CONVEGNO AIRO LOMBARDIA

TUMORI DEL DISTRETTO CERVICO-CEFALICO

DALLA DEFINIZIONE DEI VOLUMI DI TRATTAMENTO ALL'ADAPTIVE RADIOTHERAPY

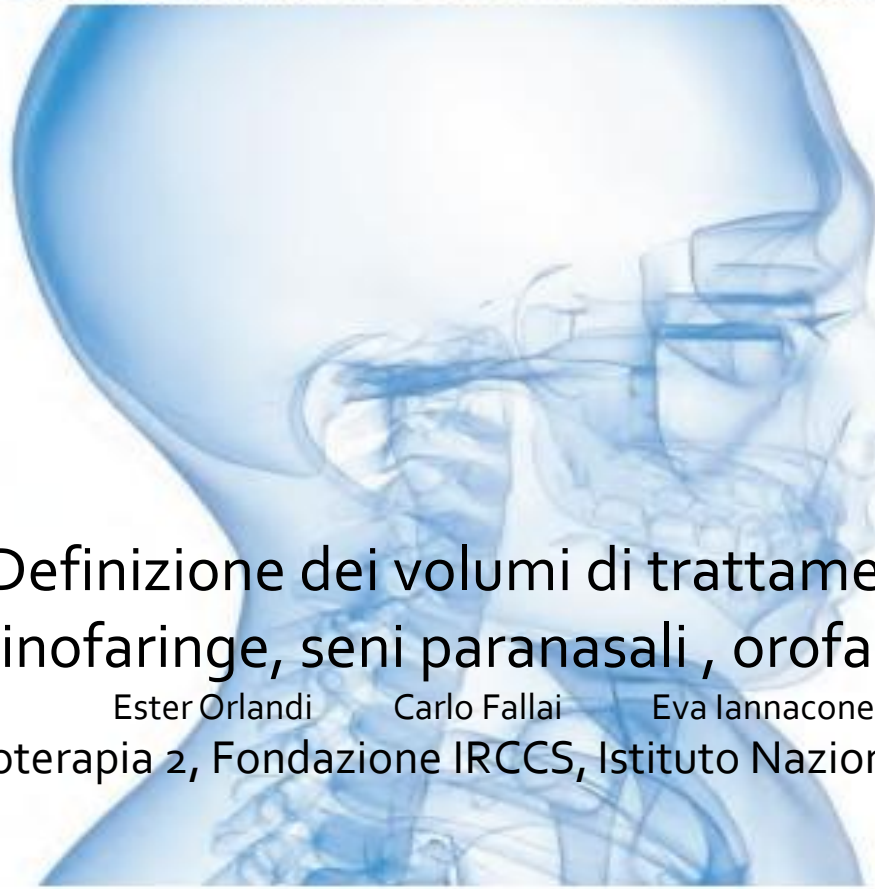
22 Giugno 2013 ore 8:30

Via Francesco Nava 31, 20159 Milano

PRESIDENTI DEL CONVEGNO
Roberto Orecchia
Presidente AIRO Lombardia
Simona Castiglioni - Milano

COMITATO SCIENTIFICO
Paolo Antognoni (Varese)
Ernestina Bianchi (Como)
Lorenza Bruschieri (Treviglio)
Simona Castiglioni (Milano)
Nadia Di Muzio (Milano)
Francesco Filippone (Bergamo)
Giovanni Ivaldi (Pavia)
Anna Merlotti (Busto Arsizio)
Roberto Orecchia (Milano)

COMITATO ORGANIZZATIVO
Simona Castiglioni
Maddalena Catalano
Ezio Colombo
Mara Migliazza



Definizione dei volumi di trattamento: rinofaringe, seni paranasali , orofaringe

Ester Orlandi Carlo Fallai Eva Iannacone
Radioterapia 2, Fondazione IRCCS, Istituto Nazionale Tumori

Background

- **Le tecniche ad intensità modulata rappresentano oggi il trattamento radioterapico d'elezione per le neoplasie del distretto orl, in particolare per il carcinoma rinofaringeo, orofaringeo e per I tumori sinunasali**

- **La fase di definizione dei volumi bersaglio tumorali è step critico nel processo IMRT (rischio di missing geografico)**

- **Mancanza di consenso relativamente a tutte le fasi del *treatment planning* in particolare riguardo a:**

  - **definizione e contornazione di GTV e High Risk CTV**
  - **prescrizione della dose**

Fleury B, Cancer Radiother, 2010
Wang T.J.C. J Radiat Oncol , 2012

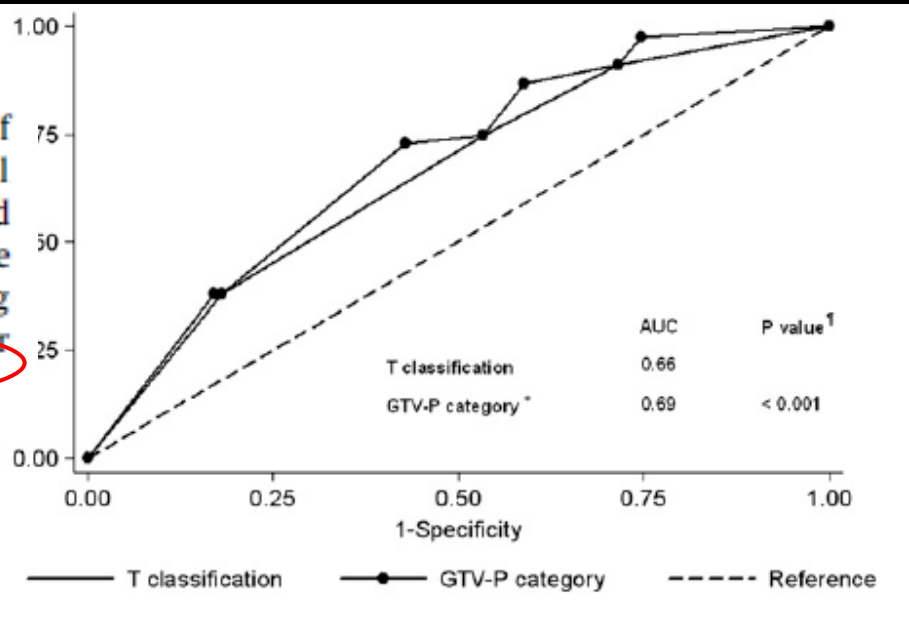
Rinofaringe

Is primary tumor volume still a prognostic factor in intensity modulated radiation therapy for nasopharyngeal carcinoma?

GTV

Endpoint	Variable	HR	HR (95% CI)	*P*-value
*Early T1-T2 patients**				
Disease-free survival	GTV-P (⩾19 ml vs.<19 ml)	7.678	3.735–15.785	<0.001
	N classification* (N1–3 vs. N0)	2.562	0.884–7.429	0.083
Overall survival	GTV-P (⩾19 ml vs.<19 ml)	8.714	3.613–21. 016	<0.001
	N classification* (N1–3 vs. N0)	3.866	0.894–16.721	0. 070
Local relapse-free survival	GTV-P (⩾19 ml vs.<19 ml)	NS		
Distant metastasis-free survival	GTV-P (⩾19 ml vs.<19 ml)	9.636	4.071–22.812	<0.001
*Advanced T3-T4 patients**				
Disease-free survival	GTV-P (⩾19 ml vs.<19 ml)	7.256	2.284–23.057	0.001
	Age (⩾45 vs.<45 years)	1.613	1.118–2.328	0.011
	N classification* (N1–3 vs. N0)	1.877	1.049–3.359	0.034
Overall survival	GTV-P (⩾19 ml vs.<19 ml)	5.725	1.804–18.172	0.003
	Age (⩾45 vs.<45 years)	2.146	1.378–3.342	0.001
Local relapse-free survival	GTV-P (⩾19 ml vs.<19 ml)	NS		
Distant metastasis-free survival	GTV-P (⩾19 ml vs.<19 ml)	6.961	1.692–28.634	0.007
	N classification* (N1–3 vs. N0)	2.208	1.014–4.811	0.046

ROC curves were used to compare the prognostic validity of adding GTV-P to the T classification of TNM staging system. In all patients ($n = 694$), the AUC was 0.66 for T classification alone and 0.69 ($P < 0.001$) when GTV-P (<19 and ⩾19 ml) was added to the T classification (Fig. 2). The results revealed that, in predicting outcomes, the addition of GTV-P to T classification was superior to T classification alone.



Guo R, Rad Oncol , 2012

GTV

- es.clinico e endoscopico
- **MRI massiccio facciale e collo con mdc: imaging di riferimento** per invasione locale e dei linfonodi retrofaringei (RPN)
- **FDG-PET:** accuratezza diagnostica simile a MRI in nodal staging , eccetto per RPN
- Fusione immagini con MRI/PET

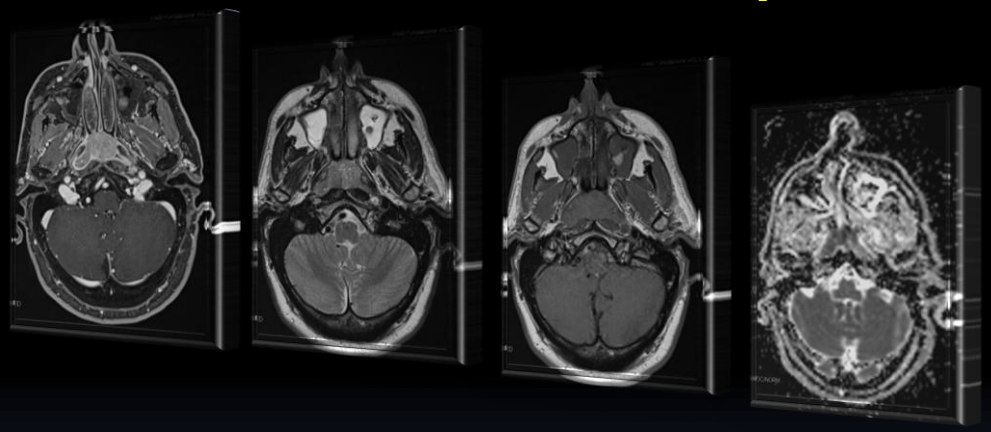
Manavis J, Clin Imaging, 2005
Ng SH, Eur J Nucl Med Mol Imaging, 2004
King AD, Br J Radiol, 2008
Nishioka T , Int J Rad Oncol Biol Phys, 2002

GTV–T/MRI

Sequenze:

- **T1 e T2 basali e dopo mdc**

  3D ultra fast gradient echo- fat-sat (es. VIBE , THRIVE ...)



Diffusion (DWI)

- caratterizzazione biologica del tumore

- diagnosi differenziale con altre neoplasie in aree endemiche

- valutazione della risposta e tossicità dopo CT neo e dopo RT

Manavis J, Clin Imaging, 2005

GTV–N/MRI

Criteri diagnostici per metastasi linfonodali:

- **Linfonodi retrofaringei (RPN)**

- Diametro assiale minimo (MID) ≥ 5 mm per i RPN laterali
- Qualsiasi dimensione per i RPN mediali

- **Linfonodi Cervicali**

- MID ≥ 11 mm al II-III livello o ≥ 10 mm se altri livelli
- Qualsiasi dimensione con necrosi centrale
- Raggruppamento linfonodale con presenza di 3 o più LNs contigui o confluenti, ognuno con MID di 8-10 mm
- Qualsiasi dimensione con estensione extracapsulare (ECS)

Tang L, 2008
Van den Brekel MW, 1990

GTV T-N/PET

- **Esistenza di correlazione SUV max e prognosi**

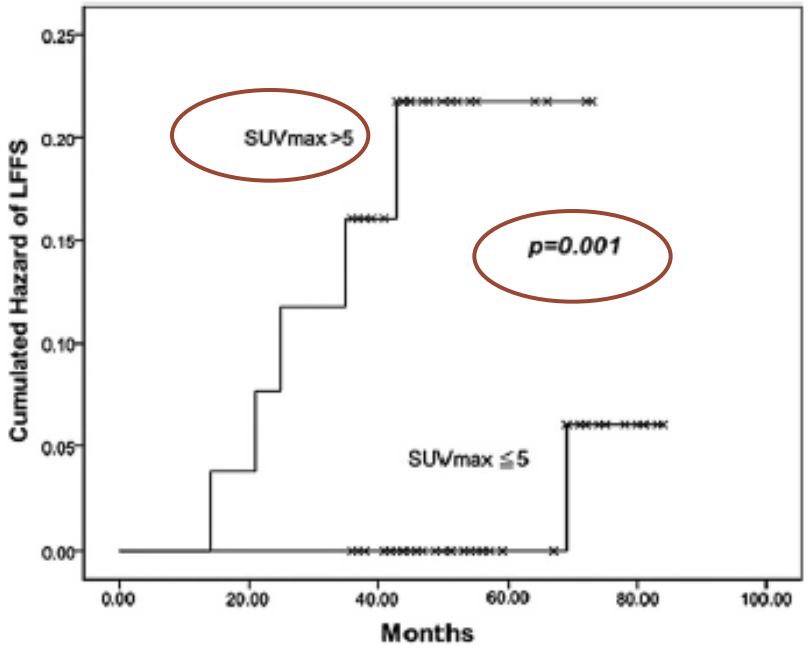


Fig. 2. The cumulative hazards of 5-year local failure-free survival (LFFS) for maximum standardized uptake value (SUVmax) ≤5 and >5 ($p = 0.001$).

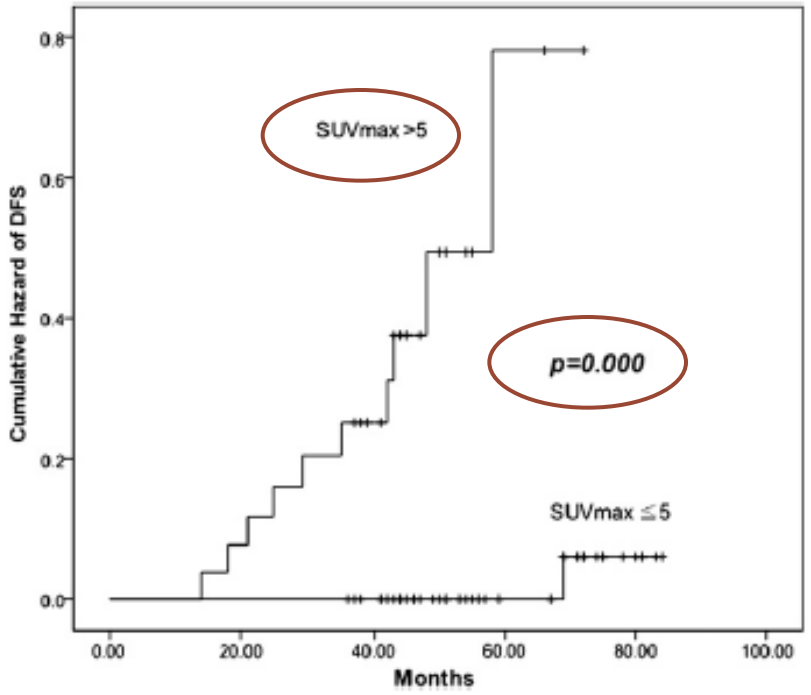


Fig. 3. The cumulative hazards of 5-year disease-free survival (DFS) for maximum standardized uptake value (SUVmax) ≤5 and >5 ($p = 0.000$).

- **Identificati cut-off di SUV max variabili (2.5-10), piu elevati per T rispetto a N**

Liu WS, Int j Rad Oncol Biol Phys, 2012

18 Studi+1 (INT)

Table 1 Results from series treating NPC with IMRT with or without chemotherapy

Study	Year	Stage	No.	Median follow-up (months)	Time point (years)	Local control rate (%)	Regional control rate (%)	Distant met-free rate (%)	OS (%)
Lee et al. [19] (UCSF)	2002	All	67	31	4	97	98	66	88
Kwong et al. [20] (Hong Kong)	2004	T1 N0–1[a]	33	24	3	100	92	100	100
Kam [21] (Hong Kong)	2004	All	63	29	3	92	98	79	90
Wolden et al. [22] (MSKCC)	2006	All	74	35	3	91	93	78	83
Kwong et al. [23] (Hong Kong)	2006	III–IVB[a]	50	25	2	96	NA	94	92
RTOG 0225 [5]	2009	All	68	31	2	93	91	85	80
Tham et al. [32] (Singapore)	2009	All	195	37	3	90	NA	89	94
Lin et al. [29] (China)	2009	II–IV[a]	323	30	3	95	98	90	90
Wong et al. [33] (China)	2010	All	175	34	3	94	93	87	87
Lin et al. [28] (China)	2010	IIB–IVB[a]	370	31	3	95	97	86	89
Kam et al. [57] (Hong Kong)	2010	All	231	59	6	82	91	75	66
Ng et al. [30] (Hong Kong)	2011	All	193	30	2	95	96	90	92
Xiao et al. [34] (China)	2011	III–IVA[a]	81	54	5	95	NA	NA	75
Bakst et al [35] (MSKCC)	2011	II–IVB[a]	25	33	3	91	91	91	89
Xiayun et al. [37] (China)	2011	IIB–IVB[b]	54	30	3	95	98	86	88
Ma et al. [36] (Hong Kong)	2011	III–IVB[b]	30	32	2	93	93	93	90
RTOG 0615 [27]	2012	IIB–IVB[c]	42	30	2	NA	NA	91	91
Su et al. [31] (China)	2012	I–IIB[b]	198	51	5	97	98	98	NA
Orlandi et al. (INT)	**2013**	**80%IIII-IV**	**106**	**43**	**5**	**88**	**88**		**82**

Wang T.J.C. J Radiat Oncol , 2012

GTV / MR-PET

Metodiche di immagine utilizzate per la definizione del GTV

- **Tutti gli autori utilizzano la RM pretrattamento (14 /19 in più del 95% dei pazienti)**
- **La PET è stata utilizzata in 8 studi → 7 + 1 (INT)**
- **Le immagini di PET o RM sono state coregistrate o fuse con la CT di centratura solo in 11 studi → 10 + 1 (INT)**

"The use of MRI is mandatory"

Wang TJC, J Radiat Oncol , 2012

GTV / MR-PET

Definizione e contornamento del GTV

- **GTV-T: definita come "all macroscopic disease at MRI" eccetto in**

Kwong et al.

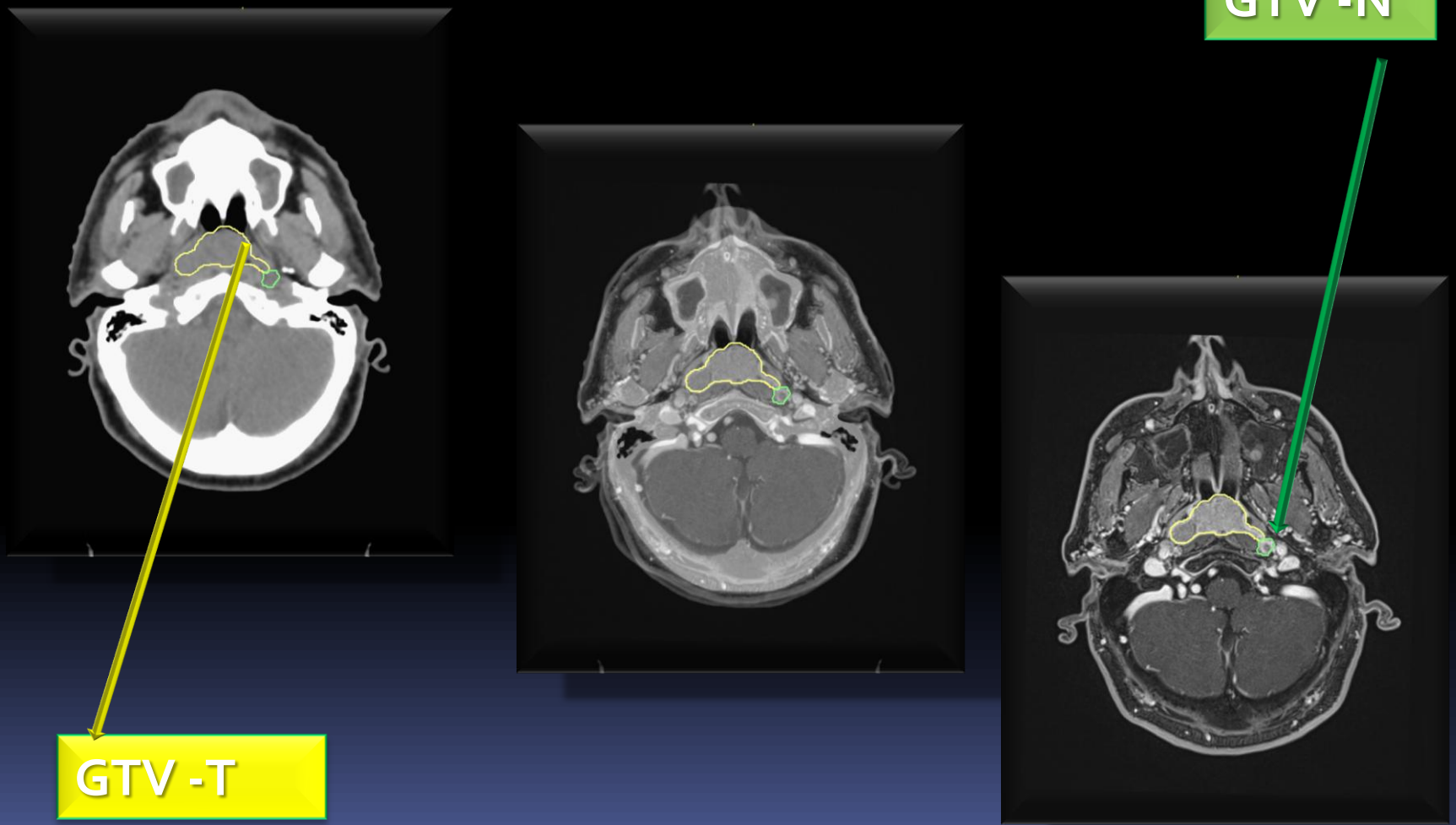
-GTV = "macroscopic tumor and the whole nasopharynx, including bilateral Eustachian cushions and prevertebral muscles" ***Cancer , 2004***

GTV-N:

"In general, all lymph nodes that are PET positive or greater than 1 cm in short axis should receive definitive treatment"

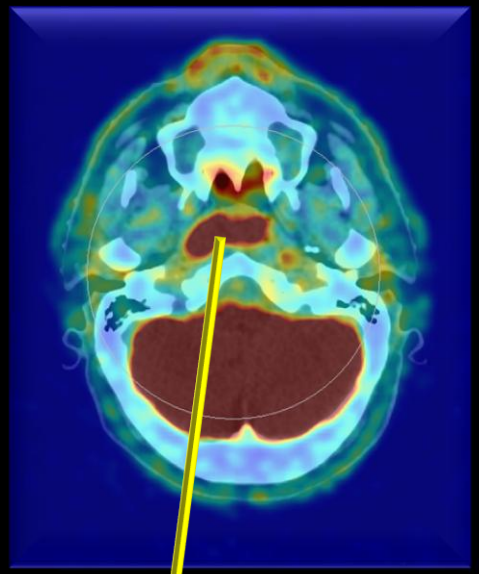
Wang TJC, J Radiat Oncol , 2012

GTV / MRI

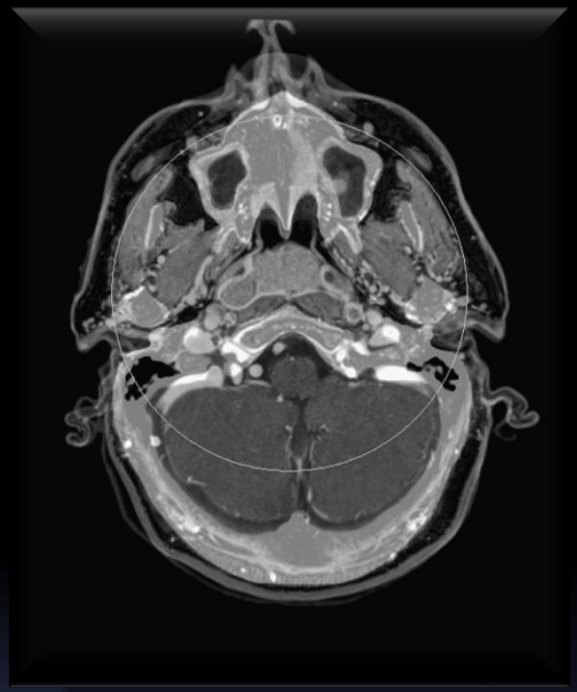


INT

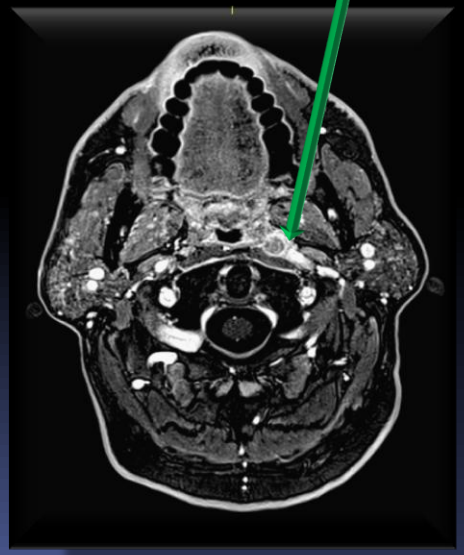
GTV / MRI e FDG-PET



GTV -T



GTV –N miglior caratterizzazione con MRI



INT

High Risk CTV (≥70 Gy)

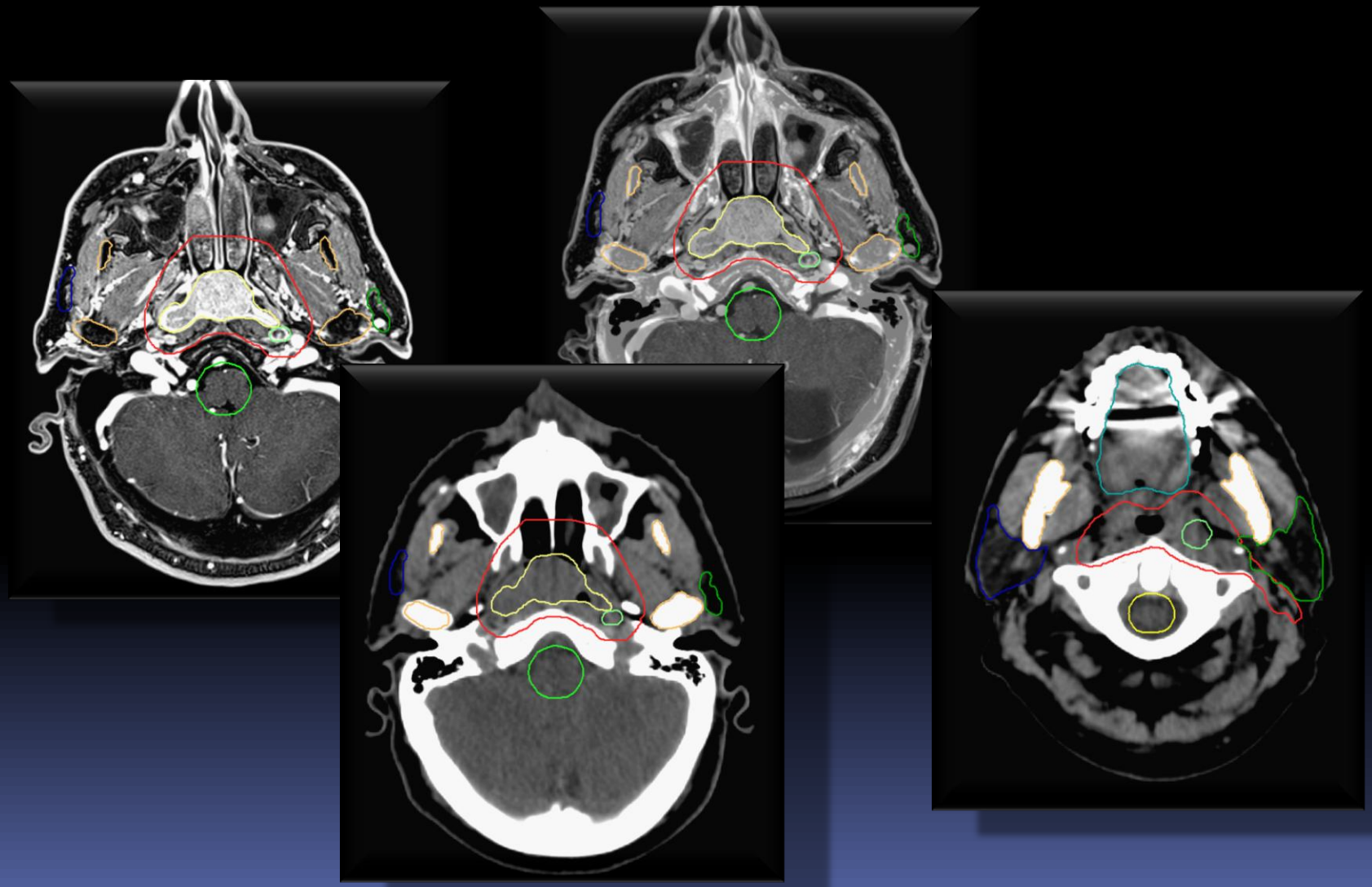
Variabilità nella definizione di HR-CTV
GTV+ 1 cm (3/18), ≥0,5 cm (8/18), ≥0,2 cm (1/19)

- **HR-CTV = nasofaringe (3/18)**
- **~~HR-CTV~~ = PTV = (GTV + 1 cm) (2/18)**
- **In 7 Studi il margine GTV-CTV è stato ridotto posteriormente fino a 0.1 cm quando il CTV risultava vicino alle strutture critiche (es. tronco encefalico).**
- **INT: GTV T /N più una espansione volumetrica ed anatomica da 0.5 a 2.5 cm (In molti casi l'intero Rinofaringe e i livelli dei linfonodi coinvolti)**

"A margin of 0.5-1 cm around GTV is generally adopted and recommended with an optional posterior margin reduction of 0.1–0.5 cm".

Wang TJC, J Radiat Oncol , 2012

High Risk CTV (≥70 Gy)



INT

Intermediate Risk CTV (59.4-68 Gy)

- **In generale nell'IR- CTV vengono inclusi:**

il clivus, il basicranio, il seno sfenoidale inferiore, il seno cavernoso, la fossa pterigoidea, lo spazio parafaringeo, la parte posteriore della cavità nasale e del seno mascellare, i linf. retrofaringei, e i linf. dal II al V livello.

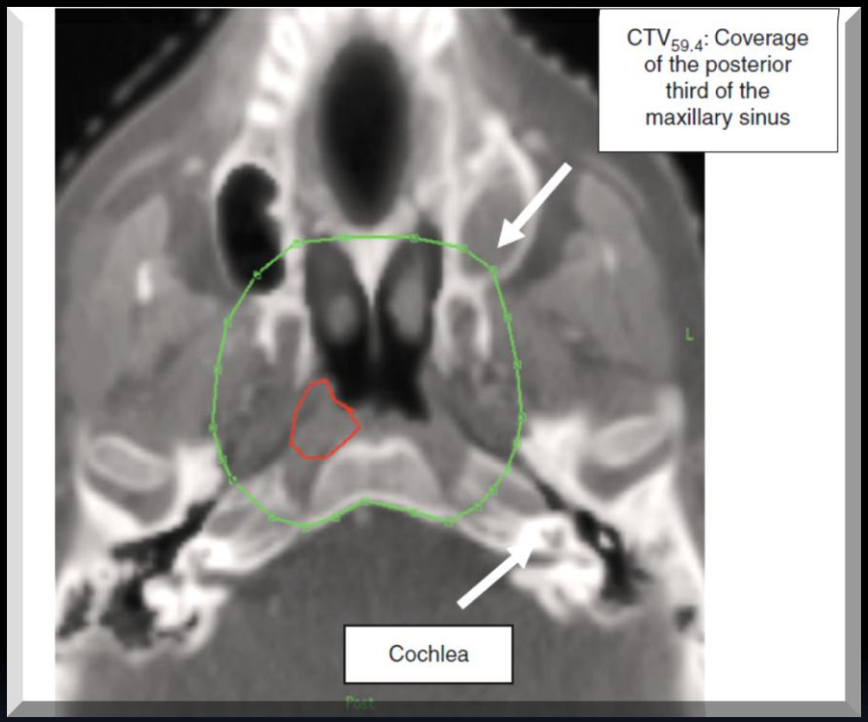
- **CLIVUS** (terzo o la metà anteriore se non coinvolto, intero se coinvolto) 8/18
- **BASE CRANICA:**

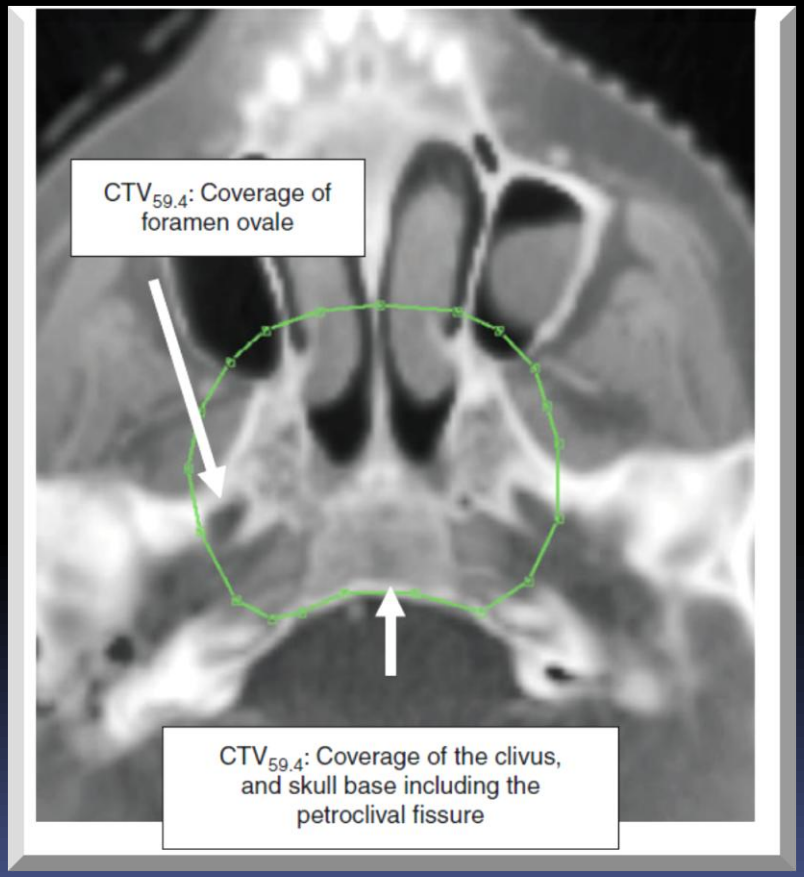
rocca petrosa e/o il forame ovale 6/18.
forame rotondo (1/18)
forame spinoso (2/18)

- **FESSURA ORBITARIA INFERIORE** (2/18)
- **ARCO ANTERIORE DELL'ATLANTE** (un terzo anteriore o la metà anteriore) (4/18)

Wang TJC, J Radiat Oncol , 2012

Intermediate Risk CTV (59.4-68 Gy)





Nancy J. Lee, Jade J. Lu 2013
Lee N et al. RTOG 0225, J Clin Oncol. 2009

Intermediate Risk CTV (59.4-68 Gy)

l'IR-CTV può comprendere:

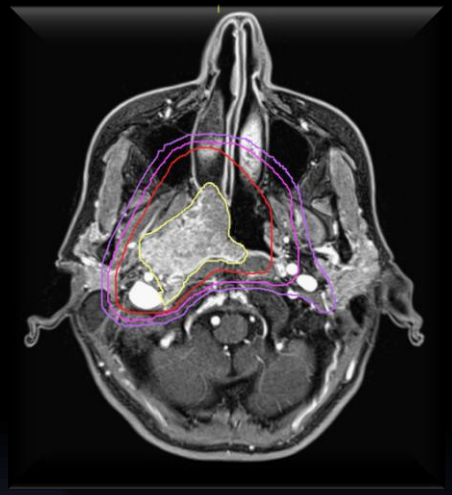
- **I livelli linfonodali non coinvolti nel collo *violato* o nel collo in cui vi è un massiccio coinvolgimento linfonodale.**
- **Le intere stazioni linfonodali retrofaringee, quando sono interessati i retrofaringei alti.**
- **Tutti i linfonodi sospetti in RM, anche se clinicamente negativi e non captanti alla PET.**

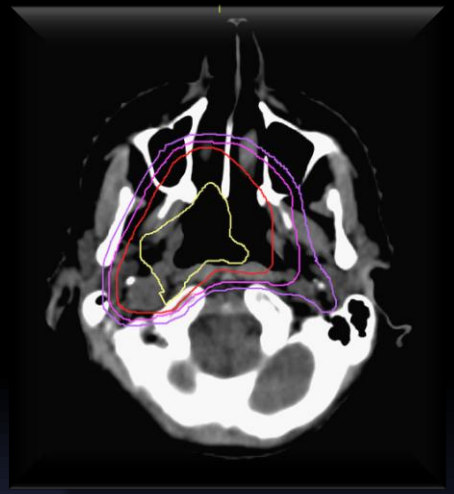
Orlandi, Future Oncology, 2013

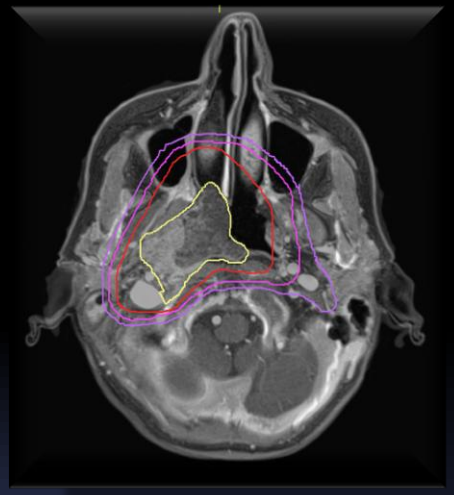
CT di induzione e Volumi

- E’ in genere raccomandato definire il GTV pre-CT e quindi prescrivere ad HR-PTV pre-CT

Wang TJC, J Radiat Oncol , 2012







- E’ possibile ridurre il volume dopo CT di induzione?

CT di induzione e Volumi

25 PZ (II B-IV)
CT Induzione: PF o TPF
Follow up medio: 29 mesi

INTENSITY-MODULATED RADIATION THERAPY WITH SIMULTANEOUS INTEGRATED BOOST TECHNIQUE FOLLOWING NEOADJUVANT CHEMOTHERAPY FOR LOCOREGIONALLY ADVANCED NASOPHARYNGEAL CARCINOMA

CTV1: **"GTV T e N post-CT"** + 5mm.
CTV2: rinofaringe, muscoli prevertebrali, fossa pterigopalatina, spazio parafaringeo, terzo post. cavità nasali e seno mascellare, seno sfenoidale inferiore, clivus, base cranica, N+ , linfonodi retrofaringei e II livello, estensione della malattia pre-CT.
CTV3: III- IV V livello non coinvolti
PTV: CTV + 3mm

PTV1 (**67,5Gy** , 2,25Gy/fx) *Normalized total dose of 74 Gy.8*
PTV2 (**54Gy** ; 1,8/fx, in 4 casi 60 Gy, 2Gy/fx)
PTV3 (**48 Gy**; 1,6Gy/fx)

" 3 locoregional recurrences within the 67.5-Gy volume
1 in the 60-Gy (where it was free of tumor the initial imaging work-up)
1 in the 48-Gy volume "

Kim K et al, Head and Neck 2009

Low-Risk CTV

"Lymph node metastasis in NPC follows a predictable and orderly pattern".

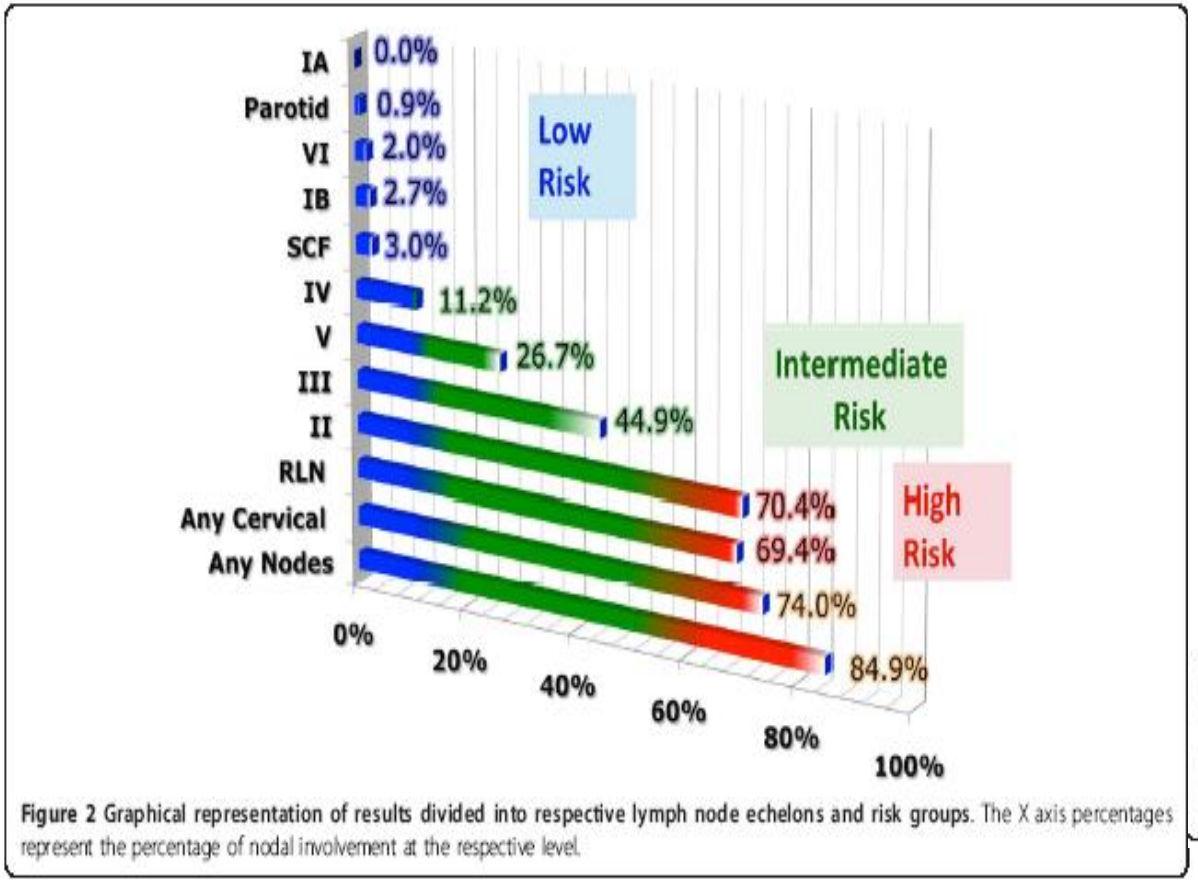


Figure 2 Graphical representation of results divided into respective lymph node echelons and risk groups. The X axis percentages represent the percentage of nodal involvement at the respective level.

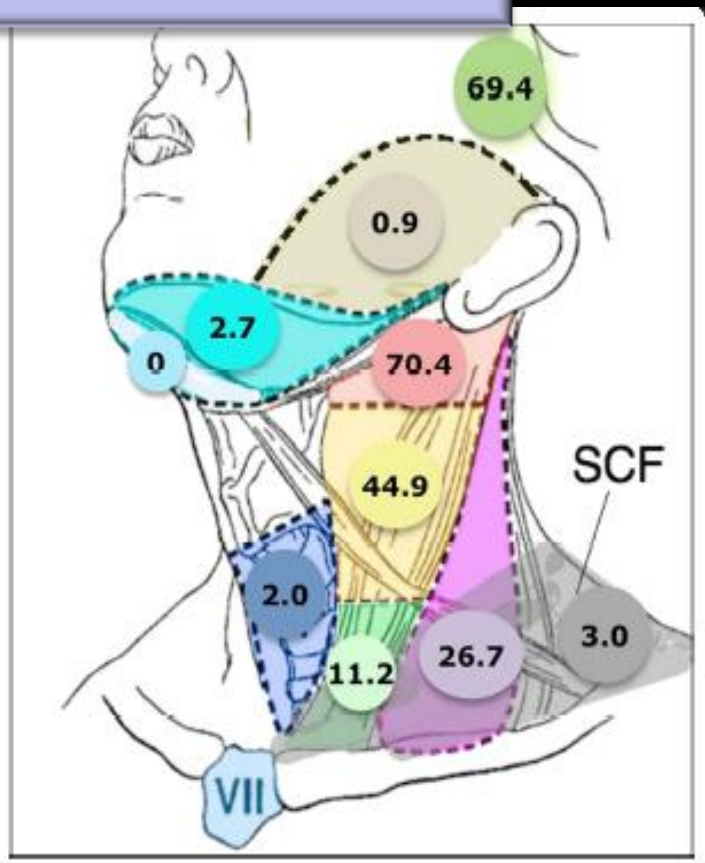


Figure 14 Pictorial summary of incidence of LN metastasis in NPC. This is a pictorial representation of the neck. The respective numbers represent the overall percentage of NPC patients presenting with positive LN metastasis at the particular nodal station.

Ho FCH, BMC Cancer , 2012

LR-CTV

La maggiore variabilità è nell'inclusione del livello I:

- **In 2 Studi, il livello IA è coperto elettivamente solo se interessato il livello IB o la cavità orale.**
- **In 3 studi il livello IB viene sempre incluso.**
- **In 3 studi il livello IB viene risparmiato solo negli N0.**
- **In 2 studi il livello IB non viene incluso (il LRC è stato superiore al 95%).**

"Non è raccomandabile includere il livello IA"

Per i RPNs, il bordo inferiore è:

- **In 2 Studi a livello del margine craniale del corpo dell'osso ioide**
- **In 2 studi a livello del margine craniale della seconda vertebra cervicale**

Wang T.J.C. J Radiat Oncol , 2012

LR-CTV

E’ perseguibile un’irradiazione linfonodale selettiva in determinati stadi di malattia?

Nel collo No è possibile differenziare la dose?

IS ELECTIVE IRRADIATION TO THE LOWER NECK NECESSARY FOR N0 NASOPHARYNGEAL CARCINOMA?

YUNSHENG GAO, M.D.,* GUOPEI ZHU, M.D.,* JIADE LU, M.D., M.B.A.,*† HONGMEI YING, M.D.,* LING KONG, M.D.,* YONGRU WU, M.D.,* AND CHAOSU HU, M.D.*

Purpose: To summarize our experience and treatment results in lymph node–negative nasopharyngeal carcinoma treated in a single institution.

Methods and Materials: From January 2000 to December 2003, 410 patients with lymph node–negative nasopharyngeal carcinoma were retrospectively analyzed. The T-stage distribution was 18.8% in T1, 54.6% in T2 (T2a, 41 patients; T2b, 183 patients), 13.2% in T3, and 13.4% in T4. All patients received radiotherapy to the nasopharynx, skull base, and upper neck drainage areas, including levels II, III, and VA. The dose was 64–74 Gy, 1. 8–2.0 Gy per fraction over 6.5–7.5 weeks to the primary tumor with ^{60}Co or 6-MV X-rays, and 50–56 Gy to levels II, III, and VA. Residual disease was boosted with either ^{192}Ir afterloading brachytherapy or small external beam fields.

Results: The median follow-up time was 54 months (range, 3–90 months). Four patients developed neck recurrence, and only 1 patient (0.2%) experienced relapse outside the irradiation fields. The 5-year overall survival rate was 84.2%. The 5-year relapse-free survival rate, distant metastasis-free survival rate, and disease-free survival rate were 88.6%, 90.6% and 80.1%, respectively. Both univariate and multivariate analyses demonstrated that T classification was the only significant prognostic factor for predicting overall survival. The observed serious late toxicities were radiation-induced brain damage (7 cases), cranial nerve palsy (16 cases), and severe trismus (13 cases; the distance between the incisors was ≤1 cm).

Conclusion: Elective levels II, III, and VA irradiation is suitable for nasopharyngeal carcinoma without neck lymph node metastasis.

Escludendo i livelli IV, VB, SCF
4 recidive linfonodali: solo 1 out-field!

AJCC 1997, RPNs non valutati

Int J Rad Oncol Biol Phys, 2010

Lei Zeng MD, Xue-Ming Sun MD, Chun-Yan Chen MD et al.
A comparative study on prophylactic irradiation to the whole neck and to the upper neck for neck lymph node-negative nasopharyngeal carcinoma patients.
Head & Neck In press.

- Studio retrospettivo
- 270 PZ
- FU:65,1 m

AJCC 2002, RPNs non valutati

171 pz PROPHYLACTIC UPPER NECK IRRADIATION		*vs*	**99 pz PROPHYLACTIC WHOLE NECK IRRADIATION**	
OS	93,6%	*ns*	90,9%	
NRFS	99,4%		99%	
DMFS	98,8%		94,9%	

A Randomized Clinical Trial Comparing Prophylactic Upper Versus Whole-Neck Irradiation in The Treatment of Patients With Node-Negative Nasopharyngeal Carcinoma

Jin-Gao Li, MD[1]; Xia Yuan, MD[1]; Ling-Ling Zhang, MD[2]; Yi-Qiang Tang, MD[1]; Lan Liu, MD[3]; Xiao-Dan Chen, MSc[4]; Xiao-Chang Gong, MD[1]; Gui-Fen Wan, MD[1]; Yu-Lu Liao, MD[1]; Jian-Ming Ye, MD[5]; and Fan Ao, MD[1]

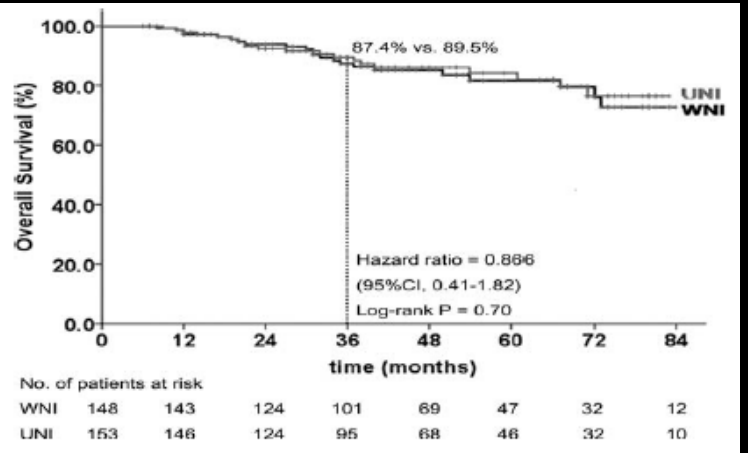


Figure 2. Cumulative overall survival rates are shown between the 2 groups.

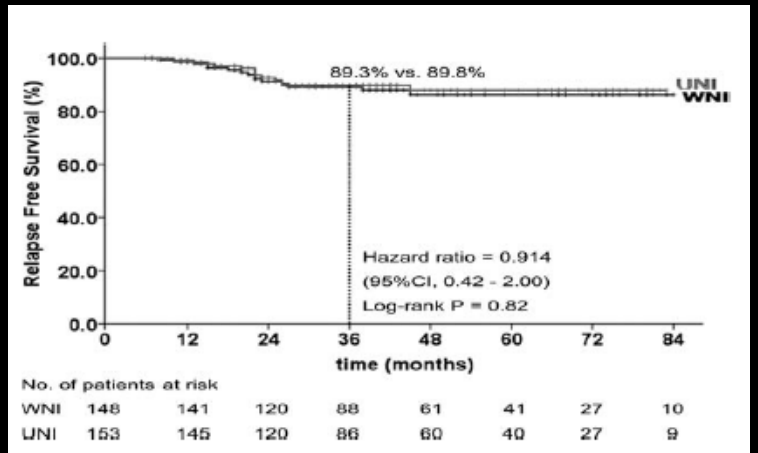


Figure 3. Cumulative relapse-free survival rates are shown between the 2 groups.

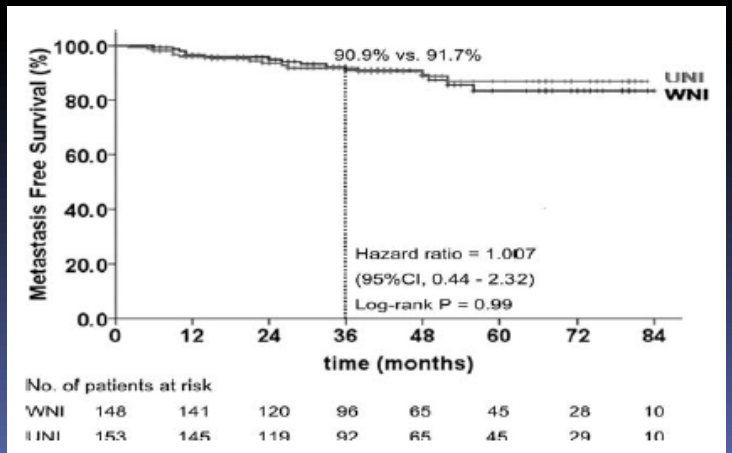


Figure 4. Cumulative metastasis-free survival rates are shown between the 2 groups.

Treatment outcome of nasopharyngeal carcinoma with retropharyngeal lymph nodes metastasis only and the feasibility of elective neck irradiation

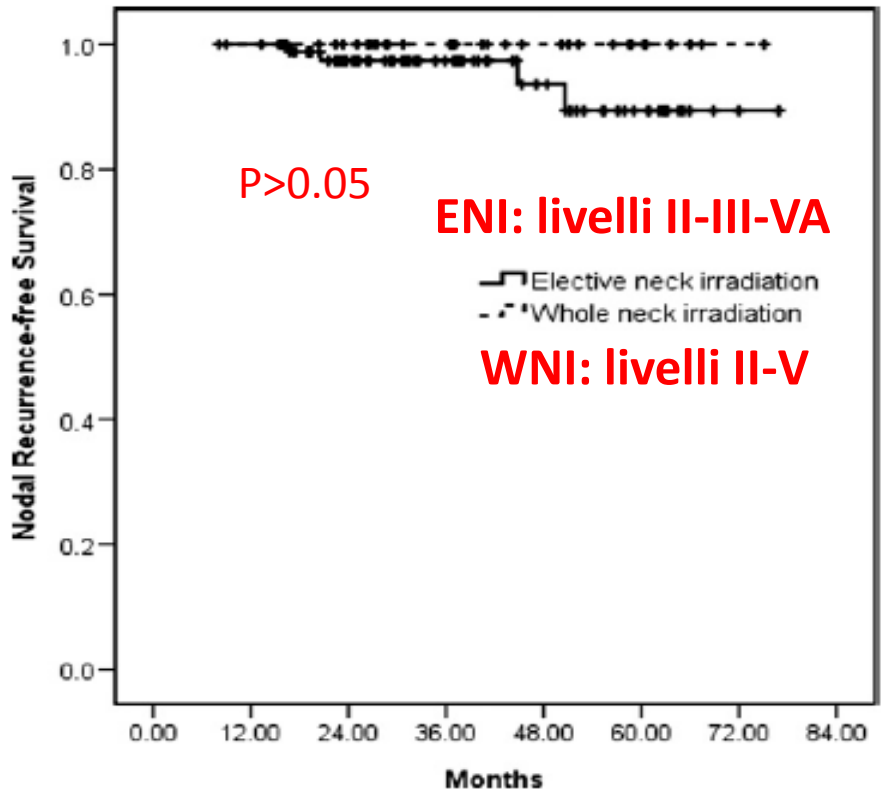


Fig. 1 Nodal recurrence-free survival between the two groups: elective neck irradiation and whole neck irradiation. There wasn't significant difference between the two groups ($p > 0.05$). The 95% of confidence interval of nodal recurrence-free survival was 69.4–76.7 months in the group of elective neck irradiation. Since there was no nodal recurrence in the group of whole neck irradiation, the 95% CI was not reached.

- Studio retrospettivo
- 119 PZ, ~50% Stadio II
- 89 ENI; 30 WNI
- Follow-up mediano: 36.6 mesi

Ou X, Oral Oncology, 2012

Etmoide, seno mascellare, fossa nasale,

Malattia non resecabile,

SCC, SNUC-ENB-SNEC-ACC

GTV

- **malattia macroscopica (se CT di induzione> volume pre-CT) definita su immagini MRI**

- **Ruolo emergente FDG-PET**

Table 2
Statistics of PET/CT divided by site and indication

	Primary staging	Primary restaging	Neck staging	Neck restaging	Distant staging	Distant restaging
PPV	100 (0.69-1)	56 (0.31-0.78)	–*	54 (0.26-0.80)	50 (0.02-0.97)	63 (0.26-0.90)
NPV	100 (0.05-1)	93 (0.81-0.98)	100 (0.69-1)	100 (0.91-1)	100 (0.68-1)	98 (0.89-0.99)
Sensitivity	100 (0.69-1)	77 (0.50-0.94)	–*	100 (0.56-1)	100 (0.05-1)	83 (0.36-0.99)
Specificity	100 (0.05-1)	84 (0.71-0.93)	92 (0.62-0.99)	89 (0.78-0.96)	92 (0.60-0.99)	95 (0.85-0.99)

All values are expressed as percentage (%).
95% confidence intervals listed in parentheses.
* No true-positive study was found.

"When viewed in conjunction with clinical examination, endoscopic assessment, and focused biopsies, they may effectively result in a more accurate assessment of the extent of disease".

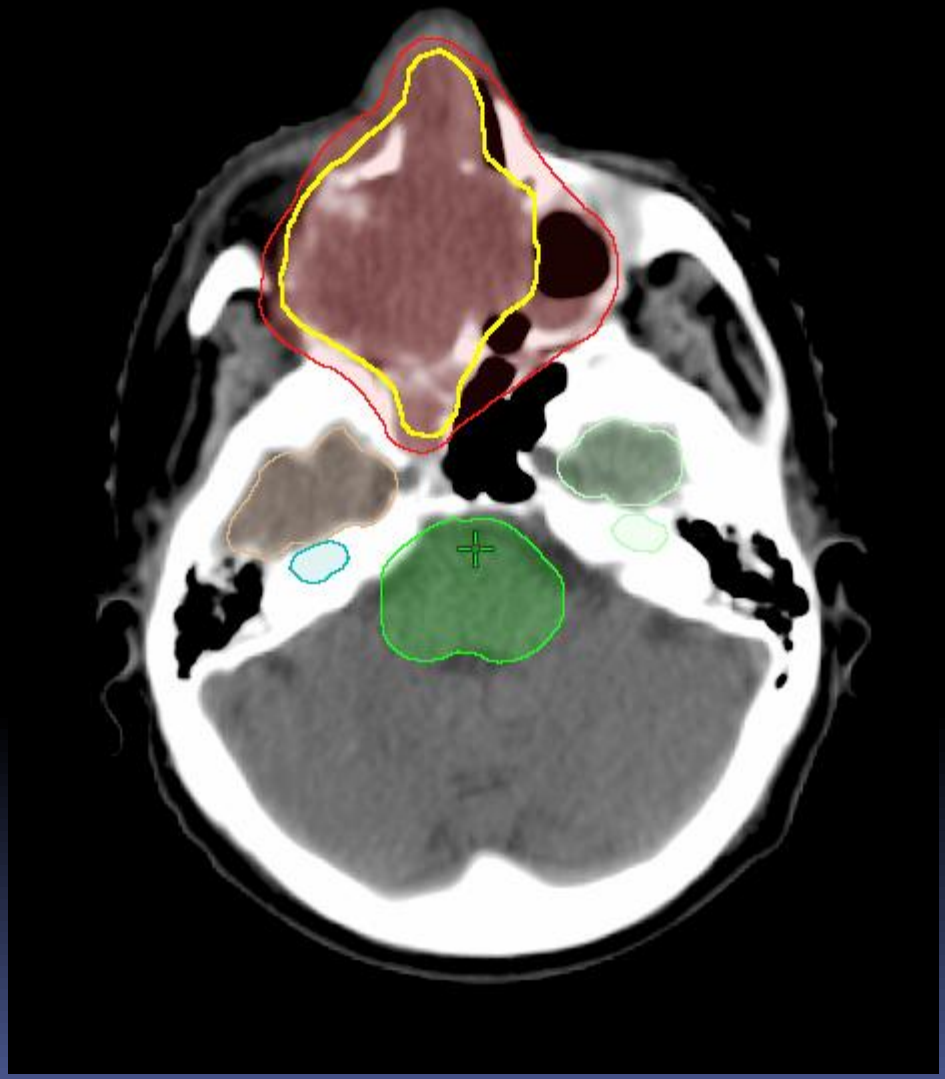
HR-CTV

- **Definizione compartimento- relata**

"HR-CTV encompasses the GTV with a margin at least 0.5 cm; however, in those region in which the GTV flanked by intact bone, no margin is added in that direction.
In the regions in which the GTV invades other paranasal sinuses or spreads up to their ostia, the whole compartment is included in the CTV contours.
In those regions in which the GTV invades the orbit or spreads intracranially, either the entire space or a margin of 0.5–1.0 cm will be added to the GTV.

If there is/are positive lymph node(s), HR-CTV includes these nodes with a margin of at least 1 cm or the whole node level according to the number and nodal level(s) involved. If there are pathological nodes with extracapsular extension (ECE) HR-CTV includes the whole node level (s)"

Claus F



LR-CTV

- **Non consenso univoco sul trattamento del collo N0**
- **Rischio di REC linfonodale: 8-29%**
- **Collo N+: in genere compresi i livelli linfonodali non immediatamente contigui ai livelli coinvolti**

Shah, In: Harrison LB 1999
Cantù, Arch Otolaryngol Head Neck Surg 2008

Table 3. Crude Cumulative Incidence (CCI) Estimates of Lymph Node Recurrence According to Tumor Site and Other Disease Characteristics

Characteristic	Ethmoid Sinus 305 pz			Maxillary Sinus 399 pz		
	First Events, No.	CCI Estimate (SE), %		First Events, No.	CCI Estimate (SE), %	
		2-Year	5-Year		2-Year	5-Year
Tumor histologic characteristic						
Adenocarcinoma	5	3.3 (1.4)	3.3 (1.4)	4	22.2 (10.1)	22.2 (10.1)
Esthesioneuroblastoma	2	NE	NE			
Adenoid cystic carcinoma				3	1.1 (1.1)	2.3 (1.6)
Melanoma	1	NE	NE			
Sarcoma				3	NE	NE
Squamous cell carcinoma	1	NE	NE	32	18.7 (3.1)	20.7 (3.3)
Undifferentiated carcinoma	4	25.5 (11.9)	25.5 (11.9	3	8.0 (5.6)	13.0 (7.4)
Mucoepidermoid carcinoma				1	NE	NE
Other	2	NE	NE	5	13.6 (7.6)	18.2 (8.6)
AJCC-UICC 2002 classification						
T2				30	15.4 (2.9)	18.0 (3.1)
T3	7	8.3 (3.0)	8.3 (3.0)	2	NE	NE
T4A/B	8	4.2 (1.7)	4.2 (1.7)	19	8.9 (2.0)	9.4 (2.1)
Nodal status at baseline						
N–	13	3.7 (1.1)	3.7 (1.1)	39	8.5 (1.5)	10.3 (1.6)
N+	2	NE	NE	12	36.4 (8.5)	36.4 (8.5)

Abbreviations: AJCC-UICC, American Joint Committee on Cancer–International Union Against Cancer TNM classification[6]; NE, not estimated.

Non- ITAC

Cantù, Arch Otolaryngol Head Neck Surg 2008

In altre serie, per stadi T3-T4, SCC e ca indifferenziati rischio di coinvolgimento> 20%

Linfonodi retrofaringei (RFN)

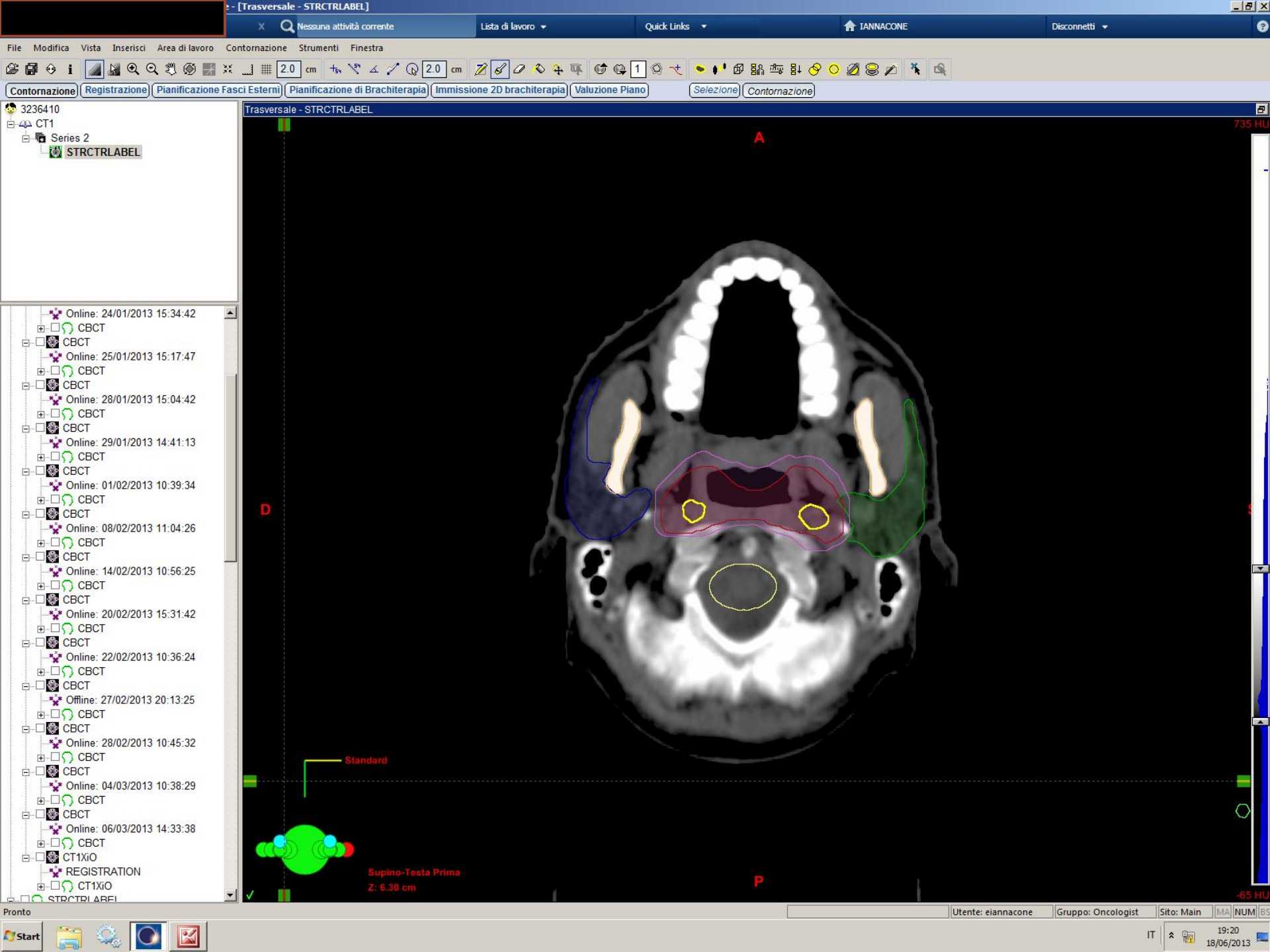
Lymph node metastasis in sinonasal squamous cell carcinoma treated with IMRT/3D-CRT

Xiyin Guan, Xiaoshen Wang, Yujie Liu, Chaosu Hu, Guopei Zhu *

Table 3
Distribution of lymph node metastases in 18 patients with positive lymph node on admission.

Nodes	Unilateral	Bilateral	Total (%)
Retropharyngeal lymph node	8	3	11(66.1)
Level I	7	3	10(55.5)
Level Ia	2	1	3(16.7)
Level Ib	6	2	8(44.4)
Level II	6	5	11(66.1)
Level IIa	6	5	11(66.1)
Level IIb	1	2	3(16.7)
Level III	2	1	3(16.7)
Level IV	2	0	2(11.1)
Level V	1	0	1(5.6)
Facial lymph node	2	0	2(11.1)

Oral Oncology 2012


- [Trasversale - STRCTRLABEL]
Nessuna attività corrente
Lista di lavoro
Quick Links
IANNACONE
Disconnetti
File
Modifica
Vista
Inserisci
Area di lavoro
Contornazione
Strumenti
Finestra
Contornazione
Registrazione
Pianificazione Fasci Esterni
Pianificazione di Brachiterapia
Immissione 2D brachiterapia
Valuzione Piano
Selezione
Contornazione
3236410
CT1
Series 2
STRCTRLABEL
Trasversale - STRCTRLABEL
735 HU
A
D
P
-65 HU
Standard
Supino-Testa Prima
Z: 6.30 cm
Online: 24/01/2013 15:34:42
CBCT
Online: 25/01/2013 15:17:47
Online: 28/01/2013 15:04:42
Online: 29/01/2013 14:41:13
Online: 01/02/2013 10:39:34
Online: 08/02/2013 11:04:26
Online: 14/02/2013 10:56:25
Online: 20/02/2013 15:31:42
Online: 22/02/2013 10:36:24
Offline: 27/02/2013 20:13:25
Online: 28/02/2013 10:45:32
Online: 04/03/2013 10:38:29
Online: 06/03/2013 14:33:38
CT1XiO
REGISTRATION
Pronto
Utente: eiannacone
Gruppo: Oncologist
Sito: Main
Start
IT
19:20
18/06/2013

Invasione perineurale

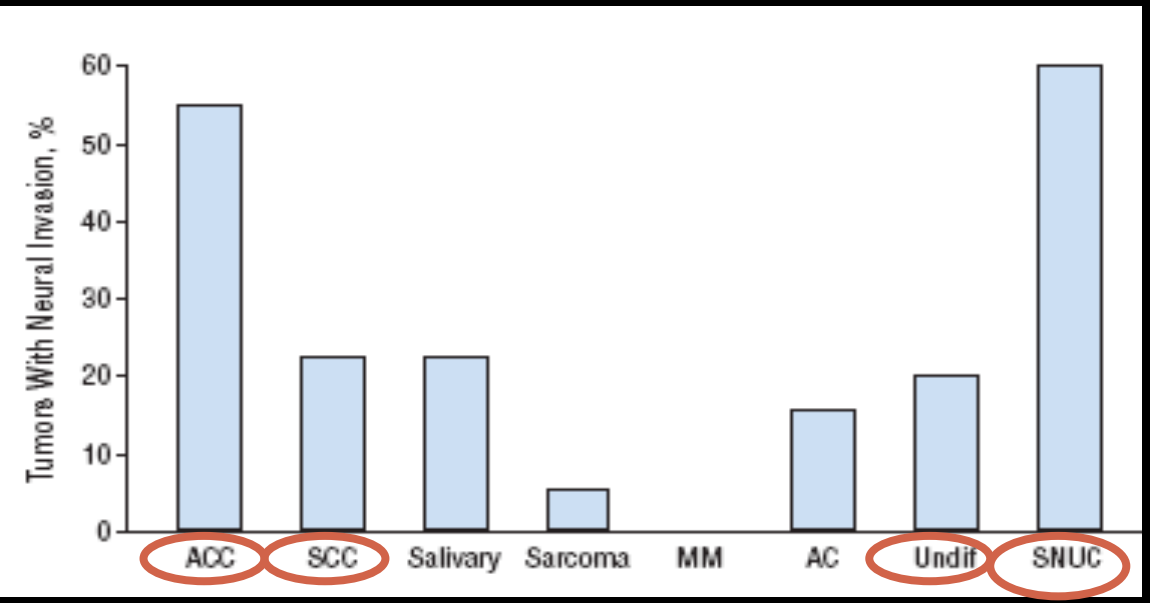


Table 3. Histopathologic An

Histologic Type	Nerve Diameter, No. (%) <2.5 mm	≥2.5 mm
Squamous cell carcinoma	5 (38)	8 (62)
Sarcoma[b]	1 (100)	0
Minor salivary gland AC	2 (66)	1 (33)
Minor salivary gland AC	5 (50)	5 (50)
Undifferentiated carcinoma	0	2 (100)
Non-ACC/AC minor salivary gland tumors[c]	1 (50)	1 (50)
SNUC	1 (33)	2 (66)
Total	**14** (42)	**19** (58)

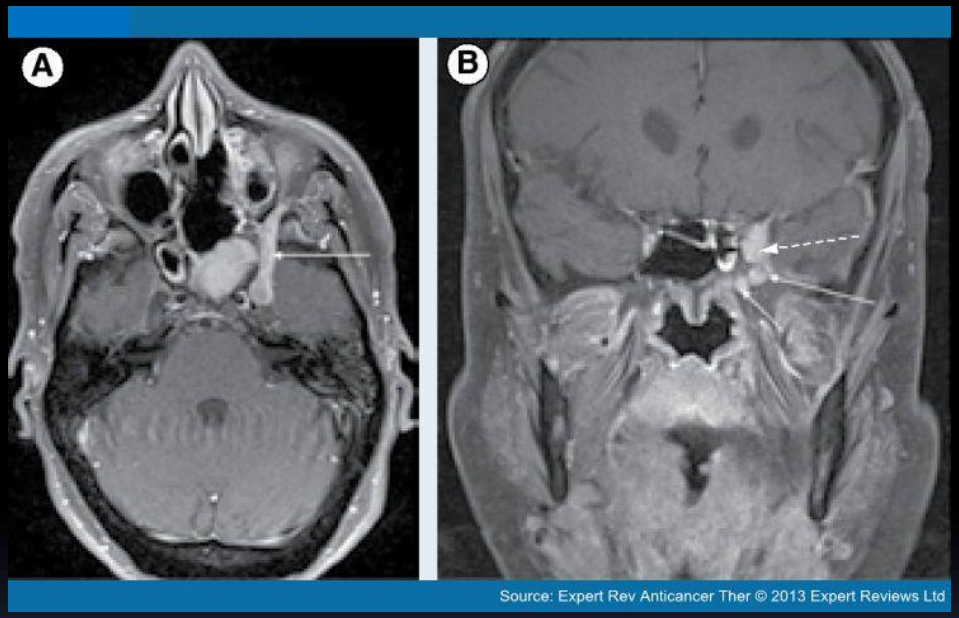
Table 5. The Different Variables Among Patients With and Without Neural Invasion (NI)

Variable	No. (%) With NI	Without NI	*P* Value (RR [95% CI])
Sex			.70
Male	26 (63)	108 (66)	
Female	15 (37)	55 (33)	
Age, y			.90
≤21	1 (2)	12 (7)	
>21	40 (98)	151 (93)	
Cranial nerve deficits			.20
No	37 (90)	155 (95)	
Yes	4 (10)	8 (5)	
Site			.04
Maxilla	18 (55)	44 (28)	
Adjuvant radiotherapy			.003 (1.4 [1.12-1.63])
Yes	34 (83)	100 (61)	
No	7 (17)	63 (39)	
Orbital/periorbital involvement			.06
Yes	6 (15)	48 (29)	
No	35 (85)	115 (71)	
Intracranial extension[a]			.90
Yes	8 (20)	30 (18)	
No	33 (80)	133 (82)	
Stage[b]			.20
T1-2	2 (6.7)	12 (18)	
T3-4	28 (93.3)	55 (82)	
Margins			<.001 (1.8 [1.3-2.3])
Positive	30 (73)	67 (41)	
Negative	11 (27)	95 (5)	

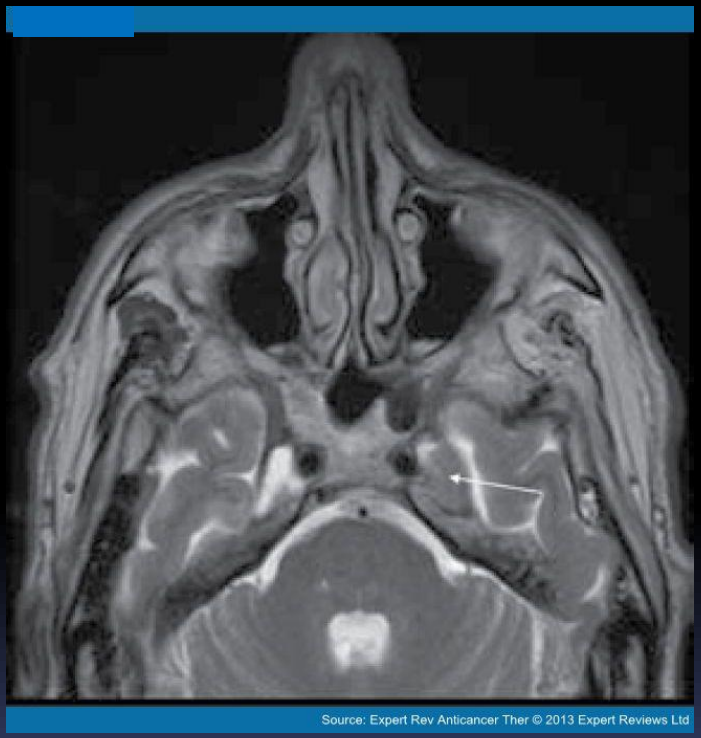
Abbreviations: CI, confidence interval; RR, relative risk.
[a]Intracranial extension includes bone and dura.
[b]There was no correlation between stage and pattern of NI.

Gill, Arch Otolaryngol Head Neck Surg 2009

Immagini esempio di invasione perineurale



Perineural tumor spread. **(A)** Axial and **(B)** coronal gadolinium-enhanced T1-weighted images show marked enlargement and enhancement along the left V2 as it travels in the foramen rotundum (arrow in **A** and long solid arrow in **B**). The short solid arrow in **(B)** also shows a similar process involving the left vidian nerve. **(B)** also shows asymmetric thickening in the region of the left orbital apex (dashed arrow).



Meckel's cave involvement. Axial T2-weighted magnetic resonance image demonstrates abnormal low signal soft tissue within the left Meckel's cave (arrow). Note the normal fluid signal within Meckel's cave on the right side.

	RT radicale
***High risk CTV* (HR-CTV)**	**T:** **malattia all'esordio o pre-CT, parti molli se pos.;** **sedi di R2*** **cN+ e livelli immediatamente adiacenti**
***Intermediate risk CTV* (IR-CTV)**	**T: sedi adiacenti a HR-CTV; base cranica-forami se IP identificata (volume dipendente da interessamento neurale)** **N: LN RP + livelli LN adiacenti a quelli inclusi in HR-PTV**
Low risk CTV (LR-CTV)	**cN0 (T2-4 SCC, SNUC, SNEC, Adenoca mascellare e fossa nasale) RPNs + livelli I-III** **cN+ : collo in toto mono o bilaterale in considerazione di estensione di T**

INT

Orofaringe

INTENSITY-MODULATED RADIATION THERAPY IN OROPHARYNGEAL CARCINOMA: EFFECT OF TUMOR VOLUME ON CLINICAL OUTCOMES

GTV

Table 2. Impact of prognostic factors on overall survival and disease control

			UVA		MVA*	
Outcome	Factor	Dichotomization	HR	*p* value	HR	*p* value
OS	pGTV	(>32.79 vs. ≤32.79)	4.40	< 0.0001†	3.74	0.0003†
	nGTV	(>19.04 vs. ≤19.04)	1.68	0.07	0.99	0.97
	T-stage	(3–4 vs. 1–2)	2.25	0.004†	1.46	0.2
	N-stage	(N2–3 vs. N0–1	3.39	0.005†	3.44	0.0073†
LF	pGTV	(>32.79 vs. ≤32.79)	6.01	0.004†	‡	‡
	T-stage	(T3–4 vs T1–2)	2.59	0.03†	‡	‡
RF	nGTV	(>19.04 vs. ≤19.04)	1.55	0.36	‡	‡
	N-stage	(N2–3 vs. N0–1)	6.98	0.055	‡	‡
DMF	pGTV	(>32.79 vs. ≤32.79)	3.03	0.0008†	3.01	0.0008†
	nGTV	(> 19.04 vs. ≤19.04)	1.78	0.64	NS	NS
	T-stage	(T3–4 vs. T1–2)	1.33	0.36	NS	NS
	N-stage	(N2–3 vs. N0–1)	9.42	0.002†	9.24	0.002†

Table 4. Literature on oropharyngeal cancer primary gross tumor volume and disease control

					pGTV	
					p value	*p* value
Author	Year	N	RT technique	Patients on CCRT	LC/LRC	DMFS
Nathu *et al.*	2000	114	3D-CRT	11%*	0.1	–
Mendenhall *et al.*	2003	190	3D-CRT	4%	0.0892–0.9493	–
Keberle *et al.*	2003	80	3D-CRT	NR	0.19	–
Been *et al.*	2008	79	3D-CRT/IMRT	49%	0.6244	–
Hermans *et al.*	2001	112	3D-CRT	NR	**0.047**	–
Chao *et al.*	2004	31†	IMRT	55%	**0.03**	**0.03**
Studer *et al.*	2007	85†	IMRT	75%‡	**<0.001**	–

Lok BH, Int J Rad oncol Biol Phys , 2012

GTV-MRI

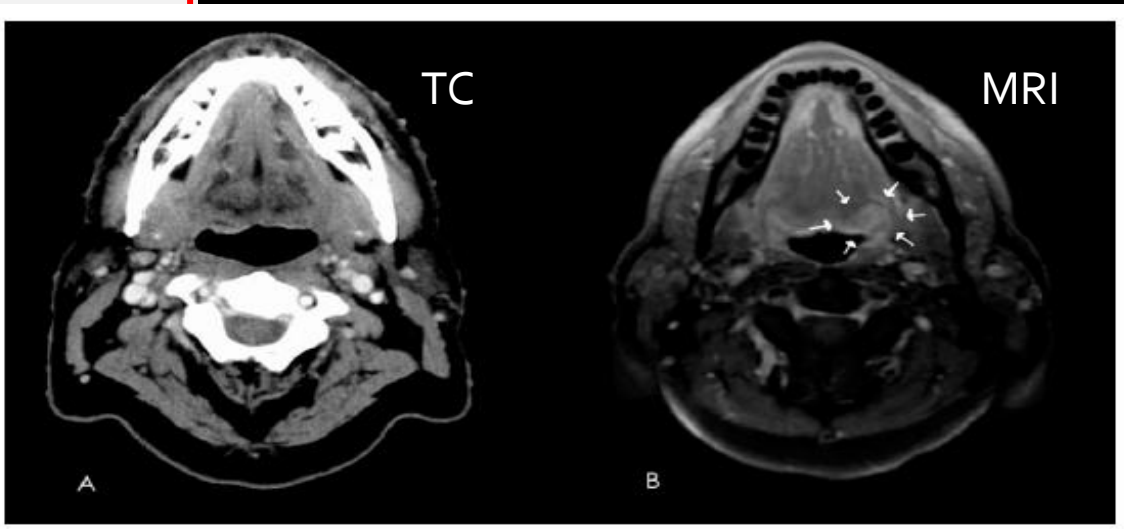
MRI: esame morfologico di riferimento

Sigal R. Radiographics 1996
Lam P. Am J Roentgenol 2004

Table 1
MRI and CT volumes for GTV, CTV and PTV and OAR. A difference between CT GTV and MRI GTV was detected. This difference was confirmed to be significant following the assessment of volumes delineated by other clinicians ($p = 0.003$).

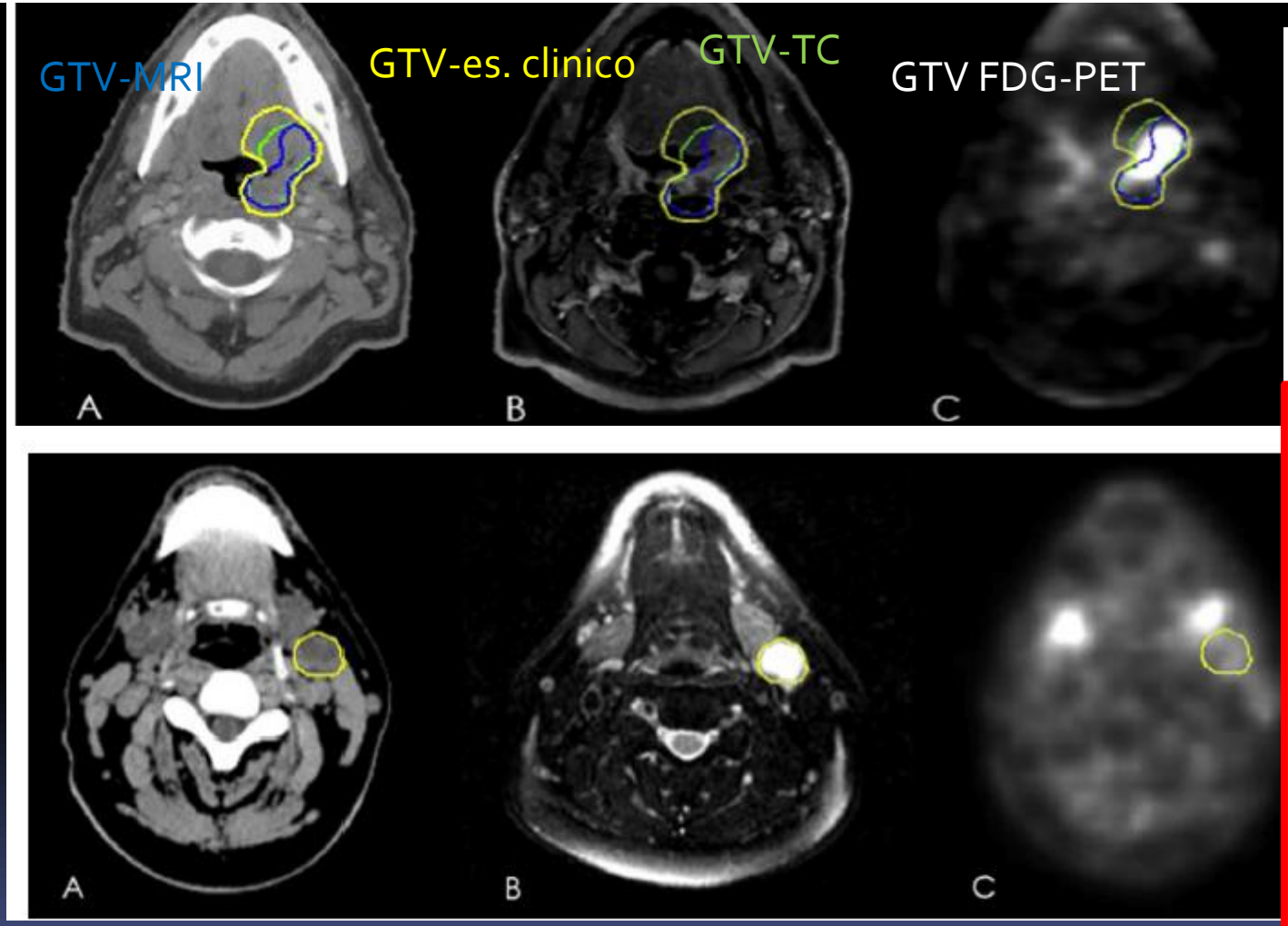
Mean volume units in cm^3 (SEM)	Mean volume on MR (cm^3) ± SE	Mean volume on CT (cm^3) ± SE	VOI	*p* value
GTV primary	22.2 (11.1)	9.5 (5.9)	0.34	0.05
GTV primary for all clinicians	24.6 (5.7)	14.4 (3.1)	N/A	0.003
GTV primary and lymph nodes	30.2	16.2	0.5	0.05
GTV primary and lymph nodes for all clinicians	30.8 (8)	18.5 (4)	N/A	0.01
GTV nodes only	5.8 (1.3)	5.8 (1.1)		

Ahmed M, Radioth Oncol, 2010



Thiagarajan, Int J Rad Oncol Biol Phys , 2012

Target Volume Delineation in Oropharyngeal Cancer: Impact of PET, MRI, and Physical Examination



Summary

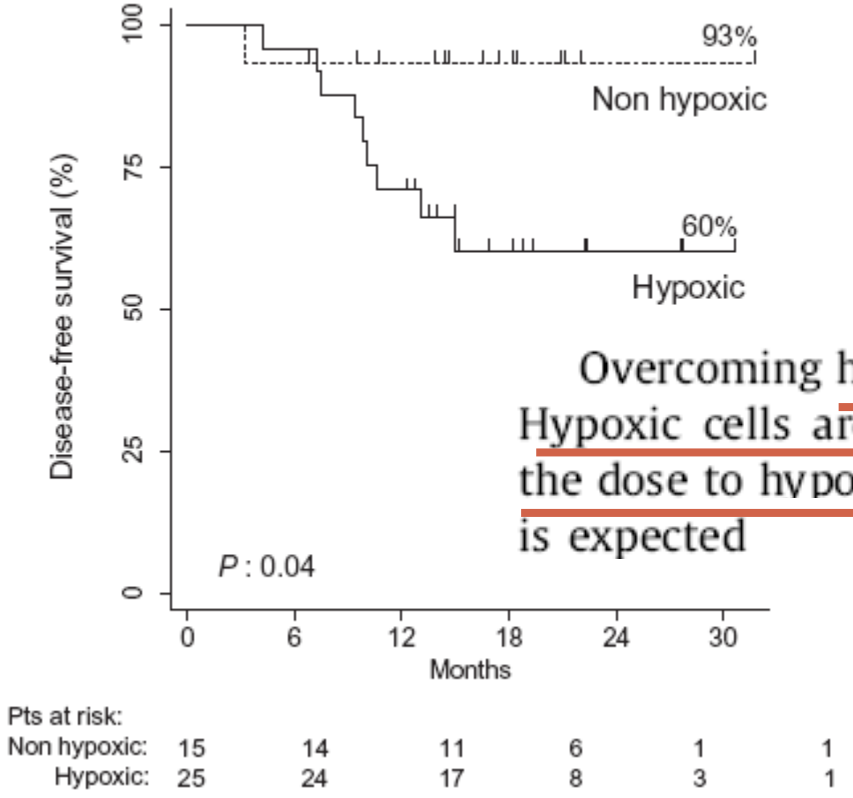
In the era of high precision radiotherapy, accurate target delineation is crucial. Sole utilization of computed tomography scans in gross tumor volume delineation for head and neck cancers is subject to significant inter-observer variation. This paper demonstrates that magnetic resonance imaging and positron emission tomography add valuable complementary information, and that their combined use is recommended. In addition, it shows that thorough physical examination is invaluable in assessing superficial tumor extent in oropharyngeal malignancies, a dimension that is often missed or underestimated by imaging alone.

Thiagarajan, Int J Rad Oncol Biol Phys , 2012

GTV-FAZA/MISO- PET

FAZA PET/CT hypoxia imaging in patients with squamous cell carcinoma of the head and neck treated with radiotherapy: Results from the DAHANCA 24 trial

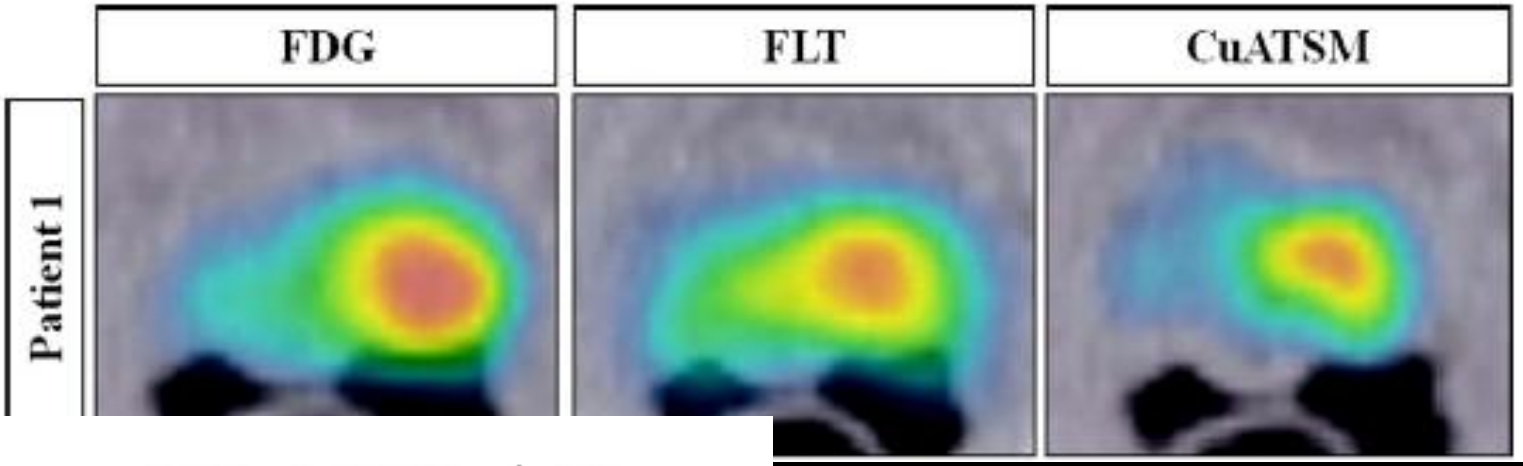
62.5% of pts:OPC



Overcoming hypoxia by dose painting is an intriguing concept. Hypoxic cells are more radiation resistant; hence by increasing the dose to hypoxic volumes of the tumor a higher tumor control is expected

Mortensen LS, Radioth Oncol, 2012

Correlation of PET images of metabolism, proliferation and hypoxia to characterize tumor phenotype in patients with cancer of the oropharynx



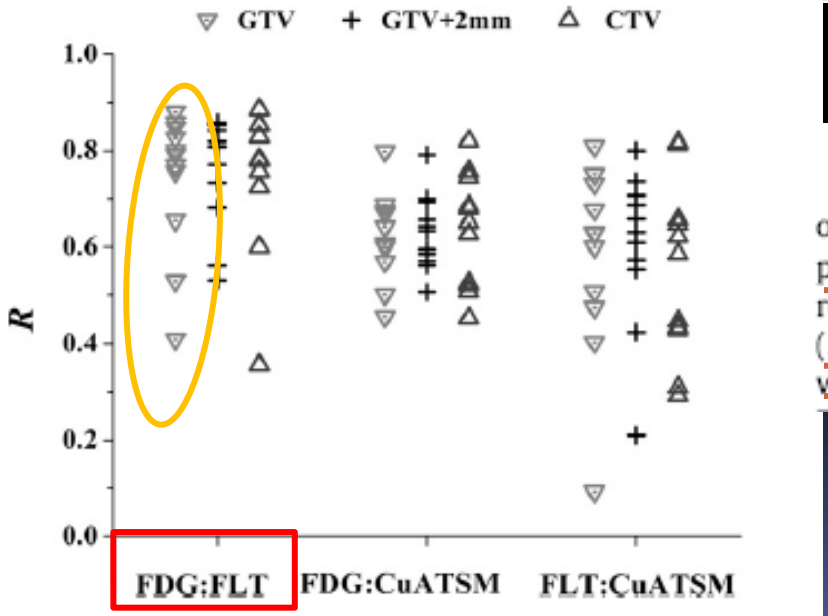


Fig. 2. Correlation coefficients for GTV, expanded GTV, and CTV volumes. Although expanded GTV showed greatest visual concordance with PET uptake, no significant differences were measured between the three regions.

In this study, high correlation between FDG and FLT uptake was observed ($R \sim 0.5–0.9$), suggesting that metabolic and proliferative phenotypes are highly correlated in cancers of the oropharynx. Correlations of FDG and FLT to Cu-ATSM exhibited wider variability ($R \sim 0.2–0.9$), indicating that hypoxia status is less clearly associated with metabolic or proliferative status. Correlation coefficients for

Nyflot MG, Radioth Oncol, 2012

HR-CTV-T; IR-CTV-N

- **Certa variabilità nella definizione di HR-CTV attorno a T**

RT-CT concomitante o RT esclusiva*, GTV definito su TC>MRI

Table 4
Published studies of intensity-modulated radiotherapy in oropharyngeal squamous cell carcinoma: primary tumour clinical target volume definition and patterns of local failure

Reference	Method of CTV-T definition	Dose fractionation to primary tumour PTV	Details of local failures
			All in-field
Yao 2006	Volumetric. High-risk CTV-T = GTV + 0.5–1.0 cm margin Intermediate-risk CTV-T = GTV + 2 cm margin	70–74 Gy at 2 Gy per fraction once daily to high-risk PTV 60 Gy at 2 Gy per fraction once daily to intermediate-risk PTV	1 local failure Pattern of local failure not reported
Garden 2007 *6%: pz IC/AC	Volumetric. High-risk CTV-T = GTV + minimum margin of 0.5 cm. Larger margins were usually used especially where tumour borders were poorly defined	Most received 63–66 Gy in 30 fractions once daily	2 local failures All in-field
Sanguineti 2008	Volumetric. High-risk CTV-T = GTV + 0–1.0 cm margin Intermediate-risk CTV-T = high-risk CTV-T + manual expansion to include possible microscopic extension	Accelerated hyperfractionated radiotherapy: 78 Gy to high-risk PTV and 69 Gy to intermediate-risk PTV in 60 fractions twice daily Conventional fractionation: 70 Gy to high-risk PTV and 63 Gy to intermediate-risk PTV in 35 fractions once daily	3 local failures 2 in-field 1 marginal
Huang 2008	Anatomical and volumetric. High-risk CTV-T included the parapharyngeal space and oropharynx with margins of up to 2.0 cm depending on anatomic boundaries and adjacent critical structures	59.4 Gy at 1.8 Gy per fraction once daily	5 local failures All in-field
Daly 2010	Volumetric. High-risk CTV-T = GTV + 0.5–1.0 cm margin Standard-risk CTV-T = high-risk CTV-T + 0.5–1.0 cm margin	Most received 66 Gy at 2.2 Gy per fraction to high-risk PTV and 54 Gy at 1.8 Gy per fraction to standard-risk PTV once daily	7 local failures 6 in-field 1 marginal
Setton 2012	Volumetric. High-risk CTV-T = GTV + 1.0–1.5 cm margin	Most received 59.4 Gy at 1.8 Gy per fraction once daily	23 local failures Pattern of local failure not reported
RTOG (1016)	HR-CTV:volumetric 0.5-1.5 cm. IR-CTV: natomical and volumetric margin depending on aatomical site.	70GY/56 Gy/52.5 GY in 6 weeks	ongoing.
Orlandi, ICHNO '03 ^^IC 45%, 100%MR	HR –CTV: anatomical and volumetric. At least 0,5 cm R-CTV: anatomical and volumetric	70 GY/60GY/50-54 Gy in 6-7 weeks	4 LR failure s, in fields

- **Espansione volumetrica (rec soprattutto in campo di alta dose) ma necessità di considerare un'espansione anatomica in determinate situazioni cliniche**

Lu SW, Clin Oncol 2013

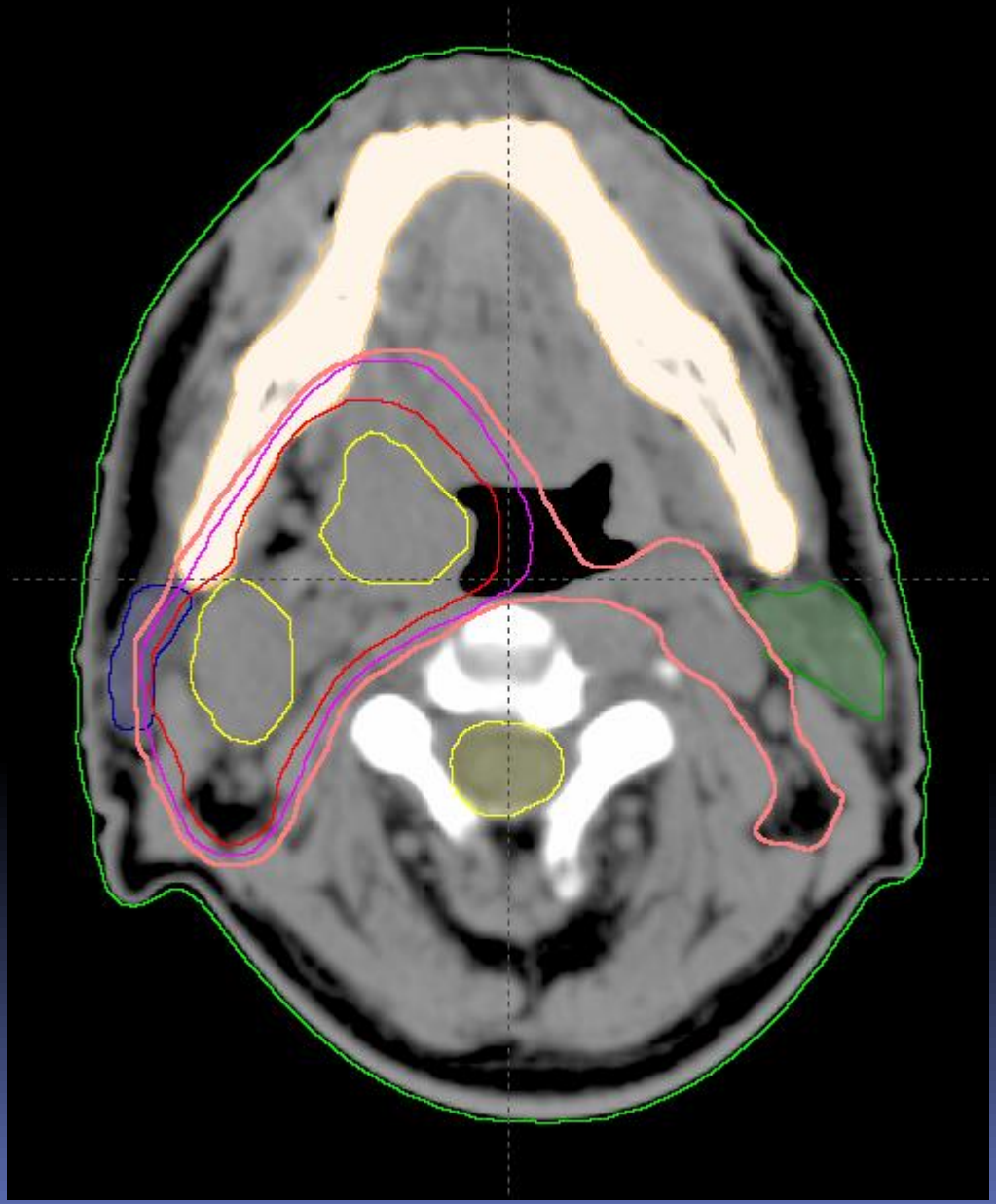
GTV-N; HR-CTV-N; IR-CTV-N

- **GTV-N: linfonodi di dimensione massima ≥ 1cm se livello IB-V, ≥ 0.5 cm se RPNs**

- **HR-CTV-N : espansione volumetrica di almeno 0.5 cm e/o livelli linfonodali interessati**

- **IR-CTV: livello/i linfonodali immediatamente contigui a quello interessato o prima stazione linfonodale potenzialmente interessata nel collo N0)**

Yao 2006, Garden 2008, Sanguineti 2008, Huang 2008, Setton 2012, Daly 2010



LR-CTV

- **Nei casi N+ include tutti i livelli a rischio non immediatamente adiacenti al livello linfonodale coinvolto; sovente nei casi N2-N3 comprende il collo in toto.**

- **Nei casi N0-N1 con primitività tonsillare (T1-T2) il collo profilattico può comprendere solo il collo omolaterale.**

- **Nei casi N1 a partenza da base lingua o se T ≥ 3, LR-CTV dovrebbe comprendere anche il collo controlaterale**

- **Nei casi N0, anche a partenza dal base lingua, può essere proposta irradiazione selettiva II-IV livello**

Yao 2006, Garden 2008, Sanguineti 2008, Huang 2008, Setton 2012, Daly 2010, Chung EG 2011, RTOG 1016, Brussel 2006, Lym 2006

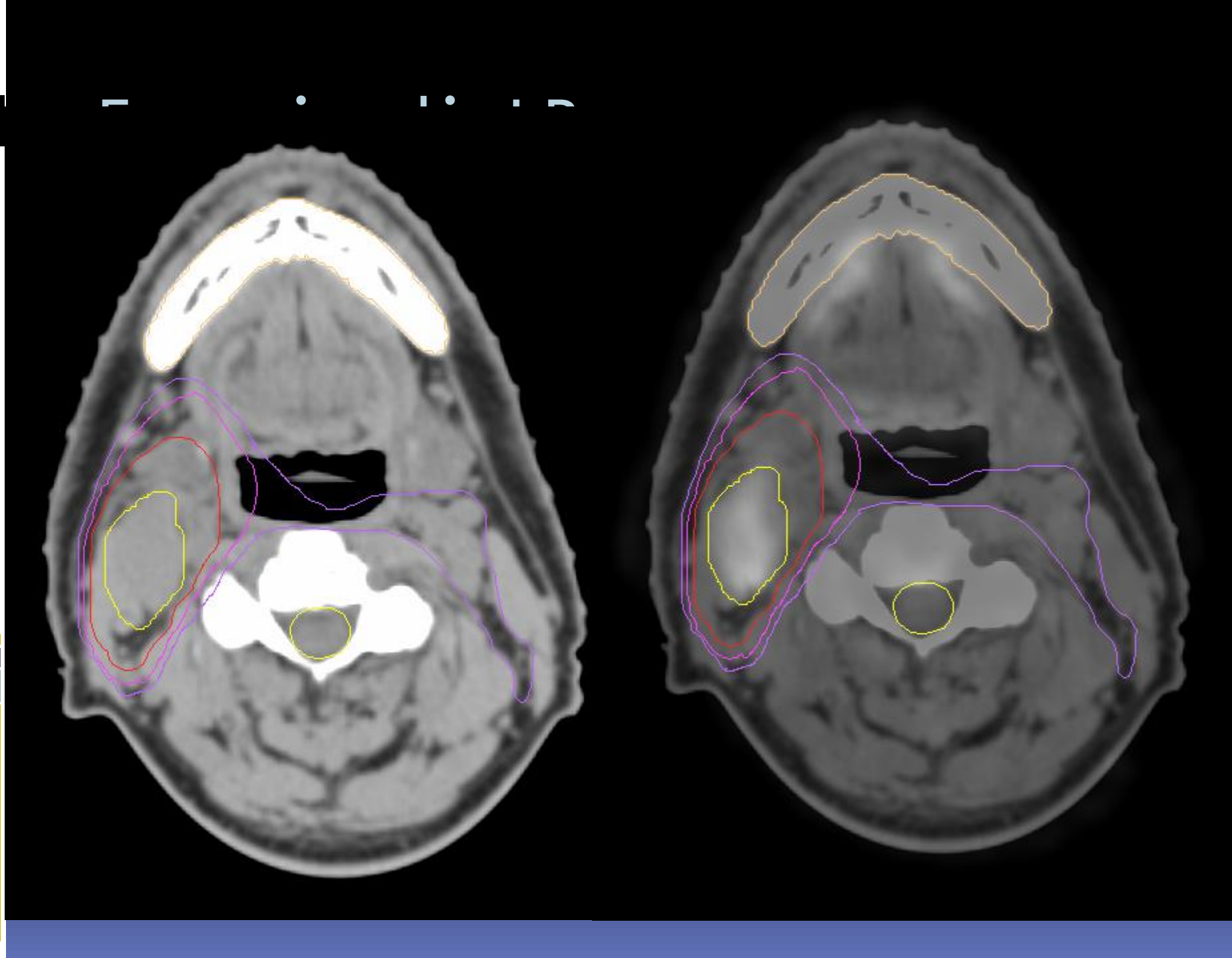
LR-CTV:RPNs

Table 6
Predictive factors of RPLN metastasis in Tonsillar Cancer Patients.

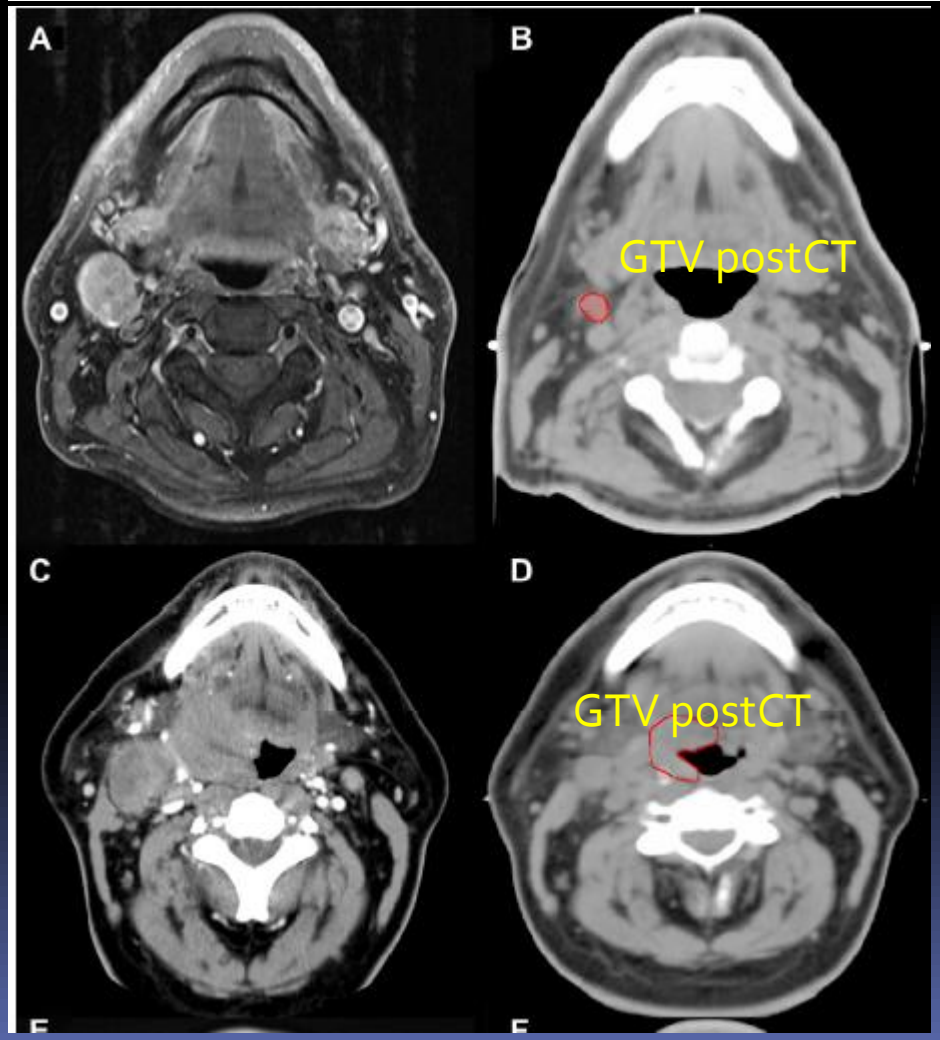
Factor	RPLN-	RPLN+	*p*-value(univariate)	*p*-value(multivariate)	95% CI
pT stage					
T1	45	4	0.266	-	
T3	22	5			
pN stage					0.000 -
N0	27	0	**0.023***	0.998	
N2	40	9			
PPW invasion					0.007 – 0.854
Negative	52	1	**<0.001***	**0.037***	
Positive	15	8			
Contra neck node					0.028 – 3.712
Negative	63	4	**0.001***	0.366	
Positive	4	5			
Ipsi multilevel					0.015 – 2.969
Negative	44	1	**0.003***	0.247	
Positive	23	8			

Abbreviations: RPLN, retropharyngeal lymph node; BOT, base of tongue; PPW, posterior pharyngeal wall; Ipsi, ipsilateral; Contra, contralateral.
* Values are statistically significant.

Chung EG, Oral Oncology, 2006



Target Volume Definition for Intensity-modulated Radiotherapy after Induction Chemotherapy and Patterns of Treatment Failure after Sequential Chemoradiotherapy in Locoregionally Advanced Oropharyngeal Squamous Cell Carcinoma



- **Non attuale evidenza dell'impiego della CT di induzione nelle forme**
- **head and neck avanzate**

- **Benasso, Oral la oncology, 2013**

HR-CTV definito su GTV post CT (+1cm)

FU mediano di 32 mesi

7 Recidive LR in campo di alta dose

(ma non chiaro se in HR-CTV che esclude GTVpostCT!!!)

Lu SW, Clin Oncol 2013

Tumori HPV positivi e negativi

I tumori HPV relati tendono a presentarsi con bassi stadi di T (T1-T2), a partenza maggiormente da tonsilla palatina e linguale (anello Waldeyer) con avanzati stadi di N (N2-N3) e adenopatie hanno prevalentemente aspetto cistico , contrariamente alle caratteristiche solide e necrotiche dei casi HPV negativi.

Gillison ML JCO 2008.

Predictive Value of HPV in Oropharyngeal Carcinoma Treated with Radiotherapy:

An updated Systematic Review and Meta-Analysis of 30 trials

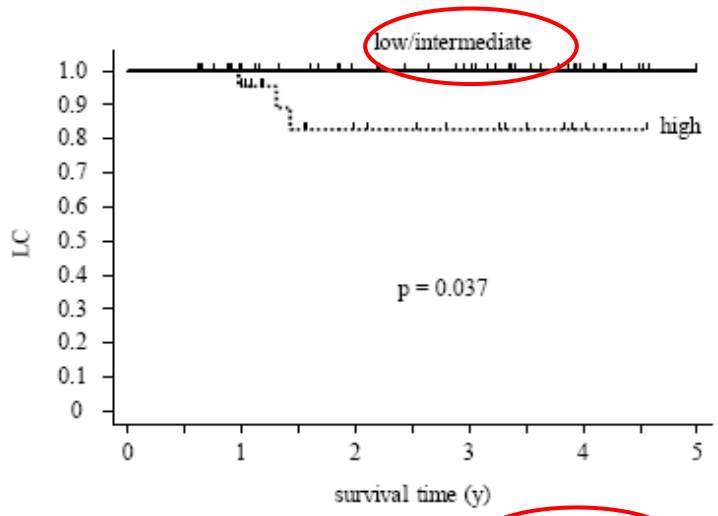
Fausto Petrelli, Enrico Sarti and Sandro Barni

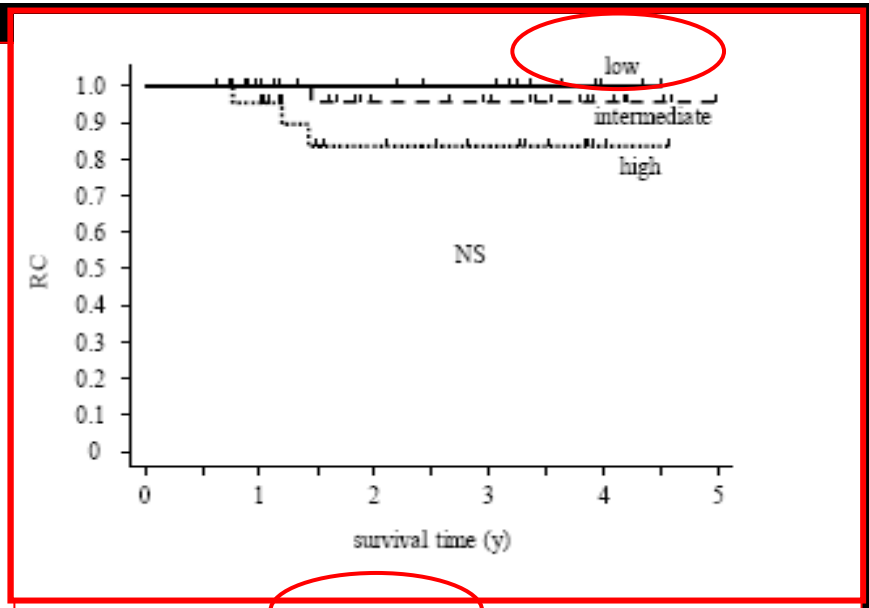
"Thirty trials were available for HPV analysis. HPV+ status is associated with better OS (HR = 0.33; p < 0.00001), DSS (HR = 0.24; p < 0.00001) and DFS (HR = 0.31; p < 0.00001). Conclusions: HPV+ OSCC has a better survival compared to HPV-negative disease when treated with radiotherapy-based modality therapy."

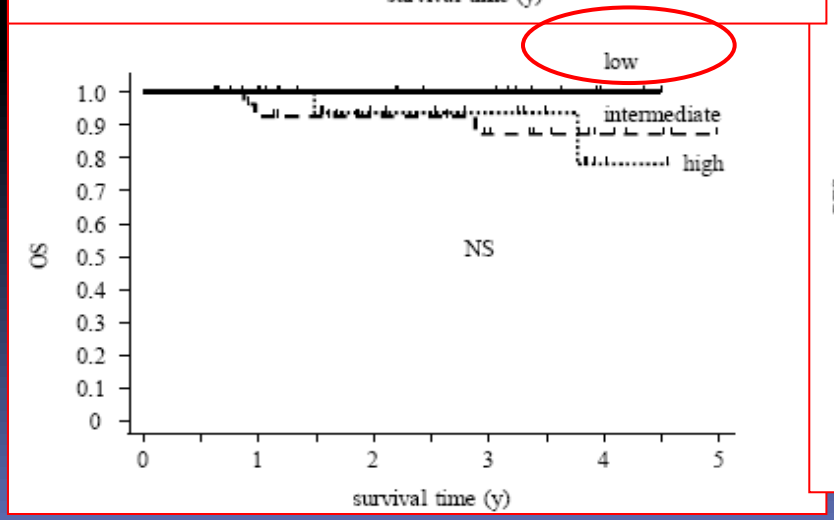
Head and Neck, 2013 in press

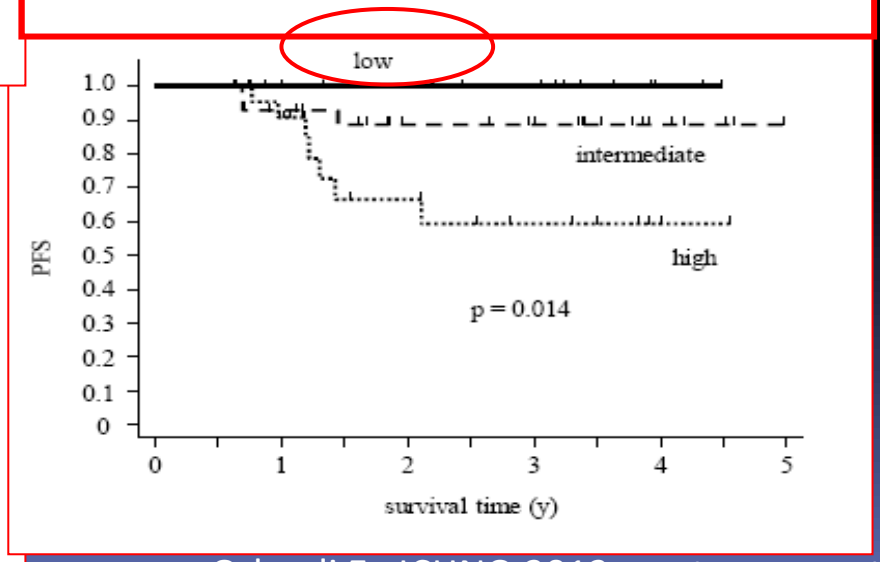
IMRT for locally advanced oropharyngeal carcinoma: preliminary results focusing on the impact of human papillomavirus (HPV) status and clinical risk categories.

71 pz,2006-2011, FU mediano 34.4 mesi









Orlandi E, ICHNO 2013, poster presentation

FAZA PET/CT hypoxia imaging in patients with squamous cell carcinoma of the head and neck treated with radiotherapy: Results from the DAHANCA 24 trial

62.5% of pts:OPC

Table 2
Relationship between FAZA uptake and HPV status.

FAZA PET data	All patients ($n = 40$)	HPV negative ($n = 24$)	HPV positive ($n = 16$)	P^*
T_{max}/M				
Median	1.5	1.5	1.7	
Mean	1.7	1.7	1.8	n.s.
Range	(1.1–2.9)	(1.2–2.9)	(1.1–2.9)	
T_{med}/M				
Median	1.1	1.1	1.1	
Mean	1.1	1.1	1.1	n.s.
Range	(0.8–1.7)	(0.8–1.6)	(0.9–1.7)	
HV ⩾ 1.4 (cm^3)				
Median	0.3	0.2	1.9	
Mean	4.4	3.9	5.2	n.s.
Range	(0.0–30.9)	(0.0–30.9)	(0.0–30.8)	
FHV ⩾ 1.4 (%)				
Median	2.8	1.0	13.6	
Mean	15.9	13.7	19.1	n.s.
Range	(0–91.7)	(0–71.7)	(0–91.7)	

HV: Volume ipossico

n.s., not significant.
* Mann–Whitney–Wilcoxon test for comparison between HPV-negative and HPV-positive groups.

The HPV-positive and the HPV-negative tumors were found to be equally hypoxic (Fig. 3), as no significant difference was found

Mortensen LS, Radioth Oncol, 2012

HPV-associated p16-expression and response to hypoxic modification of radiotherapy in head and neck cancer

OPC: 43% of pts

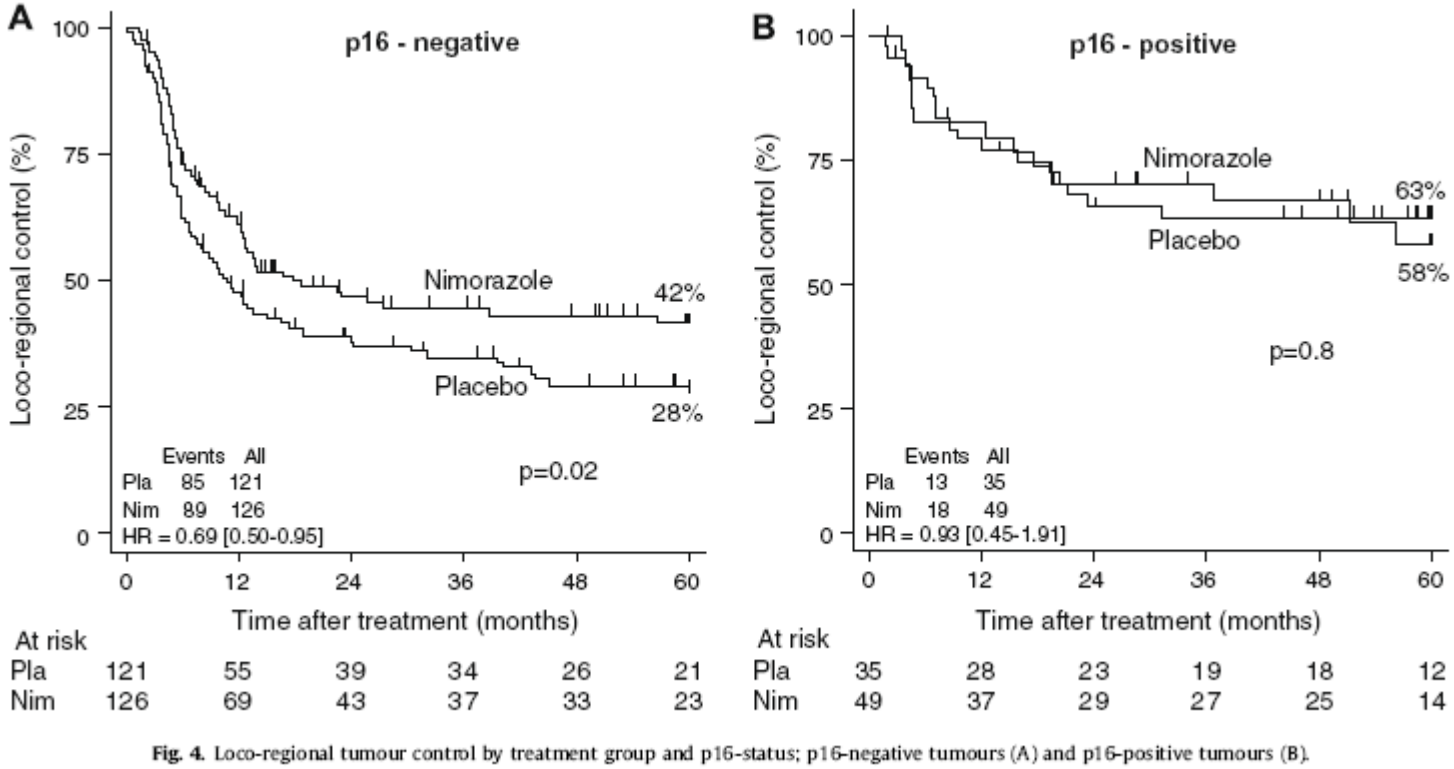


Fig. 4. Loco-regional tumour control by treatment group and p16-status; p16-negative tumours (A) and p16-positive tumours (B).

Conclusions: HPV/p16-expression significantly improved outcome after radiotherapy in HNSCC. Hypoxic modification improved outcome in HPV/p16-negative tumours but was of no significant benefit in HPV/p16-positive tumours, suggesting that hypoxic radioresistance may not be clinically relevant in these tumours.

Lassen P , Radioth Oncol, 2010

Diverso profilo genetico che regola l'ipossia
Maggior radiosensibilità dei tumori HPV positivi

Data la migliore prognosi,

Oltre a protocolli di deintensificazione di RT e CT (ECOG, RTOG 1016, in corso)

È possibile differenziare /ridurre i volumi di trattamento negli HPV positivi?

Necessario studiare patterns di presentazione clinica del tumore primitivo linonodale e patterns di recidiva

Grazie per l’attenzione!