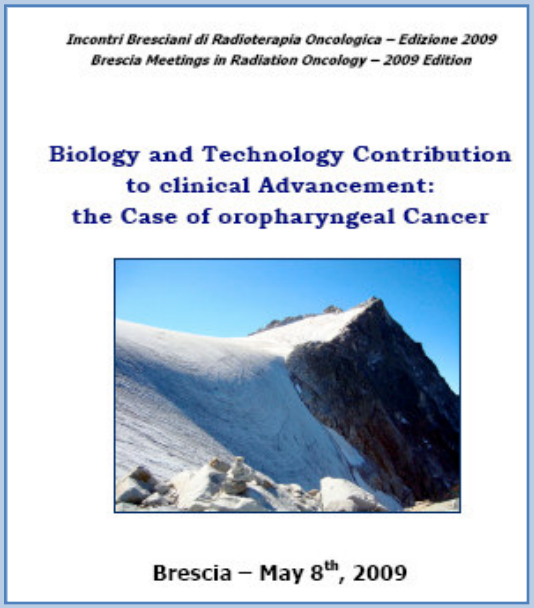

Combined radiotherapy and chemotherapy in the treatment of oropharyngeal cancer

Pietro Ponticelli
U.O. Radioterapia – Ospedale San Donato - Arezzo

Istituto Toscano Tumori

SUMMARY:

- Rationale and mechanisms of action
- Non site-specific trials either with CFRT and AFRT
- Site-specific trials either with CFRT and AFRT
- Unanswered questions:
    - induction chemotherapy
    - predictive factors
    - optimal concurrent chemotherapy
    - integration with targeted therapy
    - acute and late toxicity

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Rationale

- LC ≤ 50-60% with radiotherapy alone in stage III-IV head & neck cancer; better LRC with hyperfractionated accelerated radiotherapy (Horiot JC el al, 1997)
- 5 y OS = 30-35%
- 1/5 patients developed distant metastasis, unless achieved LC
- High activity of many drugs in squamous cell carcinomas

The main mechanisms of chemoradiation

- **Temporal modulation:** enhances tumor response to fractionated RT through the “4 R’s” of radiotherapy: repair, repopulation, reoxygenation, and redistribution

- **Biological cooperation:** refers to strategies targeting distinct cell population or using different mechanisms of cell killing or inducing tumor regrowth delay

- **Cytotoxic enhancement:** this mechamism enhances cell killing by modulating the induction or processing of intracellular demage

Bernier J et al, 2009

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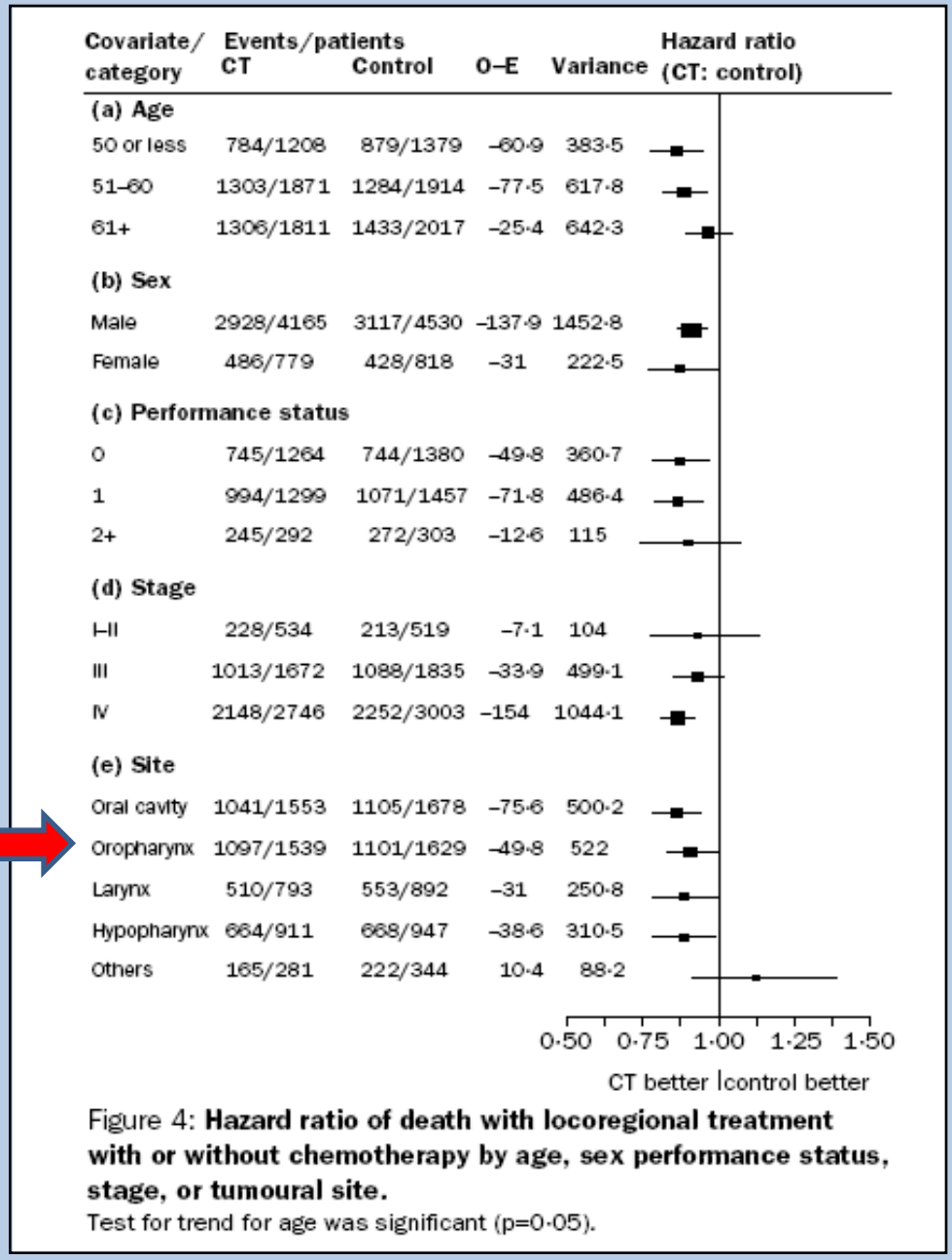
MACH-NC Collaborative Group

(Meta-Analysis of Chemotherapy on Head and Neck Cancer)

Trials performed in the period 1965-1993 to investigate the impact of chemotherapy associated to radiation therapy in patients with larynx, hypopharynx, oropharynx and oral cavity cancer.

Pignon JP et al, 2000

MACH-NC Collaborative Group



Covariate/ category	Events/patients CT	Control	O–E	Variance	Hazard ratio (CT: control)
(a) Age					
50 or less	784/1208	879/1379	–60·9	383·5	
51–60	1303/1871	1284/1914	–77·5	617·8	
61+	1306/1811	1433/2017	–25·4	642·3	
(b) Sex					
Male	2928/4165	3117/4530	–137·9	1452·8	
Female	486/779	428/818	–31	222·5	
(c) Performance status					
0	745/1264	744/1380	–49·8	360·7	
1	994/1299	1071/1457	–71·8	486·4	
2+	245/292	272/303	–12·6	115	
(d) Stage					
I–II	228/534	213/519	–7·1	104	
III	1013/1672	1088/1835	–33·9	499·1	
IV	2148/2746	2252/3003	–154	1044·1	
(e) Site					
Oral cavity	1041/1553	1105/1678	–75·6	500·2	
Oropharynx	1097/1539	1101/1629	–49·8	522	
Larynx	510/793	553/892	–31	250·8	
Hypopharynx	664/911	668/947	–38·6	310·5	
Others	165/281	222/344	10·4	88·2	

Figure 4: **Hazard ratio of death with locoregional treatment with or without chemotherapy by age, sex performance status, stage, or tumoural site.**
Test for trend for age was significant (p=0·05).

Pignon JP et al, 2000

MACH-NC Collaborative Group

Trial category	Hazard ratio (95% CI)	Chemo-therapy effect (p)	Heterogeneity (p)	Absolute benefit	
				At 2 years*	At 5 years*
Adjuvant	0·98 (0·85–1·19)	0·74	0·35	1%	1%
Neoadjuvant	0·95 (0·88–1·01)	0·10	0·38	2%	2%
Concomitant	0·81 (0·76–0·88)	<0·0001	<0·0001	7%	8%
Total	0·90 (0·85–0·94)	<0·0001	<0·0001	4%	4%

*Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups.

Pignon JP et al, 2000

MACH-NC collaborative group

- Absolute survival benefit of 8% at 5 years with concurrent chemoradiation
- Platinum-based regimens are more effective than the others
- No significant difference in efficacy between mono- and multidrug platinum regimens
- In comparison with radiation alone, small reduction in distant metastasis with chemoradiation
- No difference between CT+ CFRT and CT+AFRT
- Inverse relationship between patient age and the impact of chemotherapy on treatment outcome: the benefit disappeared for patients > 70 years old

Pignon JP et al, 2000
Bourhis J et al, 2004
Pignon JP et al, 2007

Budach metanalysis

32 randomised trials testing curatively intended RT (= 60 Gy), published between 1975 and 2003. Trials comparing RT alone with concurrent or alternating chemoradiation were analysed.

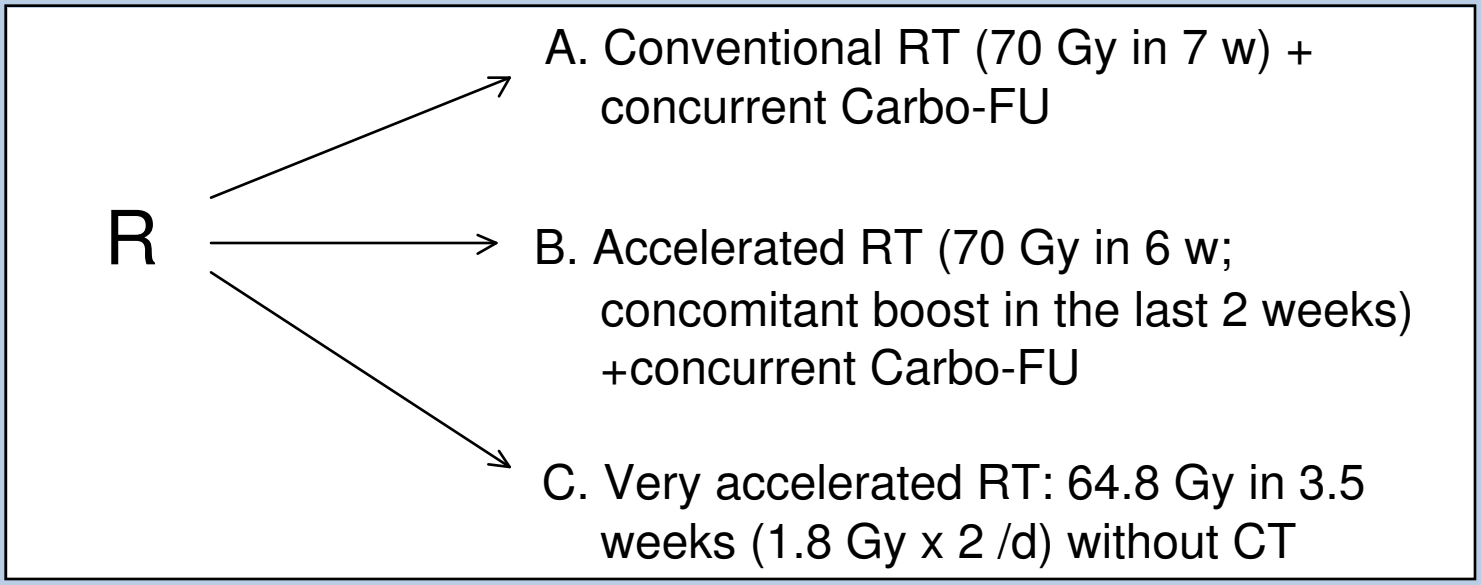
Overall survival benefit of 12 months with CRT (any RT fractionation) ($p<0.001$)

Survival significant benefit ($p<0.01$) with all the drugs used, especially with 5FU (24 mo.) and with cisplatin (16.8 mo.)

Significant survival improvement ($p< 0.001$) with hyperfractionation in comparison with conventional fractionation RT (without CT)

Budach W et al, 2006

GORTEC 99-02 trial
850 pts with locally advanced HNSCC



With a median f.up of 3.5 years, there was no difference between the 3 arms regarding LRC and survival.

PFS at 3 years was not different between the 2 chemotherapy arms, however PFS was significantly better in the conventional RT-CT arm as compared to the very Acc-RT ($p<0.03$)

Bourhis J et al, 2008

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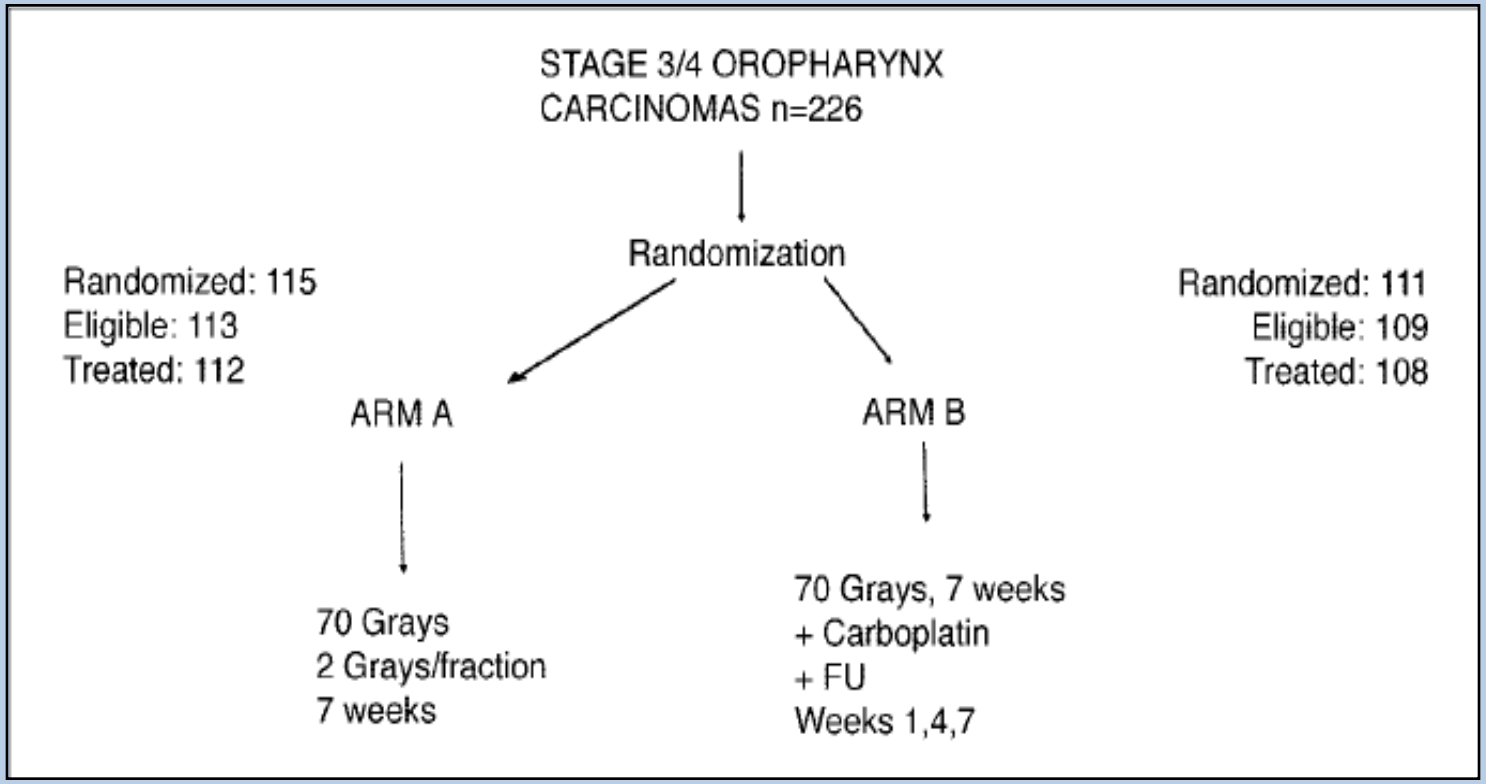
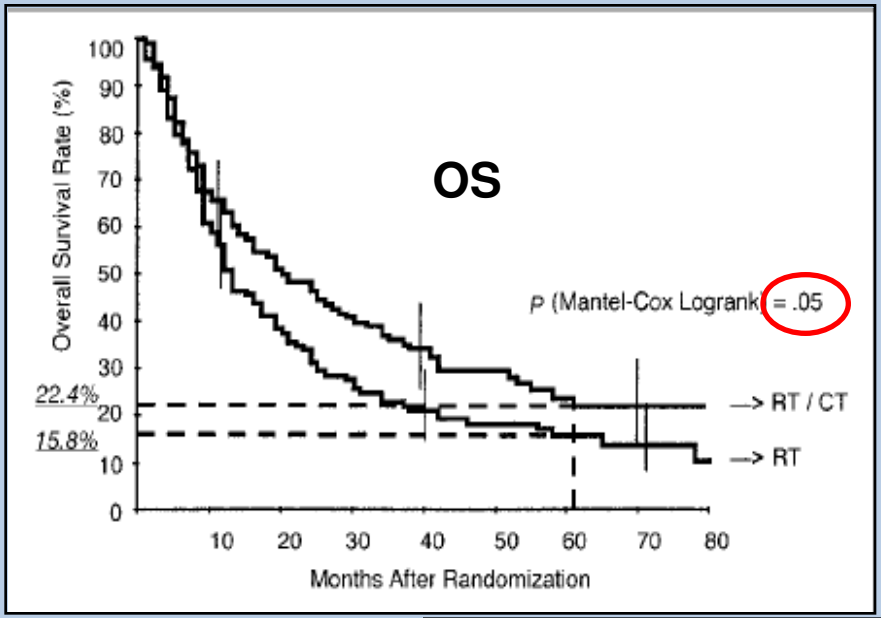
GORTEC 94-01 randomized trial in advanced-stage oropharynx carcinoma

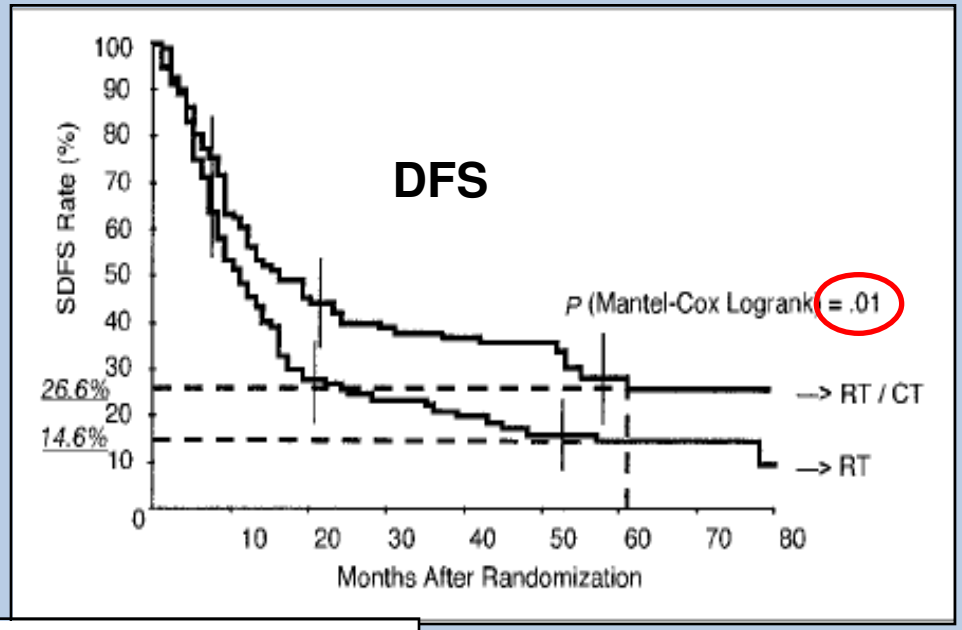


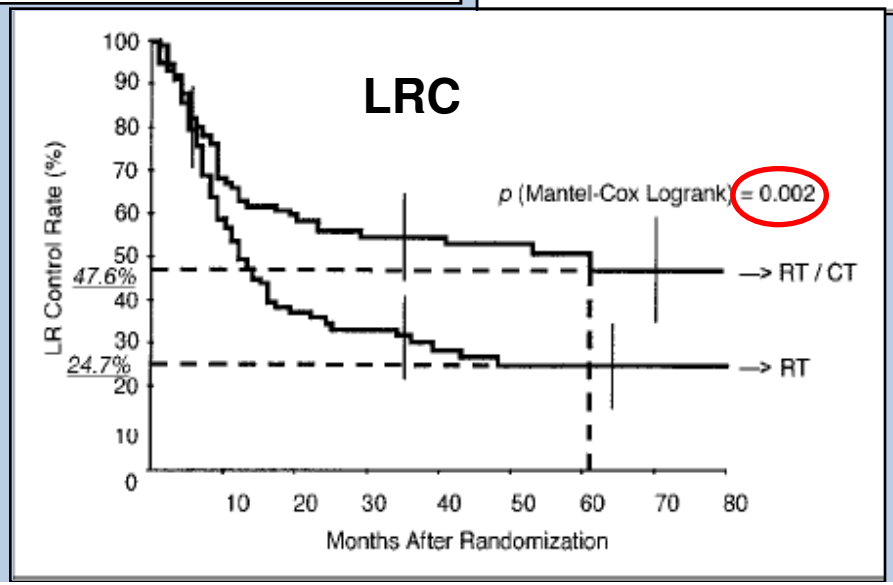
Carboplatin 70 mg/m² days 1-4; 5-FU 600 mg/m² continous infusion days 1-4

Denis F et al, 2004

GORTEC 94-01 randomized trial in advanced-stage oropharynx carcinoma







Denis F et al, 2004

GORTEC 94-01 randomized trial in advanced-stage oropharynx carcinoma

Table 2. Toxicity Scales Used for the Assessment of the Late Effect on Normal Tissues, and 5-Year Grade 3 to 4 Late Toxicity Rates of Combined Treatment Versus Radiation Alone According to the Organs Involved

Organs	Late Toxicity Scales Involved	Percentage of Patients (grade 3 to 4 toxicity)		
		RT (n = 17)	RT + CT (n = 27)	*P*
Neurological toxicity	NCI/CTC	0	0	NS
Taste	NCI/CTC	6	19	NS
Hearing	NCI/CTC	6	0	NS
Mandibula	NCI/CTC	0	6	NS
Teeth	NCI/CTC	12	4	NS
Xerostomia	RTOG/EORTC	18	15	NS
Skin and subcutaneous tissue	RTOG/EORTC	6	7	NS
Mucosa	RTOG/EORTC	18	15	NS

Abbreviations: RT, radiotherapy alone; RT + CT, radiotherapy and chemotherapy (concomitant radiotherapy); NCI/CTC, National Cancer Institute Common Toxicity Criteria; NS, not significant; RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema.

Denis F et al, 2004

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 1, pp. 161–166, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/S0360-3016(03)01370-1

CLINICAL INVESTIGATION **Head and Neck**

RADIOTHERAPY WITH CONCOMITANT WEEKLY DOCETAXEL FOR STAGES III/IV OROPHARYNX CARCINOMA. RESULTS OF THE 98-02 GORTEC PHASE II TRIAL

GILLES CALAIS, M.D.,* ETIENNE BARDET, M.D.,† CHRISTIAN SIRE, M.D.,‡ MARC ALFONSI, M.D.,§ JEAN BOURHIS, M.D.,‖ BÉATRIX RHEIN, M.D.,¶ JACQUES TORTOCHAUX, M.D.,# YOOYE TAO KONG MAN, M.D.,** HUGUES AUVRAY, M.D.,†† AND PASCAL GARAUD, PH.D.‡‡

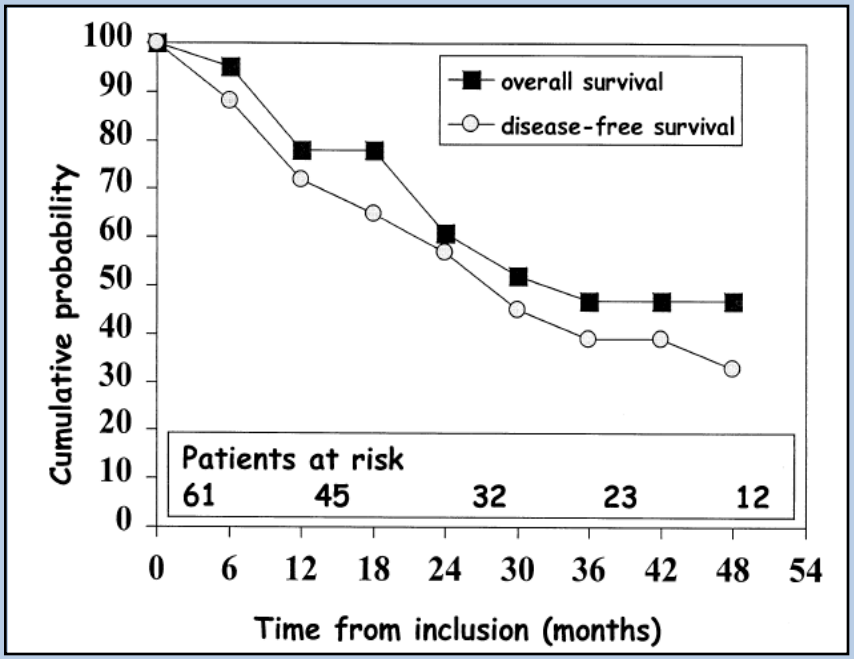
*Centre Hospitalier Universitaire, Tours, France; †Centre René Gauducheau, Nantes, France; ‡Centre Hospitalier, Lorient, France; §Clinique Sainte Catherine, Avignon, France; ‖Institut Gustave Roussy, Vellejuif, France; ¶Centre Hospitalier Universitaire, Limoges, France; #Centre Jean Perrin, Clermont-Ferrand, France; **Centre de Radiothérapie J. Belot, Montluçon, France; ††Centre Hospitalier, Moulins, France; ‡‡Département de Biostatistiques Université de Tours, Tours, France

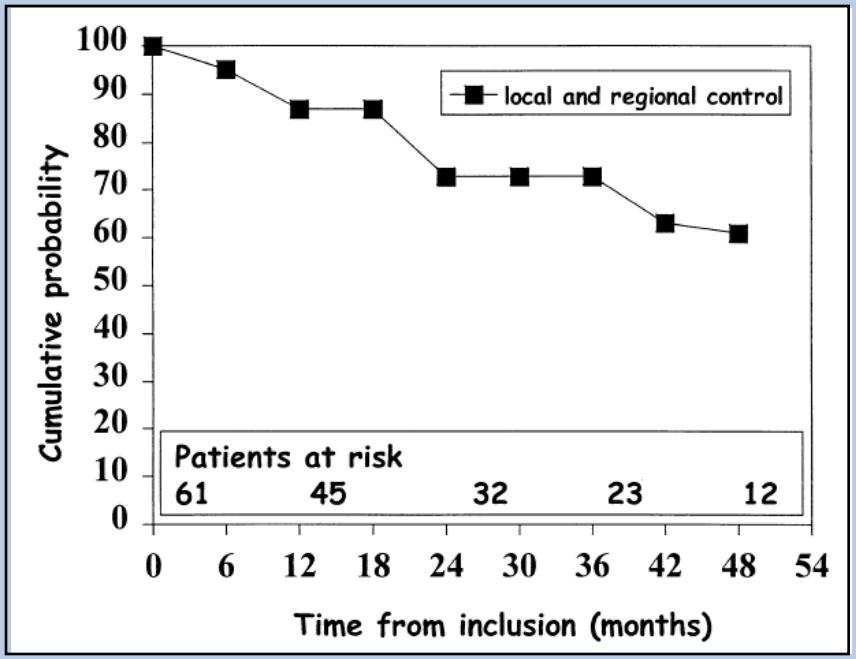
63 patients treated with CFRT : 70 Gy in 35 fractions and seven cycles of Docetaxel (20 mg/m² each week) during the period of radiotherapy

Table 2. Compliance with radiotherapy

Radiation parameter	RT + Docetaxel (n = 61)
Mean overall treatment time, days (range)	49.8 (1–77)
Treatment interruptions ≥3 days (%)	7 (11)
Mean duration of treatment break, days (range)	6.2 (3–17)
Radiotherapy stopped before completion, no (%)	2 (3%)
Mean value of maximal tumor dose, Gy (range)	71.3 (4–82)
Mean value of minimal tumor dose, Gy (range)	66.5 (4–74)

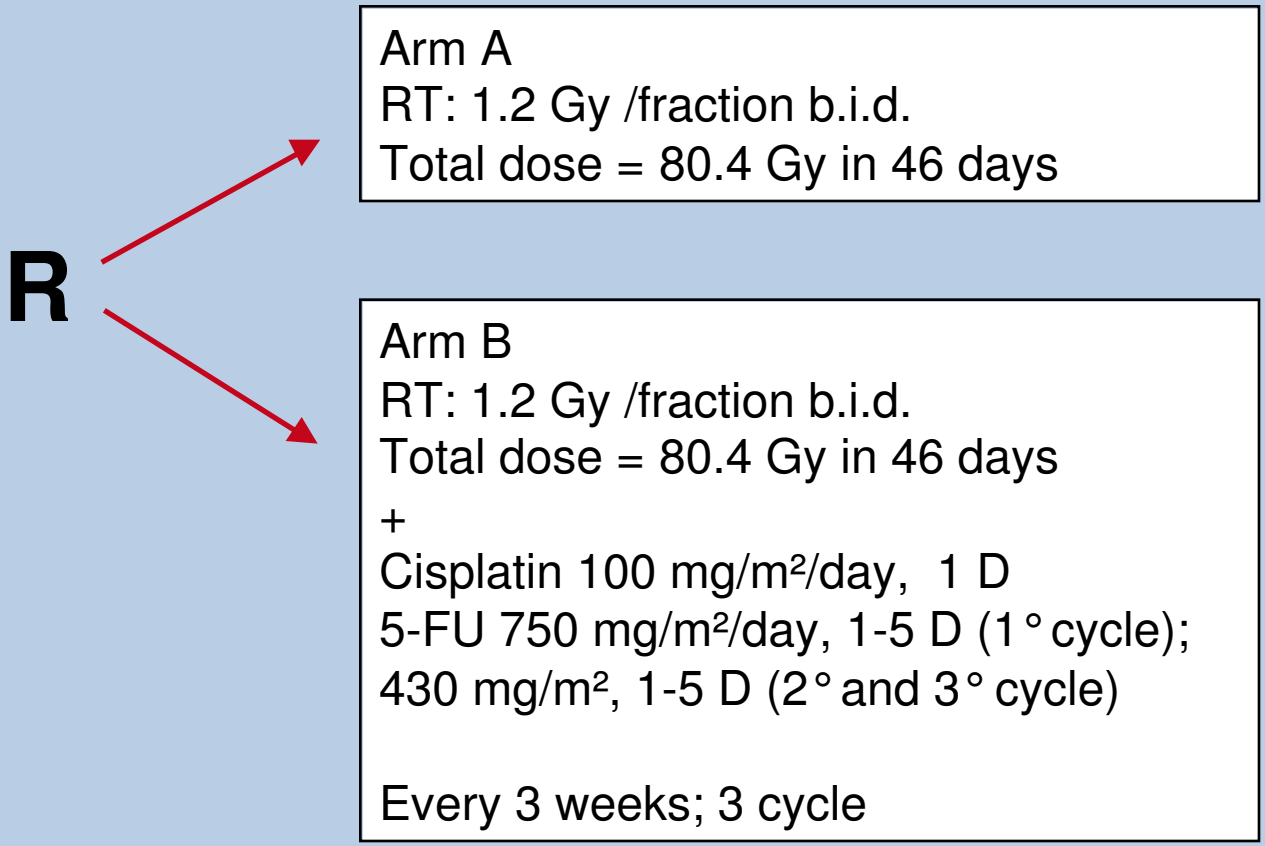
GORTEC 98-02 phase II trial





Calais G et al, 2004

FNCLCC-GORTEC French phase III trial in unresectable pharyngeal carcinoma

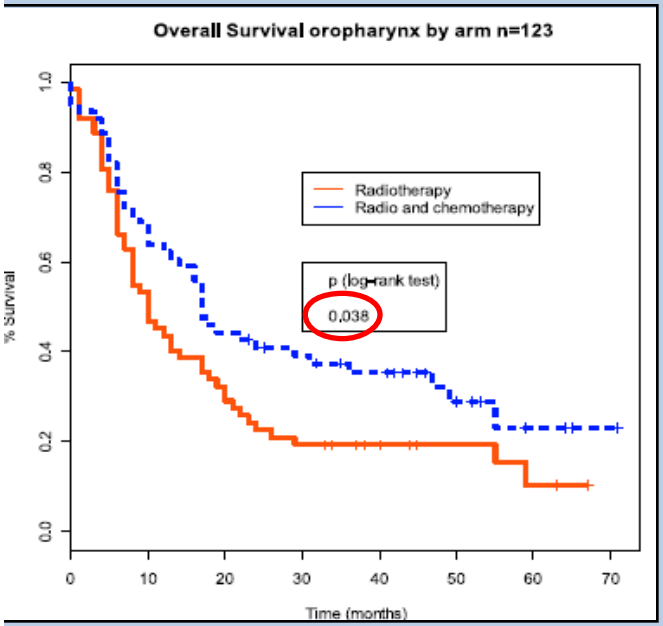


171 patients were enrolled (163 assessable at time of analysis: **123 with oropharynx** and 40 with hypopharynx cancer)

Bensadoun RJ et al, 2006

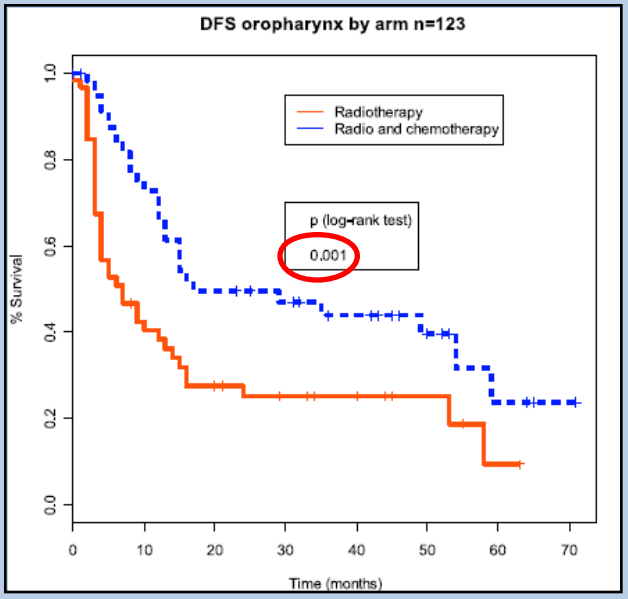
FNCLCC-GORTEC French phase III trial in unresectable pharyngeal carcinoma

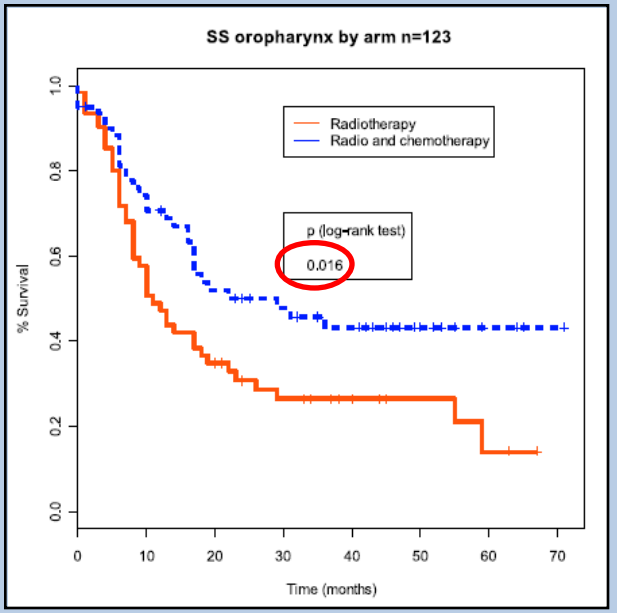
Results in **oropharynx** patients by arm



Overall Survival

DFS





Specific Survival

FNCLCC-GORTEC French phase III trial: toxicity

Acute

Table 3. Grade 3–4 acute toxic effects of treatment

Toxic effect	Arm A (n = 82)	Arm B (n = 81)	p
Mucositis			
Grade 3	52 (63.4%)	62 (76.5%)	NS
Grade 4	5 (6.1%)	5 (6.1%)	
Dermatitis			
Grade 3	22 (26.8%)	30 (37%)	NS
Grade 4	0	1 (1.2%)	
Nausea and diarrhea			
Grade 3	0	5 (6.2%)	NS
Grade 4	0	0	
Neutropenia			
Grade 3	2 (2.4%)	20 (24.7%)	<0.05
Grade 4	0	7 (8.6%)	
Early deaths	6 (7.3%)	11 (13.6%)	NS

Late

Table 4. Prevalence of gastrostomy tube in the two arms; before treatment; and 6, 12, and 18 months after primary treatment

	Arm A		Arm B		
	Patients alive (Number)	Gastrostomies (Number and percentage)	Patients alive (Number)	Gastrostomies (Number and percentage)	
Before treatment	82	38/82 (43.4%)	81	54/81 (66.7%)	p = 0.009
6 months	41	2/41 (4.9%)	49	10/49 (20.4%)	p = 0.003
12 months	26	1/26 (3.8%)	39	3/39 (7.7%)	p = 0.7 (NS)
24 months	15	0/15 (0%)	28	1/28 (3.6%)	p = 1 (NS)

ORO 93-01 multicentric phase III trial in 192 patients with locoregionally advanced carcinoma of the oropharynx. Long-term results

R

Arm A = CFRT (66-70 Gy in 33-35 fr)

Arm B = S-AHR (64-67.2 Gy with 2 daily fractions of 1.6 Gy each; 2 weeks split-course after 38.4 Gy)

Arm C = CRT (CFRT + CT with Carboplatin 75 mg/m², days 1-4; 5-FU 1000 mg/m² i.v. over 96 h, days 1-4; recycling every 28 days)

	A	B	C	Sign
5 y OS	21%	21%	40%	n.s.
5y RFS	15%	17%	36%	n.s.
5y LRCS	21%	18%	48%	P=0.07
DM	14	9	11	n.s.

Fallai C et al, 2006

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1. With better locoregional control, is there a role for the reintroduction of induction chemotherapy in an effort to decrease distant metastases?

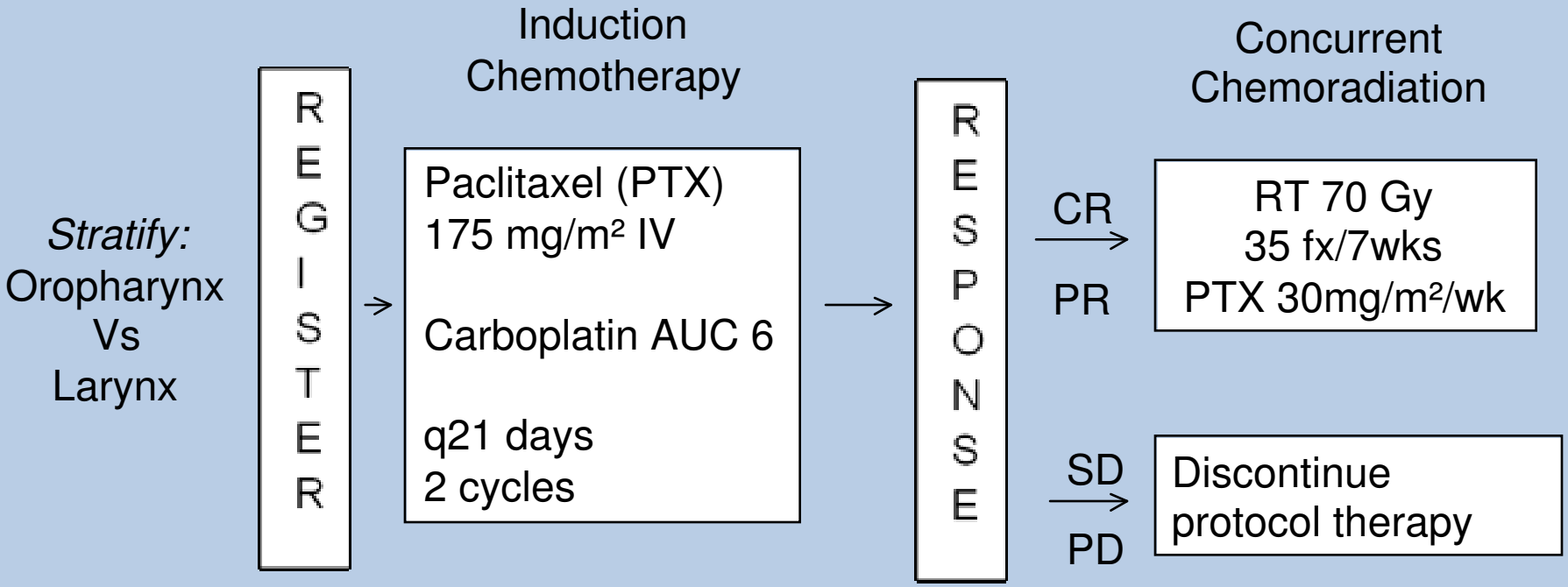
(Adelstein DJ, 2007)

Direct comparison: induction CT vs RT-CT concomitantly

	Nb of death/ Nb of pts included	HR (95% IC)	Interaction test
Locoregional control			
• CT-RT	4882/9615	0.74 (0.70-0.79)	p < 0.0001
• Induction CT	2189/5311	1.03 (0.95-1.13)	
Distant metastases			
• CT-RT	949/8612	0.88 (0.77-1.00)	p = 0.12
• Induction CT	444/3875	0.73 (0.61-0.88)	

Data from MACH-NC

Phase II Trial of Chemoradiation for Organ Preservation in Resectable Stage III or IV Squamous Cell Carcinomas of the Larynx or Oropharynx: Results of Eastern Cooperative Oncology Group Study E2399



Cmelak AJ, 2007

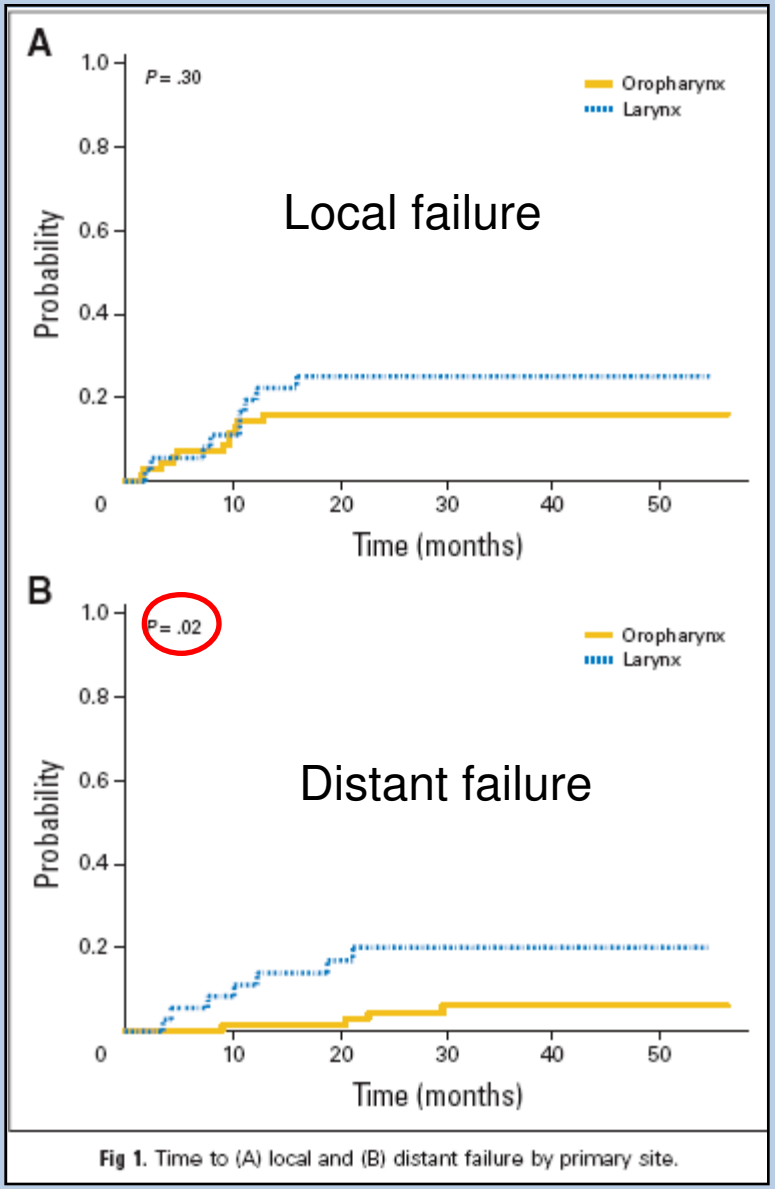


Fig 1. Time to (A) local and (B) distant failure by primary site.

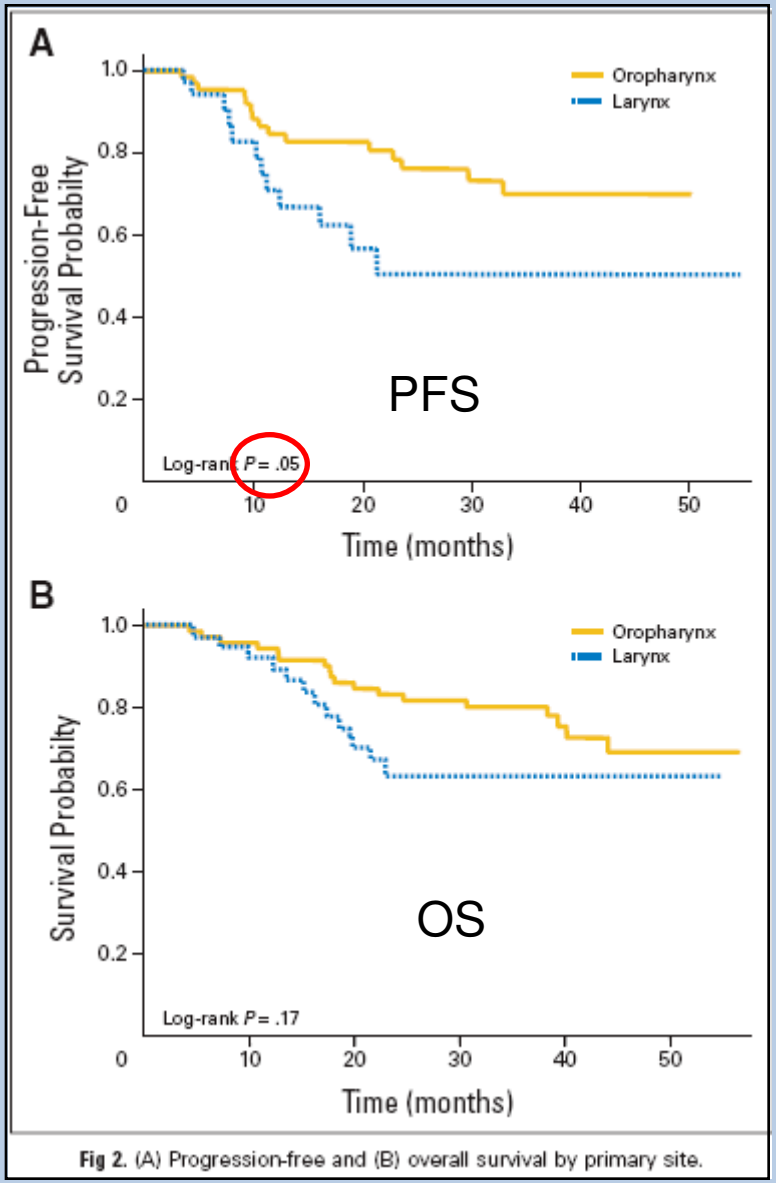


Fig 2. (A) Progression-free and (B) overall survival by primary site.

Cmelak AJ et al, 2007

Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN: Randomized Phase III trials

TRIAL	INCLUSION CRITERIA	N° CYCLES OF ICT	RADIOTHERAPY
EORTC 24971/TAX 323*	Unresectable stage III-IV	4	RT alone (CFRT or AFRT)
TAX 324**	Resectable or unresectable stage III-IV	3	CFRT + Carboplatin AUC 1.5 weekly

- TAX 323: median PFS 11 months in the TPF group and 8.2 months in the PF group (p=0.007); while median OS was 18.8 months vs 14,5 months (p=0.02)
- TAX 324: In the TPF group better survival (p= 0.006) and better LRC (p= 0.04) than PF group.
- More grade 3 or 4 events of leukopenia and neutropenia in the TPF group

** Vermorken JB et al, 2007; ** Posner MR et al, 2007*

Docetaxel-cisplatin based induction chemotherapy (ICT) in locally advanced head and neck cancer (LAHNC): A meta-analysis of randomized controlled trials (RCTs) using indirect comparisons

	Overall survival RR [95% CI]	Progression-free survival RR [95% CI]
Docetaxel-based ICT (TPF,TP) *Vs* PF ICT	0.79 [0.69;0.91] k=4 n=1154	0.72 [0.61;0.84] k=2 n=859
TPF ICT *Vs* PF ICT	0.78 [0.68;0.90] k=3 n=1072	0.72 [0.61;0.84] k=2 n=859
PF ICT *Vs* no ICT	0.89 [0.82;0.97] k=15 n=2785	0.91 [0.82;1.00] k=3 n=857
Extrapolated docetaxel-based ICT *Vs* no ICT	0.70 [0.60;0.83]	0.66 [0.54;0.79]
Extrapolated TPF *Vs* no ICT	0.69 [0.59;0.82]	0.66 [0.54;0.79]

Hitt R et al, 2008

2. Can we identify those patients most likely to benefit from this treatment approach?

(Adelstein DJ, 2007)

ECOG 2399: efficacy by HPV status

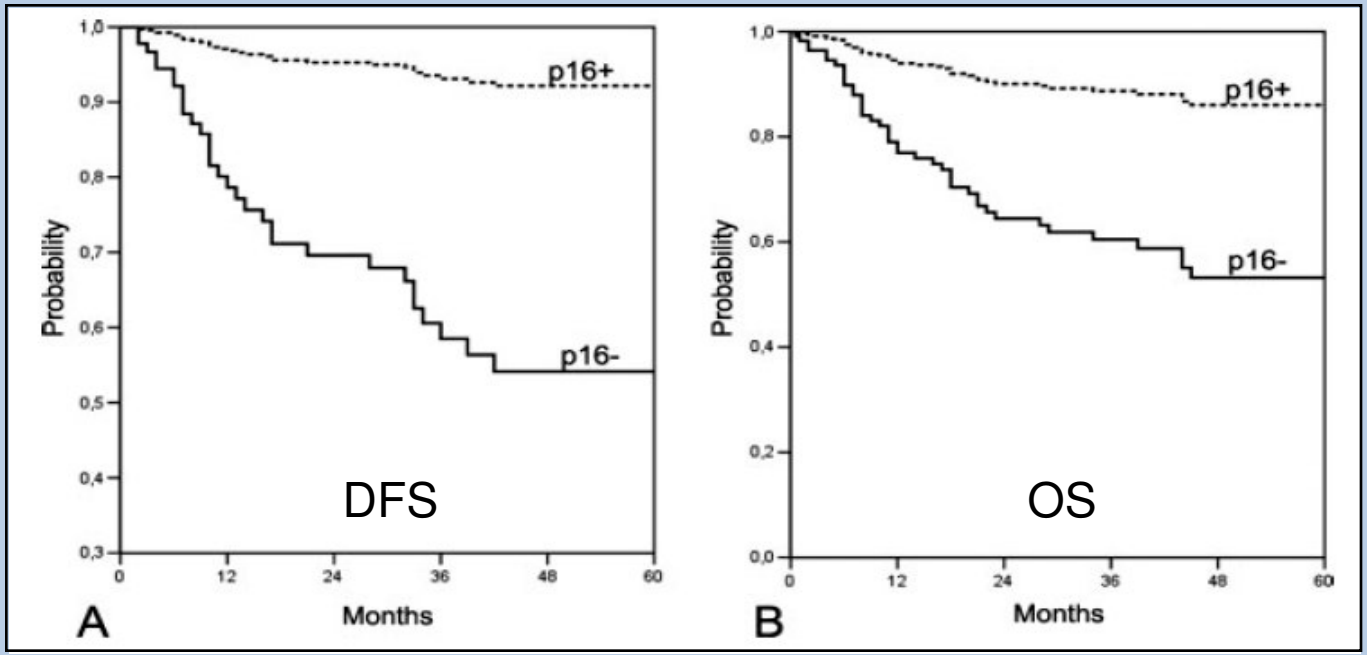
	HPV+	HPV-	P value
Response - induction - protocol	 82% 84%	 55% 57%	 .01 .007
2-Years PFS	86%	53%	.02
2-Years OS	95%	62%	.005

Response rates in HPV cases: 58% vs 52% during induction and 54% vs 59% final for oropharynx and larynx respectively

Combined analysis of HPV-DNA, p16, and EGFR expression to predict prognosis in oropharyngeal cancer

Conclusions:

- p16 expression is highly correlated with the presence of HPV-DNA
- Univariate analysis revealed a significant better outcome for patients with p16-positive and EGFR-negative tumors
- In multivariate analysis p16 remained a highly significant prognostic marker for DFS and OS



Reimers N et al, 2007

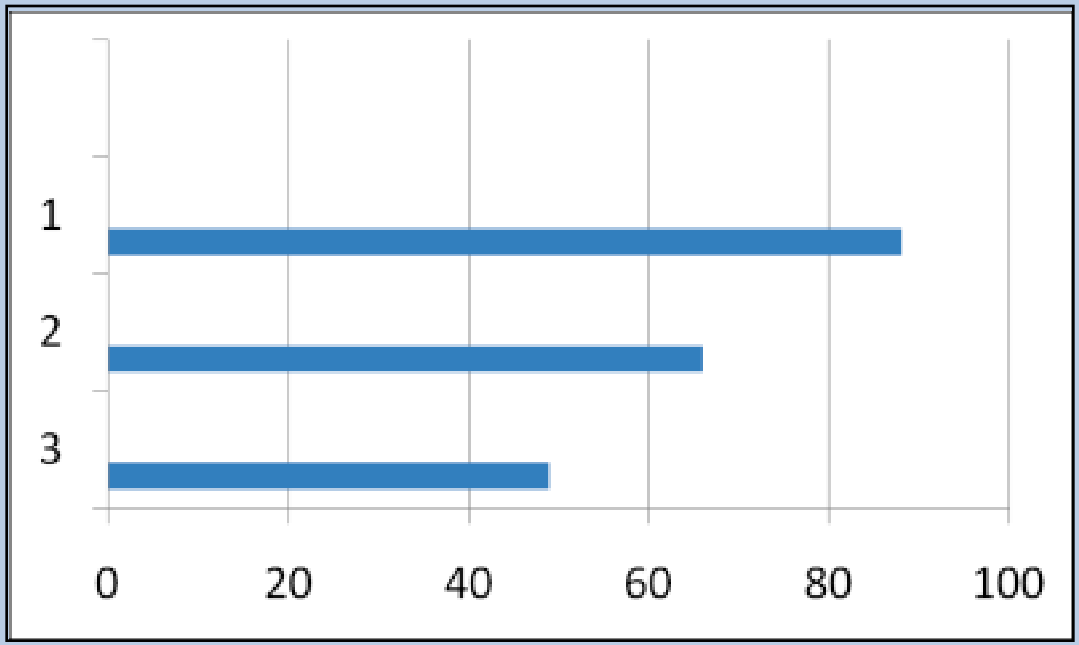
3. Is single-agent cisplatin the optimal concurrent chemotherapy regimen?

(Adelstein DJ, 2007)

Cisplatin 100 mg/m^2 every 3 weeks is the more largely used scheme in phase III trials, but the compliance of this schedule is low and there are a few trials comparing different CT schedules.

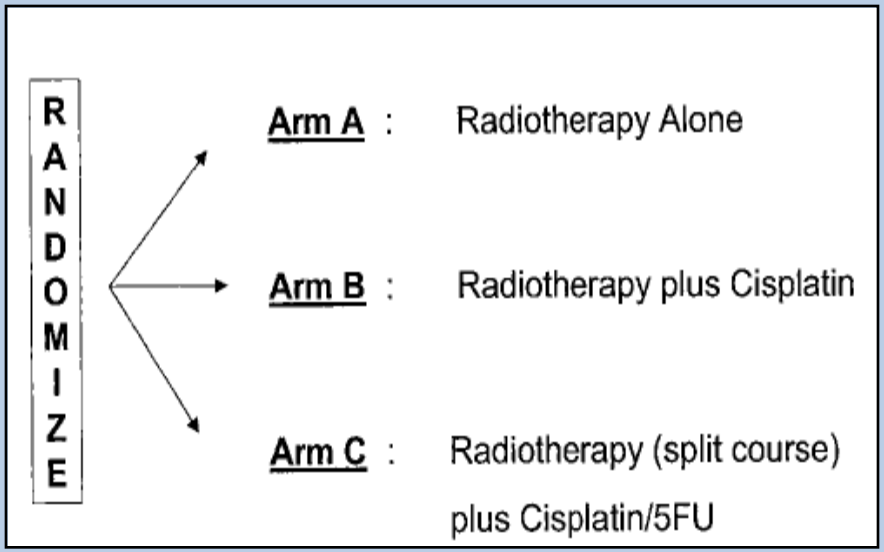
CRT compromised adherence to CT

The number of patients receiving cisplatin on time without delay decreased over time



Bernier J et al, 2004

Intergroup phase III trial in unresectable HNSCC



Major end-point = OS

Table 2. Clinical Characteristics

	Arm		
	A (n = 95)	B (n = 87)	C (n = 89)
Age (years)			
Mean (range)	56.7 (33-38)	56.8 (25-80)	57.8 (27-78)
Sex			
Male	86 (90.5%)	76 (87.4%)	76 (85.4%)
Female	9 (9.5%)	11 (12.6%)	13 (14.6%)
Race			
White	61 (64.2%)	53 (60.9%)	55 (61.8%)
African American	24 (25.3%)	28 (32.2%)	26 (29.2%)
Other	10 (10.5%)	6 (6.9%)	8 (9.0%)
Performance status			
0	32 (33.7%)	27 (31.0%)	32 (36.0%)
1	63 (66.3%)	60 (69.0%)	57 (64.0%)
Primary tumor site			
Oral cavity	16 (16.8%)	11 (12.7%)	9 (10.2%)
Oropharynx	52 (54.7%)	52 (59.8%)	56 (62.9%)
Hypopharynx	19 (20.0%)	17 (19.5%)	14 (15.7%)
Larynx	8 (8.5%)	7 (8.0%)	10 (11.2%)

Adelstein DJ et al, 2003

Intergroup phase III trial in unresectable HNSCC

RESULTS

	CR	Sign	3y OS	Sign	DFS	Sign
A	27.4%		23%		33%	
B	40.2%	B*v*A: p=0.07	37%	B*v*A: p=0.014	51%	B*v*A: P=0.01
C	49.4%	C*v*A: p=0.002	27%	C*v*A and C*v*B: n.s.	41%	C*v*A and C*v*B:n.s.

Nausea and vomiting were significantly worse for patients enrolled on arm B, the high-dose cisplatin arm.

When all grade 3, 4, and 5 toxicities are combined, arm B seemed most toxic.

4. How do we integrate targeted therapies into these concurrent chemoradiotherapy programs?

Adelstein DJ, 2007

Radiotherapy only vs radiotherapy + cetuximab in 424 patients with stage III-IV H&N cancer (oropharynx = 253/ 424 patients)

	RT only Median duration (mo)	RT+ cetuximab Median duration (mo)	Sign
LRC	14.9	24.4	P=0.005
LRC (oropharynx)	23	49	
PFS	12.4	17.1	P=0.006
OS	29.3	49	P=0.03
OS (oropharynx)	30.3	>66	

Bonner JA et al, 2006

RTOG phase III 0522 trial

Stage III-IV SCC of:
- Oropharynx
- Hypopharynx
- Larynx

Statify:
- Larynx vs others
- N0-N1, 2a,2b vs N2c-3
- 3-D vs IMRT
- Pre-Rx PET (yes vs no)

RANDOMIZE

→ Accelerated Fx + CDDP 100 mg/m^2 , q3wx2

→ Accelerated Fx + CDDP 100 mg/m^2, q3wx2
Cetuximab 400mg/m^2 pre-RT; then 250 mg/m^2/wx7

CERCEFA phase II Italian trial

Major end-points: LRC and toxicity

Inclusion criteria: resectable and unresectable stage III and IV oral cavity, oropharynx, hypopharynx, larynx and nasopharynx carcinomas

Design:

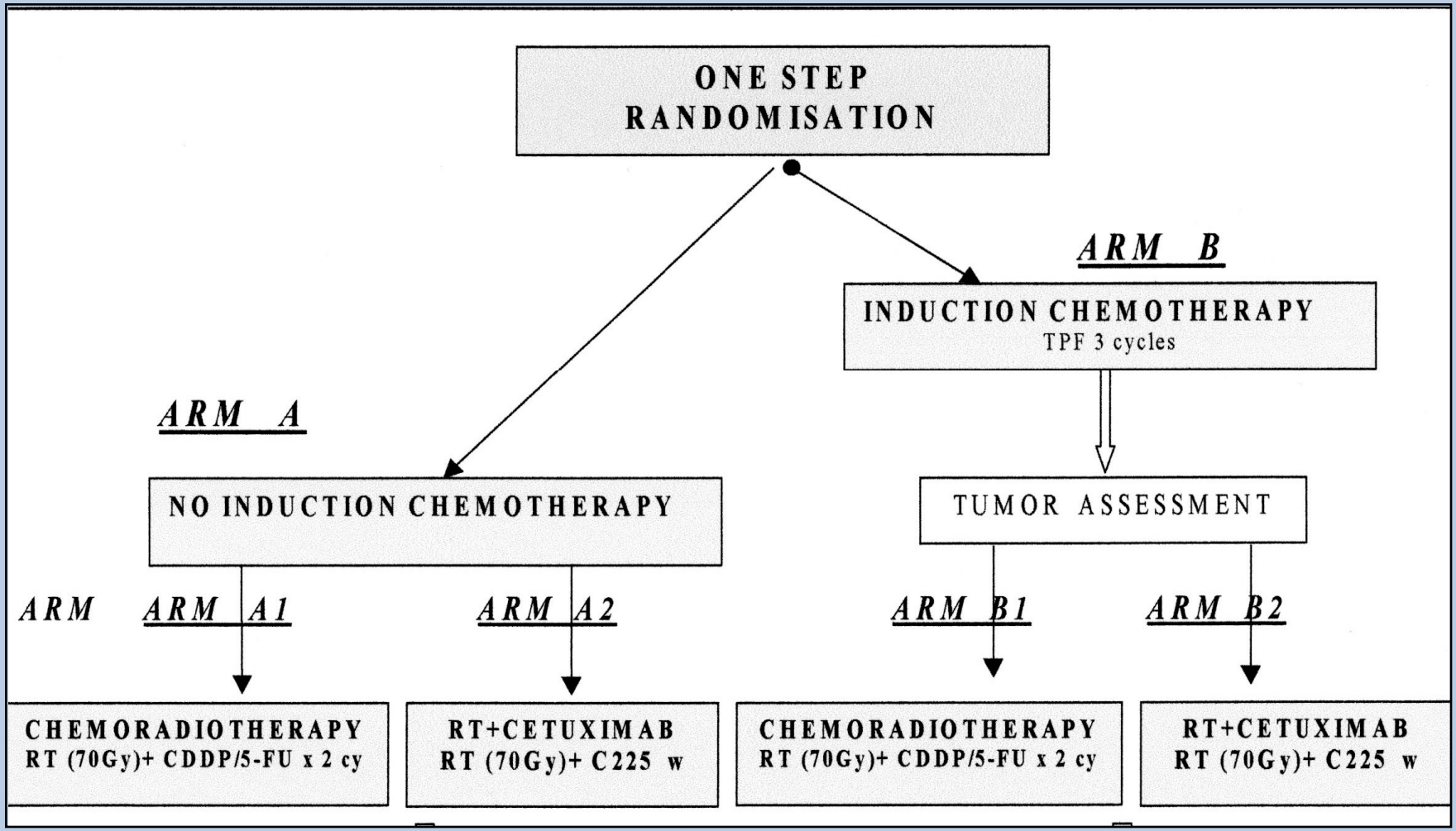
TPF: Docetaxel 75 mg/m² D1; Cisplatin 25 mg/m² D1-3; 5 FU 250 mg/m² D 1-3 q3w x2

↓

CETUXIMAB 400 mg/m² 1st week; from 2nd week 250 mg/m² weekly concomitant to RADIOTHERAPY (70-72 Gy/35-36 fx)

Coordinator: U. Ricardi (Torino)

GSTTC Italian phase III trial



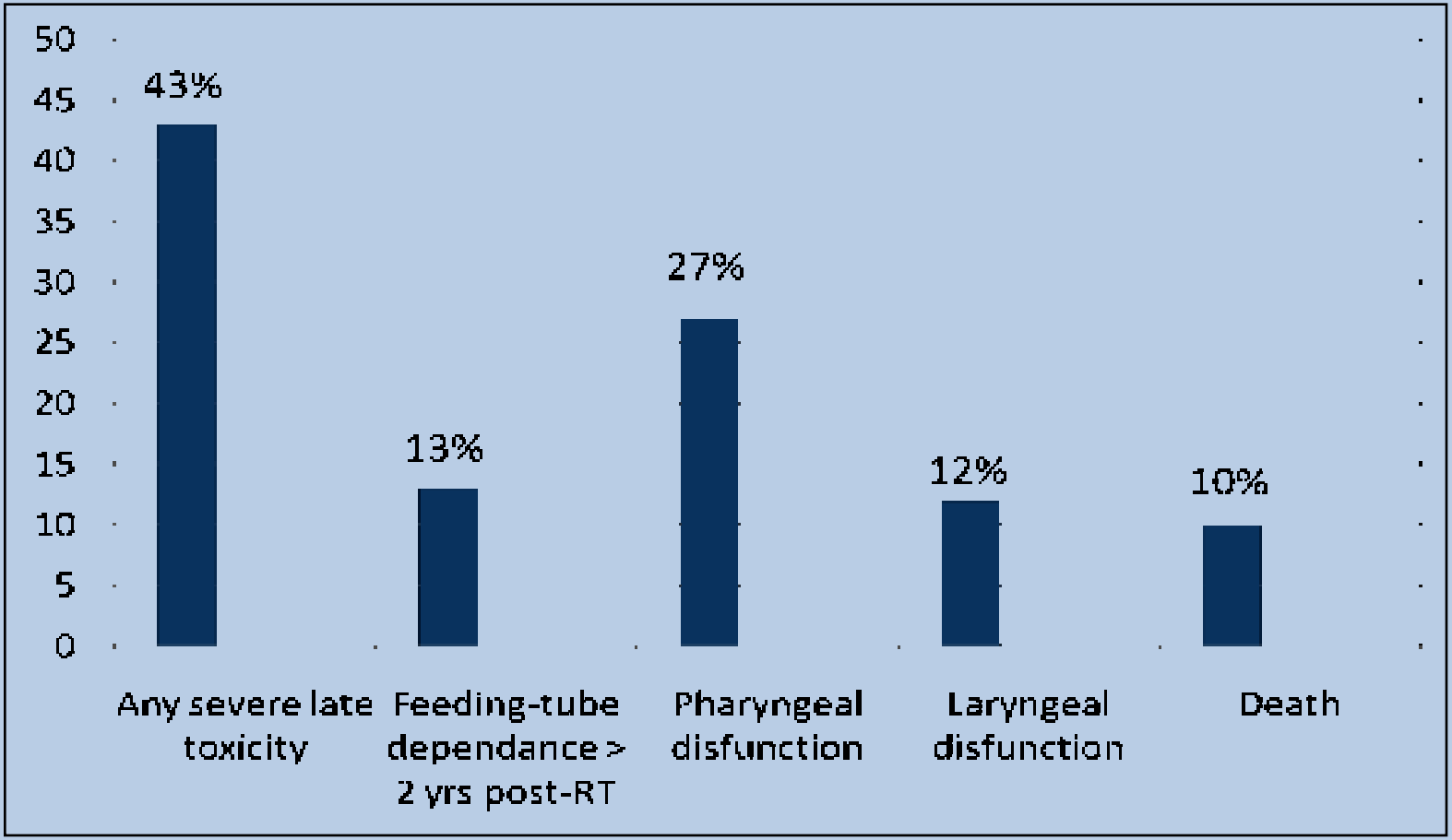
Coordinator: A. Paccagnella

5. How can we reduce and manage both the acute and the consequential late toxicities of concurrent chemoradiotherapy?

(Adelstein DJ, 2007)

- Knowledge of incidence of acute and late toxicity
- Knowledge of variables involved in incidence of toxicity
- Optimization of radiotherapy (IMRT?)
- Optimization of chemotherapy

Analysis of 230 patients receving CRT in 3 studies (RTOG 91-11, 97-03,99-14)



Macthay M et al, 2008

Table 3
Univariate and multivariate logistic regression analyses with grade 2–4 RTOG swallowing dysfunction at 6 months as primary endpoint.

Variable	Number with grade 2 4 RTOG swallowing	%	Univariate analysis		
			Odds ratio	(95% CI)	*P*-value
Sex					
Male	83	20.9%	1.00		
Female	39	29.8%	1.61	(1.03–2.51)	$p = 0.037$
Age					
>60 years	54	18.8%	1.00		
18–60 years	68	28.2%	1.70	(1.13–2.56)	$p = 0.010$
T-classification					
T0, Tis-T2	51	14.3%	1.00		
T3–T4	71	41.0%	4.16	(2.73–6.36)	$p < 0.001$
N-classification					
N0	48	14.4%	1.00		
N1–N2b	44	32.1%	2.81	(1.75–4.50)	$p < 0.001$
N2c–N3	30	50.8%	6.14	(3.39–11.1)	$p < 0.001$
Primary site					
Larynx	27	11.4%	1.00		
Oral cavity	16	17.8%	1.67	(0.85–3.28)	$p = 0.134$
Oropharynx	52	40.0%	5.16	(3.02–8.79)	$p < 0.001$
Nasopharynx	10	50.0%	7.74	(2.95–20.3)	$p < 0.001$
Hypopharynx	9	31.0%	3.48	(1.44–8.42)	$p = 0.006$
Unknown primary	8	33.3%	3.87	(1.51–9.89)	$p = 0.005$
Treatment modality					
Postoperative radiotherapy	29	20.7%	1.00		
Radiotherapy conventional fractionation	14	9.8%	0.42	(0.21–0.83)	$p = 0.012$
Accelerated radiotherapy	49	25.5%	1.31	(0.78–2.21)	$p = 0.308$
Concomitant chemoradiation	30	55.6%	4.78	(2.44–9.39)	$p < 0.001$
Radiation technique					
Conventional 3D-CRT	86	19.5%	1.00		
Bellinzona technique	19	55.9%	5.23	(2.55–10.7)	$p < 0.001$
IMRT	17	31.5%	1.90	(1.02–3.53)	$p = 0.043$
Neck irradiation					
Local or unilateral irradiation	9	4.7%	1.00		
Bilateral irradiation	113	33.3%	10.01	(4.96–20.4)	$p < 0.001$
Baseline swallowing (grading according to RTOG)					
Grade 0	100	21.2%	1.00		
Grade 1	22	38.6%	2.34	(1.31–4.16)	$p = 0.004$
Weight loss (baseline)					
No weight loss	65	16.3%	1.00		
1–5%	28	38.9%	3.28	(1.91–5.65)	$p < 0.001$
6–10%	18	48.6%	4.88	(2.43–9.81)	$p < 0.001$
>10%	11	55.0%	6.30	(2.51–15.8)	$p < 0.001$

Univariate analysis

Macthay M et al, 2008

Table 4. Univariate and Multivariable Logistic Regression Models to Identify Covariates that are Associated With Severe Late Toxicity

Covariate	Univariate Analysis		Multivariate Analysis		
	Odds Ratio	*P*	Odds Ratio	95% CI	*P*
Age					
Continuous variable	1.043*	.0038	1.05*	1.02 to 1.09	.001
Sex					
Female	RL				
Male	1.140	.6846			
Race					
Nonblack	RL				
Black	1.165	.7458			
KPS					
60-80	1.892	.0612			
90-100	RL				
Hemoglobin, g/dL					
Continuous variable	1.005	.9528			
Weight loss, kg					
Continuous variable	1.018	.3733			
T stage					
T1/T2	RL		RL		
T3/T4	2.041	.0349	3.07	1.444 to 6.54	.0036
N stage					
NX/N0/N1	RL				
N2	0.942	.8464			
N3	1.297	.6108			
Tumor site					
Oral cavity/oropharynx	RL		RL		
Larynx/hypopharynx	2.955	.0131	4.17	1.57 to 11.03	.0041
BED (toxicities) based on actual dose/Fx, Gy					
Continuous variable	0.842	< .0001			
Neck dissection after RT†					
Yes	1.632	.145	2.39	1.16 to 4.92	.018
No	RL		RL		
Chemotherapy received relative to the protocol amount, %					
< 85	1.033	.9216			
≥ 85	RL				

Abbreviations: KPS, Karnofsky performance status; RL, reference level; BED, biologically equivalent dose; Fx, fraction; RT, radiation therapy.

*The odds ratio of 1.043 for age indicates that for each one year increase in age, patients have 1.043 times higher odds of being in the case group (having a severe late toxicity) than being in the control group (not having a severe late toxicity).

†This excludes two patients who had neck dissection after having already experiencing a severe late toxicity.

Macthay M et al, 2008

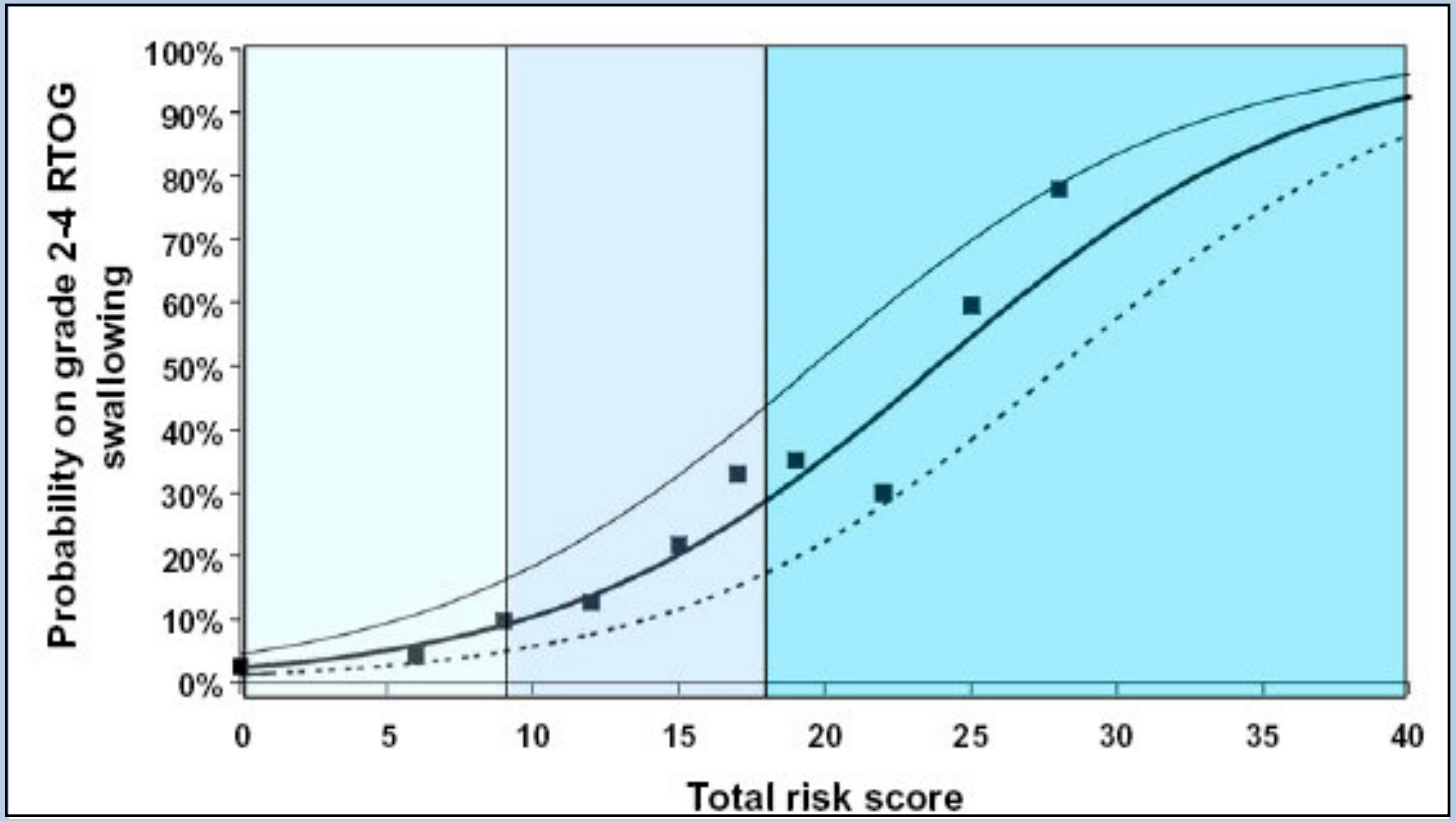
Predictive model for swallowing disfunction

Multivariate logistic regression analysis with grade 2–4 RTOG swallowing dysfunction at 6 months as primary endpoint.

Variable	*B*	SE(B)	OR	95% CI (OR)	*P*-value	Risk points
T-classification						
T1–T2			1.00			0
T3–T4	0.868	0.288	2.38	(1.36–4.19)	$p = 0.003$	4
Neck irradiation						
Primary alone ± ipsilateral neck			1.00			0
Primary + both necks	1.715	0.404	5.55	(2.52–12.2)	$p < 0.001$	9
Weight loss (baseline)						
No weight loss			1.00			0
1–5%	0.981	0.324	2.67	(1.41–5.03)	$p = 0.002$	5
6–10%	1.053	0.417	2.87	(1.27–6.49)	$p = 0.012$	5
>10%	1.324	0.545	3.76	(1.29–10.9)	$p = 0.015$	7
Primary tumour site						
Larynx			1.00			0
Oropharynx	1.376	0.340	3.96	(2.03–7.70)	$p < 0.001$	7
Nasopharynx	1.816	0.498	6.15	(1.89–20.0)	$p = 0.003$	9
Treatment modality						
Conventional radiotherapy			1.00			0
Accelerated radiotherapy	1.170	0.371	3.22	(1.56–6.67)	$p = 0.002$	6
Concomitant chemoradiation	0.975	0.415	2.65	(1.17–5.98)	$p = 0.019$	5

Langendijk JA et al, 2009

Predictive model for swallowing disfunction



Langendijk JA et al, 2009

Conclusions

- Platinum based CRT is the standard treatment of advanced H&N cancer and also in organ preservation strategy
- Concurrent CRT did not show any benefit in terms of survival in patients > 70y
- Concurrent AFRT+CT seems not to produce any advantage compared to CFRT+CT, but further investigations are needed
- Although concurrent CRT significantly improves LC, DFS and OS, the incidence of distant metastases remains disappointing
- There are ongoing trials focusing on the role of cetuximab and RT, and on the role of induction CT
- Patients selection, development of new technologies, and multidisciplinary approach aim at reducing severe acute and late toxicity