Physics aspects of HIFU clinical trials for cancer treatments

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Making the discoveries that defeat cancer

A HIFU Team must be:

Multidisciplinary

Interventional radiologist: Nandita deSouza
MR Radiographer: Sharon Giles
Pain specialist: Matt Brown & anaesthetic team
MR physicists: David Collins, Jessica Winfield
HIFU physicists: Ian Rivens, John Civale, Gail ter Haar,

The role of the physicist

- Screening & Baseline Measurements
- HR-HIFU Treatment (Day 0)
- 90-day Follow-up Period
- Study Completion
The role of the physicist

Primarily:

Calibration & QA of device

Treatment delivery

HIFU Calibration and QA

Why?

- Confidence in system output (power, field distribution etc.)
- System safety
- Interpretation of results from pre-clinical/clinical studies using different systems/equipment
HIFU Calibration and QA

**Why?**

- Necessary for wider acceptance of HIFU as a non-invasive therapeutic modality
- Need for well established protocols

**HIFU devices are complex**

Comprised of:

- Ultrasound transducer
- Positioning system
- Drive electronics
- Cooling system
- Degassing system
- MR/US scanner
- HIFU table

**Philips Sonalleve MRg-HIFU System**

- Installed at The Royal Marsden, Sutton, Oct 2013
- Existing 3T Achieva scanner
- Focused Ultrasound Foundation funded European Centre of Excellence
Volumetric Heating

Electronic beam steering:
Outwards-moving concentric circles
4 – 16 mm ø
15-77% exposures

For details see: M. Köhler et al., Med.Phys. 36 (8), 3521, August 2009

### QA Procedure

Purpose of a QA Test is to ensure that the HIFU system performance is 'normal' prior to the therapy.

- **Sonication test**
  - To check that sonication accuracy and power levels are normal
  - Heating location accuracy
  - Temperature accuracy
  - Heating volume accuracy.

- **Air bubble check**
  - Is done always prior to any sonication.
  - To avoid reflection which might cause transducer damage.

### QA Phantom

**Tissue mimicking**

Allows checking of focal position & thermometry

AAPM MRI-guided focused ultrasound task group-241

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Length (mm)</th>
<th>Volume (ml)</th>
</tr>
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<tbody>
<tr>
<td>4</td>
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<td>0.1</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>0.6</td>
</tr>
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<td>12</td>
<td>30</td>
<td>2.3</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>5.4</td>
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MRgHIFU

Purpose of a QA Test is to ensure that the HIFU system performance is 'normal' prior to the therapy.

- **Sonication test**
  - To check that sonication accuracy and power levels are normal
  - Heating location accuracy
  - Temperature accuracy
  - Heating volume accuracy.

- **Air bubble check**
  - Is done always prior to any sonication.
  - To avoid reflection which might cause transducer damage.
Air bubbles in QA tests

Acceptable, no large air bubbles

Check air bubbles visually and by imaging.
Keep a record

Look for sudden changes, or drift, over time

MRgHIFU Calibration

Challenges to working on an MRgHIFU clinical system:

- MR compatibility/safety
- Space limitations
- Technology limitations
- Access to and control over the transducer

Quantities that should be recorded

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aperture (D)</td>
<td>Physical dimensions of transducer</td>
</tr>
<tr>
<td>Focal Length (L)</td>
<td>Spherical transducer: radius of sphere</td>
</tr>
<tr>
<td>Element Configuration (N_{\text{elem}})</td>
<td>Defined by transducer design.</td>
</tr>
<tr>
<td>Frequency (f)</td>
<td>Driving frequency of the transducer element(s)</td>
</tr>
<tr>
<td>f#</td>
<td>The ratio, L/D, is defined to be the f# number (f#) of the transducer; the smaller the f#, the smaller the focal spot increasing the energy deposited at that point.</td>
</tr>
<tr>
<td>Beam Full Width Half Maximum (FWHM)</td>
<td>Hydrophone measurement</td>
</tr>
<tr>
<td>Efficiency</td>
<td>Radiation force balance or hydrophone scans of intensity over full cross-sectional area of the ultrasound beam</td>
</tr>
</tbody>
</table>

AAPM MRI-guided focused ultrasound task group 241 report - Draft
Acoustic Power Measurements

**Aim:** to develop MR compatible system

- Develop and build:
  - Tank – couples to membrane
  - Target – castor oil buoy
  - Stand – fit on Sonalleve couch

Validate the use of a load cell (Tedea-Hunt) used to measure the forces acting on the target.

**Equation:**

\[ W = F \times c \]

\[ W = \frac{G}{(k t)} \]
Load Cell Calibration

- Lab balance (Sartorius LA230S)
- Load cell

Signal noise:
- ~2 mg (30 mW)
- ~30 mg (440 mW)
- ~5 mg following filtering (70 mW)

Sonalleve Power Measurements

- 1.2 MHz – 20s CW sonication

Measurements at the Focal Peak

Pressure parameters vs. drive (1.2 MHz)
Sonalleve Power Measurements

<table>
<thead>
<tr>
<th>Method / Normal Force</th>
<th>Measured / Nominal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside Magnet - Maintenance mode</td>
<td>86%</td>
</tr>
<tr>
<td>Inside Magnet - Maintenance mode</td>
<td>88%</td>
</tr>
<tr>
<td>Inside magnet - TP with thermometry</td>
<td>90%</td>
</tr>
</tbody>
</table>

Radiation Force (on) vs Radiation Force (off) vs Buoyancy (net weight change)

Determined from 3 repeats at 100, 125, 150 and 175 W, 1.2 MHz 20s CW exposures.

MR compatible positioning system

**Features:**
- MR compatible
- Motors with no fixed magnets
- Drive and encoders signals transmitted via fibre-optic cables
- Onda HGL-0200 hydrophone
- MR safe
- Robust
- Compact size
- Flat frequency response
- Spatial resolution 0.2 mm

Beam steering
Testing frequency

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Frequency</th>
<th>Testing Parameters</th>
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</thead>
<tbody>
<tr>
<td>Motor system evaluation</td>
<td>Comparison to baseline*</td>
<td>Acceptance, Commissioning, Periodic, Every 20 patients or 6 months</td>
</tr>
<tr>
<td>Transducer focusing capability</td>
<td>Comparison to baseline*</td>
<td>Acceptance, Commissioning, DQA, Either daily or before every patient</td>
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<tr>
<td>Transducer steering</td>
<td>Comparison to baseline*</td>
<td>Acceptance, Commissioning, DQA, Either daily or before every patient</td>
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<td>Imaging SNR</td>
<td>Comparison to baseline*</td>
<td>Acceptance, Commissioning, DQA, Either daily or before every patient</td>
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<tr>
<td>Ultrasound temperature imaging accuracy</td>
<td>Comparison to invasive fiberoptic probe</td>
<td>Acceptance, Commissioning, Periodic, Every 20 patients or 6 months</td>
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<tr>
<td>Planning/delivery software function evaluation</td>
<td></td>
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<tr>
<td>Cavitation detection</td>
<td></td>
<td>Acceptance, Commissioning, Periodic, Every 20 patients or 6 months</td>
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<tr>
<td>Safety interlock evaluation</td>
<td>Functionality</td>
<td>Acceptance, Commissioning, DQA, Either daily or before every patient</td>
</tr>
<tr>
<td>Acoustic output (radiation force balance)</td>
<td></td>
<td>Acceptance, Commissioning, Periodic, Every 100 patients or 1 year</td>
</tr>
<tr>
<td>Ultrasound beam characterization (hydrophone)</td>
<td>FWHM, ISPPA</td>
<td>Acceptance, Commissioning, Periodic, Every 100 patients or 1 year</td>
</tr>
<tr>
<td>Visual check of the equipment for damage</td>
<td>Comparison to baseline*</td>
<td>Acceptance, Commissioning, DQA, Either daily or before every patient</td>
</tr>
<tr>
<td>Degassing system</td>
<td>Oxygen content (ppm)</td>
<td>Acceptance, Commissioning, Periodic, Every 20 patients or 6 months</td>
</tr>
<tr>
<td>Coupling membrane integrity inspection</td>
<td>Comparison to baseline*</td>
<td>Acceptance, Commissioning, DQA, Either daily or before every patient</td>
</tr>
</tbody>
</table>

The role of the physicist

Treatment delivery

HIFU exposure (cell) sizes

Treatment Planning:
- Discrete treatment "cells" planned to cover target

Diagrams courtesy of Philips

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Treatment planning

Yellow box: DTV

Contour plots showing field distribution inside the DTV

Treatment planning

Treatment monitoring

- Proton resonance frequency shift (PRFS) thermometry acquired using echo planar imaging (EPI) at 1s intervals
- Monitors heating seen in soft tissues adjacent to bone surface

Diagram courtesy of Philips
Background

- Bone metastases commonly cause significant pain, functional limitations and decreased quality of life
- Bone pain arises in part from:
  - increased sensory innervation
  - Sensitisation of nerve cell fibres
- External beam radiotherapy (EBRT):
  - Up to 30% non-responders
  - Up to 50% recurrence in responders
  - Re-treatment potential is limited
- HIFU:
  - Non-invasive, but non-ionising (pressure) wave
  - Thought to alleviate pain by thermal denervation of the periosteum

Bone metastases

- Common in breast, prostate & lung cancer
- Primary bone cancers – osteosarcoma
- Unifying feature = PAIN
- Multifactorial origin
- Periosteal disruption
- Local tissue destruction
- Changes in sensory innervation
- Changes in tissue pH

Images courtesy of Dr Matthew Brown

Pathological sprouting of periosteal sensory nerve fibres

↑ [H⁺] Release of growth factors and Ca²⁺

Tumour associated immune cells

Central sensitisation

Common in breast, prostate & lung cancer

Primary bone cancers – osteosarcoma

Multifactorial origin

Periosteal disruption

Local tissue destruction

Changes in sensory innervation

Changes in tissue pH
How does HIFU deliver analgesia?

MR-HIFU for Bone Metastases - Multicentre

Rationale: MR-HIFU can palliate pain from bone metastases by local denervation of the periosteum, e.g. Hurwitz, et al JNCI 2014

Objective: Efficacy without side effects

Patients: Bone pain unresponsive to standard care (radiotherapy (EBRT), systemic therapy and analgesia) - survival is months, rather than years

Design: Multi-centre, single arm, non-randomized, non-blinded

Planned patient enrolment:
- The Netherlands: 14 study + 2 roll-in
- Korea: 14 study + 2 roll-in
- United Kingdom: 13 study + 2 roll-in
- India: 13 study + 2 roll-in

Intervention: Single HIFU session under sedation

Study Endpoints

- Primary Endpoint: Pain response (NRS) after 30 days
  - Complete response – pain score 0, no in analgesia
  - Partial response – pain score 2 points or 25% in analgesia
  - Progression – pain score 2 points or 25% in analgesia

- Secondary endpoints:
  - Adverse events
  - EORTC Quality of life (Q of L) measurements
  - Pain at 60 & 90 days
  - (Changes in lesion size post treatment)

- Patients may withdraw after day 30 e.g. for other treatment
Entry Criteria

Inclusion Criteria

- Men and women ≥ 18 years
- Weight < 140kg
- ≤ 3 painful lesions
- Patient able to:
  - give informed consent
  - communicate sensation
  - be on stable pain medication for ≥1 week

Target tumour:

- Bone metastasis (NRS ≥4/10), after standard care
- MR visible (non-contrast)
- ≤ 8cm maximum dimension
- ≥ 1cm from skin
- Accessible with HIFU
- No local treatment for 4 weeks

Exclusion Criteria

- Sedation or contrast MR contraindicated
- Enrollment in another bone/pain relief clinical study
- Need for surgical bone stabilisation
- Medical history that could threaten patient safety
- Unable to tolerate treatment position
- Target tumour: is a primary tumour, lymphoma, multiple myeloma, or leukemia
- < 3cm from bladder/bowel/nerves or < 1cm in plane orthogonal to the beam in contact with hollow viscera
- Located in skull, joints, spine (exc. sacrum), ribs or sternum (if HIFU exposes lung), close to an internal or external fixation device, previous surgery or minimally invasive therapy

Pain due to:

- Impending fracture
- Involvement of a major nerve

Patient Pathway – 1 week pre-treatment

1. Pain rigorously assessed & measured (pain must be from target tumour)
2. 3D MR scanned for suitability:
   - Tumour size & location
   - Acoustic window
   - Organs/structures at risk (nerves)
3. Preliminary treatment planning:
   - Patient position
   - No. and size of exposure cells

Treatment planning & follow up

1. Treatment planned using 3D T1-w images
2. (Post treatment contrast T1-w imaging)
3. Sedation reversed for:
   - Skin examination
   - Pain examination
4. Discharged after 2-3 hrs
5. Daily pain (BPI)/QoL (EORTC) diary for 30 days
6. Contacted by Radiographer Days 7 & 14
7. Day 30, 60, 90: MR scans and hospital questionnaire
**Patient setup**

- HIFU transducer in oil bath
- Acoustically transparent membrane
- Degassed water coupling
- Gel pad coupling to patient

**Treatment planning**

- Acoustic gel couplant
- Water
- MR coil

**Treatment delivery**

- Number of discrete treatment cells planned to cover lesion / periosteum

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<table>
<thead>
<tr>
<th>Diameter</th>
<th>Length</th>
<th>Volume</th>
</tr>
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<tbody>
<tr>
<td>16 mm</td>
<td>40 mm</td>
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<td>14 mm</td>
<td>35 mm</td>
<td>3.8 ml</td>
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<td>12 mm</td>
<td>30 mm</td>
<td>2.3 ml</td>
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<tr>
<td>8 mm</td>
<td>25 mm</td>
<td>1.2 ml</td>
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<tr>
<td>6 mm</td>
<td>20 mm</td>
<td>0.8 ml</td>
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<tr>
<td>4 mm</td>
<td>15 mm</td>
<td>0.6 ml</td>
</tr>
<tr>
<td>2 mm</td>
<td>10 mm</td>
<td>0.1 ml</td>
</tr>
<tr>
<td></td>
<td>5 mm</td>
<td>0.6 ml</td>
</tr>
</tbody>
</table>

(Images and diagrams courtesy of Philips)
Placement of “cells”

View in orthogonal planes

3 case studies

2 “easy”; 1 more difficult than usual

Patient 1

Setup

Patient positioning challenges:

- “Normal” incidence on bone surface
- Required shaping and cutting of gel pads
- Tendency to slip
- Larger patient would not fit in the bore
- Central lesion

Patient 1 - Setup

- Pain uncontrolled, NRS 8-10 (3 months after 8 Gy ERBT)
- 51 year old female with painful metastasis (breast) in right shoulder

Patient positioning challenges:

- “Normal” incidence on bone surface
- Required shaping and cutting of gel pads
- Tendency to slip
- Larger patient would not fit in the bore
- Central lesion
Patient 1 – Treatment (June 2014)

- 11 exposures at 1.2 MHz
- "Near-field heating"
- 3 x 4mm cells, 8 x 8mm cells, Powers 20-60W
- Treatment time: 1 hour

Results: Patient 1

- 51 year old female with metastatic breast cancer, painful metastasis right shoulder
- Challenging positioning for treatment (space, coupling)
- Post treatment imaging shows no adverse features
- Pain scores reduced
- Range of movements greatly increased
- No analgesia now being used

Patient 1 Pain Scores

Day
Worst pain experienced today

0
1
2
3
4
5
6
7
8
9
10
-5 0 5 10 15 20 25 30 35

At Day 90, pain score 0 at rest and also 0 at maximal abduction (previously unable to abduct arm)
6 months post HIFU, pain response maintained
No adverse events

Patient 1 – Imaging Results

- Post treatment imaging
  - no break in cortex up to day 90
  - no adverse features
  - no lesion growth up to day 90
  - Temporary oedema at day 60
- Imaging changes suggestive of response:
  - Less contrast enhancement
  - Marrow fat returning to volume
Clinical Case Studies: Patient 10

Planning row 1
Planning row 2
Planning row 5
Planning all rows coronal

Clinical Case Studies: Patient 10

Test shot 30W Cell 3
80W Cell 3
90W Cell 4
90W Cell 5
Patient 5

Results: Patient 5
56 year old female with metastatic breast cancer
36 Gy Feb 2010
Painful metastases right first rib
Pain not well controlled (5/10 at rest, 9/10 on palpation)
Challenges: avoiding lung damage, whole rib affected, implanted portacath, gel pad coupling (wedge required), breast reconstruction

Patient 5 - Treatment
• High risk of failure or adverse events
• MRgHIFU Jan 2015
• 11 x sonication
  • 3 x 4mm cells, 8 x 8mm cells, 1.2MHz, Powers 20-90W
• Treatment time 1 hour

Wedge of fat
Patient 5 - Results

- Pain score reduced to 0 by Day 10
- Flare up of pain after Day 21, but returned to 0 by day 30, maintained at 0 at Day 60
- However, new neuropathic pain developed down right arm from Day 21 still ongoing at Day 60
  (caused by posterior rib disease – compression)
- Resolved with medication Day 30

Results: Outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pain score</th>
<th>Day 30 T1W</th>
<th>Day 30 T1c + Gad</th>
<th>Results: Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 5</td>
<td>Pain score</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: Treatments

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumour type</th>
<th>Target lesion</th>
<th>Number of sonications</th>
<th>Total energy delivered (KJ)</th>
<th>Treatment time (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast</td>
<td>Humeral head</td>
<td>12</td>
<td>9.28</td>
<td>61.0</td>
</tr>
<tr>
<td>2</td>
<td>Breast</td>
<td>Anterior Iliac bone</td>
<td>17</td>
<td>20.75</td>
<td>121.0</td>
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<tr>
<td>4</td>
<td>Renal</td>
<td>Posterior Iliac bone</td>
<td>11</td>
<td>15.00</td>
<td>52.0</td>
</tr>
<tr>
<td>5</td>
<td>Breast</td>
<td>1st Rib</td>
<td>11</td>
<td>14.84</td>
<td>51.7</td>
</tr>
<tr>
<td>6</td>
<td>Breast</td>
<td>Posterior Iliac bone</td>
<td>17</td>
<td>43.41</td>
<td>79.5</td>
</tr>
<tr>
<td>7</td>
<td>Renal</td>
<td>Sacrum</td>
<td>15</td>
<td>29.00</td>
<td>79.8</td>
</tr>
<tr>
<td>8</td>
<td>Lung</td>
<td>2 lesions Iliac bone</td>
<td>25</td>
<td>56.07</td>
<td>101.5</td>
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<tr>
<td>9</td>
<td>Breast</td>
<td>Greater Trochanter</td>
<td>17</td>
<td>20.92</td>
<td>86.1</td>
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<tr>
<td>11</td>
<td>Breast</td>
<td>Greater Trochanter</td>
<td>17</td>
<td>27.64</td>
<td>79.0</td>
</tr>
<tr>
<td>12</td>
<td>Breast</td>
<td>Ischial tuberosity</td>
<td>17</td>
<td>27.75</td>
<td>88.9</td>
</tr>
</tbody>
</table>

Day 30 T1W

Day 30 T1c + Gad

Patient 5 pain scores

-1 0 1 2 3 4 5

-5 0 5 10 15 20 25 30 35

Day
Worst pain experienced today

Pt Successful outcome? Adverse Event?

1 ✔ Day 30: PR
   ✔ Day 60: PR
   ✔ Day 90: CR
   None

2 ✔ Day 30: CR
   Patient had concurrent progressive H&N cancer. Withdrawn after Day 30

4 ✔ Day 30: PR
   Patient had rapidly progressive disease. Withdrawn after Day 30

5 ✔ Day 30: PR
   ✔ Day 60: PR
   ✔ Day 90: CR
   Patient developed new neuropathic pain down right arm at Day 23, related to progressive disease affecting brachial plexus, which subsequently resolved.
   Systemic treatment change after Day 90

6 ✔ Day 30: PR
   ✔ Day 60: PR
   Progressive painful disease elsewhere in pelvis
   Withdrawn after Day 60 for further EBRT

7 ✔ Day 30: PR
   ✔ Day 60: PR
   ✔ Day 90: PR
   None

8 ✖ Day 30: No response
   ✔ Day 60: PR
   ✔ Day 90: PR
   None
   The nature of the patient's pain initially changed, but did not improve due to muscle stiffness that restricted movement. This subsequently resolved.

9 ✔ Day 30: PR
   ✔ Day 60: PR
   ✔ Day 90: PR
   None
   Patient had rapidly progressive disease, developing necrogenic sepsis related to chest infection
   Withdrawn before Day 30

11 ✔ Day 7: PR
   ✔ Day 14: PR
   ✖ Day 30: No data
   Patient had rapidly progressive disease, developing neutropenic sepsis related to chest infection

17 ✔ Day 30: PR
   ✔ Day 60: due mid Sep
   None to date
Trial Conclusions I

- MRgHIFU effective in reducing pain from bone metastases (CR in 3/10 patients, partial response in all others)

- Careful patient selection, screening and preparation required to ensure:
  - Safe treatment delivery without damage to neighbouring structures
  - Treatments confer a meaningful improvement in quality of life

- Further work underway to refine methods for planning and monitoring treatments

Trial Conclusions II

- Works well for right patient in the right circumstances

- Only small minority of patients are suitable: reviewed ~200, recruited 18, treated 10

- By time HIFU considered because of poor pain control, multiple lesions or patient too unwell for treatment. Oncologists increasingly refer these for re-treatment with radiotherapy

- Only small proportion of the painful lesion can usually be targeted.

Initial analysis of m/c trial

Response rate

<table>
<thead>
<tr>
<th>Day</th>
<th>% responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>14</td>
<td>60</td>
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<tr>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>60</td>
<td>70</td>
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</tbody>
</table>
Conclusions

The Physicist has a crucial role to play in HIFU treatments:

Device QA & Calibration
Patient selection
Treatment planning & guidance
Post treatment assessment