ICR The Institute of Cancer Research

in partnership with The ROYAL MARSDEN NHS Foundation Trust

Physics aspects of HIFU clinical trials for cancer treatments

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Joint Department of Physics

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Making the discoveries that defeat cancer

A HIFU Team must be:

Multidisciplinary

Interventional radiologist : Nandita deSouza

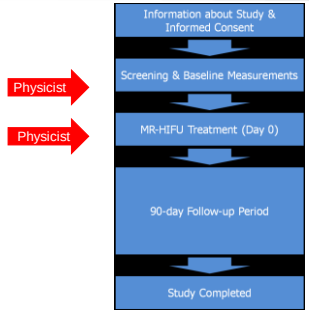
MR Radiographer : Sharon Giles

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



The role of the physicist

Primarily:

Calibration & QA of device

Treatment delivery

The role of the physicist

Calibration & QA of device

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

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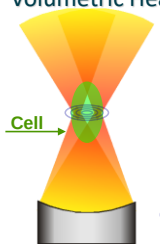
- Installed at The Royal Marsden, Sutton, Oct 2013
- Existing 3T Achieva scanner
- Focused Ultrasound Foundation funded European Centre of Excellence

FOCUSED ULTRASOUND FOUNDATION

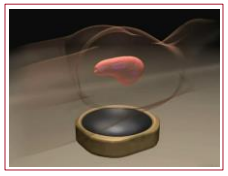
PHILIPS

MRgHIFU

Volumetric Heating



Electronic beam steering:
Outwards-moving concentric circles
4 – 16 mm ⌀
15-??s exposures



Diameter (mm)	Length (mm)	Volume (ml)
4	10	0.1
8	20	0.6
12	30	2.3
16	40	5.4

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

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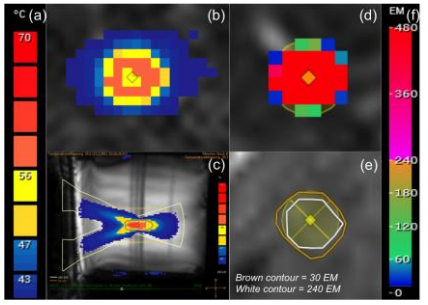
Philips QA Phantom

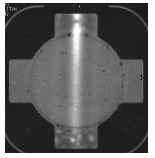
Philips QA Phantom



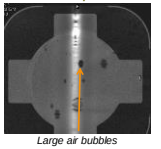
PHILIPS

Air bubbles in QA tests

***Acceptable**, no large air bubbles*

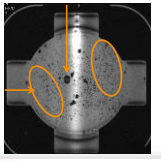


Not acceptable



Large air bubbles

Small but too many air bubbles



Check air bubbles visually and by imaging.

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Keep a record

Look for sudden changes, or drift, over time

QA Wizard Cell 1							
DATE [YYYY-Mon-DD] & User's Initials	HEATING OFFSETS (mm)			HEATING LENGTH (mm)	HEATING DIAMETER (mm)	MAX TEMP (°C)	REASON IF FAILED

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

Transducer Characteristic	Characterization Technique	Relevance
Aperture (D)	Physical dimensions of transducer	In general, the size of the focal spot is inversely proportional to the aperture size.
Focal Length (L)	Spherical transducer: radius of sphere	Distance of transducer face to geometric focal point
Element Configuration (N_{elem})	Defined by transducer design.	Single element transducers must be mechanically moved to move the focal point. Phased-array transducers allow for electronic steering allowing for multi-focus and volumetric ablation
Frequency (f)	Driving frequency of the transducer element(s)	Affects both the wavelength and attenuation of the ultrasound beam. The frequency of a HIFU system is application dependent.
f-Number (f#)	L/D	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.
Beam Full Width Half Maximum (FWHM)	Hydrophone measurement	The width of the beam measured at the focal point, assessed with pressure or intensity (should be specified).
Efficiency	Radiation force balance or hydrophone scans of intensity over full cross-sectional area of the ultrasound beam	Defines the relationship between electrical and acoustic power. A larger efficiency will result in a higher acoustic output for a given electrical input.

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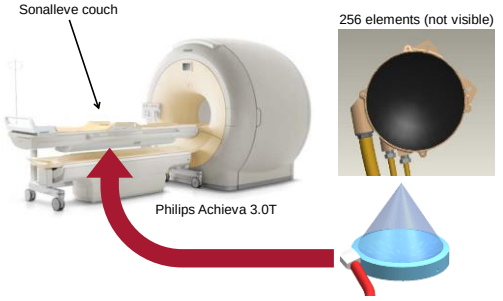
Philips Sonalleve system



Courtesy of Philips Healthcare

Acoustic Power Measurements

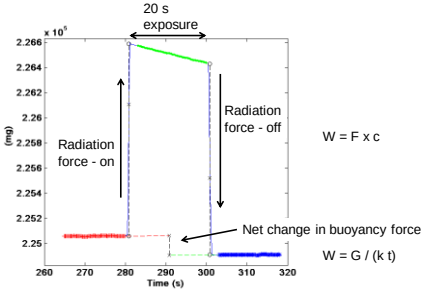
Aim: to develop MR compatible system

Develop and build:

- Tank – couples to membrane
- Target – castor oil buoy
- Stand – fit on Sonalleve couch

Validate the use of a load cell (Tedea-Huntle
used to measure the forces acting on the ta

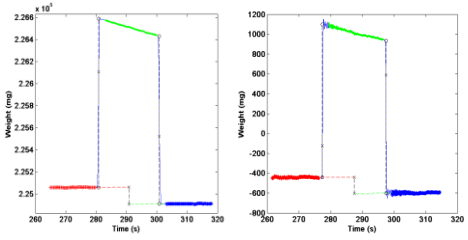
Acoustic Power Measurements



$W = F \times c$

$W = G / (k\ t)$

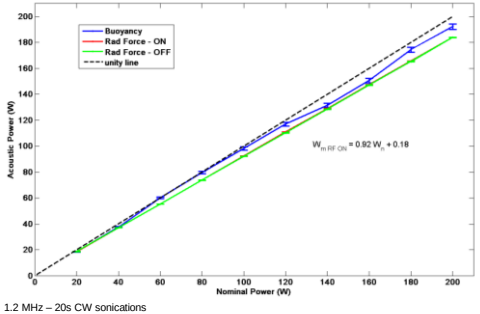
Load Cell Calibration



Lab balance (Sartorius LA230S) Load cell

Signal noise: ~2 mg (30 mW) ~30 mg (440 mW)
(Rad. force power equiv.) ~5 mg following filtering (70 mW)

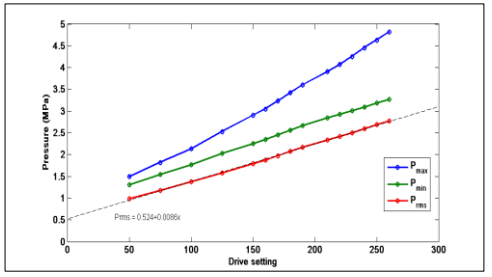
Sonalleve Power Measurements



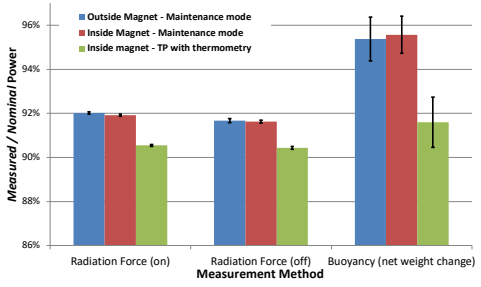
1.2 MHz – 20s CW sonications

Measurements at the Focal Peak

Pressure parameters vs. drive (1.2 MHz)



Sonalleve Power Measurements



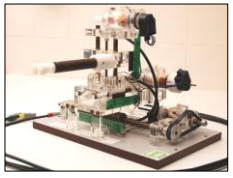
Determined from 3 repeats at 100, 125, 150 and 175 W, 1.2 MHz 20s CW exposures

MR compatible positioning system

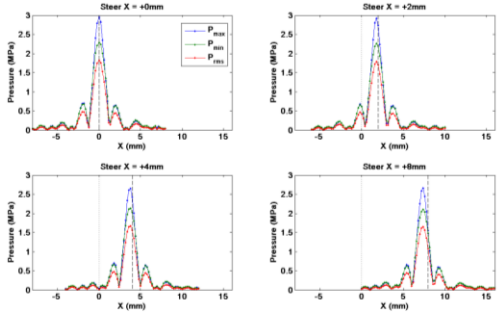
Features:

- Mc ets – make use of MRI B_0 static magnetic field
- Drive and sensors signals transmitted via fibre-optic cables
- MR safe
- Robust
- Compact size
- Flat frequency response
- Spatial resolution 0.2 mm

Onda HGL-0200 hydrophone



Beam steering



Testing frequency

Test description	Measured parameter	Testing subset	Frequency
Motor system evaluation	Comparison to baseline*	Acceptance, Commissioning, Periodic	Every 20 patients or 6 months
Transducer focusing capability	FWHM of beam	Acceptance, Commissioning, DQA	Either daily or before every patient
Transducer steering	Distance of beam steering	Acceptance, Commissioning, DQA	Either daily or before every patient
Table positioning and homing capability	Comparison to baseline*	Acceptance, Commissioning, Periodic	Every 20 patients or 6 months
Imaging SNR	Comparison to baseline*	Acceptance, Commissioning, DQA	Either daily or before every patient
MR temperature imaging accuracy	Comparison to invasive fiberoptic probe	Acceptance, Commissioning, Periodic	Every 20 patients or 6 months
Planning/delivery software function evaluation	??	Acceptance, Commissioning, Periodic	Every 20 patients or 6 months
Cavitation detection	??	Acceptance, Commissioning, Periodic	Every 20 patients or 6 months
Safety interlock evaluation	Functionality	Acceptance, Commissioning, DQA	Either daily or before every patient
Acoustic output (radiation force balance)	Transducer output (in W)	Acceptance, Commissioning, Periodic	Every 100 patients or 1 year
Ultrasound beam characterization (hydrophone)	FWHM, I_{SPPA}	Acceptance, Commissioning, Periodic	Every 100 patients or 1 year
Visual check of the equipment for damage	Comparison to baseline*	Acceptance, Commissioning, DQA	Either daily or before every patient
Degassing system	Oxygen content (ppm)	Acceptance, Commissioning, Periodic	Every 20 patients or 6 months
Coupling membrane integrity inspection	Comparison to baseline*	Acceptance, Commissioning, DQA	Either daily or before every patient

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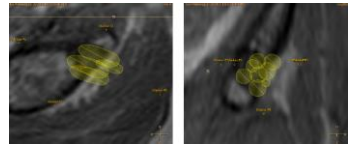
The role of the physicist

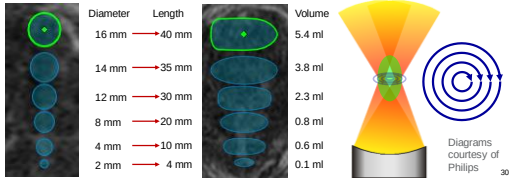
Treatment delivery

HIFU exposure (cell) sizes

Treatment Planning:

- Discrete treatment "cells" planned to cover target





Treatment planning

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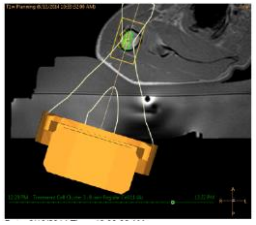

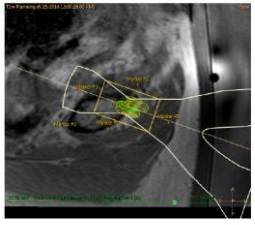

Yellow box:DTV

Treatment planning

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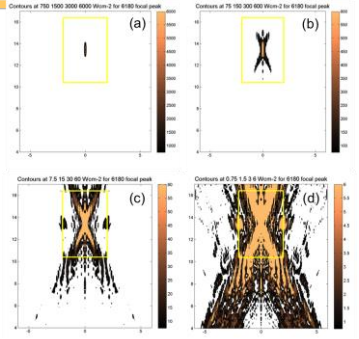
Contour plots showing field distribution inside the DTV



Treatment monitoring

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- Proton resonance frequency shift (PRFS) thermometry acquired using echo planar imaging (EPI) at 1s intervals

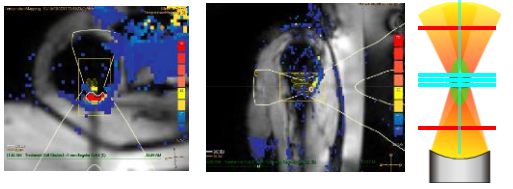

Diagram courtesy of Philips

- Monitors heating seen in soft tissues adjacent to bone surface

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Pain Palliation

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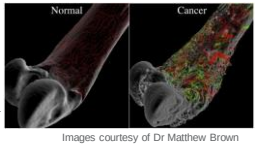
Making the discoveries that defeat cancer

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)[1]
  - Up to 30% non-responders
  - Up to 50% recurrence in responders
  - Re-treatment potential is limited[2]



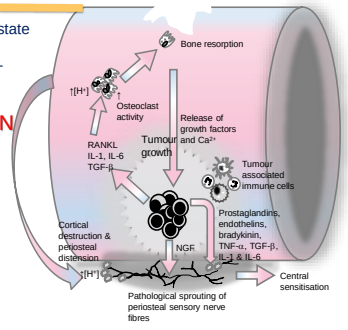
Images courtesy of Dr Matthew Brown

- HIFU
  - Non-invasive, but non-ionising (pressure) wave
  - thought to alleviate pain by thermal denervation of the periosteum

1: Steenland E et al, Radiother Oncol 1999; 52(2):101-9; 2: Huisman M et al, Int J Radiat Oncol Biol Phys 2012; 84(1):8-14

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

How does HIFU deliver analgesia?

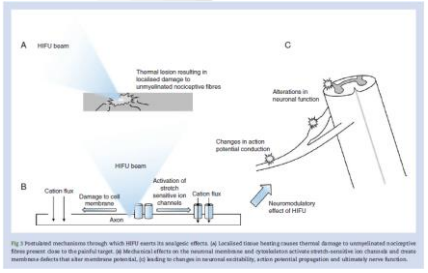


Fig 1 Postulated mechanisms through which HIFU exerts its analgesic effects. (a) Localised tissue heating causes thermal damage to unmyelinated nociceptive fibres present close to the painful target. (b) Mechanical effects on the neuronal membrane and cytoskeleton activate stretch-sensitive ion channels and create membrane defects that alter membrane potential, (c) leading to changes in neuronal excitability, action potential propagation and ultimately nerve function.

The use of high-intensity focused ultrasound as a novel treatment for painful conditions—a description and narrative review of the literature

M. R. D. Brown[1,2,*], P. Farquhar-Smith[1], J. E. Williams[3], G. ter Haar[2] and N. M. deSouza[1,2]

British Journal of Anaesthesia, 115 (4): 520–30 (2015)
doi: 10.1093/bja/aev302
Review Article

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
Enrolment 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/nerve 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), beneath a scar
- 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

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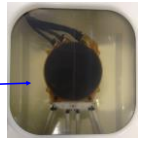
Patient setup



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

Courtesy of Philips

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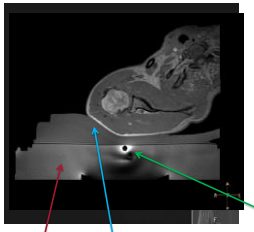
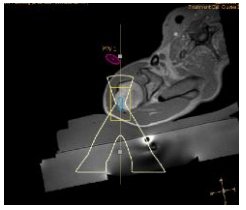
Treatment planning



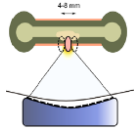


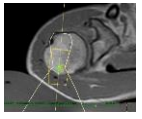
MR coil

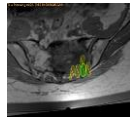
Water Acoustic gel couplant

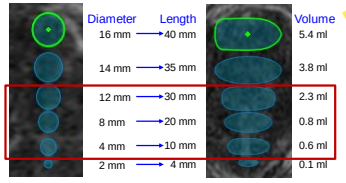
Treatment delivery

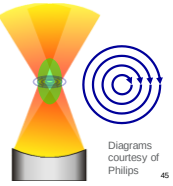
- Number of discrete treatment cells planned to cover lesion / periosteum











Diagrams courtesy of Philips

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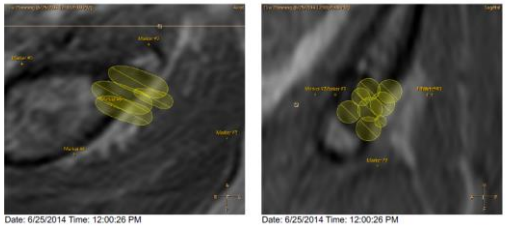
Placement of “cells”



View in orthogonal planes

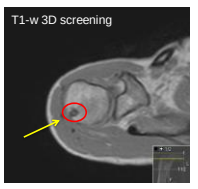
3 case studies

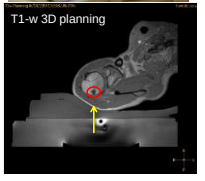
2 “easy”; 1 more difficult than usual

Patient 1

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



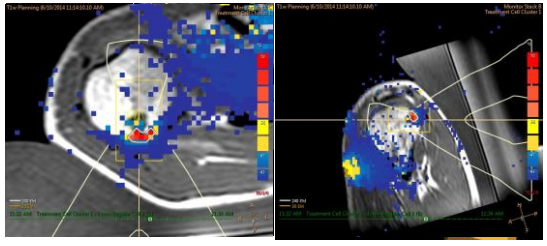


Patient positioning challenges:

- “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)

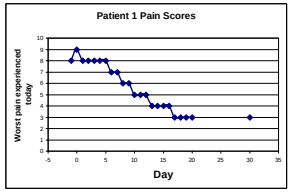
- 11 exposures at 1.2 MHz
  - "Near-field heating"
  - 3 x 4mm cells, 8 x 8mm cells, Powers 20-60W
- Treatment time: 1 hour



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



At Day 90, pain score 0 at rest and also 0 at maximal abduction (previously unable to abduct arm)

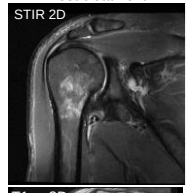
6 months post HIFU, pain response maintained

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

Post-treatment



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3 case studies

Patient 10

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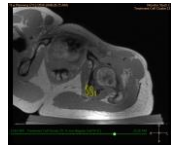
Clinical Case Studies: Patient 10


Planning row 1


Planning row 2


Planning row 5


Planning all rows coronal

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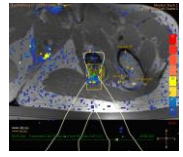
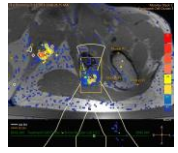
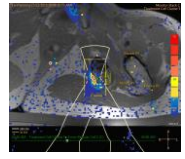
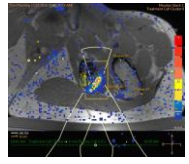
Clinical Case Studies: Patient 10


Test shot
30W
Cell 3


Cell 3
80W


Cell 5
90W


Cell 4
90W

55

3 case studies

Patient 5

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Results: Patient 5

www.nerveblock.ca

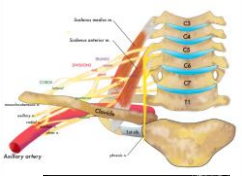
56 year old female with metastatic breast cancer

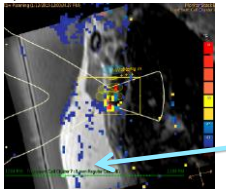
36 Gy Feb 2010

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, gelpad coupling (wedge required), breast reconstruction





Wedge of fat

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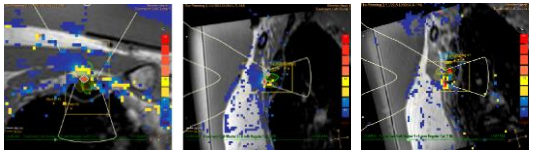
Patient 5 - Treatment

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



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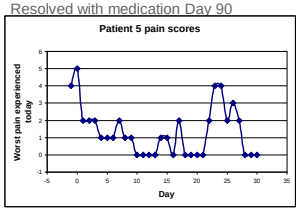
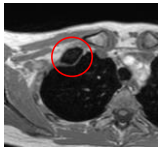
Patient 5 - Results

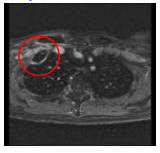
- Pain score reduced to 0 by Day 10
- Flare up of pain after Day 21, but returned to 0 by day 30, maintained at 0 at Day 60
- However, new neuropathic pain developed down right arm from Day 21 still ongoing at Day 60 (caused by posterior rib disease – compression)
- Resolved with medication Day 90



Day 30 T1W



Day 30 Thrive + Gad



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Results: Outcomes

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
11	✓ Day 7: PR ✓ Day 14: PR ✗Day 30: no data	Patient had rapidly progressive disease, developing neutropenic sepsis related to chest infection **Withdrawn before Day 30**
17	✓ Day 30: PR Day 60: due mid Sep	None to date

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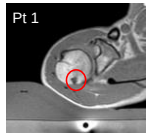
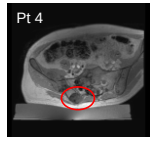
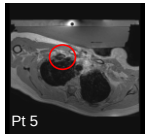
Results: Treatments

Patient	Tumour type	Target lesion	Number of sonications	Total energy delivered (KJ)	Treatment time (mins)
1	Breast	Humeral head	12	9.28 *	61.0
2	Breast	Anterior Iliac bone	17	20.75 *	121.0
4	Renal	Posterior Iliac bone	11	15.00	52.0
5	Breast	1st Rib	11	14.84 *	51.7
6	Breast	Posterior Iliac bone	17	43.41	78.5
7	Renal	Sacrum	15	29.00	79.8
8	Lung	2 lesions Iliac bone	25	56.07	101.5
9	Breast	Greater Trochanter	17	20.92	86.1
11	Breast	Greater Trochanter	17	27.64	73.0
17	Breast	Ischial tuberosity	17	27.75	48.9







Trial Conclusions I

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- 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

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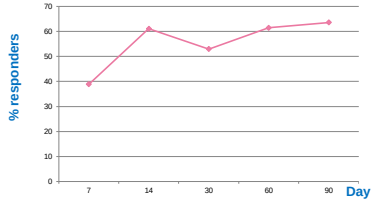
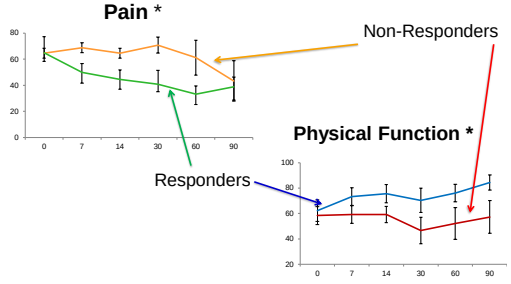
- Works well for right patient in the right circumstances
- Only small minority of patients are suitable : reviewed ~200; recruited 18; treated 10
- By time HIFU considered because of poor pain control, multiple lesions or patient too unwell for treatment. Oncologists increasingly refer these for re-treatment with radiotherapy
- Only small proportion of the painful lesion can usually be targeted.

Initial analysis of m/c trial

Response rate



Initial analysis of m/c trial



Conclusions

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

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