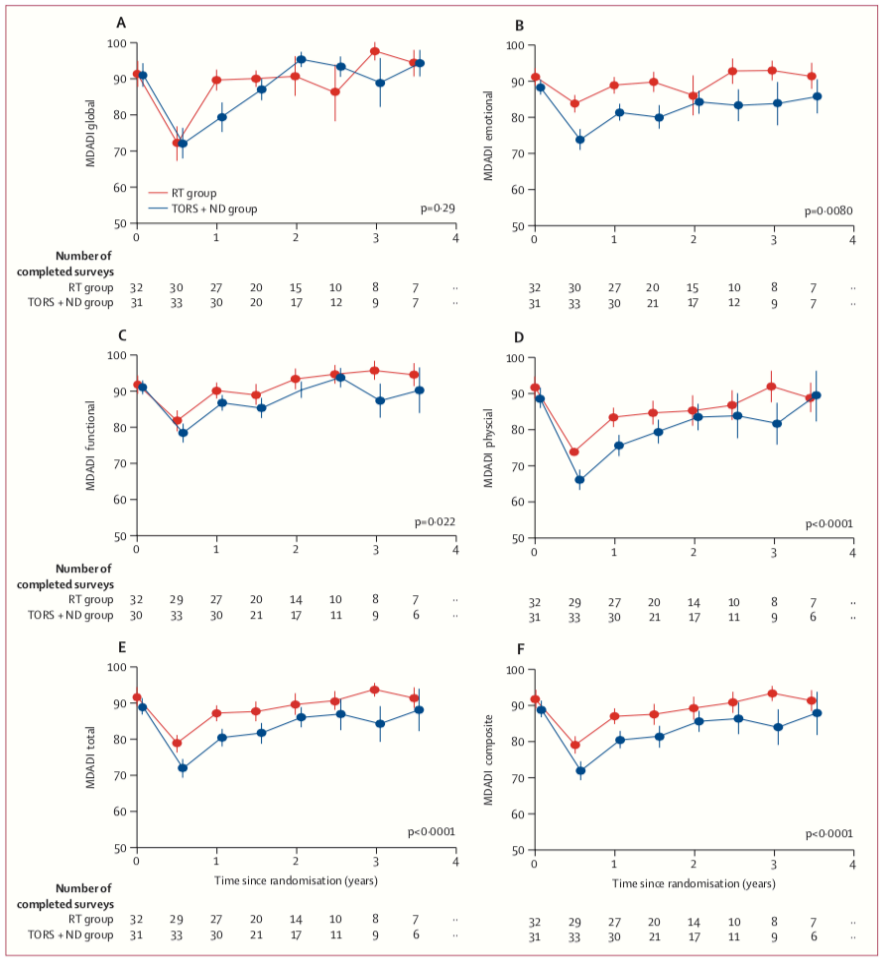

MDADI=MD Anderson Dysphagia Inventory

	1 year				Clinically meaningful decline*		
	RT group	TORS + ND group	Effect estimate (95% CI)	p value†	RT group	TORS + ND group	p value
Total (primary endpoint)	86·9 (11·4)	80·1 (13·0)	6·7 (0·2 to 13·2)	0·042	7/27 (26%)	11/27 (41%)	0·25
Global	89·6 (15·1)	79·3 (22·6)	10·3 (0·2 to 20·4)	0·046	6/27 (22%)	14/27 (52%)	0·024
Emotional	88·8 (12·0)	81·3 (12·5)	7·4 (0·9 to 14·0)	0·027	5/27 (19%)	13/27 (48%)	0·021
Functional	89·9 (11·5)	86·5 (12·0)	3·4 (−2·9 to 9·6)	0·28	7/27 (26%)	9/26 (35%)	0·49
Physical	83·1 (14·1)	75·3 (16·5)	7·9 (−0·3 to 16·0)	0·058	12/27 (44%)	16/27 (59%)	0·28
Composite (total score excluding global score)	86·7 (11·4)	80·2 (13·1)	6·5 (0·0 to 13·1)	0·049	6/27 (22%)	11/27 (41%)	0·14

Data are presented as mean (SD) unless otherwise stated. RT=radiotherapy. TORS + ND=transoral robotic surgery and neck dissection. *Defined as a decrease of at least 10 points. †p values adjusted for stratification by p16 status (post-hoc analysis): total (p=0·054), global (p=0·071), emotional (p=0·040), functional (p=0·29), physical (p=0·064), and composite (p=0·062).

Table 2: Quality-of-life scores at 1 year for the MD Anderson Dysphagia Inventory

* Lo scarto non ha soddisfatto la soglia prefissata (10 punti) per una differenza clinicamente significativa

Nichols A.J. 2019

TORS plus neck dissection was not associated with better QOL.

Deintensificazione di terapia

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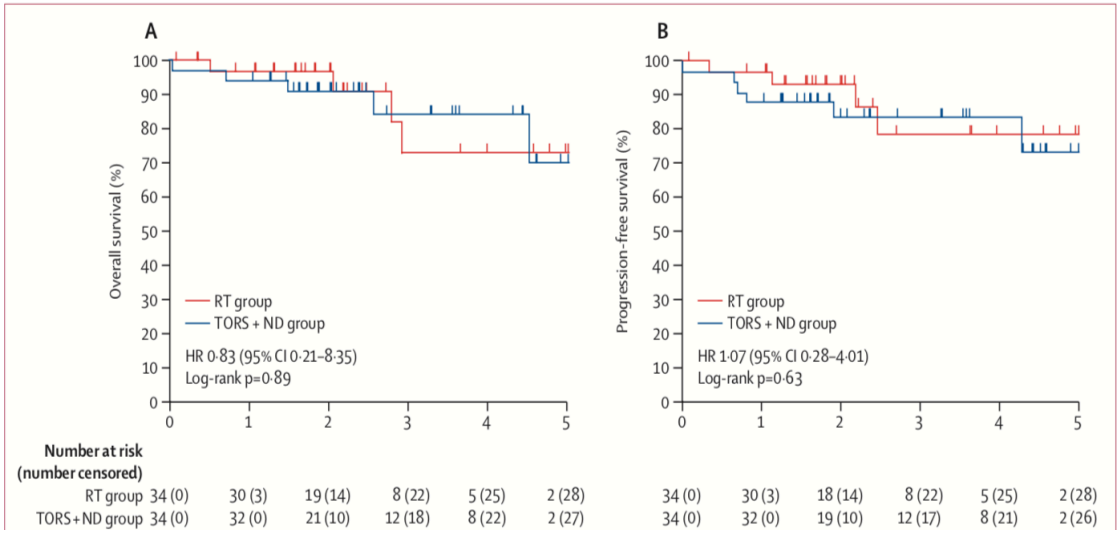

N. 4 sanguinamenti TORS:

- 2 grado 2
- 1 grado4
- 1 decesso

	Radiotherapy group (n=34)				TORS + ND group (n=34)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
p=0·004 Constipation*	9 (26%)	0	0	0	2 (6%)	0	0	0
p=0·037 Bleeding (oral cavity)	1 (3%)	0	0	0	4 (12%)	0	1 (3%)	1 (3%)
p=0·025 Neutropenia*	3 (9%)	2 (6%)	1 (3%)	0	0	0	0	0
p=0·030 Weakness (subjective)*	4 (12%)	0	0	0	11 (32%)	0	0	0
p=0·0055 Tinnitus*	11 (32%)	1 (3%)	0	0	2 (6%)	0	0	0
p=0·020 Trismus*	1 (3%)	0	0	0	8 (24%)	1 (3%)	0	0
p=0·028 Hearing loss (audiogram)*	7 (21%)	6 (18%)	0	0	5 (15%)	0	0	0

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Deintensificazione di terapia

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- Outcome clinici paragonabili nei due gruppi
- Molti dati derivanti dalle scale di tossicità sono a favore della Radiochemioterapia

- 4 sanguinamento di cui 1 mortale nel gruppo TORS

Nichols A.J. 2019

Associazione farmacologica

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma

Studio multicentrico randomizzato di fase 3

End point primario:

- recurrence-free survival,

End points secondario:

- all survival
- distant recurrence–free survival,
- locoregional recurrence–free survival,
- treatment response,
- treatment adherence,
- safety.

480 pz

IC(242 pz)
Cemcitabina+cisplatino$_{43}$
Gem 1g/mq gg 1-8 + CDPP 100 mg/mq
gg 1 ogni 3 settimane per 3 cicli

Radiochemioterapia
100 mg/mq gg 1-22-43

CCRT(238pz)
Cisplatino (CDDP) 100 mg/mq gg 1-22-43-

Radioterapia (IMRT)
CTV 1 64-66/70 Gy
CTV 2 60–62 Gy *30-33/frazioni*
CTV 3 54–56 Gy

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The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Induction Chemotherapy (N=242)	Standard Therapy (N=238)
Median age (range) — yr	46 (18–64)	45 (20–64)
Sex — no. (%)		
Male	182 (75.2)	164 (68.9)
Female	60 (24.8)	74 (31.1)
Karnofsky performance-status score†		
100	10 (4.1)	10 (4.2)
90	189 (78.1)	198 (83.2)
80	36 (14.9)	21 (8.8)
70	7 (2.9)	9 (3.8)
Tumor category — no. (%)‡		
T1	2 (0.8)	3 (1.3)
T2	16 (6.6)	16 (6.7)
T3	115 (47.5)	116 (48.7)
T4	109 (45.0)	103 (43.3)
Node category — no. (%)‡		
N1	114 (47.1)	106 (44.5)
N2	101 (41.7)	108 (45.4)
N3A	12 (5.0)	8 (3.4)
N3B	15 (6.2)	16 (6.7)
Disease stage — no. (%)‡		
III	111 (45.9)	120 (50.4)
IVA	104 (43.0)	94 (39.5)
IVB	27 (11.2)	24 (10.1)

- 96.7% ha completato i tre cicli di induzione

Compliance to concurrent cisplatin chemotherapy and radiotherapy

Variable	Induction Chemotherapy		Standard Therapy
Safety population*	239		237
Patients receiving concurrent cisplatin, no. (%)	234 (97.9)		237 (100)
Patients completing at least two cycles CC, no. (%)	220 (92.1)		233 (98.3)
Patients completing three cycles CC, no. (%)	93 (38.9)		177 (74.7)
Patients receiving concurrent cisplatin $\geq$ 200 mg/m^2, no. (%)	191 (79.9)	P<0,001	227 (95.8)
Patients receiving concurrent cisplatin 300 mg/m^2, no. (%)	63 (26.4)		140 (59.1)
Patients receiving RT, no. (%)	239 (100%)		237 (100%)
Patients completing RT, no. (%)	239 (100%)		235 (99.2%)

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Corrisponde to overall survival at 3 years that was 4.3 percentage points higher with induction chemotherapy than with standard therapy.

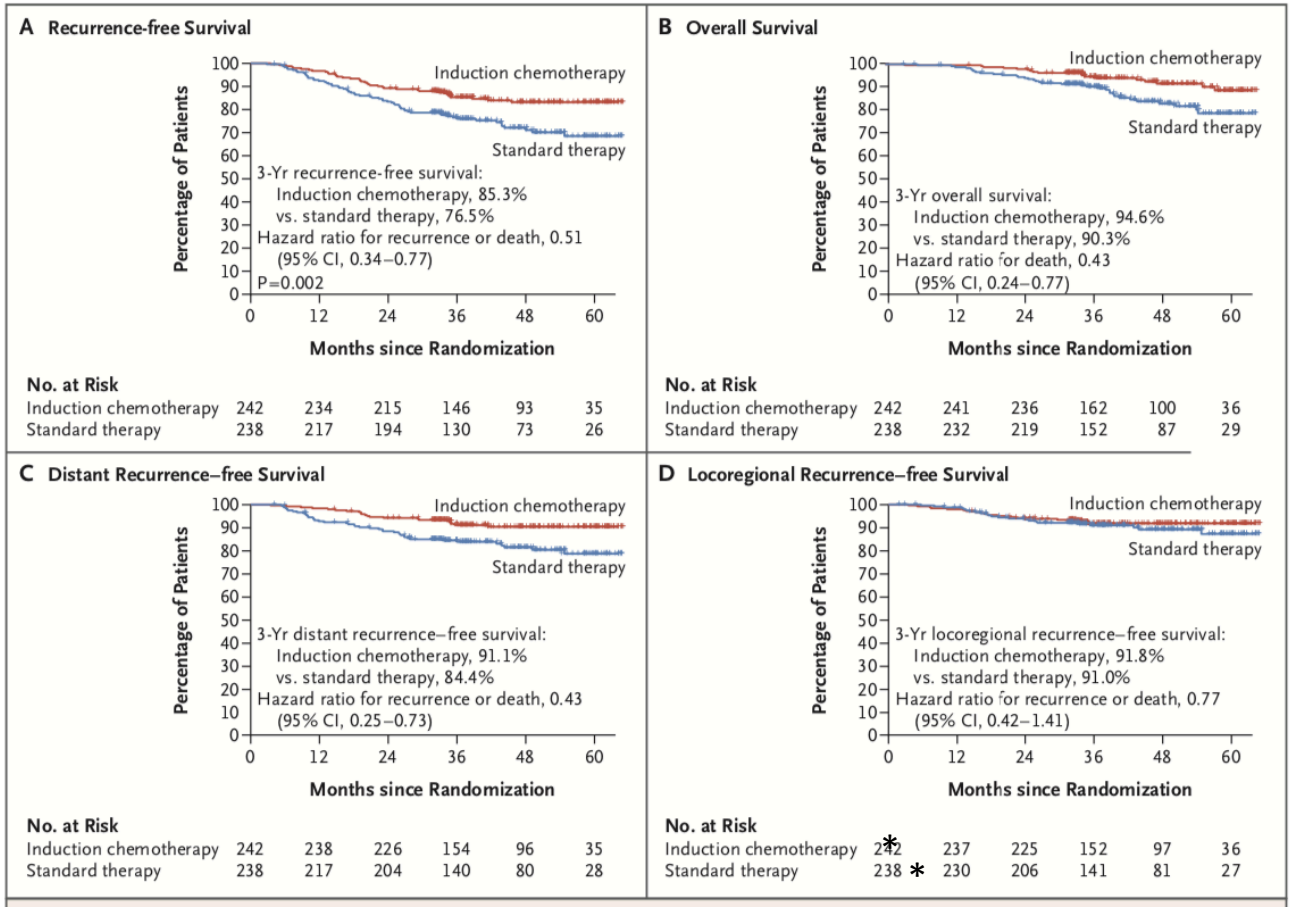

Table 2. Survival and Response to Treatment.*

Variable	Induction Chemotherapy (N=242)	Standard Therapy (N=238)	Hazard Ratio (95% CI)
Recurrence-free survival			
Recurrence or death — no. (%)	37 (15.3)	63 (26.5)	
Percentage of patients alive and without recurrence at 3 yr (95% CI)	85.3 (80.0–89.3)	76.5 (70.4–81.5)	0.51 (0.34–0.77)
Overall survival			
Death — no. (%)	18 (7.4)	35 (14.7)	
Percentage of patients alive at 3 yr (95% CI)	94.6 (90.6–96.9)	90.3 (85.6–93.5)	0.43 (0.24–0.77)
Distant recurrence–free survival			
Distant metastasis or death — no. (%)	23 (9.5)	40 (16.8)	
Percentage of patients alive and without distant metastasis at 3 yr (95% CI)	91.1 (86.4–94.2)	84.4 (79.1–88.5)	0.43 (0.25–0.73)
Locoregional recurrence–free survival			
Locoregional recurrence or death — no. (%)	17 (7.0)	22 (9.2)	
Percentage of patients alive and without locoregional recurrence at 3 yr (95% CI)	91.8 (87.3–94.7)	91.0 (86.2–94.0)	0.77 (0.42–1.41)
Response to induction chemotherapy†			
Complete response — no./total no. (%)	24/239 (10.0)	—	
Partial response — no./total no. (%)	202/239 (84.5)	—	
Stable disease — no./total no. (%)	10/239 (4.2)	—	
Progressive disease — no./total no. (%)	3/239 (1.3)	—	
Response to whole treatment — no. (%)			
Complete response	235 (97.1)	230 (96.6)	
Partial response	2 (0.8)	5 (2.1)	
Progressive disease	1 (0.4)	1 (0.4)	
Could not be assessed	4 (1.7)	2 (0.8)	

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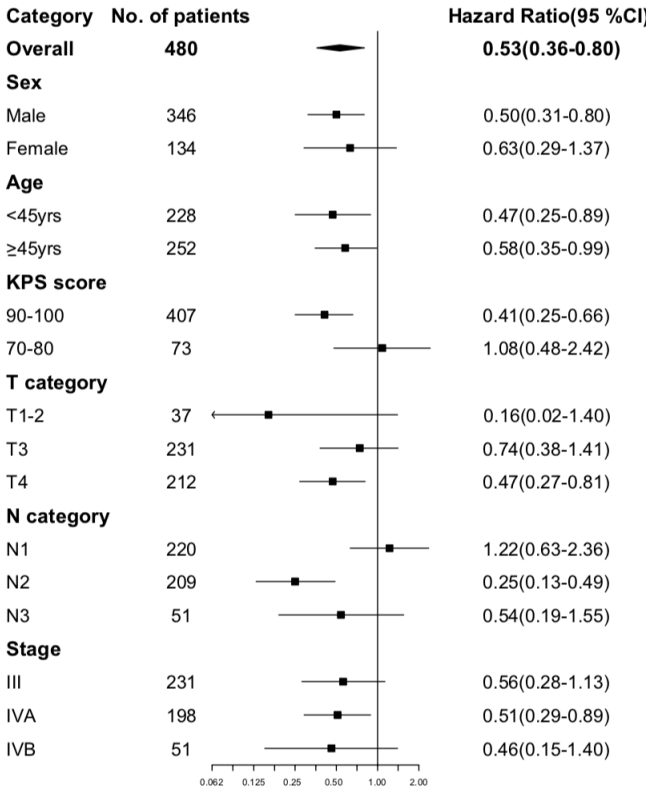

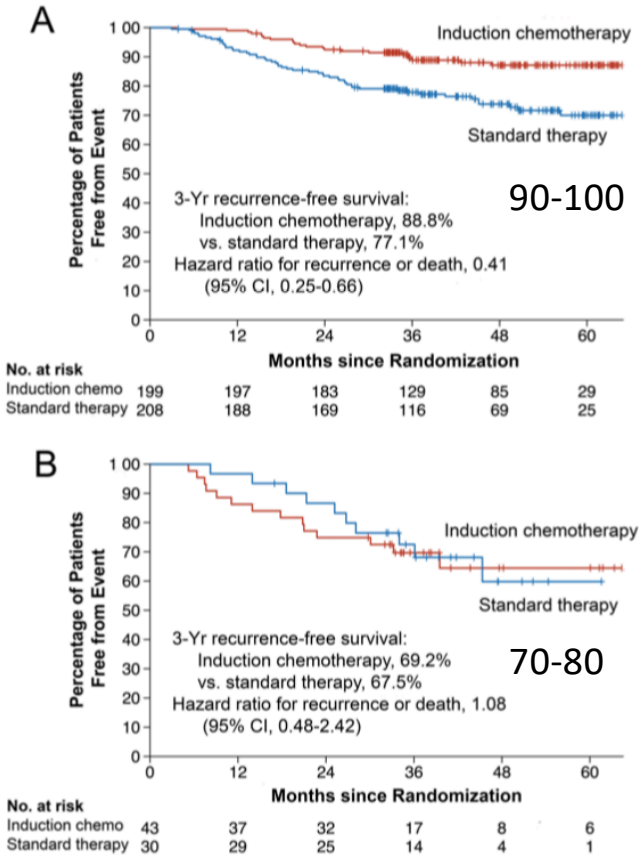

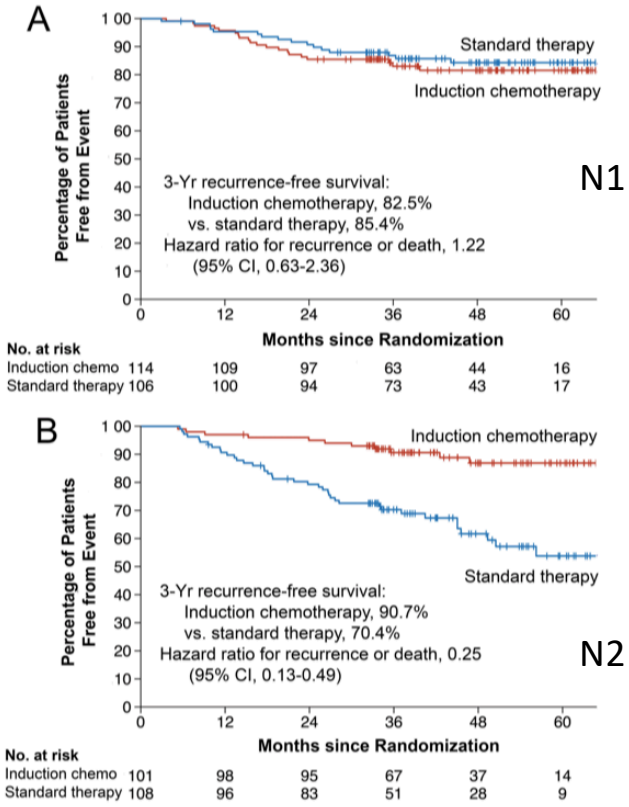

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Event	Induction Chemotherapy (N=239)		Standard Therapy (N=237)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
	number of patients with event (percent)			
Any acute adverse event	58 (24.3)	181 (75.7)	105 (44.3)	132 (55.7)
Leukopenia	168 (70.3)	63 (26.4)	178 (75.1)	48 (20.3)
Neutropenia	135 (56.5)	67 (28.0)	147 (62.0)	25 (10.5)
Febrile neutropenia	0	1 (0.4)	0	0
Neutropenic infection	0	0	0	0
Anemia	178 (74.5)	23 (9.6)	157 (66.2)	2 (0.8)
Thrombocytopenia	91 (38.1)	27 (11.3)	54 (22.8)	3 (1.3)
Mucositis	139 (58.2)	69 (28.9)	154 (65.0)	76 (32.1)
Vomiting	85 (35.6)	54 (22.6)	52 (21.9)	33 (13.9)
Nausea	176 (73.6)	55 (23.0)	188 (79.3)	33 (13.9)
Dry mouth	168 (70.3)	12 (5.0)	166 (70.0)	6 (2.5)
Diarrhea	18 (7.5)	6 (2.5)	15 (6.3)	4 (1.7)
Dermatitis	141 (59.0)	5 (2.1)	152 (64.1)	9 (3.8)
Weight loss	148 (61.9)	5 (2.1)	145 (61.2)	4 (1.7)
Deafness or otitis	172 (72.0)	0	178 (75.1)	0
Nephrotoxic event	46 (19.2)	6 (2.5)	27 (11.4)	1 (0.4)
Hepatotoxic event	68 (28.5)	6 (2.5)	53 (22.4)	0
Any late adverse event	203 (84.9)	22 (9.2)	208 (87.8)	27 (11.4)
Symptomatic temporal-lobe necrosis	14 (5.9)	0	19 (8.0)	2 (0.8)
Cranial neuropathy	6 (2.5)	2 (0.8)	8 (3.4)	2 (0.8)
Peripheral neuropathy	21 (8.8)	3 (1.3)	4 (1.7)	0
Eye damage	3 (1.3)	0	2 (0.8)	0
Deafness or otitis	60 (25.1)	13 (5.4)	65 (27.4)	16 (6.8)
Dry mouth	179 (74.9)	7 (2.9)	190 (80.2)	5 (2.1)
Neck tissue damage	62 (25.9)	1 (0.4)	74 (31.2)	3 (1.3)
Bone necrosis	4 (1.7)	0	6 (2.5)	2 (0.8)
Trismus	7 (2.9)	0	9 (3.8)	0
Nephrotoxic event	7 (2.9)	0	5 (2.1)	0

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Table S7: Comparison of acute adverse events of concurrent chemoradiotherapy with induction GP versus induction TPF

Maximum grade per patient during treatment	GP			TPF *		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Induction phase						
Any	33.5%	5.4%	0	27.6%	15.1%	0.4%
Hematologic						
Neutropenia	17.2%	3.3%	0	20.5%	14.6%	0.4%
Febrile neutropenia	0	0	0	1.3%	0.4%	0
Neutropenic infection	0	0	0	0.4%	0	0.4%
Leukopenia	10.0%	0.8%	0	23.0%	4.2%	0
Anemia	1.2%	0.4%	0	0.4%	0	0
Thrombocytopenia	4.6%	0.8%	0	0	0	0
Non-hematologic						
Nausea	7.9%	1.3%	0	4.2%	0	0
Vomiting	10.0%	0.8%	0	3.4%	0	0
Diarrhea	0.4	0	0	8.0%	0	0
Stomatitis (mucositis)	0.8	0	0	5.4%	0.8%	0
Hepatoxicity	2.1%	0	0	2.5%	0	
Renal toxicity	1.3%	0	0	0	0	0
Allergic reaction	0.4%	0	0	0.8%	0	0
Concurrent Phase						
Any	62.3%	2.9%	0	56.5%	2.9%	0
Hematologic						
Leukopenia	19.7%	0	0	18.4%	1.3%	0
Neutropenia	11.7%	0	0	11.3%	1.3%	0
Febrile neutropenia	0	0	0	0.8%	0.4%	0
Anemia	7.5%	0.4%	0	1.7%	0	0
Thrombocytopenia	5.9%	1.3%	0	2.1%	0.4%	0
Non-hematological						
Mucositis	27.6%	0.4%	0	38.5%	0	0
Vomiting	16.7%	0.8%	0	20.5%	1.7%	0
Nausea	17.2%	0.8%	0	18.8%	1.7%	0
Dry mouth	5.0%	0	0	5.4%	0	0
Diarrhea	2.1%	0	0	0	0	0
Dermatitis	2.1%	0	0	3.3%	0.4%	0
Weight loss	2.1%	0	0	1.3%	0	0
Renal toxicity	1.3%	0	0	0	0	0
Hepatoxicity	0.4%	0	0	0.4%	0	0

Zhang Y. 2019 Sun Y. 2016

Associazione farmacologica

Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: Long-term results of phase 3 randomized controlled trial

Studio multicentrico randomizzato di fase 3

End point primario: failure-free survival (FFS)

End points secondario:

Overall survival (OS)
distant failure–free survival (D-FFS)
locoregional failure–free survival (LR-FFS)
Response rates
toxicity profile
compliance to treatment
quality of life.

480 pz

IC(n = 241)
TPF

Docetaxel 60 mg/m2 gg1, CDPP 60 mg/m2 gg1, 5-FU
600 mg/m2 gg 1-5 every 3 weeks per 3 cicli

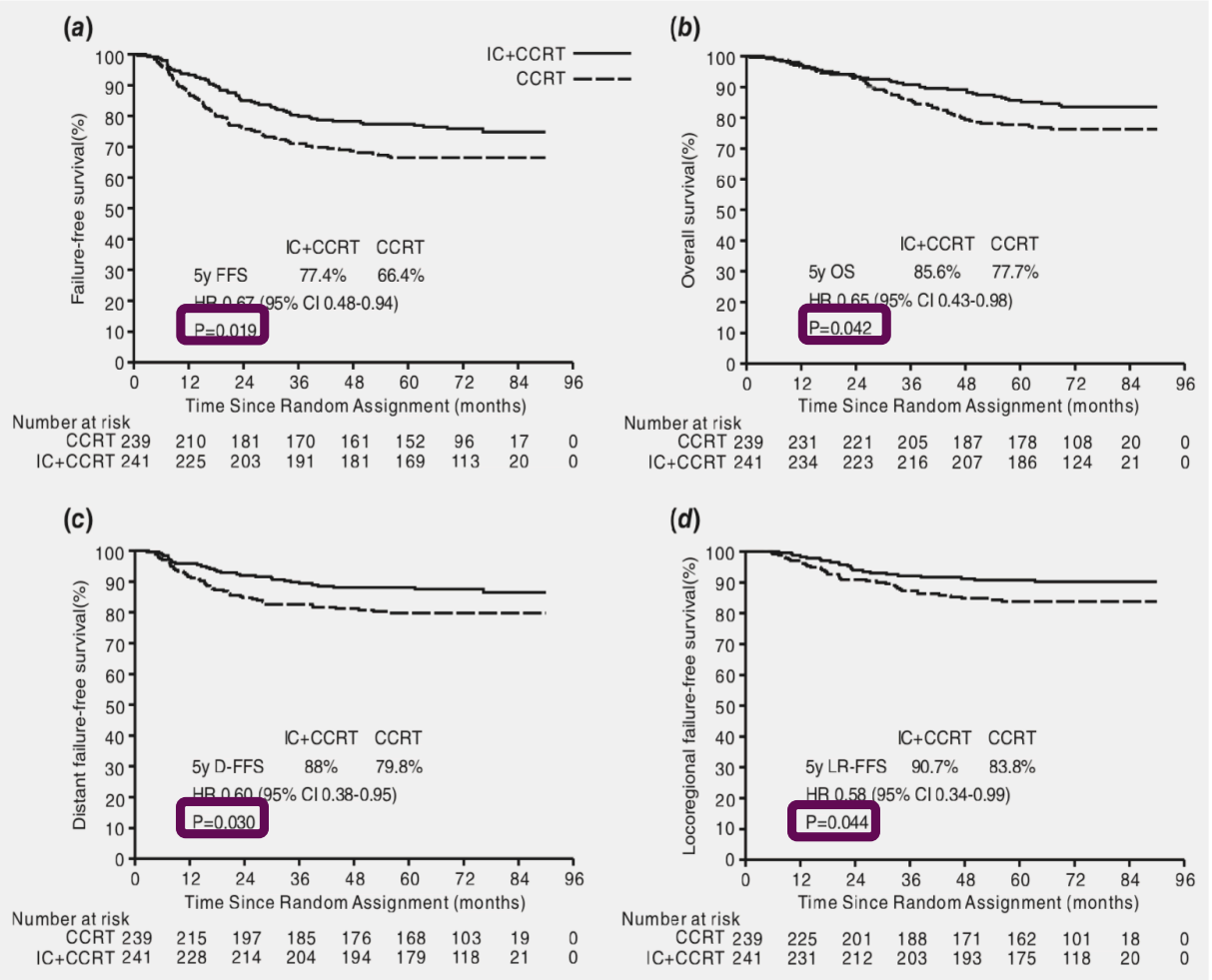
CCRT
100 mg/mq gg 1-22-43

CCRT (n = 239)
100 mg/mq gg 1-22-43

Li W.F. 2019

Associazione farmacologica

Characteristic	IC plus CCRT group (n = 241)	CCRT group (n = 239)	p Value[1]
Age, years			0.414[2]
Median	42	44	
Rang	18–59	18–59	
Sex, No. (%)			0.060
Male	193 (80.1)	174 (72.8)	
Female	48 (19.9)	65 (27.2)	
Karnofsky score, No. (%)			0.536
90–100	217 (90)	211 (88.3)	
70–80	24 (10)	28 (11.7)	
T category, No. (%)			0.122
T1	15 (6.2)	6 (2.5)	
T2	27 (11.2)	19 (7.9)	
T3	112 (46.5)	121 (50.6)	
T4	87 (36.1)	93 (38.9)	
N category, No. (%)			0.307
N1	97 (40.2)	107 (44.8)	
N2	105 (43.6)	106 (44.4)	
N3a	13 (5.4)	11 (4.6)	
N3b	26 (10.8)	15 (6.3)	
Stage, No. (%)			0.226
III	129 (53.5)	133 (55.6)	
IVA	73 (30.3)	80 (33.5)	
IVB	39 (16.2)	26 (10.9)	



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Associazione farmacologica

Failure-free survival (a) and overall survival (b)

(a)

Subgroup	IC+CCRT (events/total)	CCRT (events/total)	HR (95% CI)
Overall	58/241	80/239	0.67 (0.48, 0.94)
Sex			
Female	9/48	18/65	0.65 (0.29, 1.46)
Male	49/193	62/174	0.65 (0.45, 0.95)
Age			
< 45yrs	30/136	45/126	0.55 (0.34, 0.87)
≥ 45yrs	28/105	35/113	0.85 (0.52, 1.40)
KPS score			
90-100	52/217	68/211	0.69 (0.48, 0.99)
70-80	6/24	12/28	0.53 (0.20, 1.42)
T category			
T1-2	8/42	9/25	0.47 (0.18, 1.22)
T3	22/112	29/121	0.79 (0.45, 1.37)
T4	28/87	42/93	0.63 (0.39, 1.02)
N category			
N1	16/97	33/107	0.48 (0.27, 0.88)
N2	30/105	37/106	0.76 (0.47, 1.22)
N3	12/39	10/26	0.74 (0.32, 1.72)
Stage			
III	25/129	32/133	0.77 (0.46, 1.31)
IVA	21/73	38/80	0.51 (0.30, 0.87)
IVB	12/39	10/26	0.74 (0.32, 1.72)
LDH			
< 170 U/L	19/100	31/114	0.65 (0.37, 1.15)
≥ 170 U/L	37/132	48/114	0.60 (0.39, 0.93)
EBV DNA			
< 6000 copies/mL	9/52	16/60	0.51 (0.22, 1.15)
≥ 6000 copies/mL	13/58	28/63	0.45 (0.23, 0.87)

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(b)

Subgroup	IC+CCRT (events/total)	CCRT (events/total)	HR (95% CI)
Overall	38/241	56/239	**0.65 (0.43, 0.98)**
Sex			
Female	5/48	12/65	**0.56 (0.20, 1.58)**
Male	33/193	44/174	**0.65 (0.42, 1.02)**
Age			
< 45yrs	19/136	30/126	**0.55 (0.31, 0.98)**
≥ 45yrs	19/105	26/113	**0.79 (0.44, 1.43)**
KPS score			
90-100	32/217	47/211	**0.64 (0.41, 1.00)**
70-80	6/24	9/28	**0.82 (0.29, 2.32)**
T category			
T1-2	7/42	9/25	**0.43 (0.16, 1.16)**
T3	12/112	18/121	**0.71 (0.34, 1.47)**
T4	19/87	29/93	**0.68 (0.38, 1.21)**
N category			
N1	9/97	20/107	**0.46 (0.21, 1.01)**
N2	22/105	26/106	**0.85 (0.48, 1.49)**
N3	7/39	10/26	**0.46 (0.17, 1.20)**
Stage			
III	16/129	21/133	**0.77 (0.40, 1.48)**
IVA	15/73	25/80	**0.62 (0.33, 1.18)**
IVB	7/39	10/26	**0.49 (0.17, 1.20)**
LDH			
< 170 U/L	10/100	21/114	**0.52 (0.25, 1.11)**
≥ 170 U/L	26/132	34/114	**0.64 (0.38, 1.06)**
EBV DNA			
< 6000 copies/mL	5/52	10/60	**0.46 (0.16, 1.35)**
≥ 6000 copies/mL	10/58	20/63	**0.52 (0.24, 1.10)**

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Table 3. Adverse events

Maximum-grade acute adverse events during treatment	IC plus CCRT group (n = 239) Grade 3 No. (%)	IC plus CCRT group (n = 239) Grade 4 No. (%)	CCRT group (n = 238) Grade 3 No. (%)	CCRT group (n = 238) Grade 4 No. (%)	p Value for grade 3 adverse events[1]	p Value for grade 4 adverse events[1]
Any	132 (55.2)	42 (17.6)	125 (52.5)	3 (1.3)	0.553	<0.001
Hematologic						
Neutropenia	64 (26.8)	37 (15.5)	16 (6.7)	1 (0.4)	<0.001	<0.001
Febrile neutropenia	5 (2.1)	2 (0.8)	0	0	0.061	0.499
Neutropenic infection	1 (0.4)	0	0	0	1.000	-
Leukopenia	86 (36)	12 (5)	40 (16.8)	1 (0.4)	<0.001	0.002
Anemia	4 (1.7)	0	5 (2.1)	0	0.751	-
Thrombocytopenia	5 (2.1)	1 (0.4)	2 (0.8)	0	0.450	1.000
Nonhematologic						
Stomatitis (mucositis)	96 (40.2)	2 (0.8)	82 (34.5)	2 (0.8)	0.197	1.000
Vomiting	52 (21.8)	4 (1.7)	45 (18.9)	0	0.439	0.123
Nausea	46 (19.2)	4 (1.7)	40 (16.8)	0	0.488	0.123
Dry mouth	13 (5.4)	-	13 (5.5)	-	0.991	-
Dermatitis	8 (3.3)	1 (0.4)	10 (4.2)	0	0.624	1.000
Esophagitis, dysphagia, or odynophagia	5 (2.1)	0	9 (3.8)	0	0.274	-
Hepatoxicity	7 (2.9)	0	2 (0.8)	0	0.176	-
Allergic reaction	2 (0.8)	0	0	0	0.499	-
Maximum-grade late adverse events	Grade 1–2 No. (%)	Grade 3–4 No. (%)	Grade 1–2 No. (%)	Grade 3–4 No. (%)	p Value for grade 1–2 adverse events[1]	p Value for grade 3–4 adverse events[1]
Any	214 (89.5)	21 (8.8)	221 (92.9)	22 (9.2)	0.201	0.862
Symptomatic temporal lobe necrosis	19 (7.9)	0	23 (9.7)	0	0.509	-
Cranial neuropathy	5 (2.1)	3 (1.3)	6 (2.5)	4 (1.7)	0.755	0.724
Peripheral neuropathy	8 (3.3)	1 (0.4)	4 (1.7)	0	0.245	1.000
Eye damage	1 (0.4)	0	4 (1.7)	0	0.216	-
Ear (deafness/otitis)	80 (33.5)	16 (6.7)	88 (37.0)	15 (6.3)	0.423	0.862
Dry mouth	195 (81.6)	4 (1.7)	204 (85.7)	2 (0.8)	0.223	0.686
Neck tissue damage	102 (42.7)	0	113 (47.5)	0	0.292	-
Bone necrosis	6 (2.5)	1 (0.4)	13 (5.5)	1 (0.4)	0.099	1.000
Trismus	13 (5.4)	0	13 (5.5)	0	0.991	-

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Associazione farmacologica

Entrambi gli schemi di terapia con induzione mostrano miglioramento degli outcome clinici.

- **Gemcitabina e Cisplatino**: migliore recurrence free survival 85.3 vs 76.5 rispetto alla CRT.
  Questa differenza corrisponde ad un aumento della sopravvivenza a 3 aa di 4.3 punti percentuale.
- **TPF**= miglior FFS, OS, DFFS e LFFS
- Per entrambi gli schemi la tossicità è elevata

Data la scarsità di dati comparativi, la scelta di un regime di chemioterapia di induzione a base di gemcitabina o a base di taxani potrebbe essere fatta sulla base degli effetti tossici attesi abbinati allo stato del paziente in relazione alle condizioni preesistenti alla terapia

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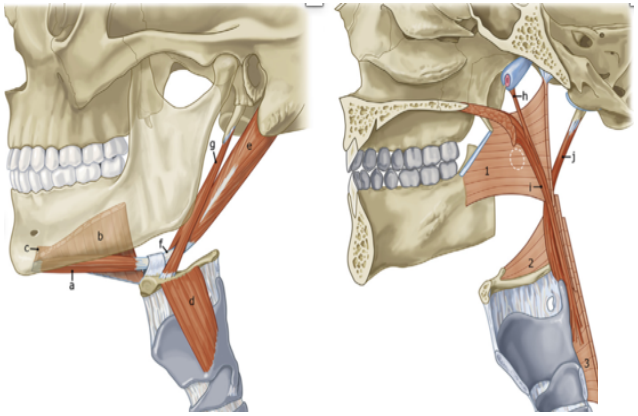
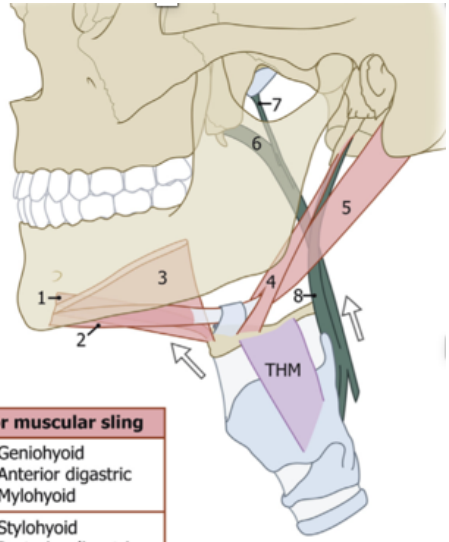
Contornazione

Functional Swallowing Units (FSUs) as organs-at-risk for radiotherapy. PART 1: Physiology and anatomy

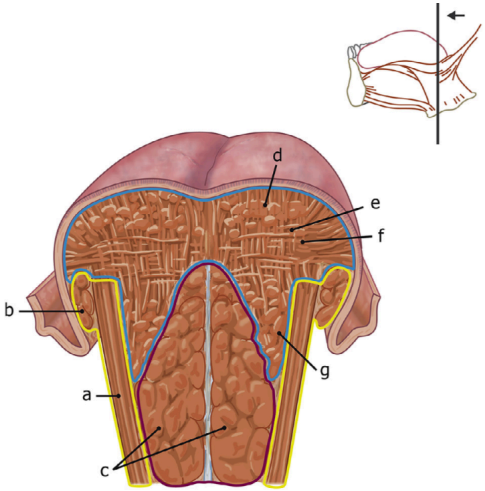




Anterior muscular sling	
FOM	1. Geniohyoid 2. Anterior digastric 3. Mylohyoid
PDS	4. Stylohyoid 5. Posterior digastric
Posterior muscular sling	
LPM	6. Palatopharyngeus 7. Salpingopharyngeus 8. Stylopharyngeus

3FSUs: 3 gruppi di muscoli:

- elevano l'osso ioide e la laringe(HLE)
- retraggono la base lingua(TBR)
- Garantiscono il movimento della lingua



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Contornazione

Functional Swallowing Units (FSUs) as organs-at-risk for radiotherapy. PART 2: Advanced delineation guidelines for FSUs

Table 1
Overview of all FSUs and their corresponding anatomic borders.

FSU involved in HLE	Anatomical border					
	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Floor of mouth FOM	Free edges of mylohyoids	Caudal edge of anterior digastric	Caudally: platysma Cranially: posterior border of level 1a/mandible	Hyoid/tongue muscles/posterior edges of mylohyoids (anterior border of submandibular glands)	Lateral edge of anterior digastric/ lateral edge of mylohyoids (medial border of level 1b)	Not defined
Thyrohyoid muscles THM	Caudal edge of hyoid	Slice where lamina of thyroid cartilage appears	Anterior end of the muscle reaching laryngeal prominence	Posterior end of the muscle (oblique line of the thyroid)	Platysma	Thyroid cartilage
Posterior digastric/ stylohyoid muscles complex PDS	Mastoid notch of temporal bone	*Tendon intermediate* medially to submandibular gland (cranial tip of grater cornu of hyoid appears)	Anterior end of stylohyoid or posterior digastric	Posterior end of posterior digastric	Posterior part of sternocleidomastoideus, deep lobe of parotid gland	Cranially: transversal process of C1, jugular vein lateral border of level 2 Caudally: hyoglossus muscle (HSG)
Longitudinal pharyngeal muscles LPM	Torus tubarius (left and right)/ first slice where hard palate appears	The last slice where posterior pharyngeal folds are visible	Cranially: anterior edge of torus tubarius and soft palate Caudally: anterior edge of posterior pharyngeal folds	Posterior edge of soft palate and posterior pharyngeal folds/superior PCM	Lateral edge of torus tubarius/ superior PCM	Pharyngeal lumen or not defined
FSU involved in TBR/ Tongue motion	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Hyoglossus/ styloglossus muscles complex HSG	One slice under the point where styloglossus appears as separate muscle not connected with the body of the tongue	Lateral part (greater cornu) of hyoid	Caudally: anterior end of hyoglossus Cranially: anterior edge of styloglossus	Caudally: posterior edge of hyoglossus Cranially: posterior edge of styloglossus (lingual part)	Caudally: PDS (*tendon intermediate* of digastric muscle)/submandibular gland/ mylohyoid Cranially: mylohyoid/mandible	Caudally: pharyngeal lumen/ BOT Cranially: ITM (inferior longitudinal muscle)/BOT
Genioglossus muscles GGS	Cranial end of septum linguae/ ITM	Caudal end of septum linguae just above hyoid	Caudally: posterior border of FOM Cranially: apex of the tongue	Anterior border of BOT	Caudally: anterior ends of hyoglossus muscles (HSG) Cranially: ITM (inferior longitudinal muscles)	Not defined
Intrinsic tongue muscles ITM	The last slice where the body of the tongue is visible	The first slice where the inferior longitudinal muscles become visible (between GGS and HSG)	Anterior edge of the body of the tongue	BOT/posterior edge of the body of the tongue	Caudally: medial border of HSG Cranially: lateral edge of the body of the tongue	Lateral edge of GGS or not defined

HLE-hyolaryngeal elevation, TBR-tongue base retraction; BOT-base of tongue.

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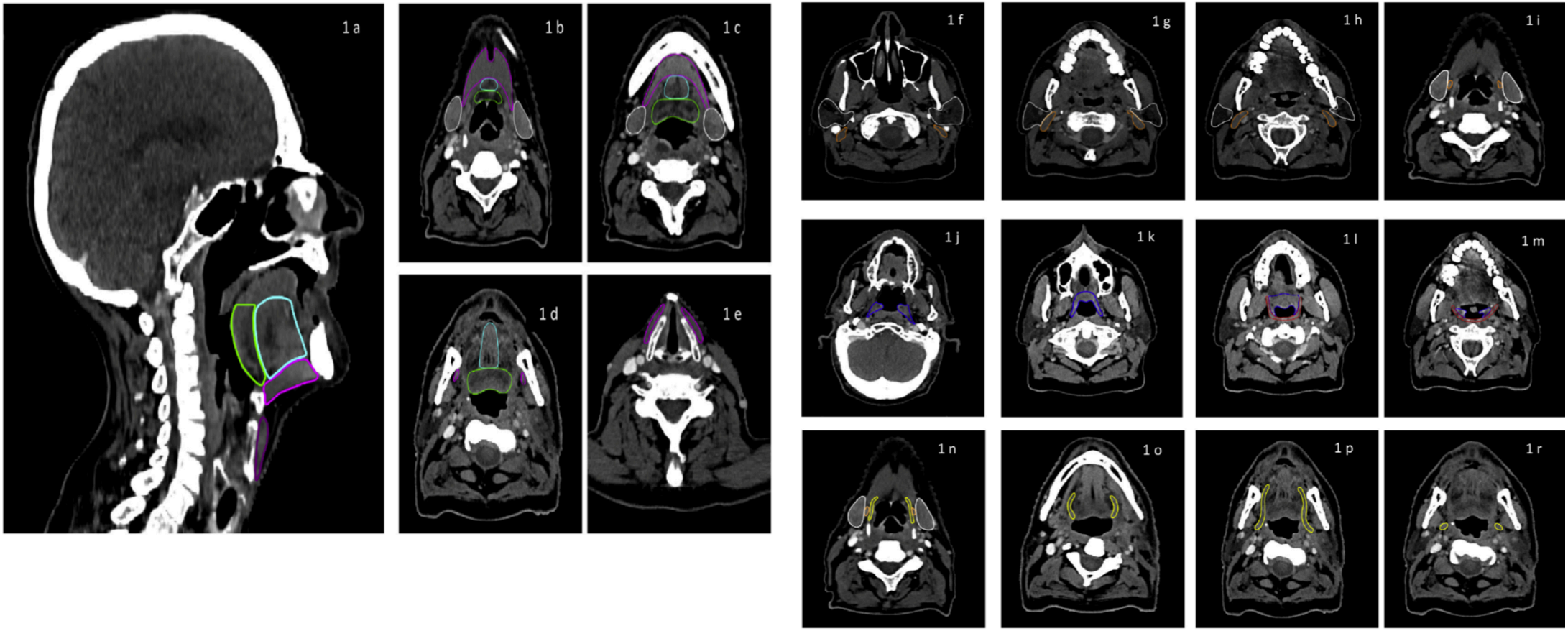
Contornazione

Functional Swallowing Units (FSUs) as organs-at-risk for radiotherapy. PART 2: Advanced delineation guidelines for FSUs



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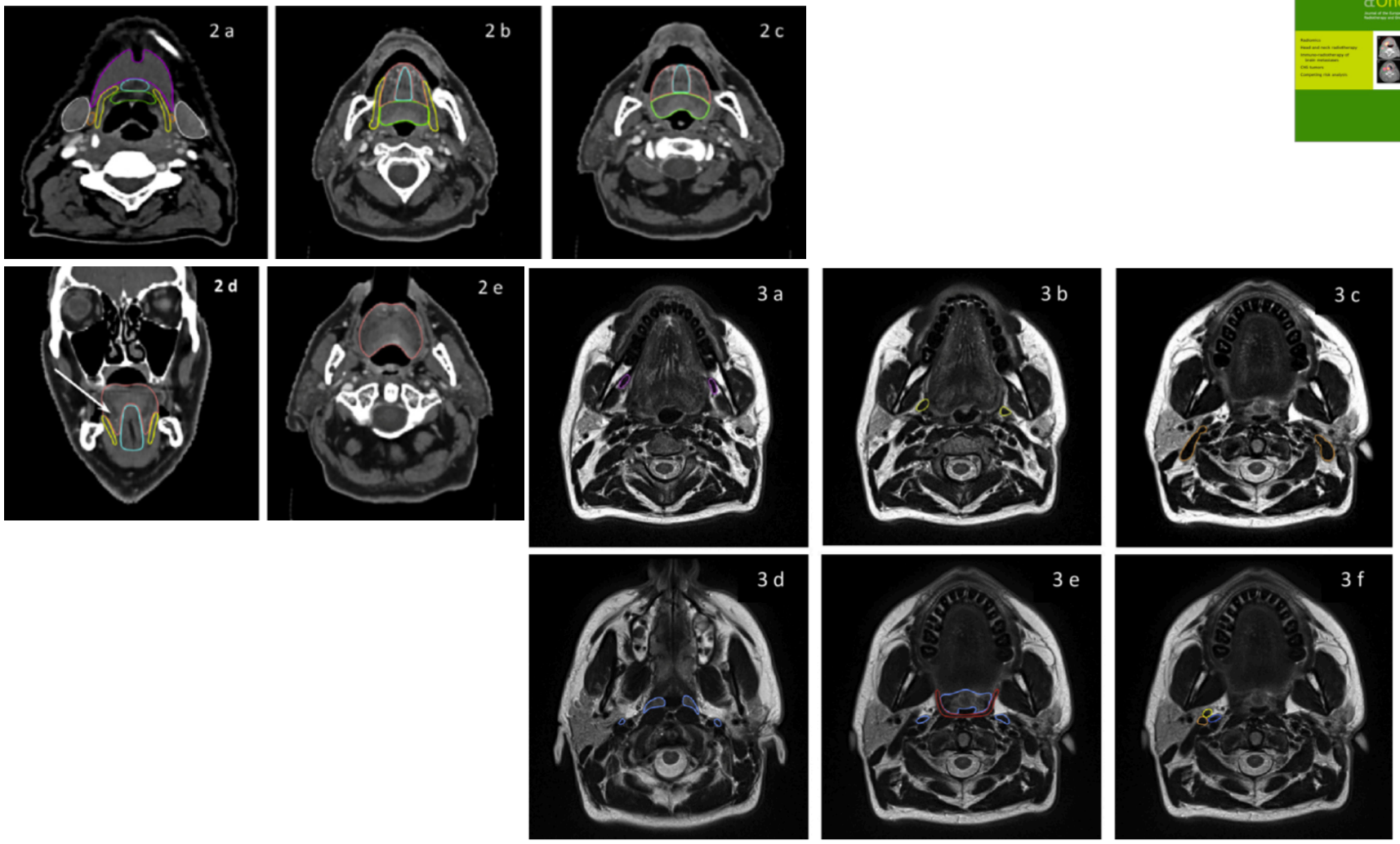

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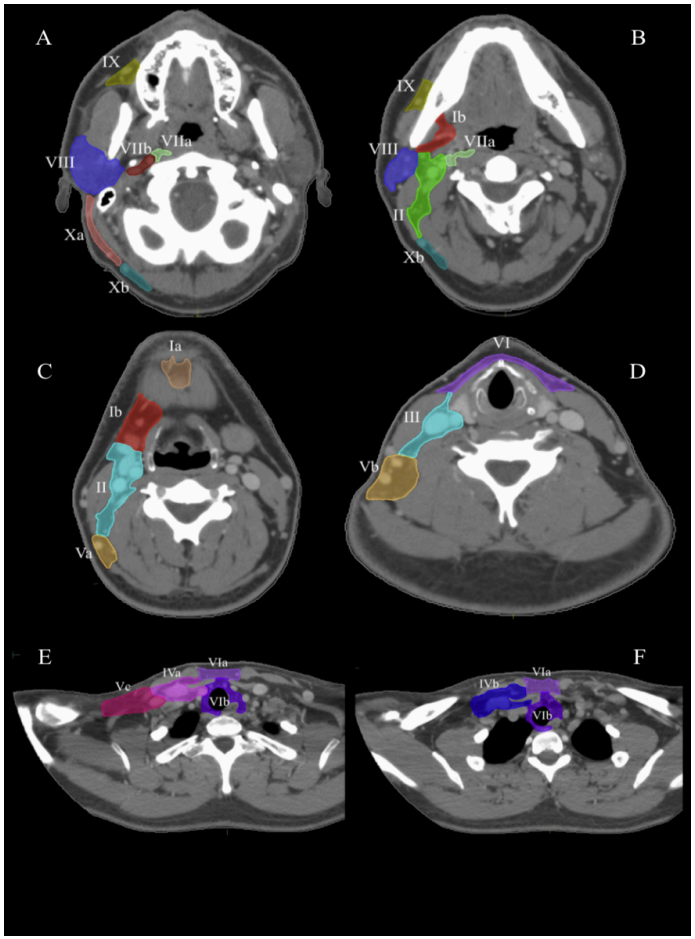
Contornazione

Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update

Raccomandazioni per i livelli linfonodali da includere sia per N+ che per N- in base alla sottosede anatomica di localizzazione della malattia

8th edition
UICC/AJCC TNM



Robbins' classification

Livelli:

- Ia(suttomentonieri)
- Ib (suttomandibolari)
- II (giugulari sup)
- III (giugulari medi)
- IVa (giugulari inferiori)
- IVb (sovraclaveari mediali)
- Va and Vb (del triangolo posteriore sup. ed inf.)
- Vc (sovraclaveari laterali),
- VIa (giugulari ant)
- VIb (prelaringei, pretracheali, paratracheali)
- VIIa (retrofaringei)
- VIIb (retro-stiloidei)
- VIII (parotidei)
- IX (buccofaciali)
- Xa (retroauricolari and subauriculari)
- Xb (occipitali).

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Contornazione

Selection of low risk nodal target volumes for nasopharyngeal cancers (according to recent international guidelines [68]).

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck
N0	II-V, VIIa, VIIb[1]	II-V, VIIa, VIIb[1]
N1, N2	II-V, VIIa, VIIb[1,2,3,4]	II-V, VIIa, VIIb[1,2,3,4]
N3	Ib-IVb, Va,b,c, VIIa, VIIb	Ib-IVb, Va,b,c, VIIa, VIIb

Selection of low risk nodal target volumes for oral cavity cancers.

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck[1]
N0-1 (in level I, II, or III)	I, II[2], III, +IVa[3], +IX[4]	I, II[2], III, +IVa[3]
N2a-b	I, II, III, IVa[5], Va,b[6,7], +IX[4]	I, II[2], III, +IVa[3]
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	I, II, III, IVa[5], Va,b, +VIIb[7], +IX[4]	I, II, III, +IVa[3]

8th edition UICC/AJCC TNM

Selection of low risk nodal target volumes for nasal and paranasal sinuses cancers.

Localization	Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
		Ipsilateral Neck	Contralateral Neck[1]
Maxillary sinus	N0[2]	Ib-III, VIIa, IX	Ib-III, VIIa
	N1-N3	Ib-V[3,4], VIIa, IX	Ib-V[3,4], VIIa
Ethmoid sinus	N0	_[5]	_[5]
	N1-N3	Ib-V[3,4], VIIa	Ib-V[3,4], VIIa
Nasal cavity	N0[2]	Ib-III, VIIa, +IX for anterior third nasal cavity involvement	Ib-III, VIIa
	N1-N3	Ib-V[3,4], VIIa, +IX for anterior third nasal cavity involvement	Ib-V[3,4], VIIa

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Contornazione

Selection of low risk nodal target volumes for hypopharyngeal cancers.

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck[1]
N0	II, III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for apex of piriform sinus, postcricoïd and/or esophageal extension	II[2], III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for esophageal extension
N1, N2a-b	Ib, II, III, IVa[3], Va,b, +VIIa + VIIb[4] + VI for apex of piriform sinus, postcricoïd, esophageal extension, and/or possibly N2b	II[2], III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for esophageal extension
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IVa[3], Va,b, +VIIa + VIIb[4], +VI	II[2], III, IVa, +VIIa for posterior pharyngeal wall tumor + VI for esophageal extension

8th edition UICC/AJCC TNM

Selection of low risk nodal target volumes for laryngeal cancers (glottic T1 excluded).

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in the CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck
N0-1 (in level II, III, or IV)	II[1,2], III, IVa[3], +VI for transglottic or subglottic extension	II[1], III, IVa, +VI for transglottic or subglottic extension
N2a-b	II[2,3,4], III, IVa[3], Va,b, +VI for transglottic or subglottic extension	II[1], III, IVa, +VI for transglottic or subglottic extension
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IVa[3], Va,b, +VIIb[4] + VI	II[1], III, IVa, +VI for transglottic or subglottic extension

Selection of low risk nodal target volumes for p16+ and p16– oropharyngeal cancers.

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck[1]
N0-1 (in level II, III, or IV)	(Ib)[2], II, III, IVa[3], +VIIa for posterior pharyngeal wall tumor	II, III, IVa, +VIIa for posterior pharyngeal wall tumor
N2a-b	Ib, II, III, IVa[3], Va,b, +VIIa, +VIIb[4]	II, III, IVa, +VIIa for posterior pharyngeal wall tumor
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IVa, Va,b, +VIIa, +VIIb[4]	II, III, IVa, +VIIa for posterior pharyngeal wall tumor

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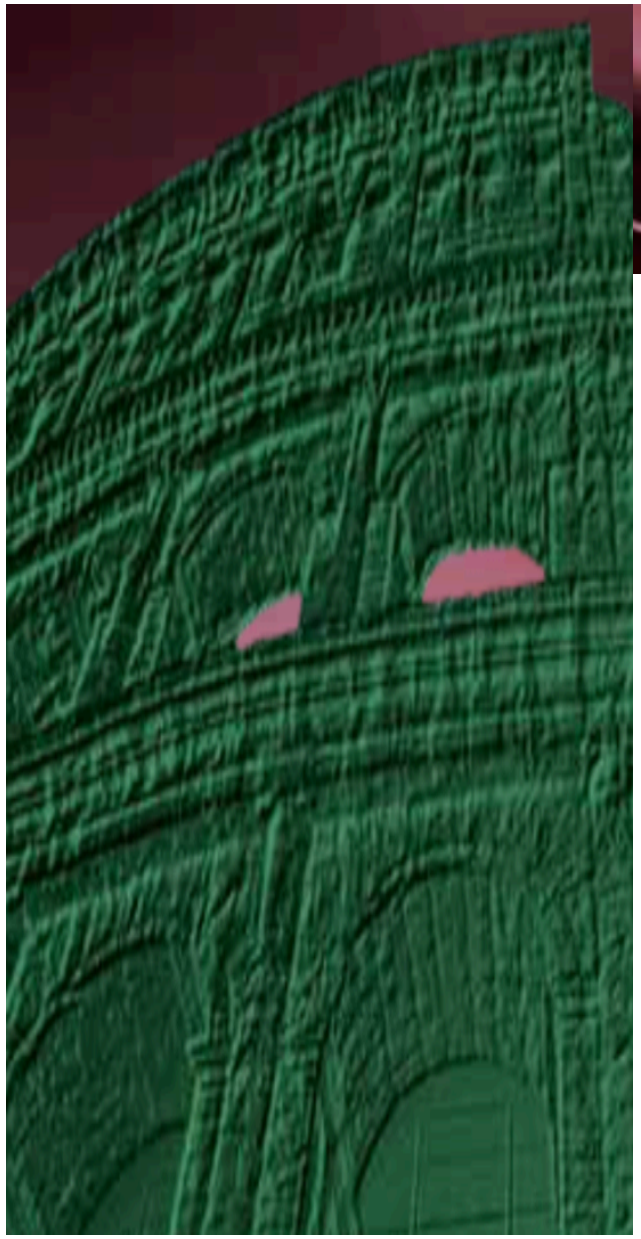

HIGHLIGHTS in RADIOTERAPIA

….discussione