Principles of focused ultrasound surgery

If we were to carry out a poll of patients regarding what aspects they would like to see in the development of invasive therapies (encompassing the full range from surgery to interventional radiology and oncology), we suspect that the following would be listed as priorities, with some more important than others:

- Treatment that is always effective at curing the disease in question
- Treatment that has as little invasion/disruption as possible
- Minimal associated hospital stay
- Treatment associated with minimal procedural pain and nausea
- Treatment that allows an almost immediate return to normal activities
- Treatment that has minimal complications either short or long term.

How do our current therapies match up to such a list of desires? Conventional surgery certainly does not come very close to meeting most of these requirements at all, and bigger and more complex operations, with some obvious exceptions, seem to be a cul-de-sac in terms of delivering therapy in the future. The majority of oncological treatments are still associated with extremely variable outcomes, albeit much more effective than 20 years ago, and have substantial side effects, which most patients find highly undesirable. Interventional radiology fares a little better, but is still usually associated with short hospitalizations and significant needle punctures to access appropriate target organs in the body, with the associated complications of such procedures. Therefore, when analyzed in this manner, most of our currently utilized therapies do not really match up with the majority of the aforementioned simple and obvious patient desires and future expectations for therapies. It does seem that the medical profession should spend more time not only perfecting treatments, as it does now, but also concentrating substantially on their short-and long-term acceptability to patients.

Focused ultrasound surgery (FUS) is a completely noninvasive method of thermally destroying a target tissue while sparing adjacent tissues and organs. Treatment is relatively painless and can be carried out under conscious sedation on an out-patient basis. The combination of magnetic resonance guidance with FUS (MRgFUS) provides the ability to plan and monitor treatments in near real-time, further increasing the safety profile of MRgFUS. This technology provides a very personalized treatment, adjusted to the individual patient anatomy, pathology and treatment response, hence it meets the needs of patients, as well as of physicians. MRgFUS has been used extensively in the successful treatment of uterine fibroids, and has been shown to be an effective treatment in the breast and in bone metastases in smaller scale studies. It shows great potential in the treatment of prostate and liver tumors, as well as in the brain and facet joints.

Keywords: focused ultrasound • magnetic resonance imaging • non-invasive
is delivered from a high-power ultrasound source, which can be focused to a very small point in the tissues, provided there is a suitable acoustic window to reach the target. The tissue effect of FUS is to deposit acoustic energy, causing rapid vibration of molecules within the focal spot. This is converted to thermal energy so that the temperature at the focal point rises to 70–80°C, resulting in cell death.[1–3] The same physical parameters for an acoustic window that are required by conventional diagnostic ultrasound apply to focused ultrasound; therefore, gas and bone interfere with the passage of ultrasound to a target site. When targeted correctly, focused ultrasound acts as a thermal ablation modality that causes no tissue damage outside of the treated volume (however, skin burns have been observed with incorrect coupling of the FUS source, gel pads and skin).[4] Each sonication only heats a relatively small volume of tissue, and in order to build up a larger area of destruction, multiple sonications must be used. This aspect is both a strength and a weakness of this technology. Whilst it takes time to carry out multiple sonications building up into a larger confluent area of destruction, this process allows careful construction of an ablative lesion to match the target (which is frequently not a regular symmetrical shape), and allows construction of appropriate margins of destruction around the target in a personalized manner that can be different in each patient treated.

Such a system can therefore destroy a variety of targeted areas in the body, potentially overcoming the requirements for surgery or radiotherapy, or perhaps more realistically, limiting such requirements so that debulking procedures are not required so frequently and smaller, less damaging procedures can be used. Side effects and complications of magnetic resonance-guided FUS (MRgFUS) are usually minimal when correct targeting is achieved and there is no constraint on repeating procedures. Similarly, the well-known limitations of radiotherapy, such as adverse histology, do not seem such a problem for focused ultrasound therapy, which is more limited by physical aspects such as a very rapid tissue perfusion and tissue water content. Unlike radiotherapy, with appropriate planning, there are no effects on tissue in the line of the FUS beam. Almost all focused ultrasound procedures can be carried out as an outpatient procedure, minimizing hospitalization of patients, and therefore substantially reducing overall procedural costs.

**Basic technology & set up**

The description of the machinery given below will be confined to the ExAblate® 2000. This is a MRgFUS system that is manufactured by InSightec Ltd (Haifa, Israel), and is the first MRgFUS system to make a significant commercial impact. The complete system consists of a focused ultrasound source that integrates into a MR scanner (1.5 T or 3 T) and takes over the running of the scanner via its work station during the focused ultrasound procedure. This system can at the moment only be utilized on General Electric Healthcare MR machinery. Philips Medical has also recently developed an MRgFUS system, which is currently undergoing early trials.

The ExAblate system consists of an operator console, patient table with detachable cradles for treating multiple clinical applications, equipment cabinet and a chiller. The physician plans and monitors the treatment from the operator console located in the control room next to the standard MR console. The patient table and detachable cradles are located in the MR scanner and, therefore, have to be entirely MR compatible so that it can work without hindrance in the very hostile MR environment, and so that MR imaging can be used effectively for guidance without image degradation. It should be stressed at this point that in addition to ensuring that all hardware components are MR compatible, careful shielding of all onboard electrical components and connections must be maintained to prevent extraneous radiofrequency energy being produced or released, which could degrade MR imaging. Therefore, both the MR imaging and FUS ablation systems must not interfere with each other in any way. The equipment cabinet containing electrical components, the main power switch and the chiller water cooling system are usually in the MRI equipment room.

Treatments are conducted with the patient lying on the modified patient table, which replaces the conventional table in the MR scanner (Figure 1). Detachable cradles are used for different clinical indications and connected to the table by a cradle docking unit. The focused ultrasound source in the ExAblate 2000, used for uterine fibroid, breast and bone treatments, is an electronic phased array of 211 transducers in a water bath housed in the modified MR table. The water bath extends slightly beyond the normal tabletop and therefore does decrease the space available for the patient within a conventional non-wide-bore MR scanner. The transducer can be moved swiftly within the water bath using four MR compatible piezoelectric motors. Earlier versions of the motion systems used hydraulics or pneumatics to move the transducer and were not as responsive. The transducer can be moved superiorly-inferiorly, to the left and right of the field of view, as well as being rolled and pitched to maximize access to a particular area.

The water bath consists of degassed water covered with a mylar membrane. Furthermore, degassed water and ultrasound gel are placed on top of the membrane, together with a large gel pad to optimize acoustic coupling. The part of the body through which the focused ultrasound energy will enter is placed into this shallow water bath to make good acoustic contact with the above

![Figure 1. The adapted MR patient table with water bath visible.](image-url)
Device Profile
ExAblate® MR-guided focused ultrasound system in multiple body applications

Materials. This is an area of immense importance in the whole process, because any residual gas bubbles at the coupling site can either distort the beam or, if they are at the patient skin–gel interface, be a site of heat production owing to ultrasound reflection, which may potentially cause skin burning. The whole assembly together with the patient is then moved into the MR scanner bore.

Treatment process: planning, safety assurance, sonications & thermal monitoring

Once the patient is comfortably positioned the treatment is planned. Treatment planning takes into account the tissue to be targeted and the adjacent tissues, such as bowel and nerves, to be avoided for safety reasons. Multiple images in all places are obtained through the target and its surrounding organs. A treatment plan is drawn up and the images are used to confirm that there is a safe acoustic pathway to the target that does not transgress bone or bowel, or other vulnerable structures (Figure 2) [5]. The density of focal treatment spots can be varied based upon the type of lesion to be treated. Treatment starts with initial very low-power sonications to verify the concordance of the ultrasound beam and the MR scanning parameters. Subsequently, the operator can set a very large range of different types of sonication volumes, and alter the ultrasound frequency and other factors to achieve the desired effect in the individual tissues. This flexibility to adapt the size of the sonication volume within the tissue is critical to overcome constraints imposed by sensitive tissues and other organs in the beam pathway. Sonication power and cooling duration between sonications can also be changed accordingly.

The treatment is monitored in near real time with thermal mapping using phase-sensitive fat-saturated gradient echo sequences (Figure 3). If organs shift, repeated MR scans allow this to be taken into account. Multiple images are obtained during and immediately after each sonication. This information is transformed into a colorized, thermal-sensitive MR map, which allows temperature to be assessed at each site in the individual scan ± 2°C (Figure 4). This allows the operator to visualize the tissue response to the focused ultrasound beam and titrate the tissue response against the machine settings to optimize this tissue response and ensure patient safety. The size of each sonicated area is displayed easily and the size of the thermal focus can be altered to vary the ablation size per sonication from 2 × 2 × 8 mm to 10 × 10 × 45 mm, providing flexibility to treat targeted tissue of variable shapes, sizes and depths, including relatively large lesions or tumors. Each heating period or ‘sonication’ lasts 20 s or less, followed by a cooling interval [5,6]. Depending on the anatomical site being treated, 50 sonications or more may be performed in a single procedure [7]. Total procedure time depends on the volume of tissue to be ablated and varies between 1.5 and 3.5 h for a fibroid FUS ablation.

Patients are usually treated under conscious sedation and are able to effectively communicate the site and nature of any discomfort they experience, which further improves the safety of the procedure [8]. The result of all this is that each treatment is adjusted appropriately to individual patient anatomy, pathology and tissue response producing a very personalized form of therapeutic procedure that varies between each patient in its precise details.

Why use MR to guide FUS?

Focused ultrasound is not a new technology and researchers have been attempting to harness this modality for treatment since 1942 [9]. Early manifestations of this technology, whilst promising, were hampered severely by lack of a careful and easily utilized targeting technology, and also by the lack of thermal mapping of the result of their sonications. Diagnostic ultrasound has been utilized for some time to provide a targeting modality for focused ultrasound when linked to the much more powerful focused ultrasound transducers in a single machine [10]. Whilst this combination

Figure 2. Sagittal image with focused ultrasound system beam focused on the sonication site within a uterine fibroid.

Figure 3. Phase map acquired in near real-time during sonication. Demonstrates the change in signal in the sonicated target zone.
does provide approximate targeting of abnormal tissue, the well-known drawbacks of diagnostic ultrasound can make optimal tissue targeting difficult. In comparison, the high soft-tissue contrast capabilities of MR imaging (which is also the most commonly used method for exact tumor staging) make it the best possible modality for visualizing complex tissue targets, and for identifying the acoustic pathway to a tissue and the adjacent sensitive tissue structures, such as bowel gas, bones and nerves, which could either interfere with the focused ultrasound beam or be damaged by it. MR is currently also the only modality that can easily produce reliable, repeatable and accurate real-time temperature maps of the whole sonication pathway \[4\], so that the whole process of tissue heat ablation can be monitored. This process allows appropriate measures to be taken to titrate the tissue response to produce an appropriate ablated area against input focused ultrasound parameters, such as power, spot size, transducer frequency, transducer angulation and cooling duration. Diagnostic ultrasound FUS guidance has to date not been able to produce a consistent easily reproduced method of temperature measurement that matches the capabilities of MRI.

The addition of MR to focused ultrasound produces a unified technology that has the best possible tissue targeting coupled with tissue temperature measurement at the sonication target site and in its path, which produces what is sometimes described as a closed loop energy deposition system. MR is a much more expensive technology to utilize than simple diagnostic ultrasound, but its many advantages allow a repeatable, accurate, safe outpatient procedure to be performed each time. This means that procedures that are commonly carried out by surgery and need substantial hospitalization can be converted into day cases with very substantial cost–benefit gains, which more than offset the requirement of using this more complex technology. There are already useful cost–effectiveness studies confirming this aspect when applied to the treatment of uterine fibroids \[11\].

This last aspect discussing the unification of MRI guidance and focused ultrasound application is of course not a universally accepted point of view, and many researchers remain dedicated to using focused ultrasound guided only by diagnostic ultrasound. Jolesz, in a recent wide-ranging article, makes an effective argument that systems using only diagnostic ultrasound guidance will have a very narrow application area and will in most cases not be sufficiently better than surgery to be competitive with it as a therapeutic application \[4\]. He goes on to make the argument that MR guided systems, because of the inherent advantages of targeting and thermal mapping, will be able to potentially replace many surgical and oncological therapies in multiple body areas.

**Clinical applications**

**MRgFUS of fibroids**

Fibroids are the lesions in which MRgFUS has been applied most widely, with the aim of reducing fibroid volume and related symptoms. Uterine leiomyomas (fibroids) are benign uterine tumors affecting at least 25% of women of child-bearing age \[5\]. They cause menorrhagia and pressure symptoms and have significant social and economic costs \[1,5\]. MRgFUS for fibroids has been shown to be a safe and effective treatment, and is now offered by at least 80 hospitals worldwide. More than 5000 women have had their fibroids ablated with MRgFUS therapy, and the results published in Phase II and III trials with follow-up of between 6 and 24 months \[3\]. The main outcome measure is the symptom severity (SS) score, a validated symptom and health-related quality of life questionnaire specific to uterine leiomyomata. A score of between 0 and 100 is allocated, with higher scores indicating more severe symptoms \[3\]. Women with fibroids often score 40 or greater \[6\]. In early feasibility studies with relatively small treatment volumes, 79% of patients...
experienced SS score symptom reduction of at least 10, rising to 91% in more recent studies where larger volumes were treated [2,12]. A 24-month follow-up of 359 patients demonstrated that when a large volume of fibroid had been ablated, the improvement in SS scores was both significant and sustained, and shrinkage of the fibroid was maintained over the following 21 months, indicating the effects are durable [6]; only 15% sought alternative therapy for their fibroid symptoms within the 12 months following FUS [6].

In the short term, MRgFUS appears to enable women to avoid surgery. In a prospective study of 35 women who underwent MRgFUS while awaiting hysterectomy, only four chose to proceed to surgery in the 6 months following MRgFUS [13]. MRgFUS and hysterectomy have been compared for a contemporaneous group of patients: MRgFUS causes fewer complications, but there are greater health satisfaction scores for hysterectomy at 6 months [14]. MRgFUS is particularly appealing to patients who wish to avoid intervention or surgical treatment. It has an efficacy comparable with other minimally-invasive treatment modalities such as uterine artery embolization and laparoscopic or hysteroscopic myomectomy, but has the advantage of being fully noninvasive, performed without anaesthesia in an outpatient setting and potentially does not compromise fertility [10].

The procedure is performed with the patient prone on the table so that the FUS beam can pass through the anterior abdominal wall to the uterine fibroids. Planning of the treatment includes ensuring that the FUS beam does not pass through bowel loops or skin scar tissue, or run close to the sciatic nerve and sacral plexus branches (Figure 5) [5]. Once the multiple planned sonication have been completed, gadolinium-enhanced MRI is performed to demonstrate the volume of necrosis (corresponding to nonenhancement): the greater the nonperfused percentage of the target, the greater the improvement in symptoms (Figure 6) [15]. Most adverse effects are minor and reversible, and include pelvic pain, leg and buttock pain, which usually disappears within 48 h of treatment [1,6,12].

In recent years there have been considerable advances in understanding the importance of maximizing the ablation volume to maximize symptom relief post-MRGFUS and the ability to ablate to within 10 mm of the uterine serosa has been demonstrated [16]. The existence of a ‘learning curve’ for operators to produce the optimal nonperfused volume has been identified, which is important as more centers open worldwide. Increased clinical expertise has also led to greater understanding of who will benefit from treatment and expansion of the criteria for suitability for treatment, including the upper limit for number of fibroids [17,18]. The technique continues to be developed and refined, and indicators of success have been identified to guide patient selection in future. For example, fibroids that are of low signal intensity on T2W imaging pretreatment are those that are most likely to be successfully treated with FUS as judged by nonperfused volume and patients’ symptoms [15].

Concerning cost-effectiveness, a recent study comparing MRgFUS with other treatments, including uterine artery embolization, demonstrated a small gain in quality of life scores for MRgFUS and indicated it was the dominant therapy in 90% [7]. ExAblate 2000 for fibroid ablation received US FDA approval in October 2004.

Figure 6. T1-weighted postgadolinium fat-saturated MRI demonstrates nonperfusion of ablated fibroid tissue post successful magnetic resonance-guided focused ultrasound system procedure.

There are several areas of future promise in MRgFUS of fibroids: since MRgFUS selectively destroys leiomyomatous tissue, it should theoretically be safe for women who want to preserve their fertility. World experience from 13 sites of pregnancy outcome after MRgFUS reveals 54 pregnancies without any excess in pregnancy complications [19]. This is particularly important for women who wish to undergo treatment of their fibroids without compromising their fertility.

MRgFUS of the brain
Attempts to utilize focused ultrasound to treat brain tissue are probably the oldest application of this technology [20]. In 1942, Lyn carried out focused ultrasound on animal brain tissue and this pioneering work was continued by the Fry brothers in the late 1950s and early 1960s [9]. This group developed a complex four-transducer machine that was capable of creating discrete focused ultrasound ablative lesions in the brain [4]. However, all of these early applications required a craniotomy to be performed to allow focused ultrasound to reach and be focused on a suitable target within the brain, because even high power ultrasound does not readily penetrate the intact skull [11]. However, if enough power is used, some focused ultrasound will penetrate into the brain through the intact calvarium and this residue can potentially be used to carry out focused ultrasound treatments. InSightec has created an MR-guided focused ultrasound system that encompasses the skull in a hemispherical array of 1000 transducer elements that can overcome the refocusing aspects of the cranial curvature and still produce a coherent controlled focused beam of therapeutic-strength ultrasound within the brain. Early work is underway with trials in the treatment of brain malignancy using heat ablation of tissue with this system at several sites. Functional neurosurgery using focused ultrasound
as a method of selectively destroying targeted neural structures to interrupt selected pathways is a very promising development of a very old neurosurgical principal [9,21]. A variety of effects can be induced in this manner, which in the past required the performance of a craniotomy. Such procedures were not carried out commonly because of the need for surgery, but the noninvasiveness of the focused ultrasound procedure has created a resurgence of interest in this approach, which may allow treatment of chronic intractable pain, epilepsy, Parkinson’s disease and its related conditions, and other chronic benign conditions by using such a simple noninvasive technique to accurately place an ablative interruptive lesion in a critical neural pathway, without any surgery being required.

A further new application of brain-focused ultrasound is the use of lower power sonications targeted to specific areas of the brain using energy levels that do not cause tissue necrosis. Such a sonication can cause temporary opening of the blood–brain barrier (BBB) at the selected focus without causing tissue necrosis [11]. This procedure may allow large circulating molecules, such as certain drugs or complex contrast agents which are given at the same time, to enter the brain at this site and have a therapeutic effect within the brain, whereas normally they would not be able to cross into the brain because of the intact BBB. The BBB re-establishes itself naturally within 24–36 h of such a procedure. Extensive investigations into the use of MRgFUS in the brain are ongoing at several sites in the world.

**MRgFUS of the bone**

Focused ultrasound is absorbed very avidly by bone, and almost the entirety of this absorption is at the cortical and periosteal margin. Under normal circumstances bone in the acoustic pathway prevents a suitable acoustic window being obtained to a soft-tissue target such as a fibroid. However on the benefit side of this physical aspect in this application is the fact that it is easy to produce a broad area of heating at the periosteal margin with relatively low powers. The heating produced at the periosteal/cortical borders using this technique can destroy neural pain fibers in the periosteum, which can result in excellent palliation of painful bone lesions. There is huge potential benefit to MRgFUS of bone; up to 30% of all cancer patients develop bone secondaries, and approximately 50% of these patients will develop pain from these lesions [22]. Radiotherapy is the current primary treatment of such lesions, but between 20 and 30% of patients do not gain any benefit at all from such treatment, and in up to 27% of patients who are successfully treated, pain recurs after radiotherapy [22].

Magnetic resonance-guided focused ultrasound can therefore be used to produce palliation of pain from painful bone metastases by destroying local pain fibers on the surface of the secondaries. This procedure seems to work when only the outside surface of the bone lesion is treated. For instance, in a secondary deposit involving the iliac blade it is only necessary to treat the outside accessible metastatic margin to get significant pain palliation, the inner inaccessible margin, which would be obscured by intestinal bowel gas, does not need to be treated to get a substantial effect. Early results using MRgFUS for this palliative application demonstrated great promise and have rapidly lead to larger multinational studies investigating the use of this technology [22]. The largest current study enrolled 31 patients who had failed to respond to radiotherapy or refused to undergo radiotherapy. The focused ultrasound procedure was performed as a single study using conscious sedation as an outpatient. The average treatment time per metastatic lesion in this study was 66 min, and no significant adverse events were recorded. Of those patients who could be assessed at 3 months following this therapy, 72% had a significant reduction in pain as judged by a significant fall in their visual analogue pain scores (VAS). In total, 50% of this group reported a fall of their VAS score to zero, 24% of patients in this group had no response to the MRgFUS procedure and one patient worsened over the course of the 3 months. A total of 52% of this group demonstrated significant improvement in VAS pain scores within 3 days of the procedure. Overall, in this group of radiotherapy failures, 36% of patients showed a partial but significant response, and 36% showed a complete pain response. However, it is worthwhile remembering that this is only a palliative procedure at the moment, and that focused ultrasound does not currently penetrate deeply into the diseased bone when there is an intact cortex, and does not therefore cause substantial destruction of the underlying bone lesion. This may be possible in the future as the frequency of available transducers is lowered, which will allow greater penetration through bone; as yet, systems in common use cannot achieve this. However, focused ultrasound can be repeated easily if required locally, with no maximum dosage known.

Randomized sham studies are underway in a multinational collaboration to assess the efficacy of this therapy further; this will hopefully be followed by randomized studies comparing MRgFUS with radiotherapy to try and further establish the correct place of this modality in the treatment of painful bone secondaries. Currently, it is not really possible to treat bone lesions that are very close to neural structures such as the cervical, thoracic and upper lumbar spine, and in the calvarium. However, as the application of MRgFUS is already so promising in bone metastases, it is very likely to play a much larger role in the future treatments in this field when it becomes fully integrated into other treatment regimes.

**MRgFUS of the prostate**

Ultrasound-guided FUS ablation of the prostate in patients with prostatic cancer has been a reality for many years using an endorectal approach [23,24]. This approach, until recently, usually involved ablation of as much of the prostate as possible — that is, total gland ablation. The result of this type of focused ultrasound procedure was that whilst admittedly less invasive than surgery, these procedures reported similar rates of complications in terms of impotence and incontinence as those of conventional surgery or radiotherapy for prostate cancer. Modern state-of-the-art MRI using not only parenchymal imaging, but also molecular imaging such as diffusion, perfusion and spectroscopy, can localize prostatic malignancy much more effectively than all other imaging modalities could in the past [21]. The result is that prostatic malignancy can now be frequently localized to an individual quadrant of the prostate allowing this individual area to potentially
be targeted for ablation procedure. The quality of the information that MR can now provide may, therefore, allow much more localized procedures to be carried out to destroy individual areas of malignancy, whilst still allowing very careful follow-up of the residue of the prostate, with the same techniques described earlier. Whilst multiple biopsies of the prostate remain a key diagnostic part of any prostatic cancer workup, modern MRI may allow much better targeting of concerning areas than previously. Endorectal MRgFUS systems will be available in the very near future and will explore the possibility of hemi- or quadrant-gland ablations targeted at precisely such areas visualized by modern MR imaging. The greatly improved parenchymal visualization that can be achieved during the MRgFUS prostatic ablation procedure when coupled with accurate thermal maps of the prostate showing areas of destruction as they are produced, may also mean that much less neural damage is created because the neurovascular bundles will be easily visualized at this time. Such an advance may mean that the concerning and common complications of impotence which are commonly seen could be reduced substantially in the future.

**MRgFUS of the liver**

Local ablative techniques have developed as a common method of treating liver tumors over the last decade. Radiofrequency probes, laser fibers or microwave probes are placed into the target tumor percutaneously and power applied over a period of time, causing local heating and tissue destruction [11]. These procedures have allowed many more patients with liver tumors to be treated than in the past, but these techniques are still quite invasive, particularly in patients who have hepatocellular carcinoma who invariably have underlying severe liver disease with all of its associated complications. However, these procedures have established the firm principal that local heat ablation is a useful technique in the treatment of liver tumors and prolongs these patients lives in many instances [11]. Multiple Chinese groups have explored the use of ultrasound-guided focused ultrasound therapy in liver tumors, particularly hepatocellular carcinoma, which has a high incidence in Asia over the past 8 years. These groups have demonstrated that it is possible to easily create effective thermal lesions using focused ultrasound in targeted tumors in the liver [25].

However, applying focused ultrasound to the liver has many problems and is perhaps the most difficult area of application of focused ultrasound technology at the moment. Respiratory movement makes accurate and repeatable focused ultrasound application currently very difficult, unless respiratory motion is controlled externally by artificial ventilation. In addition, the bones of the rib cage cause extensive masking of the liver from the focused ultrasound beam, and absorb and distort focused ultrasound sonications. Much of the initial Chinese work in this area found these problems were so severe that these procedures were commonly carried out under general anesthesia post-resection of the lower six right ribs.

Early MRgFUS approaches have been undertaken, but are currently confined to portions of the liver that are not covered by the ribs, such as the mid-part of the left lobe or an abnormally large right lobe that extends below the right rib margin [11]. Currently, this procedure is carried out using artificial ventilation to overcome respiratory problems. Using this technique, a small number of patients have had tumors treated in the left lobe successfully using online thermal mapping under MR control. Current MRgFUS technology cannot reach the rest of the liver predominately because of the masking by the rib cage. However, it is anticipated that over the next 12 months, technology improvements with switchable large multitransducer flat plate applicators will allow MRgFUS to be applied consistently to the liver, overcoming rib interference [4]. This will hopefully be accompanied by improvements in rapid MR scanning and tracking techniques, which will be able to lock on to the target tumor and overcome the requirement for ventilation control, to allow consistent targeting of a discreet liver lesion. We believe that successful application of this type of technology in the liver will potentially have the greatest immediate impact on patient treatment of all MRgFUS applications, because these lesions are very common, frequently multiple and often occur in patients who have either severe liver disease or severe medical conditions. Surgery for metastatic liver lesions from colorectal cancers, whilst being carried out regularly, is only possible in a small amount of patients, and therefore a huge residue of patients with these problems exist, for whom currently there are only limited treatments available.

**MRgFUS of the breast**

MRI is the most sensitive technique that is available for the diagnosis and extent of breast cancer [26]. This capability allows MRgFUS to carry out a very accurate targeting of such lesions for ablation procedures. Theoretically, the position of the breast is very advantageous for MRgFUS because it is easily accessible, essentially lying outside of the body, and has no complicated intervening structures such as bowel or bone interfering with the acoustic window. Thermal mapping is used to assess tissue heating and this combination makes MRgFUS procedures an excellent potential technology for reaching and treating breast tumors.

Several relatively small-scale studies have been carried out to date using MRgFUS to ablate breast cancer. Furusawa treated 30 patients who were diagnosed with breast cancer using MRgFUS prior to these patients proceeding to a conventional surgical lumpectomy [27]. Following this, careful assessment of tumor necrosis in the resected specimen was carried out and an average necrosis rate across the whole study group of 97% was achieved, with 50% of patients having 100% necrosis. More recently, the same author has described a further small cohort of 21 patients who had local MRgFUS therapy without undergoing subsequent surgical resection of the tumor [28]. Regular follow-up was carried out of this group using ultrasound and MRI over a follow-up with a mean length of 14 months. One minor recurrence was documented in their series, which was based on MR imaging criteria in this time frame. These patients also received other regular therapies for breast cancer, such as radiotherapy and tamoxifen, making the overall assessment a little more difficult.

Nevertheless, this type of data is extremely promising, and it seems likely that MRgFUS of the breast could be used to replace surgical lumpectomy with the possibility of substantial...
improvement in cosmetic outcomes for women and reducing surgical complications seen with breast surgery. The size of the margin treated around the malignancy appears to be of great relevance in recurrence rates postprocedure. The literature suggests that the greater the margin of apparently normal tissue removed or destroyed around the tumor, the lower the subsequent recurrence rate of malignancy locally. A margin of at least 0.5 cm in all directions around the breast tumor appears to be a good compromise, and therefore should be built into all MRgFUS procedures [27,28].

For successful MRgFUS to be achieved, tumors should be at least 1 cm away from the skin surface and the chest wall to prevent collateral damage during ablation to these structures [29]. Currently, tumors greater than 5 cm in diameter are not treated since they appear to be too large for easy treatment, and ductal carcinoma in situ is a contraindication because of the widespread nature of this disease and a lack of a reliable method for identification of the extent of ductal carcinoma in situ. Early information indicates that MRgFUS does not impair or interfere with any sentinel node procedures, and that these can be carried out in the normal way [30].

Magnetic resonance-guided focused ultrasound appears to be a very promising method for replacing some surgical breast procedures with potential cosmetic benefits. Obviously, multiple further studies are required in many areas in this field before MRgFUS becomes an accepted part of breast cancer therapy, but the potential in this field is exciting.

Conclusion
Magnetic resonance-guided focused ultrasound is an emerging new technology that has the potential, when it is integrated properly in the future with other more conventional therapeutic regimes, to come much closer to our desires and expectations for new therapeutic applications. MRgFUS is a method of delivering destructive energy into deep tissues under continuous MR guidance and targeting without the requirement of any needles or other instruments passing through the skin, and yet still has the ability to destroy discrete tissue targets in a completely noninvasive manner with greater accuracy than any other technique. MRgFUS requires precise integration between the delivery of the FUS beam and MR-guided planning monitoring, but the ability to thermally monitor therapy delivery as it is carried out cannot be matched by any other noninvasive ablation technique. While MRgFUS is already well established in the treatment of fibroids, its potential for success in other anatomical areas, including the prostate, brain, bones and liver is potentially very far reaching, and may change how we apply therapy over the next 20 years.

Expert commentary: authors’ recommendation regarding current impact
Both cost constraints and patients’ expectations will influence the development of new treatment techniques profoundly. From both of these perspectives, MRgFUS is appealing; by providing a noninvasive focused treatment requiring minimal hospitalization, preparation and after-care, it satisfies health economists and patients.

Five-year view
Magnetic resonance-guided focused ultrasound shows great promise in several anatomical areas:

- **Prostate:** MRgFUS combines the diagnostic capabilities of MRI and the appeal of focal treatment, with less adverse effects than current surgical treatment;
- **Breast:** again, superb diagnostic capabilities of MRI enable optimal treatment planning. The potential to avoid surgery is important for this common disease;
- **Liver:** although the technique required is challenging, MRgFUS represents a treatment for patients who are generally considered to be inoperable, for example those with liver metastases. This is not an alternative to treatment, but a new treatment option for patients who are unsuitable for surgery.

Alternative devices
Percutaneous thermal ablation with laser, radiofrequency or cryo-ablation are widely performed techniques that have the disadvantage of being invasive. One other company (Philips) is trialing an MRgFUS system at present.

Financial & competing interests disclosure
EA Dick is a minor share holder in St Mary’s Therapy Center, which offers focused ultrasound therapy. WMW Gedroyc is an occasional consultant to Insightec and a shareholder in St Mary’s Therapy Center. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.
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Device Profile

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