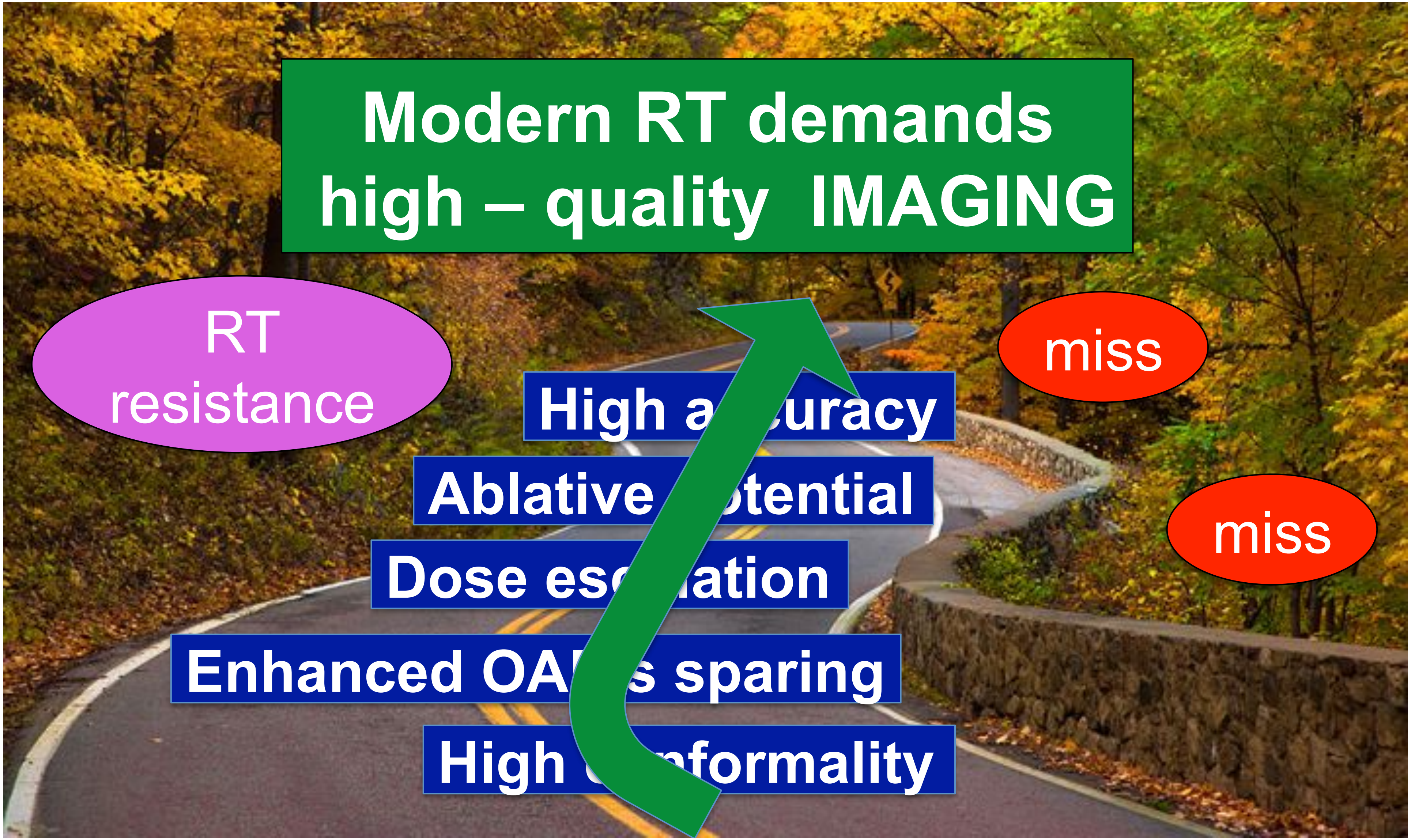
Impatto dell’imaging nel planning radioterapico

Pierluigi Bonomo
Radioterapia Oncologica
Azienda Ospedaliero – Universitaria Careggi
Firenze

The winding road of modern RT



Impact of imaging on Radiation Oncology workflow

- Diagnosis
- Staging
- Target selection
- Image registration
- Image segmentation
- Target delineation
- Theragnostics
- Prognostic value
- Predictive value
- Delivery verification
- Delivery guidance
- Adaptive replanning
- Response evaluation
- Follow-up

Impact of imaging on Radiation Oncology workflow

- ~~Diagnosis~~
- ~~Staging~~
- Target selection
- ~~Image registration~~
- ~~Image segmentation~~
- Target delineation
- Theragnostics
- ~~Prognostic value~~
- Predictive value
- ~~Delivery verification~~
- ~~Delivery guidance~~
- ~~Adaptive replanning~~
- ~~Response evaluation~~
- ~~Follow-up~~

WHERE

and

HOW

is Radiotherapy planned (& delivered) ?

Clinical practice cannot resist fashion!

Editorial

PET in radiotherapy planning: Particularly exquisite test or pending and experimental tool?

Vincent Gregoire [a,*], Arturo Chiti [b]

The Value of Magnetic Resonance Imaging for Radiotherapy Planning

Piet Dirix, MD, PhD,[*,‡] Karin Haustermans, MD, PhD,[*,‡] and Vincent Vandecaveye, MD, PhD[†,§]

Gregoire V, Radiother Oncol 2010
Dirix P, Semin Radiat Oncol 2014

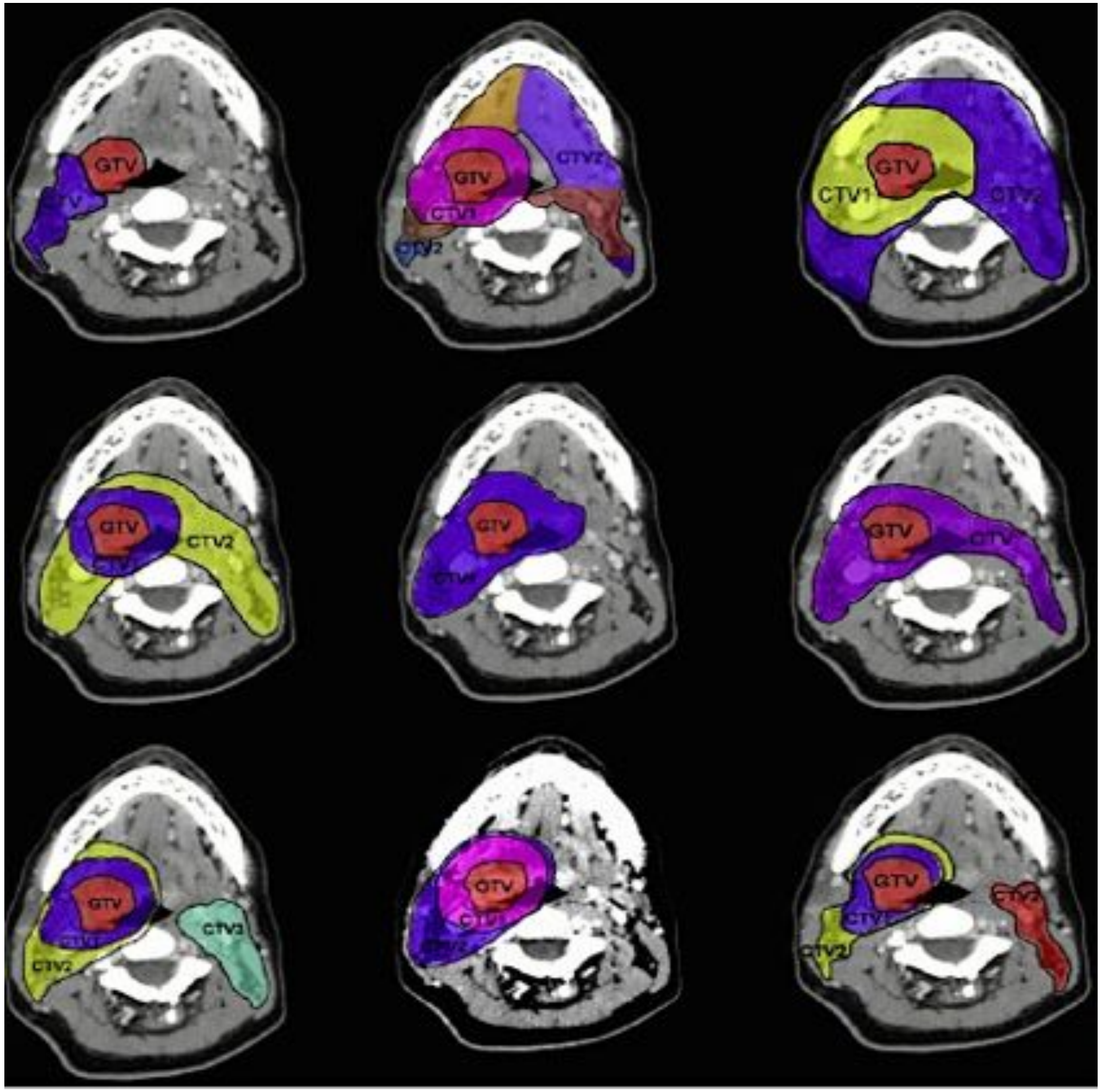
Outline

- Imaging influences **where** RT is planned
  - accurate target definition: allowed?
  - what evidence do we rely on?

- Imaging influences **how** RT is planned
  - optimized prescription: feasible?
  - what therapeutic gain can we expect?

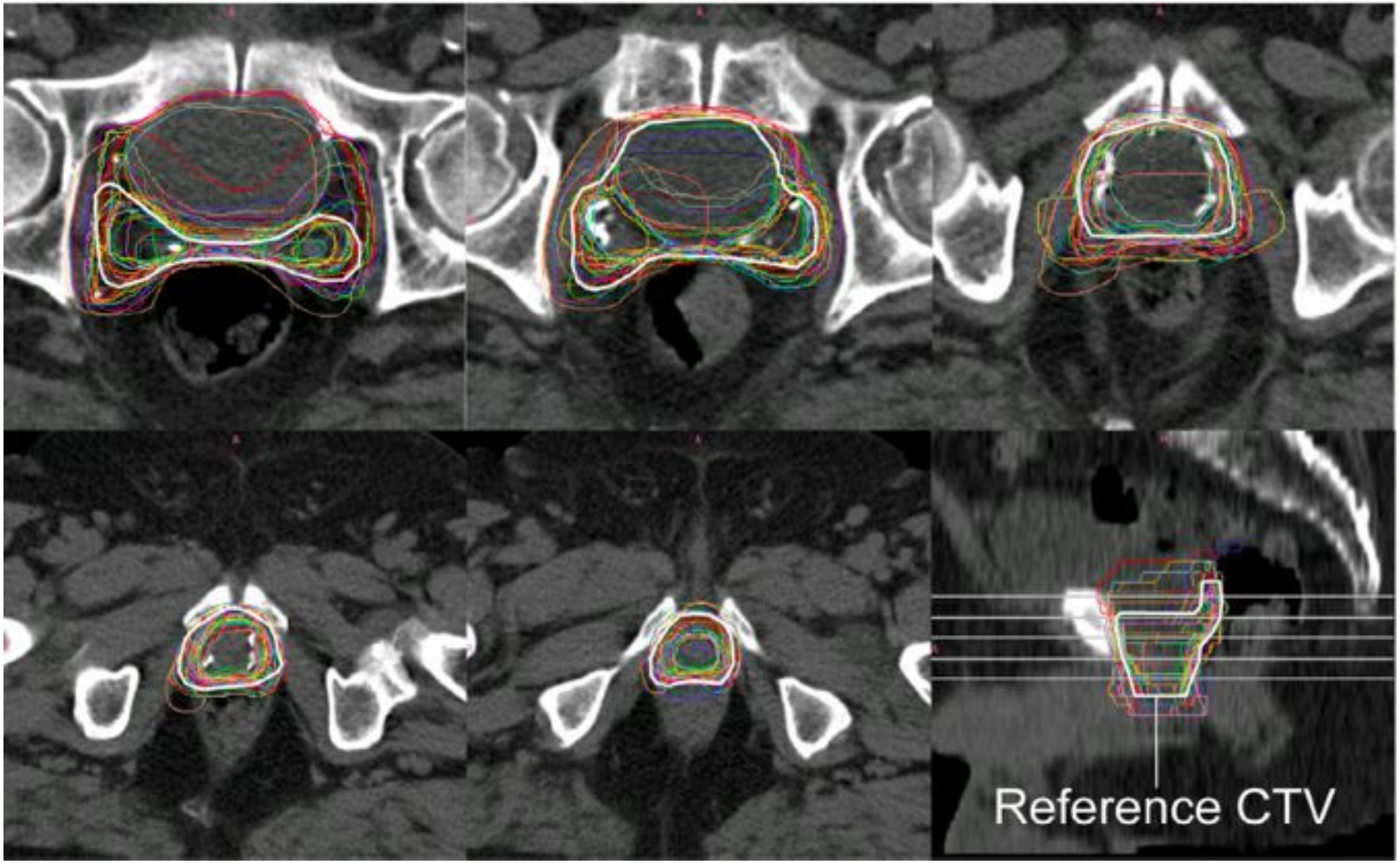
- Open issues & future directions

Heterogeneity in clinical practice



Hong TS, Radiother Oncol 2012

Heterogeneity in clinical trials



Fenton PA, Radiother Oncol 2013

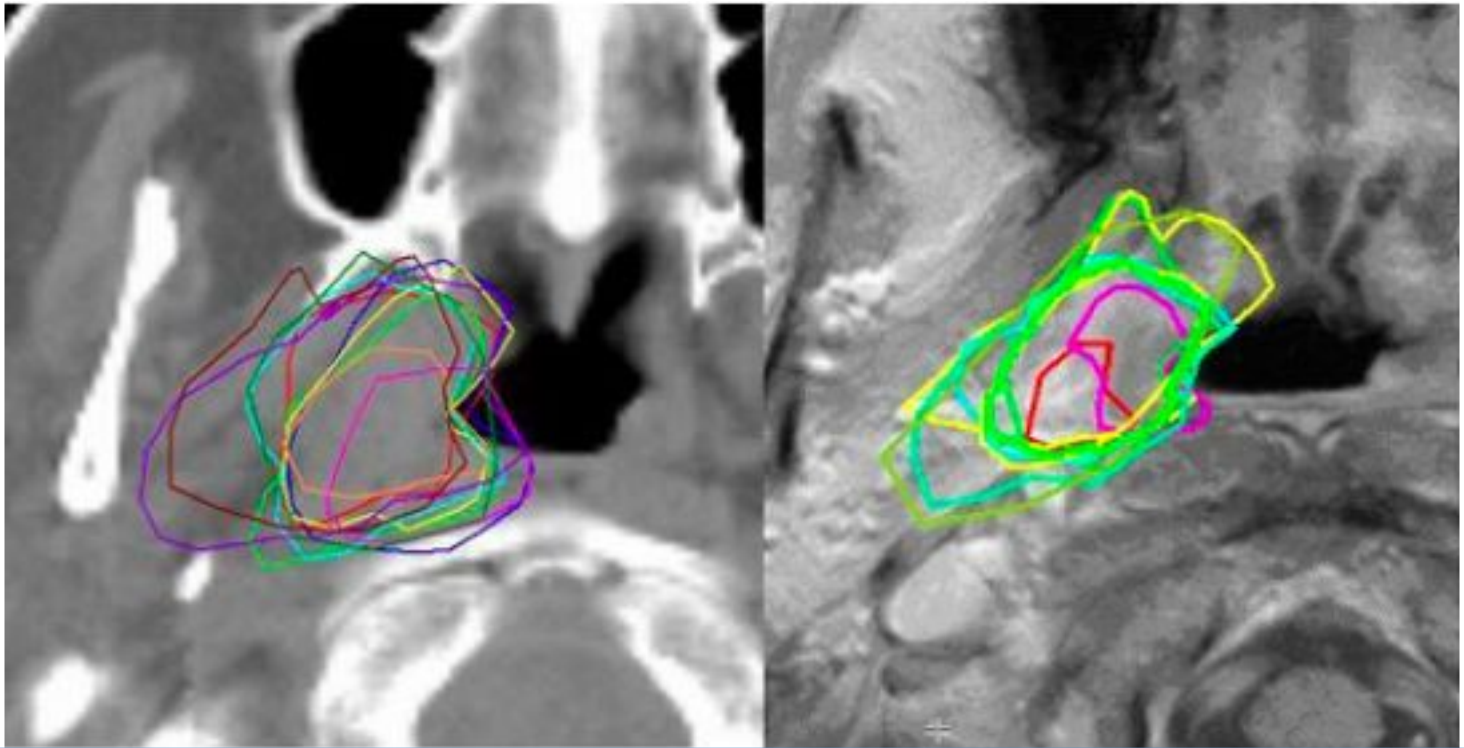
Weakest link in RT chain

- Target definition: **large source of error**

- Main reasons for delineation variation:
  – visibility of the target
  – disagreement on the target extension
  – interpretation, or lack, of delineation protocols

- Impact of multimodality imaging assessed with
  – intra/inter observer variability
  – pathologic validation
  – clinical endpoints (outcome & toxicity)

Target definition: head and neck



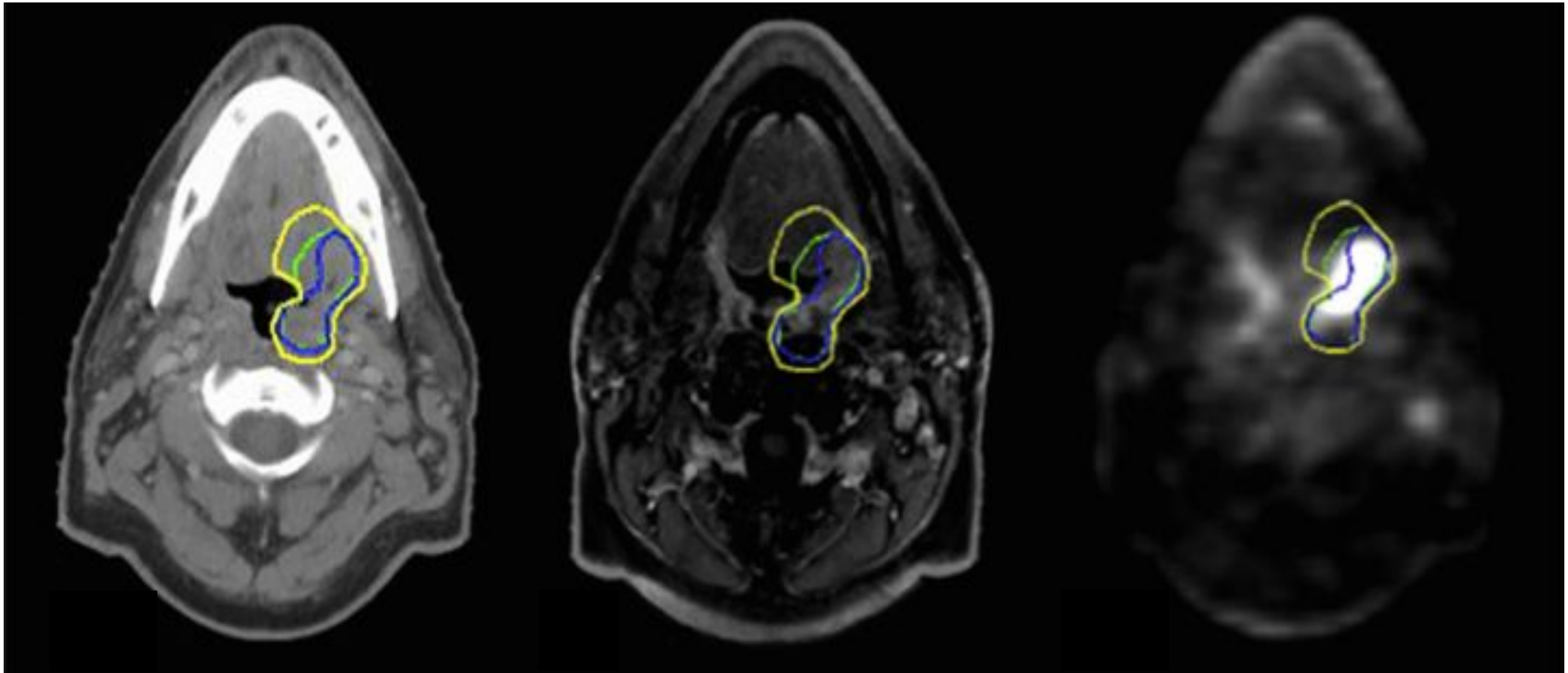
- C

Nasopharyngeal & sinonasal cancers: MR - guided planning standard of care

mm

(SD)

Rasch C, Radiat Oncol 2010

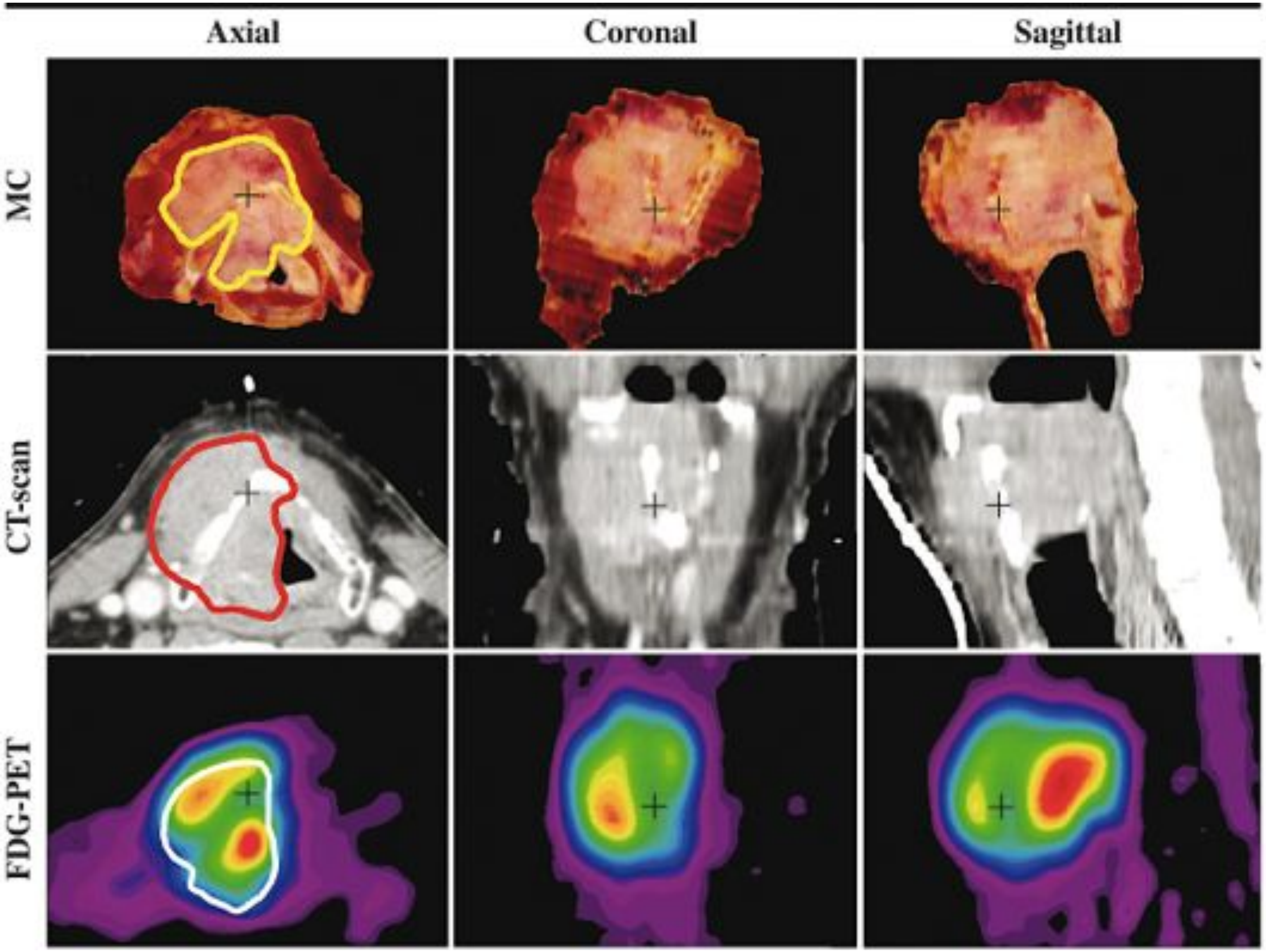


- Pet & MR: complementary, combined use is ideal
- Superficial extent of disease underestimated if clinical findings are not integrated in GTV contour

GTV Comparisons	Concordance Index (CI)
GTVctpet VS GTVctmr	0.62
GTVctpet VS GTVref	0.54
GTVctmr VS GTVref	0.55
GTVctpetmr VS GTVref	0.62

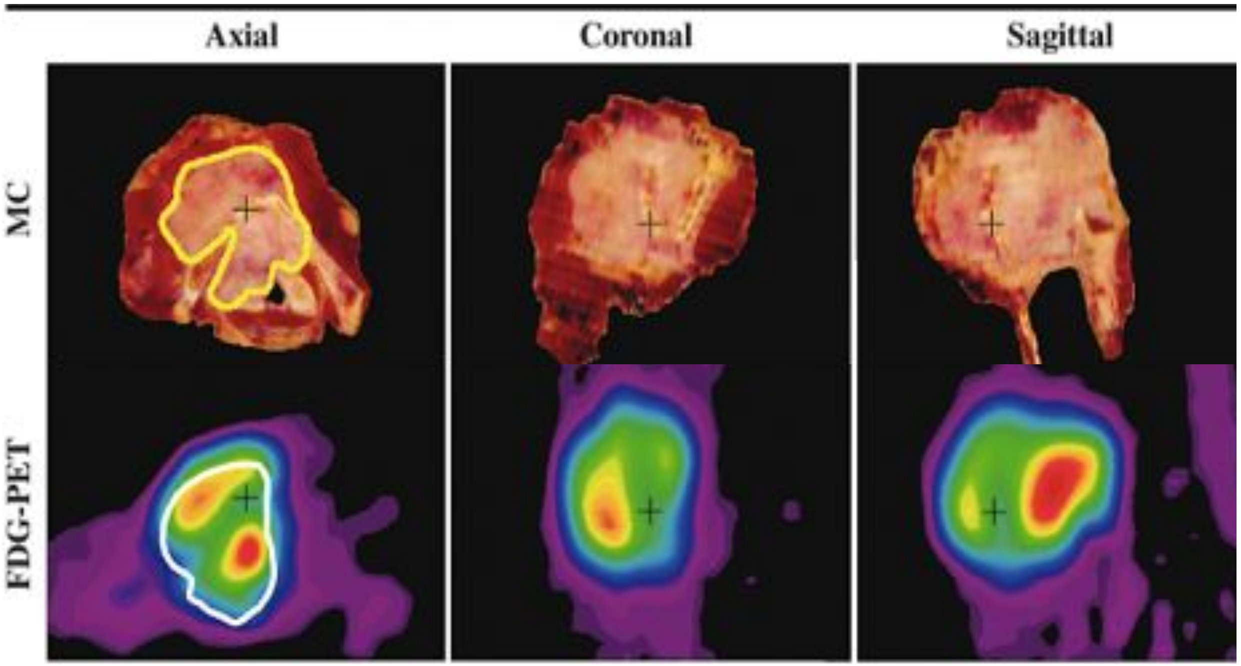
Thiagarajan A, Int J Radiat Oncol Biol Phys 2012

Ground truth: pathologic correlation



Daisne JF, Radiology 2004

Ground truth: pathologic correlation

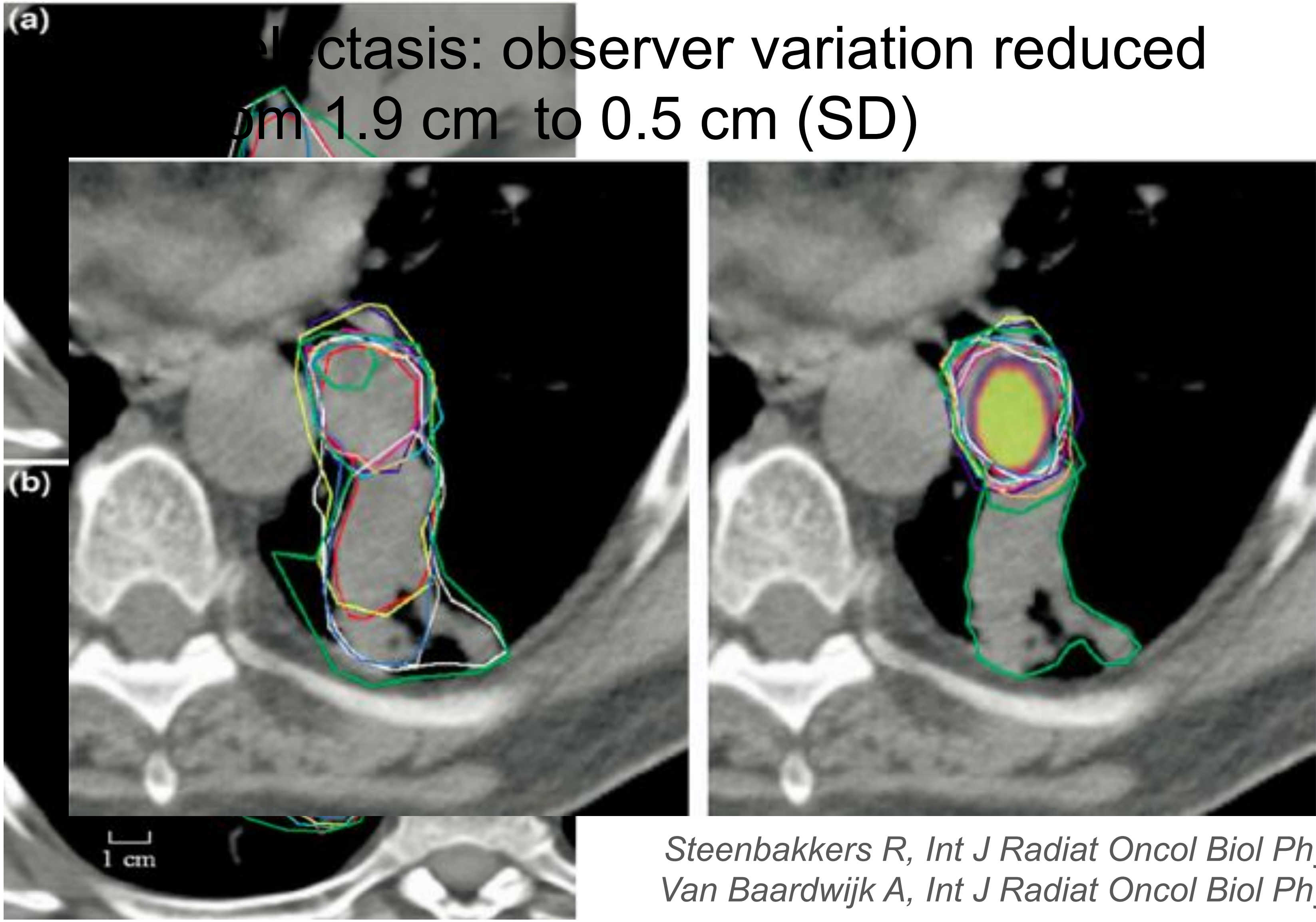


Average GTV	
@ macro	12.6 cm^3
@ PET	16.3 cm^3
@ CT	20.8 cm^3
@ MR	23.8 cm^3

The incremental value of MRI & FDG PET for non-nasopharyngeal head and neck cancer is controversial

Daisne JF, Radiology 2004

Target definition: NSCLC

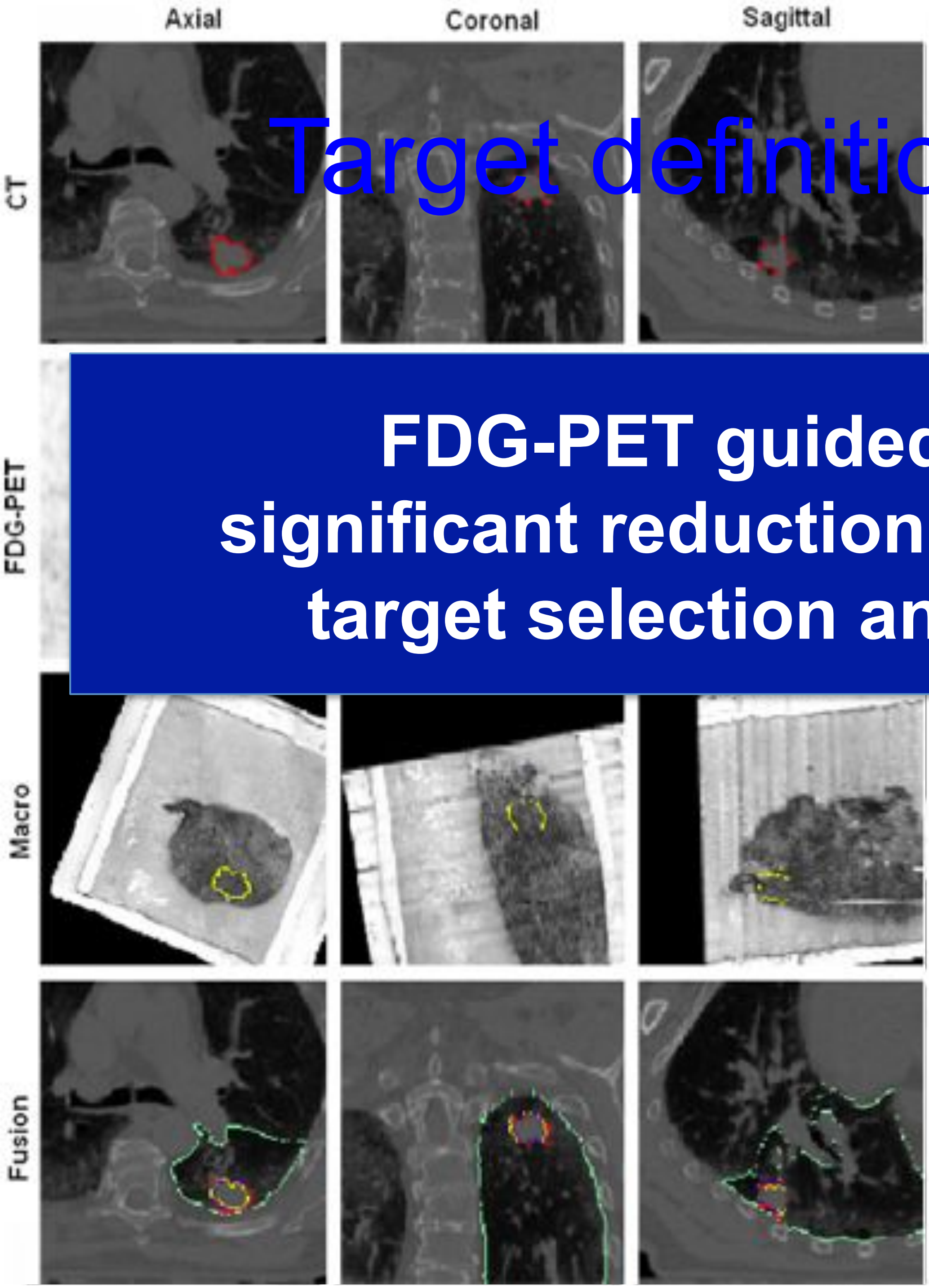


ctasis: observer variation reduced
m 1.9 cm to 0.5 cm (SD)

ET:
uced
SD)

Steenbakkers R, Int J Radiat Oncol Biol Phys 2006
Van Baardwijk A, Int J Radiat Oncol Biol Phys 2007

Target definition: NSCLC



FDG-PET guided planning: significant reduction of variability in target selection and delineation

@ PET 17.4 cm^3

Wanet M, Radiother Oncol 2011
V. Loon J, Int J Radiat Oncol Biol Phys 2012

Target definition: NSCLC

PET volume in lung cancer

The use of fused PET/CT images for patient selection and radical radiotherapy target volume definition in patients with non-small cell lung cancer: Results of a prospective study with mature survival data

Michael P. Mac Manus[a,b,*], Sarah Everitt[c], Mike Bayne[d], David Ball[a,b], Nikki Plumridge[a,b], David Binns[e], Alan Herschtal[f], Deborah Cruickshank[a], Mathias Bressel[f], Rodney J. Hicks[b,e]

- 76 NSCLC patients eligible to radical CTRT: after PET, 34% were upstaged
- Without PET:
  - FDG+ disease would stay outside of PTV in 36% of radical cases
  - 95% prescribed dose would cover <90% PTV in 25% of radical cases

McManus MP, Radiother Oncol 2013

Impact of multimodality imaging

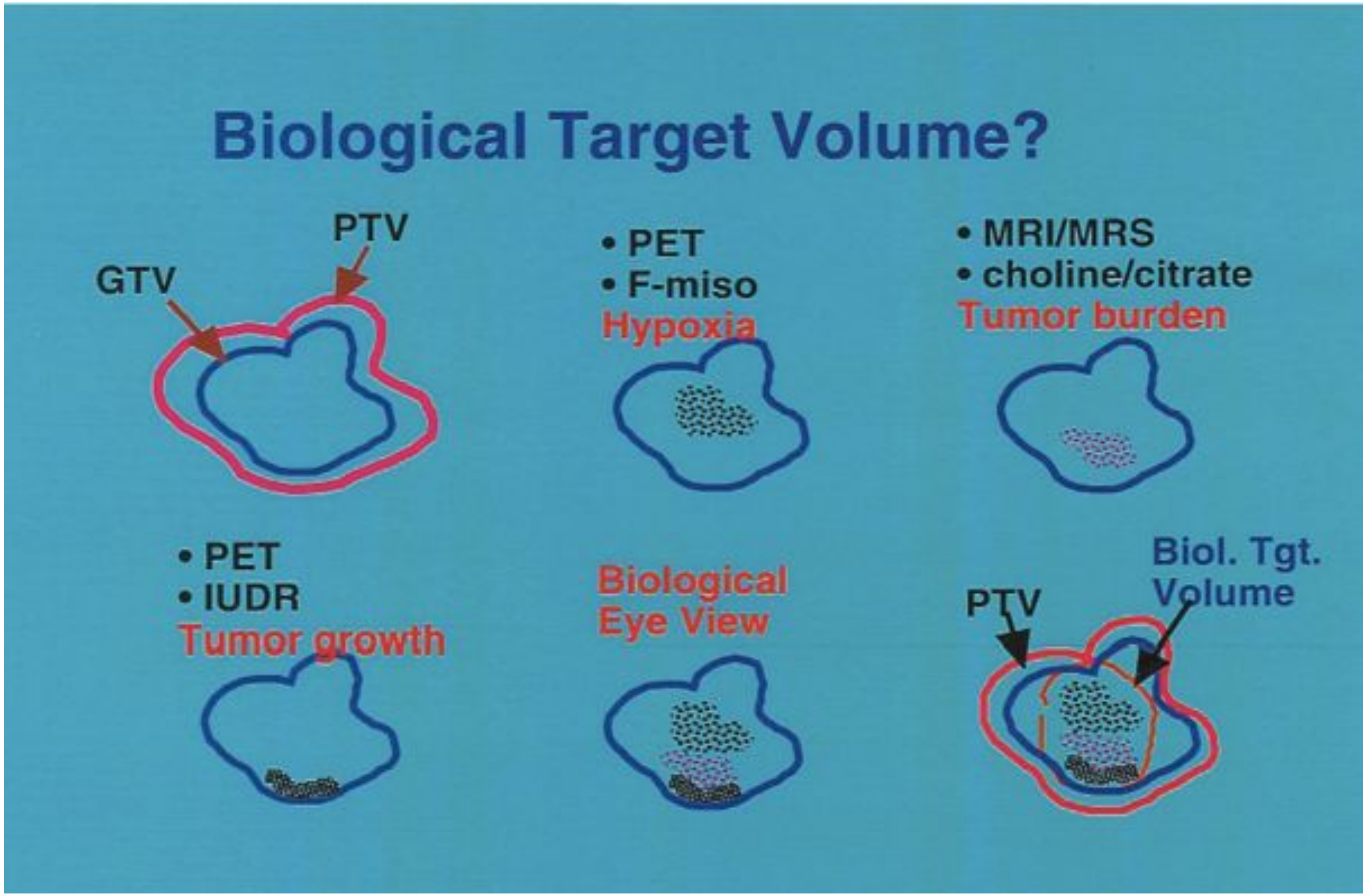
- Increased accuracy in **where** to irradiate
  - **selection:** NSCLC, esophagus, anal, cervix, HL...
  - **delineation:** NSCLC, gliomas, rectum, prostate…

- Is this all evidence-based medicine?
  - **YES**: consistent surrogate endpoints (Coefficient of Variation, CI, DICE index, pathology as benchmark)
  - **BUT**...hard to correlate the benefits of more accurate planning on outcome & toxicity!

Outline

- Imaging influences **where** RT is planned
  - accurate tumor delineation: allowed?
  - what evidence do we rely on?
- Imaging influences **how** RT is planned
  - optimized prescription: feasible?
  - what therapeutic gain can we expect?
- Open issues & future directions

BTV: customized dose delivery



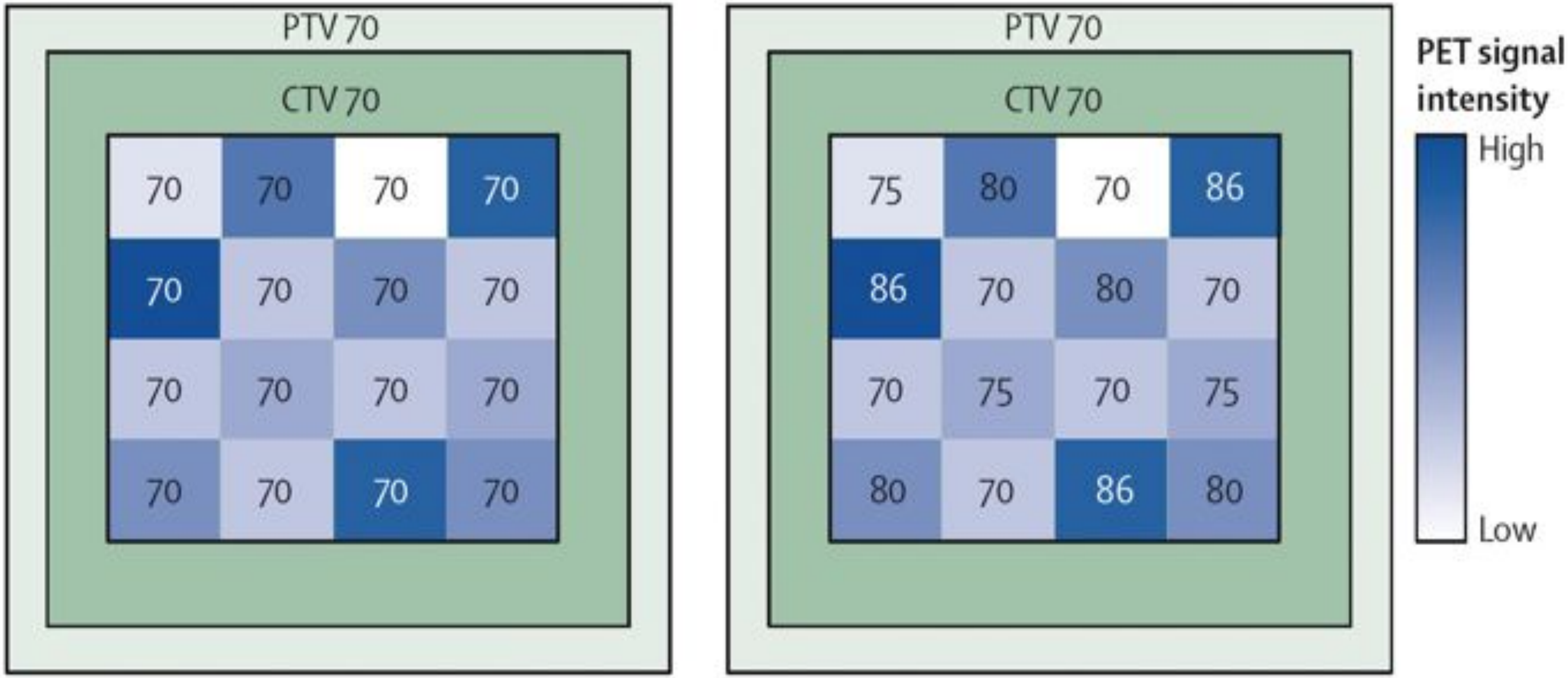
Ling CC, Int J Radiat Oncol Biol Phys 2000

Theragnostics

- **Theragnostic imaging:**
  - maps in 3 dimensions the distribution of a tumor or of microenviromental features within a tissue
  - provides information about the clinical response to RT, *before* and *during* treatment
- **Dose painting:**
  - prescription of non-uniform radiation dose distribution based on molecular imaging

Bentzen SM, Lancet Oncol 2005

Heterogeneous irradiation



Gregoire V, Lancet Oncol 2012

Dose painting targets

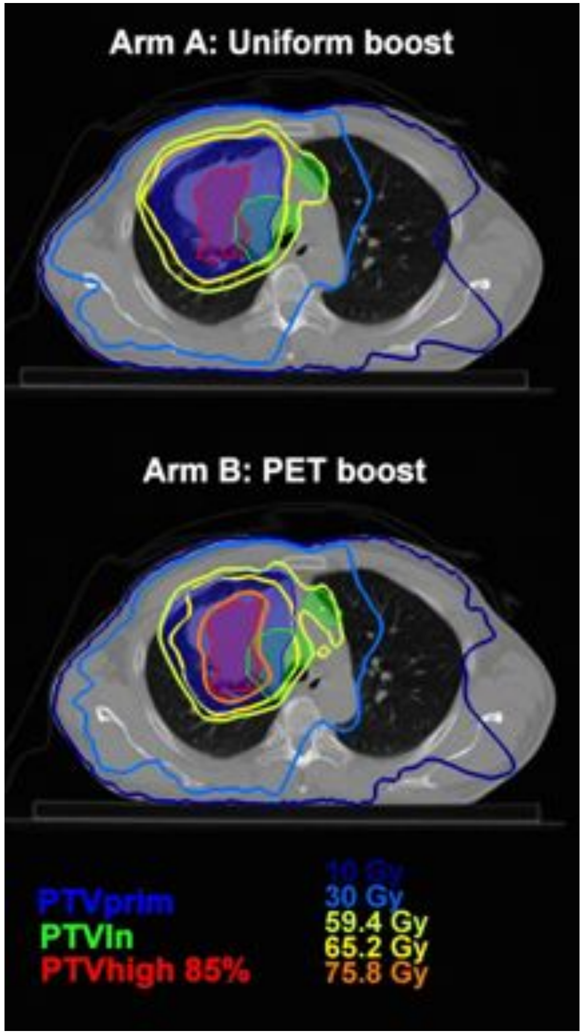
1. Tumor burden
2. Tumor proliferation & cancer stem cells
3. Tumor hypoxia

Bentzen SM, Semin Radiat Oncol 2011

PET in lung cancer RT

The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer

Wouter van Elmpt[a,*], Dirk De Ruysscher[a], Anke van der Salm[a], Annemarie Lakeman[b], Judith van der Stoep[a], Daisy Emans[a], Eugène Damen[b], Michel Öllers[a], Jan-Jakob Sonke[b], José Belderbos[b]



- **Hypothesis:**

boosting the high FDG region (>50% SUV max) inside the primary tumor improves local control

- **Planning feasibility:**

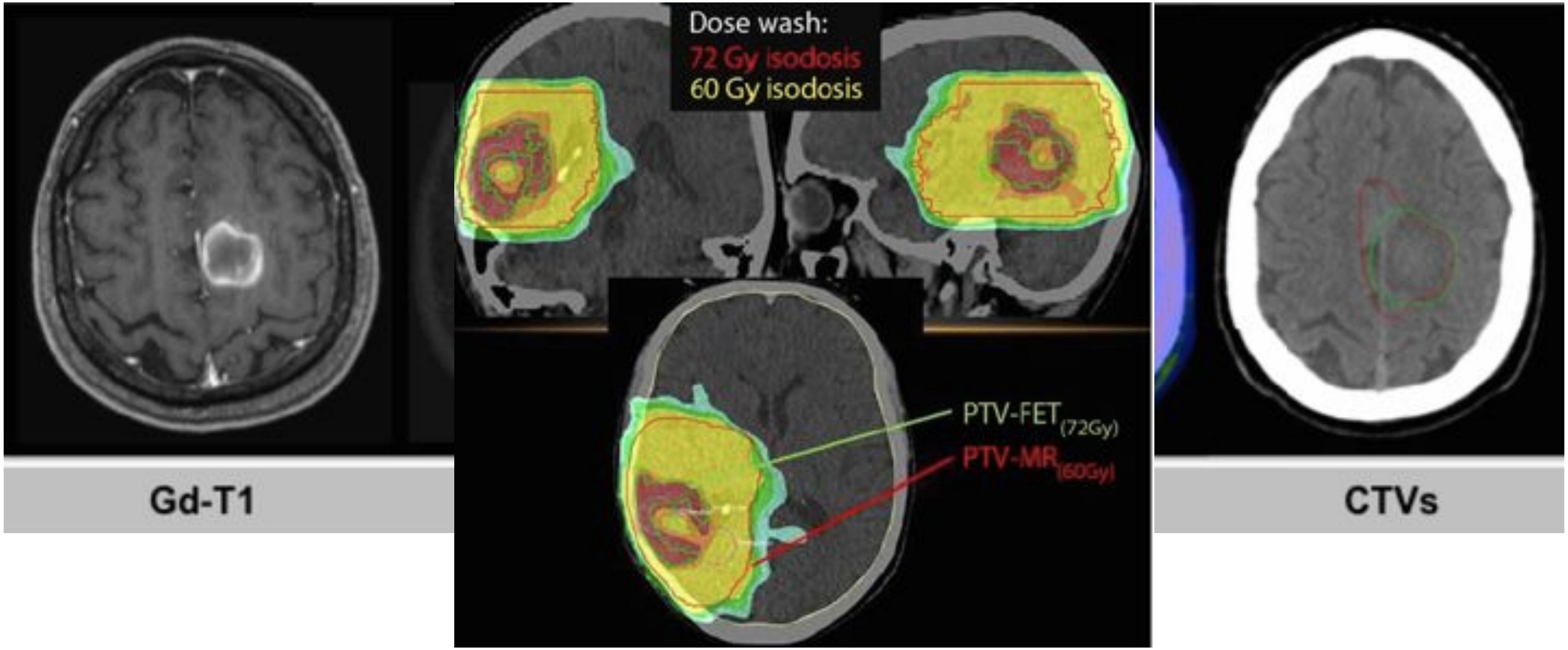
dose escalation in arm B on average 8 Gy > than in arm A

Van Elmpt W, Radiother Oncol 2012

Tumor proliferation: gliomas

- Most promising: PET-MR integration
  - ^{18}F-fluoroethyltyrosine PET *Rieken S, Radiother Oncol 2013*
  - ^{11}C-methionine PET *Navarria P, Radiother Oncol in press*

- Dose escalation, FET-PET based phase II study: no survival benefit *Piroth MD, Strahlenter Onkol 2012*
  - protons? concept of PETra trial *M. Baumann ESTRO 2014*



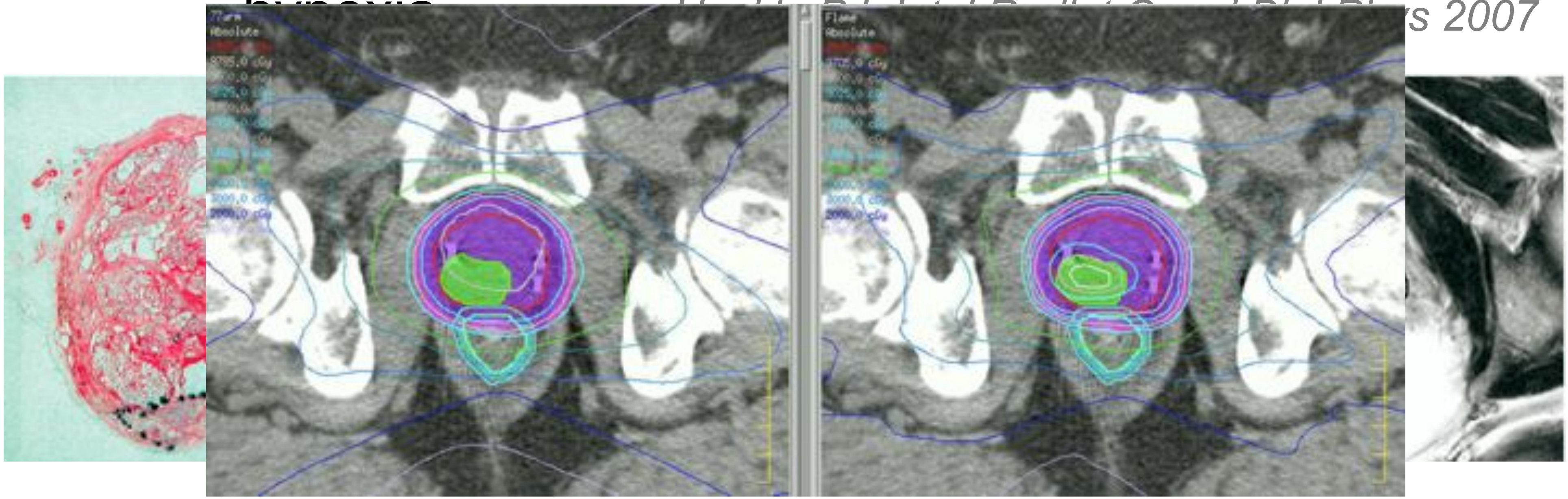
Tumor hypoxia: prostate

- Focal boost trials
  - FLAME trial Europe
  - HEIGHT trial US
  - TARGET trial Canada

Bauman G, Radiother Oncol 2013

- Most promising: with multiparametric MRI blood oxygen level dependent (BOLD) MRI
  - High correlation between pimonidazol staining and R_2 signal
  - high sensitivity to define intraprostatic tumor hypoxia

s 2007



What therapeutic gain can we expect?

- **Adaptive dose painting**:

use of imaging as a biomarker of response

  – repeated imaging during treatment

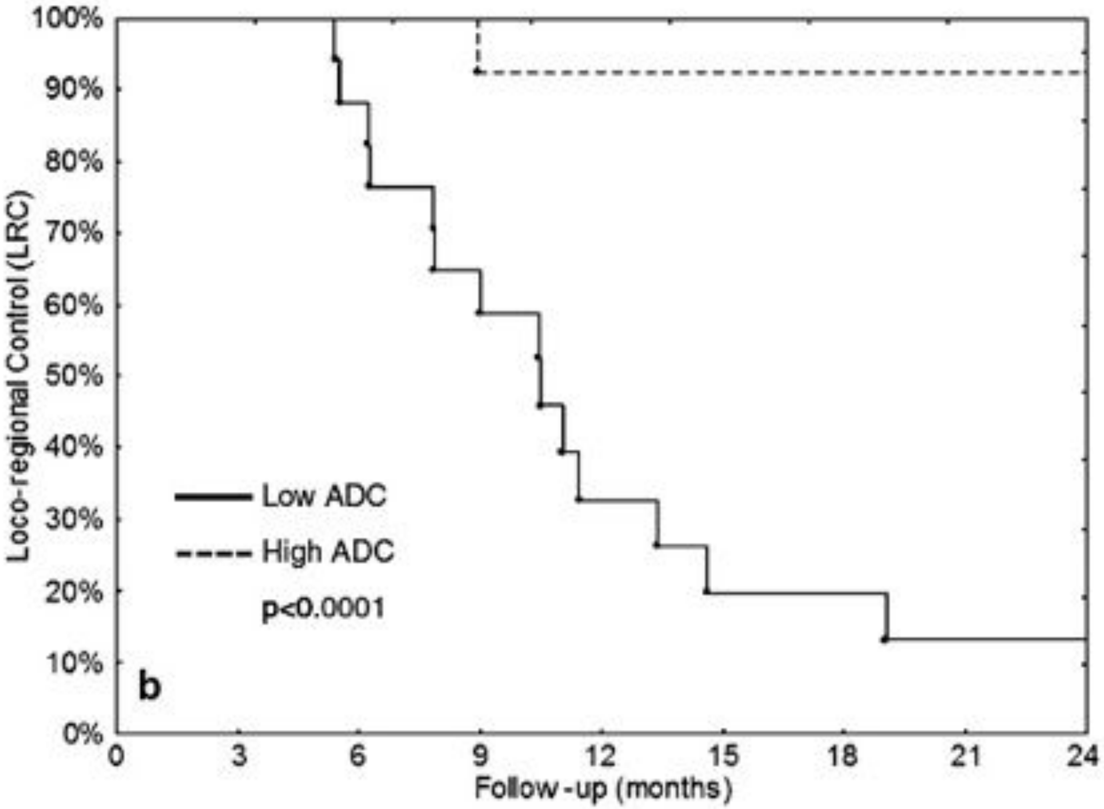
- Most promising:

  diffusion-weighted MRI (DWI)

Dirix P, Semin Radiat Oncol 2014

DWI: predictive value

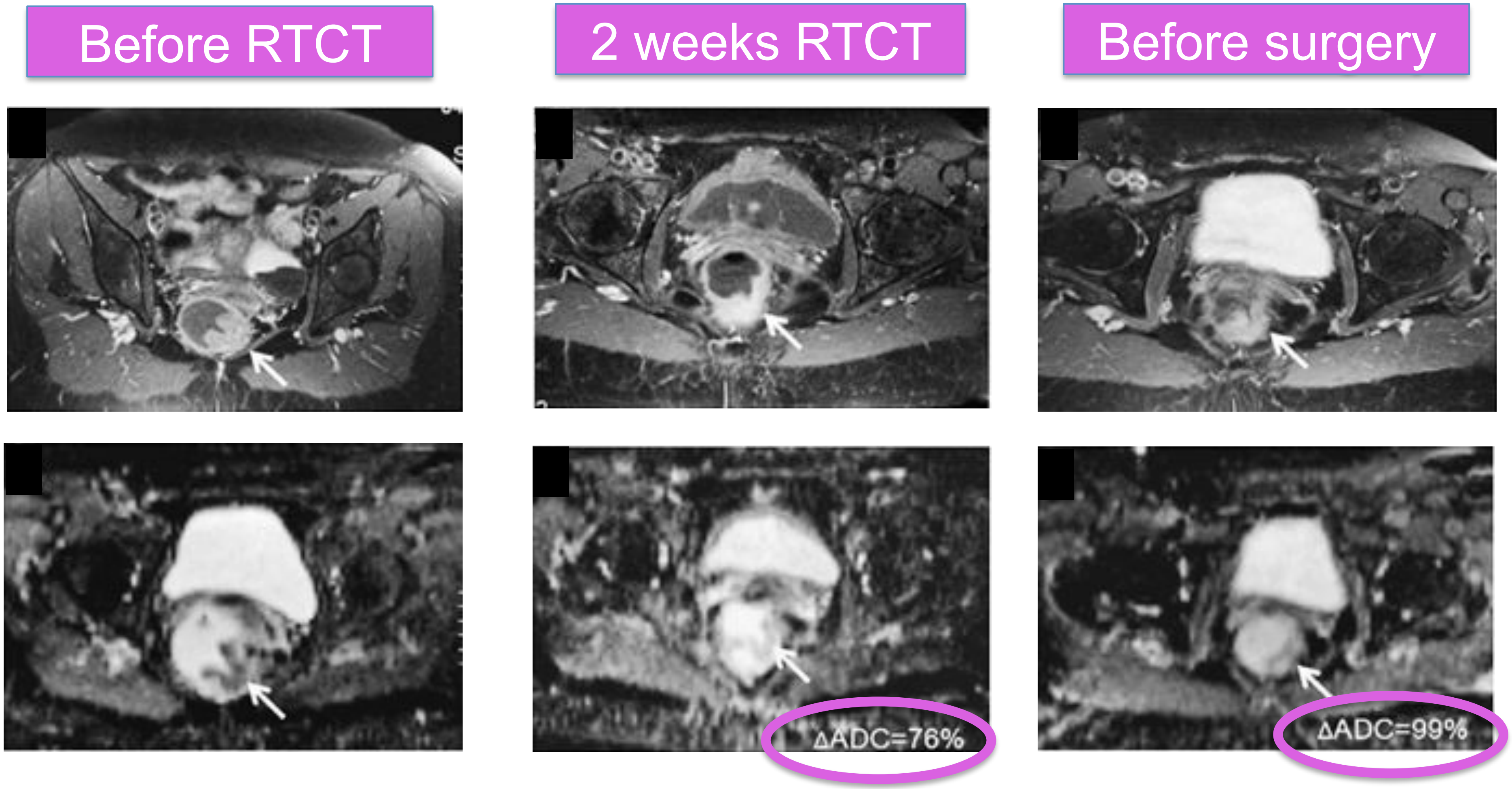
- During RTCT in head and neck cancer:
  - ⬆ ADC at 2 and 4 weeks correlates with 2-year LRC



Vandecaveye V, Eur Radiol 2010

- During and after neoadjuv RTCT in rectal cancer:
  - exquisite accuracy in prediction of pathologic CR

Lambrecht M, Int J Radiat Oncol Biol Phys 2012



Outline

- Imaging influences **where** RT is planned
  - accurate tumor delineation: allowed?
  - what evidence do we rely on?

- Imaging influences **how** RT is planned
  - optimized prescription: feasible?
  - what therapeutic gain can we expect?

- Open issues & future directions

Caveats to keep in mind

- Extreme variability in methods used for target definition
  - PET segmentation:
    1. visual-manual approach
    2. fixed treshold (i.e., 50% SUV max)
    3. adaptive treshold (signal to background ratio)
  - functional MRI: no standardized tresholds to be used
  - large degree of technical parameters

- Theragnostics: assumed stability of biology
  - microenviromental variables are not constant!

Rasch C, Semin Radiat Oncol 2006

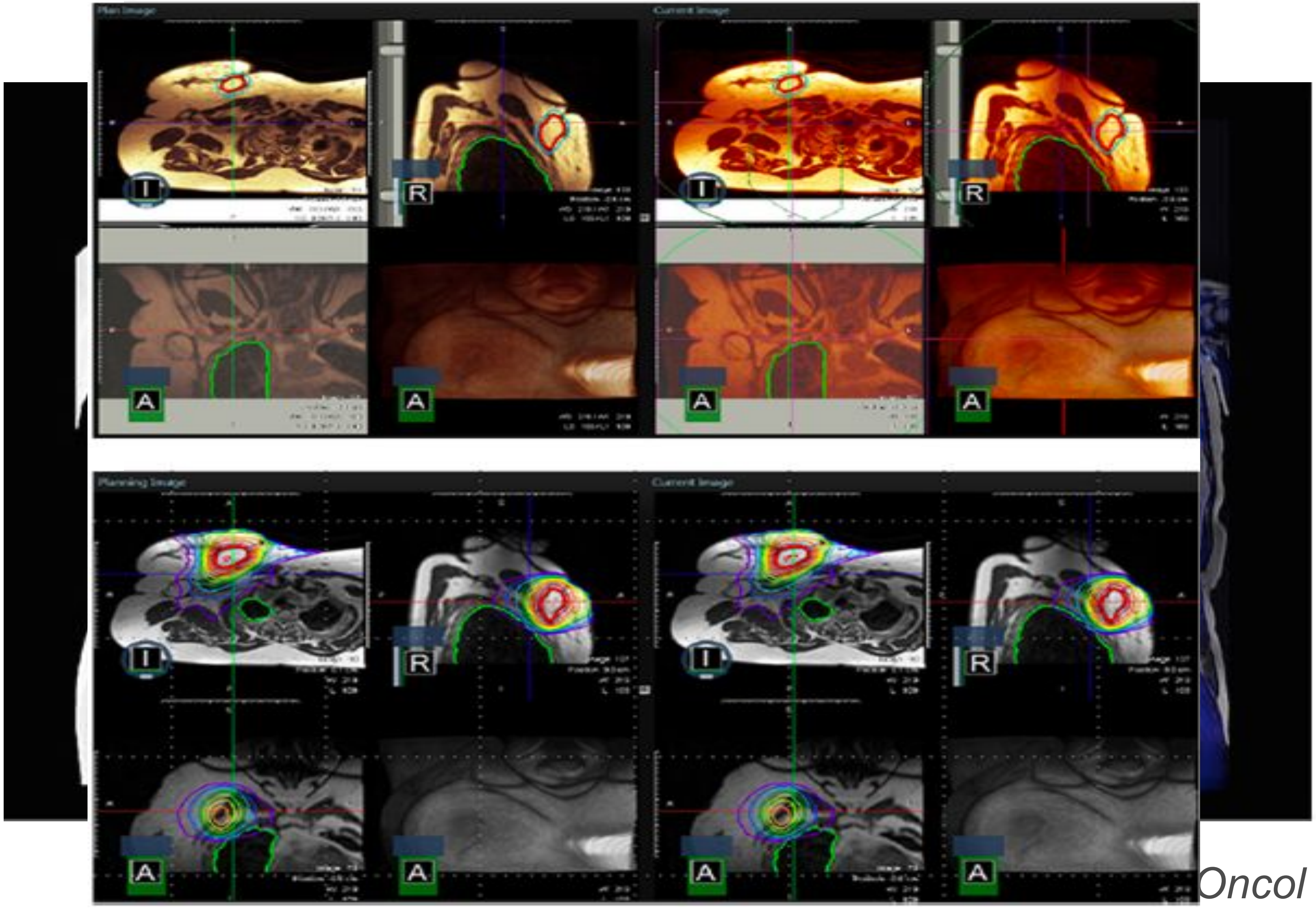
Future directions

- Molecular imaging for target definition
  - randomization is required to show clinical benefit: too complex? ethical?
  - justified by surrogate endpoints of efficacy?

- Dose painting strategies
  - priority: preclinical research & early clinical trials
  - phase I/II studies with subvolume boosting
  - phase III trials endpoints: locoregional control and late toxicity

Matsuo M, Semin Radiat Oncol 2014

Future directions



Oncol 2014

Summary - WHERE

- **The use of multimodality imaging**
  - allows better target visibility
  - allows better accuracy in target selection and delineation
  - does it improve treatment outcome?

- **Interpretation of target extension: still to be improved!**
  - multicenter guidelines, strict in-house protocols, semi-automatic tools, **TRAINING**!

Summary - HOW

- **Molecular – imaging guided dose painting**
  – technically feasible
  – biologically driven, heterogeneous irradiation

- **Advanced dose escalation strategies: likely to provide a therapeutic gain?**

- **Clinical impact remains to be validated**