Multimodal imaging

Enlight Meeting
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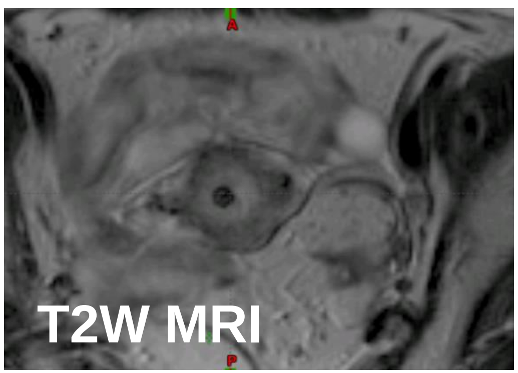
Thanks to:

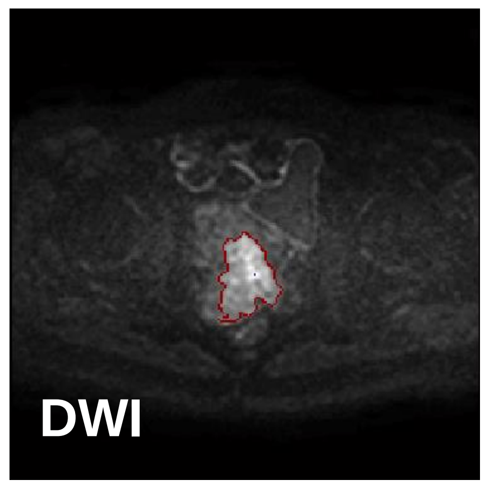
- **Uulke van der Heide (Amsterdam NKI)**
- **Daniela Thorwarth (University Tübingen)**
- **Renata Raidou (Technical University of Eindhoven)**
- **Jesper Kallehauge (Aarhus University Hospital)**

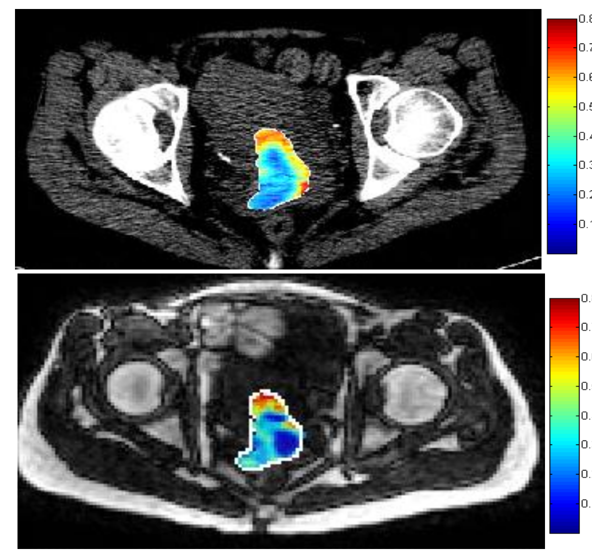
Multimodal imaging

Morphological imaging:
- Where is the tumour?
- What are the tumour characteristics?

Functional imaging:
- Where is the tumour?
- What are the tumour characteristics?



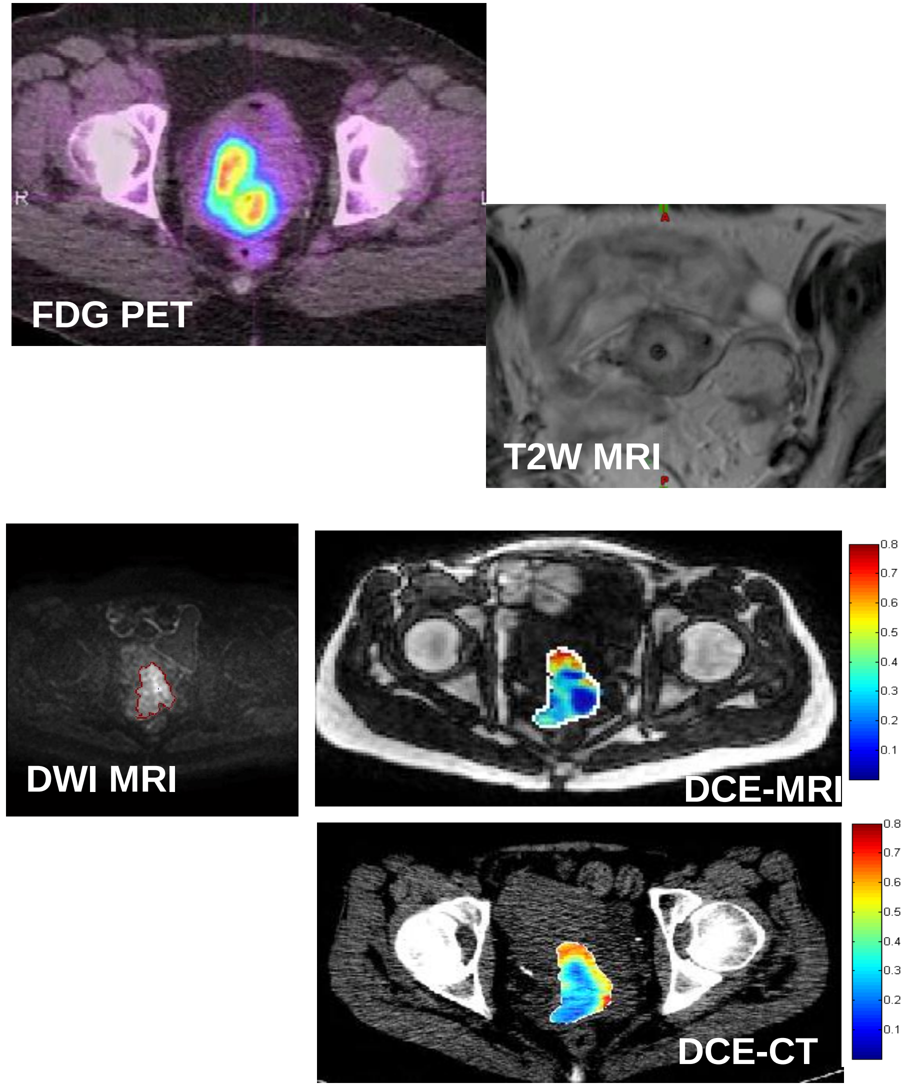




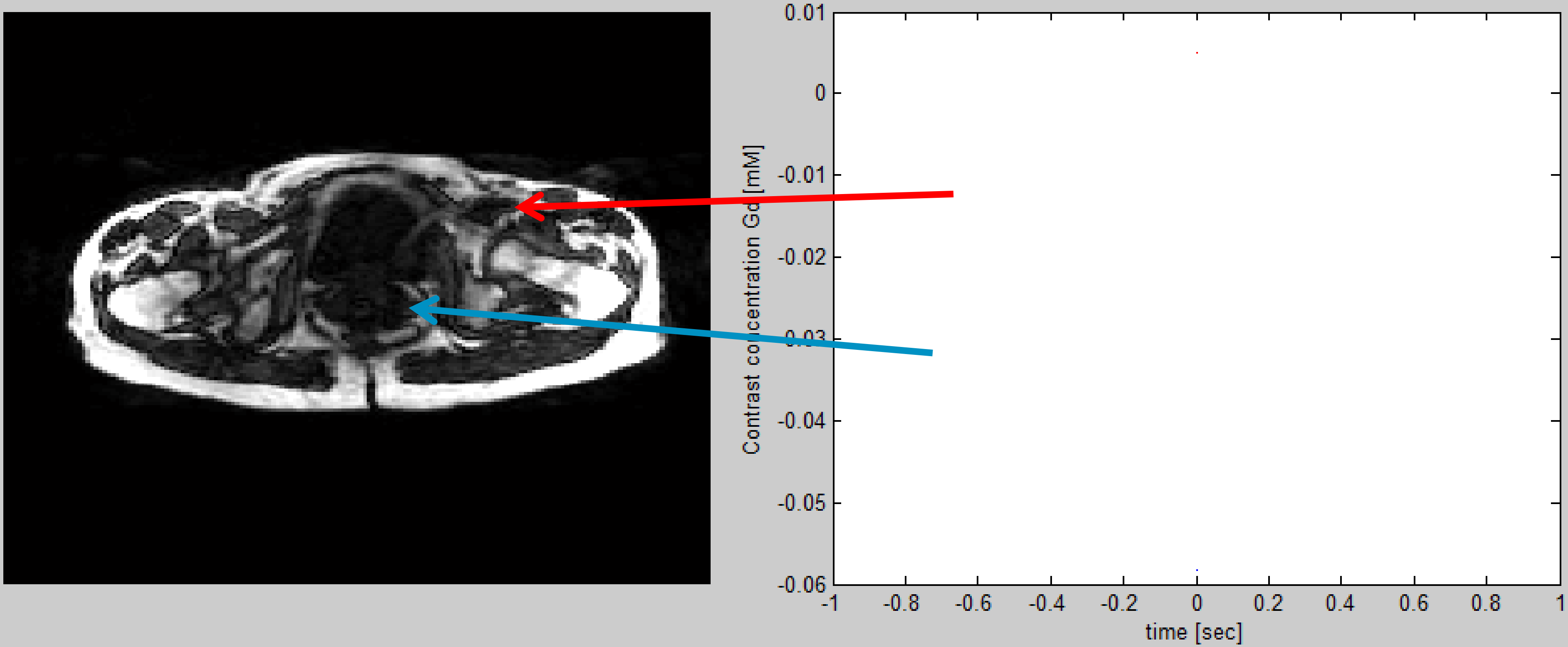
DCE-CT/MRI

Functional imaging modalities

- **PET**
  - **Tracers accumulation reflect biologic processes as e.g. metabolism**
  - **Kinetics**
- **MRI**
  - **Spin relaxation depends on tissue structure**
  - **Contrast agents: kinetics**
- **CT**
  - **Contrast agents: kinetics**

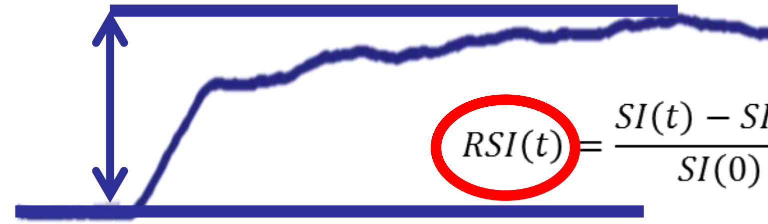


DCE-MRI



Contrast concentration Gd [mM]
0.01
0
-0.01
-0.02
-0.03
-0.04
-0.05
-0.06
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
time [sec]

DCE-MRI

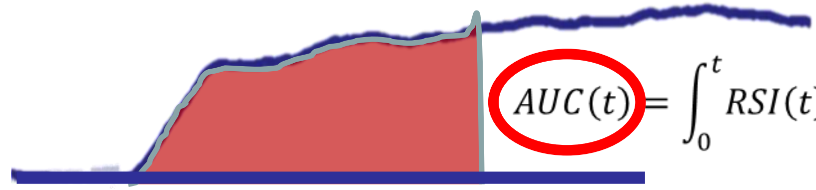


$$RSI(t) = \frac{SI(t) - SI(0)}{SI(0)}$$

Semi-quantitative analysis

-Relative Signal Increase

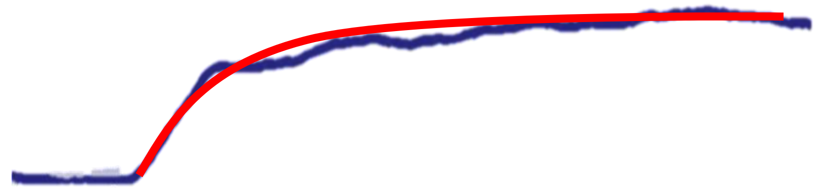
-Area Under Curve



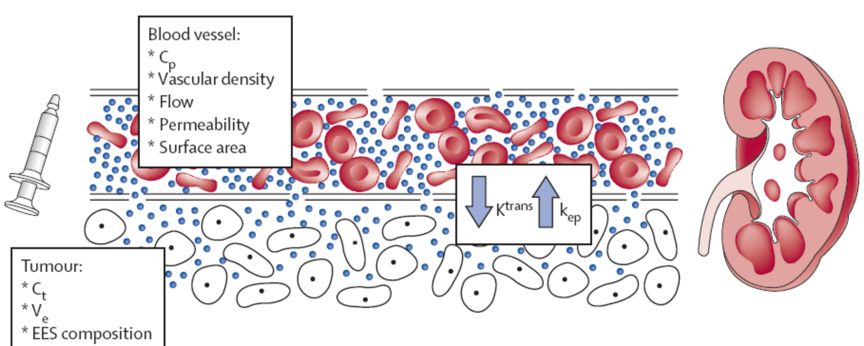
$$AUC(t) = \int_0^t RSI(t)\,dt$$

Quantitative analysis

-Extended Toft model (K^{trans}, k_{ep}, v_p) implemented as Murase et al.

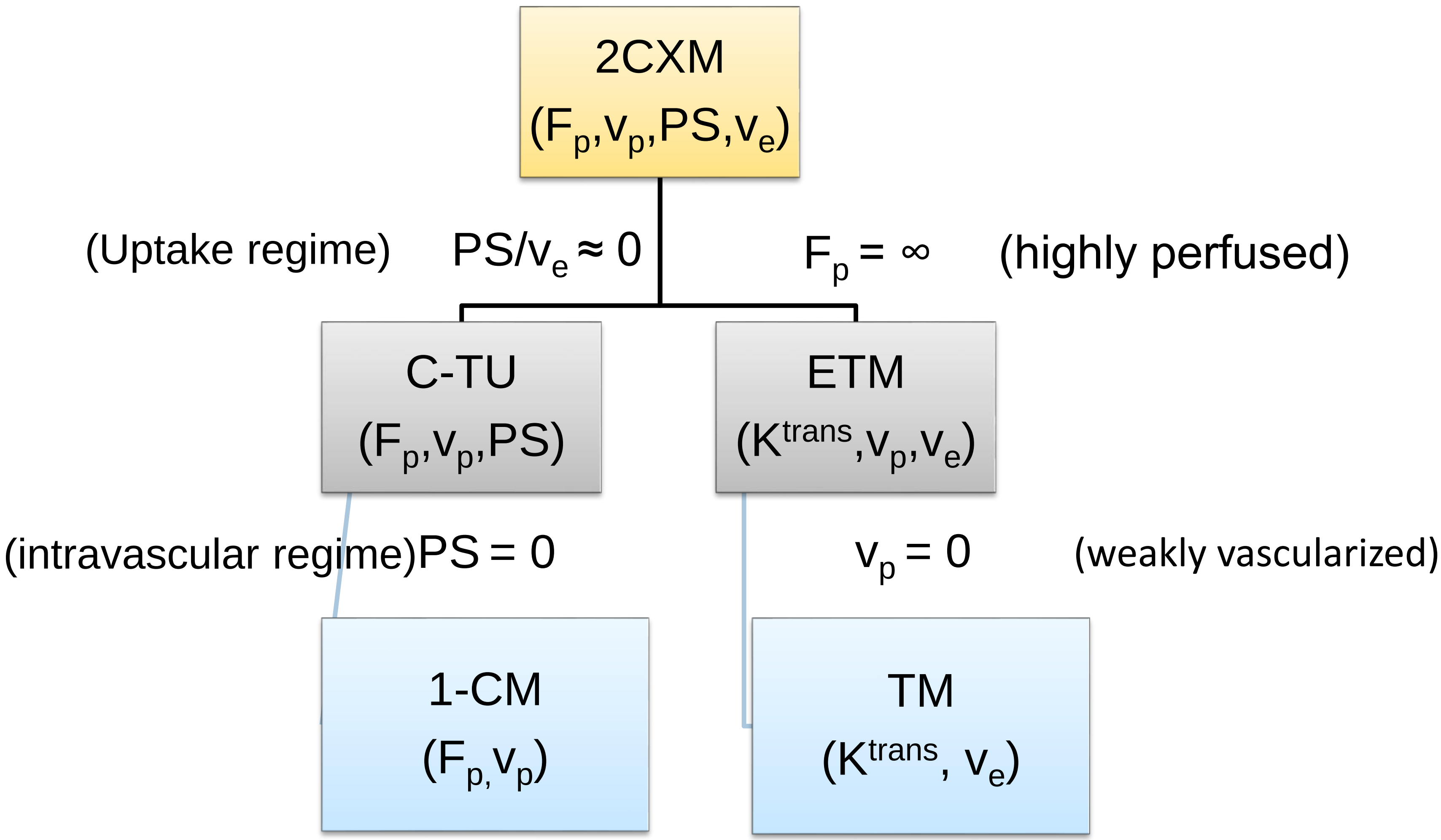


$$C_t(t) = K^{trans} e^{-k_{ep}t} \otimes C_p(t) + v_p C_p(t)$$



Zahra et al. 2007

Hierarchy of models

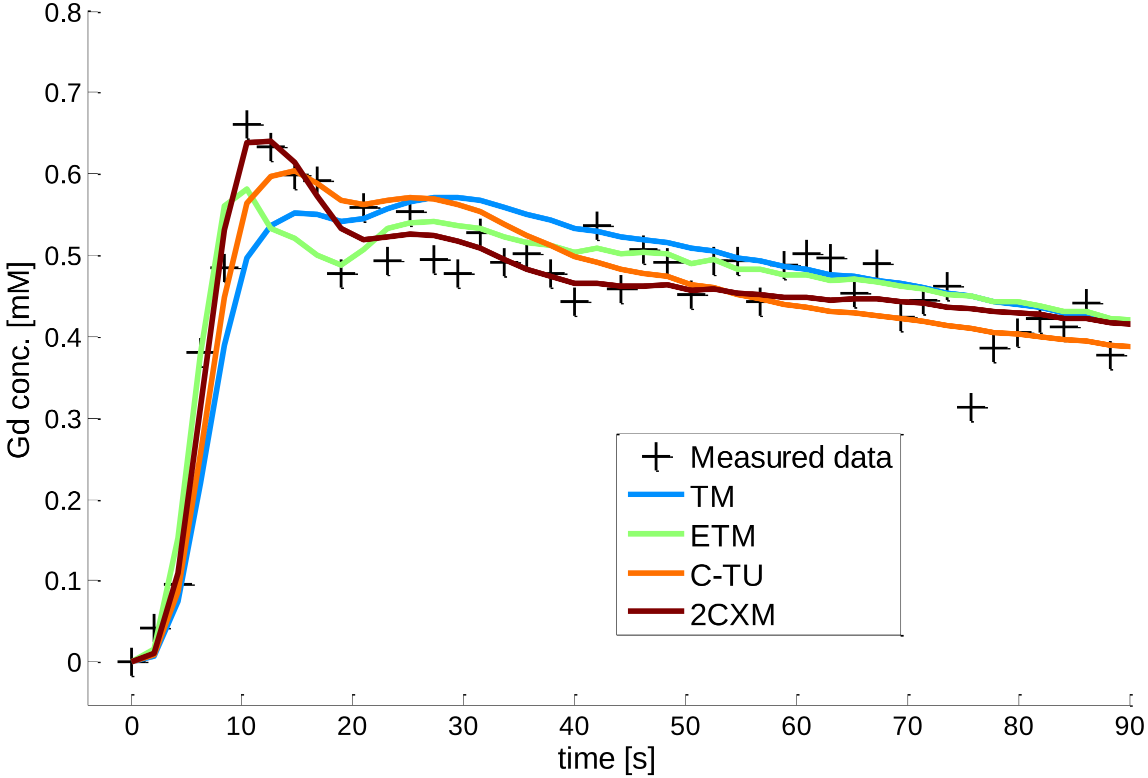


Fitting of models

Fit comparison:

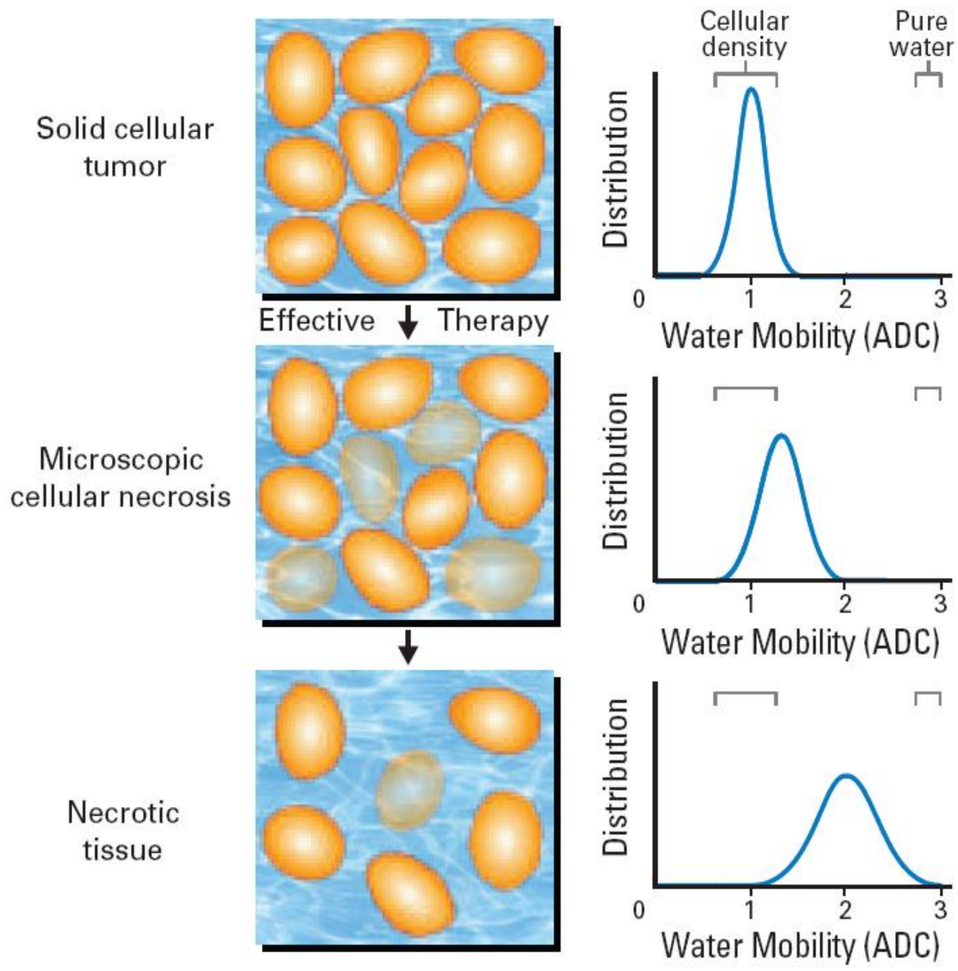
$$AICc_m = n \cdot ln\left(\frac{SS_m}{K_m}\right) + 2K_m + \frac{2K_m(K_m+1)}{n-K_m-1}$$

K_m: # fit parameters (TM=2, ETM=3, C-TU=3, 2CXM=4)



Diffusion weighted MRI (DWI)

- Measurement of diffusion of water molecules
- DWI is a quantitative method

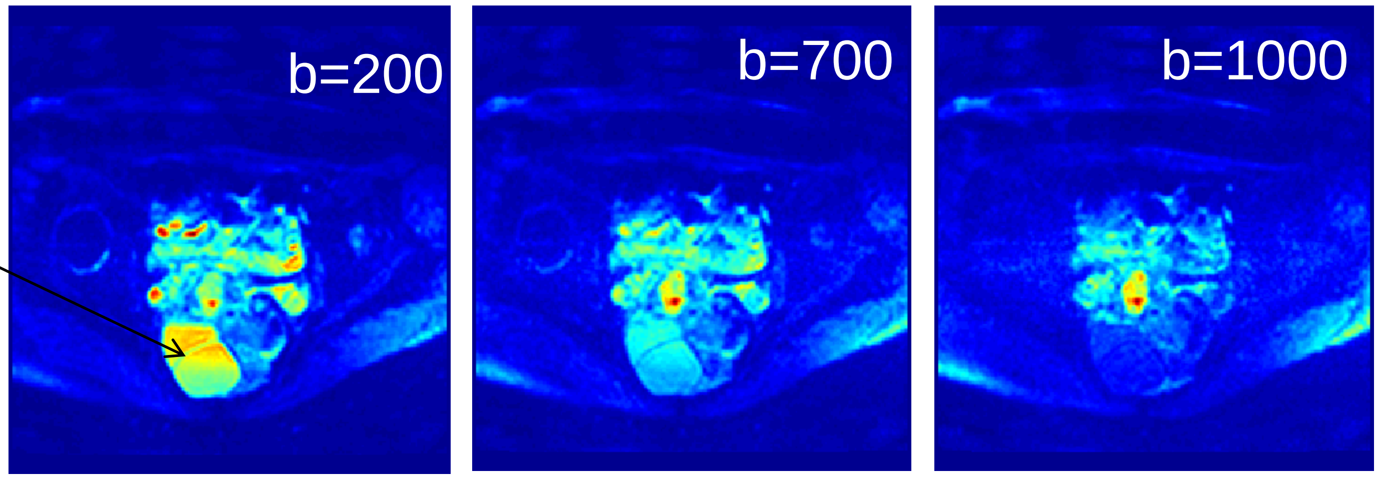


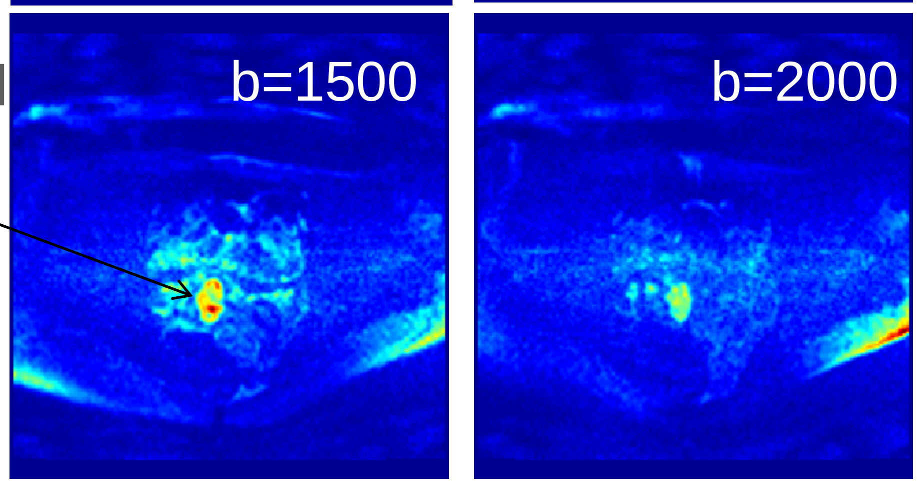
D. Hamstra et al. Diffusion Magnetic Resonance Imaging: A Biomarker for Treatment Response in Oncology. Journal of Clinical Oncology Vol. 25:4104-4109, 2007

Acquired data

Free diffusion

Restricted diffusion





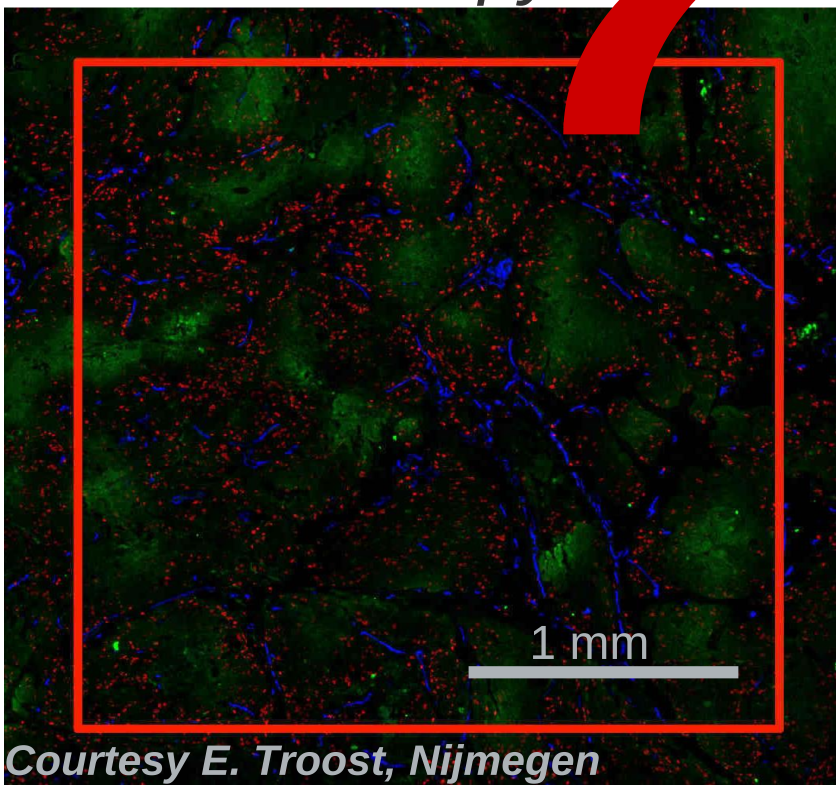
b-value: *changes the sensitivity of the diffusion length*

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

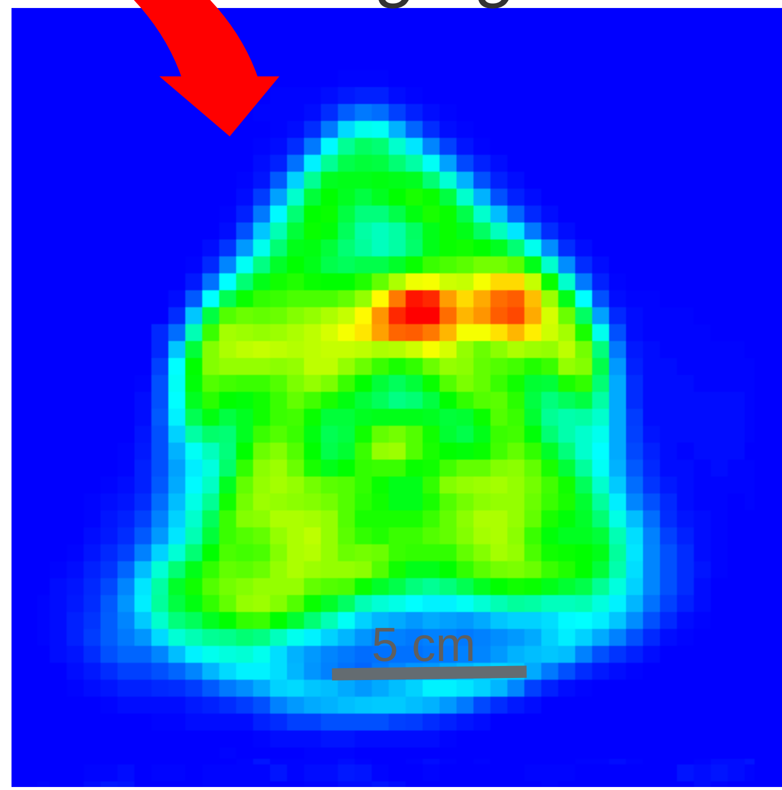
Provided by Jesper F. Kallehauge, Dept of Med Phys, AUH

Spatial resolution of functional imaging is challenging

Microscopy ? *Imaging*

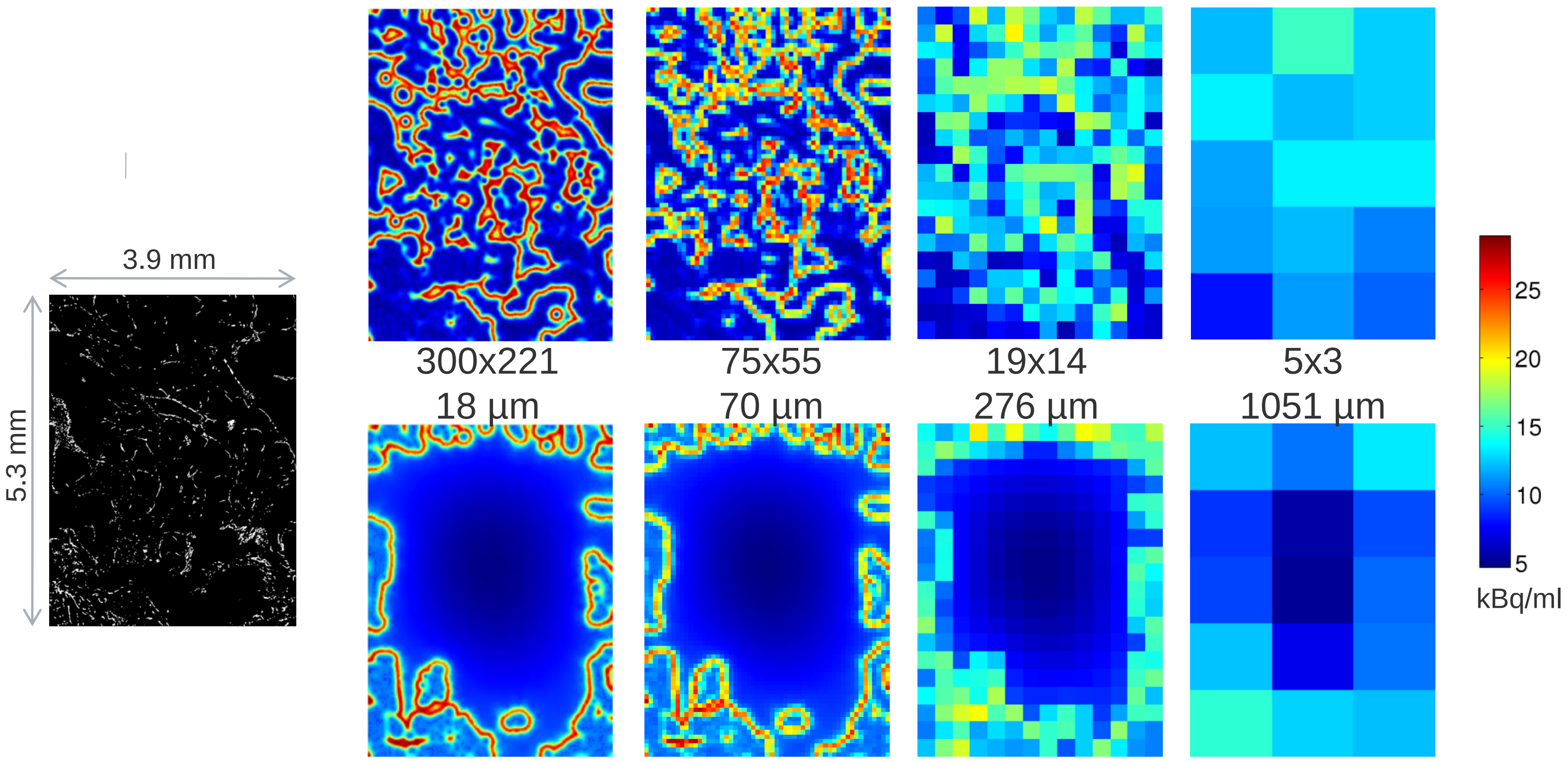


Immunohistochemistry
(vascularization, perfusion, hypoxia)



Clinical FMISO PET image, 4h pi

Image resolution



FMISO PET simulation 4 h pi

Functional Imaging with MRI and PET

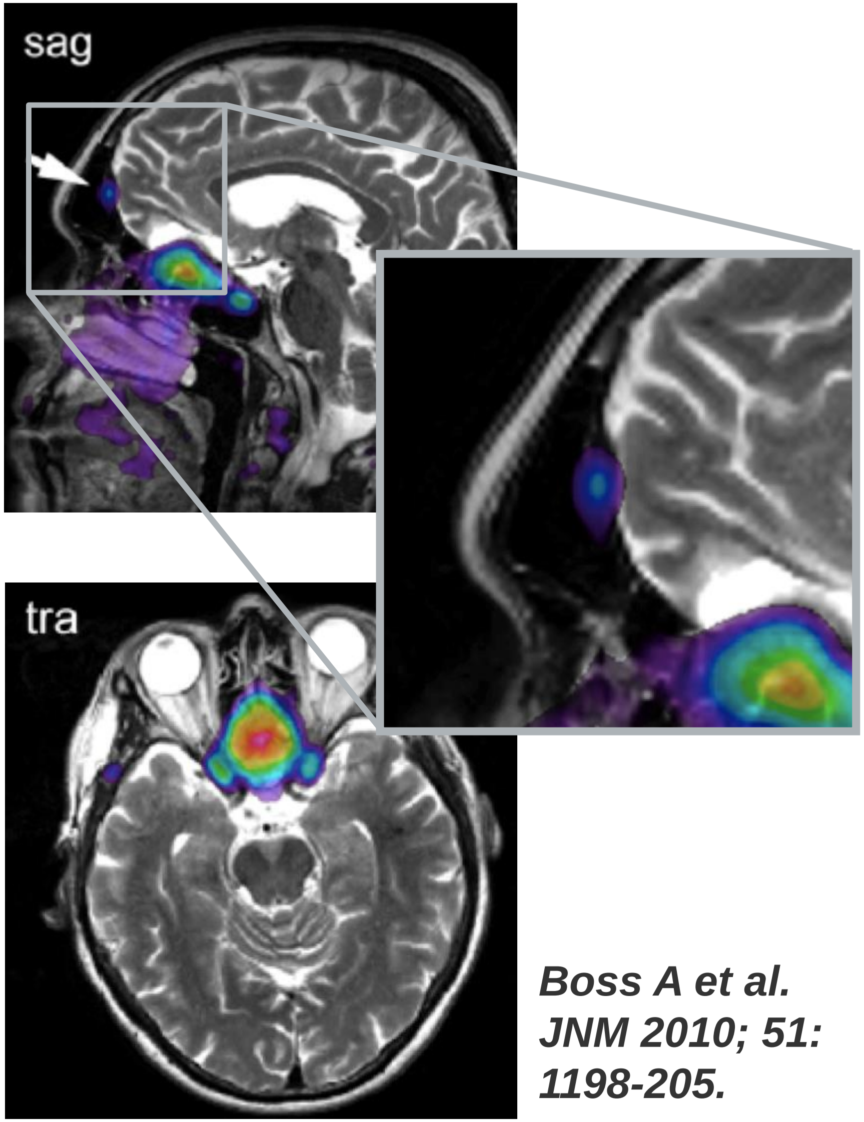
Cell density, microanatomy	
• **DWI, DTI,**	**[^{18}F]FDG**
Perfusion, permeability of microvasculature	
• **DSC-MRI, DCE-MRI,**	**[^{18}F]Galacto RGD, [^{15}O]H_2O**
Cell membrane synthesis	
• **MRSI (choline),**	**[^{11}C]Choline, [^{18}F]Choline**
Metabolism	
• **^{31}P-MRSI**	**[^{18}F]FDG**
Hypoxia	
• **R2* (BOLD), MRSI (lactate)**	**[^{18}F]FMISO, [^{18}F]FAZA, [^{18}F]HX4**

Combined PET/MR for Radiation Oncology

Visualization of anatomical, functional and molecular information of tumor tissue

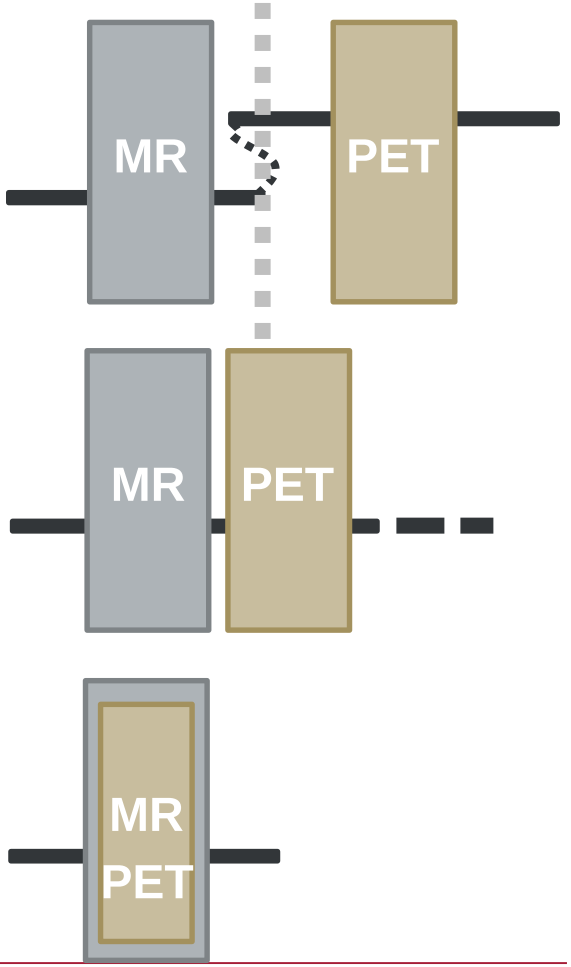
Improved accuracy of target volume delineation based on PET/MR

Multi-parametric functional PET/MR imaging for biologically adapted RT dose prescriptions



Boss A et al. JNM 2010; 51: 1198-205.

Combined PET/MR: Technical Realization



1. **Separate PET- and MR-systems**
   - Imaging systems in different rooms
   - Patient couch on rails
   - Time delay between PET- and MR image acquisition
2. **Co-planar PET/MR systems**
   - PET and MR back to back
   - Rotating table platform
   - 3T MRI plus TOF PET
3. **Integrated PET/MR**
   - MR-compatible PET detector ring inside clinical 3T-MR scanner

Integrated PET/MR: Technical Realization

- Simultaneous PET and MR acquisition

MR specification:

- 3T static magnetic field
- 60 cm bore size
- Spatial resolution < 1-3 mm

PET detector:

- MR-compatible PET components (APDs instead of PMTs)
- No time-of-flight (TOF) PET possible

Siemens Biograph mMR

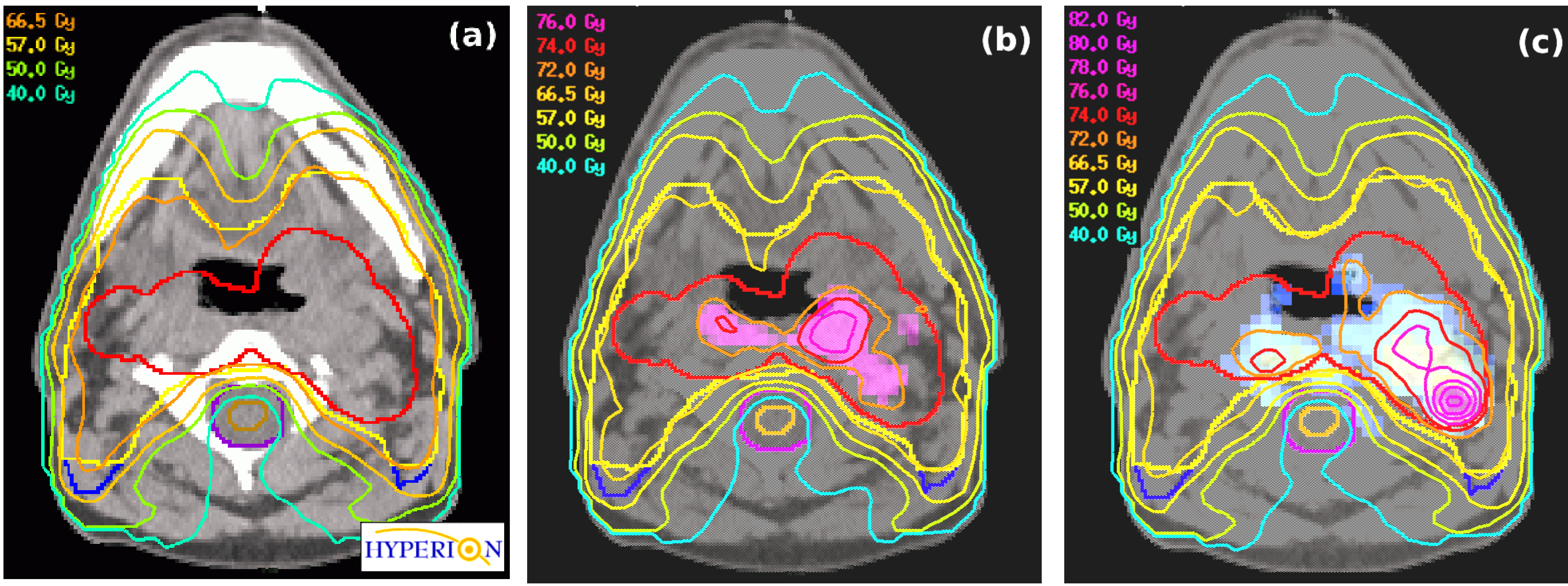
Timing and purpose of imaging

- **Pre-treatment imaging:**
  - **Location and characterisation of tumour**
  - **Target delineation**
  - **Differential dose prescription (e.g. dose painting)**

- **Imaging during radiotherapy:**
  - **Response monitoring**
  - **Adaptation of target volumes and treatment**
  - **Differential boosting**

Pre-RT imaging and dose painting

Dose escalation in a functional PTV (*f*-PTV) vs. Hypoxia- guided Dose Painting by Numbers (DPBN) in Head and Neck Cancer.



(a) 54/60/70 Gy, standard IMRT

(b) 54/60/70/77 Gy, FDG-guided IMRT, *f*-PTV

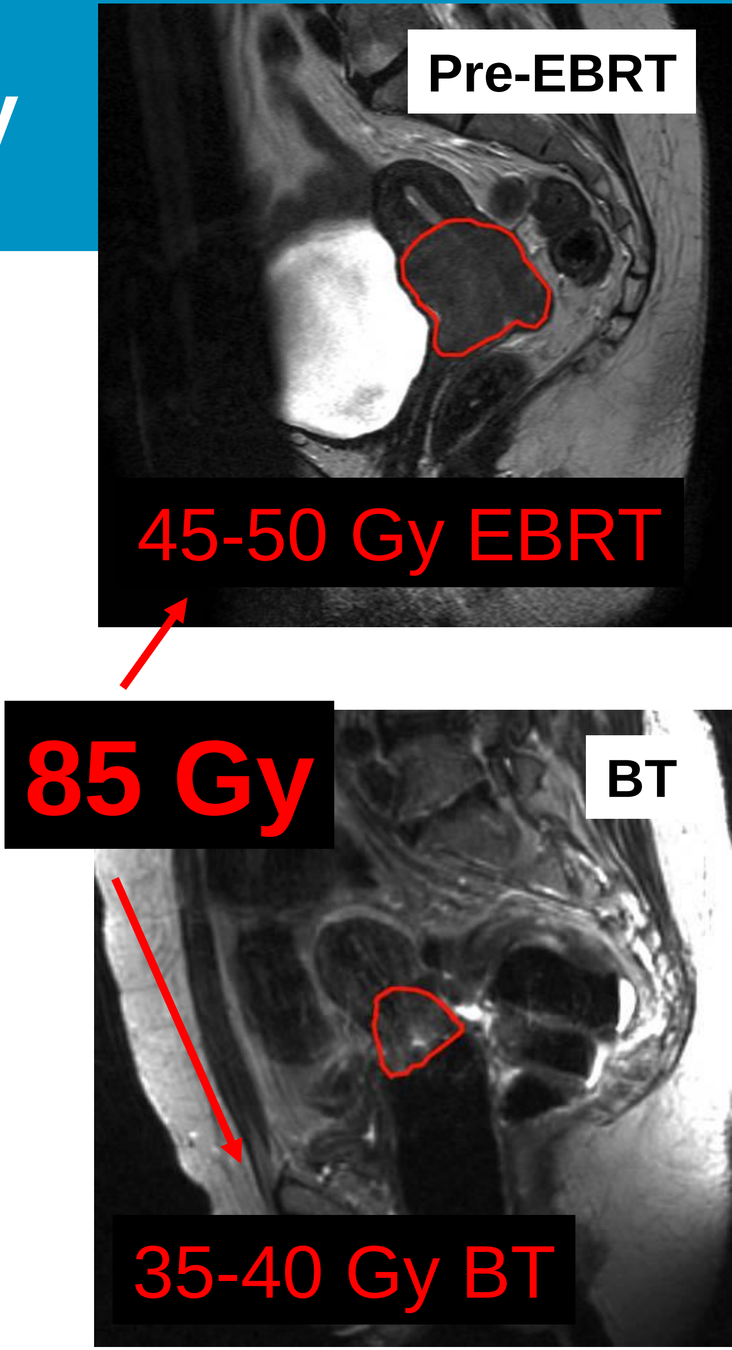
(c) 54/60/70/84 Gy, FMISO-guided IMRT, DPBN

***Thorwarth et al.** IJROBP 2007*

Imaging during radiotherapy

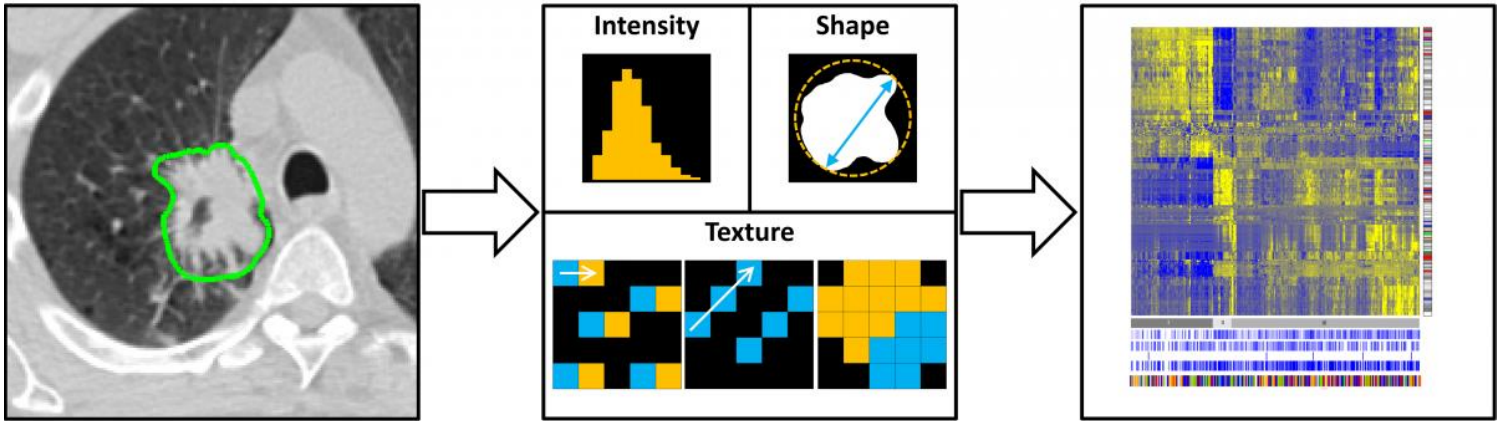
- **Adaptation based on response**
  - **Imaging (or clinical assessment) during radiotherapy**
  - **Decision on treatment for residual target volume**
  - **Focal boosting with brachytherapy**

- ***ICRU89: introduction of adaptive target concept (for CTV and GTV)***



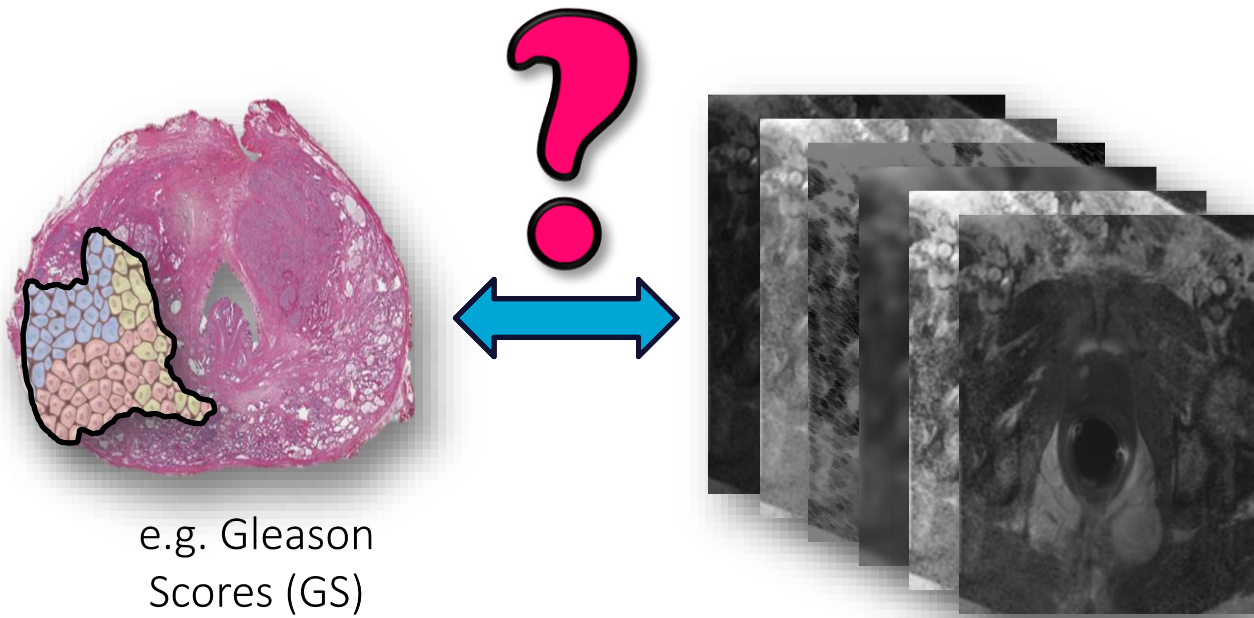
Radiomics

- Radiomics extracts a high number of features based on e.g. contrast, shape, texture, gradients etc.
- Patterns predicting disease failure are obtained with use of statistical modelling



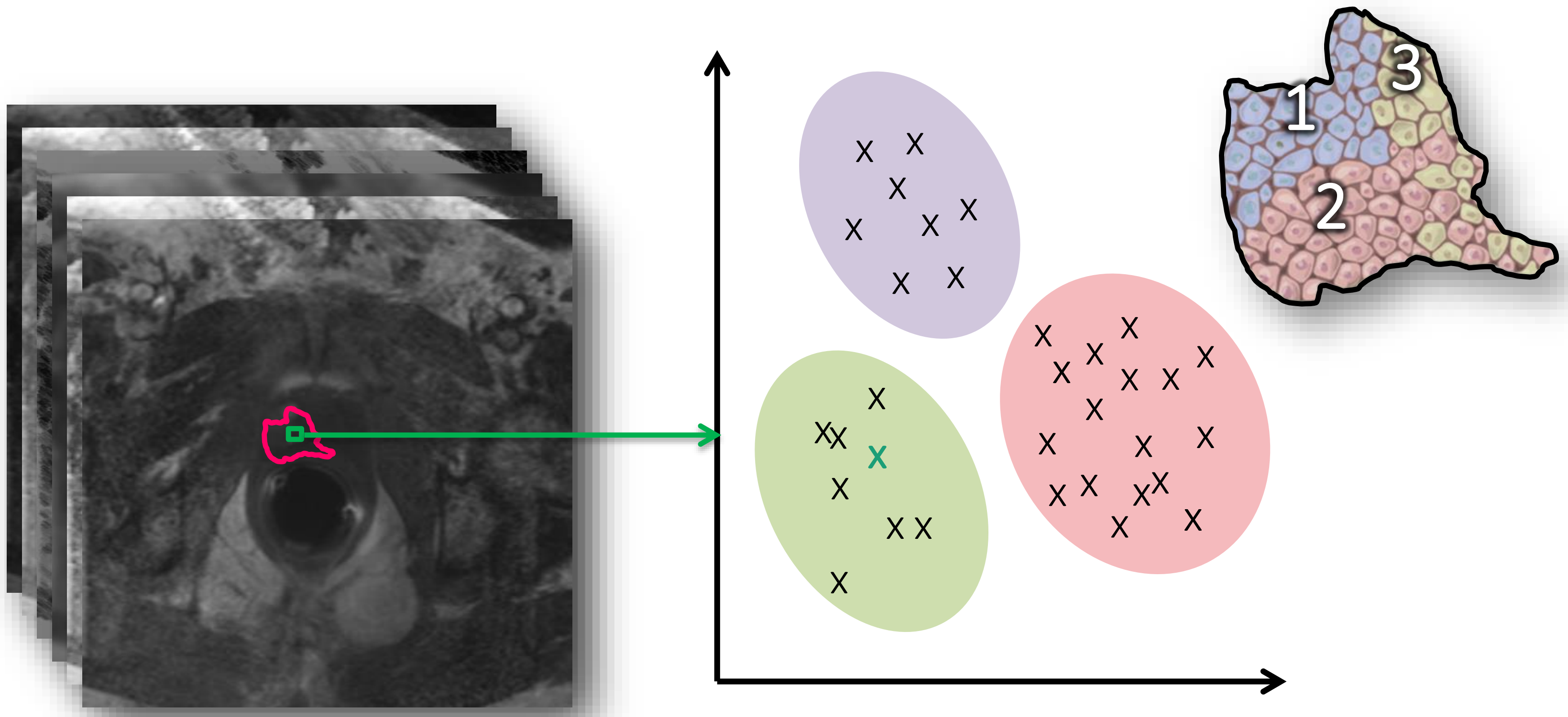
MAASTRO RADIOMICS

Advanced tools for visualisation of multimodal imaging



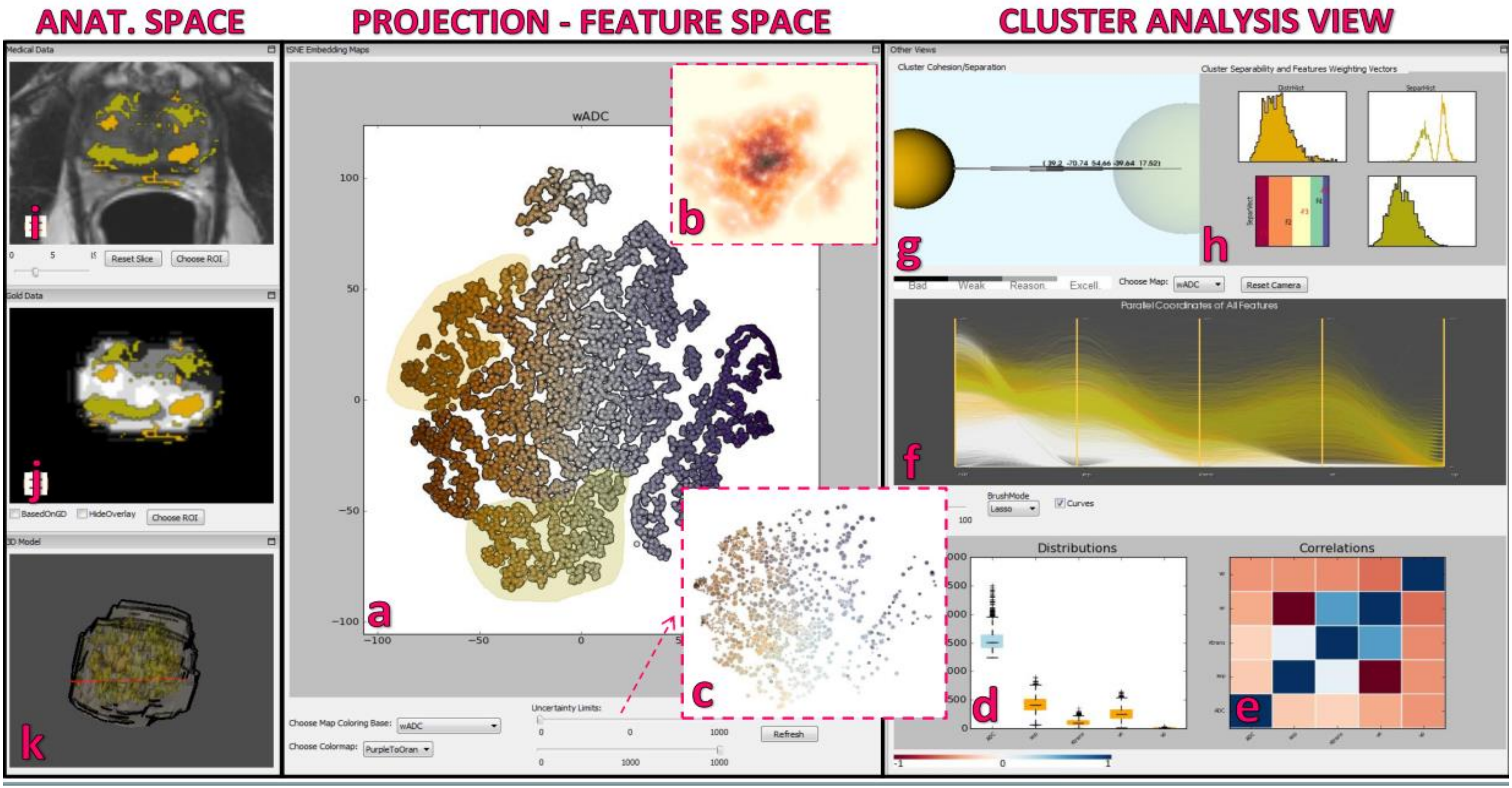
e.g. Gleason
Scores (GS)

Identification and Exploration of Intra-tumor Regions



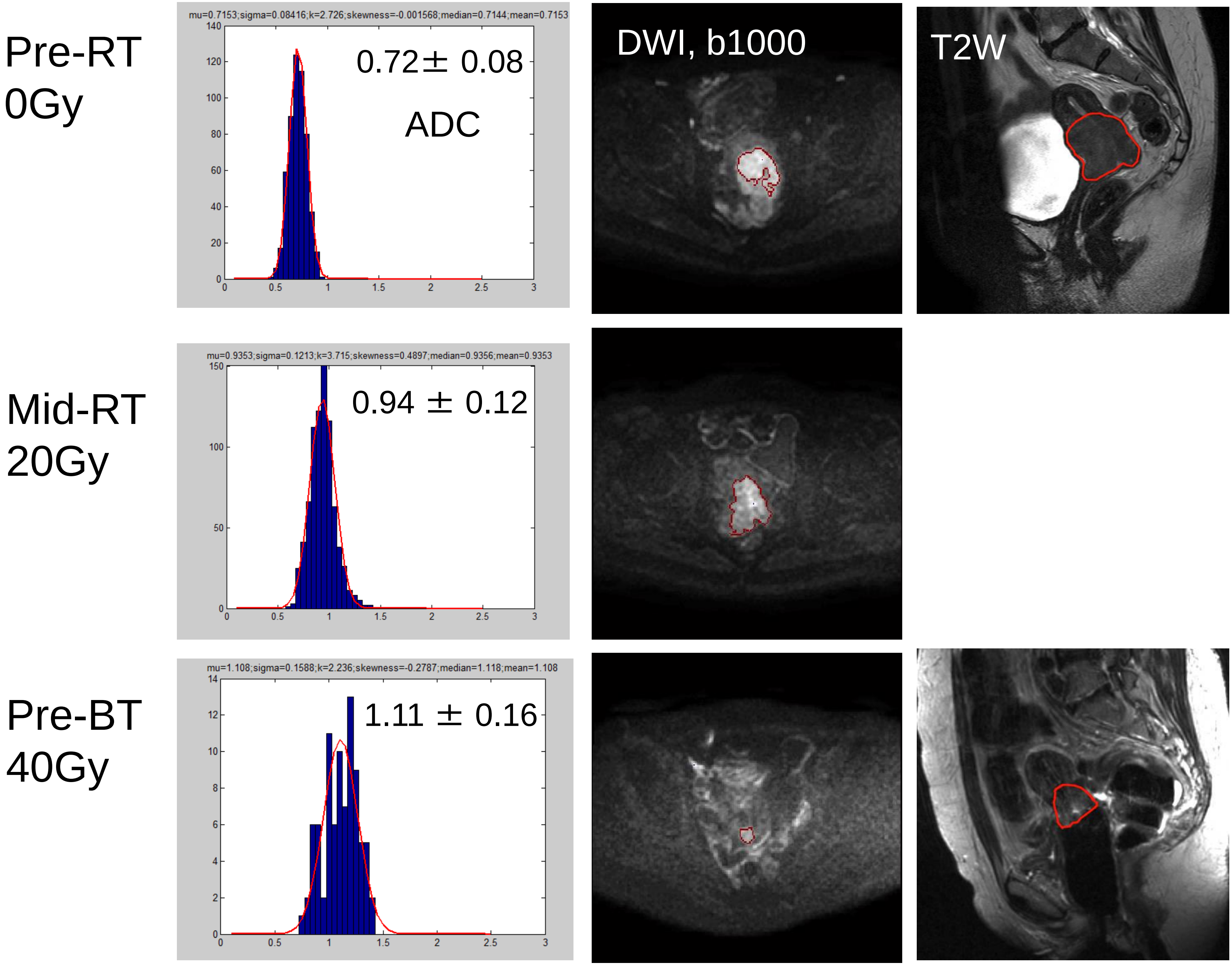
t-Distributed Stochastic Neighborhood Embedding (**tSNE**) - L. van der Maaten, 2008

Anatomical space – feature space – cluster analysis



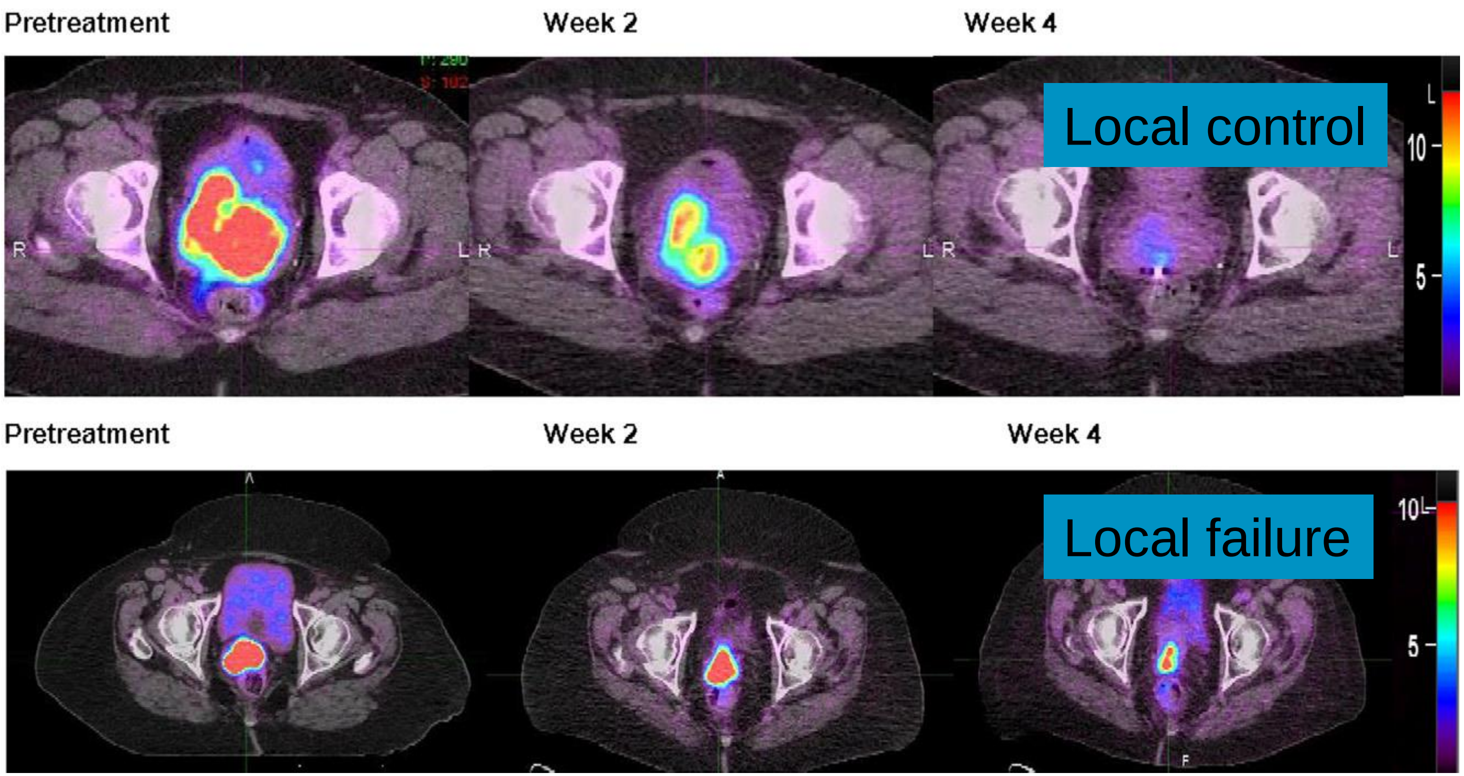
Example cervix

- **Why multimodality imaging in cervix cancer?**
  - **Significant response during radiotherapy**
    - **Repeated imaging during radiotherapy**
    - **Individualised boosting with brachytherapy**
  - **Hypoxia has significant impact on clinical outcome**
    - **Hypoxia imaging: DCE-MRI, FAZA, FMISO**


Pre-RT
0Gy
mu=0.7153;sigma=0.08416;k=2.726;skewness=-0.001568;median=0.7144;mean=0.7153
0.72± 0.08
ADC
DWI, b1000
T2W
Mid-RT
20Gy
mu=0.9353;sigma=0.1213;k=3.715;skewness=0.4897;median=0.9356;mean=0.9353
0.94 ± 0.12
Pre-BT
40Gy
mu=1.108;sigma=0.1588;k=2.236;skewness=-0.2787;median=1.118;mean=1.108
1.11 ± 0.16

FDG PET

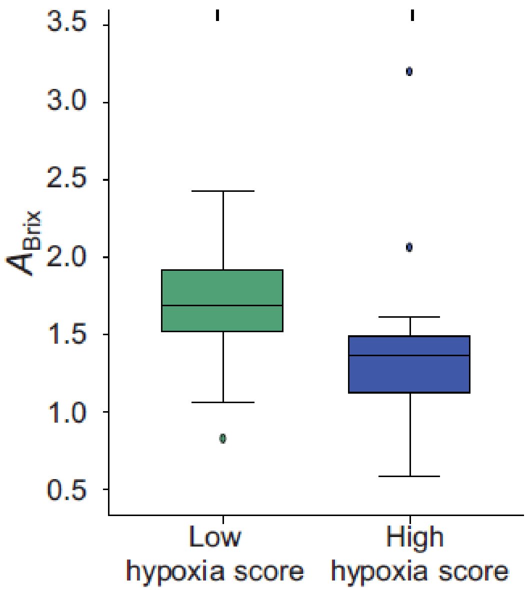
- **Persistent PET to identify non-responders**



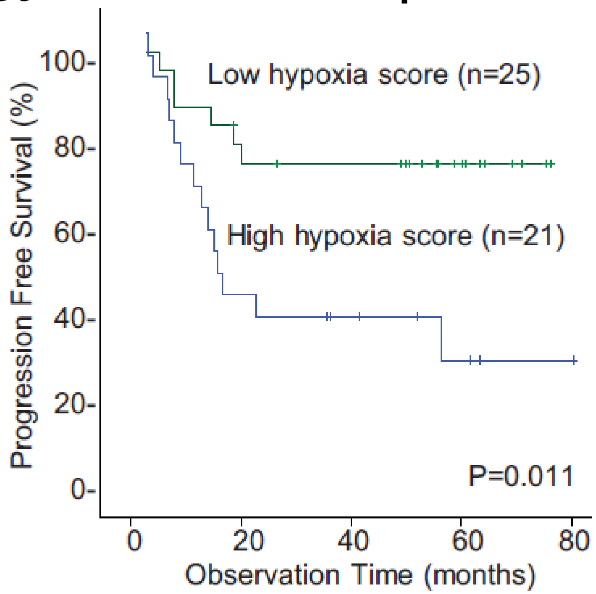
Kidd et al, IJROBP, 2013 85(1):116-22.

Rationale: Link between imaging and biology

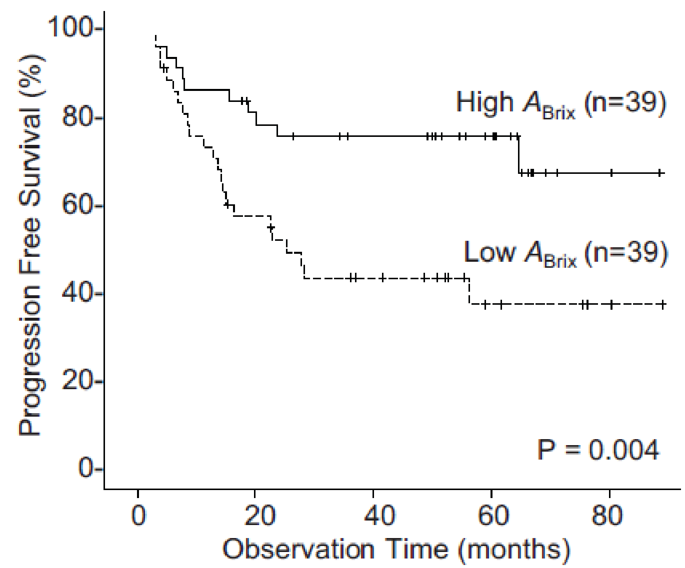
Imaging and biology



Genetic profile



DCE MRI



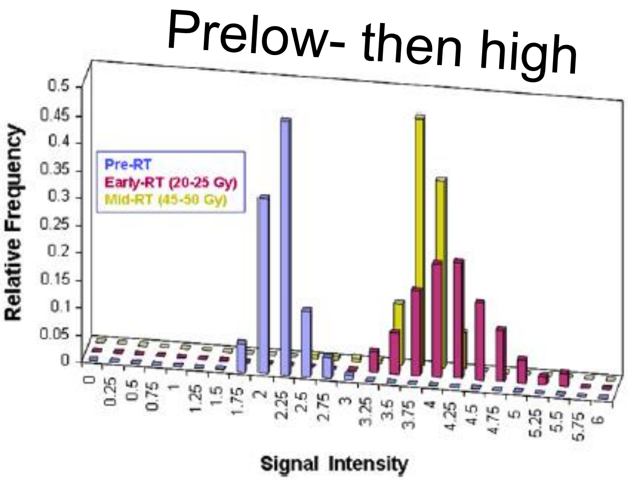
Cancer Research

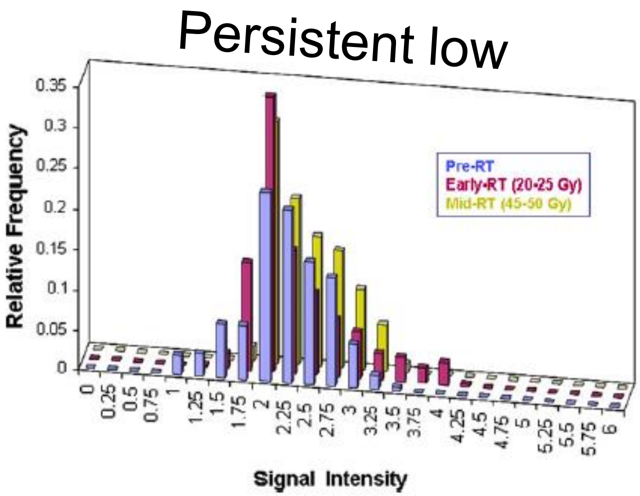
Hypoxia-induced gene expression in chemoradioresistant cervical cancer revealed by dynamic contrast enhanced MRI

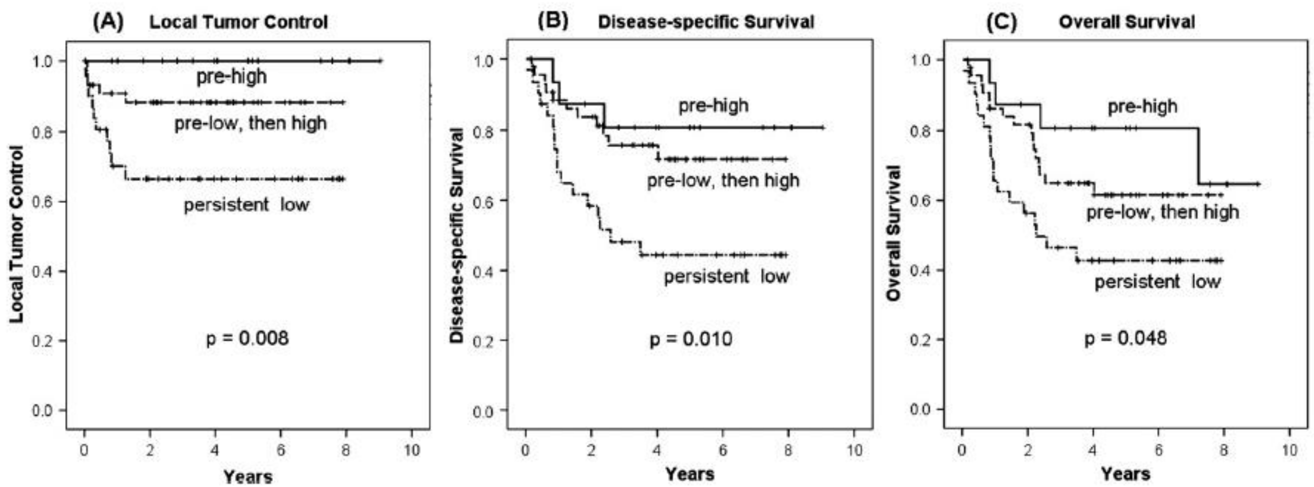
Cathinka Halle, Erlend Andersen, Malin Lando, et al.

Cancer Res Published OnlineFirst August 13, 2012.

DCE-MRI (RSI)
Mayr, Ohio



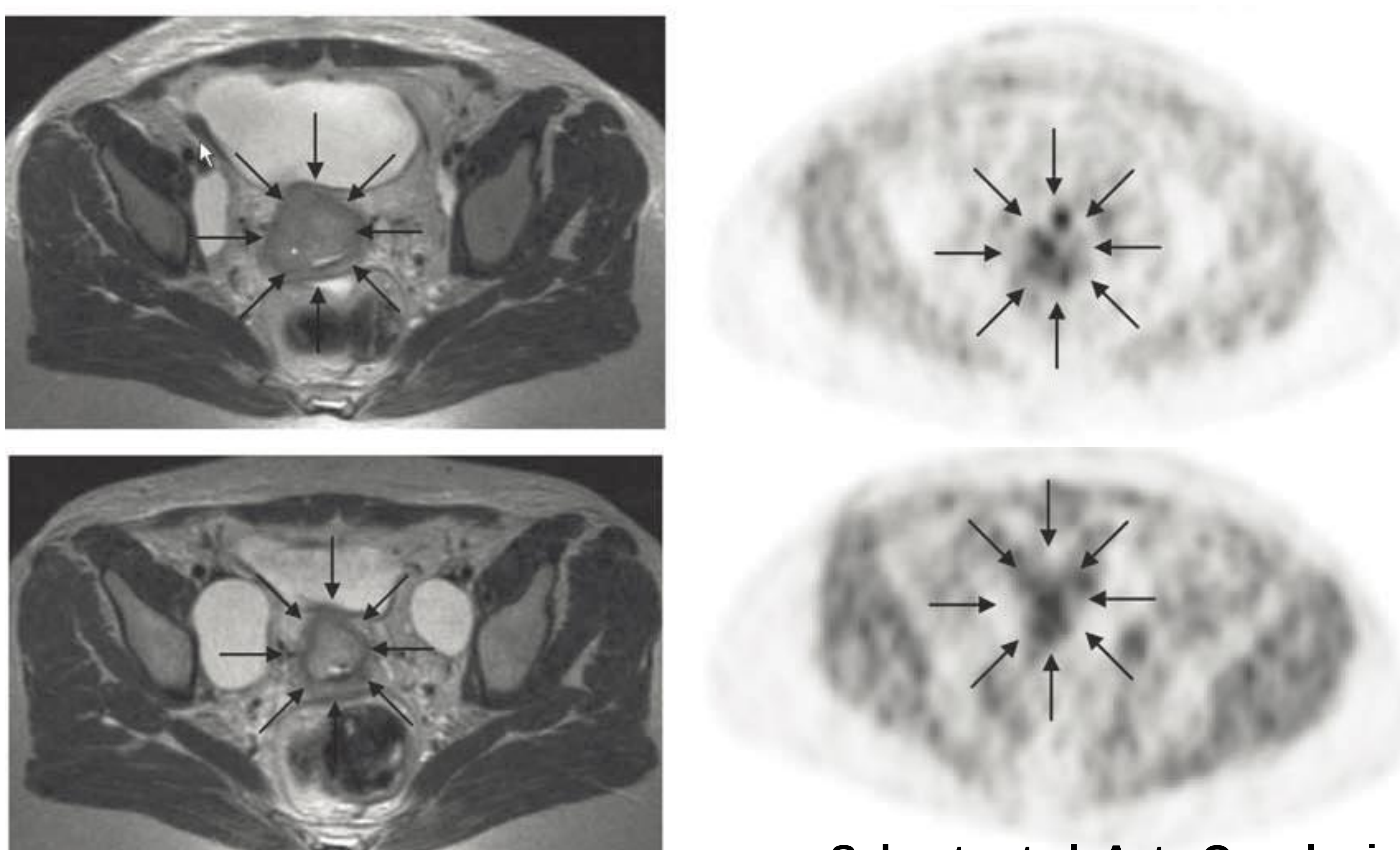




Mayr IJROBP 2010

18F-FAZA PET

- **15 pts repeated imaging:**
  - **pre-EBRT + after 30-40Gy**



Schuetz et al, Acta Oncologica 2010

Example prostate cancer

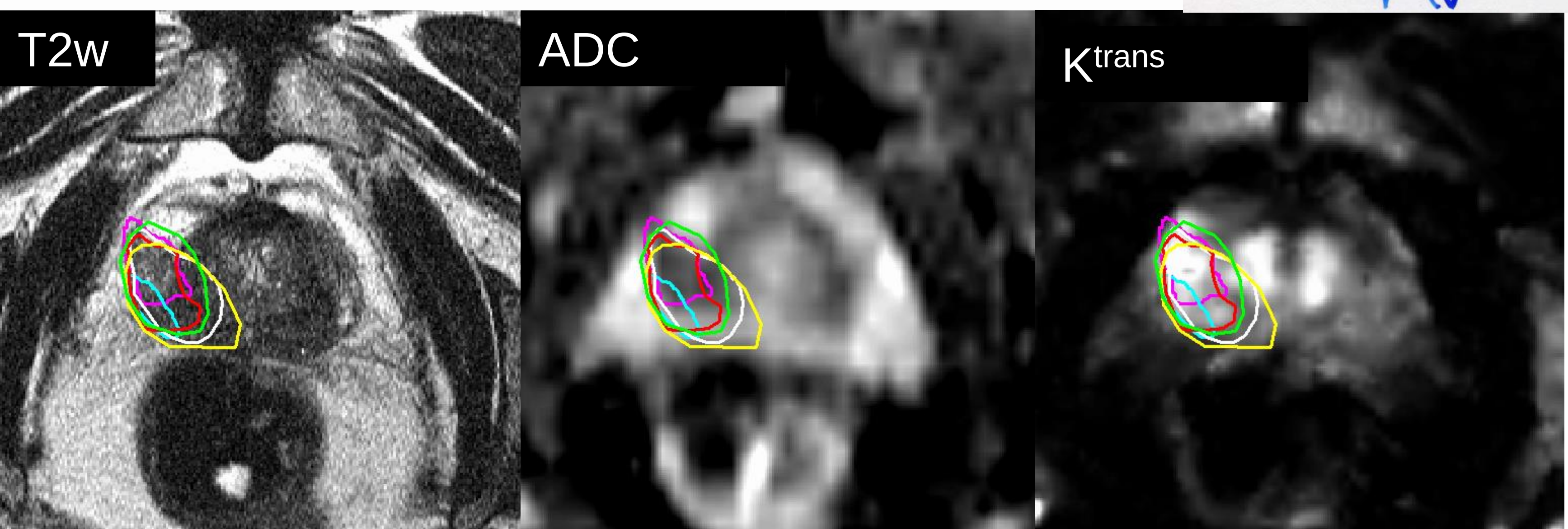
- Currently, the majority of prostate cancer patients, the entire gland is treated:
  - Surgery
  - EBRT whole gland irradiation
  - Brachytherapy LDR and HDR
- Focal treatment upcoming:
  - Multiple modalities: Radiotherapy: integrated boost or focal only, HIFU, Cryotherapy,...
  - Question: how to delineate GTV?

How well can we delineate prostate tumors?

Universitair Medisch Centrum Utrecht
UZ LEUVEN
NETHERLANDS CANCER INSTITUTE ANTONI VAN LEEUWENHOEK

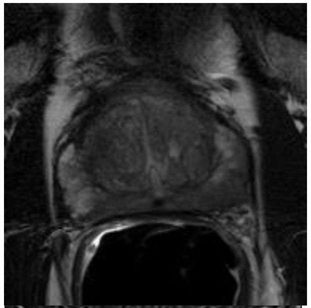
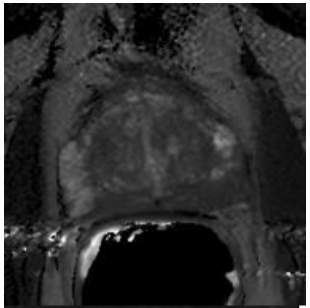
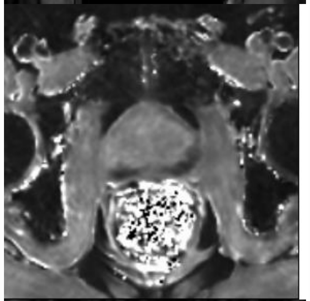
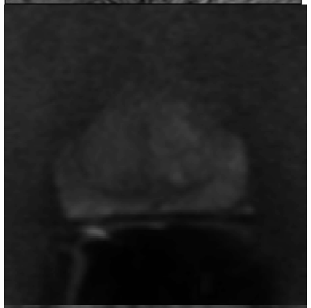
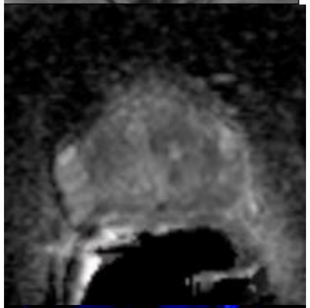
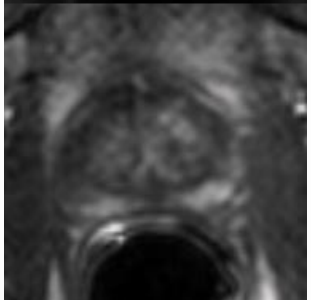
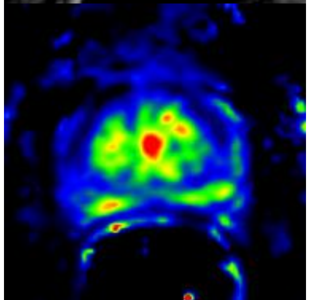
- 20 patients received mp-MRI prior to prostatectomy
- Tumors were delineated by 6 teams of a radiation oncologist and a radiologist

- Uncertainty about boundaries of tumors
- Difficult to detect small tumors (<0.5 cc)

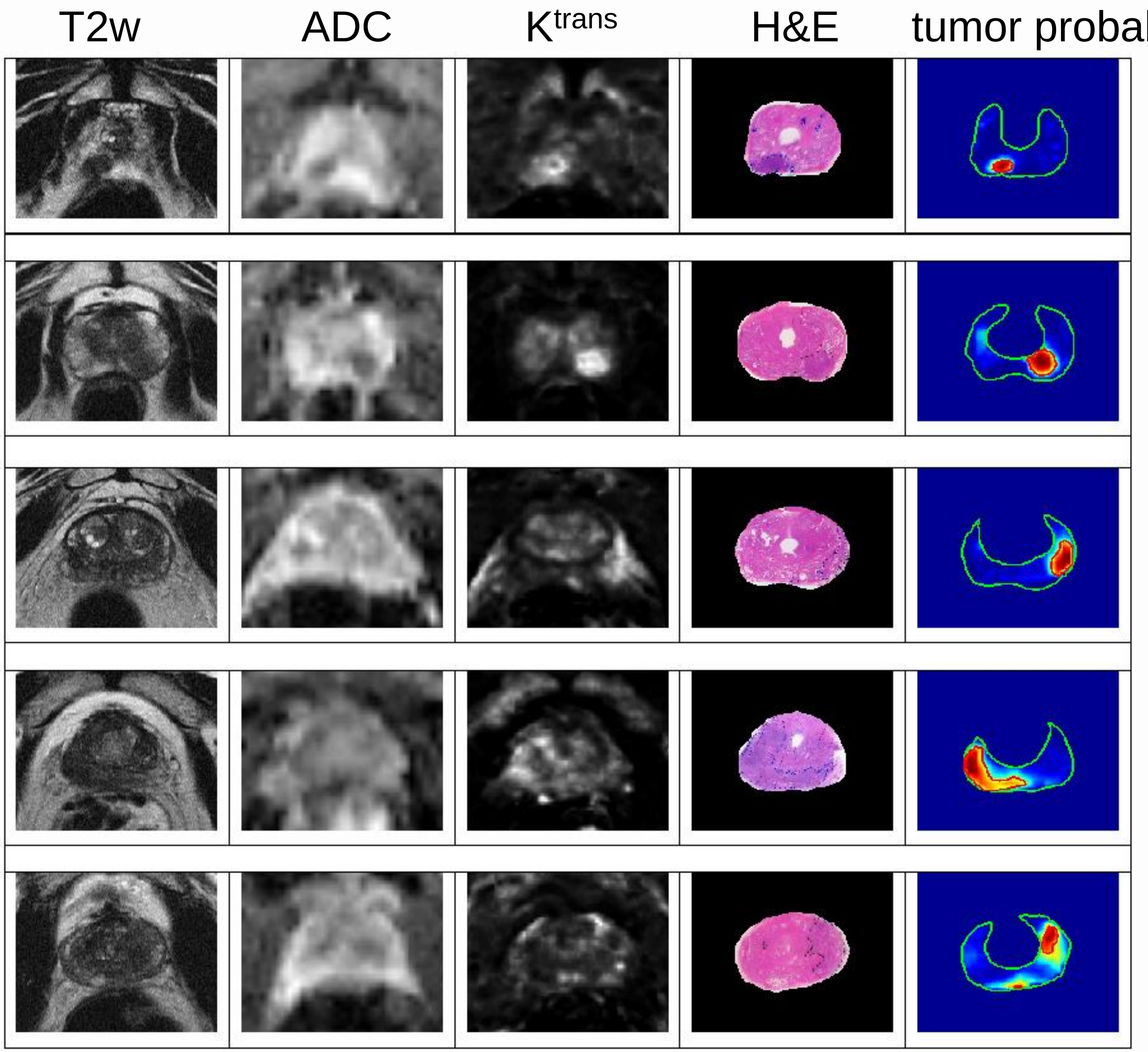


Steenbergen et al. Radiother Oncol. 2015;15:186-90.

From qualitative to quantitative imaging

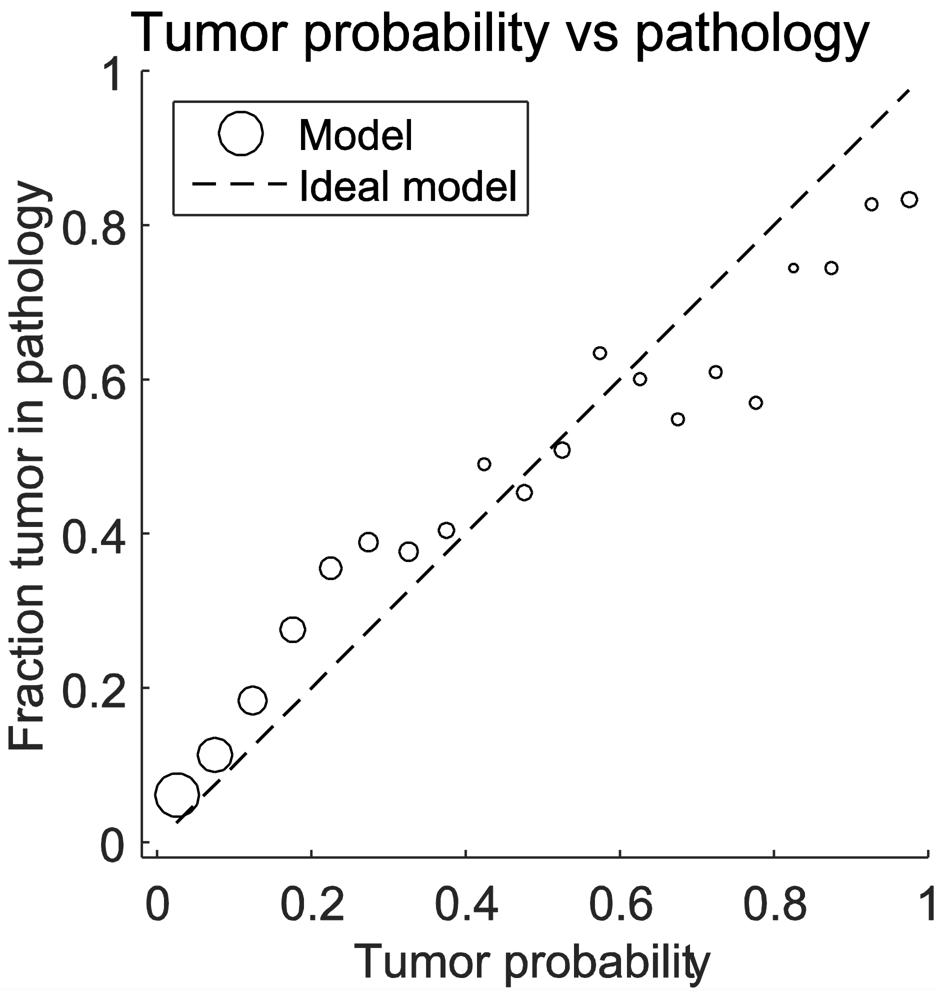
- T2w  → T2 map 
- T1w  → T1 map 
- DWI  → ADC 
- DCE-MRI  → K^{trans} 

Validation of tumor probability model



Dinh et al. Phys Med. 2016 Mar;32(3):446-51

Calibration of tumor probability



in 100 voxels that each have a probability of tumor presence of 50%, the histology should show that 50% of those voxels contain tumor and 50% do not.

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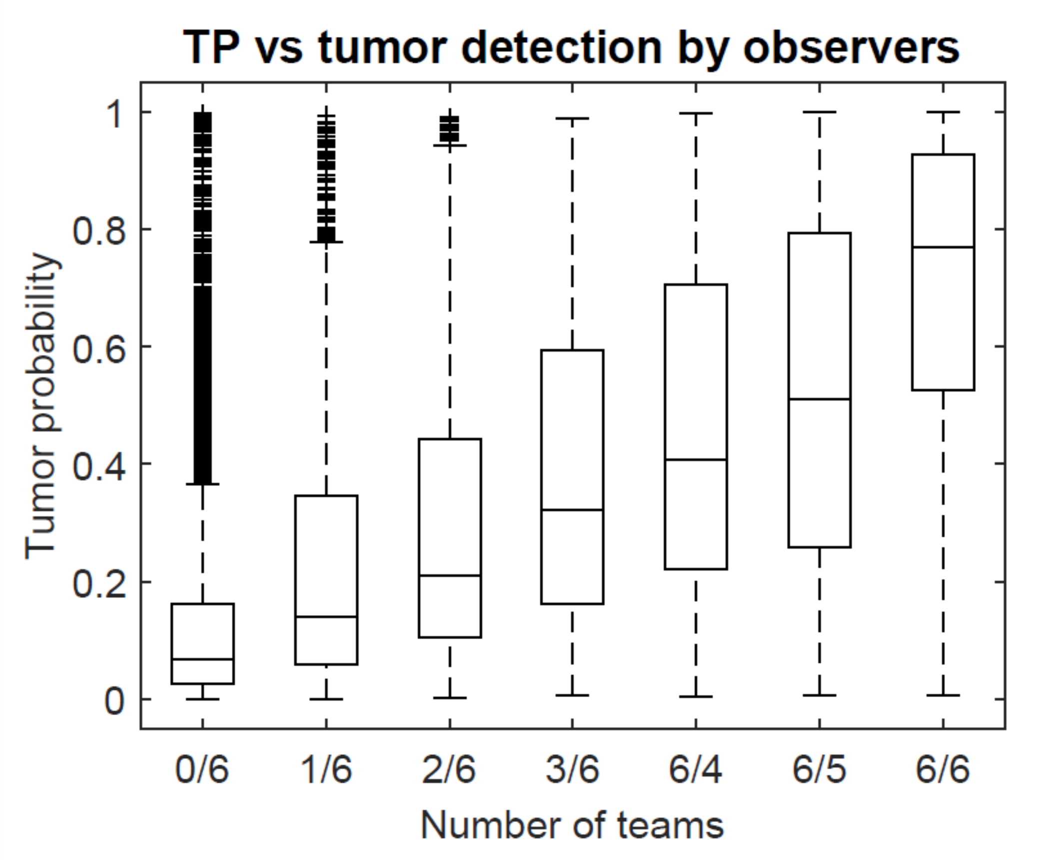
Tumor probability and inter-observer variation



- Tumor probability model applied to the patients in the delineation study

- The tumor probability correlates with the number of observers identifying a voxel as cancer

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Dinh et al. Phys Med. 2016 Mar;32(3):446-51

Where should the field move?

- **Novel image sequences and PET tracers**
- **Novel methods of image analysis**
- **Validation of link between imaging and biology**
- **Validation of link between imaging and outcome**
- **Exploitation of imaging for individualised, personalised, and adaptive radiotherapy**