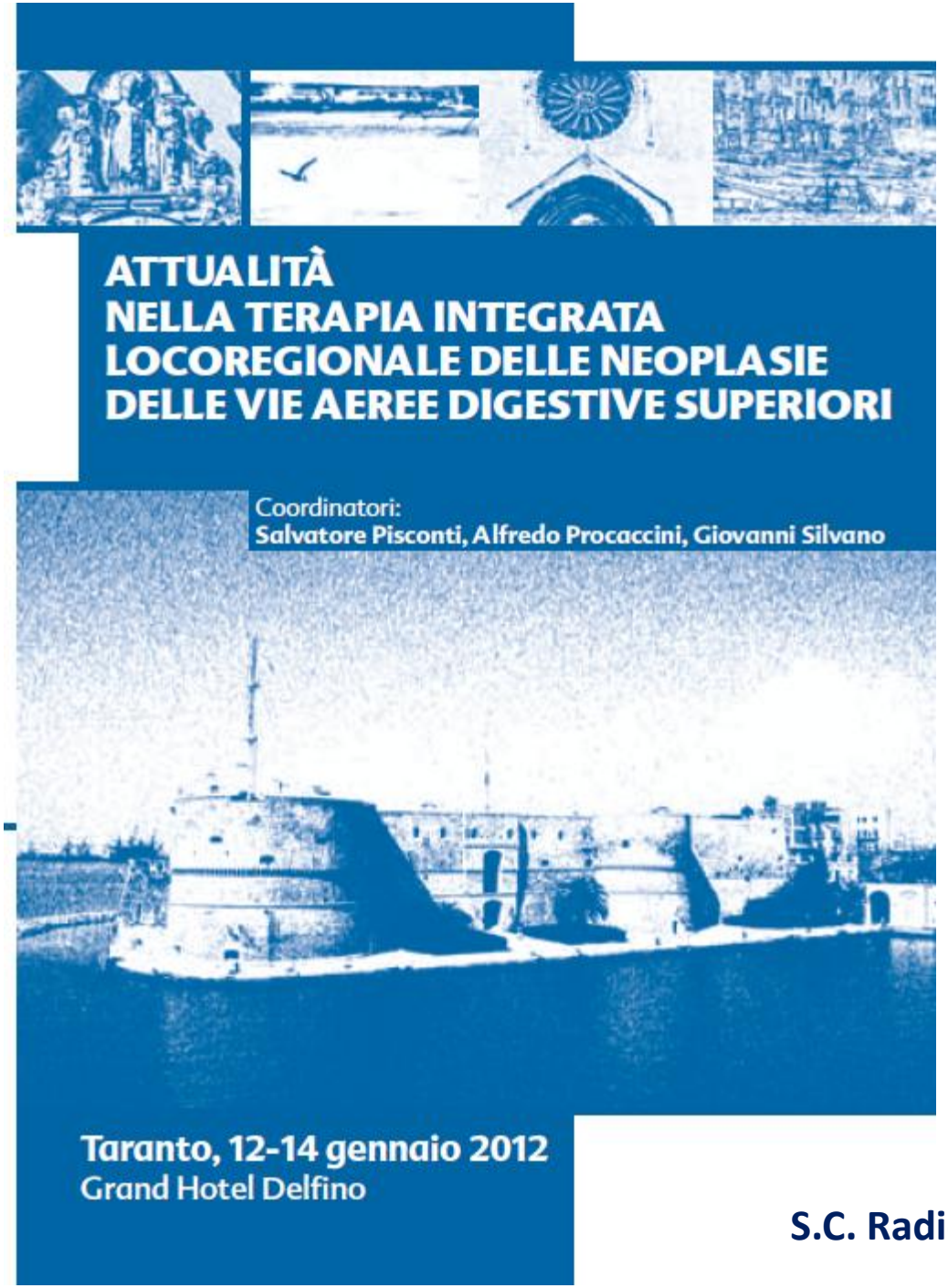


Radiochemioterapia farmaci biologici e radioprotezione

nel trattamento esclusivo

Giovanni Silvano
Mariantonietta Soloperto

S.C. Radioterapia Oncologica Taranto

HNSCC localmente avanzato

E' caratterizzato da meccanismi radiobiologici di radioresistenza

- **elevato numero di cellule clonogene**
- **ripopolamento accelerato durante la RT**
- **cellule ipossiche con neoangiogenesi circostante**
- **sovraespressione di EGF-recettore**

La RT convenzionale: 70 Gy possono controllare il 50-60% dei T3-T4 ed il 50-70% dell'N positivo fino a 3-5 cm, con un tasso di sopravvivenza a 5 anni del 30%

Antognoni P et al. Tumori. 2005
Baumann M et al. Radiother Oncol 2004
Laskar SG et al. Expert Rev Anticancer Ther. 2006

Attuali strategie terapeutiche

per migliorare il controllo locoregionale e OS

- RT con frazionamento alterato
- RT + modificatori dell'ipossia
- RT + farmaci antiblastici e/o biologici:
  - **RCT concomitante**
  - **CT di induzione + RT/RCT concomitante**
  - **RT + Cetuximab**
  - **RCT concomitante +/- Cetuximab**

Attuali strategie terapeutiche

per contenere la tossicità acuta e cronica

- Radioprotettori:
  - **amifostina**
- Nuove tecniche RT:
  - **IMRT**
  - **Radiazioni non convenzionali**
- Supporto nutrizionale

RT con frazionamento alterato

Aumentare la dose-intensity della RT:

- **RT iperfrazionata (HF):** aumenta la dose totale al tumore erogando dosi più piccole, più volte al giorno
- **RT accelerata (AF):** riduce il tempo totale di trattamento ostacolando il ripopolamento delle cellule clonogene

AF comprende regimi senza riduzione della dose totale, con riduzione della dose totale o split-course.

RT convenzionale *vs* RT iperfrazionata o accelerata

Evidenze dalle metanalisi

Il frazionamento alterato produce:

- beneficio sul controllo loco-regionale a 5 anni del **6.4%**
- beneficio sulla OS a 5 anni con HF dell' **8%**
- beneficio sulla OS a 5 anni con AF del **3.4%** *(n.s.)*
- nessun beneficio per la AF senza aumento della dose o split-course

Il beneficio è più evidente nei pazienti giovani

Bourhis J, Lancet 2006

Frazionamenti RT alterati più efficaci

RTOG 90-03: HF 81,6 Gy dose totale in 68 frazioni da 1.2 Gy, due volte al giorno, 5 giorni a settimana per 7 settimane

RTOG 90-03: AF con concomitant boost: 72 Gy in 6 settimane (1.8 Gy sul volume grande più 1.5 Gy di boost come seconda frazione sul piccolo volume dopo 12 giorni dall'inizio della RT)

DAHANCA 6 & 7 (2003) & IAEA-ACC (2010): AF sei frazioni a settimana

(AF migliora il controllo loco-regionale, la sopravvivenza malattia-specifica, non migliora la OS)

Articles

Lancet, 2003

Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group

Vantaggio significativo per età < 65aa, PS <1, T1-2, N0

Incremento della tossicità acuta, ma non della tardiva

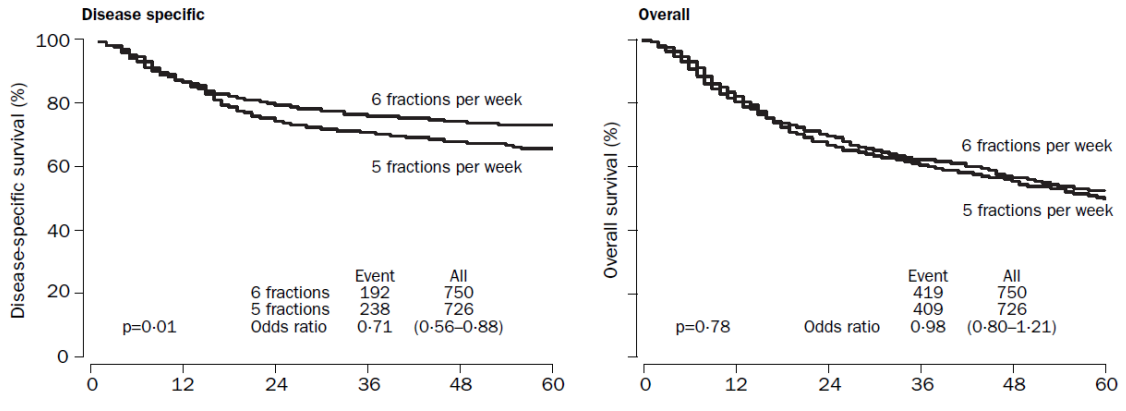
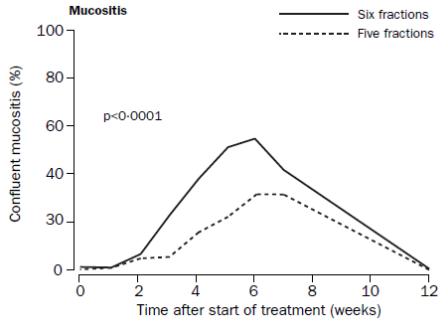
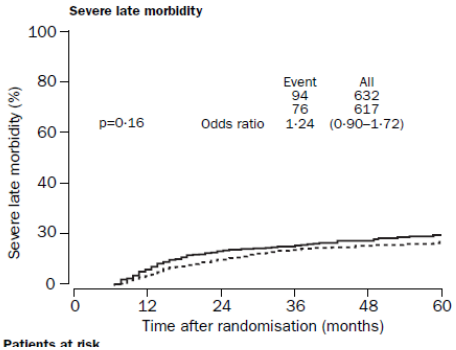


Figure 5: **Effect of overall treatment time on disease-specific survival and overall survival**





Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial

Jens Overgaard, Bidhu Kaylan Mohanti, Naseem Begum, Rubina Ali, Jai Prakash Agarwal, Maire Kuddu, Suman Bhasker, Hideo Tatsuzaki, Cai Grau

Summary

Background Several large randomised studies from western Europe and the USA have shown that accelerated fractionation of radiotherapy might be beneficial in the treatment of squamous-cell carcinoma of the head and neck (HNSCC). The aim of this study—the International Atomic Energy Agency (IAEA) ACC trial—was to determine whether accelerated fractionation could be applied in developing countries, where there are fewer therapeutic resources and where tumour burdens can be heavier.

Lancet Oncol 2010; 11: 553–60
Published Online
April 9, 2010
DOI:10.1016/S1470-2045(10)70072-3

948 pz

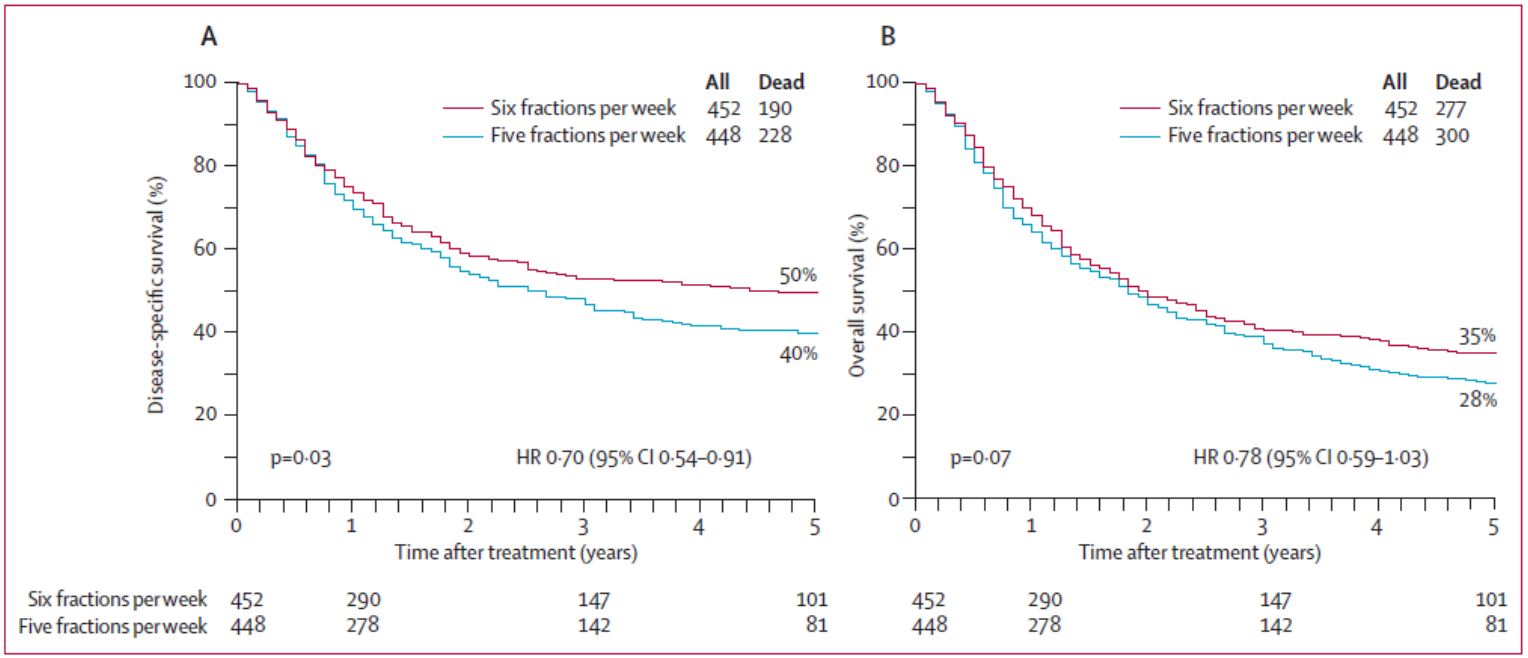


Figure 5: Disease-specific survival (A) and overall survival (B)

Hyperfractionated or accelerated RT for head and neck cancer (Cochrane Review, August 2010)

Individual patient data from 15 randomised trials beginning recruitment from 1970 to 1997 (6515 pts)

OS absolute benefit of 3.4% at five years

Hyperfractionated RT (8%); accelerated RT (2% /1,7%), p = 0.003

LRC in favour of altered fractionation versus conventional RT

(6.4% at five years; P < 0.0001), T *vs* N for younger pts

Authors' conclusions

Altered fractionation RT improves survival in patients with head and neck squamous cell carcinoma. Comparison of the different types of altered RT suggests that hyperfractionation provides the greatest benefit.....

Andre A. Konski, et al
Head Neck , 2009

Quality-Adjusted Survival Analysis of Radiation Therapy Oncology Group (RTOG) 90-03: Phase III Randomized Study Comparing Altered Fractionation to Standard Fractionation Radiotherapy for Locally Advanced Head and Neck Squamous Cell Carcinoma

Quality Adjusted Survival for Utility of 0.8 for Tox and 0.5 for Rel

Treatment Arm	Mean Quality Adjusted Survival (Months)	p-value*
SFX (n=266)	12.99	------
HFX (n=261)	14.27	0.057
AHFXS (n=274)	13.55	0.38
AFXC (n=267)	13.60	0.36

*Comparing mean QAS to SFX arm. SFX- Standard Fractionated radiotherapy; HFX-Hyp
hyperfractionated radiotherapy with split; AFXC- Accelerated fractionated radiotherapy with co

a causa della tossicità nessun vantaggio statisticamente significativo con i frazionamenti alterati se consideriamo anche la qualità di vita

Mean Survival partitioned into TwiST, Tox, and Rel (Months)

Treatment Arm	TwiST	Tox	Rel
SFX (n=266)	4.9	6.9	5.0
HFX (n=261)	5.2	9.0	3.8
AHFXS (n=274)	5.8	7.1	4.1
AFXC (n=267)	5.2	7.1	3.8

SFX- Standard Fractionated Radiotherapy; HFX-Hyperfractionated radiotherapy; AHFXS-Accelerated Hyperfractionated Radiotherapy with Split; AFXC-Accelerated Fractionated Radiotherapy with Concomitant Boost; Twist- Time without toxicity or relapse; Tox- Toxicity; Rel-Relapse

Modificatori dell'ipossia

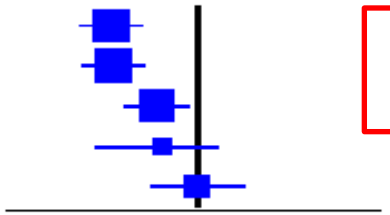
Evidenze dalla metanalisi

Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – A systematic review and meta-analysis

32 studi randomizzati

Head and neck cancer - meta analysis - summary

Endpoint	Events / Total		Odds ratio and 95% CI			
	Hypoxic modification	Control		Odds ratio	Risk Reduction	NNT**
Loco-regional control	1203 / 2406	1383 / 2399		0.71 (0.63-0.80)*	8% (5-10%)*	13
Disease specific survival	1175 / 2335	1347 / 2329		0.73 (0.64-0.82)	7% (5-10%)	14
Overall survival	1450 / 2312	1519 / 2305		0.87 (0.77-0.98)	3% (0-6%)	31
Distant metastasis	159 / 1427	179 / 1391		0.87 (0.69-1.09)	2% (-1-4%)	57
Radiotherapy complications	307 / 1864	297 / 1822		1.00 (0.82-1.23)	0% (-3-2%)	>>



*** con tutti i tipi di modificatori dell'ipossia**

Overgaard J, Radiat Oncol, 2011

Radiotherapy and Oncology 100 (2011) 22–32

Contents lists available at ScienceDirect

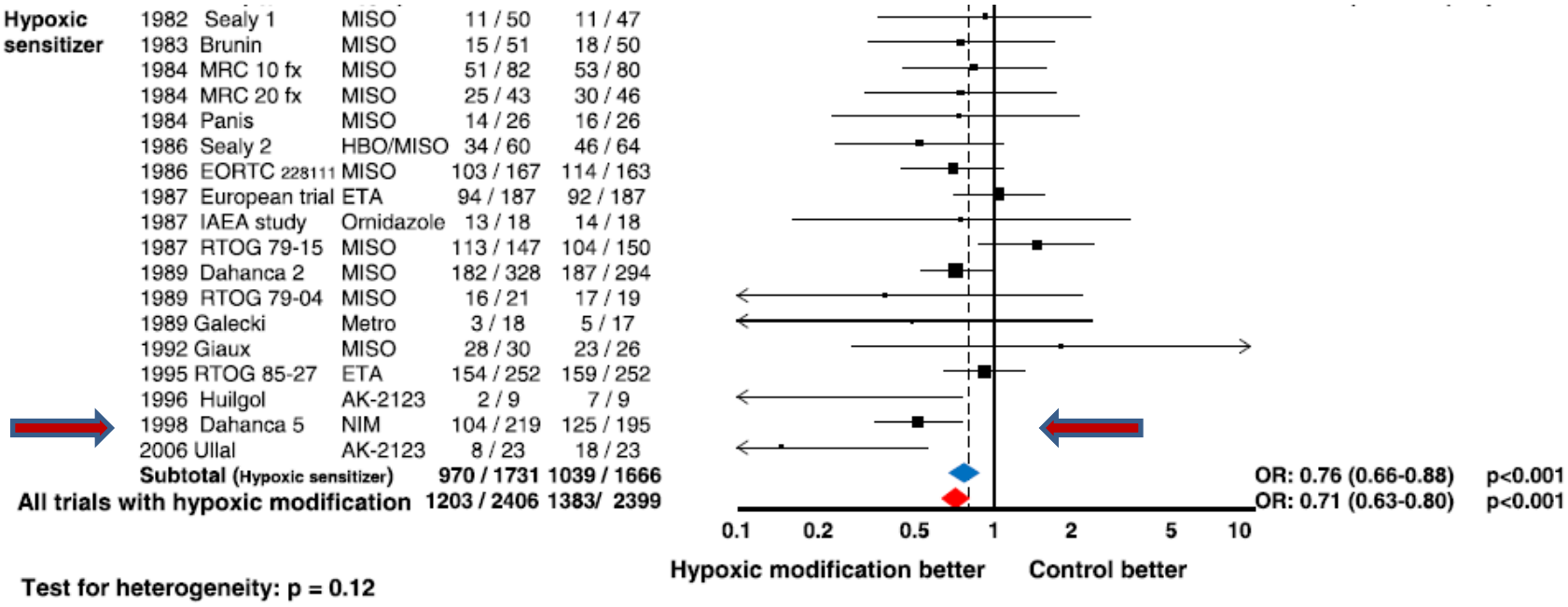
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Meta-analysis of hypoxia in HNSCC

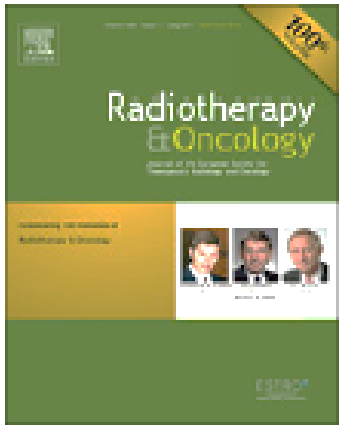
Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – A systematic review and meta-analysis

Jens Overgaard *



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

La maggior parte degli studi randomizzati (17) hanno utilizzato quali modificatori i radiosensibilizzanti delle cellule ipossiche



DAHANCA Protocol 5-85: 414 pazienti
(faringe e laringe sopraglottico anche in pz. localmente avanzati)
Nimorazole + RT *vs* RT esclusiva 66/68Gy

- miglior controllo loco-regionale : 49% vs 33%
- migliore sopravvivenza malattia-specifica: 52% vs 41%
- risultati non significativi per la OS: 26% vs 16%

RT 6 frazioni + Nimorazole è uno standard nelle linee guida danesi

Overgard J, Radiot Oncol 1998

Radiother Oncol.2011 Jan;98(1):28-33. Epub 2010 Oct 20

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

The importance of haemoglobin level and effect of transfusion in HNSCC patients treated with radiotherapy – Results from the randomized DAHANCA 5 study

Camilla Molich Hoff [a,*], Hanne Sand Hansen [b], Marie Overgaard [c], Cai Grau [c], Jørgen Johansen [d], Jens Bentzen [e], Jens Overgaard [a]

Vantaggio per i pz. con Hb > 13 g/dl se donne e 14,5 g/dl se uomini
Le emotrasfusioni nei pazienti con bassi valori di Hb non impattano sul risultato

414 pz. ogni T e N; random RT +/- Nimorazolo

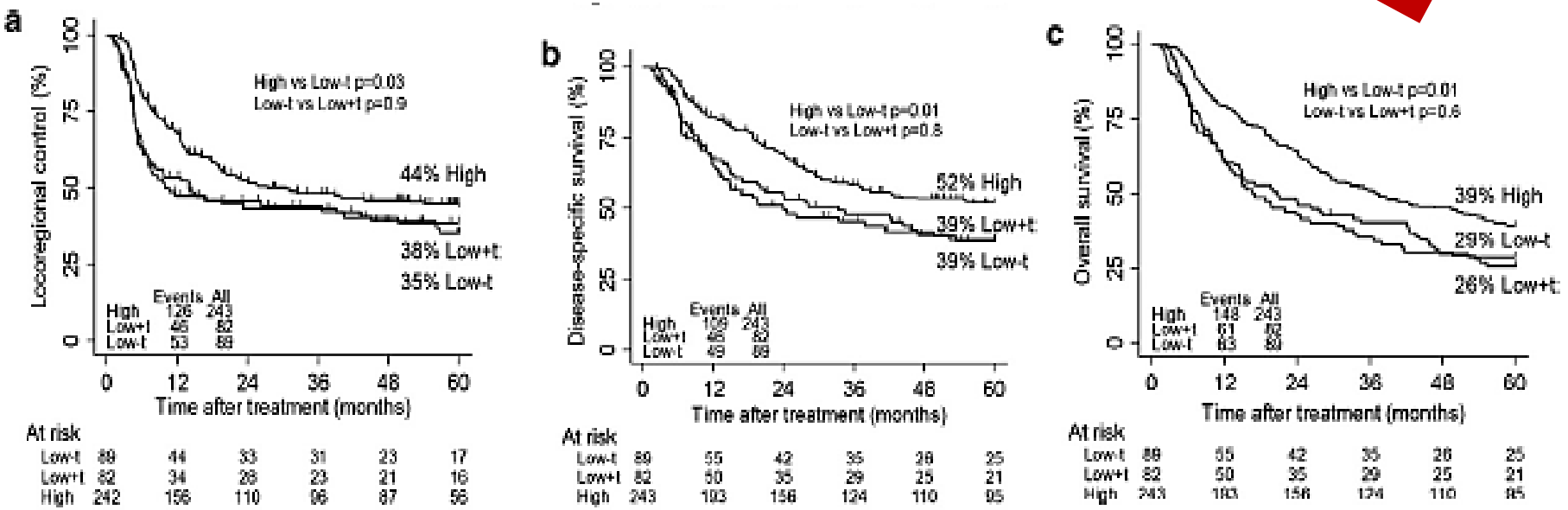


Fig. 3. Locoregional control (a), disease-specific (b) and overall survival (c) probability curves (Kaplan–Meier method) according to haemoglobin group.

Radiochemioterapia

La **radiochemioterapia con cisplatino** è l'attuale standard di cura nel HNSCC localmente avanzato.

Evidenze dalla recente metanalisi

Radiotherapy and Oncology 100 (2011) 33–40

Contents lists available at ScienceDirect

Radiotherapy and Oncology

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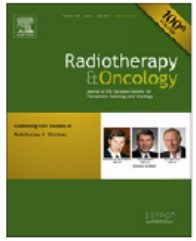


Meta-analysis of radiotherapy in HNSCC

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumour site

Pierre Blanchard [a,b,1], Bertrand Baujat [c,1], Victoria Holostenco [a], Abderrahmane Bourredjem [a], Charlotte Baey [a], Jean Bourhis [b], Jean-Pierre Pignon [b,*], on behalf of the MACH-CH Collaborative group [2]

Radiochemioterapia

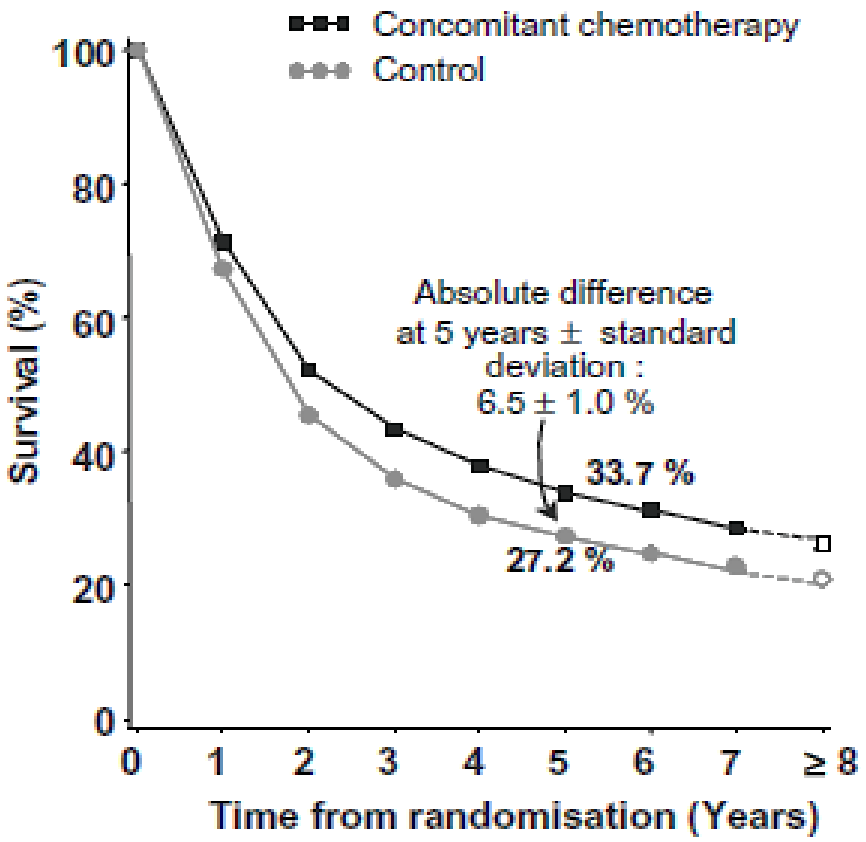
trials1965-1993

La RT-CT neoadiuvante, concomitante, adiuvante migliora la sopravvivenza:
HR 0.90, CI 95%, beneficio OS a 5 anni **4.5%**

La RCT concomitante= maggiore beneficio: OS **6.5%**

Pignon JP, Lancet 2000 & 2009

Radiochemioterapia concomitante



- **sopravvivenza globale**

HR di morte: 0.81, CI 95%, p<0.0001

beneficio assoluto 5 anni: **6.5%**

Il beneficio della sopravvivenza è dovuto alla riduzione delle morti cancro correlate

- **sopravvivenza libera da eventi**

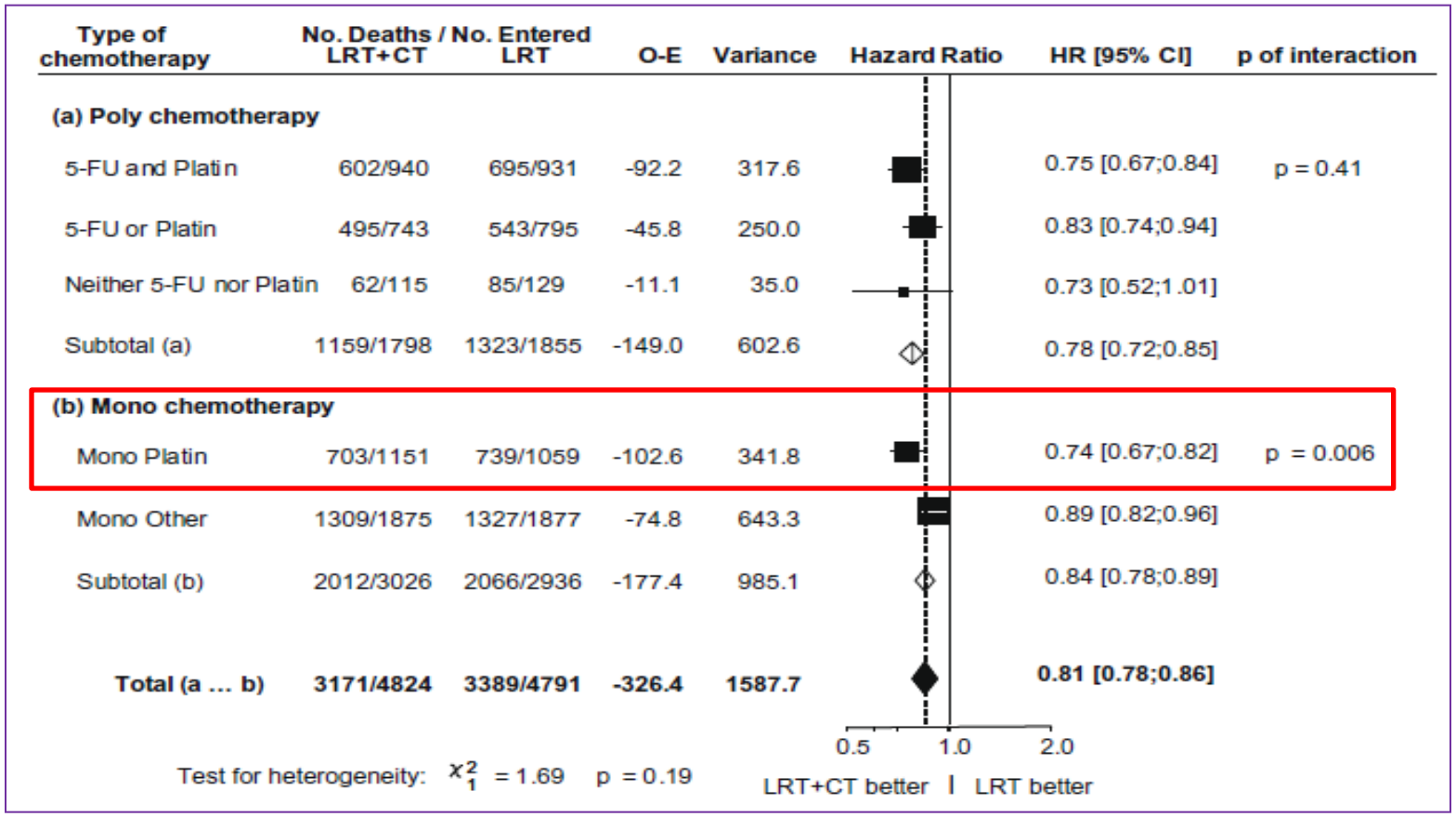
beneficio assoluto a 5 anni: **6.25%**

Pignon JP, Radiot Oncol, 2009

La radiochemioterapia concomitante

ha mostrato un beneficio significativamente più alto di OS

con il **cisplatino in monochemioterapia**

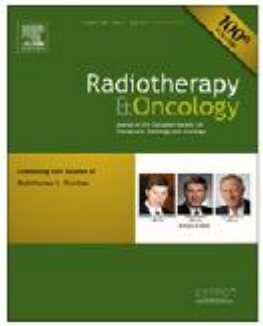


Type of chemotherapy	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]	p of interaction
(a) Poly chemotherapy							
5-FU and Platin	602/940	695/931	-92.2	317.6		0.75 [0.67;0.84]	p = 0.41
5-FU or Platin	495/743	543/795	-45.8	250.0		0.83 [0.74;0.94]	
Neither 5-FU nor Platin	62/115	85/129	-11.1	35.0		0.73 [0.52;1.01]	
Subtotal (a)	1159/1798	1323/1855	-149.0	602.6		0.78 [0.72;0.85]	
(b) Mono chemotherapy							
Mono Platin	703/1151	739/1059	-102.6	341.8		0.74 [0.67;0.82]	p = 0.006
Mono Other	1309/1875	1327/1877	-74.8	643.3		0.89 [0.82;0.96]	
Subtotal (b)	2012/3026	2066/2936	-177.4	985.1		0.84 [0.78;0.89]	
Total (a ... b)	**3171/4824**	**3389/4791**	**-326.4**	**1587.7**		**0.81 [0.78;0.86]**	

Test for heterogeneity: $\chi^2_1 = 1.69$ p = 0.19

Pignon JP, Radiot Oncol, 2009

Meta-analysis of chemotherapy in head and neck (MACH-NC): A comprensive analysis by tumor site



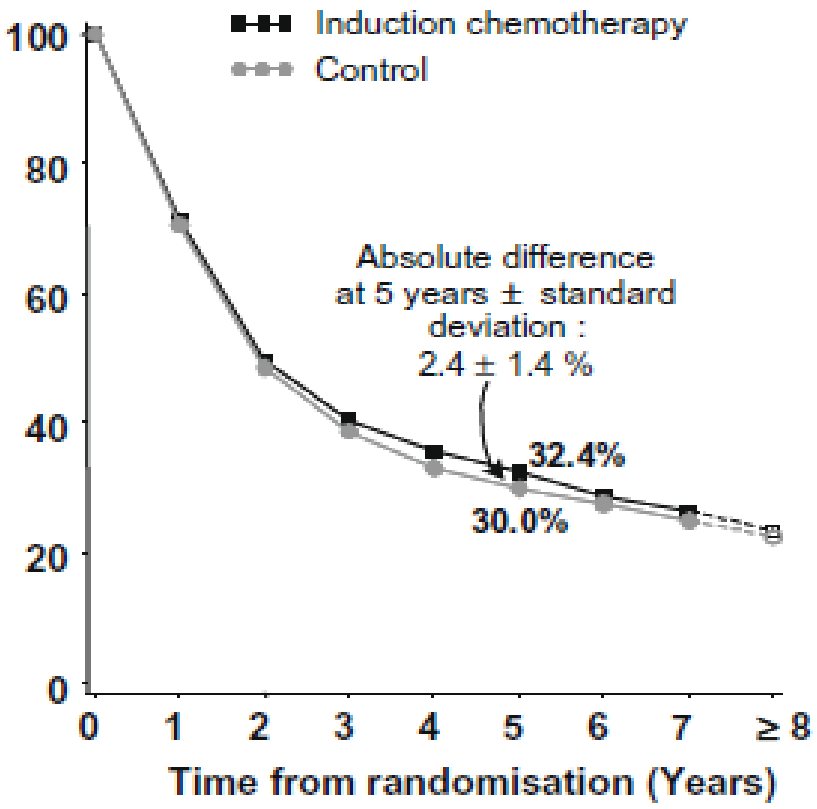
La CT concomitante produce un beneficio assoluto in **OS** a 5 anni per tutte le sedi del tumore, ma il beneficio è maggiore per i tumori dell'orofaringe e cavo orale

- **cavità orale: 8.9%**
- **orofaringe: 8.1 %**
- **laringe: 5.4%**
- **ipofaringe: 4.0%**

16.192 pz in 87 trials

Blanchard P, Radiot Oncol, 2011

Chemioterapia di induzione



- **sopravvivenza globale**

HR di morte: 0.96, p=0.18

beneficio assoluto a 5 anni: **2.4%**

- **sopravvivenza libera da eventi**

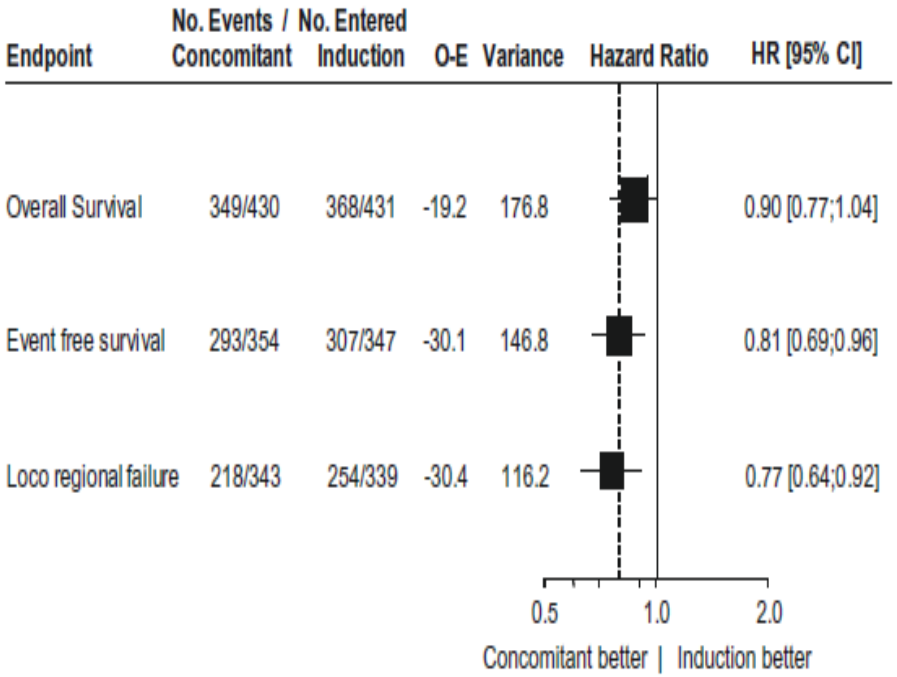
HR 0.93, p=0.67

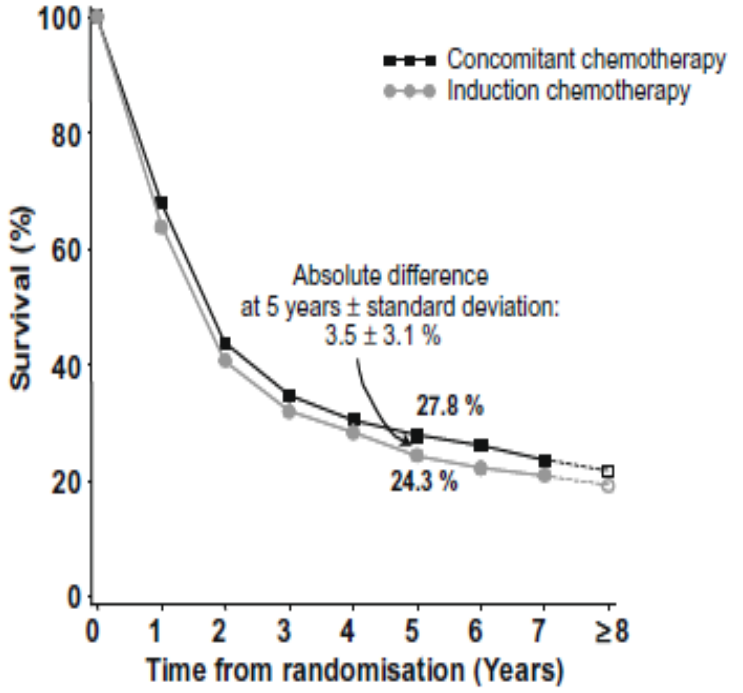
beneficio assoluto a 5 anni: **1.3%**

Pignon JP, Radiot Oncol, 2009

CT concomitante vs induzione

6 studi randomizzati: concomitante *vs* induzione, stessi farmaci, uguale RT. Follow-up 10.9 anni





I tre endopoint studiati hanno mostrato risultati a favore della CT concomitante

Beneficio assoluto di **OS** a 5 anni del **3.5%**

Pignon JP, Radiot Oncol, 2009

Nuove combinazioni terapeutiche

- regimi intensificati di RCT con frazionamenti alterati
- chemioterapia di induzione con Taxani
- RCT + farmaci biologici

studi randomizzati di fase III
studi di fase II e studi retrospettivi
studi in corso

Intensificazione: RCT con frazionamenti alterati

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Accelerated radiotherapy and concomitant high dose chemotherapy in non resectable stage IV locally advanced HNSCC: Results of a GORTEC randomized trial

Studio di fase III multicentrico:109 pz N3 –N2b-c e/o T non resecabile

RT 64 Gy in 32 frazioni in 23gg (2Gy BID)

vs

RT 64 Gy in 32 frazioni in 35gg + CT concomitante

(RT 2Gy BID a settimane alterne)

CT = CDDP 100 mg/m^2 , 3 cicli nei giorni 2,16 e 30 +
5FU 1000 mg/m^2 , 2 cicli nei giorni-5 e 29-33.

Se RC dopo RCT due cicli di CT adiuvante CDDP-5FU (26 pz)

Bohuris J,
Radiot Oncol 2011

Intensificazione: RCT con frazionamenti alterati

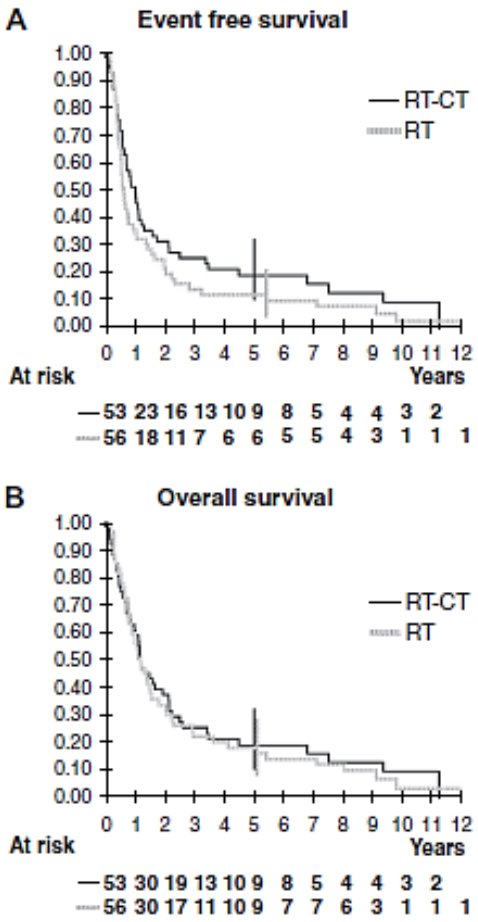


Fig. 1. Kaplan–Meier curves for event-free survival (1A) and survival (1B). Vertical bars denote 95% confidence interval of the actuarial rates.

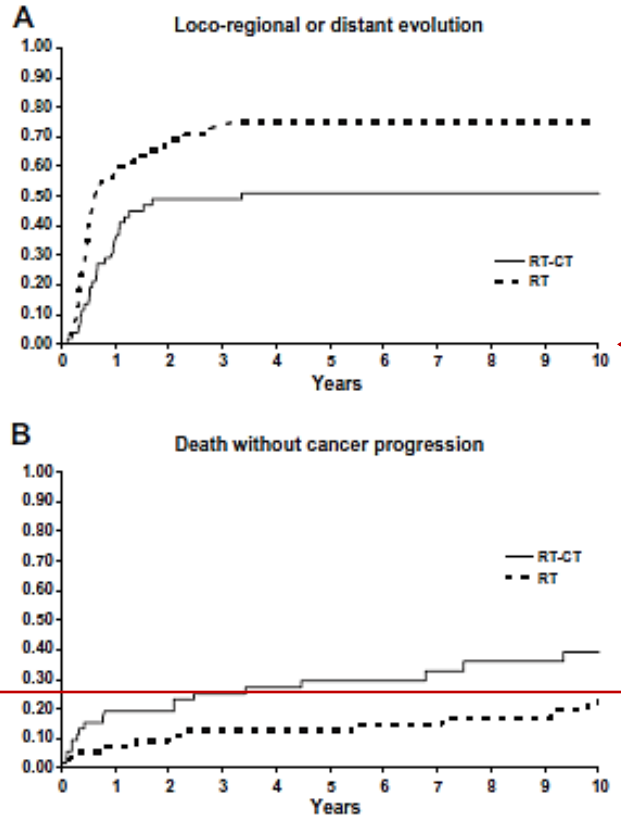
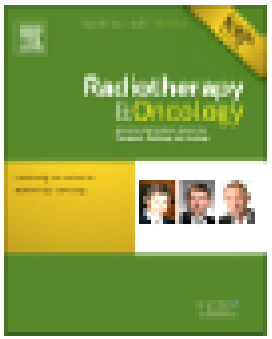


Fig. 2. Cumulative incidence of loco-regional or distant evolution (2A) and of death without cancer progression (2B).



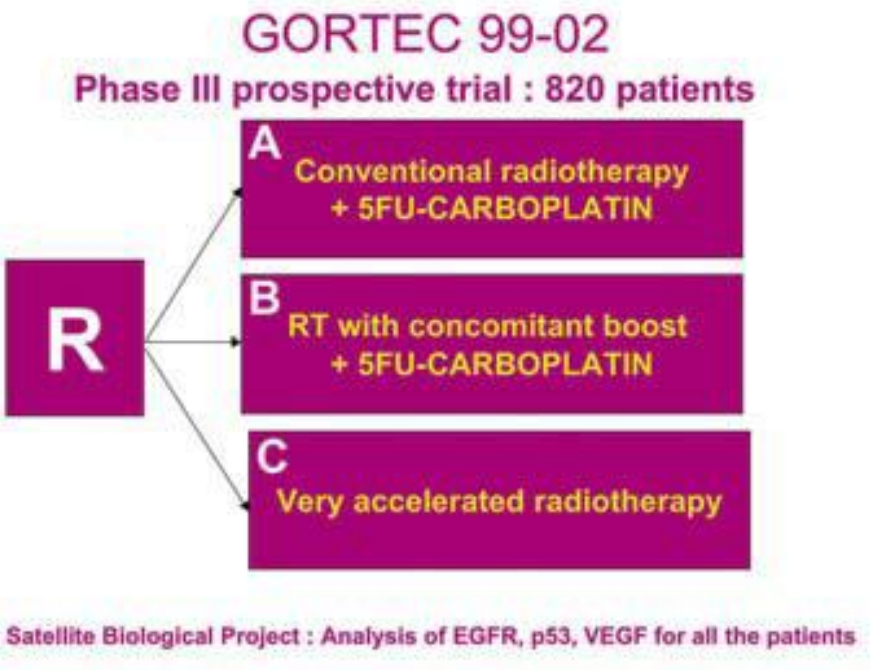
RCT intensifica: maggior controllo loco-regionale

maggiori effetti tossici **(20% early deaths)**

Nessun miglioramento dell'indice terapeutico

ospedalizzazione > 85% ; feeding tube = 94%

Bohuris J, Radiot Oncol 2011



A: conventional RT given once daily;
70 Gy in 7 weeks (5 fractions of 2 Gy per week) and chemotherapy: 5FU : 600 mg/m²/d, Paraplatin: 70 mg/m²/d, D1-4 and D22-25 and D43-46

B: middle accelerated RT
70 Gy in 6 weeks and chemotherapy: 5FU : 600 mg/m²/d, Paraplatin: 70 mg/m²/d, D1-5 and D29-33
first part: radiotherapy given once daily delivering 40 Gy in 4 weeks and 20 fractions of 2 Gy
second part: radiotherapy given twice daily with "concomitant boost" delivering 30 Gy in 20 fractions in 2 weeks (1,5 Gy x 2 / day)

C: very accelerated RT given twice daily delivering 64.8 Gy in 3.5 weeks in 36 fractions of 1.8 Gy

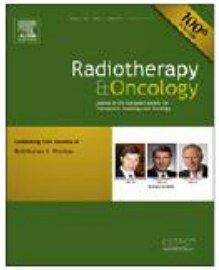
CONCLUSIONI:

- Sopravvivenza migliore nel braccio **A** trattato con RT-CT con 3 cicli di CT concomitante
- Importante la dose complessiva di CT somministrata che non può essere surrogata da frazionamenti alterati

Bourhis J, ESTRO 2010, abs n.296

Intensificazione: CT di induzione con Taxani

TAXANE-CISPLATIN-5FU AS INDUCTION CHEMOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA: AN INDIVIDUAL PATIENT DATA META-ANALYSIS OF THE MACH-NC GROUP



Abs: Metanalisi su 1759 pz su la CT di induzione nel H&N

PF	*vs*	**TPF**
(cisplatino + 5FU)		(PF + taxani)

Follow up mediano 4.9 anni

HR = 0.73 (95% CI: 0.64-0.83)
per progressione o decesso a favore del gruppo trattato con TPF

Blanchard P, Radiot Oncol Vol. 98 Supplement 1, 2011

Intensificazione: CT di induzione con Taxani

Neo TPF + RCT° (255 pz) *vs* Neo PF + RCT° (246 pz)

° RCT con carboplatino settimanale

follow-up mediano di 72.2 mesi *

TPF: OS stimata a 5 anni: **52%** HR 0·74

sopravvivenza mediana: **70.6** mesi p=0·014

sopravvivenza libera da progressione: **38.1**mesi HR 0·75

PF: OS stimata a 5 anni: **42%**

sopravvivenza mediana: **34.8** mesi

sopravvivenza libera da progressione: **13.2** mesi

Nessuna differenza significativa nella dipendenza da sondino nasogastrico e tracheostomia tra i due gruppi

Lorch JH, TAX 324. Lancet Oncol 2011

Intensificazione: CT di induzione con Taxani ?

Nessuno studio di fase III ha ancora pubblicato i risultati di un confronto diretto

Dati preliminari dello studio di Hitt sono stati presentati all'ASCO 2009:

Final results of a randomized phase III trial comparing induction chemotherapy with cisplatin/5-FU or docetaxel/cisplatin/5-FU followed by chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer

con CT di induzione:

- migliore TTF* tempo al fallimento: 12.5 mesi vs 4.9
- migliore controllo loco-regionale: 60.9% vs 44.5%
- aumento della tossicità di grado 3-4: 83% vs 69%

*(morte, progressione, chirurgia)

Intensificazione: CT di induzione con Taxani

Studio randomizzato di fase II su 101 pz

Neo TPF + RCT° *vs* RCT°

RCT°: 2 cicli di CDDP 20 mg/m2, 1-4 + 5-Fu 800 mg/m2 ic per 96 ore, I e VI sett. di RT

TPF: sopravvivenza globale: **39.6** mesi
sopravvivenza libera da progressione: **33.3** mesi
CR radiologica: **50%**

RCT sola: sopravvivenza globale: **30.4** mesi
sopravvivenza libera da progressione: **19.7** mesi
CR radiologica: **21.2%**

L'induzione TPF seguita da RCT è fattibile ; non c'è differenza negli effetti tossici ematologici e non

Paccagnella A, Ann Oncol 2010

Intensificazione: CT di induzione con Taxani

Induction Chemotherapy Before Chemoradiotherapy in Locally Advanced Head and Neck Cancer: The Future?

The Oncologist
Marzo 2011

A. PACCAGNELLA, C. MASTROMAURO, P. D'AMANZO, M.G. GHI

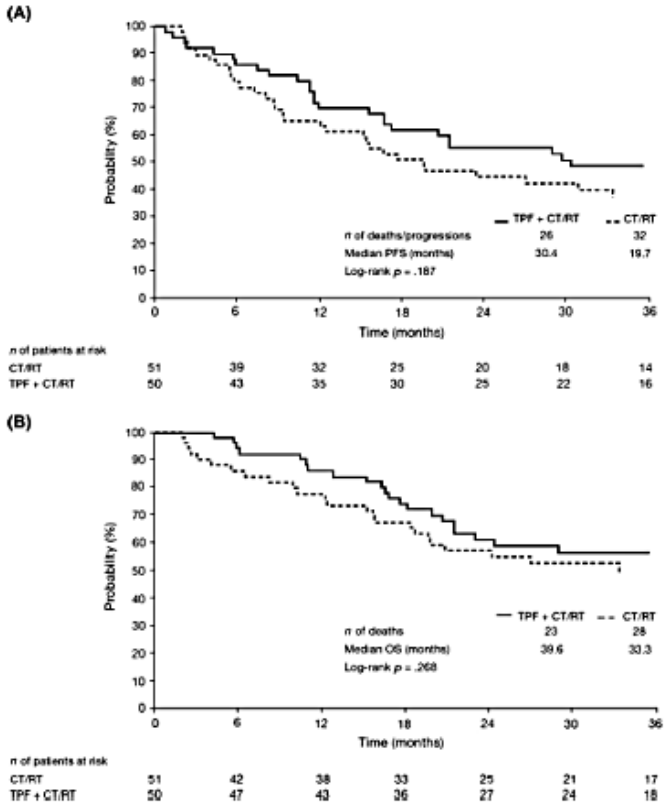


Figure 1. Progression-free survival (**A**) and overall survival (**B**) in patients treated with chemoradiotherapy alone or docetaxel, cisplatin, and 5-fluorouracil induction chemotherapy plus chemoradiotherapy.
Abbreviations: CT/RT, chemoradiotherapy; OS, overall survival; PFS, progression-free survival; TPF, docetaxel, cisplatin, and 5-fluorouracil.

Table 2. Clinical response following treatment with chemoradiotherapy alone or docetaxel, cisplatin and 5-fluorouracil induction chemotherapy plus chemoradiotherapy

	n of patients (%)	
	CRT, *n* = 47	TPF + CRT, *n* = 46
Complete response[a]	10 (21)	23 (50)
Partial response	29 (62)	13 (28)
Stable disease	0	1 (2)
Progressive disease	8 (17)	9 (20)
Objective response rate	39 (83)	36 (78)

[a] $p = .004$, χ^2 test.
Abbreviations: CRT, chemoradiotherapy; TPF, docetaxel, cisplatin, and 5-fluorouracil.

Farmaci biologici

Il recettore EGF è iperespresso nel 90% dei HNSCC
L'iperespressione del EGFR è associata ad una prognosi sfavorevole

Il Cetuximab, un anticorpo monoclonale contro l'EGFR, è stato associato alla RT nel HNSCC localmente avanzato

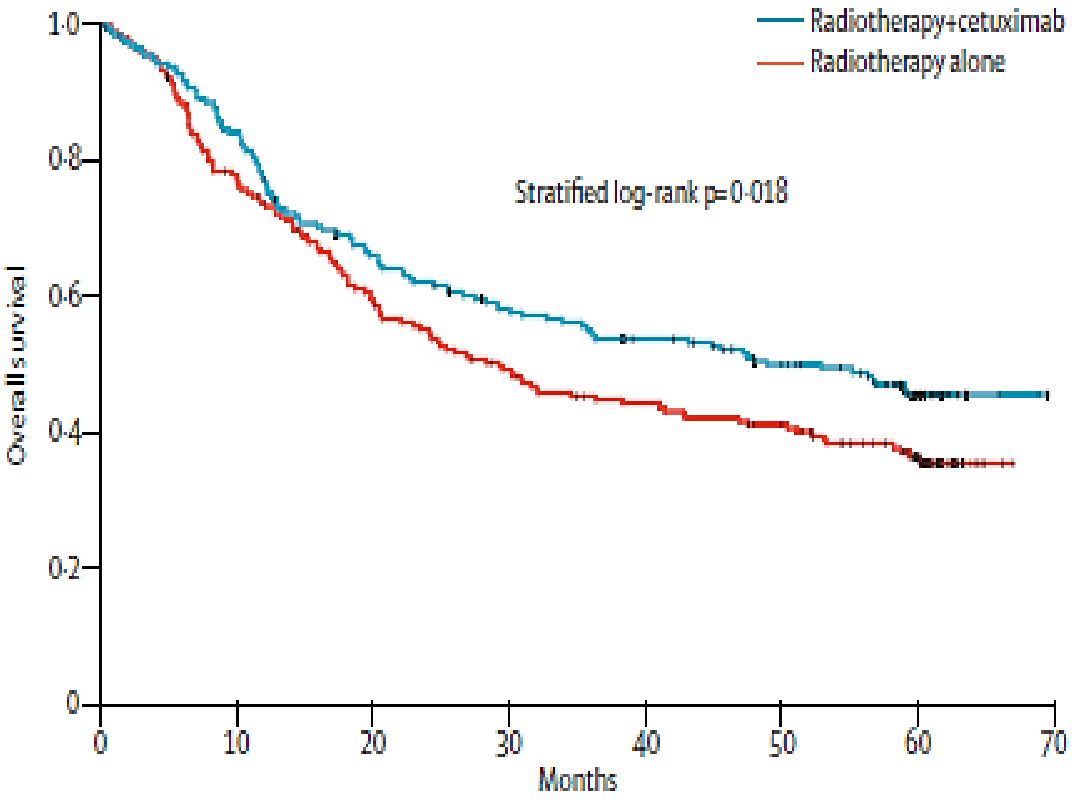
Evidenza di uno studio randomizzato di fase III

Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival

Bonner JA, Lancet Oncol. 2010

Farmaci Biologici: RT + Cetuximab *vs* RT

RT convezionale, HF, AF concomitant boost



RT+ Cetuximab:

OS mediana: **49** mesi

OS a 5 anni: **45.6%**

RT:

OS mediana: **29.3** mesi

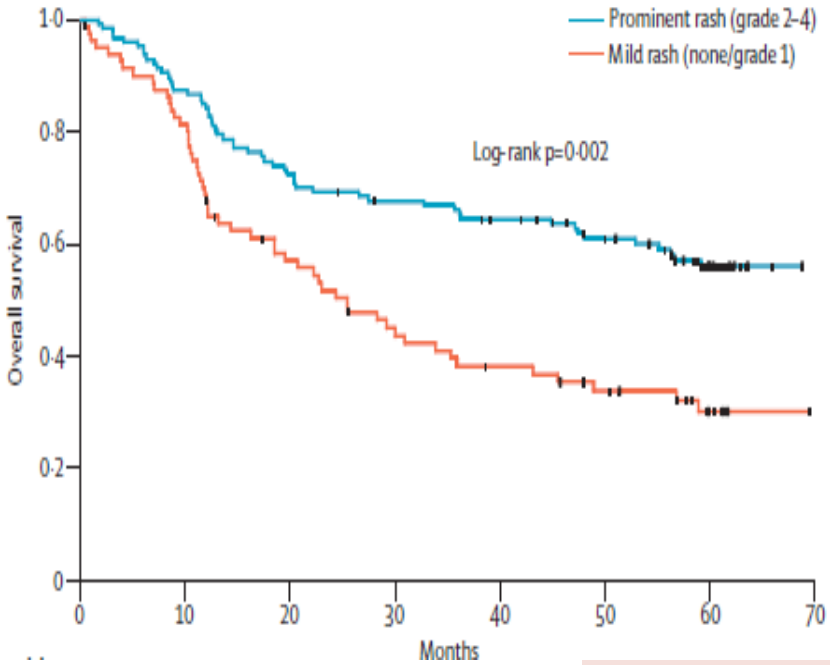
OS a 5 anni: **36.4%**

HR 0.73 p= 0.018

Bonner JA, Lancet Oncol. 2010

Farmaci Biologici: RT + Cetuximab *vs* RT

Rash acneiforme G 2-4 è associato ad una migliore OS vs G 0-1



Tossicità acuta severa simile in entrambi i gruppi ad eccezione del rash acneiforme e delle reazioni da infusione

	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	63 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35(16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)

Bonner JA,
Lancet Oncol. 2010

Integrazione di Cetuximab con RT e chemioterapia

Risultati di studi di fase I

Kuhnt T, Sandner A, Wendt T et al. Phase I trial of dose-escalated cisplatin with concomitant cetuximab and hyperfractionated-accelerated radiotherapy in locally advanced squamous cell carcinoma of the head and neck. *Ann Oncol,* 21(11), 2010.

Argiris A, Heron DE, Smith RP et al. Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and neck cancer. *J Clin Oncol,* 2010.

Koukourakis MI, Tsoutsou PG, Karpouzis A et al. Radiochemotherapy with cetuximab, cisplatin, and amifostine for locally advanced head and neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys,* 2010.

Argiris A, Karamouzis MV, Smith R et al. Phase I trial of pemetrexed in combination with cetuximab and concurrent radiotherapy in patients with head and neck cancer. Ann Oncol, 2011.

CDDP
40 mg/m^2
sett

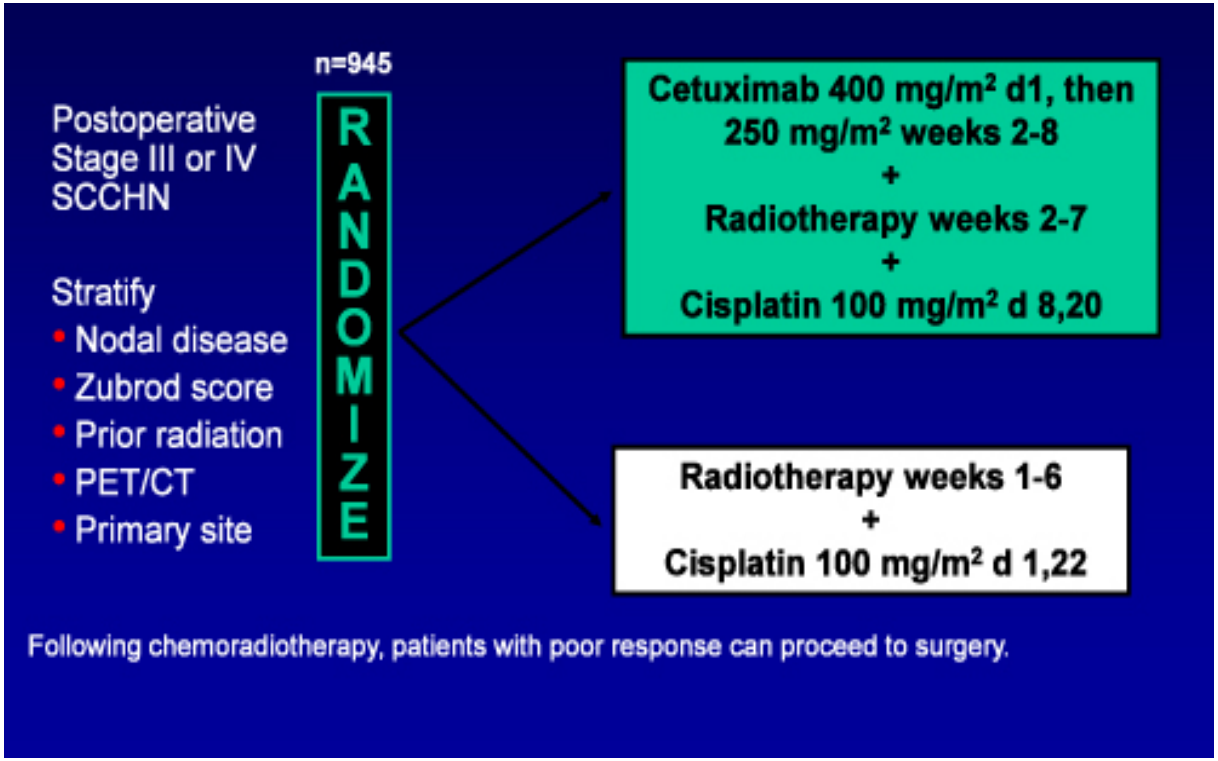
CDDP
30 mg/m^2
sett

CDDP
30 mg/m^2
sett + die
Amifostina
0.5- 1 gr

PEM [1,22,43]
500 mg/m^2

A Randomized Phase III Trial (RTOG 0522) of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III-IV Head and Neck Squamous Cell Carcinomas (HNC)

Ang KK[1] Initial Results Reported at ASCO 2011



No Survival Benefits or PFS by the addition of Cetuximab to Chemoradiation treatment for pts with locally advanced head and neck cancer

higher rates of mucositis and cetuximab-induced skin reactions within the range of that reported in other prospective trials

Further analysis is underway to determine the role of tumor human papillomavirus status.

GORTEC-CETTEC (TREMPLIN), Phase II, n:153 — 2012

Neo TPF + RT-CDDP *vs* Neo TPF + RT-Cetuximab

Cetuximab is a reasonable substitute for cisplatin in combination with full dose RT in patients with laryngeal carcinoma who received induction TPF prior to RT

Overall PFS and OS were similar but Cetuximab-RT arm was far better tolerated

Arm	Cisplatin	CETUXIMAB
Number	60	56
Local Failure	8%	14%
Salvage Laryngectomy	0/4	7/8
Larynx Function Preservation	86%	82%
Overall Survival	92%	89%

Lefebvre et al, A-5501, ASCO 2011

Integrazione di Cetuximab con RT e chemioterapia

Studi di fase II/III in corso

GORTEC 2007-01 Phase III trial, n: 406 ***iniziato 2008***

RT + Cetuximab

vs

RT + Cetuximab + CT

GORTEC 2007-02 Phase III trial, n: 360 ***iniziato 2009***

Neo TPF + RT + Cetuximab

vs

RT + CT

LOCOREGIONALLY ADVANCED HEAD AND NECK CANCER TREATED WITH PRIMARY RADIOTHERAPY: A COMPARISON OF THE ADDITION OF CETUXIMAB OR CHEMOTHERAPY AND THE IMPACT OF PROTOCOL TREATMENT

Caudell JJ, Int J Radiat Oncol Biol Phys 2008

Studio retrospettivo

confronto tra RT + cetuximab e RCT

29 paz trattati con RT + cetuximab: follow-up 83 mesi
103 paz trattati con RCT: follow-up 53 mesi

nessuna differenza significativa a 3 anni per:

controllo locoregionale: **71% vs 75%**

sopravvivenza libera da metastasi: **92% vs 86%**

sopravvivenza malattia-specifica: **79% vs 77%**

sopravvivenza globale: **75% vs 61%**

CONCURRENT CISPLATIN AND RADIATION VERSUS CETUXIMAB AND RADIATION FOR LOCALLY ADVANCED HEAD-AND-NECK CANCER

Koutcher L, Int J Radiat Oncol Biol Phys 2011

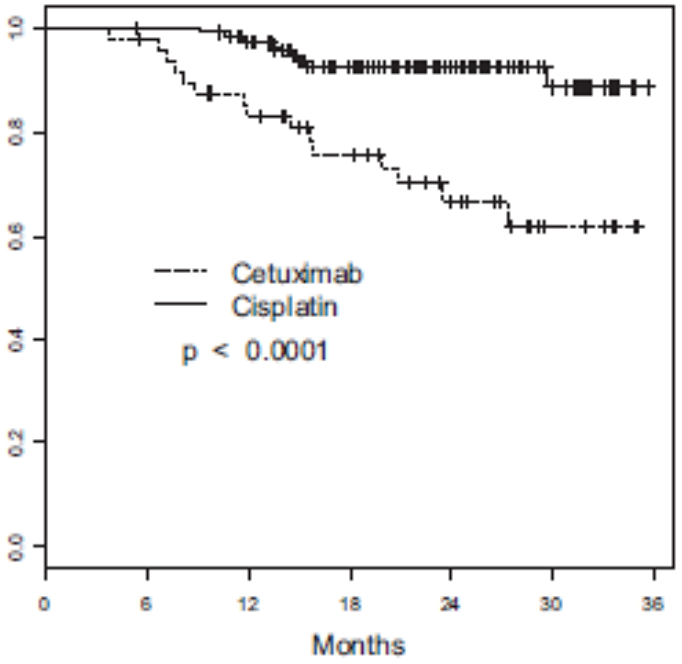
Studio retrospettivo H&N 2006-2008

follow-up medio 22.5 mesi

49 paz trattati con RT + cetuximab

vs

125 paz trattati con RCT

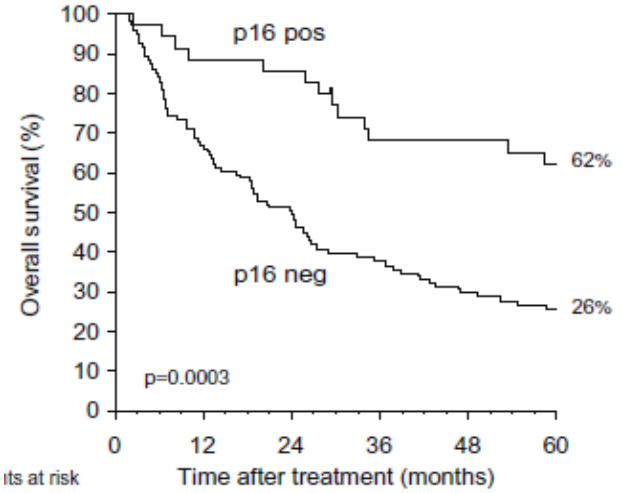


differenze significative a 2 anni per:

recidiva locoregionale:	**40% vs 6%**	**p=0.001**
sopravvivenza libera da malattia:	**87% vs 93%**	**p=0.001**
sopravvivenza globale:	**45% vs 67%**	**p=0.01**
Tossicità tardiva G3-4	**24% vs 21%**	**p=0.66**

HPV status positivo *vs* negativo

- lo stato HPV p16+ manifesta una prognosi migliore con la RT
- un trattamento intensivo può non essere ottimale
- necessità di considerare strategie separate



status HPV p16+:

- non beneficio con modificatori dell'ipossia
- beneficio (controllo loco-regionale) con AF 6 frazioni (ripopolamento anche con HPV+)
- beneficio con RCT
- non ci sono dati con Cetuximab

Pernille L, Radiot Oncol 2010

La riduzione della tossicità

- **Acuta: OTD70DERM**
  inibitore della radiodermite

- **Cronica: Amifostina**
  radioprotettore muccose e ghiandole salivari

Ridurre la Radiodermite da cetuximab

Le journal du GORTEC
Semestriel
Septembre 2011
NUMERO 3
Groupe d'Oncologie Radiothérapie Tête Et Cou

ESSAI GORTEC 2009-01

Y. TAO, Villejuif

Yungan TAO
tao@igr.fr

Cet essai randomisé multicentrique évalue l'effet du RGTA (*ReGeneraTing* Agents) — l'OTD70DERM sur les dermites induites par l'association radiothérapie-Erbitux® qui est un analogue structurel et fonctionnel des glycosaminoglycanes (GAG) - Heparane mimétics. Il peut protéger la matrice extracellulaire et stimuler la régénération tissulaire **(Figure 8)**. Il est appliqué 1 à 4 heures après la séance pendant une durée de 5 à 10 minutes. L'objectif principal est de comparer le taux de survenue des radiodermites de grade ≥ 2 entre deux groupes randomisés OTD70DERM® et Placebo (avec du sérum physiologique). Tous les patients sont traités par radiothérapie (70 Gy en 35 fractions) et Erbitux® hebdomadaire. Actuellement, un total de 17 patients est inclus sur les 70 prévus **(Figure 9)**.

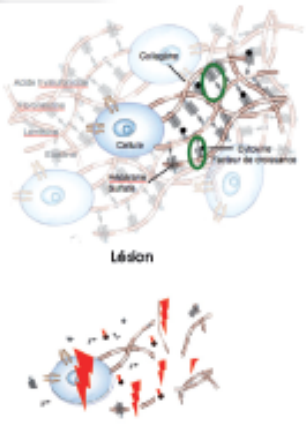


Figure 8 : Mode d'action de l'OTD70DERM

OTD70DERM = analogue des glycosaminoglycanes, GAG, Ils fixent et protègent les protéines de la Matrice Extra-cellulaire

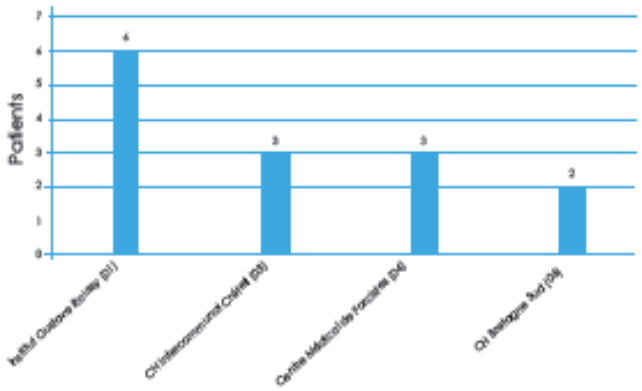


Figure 9 : Bilan des inclusions de l'étude GORTEC 2009-01 (Point au 9 mai 2011 mais majoration de l'effectif depuis).

Random fase II
Prospettico

70Gy in 35 fr.

OTD70DERM
vs
PLACEBO

Arruolati 17/70 pz previsti

Amifostine and RT in H&N cancer

Amifostine can ameliorate RT side effects without compromising treatment effectiveness

JCO, 2000;18:3339

Phase III Randomized Trial of Amifostine as a Radioprotector in Head and Neck Cancer

By David M. Brizel, Todd H. Wasserman, Michael Henke, Vratislav Strnad, Volkar Rudat, Alain Monnier, Francois Eschwege, Jay Zhang, Lesley Russell, Wolfgang Oster, and Rolf Sauer

RT: Chronic xerostomia ≥ 2

57% vs 34% p= 0.002

Acute mucositis: n.s.

IJROBP, 2002; 52: 739

CLINICAL INVESTIGATION Head and Neck

PROPHYLACTIC USE OF AMIFOSTINE TO PREVENT RADIOCHEMOTHERAPY-INDUCED MUCOSITIS AND XEROSTOMIA IN HEAD-AND-NECK CANCER

Dosia Antonadou, M.D., Marizenia Pepelassi, M.D., Maria Synodinou, M.D., Maria Puglisi, M.D., and Nicolas Throuvalas, M.D.

RCT: Chronic xerostomia ≥ 2
30% vs 5% p= 0.047

G4 Acute mucositis:
52% vs 5% p=0.0006

IJROBP, 2006;64:684

CLINICAL INVESTIGATION Head and Neck

INTRAVENOUS AMIFOSTINE DURING CHEMORADIOTHERAPY FOR HEAD-AND-NECK CANCER: A RANDOMIZED PLACEBO-CONTROLLED PHASE III STUDY

Jens Buentzel, M.D.,* Oliver Micke, M.D.,† Irenaus A. Adamietz, M.D.,‡ Alain Monnier, M.D.,§ Michael Glatzel, M.D.,‖ and Alexander de Vries, M.D.¶

RCT randomized trial:

Acute mucositis: n.s.

Chronic xerostomia ≥ 2 n.s.

Our experience with Amifostine

- 243 pts with H&N cancer treated with 3D RT o RCT Between 2005 and 2010
- Dose prescription:
  - 70 Gy were prescribed to tnPTV for definitive RT;
  - 60 Gy after R0 surgery (66 - 70Gy to R1-2 pts)
  - 50 Gy to pnPTV

- 170/243 pts received a radiation dose ≥ 50Gy on both parotid glands *(standard fractionation)*
- Amifostine (200mg/m^2) was daily administered i.v. to
  - 86/170 pts 15-30 minutes before RT: RTA group
  - 84/170 pts did not received Amifostine: RT group

G2-3 chronic xerostomia according to Amifostine Dose-Intensity (DI) and CDDP administration

Amifostine DI 81 pts*	100 mg/m2 3wks n. pts	30 mg/m2 weekly n. pts	CTX n. pts	RT only n. pts	Tot. %
Definitive RT/RCT	**25**	**15**	**1**	**7**	**48**
0.81 – 1.0	2/9	2/8	0/1	2/5	6/23 **26%**
0.61 – 0.80	2/4	3/6	0	0/1	5/11 **45%**
≤ 0.60	9/12	0/1	0	0/1	9/14 **64%**
PORT	**9**	**14**	**0**	**10**	**33**
0.81 – 1.0	1/2	1/6	0	1/4	3/12 **25%**
0.61 – 0.80	0/1	3/3	0	0/1	3/5 **60%**
≤ 0.60	2/6	2/5	0	1/5	5/16 **31%**

Chronic Xerostomia ≥ 2: 31/81 pts = 38% (RTA group) vs 50% (RT group) n.s.

Amifostine DI > 80% *vs* ≤ 80% : 26% *vs* 48% p 0.04 χ 2 4.11 OR 2.65 (1.02-6.87)

"" "" > 60% *vs* ≤ 60% : 30% *vs* 56% p 0.03 χ 2 4.81 OR 2.92 (1.10-7.73)

"" "" > 60% *vs* no amifostine: 30% *vs* 50% p 0.03 χ 2 4.77 OR 0.47 (0.21-1.07)

Effect of amifostine on survival among patients treated with radiotherapy: a meta-analysis of individual patient data

PURPOSE:
Controversy exists regarding whether or not amifostine might reduce the efficacy of cancer treatment. The aim of this meta-analysis was to evaluate the impact of amifostine on overall survival (OS) and progression-free survival (PFS) in patients treated with radiotherapy or chemoradiotherapy.

MATERIAL AND METHODS:
Updated data from individual patients with non-small-cell lung cancer, head and neck squamous cell carcinoma, and pelvic cancer treated with radiotherapy or chemoradiotherapy and randomly assigned to amifostine or not were included. The primary end point was OS.

RESULTS:
12 trials and 1119 patients were analyzed. A total of 431 patients were treated with radiotherapy alone (three trials), and 688 patients were treated with chemoradiotherapy (nine trials). Thirty-three percent of patients had lung cancers, 65% had head and neck cancers, and 2% had pelvic carcinomas. Ninety-one percent of patients had locally advanced disease (early stage, 9%). Median follow-up was 5.2 years. The hazard ratio (HR) of death was 0.98 (95% CI, 0.84 to 1.14; P = .78). On the basis of 11 trials (1091 patients), the HR of progression, relapse, or death was 1.05 (95% CI, 0.90 to 1.22; P = .53). The tests for heterogeneity were not significant (P ≥ .73), and there was no significant variation of treatment effect according to sex, age, tumor site, stage, histology, locoregional treatment, or type of administration for either end point.

CONCLUSION:
Amifostine did not reduce OS and PFS in patients treated with radiotherapy or chemoradiotherapy

Bourhis J, J Clin Oncol 2011

Tecniche di radioterapia

L' IMRT rappresenta la tecnica emergente

PRO:

- migliore distribuzione della dose
- riduzione della dose a strutture normali
- possibilità di aumentare la dose al tumore

CONTRA:

- rischio di recidive marginali
- diminuzione della omogeneità della dose
- incremento della dose totale al corpo

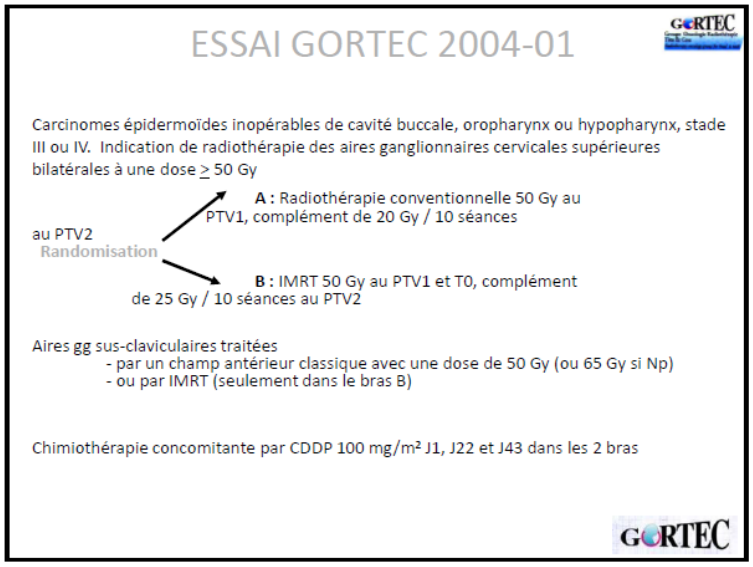
GORTEC 2004-01

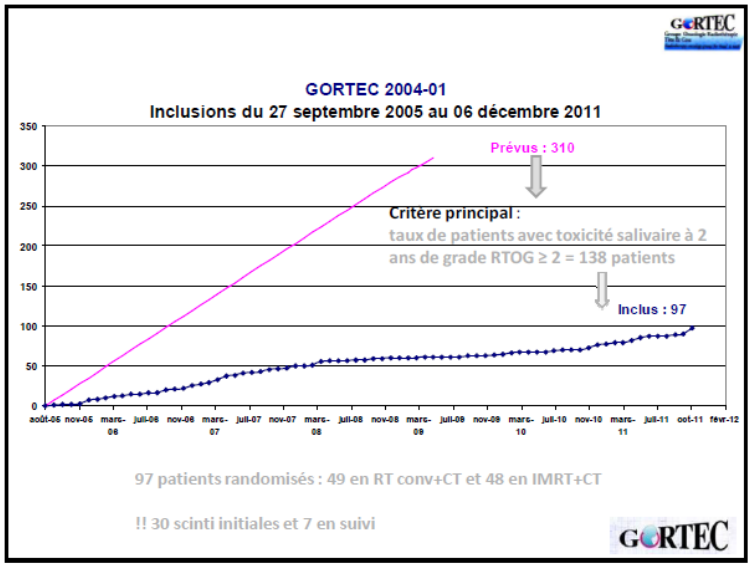
Studio randomizzato di fase III di confronto tra RT 3D conformata (70 Gy) e IMRT (75 Gy) per le neoplasie del testa-collo in stadio III e IV (escluso rinofaringe)

Coordinatore : Pr BOURHIS

Start-up: 2005

N. Pz previsti 310, arruolati a fine 2011: **97**





Problematiche della RCT concomitante

Tossicità acuta

Revisione sistematica dei dati di 33 studi (1996-1999)

Treatment	*n*	Mucositis incidence (% of patients)	Grade 3–4 mucositis (% of patients)
Total[b]	6181	80	39
RT-C	2875	97	34
RT-AF	1096	100	57
RT+CT[c]	1505	89	43
CT only	318	22	0

un terzo dei pazienti sono stati ospedalizzati

Trotti A, Radiot & Oncol 2003

Gastrostomy tube placement and use in patients with head and neck cancer

Surveillance, Epidemiology, and End Results (SEER) Medicare Data per pazienti con neoplasia del testa- collo diagnosticata tra il 2000 to 2005 (N = 16,458) e trattati con RT +/- CT o Cetuximab

35% di pazienti portatori di gastrostomia

CONCLUSIONS:
Future work is warranted to identify predictors and outcomes associated with provision and timing of enteral nutrition support for patients with head and neck cancer. Head Neck, 2011

Locher JL, Head Neck 2011

Impact of nutrition support on treatment outcome in patients with locally advanced head and neck squamous cell cancer treated with definitive RT: a secondary analysis of RTOG trial 90-03

Rabinovitch R, Head Neck. 2006

Relazione tra supporto nutrizionale (NS) , tossicità acuta e risultati della RT curativa

1073 pazienti NS dato: Prima del trattamento (BNS); Durante il trattamento (TNS);

NS	Perdita di peso	mucosite G3-4	CLR % 5aa	OS % 5aa	note
BNS	<	<	29	16	stadio >
TNS	>	>	55	36	stadio <
no NS	>	>	57	49	stadio <
Significatività mantenuta anche all'analisi multivariata			p .0001	p .0001	

Conclusioni

- **Frazionamenti alterati + efficienti della RT standard**
- **RCT + efficace della sola RT**
- **RCT concomitante + efficace della sequenziale**
- **CT neoadiuvante deve ancora definire il suo ruolo**
- **RT & CTX + efficace della RT da sola**
- **RT & CT + CTX: ruolo ancora da definire**
- **Con la IMRT minore tossicità acuta**