

Re-irradiazione delle neoplasie testa – collo

*Re-irradiazione:
standard clinico o ricerca?*

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DICHIARAZIONE

Relatore: Pierluigi Bonomo

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board **NIENTE DA DICHIARARE**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**

Outline

- The burden of loco-regional recurrence
- Re-irradiation: is there any evidence?
 - **after salvage surgery**
 - **unresectable disease**
- Open issues & future perspectives

Where do we fail in head and neck cancer?

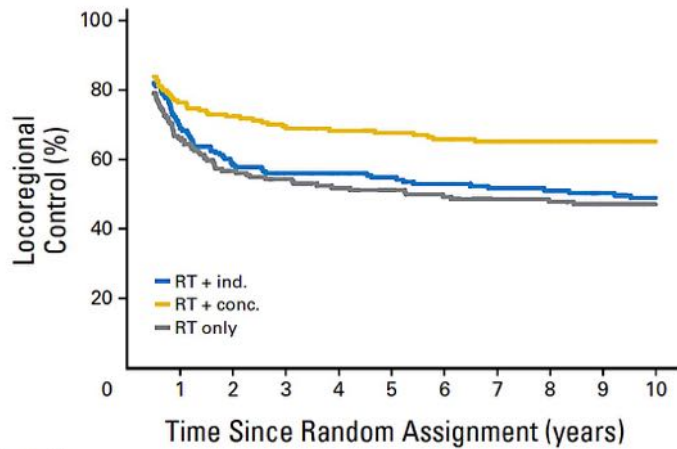
	Patients, N (number of comparisons)	Locoregional events	
		N	% in first 2 years
104 trials (1965 – 2000)			
MARCH¹ Radiotherapy	6515 (17)	51%	92
Concomitant chemotherapy	9530 (56)	50%	93
MACH-NC² Induction chemotherapy	4631 (32)	47%	91
Adjuvant chemotherapy	2068 (11)	27%	91

¹Bourhis J, Lancet 2006

²Pignon JP, Radiother Oncol 2009

Michiels S, Lancet Oncol 2009

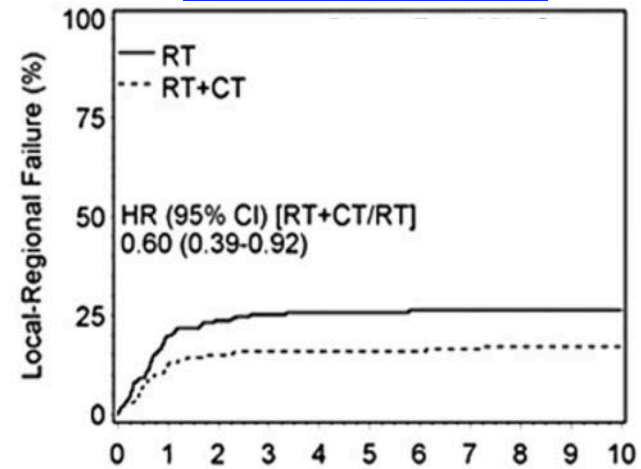
RTOG 91-11



No. at risk
RT + ind.
RT + conc.
RT only

46% vs 33% vs 49% (5-y)

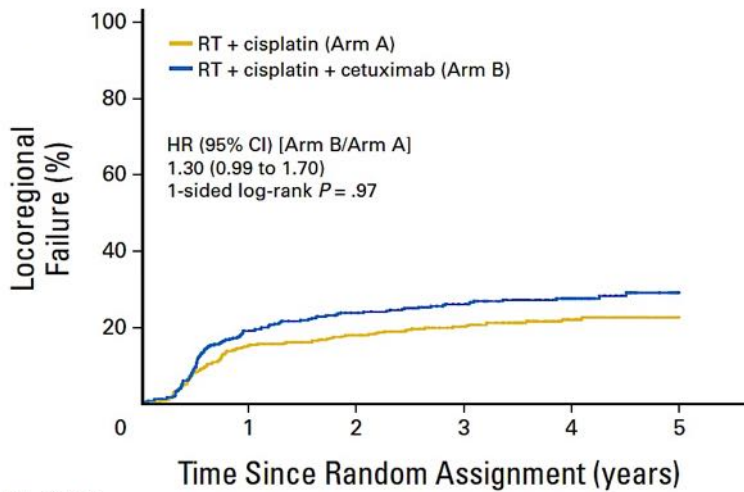
RTOG 95-01



No. at risk
RT
RT+CT

25% vs 16% (5-y)

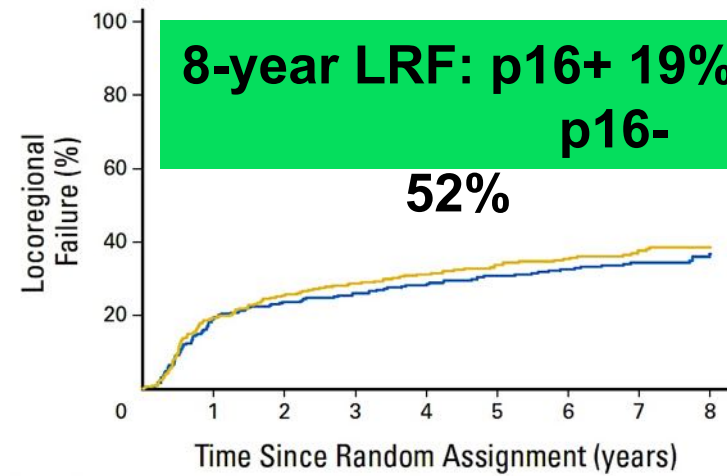
RTOG 0522



No. at risk
Arm A
Arm B

20% vs 26% (3-y)

RTOG 0129



No. at risk
SFX
AFX-C

31% vs 34% (5-y)

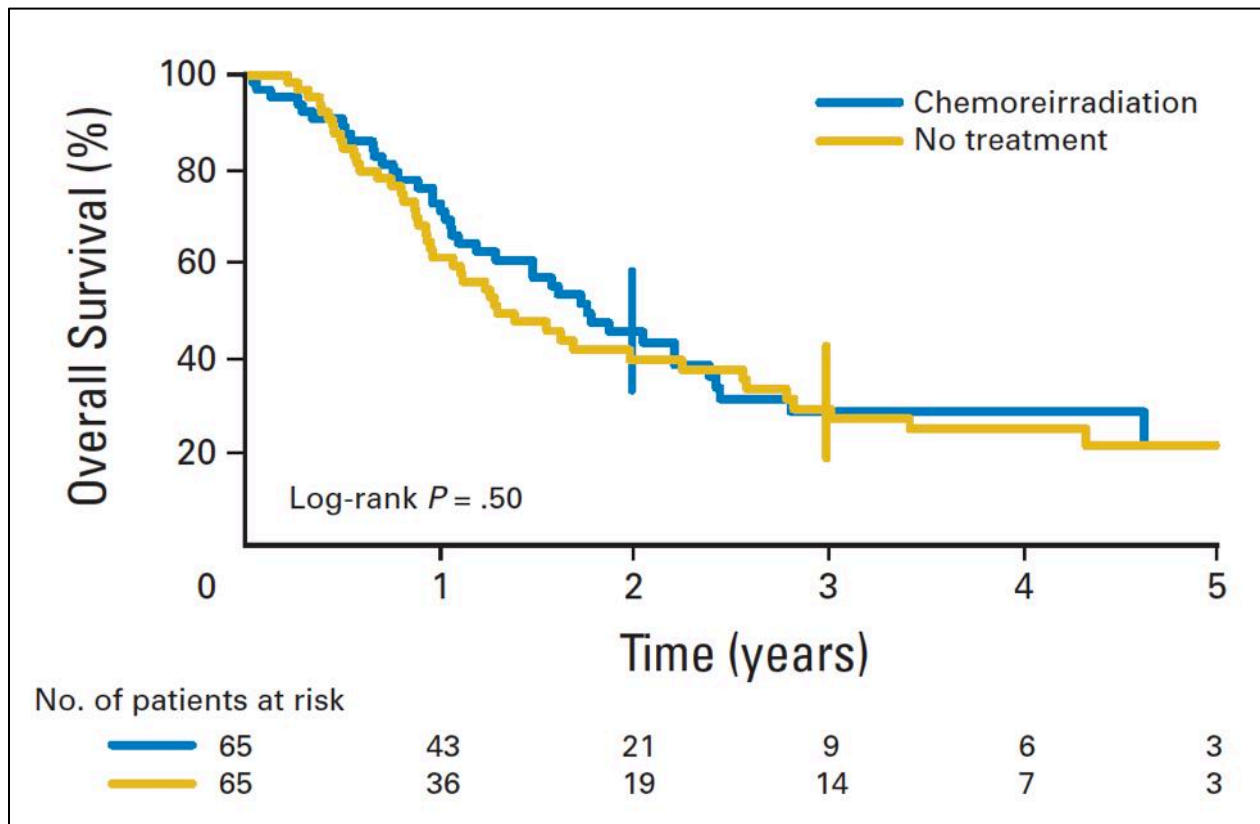
The burden of loco-regional recurrence

- **Surgery: the most effective curative-intent tx**
 - half or less of pts are amenable to salvage
 - $\geq 25\%$: major post-op complications
- **Long-term survival achieved in 1/3 of cases**
 - best if: rT1; larynx vs other sites
 - meta-analysis on 1080 pts: 5-y DFS 39%
- **Rate of 2nd recurrence still high (up to 60%)**
 - poor outcome if adverse pathologic features

Goodwin WJ, Laryngoscope 2000




Re-irradiation after salvage surgery

- 130 pts randomized to 60 Gy, 2 Gy/fx (d 1–5; 9-d break) with concomitant HU, FU vs observation



- LRC: HR 2.73 (95% CI, 1.66 to 4.51; $p < .0001$)
- G3/G4 late toxicity (2-y): 39% vs 10%
- DFS: HR 1.68 (95% CI, 1.13 to 2.50; $p < .01$)

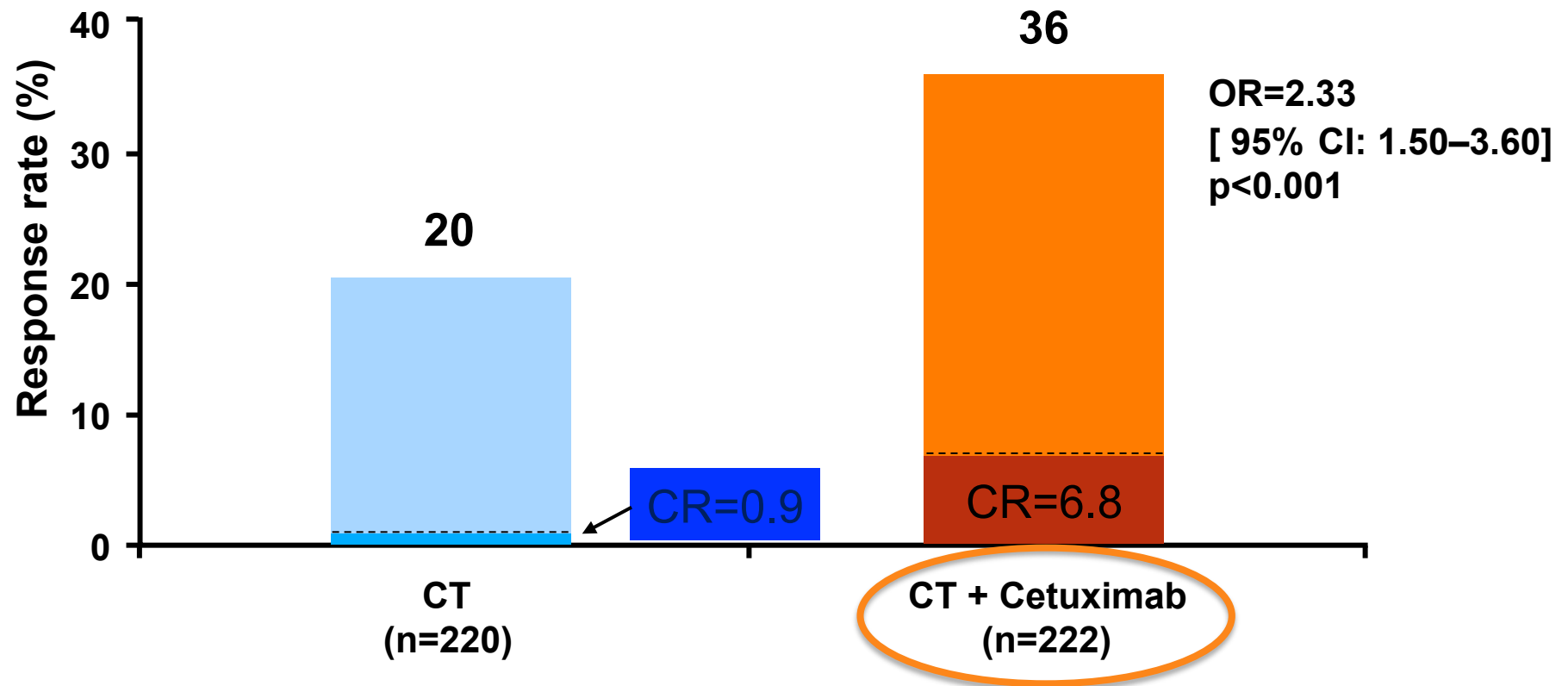
So, is it standard practice?

- Selected pts with high risk features (R1, ECE) should be considered for post-op re-RT 
- 40-50% OS @ 2 years may be achieved 
- Severe toxicity in > 1/3 of pts; treatment mortality up to 8% 

- 1. 60 Gy/2 Gy fx, split-course over 11 weeks?**
- 2. role of chemotherapy?**
- 3. impact of hyperfractionation? IMRT?**

Unresectable recurrence: real world scenario

Median **PFS: 5.6 mo** with cetuximab vs 3.3 mo without (HR 0.54; 95% CI, 0.43 to 0.67; $p < 0.001$)



Unresectable recurrence: real world scenario

	Cetuximab plus Platinum–Fluorouracil (N = 222)	Platinum–Fluorouracil Alone (N = 220)
Extent of disease — no. (%)		
Only locoregionally recurrent	118 (53)	118 (54)
Metastatic with or without locoregional recurrence	104 (47)	102 (46)

- no difference in OS between pts with metastatic/recurrent and locoregional recurrence only $p=0.06$

Re-irradiation for unresectable disease

- **3D-CRT**
- **IMRT**
- **SBRT**
- **Brachytherapy**
- **The case of nasopharynx**
- **Protons/heavy ions**

Re-irradiation for unresectable disease

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- ~~**Protons/heavy ions**~~

Benchmark data: 3D-CRT

Author	N, study type	Interval to ReRT (months)	Re-irradiation	CT	G3/G4 late toxicity, TRD	2-year outcome
Salama et al, 2006 ²³ (1986–2001)	66, prospective	N.S.	TD 66–67 Gy, 2 Gy/tx q.d. or 1.5 Gy/tx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: GTV + 10 mm ± ELN-RT	HU + 5FU, CDDP, gemcitabine, paclitaxel, irinotecan	N.S.	3-y LRC, 36% 3-y OS, 11%
Langer et al, 2007 ²⁸ (2000–2003)	99, prospective RTOG 9911	40 (6–318)	TD _{median} 60 Gy, 1.5 Gy/tx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: GTV + ≥20 mm	CDDP + paclitaxel	N.S. TRD, 8%	OS, 25.9%
Spencer et al, 2008 ²⁷ (1996–1999)	79, prospective RTOG 9610	30 (7–238)	TD 60 Gy, 1.5 Gy/tx b.i.d. (d 1–5 → 9-d break) Reirradiation volume: GTV + ≥20 mm	HU + 5FU	At 2–5 y, 9.4% TRD, 7.6%	OS, 25.9%
Berger et al, 2010 ⁴⁸ (1997–2007)	57 [‡] , prospective	16 (7.5–188)	TD 40 Gy, 2 Gy/tx (wk 2 + 3, 5 + 6) or TD 49.6 Gy, 2 Gy/tx (wk 2 + 3, 5 + 6, CB with 1.6 Gy 2nd fx after 28 Gy) Reirradiation volume: PTV = GTV + 10 mm	CDDP + docetaxel	40% TRD, 7%	40 Gy group: OS, 16% [†] 49.6 Gy group: OS, 31%
Tortochaux et al, 2011 ²⁶ (1999–2005)	30 [¶] , randomized GORTEC 98-03	N.S.	TD _{median} 60 Gy, 2 Gy/tx, (d 1–5 → 9-d break) Reirradiation volume: GTV + ≥2 cm + ELN-RT	HU + 5FU	37% TRD, 7%	OS, 8% [†]

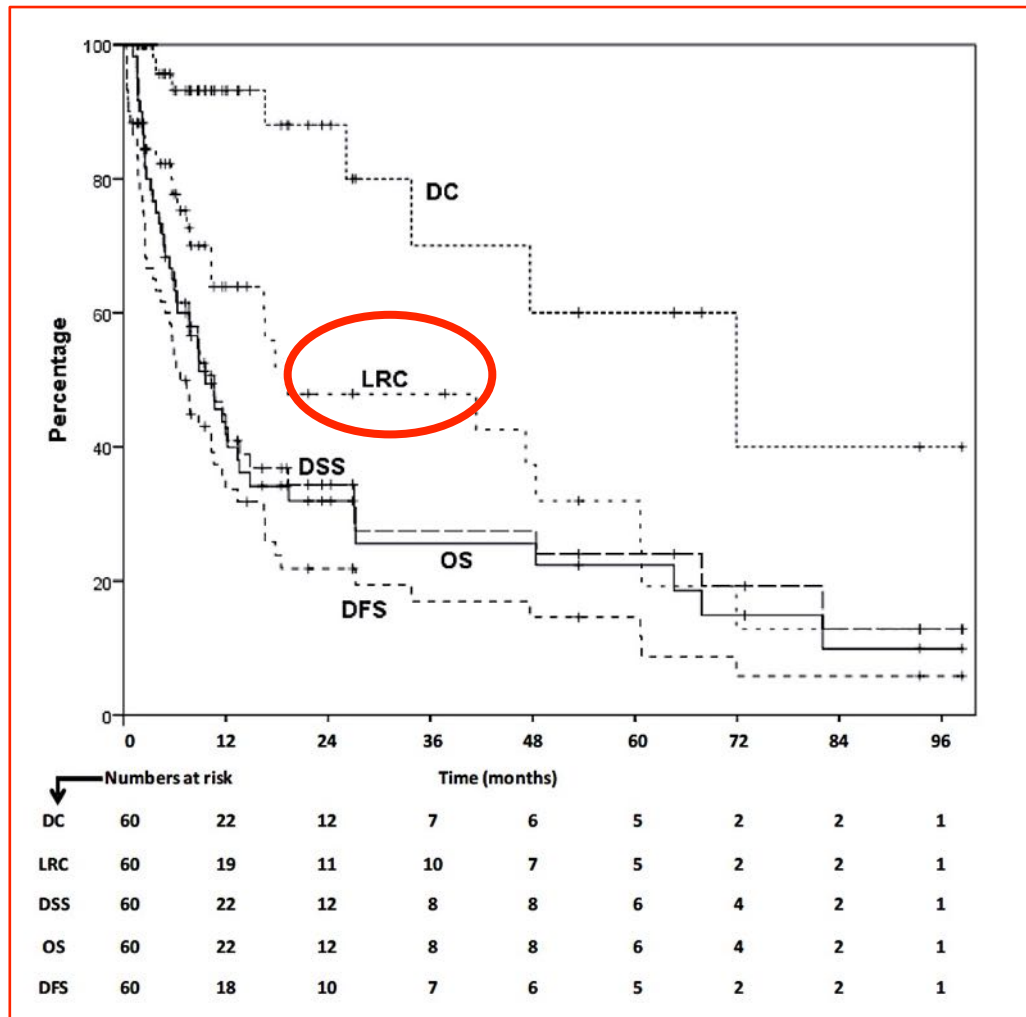
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G3/G4: up to 40%
2-year OS: 10 to 30%
TRD: up to 10%

IMRT: Ghent University

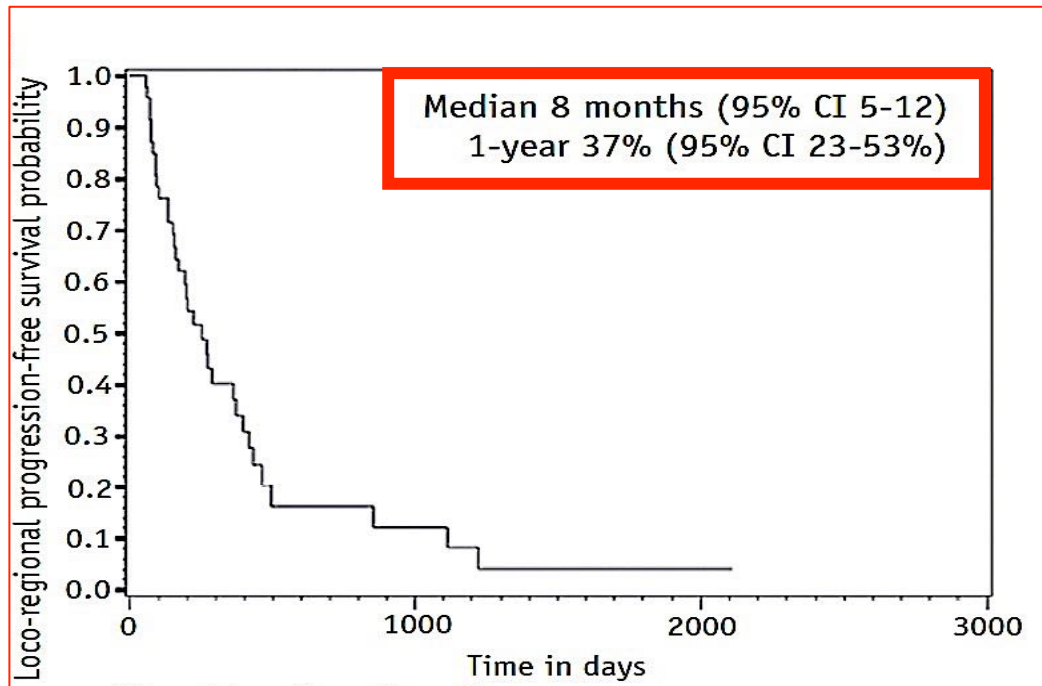
- 60 patients (1997 – 2011); 69.1 Gy/212 cGy fx



- LRC:
 - 1-y: 64%
 - 2-y: 48%
- PFS (median):
6.7 months
- G3/G4 late toxicity:
27% (2-y)

SBRT: Pittsburgh phase II

- 50 patients (2007 – 2013)
 - 40/45 Gy in 5 fx + 3 cycles Cetuximab
- Endpoint: 1-year locoregional PFS from 35% to 55%

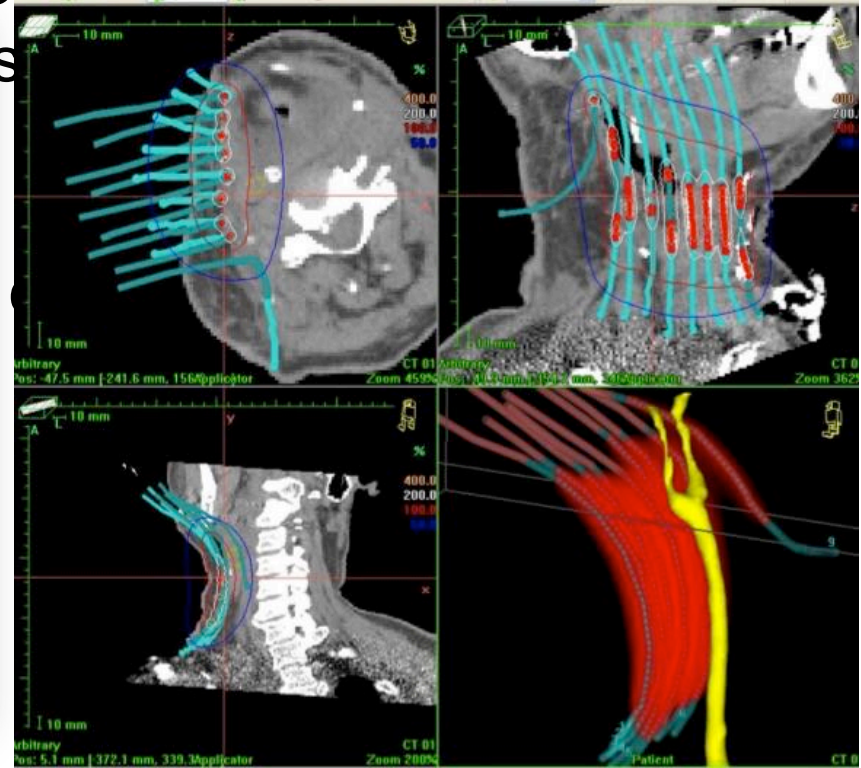


- PFS (median):
7 months
- G3/G4
late toxicity:
6% (no G4)

- local progression-free survival: 60% (1-y)

Interstitial brachytherapy

- 104 patients (1999 – 2008). PDR up to 55 Gv



G3/G4 toxicity.

10 – 18%

PERIOPERATIVE INTENSITY-MODULATED BRACHYOTHERAPY

COURTESY BY DR. L.TAGLIAFERRI – UCSC Rome

The case of nasopharynx

- **Locoregional failure:**
first PFS event in 5 to 15% of patients
- **rT1/rT2: best treated with**
 - HDR brachytherapy; SBRT; ENPG
 - surgery preferred if within a year of primary RT
- **rT3/rT4 best treated with**
 - IMRT
 - palliative CT

So, is it standard practice?

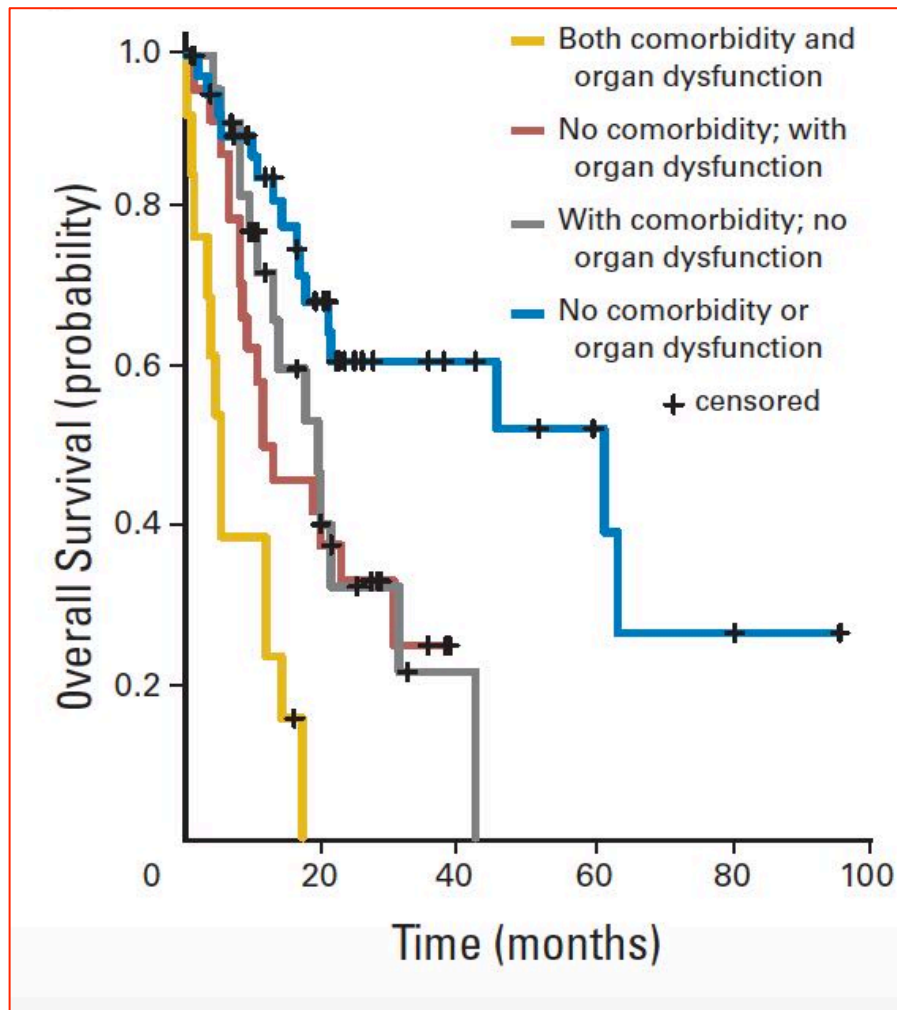
NO

- **Lack of high quality data to recommend re-RT for unresectable disease**
 - heterogeneity
 - case mix
 - significant sources of bias
 - difficult interpretation

Open issues

- **Technical feasibility: challenging**
 - dose constraints? Normal tissues recovery?
 - GTV-CTV expansion? Volumes?
- **Recurrent SCCHN: heterogeneous group**
 - HPV positive
 - HPV negative
 - SPT's
- **Integration with CT**
 - what drugs? Sequential or concurrent schedule? Maintenance?

Who may then benefit from re-RT?



- Organ dysfunction
- Comorbidity
- Interval from 1st RT: ≥ 6 mo
- rT stage: $\leq T2$
- Tumor bulk: ≤ 25 cm³
- Re-RT dose: ≥ 60 Gy

Future perspectives

A Feasibility Study on Adaptive 18F-FDG-guided Radiotherapy for Recurrent and Second Primary Head and Neck Cancer in the Previously Irradiated Territory.

This study is currently recruiting participants. (see Contacts and Locations)

Verified June 2015 by University Hospital, Chart

ClinicalTrials.gov Identifier:

NCT01427010

Reirradiation With MK-3475 in Locoregional Inoperable Recurrence or Second Primary Squamous Cell CA of the Head and Neck

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2015 by University of Maryland

Sponsor:

Dan Zandberg

Collaborator:

Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):

Dan Zandberg, University of Maryland

ClinicalTrials.gov Identifier:

NCT02289209

First received: October 17, 2014

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[History of Changes](#)

Verified July 2015 by University of Pittsburgh

Sponsor:

University of Pittsburgh

Information provided by (Responsible Party):

University of Pittsburgh

NCT02057107

First received: January 30, 2014

Last updated: July 29, 2015

Last verified: July 2015

[History of Changes](#)

Summary #1

- **Proper patients' selection:**
crucial factor
- **Re-irradiation after salvage surgery:**
increases LRC but also late toxicity
- **Re-irradiation for unresectable disease:** **tailored decision on a case-by-case basis**

Summary #2

- **Urgent need to fill the gap of evidence**
- **Prospective data required to assess:**
 - **technical issues**
 - **patterns of failure**
 - **late toxicity**
 - **imaging & translational research**

