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Review Article

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

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Abstract

High-intensity focused ultrasound (HIFU) is a non-invasive technique that allows a small, well-circumscribed thermal lesion to be generated within a tissue target. Tissue destruction occurs due to direct heating within the lesion and the mechanical effects of acoustic cavitation. HIFU has been used in a broad range of clinical applications, including the treatment of malignancies, uterine fibroids and cardiac arrhythmias. Interest in the use of the technique to treat pain has recently increased. A number of painful conditions have been successfully treated, including musculoskeletal degeneration, bone metastases and neuropathic pain. The exact mechanism by which HIFU results in analgesia remains poorly understood, but it is thought to be due to localised denervation of tissue targets and/or neuromodulatory effects. The majority of studies conducted investigating the use of HIFU in pain are still at an early stage, although initial results are encouraging. Further research is indicated to improve our understanding of the mechanisms underlying this treatment and to fully establish its efficacy; however, it is likely that HIFU will play a role in pain management in the future. This narrative review provides a synthesis of the recent, salient clinical and basic science research related to this topic and gives a general introduction to the mechanisms by which HIFU exerts its effects.

Key words: cancer; High Intensity Focused Ultrasound, HIFU; pain, mechanism; pain, neuropathic; pain

The development, trialling and subsequent introduction into clinical practice of a novel treatment for pain is a rare occurrence. Here we describe high-intensity focused ultrasound (HIFU), a non-invasive thermal ablation technique that represents an emerging and potentially efficacious intervention for pain, and review the literature relevant to its clinical application.

The potential for HIFU to ablate selected anatomical targets precisely makes the modality suitable for adoption in the field of pain. Therefore interest in the use of HIFU to alleviate pain is increasing and, correspondingly, a number of case studies, case series and trials have recently been published. In addition, clinical trials encompassing a range of different painful conditions are actively recruiting participants. In order to give an overview of these individual publications, each broad area of pain investigated is summarized and the salient features of clinical studies conducted in a variety of painful conditions is provided. A particular focus is on the treatment of painful bone metastases, the clinical area where the most robust evidence exists. We also outline the technical requirements of specific HIFU treatments and elaborate on the current limitations and potential future developments of this novel intervention for painful conditions.

Methodology

We conducted a PubMed literature search for all types of articles using the search terms ‘focused ultrasound & pain’, ‘HIFU & pain’,

'high-intensity focused ultrasound & pain', 'MRgFUS & pain', 'focused ultrasound & pain', 'HIFU & analgesia', 'high-intensity focused ultrasound & analgesia', 'MRgFUS & analgesia', 'focused ultrasound & neuropathic', 'HIFU & neuropathic', 'high-intensity focused ultrasound & neuropathic', 'MRgFUS & neuropathic', 'focused ultrasound & bone metastases', 'HIFU & bone metastases', 'high-intensity focused ultrasound & bone metastases', 'MRgFUS & bone metastases', 'focused ultrasound & nerve', 'HIFU & nerve', 'high-intensity focused ultrasound & nerve', 'MRgFUS & nerve', 'focused ultrasound & spine', 'HIFU & spine', 'high-intensity focused ultrasound & spine' and 'MRgFUS & spine'. Additional articles were identified by manually searching the references of previously identified publications. Articles not written in English were not considered.

High-intensity focused ultrasound

Ultrasound comprises acoustic pressure waves in the kilohertz to megahertz frequency range. Like any energy wave, ultrasound can be focused in a fashion analogous to light being focused by a magnifying glass. The high-intensity focal spot characteristic of HIFU is produced using a plane transducer and an acoustic lens focusing bowl, which concentrate acoustic energy and enable the position of the thermal lesion to be adjusted. Figure 1 shows schematically an extracorporeal HIFU source being used to target a deep-seated tissue volume.

At megahertz frequencies, the focus produced may only be a few cubic millimetres in size, permitting high precision of the ablative energy at the selected target.[1] At the focal spot, localised areas of high temperature (60–80°C) are generated very rapidly (typically 1–20 s), resulting in cell damage and subsequent tissue destruction due to both protein denaturation and coagulation necrosis.[2] Multiple sonications can be performed in a relatively short time, although care must be taken not to inadvertently cause heating in the wider prefocal areas of tissue that may overlap during adjacent focal sonications.

In addition to the thermal effects of HIFU, a secondary mechanical phenomenon, acoustic cavitation, can occur in tissue wherever the acoustic pressure exceeds the relevant threshold level. Acoustic cavitation occurs because of the formation, rapid oscillation and subsequent collapse of bubbles within tissues. This occurs first in the focal region, contributing to damage,

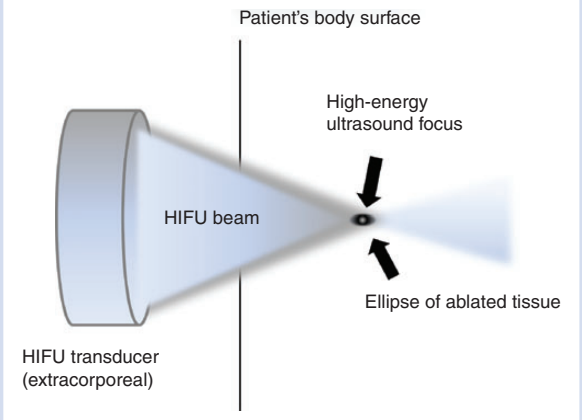

Fig 1 Diagram showing the extracorporeal generation of HIFU and its use to form a thermal lesion within a tissue target.

albeit in a less deterministic (and less well-understood) manner than that observed with localised hyperthermia.[3]

Damage to tissues surrounding the focus is avoided during treatment with HIFU since the ultrasound wave passing through intervening tissues is of lower acoustic energy and does not, under normal conditions, result in the production of either thermal or mechanical effects. Adverse events associated with HIFU treatment are rare; transitory effects such as fever, increased pain and localised skin reactions such as oedema and erythema at the site of treatment have been reported. The most important side effect is a skin burn that occurs when acoustic coupling between the transducer and skin is inadequate because of air entrapment, leading to defocusing of the beam and deposition of energy at the skin surface. The nature and incidence of adverse events is influenced by the nature of the target and the type of HIFU device utilised.[4]

The potential of HIFU to ablate tissues has been recognised since its first description in the early 1940s when experimental equipment was used to lesion a sample of liver *in vitro*.[5] Initially, however, the lack of suitable methods to precisely target HIFU hampered its introduction into the clinical environment. The development of ultrasound guidance (USgFUS) and later MRI guidance (MRgFUS) has rectified this problem and the clinical use of HIFU has expanded. MRgFUS has some distinct advantages over USgFUS inasmuch as it enables not only the precise planning and targeting of the therapy, but, by using MR thermometry to monitor tissue temperature, the ablated areas may be defined in real time, avoiding damage to adjacent structures.[6]

Focused ultrasound is now used in a wide variety of routine clinical applications. These include the ablation of malignant prostate tumours;[7 8] the treatment of pancreatic,[9] renal[10] and breast cancer;[11] the ablation of non-resectable liver tumours and metastases[12 13] and the destruction of uterine fibroids.[14] Ongoing research is addressing the application of HIFU in a number of additional clinical fields. These include neurology, where HIFU can be used to stimulate or ablate areas of the brain that are challenging to reach using traditional neurosurgical approaches;[15 16] cardiology, where dysrhythmias may be terminated through selective endocardiac ablation;[17] and obstetrics, with intrauterine procedures performed on the developing foetus.[18] The use of HIFU in pain control is, in comparison, less well developed, but nonetheless is emerging as an important application of the technology.

MRgFUS treatments occur within the radiology suite. The equipment required to administer MRgFUS comprises a HIFU transducer and an adapted MRI machine (Fig. 2A). The HIFU transducer may either be portable or fixed within the MRI table upon which the patient being treated lies. Gel pads are used to ensure a gas-free interface between the transducer and the patient's skin, minimising the risk of energy deposition and subsequent skin burns. The number, size and positioning of the individual sonications are determined from planning MRI scans conducted prior to the HIFU treatment (Fig. 2B). During sonication, real-time MR thermometry gives an indication of the degree and location of tissue heating (Fig. 2C). The application of an MRgFUS treatment relies on close multidisciplinary cooperation between radiologists and radiographers (who plan and administer the treatment), the patient's clinicians (who identify potential patients and provide post-sonication follow-up) and anaesthetists and operating department practitioners (who provide the anaesthetic support required to undertake the procedure).

Typical treatments are conducted on a day-case basis, with patients admitted on the morning of the procedure and,

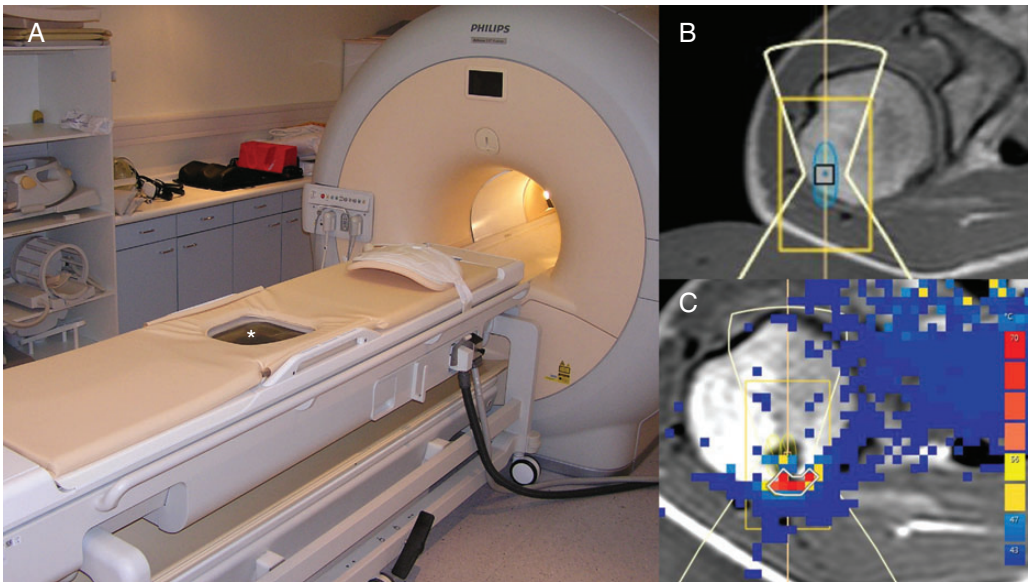

Fig 2 (A) MRI scanner with HIFU transducer located in patient table (*). (B) Planning scans allow a sonication matrix to be accurately targeted prior to treatment. (C) Real-time MRI thermometry displays tissue temperatures during treatment, providing confirmation of the sonication site.

following sonication, which may last 1–2 h, discharged home once standard day-case criteria are met.[19] Anaesthetic requirements vary between patients and are influenced by the anatomical position of the target being sonicated. The actual treatment process itself may be transiently painful due to localised tissue heating and a number of anaesthetic approaches have been adopted, including sedation, local anaesthetic infiltration, general anaesthesia and neuraxial block.[20] Anaesthetic provision for MRgFUS treatment is potentially challenging due its remote-site nature, the equipment and access restrictions imposed by the presence of an MRI magnet and the possible frailty of treated patients. However, it does share features with a number of other commonly encountered remote-site anaesthetic environments such as interventional cardiology and vascular suites, allowing relatively standardised approaches to be adopted and guidelines to be followed.[21]

HIFU in painful conditions

Mechanism

The actual mechanism by which HIFU exerts its effects in painful conditions remains poorly understood. It is likely, however, that thermal effects result in localised denervation of the target, reducing the density of nociceptive fibres present. This hypothesis is reinforced by evidence that unmyelinated nerve fibres are particularly vulnerable to (non-HIFU) thermal injury[22] and that direct sonication of neuronal structures *in vivo* results in demyelination and neural degeneration.[23] At lower temperatures, reversible blockade of nerve action potential conduction occurs,[24 25] with unmyelinated fibres again proving more susceptible to this phenomenon.

The application of focused ultrasound to both the central nervous system[26] and peripheral nerves[27] in animal and human subjects has been shown to induce transient neuromodulation, resulting in changes in neuronal excitation levels. The precise mechanism has not been fully elucidated, but it is postulated that it causes temporary distortion of the cell membrane, thereby altering the function of stretch-activated ion channels present on the surface of neurones.[28] HIFU may also result in acoustic pressure and cavitation-driven changes in ion flux through both existing ion channels and defects formed in the neuronal membrane, thereby generating action potentials.[29] It is therefore possible that HIFU exerts its effects through more than one distinct mechanism, summarised in Figure 3.

It has been suggested that HIFU may have a role in the detection, diagnosis and investigation of neuropathic pain,[30] and recent studies have attempted to elaborate on this theme. Paw withdrawal in response to focused ultrasound stimulation was assessed in a rat tibial nerve neuroma model of neuropathic pain by McClintic and colleagues.[31] This group demonstrated the ability of focused ultrasound to preferentially stimulate neuropathic tissue when compared with normal tissue. Results from similar work in a rat sciatic ligation model of neuropathic pain[32] mirrored these findings, with a significantly lower paw withdrawal threshold to focused ultrasound stimulation in lesioned rats when compared with both a control group and a 'sham surgery' group. This work raises the possibility of HIFU being used in the detection, delineation and quantification of neuropathic tissue in the future.

Musculoskeletal pain

Back pain

Facet joint arthropathy

Back pain represents a significant health and economic burden on society and the use of HIFU has been investigated in this condition. To date, a single case series has been published investigating the use of MRgFUS in the treatment of low back pain caused by facet (zygapophyseal) joint arthropathy.[33] A total of 18 patients were treated with sonications of multiple lumbar facet

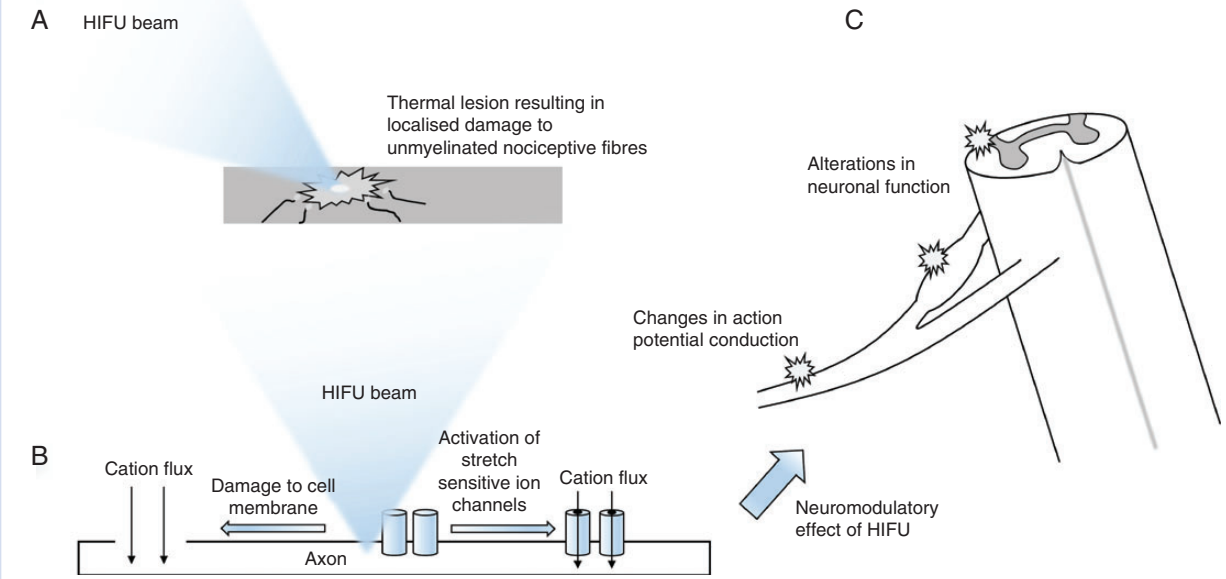

Fig 3 Postulated mechanisms through which HIFU exerts its analgesic effects. (A) Localised tissue heating causes thermal damage to unmyelinated nociceptive fibres present close to the painful target. (B) Mechanical effects on the neuronal membrane and cytoskeleton activate stretch-sensitive ion channels and create membrane defects that alter membrane potential, (C) leading to changes in neuronal excitability, action potential propagation and ultimately nerve function.

joints (mean number 5, range 2–8), with treatment lasting on average 188 min. Ten patients received sedation during the procedure and there were no reported adverse events. In 13 patients followed to 6 months, post-treatment reduction in average numerical rating scale (NRS) pain scores to 3.87 from a pretreatment average of 6.42 (60.2% reduction) was observed. This was accompanied by a 45.8% improvement in the Oswestry Disability Questionnaire score and a 61.9% reduction in the Brief Pain Inventory interference score. The results of this small series compare favourably with the outcomes observed with lumbar facet intra-articular injections, for which there is only moderate (level III) evidence of long-term efficacy.[34]

Discogenic back pain

A modest amount of work has also been undertaken exploring the use of focused ultrasound in low back pain caused by intervertebral disc herniation. *In vitro* 'proof of concept' experiments have shown that HIFU is effective in producing localised heating resulting in protein degradation and subsequent disc shrinkage.[35] However, the anatomical complexity of the spine means that achieving uninterrupted sonication of intervertebral discs is difficult. To overcome this challenge, a minimally invasive approach has been proposed, using a small probe inserted percutaneously to abut the disc.[36] This study has progressed from *in vitro* proof of concept studies to *in vivo* animal work, with Forslund and colleagues[37] successfully performing percutaneous thermolesioning of porcine lumbar intervertebral discs. Post-mortem histological analysis of tissues showed that disruption of collagen fibres occurred within the area of disc lesioning and that, importantly, no thermal damage to nerve roots was observed. Despite these promising findings from preclinical work, no trials of HIFU in the treatment of discogenic low back pain in humans have so far been reported.

Joint pain due to osteoarthritis

Another common cause of pain in the ageing population is large joint osteoarthritis, where the use of focused ultrasound has also been investigated. Izumi and colleagues[38] describe the novel use of MRgFUS to alleviate pain experienced by patients with advanced osteoarthritis of the knee joint awaiting knee arthroplasty. MRgFUS was used to sonicate osteophytes inferior to the medial tibial plateau. The procedure was performed solely under analgesia provided by infiltration of the periosteum with local anaesthetic. No intraprocedural complications were reported and cases took on average of 74 min to complete. A post-treatment reduction in visual analogue scale (VAS) scores on walking at 3, 10 and 28 days was recorded in six of eight cases, and four of these experienced attenuation of pain at 6 months. In addition, a statistically significant increase in pressure pain thresholds (PPTs) at sites close to sonication was observed in responders but not in non-responders, suggesting denervation of hypersensitive pressure-responsive nerve fibres in this group. No attempt was made to assess changes in functional level and quality of life scores in this small study.

Although there are no other published studies investigating HIFU in osteoarthritis, its use in treating the pain caused by osteoid osteomas (a painful benign bone tumour) has been explored. A small pilot study[39] in six patients demonstrated notable reductions in pain scores following osteoma sonication, from a pretreatment average of 7.9 (SD 1.4) to 0 (SD 0) on an 11-point VAS at 1, 3 and 6 months, accompanied by a corresponding reduction in analgesic requirements. A larger follow-on study of 29 patients conducted by the same investigators reinforced these findings, with reductions in self-reported pain scores on a VAS at 12 months from a mean of 8 (SD 1) pretreatment to 1 (SD 2) ($P<0.001$).[40] There were no reported adverse events or complications in either study.

Table 1 Summary of research published to date investigating the use of focused ultrasound to treat pain arising from bone metastases. [a]Patient demographics not detailed. [b]No comment on the statistical significance of this finding. [c]Details of reduction in analgesia intake not included in the paper. [d]Fifty-one adverse events in the sonication group comprising 36 incidents of pain during sonication, 9 incidents of positioning pain, 5 incidents of post-procedural pain, 2 episodes of fatigue, 2 incidents of neuropathy in the leg, 2 fractures, 2 skin burns, 1 febrile episode, 1 myositis, 1 skin rash and 1 episode of numbness. [e]The design of this study is described in more detail in the main text. BPI: Brief Pain Inventory; IQR: interquartile range; MEDD, morphine equivalent dose; NRS: numerical rating scale; SF-36: 36-item Short Form Health Survey; VAS, visual analogue scale

Study	Sample	Patient characteristics	Intervention	Setting	Outcome measures	Follow-up	Dropout rate	Results	Adverse events
Catane *et al.*,[48] 2007, case series, level 4 evidence	13 patients[a]	Bone metastases from a variety of primary cancers, including breast and prostate	MRgHIFU of single painful lesion	Two centres: one in Israel and one in Germany	Change in pain recorded on 11-point VAS Analgesia requirements	Total 6-month follow-up	2 patients	Reduction in mean pain scores from 5.4 to 1.65 at 1 month[b] Reduced analgesia requirements[c]	None reported
Gianfelice *et al.*,[49] 2008, case series, level 4 evidence	11 patients (7 female, 4 male), mean age 58.6 yr	Painful metastases of non-weight-bearing bones from mainly breast and renal primaries	MRgHIFU of single painful lesion (one patient with two lesions sonicated)	Single centre, Canada	Change in pain recorded on 11-point VAS Analgesia requirements Quality of life (SF-36)	Total 3-month follow-up	0 patients	Reduction in mean pain scores from 6.0 (SD 4–9) to 0.5 (SD 0–1) at 3 months ($P<0.01$) Reduction or cessation of analgesia intake[c] Minimal change on SF-36	None reported
Liberman *et al.*,[50] 2009, case series, level 4 evidence	31 patients (16 female, 15 male), mean age 61.0 yr	Bone metastases from a variety of primary cancers, including breast, prostate and renal	MRgHIFU of a single painful lesion	Three centres: one each in Israel, Canada and Germany	Change in pain recorded on 11-point VAS Analgesia requirements (MEDD)	Total 3-month follow-up	2 patients	Reduction in mean pain scores from 5.9 (IQR 3.5–8.5) to 1.8 (IQR 0–8) at 3 months ($P<0.003$) 67% of patients reduced opioid intake[b]	None reported
Li *et al.*,[52] 2010, case series, level 4 evidence	25 patients (12 female, 13 male), mean age 39.6 yr	Bone metastases from a variety of primary cancers, including lung, liver and renal Primary osteosarcoma	USgFUS of a single painful lesion (mean 2.29 sessions)	Single centre, China	Change in pain score on a 3-point numerical rating scale (0=no pain, 3=worst pain)	Not detailed in the paper	0 patients	Reduction in pain scores (out of 3) from 1.84 (SD 0.85) prior to treatment to 0.12 (SD 0.33) after treatment ($P<0.001$)	Skin burns occurred in 14 patients, low grade fever in 4 patients
Hurwitz *et al.*,[54] 2014, randomised, placebo-controlled single-blind trial[e] Level 1b evidence	147 patients (89 female, 58 male), mean age 60.7 yr	Bone metastases from a variety of primary cancers the majority being breast and prostate	MRgHIFU of a single painful lesion	Multicentre; 17 sites in USA, Canada, Israel, Italy and Russia	Change in pain recorded on 11-point VAS Analgesia requirements (MEDD) Quality of life (BPI) Treatment-related adverse events	Total 3-month follow-up	26 patients in sonication arm did not complete 3-month follow-up. No subjects excluded from analysis	64% of subjects in sonication arm of study were 'responders' at 3 months (defined as a 2 point reduction from baseline in pain on the NRS or <25% increase in MEDD from baseline) ($P<0.001$)	51 total adverse events reported in sonicated patients[d]
Huisman *et al.*,[53] 2014, case series, level 4 evidence	11 patients (4 female, 7 male), mean age 67.7 yr	Bone metastases from a variety of primary cancers, including lung, liver, renal and breast	MRgHIFU of a single painful lesion	Single centre, Holland	Change in pain recorded on 11-point VAS Analgesia requirements (MEDD)	Total 1-month follow-up	2 patients between day 3 and 1-month follow-up	Day 3, decrease in pain score from median of 8 (IQR 6–9) to 6 (IQR 4–8) ($P<0.045$), 1 month decrease of median pain score to 4 (IQR 1–5) ($P<0.028$)	First-degree skin burn in one patient

Table 2 Summary of research published to date on the use of focused ultrasound in a range of painful conditions. See the text for further details of these studies. [a]No formal pain score used. [b]Preliminary data; study continued and described in full below.[61] [c]Participant demographics not detailed in paper. BPI: brief pain inventory; IQR: interquartile range; ODQ: Oswestry disability questionnaire; PPTs: pressure pain thresholds; VAS: visual analogue scale

Study	Sample	Patient characteristics	Intervention	Setting	Outcome measures	Follow-up	Dropout rate	Results	Adverse events
Weeks *et al.*,[33] 2012, case series, level 4 evidence	18 patients treated, 13 followed up (8 female, 5 male), mean age 48.2 yr	Low back pain attributed to lumbar facet joint arthropathy	MRgFUS of 2–8 lumbar facet joints (mean of 5)	Single centre, UK	Change in pain recorded on 11-point VAS BPI and ODQ scores	Total 6-month follow-up	5 patients	60.2% reduction in mean pain scores at 6 months 61.9% reduction in BPI score 45.8% improvement in ODQ score	None
Izumi *et al.*,[38] 2013, case series, level 4 evidence	8 patients (6 female, 2 male), mean age 78 yr	Advanced osteoarthritis of knee medial compartment	MRgFUS of osteophytes	Single centre, Japan	Change in pain on walking recorded on 100-mm VAS PPTs[c] measured with algometer	Total 12-month follow-up	None	72.6% reduction in mean pain scores at 6 months Significant increase in PPTs at treatment sites	None
Napoli *et al.*,[39] 2013, case series, level 4 evidence	8 patients (2 female, 6 male), mean age 24.8 yr	Painful osteoid osteoma	MRgFUS of osteoid osteoma	Single centre, Italy	Change in pain recorded on 11-point VAS Analgesia requirements	Total 6-month follow-up	None	Reduction in mean pain scores from 7.9 (SD 1.4) to 0 (SD 0) at 1, 3 and 6 months (P=0.003) All patients stopped analgesic intake	None
Geiger *et al.*,[40] 2014, case series, level 4 evidence	29 patients (9 female, 20 male), mean age 25 yr	Painful osteoid osteoma	MRgFUS of osteoid osteoma	Three centres, Italy	Change in pain recorded on 11-point VAS Pain score 0/10=complete response Reduction in pain score of >2 points=partial response	Total 12-month follow-up	None	Complete response at 12 months in 26 (90%) patients Partial response in 3 patients [mean VAS 5 (SD 0) points] Significant reduction in pain scores (P<0.001)	None
Machtinger *et al.*,[58] 2008, case report, level 4 evidence	1 patient (27-yr-old female)	Recurrent carcinoma of the cervix	MRgFUS of the cervix (2 sonications)	Single centre, Israel	Verbal reports of pain severity[a] Analgesia requirements	Total 4-month follow-up	None	'Pain free' for 4 months after treatment 50% reduction in daily opioid intake	None
Wu *et al.*,[59] 2003, case series, level 4 evidence	13 patients (4 female, 9 male), mean age 56.3 yr	Advanced, biopsy-proven renal malignancy	USgFUS of the target renal tumour	Single centre, China	Verbal reports of pain severity[a]	Median follow-up 18 months	1 patient lost to follow-up at 6 months	'Severe renal pain' relieved in 90% of patients treated	1 minor skin burn

Continued

Table 2 Continued

Study	Sample	Patient characteristics	Intervention	Setting	Outcome measures	Follow-up	Dropout rate	Results	Adverse events
Martin *et al.*,[60] 2009, case series[b], level 4 evidence	9 patients[c]	Neuropathic pain, central origin *n*=3, peripheral *n*=6	MRgFUS ablation of the medial thalamus	Single centre, Switzerland	Verbal reports of pain severity[a]	Day 2 post-MRgFUS	None	Mean pain relief at day 2 post-ablation of 68% (IQR 30–100%)	None
Jeanmonod *et al.*,[61] 2012, case series, level 4 evidence	12 patients[c]	Neuropathic pain, variety of causes (detailed in text)	MRgFUS ablation of the medial thalamus	Single centre, Switzerland	Change in pain recorded on 100-mm VAS	Total 12-months follow-up	2 patients (completed 3-month follow-up)	Reduction from pre-procedure VAS score of 59.5 to 34.3 at 3 months and 35.3 at 12 months	1 patient had intracerebral haemorrhage

Cancer pain

Pain from bone metastases

Approximately one-third of patients with bone metastases experience pain,[41] which usually manifests as a background gnawing pain accompanied by severe episodic pain commonly triggered by weight-bearing or movement.[42] A variety of treatment options for bone metastases exist, including drugs, radioisotopes and radiotherapy, however, HIFU is not currently part of the treatment arsenal.[43] The relatively benign nature of focused ultrasound when compared with the alternative, established treatment (ionising radiation) for painful bone metastases has led to interest in its use to treat these lesions. The pain from bone metastases arises due to a combination of factors, including the release of chemical mediators, microfractures and increased pressure within the bone resulting in stretching of the periosteum.[44] The effect of these painful factors is amplified by the pathological sprouting of nociceptive nerve fibres in the periosteum associated with the metastases.[45 46] It is thought that HIFU reduces pain by thermal denervation of the bone and periosteum, although debulking of the metastases may also contribute. The use of MRgFUS to treat bone metastases allows sonication cells to be accurately placed to heat the cortical margin of the lesion and provides near real-time monitoring of tissue temperature. The higher absorption of acoustic energy by bone when compared with soft tissue means that fewer sonications are required to achieve tissue heating, permitting rapid treatment.[47]

Pilot studies investigating the use of focused ultrasound in bone metastases have demonstrated its efficacy and safety, albeit in small numbers of patients in most reports.[48–53] A larger recent placebo-controlled study also demonstrated the efficacy of MRgFUS for pain from bone metastases that had failed control by standard treatments.[54] A 3:1 randomisation of 142 patients to either the intervention or placebo arms allowed subjects allocated to the placebo arm to cross over into the treatment arm of the study if they requested 'rescue treatment' within the 3-month follow-up period. Participants were deemed to be 'responders' if MRgFUS was found to be superior to placebo at 3 months, with 64.3% of participants in the intervention arm responding to treatment compared with 20% in the placebo arm [$P<0.001$, response being defined as a reduction in worst pain rating on the NRS of ≥2 points from baseline and analgesic requirements assessed using the morphine equivalent daily dose (MEDD) not increasing by >25% from baseline]. Interestingly, 17 patients crossed over from the placebo to the intervention arm during follow-up and were treated with MRgFUS; 70.7% of these patients were deemed to be treatment responders, although these data were not included in the primary efficacy analysis. Statistically significant differences at 3 months were also observed in worst pain on the NRS and quality of life scale (from brief pain inventory scores). The various feasibility studies and this randomised control trial are summarised in Table 1; Table 2 details work investigating the use of HIFU in other painful conditions. Investigation into the use of MRgFUS to treat painful bone metastases is ongoing, with a number of multicentre studies currently actively recruiting participants (http://www.clinicaltrials.gov).

Pain from primary tumours

HIFU has been used successfully to reduce the pain associated with a number of primary tumours. One of the most common applications is in the palliation of inoperable pancreatic cancer,[55] which is often associated with severe, intractable pain. A recently published systematic review by Keane and colleagues[56]

Table 3 Summary of technical parameters of focused ultrasound used to treat a range of painful conditions. Note the absence of certain values for a number of studies. This is due to the current lack of a standardised reporting doctrine for HIFU parameters

Study	HIFU type	Frequency	Treatment time	Focal peak intensity	Energy	Temperature achieved
Catane *et al.*,[48] 2007, cohort study	MRgHIFU	1.0–1.5 MHz	80 min (avg)	Not detailed in paper	1025 J (avg)	Not detailed in paper
Gianfelice *et al.*,[49] 2008, cohort study	MRgHIFU	1.0–1.5 MHz	28–103 min	Not detailed in paper	466–1853 J	>65°C
Liberman *et al.*,[50] 2009, cohort study	MRgHIFU	1.0–1.5 MHz	22–162 min, 66 min (avg)	Not detailed in paper	1135 J (avg)	Not detailed in paper
Li *et al.*,[52] 2010, cohort study	USgHIFU	0.8 MHz	27.5–647.6 min	70–160 W cm^{-2}	Not detailed in paper	Not detailed in paper
Hurwitz *et al.*,[54] 2014, randomised, placebo-controlled, single-blind trial	MRgHIFU	Not detailed in paper	176 (SD 57) min (scanner time) 83 (SD 43) min (sonication time)	Not detailed in paper	Not detailed in paper	65–85°C
Huisman *et al.*,[53] 2014, cohort study	MRgHIFU	1.2 MHz	20–73 min, 45 min (avg)	80–190 W cm^{-2}	3000 J (max)	>55°C
Weeks *et al.*,[33] 2012, cohort study	MRgHIFU	1.0–1.5 MHz	188 min (avg scanner time), 97 min (avg sonication time)	Not detailed in paper	450–750 J, 600 J (avg)	Not detailed in paper
Izumi *et al.*,[38] 2013, cohort study	MRgHIFU	1.0–1.5 MHz	Not detailed in paper	Not detailed in paper	Not detailed in paper	>60°C
Napoli *et al.*,[39] 2013, cohort study	MRgHIFU	1.0–1.5 MHz	40 (SD 21) min (scanner time), 12.7 (SD 5) min (sonication time)	Not detailed in paper	866 (SD 211) J	65°C
Geiger *et al.*,[40] 2014, cohort study	MRgHIFU	1.0–1.5 MHz	13 (SD 5) min	Not detailed in paper	1180 (SD 736) J	65°C
Machtinger *et al.*,[58] 2008, case report	MRgHIFU	1.0–1.5 MHz	<3 h	Not detailed in paper	Not detailed in paper	Not detailed in paper
Wu *et al.*,[59] 2003, cohort study	USgHIFU	0.8 MHz	1.5–9 h, 5.4 h (avg)	5000–20 000 W cm^{-2}	Not detailed in paper	Not detailed in paper
Martin *et al.*,[60] 2009, cohort study	MRgHIFU	1.0–1.5 MHz	Not detailed in paper	Not detailed in paper	12 000 J (max)	51–60°C
Jeanmonod *et al.*,[61] 2012, cohort study	MRgHIFU	1.0–1.5 MHz	Not detailed in paper	800–1200 W cm^{-2}	12 000 J	53 (3.3)°C

comprehensively summarises the findings of 14 prospective studies, the bulk of which were undertaken in China. A total of 659 patients were treated with MRgFUS, and the majority included change in pain scores as an outcome measure. On average, 86.4% of patients reported a reduction in pain scores following treatment, with minimal complications. However, these favourable results are from studies that are predominantly unblinded and did not include placebo or sham treatments. A subsequent single-centre cohort study of six patients with non-resectable pancreatic cancer also demonstrated notable reductions in pain scores (from 7 to 3) 1 week after treatment (P=0.017) and all but one patient completely stopped analgesic medication.[57] Interestingly, tumour volumes remained stable post-treatment, with no tumour regrowth in five of the six patients.

Several published case reports describe impressive reductions in pain emanating from other isolated primary malignancies, including carcinoma of the cervix[58] and renal malignancies.[59]

Neuropathic pain

The use of HIFU in the treatment of neuropathic pain has also been investigated. Transcranial MRgFUS is technically feasible and the ability to safely and accurately ablate cerebral structures has been demonstrated in the clinical environment.[15]

Martin and colleagues[60] were the first to describe the MRgFUS treatment of both central and peripheral intractable neuropathic pain by ablating the medial thalamus of patients due to undergo central lateral thalamotomy. A total of nine patients were treated and preliminary mean reductions in pain scores of 68% were demonstrated. This group then continued to treat a further 12 patients with chronic neuropathic pain caused by a range of conditions, including post-herpetic neuralgia, avulsion of the brachial plexus and lumbar nerve root compression. In those patients in whom an adequately sized lesion in the thalamus was judged to have been created (n=9), a reduction from preoperative mean VAS scores of 59.5/100 to 34.3/100 at 3 months and 35.3/100 at 1 yr (n=8) occurred following treatment. In addition, the use of analgesic drugs in five of the eight patients had ceased entirely at the 1 yr time point, although the authors urged caution in drawing conclusions from this surrogate marker of pain levels. Adverse events were limited to one patient who developed an intracerebral haemorrhage at the target in the thalamus that resulted in persistent neurological impairment at 1 yr.

The use of transcranial MRgFUS sonication for trigeminal neuralgia has been explored in a cadaveric feasibility study in which the root entry zone (REZ) and cisternal segments of six nerves were targeted.[62] No evidence of aberrant heating of surrounding structures was demonstrated. Further clinical

Table 4 Summary of the relative advantages and disadvantages of MRgFUS when used as a treatment for pain

Advantages of MRgFUS	Disadvantages of MRgFUS
Small, well-circumscribed lesion produced	Requires MRI scanner and specialist transducer equipment with associated cost implications
Precise targeting of lesion possible with MRI guidance	Requires training of staff to administer treatment
MR thermometry permits therapy monitoring in real time	Anaesthetic input (often) required during sonication
Non-invasive treatment with a good safety profile	Remote-site anaesthetic environment with added complication of presence of MRI magnet
Appears efficacious in published studies	Exact mechanism of action in pain states not fully elucidated
No use of ionising radiation and associated risk of radiotoxicity	Evidence base for efficacy in painful conditions is predominantly limited to level 4 evidence

work that builds on these findings of transcranial MRgFUS is warranted.

Discussion

Focused ultrasound is emerging as a viable treatment option for painful bone metastases and other musculoskeletal disorders. Furthermore, its use is being actively investigated in a range of painful conditions that differ both in phenotype and underlying pathological process. The potential benefits of the use of MRgFUS to target specific pain generators or structures involved in the transmission of pain signals are apparent, with the safe generation of precise, well-circumscribed thermal lesions possible. This precision, and the quality of the monitoring of the lesion as it is generated, is likely to improve as the image-based technology utilised in the treatment progresses and operators gain experience with its use.[63]

HIFU is a safe treatment; adverse events, although possible, are uncommon, with the vast majority of patients described in the various studies outlined above experiencing uncomplicated treatments. The majority of adverse events that are reported are localised minor burns arising at the site of the window through which the HIFU beam passes at the skin surface. These often arise due to the presence of air bubbles from incomplete 'degassing' of the skin–transducer interface. Again, it is conceivable that as HIFU technology improves and as operator experience increases, adverse events are likely to become even less common.

Another beneficial feature of HIFU treatment for pain is the relative rapidity (within a day of sonication) of the onset of pain relief and its duration, with many patients exhibiting benefit 1 yr after treatment; notably, these features appear to transcend the type of painful condition treated. Interestingly, many of the patients treated in preliminary studies had pain that had proved refractory to treatment with more traditional methods, thereby increasing the therapeutic value of MRgFUS as a 'rescue' or adjuvant therapy. In cancer patients (who make up a significant number of participants in clinical HIFU studies), marked reductions in opioid intake have been possible following sonication of painful lesions. This opioid-sparing aspect of HIFU is clinically relevant, as evidence exists that opioids may influence rates of recurrence or metastasis formation,[64 65] therefore any opioid dose reduction achieved in these patients is potentially beneficial.

The limitations of HIFU as a treatment for pain revolve around its application in the clinical environment. Complex equipment and well-trained staff are required to perform MRgFUS, and the positioning of patients within the MRI scanner to enable unobstructed passage of the HIFU beam to the target can sometimes prove challenging. In addition, the majority of patients treated for painful conditions have required sedation, general anaesthesia or regional local anaesthetic blocks to tolerate the pain that may arise during treatment, both from the thermal effects and the fact that the patient often needs to lie on the painful site. These factors all result in the cost per treatment being greater than more traditional nerve blocks, which may restrict its use to specialist centres. The relative advantages and disadvantages of MRgFUS when used to treat pain are outlined in Table 4.

Further basic science and clinical research regarding HIFU and pain is warranted. Our understanding of the exact mechanisms by which HIFU exerts it analgesic effects remains somewhat incomplete and a greater appreciation of what occurs in nociceptive pathways following sonication at the cellular level would be beneficial. Clinically, although the effects of HIFU in pain have been encouraging, the majority of the results have come from small observational trials, often uncontrolled and the majority non-blinded. In the future, larger studies with robust methodological design are needed, not only to further delineate the analgesic efficacy of the treatment, but to enable the detection of rarer adverse events that smaller studies may not have been adequately powered to show.

High-intensity focused ultrasound is an emerging, novel and potentially effective treatment for certain painful conditions, with a good safety profile and, in the clinical literature published to date, encouraging efficacy. The ability to selectively and accurately lesion structures in both the peripheral and central nervous systems in a minimally invasive fashion distinguishes it from existing treatments at the disposal of pain clinicians, who currently rely on the introduction of a needle, catheter or probe in close proximity to the target.

Ongoing developments in the technology used to deliver treatment and an expansion in the clinical research supporting its adoption make it likely that HIFU will have a role in pain management in the future.

Authors' contributions

The authors (M.R.D.B., J.E.W., P.F.-S., G.t.H. and N.M.dS.) contributed equally to the development, drafting and final review of the manuscript. M.R.D.B. produced Figures 1, 2 and 3.

Declaration of interest

M.R.D.B., J.E.W., G.t.H. and N.M.dS.: none declared. P.F.-S. has previously undertaken paid consultancy work for Astellas, Napp, Pfizer and Grunenthal.

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