Sabato 27 Novembre 2021

RADIOTERAPIA OGGI E DOMANI,

20 (+1) anni della U.O.C. di Radioterapia dell'Ospedale Manzoni di Lecco

STATO DELL'ARTE, PROBLEMATICHE ATTUALI E PROSPETTIVE FUTURE NEL TRATTAMENTO DELLE NEOPLASIE DEL DISTRETTO ORL

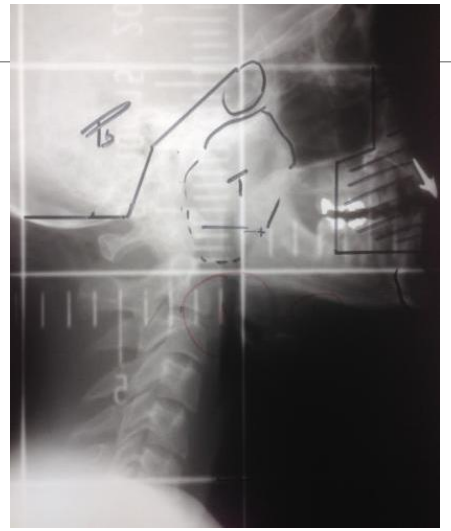
SANDRO TONOLI

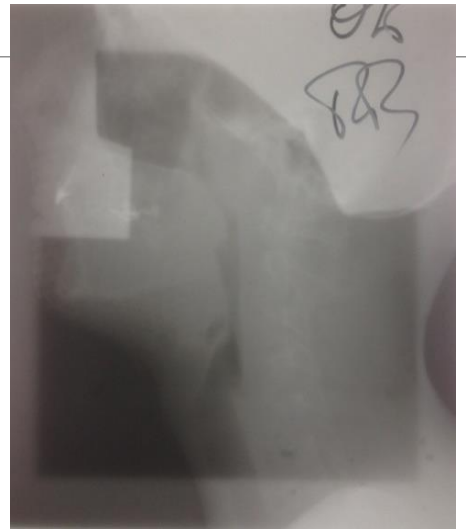
DIRETTORE UOC RADIOTERAPIA E MEDICINA NUCLEARE

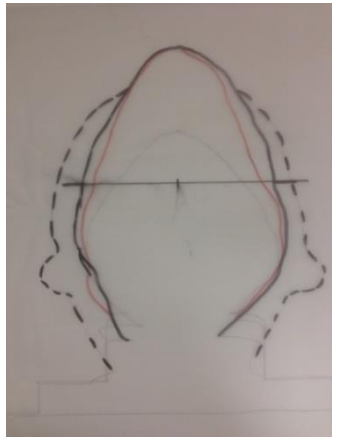
ASST DI CREMONA

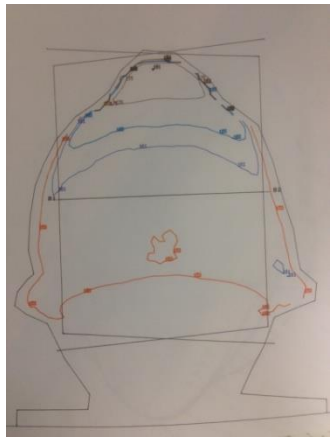
Sistema Socio Sanitario
Regione Lombardia
ASST Cremona

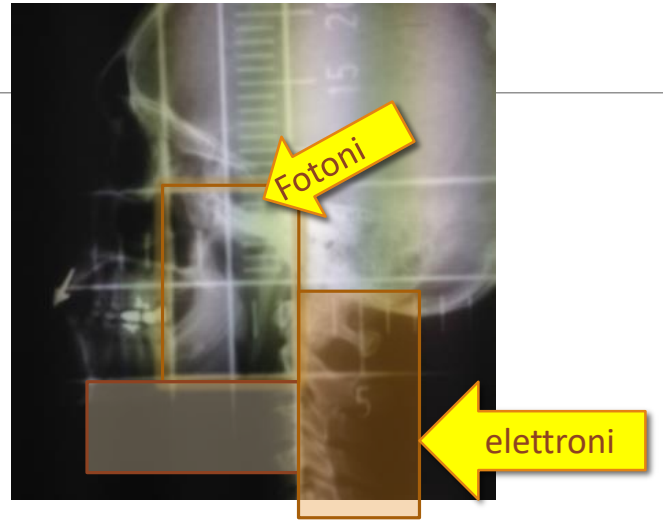
Radioterapia come trattamento elettivo trattamenti negli anni ‘90









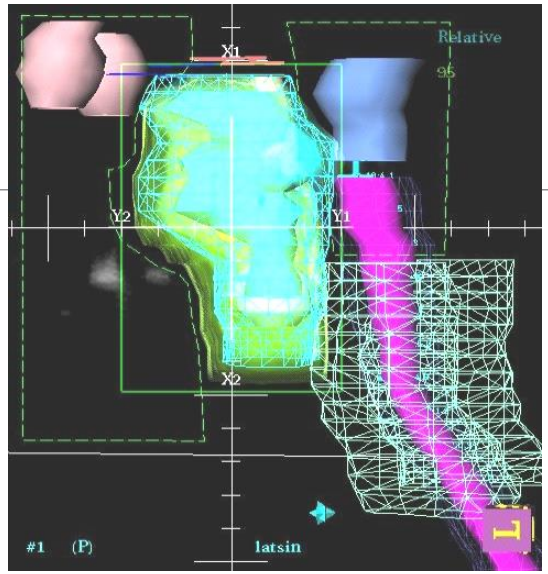


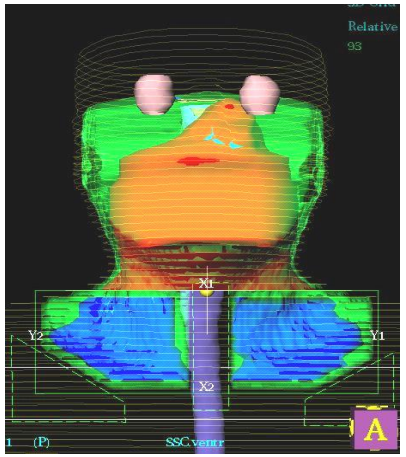
T2 N2c M0 (1993)

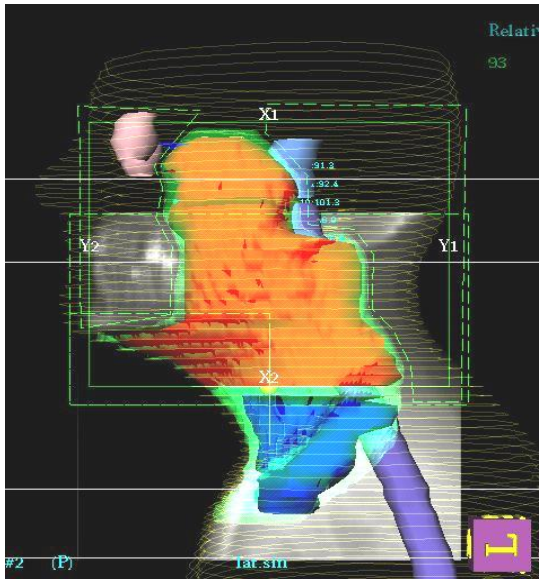
- Diagnosi su TC collo
- Definizione dei volumi: ricostruzione proiezione su radiogrammi
- Calcolo su profili corporei

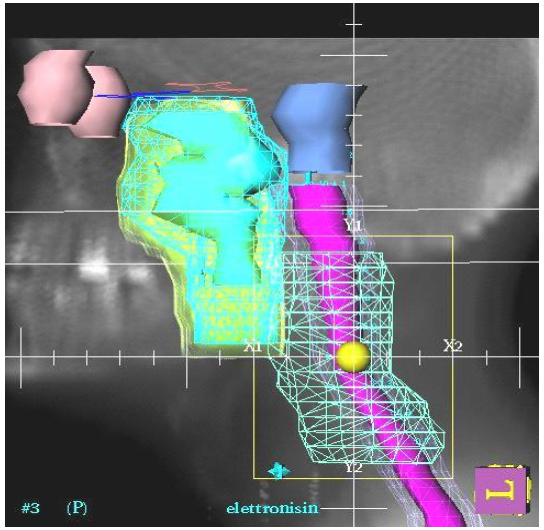
Un po’ meno passato… Tecnica tre emicampi (sino 2004)
I e II tempo di trattamento: isodose del 93%

- Utilizzo della RM nello studio dell’estensione di malattia
- Definizione dei volumi su TC
- Schermi personalizzati
- Corridoio di isodose per emicampi laterali
- Maggiore accuratezza (target e dosimetria)
- Parotidi incluse nei volumi di trattamento



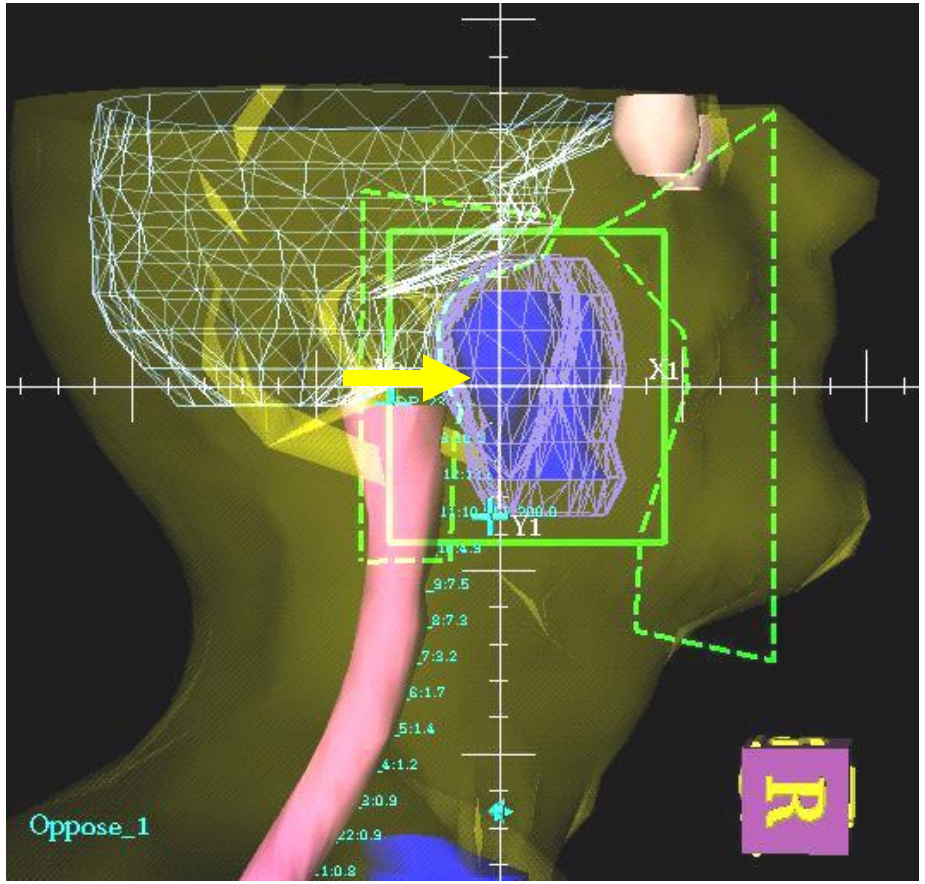


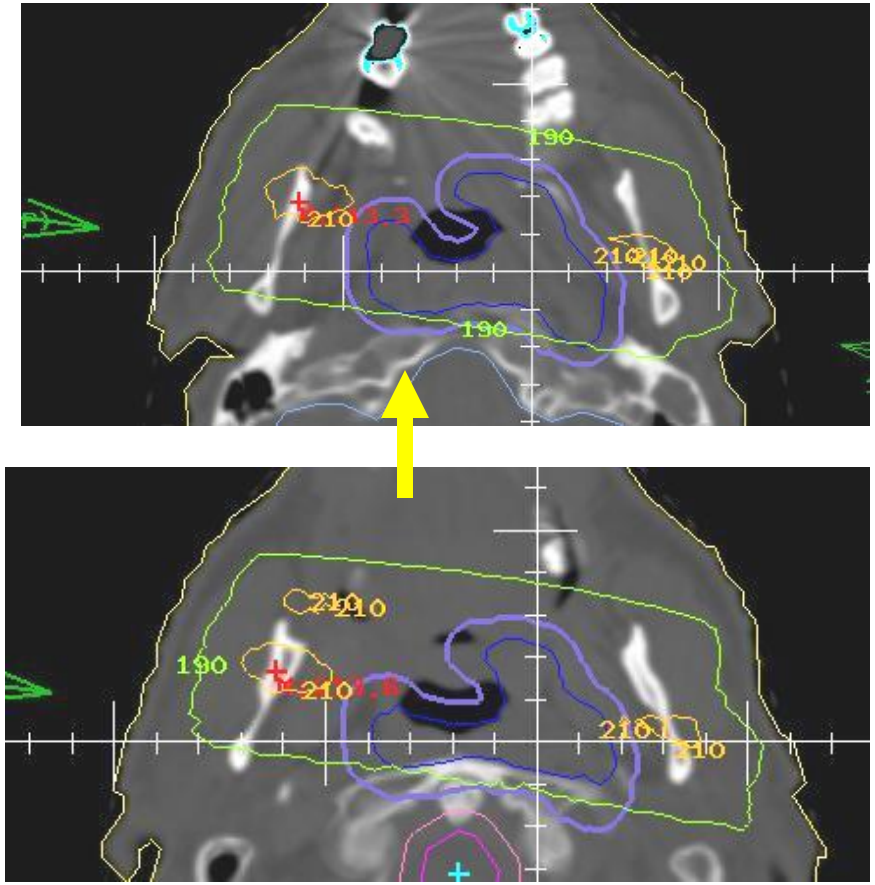




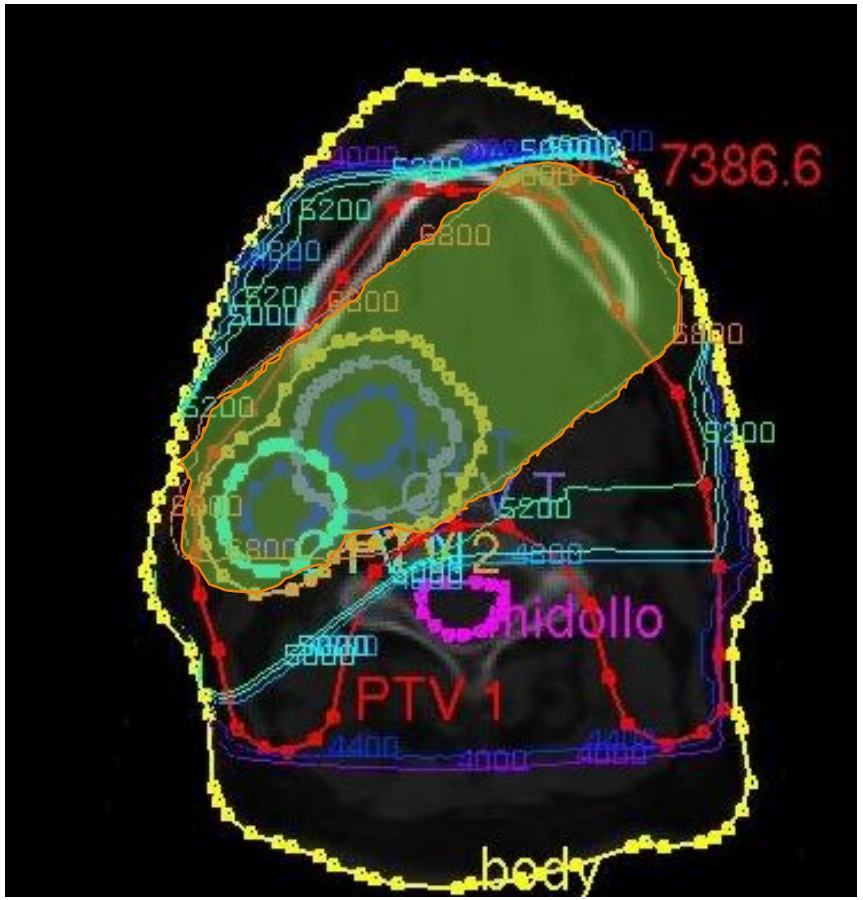
Il tempo “3D CRT corretta” (boost)

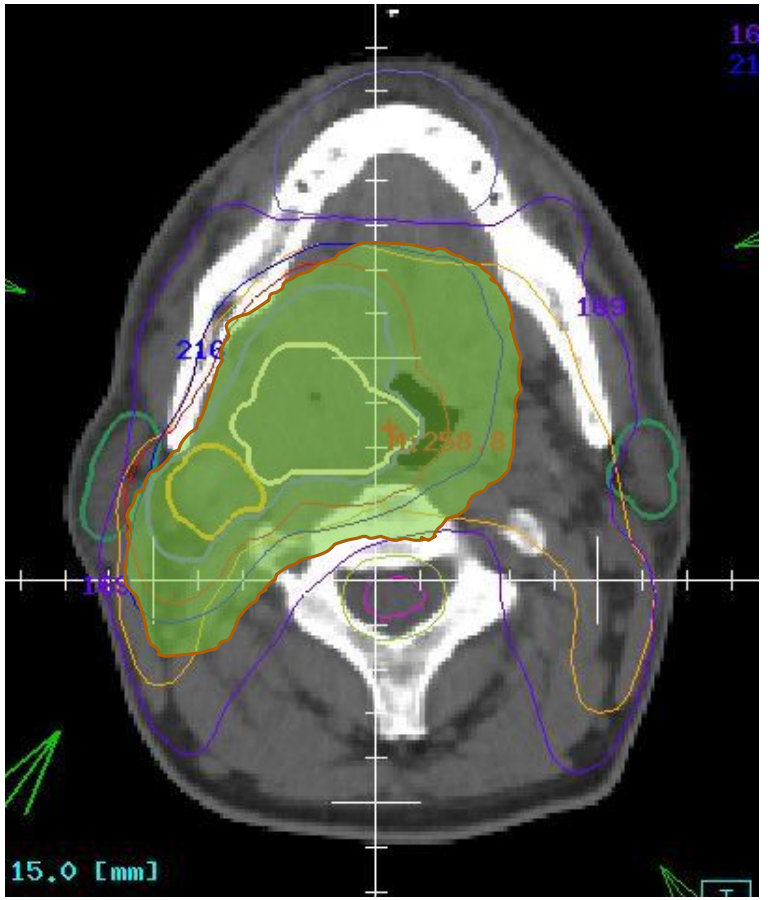
…il limite dorsale del PTV TN non è comunque adeguato per la vicinanza degli organi critici!





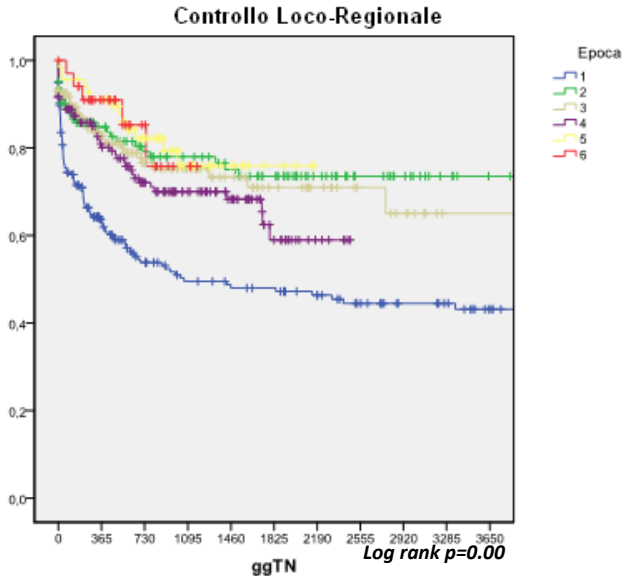
3DCRT vs IMRT

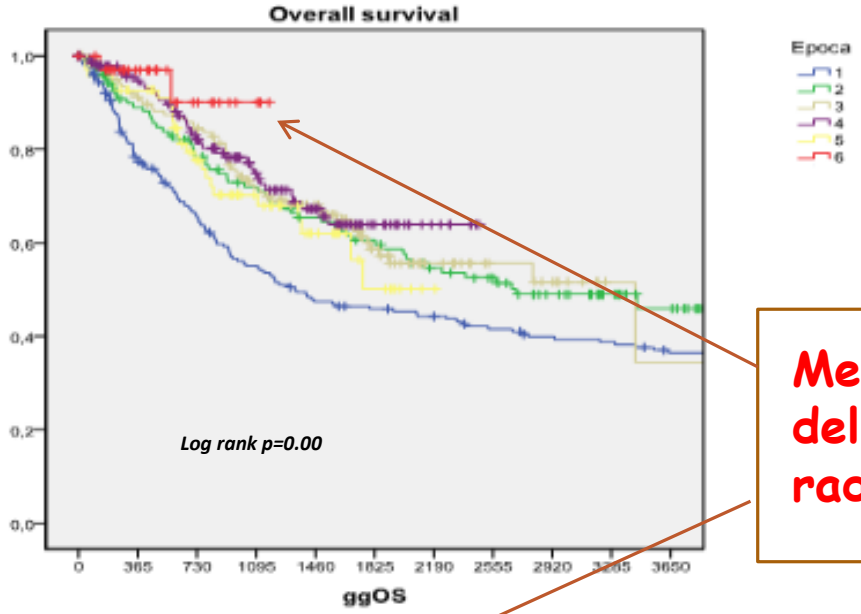




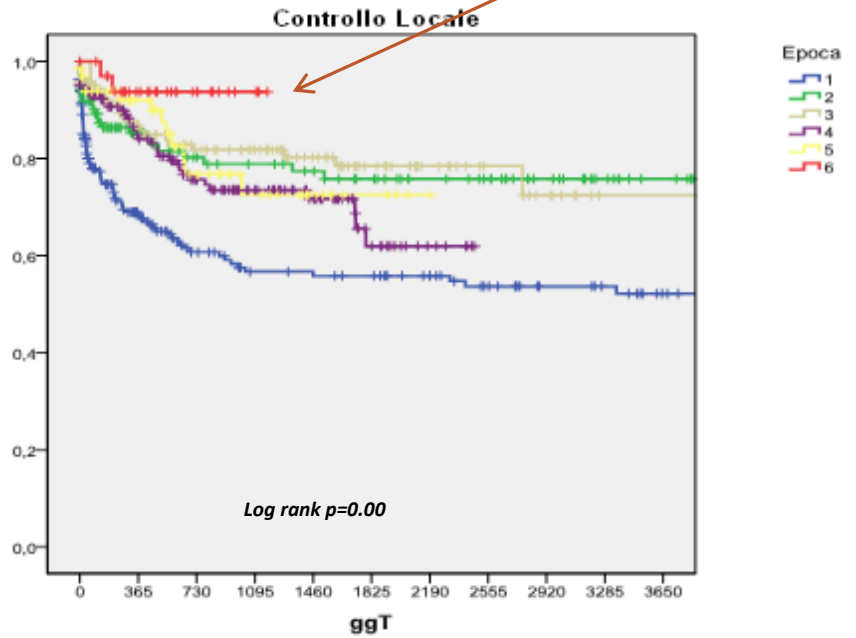
Sopravvivenza e controllo locale - Rinofaringe – Radioterapia Brescia (1985-2006)

Epoca	Frequenza
1: ≤ 1985	215 (29,4%)
2: >'85 ≤ '90	124 (16,9%)
3: > '90 ≤ '95	145 (19,8%)
4: > '95 ≤ 2000	144 (19,7%)
5: > 2000 ≤ luglio 2006	69 (9,4%)
6: > agosto 2006	35 (4,6%)
Totale	732 (100%)





Merito solo della tecnica radioterapica?

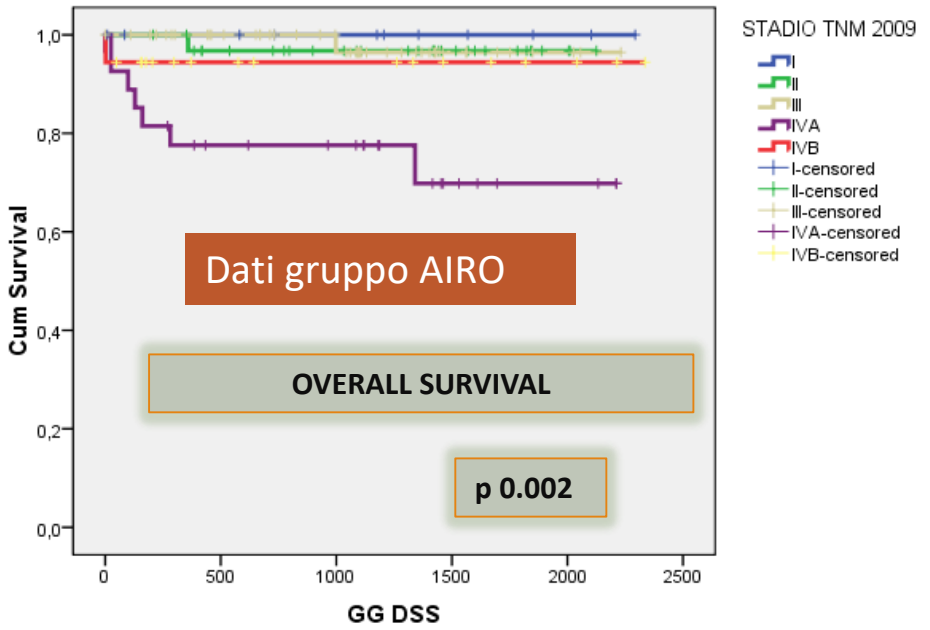


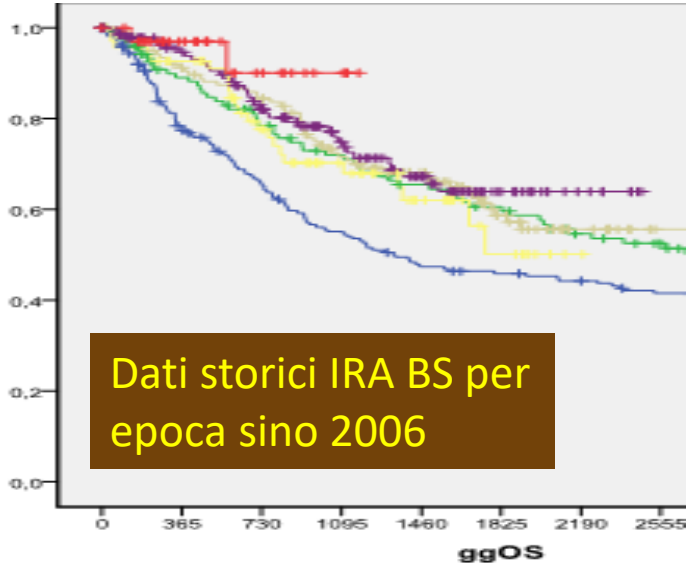
S. Tonoli, D. Alterio et al

Nasopharyngeal carcinoma in a low incidence European area :

A prospective observational analysis from the Head and Neck Study Group of the Italian Society of Radiation Oncology (AIRO)

End point	5 yrs results
DSS	92+/-3%
OS	91+/-3%
DMFS	79+/-5%
DFS	73+/-5%
LC	89+/-3%
RC	93+/-3%
LRFS	85+/-4%





Strahlenther Onkol . 2016 Dec;192(12):931-943.

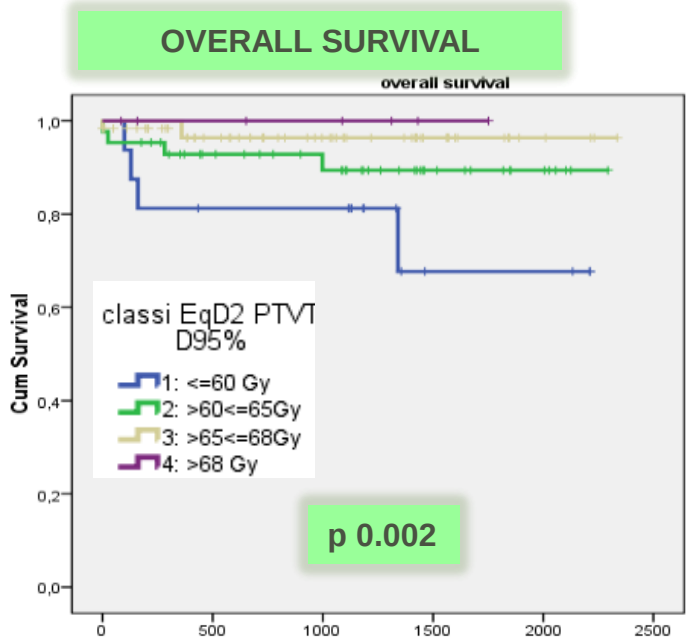
Casistica gruppo AIRO H&N

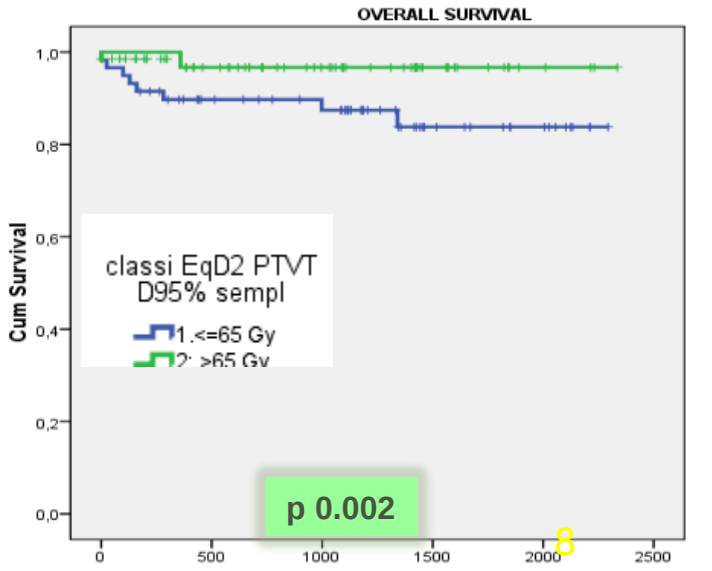
D95% $_{2GyEqD}$ PTV T

Parametro più interessante predittivo della sopravvivenza anche se stratificato per

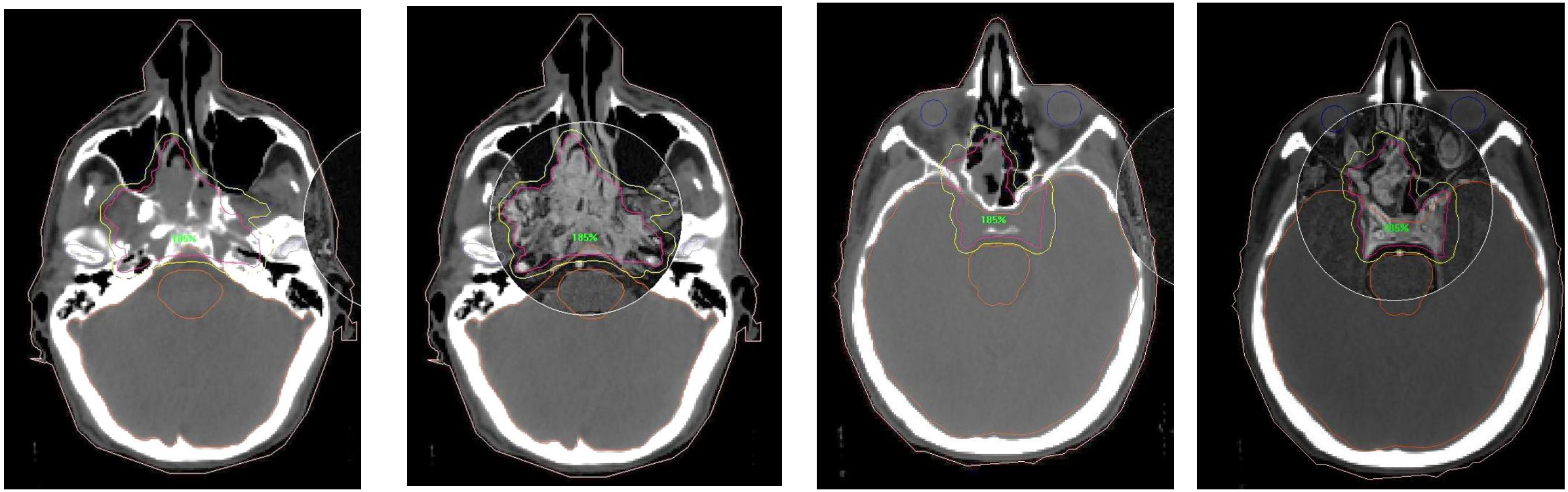
- volume GTV T classi,
- vol GTV TN 30cc,
- vol GTV TN 50cc
- chemioterapia associata.

Indipendentemente dalla metodica utilizzata e compatibilmente con la fattibilità, la D95% al PTV T > 65 Gy dovrebbe essere considerata un criterio di adeguatezza del piano di trattamento.

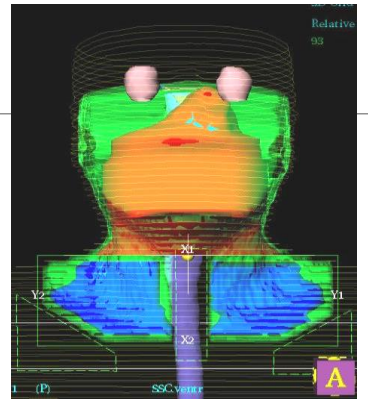


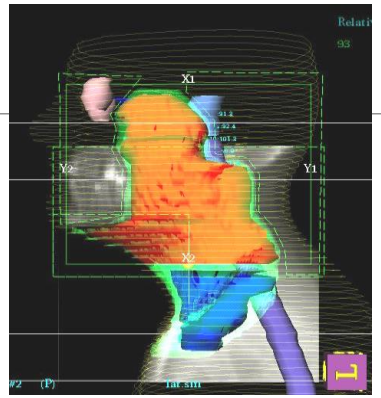


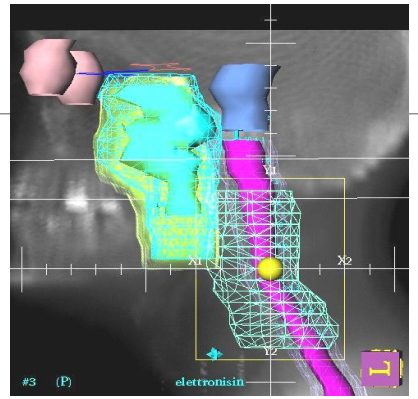
Le metodiche di coregistrazione di immagini nella definizione dei volumi di interesse



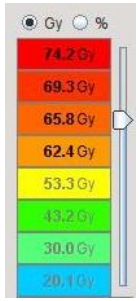
La maggiore capacità di conformazione della IMRT è associata con un incremento del volume con “basse dosi”

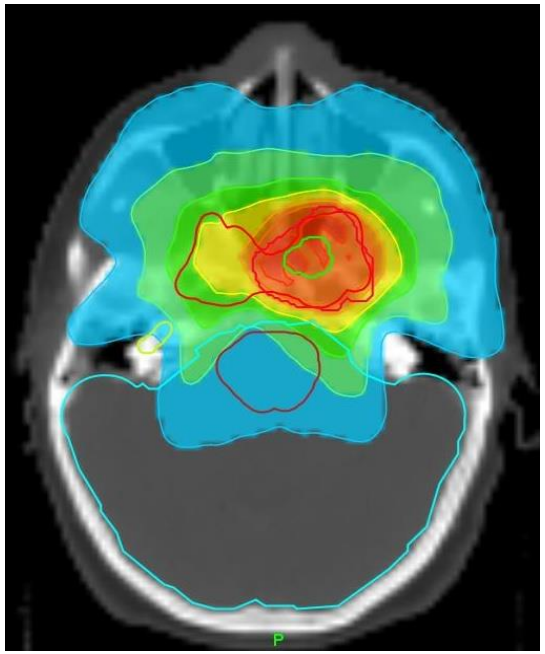


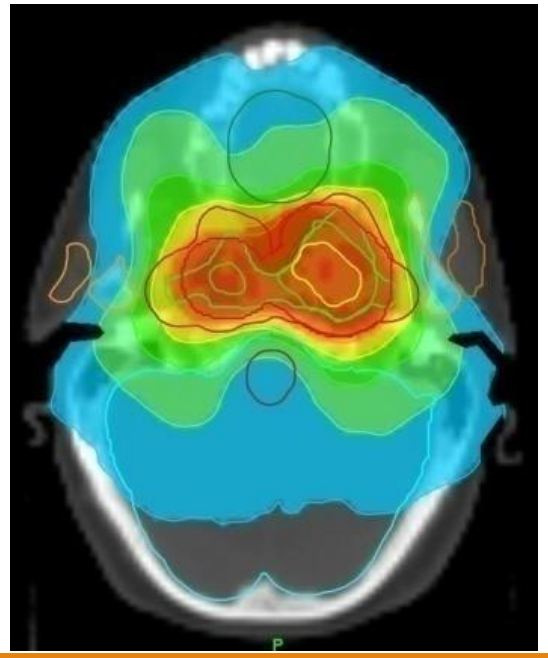


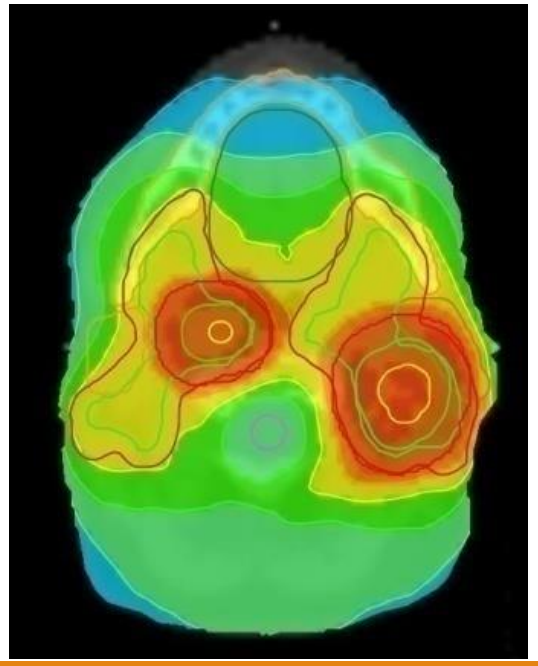


2D (e mezzo)









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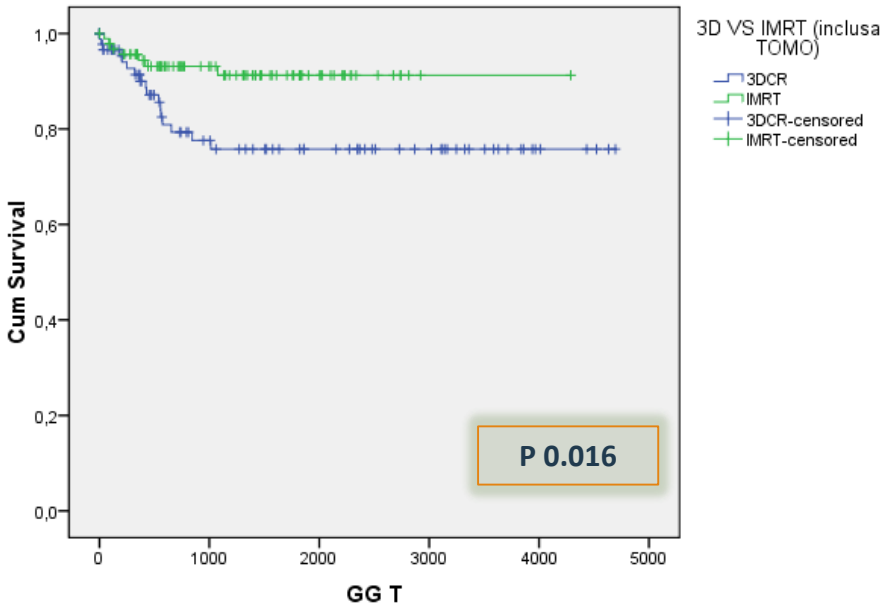
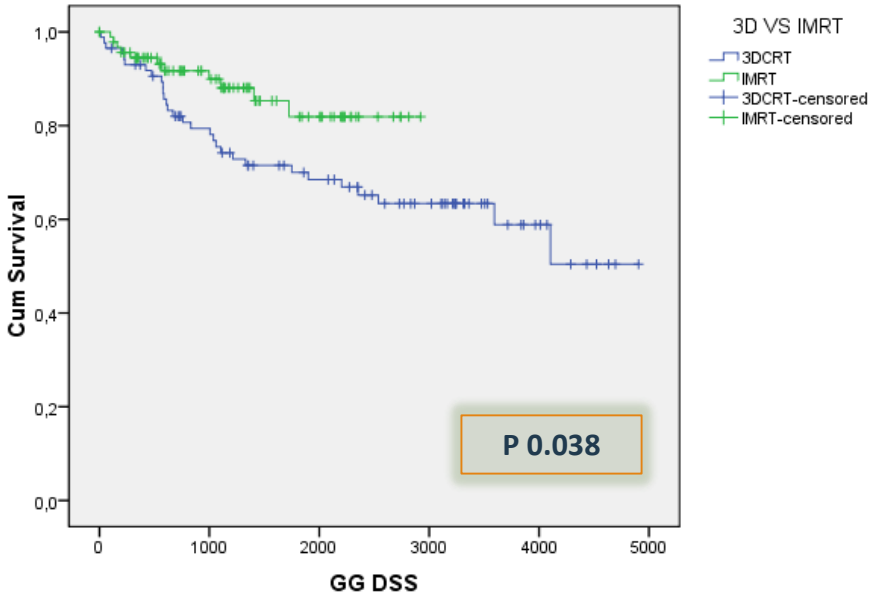
“3D” vs IMRT S&S (inclusa tomo)

CONTROLLO LOCALE



OVERALL SURVIVAL

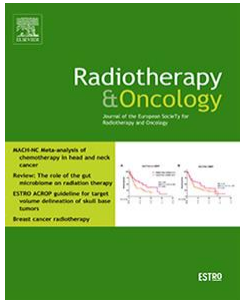


HEAD & NECK TUMORS

CURRENT STANDARD

- Associazione con chemioterapia negli stadi localmente avanzati
- Co-registrazione fra immagini multimodali (RM e TC-PET)
- Trattamenti IMRT/volumetrici
- IGRT

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group



Main question: addiction of chemotherapy to locoregional treatment

Concomitant chemoradiotherapy:

- **mainstay of treatment for locally advanced HNSCC** whether as sole treatment or given as adjuvant after surgery,
- with a longer follow-up of 9.2 years, this analysis confirm **the OS benefit it of 6.5% and 3.6% at 5 and 10 years respectively.**

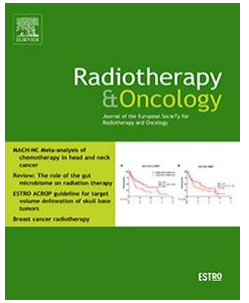
The decreasing effect of concomitant chemotherapy **with increasing patient age** is reinforced; thus, the use of concomitant chemotherapy should be carefully weighed after 70 years.

The subset analysis confirmed as well that **platin containing mono or polychemotherapy is the standard of care** due to higher OS or EFS benefit.

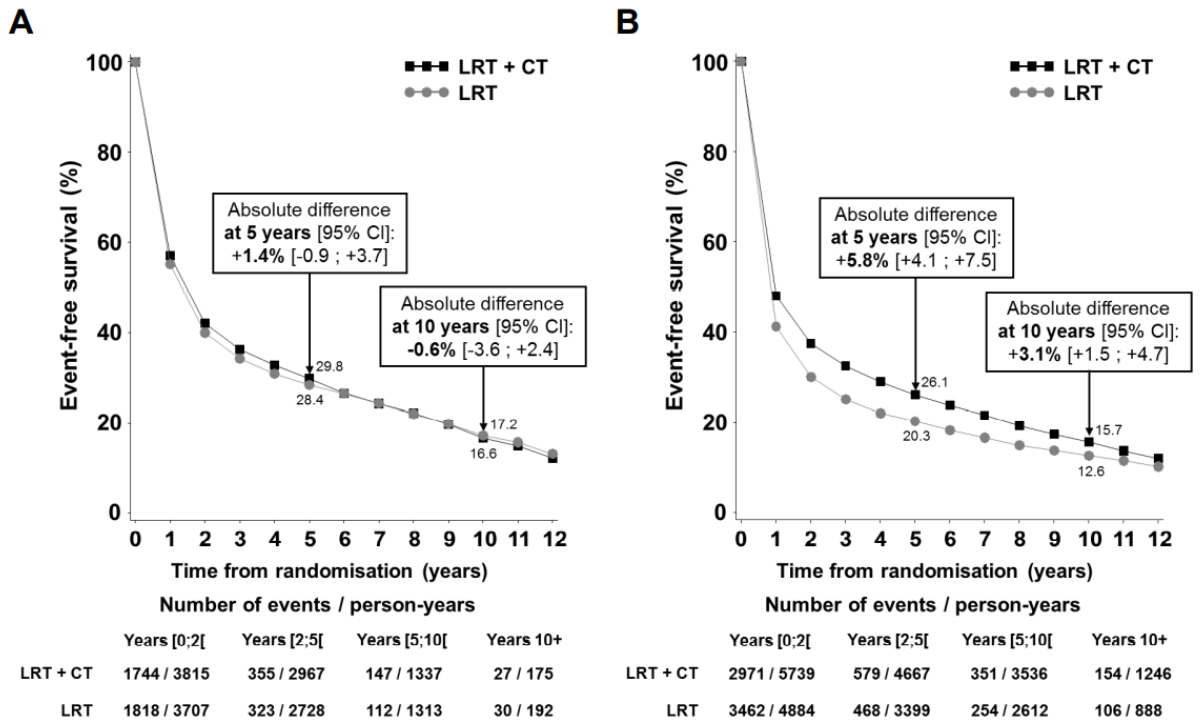
	Timing of chemotherapy						All timings	
	Induction		Concomitant		Adjuvant			
	N	%	N	%	N	%	N	%
Stage 0	0	-	0	-	2	*0.1*	2	*< 0.1*
Stage I-II	423	*6.0*	587	*5.5*	607	*20.8*	1617	*7.8*
Stage III	2393	*33.9*	2574	*24.1*	967	*33.2*	5934	*28.7*
Stage IV Low	974	*13.8*	2132	*20.0*	226	*7.8*	3332	*16.1*
Stage IV High	3072	*43.6*	4851	*45.4*	740	*25.4*	8663	*42.0*
Stage IV M+	11	*0.2*	14	*0.1*	0	-	25	*0.1*
Stage IV (unspecified)	32	*0.5*	197	*1.8*	125	*4.3*	354	*1.7*
Unknown	149	*2.1*	325	*3.1*	248	*8.5*	722	*3.5*
Smoking status								
Never	177	*2.5*	384	*3.6*	0	-	561	*2.7*
Former	267	*3.8*	1025	*9.6*	0	-	1292	*6.3*
Current	91	*1.3*	1119	*10.5*	0	-	1210	*5.9*
Unknown	6519	*92.4*	8152	*76.3*	2915	*100*	17586	*85.2*
HPV status								
Negative	8	*0.1*	40	*0.4*	0	-	48	*0.2*
Positive	44	*0.6*	3	*< 0.1*	0	-	47	*0.2*
Unknown	7002	*99.3*	10637	*99.6*	2915	*100*	20554	*99.5*
Total	**7054**	***100***	**10680**	***100***	**2915**	***100***	**20649**	***100***

* Overall rate of missing data is 5.4% after exclusion of the 40 comparisons that did not collect performance status: 17 (2070 patients) for induction, 19 (2061 patients) for concomitant and 4 (708 patients) for adjuvant
IQR: interquartile range

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group



Web-Figure 3: Event-free survival - Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing
A: Induction chemotherapy, B: Concomitant chemotherapy, C: Adjuvant chemotherapy.



CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

INDUCTION CONCOMITANT ADJUVANT

MAÏMOUNA MANÉ et al,

Meta-Analysis on Induction Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma

- Out of 292 studies identified by our search, 8 RCTs included in the meta-analysis,
- 2,384 randomized patients (1,200 and 1,184 were assigned to receive ICT plus CCRT and CCRT)
- 69% had N2–N3 disease

Treatment compliance:

- median rate of 92% (range, 86%–100%) of patients receiving all cycles of ICT.
- The percentage of patients completing radiotherapy was 96% and 95% in the ICT group and CCRT group
- **Chemotherapy during RT completed in only 28% of the ICT group vs 61% in the CCRT group** (p 0.003)

Grade 3–4 acute toxicity

- mostly hematologic during the ICT phase (496 events vs. 191 nonhematologic)
- **predominant in the ICT group during the CCRT.**

Adding ICT to CCRT provided a significant benefit in overall survival (hazard ratio [HR], 0.680; 95% CI, 0.511–0.905; p = .001) and progression-free survival (HR, 0.657; 95% CI, 0.568–0.760; p < .001)

Table 3. Compliance to treatment

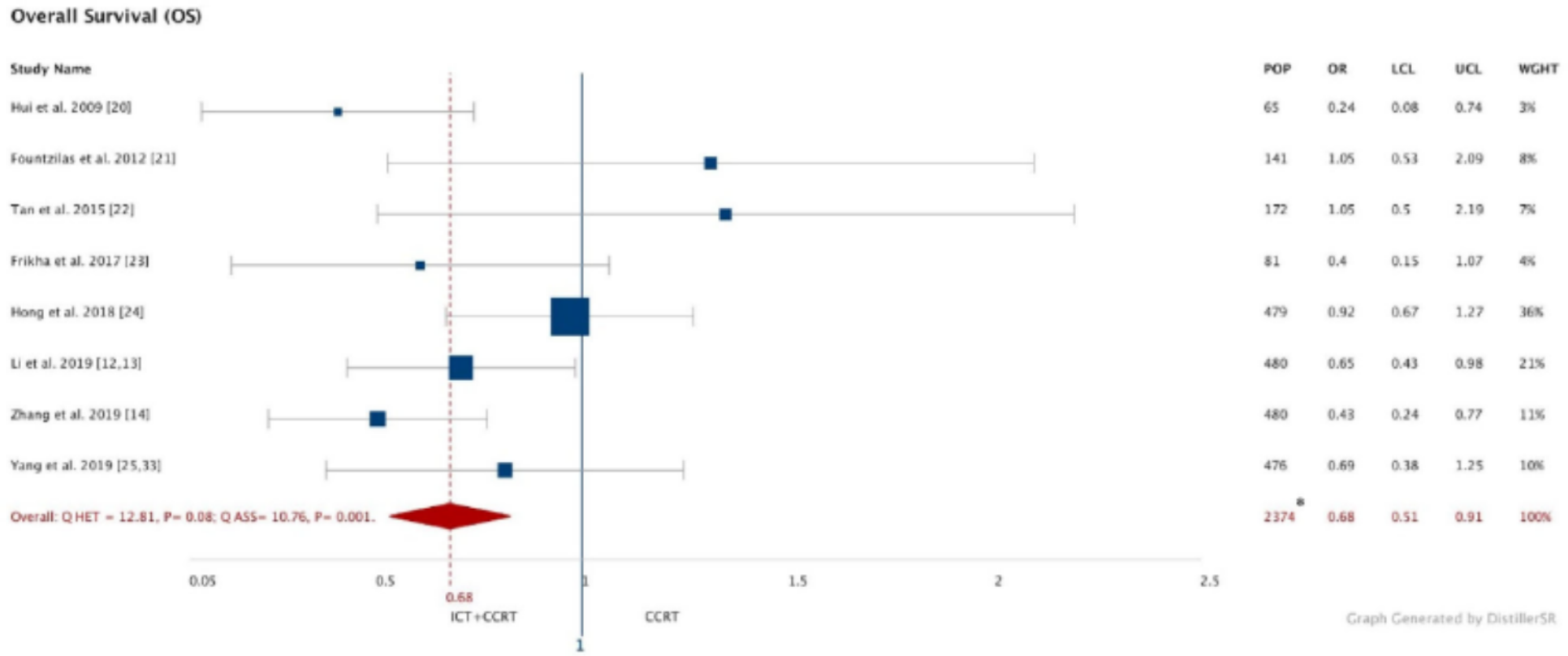
				Concurrent chemoradiation (calculated on number starting RT)								
				Radiotherapy				Chemotherapy				
Trial	Arm	*n*[a]	ICT completed, calculated on ITT, %	*n*[b]	Completed, %	Duration, d	Total dose, Gray	Weekly or 3-weekly	Planned dose/cycle mg/m^2	Planned number of cycles	% pts receiving dose as planned	% pts with ≥ 200 mg/m^2 cumulative cisplatin dose
Hui et al. 2009 [20]	ICT+CCRT	34	100	34	100	58.8[c]	78.4[c]	Weekly	40	8	3	74[d]
	CCRT	31		26	100	56.6[c]	76.5[c]	Weekly	40	8	0	76[d]
Fountzilas et al. 2012 [21]	ICT+CCRT	72	86	65	94	51.8[e]	70[e]	Weekly	40	8	8	58
	CCRT	69		68	94	51.1[e]	70[e]	Weekly	40	8	9	75
Tan et al. 2015 [22]	ICT+CCRT	92	86[f]	86	100	NR	NR	Weekly	40	8	26	61[d]
	CCRT	88		86	99	NR	NR	Weekly	40	8	42	72[d]
Frikha et al. 2017 [23]	ICT+CCRT	42	93[f]	41	83	53.1[c]	NR	Weekly	40	7	32	NR
	CCRT	41		40	90	51.8[c]	NR	Weekly	40	7	55	NR
Hong et al. 2018 [24]	ICT+CCRT	239	95	232	NR	NR	NR	Weekly	30	7	26	NR
	CCRT	240		227	NR	NR	NR	Weekly	30	7	73	NR
Li et al. 2019 [12,13]	ICT+CCRT	241	88	238	100	46[e,g]	70[e]	3-weekly	100	3	31	86
	CCRT	239		238	99	46[e,g]	70[e]	3-weekly	100	3	56	98
Zhang et al. 2019 [14]	ICT+CCRT	242	96	239	100	NR	NR	3-weekly	100	3	39	80
	CCRT	238		237	99	NR	NR	3-weekly	100	3	75	96
Yang et al. 2019 [25,33]	ICT+CCRT	238	91	219	100	NR	NR	3-weekly	80	3	23	23
	CCRT	238		214	100	NR	NR	3-weekly	80	3	71	71

[a]Refers to number of patients randomized.

Compliance to treatment

MAÏMOUNA MANÉ et al,

Meta-Analysis on Induction Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma



Frazionamenti Alterati

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis
MARCH collaborative group – Lancet 2006

15 studi, 6515 pazienti, mediana FU 6 anni, prevalentemente orofaringe e laringe, 74% stadio III-IV

Overall survival

Beneficio a 5 anni: 3.4%

- Iperfrazionamento: 8%
- RT accelerata: 2%
- RT accelerata con riduzione della dose totale: 1.7%

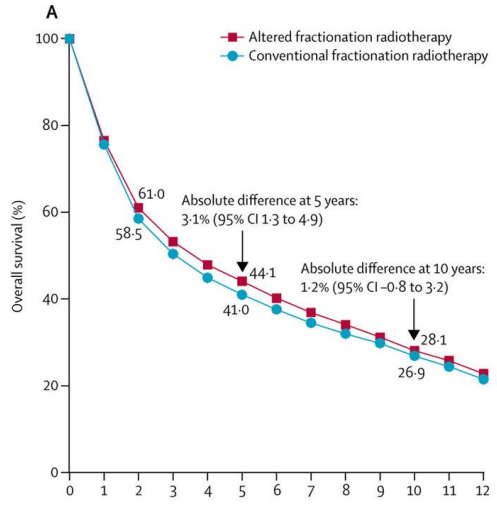
Controllo locoregionale

Beneficio a 5 anni: 6.4%

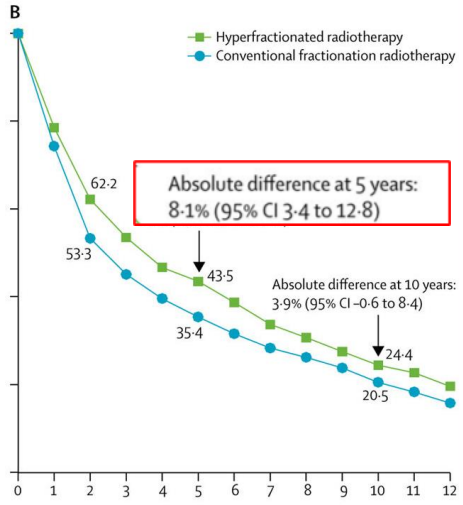
- Iperfrazionamento: 9.4%
- RT accelerata: 7.3%
- RT accelerata con riduzione della dose totale: 2.3%

Benjamin Lacas, Jean Bourhis et al.
Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

OVERALL SURVIVAL

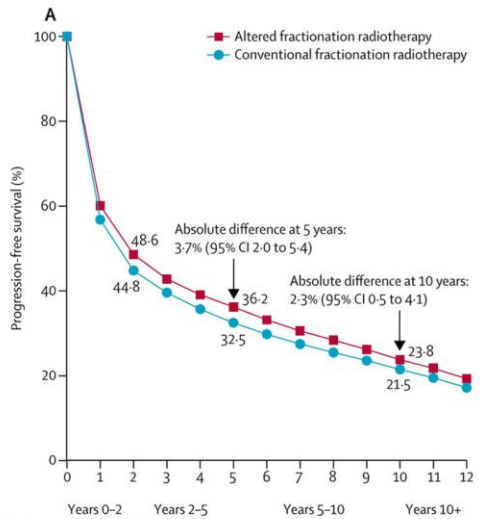


	Years 0–2	Years 2–5	Years 5–10	Years 10+
Altered fractionation radiotherapy (deaths/person-years)	2340/9351	936/8374	548/6153	220/1931
Conventional fractionation radiotherapy (deaths/person-years)	2401/8866	918/7531	452/5431	199/1723

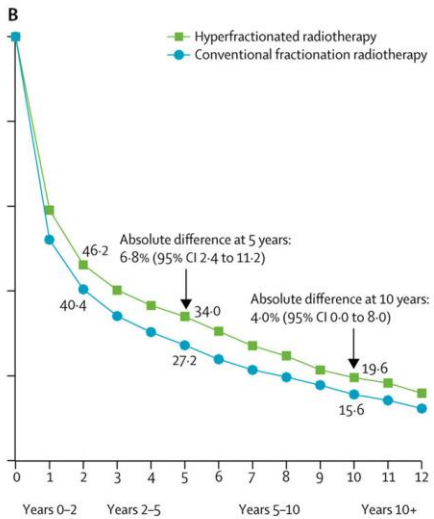


	Years 0–2	Years 2–5	Years 5–10	Years 10+
Hyperfractionated radiotherapy (deaths/person-years)	320/1359	152/1210	120/1035	57/442
Conventional fractionation radiotherapy (deaths/person-years)	395/1250	137/988	87/808	45/330

PROGRESSION FREE SURVIVAL



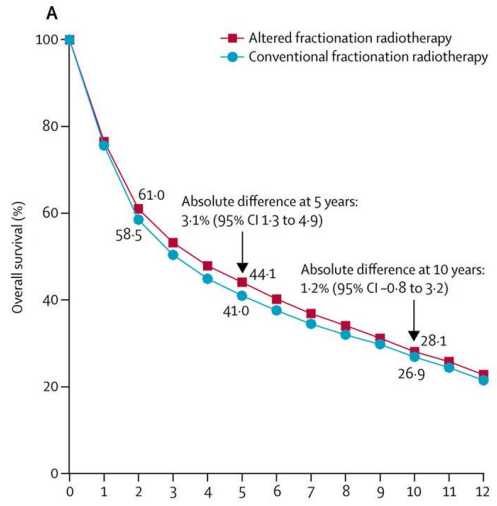
	Years 0–2	Years 2–5	Years 5–10	Years 10+
Altered fractionation radiotherapy (deaths/person-years)	3044/7908	715/7002	437/5241	197/1727
Conventional fractionation radiotherapy (deaths/person-years)	3166/7208	663/6145	368/4457	168/1457



	Years 0–2	Years 2–5	Years 5–10	Years 10+
Hyperfractionated radiotherapy (deaths/person-years)	449/1122	106/985	94/861	46/366
Conventional fractionation radiotherapy (deaths/person-years)	507/980	106/773	71/628	34/272

Benjamin Lacas, Jean Bourhis et al.
Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

OVERALL SURVIVAL



	Years 0–2	Years 2–5	Years 5–10	Years 10+
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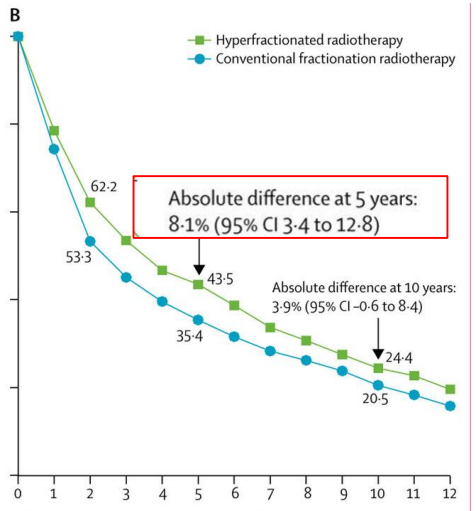

	Years 0–2	Years 2–5	Years 5–10	Years 10+
Hyperfractionated radiotherapy (deaths/person-years)	320/1359	152/1210	120/1035	57/442
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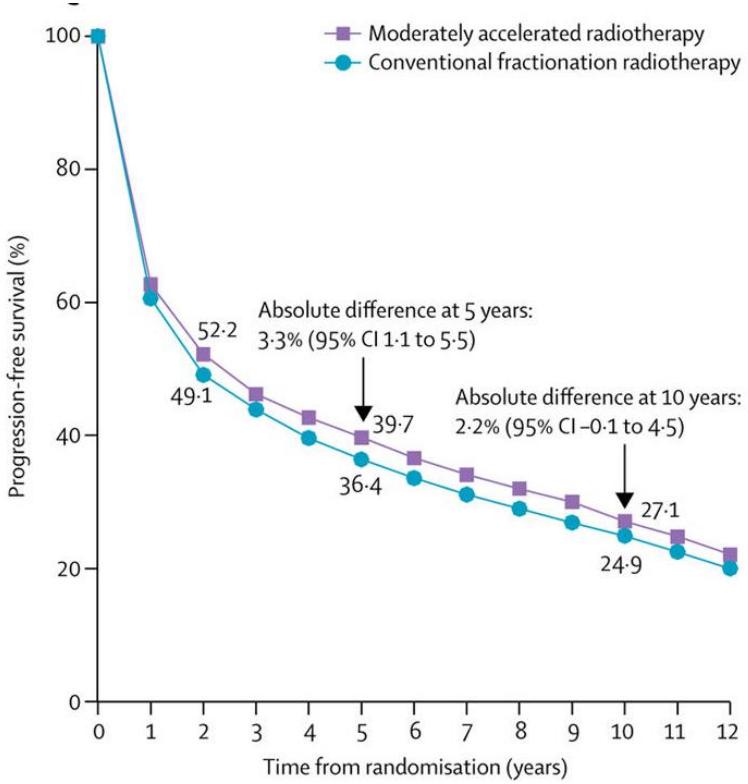
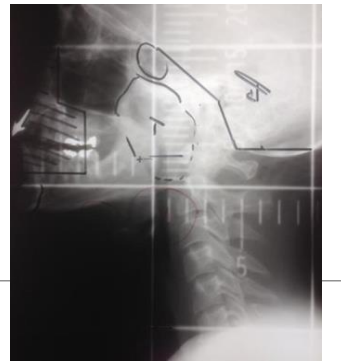
PROGRESSION FREE SURVIVAL

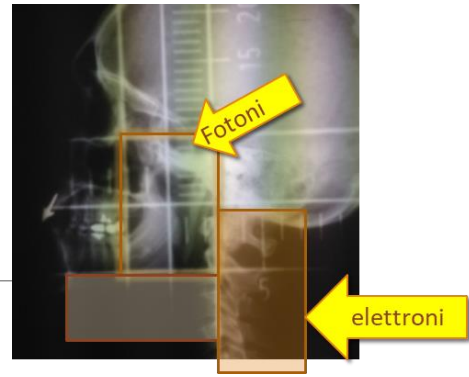


Lancet Oncol. 2017 September ; 18(9): 1221–1237.

Benjamin Lacas, Jean Bourhis et al.

Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis





Altered fractionation RT vs standard fractionation RT

- small but significant improvement in overall survival (3.1% at 5 yrs)
- Hyperfractionation: absolute difference at 5 years 8.1%
  - clear benefit on local control,
  - smaller benefit on regional (nodal) control and cancer mortality,
  - no benefit on distant metastases and non-cancer-related mortality.
- Node-positive patients:
  - significant only for hyperfractionation
- Pure acceleration (the delivery of 66–70 Gy in 5.5–6 weeks) should therefore be considered only for patients with a low nodal burden

LIMITATIONS

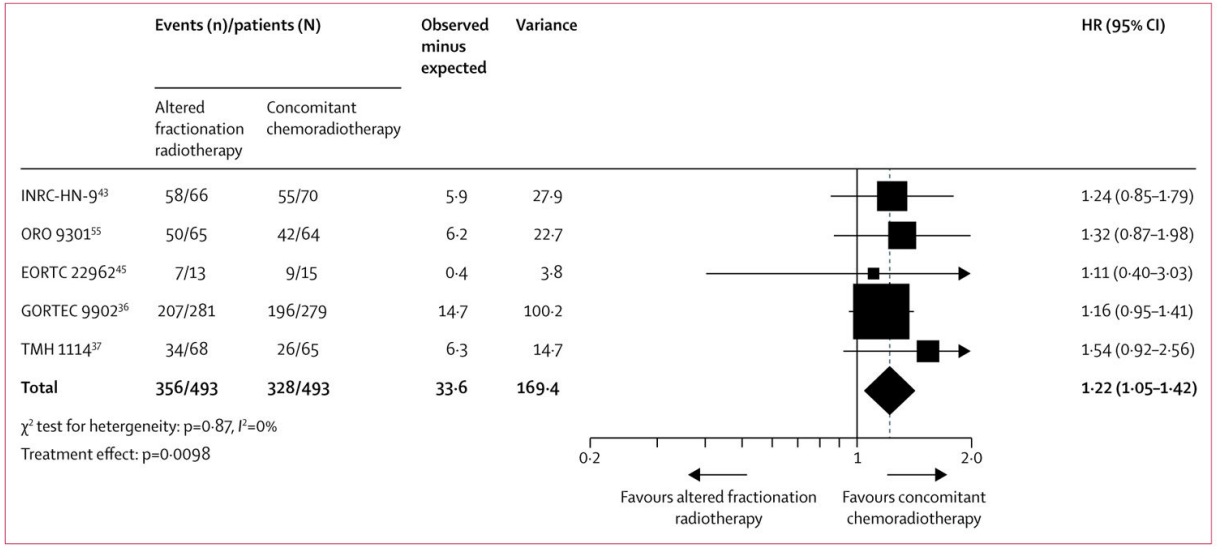
- Almost all of the trials included used **outdated radiotherapy techniques (1965-2016!!)**
- The included trials also come **before HPV era** and **often did not record smoking status**, with data for these variables available in very few trials in the meta-analysis
- **Low quality of data collected for the toxicity analysis**
  - Only five trials compared altered fractionation radiotherapy with standard radiotherapy plus chemotherapy in both groups,
  - three trials have a lower dose of chemotherapy in the group with altered fractionation radiotherapy than in the standard radiotherapy group

Lancet Oncol. 2017 September ; 18(9): 1221–1237.

Benjamin Lacas, Jean Bourhis et al.

Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

Overall survival for trials comparing **altered fractionation radiotherapy and concomitant chemoradiotherapy (using conventional fractionation)**



	Events (n)/patients (N)		Observed minus expected	Variance	HR (95% CI)
	Altered fractionation radiotherapy	Concomitant chemoradiotherapy			
INRC-HN-9[43]	58/66	55/70	5·9	27·9	1·24 (0·85–1·79)
ORO 9301[55]	50/65	42/64	6·2	22·7	1·32 (0·87–1·98)
EORTC 22962[45]	7/13	9/15	0·4	3·8	1·11 (0·40–3·03)
GORTEC 9902[36]	207/281	196/279	14·7	100·2	1·16 (0·95–1·41)
TMH 1114[37]	34/68	26/65	6·3	14·7	1·54 (0·92–2·56)
Total	**356/493**	**328/493**	**33·6**	**169·4**	**1·22 (1·05–1·42)**

χ^2 test for hetergeneity: p=0·87, I^2=0%
Treatment effect: p=0·0098

The direct comparison between altered fractionation radiotherapy and concomitant chemoradiotherapy showed the superiority of the addition of concomitant chemotherapy over pure fractionation modification.

Concomitant chemo radiotherapy should remain the standard of care for locally advanced node-positive tumours.

L. G. Sapienza et al.

Altered-fractionation radiotherapy improves local control in early-stage glottic carcinoma: A systematic review and meta-analysis of 1762 patients

Table 1
Characteristics of the randomized clinical trials.

Author/study	Year	N	Stage (%T1)	A-com (%)	Beam energy	ART strategy	Fraction Size		MNTDR
							CRT	ART	
Yamazaki	2006	180	T1 (100%)	14.4%	4 MV	Hypo	2.0 Gy qd	2.25 Gy qd	5 days
KROG 0201	2014	156	T1 (89%) and T2	28.8%	4–6 MV	Hypo	2.0 Gy qd	2.25 Gy qd	5 days
RTOG 9512	2014	239	T2 (0% T1)	NA	Cobalt-60 or 4–6 MV	Hyper	2.0 Gy qd	1.2 Gy bid	2 days
JCOG 0701	2018	370	T1 (74.8%) and T2	3.5%	3–6 MV	Hypo	2.0 Gy qd	2.4 Gy qd	8 days

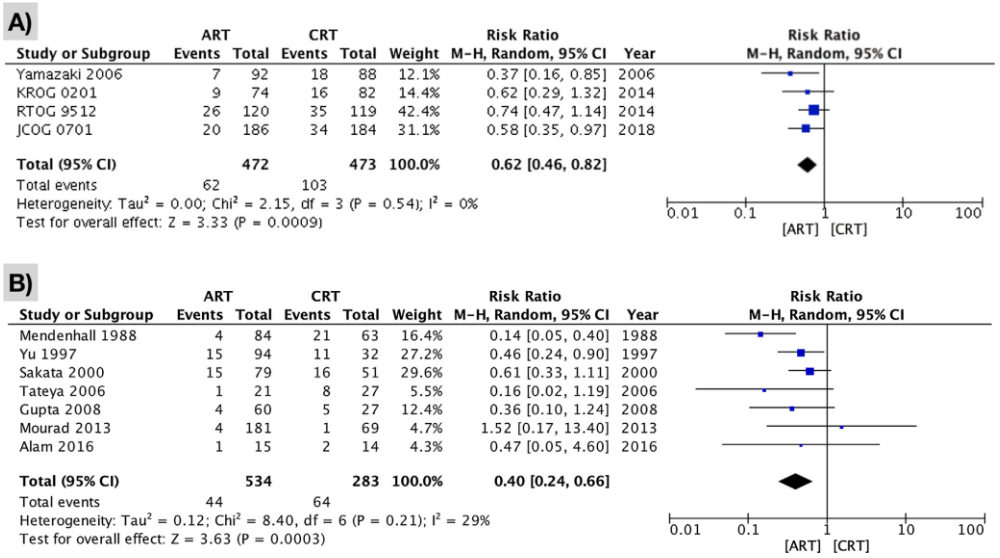
A-com: anterior commissure involvement. MNTDR – minimum number of treatment days reduced. ART: accelerated radiotherapy. CRT: conventional radiotherapy. Hypo: hypofractionation. Hyper: hyperfractionation.

Table 2
Characteristics of the retrospective cohorts.

Author	Year	N	Stage (%T1)	A-com (%)	Beam energy	ART strategy	Fraction Size		MNTDR
							CRT	ART	
Mendenhall	1988	147	T1 (51%) and T2	NA	Cobalt-60 or 2–8 MV	Hypo	< 2.25 Gy qd	≥2.25 Gy qd	NA
Yu	1997	126	T1 (100%)	53.9%	Cobalt-60 or 4 MV	Hypo	2.0 Gy qd	2.25 or 2.5 Gy qd	13 days**
Sakata	2000	130	T1 (63%) and T2	NA	Cobalt-60	Hyper	2.0 Gy qd	1.72 Gy bid	15 days
Tateya	2006	48	T2 (0% T1)	43.7%	Cobalt-60	Hyper	2.0 Gy qd	1.2 Gy bid	2 days
Gupta	2008	87	T1 (65.5%) and T2	NA	4–6 MV	Hypo	2.0 Gy qd*	3.18 Gy qd*	22 days#
Mourad	2013	250	T1 (77%) and T2	NA	Cobalt-60 or 6 MV	Hypo	2.0 Gy qd	2.25 Gy qd	NA
Alam	2016	29	T1 (41.3%) and T2	48.2%	Cobalt-60	Hypo	2.0 Gy qd	2.5 Gy qd	10 days

A-com: anterior commissure involvement. MNTDR – minimum number of treatment days reduced. ART: accelerated radiotherapy. CRT: conventional radiotherapy. Hypo: hypofractionation. Hyper: hyperfractionation. NA: not available.
* Most common fraction size.
\# Mean time difference.
** Majority (68%) have MNTDR of 13 days.

Both hypofractionation and hyperfractionation improve local control in ESGC, including T1 tumors and for anterior commissure involvement.
This benefit may not persist for T2 tumors, for which alternative strategies should be considered.



Altered fractionation and concomitant chemotherapy

Jan Haussmann et al.

Addiction of chemotherapy to hyperfractionated radiotherapy in advanced head and neck cancer - a meta-analysis

6 studies (n = 1280 patients) randomizing HFX-RT alone and the concurrent addition of CTx in patients with LA-HNSCC undergoing definite RT.

- **OS was significantly improved in the HFX-RT + CTx group** (HR = 0.77, CI95% = 0.66-0.89; p = <0.001).
- Similar results in
  - **PFS** (HR = 0.74, CI95% = 0.63-0.87; p < 0.001)
  - **CSS** (HR = 0.72, CI95% = 0.60-0.88; p = 0.001).
- **Acute toxicities** (≥grade 3) and late adverse events (≥grade 3) **did not significantly differ between the two groups.**

Conclusion:

The addition of CTx to HFX-RT in the definitive treatment of advanced LA-HNSCC improves OS, CSS, PFS, and LRR without a significant increase in high-grade acute and late toxicities.

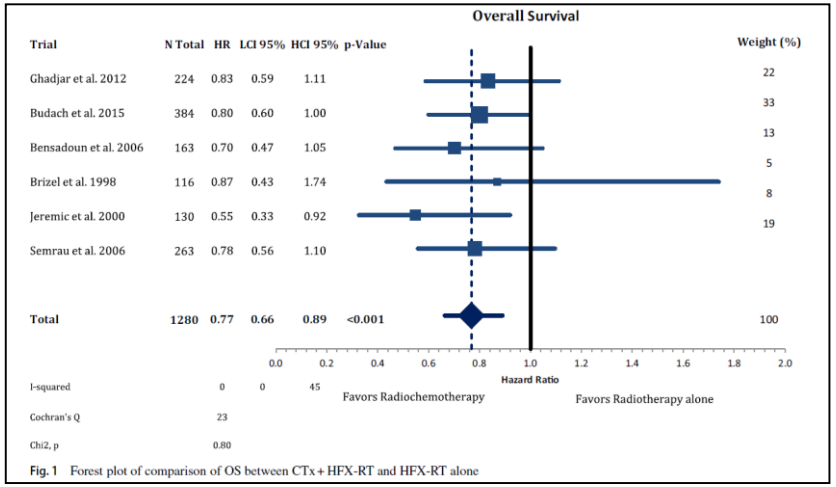


Fig. 1 Forest plot of comparison of OS between CTx + HFX-RT and HFX-RT alone

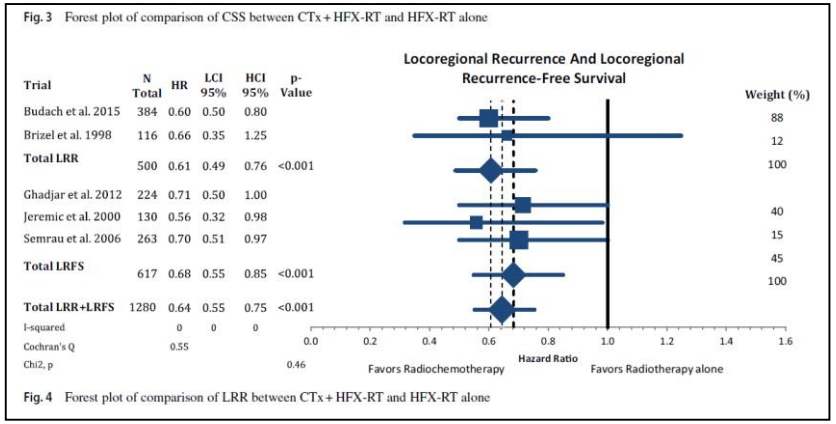


Fig. 3 Forest plot of comparison of CSS between CTx + HFX-RT and HFX-RT alone

Fig. 4 Forest plot of comparison of LRR between CTx + HFX-RT and HFX-RT alone

Claire Petit et al. - **On behalf of the MACH-NC and MARCH Collaborative Groups**

Chemotherapy and radiotherapy in locally advanced head and neck cancer: an individual patient data network meta-analysis

- **Hyperfractionated radiotherapy with concomitant chemotherapy** had the highest efficacy for overall survival, event-free survival, locoregional control, and cancer death.
- For **distant control**, locoregional treatment with **adjuvant chemotherapy** had the best results.
- The other modalities of treatment that had good results were **taxanes, cisplatin, and fluorouracil-based induction chemotherapy** followed by locoregional treatment with or without concomitant chemotherapy and accelerated radiotherapy with concomitant chemotherapy

Altered fractionation concomitant chemoradiotherapy is the most effective treatment for locally advanced head and neck cancer and **especially hyperfractionated radiotherapy** with concomitant chemotherapy.

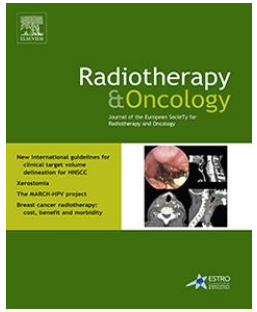
Taxane-based induction chemotherapy followed by locoregional therapy, ideally with concomitant chemotherapy, is another **good option in selected patients with a good performance status and minor comorbidities.**

Lancet Oncol. 2021 May;22(5):727-736

HEAD & NECK TUMORS

TOOLS FOR RADIATION ONCOLOGISTS

Anne W. Lee et al: International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma



High risk primary tumor CTV (CTVp1) for full therapeutic dose

- CTVp1 = GTV + 5 mm margin (consider exclusion of the clivus if not involved). [Consensus: High (90%)]
- CTVp1 = inclusion of whole nasopharynx (as well as GTV + 5 mm margin [Consensus: Low (55%)]

Intermediate risk (prophylactic dose) CTV (CTVp2)

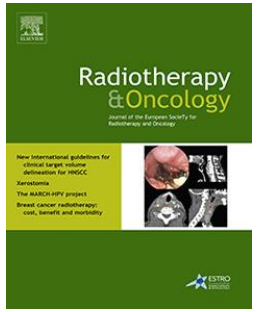
- CTVp2 = 5 mm expansion from CTVp1 [Consensus: Moderate (76%)]

Delineation of the nodal CTV

The diagnostic criteria used for defining LN involvement are:

- - Retropharyngeal LNs > 5 mm or cervical LNs > 10 mm in shortest diameter (11 mm for subdigastric node)
- - Three or more contiguous and confluent LNs, each with shortest diameter of 8–10 mm
- - LNs of any size with central necrosis or a contrast-enhanced rim
- - LNs of any size with extracapsular extension
- - LNs of any size with overt FDG uptake on FDG-PET scan

Anne W. Lee et al: International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma



Geometric GTVn + 5 mm expansion for CTVn1 and GTVn + 5+5 mm expansion for CTVn2

(1) CTVn1 = GTVn + 5 mm in cases with no extracapsular extension (Consider 10 mm expansion if extracapsular extension present)

(2) CTVn2 = CTVn1 + 5 mm expansion (i.e. GTVn + 5 mm + 5 mm). [Consensus: Low (64%)]

Intermediate risk cervical lymph node levels (prophylactic dose) CTV (CTVn2)

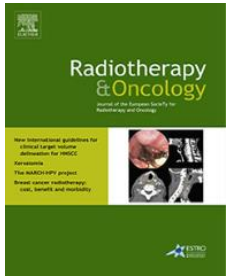
(3) Prophylactic coverage of the retropharyngeal lymph nodes (RPLN) in CTVn2 should extend from the base of the skull to the caudal border of the hyoid bone or caudal border of C3 as the lower limit. Only the lateral nodes need prophylactic coverage. [Consensus: Moderate (77%)]

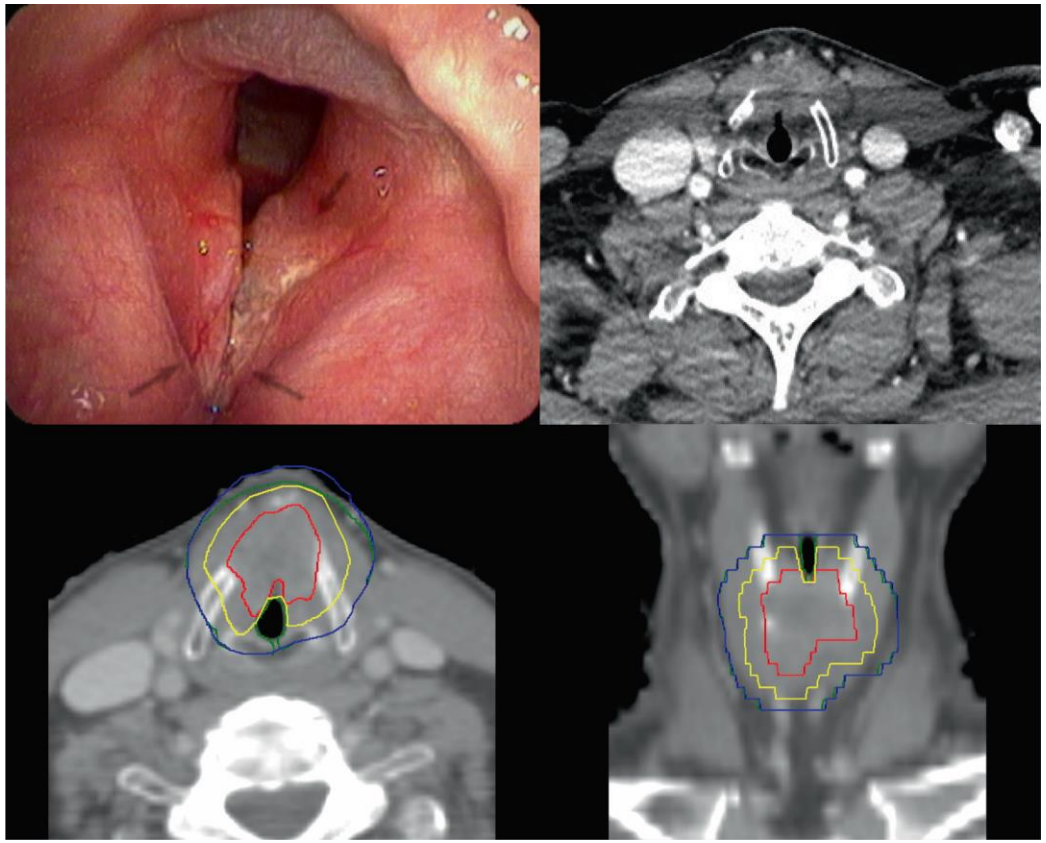
(4) Prophylactic coverage of ipsilateral Level Ib lymph node level in CTVn2 if there is:

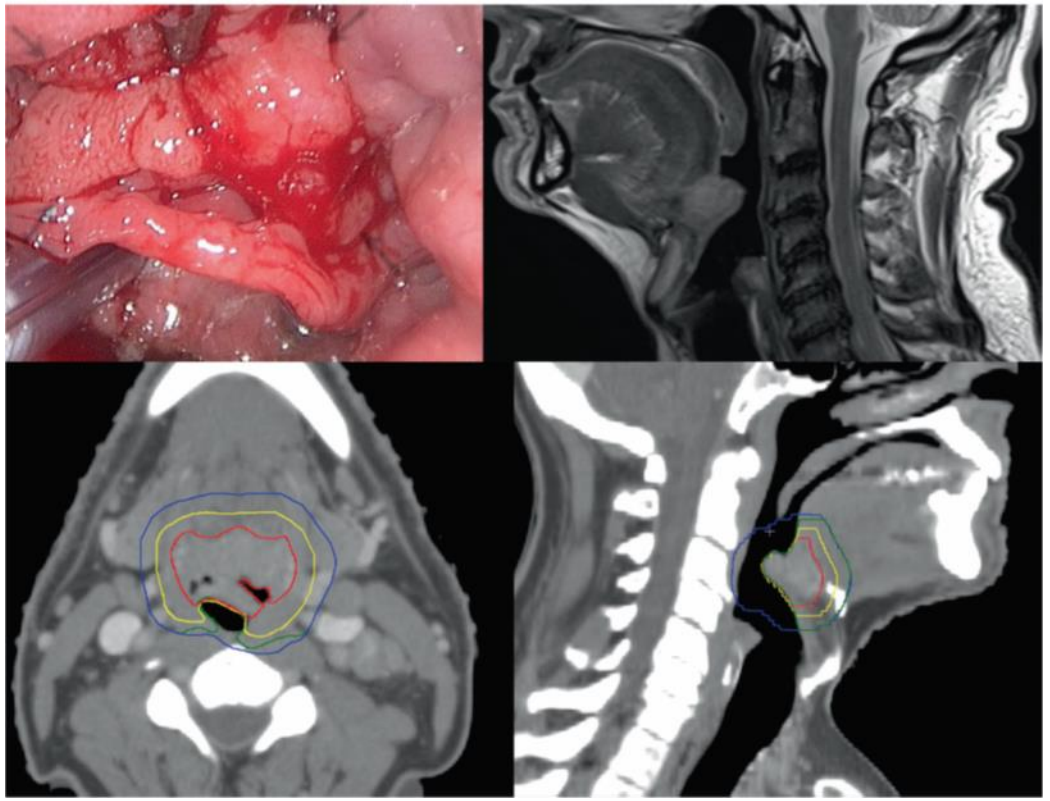
- - disease involvement of the submandibular gland, or;
- - involvement of structures that drain to level Ib as the first
- echelon site (namely the oral cavity, anterior half of nasal cavity), or;
- - involvement of level II LNs with extracapsular extension.
- [Consensus: High (91%)]
- - level II nodal involvement with maximum nodal axial diameter greater than 2 cm

V. Gregoire et al.:

Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines

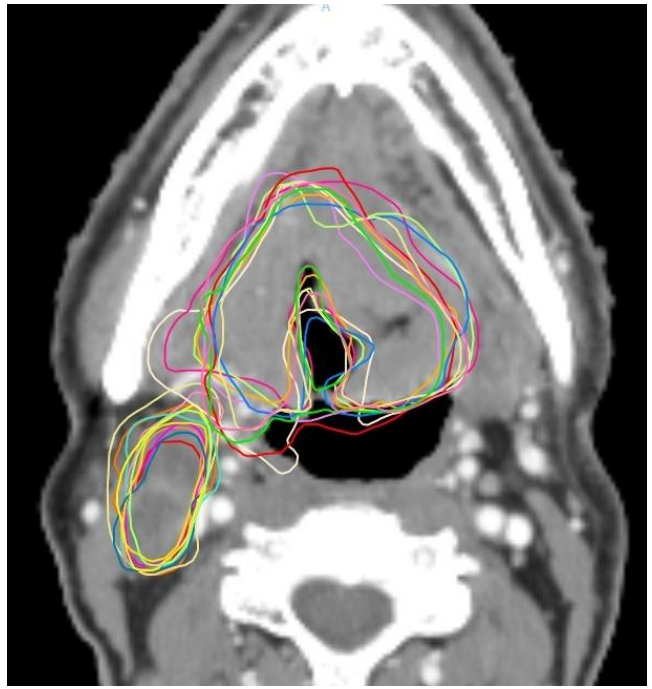


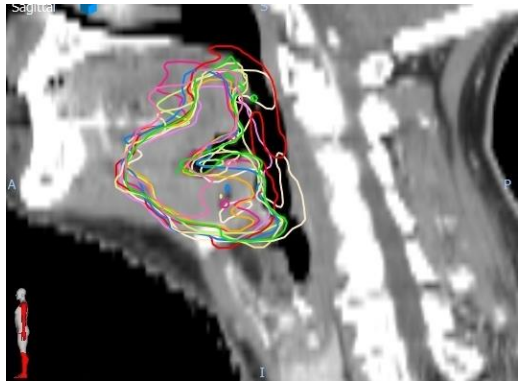




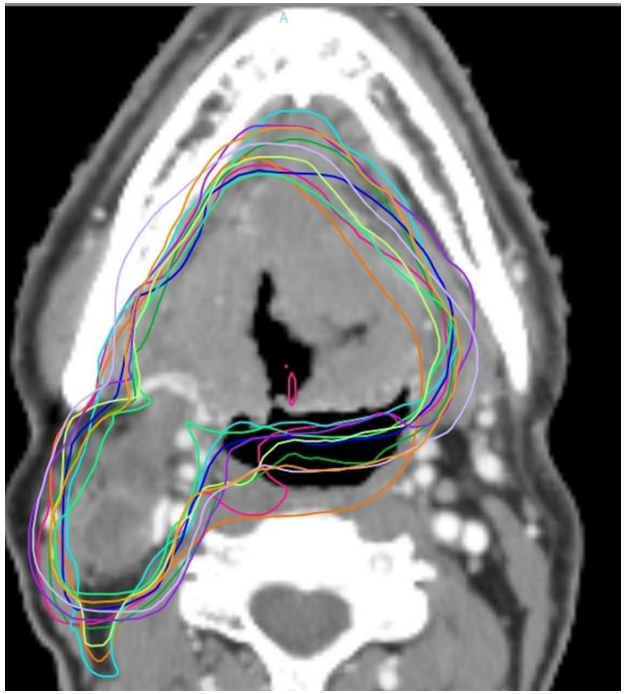
Radiotherapy and Oncology 126 (2018) 3–24

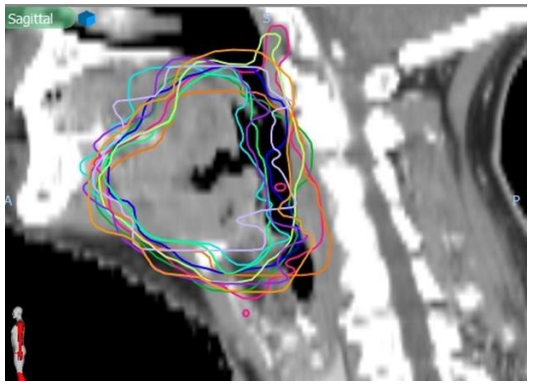
Definizione GTV





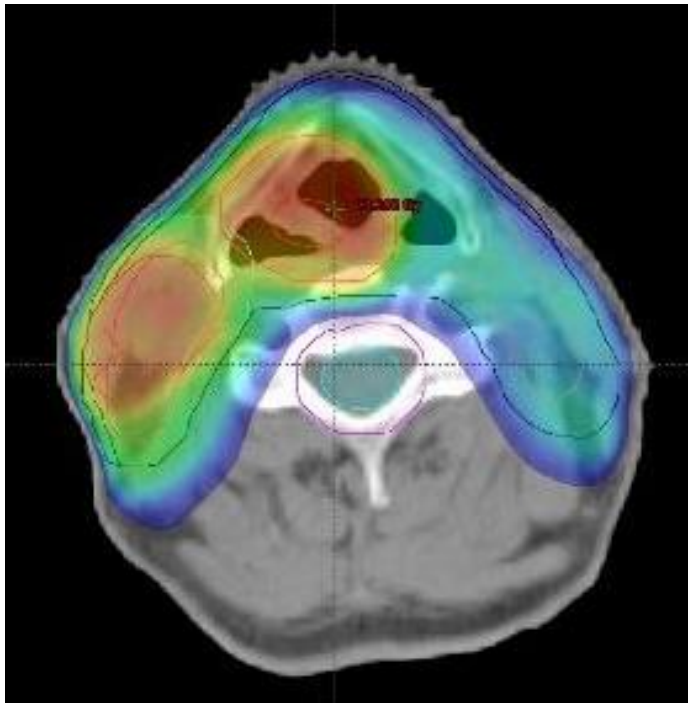
Definizione CTV ad alta dose

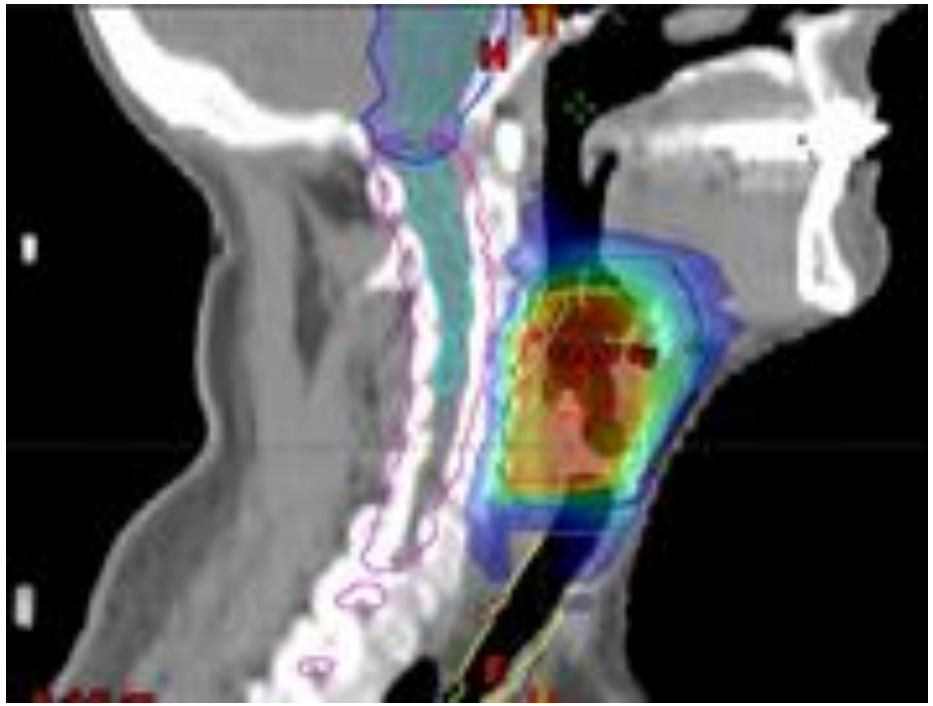


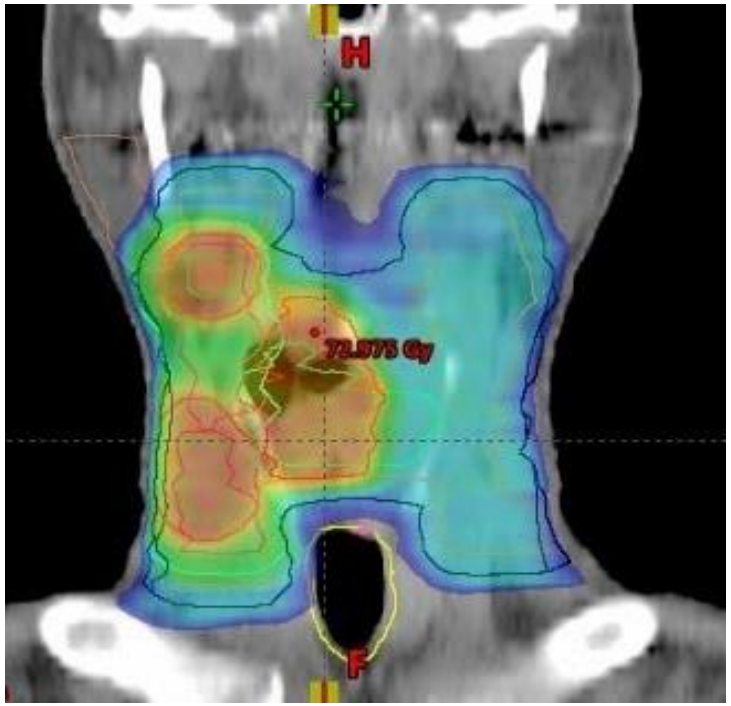


Corso teorico-pratico sul contouring nei tumori della mesofaringe
Gruppo AIRO H&N

SCC laringeo sovraglottico, T1N2b stadio IVa
Risultati dosimetrici ottenibili con trattamento IMRT volumetrico.







IGRT & Adaptive Radiotherapy

Review article

Adaptive radiation therapy: When, how and what are the benefits that literature provides?

An electronic research of articles published from January 2004 to October 2020

Among a total of 127 studies assessed for eligibility, 85 articles were ultimately retained for the review.

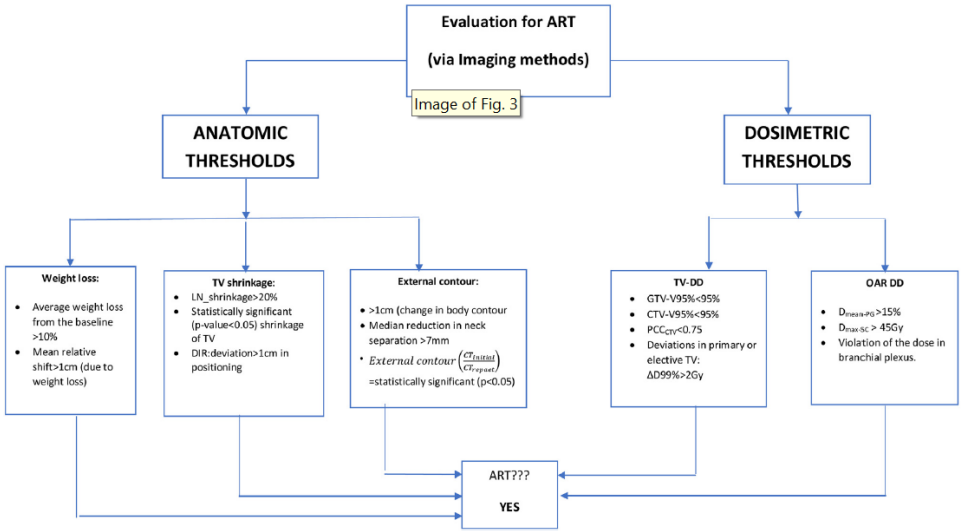


Fig. 3. Results conducted from the studies, which lead to ART implementation.

The most noticeable changes have been reported in the middle fraction of the treatment.

The suggested optimal time to replan is between the third and the fourth week.

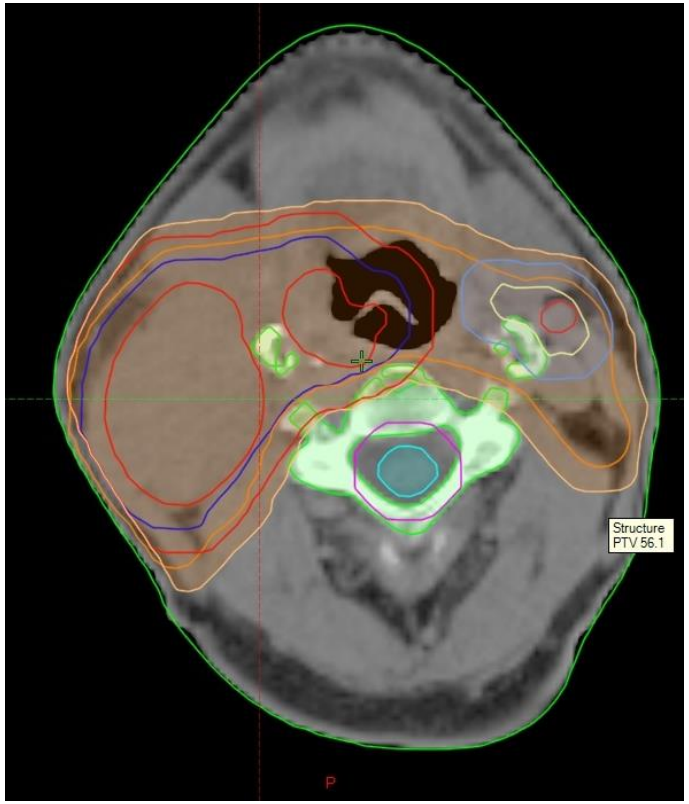
- Anatomical deviations > 1 cm in the external contour,
- average weight loss > 10%,
- violation in the dose coverage of the targets > 5%,
- violation in the dose of the peripherals

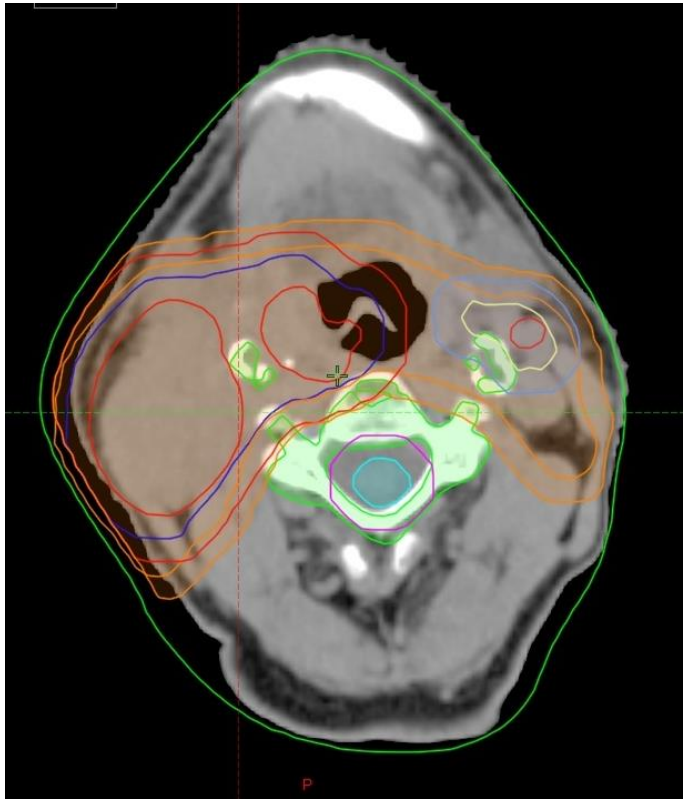
were some of the thresholds that are currently used, and which lead to replanning.

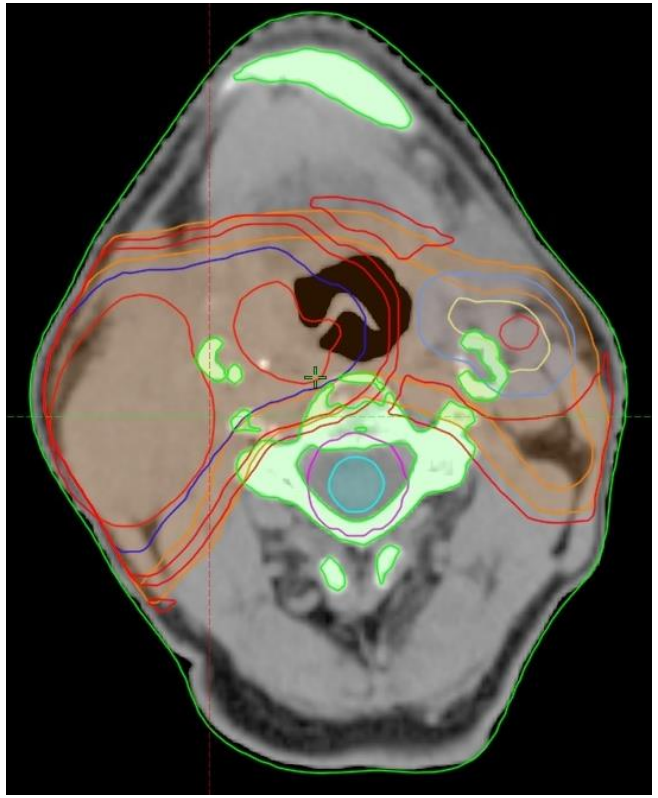
No clear benefits of ART but…

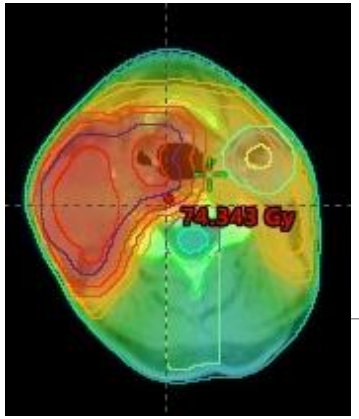
R. Avgousti et al. Cancer/Radiothérapie *in press*

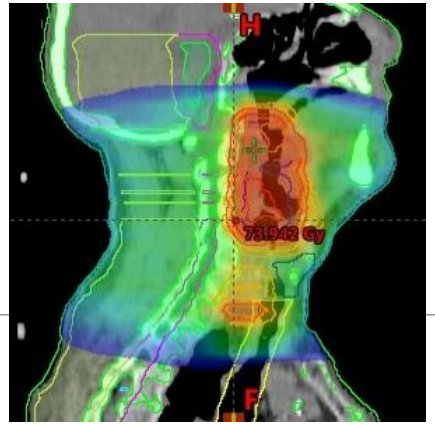
In presenza di voluminose adenopatie le modifiche in corso di radioterapia sono più evidenti

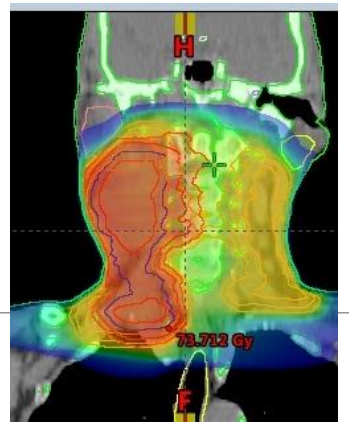


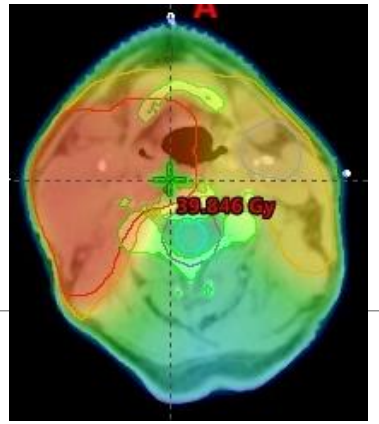


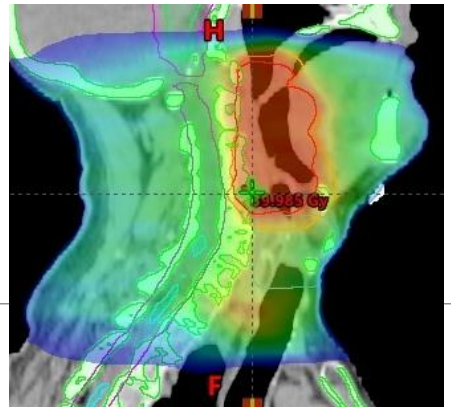


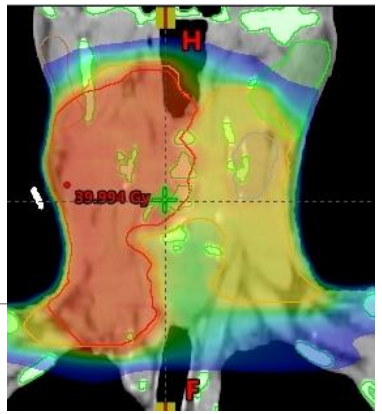

74.343 Gy

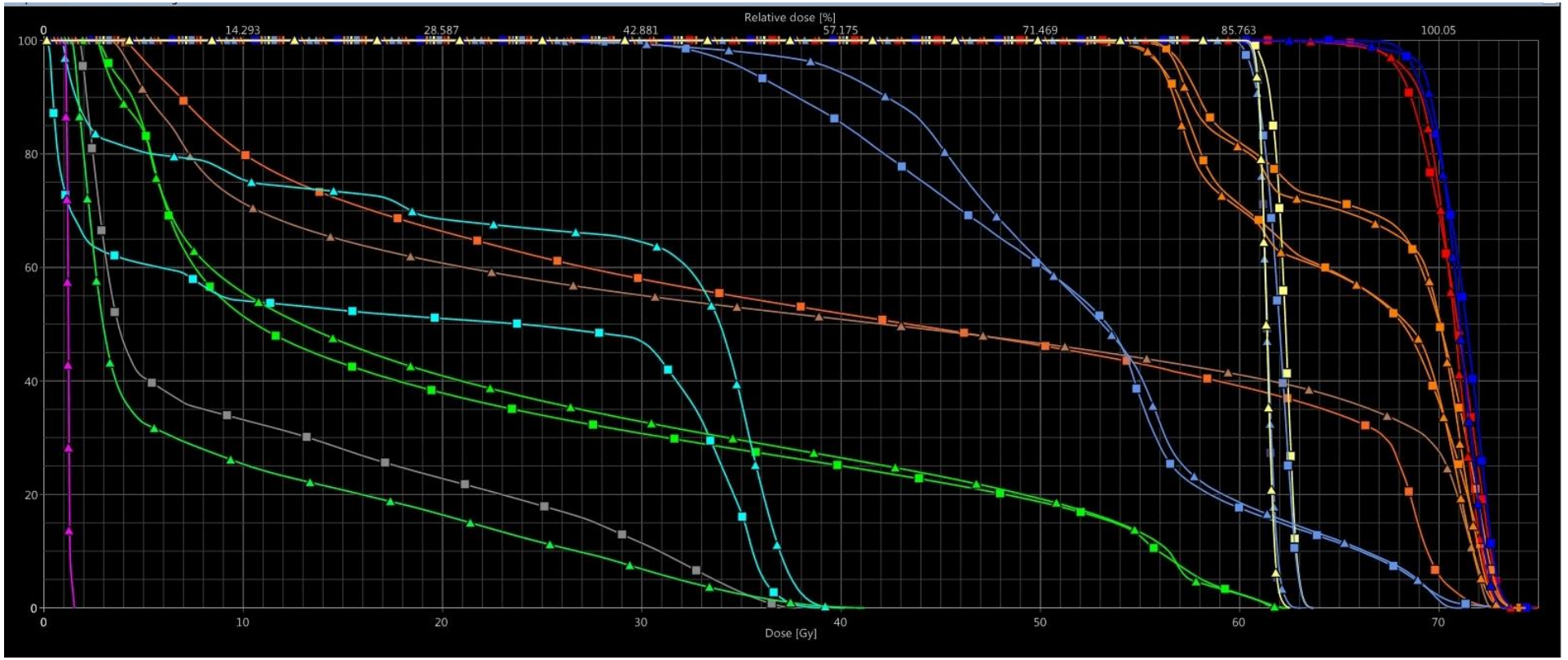

H
73.942 Gy
F


H
73.712 Gy
F

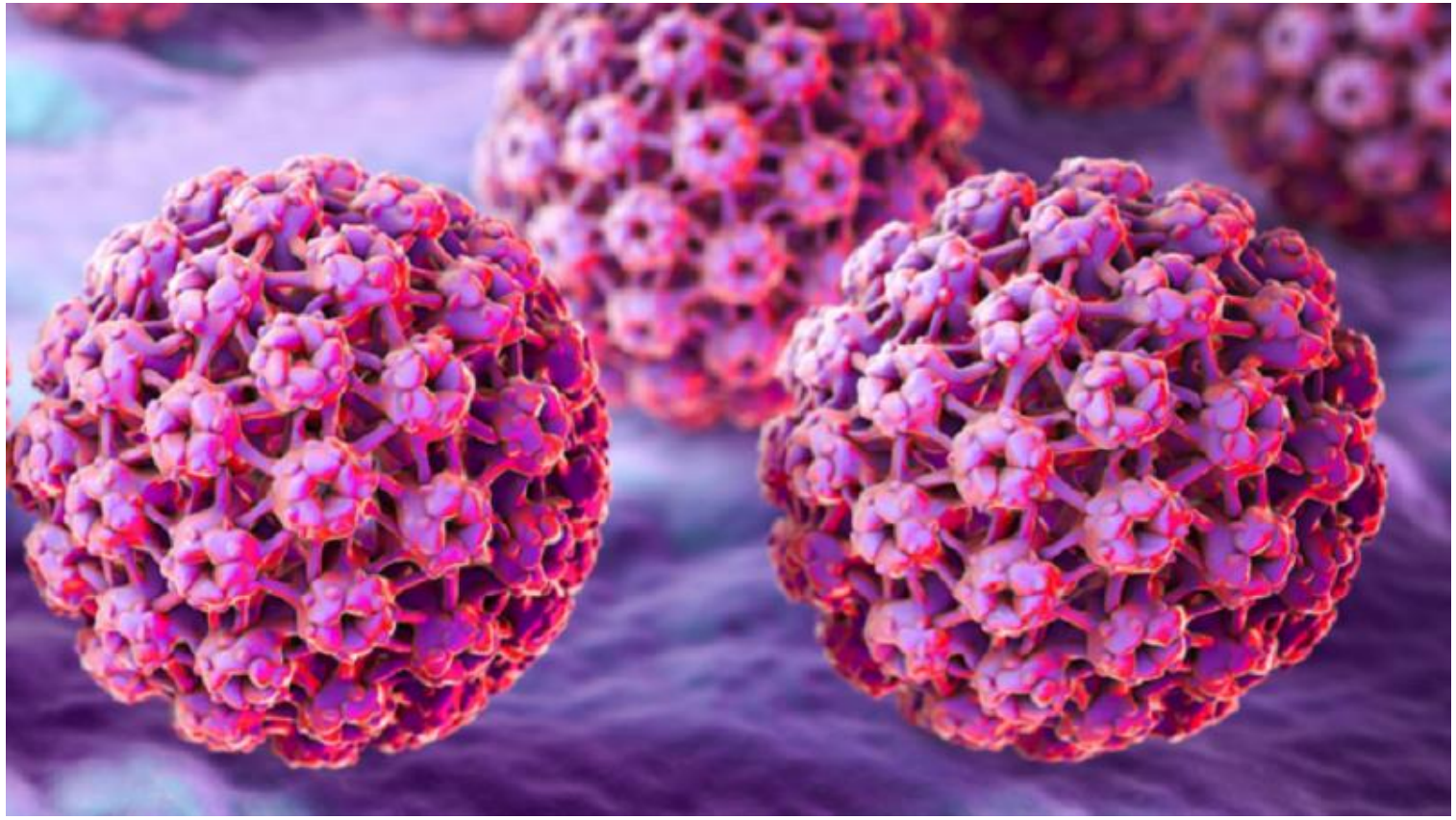

A
39.946 Gy


H
F


H
39.994 Gy
F


Relative dose [%]
0
14.293
28.587
42.881
57.175
71.469
85.763
100.05
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Dose [Gy]

HPV +



Nguyen-Tan PF, Zhang Q, Ang KK et al.
Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the **RTOG 0129 trial**: Long-term report of efficacy and toxicity.

Patients were randomized

- to either high-dose cisplatin 100 mg/m^2 every 3 weeks for 3 doses concurrent with standard fractionation of 70 Gy in 35 fractions over 7 weeks
- or cisplatin 100 mg/m^2 every 3 weeks for 2 doses concurrent with accelerated fractionation of 72 Gy in 42 fractions over 6 weeks.

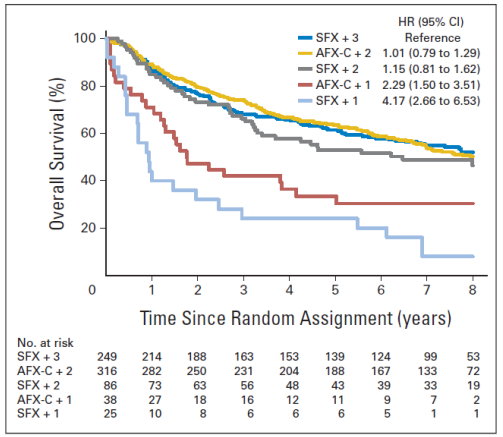


Fig 3. Overall survival by fractionation and number of cisplatin cycles delivered. AFX-C, accelerated fractionation with a concomitant boost; HR, hazard ratio; SFX, standard fractionation.

Conclusion

When combined with cisplatin, **AFX-C neither improved outcome nor increased late toxicity in patients with LA-HNC.**

Long-term high survival rates in p16-positive patients with oropharyngeal cancer support the ongoing efforts to explore de-intensification

NB.

- Tecniche a campi contrapposti,
- IMRT non permessa

J Clin Oncol 2014;32:3858–3866.

De escalation in HPV+ OPC

RT+Cetuximab vs RT+CDDP

Maura L. Gillison et al. RTOG 1016

Radiotherapy plus cetuximab or cisplatin for human papillomavirus (HPV)-positive oropharyngeal cancer: a randomized, multicenter, non-inferiority clinical trial

Patients with **locoregionally advanced p16-positive OPC** stratified for

- T1-T2 vs. T3-T4
- N0-N2a vs. N2b-N3
- Zubrod Performance Status (0 vs. 1)
- tobacco smoking history (≤ vs. >10 pack-years)

Randomized 1:1 to

- RT + cetuximab 400 mg/ m^2, followed by 250 mg/m^2 for seven weekly doses
- RT +cisplatin 100 mg/m^2 for two doses, 21 days apart.

The primary endpoint was overall survival (OS) with non-inferiority margin 1.45 (hazard ratio).

All patients received **accelerated IMRT delivered to 70 Gy in 35 fractions over 6 weeks**, 6 fractions per week (with 2 fractions 1 day per week, at least 6 hours apart)

849 patient, Median FU 4-5 years

Results at 5 years (Cetuximab group vs cisplatin group)

OS: 77,9% vs 84,6% (p 0,0163)

PFS: 67,3% vs 78,4%

LRF: 17,3% vs 9,9%

Conclusion:

- **RT + Cetuximab demonstrated inferior OS and PFS compared with RT + CDDP**
- Moderate to severe **toxicity** (acute and late) **similar** in the two groups

Lancet 2019 January 05; 393(10166): 40–50

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

32 head and neck treatment centres in Ireland, the Netherlands, and the UK

patients with HPV-positive low-risk oropharyngeal cancer (non-smokers or lifetime smokers with a smoking history of <10 pack-years).

In addition to radiotherapy (**70 Gy in 35 fractions**), Randomisation to receive:

- **intravenous cisplatin** (100 mg/m² on days 1, 22, and 43 of radiotherapy)
- or **intravenous cetuximab** (400 mg/m² loading dose followed by seven weekly infusions of 250 mg/m²).

2012-2016: **334 patients recruited**

Overal (acute and later) severe (G4-5) toxicity did not differ significantly between groups

Results at two years (**cisplatin vs cetuximab**)

- **Overall survival: 97,5% vs 89,4** p=0,001
- **Recurrence: 6% vs 16.1%,** p=0,0007

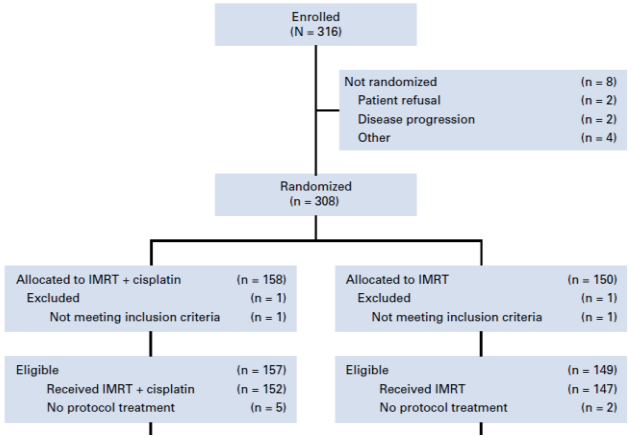
Cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control.

Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

Lancet 2019; 393:51-60

Sue S. Yom et al.
Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002)

Patients with p16-positive, T1-T2 N1-N2b M0, or T3 N0-N2b M0 OPSCC (7th edition staging) with ≤ 10 pack-years of smoking received **60 Gy of IMRT over 6 weeks with concurrent weekly cisplatin** (C) or **60 Gy IMRT over 5 weeks**.



CONCLUSION

- The IMRT + C arm met both prespecified end points justifying advancement to a phase III study.
- Higher rates of grade ≥ 3 acute AEs were reported in the IMRT 1 C arm.

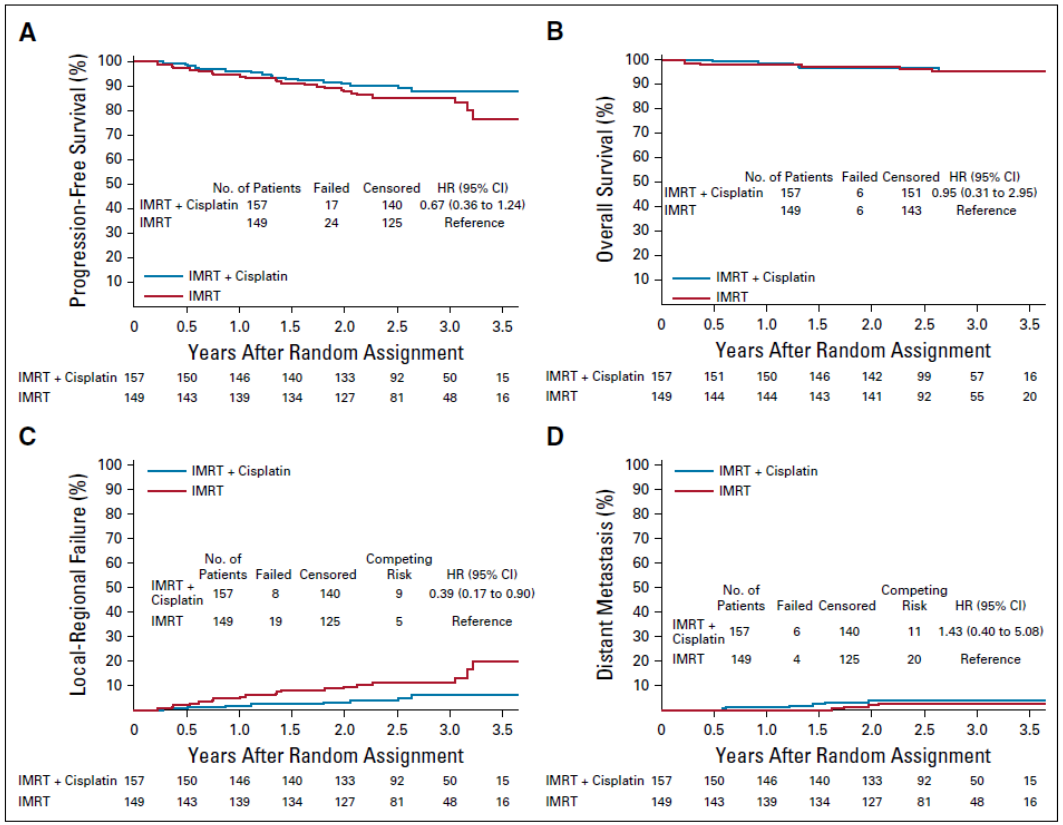
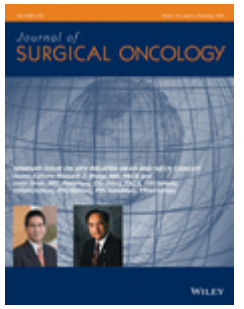


FIG 2. NRG-HN002 progression-free (A) and overall survival (B), local-regional failure (C), and distant metastasis (D). HR, hazard ratio; IMRT, intensity-modulated radiation therapy.

Chen L et. al. - Review Article

Current considerations for radiotherapy in HPV-associated head and neck cancer



- Distinct epidemiology: a younger patient population without a significant tobacco or alcohol history
- Distinct staging systems for HPV-negative and HPV-positive carcinomas
- RTOG 0129: Patients can be risk-stratified based using HPV status as well as tobacco use, with statistically significant differences in
  - 3-year locoregional relapse rates (13.6% in HPV-positive vs. 35.1% in HPV-negative patients)
  - 3-year OS (82.4% in HPV-positive and 57.1% in HPV-negative).
- HPV-mediated oncogenesis has been hypothesized to confer increased radiosensitivity by rewiring the DNA damage response, improving antitumor immunity, altering the cell cycle, and increasing apoptosis following radiation exposure.

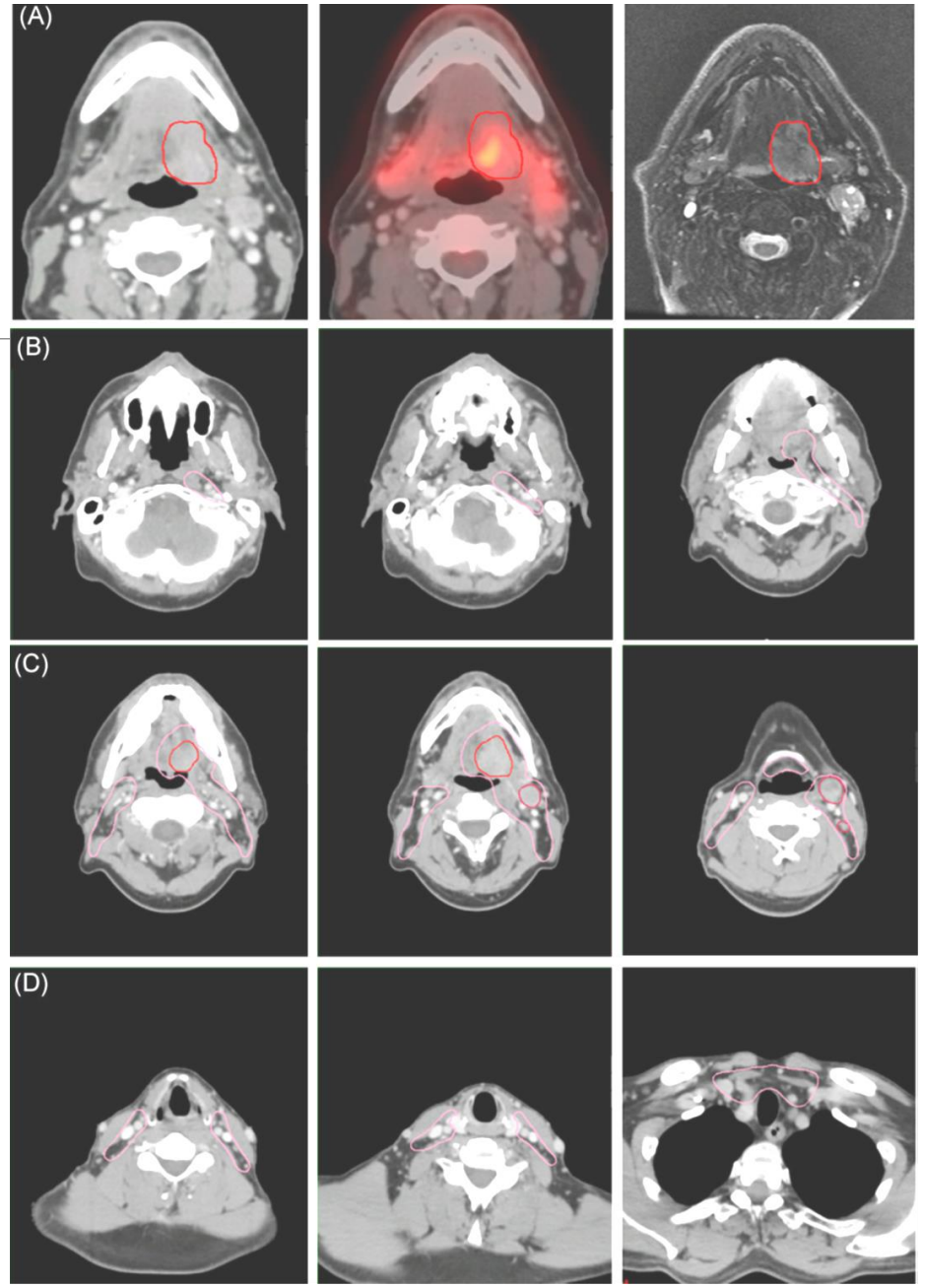
A multidisciplinary approach should balance maximizing locoregional control with preserving organ function, maintaining the quality of life, and minimizing treatment related toxicity.

Chen L et. Al. -Review Article

Current considerations for radiotherapy in HPV-associated head and neck cancer

Memorial Sloan Kettering Cancer Center NY

- Routinely omission of uninvolved level Ib and level V for HPV-positive oropharynx cancer
- In the uninvolved neck, routinely omission of high retropharyngeal and level 2 lymph nodes
- For the base of tongue tumors with significant involvement of the oral tongue, ipsilateral coverage of level Ib, on a case-by-case basis.



Chen L et. al. - Review Article

Current considerations for radiotherapy in HPV-associated head and neck cancer

276 patients (32% cT3-4 and cN2-N3)

CT PET and RM for local staging

Dose prescribed:

- Elective nodal regions: 30 Gy
- GTV: 70 Gy

The majority of patients completed 300 mg/m^2 of high dose cisplatin

Results after 2 years

- **Locoregional control:** 97%,
- **Distant metastasis-free survival:** 95.2%,
- **OS**: 95.1%

Seven patients developing recurrence at the primary site (with received 70 Gy)

Nichols et al.

Treatment de-escalation for HPV-associated oropharyngeal squamous cell carcinoma with **radiotherapy vs. trans-oral surgery (ORATOR 2):** study protocol for a randomized phase II trial

- Multicenter phase II study - 140 patients T1–2 N0–2 HPV+ OPC
- Patients will be stratified based on smoking status (< 10 vs. ≥ 10 pack-years).
- Hypothesis: to achieve 2 years OS of 85% or greater

ARM 1:De-escalated primary radiotherapy (60 Gy) ± concomitant chemotherapy

- 60 Gy in 30 fractions: Gross Tumor and Involved Nodes
- 54 Gy in 30 fractions: High risk subclinical areas.
- 48 Gy in 30 fractions: Low-risk nodal areas

- 6 fraction a week if no Chemo and < 70 yrs

Concurrent chemotherapy: Weekly CDDP 40 mg/m^2 for 6 cycles

ARM 2: patients submitted to TOS.

- Patients with positive margins or ENE will receive a 6-week course of radiation as follows:
  - 60 Gy in 30 fractions: Area of positive margins or ENE
  - 54 Gy in 30 fractions: Operative bed, including primary tumor location and all dissected nodal levels
  - 48 Gy in 30 fractions: Undissected areas considered to be at low-risk of harbouring microscopic disease.

- Patients without positive margins or ENE will receive a 5-week course of radiation as follows:
  - 50 Gy in 25 fractions: Operative bed, including primary tumor location and all dissected nodal levels
  - 45 Gy in 25 fractions: Undissected areas considered to be at low-risk of harbouring microscopic disease

Ferris RL, Flamand Y, Weinstein GS et al.

Phase II Randomized Trial of **Transoral Surgery and Low-Dose IMRT** in Resectable p16+ Locally Advanced Oropharynx Cancer: An ECOG-ACRIN Cancer Research Group Trial (E3311)

RESULTS

TOS for 495 patients.

Eligible and treated patients were assigned as follows:

- arm A (**low risk**, n = 38, observation) enrolled 11%,
- **intermediate risk** arms B (50 Gy, n = 100) or C (60 Gy, n = 108) randomly allocated 58%,
- arm D (**high risk**, n = 113)

2-year PFS

- 96.9% for arm A (observation, no RT),
- 94.9% for arm B (50 Gy),
- 96.0% for arm C (60 Gy),
- 90.7% for arm D (66 Gy plus weekly cisplatin).

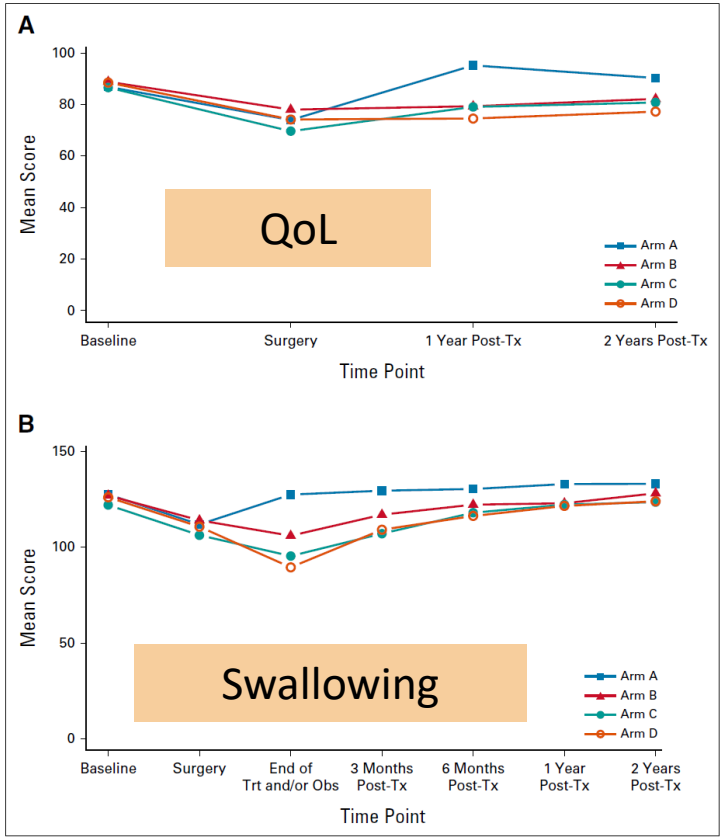


FIG 4. (A) QOL and (B) swallowing. QOL, quality of life; Trt and/or Obs, treatment and/or observation; Tx, treatment.

J Clin Oncol 2020;38 (15suppl):6500a.

Rainer Fietkau et al.
Randomized phase-III-trial of concurrent chemoradiation for locally advanced head and neck cancer comparing dose reduced radiotherapy with paclitaxel/cisplatin to standard radiotherapy with fluorouracil/cisplatin: **The PacCis-trial**

SCCHN, stage III–IVB, randomized to receive

- ARM A: paclitaxel/cisplatin (PacCis)–CRT
  (paclitaxel 20 mg/m2 on days 2, 5, 8, 11 and 25, 30, 33, 36; cisplatin 20 mg/m2, days 1–4 and 29–32; RT to a total dose of **63.6 Gy**)
- ARM B: fluorouracil/cisplatin (CisFU)–CRT
  fluorouracil 600 mg/m2; cisplatin 20 mg/m2, days 1–5 and 29–33; RT: **70.6 Gy**).

221 patients enrolled between 2010 and 2015.

Paclitaxel/cisplatin–CRT with a reduced **RT-dose is not superior to standard fluorouracil/cis platin–CRT**.

Subgroup analyses indicate that a reduced radiation dose seems to be sufficient for p16+ oropharyngeal cancer or non-smokers.

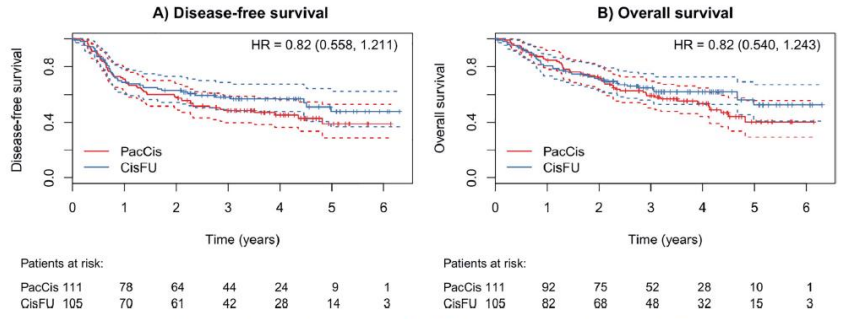


Fig. 2. Disease-Free (a) and Overall survival (b) for both treatment arms, including hazard ratios.

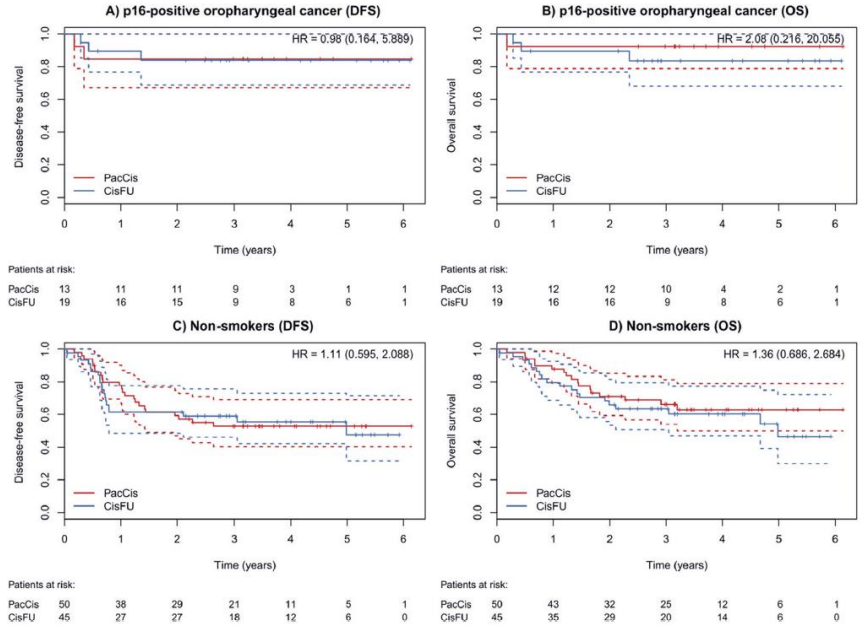
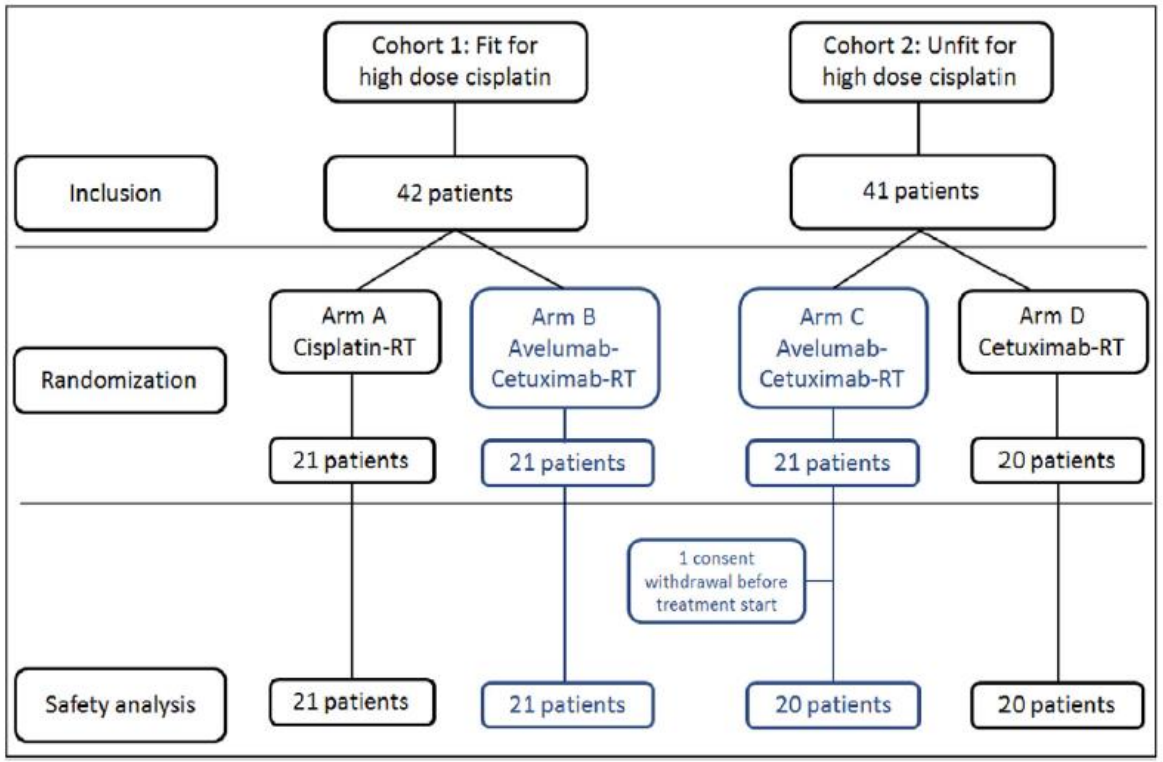


Fig. 3. Disease-Free and Overall survival for p16-positve oropharyngeal cancer patients (a, b), and non-smokers (c, d).

Radiother Oncol. 2020 Mar;144:209-217

Avelumab-cetuximab-radiotherapy versus standards of care in locally advanced squamous-cell carcinoma of the head and neck: The safety phase of a randomised phase III trial GORTEC 2017-01 (REACH)



Number (%) of patients with adverse events by grade in experimental and SOC arms.

Characteristics	Arm A (SOC cisplatin)	Arms B + C (experimental)	Arm D (SOC cetuximab)
Any grade	21 (100%)	41 (100%)	20 (100%)
Grade I	20 (95%)	39 (95%)	20 (100%)
Grade II	20 (95%)	41 (100%)	16 (80%)
Grade III	18 (86%)	35 (85%)	19 (95%)
Grade IV	2 (10%)	5 (12%)	2 (10%)
Grade V	1 (5%)	0 (0%)	0 (0%)

SOC, standard of care.

Skin toxicity in experimental and SOC arms.

Characteristics	Arm A (SOC cisplatin) (N = 21)	Arms B + C (experimental) (N = 41)	Arm D (SOC cetuximab) (N = 20)
Radiation Dermatitis			
Grade I	11 (52%)	8 (20%)	1 (5%)
Grade II	7 (33%)	11 (27%)	7 (35%)
Grade III	4 (19%)	20 (49%)	11 (55%)
Grade IV	0	1 (2%)	0
Rash acneiform/maculo-papular			
Grade I	0	15 (37%)	7 (35%)
Grade II	0	16 (39%)	6 (30%)
Grade III	0	2 (5%)	3 (15%)
Grade IV	0	0	0
Erythema			
Grade I	1 (5%)	1 (2%)	0
Grade II	0	2 (5%)	0
Grade III	0	0	0
Dry skin			
Grade I	0	5 (12%)	1 (5%)
Grade II	0	3 (7%)	0
Skin infection			
Grade I	0	0	1 (5%)
Grade II	0	1 (2%)	0
Vitiligo			
Grade I	0	1 (2%)	0

SOC, standard of care.

Tao Y. et al. European Journal of Cancer 141 (2020) 21-29

Reduction in Radiotherapy Dose Following Induction Chemotherapy

Seiwert TY, Foster CC, Blair EA et al. OPTIMA: A phase II dose and volume de-escalation trial for human papillomavirus positive oropharyngeal cancer.

Effort to limit treatment elated toxicity while preserving efficacy.

- low-risk Patients (≤T3, ≤ N2B, ≤ 10 pack-year history)
- high-risk patients (T4 or ≥N2C or>10 PYH).

After three cycles of carboplatin/nab-paclitaxel,

- Low-risk patients with ≥ 50% response received 50 Gray (Gy) RT **(RT50)**
- Low-risk patients with 30%–50% response or high-risk patients with ≥ 50% response received 45 Gy CRT **(CRT45).**
- Patients with lesser response received standard of care 75 Gy CRT (CRT75).

RT/CRT was limited to the first echelon of uninvolved nodes.

The primary end point was 2-year progression-free survival compared with a historic control of 85%. Secondary end points included overall survival and toxicity.

Reduction in Radiotherapy Dose Following Induction Chemotherapy

Seiwert TY, Foster CC, Blair EA et al. OPTIMA: A phase II dose and volume de-escalation trial for human papillomavirus positive oropharyngeal cancer.

Results:

Sixty-two patients (28 low risk/34 high risk) were enrolled.

- Of low-risk patients, 71% received RT50 while 21% received CRT45.
- Of high-risk patients, 71% received CRT45.

Median follow-up of 29 months,

2-year PFS and OS were **95% and 100% for low-risk patients** and **94% and 97% for high-risk patients**, respectively.

The overall 2-year PFS was 94.5% and within the 11% non inferiority margin for the historic control.

Grade 3+ mucositis occurred in 30%, 63%, and 91% of the RT50, CRT45, and CRT75 groups, respectively (P=0.004).

Rates of any PEG-tube use were 0%, 31%, and 82% for RT50, CRT45, and CRT75 groups, respectively (P<0.0001).

Conclusions: Induction chemotherapy with response and risk-stratified dose and volume de-escalated RT/CRT for HPVþ OPSCC is associated with favorable oncologic outcomes and reduced acute and chronic toxicity.

Ann Oncol 2018; 30:297–302

Reduction in Radiotherapy Dose Following Induction Chemotherapy

Seiwert TY, Foster CC, Blair EA et al.

OPTIMA: A phase II dose and volume de-escalation trial for human papillomavirus positive oropharyngeal cancer.

Table 2. Worst acute toxicity and functional outcomes by treatment arm and risk group

Treatment arm	Acute toxicity [no. (%)][a]						PEG dependency [no. (%)]			
	Grade 3+ mucositis	*P*-value	Grade 3+ dermatitis	*P*-value	Grade 3+ neutropenia	*P*-value	Ever required	6 months	12 months	*P*-value[b]
RT50	6 (30)	0.004	0 (0)	<.0001	10 (50)	0.67	0 (0)	0 (0)	0 (0)	<0.001
CRT45	19 (63)		6 (20)		14 (47)		9 (31)	1 (3)	1 (4)	
CRT75	10 (91)		6 (55)		5 (46)		9 (82)	2 (18)	1 (9)	
Risk status										
Low risk	11 (39)	0.009	2 (7)	0.02	13 (46)	0.87	2 (7)	1 (4)	0 (0)	0.0005
High risk	24 (71)		10 (29)		16 (47)		16 (50)	2 (6)	2 (7)	

[a]There was one grade 5 death due to sepsis during cycle 1 of CRT45.

[b]*P*-value for ever requiring PEG tube placement over the course of treatment and follow-up.

PEG, percutaneous endoscopic gastrostomy tube, RT50, radiation to 50 Gy, CRT45, chemoradiation to 45 Gy, CRT75, chemoradiation to 75 Gy.

Ann Oncol 2018; 30:297–302

Shanthi Marur et al.

E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx

ECOG-ACRIN Cancer Research Group

Patients with HPV16 and/or p16-positive, stage III-IV OPSCC

Three cycles of IC with cisplatin, paclitaxel, and cetuximab.

- Patients with primary-site cCR to IC received IMRT 54 Gy with weekly cetuximab;
- Patients with less than cCR to IC at the primary site or nodes received 69.3 Gy and cetuximab

The primary end point was 2-year progression-free survival.

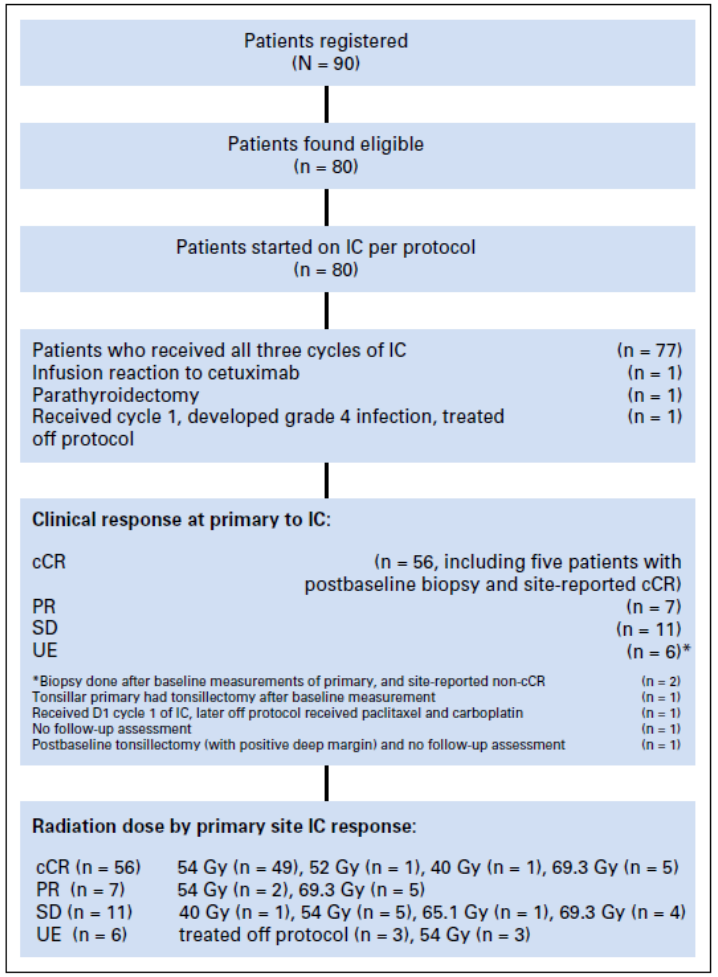


Fig 1. Patient flow diagram. cCR, clinical complete response; IC, induction chemotherapy; PR, partial response; SD, stable disease; UE, unevaluable.

Shanthi Marur et al.

E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx

ECOG-ACRIN Cancer Research Group

Results

90 patients enrolled, 80 valuable.

the majority had stage T1-3N0-N2b OPSCC and a history of 10 pack-years of cigarette smoking.

Three cycles of IC were delivered to 77 of the 80 patients.

Fifty-six patients (70%) achieved a primary-site cCR to IC and 51 patients continued to cetuximab with IMRT 54 Gy.

Median follow-up of 35.4 months, 2-year PFS and OS

- 80% and 94%, respectively, for patients with primary-site cCR treated with 54 Gy of radiation (n = 51);
- 96% and 96%, respectively, for patients with < T4, < N2c, and ≤ 10 pack-year smoking history who were treated with ≤ 54 Gy of radiation (n = 27).

At 12 months, significantly fewer patients treated with a radiation dose 54 Gy had difficulty swallowing solids (40% vs 89%; P = .011) or had impaired nutrition (10% vs 44%; P = .025).

Conclusion

For IC responders, reduced-dose IMRT with concurrent cetuximab is worthy of further study in favorable-risk patients with HPV-associated OPSCC.

Radiation dose reduction resulted in significantly improved swallowing and nutritional status.

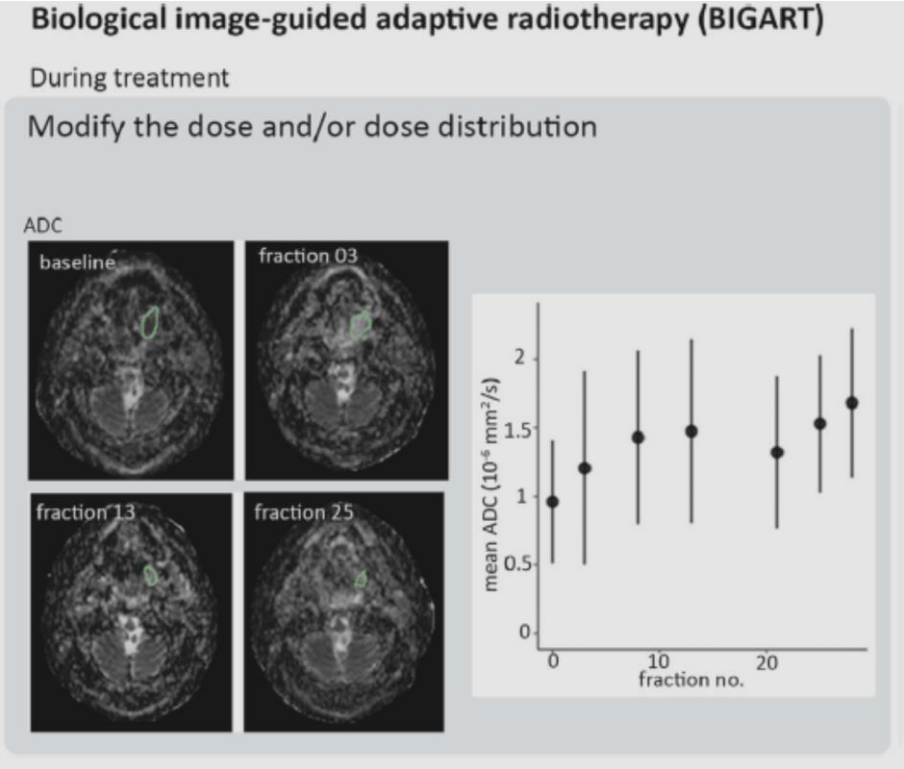
NEXT FUTURE

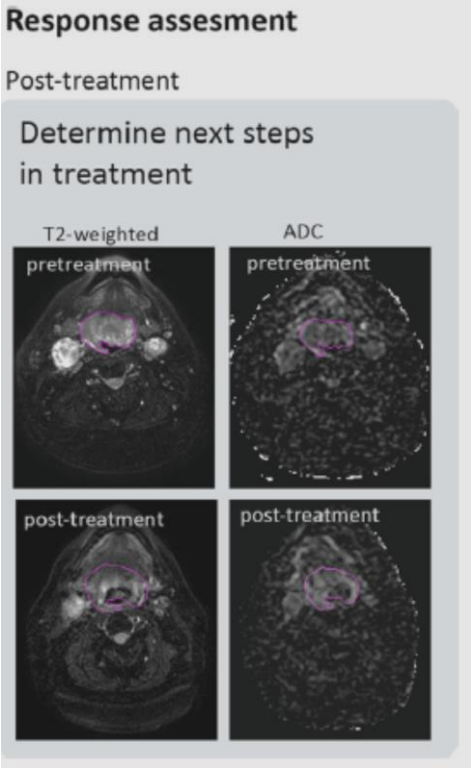
MR LINACS

Petra J. van Houdt, Hina Saeed, Daniela Thorwarth et al.

Integration of quantitative imaging biomarkers in clinical trials for **MR-guided radiotherapy**:

Conceptual guidance for multicentre studies from the MR-Linac Consortium Imaging Biomarker Working Group



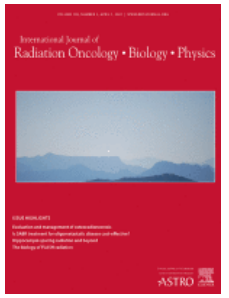


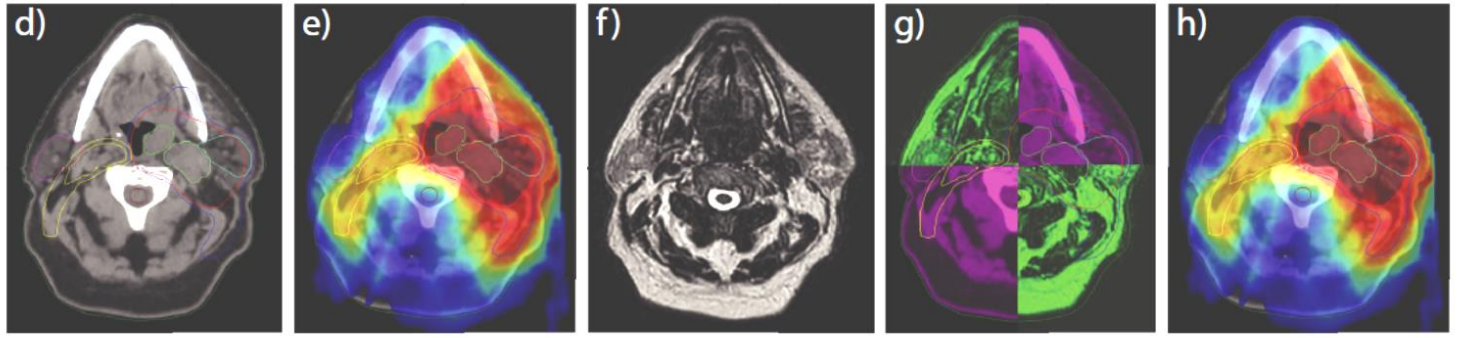
Quantitative imaging biomarkers (QIBs) derived from MRI techniques have the potential to be used for the personalised treatment of cancer patients.

The most important need is to gather and understand **how the QIBs collected during MRIgRT correlate with clinical outcomes.**

Brigid A. McDonald et al. - MR-Linac Consortium Head and Neck Tumor Site Group

Initial Feasibility and Clinical Implementation of **Daily MR-Guided Adaptive Head and Neck Cancer Radiation Therapy** on a 1.5T MR-Linac System: Prospective R-IDEAL 2a/2b Systematic Clinical Evaluation of Technical Innovation





Methods and Materials:
Ten patients with HNC received daily ART on a 1.5T/7MV MR-linac, 6 using ATP only and 4 using ATP with 1 offline adapt-to-shape replan.

Conclusions: Daily ART on a 1.5T MR-linac using an online ATP workflow is safe and clinically feasible for HNC
and results in delivered doses consistent with planned doses.

Int J Radiation Oncol Biol Phys, Vol. 109, No. 5, pp. 1606e1618, 2021

Rosie B Hales et al.

The impact of gadolinium-based MR contrast on radiotherapy planning for oropharyngeal treatment on the MR Linac

Purpose: Gadolinium-based contrast agents (GBCAs) may add value to magnetic resonance (MR)-only radiotherapy (RT) workflows including on hybrid machines such as the MR Linac.

Methods: Ten patients with oropharyngeal squamous cell carcinoma receiving RT from November 2018 to April 2020 were included in this study

Results: The median percent dose differences for key reportable dosimetric parameters between non-contrast and simulated contrast plans were <1.2% over all fractions over all patients for reportable target parameters (mean 0.34%, range 0.22%–1.02%).

Conclusion: **Dose differences to targets and OARs in oropharyngeal cancer treatment due to the presence of GBCA were minimal,** and this work suggests that prospective in vivo evaluations of impact may not be necessary in this clinical site.

NEW BIOMARKERS

Actual and next generation biomarker

Prognostic and predictive biomarker

- HPV positivity
- T4 tumor stage
- Bilateral nodal disease or N3
- Smoking history: high risk feature in HPV+
- Response to induction therapy

Poor prognostic value:
high MATH, low ERα and HPV-negative status
Goodprognosis values:
low MATH, high ERα and HPV-positive status

Next generation biomarker

PIK3CA mutations in HPV+ OPSCC Worse DFS vs PK3CA wild-type in de-escalation trials	Beaty BT et al. PIK3CA mutation in HPV-associated OPSCC patients receiving deintensified chemoradiation. J NatlCancer Inst 2019;112:855–858.
Mutation in P54: Associated with smoking-related HPV neg cancer May identify a poor risk population	Carlos de Vicente J et al. Prognostic significance of p53 expression in oral squamous cell carcinoma without neck node metastases. Head Neck. 2004;26: 22–30.
Mutant allele tumor heterogeneity (MATH) Quantitativ measure of intratumor genetic heterogeneity Worse outcome	Krupal B. et al. A combination of intra-tumor genetic heterogeneity, estrogen receptor alpha and human papillomavirus status predicts outcomes in H&NSCC following chemoradiotherapy Oral Oncology 120 (2021) 105421
Estrogen receptor (ER)-α: Favorable prognosis	C. P. De Oliveira et al. Is There a Role for Sex Hormone Receptors in Head-and-neck Cancer? Links with HPV Infection and Prognosis ANTICANCER RESEARCH 41: 3707-3716 (2021)
TRAF3 and CYLD loss by inactivating mutations or delection Favorable prognosis among HPV+ OPSCC	Hajek M, Sewell A, Kaech S et al. TRAF3/CYLD mutations identify a distinct subset of human papillomavirus-associated head and neck squamous cell carcinoma. Cancer 2017;123:1778–1790.

Take Home messages

Stato dell'arte

- Imaging multimodale per definizione VOIs
- Trattamenti volumetrici
- Associazione con chemioterapia nei casi avanzati, in particolare con adenopatie voluminose
- Controlli IGRT
- Iperfrazionamento?? Limiti logistici
- Supporto nutrizionale
- Per ora non indicazioni a de-intensificazione per HPV+ al di fuori di trial clinici

Next step

- Riduzione della tossicità tardiva a parità di risultato oncologico
- Personalizzazione dei trattamenti sulla base di fattori prognostici/predittivi
- Identificazione di nuovi biomarkers
- Sperando in una riduzione dell'incidenza di casi HPV+ con il programma di vaccinazioni già in atto

Grazie per l’attenzione