Molecular imaging-based adaptive treatment for locally advanced head and neck cancers: where are we?

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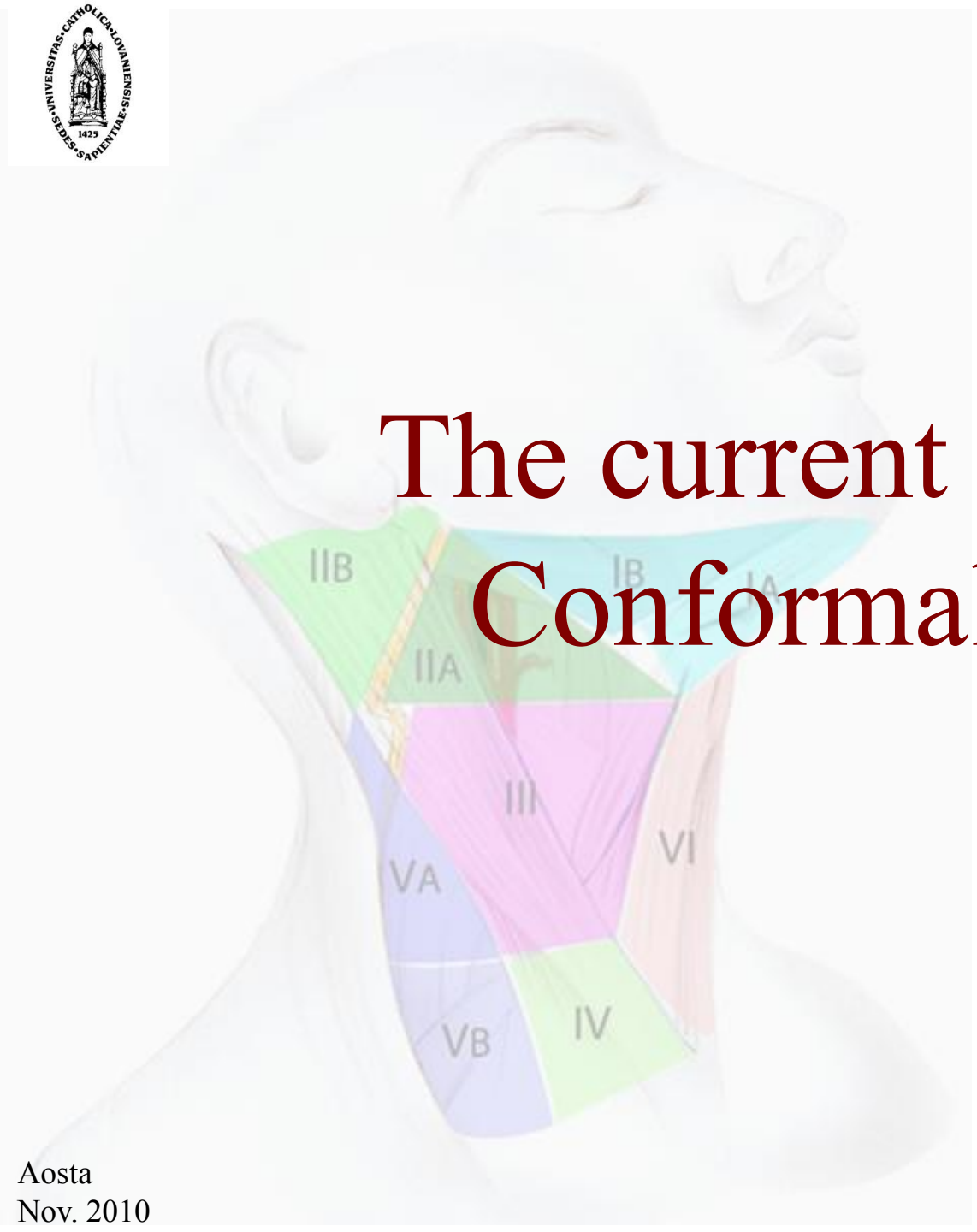
Aosta
Nov. 2010

This house believes that …

- RO will be (even more) multidisciplinary…
- RO will be conformal (e.g. IMRT, proton, hadrons)…
- RO will be tailored (based on imaging and molecular profiling) and adaptive …
- RO will be associated with targeted agents …



The current practice: Conformality…?

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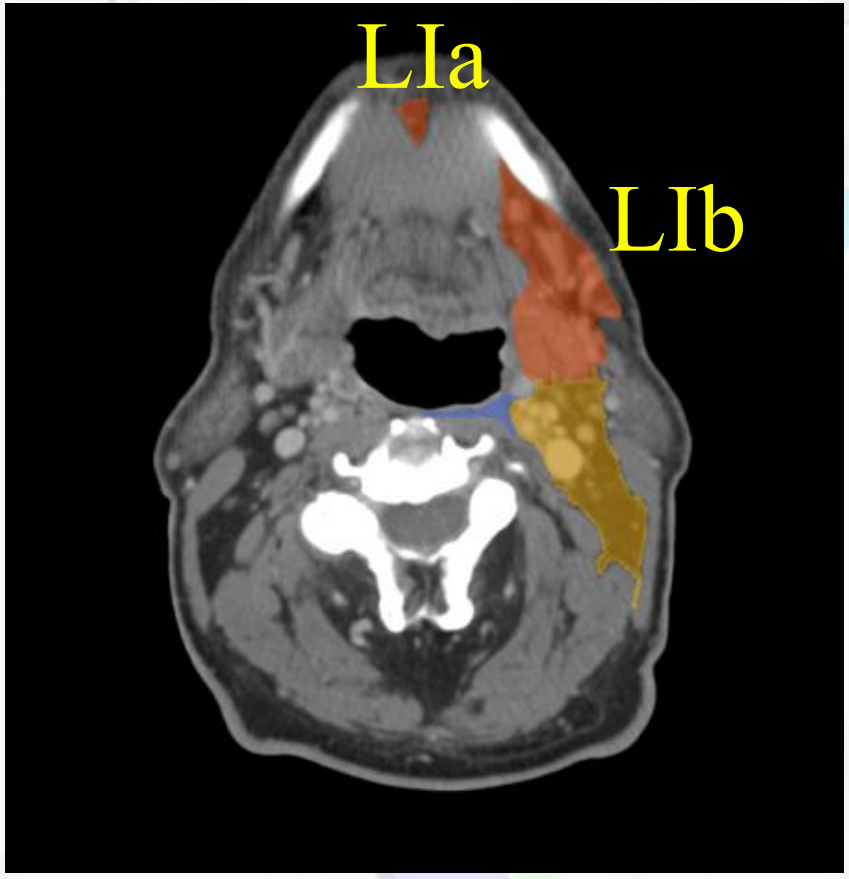
Radiotherapy in HNSCC

2

Adaptive IMRT

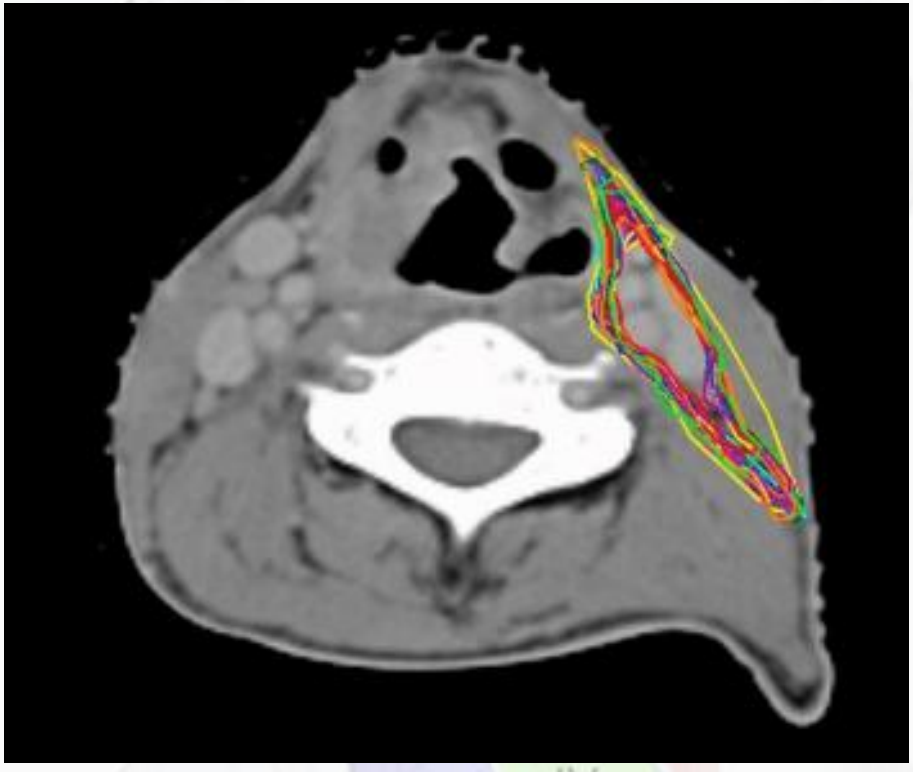
CT-based delineation of lymph node levels in the neck: Brussels- Rotterdam consensus guidelines

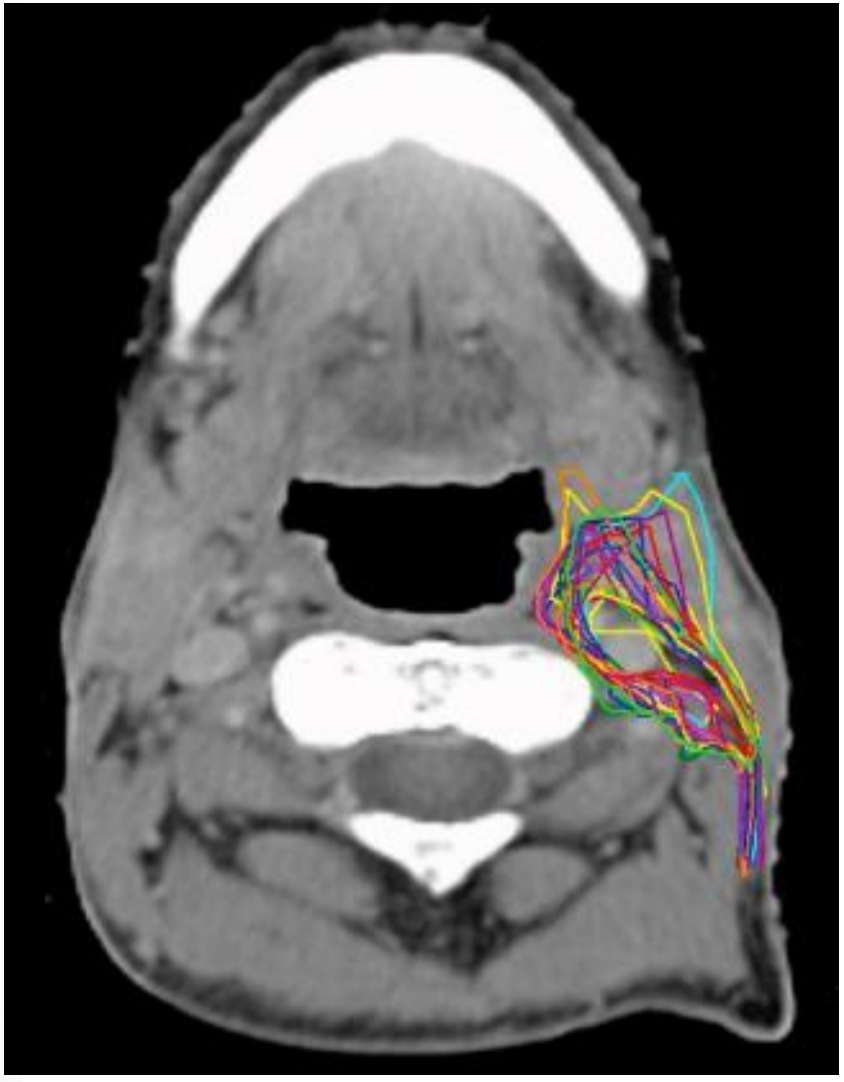


Level Ia and Ib

Ant.	symphysis menti / platysma
Post.	hyoid bone / submandibular gland
Lat.	ant. belly of digastric m. (Ia) mandible / platysma (Ib)
Med.	ant. belly of digastric m. (Ib)
Cra.	geniohyoid m./mandible (Ia) mylohyoid m, submandibular gland (Ib)
Cau.	hyoid bone

H&N IMRT practice heterogeneity among Dutch Radiation Oncologists





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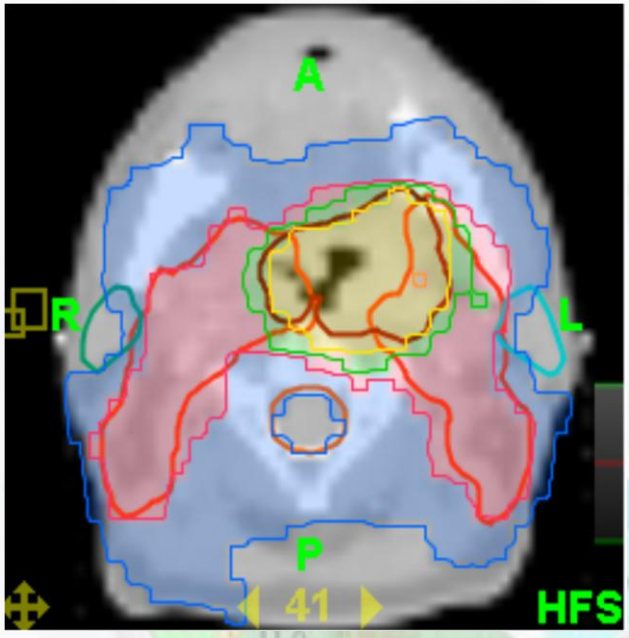
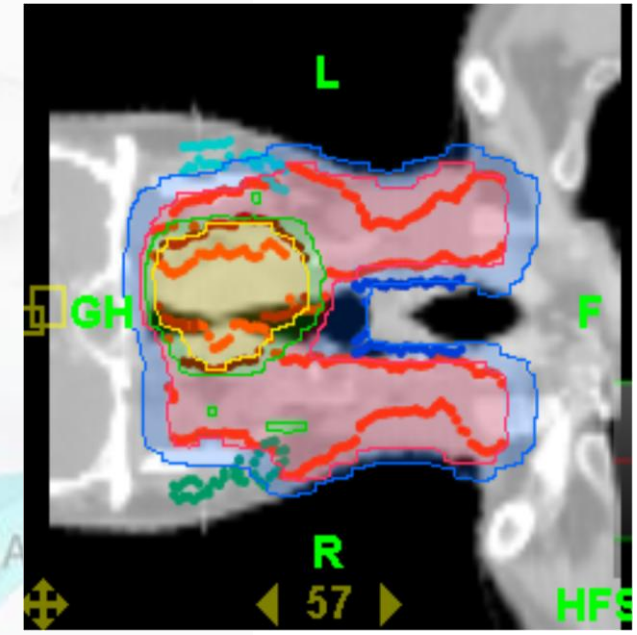
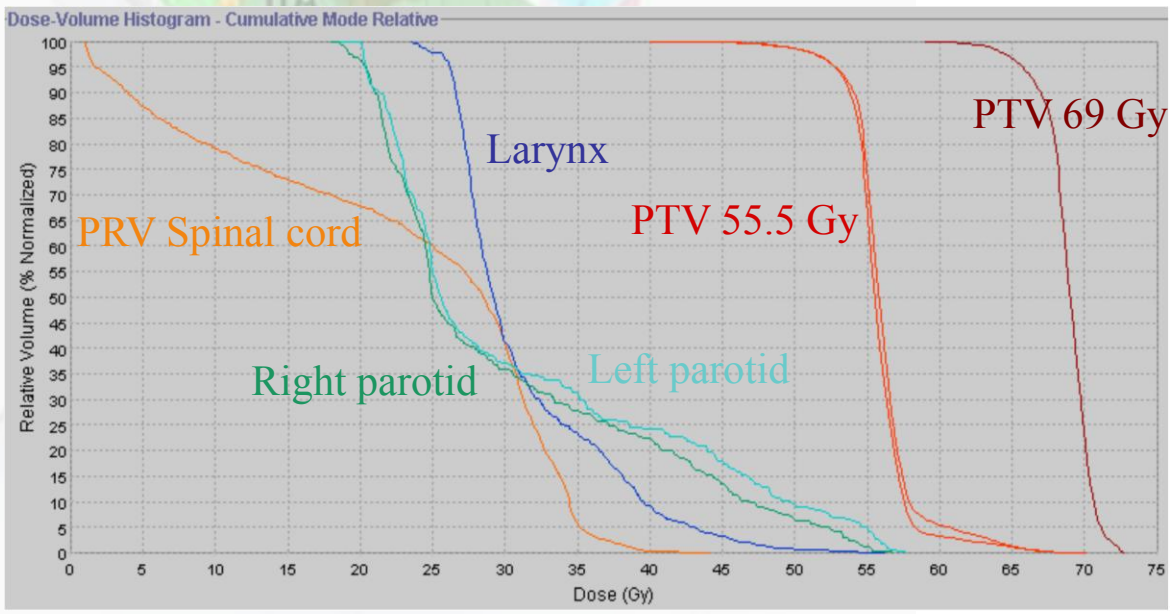
Rasch et al., 2007

IMRT for Head and Neck Tumors







Oropharyngeal SCC

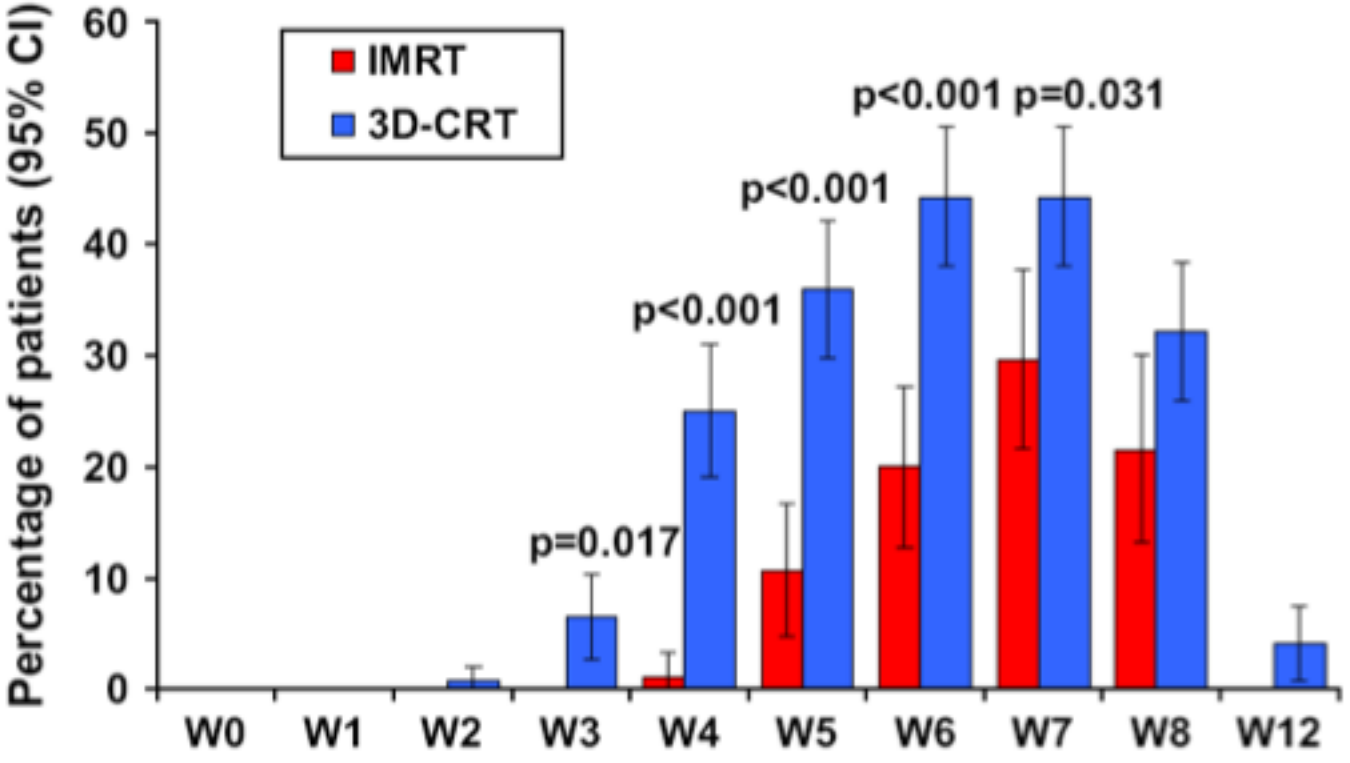
T2-N0-M0

SIB-IMRT: 30x2.3 Gy

30x1.85 Gy

Acute toxicity with IMRT

≥ grade 3 mucositis: IMRT vs 3D-CRT

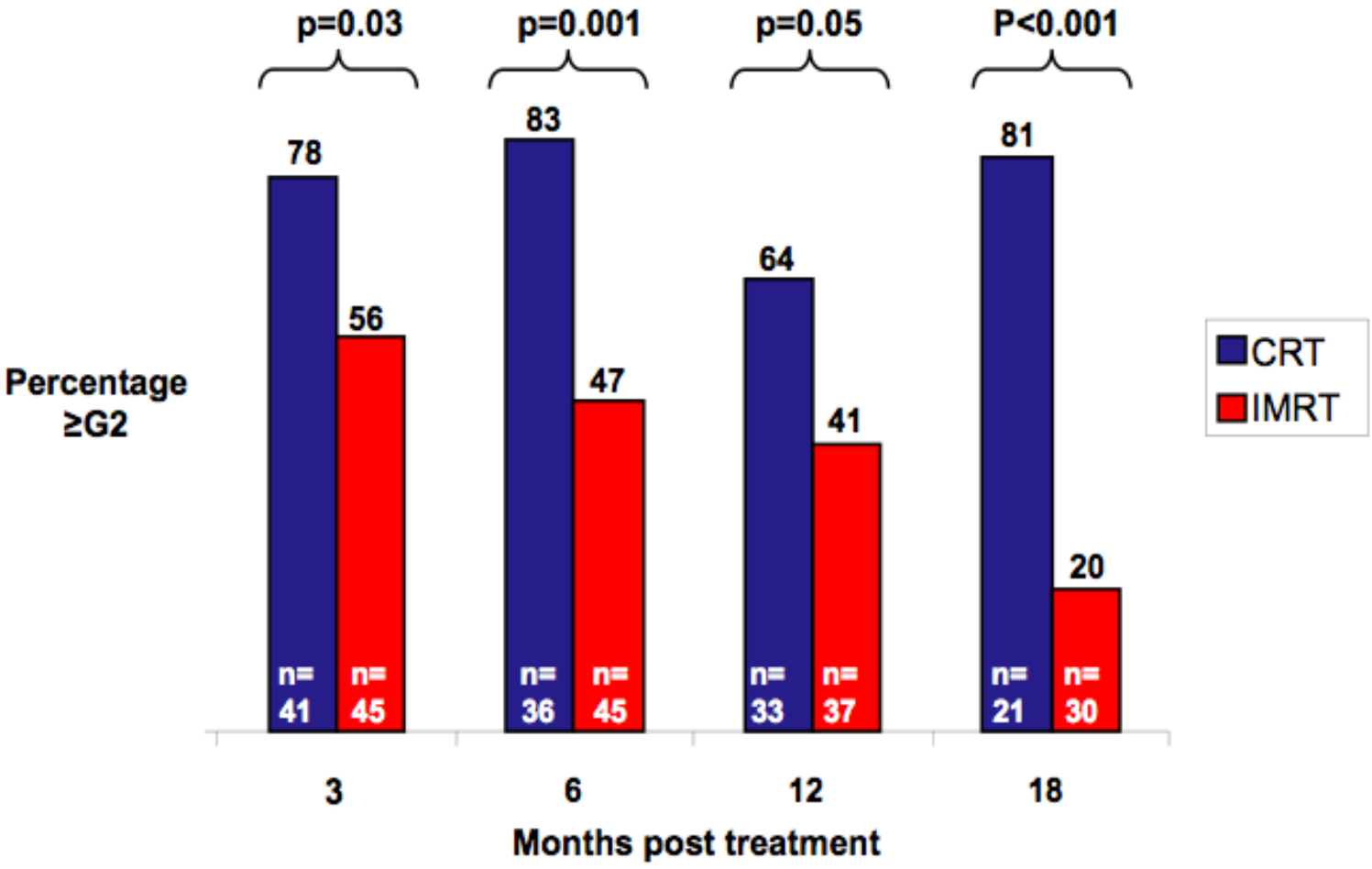


Note: The prevalence of grade 3 or higher mucositis was significantly lower among IMRT-treated patients. This is most likely due to the SIB-technique used with a lower dose per fraction and a longer overall treatment time of radiation for the elective part of the target volume.

Vergeer, 2009

Parotid gland sparing in IMRT for HNSCC

RTOG Subjective Salivary Gland toxicity ≥G2*



*Moderate or complete dryness of mouth poor or no response on stimulation

Nutting et al. JCO 2009:27 (18s);799s (LBA6006)

Nutting, 2009

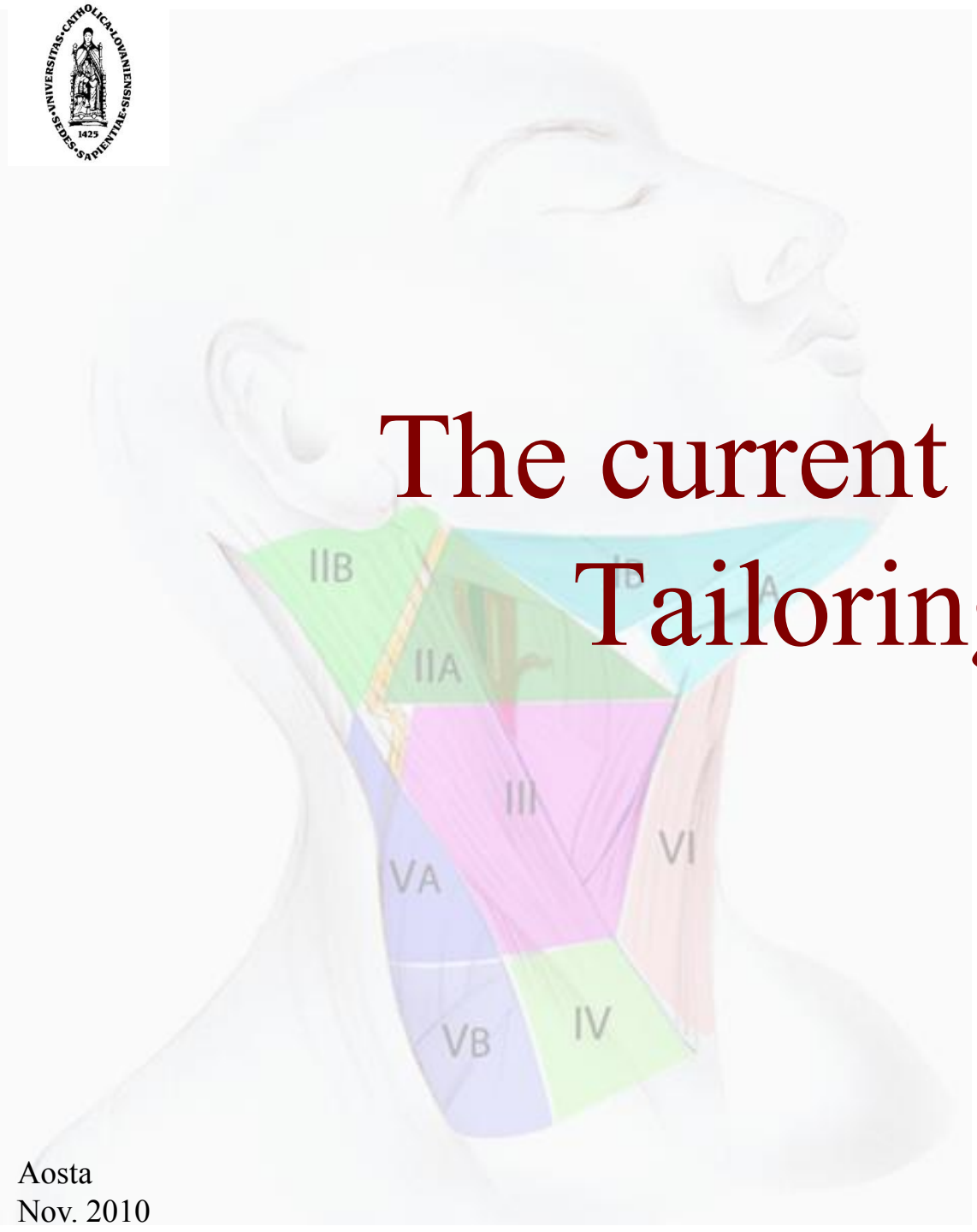
IMRT: revisiting the fractionation dogma?

- Option 1: 2-phase IMRT
  - elective PTV: 25 x 2.0 Gy
  - therapeutic PTV: 35 x 2.0 Gy
- Option 2: high dose per fraction SIB-IMRT
  - elective PTV: e.g. 30 x 1.85 Gy
  - therapeutic PTV: e.g. 30 x 2.3 Gy
- Option 3: low dose per fraction SIB-IMRT
  - elective PTV: e.g. 35 x 1.55 Gy
  - therapeutic PTV: e.g. 35 x 2.0 Gy

The current practice: Conformality…?

Yes !

The current practice: Tailoring…?



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The Gross Tumor volume (GTV)

Radiology

Jean-François Daisne, MD
Thierry Duprez, MD
Birgit Weynand, MD
Max Lonneux, MD, PhD
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Hervé Reychler, MD, DDS
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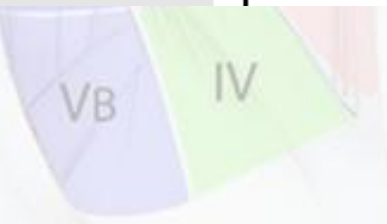
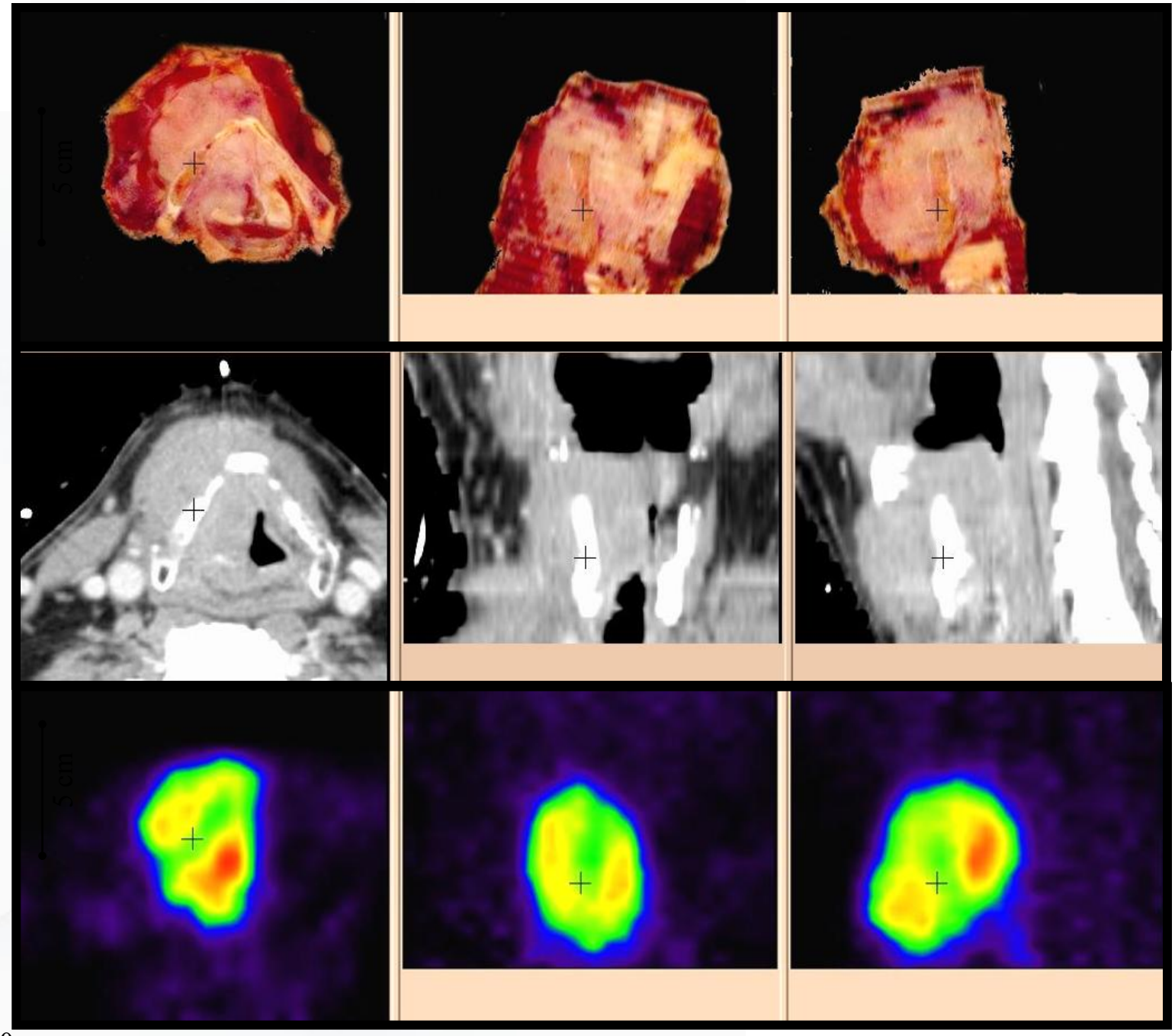
Index terms:
Head and neck neoplasms, CT, 26.1211, 27.1211
Head and neck neoplasms, MR,

Tumor Volume in Pharyngolaryngeal Squamous Cell Carcinoma: Comparison at CT, MR Imaging, and FDG PET and Validation with Surgical Specimen[1]



Daisne et al., *Radiology*, 233: 93-100, 2004



Macroscopy

CAT Scan

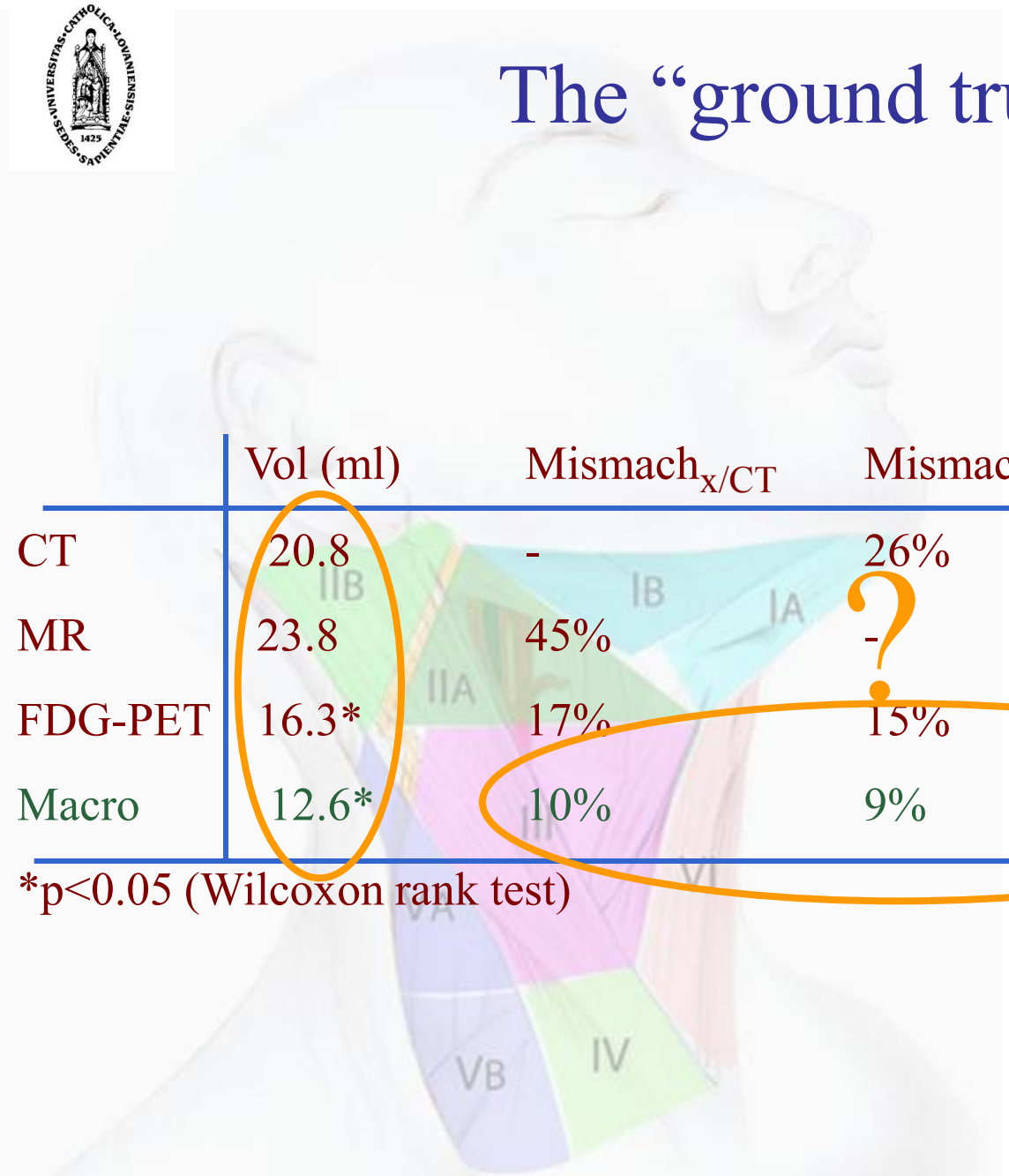
^{18}F-FDG PET

Daisne *et al*, 2004

The "ground truth" GTV

	Vol (ml)	Mismach$_{x/CT}$	Mismach$_{x/MR}$	Mismach$_{x/PET}$	Mismach$_{x/macro}$
CT	20.8	-	26%	48%	81%
MR	23.8	45%	-	67%	107%
FDG-PET	16.3*	17%	15%	-	47%
Macro	12.6*	10%	9%	13%	-

*p<0.05 (Wilcoxon rank test)



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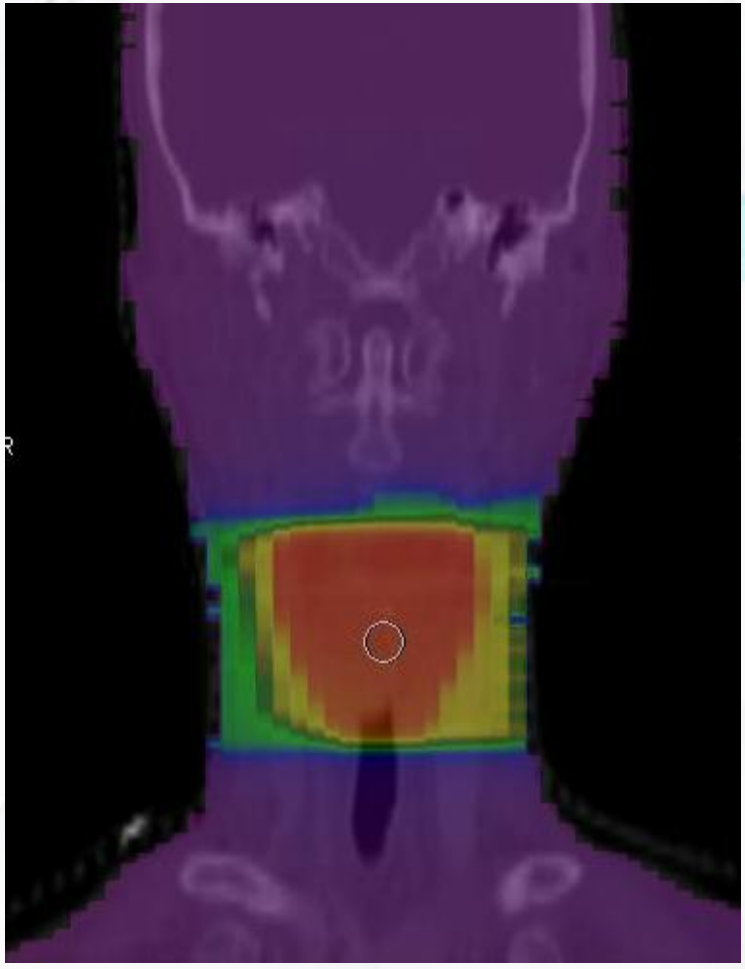
Daisne *et al*, 2004

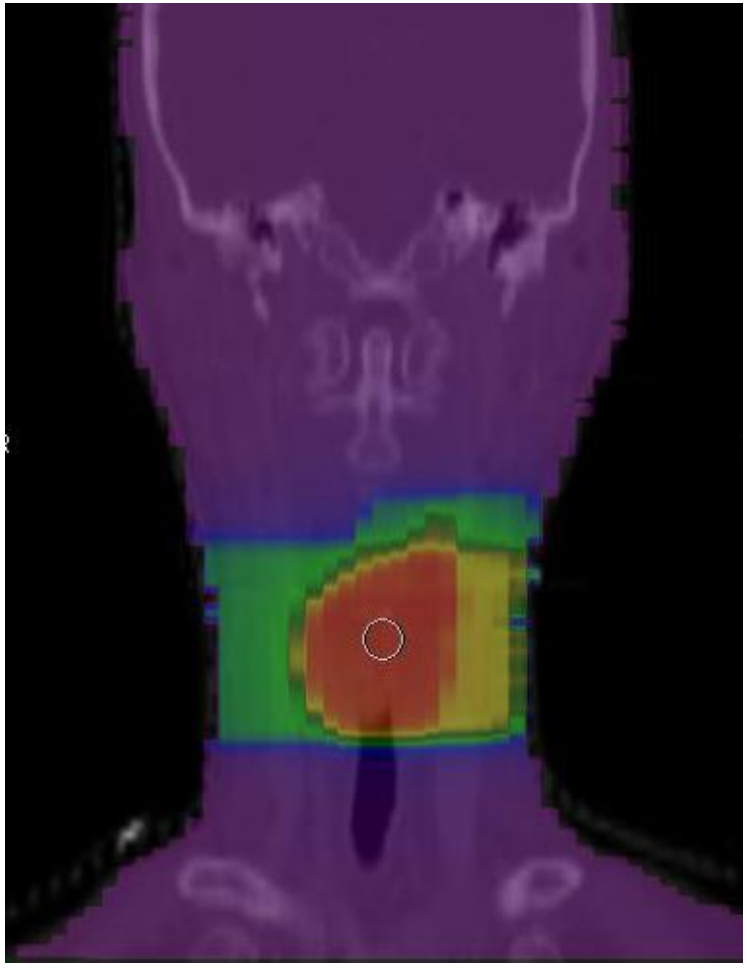
Image-Guided Radiation Therapy in HNSCC

Impact of imaging modality on dose distribution

CT-based target volume



FDG PET-based target volume



Validation protocol in locally advanced HNSCC

Apport de l'imagerie fonctionnelle par Tomographie
par Emission de Positrons (TEP) dans le ciblage biologique
par radiothérapie de conformation (3D-CRT)
et par modulation d'intensité (IMRT) de tumeurs ORL

Use of functional imaging with PET for target volume delineation in 3D-CRT/IMRT for head and neck tumors

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Prof. E. Lartigau, COL, Lille, France
Dr. JF Daisnes, Cliniques St-Elisabeth, Namur, Belgium

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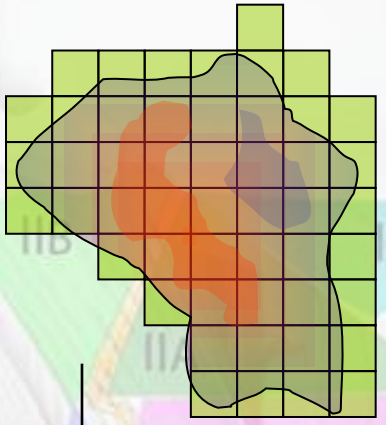
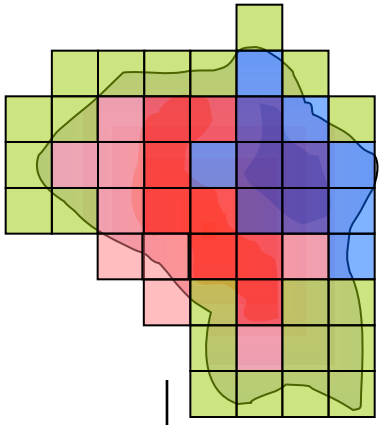
“Dose painting” by number…

Flat dose

Non-flat dose





Far more efficient use of dose

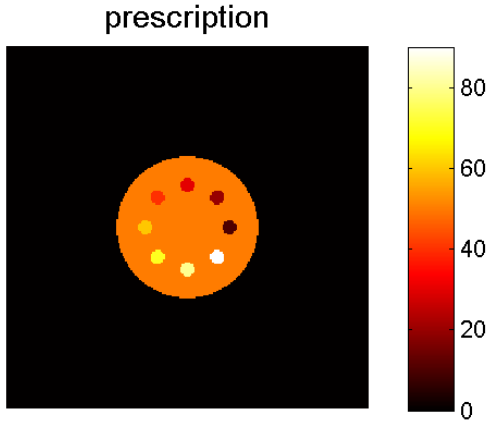
Mean Tumor Dose = 2 Gy

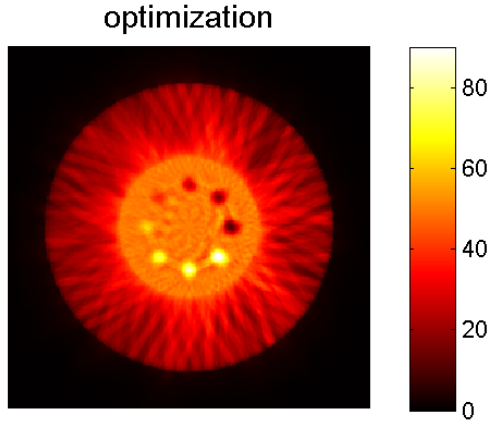
Survival is non-flat
(higher in resistant areas)

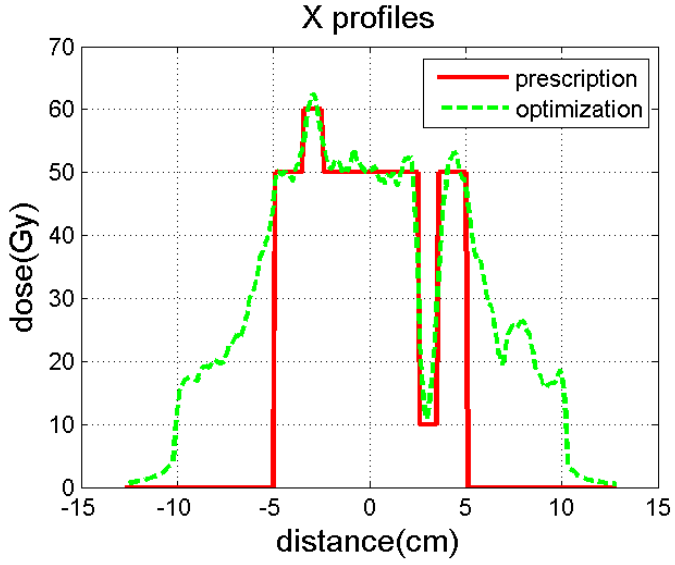
More similar survival
across entire tumor

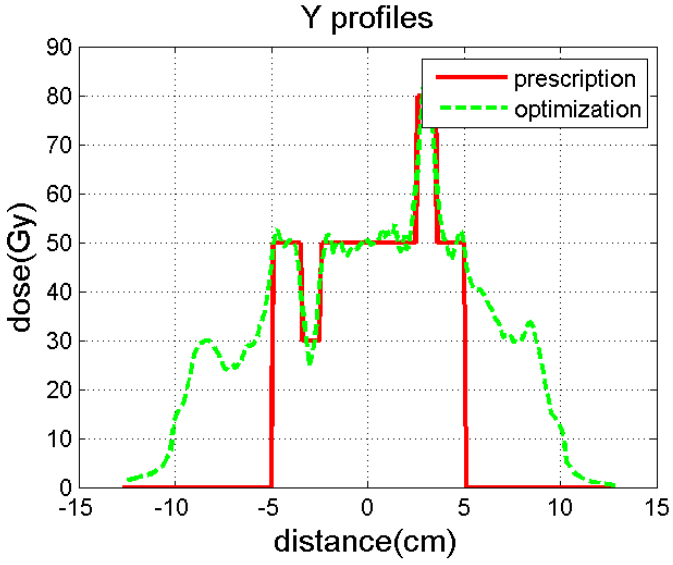
Courtesy of D. De Ruysscher

“Dose painting” : the physics issue



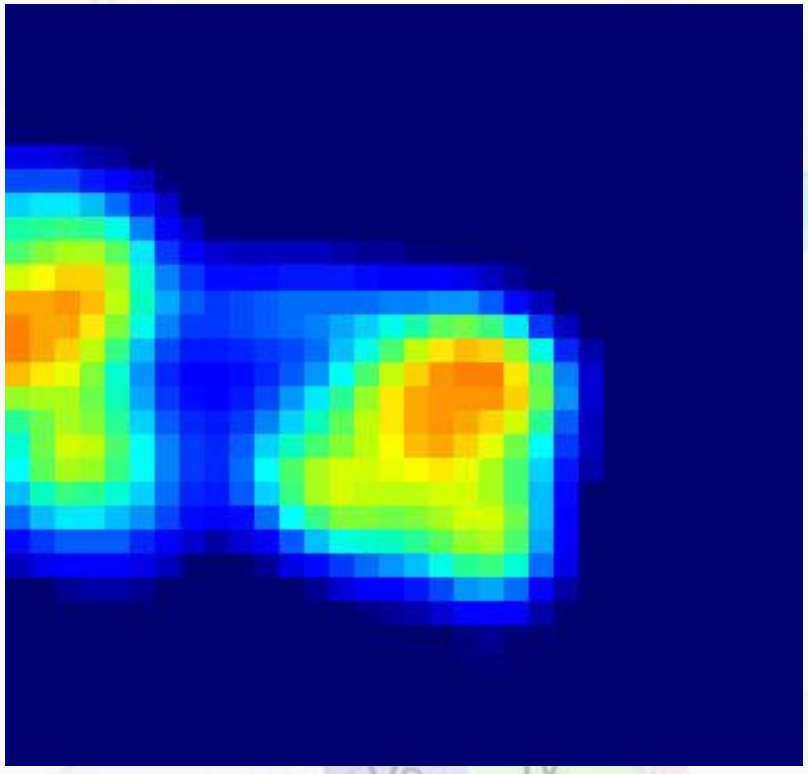






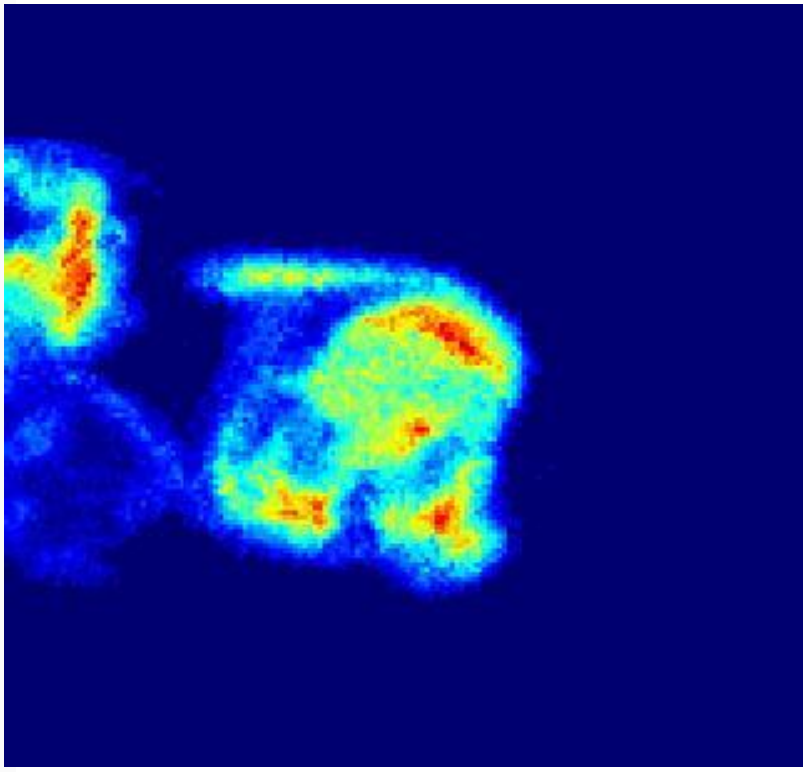
Biological heterogeneity

[^{18}F]-FDG TEP



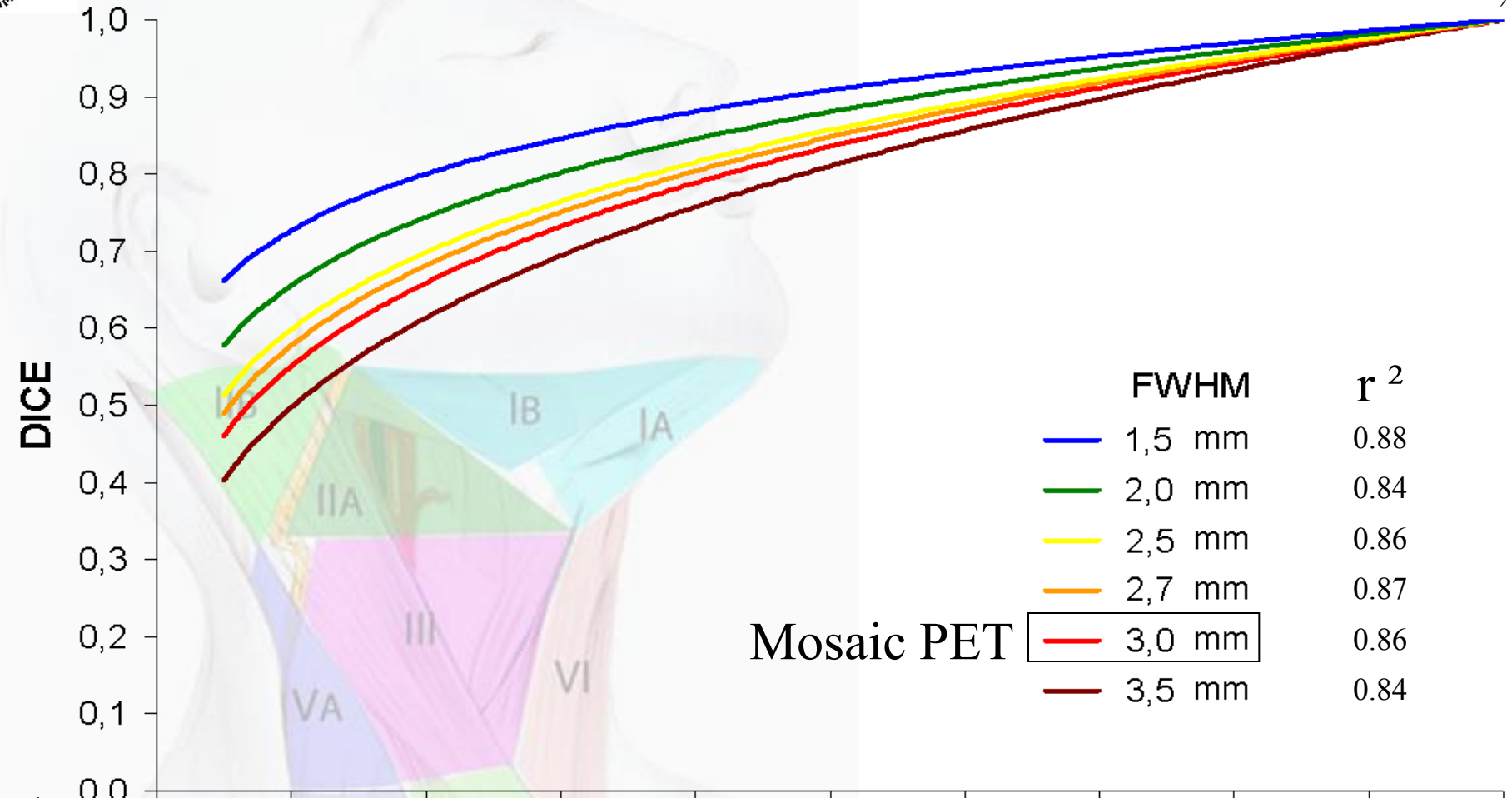
Résolution 2.3 mm

Registered autoradiography



Résolution 0.1 mm

Effect of resolution



% vol

0 0,1 0,2 0,3 0,4 0,5 0,6 0,7 0,8 0,9 1

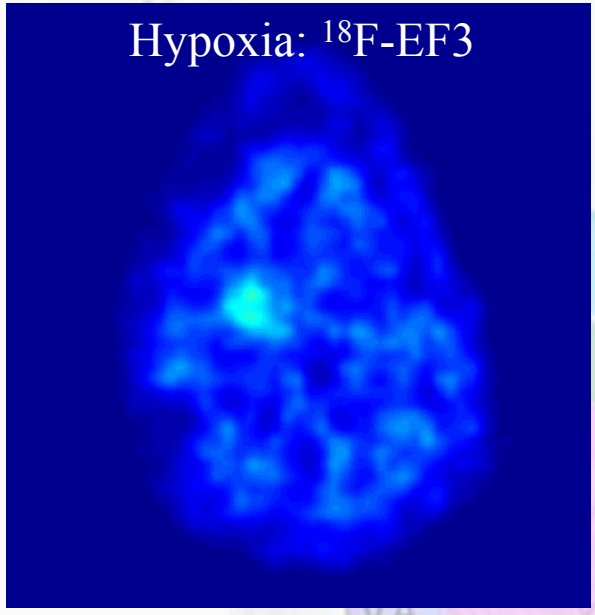
Mouse T ø

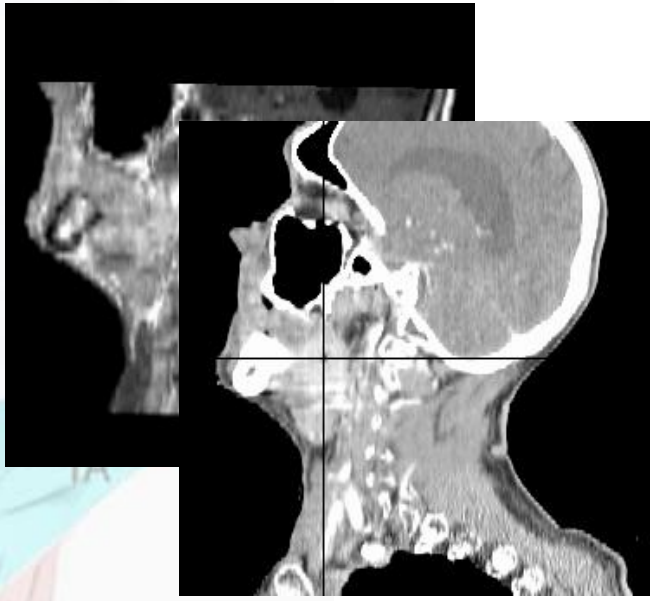
0.0 7.0 8.7 10.0 11.0 12.1 12.7 13.1 13.9 14.5 15.0

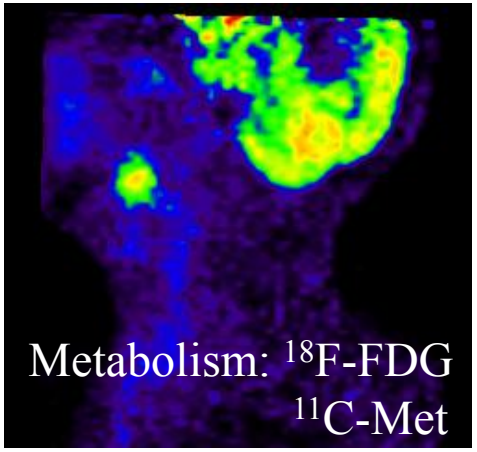
Human T ø

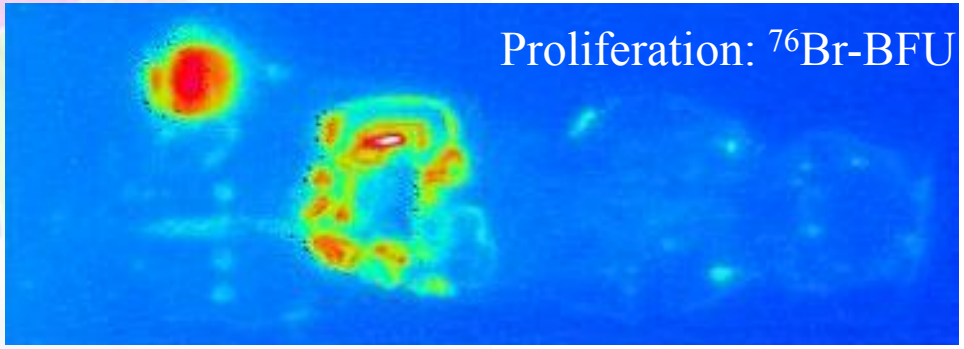
0.0 13.9 17.5 20.1 22.1 23.8 25.3 26.6 27.8 28.9 30.0

Which biological pathways? …

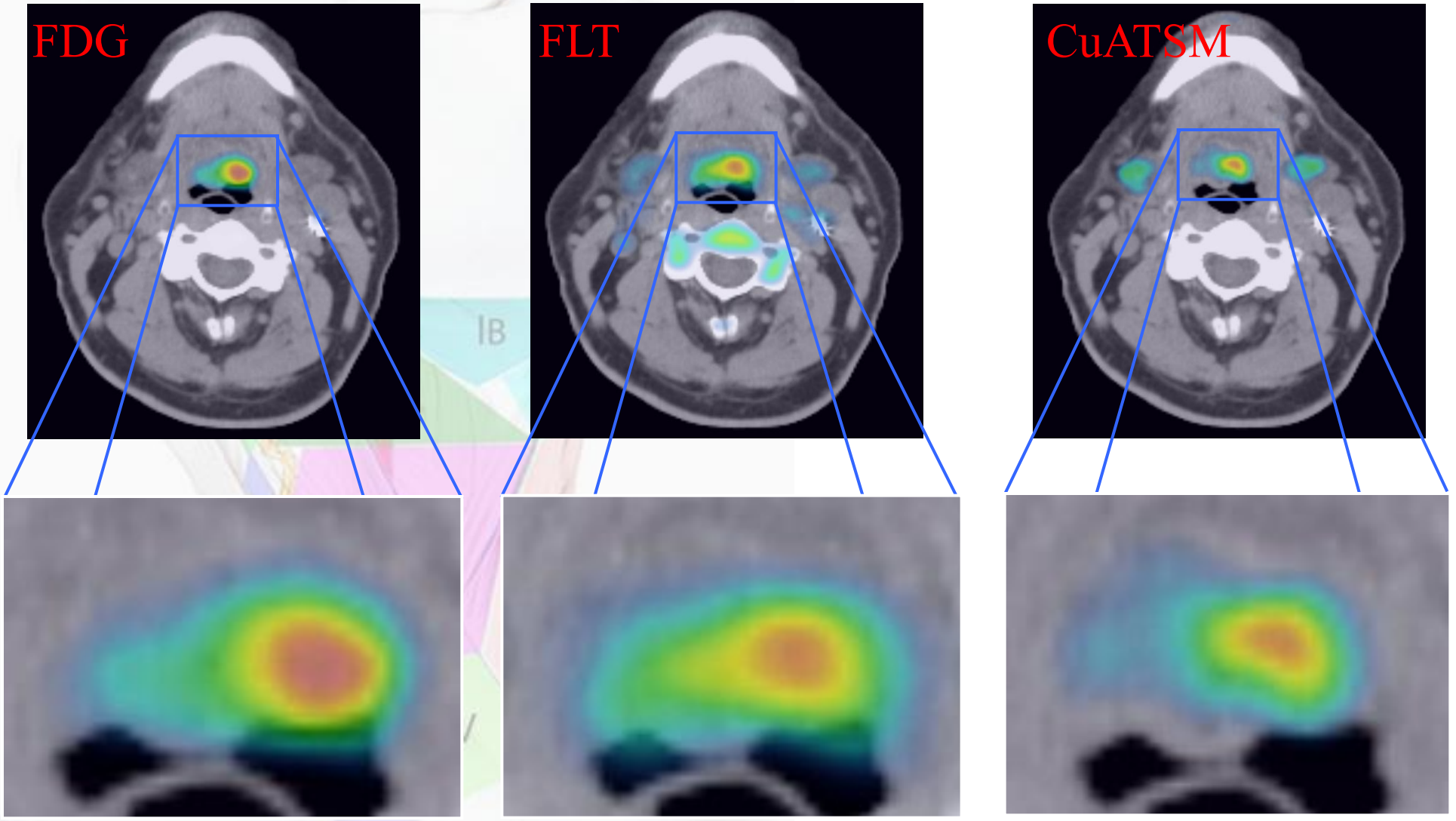








Spatially “similar” target



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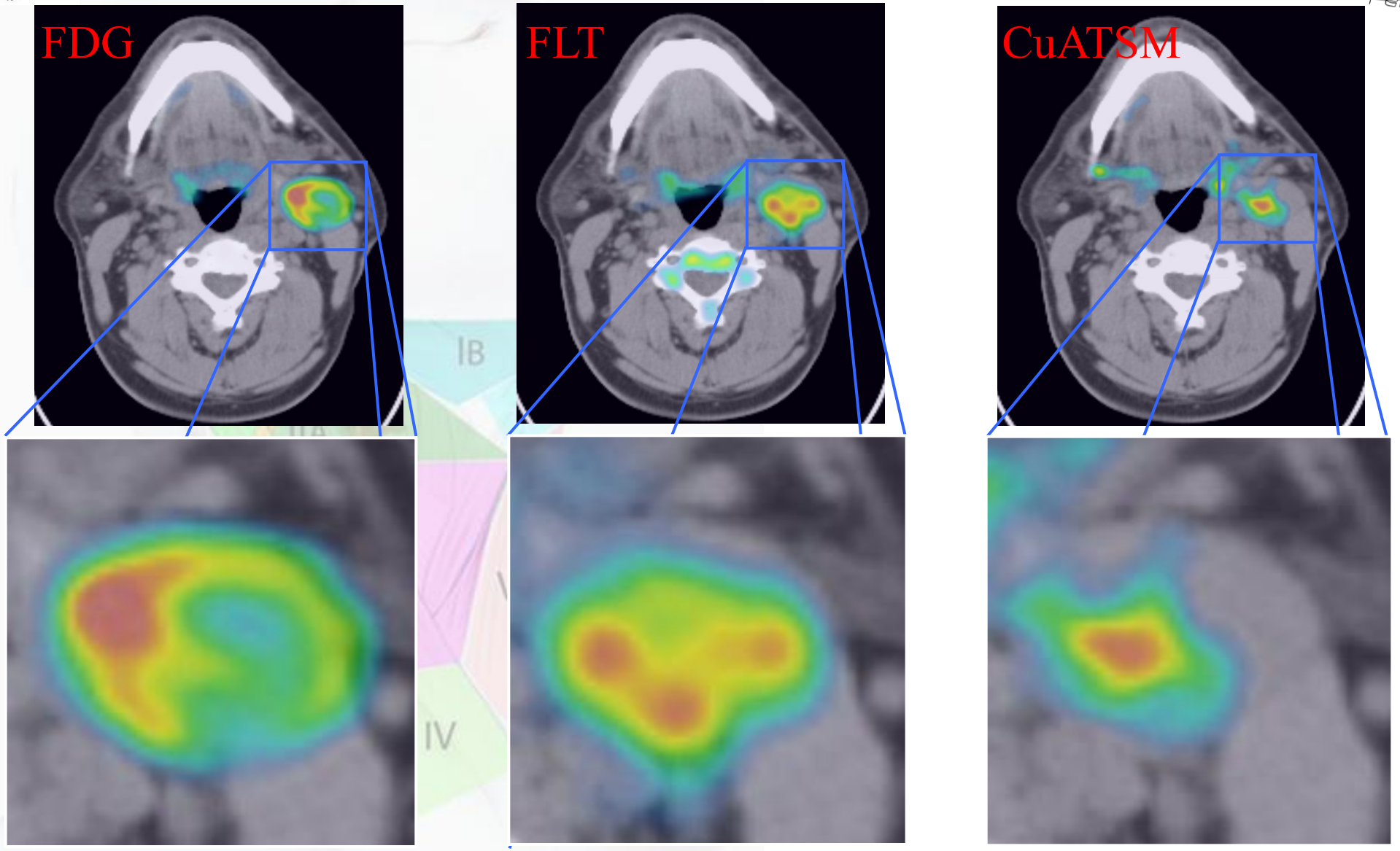
Jeraj *et al*, 2010

Spatially “complex” target



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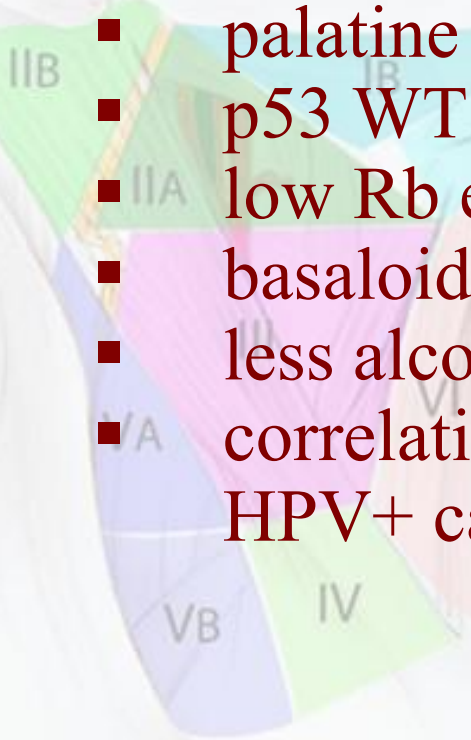
Jeraj *et al*, 2010

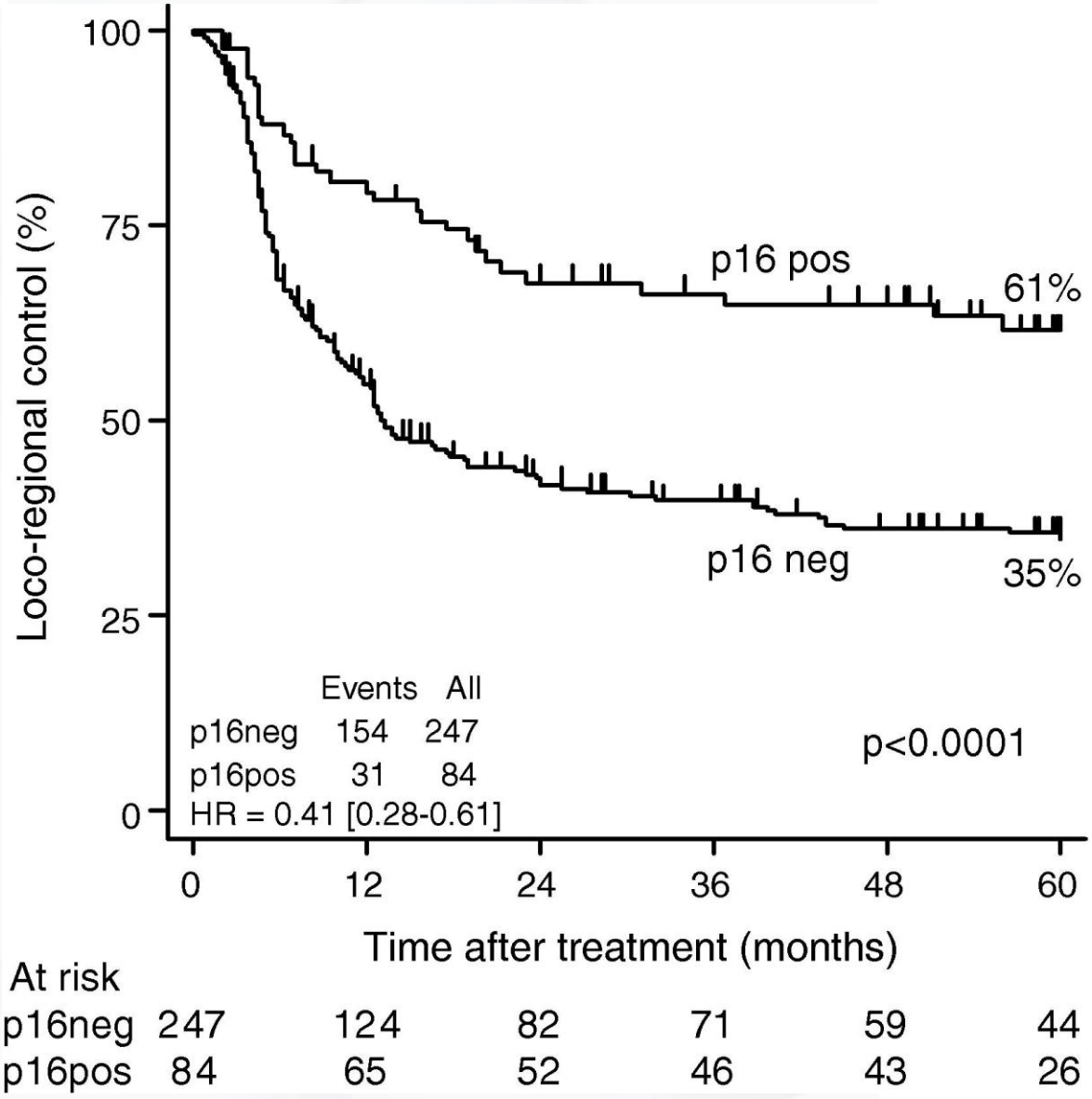
Molecular personalization (tailoring)

Molecular and epidemiological evidence suggest that HPV is associated with a distinct subset of HNSCC

- palatine and lingual tonsils
- p53 WT
- low Rb expression
- basaloid
- less alcohol and tobacco exposure
- correlation with HIV+ and ano-genital HPV+ cancer



Molecular profiling: HPV in HNSCC



Pharyngo-laryngeal SCC

RxTh: 66-68 Gy

p16 IHC

Lassen et al., *Radiother. Oncol.*, 2009

The current practice: Tailoring…?

Great hope but still in the research arena!

The current practice: Adaptation…?

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4D-IMRT

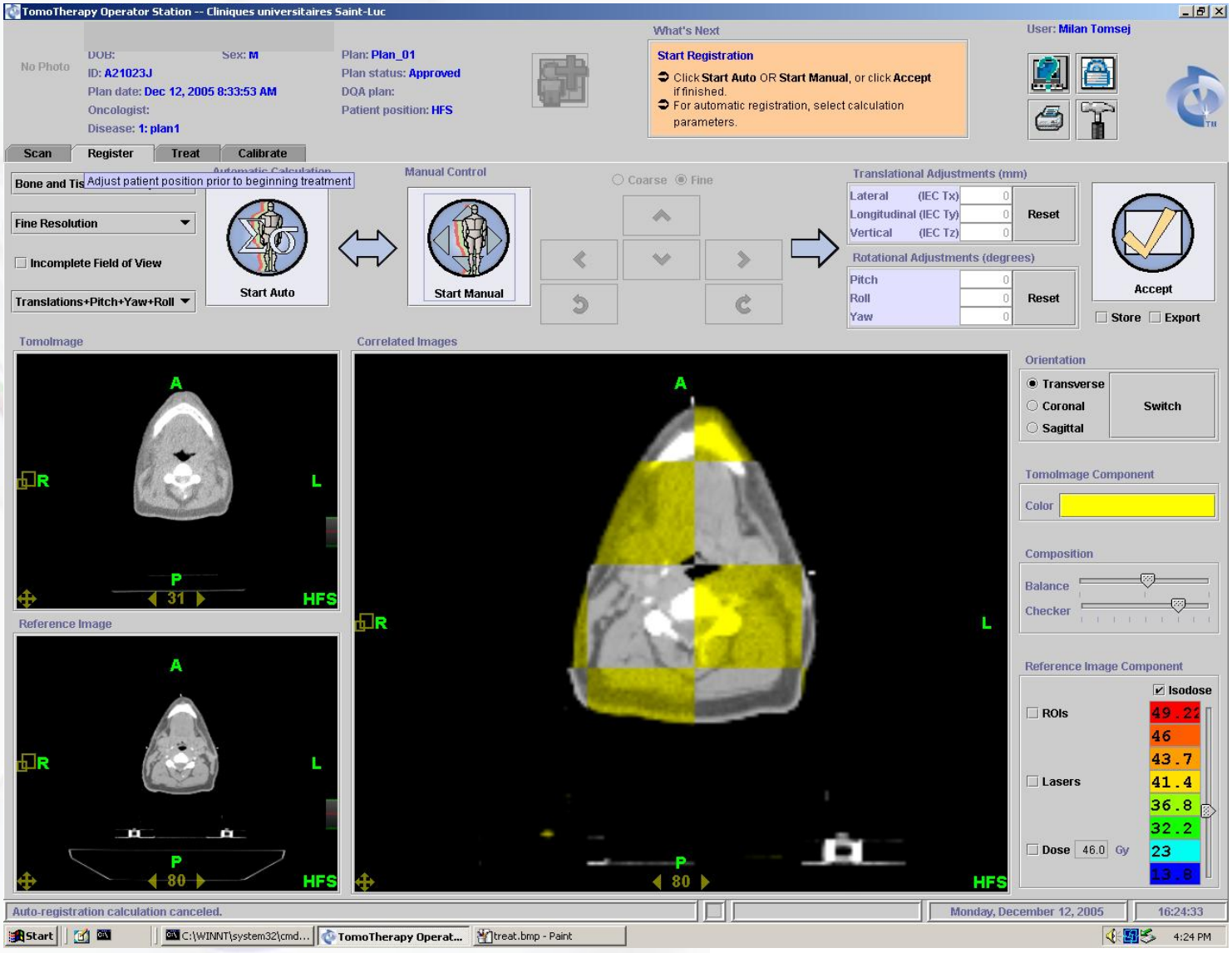
The Cathedral of Rouen

C. Monet, 1894

Geometric 4D-IMRT

MVCT

kVCT



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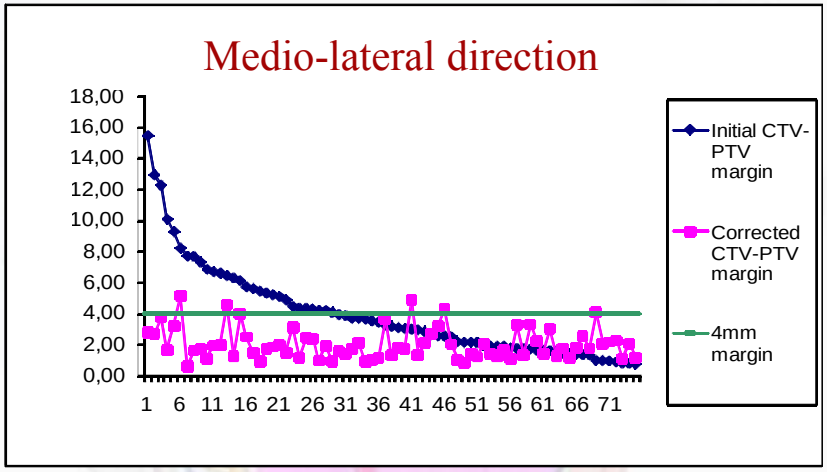
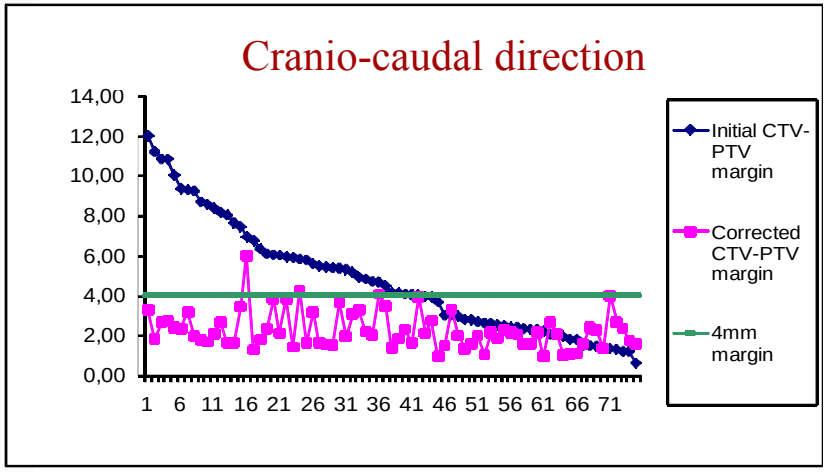
Vaandering, 2006

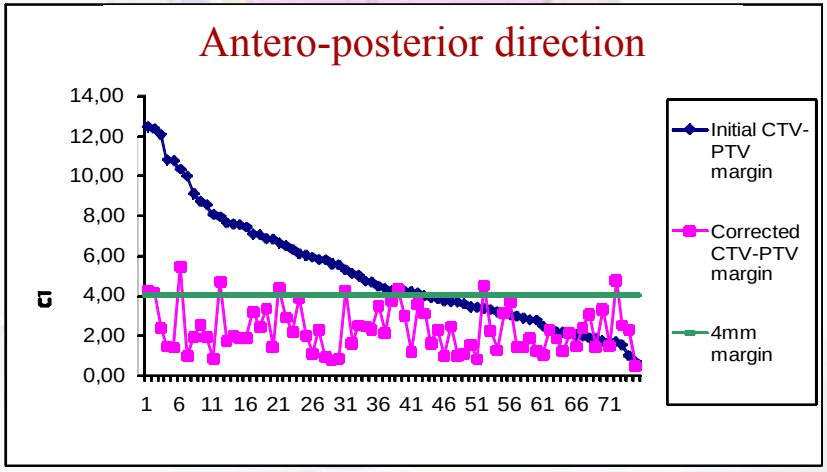
Geometric 4D-IMRT

Alternate week MVCTs: CTV-PTV margins

CTV to PTV margin







- 75 patients
- total of 1481 MVCT
- CTV-PTV: $(2*\Sigma + 0.7\sigma)$

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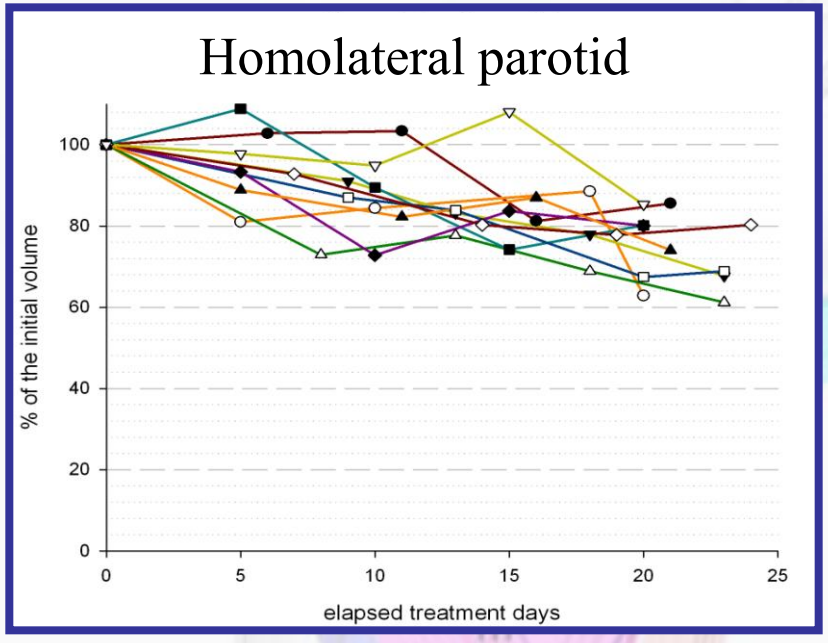
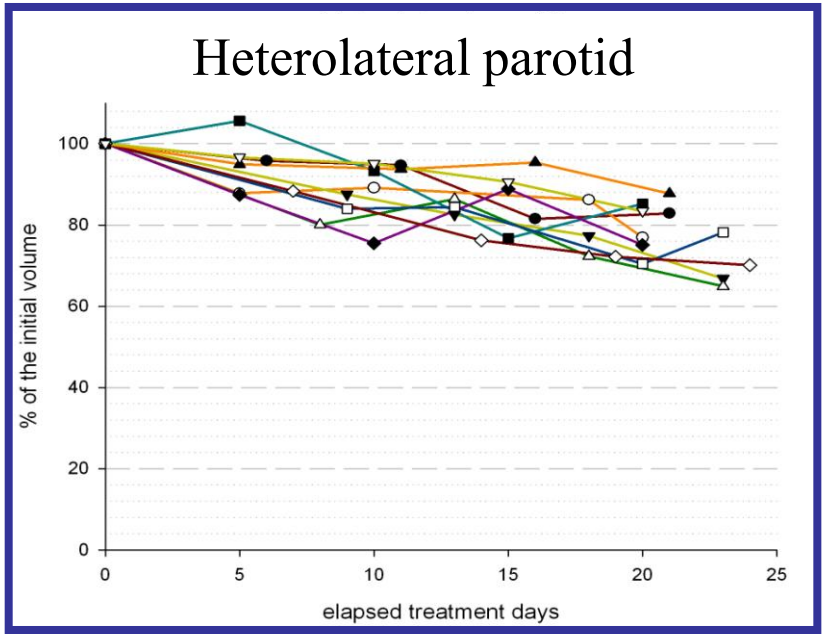
Vaandering, 2009

Variation in parotid volumes during RT-CH… (70 Gy – 3 courses on w1, w4, w7)





Mean slope: -0.93% / treat day ($p<0.05$)

Medial shift: 3.21mm after 25# ($p<0.05$)

Mean slope: -1.03% / treat day ($p<0.05$)

No shift

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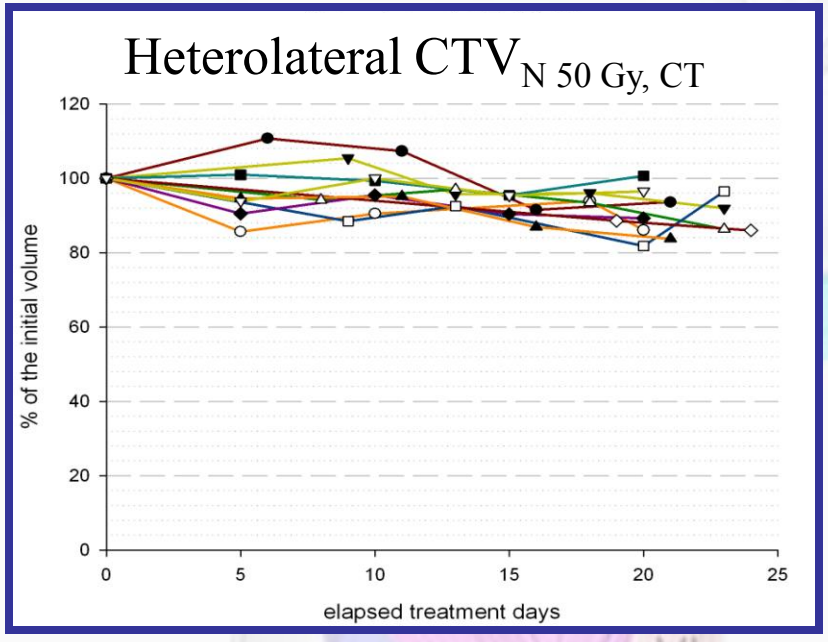
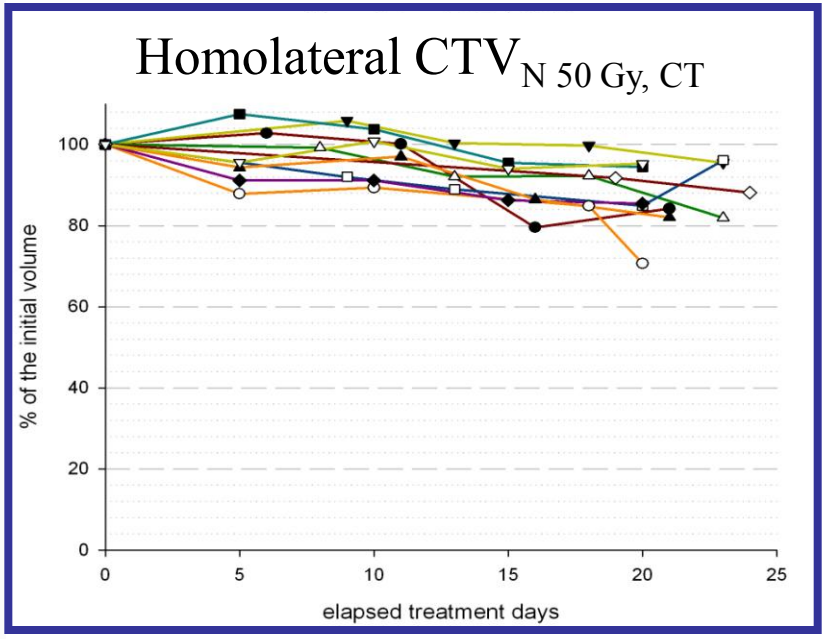
Castadot & Lee, 2010

Variation in prophylactic CTVs during RT-CH… (70 Gy – 3 courses on w1, w4, w7)



Mean slope: -0.47% / treat day ($p<0.05$)

No shift



Mean slope: -0.41% / treat day ($p<0.05$)

Medial shift: 1.76mm after 25# ($p<0.05$)

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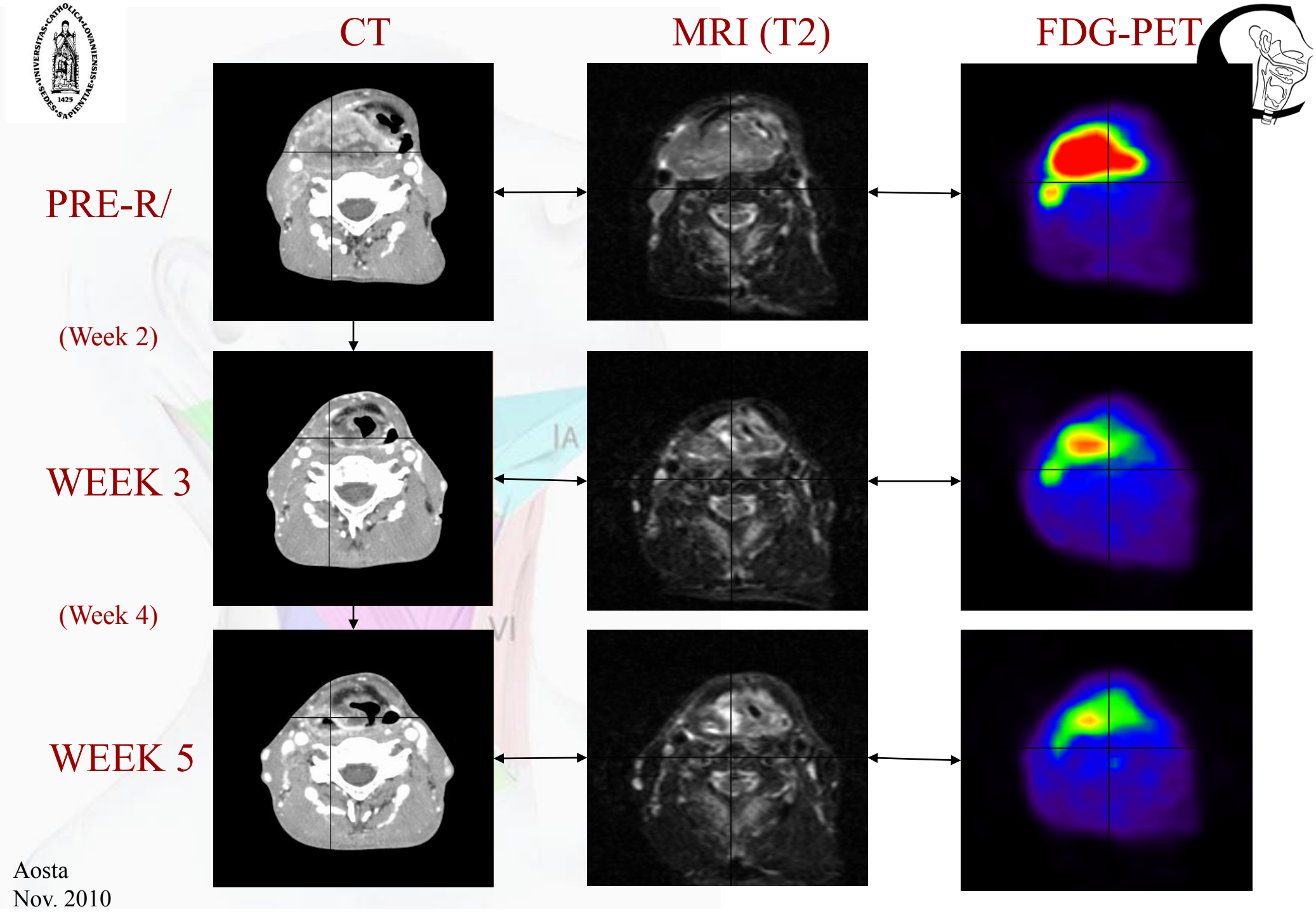
Castadot & Lee, 2010



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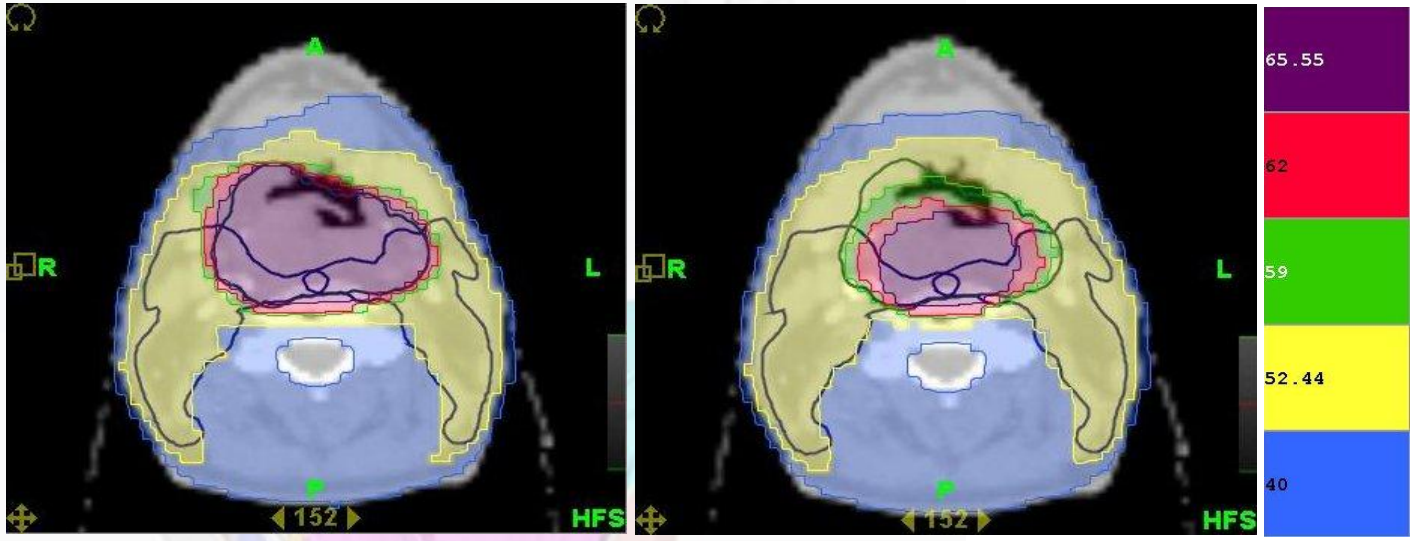
Impact on dose distribution

Classic CT-based planning Adaptive PET-based planning



SIB-IMRT

30x2.3 Gy

30x1.85 Gy

P<0.001

Planning	V_{10}	V_{50}	V_{80}	V_{90}	V_{95}	V_{100}
Classic CT-based	100%	100%	100%	100%	100%	100%
Adaptive CT-based	99%	100%	100%	85%	80%	66%
Classic PET-based	99%	99%	98%	83%	82%	81%
Adaptive PET-based	99%	100%	98%	73%	67%	58%

Geets, 2007

Dose distribution after biological adaptive IMRT

	« Classical » CT-based	« Classical » PET-based	« Real » CT-based	« Real » PET-based	Adaptive CT-based	Adaptive PET-based
Homolat Parotid D_{mean} (Gy)	22.05	21.63	23.80	23.27	22.91	22.09
Heterolat Parotid D_{mean} (Gy)	18.15	20.00	18.52	19.34	18.57	18.40
SC D_2 (Gy)	39.49	39.76	41	42.04	37.90	38.26
Larynx D_5 (Gy)	65.63	66.33	65.37	66.35	65.57	65.37
Oral cavity D_{mean} (Gy)	37.80	35.18	38.79	36.16	36.01	33.35
Mandible D_2 (Gy)	60.59	57.51	59.52	56.77	58.30	57.27
Homolat Submax gl D_{mean} (Gy)	65.04	62.96	65.52	63.59	64.57	63.09
Heterolat Submax gl D_{mean} (Gy)	54.92	53.77	54.97	53.63	55.11	54.58
Skin V_{65Gy} (cc)	11.66	8.78	12.08	9.25	10.25	7.24
$V_{95\%}$ (cc)	308.89	297.00	400.11	327.56	311.39	254.40

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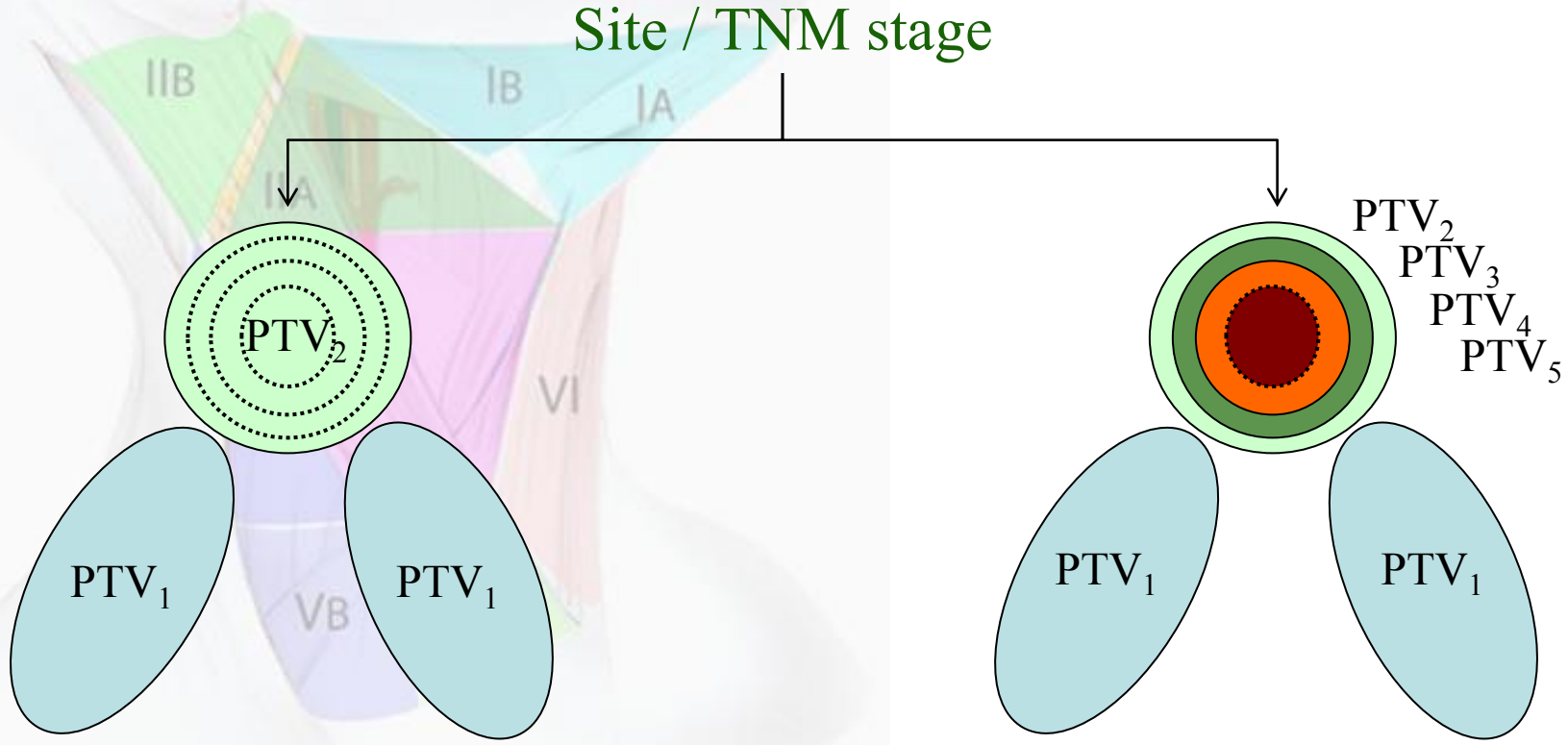
Castadot & Lee, 2010

Concept validation: a clinical trial ?

IMRT >< geometrical adaptive IMRT ?

Geometrical adaptive IMRT >< biological adaptive IMRT ?



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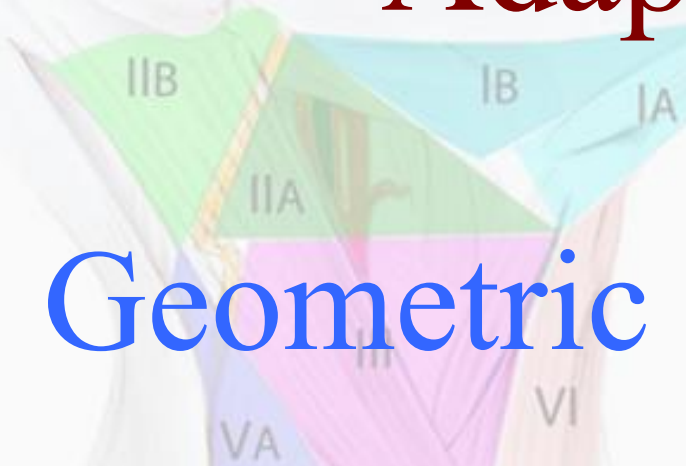
The current practice: Adaptation…?



Geometric adaptation, yes!

Biologic & dosimetric adaptation, under validation!

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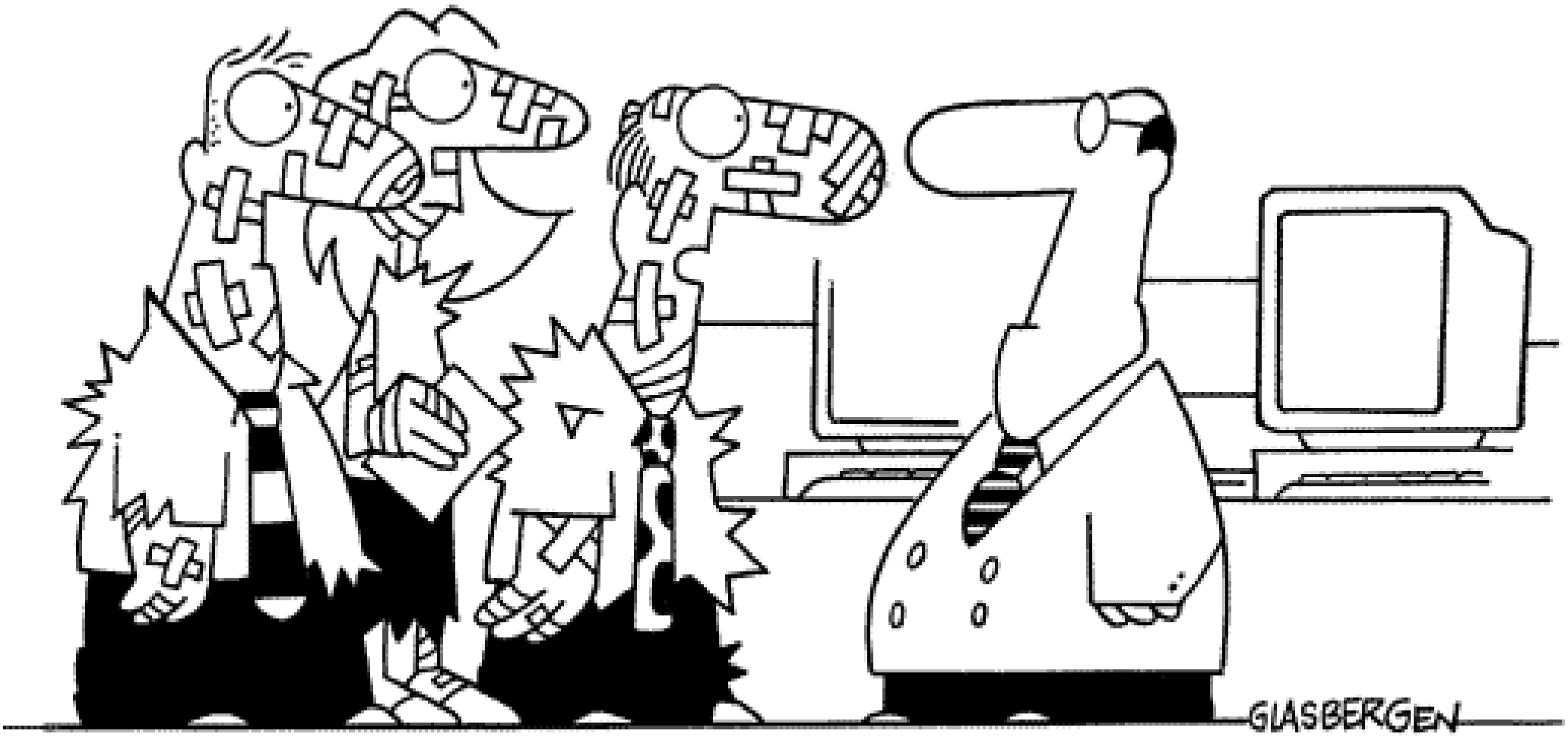


"Frankly sir, we're tired of being on the cutting edge of technology."

This house believes that …

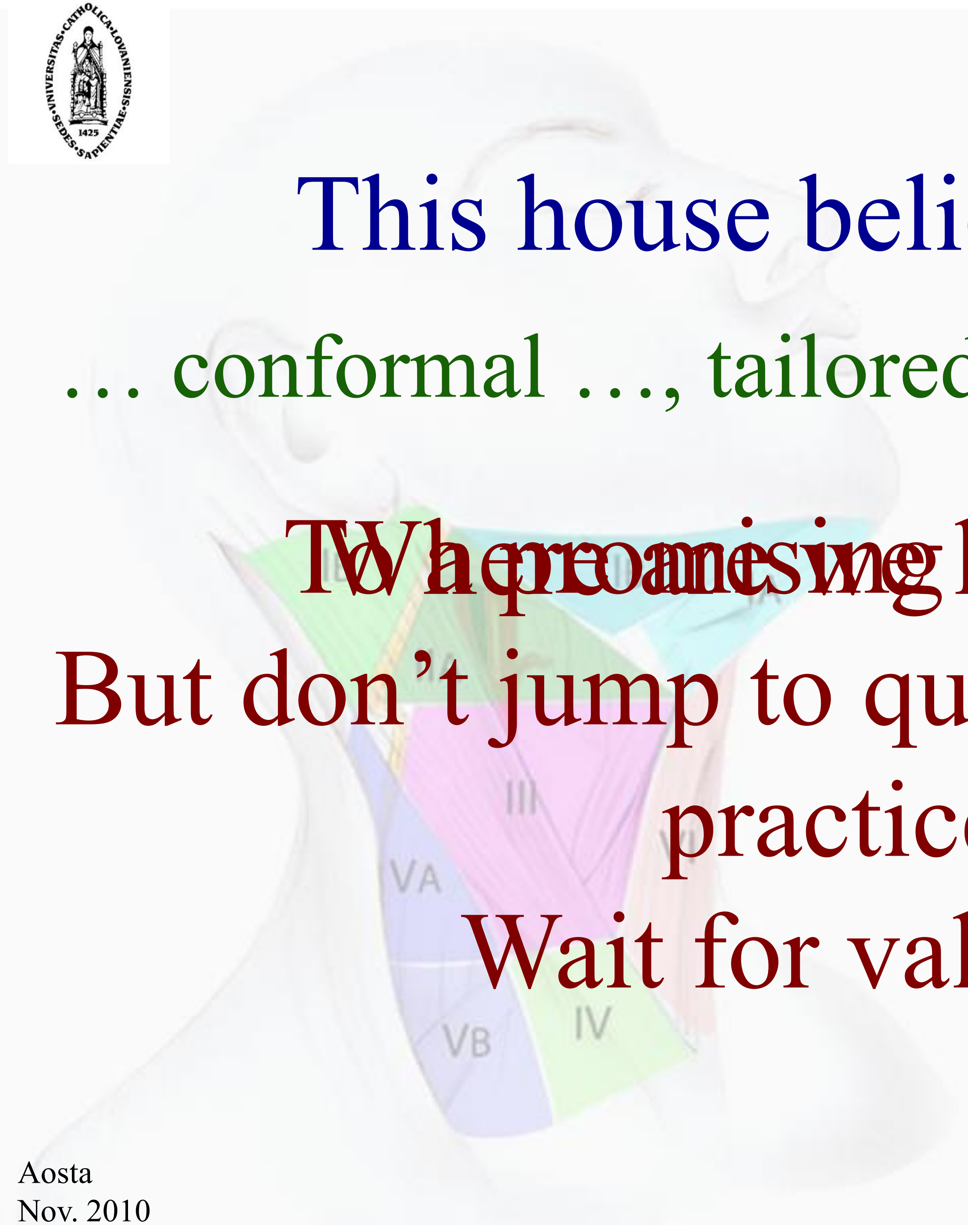
… conformal …, tailored …, and adaptive …

Where are we heading to?

To a promising direction…

But don't jump to quickly into routine practice…

Wait for validation!



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