

Prague, 24-25 April 2009

**ALTERNATING CHEMORADIATION:
FOR WHOM?**
M. Merlano MD
Holy Cross Gen. Hospital
Cuneo - Italy

**ALTERNATING CHEMORADIATION:
FOR WHOM?**

- Definition of alternating chemoradiation
- Targets of alternating chemoradiation
- Comparison of alternating vs concurrent chemoradiation
 - Efficacy
 - Toxicity
- Selection of patients

alternating chemoradiation

- A minor variation of concurrent chemoradiation aimed at minimizing toxicity ⁽¹⁾...

1) Halfy GB. Concurrent chemoradiation in the treatment of head and neck cancer. Hematol. Oncol. Clin. North Am. 1998;13:719-742

**Split course RT?
No, thanks!**

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No, thanks!**

What is the real principle?
The uninterrupted radiotherapy
Or
The uninterrupted tumor treatment?

"Alternating radiotherapy and chemotherapy produces less acute mucosal toxicity than synchronous therapy but may prolong the overall treatment time... Although longer treatment times adversely affect efficacy in programs of standard RT alone due to tumor repopulation, the significance of RT overall treatment time in a continuous course of alternating RT and CT is controversial. Some investigators have suggested that the usual time-dose relationship do not apply⁽¹⁾."

From:
David M. Brizel: The Role of Combined Radiotherapy and Chemotherapy in the Management of Locally Advanced Squamous Carcinoma of the Head and Neck. In *Perez and Brady's Principles and Practice of Radiation Oncology* (Editors Edward C. Halperin MD, MA, FRCR, Carlos A. Perez MD, Luther W. Brady MD). V Ed. p.807. Lippincott Williams & Wilkins December 2007.

(1) Wong WW et al "Time-dose relationship for local control following alternate week concomitant radiation and chemotherapy of advanced head and neck cancer" *Int. J. Radiat. Oncol. Biol. Phys.* 1994;29:153-162

alternating chemoradiation

- A minor variation of concurrent chemoradiation aimed at minimizing toxicity⁽¹⁾
- The alternating chemoradiation allows **uninterrupted (continuous) treatment of the tumor, with radiotherapy administered during the pauses between courses of chemotherapy**⁽²⁾
- **Preclinical studies support the hypothesis that alternating chemoradiation could preserve efficacy without significantly increasing toxicity**⁽³⁾

1) Haffty GB: Concurrent chemoradiation in the treatment of head and neck cancer. *Hematol Oncol Clin North Am*. 1999;13:719-742.
 2) Merlano M: Alternating chemotherapy and radiotherapy in locally advanced head and neck cancer: an alternative? *The Oncologist* 2006;11:146-151.
 3) Lefebvre J-L et al: Alternation of chemotherapy and radiotherapy in cancer management. II. Results in experimental solid tumors systems and their relationship to clinical studies. *Cancer Treat Rep*. 1988;70:141-162.

Targets of alternating chemoradiation

“To preserve increased efficacy of chemoradiation without paying the cost of the increased toxicity”

RAPIDLY ALTERNATING CT/RT^(1,2,3)

Weeks	1	2	3	4	5	6	7	8	9	10
Chemotherapy		-----	-----		-----	-----		-----	-----	
Radiotherapy	-----			-----			-----			-----

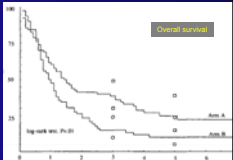
Chemotherapy: cisplatin, 20 mg/m²/die, days 1 to 5; fluorouracil bolus i.v., 200 mg/m²/die, days 1 to 5
 Radiation: 200 cGy/die, 1 fraction per day, 5 fractions per week

1) Merlano M, et al. *N Engl J Med* 1992;327:1115-1121; *J Natl Cancer Inst*. 1996;88:583-9
 2) Corvó R et al. *Cancer* 2001;92:2856-2867
 3) Lefebvre J-L et al. *J. Natl Cancer Inst* 2009;101:142-52

Alternating chemoradiation vs radiotherapy

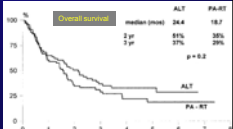
Merlano M et al: N Engl J Med 1992;327:1115-1121

	ALT	RT	p
pts	80	77	
CR (%)	42	22	0.037
On treatment deaths	7	6	



Corvò R et al: Cancer 2001;92:2886-2867

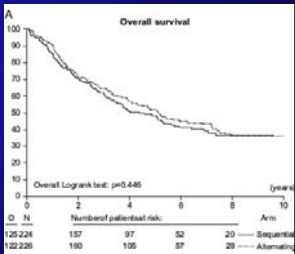
	ALT	PA-RT	p
pts	70	66	
CR (%)	51	39	0.1
On treatment deaths	7	8	



Alternating chemoradiation vs induction CT and radiotherapy

ORGAN PRESERVATION EORTC 24954

Lefebvre J.L. et al: J Natl Cancer Inst 2009;101:142-52

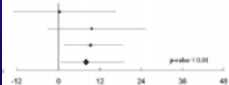


Arm	Number of patients at risk
ALT	128 228 187 97 52 20
Induction CT	122 226 190 105 57 29

Can we say that alternating chemoradiation is superior to radiation alone?

1) median OS by study

Merlano	17 m	11 m	P = 0.01
Corvò	24 m	19 m	P = NS
Lefebvre	5.1 yrs	4.4 yrs	P = NS



Keane 1993¹
Corvò 2001
Merlano 1996

Total

1) Not platinum based

Can we say that alternating chemoradiation is superior to radiation alone?

	Total RT dose (median)		Median OS	
	ALT-RT	RT	ALT-RT	RT
Merlano	60	66	17	11
Corvò	60	75	24	19
Lefebvre	62.8	71.5	5.1 y	4.4 y

Tab. 1 Selected randomized clinical trials of chemo-radiation

Author	# pts	CT	RT daily fraction	3-ys OS	3-ys OS Control arm	P
Fu (1987)	104	B	Standard	43%	24%	0.16
Browman (1994)	175	F	Standard	52%	37%	0.076
Corvò (2001)	136	CF	standard	37%	29%	0.2
Merlano (1996)	157	CF	Standard	41%	23%	0.01
Adelstein (2003)	295	C	Standard	37%	23%	0.014
Brizel (1998)	116	CF	MFD RT	55%	34%	0.07
Wendt (1998)	298	CF	MFD RT	48%	24%	0.0003
Huguenin (2004)	224	C	MFD RT	59%	49%	0.147

CT=chemotherapy, RT=radiotherapy, OS=overall survival, V=vinblastine, B=bleomycin, M=methotrexate, F=fluorouracil, C=cisplatin, MFD=multiple fractions per day

modified from: Merlano M, Polla Mattioli V: "future chemotherapy and radiotherapy options in head and neck cancer" *Expert Rev Anticancer Ther* 2006;6(3): 395-403

Targets of alternating chemoradiation

"To preserve increased efficacy of chemoradiation"

ALT CTRT > RT evidence level I (meta-analysis)

ALT CTRT = Concurrent CT/RT not evidence based (lack of direct comparison)

Targets of alternating chemoradiation

“To preserve increased efficacy of chemoradiation without paying the cost of the increased toxicity”

Toxicity analysis

From: Alternating RT and CT compared with RT alone in treatment of unresectable SCC-HN

Merlano M et al. JNCI 1996;88:583-9 (modified)

- 157 pts
- WHO G. III-IV mucositis 19% vs 18%
- Toxicity related treatment delay:

	Alt. CT/RT	RT
1 week	21%	32%
2 weeks	11%	11%
3 weeks	4%	14%
Overall	36%	47%

From: Alternating chemoradiotherapy vs partly accelerated radiotherapy in locally advanced SCC-HN

Corvò R et al. Cancer 2001;92:2856-67 (modified)

Acute mucosal reaction observed in the treatment groups according to the objective RTOG Scale				
Reaction	Combined treatment (n = 63)		Radiotherapy (n = 64)	
	n	%	n	%
Enanthema	16	25	11	17
Patchy mucositis	10	15	19	30
Confluent mucositis	34	54	33	51
Hemorrhagic mucositis	-	-	1	2

Pros and cons

	CONCURRENT CHEMORADIATION		ALTERNATING CHEMORADIATION	
	PROS	CONS	PROS	CONS
TREATMENT DURATION	≈ 7 WEEKS			≈ 10 WEEKS
COMPLEXITY	LOW			HIGH
ACUTE TOXICITY		HIGHER THAN INDUCTION CT FOLLOWED BY RT HIGHER THAN RT ALONE	LOWER THAN INDUCTION CT FOLLOWED BY RT LOWER THAN RT ALONE	
LATE TOXICITY		HIGHER (?) THAN INDUCTION CT FOLLOWED BY RT	LOWER THAN INDUCTION CT FOLLOWED BY RT LOWER THAN RT	

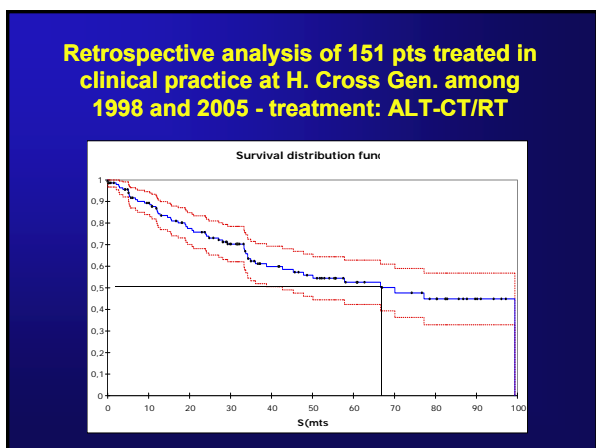
Age and chemo-radiation

Variation of treatment effect according to age in the concomitant part of MACH - NC

Concomitant CT + RT vs RT

Age(y)	No. of pts	Hazard ratio (95% CI)	Test for trend (p)
≤50	2584	0.76 (0.66-0.86)	0.003
51-60	3306	0.78 (0.70-0.87)	Tot 9208 pts > 60 y = 36.8%
61-70	2698	0.88 (0.78-1.00)	
≥71	692	0.97 (0.76-1.23)	

From: Pignon JP et al Int J Radiat Oncol Biol Phys 69 s112-S114, 2007, modified



Holy Cross General Hospital data base

# of PTS	151
Age ≥ 65 yrs	40 (36.3%)
Age < 65 yrs	111
Stage III - IV	151

From the H.C.Gen. Data base

Statistic	Observed v _i	Critical value	p-value	alpha
Log-rank	0,318	3,841	0,573	0,050
Wilcoxon	1,343	3,841	0,246	0,050
Tarone-Ware	0,914	3,841	0,339	0,050

Prog. free Survival distribution function

From the H.C.Gen. Data base

Statistic	Observed v _i	Critical value	p-value	alpha
Log-rank	0,298	3,841	0,585	0,050
Wilcoxon	0,899	3,841	0,343	0,050
Tarone-Ware	0,641	3,841	0,423	0,050

Survival distribution function

**ALTERNATING CHEMORADIATION:
FOR WHOM?**

- Elderly pts (over 65) could be treated with alternating chemoradiation
 - The treatment is superior to radiation
 - The treatment is less toxic compared to radiation
- Pts unfit for concurrent chemoradiation should be evaluated for alternating chemoradiation
 - Speculative, no data available

THANK YOU
