I. Dell'Oca

Dichiarazione conflitti di interesse: nessuno

OSPEDALE
SAN RAFFAELE

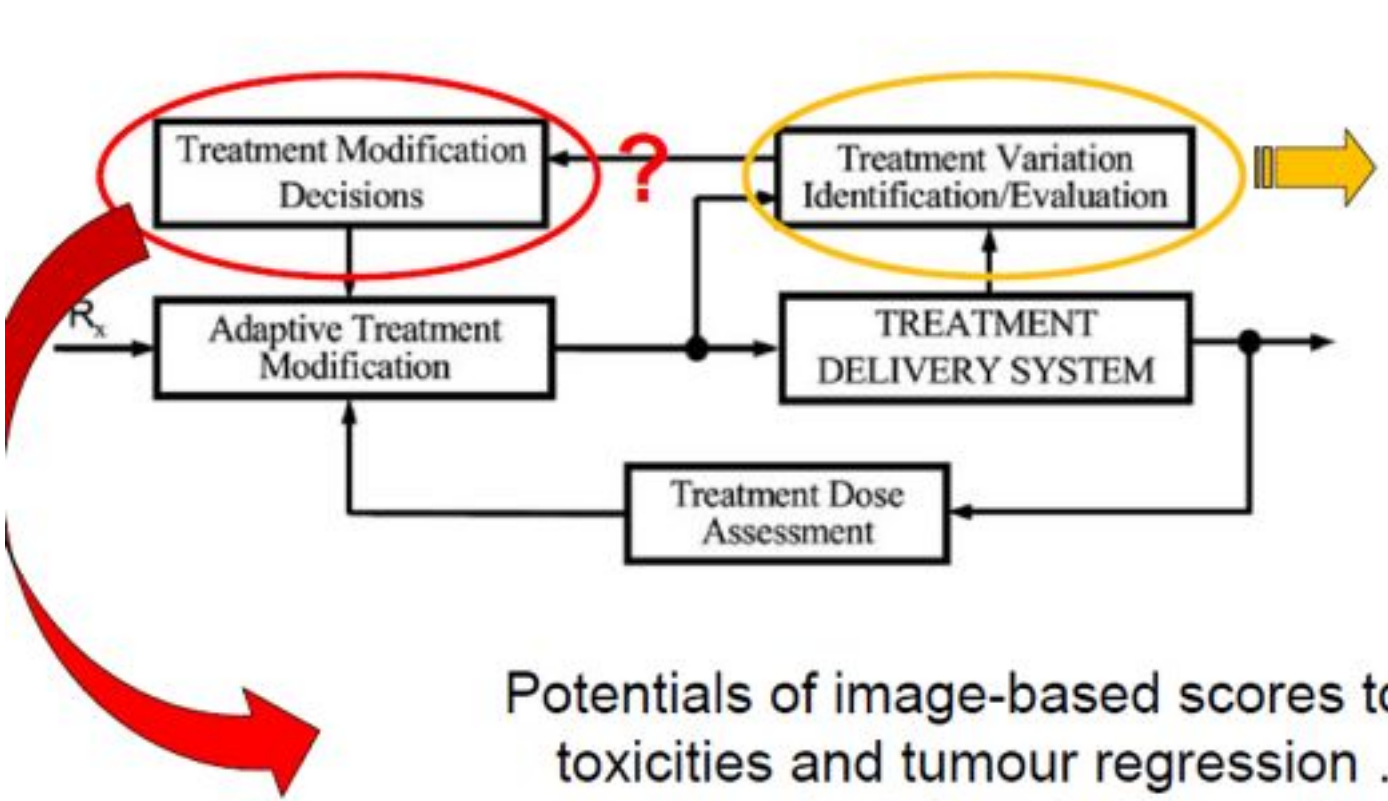
Radioterapia “adaptive”: mito o realtà?

I. Dell’Oca

Seminars in
RADIATION
ONCOLOGY

April 2010

Adaptive Radiotherapy: Merging Principle Into Clinical Practice



- tumour response
- normal tissue variations

Potentials of image-based scores to model toxicities and tumour regression …and consequently define decision rules …..???

Yan, Semin RO 2010

Image guided RT (IGRT)

daily imaging

?

Early identify sign of tissue damage

?

Predict organ dysfunction and final RT treatment outcome

?

Re-optimization of treatment strategies based on patients' risk and benefits

ART

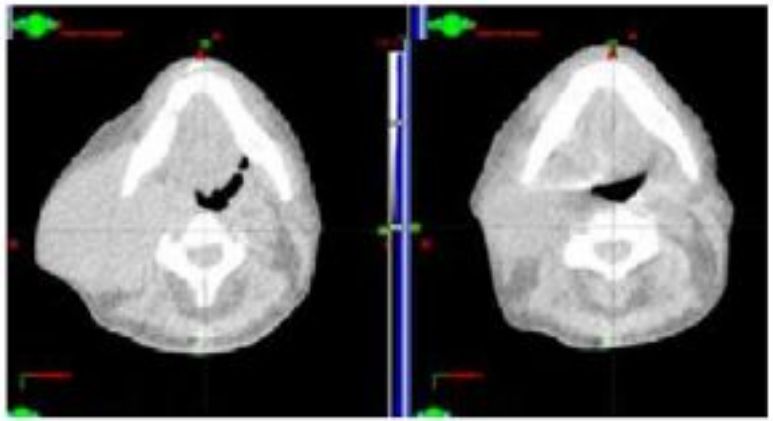


Image during RT tmt is *in-vivo* RADIOBIOLOGY!!!

- Which structures?
- When to adapt?
- Which patients?

THE LANCET Oncology

Volume 13, Issue 7, July 2012, Pages e292–e300

Review

Radiotherapy for head and neck tumours in 2012 and beyond: conformal, tailored, and adaptive?

Prof Vincent Grégoire, MD[a], Robert Jeraj, PhD[c], John Aldo Lee, PhD[b], Prof Brian O'Sullivan, MD[d]

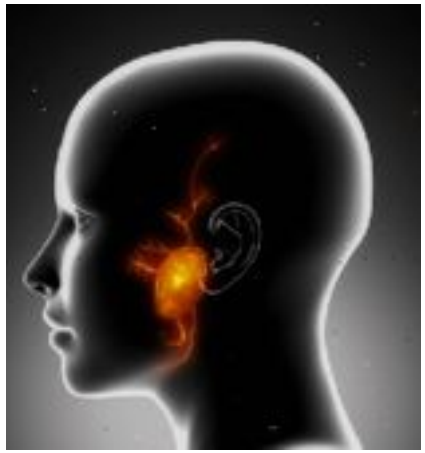
Studies of head and neck cancers have mainly focused on variations in the volumes and positions of the parotid glands and in target volumes throughout the treatment course. Progressive shrinkage of around 1% per treatment day

Nodal and primary-tumour gross target volumes assessed on repeated planning CT shrink by 2–3% per treatment day

Volumetric and positional changes of organs at risk and target volumes are generally associated with progressive increase in the delivered dose compared with the planned dose, typically because of shrinkage of the gross target volume owing to tumour tissue loss

- **Organs at Risk**

Parotid Glands (PGs)



Volume, Density

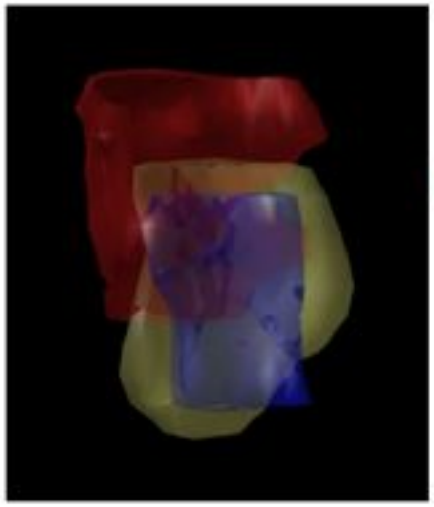
- **Tumor volumes**

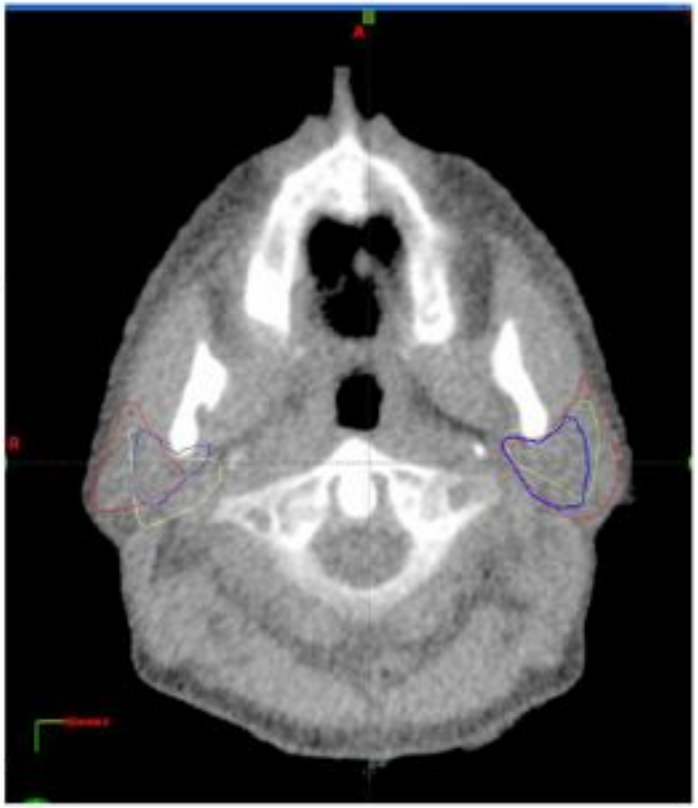
GTV, CTV, PTV

Example of PGs volume variation and shift during the RT treatment

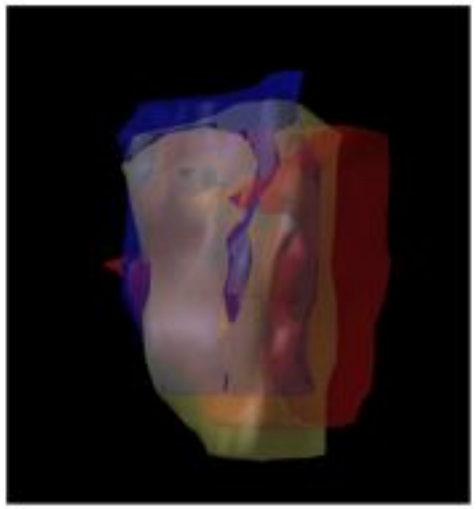
Red: day 1 Yellow: day 15 Blue: day 30

RIGHT



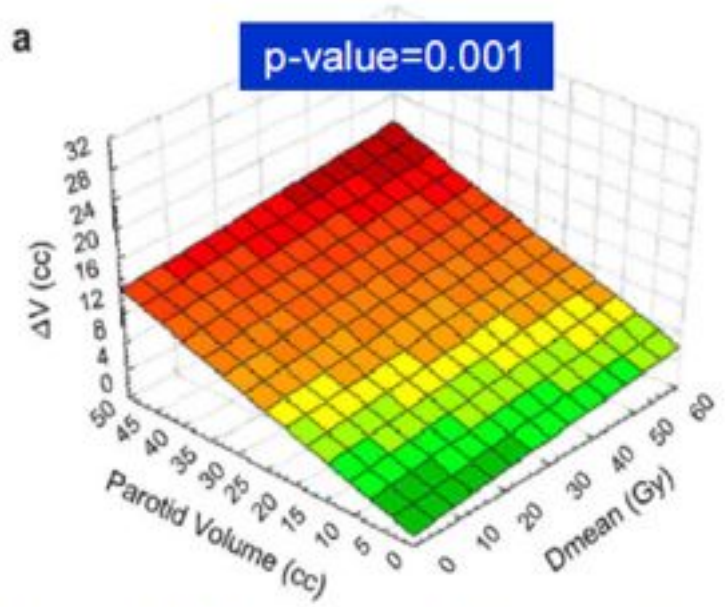


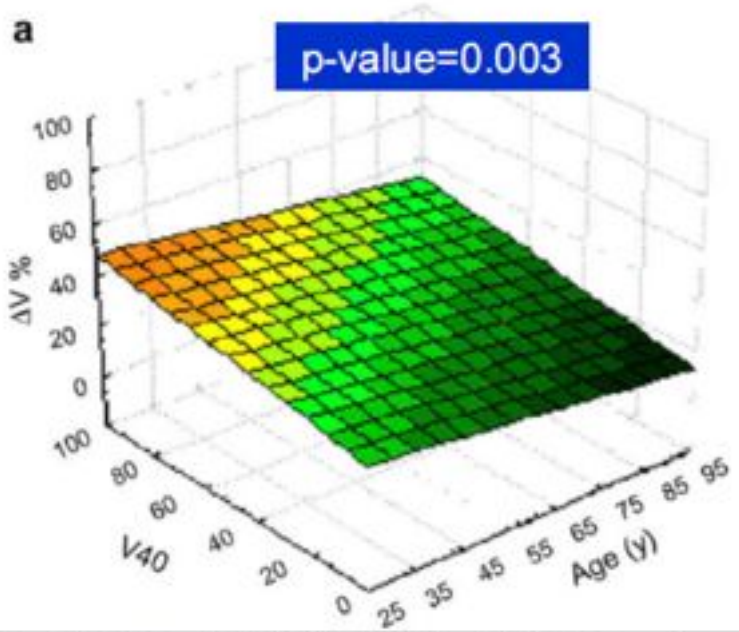
LEFT



Is it possible to **predict** the final deformation based on **pre-treatment information**?

87 pts, 174 PGs, 4 Institutes (2: diagn. kVCT, 2: Helical MVCT)





$$\Delta V[cc] = -2.44 + 0.0076\,Dmean[Gy] + 0.279\,IPV[cc]$$

$$\Delta V[\%] = 34.23 + 0.192\,V40[\%] - 0.2203\,age[year]$$

ΔVcc e ΔV% described by a **combination of pre-RT treatment parameters**: one clinical and one dosimetric

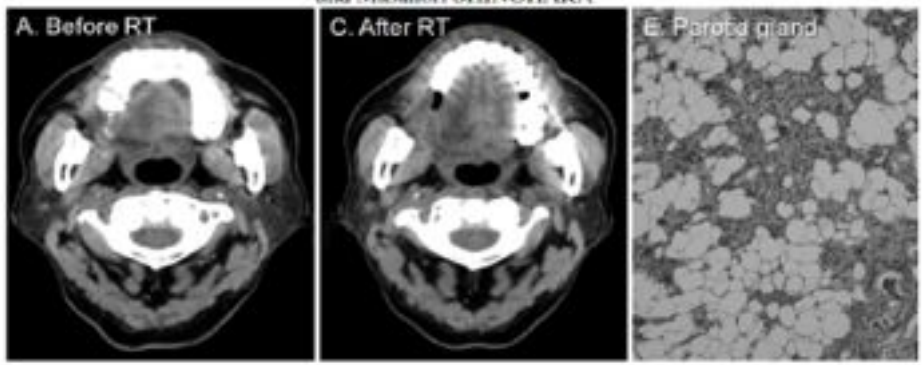
Broggi et al. R&O 2010

PG density variation as surrogate of glandular/adipose tissue variation

JRR 2012

Histopathological Changes in Parotid and Submandibular Glands of Patients Treated with Preoperative Chemoradiation Therapy for Oral Cancer

Keiko TESHIMA[1], Ryuji MURAKAMI[3,4], Ryoji YOSHIDA[1], Hideki NAKAYAMA[1], Akimitsu HIRAKI[1], Toshinori HIRAI[3], Yuji NAKAGUCHI[4], Naoko TSUJITA[2], Etsushi TOMITAKA[5], Mitsuhiro FURUSAWA[6], Yasuyuki YAMASHITA[3] and Masanori SHINOHARA[1]



- PGs kVCT imaging
- histopathological analysis
- measure of salivary flux (Saxon test)

Table 1. Histopathological quantitative analysis in the control- and CRT groups

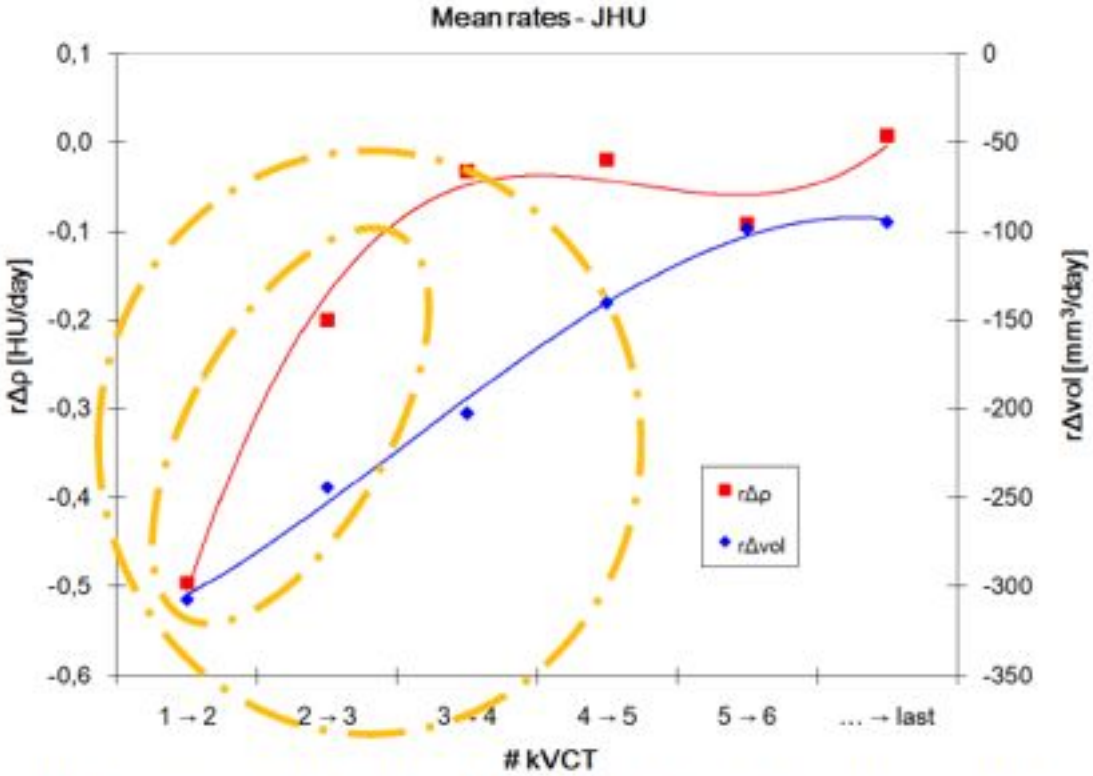
Parameter	Control group	CRT group	P value*
Parotid gland	(n = 10)	(n = 6)	
Acinar cells (%)	31.5 (17.7–49.0)	1.1 (0.3–2.2)	0.0011
Duct cells (%)	4.5 (2.3–7.7)	5.8 (3.3–7.0)	0.0875
Adipose cells (%)	41.9 (26.0–63.3)	49.7 (14.7–80.3)	0.6374
Other tissues (%)	21.1 (12.1–31.6)	43.5 (13.5–77.4)	0.0509

Acinar cell reduction!!

↓ρcould be considered a **likely surrogate** of acinar cells loss indirectly measured by the **relative increase of fat** component, being a promising **in-vivo biological score**

Early prediction of final PG deformation

25 IMRT pts,



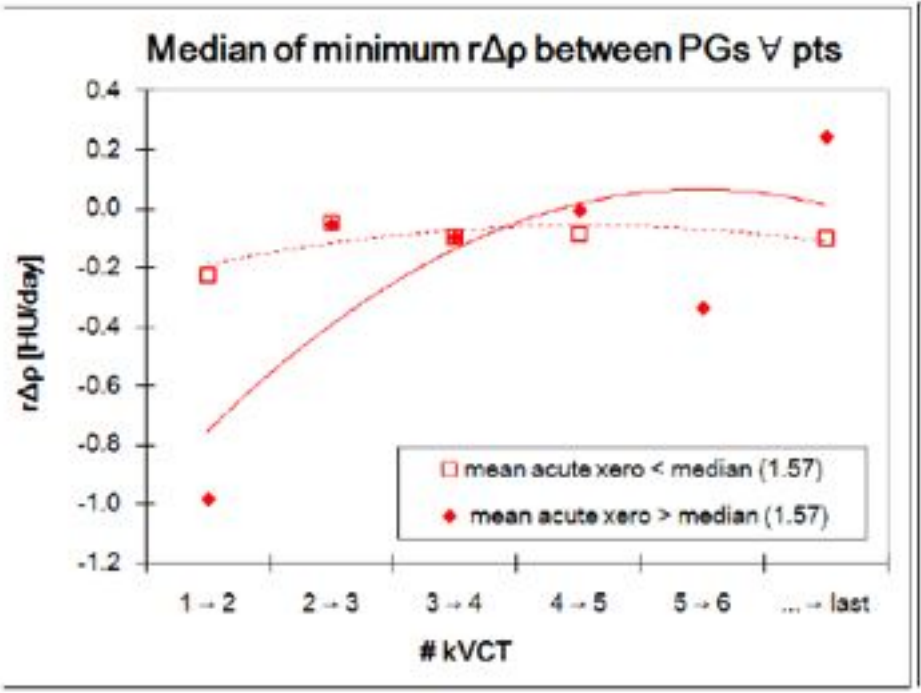
- **Larger** rΔρ and rΔvol in the **first** half of the treatment compared to the second half: paired Student T-test p-value<0.05
- **Early** variations well **predict** with the final ones
- **rΔρ** concentrated during the **early** treatment phase. i.e. first 2 weeks **1→2**

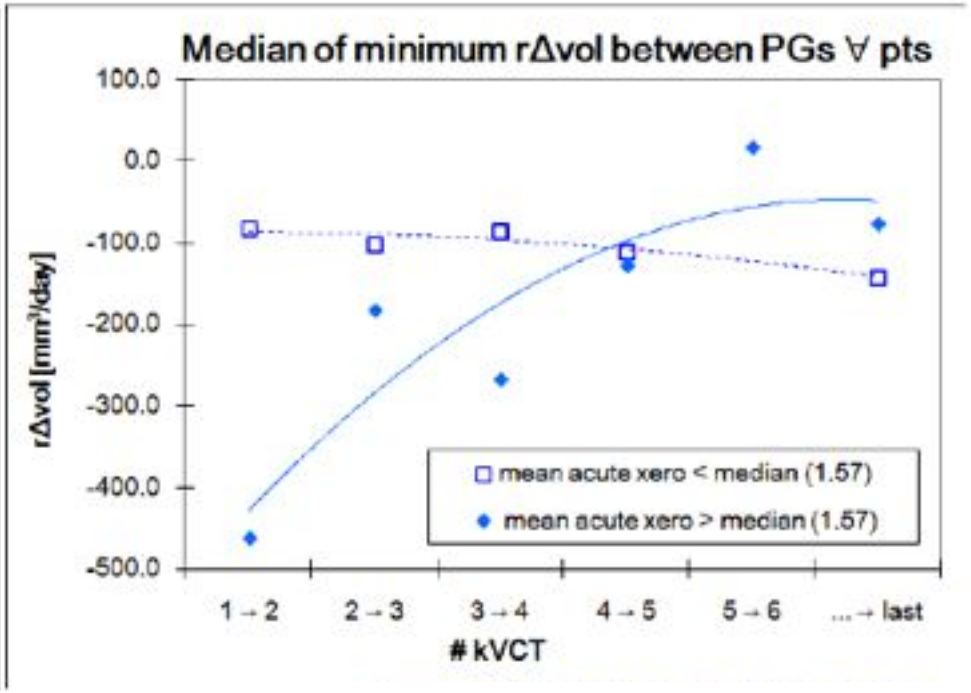
Belli et al. Strahl. Onkol. 2014

Correlation between **early** changes and **acute xerostomia**

- CTC-based prospective assessment of **acute xerostomia** (weekly) of 25 patients (CTCAE v.3.0): grade=1(good) → grade=4(bad)
- **Peak** and **longitudinal** scores (**mean** score) representing both severity and persistence

mean acute xerostomia





Belli et al. Strahl. Onkol. 2014

Correlation between **early** changes and **acute xerostomia**

		rΔρ [HU/day] 1→2		rΔvol [mm³/day] 1→2	
		mean acute xero≥ 1.57	mean acute xero< 1.57	mean acute xero≥ 1.57	mean acute xero< 1.57
Mann-Whitney test	Median	-0.98	-0.22	-455	-127
	95%CI	-1.37 to -0.43	-0,95 to 0,09	-970 to -216	-550 to 19
	p-value	0.05		0.03	

↓ ρ≈10-15 HU/ 2weeks

(≈ 0.01 g/cm³)

PG difference adipose and glandular tissues =70/80 HU

(≈ 0.05 g/cm³)

CT acquisition @ 2nd week of tmt

Early identify sensitive pts! ...potential for ART ??

Belli et al. Strahl. Onkol. 2014

Assessing **tumor response** during RT?

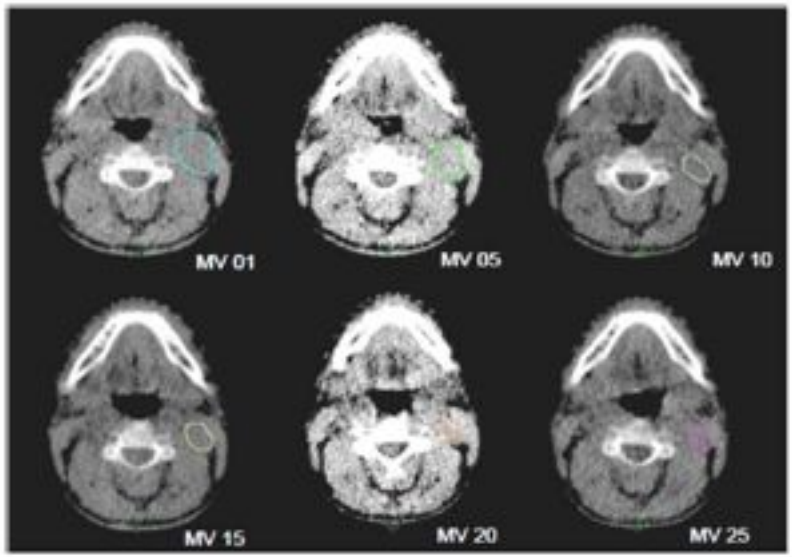
lymphnodes (PET⁺), PLs

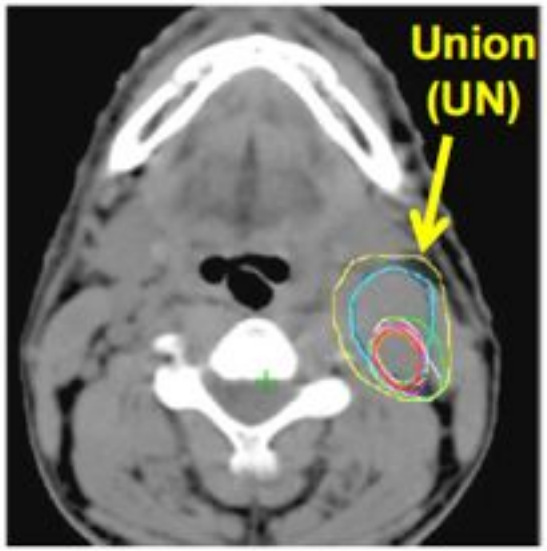
- ✓ large volume variations
- ✓ well visible with IGRT in-room systems (CBCT/MVCT)

30 pts N2/N3, 42 PET⁺ lymphnodes(PLs)

Helical Tomotherapy, radical intent, SIB 30 fr (boost PET⁺ PLs+T)

planning kVCT + weekly MVCTs





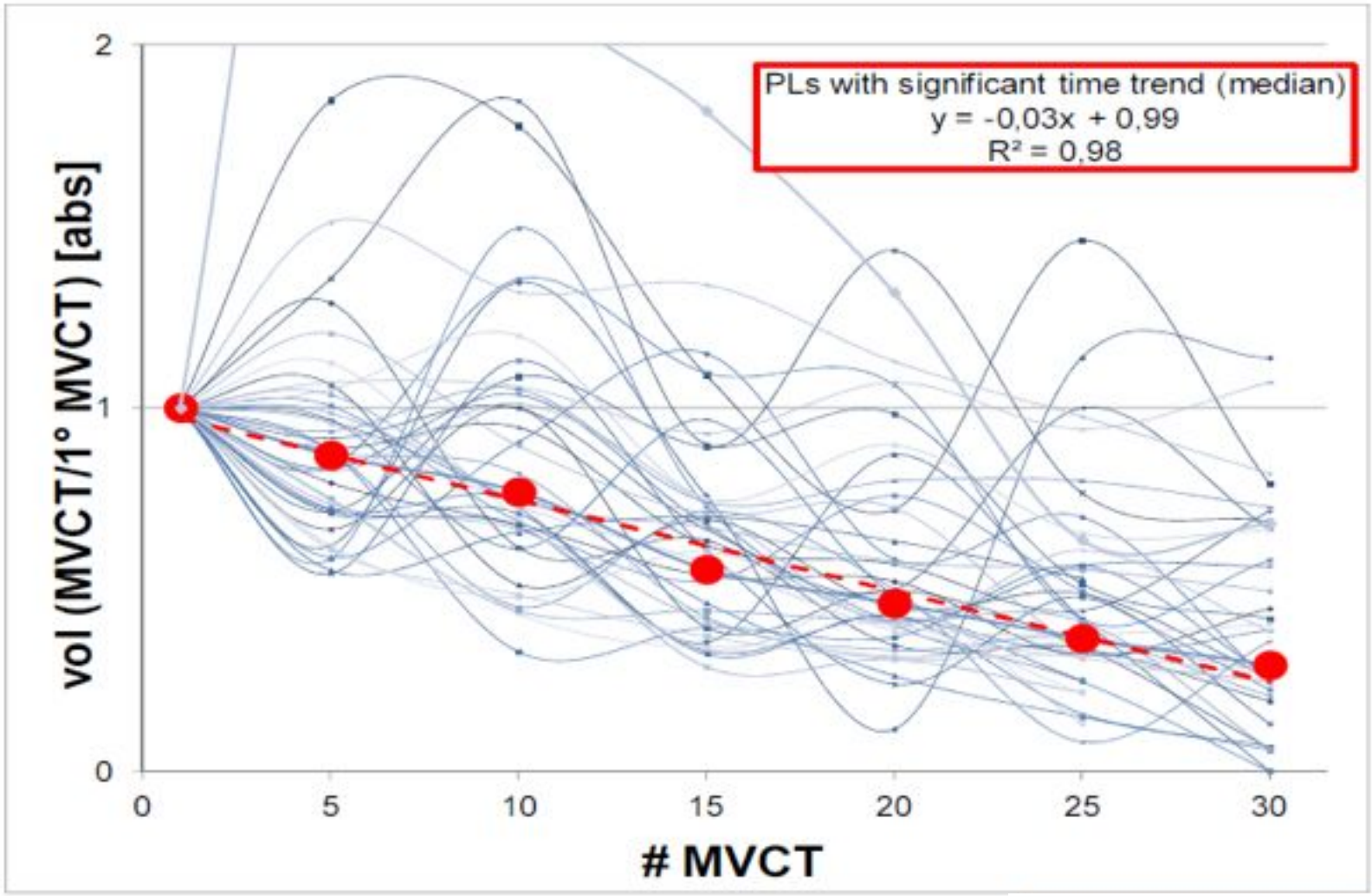
3 experties contouring

(median DICE:
kVCT: 0.92±0.02
MVCT: 0.86±0.07)

Rigid registration based on bony anatomy and high dose region

Belli et al. under review R&O

Dynamic



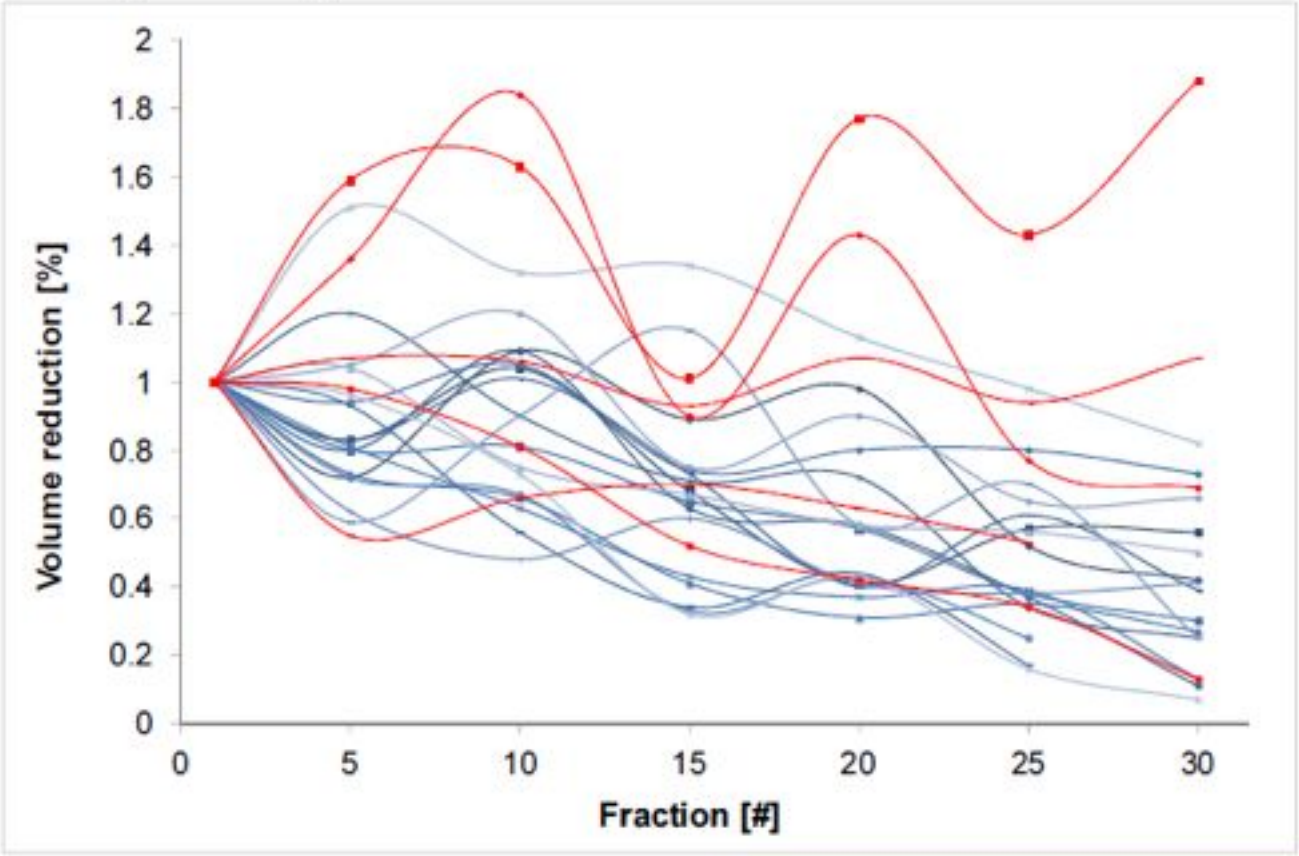
27/42 PLs: **significant volume shrinkage**
(average reduction at end of RT: 70; $p<0.05$)

Belli et al. under review R&O

Relapse

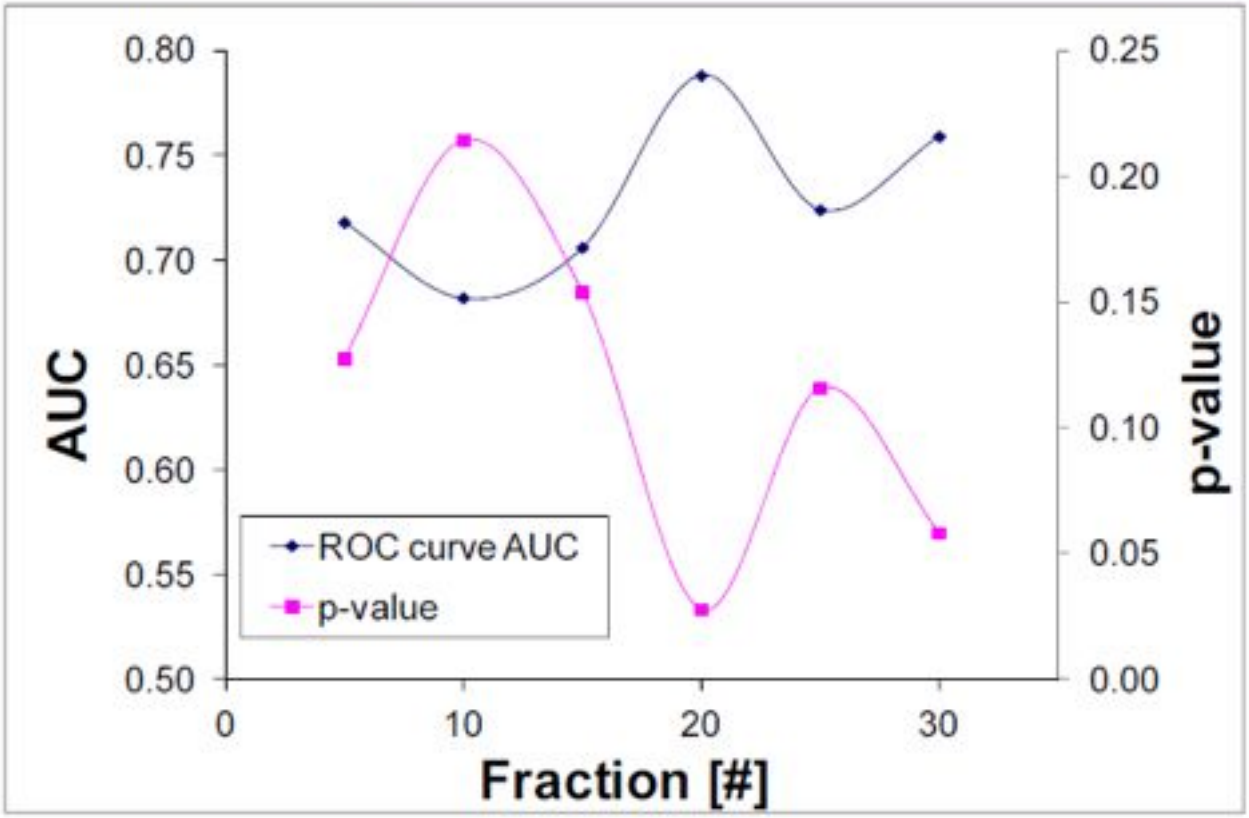
22/30 pts (29 PLs) with available follow-up information
(median: 15 mts, range: 3-69)

5 T relapse



Belli et al. under review R&O

Relapse



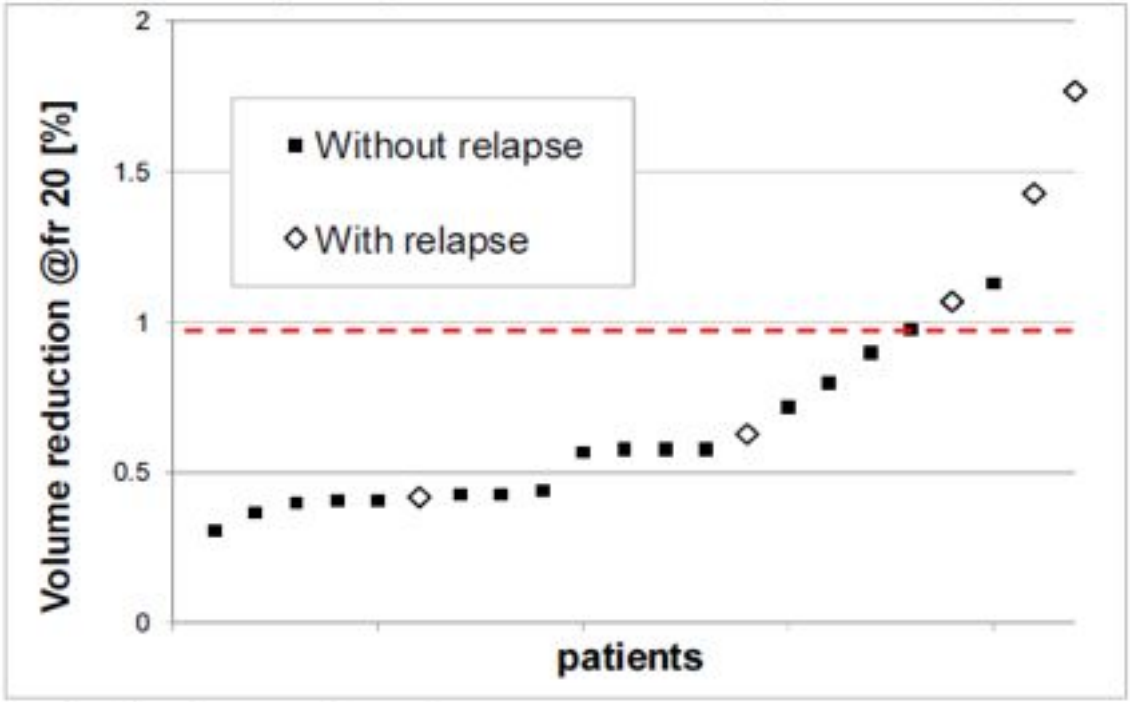
Optimal discriminantion @ **fr 20** with a best-cut off value=**0.98%** volume reduction

Volume variation @ fr 20 results to be a **significant predictive parameter of T relapse** (log-rank HR=0.15, 95% CI: 0.01-0.51, p-value=0.01)

Belli et al. under review R&O

Assessing **tumor response** during RT?

- ✓ **Morphological / functional** imaging may assess early response (in some cases in-room imaging is "enough")
- ✓ Early response may be **predictive** of long-term response



what kind of adaptation ?

...dose boosting in the remaining part, changing objectives, reducing dose, systemic therapy, adjuvant post-RT therapy….

Belli et al. under review R&O

International Journal of
Radiation Oncology
biology • physics

Replanning During Intensity Modulated Radiation Therapy Improved Quality of Life in Patients With Nasopharyngeal Carcinoma

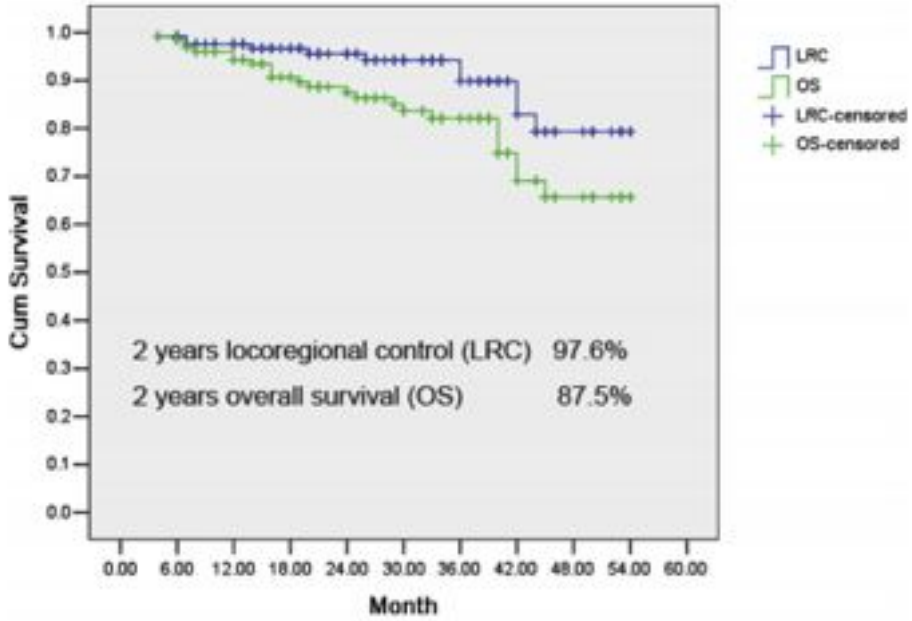


Fig. 1. Results of LRC and OS for 129 patients with NPC.

Table 1 Patient characteristics and dose differences in initial plans (n = 129)

Variable	No. of patients who underwent nonreplanning	No. of patients who underwent replanning	*P* value
Median age in y (range)	57 (26-77)	52 (28-73)	
Sex			
Male	23	55	.252
Female	20	31	
Median Karnofsky performance status (range)	90 (70-100)	90 (70-100)	
≤80	22	42	.803
>80	21	44	
AJCC stage			
I	6	9	.460
II	7	25	
III	17	29	
IV	13	23	
T stage			
T1	12	19	.193
T2	8	32	
T3	12	17	
T4	11	18	
N stage			
N0	13	16	.491
N1	14	33	
N2	13	28	
N3	3	9	
Chemotherapy			
No	6	9	.560
Yes	37	77	
GTVnx D95	73.01 ± 2.82	73.21 ± 3.01	.717
GTVnd D95	71.16 ± 1.96	71.20 ± 2.52	.942
CTV1 D95	60.89 ± 3.06	61.62 ± 2.37	.136
Left parotid gland mean dose	29.65 ± 4.01	29.93 ± 5.27	.762
Right parotid gland mean dose	29.49 ± 4.89	29.86 ± 3.73	.642

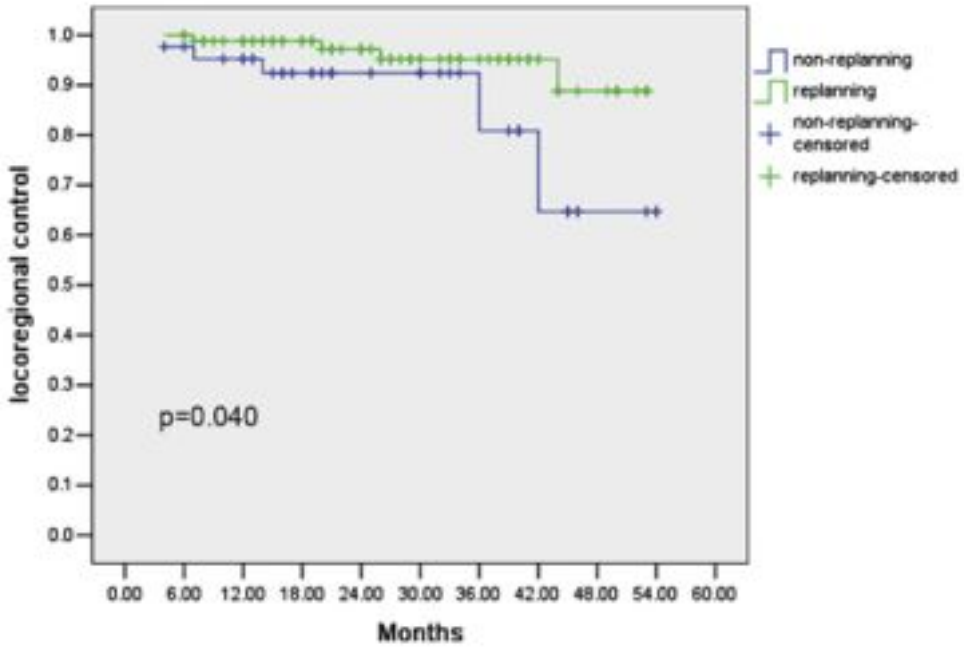


Fig. 2. Results of LRC for 86 NPC patients treated with IMRT replanning and 43 patients treated without IMRT replanning.

Summary

It is unclear whether anatomic and dosimetric alterations cause changes in clinical outcomes during intensity modulated radiation therapy (IMRT) for patients with nasopharyngeal carcinoma (NPC). The main finding of the present study was that IMRT replanning had a profound and favorable impact on the quality of life of NPC patients. Additionally, replanning during IMRT for NPC significantly improved 2-year local regional control but did not improve 2-year overall survival.

Table 3 Influence of the 13 EORTC QLQ-H&N35 scales due to replanning during intensity modulated radiation therapy for nasopharyngeal carcinoma using GLM-ANOVA test

Parameter	Before therapy	After therapy	1 mo after therapy	3 mo after therapy	6 mo after therapy	12 mo after therapy	*P* value
Teeth							
Nonreplanning	18.60 ± 24.45	23.26 ± 15.49	9.30 ± 15.13	10.85 ± 17.40	9.30 ± 15.13	10.08 ± 15.49	.031
Replanning	3.88 ± 10.75	14.73 ± 17.42	11.24 ± 15.85	8.14 ± 15.28	7.75 ± 15.06	11.63 ± 16.78	
Opening mouth							
Nonreplanning	8.53 ± 14.72	47.29 ± 16.64	38.76 ± 28.11	19.38 ± 24.38	19.38 ± 16.64	9.30 ± 15.13	.000
Replanning	4.65 ± 11.62	28.29 ± 23.16	13.18 ± 16.39	6.98 ± 13.64	6.98 ± 13.64	5.04 ± 12.01	
Dry mouth							
Nonreplanning	18.60 ± 24.45	57.36 ± 15.13	48.06 ± 24.45	56.59 ± 23.61	37.98 ± 11.69	33.33 ± 17.82	.000
Replanning	5.04 ± 15.77	50.39 ± 21.54	35.66 ± 16.80	37.21 ± 15.69	26.74 ± 14.30	24.81 ± 15.50	
Sticky saliva							
Nonreplanning	13.95 ± 16.64	43.41 ± 23.61	28.68 ± 27.78	37.98 ± 27.78	28.68 ± 21.31	24.03 ± 23.37	.015
Replanning	4.26 ± 15.16	46.90 ± 20.05	25.19 ± 16.91	29.85 ± 15.36	21.32 ± 16.10	16.67 ± 16.76	

QoL generally refers to the patient's perception of the effects of the disease and the impact on the patient's daily life. QoL is a multidimensional issue, incorporating physical, psychological, social, and emotional domains, and must be self-reported by the patient according to their own experiences. Many reports have

Our present study showed that replanning dramatically ameliorated dry mouth and sticky saliva compared with the nonreplanned therapy. This result was consistent with our previous studies in

Head & Neck
Volume 36, Issue 11, pages 1541–1546, November 2014

Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning

TABLE 1. Clinical and disease characteristics.

Characteristic	Adaptive (%)	Nonadaptive (%)
Primary site ($p = .54$)		
Oropharynx	22 (43)	105 (39)
Oral cavity	8 (16)	66 (25)
Larynx/hypopharynx	8 (16)	56 (21)
Nasopharynx	8 (16)	17 (7)
Unknown primary	5 (10)	22 (8)
Clinical T classification ($p = .63$)		
T0	5 (10)	22 (8)
T1	7 (14)	70 (26)
T2	11 (22)	65 (24)
T3	11 (22)	53 (20)
T4	17 (33)	56 (21)
Clinical N classification ($p = .30$)		
N0	6 (12)	50 (30)
N1	6 (12)	48 (18)
N2	27 (53)	129 (49)
N3	12 (24)	39 (15)
Age ($p = .01$)		
<57 y	22 (43)	140 (53)
>57 y	29 (57)	126 (47)
Radiation modality ($p = .01$)		
Definitive	39 (76)	140 (52)
Postoperative	12 (24)	126 (47)
Concurrent chemotherapy ($p = .01$)		
Yes	33 (65)	111 (41)
No	28 (55)	155 (58)

From July 2007 to January 2013, a total of 317 patients underwent IMRT for newly diagnosed, biopsy-proven squamous cell carcinoma of the head and neck. Of these 317 patients, 51 (16%) underwent adaptive radiotherapy

TABLE 2. Predominant indications for adaptive replanning.

Indication	No. of patients (%)
Weight loss	17 (33)
Tumor shrinkage	12 (24)
Poorly fitting mask	12 (24)
Prolonged break	10 (20)

Head & Neck
Volume 36, Issue 11, pages
1541–1546, November 2014

2-year OS

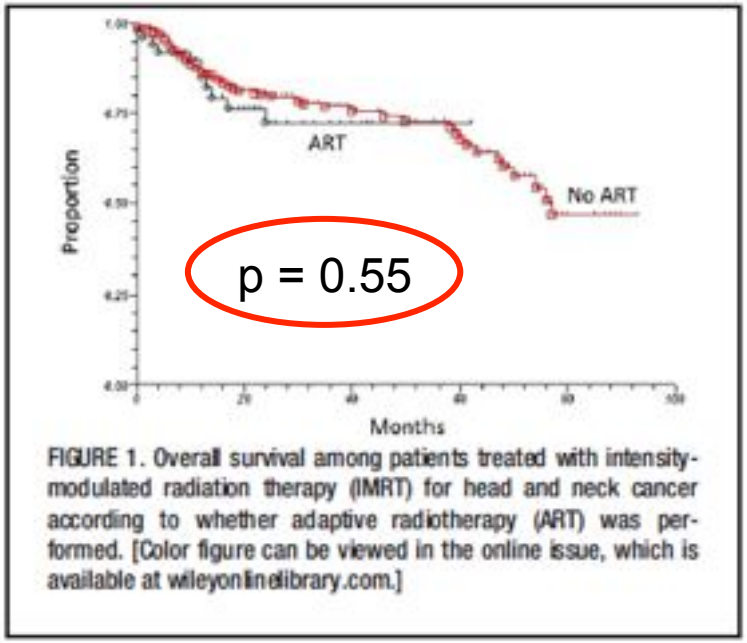


FIGURE 1. Overall survival among patients treated with intensity-modulated radiation therapy (IMRT) for head and neck cancer according to whether adaptive radiotherapy (ART) was performed. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2-year LRC

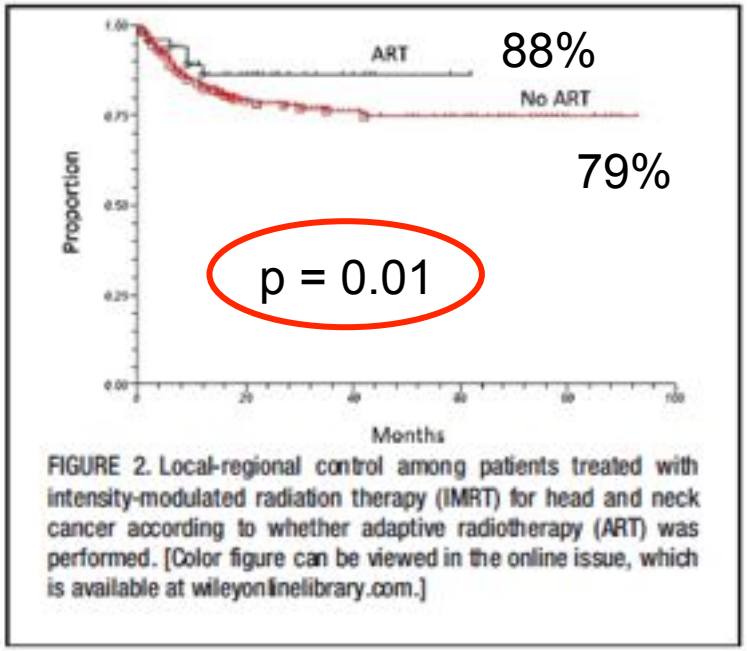


FIGURE 2. Local-regional control among patients treated with intensity-modulated radiation therapy (IMRT) for head and neck cancer according to whether adaptive radiotherapy (ART) was performed. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Based on these results, the present series is among the first to suggest that the theoretical benefits of adaptive replanning may be associated with actual clinical advantages for patients treated by IMRT for head and neck cancer. This is particularly important given the widespread

2 comparison arms. Indeed, the observation that patients treated with adaptive radiotherapy had superior local-regional control despite the significantly higher incidence of T3/T4 disease and N3 metastasis strongly highlights the importance of accurate and precise delivery of radiation therapy.

Conclusions and future trends…

- **ART** is not an automatic procedure, but rather a **process** that have to be **guided** (….continuous improvement…)
- Information acquired **during treatment** could guide the ART process

  - ✓ **PGs early** (i.e. during the **first 2 week** of treatment) volume/density variations predict **final deformation** at the end of therapy and **acute xerostomia** score. Texture parameters as global and synthetic image-based indices to describe structural modifications of PGs (**in-vivo** measurement of the reduction of acinar cells ??)
  - ✓ **PLs** volume variation well correlates with **T relapse**

adapt tmt?
supportative therapies?

boosting?
margin adapting?
concomitant therapies?

- **Simple and smart ART strategies** (cost, time and energy consuming evaluation,…)
- Need of **prospective ART trials**