



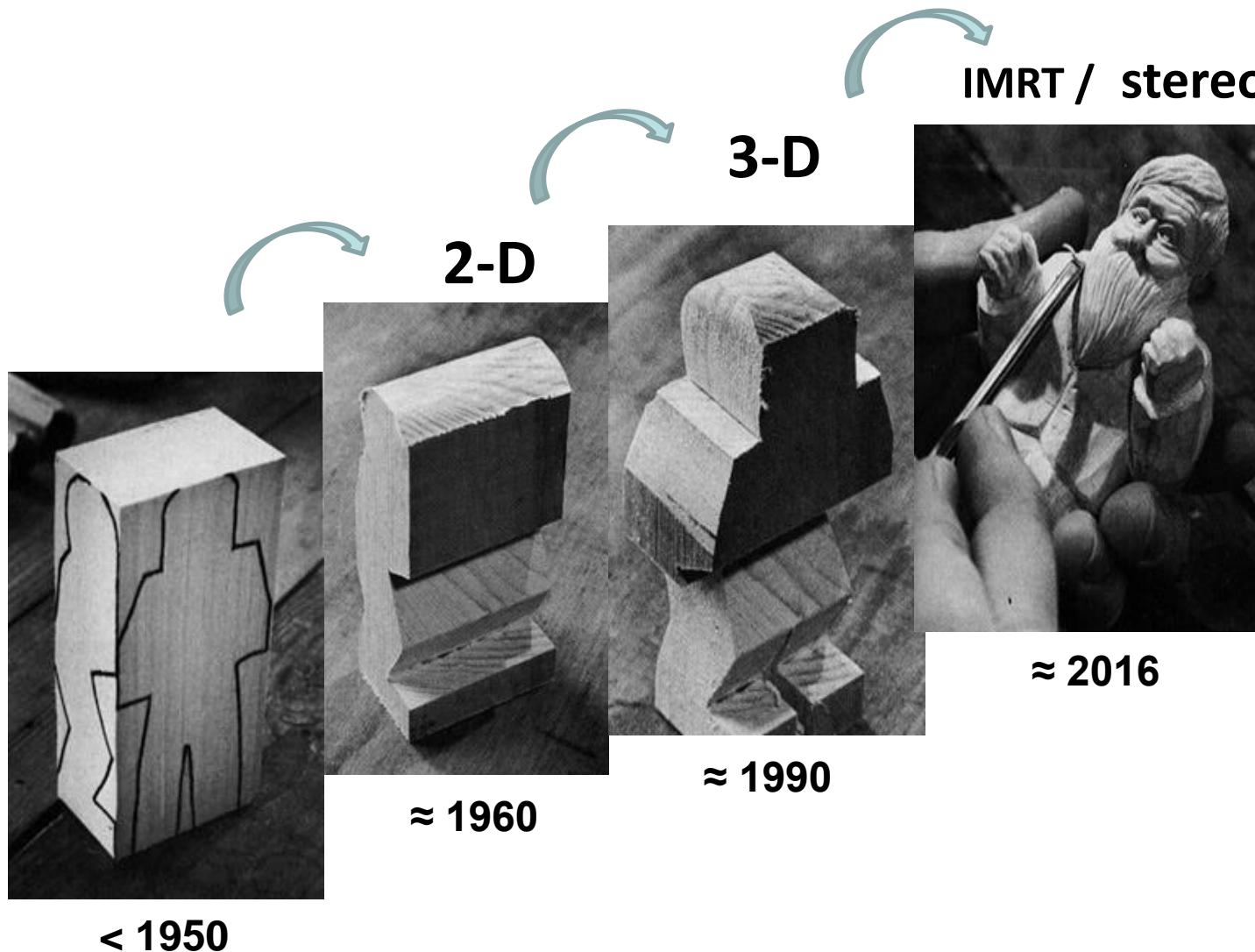
# **IMRT in Head and Neck Cancer: Beyond Parotid Sparing...**

*Prof. Jean Bourhis*

*Unil*  
UNIL | Université de Lausanne



# Better and better target definition & delivery ...



# **Head and neck cancer : radiation-induced side effects after CT-RT ...**

- **Significant impact on quality of life**
- **Xerostomia:**
  - Most frequently Grade  $\geq 2$  were reported
  - Impact on quality of life increases with time
- **Dysphagia:**
  - Most frequently Grade  $\geq 3$  were reported
  - Major impact on quality of life
  - Impact more pronounced in first 12 months after completion of RT
- **Trismus, Dental defect, Neck fibrosis ...**

**Side  
Effects  
In HNC**



**High dose (50-70 Gy)**

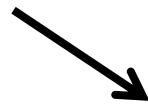


**Large volume (50Gy in 800-1600 cc)**

**Side  
effects**



**High dose : can we decrease the dose ?**

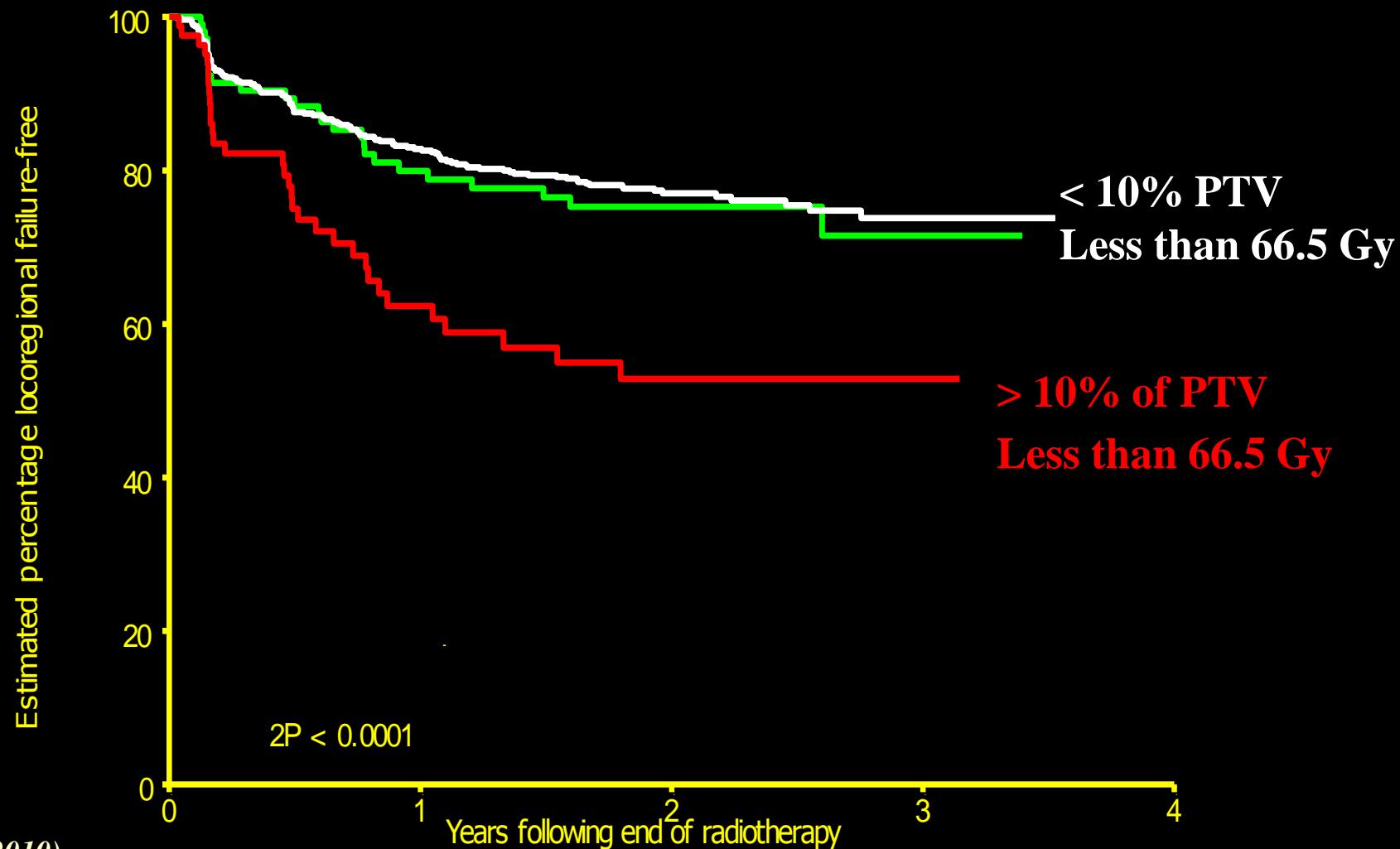


**Large volume**

**Small variations in dose → major impact**

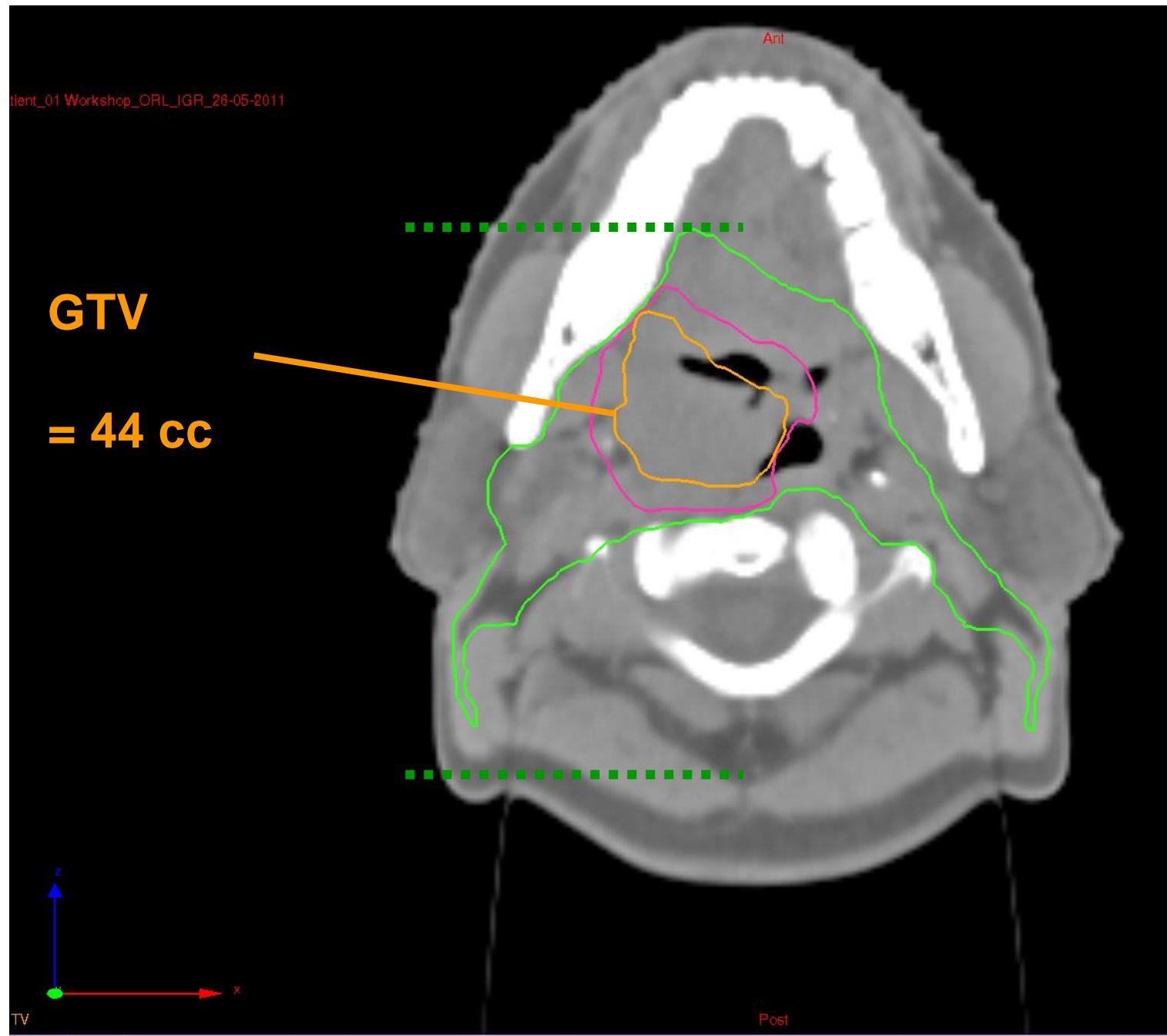
70 Gy + Cisplatin,

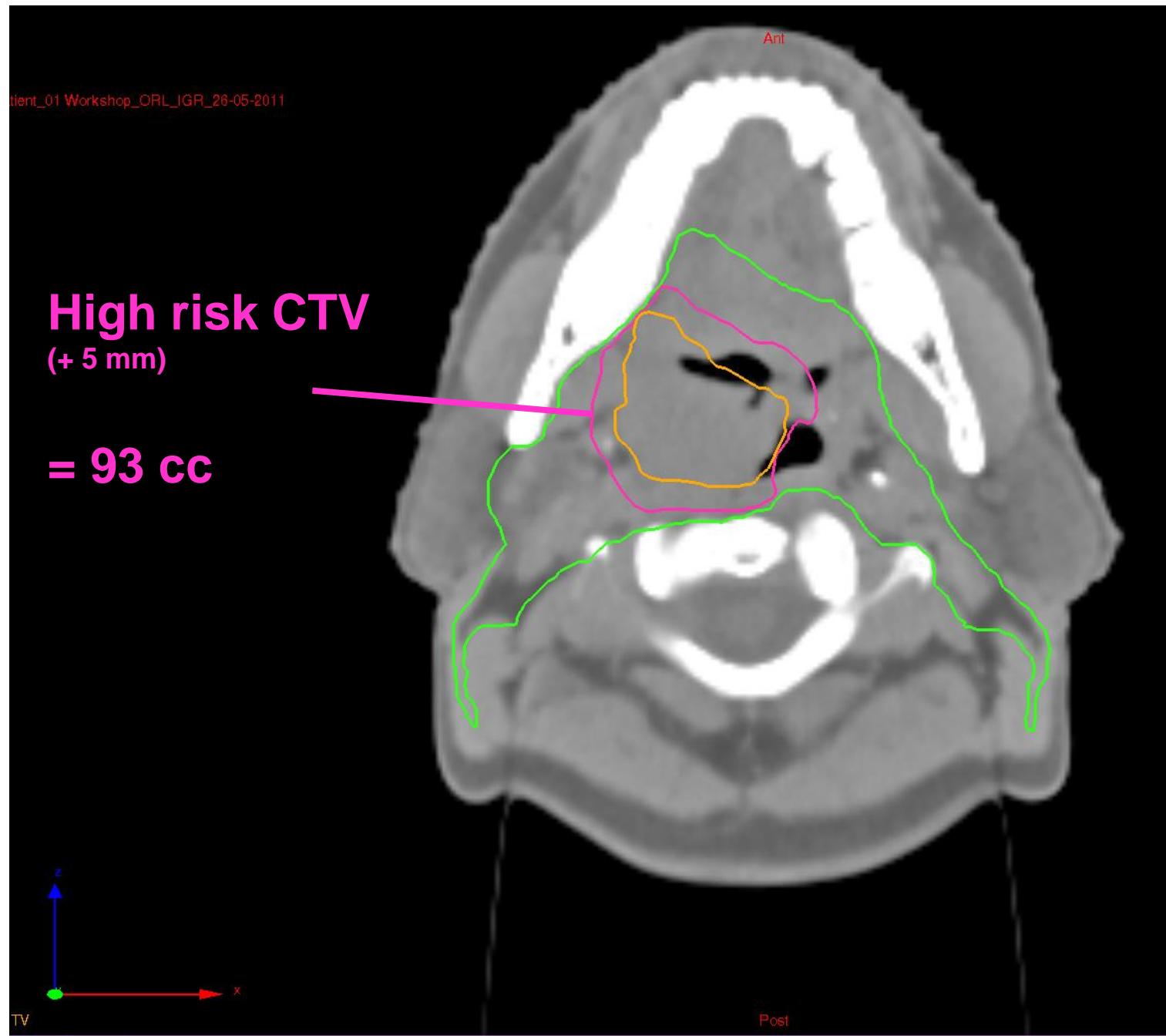
N= 840 patients randomized

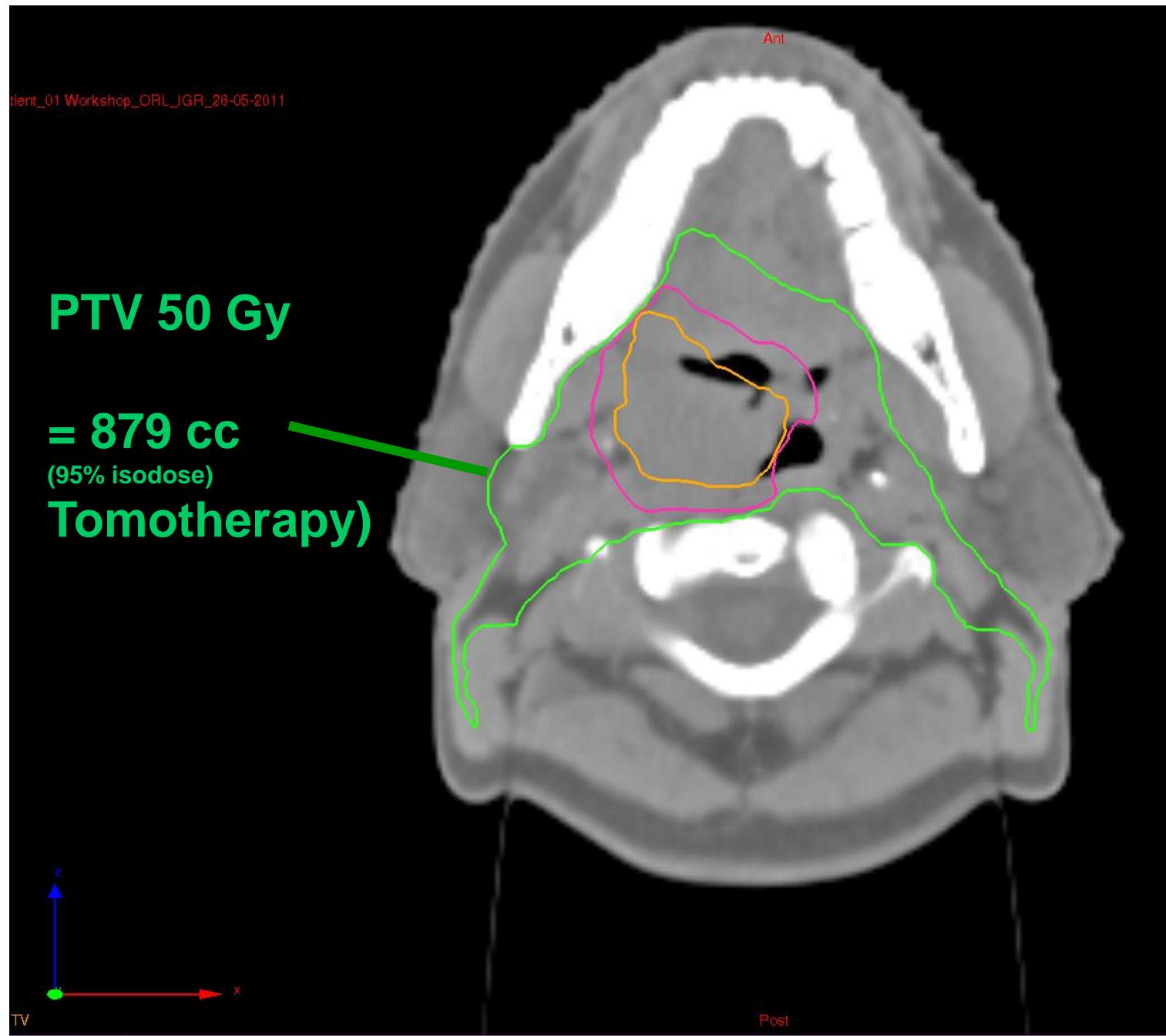


**No compromize with the RT dose +++ (HPV ?)**

but ... can we decrease safely  
the volume of RT ? to decrease side effects ?



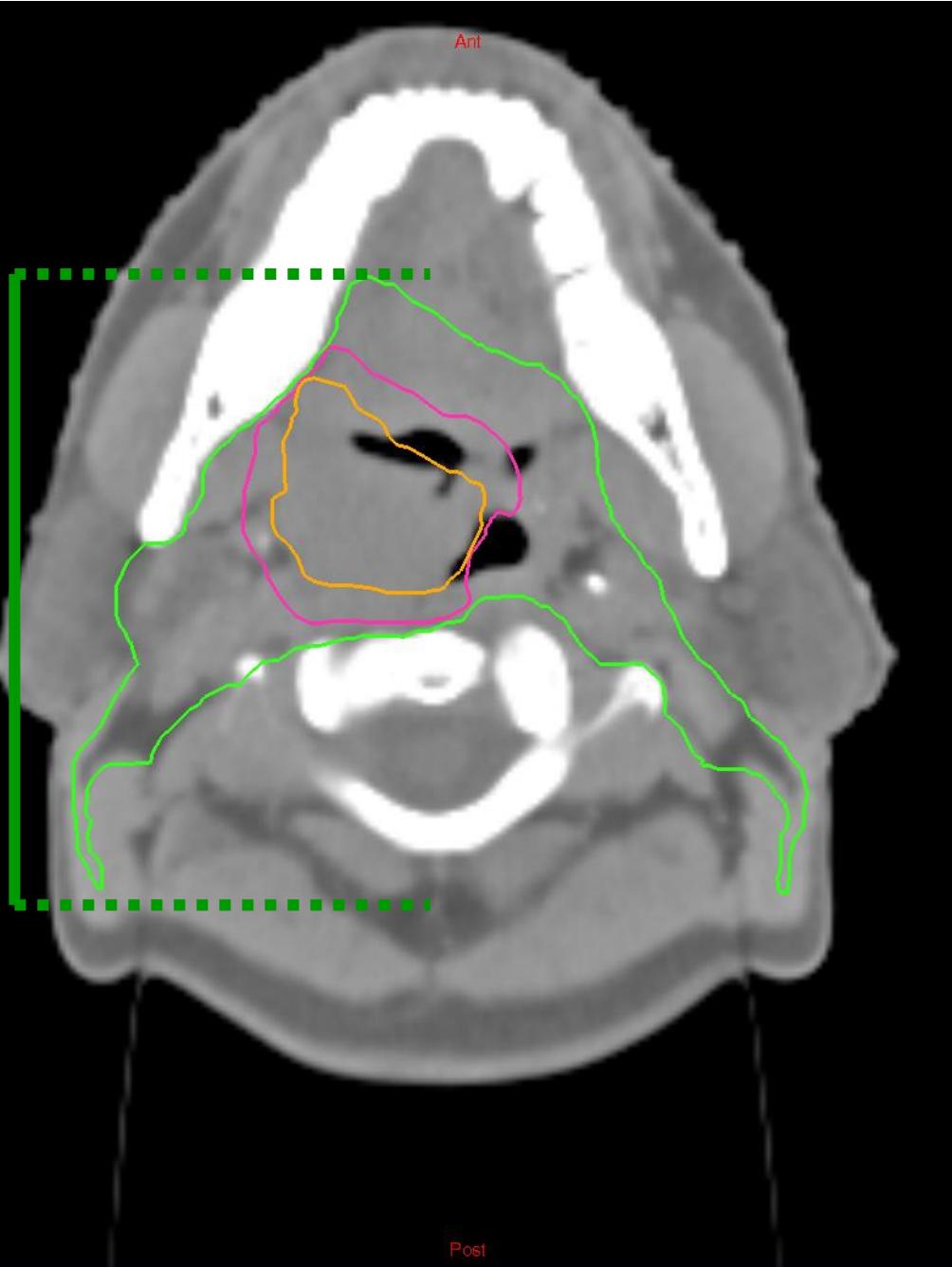




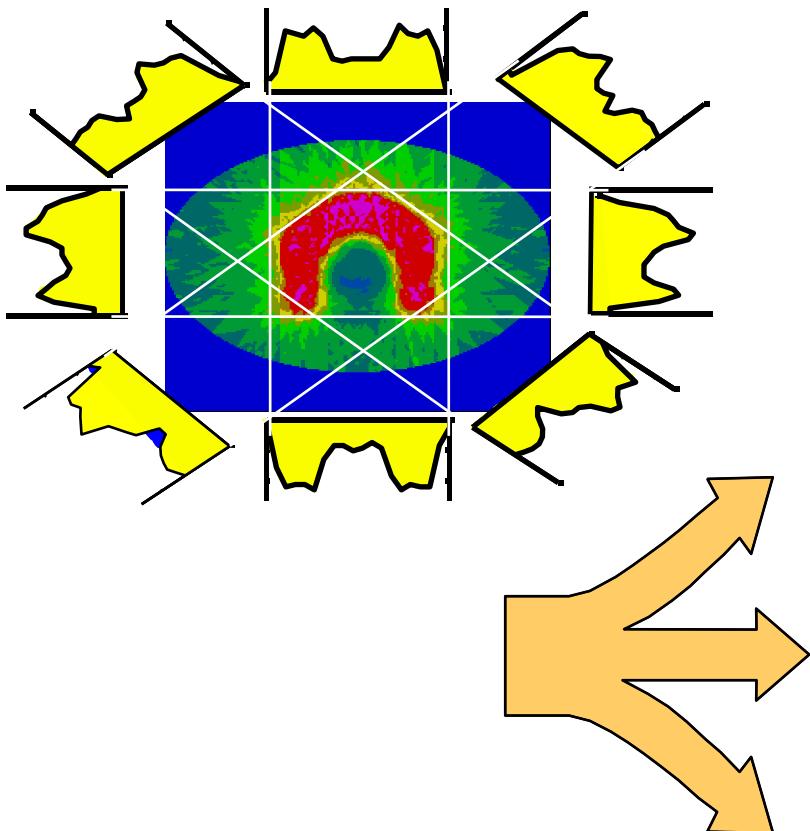
Patient\_01 Workshop\_ORL\_IGR\_26-05-2011

**PTV 50 Gy  
3D RT  
(95% isodose)**

**= 1489 cc**

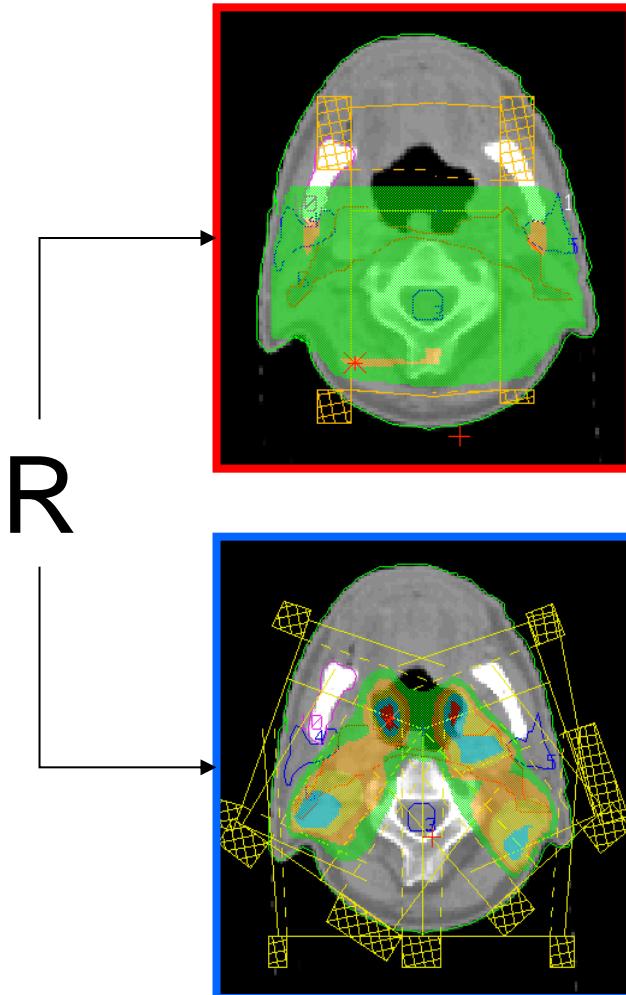


# IMRT



- 1) Better normal tissue protection**
- 2) Dose escalation to the tumor**  
*Interesting if :*
  - Most relapses in the GTV
  - Dose effect relationship
- 3) Dose sculpting**

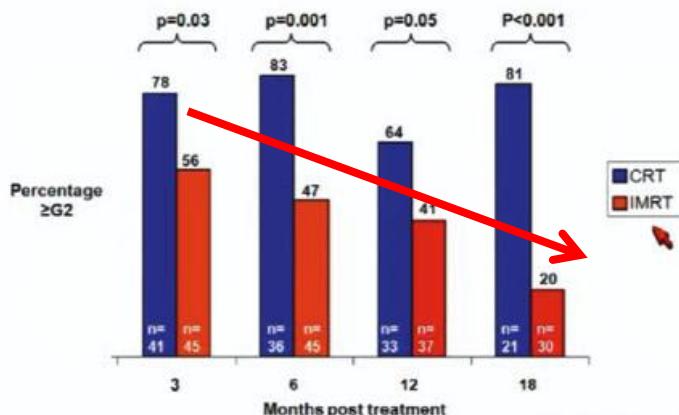
# Phase III study : 3D-CRT versus IMRT



- 3D-CRT
  - 47 patients
  - 60-65 Gy in 30 fractions
  - $D_{mean}$  parotid glands:
    - Ipsilateral: 61.0 Gy
    - Contralateral: 61.0 Gy
- IMRT
  - 47 patients
  - 60-65 Gy in 30 fractions
  - $D_{mean}$  parotid glands:
    - Ipsilateral: 46.7 Gy
    - Contralateral: 25.4 Gy

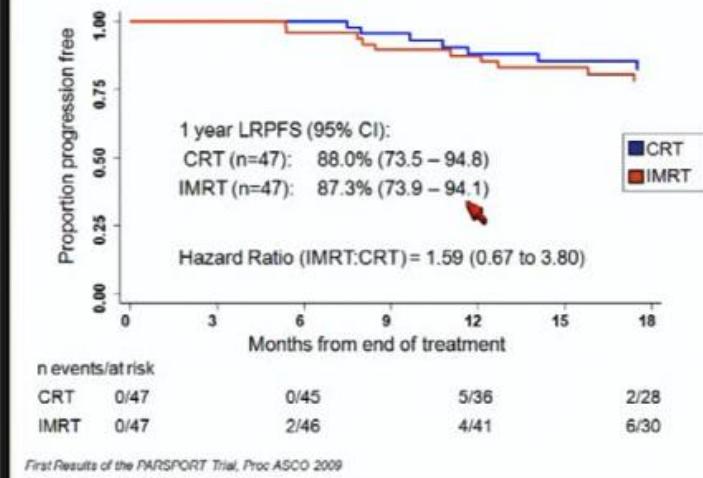
# Gain with IMRT

## RTOG Subjective Salivary Gland toxicity $\geq G2^*$



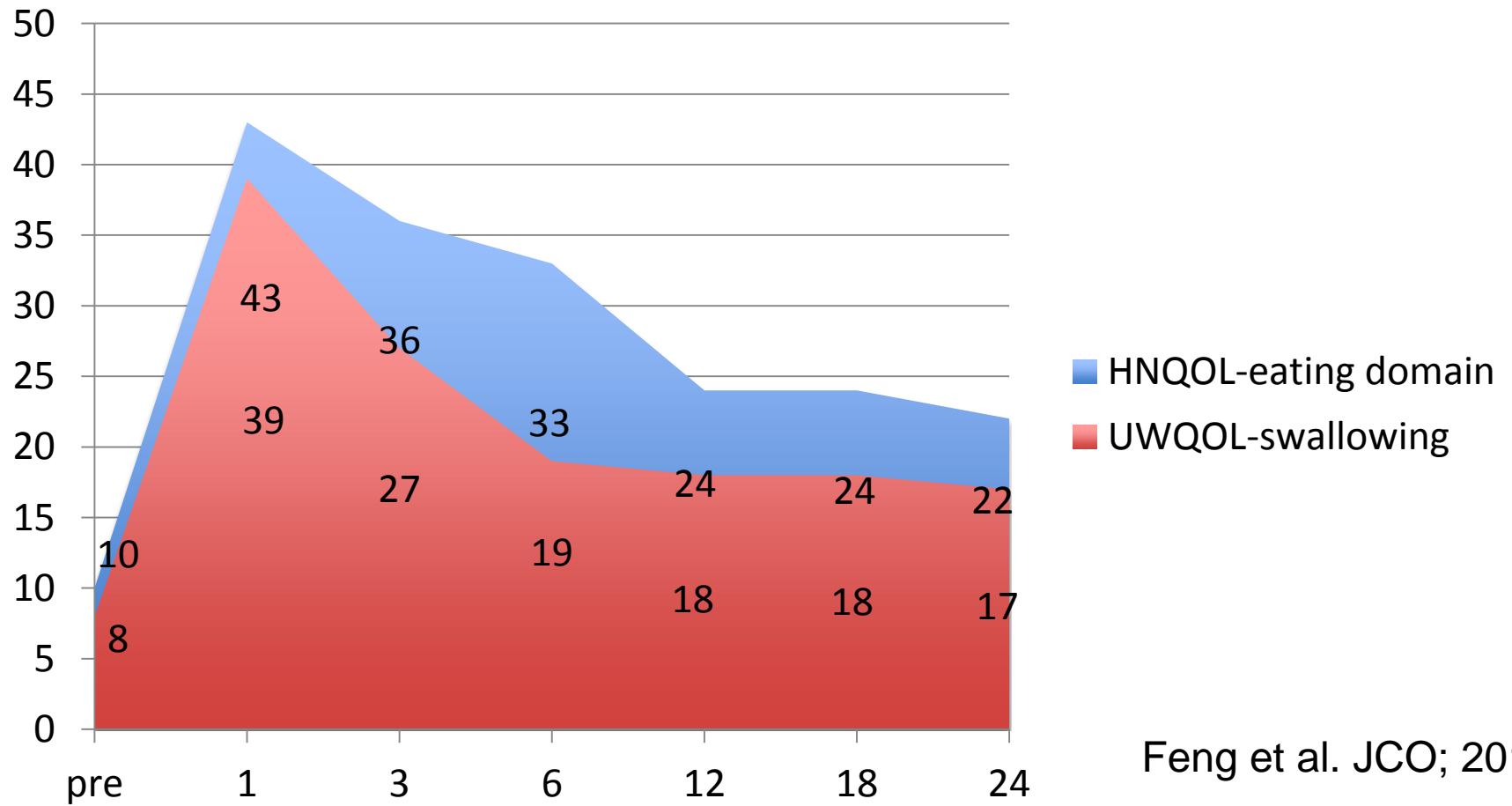
First Results of the PARSPORT Trial, Proc ASCO 2009

## Loco-Regional Progression Free Survival (LRPFS)



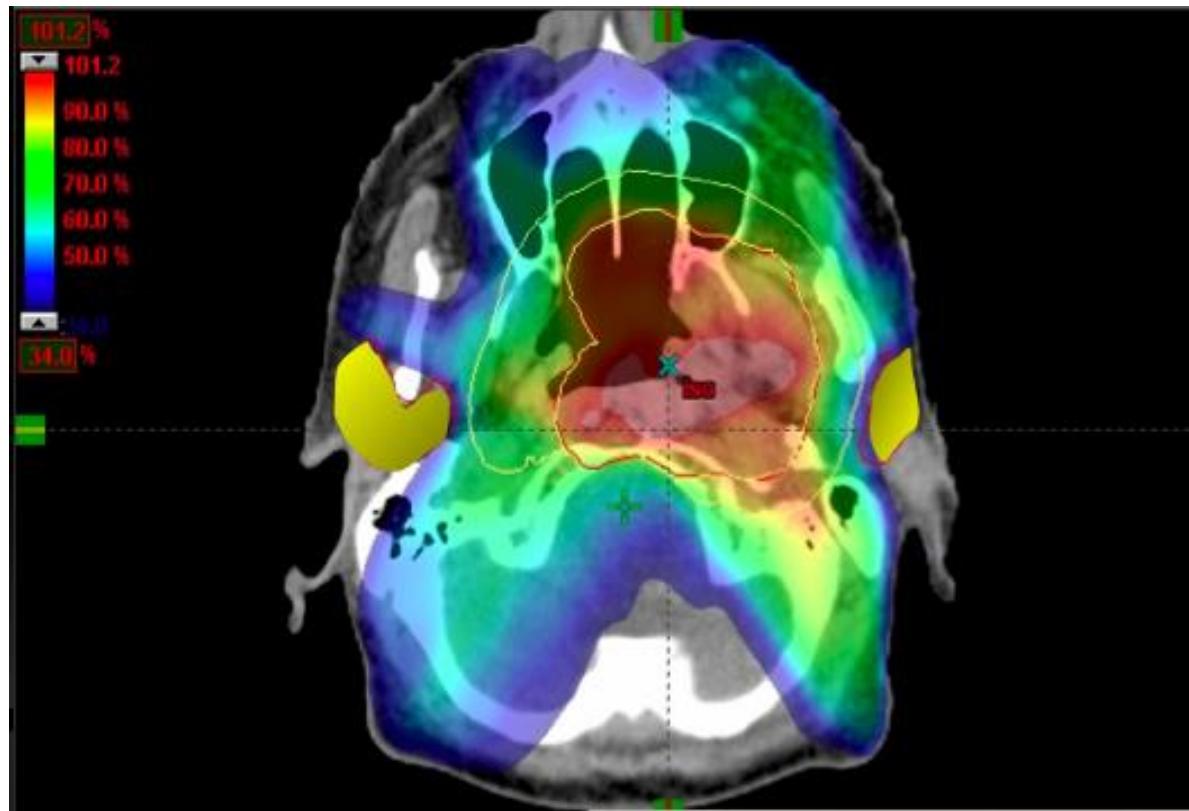
Nutting et al, Lancet Oncol 2011  
The PARSORT trial

# Dynamics of swallowing recovery after IMRT for locally advanced oropharyngeal SCC



Feng et al. JCO; 2010

# Is parotid sparing compromizing tumor control probability ?



# Does recurrence rate increase by using parotid-sparing IMRT in head and neck cancer ?



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0360-3016/04/\$—see front matter

doi:10.1016/j.ijrobp.2003.10.032

## CLINICAL INVESTIGATION

## Head and Neck

No

### RECURRENCES NEAR BASE OF SKULL AFTER IMRT FOR HEAD-AND-NECK CANCER: IMPLICATIONS FOR TARGET DELINEATION IN HIGH NECK AND FOR PAROTID GLAND SPARING

AVRAHAM EISBRUCH, M.D.,<sup>\*</sup> LON H. MARSH, C.M.D.,  
CAROL R. BRADFORD, M.D.,<sup>†</sup> THEODOROS N. TEKNOS, M.I.  
FRANCIS P. WORDEN, M.D.,<sup>‡</sup> SUSAN URBA, M.D.,<sup>‡</sup>  
MATTHEW J. SCHIPPER, M.S.C.,<sup>§</sup> AND GREGO



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PII S0360-3016(02)03940-8

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## CLINICAL INVESTIGATION

## Head and Neck

### PATTERNS OF FAILURE IN PATIENTS RECEIVING DEFINITIVE AND POSTOPERATIVE IMRT FOR HEAD-AND-NECK CANCER

K. S. CLIFFORD CHAO, M.D.,<sup>\*</sup> GOKHAN OZYIGIT, M.D.,<sup>\*</sup> BINH N. TRAN, M.D.,<sup>\*</sup>  
MUSTAFA CENGIZ, M.D.,<sup>\*</sup> JAMES F. DEMPSEY, PH.D.,<sup>†</sup> AND DANIEL A. LOW, PH.D.\*

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## Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer

Barbara Bussels<sup>a,\*</sup>, Annelies Maes<sup>b</sup>, Robert Hermans<sup>c</sup>, Sandra Nuyts<sup>a</sup>, Caroline Weltens<sup>a</sup>,  
Walter Van den Bogaert<sup>a</sup>

No..

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<sup>c</sup>Department of Radiology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

# Does recurrence rate increase by using parotid-sparing IMRT in head and neck cancer ?



Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 1, pp. 164–168, 2010

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0360-3016/\$—see front matter

doi:10.1016/j.ijrobp.2009.01.037

## CLINICAL INVESTIGATION

## Head and Neck

No

### MARGIN ON GROSS TUMOR VOLUME AND RISK OF LOCAL RECURRENCE IN HEAD-AND-NECK CANCER

JIMMY J. CAUDELL, M.D., PH.D., RUBY F. MEF  
KIMBERLEY S. KEENE, M.D., M. CHRISTIAN DOBEI

Strahlentherapie  
und Onkologie

Department of Radiation Oncology, Univers

Original Article



No

doi:10.1016/j.ijro

### Locoregional Failure Analysis in Head-and-Neck Cancer Patients Treated with IMRT

Gabriela Studer, Urs M. Luetolf, Christoph Glanzmann<sup>1</sup>

## CLINICAL INVESTIGATION

## Head and Neck

### PATTERNS OF FAILURE AND TOXICITY AFTER INTENSITY-MODULATED RADIOTHERAPY FOR HEAD AND NECK CANCER

No.

GORDON O. SCHOENFELD, M.D., ROBERT J. AMDUR, M.D., CHRISTOPHER G. MORRIS, M.S.,  
JONATHAN G. LI, PH.D., RUSSELL W. HINERMAN, M.D., AND WILLIAM M. MENDENHALL, M.D.

Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL

# Does recurrence rate increase by using parotid-sparing IMRT in head and neck cancer ? (more recent series)

Clinical Investigation: Head and Neck Cancer

## Patterns of Disease Recurrence Following Treatment of Oropharyngeal Cancer With Intensity Modulated Radiation Therapy

Adam S. Garden, MD,\* Lei Dong, PhD,† William H. Morrison, MD,\* Erich M. Stugis, MD, MPH,§|| Bonnie S. Glisson, MD,‡ Steven J. Frank, MD,\* Beth M. Beadle, MD, PhD,\* Gary B. Gunn, MD,\* David L. Schwartz, MD,¶ Merill S. Kies, MD,\* Randal S. Weber, MD,§ K. Kian Ang, MD, PhD,\* and David I. Rosenthal, MD\*

Departments of \*Radiation Oncology, †Radiation Physics, ‡Thoracic/Head and Neck Medicine, §Head and Neck Surgery, ¶Epidemiology, University of Texas MD Anderson Cancer Center, Houston, TX; and \*Department of Radiation Medicine, Long Island Jewish Medical Center, New Hyde Park, NY

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Radiation Oncology  
biology • physics  
2013

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doi:10.1016/j.ijrobp.2010.10.041

### CLINICAL INVESTIGATION

### Head and Neck Cancer

## INTENSITY-MODULATED RADIOTHERAPY IN THE TREATMENT OF OROPHARYNGEAL CANCER: AN UPDATE OF THE MEMORIAL SLOAN-KETTERING CANCER CENTER EXPERIENCE

JEREMY SETTON, B.A.,\*† NICOLA CARIA, M.D.,\*† JONATHAN ROMANYSHYN, M.D.,\* LAWRENCE KOUTCHER, M.D.,\* SUZANNE L. WOLDEN, M.D.,\* MICHAEL J. ZELEFSKY, M.D.,\* NICHOLAS ROWAN, B.A.,\* ERIC J. SHERMAN, M.D.,† MATTHEW G. FURY, M.D., Ph.D.,† DAVID G. PFISTER, M.D.,† RICHARD J. WONG, M.D.,‡ JATIN P. SHAH, M.D.,‡ DENNIS H. KRAUS, M.D.,‡ WEIJI SHI, M.S.,§ ZHIGANG ZHANG, Ph.D.,§ KAREN D. SCHUPAK, M.D.,\* DAPHNA Y. GELBLUM, M.D.,\* SHYAM D. RAO, M.D., Ph.D.,\* AND NANCY Y. LEE, M.D.\*

From the Departments of \*Radiation Oncology, †Medicine, ‡Surgery, §Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

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doi:10.1016/j.ijrobp.2009.04.006

### CLINICAL INVESTIGATION

### Head and Neck

## INTENSITY-MODULATED RADIOTHERAPY IN THE TREATMENT OF OROPHARYNGEAL CANCER: CLINICAL OUTCOMES AND PATTERNS OF FAILURE

MEGAN E. DALY, M.D., QUYNH-THU LE, M.D., PETER G. MAXIM, Ph.D., BILLY W. LOO, Jr., M.D., Ph.D., MICHAEL J. KAPLAN, M.D., NANCY J. FISCHBEIN, M.D., HARLAN PINTO, M.D., AND DANIEL T. CHANG, M.D.

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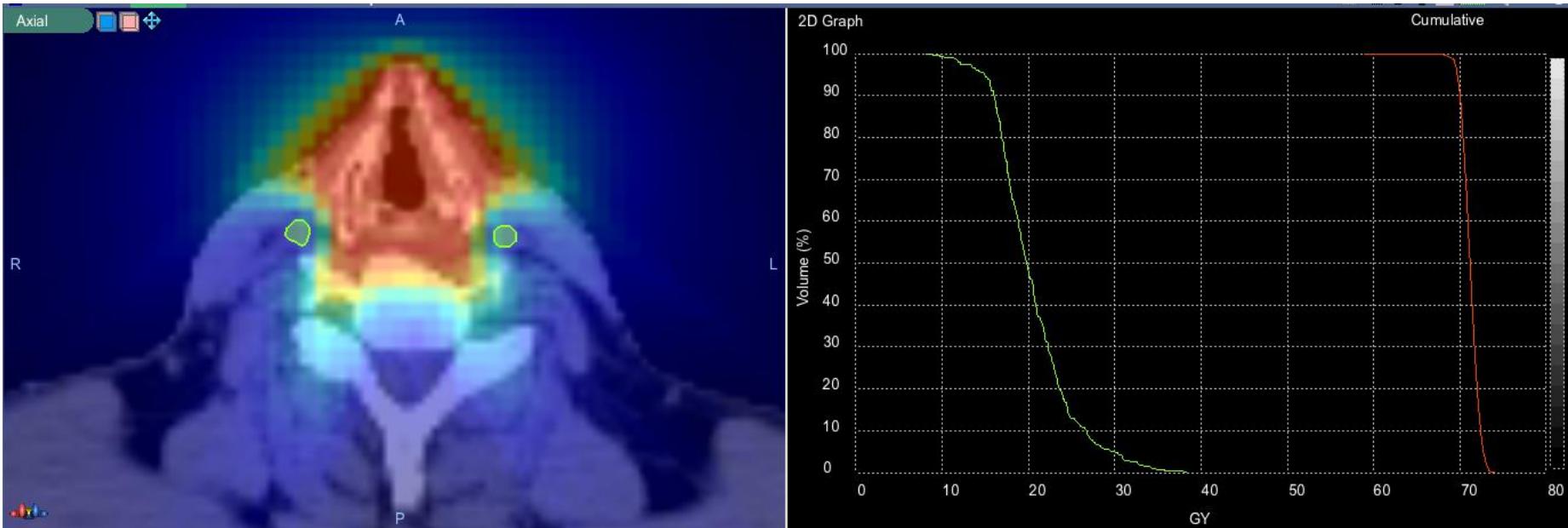
**IMRT : beyond parotid sparing ?**

## Uni or bilateral radiotherapy ?



- Well (very) lateralized tumors
- Minimal nodal involvement
- Other than base of tongue & soft palate tumors

# Carotid sparing IMRT : example in early glottic cancer



**N = 23 patients treated at CHUV  
Median Follow-up = 4 years,  
Local control = 100%**

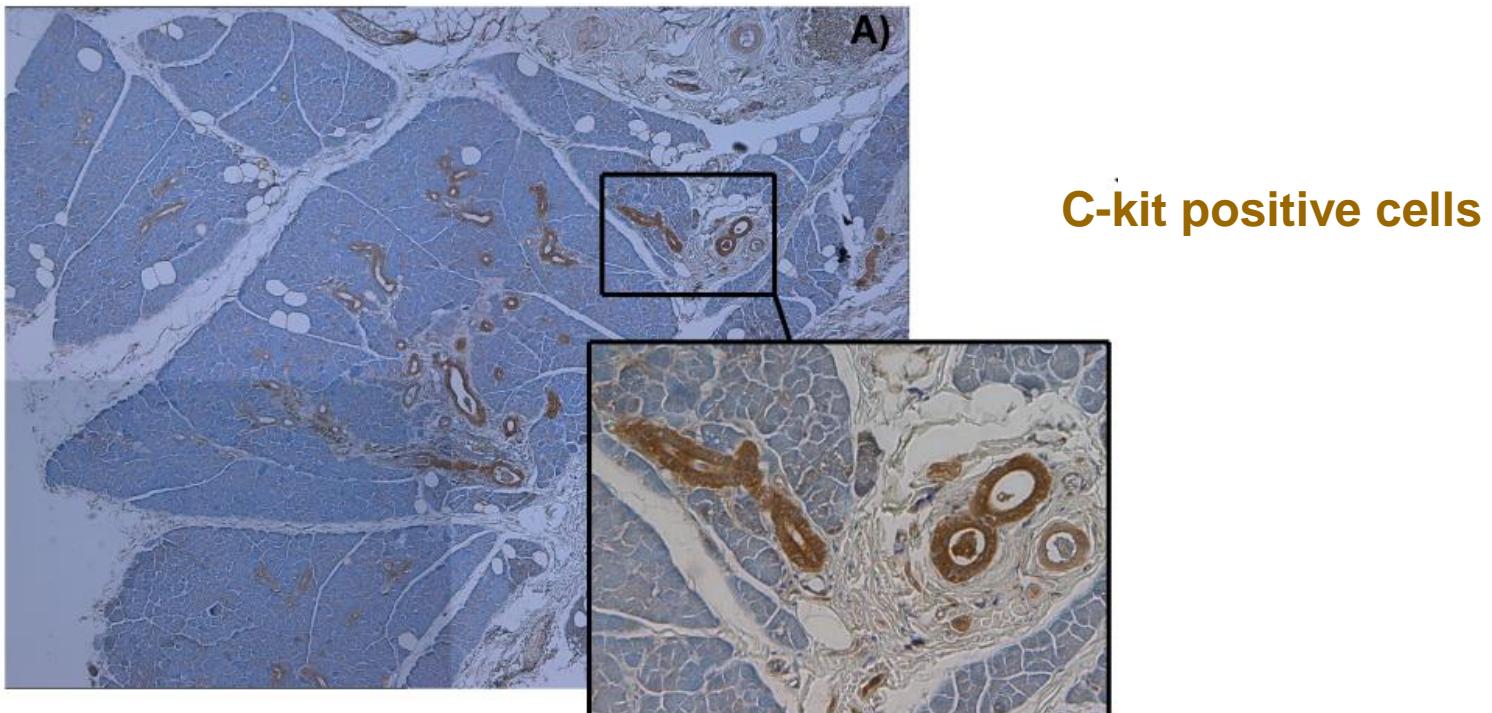
# Stem-cell sparing IMRT ?

van Luijk et al 2012 :

- **Parotid stem cells** : necessary for the maintenance of organ function
- Reductions of RT dose to some parts of the gland allow the **parotid to regenerate**
- Stem cells located **in the central part of the major ducts** of the parotid
- **Proton RT to this central part of the gland** resulted in a significant reduction in saliva production in rats

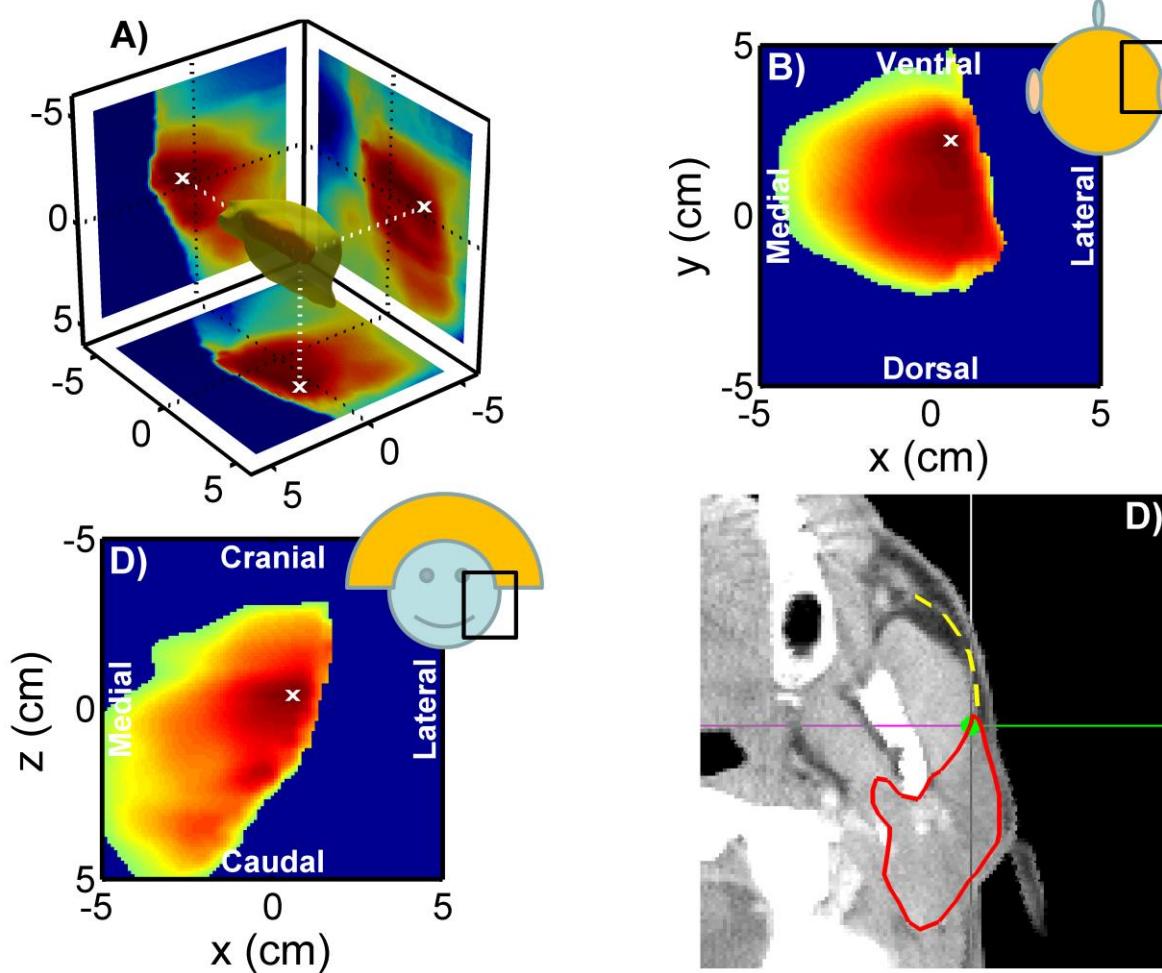
# Parotid stem cells sparing

- Region of major salivary ducts most radiosensitive part
- stem cells located along salivary ducts (*mouse, rat, humans*)



# The cranio-ventral region contains the major ducts

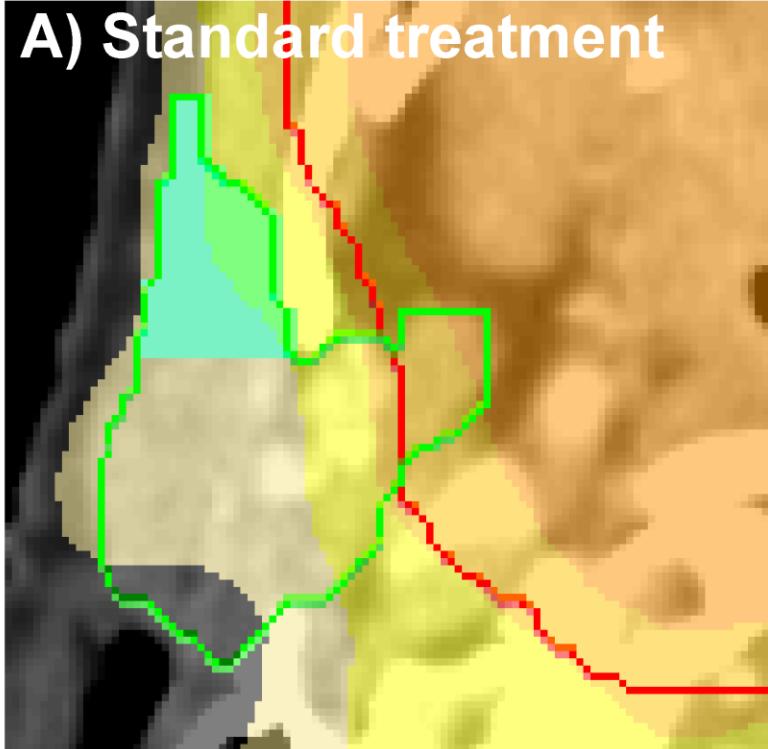
= Most predictive of saliva dysfunction at 1 year (van Luyck, N = 36 patients)



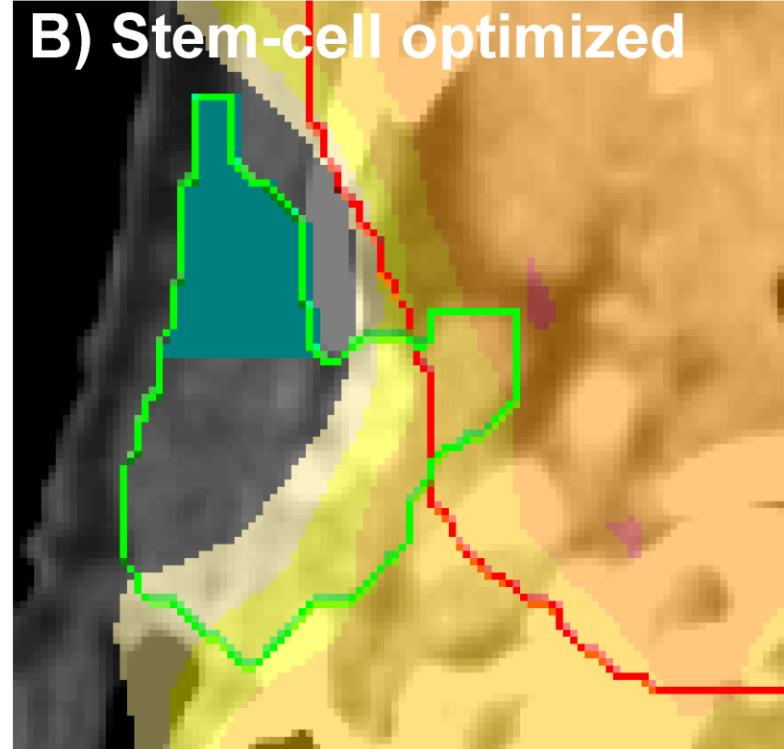
# Stem-cell sparing IMRT

Planning comparison study

A) Standard treatment

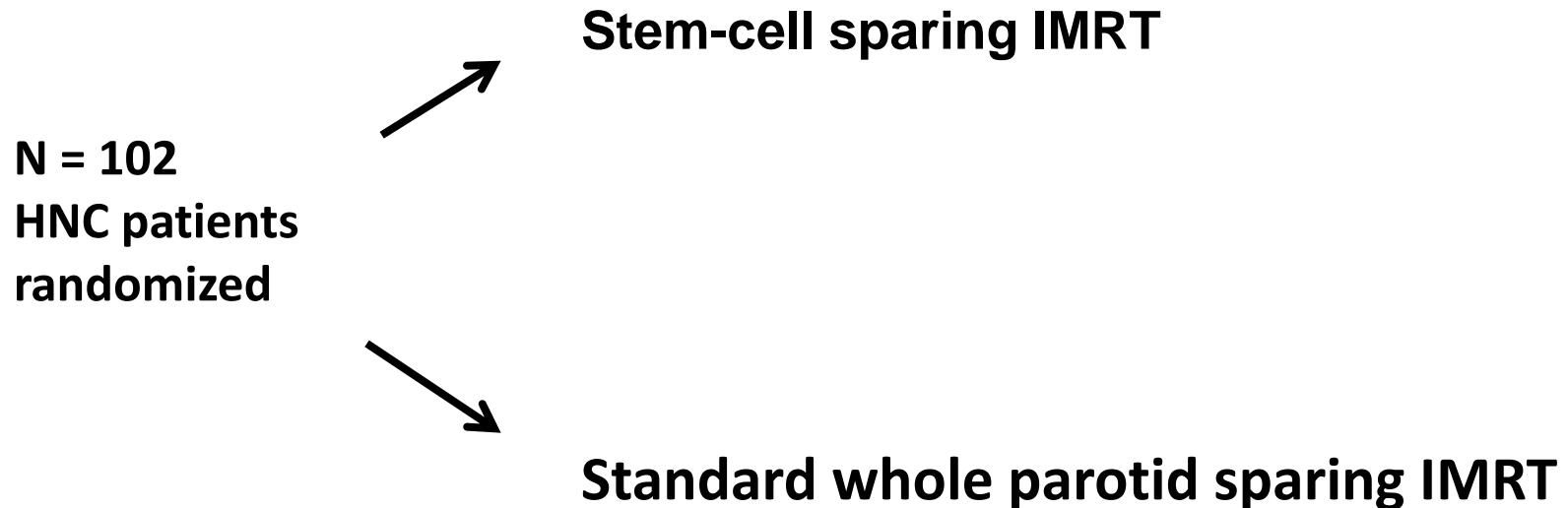


B) Stem-cell optimized



Based on planning comparison: expected reduction severe xerostomia (<25% salivary at baseline): 50% ▶ <20%

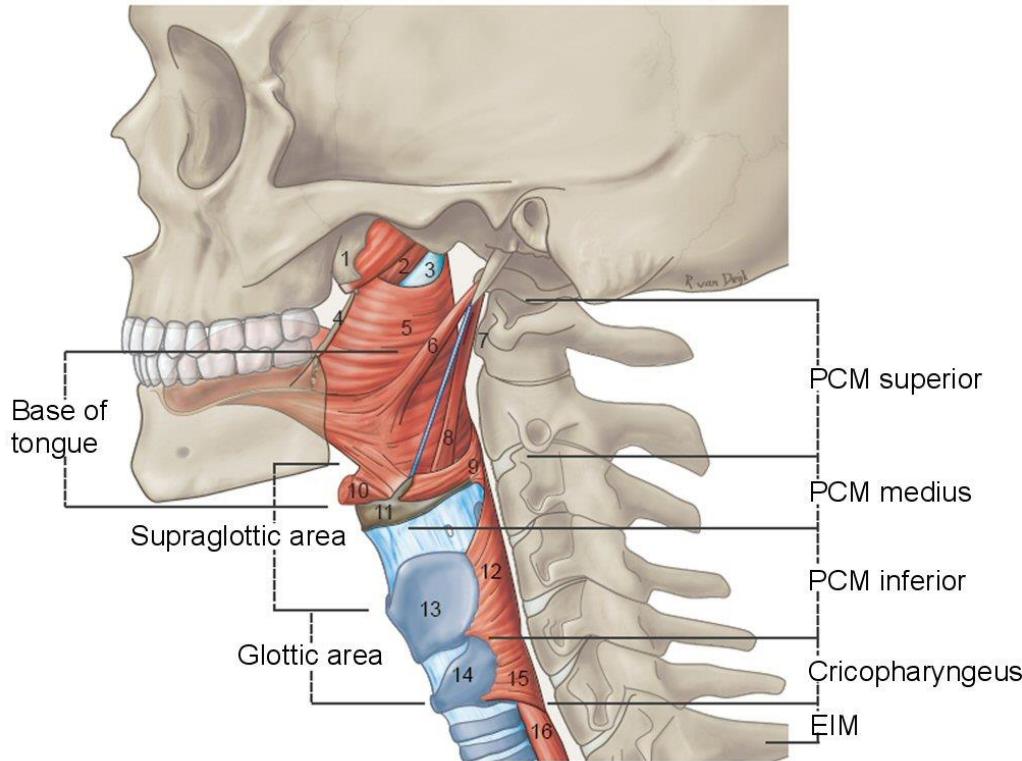
# Ongoing randomized trial (*Groningen, Netherland*)



# Swallowing sparing IMRT

Pharyngeal constrictor muscles = variables for tube feeding dependence

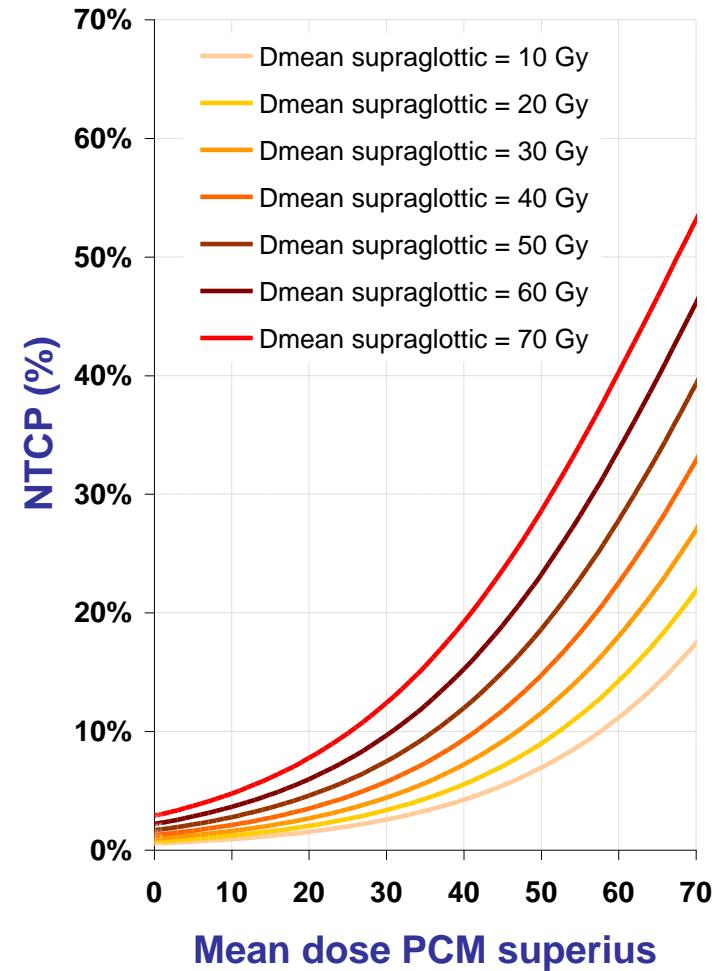
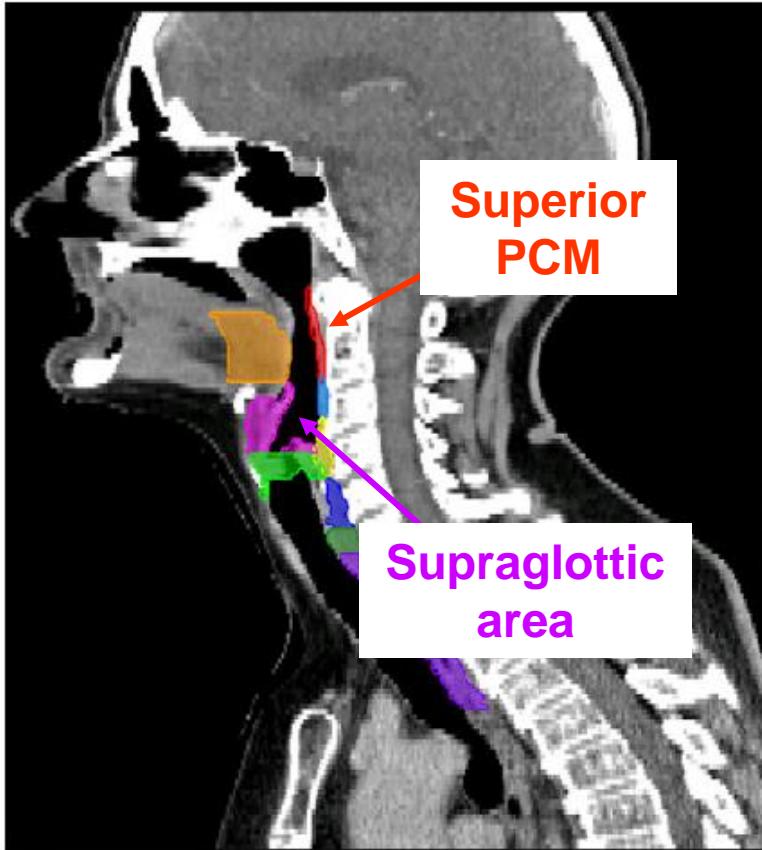
## DOSE VOLUME PARAMETERS



## OTHER FACTORS

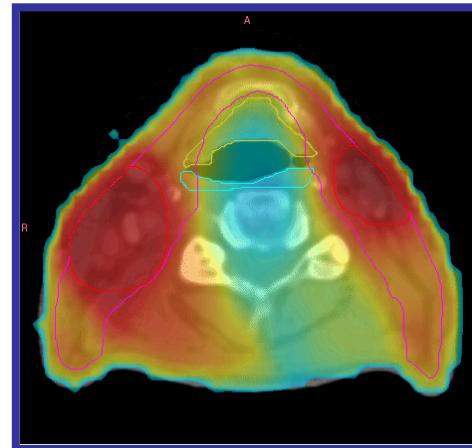
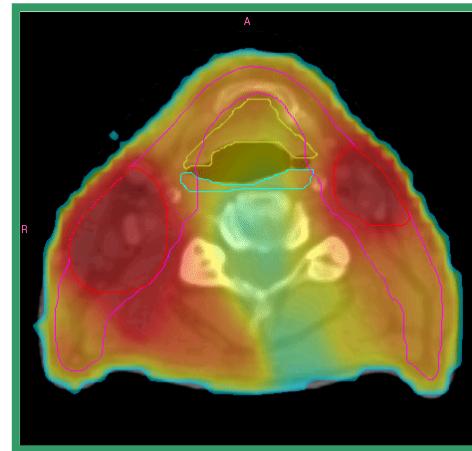
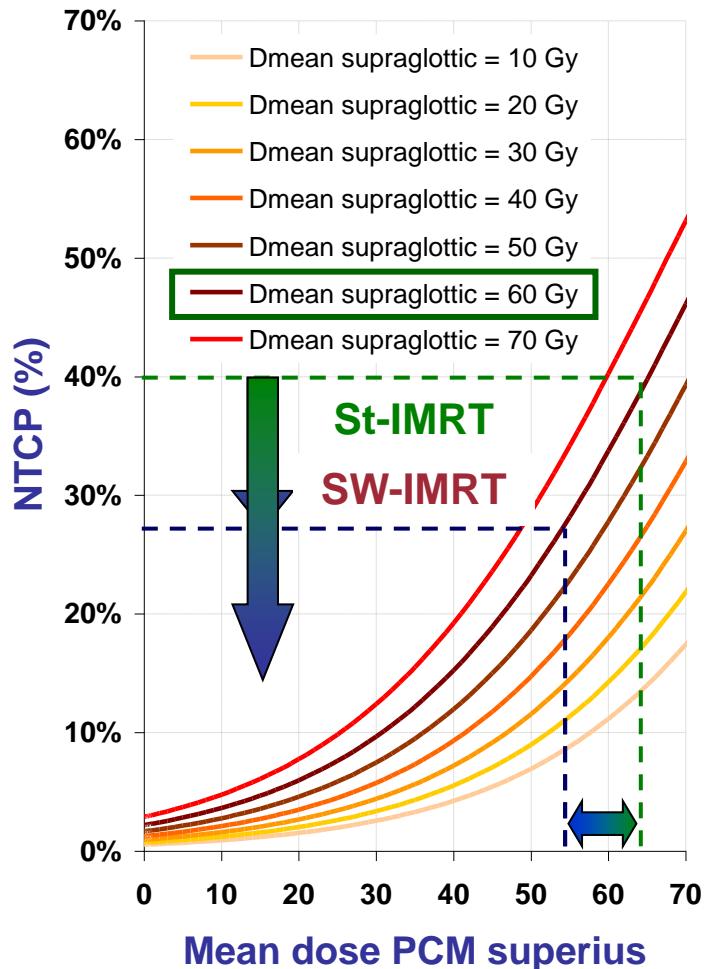
- Sex
- Age
- Tumour-stage
- Nodal-stage
- RT technique
- Chemotherapy
- Fractionation
- Site
- Baseline dysphagia
- Weight loss

# Grade $\geq 2$ dysphagia at 6 months



# Swallowing sparing IMRT

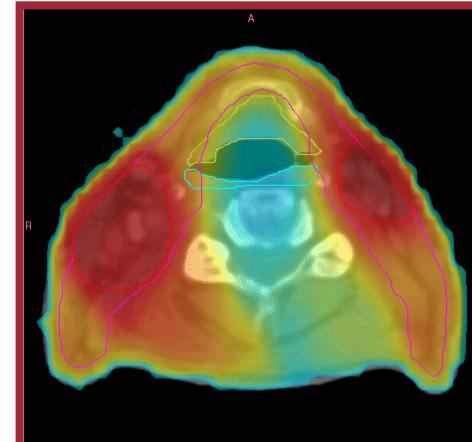
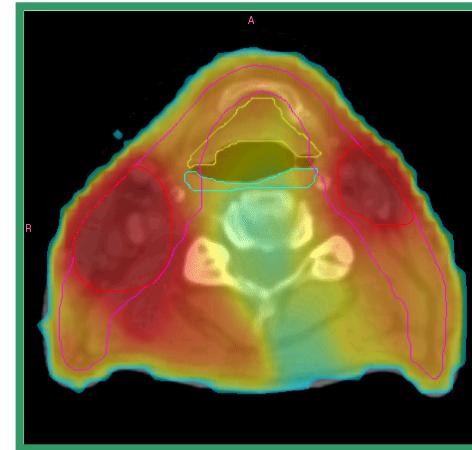
## From DOSE reduction to RISK reduction ...



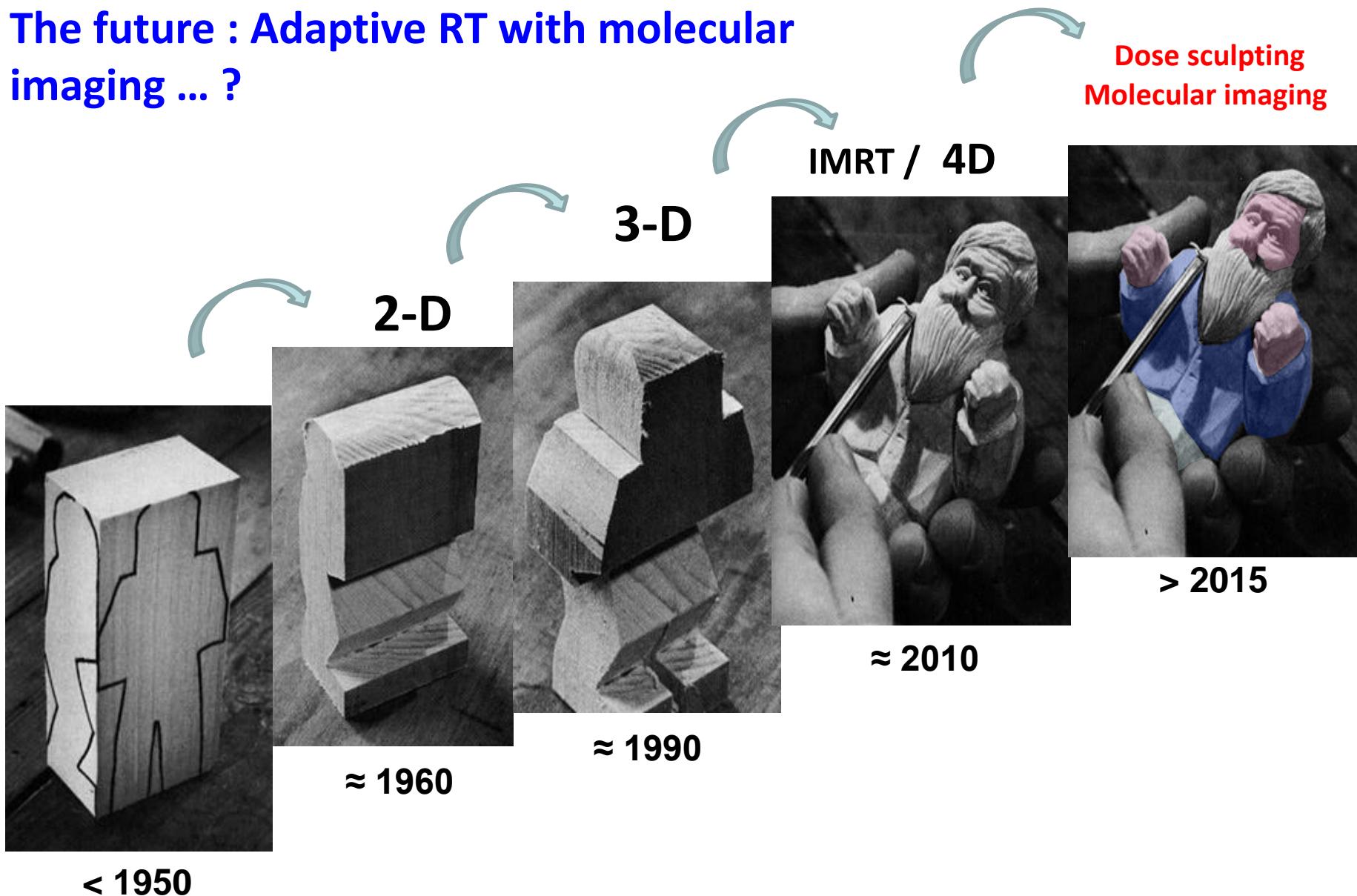
# Planning comparison

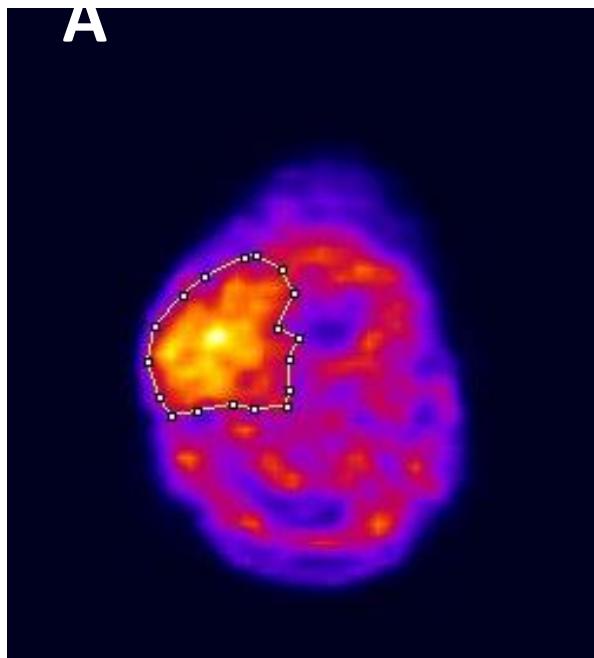
## Standard IMRT versus swallowing sparing IMRT (SW-IMRT)

- Standard IMRT:
  - Dose reduction parotid glands
  - No dose constraints for superior PCM and supraglottis
  - $D_{mean}$  superior PCM = **64 Gy**
  - $D_{mean}$  supraglottis = **60 Gy**
- Swallowing sparing IMRT:
  - Dose reduction parotid glands
  - Dose reduction superior PCM and supraglottis
  - $D_{mean}$  superior PCM = **54 Gy**
  - $D_{mean}$  supraglottis = **30 Gy**



# The future : Adaptive RT with molecular imaging ... ?



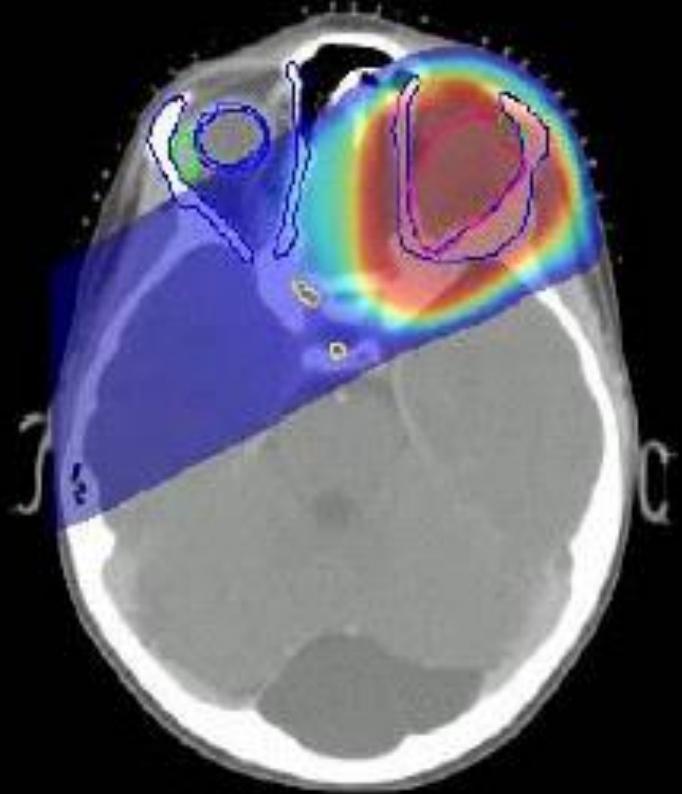


## Adaptive Radiotherapy

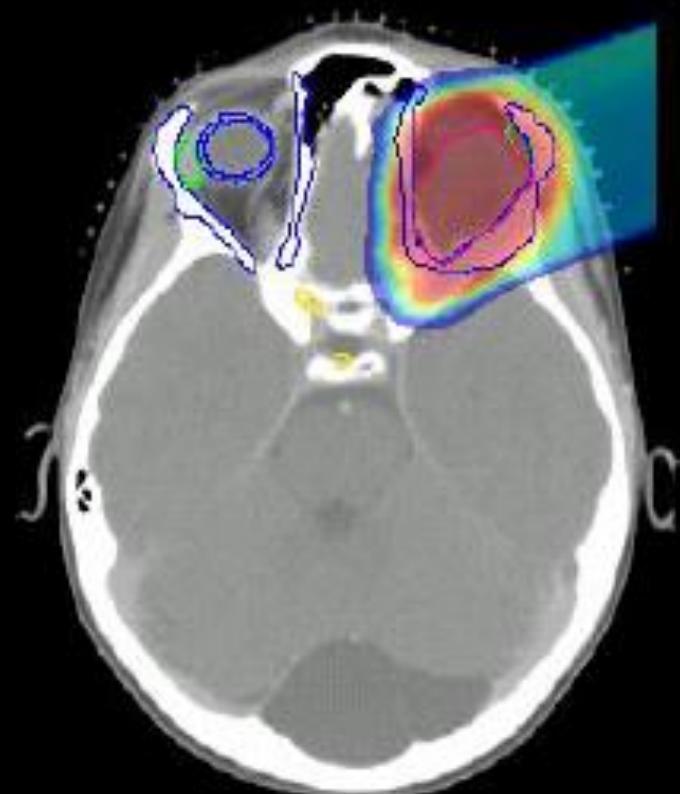
Dose sculpting based on functional  
imaging

Ex : Ga68-RGD  
imaging angiogenesis ...  
(CHUV)

# Proton better than IMRT ?

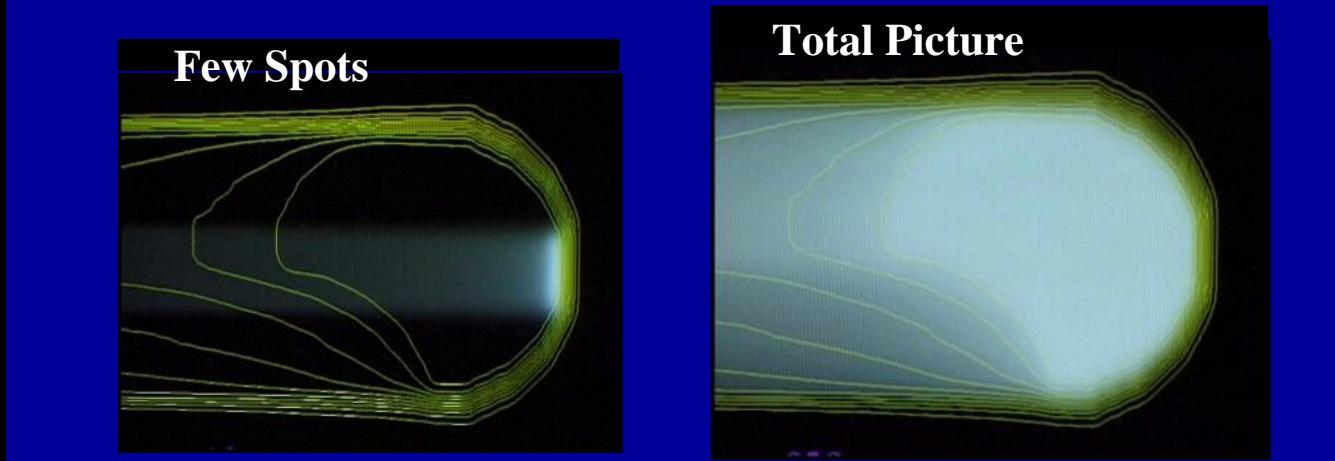
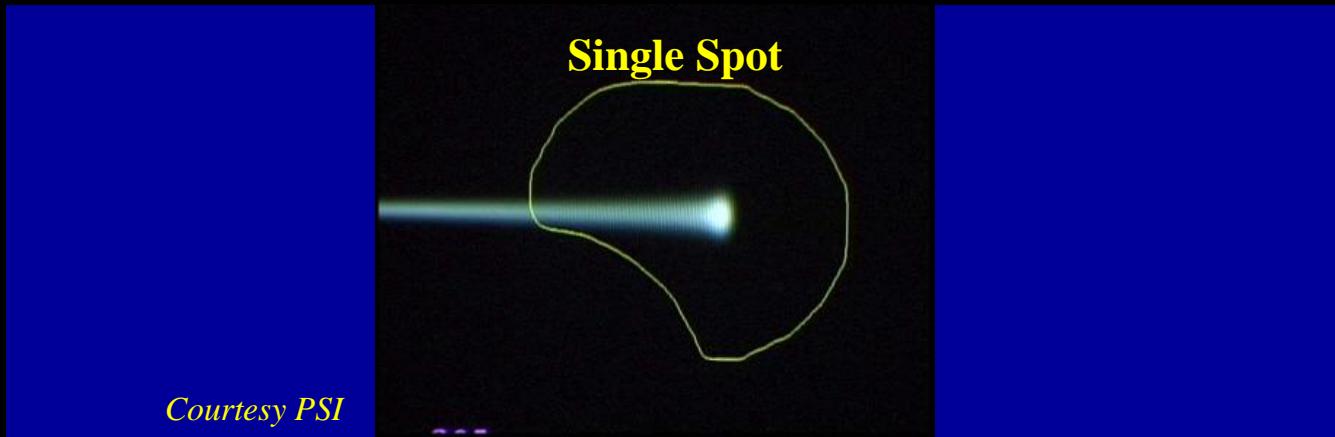


**RX**

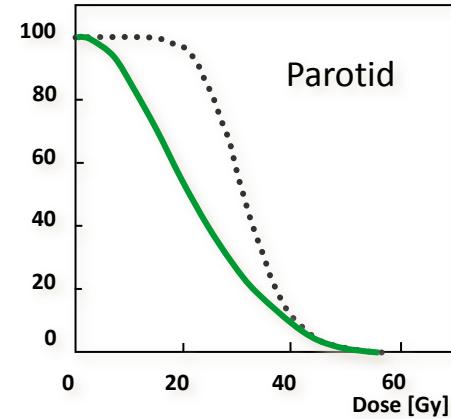
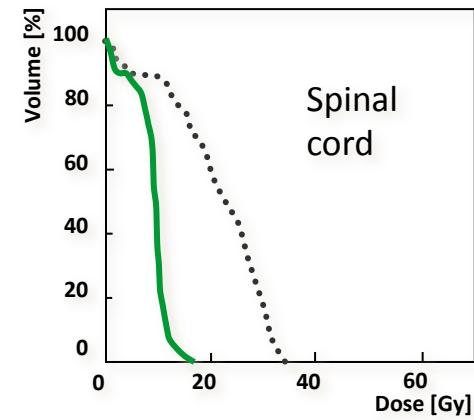
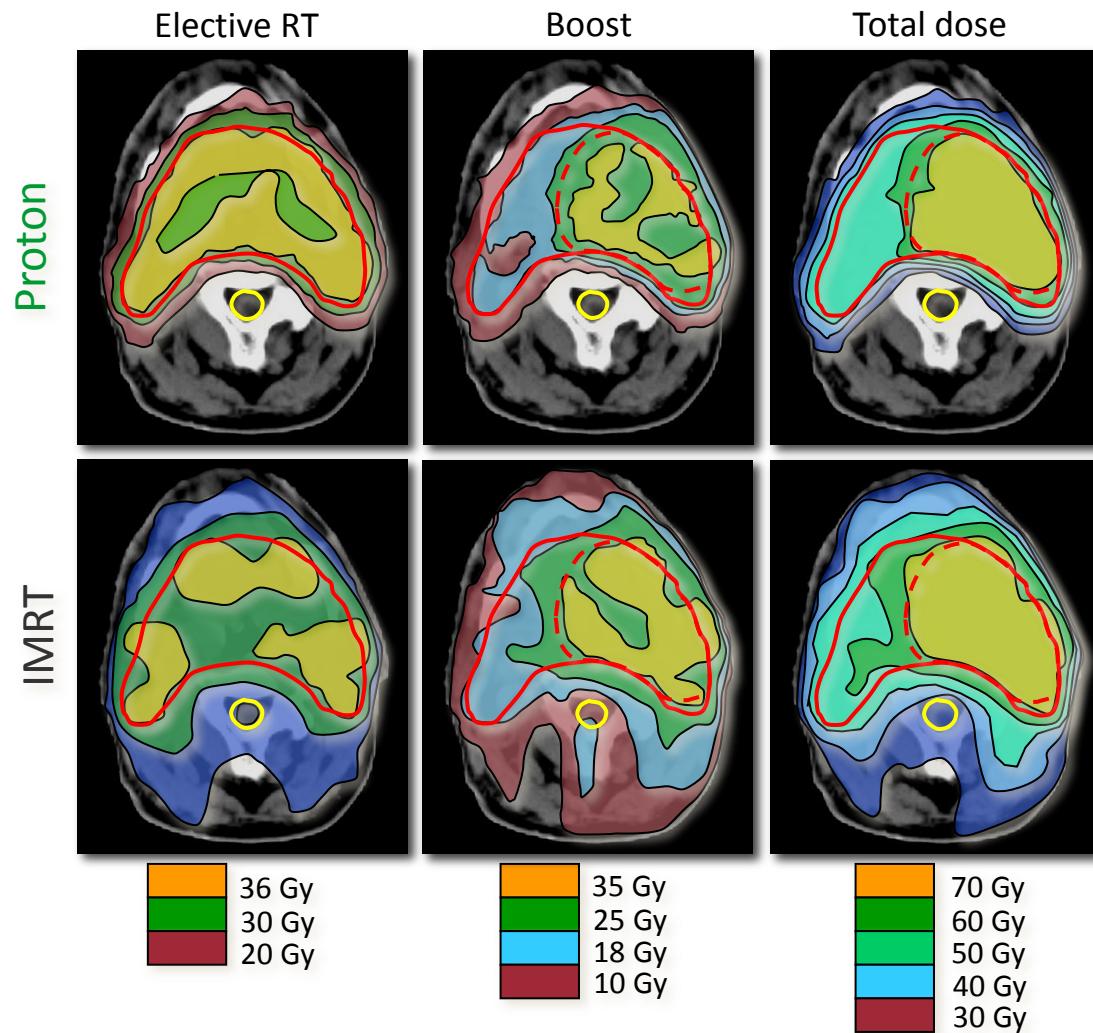


**Protons**

# Head and neck : need for spot scanning (PSI)



# Protons (IMPT) vs. IMRT



Cozzi et al, Zeit Med Phys 2004

# Avoiding IMRT ?...



*Best of RT*

# EORTC-GORTEC-SAKK Intergroup

## “Best-of”: TOS versus IMRT in early stage OPC

Assess eligibility:  
Stage I/II  
OPC T<sub>1,2</sub>N<sub>0</sub>M<sub>0</sub>

Stratification for:  
HPV-status, T, sub-site,  
institution, baseline-  
MDADI

Baseline  
function/QoL-  
status/MRI or CT-  
neck c contrast,  
CT-chest, pan-  
endoscopy,  
adequate trans-  
oral access

IMRT+SIB 66-70Gy  
definitive dose,  
54.25Gy prophylactic  
dose  
  
Trans-oral surgery +  
uni-or bilateral  
selective neck  
dissection

Basic science package

CT or MRI after 8-10 weeks:  
CR – observation  
PR – endoscopy, biopsy, salvage  
NR – endoscopy, biopsy, salvage

1. Dysphagia related QoL (MDADI)
2. QoL/function
3. OS, DSS, PFS
4. LC, LRC

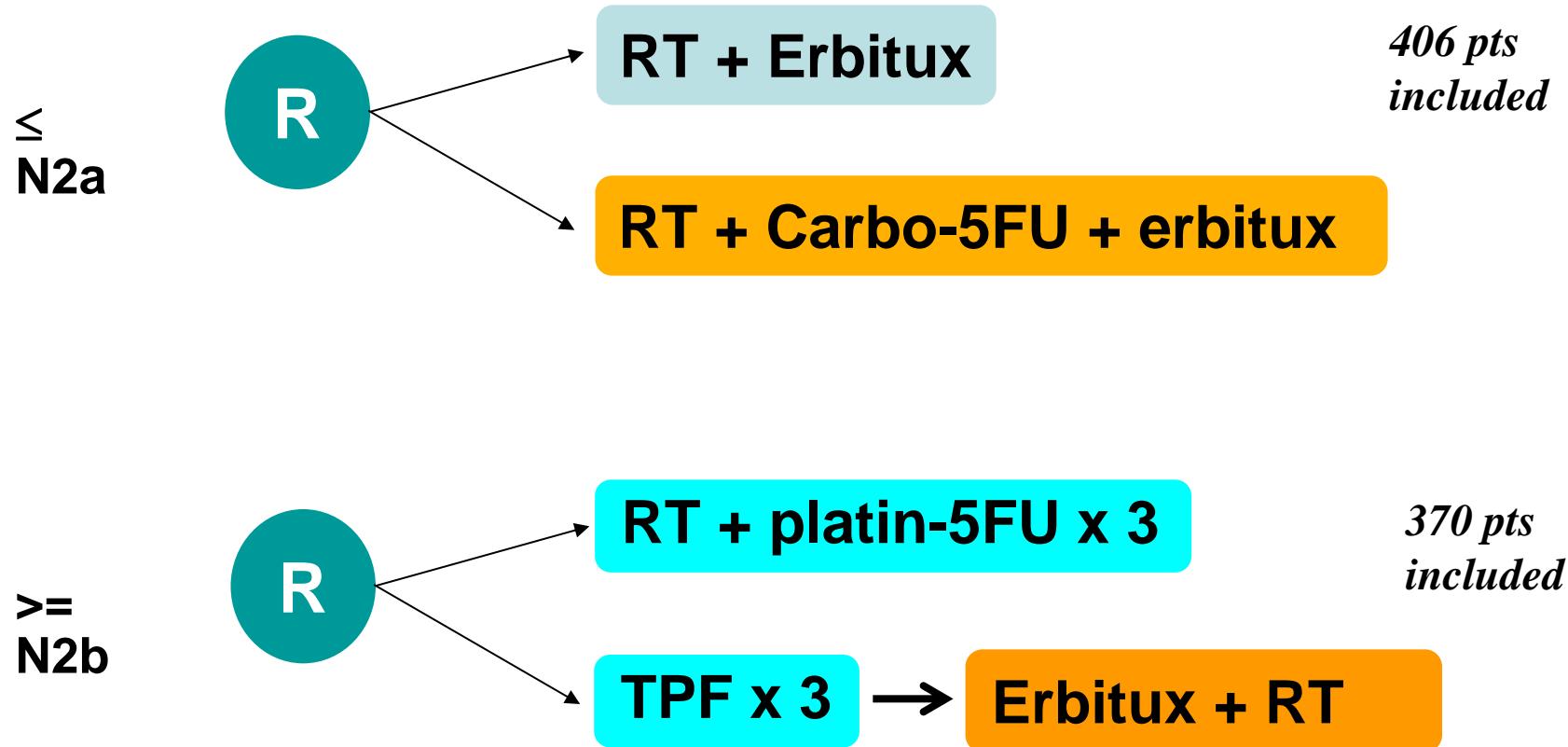
At 3, 6, 9 months,  
1 year and 2  
years

observation

Risk-stratified  
RT 60Gy for PI/LVI/CM or CRT 66Gy for pN1 with  
ECS and R1

# Up-coming ASCO

2007-01 & 02 GORTEC randomized trials



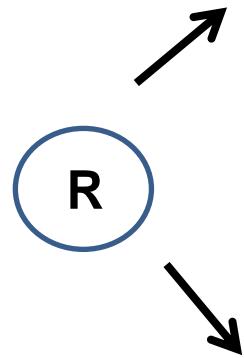
## **GORTEC 2015-03 / Debio**

**Randomized phase II in locally advanced HNSCC  
(stage III / IV, HPV- if oropharynx)**

- **CDDP-RT + Placebo**
- **CDDP-RT + Debio 11-43**

## Pemborad randomized trial

Locally advanced  
Non candidate for  
CT-RT



Pembrolizumab + RT

Cetuximab + RT

*Phase II : primary end point LRC at 15 months (60% in the Bonner study)  
to 80%. 57 patients / arm (114 patients)*

**Since November 2012: Labelised by INCA (French National Cancer Institute) as a cooperative intergroups GORTEC-GETTEC-GERCOR**

