

RADIOTERAPIA A INTENSITÀ MODULATA CON SIMULTANEOUS INTEGRATED BOOST (IMRT-SIB) NEL TRATTAMENTO DELLE NEOPLASIE DEL DISTRETTO TESTA-COLLO

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TERAPIA DELLE NEOPLASIE H&N

- × Radioterapia e Chirurgia: gold standard terapeutico in alternativa o in sequenza
- × In considerazione dell'alta percentuale di recidiva locoregionale (50%), la ricerca si è spinta in nuove direzioni:

NUOVE TECNICHE RT
→ DOSE ESCALATION

NUOVI
FRAZIONAMENTI

CHEMIOTERAPIA
CONCOMITANTE

FRAZIONAMENTI ALTERATI

Regime	D totale (Gy)	Tempo (gg)	Dose/fx (Gy)
Iperfrazionamento			
RTOG 9003	81.6	47.6	1.2 bid
Boost concomitante - Rt accelerata			
RTOG 9003	72	42	1.8 + 1.2 boost
CHART	54	12	1.5
HA-RT con split	67.2	43.4	1.6 bid
RT- DAHANCA	66-68	42	2
RT-GORTEC	62-64	22-23	2 bid
AH-RT GCS	77.6	42	2 (start) – 1.4 bid

FRAZIONAMENTI ALTERATI: METANALISI

THE LANCET

The Lancet, [Volume 368, Issue 9538](#), Pages 843 - 854, 2 September 2006

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This article can be found in the following collections: [Oncology \(Head & neck cancer\)](#)

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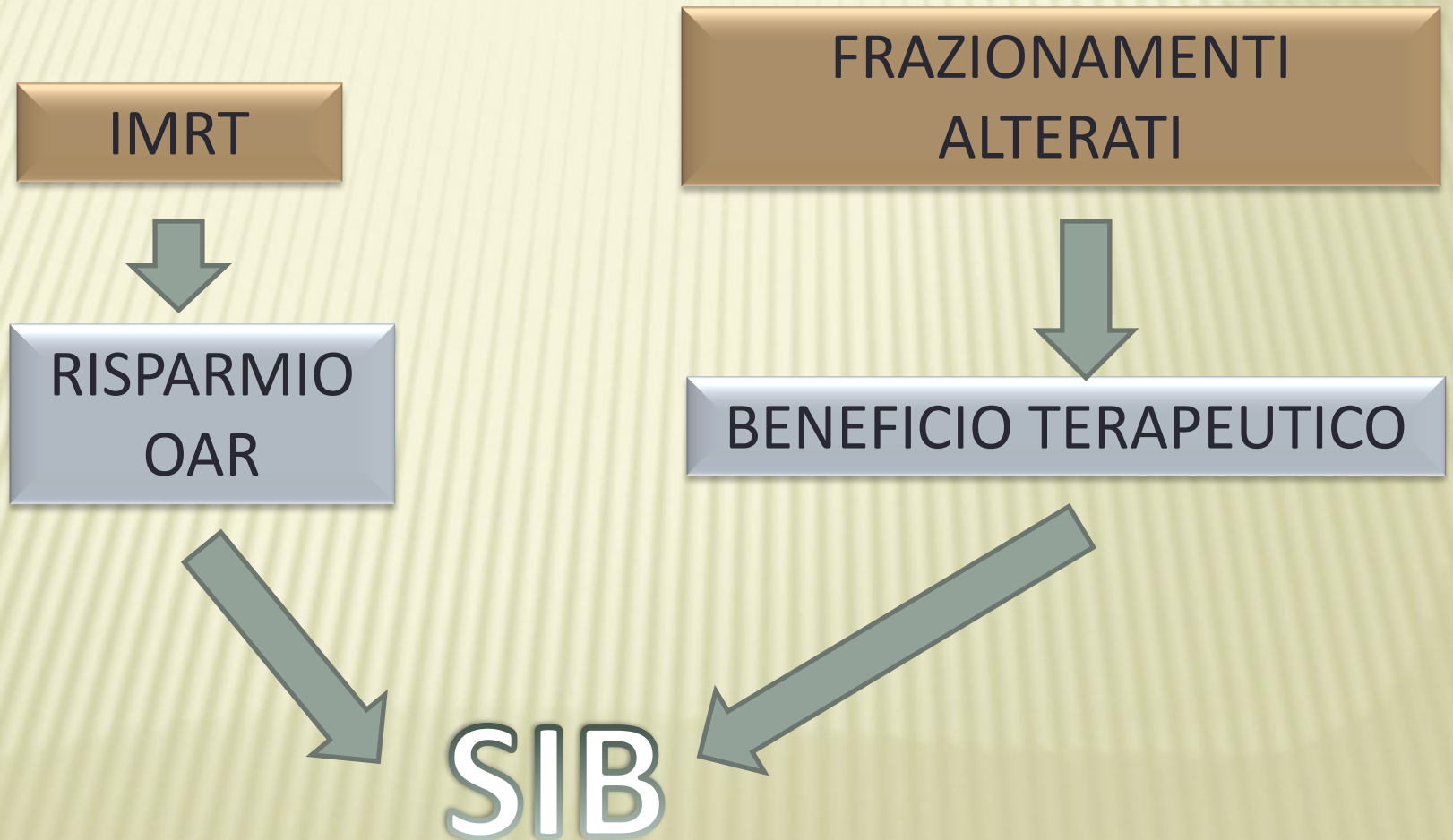
Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

Prof [Jean Bourhis](#) MD ^a, Prof [Jens Overgaard](#) MD ^c, [Hélène Audry](#) MSc ^b, Prof [Kian K Ang](#) MD ^d, Prof [Michele Saunders](#) MD ^e, [Jacques Bernier](#) MD ^f, Prof [Jean-Claude](#)

Altered fractionated radiotherapy improves survival in patients with head and neck squamous cell carcinoma.

Comparison of the different types of altered radiotherapy suggests that **hyperfractionation** has the greatest benefit

SIB: SIMULTANEOUS INTEGRATED BOOST



SIB: RAZIONALE RADIOBIOLOGICO

somministrazione simultanea di differenti livelli di dose ai diversi volumi *target* nell'ambito di una singola frazione

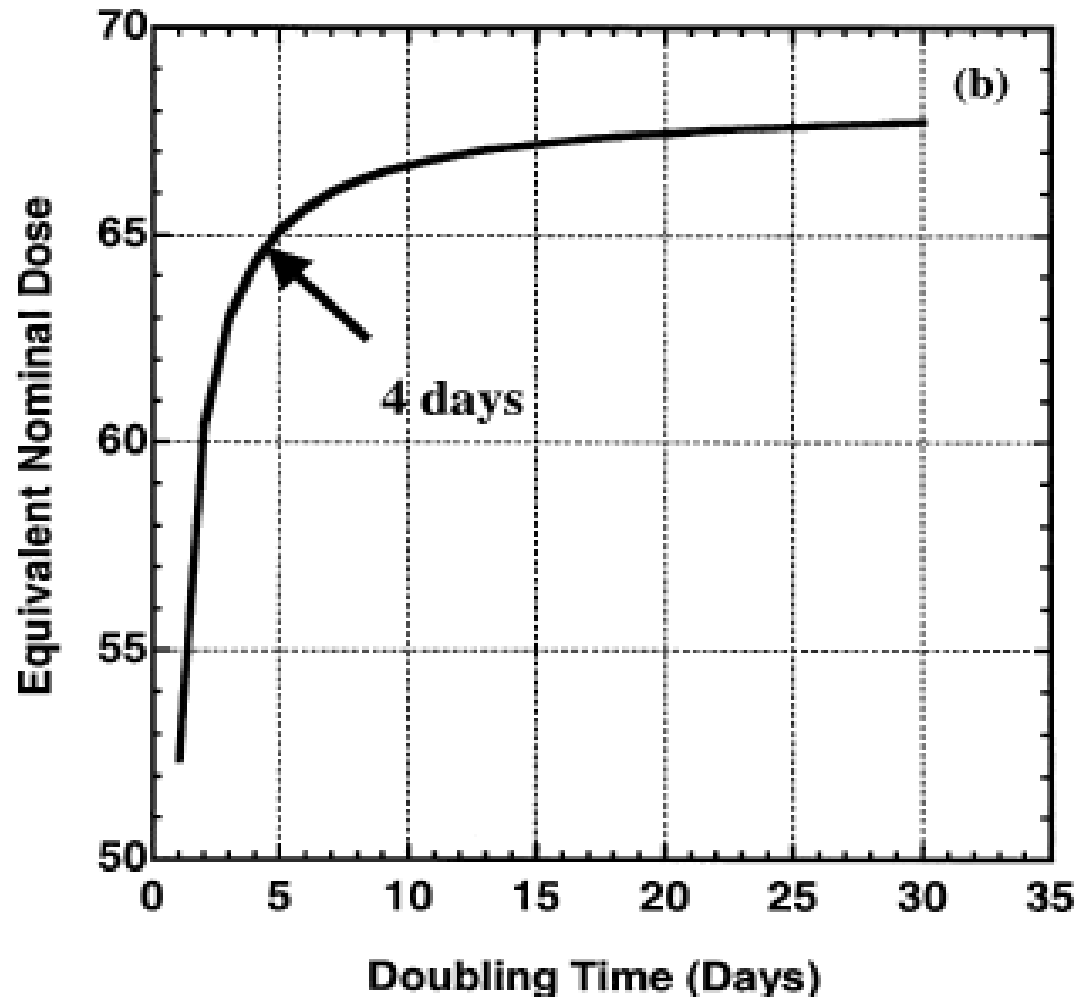
Volume (cc) outside the target (tumor and nodes) regions at specified dose level or higher

Dose level (cGy)	Conventional	Conventional with IMRT boost	Two-phase IMRT	Simultaneous integrated boost IMRT	% Difference between SIB IMRT and 2-phase IMRT
1,000	1,640	1,895	2,183	2,169	0.6
2,000	1,418	1,447	1,975	1,941	1.8
3,000	1,336	1,355	1,557	1,459	6.7
4,000	1,206	1,234	1,096	1,016	7.9
4,500	1,016	1,141	897	797	12.5
5,000	762	977	732	604	21.2
5,500	627	810	567	407	39.3
6,000	592	575	388	238	63.0
6,500	571	396	210	130	61.5
7,000	409	123	83	62	33.9

RIDUZIONE DELL'OTT

- × Aumento significativo del tempo di raddoppio tumorale mediato (Tpot) inferiori a 10 giorni
- × Influenza su tossicità

Tpot tumorale



POWER JF, *Acta Oncol* 2001; 40:712-717
Maciejewski B, *IJROBP* 1989; 16:831-843

BED

Studio	Df/nf/Dtot	Tumore		Acute responding tissues	Late reacting tissues
		BED (Gy)	NTD2Gy (Gy)	BED (Gy)	BED(Gy)
Butler	2.4/25/70	68.2	66.8	56.4	108
Chao	2/35/70				
DeArruda	2.12/33/69.9				
Guerrero Urbano	2.25/28/63				
	2.4/28/67.2				
RTOG0022	2.2/30/66	71.1	69.6	57.6	115.4

$\alpha/\beta = 15$

$\alpha/\beta = 10$

$\alpha/\beta = 3$

Table 2. α/β values of some of the normal tissue of interest for the treatment of HN carcinomas

Tissue	α/β
Mucosa	10
Spinal cord	2.5
Brainstem	2.5
Bone	0.85
Muscle	3.1
<u>Parotids</u>	<u>10</u>

Dose per frazione (indicated by a bracket on the first four rows)

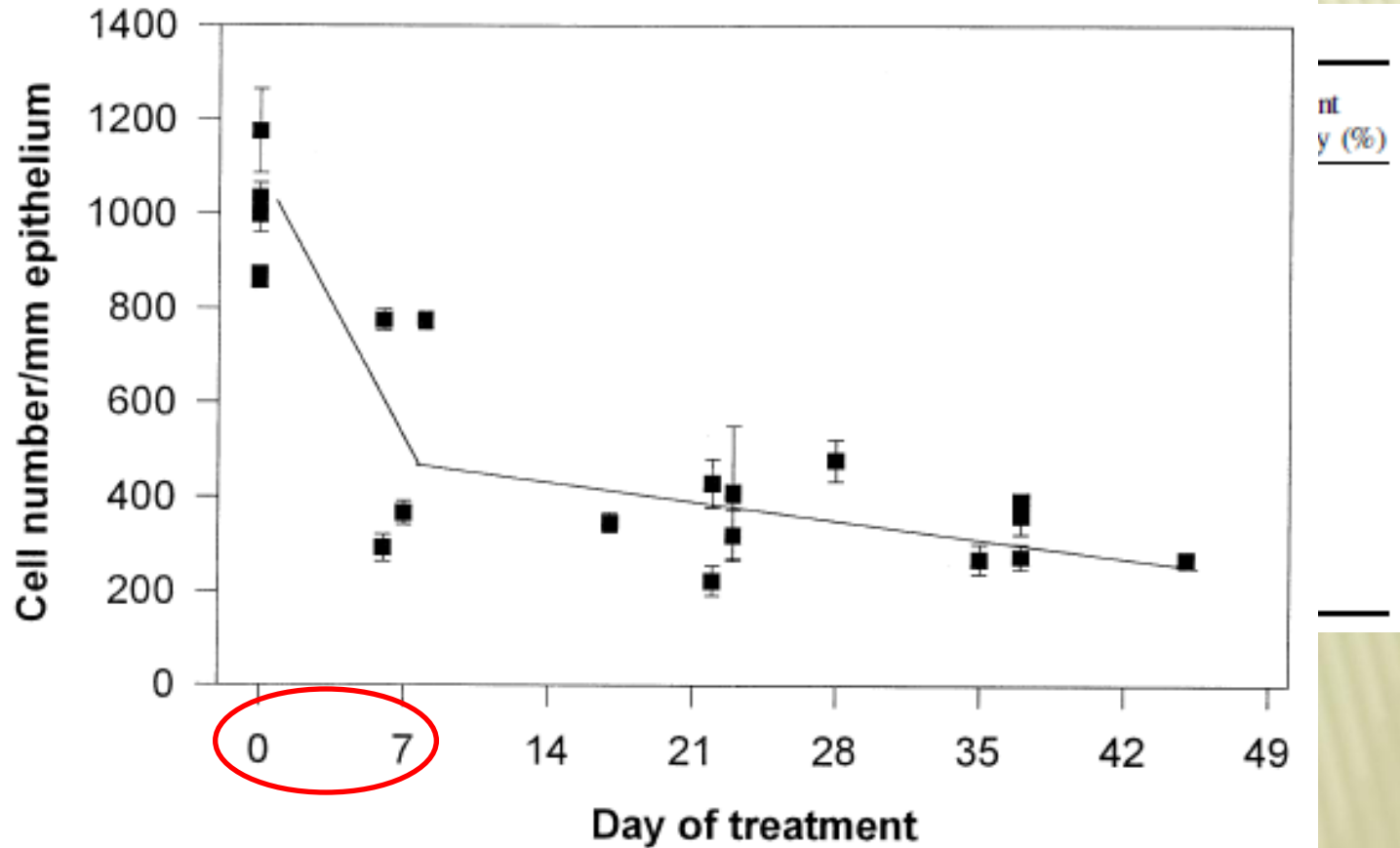
dose totale (indicated by a bracket on the last two rows)

RISULTATI

Lee et al. (36)
Lee et al. (22)
Kwong et al. (25)
Wolden et al. (24)

Chao et al. (26)
Lauve et al. (27)

de Arruda et al. (28)
Studer et al. (29)
Schwartz et al. (30)
Lee et al. (31)



Boost concomit

- LRC2y → 54-
- Aumentata to
- Fino a 41% tossicità tardiva

Montejo MR, IJROBP 2011
Dorr et al, IJROBP, 2002

INCERT
DI SE



«ADAPTIVE»
RT

MODIFICHE
ATOMICHE

VERIFICHE CON
KV-OBI

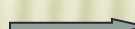
REPLANNING

ERRORI DI POSIZIONAMENTO

OFFLINE PROTOCOL	Decrease in sytematic errors mm.	random errors mm.
De Boer et al.	1.6-2.1  1.1-1.2	1.6-1.4
Van Lin et al.	2.2-2.3  0.8-1.4	1.5-1.9

On line correction provides the advantage of reducing both the systematic and random errors whereas an offline protocol can only reduce the systematic error

ON LINE
P
R
O
T
O
C
O
L

O'Daniel et al.	Use of IGRT reduce mean parotid dose in 91% of pts.	the parotid dose resulting from bone alignment is greater than the planned dose
Wang et al.	PTV margin reduction 5mm  3mm	Traslational isocenter shift of 3mm—No on line correction increasing dose in brainstem and spinal cord (10Gy) Parotid gland (7.5-8.5 Gy)

MODIFICHE ANATOMICHE

Author	No. of Patients	Per-Treatment Imaging	Image Registration	Volume Analysis	Shape and Positional Analysis
Barker et al (2004) ⁸	14	In-room CT-on-rail 3 times/wk; no iv contrast	Rigid	Reduction of: <ul style="list-style-type: none"> • GTV: 1.8% per treatment day • PGs: 0.6%/treatment day 	<ul style="list-style-type: none"> • GTV: COM displacement: 3.3 mm (asymmetric shrinkage) • PG: COM shift medially by 3.1 mm After 48 Gy: <ul style="list-style-type: none"> • Lateral and inferior regions of homolat PG: medial and posterior shift (3 mm) • Homolat SMG: medial, cranial, and posterior shift (4 mm)
(2008) ²¹		contrast	Deformable	Reduction after 48 Gy: <ul style="list-style-type: none"> • GTV: 25 ± 15% • Homolat PG: 17 ± 7% • Heterolat PG: 5 ± 4% • Homolat SMG: 20 ± 10% • Heterolat SMG: 11 ± 7% 	
Castadot et al (2008)	10	CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast	Deformable	Reduction of <ul style="list-style-type: none"> • GTV_T: 3.2%/treatment day • GTV_N: 2.1%/treatment day • Homolateral PG: 0.9%/treatment day • Heterolat PG: 1.0%/treatment day • Low dose homolat CTV_N: 0.5%/treatment day • low dose heterolat CTV_N: 0.4%/treatment day 	After 5 treatment wks: <ul style="list-style-type: none"> • Homolat PG: medial shift of 3.4 mm • GTV_T: lateral shift of 1.3 mm • GTV_N: medial shift of 0.9 mm • Low dose homolat CTV_N: medial shift of 1.8 mm No shift for the heterolat PG and heterolat low dose CTV_N.

GTV → ASYMMETRIC SHRINKAGE 9-15%

PAROTID GLAND → SHRINKAGE + MEDIAL SHIFT (3mm)

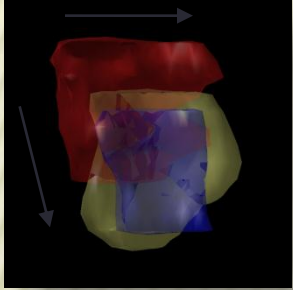
PERDITA DI PESO MEDIA: 7% (5-13%)

MOVIMENTI MIDOLLO
3.5 mm (C1) - 5.6 mm (C6)

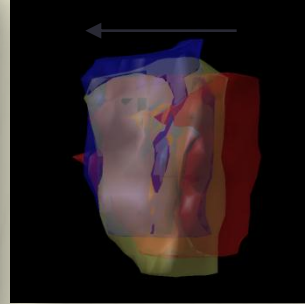
ART: modifiche anatomiche OAR

Red: day 1; Yellow: day 15; Blue: day 30

RIGHT



LEFT

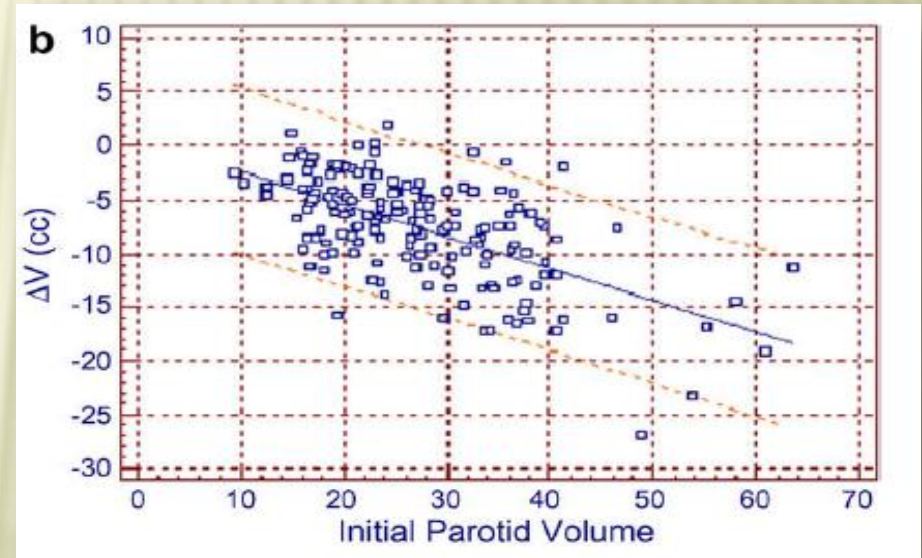
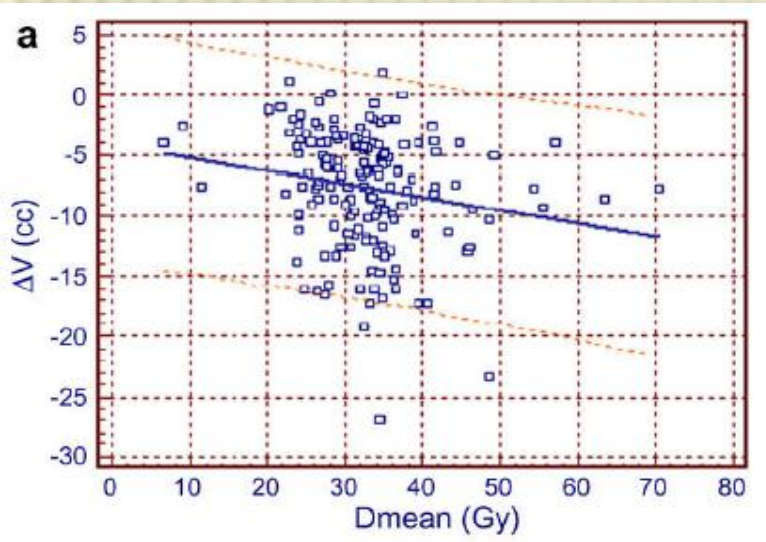


Original article

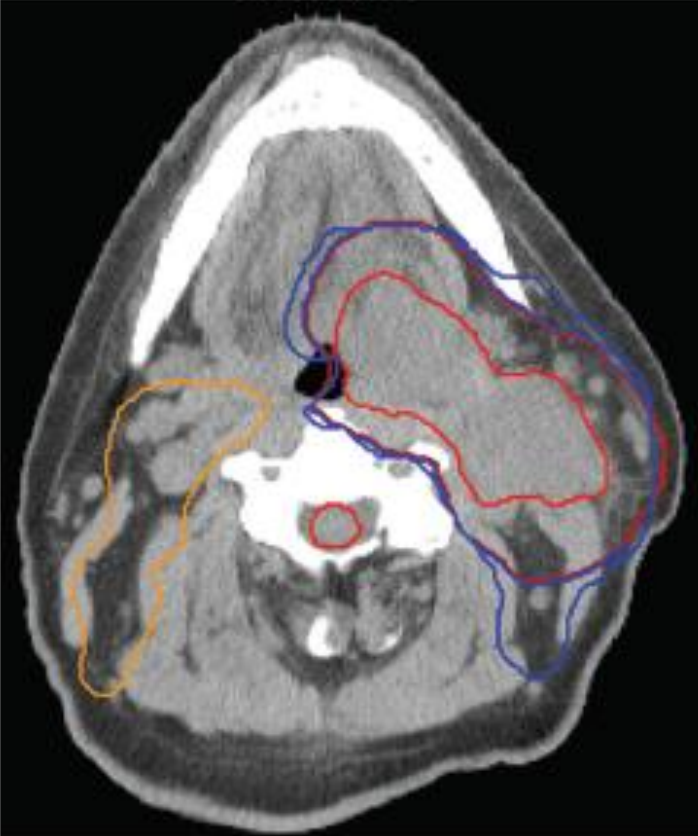

A two-variable linear model of parotid shrinkage during IMRT for head and neck cancer

Sara Broggi^{a,*}, Claudio Fiorino^a, Italo DelfOca^b, Nicola Dinapoli^c, Marta Paiusco^d, Alessandro Muraglia^e, Eleonora Maggiulli^f, Francesco Ricchetti^g, Vincenzo Valentini^g, Giuseppe Sanguineti^g, Giovanni Mauro Cattaneo^a, Nadia Di Muzio^b, Riccardo Calandrino^a

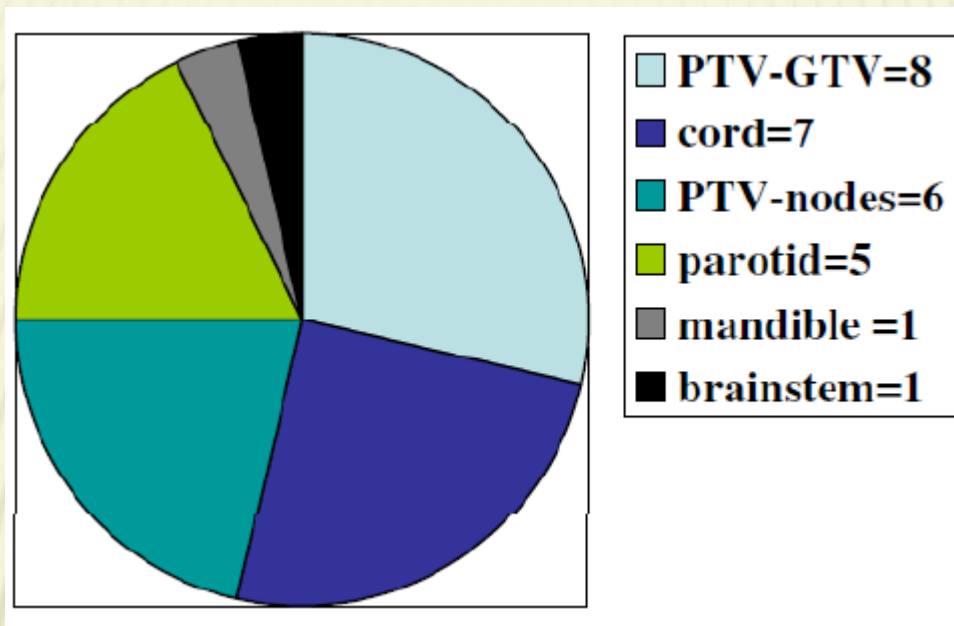
(4 Istituti, 187 parotidi)



IMPATTO DOSIMETRICO

	Imaging	Parotid	PTV	Cord	MISC	#
	Planning CT		During treatment			
H (J						
O (J						
R (J						
H (J						
L (J						
C (R						
20						

INDICAZIONI AL REPLANNING



PTV D95 < 95%prescrizione

Dmax midollo >45 Gy

Dmedia parotide >26 Gy

V60 mandibola >10%

D54 tronco >20%

L'ESPERIENZA DELL'U.O.C. DI RADIOTERAPIA DI BARLETTA

MATERIALI E METODI

- × Febbraio 2010 → Settembre 2012
- × **19** pazienti
- × Conferma istologica di tumore del distretto H&N
- × **Stadio II-IV**
- × Età media **64 anni** (range 40-80)
- × **Valutazione multidisciplinare** (oncologo medico, otorinolaringoiatra, radioterapista oncologo, nutrizionista) → indicazione a chemioterapia concomitante e valutazione locale con FLS
- × Se non eseguita, richiesta **RMN**

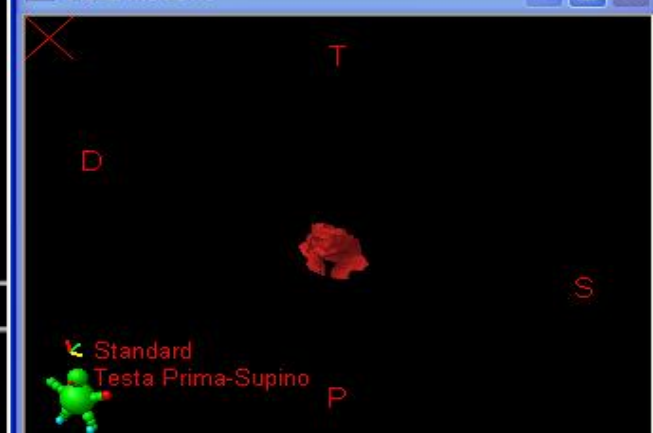
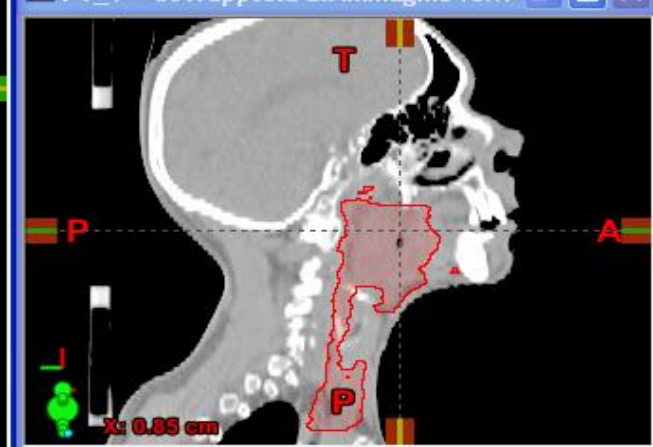
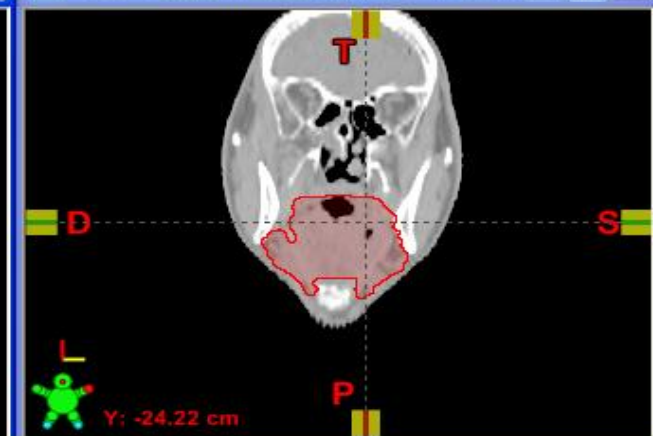
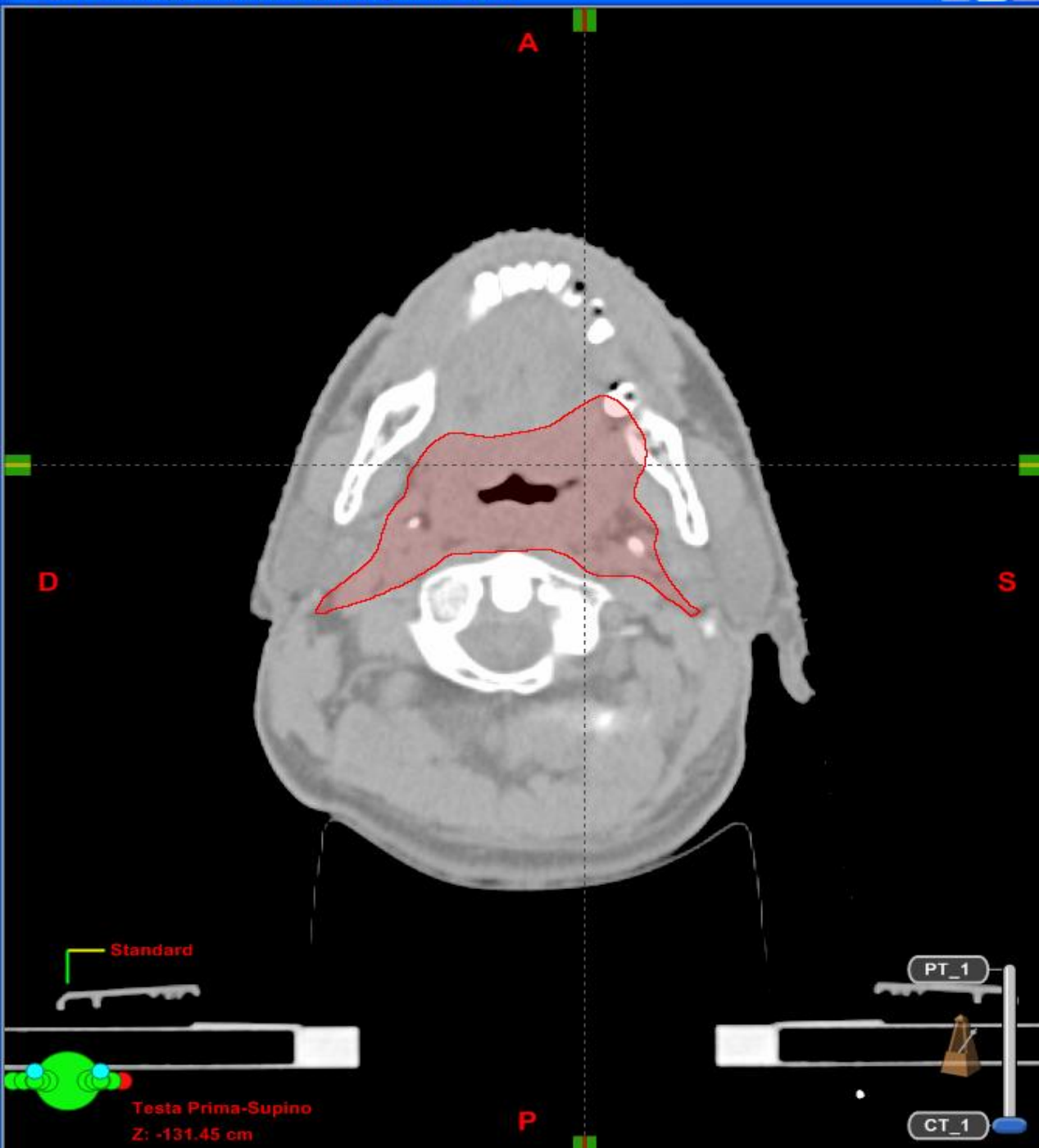
CARATTERISTICHE DEI PAZIENTI

	N. Pz (%)
GENERE	
M	14 (74)
F	5 (26)
SITO PRIMITIVO	
cavo orale	2 (11)
orofaringe	11 (58)
laringe	2 (11)
rinofaringe	3 (16)
occulto	1 (5)
TIPO ISTOLOGICO	
squamoso	17 (89.5)
indifferenziato	2 (10.5)
STADIO INIZIALE	
I	0 (0)
II	3 (15.8)
III	1 (5.3)
IV	12 (63.2)

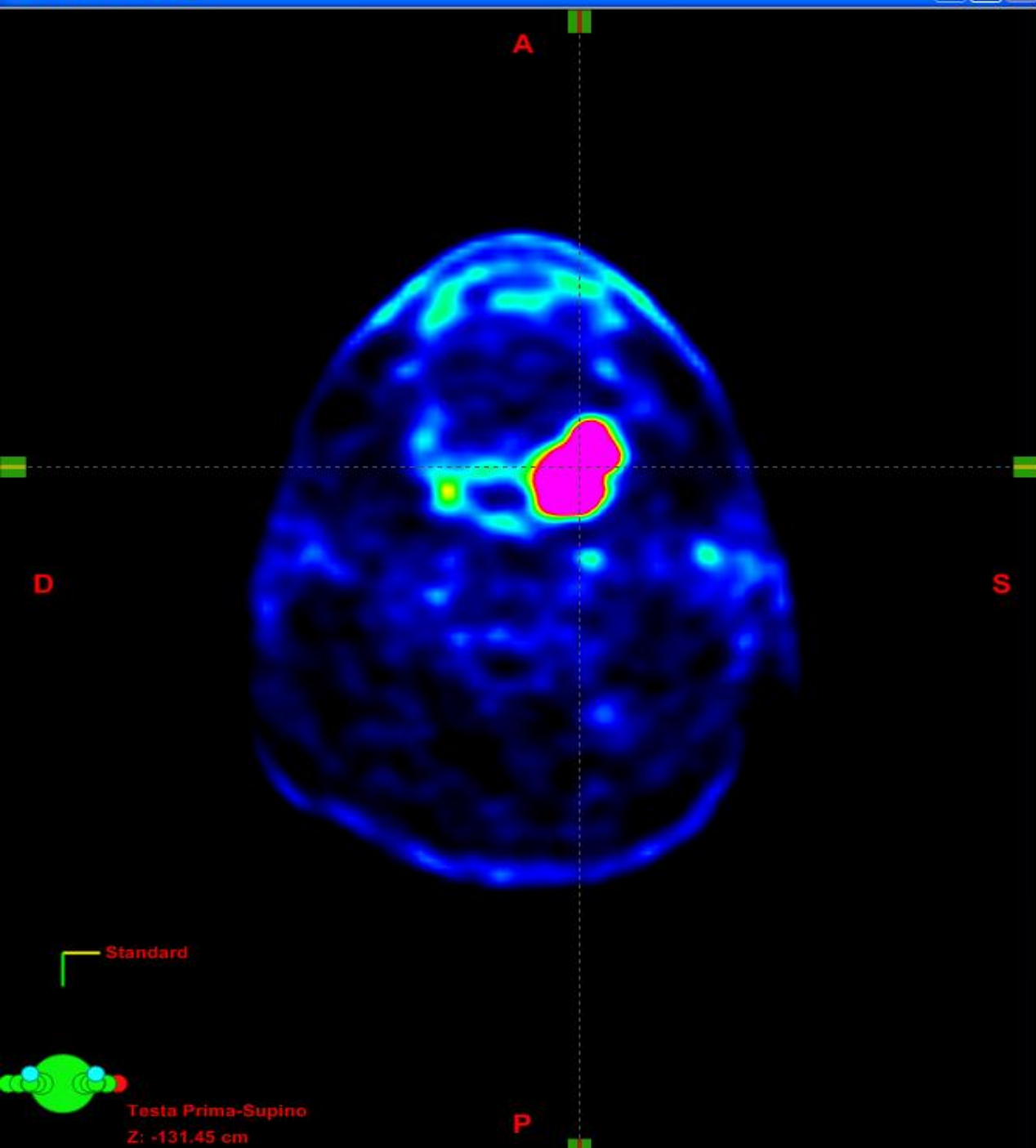
	N. Pz (%)
CHIRURGIA	
si	6 (31.6)
no	13 (68.4)
CHEMIO PRE-RT	
si	4 (21.1)
no	15 (78.9)
CHEMIO CONCOMITANTE	
CDDP q7	11 (57.9)
CDDP q21	2 (10.5)
Cetuximab	3 (15.8)
Carboplatino	3 (15.8)

PET-TC DI SIMULAZIONE

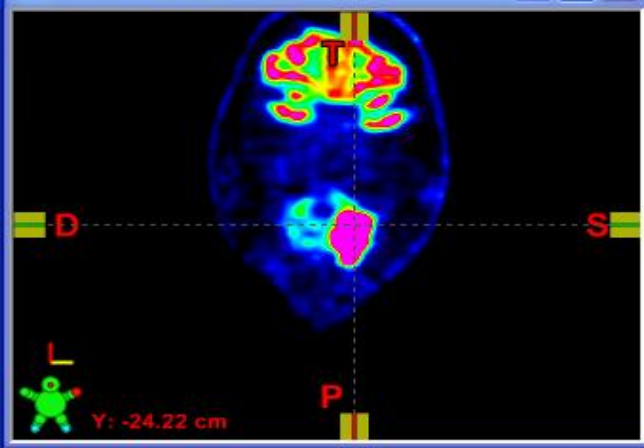
- ✘ PET-TC Siemens Biograph con TC a 40 strati, laser mobili e di un **lettino gemello** al lettino di trattamento radioterapico (su cui è possibile fissare i sistemi di immobilizzazione)
- ✘ **Immobilizzazione** del capo in iperestensione mediante maschera termoplastica
- ✘ **Acquisizione** di immagini TC con uno *slice thickness* di 3 mm e immagini PET dal vertice del cranio al bacino
- ✘ **Refertazione** da parte del Medico Nucleare e trasferimento al TPS Eclipse



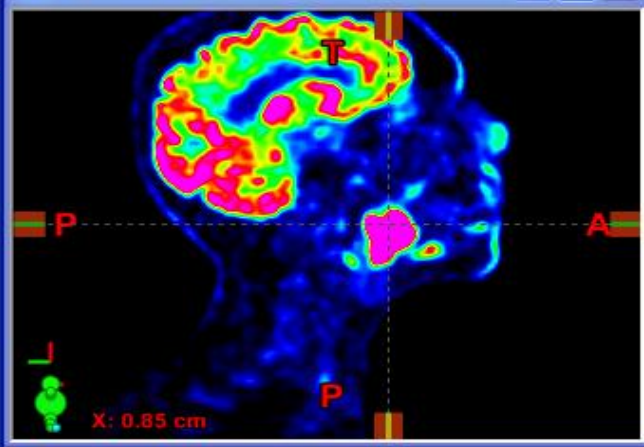
Trasversale - PT_1



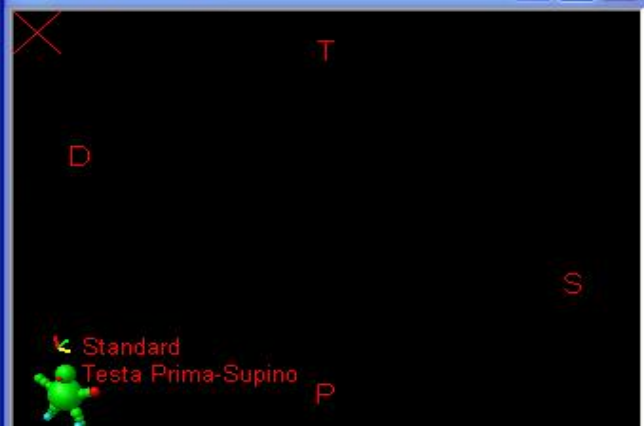
Frontale - PT_1

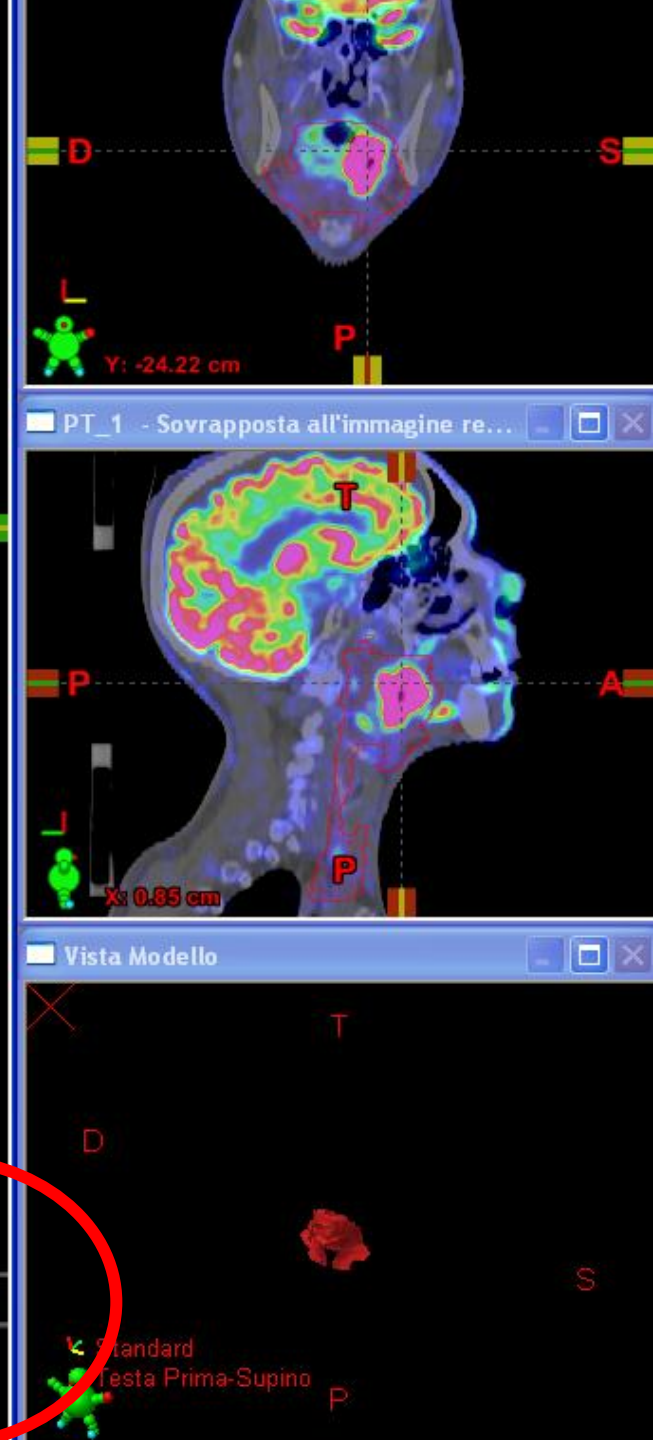
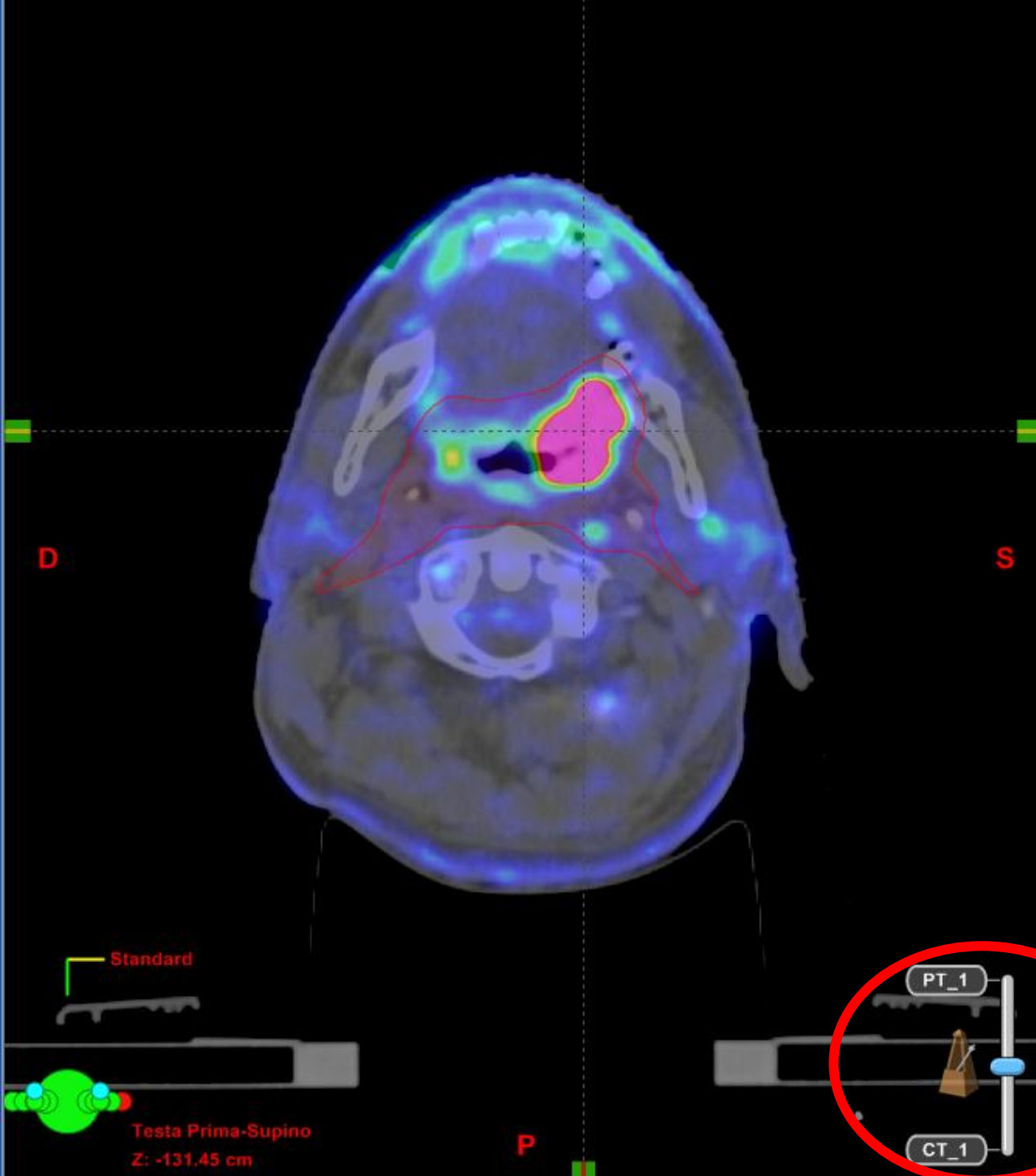


Sagittale - PT_1



Vista Modello

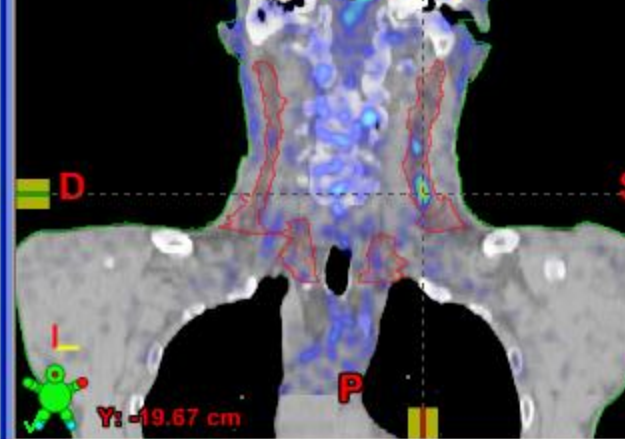
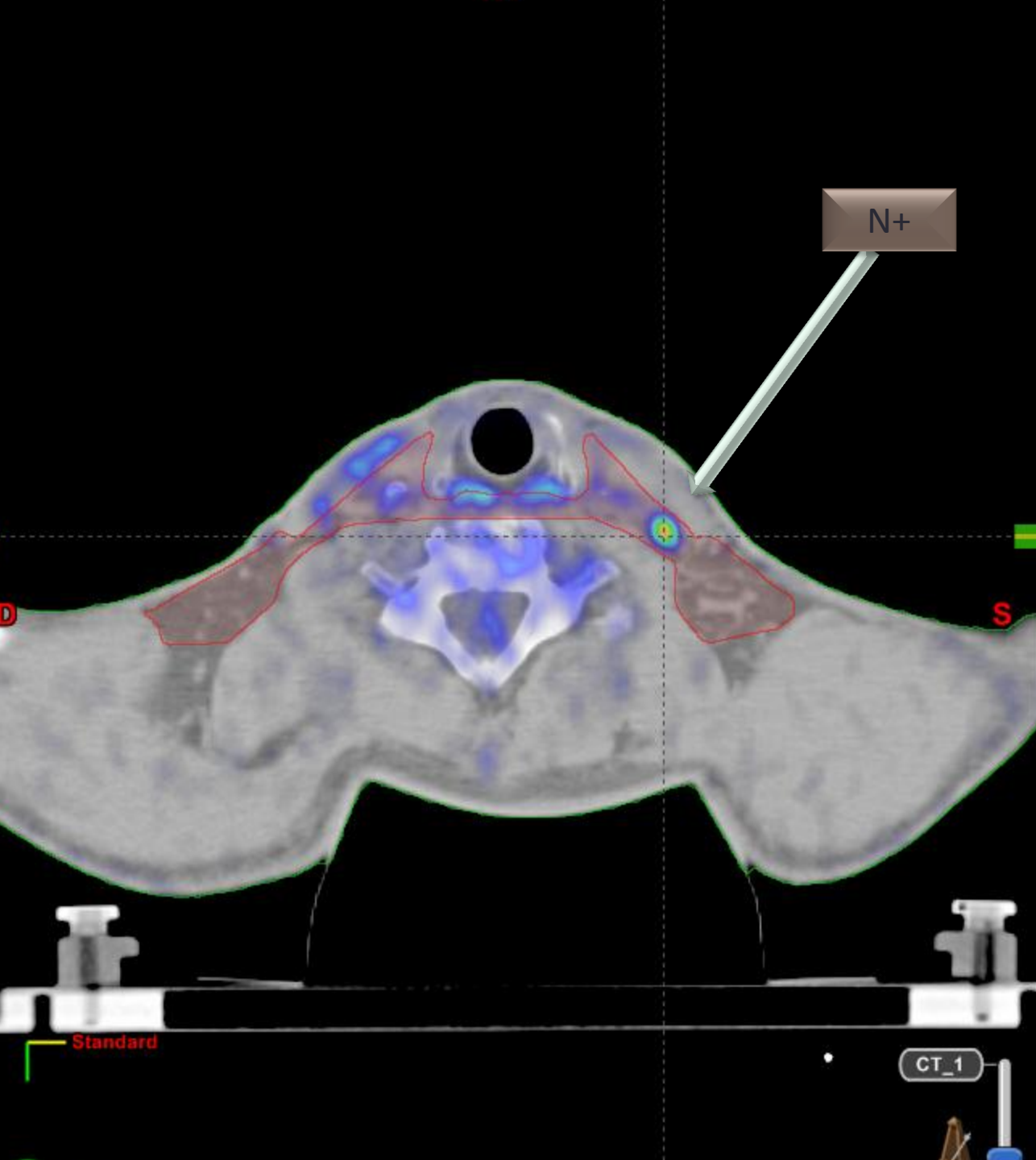




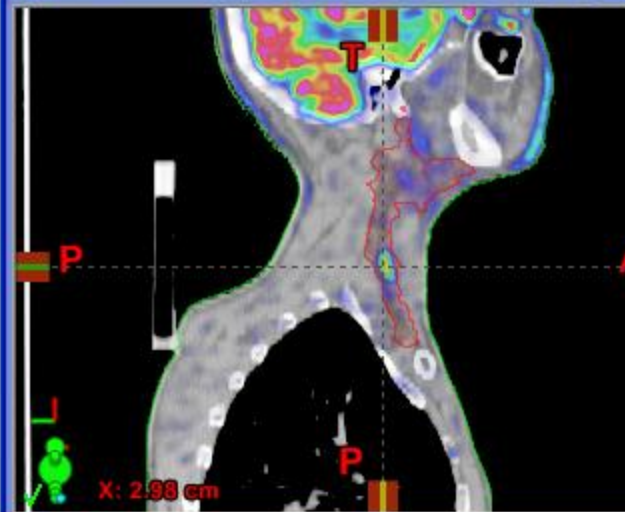
CONTORNAZIONE (2)

× Sulla base di PET-TC e RMN

- + **GTV** (malattia macroscopica)
- + **CTV66** (GTV + 1-1,5 cm per disseminazione microscopica);
- + **CTV60** (aree linfonodali ad alto rischio di diffusione metastatica e le sottosedì adiacenti a quella del tumore primitivo)
- + **CVT54** (aree linfonodali a basso rischio di localizzazione)
- + **PTV54, PTV60, PTV66** (CTV + 3mm, per tenere conto delle incertezze di *setup*)



CT_1 - Sovrapposta all'immagine re...



Vista Modello



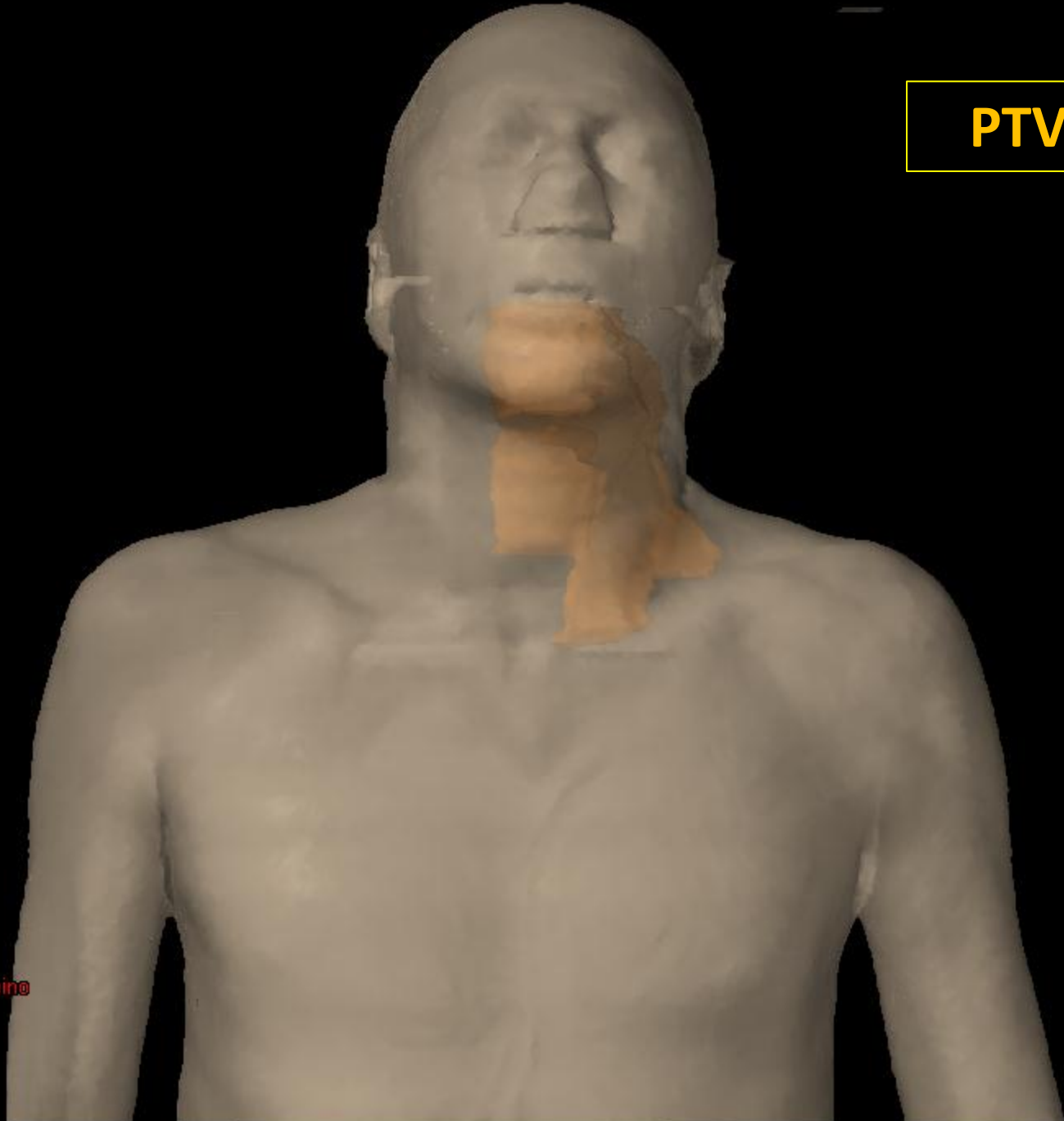
PTV54



Standard
Testa Prima-Supino



PTV60



Standard
Testa Prima-Supino



PTV66



Standard
Testa Prima-Supino



PRESCRIZIONE DI DOSE: SIB

× SIB(14 pazienti):

- + 66 Gy a 2.2 Gy/frazione per il volume PTV66
- + 60 Gy a 2 Gy/frazione per il volume PTV60
- + 54 Gy a 1.8 Gy per frazione per il PTV54

× SIB (1 pazienti operato):

- + 60 Gy a 2 Gy/frazione per il volume PTV60
- + 54 Gy a 1.8 Gy per frazione per il PTV54

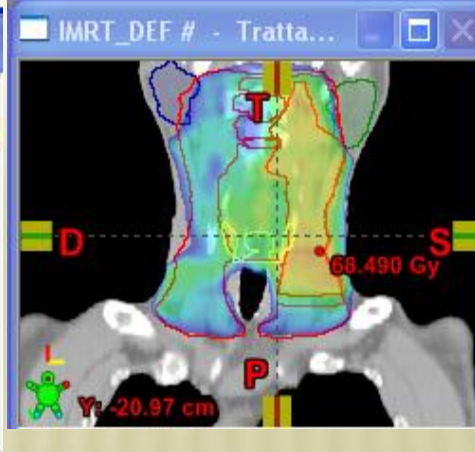
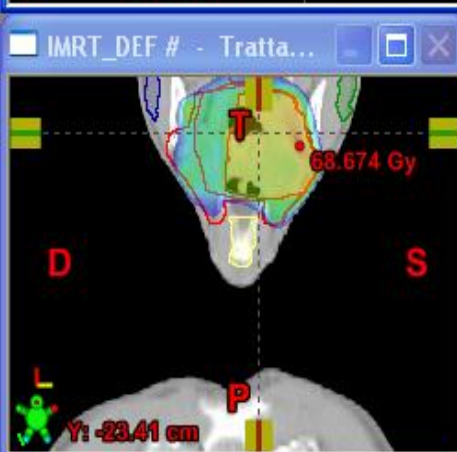
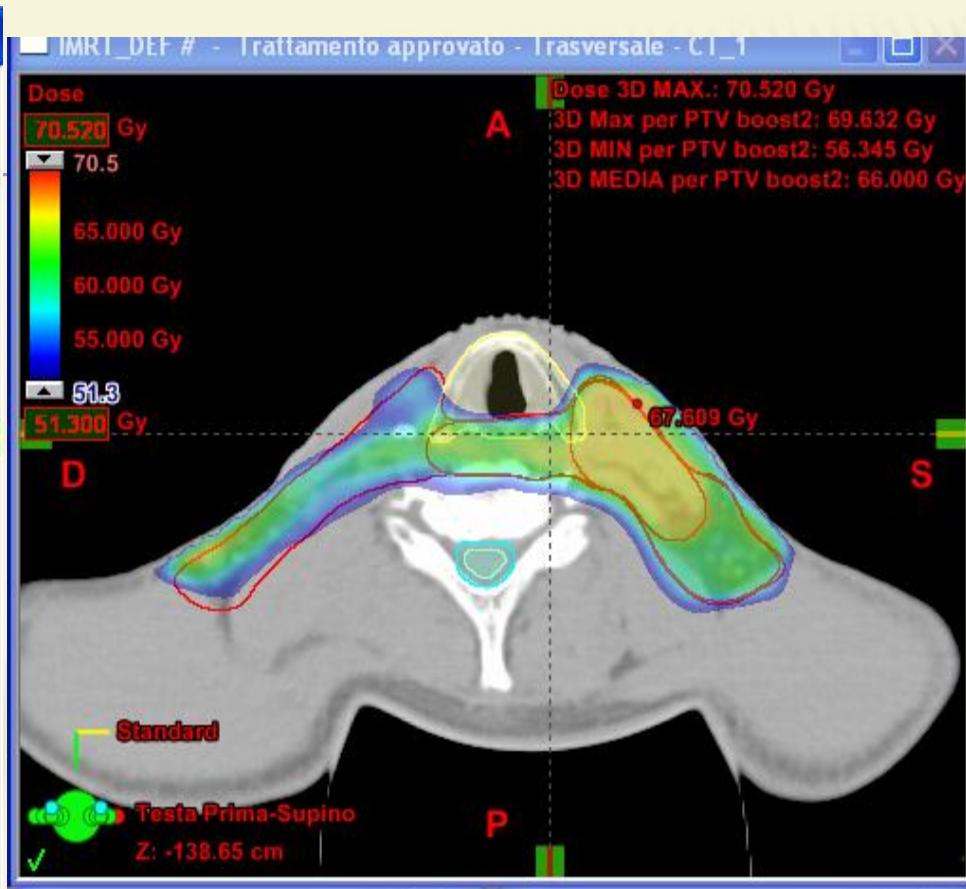
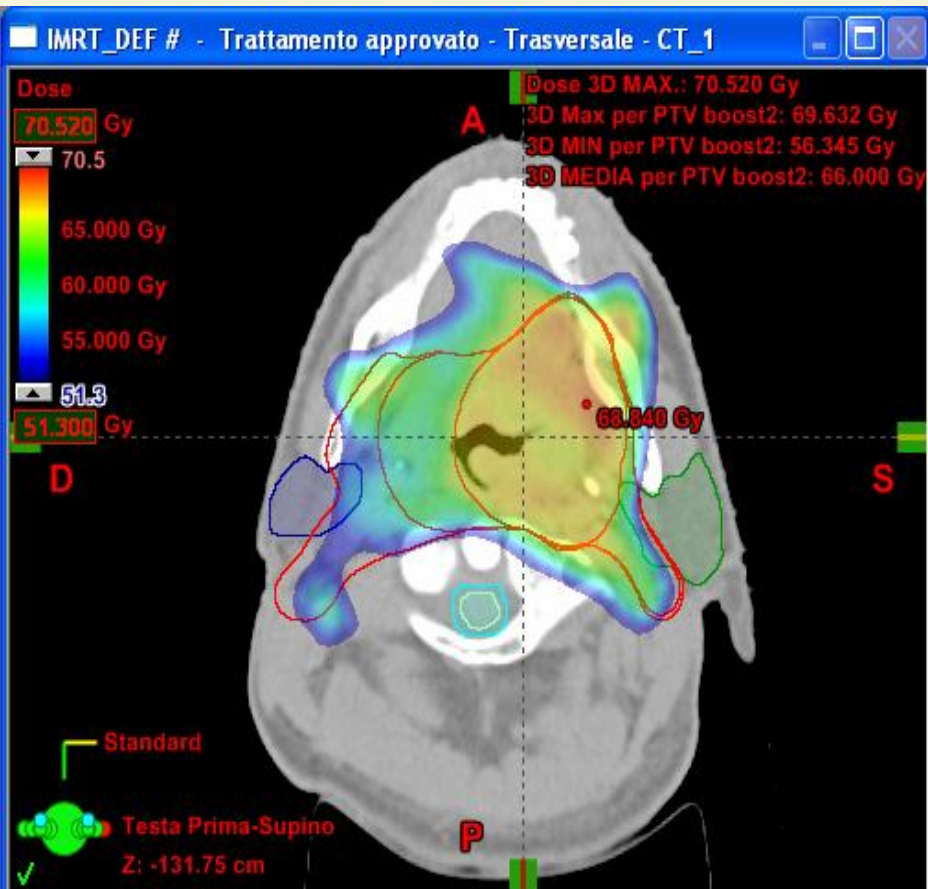
× SIB (4 pazienti):

- + 69.6 Gy a 2.12 Gy per frazione per il PTV66
- + 59.4 Gy a 1.8 Gy per frazione per il PTV60
- + 54 Gy a 1.6 Gy per frazione per il PTV54

30 frazioni

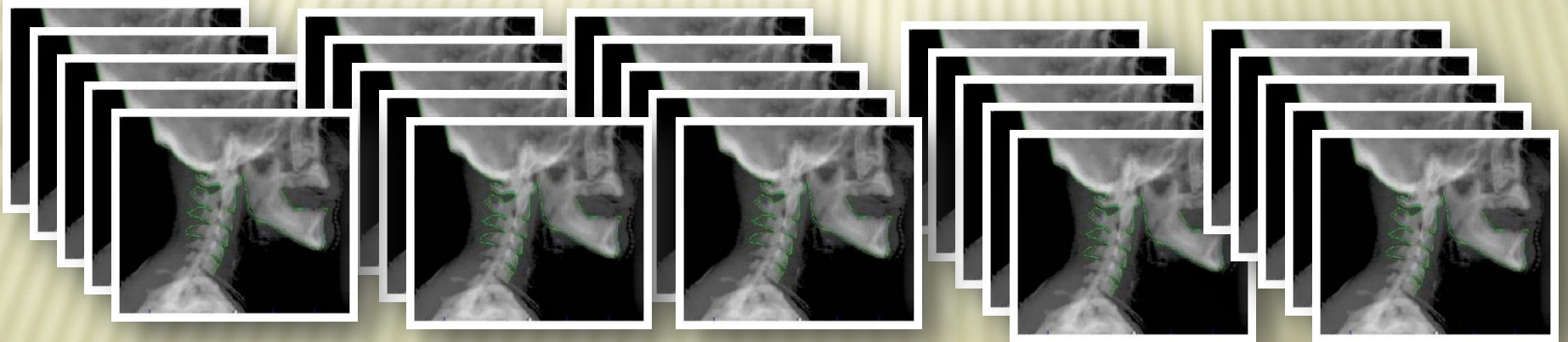
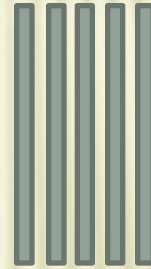
30 frazioni

33 frazioni



VERIFICHE

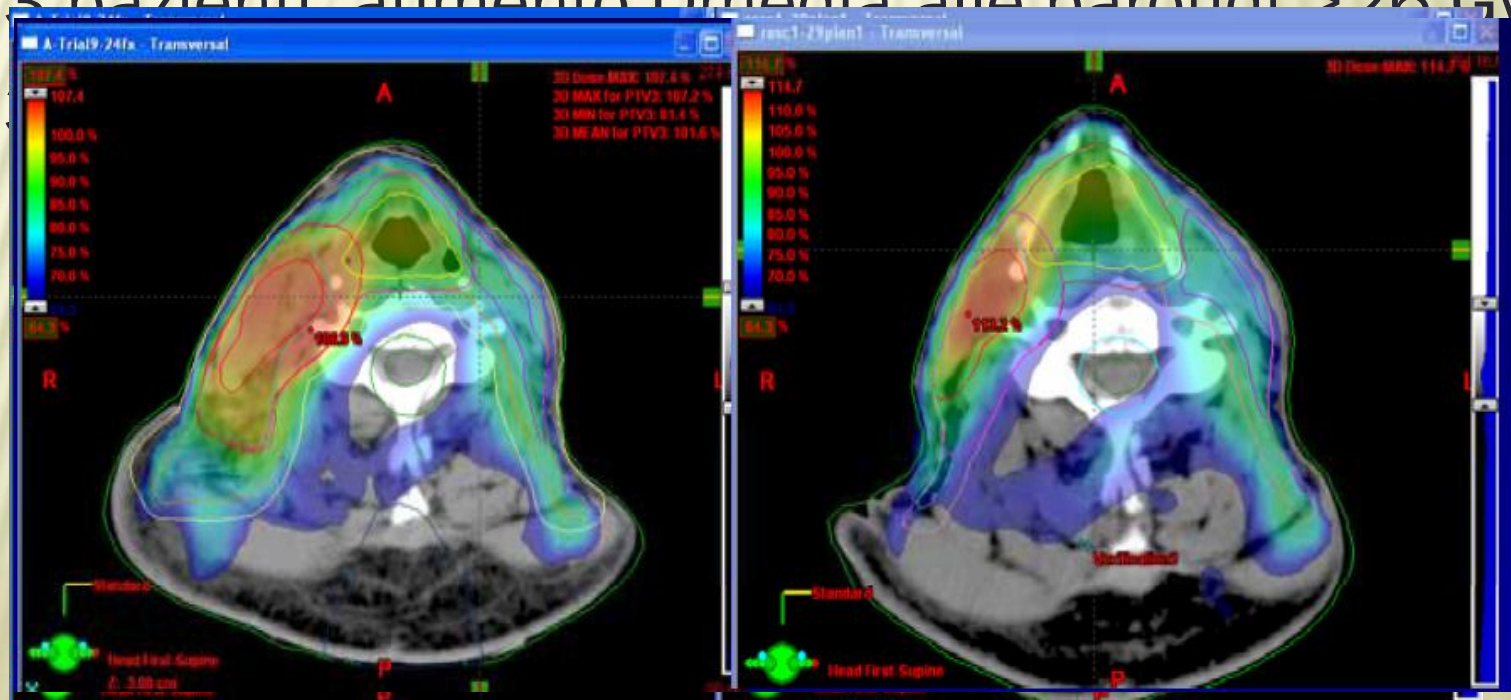
Weekly Cone Beam CT



Daily KV OBI

REPLANNING

- ✘ In 10 pazienti è stato effettuato un Replanning
 - + 4 pazienti: diminuzione D95 al PTV (per shrinking della malattia)
 - + 3 pazienti: aumento Dmedia alle parotidi >26 Gy
 - + 3 pazienti: aumento Dmax alla tiroide >63 Gy



TOSSICITÀ ACUTA

RISULTATI

OTT

- × **Interruzioni precoci del trattamento: 2 casi**
 - + 24esima seduta (dose raggiunta al PTV66: 52.8 Gy)
 - + 28esima seduta (dose raggiunta al PTV66: 61.6 Gy)
- × **Sospensioni del trattamento per tossicità: 8 pazienti**
- × **Media giorni di interruzione = 4 giorni** (*range* di 1- 16 giorni)
- × 9 pazienti (47.4%) hanno completato l'intero corso di radioterapia in maniera consecutiva

OTT mediano = 46 giorni
(*range* 40-62 giorni)

TOSSICITÀ ACUTA

	G0(%)	G1(%)	G2(%)	G3(%)	G4(%)
Xerostomia	11 (57.9)	8 (42.1)	0 (0)	0 (0)	0 (0)
Tox cute	0 (0)	14 (73.7)	5 (26.3)	0 (0)	0 (0)
Mucosite	1 (5.3)	1 (5.3)	12 (63.2)	5 (26.3)	0 (0)
Leucopenia	13 (68.4)	2 (10.6)	2 (10.5)	1 (5.3)	1 (5.3)
Disfagia	1 (5.3)	1 (5.3)	15 (78.9)	2 (10.6)	0 (0)

Nessun paziente ha avuto necessità di alimentazione con sondino naso-gastrico (SNG) o con gastrostomia endoscopica percutanea (PEG)

	Dermatite (%)					Mucosite (%)					Faringite/disfagia (%)					Alterazioni salivari (%)				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Lee 2006	0	65	35	0	0	0	10	65	25	0	0	10	45	45	0	0	0	45	55	0
Lee 2007	13	65	19	3	0	10	42	26	23	0	0	0	87	13	0	-	-	-	-	-
Kam 2004	0	57	36	7	0	0	8	51	41	0	0	43	44	13	0	0	25	75	0	0
Kwong 2006	-	-	-	46	-	-	-	-	78	-	-	-	-	-	-	-	-	-	-	-
Butler 1999	-	-	-	-	-	-	-	-	80	50	-	-	-	-	-	-
Chao 2003	-	-	-	-	-	-	-	-	38	5	-	-	-	-	-	-	-	-	-	-
Lauve 2004 dose 1	-	-	-	17	-	-	-	-	83	-	-	-	-	17	0	-	-	-	-	-
Lauve 2004 dose 2	-	-	-	33	-	-	-	-	67	-	-	-	-	42	8	-	-	-	-	-
Lauve 2004 dose 3	-	-	-	0	-	-	-	-	10 0	-	-	-	-	10 0	0	-	-	-	-	-
De Arruda 2006	0	52	42	6	0	0	8	54	38	0	6	16	62	16	0	0	48	52	0	0
Studer 2006	-	-	-	5	-	-	-	-	15	-	-	-	-	20	-	-	-	-	-	-
Schwartz 2007	3	39	59	8	0	0	12	32	55	0	40	14	24	20	0	49	36	12	3	-
Guerrero Urbano 2007 63Gy	-	-	67	20	0	-	-	33	67	-	-	-	20	67	-	-	-	60	0	-
Guerrero Urbao 2007 67.2Gv	-	-	47	20	0	-	-	47	40	-	-	-	13	87	-	-	-	73	7	-
Our study	0	77	26	0	0	5	5	63	26	0	5	5	79	11	0	58	32	10	0	0

CONTROLLO DI MALATTIA

- × Follow-up mediano: **8 mesi** (medio 8.2, *range* 0-21 mesi)

	n pazienti (%)
LR	2 (10.5)
LnR	1 (5.3)
DM	2 (10.5)
OS	17 (89.5)
LC 21mths	16 (84.2)

CHIRURGIA DI
SALVATAGGIO



TOSSICITÀ TARDIVA

× Solo **14** pazienti hanno un follow-up abbastanza lungo da valutare la tossicità tardiva

Tossicità tardiva	
Xerostomia	
G0	3
G1	7
G2	4
G3	0
G4	0
Disfagia	
G0	12
G1	1
G2	0
G3	0
G4	0

CONCLUSIONI

× Vantaggi del SIB:

- + Consente una **riduzione dell'OTT ed aumento del BED**
- + Creazione di un **unico piano di trattamento** (semplificazione di pianificazione e *delivery* e *migliore conformazione e controllo della distribuzione di dose rispetto ad IMRT-SEQ*)

× Criticità del SIB:

- + Potenziale aumento della **tossicità acuta ma soprattutto tardiva**
- + **Studi clinici eterogenei** per sito primitivo e frazionamenti utilizzati
- + Necessità di follow-up più lunghi

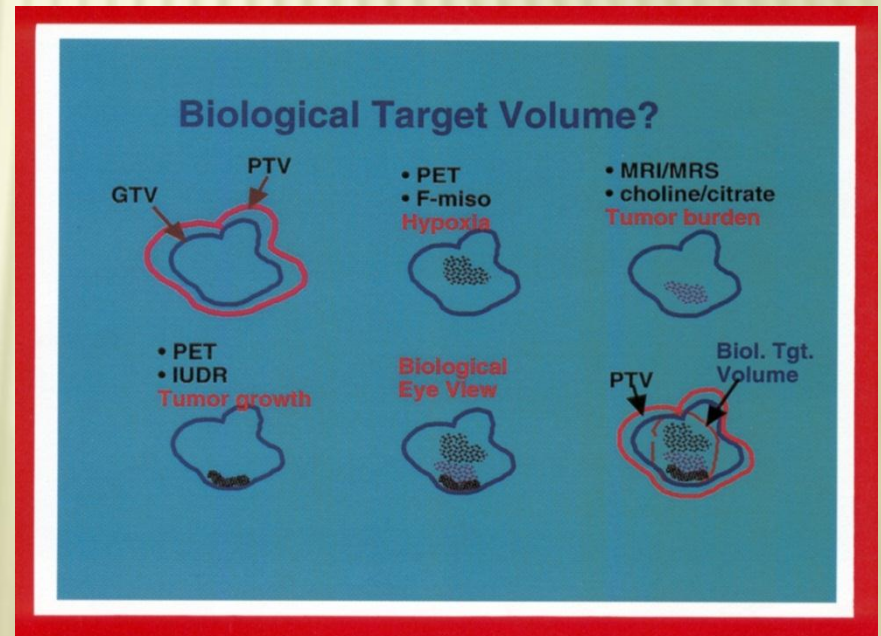
PROSPETTIVE FUTURE

recidive locali «in field»: 30-45 %

× Dalla MART (morphologic adaptive radiotherapy).....

× alla BART (biologic adaptive

radiotherapy)



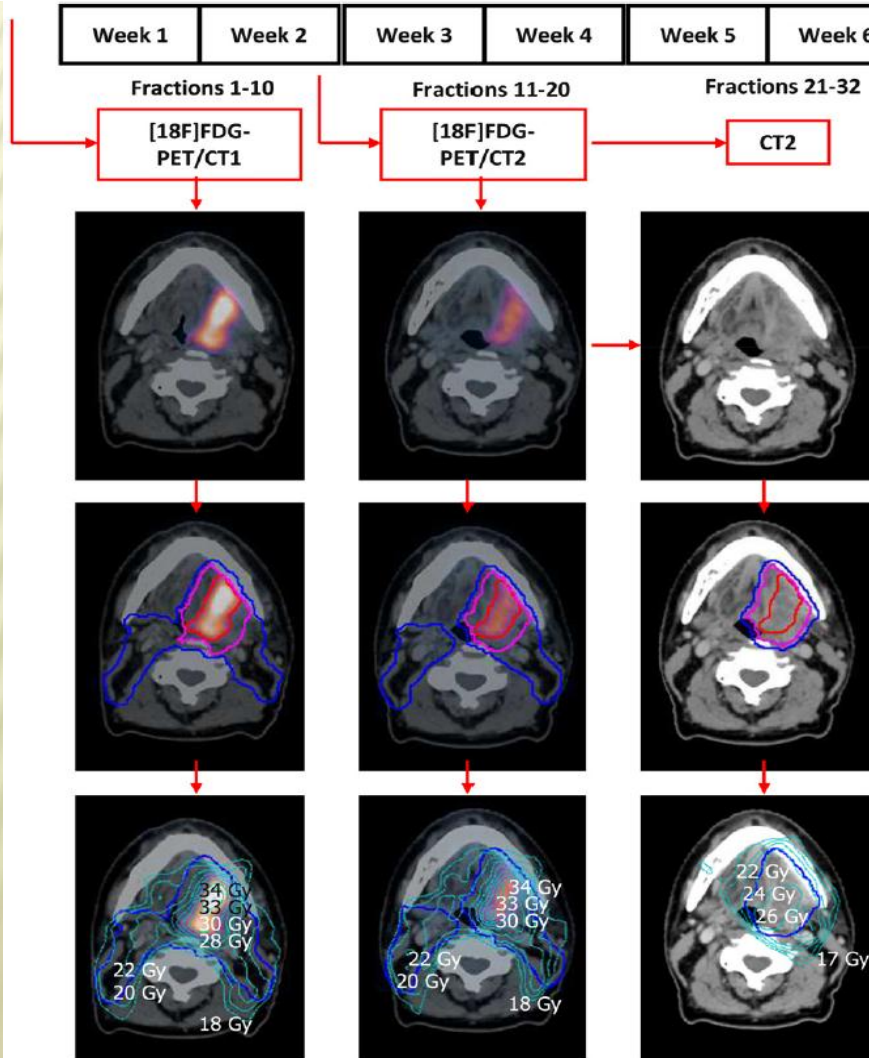
IMAGING BIOLOGICO PER IL “ DOSE PAINTING” DURANTE RT

1. **FDG:** metabolismo del glucosio

ADAPTIVE DOSE PAINTING BY NUMBERS FOR HEAD-AND-NECK CANCER

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CTV h.dose: 80.9 Gy / 3 Gy/die (step 1)

CTV h.dose: 85.9 Gy/3.5 Gy/die (step 2)

IMAGING BIOLOGICO PER IL “ DOSE PAINTING” DI GTV SUBVOLUMES

1. **FDG**: metabolismo del glucosio
2. **FLT** (fluorotimidina): proliferazione tumorale

^{18}F -FLT PET/CT for Early Response Monitoring and Dose Escalation in Oropharyngeal Tumors

Esther G.C. Troost¹, Johan Bussink¹, Aswin L. Hoffmann¹, Otto C. Boerman², Wim J.G. Oyen², and Johannes H.A.M. Kaanders¹

OROFARINGE

FLT-PET/CT ALLA SETTIMANA -1, 2 and 4 → LE VARIAZIONI SONO VISIBILI PRECOCEMENTE alla PET rispetto alle modifiche volumetriche

Diminuzione SUV max del 40-50% tra settimana -1 e 2

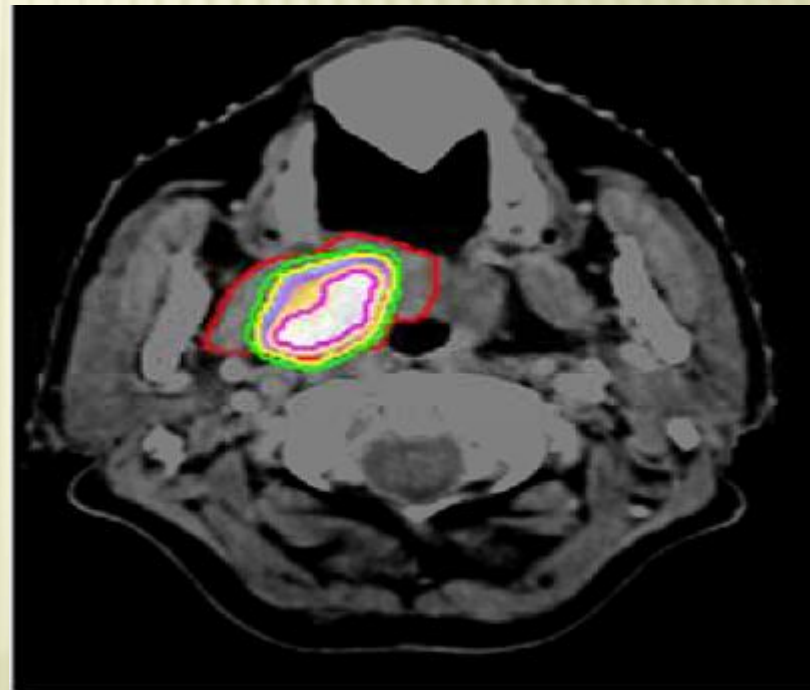


FIGURE 1. ^{18}F -FLT PET/CT image of T3N0M0 oropharyngeal tumor before radiation therapy. Shown are GTV_{CT} (red), GTV_{SBR} (green), and GTV_{50%}. GTV_{90%} is highlighted in pink.

^{18}F -FLT PET/CT for Early Response Monitoring and Dose Escalation in Oropharyngeal Tumors

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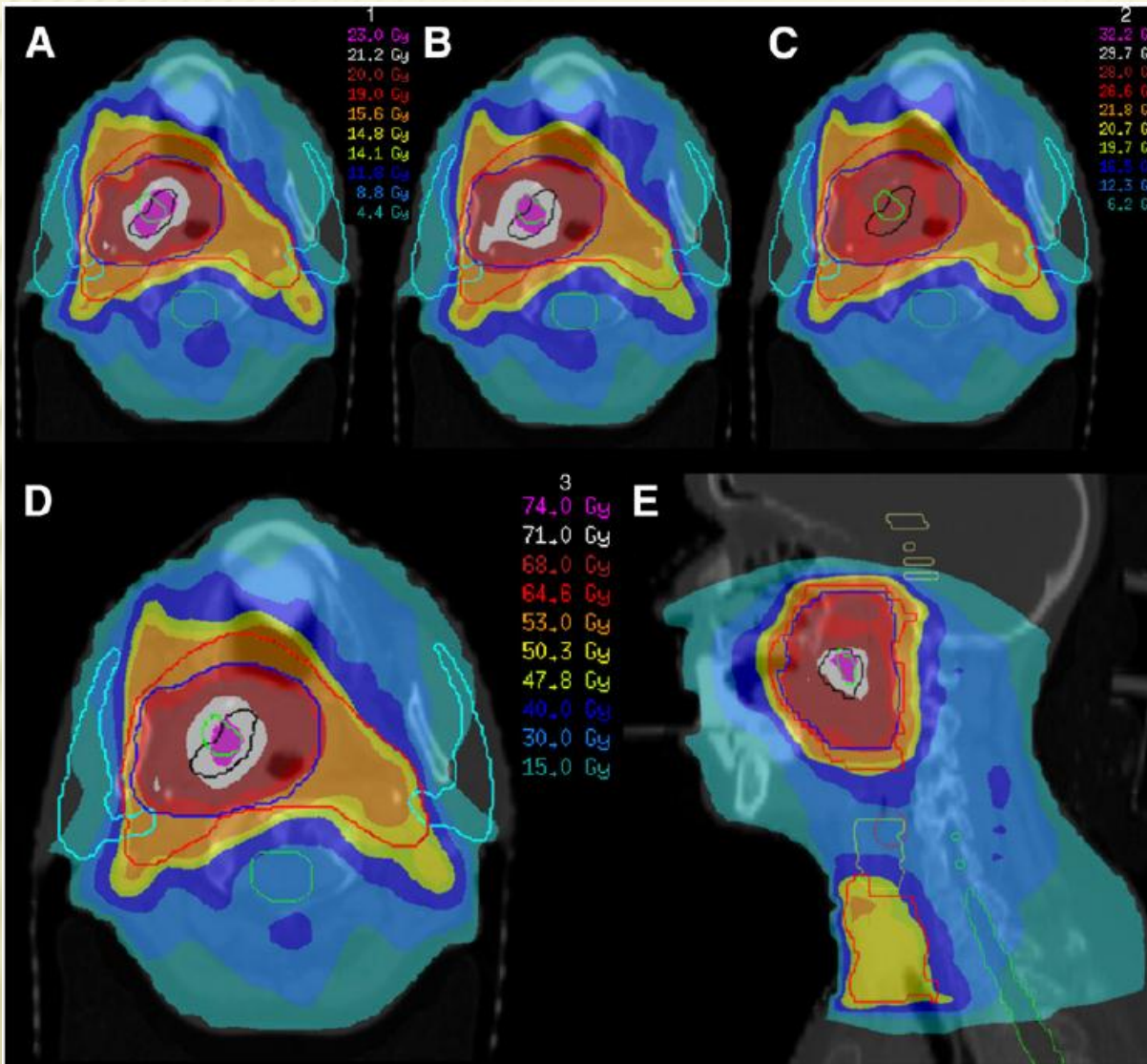


FIGURE 4. Dose escalation to $\text{GTV}_{80\%1}$ and $\text{GTV}_{80\%2}$ for T3N0M0 oropharyngeal tumor. Using IMRT with integrated simultaneous boost technique, total dose was 50.3 Gy to bilateral cervical lymph node regions (large planning target volume, red) and 68 Gy to primary tumor (small planning target volume, blue). $\text{GTV}_{80\%1}$ (black) and $\text{GTV}_{80\%2}$ (green) were consecutively irradiated with 2.3 Gy for 10 fractions, resulting in dose of 71 Gy in total and dose of 74 Gy in overlapping region. (A and B) Dose distributions for first 2 wk of treatment (A) and weeks 3 and 4 (B); see legend 1. (C) Dose distribution for remaining 14 fractions without dose escalation; see legend 2. (D and E) Dose distributions of total treatment plan in transverse (D) and sagittal (E) planes; see legend 3. Parotid glands are delineated in sky blue and spinal cord in green.

IMAGING BIOLOGICO PER IL “ DOSE PAINTING” DI GTV SUBVOLUMES

1. **FDG**: metabolismo del glucosio
2. **FLT** (fluorotimidina): proliferazione tumorale
3. **F- misonidazolo**: ipossia

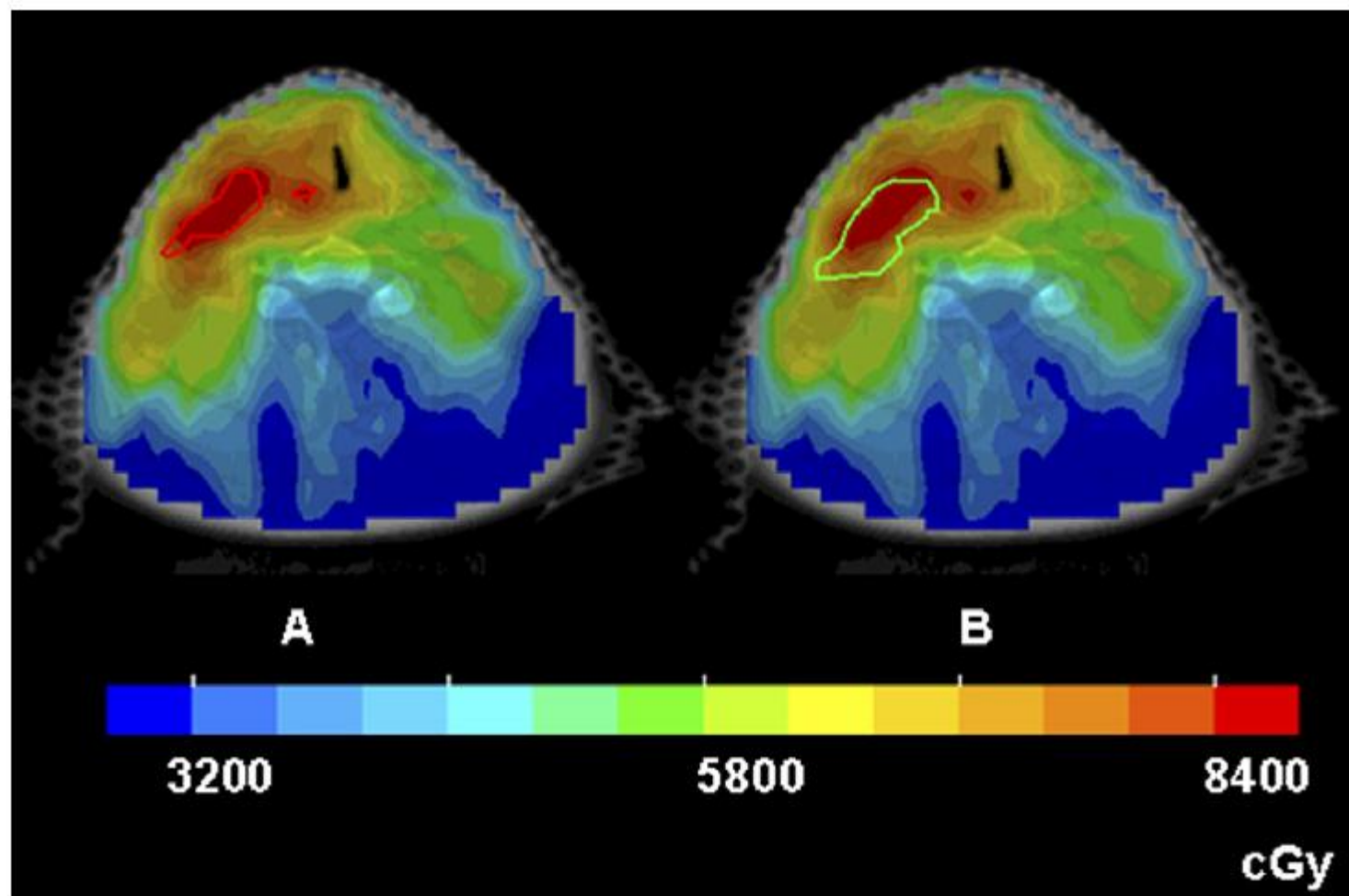
THE INFLUENCE OF CHANGES IN TUMOR HYPOXIA ON DOSE-PAINTING TREATMENT PLANS BASED ON ^{18}F -FMISO POSITRON EMISSION TOMOGRAPHY

Fig. 5. Intensity-modulated radiotherapy dose distributions in color-wash display of Patient 7, for whom the sequential hypoxia images were dissimilar. (a) Both sub-volumes of V_{H1} (the red contours) received 84 Gy. (b) When the same treatment plan was applied to V_{H2} (the green contour), part of the hypoxic volume did not receive the intended boost dose.

IMAGING BIOLOGICO PER IL “ DOSE PAINTING” DI GTV SUBVOLUMES

1.

**TIME AND RESOURCES
CONSUMING**

3.

GRAZIE...

