

## Clinical experience and outcome of functional MRI-guided RT for prostate cancer

Uulke van der Heide




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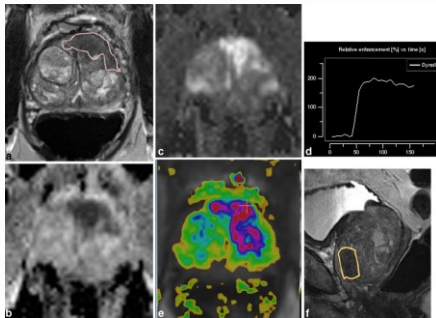
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## Diagnostic value of mp-MRI for detection and staging of prostate cancer



Barentsz et al. Eur Radiol. 2012;22:746-57.

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## Diagnostic value of mp-MRI for detection and staging of prostate cancer

- Multi-parametric MRI is used widely for prostate cancer diagnosis
  - T2-weighted
  - Diffusion-weighted (DWI)
  - Dynamic Contrast-Enhanced (DCE)
- It has a high diagnostic accuracy for localizing prostate cancer (AUC >0.90)
- Consensus papers published about acquisition and interpretation of images for detection and staging
  - PI-RADS version 2

Weinreb et al. Eur. Urol. 2016;69:16-40  
Barentsz et al. Eur Radiol. 2012;22:746-57  
Dickinson et al. J Magn Reson Imaging. 2013 Jan;37:48-58 .




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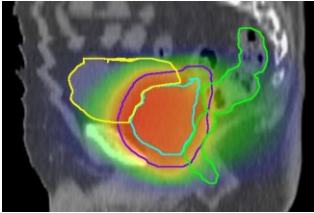
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## Prostate Cancer Radiotherapy

Planning



Delivery



- External beam radiotherapy 35-39 fractions
- Dose varying between 70 and 80 Gy
- Homogeneous dose the prostate gland
- Position verification



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## Differential boosting of the GTV in prostate cancer

### Targets for boosting

- GTV: intraprostatic lesion(s) as visible on imaging (MRI and/or PET)
- PTV<sub>GTV</sub>: PTV margin around the GTV
- CTV: prostate, possibly seminal vesicles and microscopic disease outside prostate gland

### Treatment techniques

- Integrated boost with EBRT
- Brachytherapy boost after EBRT

### Dose levels

- A wide range of dose levels and fractionation schemes
  - $\geq 35$  fractions with GTV dose between 80 and 95 Gy
  - 5 fractions, GTV dose up to 50 Gy

Bauman et al. Radiotherapy and Oncology 107 (2013) 274–281

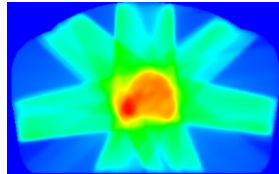
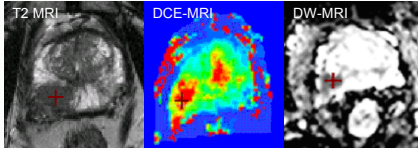
## trials of differential boosting of the GTV in prostate cancer

| Abr.         | Registration number | Study Phase | Imaging of DIL | RTH technique    | DIL / prostate dose (Gy), # | Standard arm dose (Gy), # |
|--------------|---------------------|-------------|----------------|------------------|-----------------------------|---------------------------|
| HEIGHT       | NCT01411332         | III         | MRI            | IMRT             | 89.3/78, 38#                | 80Gy, 40#                 |
| FLAME        | NCT01168479         | III         | MRI            | IMRT             | 95/78, 35#                  | 78Gy, 35#                 |
| TARGET       | NCT01802242         | II          | MRI            | IMRT or BT boost | 95/78, 38# or 10+78Gy, 38#  | N.a.                      |
| DELINTEATE   | ISRCTN04483921      | II          | MRI            | N.m.             | N.m.                        | N.a.                      |
| SPARC        | NCT02145494         | II          | MRI            | Cyberknife       | 47.5/36.25, 5#              | N.a.                      |
| PARAPLY-1    | NCT01962324         | II          | MRI/PET        | NM               | N.m.                        | N.a.                      |
| BIPROP20     | NCT02125175         | II          | MRI/PET        | IMRT             | N.m.                        | N.a.                      |
| (Alberta)    | NCT02004418         | II          | PET            | EBRT             | 78/68, 25#                  | N.a.                      |
| BRAPROST     | NCT01909388         | II          | MRI            | BT boost+EBRT    | 15+37.5, 15#                | N.a.                      |
| (California) | NCT00807820         | II          | MRS            | BT               | N.m.                        | N.a.                      |
| (Scottsdale) | NCT00956228         | II          | SPECT          | IMRT             | 82/75.6, 42#                | N.a.                      |

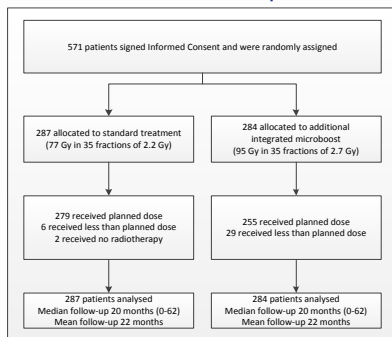
ANTONI VAN LEEUWENHOEK

## FLAME: focal dose escalation multi-center phase III randomized trial

Prostate 77 Gy  
Tumor 95 Gy  
  
571 patients  
Trial is now closed



### Trial profile



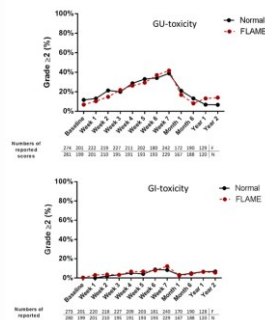
### Toxicity

#### GU adverse events

- urinary frequency/urgency, urinary retention, bladder spasms, urinary incontinence, genitourinary hemorrhage and dysuria.

#### GI adverse events

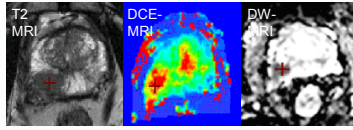
- Rectal or perirectal pain, proctitis, diarrhea, flatulence, hemorrhoids, anal incontinence, rectal fistula and rectal hemorrhage



Van Vulpen et al. Radiotherapy and Oncology 119 (2016) S132

## Tumor definition in the FLAME trial

Philips 3T: 439 pts  
Siemens 1.5T: 93 pts  
Siemens 3T: 49 pts



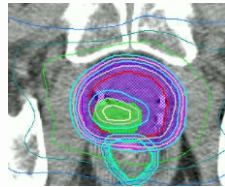
Number of GTVs defined per patient

|    |     |
|----|-----|
| 1  | 71% |
| 2  | 21% |
| ≥3 | 8%  |

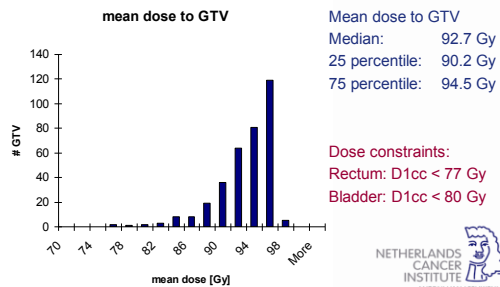


## Did we boost the tumor in the experimental arm?

- Different treatment techniques
  - IMRT: 320 pts
  - VMAT/rapid arc: 202 pts
  - Endorectal balloon: 49 pts
- 4 different treatment planning systems
  - Plato: ~160 pts
  - Monaco: ~160 pts
  - Pinnacle: 158 pts
  - Eclipse: 93 pts



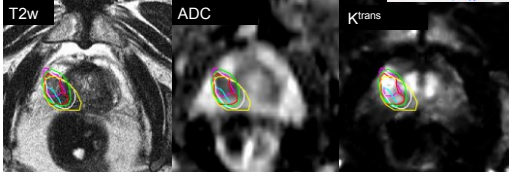
## Did we boost the tumor in the experimental arm?



How well can we delineate prostate tumors?



- 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.

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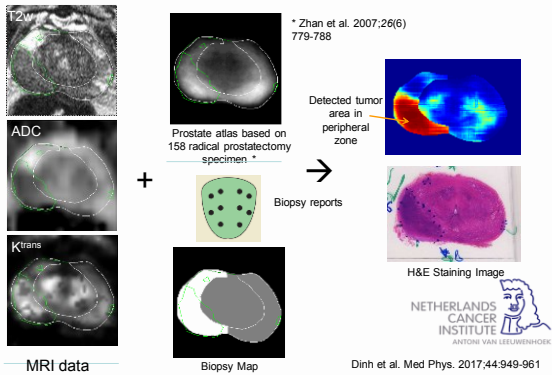
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Computer-aided detection of tumor



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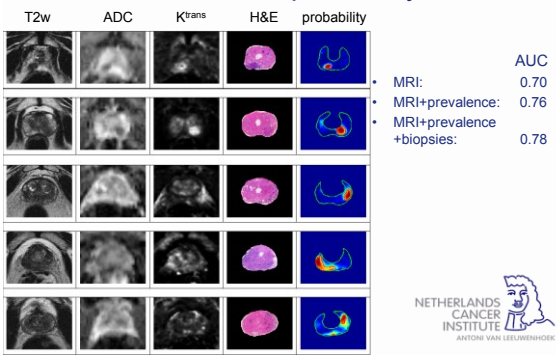
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Validation of tumor probability model



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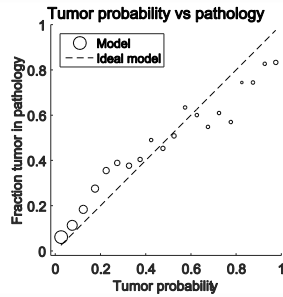
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## Calibration of tumor probability



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.



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

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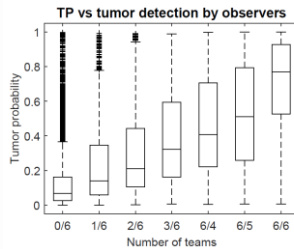
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## Tumor probability and inter-observer variation



- 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

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

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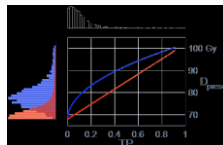
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## Dose mapping

As radiotherapy is not a binary technique, we can prescribe dose as a function of TP

- Radiobiological modeling
- Linear and square root dose mapping
  - Easy implementation
  - No radiobiological assumptions
- Between 68 and 102 Gy
  - 68 Gy: standard treatment in Dutch dose escalation trial <sup>(4)</sup>
  - 102 Gy: 107% of 95 Gy, escalated dose in FLAME trial <sup>(5)</sup>



<sup>(4)</sup> Peeters et al 2006  
<sup>(5)</sup> Lips et al 2011



Van Schie et al. Phys Med. Biol. 2017. 62(14):5575-5588

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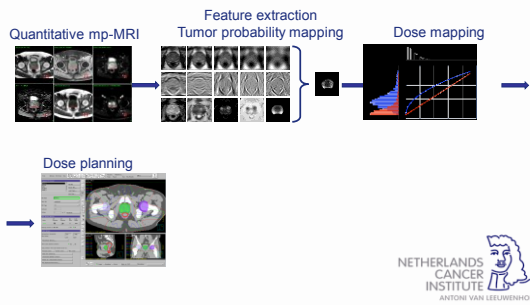
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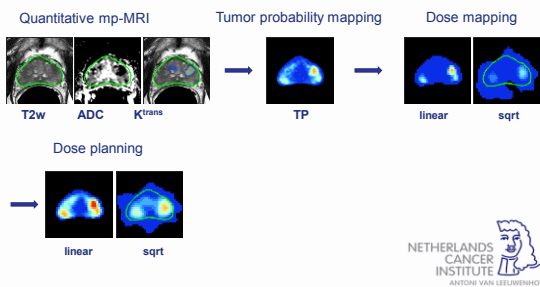
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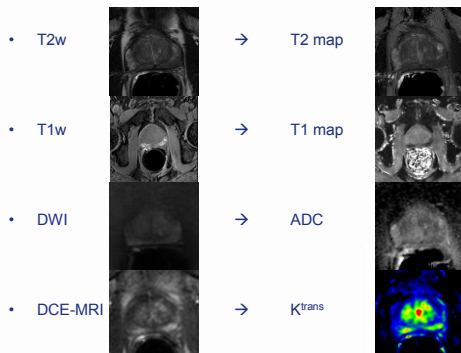
## Dose Painting by Numbers based on mp-MRI



## Dose Painting by Numbers based on mp-MRI

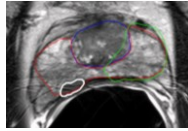
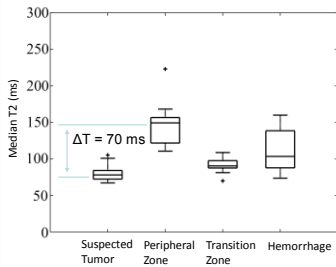


## From qualitative to quantitative imaging



## T2 mapping in prostate cancer

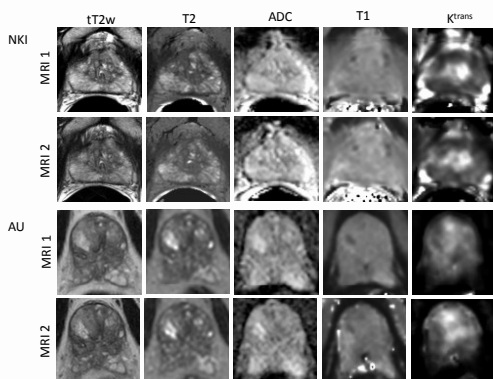
- kt-T2 mapping sequence;



Van Houdt et al. MRM in press

## Test-retest study to investigate repeatability of quantitative MRI

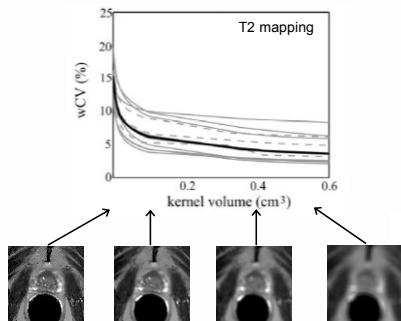
- 34 patients in 3 institutes received an mp-MRI twice prior to treatment
  - T1 mapping (T1)
  - T2 mapping (T2)
  - Diffusion-weighted MRI (ADC)
  - Dynamic Contrast-Enhanced MRI ( $K^{trans}$ )
- Determine bias and spatial resolution
  - Smallest volume for which a relevant difference in image quantity can be determined
- Determine how day-to-day variation propagates in Dose Painting by Numbers (12 patients)



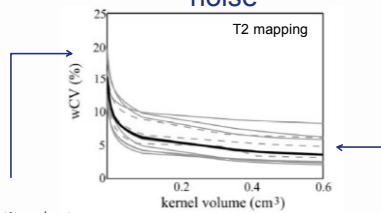


## Spatial resolution in functional imaging

What is the minimum difference that can be determined in a given VOI



## Repeatability vs. voxel size and image noise



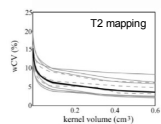
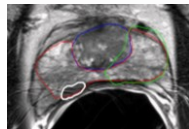
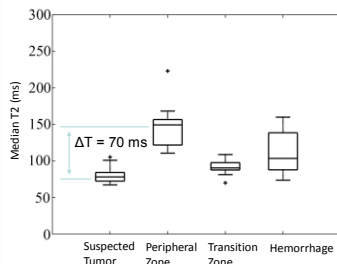
Variations due to:

- Noise
- Small registration errors
- day-to-day variations in tissue
- day-to-day scanner variations

Variations due to:

- Day-to-day variations in tissue
- Day-to-day scanner variations

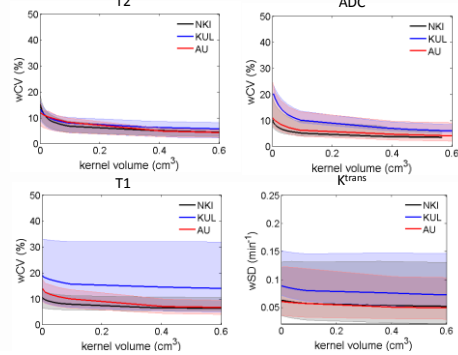
## T2 mapping in prostate cancer



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CANCER  
INSTITUTE  
ANTON VAN LEEUWENHOEK

Van Houdt et al. MRM in press

Multi-center repeatability for mp-q-MRI



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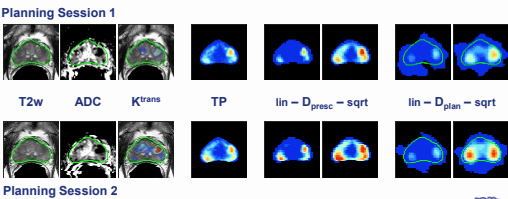
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Test-retest of Dose Painting by Numbers



Van Schie et al. Phys Med. Biol. 2017. 62(14):5575-5588



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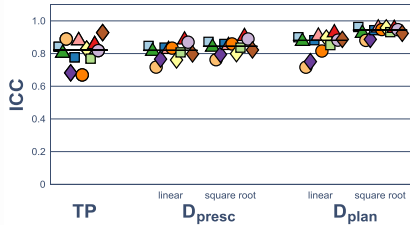
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Repeatability of Dose Painting by Numbers

Assessment with Intraclass Correlation Coefficient



Van Schie et al. Phys Med. Biol. 2017. 62(14):5575-5588



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## Conclusions

- Boosting the GTV (i.e. the visible cancer inside prostate and seminal vesicles) is tested in the FLAME trial
- Multi-parametric MRI is used for staging and tumor localization in prostate cancer
  - PI-RADS v2
- Multi-parametric MRI can be used to delineate lesions inside the prostate gland
  - Large inter-observer variability
  - Statistical approach, reflecting probability of tumor presence
- Tumor probability can be derived from multi-parametric MRI
- As radiotherapy is not a binary technique, we can modulate the dose based on tumor load and characteristics




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## Acknowledgements

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