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

Uulke van der Heide

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

Prostate Cancer Radiotherapy

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

Differential boosting of the GTV in prostate cancer

Targets for boosting
- GTV: intraprostatic lesion(s) as visible on imaging (MRI and/or PET)
- PTV/GTV: 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
  - ≥ 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Registration number</th>
<th>Study Phase</th>
<th>Imaging &amp; OIL</th>
<th>RT technique</th>
<th>GTV/PTV dose [Gy]</th>
<th>Standard [Gy] Dose [Gy]</th>
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<tr>
<td>trials of differential boosting of the GTV in prostate cancer</td>
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FLAME: focal dose escalation multi-center phase III randomized trial

Prostate 77 Gy
Tumor 85 Gy
571 patients
Trial is now closed

Trial profile

571 patients signed Informed Consent and were randomly assigned
287 allocated to standard treatment
(77 Gy in 35 fractions of 2.17 Gy)
284 allocated to additional integrated microboost
(95 Gy in 35 fractions of 2.70 Gy)

255 received planned dose
29 received less than planned dose
255 received planned dose
255 received less than planned dose

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

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?

<table>
<thead>
<tr>
<th>mean dose to GTV</th>
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<tr>
<td>0</td>
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</table>

Mean dose to GTV
- Median: 92.7 Gy
- 25 percentile: 90.2 Gy
- 75 percentile: 94.5 Gy

Dose constraints:
- Rectum: D1cc < 77 Gy
- Bladder: D1cc < 80 Gy
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)

Computer-aided detection of tumor

Prostate atlas based on 158 radical prostatectomy specimens

Detected tumor area in peripheral zone

MRI data

Bipby reports

H&E Staining Image

Validation of tumor probability model

<table>
<thead>
<tr>
<th>T2w</th>
<th>ADC</th>
<th>(K_t)</th>
<th>H&amp;E</th>
<th>Probability</th>
<th>AUC</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
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<td></td>
<td></td>
<td>MRI</td>
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<td>MRI+prevalence</td>
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<td></td>
<td></td>
<td>MRI+prevalence+bipseys</td>
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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.


Tumor probability and inter-observer variation

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


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
  – 102 Gy: 107% of 95 Gy, escalated dose in FLAME trial

Peeters et al 2006
Lips et al 2011
Dose Painting by Numbers based on mp-MRI

Feature extraction
Tumor probability mapping
Dose mapping

Dose planning

Quantitative mp-MRI

T2w
ADC
K\text{trans}

T2 map

DCE-MRI

K\text{trans}

From qualitative to quantitative imaging

- T2w
  →
  T2 map

- T1w
  →
  T1 map

- DWI
  →
  ADC

- DCE-MRI
  →
  K\text{trans}
T2 mapping in prostate cancer

- kI-T2 mapping sequence;

<table>
<thead>
<tr>
<th>Median T2 (ms)</th>
<th>Suspected Tumor</th>
<th>Peripheral Zone</th>
<th>Transition Zone</th>
<th>Hemorrhage</th>
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</thead>
<tbody>
<tr>
<td>ΔT = 70 ms</td>
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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 (Ktrans)

- 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

ΔT = 70 ms

Van Houw et al. MRM in press
Multi-center repeatability for mp-q-MRI

Test-retest of Dose Painting by Numbers

Planning Session 1

T2w ADC Ktrans TP lin – Dpresc – sqrt lin – Dplan – sqrt

Planning Session 2

Repeatability of Dose Painting by Numbers

Assessment with Intraclass Correlation Coefficient
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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