MRI guided Therapies: seeing what you treat

Universitair Medisch Centrum Utrecht

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Interventional radiology

- Vascular interventions
- Image guided biopsies
- Image guided drug infusion
- Tumor ablation
  - Radiofrequency
  - Microwave
  - Laser
  - High Intensity Focused Ultrasound (HIFU)
    - US guided HIFU
    - MRI guided HIFU
MRI guided
High Intensity Focused Ultrasound (HIFU)

Thermo-therapy

MRI with HIFU

Anatomy and temperature mapping

Position and power control

Transducer

PC
MRI guided Focused ultrasound: clinical applications

Patient 1 (Uterine Fibroid) 20/11/2008, Philips/CHU Bordeaux (Pr Trillaud)

HIFU Ablation

Before

After
Radiotherapy

- Standard-of-Care for many types of cancer
- High-Precision Treatment (Gamma-knife, linear accelerator, proton beam)
- Pre-planning is image guided
  - Definition of Gross Tumor Volume (GTV)
  - Definition of Clinical Target Volume (CTV)
  - Identification of Organ At Risk (OAR)
- Until now, treatment itself is not (real-time) image guided
- Mobile organs are generally not treated with RadioTherapy
- Modern RadioTherapy moves towards real-time image guidance (US, X-ray, MRI)
MRI offers superb soft tissue visualization

GTV primary tumor

bladder

rectum

CTV$_{\text{primary}}$ (cervix, corpus uteri)

GTV pathological lymph nodes (left)

GTV pathological lymph nodes (right)

t2 weighted MRI sequence cervix
Real time breathing related motion

irregular breathing von Hippel Lindau kidney tumour
Breathing related motion

irregular breathing von Hippel Lindau kidney tumour
New 3D T2-FFE sequence with unique potential lymph nodes breast cancer patients

- 3D T2-FFE with some intrinsic diffusion weighting, fat suppression and black blood imaging
- Resolution 0.7x0.7x1 mm
- Geometrically correct, targeting 1.5 T MRL

T2-FFE MRI axillary lymph nodes
Vision: MRI guided Therapy

- With MRI we see the GTV and we can follow/track tumours
- The GTV is hard to track with present day radiotherapy
- Tumour infiltrations are relatively well visualized
- We want to use the actual MRI to better track the GTV and spare OAR

Conclusion UMCU: MRI guided cancer treatment, **seeing what you treat**
Outline

• MRI guided RadioTherapy
• MRI guided Focused Ultrasound
• Image Guided Chemotherapy
• Center for Image Guided Oncological Interventions
Outline

- MRI guided RadioTherapy
- **MRI guided Focused Ultrasound**
- Image Guided Chemotherapy
- Center for Image Guided Oncological Interventions
Volumetric MR-HIFU ablation of breast cancer using a dedicated breast platform

• Phase 1 study on patients with pathologically proven invasive breast cancer (n=10)
  • Feasibility study to assess safety and treatment accuracy in patients with breast cancer

• Treat-and-resect protocol
  • Surgery between 48 hours and one week after HIFU treatment

• Sentinel lymph node procedure
  • Peritumoral injection of radioactive colloid just before surgery
  • Detection during surgery
Dedicated breast MR-HIFU system

“Conventional” approach

Dedicated system with lateral sonication

transducer top view
Dedicated breast platform
Sonalleve Breast MR-HIFU

Table top without covers

Water box with transducer and motors

Close-up of breast cup, single-element RF coil, and transducer
Results: 3 Tesla MRI
Results: MR-HIFU

Temp (°C)

Time (s)
Results: after MR-HIFU ablation

• Minimal pain after MR-HIFU ablation

• Lumpectomy three days after MR-HIFU ablation
  • Detection of sentinel lymph node
  • No damage to pectoral muscle

• Pathology
  • No macroscopic or microscopic changes visible in tumor tissue (patient 1)
  • Macroscopic changes visible in tumor tissue (patient 2) with diameter corresponding with thermal dose threshold
Outline

- MRI guided RadioTherapy
- MRI guided Focused Ultrasound
- Image Guided Chemotherapy
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Development of the ultimate MRI targeting system for RadioTherapy

- Diagnostic quality MRI
- Targeting accuracy 0.5-1 mm
- On line/intrafraction/breathing
- Therapy plan update continuously
- Dose accumulation
- High dose rate
- Good IMRT properties (penumbra, scatter, transmission)
- Fast MLC
Concept of MRI accelerator

- Accelerator
- MLC
- beam
Principle of active B field shielding

\[ B_{0,\text{out}} = B_{p,\text{out}} - B_{c,\text{out}} = 0 \]

\[ 0 \text{ T area} \]

Cross section through magnet
Radiation windows

Present design:
field 24 cm long x 40 cm wide
Specifications MRI accelerator

- 1.5 T diagnostic MRI
- 6 MV linac
- Simultaneous irradiation and MRI
- Continuously rotation
  - *Both directions*
  - *10 RPM*
  - *0.1 degree accuracy*
- 1 mm spherical volume as target
- MLC Field size 24x56 cm2
  - *7 mm leaves at isoc*
Philips and Elekta go MRI

- Tumor characterization
- MRI simulation: delineation
- MRI guidance
  - MRI treatment guidance external beam
- MRI treatment response assessment
Outline

- MRI guided RadioTherapy
- MRI guided Focused Ultrasound
  - Liver- preclinical (large animal)
- Image Guided Chemotherapy
- Center for Image Guided Oncological Interventions
Challenges:

1. **motion**:
   - Artifacts in MRI thermometry
   - Target tracking/gated HIFU

2. **Presence of ribs**:
   - Block propagation of HIFU
   - Burn risk in and around ribs

3. **Highly perfused organs**:
   - Cooling due to flow/perfusion
   - High HIFU energy deposition
   - Burn risk in near and far field
#1: Respiratory motion

- Motion Tracking:
  - MRI
  - Ultrasound

- HIFU guidance
  - Beam steering
  - Gated sonication
MRgHIFU for cancer therapy: Challenges for HIFU in the liver

#1: Respiratory motion

For respiratory motion this is done at a rate of 10 Hz with a latency below 100 ms.

[Diagram showing registration processes and respiratory motion correction]
## Towards clinical MR-HIFU treatment in the liver

<table>
<thead>
<tr>
<th>Interventional Pre-Planning</th>
<th>Treatment</th>
<th>Evaluation</th>
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<tbody>
<tr>
<td>• Preparatory scanning</td>
<td>• Inter-costal firing</td>
<td>• Comparison of Contrast-Enhanced MR images to thermal dose maps</td>
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<tr>
<td>• Evaluate acoustic access</td>
<td>• Respiratory motion compensation</td>
<td>• Correlation of histopathological Findings and thermal dose maps</td>
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<td>• Determine diffractive/refractive effects</td>
<td>• Feed-back control</td>
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<td>• Estimate duty-cycle/volumetric ablation rate (treatment duration)</td>
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Treatment

- Inter-costal firing
- Respiratory motion compensation
- Temperature feed-back control

Liver ablations under clinical conditions
Continuous sonication with gated thermometry

smearing of energy due to breathing motion
Reference: gated sonication

- adapted duration to duty-cycle
- isotropic shape

Layered structures in beam path strongly heated → oedema! (all sonications)
Power calibration animal 4

What about the 8mm 349W sonication?
Case study: Larger volume ablation

• ablation of region with 10mm diameter

• location: 35mm from skin, 12mm inside liver

• 7 cells @ 4mm

• cooling time between shots > 10 min

• check for oedema with T2 while waiting

⇒ feasible for unobstructed, shallow shot
Larger volume ablation: pathology puzzle
Intercostal-firing: The problem

MRI / CT based preplanning tools

Treatment simulations for patient selection
Geometric Shadow

Determine shadowed fraction of area $A_s$

If $A_s >$ threshold:
Switch Element OFF

$$P_{elem} \leftarrow P_{elem} \frac{n_{total}}{n_{active}}$$
Intensity-based thresholding

- Shadow casting ignores transmission characteristics
  - ‘Blocked’ elements can contribute to focus
  - ‘Unblocked’ elements can expose the ribs

Element Directivity Pattern

10% of focus intensity @ $|x| = 6\text{mm}$
Geometric Shadow

Pro

• Fast
• Relatively Simple

Contra

• Requires rib segmentation
• Weak correlation with exposure (depending on rib geometry)
Intensity-based switch-off

PRFS Thermometry @ rib level

Thermocouple measurements

No Rib Protection | Intensity Threshold
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• Center for Image Guided Oncological Interventions
Center for Image Guided Oncological Interventions at Utrecht

Planning, real-time guidance, and monitoring of oncological interventions

MRI guided HIFU

MRI guided Linear Accelerator

Image guided Chemotherapy
Applications of Focused Ultrasound

- MR-HIFU for Image Guided, Local Drug Delivery
  - Extravasation
  - Membrane permeabilization
  - Triggered drug release from nanocarriers
The primary hurdle to the use of drugs in the central nervous system for most small molecule agents and all large molecule agents. Methods developed to bypass the BBB are invasive, non-targeted and/or require the development of new drugs.
Focused Ultrasound and Microbubbles: BBB opening

**BBB closure dynamics**

- **Dotarem®** ($d_H \sim 1\text{nm}$)
  - $T_{1/2} \sim 4\text{h}$

- **Gd-chelate A** ($d_H \sim 4\text{nm}$)
  - $T_{1/2} \sim 1\text{h}$

- Normalized Gd concentration

- Time elapsed between BBB opening and contrast agent injection (h)

Benoit Larrat et al ISMRM 2011
Applications of Focused Ultrasound

- MR-HIFU for Image Guided, Local Drug Delivery and Gene
  - Extravasation
  - Membrane permeabilization
  - Triggered drug release from nanocarriers
Low Temperature Heat Sensitive liposomes

37°C

Leaky tumor vessels

39 < T < 42°C

Heat adds permeability / extravasation

39 < T < 42°C

Cargo deployed @ 39-42 deg

Courtesy Mark Dewhirst, Duke University
Co-release of MRI contrast agents from liposomes visualized with $T_1$-maps

de Smet et al; 2011
Present indications Cancer Therapy

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<tr>
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<td>+</td>
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<td>RT</td>
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Development MR-HIFU and MR-LINAC

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Centre for Image Guided Oncological Interventions (CIGOI)

MR-LINAC
MRI guided brachytherapy
MR-HIFU

HDR robotic brachytherapy

HIFU

MRI linac
• MRI guidance of RadioTherapy and MR guided HIFU will set the next stage in high-precision tumor therapy

• Synergy in development (motion descriptors, target tracking)

• MR-LINAC will be the next standard-of-care in RadioTherapy

• MR-HIFU offers many complementary features and may be added to the Surgical, RT and Chemo therapies

• MR-HIFU may lead to MR guided Drug Delivery
Imaging Division, UMCU; Pharmaceutical Sciences UU
Jan Lagendijk, Marco van Vulpen, Bas Raaijmakers, Baudouin Denis de Senneville, Mario Ries, Clemens Bos, Anna Yudina, Wilbert Bartels, Gert Storm, Maurice van den Bosch, Willem Mali et al

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