A new clinical multi-centre trial is underway to assess the effectiveness of pain palliation in bone metastases using the Philips Sonalleve MR-HIFU (high intensity focused ultrasound) system. Researchers at The Royal Marsden and The Institute of Cancer Research (ICR), London, are participating in the trial and this article outlines the clinical context and our experience on the study so far.

What is HIFU?
In the same way that sunlight can be focused using a lens, ultrasound can be focused using a concave transducer. When performed at high intensity, this focused ultrasound can be used therapeutically. Whereas diagnostic applications use ultrasound intensities ranging from 0.01-0.1W/cm², HIFU uses a range of 800-1500W/cm² to produce an effective ablation.

At the focus, the heating of the tissues is achieved through conversion of the mechanical energy of the sound wave into heat energy as it passes through tissue. To produce ablation, the temperature must be raised to around 60°C for more than one second. As the ultrasound beam has a low energy outside of the focus, it passes through other tissues without heating or damage.

MR-guided HIFU
Ultrasound-guided HIFU allows real-time visualisation of a target volume during therapy and has mostly been used for ablations in the prostate and some abdominal tumours. More recently, MR-guided (MRg) HIFU has become available and this has many obvious advantages. It provides higher resolution images for more accurate planning and targeting, real-time temperature monitoring and immediate post-treatment imaging to assess ablations.

Around 25,000 patients with uterine fibroids have been treated with MRg HIFU so far across the world. At The Royal Marsden and ICR we are working with its second major application in pain palliation of bone metastases.

The need for MRg HIFU in bone metastases
Some patients have residual pain after palliative radiotherapy and can’t be safely or effectively re-irradiated. Bone metastases can be extremely painful for several reasons:
- Bone destruction
- Increased sensory innervation (more nerve cell fibres)
- Sensitisation of those nerve cell fibres (nociceptors)
- Distension of the periosteum (fibrous membrane covering the bone).

The way that HIFU is thought to alleviate pain is by heating and ablating the nerves of the periosteum (thermal denervation) but there may also be an effect of tumour necrosis giving a reduced mass effect, thus relieving periosteal distension.

Our clinical trial
There have been a number of studies since 2007 that have shown evidence that MRg HIFU can be a safe and effective treatment option for palliation of pain from bone metastases. Purposely-designed equipment has now become available in the form of the Philips Sonalleve MR-HIFU. Using this system, we are involved in a trial that will evaluate HIFU as a treatment option in adult patients with painful bone metastases that have not responded to ‘standard of care’ treatments, including radiotherapy.

The eligibility criteria are very tight and the patient’s most painful lesion can be up to 8cm in its largest dimension and must be at least 1cm below the skin. The primary endpoint of the study is pain response 30 days post treatment. A successful outcome is achieved if there is a reduction in pain scores or reduction in analgesic use. Secondary endpoints include quality of life assessment, pain response at 60 and 90 days, and changes in lesion size.

Philips Sonalleve system
Our system was installed 18 months ago, when the ICR and The Royal Marsden were jointly made a Focused Ultrasound Centre of Excellence. It uses our four-year-old Philips 3.0T Achieva MR system in a standard dual-purpose scanning room. The Sonalleve table slides over the lowered MR table so we do not have to remove it. The Sonalleve’s ultrasound transducer sits in an oil bath beneath a window that is covered in a thin membrane. It can focus to a point 14cm above its centre and can be moved and angled to target a lesion as accurately as possible. It has 256 independent channels, an ultrasound frequency of either 1.2 or 1.45MHz and a maximum acoustic power of 300 watts. The single surface coil for imaging is used in conjunction with another coil that sits underneath the membrane.

Treatment planning
MR images are first acquired on the Achieva and then imported into the Sonalleve. A graphical representation of the proposed ultrasound beam allows us to visualise which tissues we are going to pass through as we target the lesion. A number of treatment cells can cover one lesion varying in size from 2-16mm in diameter. Their shape is determined by the way the transducer steers the beam in concentric circles, starting at the centre, to build up each treatment cell. The ultrasound intensity for each treatment cell can also be varied.

Preparing the patient
Prior to treatment, patients attend screening visits to establish their eligibility for the study, which includes physical examination, pain assessment and MRI scanning. On the treatment day, patients are admitted as day cases and seen by an anaesthetist. We know that patients experience pain as the treatment is delivered, so we need to manage this while making sure they stay still. After establishing IV access, the patient is helped into treatment position on the Sonalleve table while they are awake. We position the lesion directly over the transducer, having first placed a gel pad between the membrane and the skin. We then image to make sure we’re happy with the patient’s position before we administer conscious sedation.

Delivering treatment
Each element of the ultrasound treatment (sonication cell) is delivered separately for a duration of between 16 and 55 seconds, depending on the power and size of the cell. At the same time a temperature mapping MR sequence is run to check where the heat is building up. This is important because the actual shape of the treatment cell areas can vary from what we planned, depending on the acoustic prop-
erties of the surrounding tissues. For example, in bone an intact cortex reflects the ultrasound but we can exploit that to build up the heating where we want it – at the periosteum.

This temperature mapping in the soft tissues around the bone enables us to see how effective each sonification has been before moving on to the next one; or indeed terminating straightaway if heat builds up where we don’t want it. A cooling period of several minutes between each sonication avoids heat build-up in tissues outside the focus.

**Post treatment**

After treatment, immediate MR imaging takes place, while the patient is still in the treatment position. A physical examination includes checking the skin, and the patient will be seen by a pain specialist on the ward before they are discharged.

Patients are asked to keep a daily pain diary for 30 days at home. We contact them at days seven and 14 to do questionnaires, and invite them back in at day 30 to do more imaging and a physical examination. This is repeated at day 60 and day 90 if they are willing.

**Conclusion**

So far we have seen successful outcomes in the first patients treated at The Royal Marsden and are recruiting further candidates for the trial. We are carrying out a huge amount of additional study to develop better sequences in planning and monitoring our treatments, as well as pre-clinical, quality assurance and calibration work.

Our enthusiastic multidisciplinary team is now keen to expand into new clinical applications in patients who have exhausted other treatment options.

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**Case study**

A 51-year-old woman with metastatic breast cancer, treated in June 2014.

Despite previous radiotherapy, shoulder pain remained uncontrolled by analgesia which severely restricted movements in her right arm. She was unable to carry out basic functions such as opening cupboards, putting on a seatbelt and dressing herself. Baseline imaging showed a well-defined focal lesion in the humeral head at the insertion of the infraspinatus tendon. There was also a more diffuse area of disease that extended further down the humerus.

This patient’s treatment was delivered as 11 separate sonications of 3 x 4mm cells to cover the small focal lesion and 8 x 8mm cells to cover the more diffuse area. Power levels were quite low, ranging from 20-60W, in part because the lesion was quite superficial, but also because we were already seeing good heating at that level.

The treatment time, including cooling periods, was one hour plus set-up and coming off the table time. The patient was discharged after two hours.

This patient has completed the study (90 days) with a good outcome. Her pain score had reduced to less than half the baseline by day 30 with huge increase in mobility of her arm to perform basic functions. At day 90 she reported a pain score of 0 at rest as well as at maximum abduction. She is currently using no analgesia at all and has resumed an active life.

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**Targeting the lesion:**

**Temperature mapping during sonication:**

PRFS images acquired during sonication; red pixels indicate heating >57°C, indicative of achieving heating capable of ablating periosteal nerves.

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Figure 1