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Competing interests statement
The authors declare no competing financial interests.

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DATABASES
The following terms in this article are linked online to:
Cancer.gov: http://cancer.gov/
acute lymphoblastic leukaemia | acute myelogenous leukaemia | chronic myelogenous leukaemia
Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
ABL | *BCR* | *HOX11* | *HOX11L2* | *HOXA9* | *HOXB4* | *HOXD13* | *NOTCH1* | *NUP98*

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INNOVATION

High-intensity focused ultrasound in the treatment of solid tumours

James E. Kennedy

Abstract | Traditionally, surgery has been the only cure for many solid tumours. Technological advances have catalysed a shift from open surgery towards less invasive techniques. Laparoscopic surgery and minimally invasive techniques continue to evolve, but for decades high-intensity focused ultrasound has promised to deliver the ultimate objective — truly non-invasive tumour ablation. Only now, however, with recent improvements in imaging, has this objective finally emerged as a real clinical possibility.

The 1990s witnessed an explosion in minimally invasive alternatives to open surgery for localized malignancy. Quite apart from the inherent attractions of new technology, the incentives behind this movement are plain. Open surgery is associated with significant morbidity and with mortality, and causes suppression of a patient's immune system, which in turn can lead to the risk of perioperative metastatic tumour dissemination. Patients themselves usually complain of postoperative pain and recovery can be lengthy. Laparoscopic surgery might be more acceptable to patients, and leads to a quicker return to work, but usually takes longer, and both operative morbidity and mortality are broadly comparable with open surgery.

Other minimally invasive techniques use a range of energy-based methods for *in situ* tumour destruction. Apart from radiotherapy, these include radiofrequency ablation, laser ablation, cryoablation (BOX 1) and high-intensity focused ultrasound (HIFU). In principle, where surgery usually aims to remove a tumour with an adequate normal-tissue margin, if a minimally invasive technique can destroy the equivalent tissue volume, then outcome in terms of disease-free survival should be at least equal. If operative mortality is avoided, then outcome could even be better. In fact, taking the example of interstitial laser ablation for isolated colorectal liver metastases, data are now emerging to support this assertion[1].

Treatment with HIFU is the only one of these alternatives to surgery that is truly non-invasive. Theoretical advantages of this lack of invasiveness are that there is no risk of tumour seeding along a needle track, which has been reported after procedures such as percutaneous ethanol injection[2] and radiofrequency ablation[3], and there is no risk of haemorrhage from visceral or vascular puncture, which can occur during any of the minimally invasive procedures described in BOX 1. A high-energy focused ultrasound beam is directed harmlessly across the skin and intervening tissues towards the target tumour. Only at the focus of the beam is the energy level great enough to cause a temperature rise sufficient for instantaneous cell death. The mechanism of action of HIFU is not tumour-specific and so a wide range of tumour types can be targeted. In addition, in contrast to ionizing radiation, treatment can be given more than once as there is no upper limit of tissue tolerance to repeated ultrasound exposure. There are very few side effects of treatment, and serious adverse events are rare. As a result, HIFU treatment with palliative intent, aimed either towards symptom or local tumour control can also be seriously contemplated for patients with poor prognoses.

In several centres worldwide, HIFU is now being used clinically to treat solid tumours (both malignant and benign), including those of the prostate[4], liver[5,6], breast[7], kidney[8], bone and pancreas, and soft-tissue sarcoma[6]. This has only been the case for the past 5 years, so, perhaps with the exception of prostate cancer, the evidence base for long-term efficacy is far from mature. However current data are very encouraging and the role of HIFU in oncology is likely to expand as devices become more widely available.

How does HIFU work?

The term 'ultrasound' refers to mechanical vibrations above the threshold of human hearing (16 kHz). Medical ultrasound is generated by applying an alternating voltage across a piezoelectric material such as lead zirconate titanate. Such materials oscillate in thickness at the same frequency as the driving current. The resulting ultrasound wave propagates through tissues, causing alternating cycles of increased and reduced pressure (compression and rarefaction, respectively). Most of us are familiar with diagnostic ultrasound, which usually uses frequencies in the range of 1–20 MHz. By contrast, frequencies of 0.8–3.5 MHz are generally used during the clinical applications of HIFU, and the energy levels carried in the HIFU beam are several orders of magnitude greater than those of a standard diagnostic ultrasound beam. In a way analogous to the focusing of light, ultrasound waves can be focused at a given point. The high energy levels carried in a HIFU beam can therefore be magnified further and delivered with precision to a small volume, while sparing surrounding tissues[9].

Box 1 | **Minimally invasive energy-based ablative treatments**

Radiofrequency ablation (RFA)
A high-frequency electric current is delivered through needle electrodes to a target tumour. At the electrode tip, electrical energy is converted to heat, leading directly to cellular damage and death. Saline can be infused into the treatment tip to reduce local tissue dessication and therefore to enable ablation of larger volumes ('cool-tip'). RFA can be applied percutaneously, laparoscopically and at open surgery. Its main applications have been in the treatment of liver and kidney tumours of less than 4 cm diameter, although it has been shown that volumes of up to 7 cm diameter can be ablated in colorectal liver metastases[4,51].

Cryoablation
Cryoablation uses two or three freeze-thaw cycles to induce tissue damage. One or more cryoprobes are inserted directly into the target tissue, usually under ultrasound guidance, and liquid nitrogen or argon gas is circulated during the freeze cycle. A ball of ice develops over approximately 15 minutes, and its size can be monitored directly with real-time ultrasound. Intracellular and extracellular ice formation leads to osmotically induced pH changes and protein denaturation and can cause direct membrane disruption. Delayed cell death is also caused secondary to vascular thrombosis and increased vascular permeability. Liver[52], kidney[53] and prostate[54] tumours have been treated in this way. Like RFA, cryotherapy can be performed at laparotomy, laparoscopically or percutaneously.

Laser ablation
Interstitial laser thermotherapy, also known as laser-induced thermotherapy, has been used since the early 1980s[1,55]. Needles are placed percutaneously under ultrasound or magnetic-resonance imaging guidance, and laser fibres can then be inserted through these.

The volume of ablation ('lesion') following a single HIFU exposure is small and will vary according to transducer characteristics, but is typically cigar shaped with dimensions in the order of 1–3 mm (transverse) × 8–15 mm (along beam axis) (FIG. 1). To ablate clinically relevant volumes of tissue for the treatment of solid cancers, many of these lesions must be placed side by side systematically to 'paint out' the target tumour.

The two predominant mechanisms of tissue damage are by the conversion of mechanical energy into heat, and through 'inertial cavitation' (FIG. 2). Immediate thermal toxicity occurs if tissue temperatures are raised above a threshold of 56°C for at least 1 second, leading to irreversible cell death through coagulative necrosis. During HIFU treatments, the temperature at the focus can rise rapidly above 80°C[10], which, even for very short exposures, should lead to effective cell killing[11]. Inertial cavitation is less predictable, but occurs simultaneously with tissue heating. As described above, ultrasound subjects the molecular structure of the tissues to alternating cycles of compression and rarefaction. During rarefaction, gas can be drawn out of solution to form bubbles, which can collapse rapidly. Again the end result is cell necrosis, but in this case injury is induced through a combination of mechanical stresses and thermal insult at a microscopic level.

The observed tissue changes following HIFU treatment begin characteristically with appearances of homogenous coagulative necrosis[12]. A volume of necrotic tissue therefore remains following treatment, corresponding to the original target tumour along with an appropriate margin of normal tissue (FIG. 3). The subsequent inflammatory response includes formation of granulation tissue (indicated by the presence of immature fibroblasts and new capillary formation) at the periphery of the necrotic region after approximately 7 days[9] and the migration of polymorphonuclear leukocytes deep into the treated volume. Two weeks following HIFU treatment, the periphery of the treated region is replaced by proliferative repair tissue. The repair process has not been investigated in detail at the cellular level beyond this time frame, but sequential anatomical imaging shows a gradual shrinkage of treated volumes over time, which indicates replacement of the necrotic region with fibrous scar tissue.

It has been proposed that the persistence of tumour antigen in disrupted tumour cells of this necrotic volume might allow host recognition and stimulate a subsequent specific antitumour host response. Whether this phenomenon actually occurs is not yet clear. Certainly no cellular mechanism has yet been identified, but the laboratory and clinical factors leading to this proposal will be discussed below.

The placement of small lesions side by side requires precision if an entire tumour is to be ablated reliably. Patient movement or operator error might potentially lead to areas of viable tumour remaining after treatment. However, even with the most meticulous treatment planning and conduct, other tissue factors might still complicate the picture, many of which remain to be completely elucidated. Lesions placed side by side might interact with one another, making it difficult to predict the exact volume ablated by successive exposures if insufficient time is allowed between exposures[13]. In addition, highly vascularized (perfused) tissues might be more resistant to thermal ablation than poorly perfused areas owing to the heat-sink effect of their blood supply, but the precise effects of tissue perfusion on the ablated volume remain unclear. Early studies indicated that ablation by very short exposures (<3 seconds) should be independent of tissue perfusion[14,15], yet clinical exposure durations often exceed this figure. Other thermal ablation techniques that work by the principle of slower tissue heating are profoundly effected by the heat-sink effect of tissue perfusion. Despite this, pre-HIFU estimation of tissue perfusion has not yet been found to be helpful in the clinic[16]. Nonetheless, it would still seem plausible that perfusion should influence ablation, although it is likely that adjustment of exposure parameters to account for any such effects of perfusion will need to be based on real-time assessment of tissue response for the foreseeable future.

Is it safe?

An important prerequisite for any proposed cancer treatment is that the treatment itself does not worsen clinical outcome. An early concern for HIFU was that the shear forces of the ultrasound and of inertial cavitation could lead to dissemination of cancer cells and subsequent metastasis. This possibility was investigated by several groups, but seemingly answered conclusively by Oosterhof *et al.* using the highly metastatic AT-6 Dunning R3327 rat prostate cancer subline. They showed no difference in the number of observed metastases between HIFU-treated and sham-treated groups in a xenograft mouse model[17]. (Sham-treated mice were anaesthetised, shaved and positioned identically to the treated group, but not exposed to HIFU.) Tumour cells can often be detected in the peripheral blood of patients with various malignancies, and, indeed, haematogenous metastasis depends on this fact. However, in a recent study in humans, Wu *et al.* noted no apparent increase in the number of patients with detectable circulating tumour cells following HIFU[18]. From these observations, the authors conclude that HIFU does not increase the potential risk of metastasis.

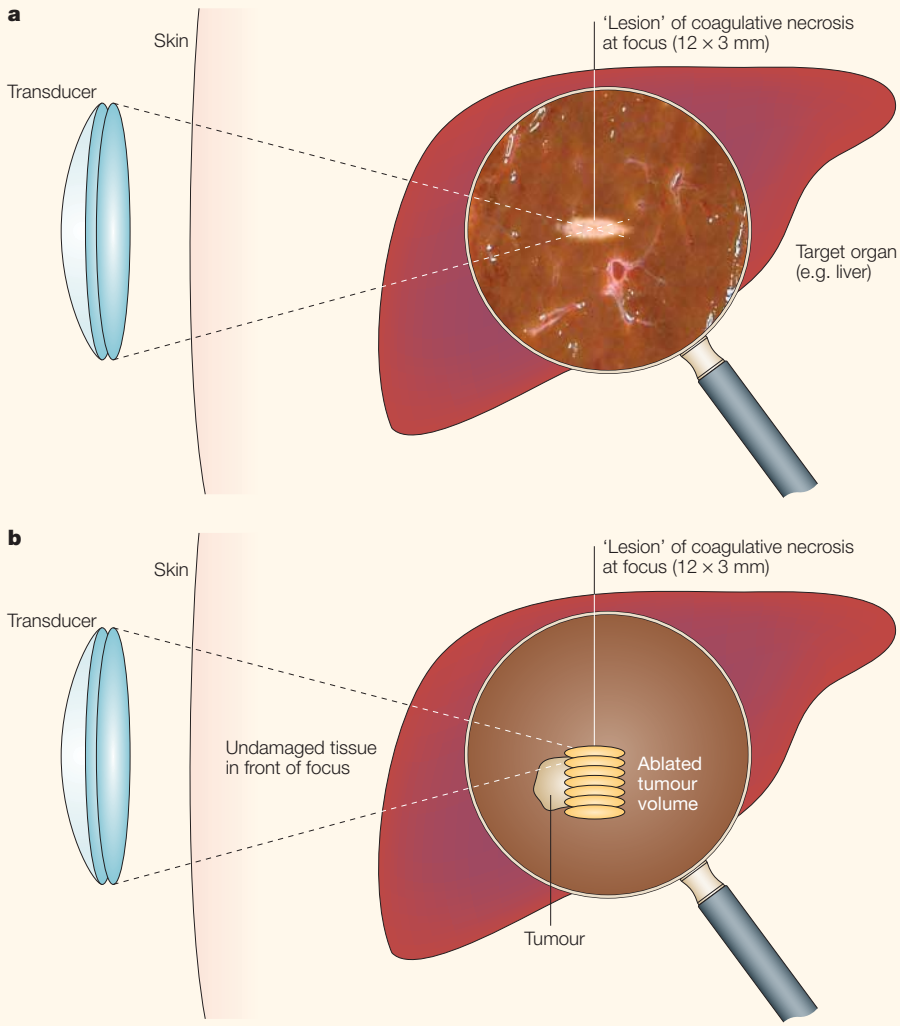

Figure 1 | **Schematic showing the principles of high-intensity focused ultrasound**. **a** | An extracorporeal source generates an ultrasound beam, which forms a cigar-shaped focus deep within the target tissue (liver). The volume of ablation ('lesion') following a single high-intensity focused ultrasound exposure is small and will vary according to transducer characteristics, but is typically in the order of 1–3 mm wide by 8–15 mm in length along the beam axis. **b** | Schematic illustrating application of sequential 'single lesions' to achieve tumour volume ablation. The lesions must be placed side by side systematically to 'paint out' the target tumour and some of the surrouding normal tissue margin.

The clinical evidence so far would also seem to refute any such early concerns. Several investigators have now described their own experience following the clinical use of HIFU in various settings (see below). There have been no reports of any apparent increase in rates of metastasis. In one series of treatments, the authors commented on the lack of clinical progression of pre-existing lung metastases following HIFU treatment of eight advanced primary renal-cell cancers[8]. Although this phenomenon has been reported previously following other local therapies for renal-cell carcinoma (including surgery), the same investigators in Chongqing, China, have also presented their observations of two separate instances of regression and disappearance of lung metastases following HIFU treatment of primary osteosarcoma in the absence of any systemic therapy (F. Wu, personal communication). By contrast, following the surgical resection of various types of primary malignancy, the phenomenon of rapid progression of distant metastases has been well documented. Many potential mechanisms have been implicated for this, including the release of growth factors in response to surgical injury, a disturbance in the balance of pro-and anti-angiogenic factors released by the tumours themselves, and a generalized post-operative state of immune suppression. The best understood of these factors is that of immune suppression[19].

As a result of the type of observation discussed above, attention has now turned full circle from original concerns regarding a possible increase in tumour metastasis following treatment with HIFU towards the exciting possibility of direct HIFU-induced enhancement of cancer-specific immunity after treatment. The T-cell-mediated immune response predominates in cellular antitumour immunity[20], and enhanced T-cell immunity is one proposed mechanism for which recent evidence has emerged[21]. Another study, which used a mouse model, has taken this one step further, indicating a specific antitumour response following tumour ablation, and proposing that *in situ* tumour ablation provides an antigen source for the generation of antitumour immunity[22]. An alternative mechanism that might also enhance cellular immunity involves the release of heat-shock proteins (HSPs), which can stimulate cytotoxic T-cell activity. Upregulated expression of HSPs has been reported following radiofrequency ablation[23], and Marberger's group in Vienna has also raised the possibility of HSP-mediated immune activation following HIFU[24].

Another important clinical consideration is the safety and side-effect profile of treatment itself. Among the early reports of extracorporeal HIFU as a cancer therapy, Visioli *et al.* described results of a Phase I study conducted at The Royal Marsden Hospital (Sutton, United Kingdom), in which they treated tumours of the liver, kidney and prostate. They encountered few treatment-related symptoms, with the most severe being moderate pain over the exposed site in 2 of 14 treated patients[25]. Using a different device in Paris to treat superficial bladder tumours, Vallancien *et al.* also documented few complications, although theirs included skin burns in 2 of 20 patients[26]. More recent reports have again identified local pain, transient fever and skin toxicity as the most frequently occurring adverse events[5,6,27]. Pain is usually transient, mild and short-lived. Fever is thought to be caused by a combination of the release of intracellular ions, nucleic acids, proteins and their metabolites into the extracellular space. Skin toxicity is usually limited to sub-centimetre superficial burns and occurs because energy deposition outside of the focal region is maximal at interfaces between tissues of differing acoustic impedances. The most significant of these interfaces is the skin surface, which explains the occurrence of skin burns.

There have also been considerable data arising from the use of transrectal HIFU for the treatment of prostate cancer. In this case, the list of potential side effects is similar to that for other existing treatments such as

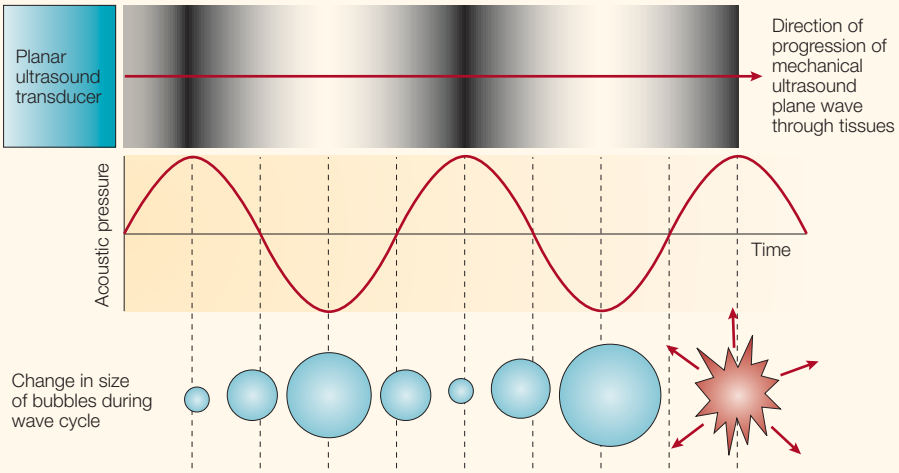

Figure 2 | **The principles of inertial cavitation.** A mechanical ultrasound wave progresses through tissues (top), causing alternating cycles of increased and reduced pressure (compression and rarefaction respectively — middle). Gas is drawn out of solution during rarefaction, creating bubbles. These can oscillate in size in a stable fashion with the changing tissue pressure, but ultimately might collapse, causing local energy release and temperature rises at the microscopic level (bottom).

surgery or radiotherapy[28]. The most severe complication has been rectal-wall injury leading to a small number of recto-urethral fistulae, although, following improvements in device design and safety features such as rectal-wall cooling, this particular complication has not been encountered with the current generation of commercially available clinical devices.

There are other potential complications such as inadvertent injury to hollow viscera adjacent to the target tumour, and abscess formation following bacterial colonization of the necrotic volume after successful ablation[6]. These have only been observed in China, where the number of treated patients is greatest (>3,000), and the combined reported incidence of these adverse events stands below 1% (F. Wu, personal communication). All of these figures must be interpreted against the background of the potential alternative of surgical resection of these target tumours, and in the case of liver resection, an operative mortality of 3–5% would not be unusual. The general consensus from all studies so far has been that extracorporeal and transrectal HIFU are both safe and acceptable to patients.

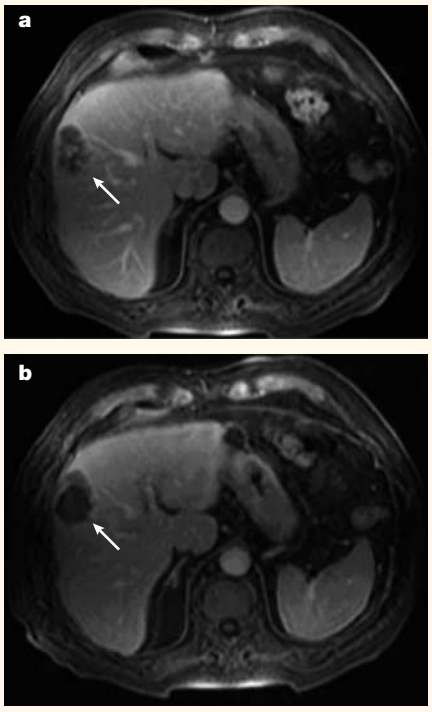

Figure 3 | **Ablation of a liver metastasis with high-intensity focused ultrasound.** Gadolinium-enhanced T1-weighted images of patient before (**a**) and 12 days after (**b**) treatment with high-intensity focused ultrasound of isolated liver metastasis from a colorectal primary tumour in a 75 year old man. The posterior portion of metastasis was treated before surgical resection during a feasibility study[5]. The treated region can be clearly identified as a region of absent contrast uptake.

Clinical applications

HIFU was first used clinically in the 1950s for the treatment of focal neurological conditions such as Parkinson's disease[29]. Although successful, the procedure required a craniotomy (surgical access to the brain) and results were short-lived. Consequently, the technique was largely relegated to the laboratory during subsequent decades until its re-emergence as a tool for the non-invasive treatment of malignancy in the 1990s. Since then, there has been considerable interest across a broad spectrum of clinical specialities. A summary of some of the more recent publications relating to the use of HIFU in the treatment of cancers can be found in TABLE 1.

The first clinical application was in the treatment of prostatic malignancy. Like many other novel treatments, clinical results and safety profiles have improved alongside technical and technological developments over the past 10 years. Current published data are at best short- to medium-term[4,30], but already several thousand patients with organ-confined prostate cancer have been treated (C. Chaussy, personal communication) and should these early results be sustained, the technique might soon rival existing treatments such as brachytherapy (local insertion of multiple small radioactive seeds) and even external-beam radiotherapy or radical surgery, both in terms of disease-free survival and, particularly, patient acceptability[4,31]. Furthermore, local recurrence of tumours following radiotherapy can be treated with HIFU[32].

Several prototype extracorporeal devices have been used in feasibility exercises during the 1990s and first years of this decade[25,26,33], but so far the use of only two commercially available devices has been reported in the medical literature[6,34]. These two devices differ principally in the type of imaging used to guide and monitor treatment, with one system using magnetic resonance imaging (MRI) and the other B-mode ultrasound. A discussion of the benefits of each approach can be found in BOX 2.

MRI-guided HIFU has only been used clinically to treat breast neoplasia[7] and uterine leiomyomata (fibroids)[27], but in each case results indicate successful ablation of their target tumours with few complications. The potential application of HIFU to treat brain tumours through an intact skull is an exciting prospect, and seems to be feasible in preclinical studies[35,36]. This application will certainly require MRI guidance, but other applications might be better suited to the use of ultrasound guidance. Ultrasound-guided HIFU has also been used to treat breast tumours and uterine fibroids[6,37], as well as a considerably more diverse group of tumour types including those of the liver[5,6] (FIG. 3), kidney[8,33,38], bone and soft tissues[6]. Most of these reports describe encouraging short-term outcomes from small patient groups (TABLE 1), but evidence of survival advantage over existing treatments is emerging for the treatment of locally advanced hepatocellular carcinoma[39].

HIFU is a local treatment and, as such, can only ever be expected to act directly on the targeted tumour. Any benefit, whether theoretical or real, in relation to immune

Table 1 | **Recent publications relating to the use of clinical high-intensity focused ultrasound in solid tumours**

Tumour type	Number of patients	Type of device	Type of study	End points or outcome measures	Outcomes	References
Prostate	20	Transrectal (Sonablate)	Preliminary report	Negative biopsy rate; PSA stability	Complete response in 100% of patients (mean follow-up 13.5 months)	31
	402	Transrectal (Ablatherm)	Phase II/III prospective multicentre trial	Safety and efficacy	87.2% negative biopsy rate (mean follow-up 407 days)	4
Liver	11	Extracorporeal (HAIFU)	Preliminary report	Safety and performance	No major complications; evidence of ablation in 10 of 11 patients (91%)	5
	474	Extracorporeal (HAIFU)	Case series	No specific criteria quoted	Complete coagulative necrosis seen on histology; absence of contrast uptake in treated region on MRI and subsequent shrinkage over time	6
Breast	23	Extracorporeal (HAIFU)	Prospective randomized controlled trial	Pathological assessment of therapeutic response	100% response — coagulative necrosis of tumour along with normal tissue margin	37
	24	Extracorporeal (Exablate)	Feasibility study	Negative biopsy rate	19 of 24 patients (79%) had negative biopsy results after 1 or 2 treatment sessions	7
Kidney	13	Extracorporeal (HAIFU)	Preliminary report	Symptoms; MRI/CT appearances	Absent contrast uptake on post-HIFU MRI with tumour shrinkage over time; symptom alleviation in most cases; stability of lung metastases	8
	1	Extracorporeal (Storz Medical prototype)	Case report	MRI appearance post-treatment	Necrosis and shrinkage over time in 2 of 3 treated tumours	33
Sarcoma	153 (bone) and 77 (soft tissue)	Extracorporeal (HAIFU)	Case series	Anatomical and functional imaging appearances	Absence of contrast uptake in treated volume on MRI; ablation of tumour on SPECT; destruction of microvasculature on DSA	6
Uterine fibroids	55	Extracorporeal (Exablate)	Feasibility study	Safety and feasibility	No major complications; MRI guidance provides safe, accurate delivery of HIFU	27

CT, computed tomography; DSA, digital subtraction angiography; HIFU, high-intensity focused ultrasound; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; SPECT, single-photon-emission computed tomography.

sensitization could not be assumed to transform HIFU into a systemic therapy. For this reason, HIFU treatment has been considered as a potential alternative to surgical resection in all of the above settings. In that context, the consideration of adjuvant or neoadjuvant systemic therapies has followed traditional principles. For example, in the treatment of prostate cancer, adjuvant hormone therapy would not routinely be used following surgery, and the same rationale should apply to treatment with HIFU. Similarly, tumour types such as renal-cell cancer, soft-tissue sarcoma and pancreatic cancer often do not respond to either chemotherapy or radiotherapy, so in these cases HIFU could be given alone. On the other hand, when HIFU is used to treat osteosarcoma, neoadjuvant and/or adjuvant chemotherapy would routinely be given (F. Wu, personal communication). Uncertainty might arise in some circumstances, such as in the treatment of breast malignancy, where the decisions regarding adjuvant therapies would usually be based heavily on histological assessment of a surgical specimen. Clearly, HIFU would not result in any surgical specimen and in these circumstances such decisions should be based on good histological specimens obtained pre-operatively from core biopsies. A further factor to be considered in the case of breast cancer would be the need for axillary lymph-node dissection after treatment with HIFU.

One issue that remains to be clarified is the possibility of combining HIFU treatment with other minimally invasive or minor procedures. In China, where most of the clinical experience of extracorporeal HIFU lies, it is not uncommon for HIFU treatment of liver or kidney tumours to be given following a single session of transarterial embolization with lipiodol. The rationale for this approach is that embolization serves to reduce the heat-sink effect of target tumour perfusion, and that the lipiodol (a radio-opaque iodine-containing oil) enhances the absorptive properties of the target tissues to ultrasound. The combination of therapies is thought to improve therapeutic efficacy and to reduce treatment time and energy requirements (so reducing the likelihood of complications)[39]. The combination of minimally invasive therapies is not a new concept, and further experience will determine whether the principle holds in this setting. Many years ago, the suggestion of synergy between HIFU and chemotherapy was raised[40], but this possibility has not yet been investigated in humans.

An important consideration following any cancer therapy surrounds selection of an optimum method for the assessment of treatment success. A surgeon can take some comfort from histological inspection of excision margins, and oncologists assess the change in volume of tumours over time.

Box 2 | **Types of device**

In considering the differences between the high-intensity focused ultrasound (HIFU) devices that are in current clinical use, there are two important distinctions. The first is between endocavitary and extracorporeal application, and the second relates to the mode of imaging modality used for treatment guidance — at present, treatment is either guided by ultrasound or magnetic resonance imaging (MRI).

Endocavitory versus extracorporeal application

The first devices to be used widely in clinical practice were transrectal probes, which have been used predominantly to treat the prostate[4,31]. With the exception of prototypes, these have all been ultrasound guided. They are necessarily small, with short focal lengths (3–4 cm), and operate at higher frequencies than extracorporeal devices. Other endocavitory devices are now emerging, and these have been designed for laparoscopic or endoscopic use for the treatment of liver, kidney, oesophageal and even biliary tumours, but these remain experimental.

Ultrasound versus MRI guidance

Ultrasound-guided devices use diagnostic ultrasound probes, which are fixed in position relative to the HIFU beam, both to locate the target and to observe response[6,56]. The position of the HIFU focal region is superimposed on the ultrasound image, and grey-scale change caused by cavitation is used as an indication of ablation following each exposure. MRI-guided devices use MRI images to locate tumour targets[27]. They use indirect MRI thermometry following sublethal exposures to confirm targeting, and following lethal exposures to measure response[57,58]. There are advantages and disadvantages of each type of device. The main advantages of ultrasound guidance are its low cost and its high spatial and temporal resolution. The main advantage of MRI is the greater clarity of three-dimensional imaging. With treatments lasting several hours, unless the cost of MRI falls considerably, MRI-guided HIFU will remain confined to large research centres, with the exception of the United States. Also, recent advances in image-fusion technology should mean that many of the disadvantages of three-dimensional image perception from ultrasound guidance might soon be overcome.

However, when a tumour has been thermally ablated, it will often have been treated along with an appreciable margin of normal tissue, and so an early assessment of tumour size might wrongly indicate an increased tumour volume when compared with pretreatment measurements. On the other hand, if ablation has been successful, tumour perfusion should have been abolished, and so there would be a volume of absent contrast uptake corresponding to the ablated region post-treatment. In the context of HIFU, this has led to the adoption of imaging modalities such as contrast-enhanced MRI[41] or ultrasound[42,43], both of which give an indication of the presence or absence of residual tumour perfusion. In fact, international guidelines have now been published on the assessment of response following ablative cancer therapies[44], and these should also be adopted following HIFU. One problem is that anatomical imaging modalities such as MRI, computed tomography or ultrasound will often fail to detect small foci of residual viable disease, and so the ideal combination would be that of anatomical and functional imaging such as positron emission tomography[45].

Advantages and limitations of HIFU

Novel treatment modalities should again be considered in comparison with existing therapeutic alternatives. In general terms, the mainstream therapies for solid malignancies include surgery, radiotherapy and systemic chemotherapy. All of these cause suppression of the host anticancer immunity, but in the case of HIFU, even when discounting the possibility of beneficial immune stimulation, treatment is not associated with generalized physiological insult and so should not impair immune function. Other than this, like most minimally invasive treatments, its main advantages over surgery are reflected in its lower side-effect profile (discussed above). Related to the lower risk of complications is another potential clinical application. Surgical debulking is not considered to be suitable for most types of cancer in the palliative setting owing to the associated morbidity. Conversely, HIFU is much less debilitating and has been found to provide effective local tumour control and, perhaps more importantly, pain relief in the palliative settings of advanced pancreatic malignancy and advanced pelvic side-wall recurrences of colorectal origin[6].

Radiotherapy is usually given in fractionated doses, necessitating multiple attendances at the clinic, and is limited by the danger of collateral damage if safe maximum exposures are exceeded. By contrast, HIFU is mainly administered in a single session, but is repeatable in the case of residual disease or local recurrence. HIFU does not preclude the use of any conventional treatment and so creates no therapeutic impasse. Other significant advantages of the technique over radiotherapy and chemotherapy are that its mechanism of action is independent of tissue type and that specific tumour resistance is unlikely given that cells of all types will be killed at the high temperatures achieved in the focal volume.

It would be wrong to depict HIFU as a panacea, as it has both disadvantages and limitations. Ultrasound cannot penetrate air-filled viscera, and HIFU will not therefore be suitable for tumours in sites such as the lung or bowel. Also, the position of tumours within target organs might limit their accessibility. If there is no adequate acoustic window, or if tumours lie close to adjacent structures such as the heart, gall bladder or bowel, it might not be feasible to treat them with HIFU. However, some targets that are currently inaccessible to HIFU might soon be reached as a result of recent advances; for example, trans-skull therapy can be used to treat brain tumours.

HIFU treatment is not fast. Although tumour size poses no absolute limitation, the duration of treatment will increase with the volume to be ablated. A superficial 3 cm diameter breast tumour might take less than 1 hour to treat, whereas a 10 cm diameter liver tumour might take more than 6 hours. These long treatment times and the need for patient immobility do make general, or at least regional, anaesthesia necessary for most treatments, but in our experience patients are not deterred by this, and in the absence of surgical insult anaesthesia is usually uncomplicated.

Future directions

As a clinical tool, HIFU is in its infancy. As its profile is raised and the technique becomes more widely available, it should be possible to coordinate the type of larger-scale clinical trials that will be necessary to develop the evidence base for the efficacy of HIFU in its various applications, whether alone or in combination.

This entire process is likely to be facilitated by improvements in equipment design. Real-time imaging and treatment monitoring are the subjects of ongoing theoretical research, and the development of techniques such as three-dimensional ultrasound[46] and elastography[47,48], which measures the change in stiffness of a tissue as it is ablated, are likely to enable improvement in clinical outcome and to bring about a reduction in treatment duration. Co-registration of ultrasound with cross-sectional imaging[49] should also provide additional

safety and improve user-friendliness of ultrasound-guided devices.

One potential overlap between current clinical application and ongoing molecular biological research is the basis for any possible immunological activation, which remains to be elucidated. In addition, focused ultrasound has been proposed as a vehicle for delivering targeted gene therapy through inducing cavitation of DNA-laden microbubble contrast agents[50] in the periphery of any zone of ablation, where temperature rises would be sublethal, but these remain secondary considerations to the direct ablative treatment intent at present.

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Competing interests statement

The author declares competing financial interests: see web version for details.

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