Oropharyngeal carcinoma
State of the Art

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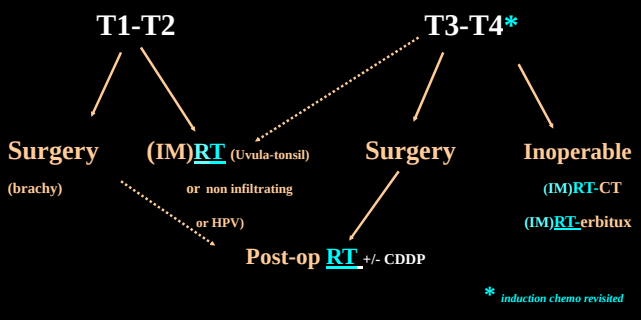
- Among HNSCC what are the specificities of the oropharyngeal sub site ?

- **Frequent among HNSCC**
- **More HPV related carcinomas** *(up to 50-75%)*
- **Importance of IMRT for parotid sparing**

- Are the results obtained in the orophaynx different from the rest of HNSCC ?

- Relative consensus on « general treatment guidelines »

Multidisciplinary approach in oropharynx carcinomas



How different are the oropharyngeal carcinomas as compared to the other HNSCC ?

How different are the oropharyngeal carcinomas as compared to the other HNSCC ?

For altered fractionation …

Is the effect of altered fractionated RT any different in oropharynx sub site ?

MARCH database of randomized trials (1970-1999)

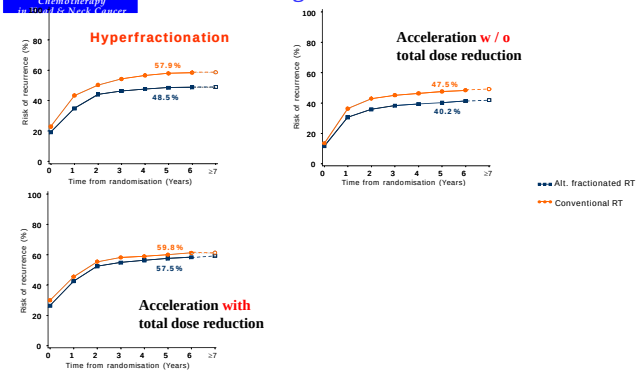
Hyperfractionated or accelerated RT

Conventional RT

Overall results (all sites)

Loco regional control

Meta-Analysis of Chemotherapy in Head & Neck Cancer

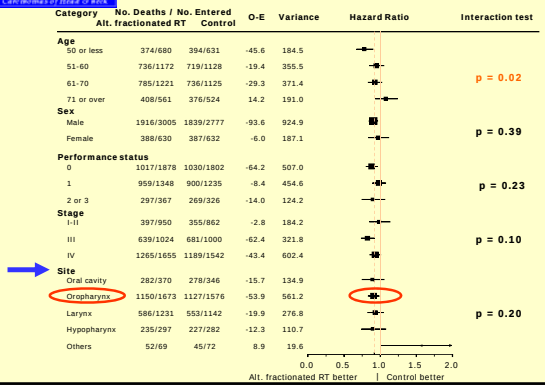


Altered fractionated RT database

(N > 6500 patients randomized)

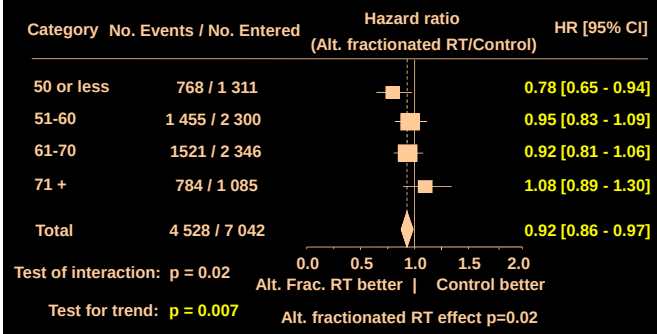
Characteristics	Altered fractionated RT (n=3,650)	Conventional RT (n=3,423)
Site of tumour		
- Oral cavity	13%	13%
- Oropharynx	44%	44%
- Larynx	34%	33%
- Hypopharynx	8%	8%
- Others	2%	2%
Stage		
- I	9%	9%
- II	18%	16%
- III	28%	29%
- IV	46%	45%

Altered fractionated *versus* conventional RT : survival by site



MARCH:

Overall survival by age (incl. oropharynx)



How different are the oropharyngeal carcinomas as compared to the other HNSCC ?

For Chemo-RT …

A few pure oropharynx randomized trials …

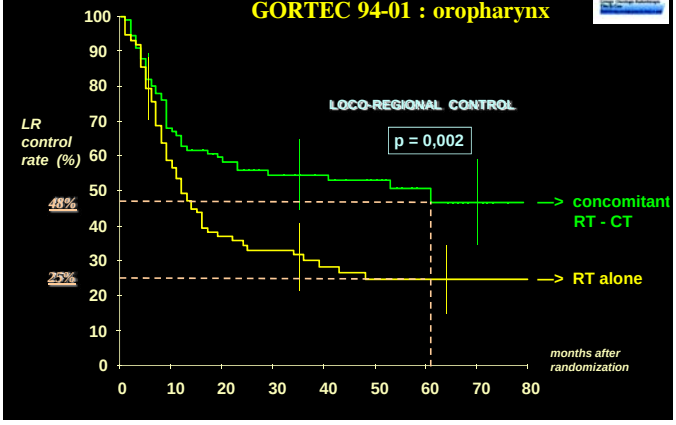
Example of specific trial : RT-CT 94-01 trial

N = 226
T3-T4
oropharynx
Non operated

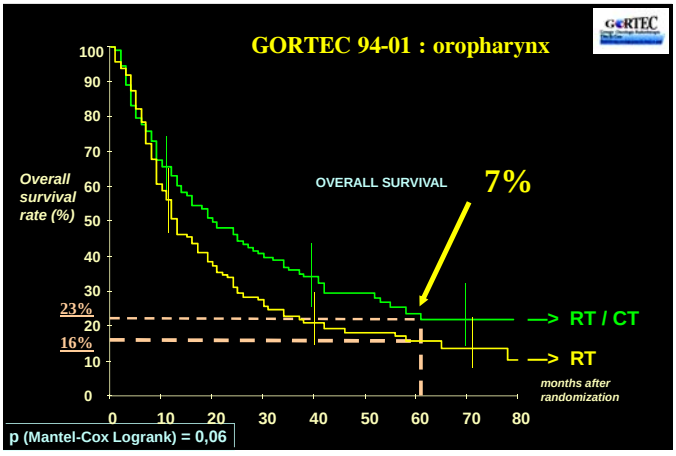
→ 70 Gy / 7 weeks

→ 70 Gy / 7 weeks + Carbo-5FU

GORTEC 94-01 : oropharynx



GORTEC 94-01 : oropharynx



Concomitant chemo : the price to pay ?

GORTEC 94-01 : oropharynx : Acute toxicity

	RT	RT+CT	*P* value
Mucositis			
Patchy	32	57	.005
Confluent	7	14	
Skin			
Erythema . Dry desquamation	47	44	.02
Moist desquamation	12	23	
Nutritional status			
Weight loss >10% of body mass	6	14	.04
Feeding tube	15	36	.02
Haematology			
Neutrophils < 0.9	0	4	.04
Platelets < 50	1	6	.04
Hemoglobin < 8 g/100mL	0	3	.05
Toxic death	0	1	

GORTEC 94-01 : oropharynx : Late toxicity

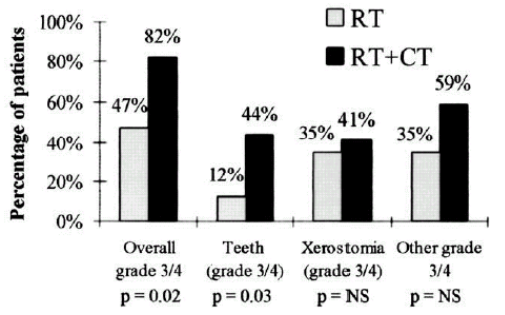


Fig. 4. Five-year rate of Grade 3–4 late toxicity for combined modality treatment (27 patients, RT+CT) vs. RT alone (17 patients, RT) assessed using three late toxicity scales simultaneously.

Is the effect of adding chemotherapy to RT any different in oropharynx sub site ?

MACH-NC database of randomized trials (1965-2000)

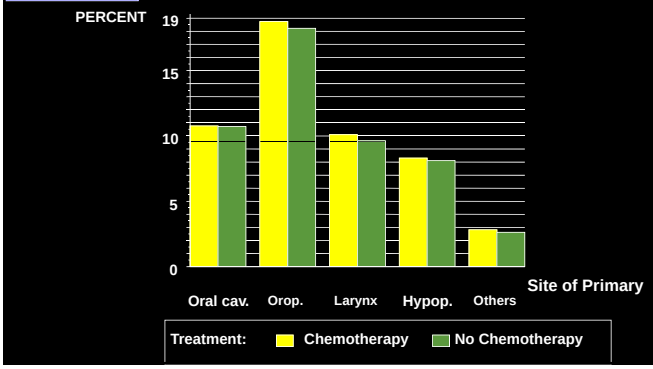
RT-CT

RT

MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Chemotherapy data base (N=9615 pts randomized)

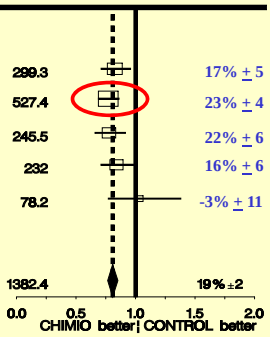


MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Effect of concomitant CT-RT *versus* RT *(survival by site)*

Category	No. Events/ No. Entered CHIMIO	CONTROL	O−E	Variance	Relative Risk Risk Redn. (CHIMIO:CONTROL) (±SD)
Oral Cavity	633/906	673/912	−57.3	299.3	17% ± 5
Oropharynx	1058/1596	1151/1551	−137.3	527.4	23% ± 4
Larynx	516/859	532/817	−61.9	245.5	22% ± 6
Hypopharynx	502/706	509/689	−40.4	232	16% ± 6
Others	179/240	161/215	2.4	78.2	-3% ± 11
Total	2888/4307	3026/4184	−294.5	1382.4	19% ±2



Test for interaction: X^2_4 = 6.72 2P = 0.15

CHIMIO effect 2P < 0.0001

MACH-NC
Meta-Analysis of Chemotherapy in Head & Neck Cancer

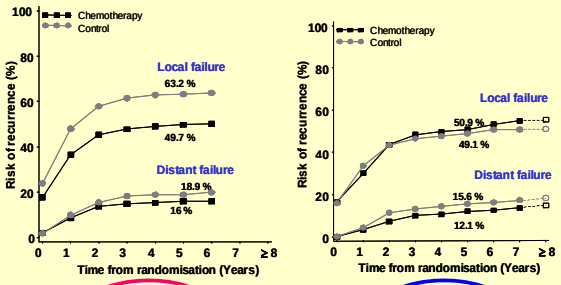
Chemotherapy is more beneficial in younger patients (N = 9615 pts randomized)

Age	Absolute survival benefit at 5 years	
< 50	12%	
51-60	9%	p< 0.001
61-70	4%	
> 71	1.5%	

IGR, June 2004

MACH-NC
Meta-Analysis of Chemotherapy in Head & Neck Cancer

Platin-5FU : concomitant *versus* induction

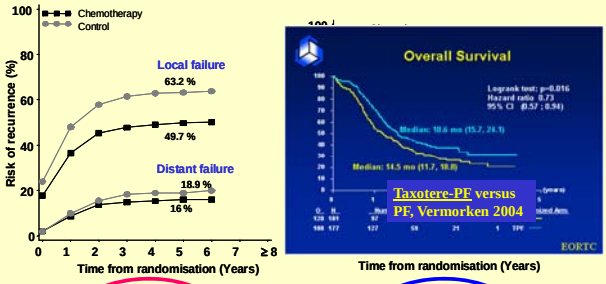


Concomitant
Absolute difference at 5 years:
Local failure: -13.5 ± 2.8 %
Distant failure: -2.9 ± 2.7%

Neoadjuvant
Absolute difference at 5 years:
Local failure: 1.8 ± 2.3 %
Distant failure: -3.5 ± 2.0 %

MACH-NC
Meta-Analysis of Chemotherapy in Head & Neck Cancer

Concomitant PF > induction PF ; but TPF > PF



Concomitant
Absolute difference at 5 years:
Local failure: -13.5 ± 2.8 %
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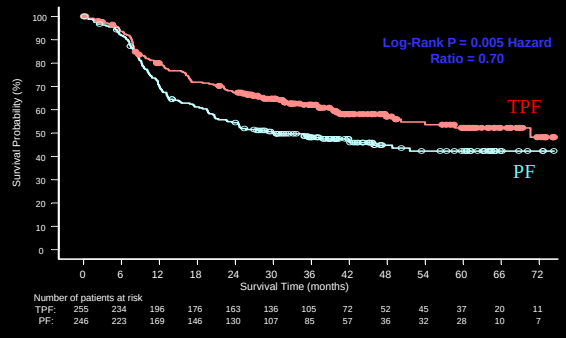
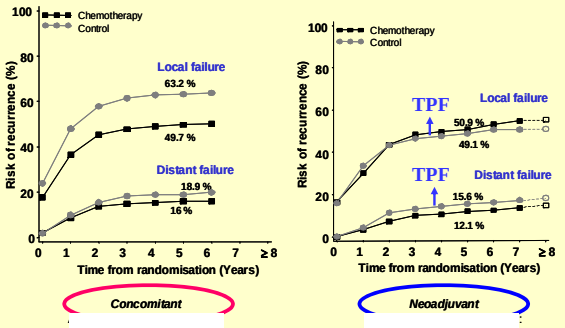
Neoadjuvant
Absolute difference at 5 years:
Local failure: 1.8 ± 2.3 %
Distant failure: -3.5 ± 2.0 %

TAX324 : Survival



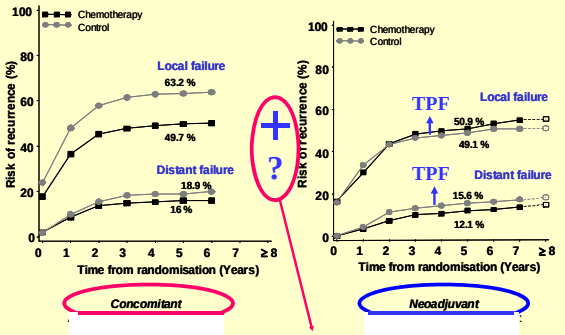
Posner M, et al. N Engl J Med 2007;357:21-31.

MACH-NC — TPF : a new standard for induction CT in HNSCC



With no significant difference in toxicity …

MACH-NC — Combining TPF induction + concomitant…?



Efficacy ? / toxicity ?…

How different are the oropharyngeal carcinomas as compared to the other HNSCC ?

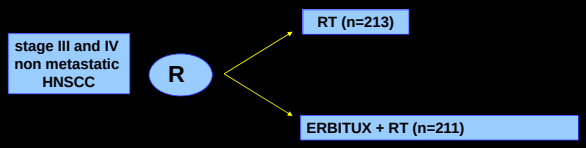
For erbitux …

Erbitux + Radiotherapy : a good ratio efficacy / toxicity

in locally advanced HNSCC …

ERBITUX + RT in locally advanced HNSCC : a phase III randomized study

(the most important sub site was oropharyngeal cancer)

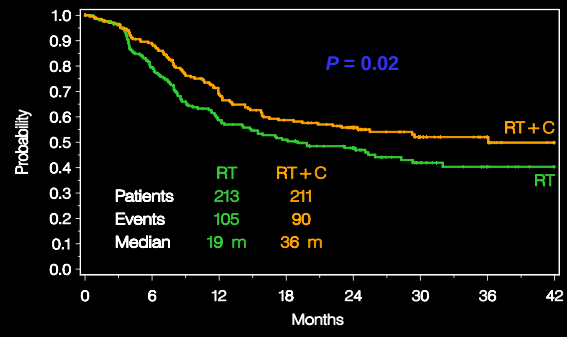


- **Primary endpoint: Locoregional control**

Bonner J, et al. N Eng J Med 2006;354:567–578

RT + cetuximab : local-regional control

(more effect was seen in oropharynx…(subgroup ?)



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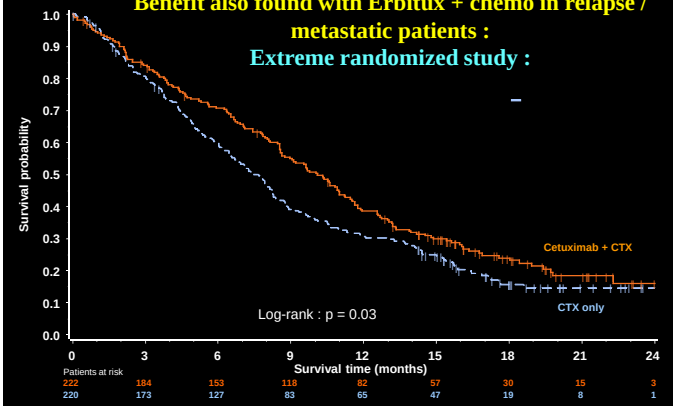
Benefit also found with Erbitux + chemo in relapse / metastatic patients :

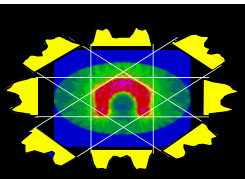
Extreme randomized study :



Vermorken JB, et al. ASCO 2007 (Abstract No. 6091; updated information presented)

Oropharyngeal carcinomas :

Importance of IMRT …



IMRT, intensity modulated RT

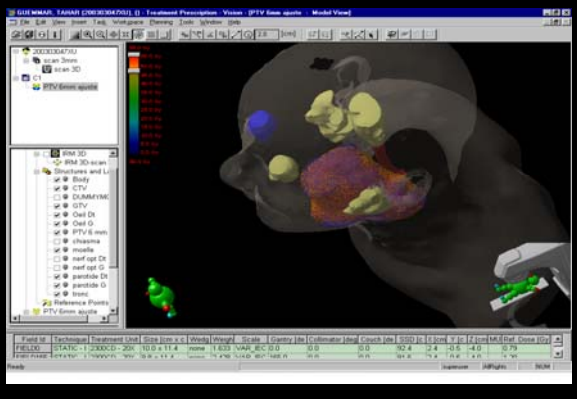
IMRT in Oropharyngeal carcinoma

1) **Better normal tissue protection (parotid)**

2) **Dose escalation to the tumor**

Potentially Interesting since **:**
- **Most relapses in the GTV**
- **Dose effect relationship**

IMRT : increased dose conformality ⟶ clinical benefit ?



IMRT in oropharynx carcinomas : carcinological results

Table 1. Locoregional Control After IMRT for Head and Neck Cancer

Study	No. of Patients	Primary Site	RT		Follow-Up (months)		Control		
			Definitive	Postoperative	Median	Range	Local (%)	Regional (%)	Interval (years)
Chao et al[10]	126	Various	52	74	26	12-66	86		2
Lee et al[5]	67	NPX	67	0	31	7-72	98		4
Chao et al[20]	74	OPX	31	43	33	9-100	87		4
Eisbruch et al*[21]	133	Various, non NPX	60	73	22	6-107	92		3
Kam et al[83]	63	NPX	63	0	29	8-45	92	98	3
Kwong et al[84]	33	NPX	33	0	29	11-42	100	92	3

Abbreviations: IMRT, intensity-modulated radiotherapy; RT, radiotherapy; NPX, nasopharynx; OPX, oropharynx.
*Patients treated from 1994 to 2002; three-dimensional conformal radiotherapy was used before 1996, and IMRT thereafter.

Mendenhall W. JCO 2006

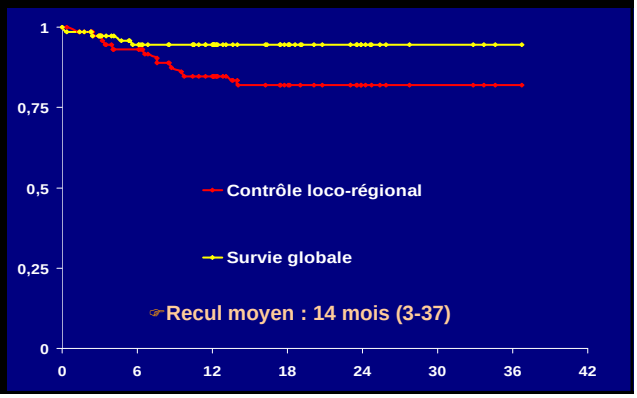
IMRT in oropharyngeal carcinomas :

a multicentric prospective study of patients necessitating a bilateral IMRT

(M Lapeyre)

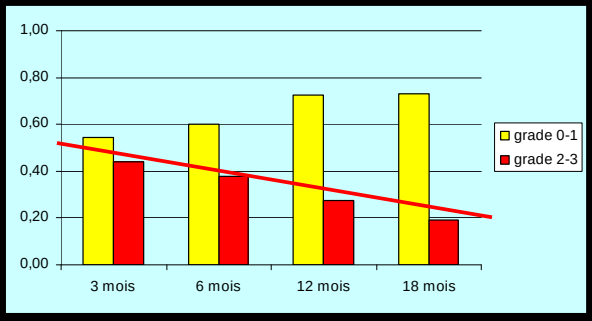
GORTEC
Groupe Oncologie Radiothérapie Tête Et Cou
Radiotherapy oncology group for head & neck

GORTEC : Loco-regional & survival (N= 93)



Late xerostomia (N =93)

(RTOG-EORTC scoring system)



Salivary toxcity at 1 year

	Grade 2-3
Controlateral parotid :	
Dose moy < 30 Gy	16 %
Dose moy > 30 Gy	43 %
	p=0,05

QOL : 7 scores in favor of IMRT

	RTE conv	IMRT	p
Scoring of symptoms			
Dolor (HN)	33,5 [28,5]	21,5 [25,0]	0,01
Deglutition	35,1 [26,2]	23,0 [25,6]	0,01
Eating in public	38,2 [31,8]	26,9 [30,3]	0,03
Dental Pbs	34,9 [40,0]	19,5 [30,6]	0,02
Opening mouth	48,3 [37,7]	28,8 [31,9]	0,001
Mouth dryness	83,1 [25,5]	57,2 [33,2]	<0,0001
Stick saliva	76,6 [30,1]	47,1 [34,7]	<0,0001

Graff P et al Int J Radiat Oncol Biol Phys. 2007 Apr 1;67(5):1309-17

Dose escalation with IMRT in oropharyngeal carcinomas ?

An ongoing randomized study with / wo IMRT

(GORTEC 2004-01)

Oropharynx + OC Stage II-IV with R

- **70 Gy + CDDP**
- **IMRT 75 Gy + CDDP**

Hypothesis = IMRT 75 Gy more efficient & less toxic ?

N = 67 pts

IMRT in oropharynx carcinomas : summary

- Better conformality / 3D, & one of the tumor sites where it is increasingly used +++
- Steep dose gradient : need for clinical validation in locally advanced disease
- Promizing & converging results (EBM 2-3) :
  - Few LR recurrence
  - Less late toxicity
- Learning curve / Re-inforced QA needed ++

Radiotherapy for oropharyngeal carcinoma :

Importance of the RT-QA …

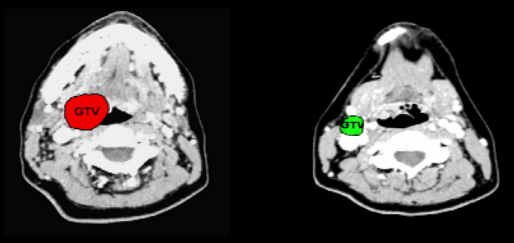
Radiotherapy for oropharyngeal carcinoma :

Importance of the RT-QA …contouring

Importance of RT-QA : contouring ; international survey : T2 Tonsil

Primary Tumor

Neck Node



Harari 2004

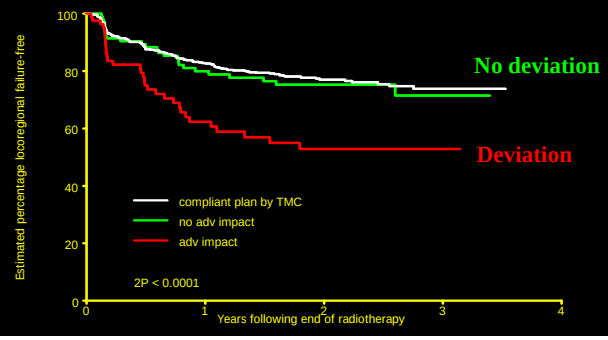
Samples : Elective CTV Designs

Harari 2004

Radiotherapy for oropharyngeal carcinomas :

Importance of the RT-QA … RT plan verification

LR Failure according to RT plan deviations yes / no (N= 820) *(Rishin, ASCO 2008)*



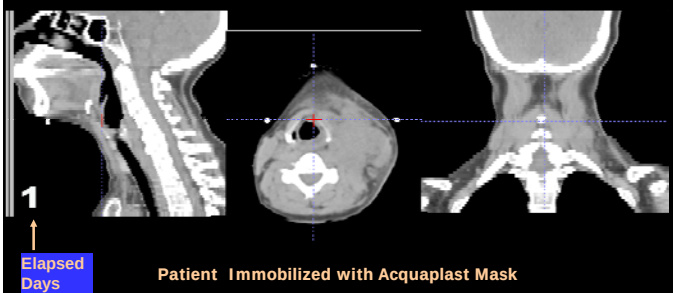
IMRT : what's next ?
New tools for radiation delivery :

Image guided RT

Adaptive RT

Dose Guided RT

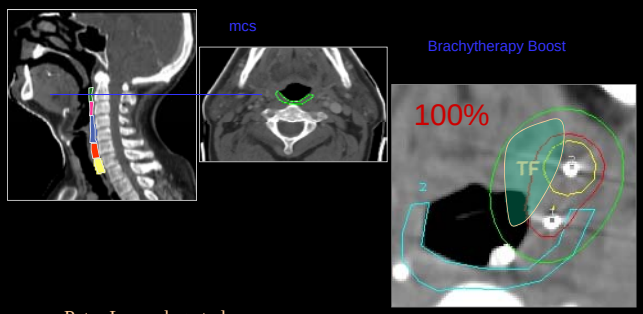
Adaptive Radiotherapy - Anatomic and set-up Changes
19 CT Scans over 47 Days



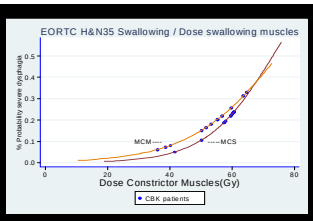
Patient Immobilized with Acquaplast Mask

Barker et al. *IJROBP* 59:960-970, 2004 (MDACC); Lei Dong et al. (MDACC)

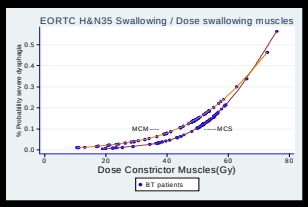
Dose distribution in Superior Constrictor Muscle from Brachytherapy in Tonsillar Fossa (< 50%)



Peter Levendag et al



Cyberknife boost



Brachytherapy boost

Peter Levendag et al

New generation of trials in locally advanced oropharyngeal carcinomas ?

Most of them do integrate concomitant CT-RT (CDDP-RT)

New generation of trials for oropharynx carcinomas :

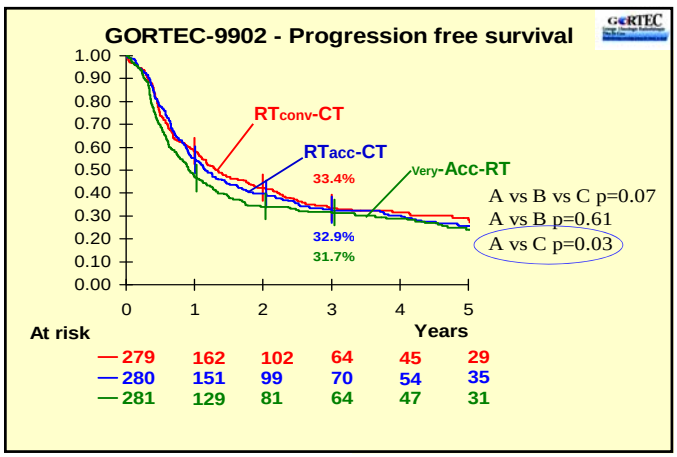
concomitant CT-RT
&
modifying the radiotherapy

GORTEC 99-02 randomized trial

Stage III/IV

- **Conventional RT + Carbo/5FU**
- **Accelerated RT + Carbo/5FU**
- **Very accelerated RT**

N = 840 pts randomized, 2/3 of oropharynx



New generation of trials in locally advanced oropharyngeal carcinomas ?

concomitant CDDP-RT
&
adding a new drug

RTOG H05-22 : Phase III

Stage III-IV
HNSCC

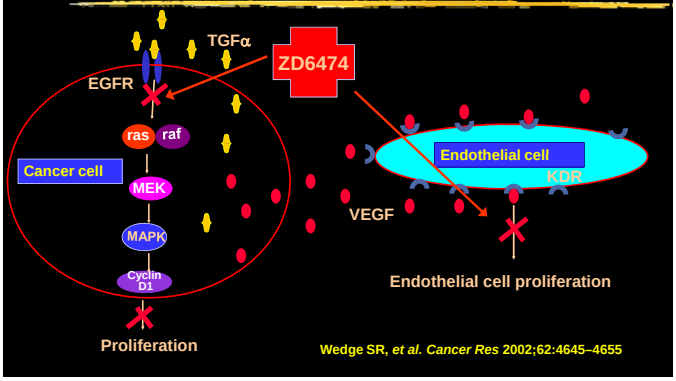
RANDOMIZE

→ Accelerated FX
CDDP

→ Accelerated FX
CDDP
Erbitux

Future directions : multiple targeting ?

Example : ZD6474 : a Dual EGFR-VEGFR TKI



Wedge SR, *et al. Cancer Res* 2002;62:4645–4655

Multiple- better than single-targeting ? several ongoing trials in HNSCC …

Phase I (Localy advanced HNC) Brizel, 2007

R
- RT- CDDP + Erlotinib
- RT- CDDP + Avastin
- RT-CDDP + Erlotinib + Avastin

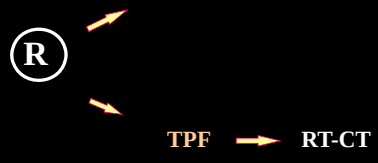
New GORTEC trial (> 2/3 oropharynx)

R (T2-T4 N0-N1)
- Erbitux - RT
- Erbitux - RT + Carbo-5FU (best arm 99-02)

New generation of trials in localy advanced oropharyngeal carcinomas ?

concomitant CT-RT
&
testing induction CT

6 ongoing randomized trials
(Decide, Paradigm, Paccagnella etc…)



Other Strategy tested : a new GORTEC trial

New generation of trials in localy advanced oropharyngeal carcinomas ?

Replacing CDDP concomitant to RT by a molecular targeted drug (erbitux)
?

Replacing chemo by a molecular targeted drug ?

larynx preservation randomized trial

(GORTEC-GETTEC)

Decreasing the dose intensity of the treatment :
a relevant question for HPV+ oropharyngeal carcinomas ?

Other directions in oropharyngeal carcinoma …

specific treatments for HPV related tumors ?…

- HPV found in 20-25% of HNSCC (and 30% benign biopsies of oropharynx)

- Up to 50% in oropharynx carcinomas (some series : 90%) :
- 85-90% HPV16 (De Souza, NEJM 2007)

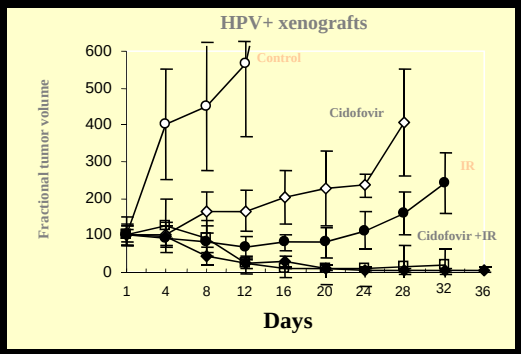
- HPV+ tumors associated with :

- **Better survival** (Richties 2003)
- **Better survival in surgically treated tumors** (Licitra JCO 2006)
- **More radiosensitivity** (Lindel 2007)
- **More response to induction chemo** (Worden JCO 2008)
- **Cellular marker of prognostic value : p16** (Lassen JCO 2009 survival 62% versus 26% with conventional RT)

Do we need different therapeutic approaches for HPV associated oropharyngeal tumors ?

- De-escalation ?
- Value of EGFr targeting instead of concomitant chemo ?
- Other specific anti-viral strategies ?

Antiviral agent Cidofovir + irradiation in HPV+ SC carcinoma xenografts (ongoing phase I)



Oropharyngeal carcinoma
- Conclusions -

- High proportion of HNSCC (about 50%)
- The effect of chemotherapy and/or altered fractionation or EGFr targeting = not different from the other HNSCC … EBM level 1a
- Importance of IMRT / IGRT / RT-QA … for normal tissue sparing in this particular sub-site
- Question : more HPV related carcinomas *(specific targeting ? Treatment Desescaltion)* ?