ARTICLE INFORMATION

Received:
17 January 2013

Accepted:
23 January 2013

doi: 10.1259/bjr.20130044

Cite this article as:
Malietzis G, Monzon L, Hand J, Wasan H, Leen E, Abel M, Muhammad A, et al. High-intensity focused ultrasound: advances in technology and experimental trials support enhanced utility of focused ultrasound surgery in oncology. Br J Radiol 2013;86:20130044.

REVIEW ARTICLE

High-intensity focused ultrasound: advances in technology and experimental trials support enhanced utility of focused ultrasound surgery in oncology

[1]G MALIETZIS, MB BS, MSc, [1]L MONZON, MB BS, MRCS, [2]J HAND, DSc, PhD, [1,3]H WASAN, MB BS, MRCP, [4]E LEEN, MD, FRCR, [1]M ABEL, MB BS, [1]A MUHAMMAD, MB, FRCR, [1]P PRICE, MD, FRCR and [1,5]P ABEL, ChM, FRCS

[1]Department of Surgery and Cancer, Faculty of Medicine, Imperial College, London, UK
[2]Imaging Sciences & Biomedical Engineering Division, King's College London, London, UK
[3]Department of Oncology, Hammersmith Hospital, Imperial College NHS Trust, London, UK
[4]Department of Medicine, Imperial College, London, UK
[5]Department of Urology, Charing Cross Hospital, Imperial College NHS Trust, London, UK

Address correspondence to: Professor Pat Price
E-mail: *p.price@imperial.ac.uk*

ABSTRACT

High-intensity focused ultrasound (HIFU) is a rapidly maturing technology with diverse clinical applications. In the field of oncology, the use of HIFU to non-invasively cause tissue necrosis in a defined target, a technique known as focused ultrasound surgery (FUS), has considerable potential for tumour ablation. In this article, we outline the development and underlying principles of HIFU, overview the limitations and commercially available equipment for FUS, then summarise some of the recent technological advances and experimental clinical trials that we predict will have a positive impact on extending the role of FUS in cancer therapy.

Focused ultrasound surgery (FUS), using high-intensity focused ultrasound (HIFU) technology in combination with modern imaging methods, has the potential to ablate internal tumour target tissue with great precision, giving it all the benefits of minimally invasive surgery [1]. Damage to adjacent or intervening tissues may be minimised with careful image-based treatment planning and the tumour target may be visualised during treatment. As it does not involve ionising radiation, it is low risk and repeat treatments are possible. The non-invasiveness of FUS reduces toxicity compared with other ablation techniques and adjacent blood vessels may be less vulnerable to damage compared with surgical risks [2,3]. FUS therefore holds great promise as a single or part of a multimodal approach for cancer treatment, especially for patients with cancers unsuitable for other established therapeutic options.

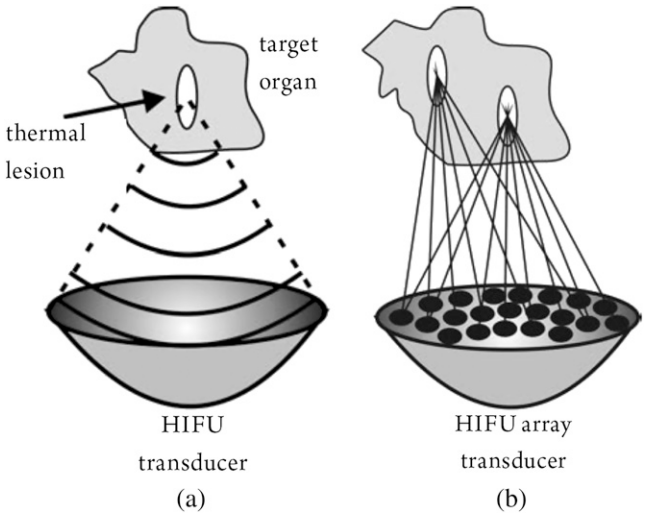
We describe how recent technical developments in HIFU equipment design, electronic control, ablation focusing and target imaging have made rapid advances that are overcoming previous limitations of HIFU for destroying target tumour tissue, especially in shortening FUS treatment times. Together with ongoing worldwide trials exploring oncology applications, this is strengthening confidence in FUS and broadening its scope. As a result, we believe that it is evolving into an increasingly more useful alternative or complementary treatment option and have continued expectation that FUS will be successfully integrated into routine future clinical practice.

PRINCIPLES OF FUS

HIFU transducers are made from piezoelectric materials that oscillate upon application of an alternating voltage, resulting in the generation of ultrasound waves in the receiving medium. They are capable of handling relatively high levels of power and focus the resulting ultrasound beam to a small "cigar"-shaped volume, typically of a few cubic millimetres. Focusing can be achieved geometrically, either by using a curved (spherical section) transducer or by using a plane transducer and a curved lens (Figure 1a). In devices that use an array of small transducers, beam focusing may also be achieved by electronic control (Figure 1b). Modern transducers can create acoustic intensities in a target tissue of ~100–10 000 W cm^{-2} and peak compression pressures of up to 30 MPa. In comparison, diagnostic ultrasound transducers deliver intensities of ~0.0001–0.1000 W cm^{-2} and a compression of 0.001–0.003 MPa [2].

Rapid elevation of the local tissue temperature is the main causative mechanism of tissue destruction. Coagulative necrosis occurs as a high amount of acoustic energy is deposited in a short period of time—a function of both tissue temperature and exposure time [3–7]. This thermal effect was the preferred mode of targeted ablation in early clinical applications of HIFU as it was most predictable and understood [4]. Mechanical tissue effects also occur at very high ultrasound intensities [3,8–10]. Cavitation, *i.e.* bubble formation, occurs as microscopic gas bodies are drawn out of solution because of alternating rarefaction and compression and local temperature elevations. A low-pressure acoustic field results in stable cavitation, where microbubbles oscillate. In turn, fluid movement leads to the production of shear forces that cause cell membrane disruption and resulting cell damage—a phenomenon known as microstreaming. With high acoustic pressures, vibration-induced changes in microbubble volume result in inertial cavitation, *i.e.* violent bubble collapse. If this happens near the cell membrane, destruction of the cell may occur [8–13]. Radiation forces are also created in tissues owing to the absorption and reflection of the ultrasound wave energy [8]. These cause additional destructive bioeffects, including cell

Figure 1. Diagram illustrating focusing principles of high-intensity focused ultrasound in single (a) and array (b) transducers. Reproduced with permission from Pioneer Bioscience Publishing Company, from Khokhlova and Hwang [16].



membrane deformation, microstreaming and organelle rotation [8,14]. Mechanical destructive effects have been increasingly exploited as HIFU understanding, experience and technological developments have advanced. Harnessing mechanical bioeffects can result in larger treatment volumes, and hence shorter treatment times, as well as achieving very sharply demarcated precise lesions. This latter effect forms the basis of "histotripsy"—a development of HIFU tissue ablation, which uses short pulses of very high-intensity ultrasound to specifically induce mechanical bioeffects for tissue destruction [3,15].

KEY LIMITATIONS OF HIFU FOR FUS

Since ultrasound is reflected at interfaces between soft tissues and air–gas and is rapidly attenuated in bone, the presence of lung, ribs or gaseous bowel in front of the FUS target region can be problematic. Sonication through the cranium is particularly challenging owing to high attenuation and variable thickness and density of the skull. In addition, non-uniform soft tissues cause the ultrasound beam to propagate variably. Therefore, an appropriate "acoustic window" may be required for an ultrasound beam to propagate through the body to the target volume, restricting the application of FUS to specific patients/tumours. Beam scattering and diffraction may also occur. Unwanted high-energy deposition to tissues in the ultrasound pathway, resulting from energy reflected from acoustically resistant media, such as air, bowel gas or bone, to tissues with strong acoustic absorbance, such as skin, muscle or the gastrointestinal tract, can lead to complications like skin burns or serious side effects like bowel perforation owing to thermal injury [3,16]. Beam scattering, diffraction and reflection therefore need to be prevented or carefully accounted for in planning and during delivery, and acoustic coupling of the transducer to the skin throughout treatment is necessary to avoid skin burns.

Compared with HIFU transducer focal volume, clinically relevant tissue target volumes may be very large. This means that the HIFU focus may have to be moved within the target volume to achieve sufficient tissue ablation, either by shooting the beam continuously while moving the transducer or by interrupting the beam and moving the HIFU focus. When combined with the need to frequently verify the location of the focus within the body by means of imaging and ensure unwanted energy deposition to avoid side effects, excessively long treatment times can result.

ADVANCES IN TRANSDUCER DESIGN AND BEAM FOCUS THAT COUNTER LIMITATIONS

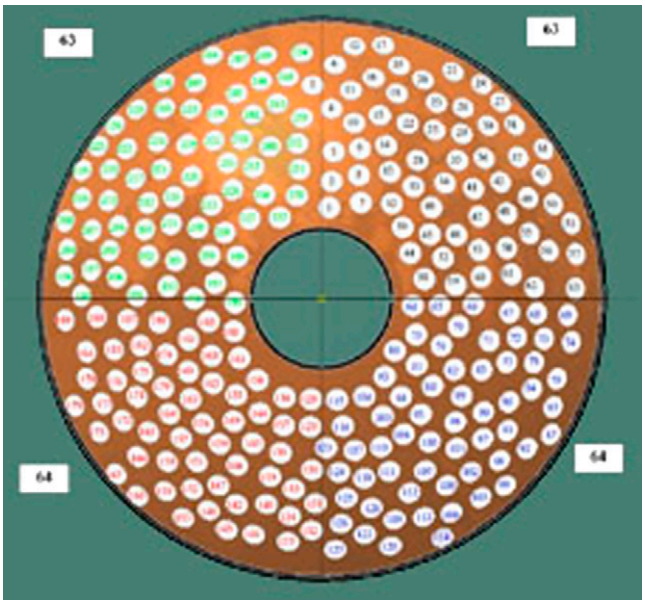
HIFU transducers need to be optimally designed for specific clinical applications. The development of piezoactive materials with specific acoustic properties, *e.g.* lead zirconate titanate-type ceramics and composites of piezoactive elements, that are capable of being driven at high power and can be tailored for the specific clinical application, has been an important step. For curved transducers, the radius of curvature, which determines the distance at which the focal volume is located, and transducer diameter, which determines the surface area, are important parameters. In the case of arrays, the size and number of individual elements required to achieve appropriate acoustic power, their spatial distribution and their relationship to operating frequency are evaluated. Often elements are placed on a curved surface to achieve some geometric focusing [17,18]. The advantage of arrays is that the electrical signals applied to each element can be varied [19]. Using multichannel electronics, the acoustic fields produced by individual elements can be used coherently to produce a single focus that can be adjusted in size, shape and position and manoeuvred through a clinically relevant volume, or several foci can be created simultaneously. This increases the overall volume that can be ablated and achieves faster treatment times. An important factor in transducer array design is the compromise between performance, which favours a large number of elements, and cost and complexity, which favours a small number of elements. Many specific designs for arrays have now been reported. For example, ablation of large deep-seated tissue volumes has been reported with a 256-element phased array [20]; high-power beam steering through human skull was demonstrated with a 200-element sparse phased array [21]; high-power acoustic fields were achieved with an intracavitary 57-element aperiodic array device designed for prostate treatment [22]; and an endorectal transducer with 1000 elements for high-resolution treatment of prostate conditions has been clinically approved [23]. One drawback associated with arrays is that of "grating lobes" caused by sound energy spreading out from the transducer in undesired directions, which occurs when the element spacing is greater than a half wavelength. Several methods to minimise this have now been reported [21,22,24,25], including a patented random array design (Figure 2), which further

reduces the time taken to deliver therapy and avoids delivering significant acoustic energy to non-targeted tissues, even when multiple simultaneous foci located off axis are produced [26].

Design and testing of a HIFU system with flexible and controllable multifocus pattern ability is another important advance. Using a 256-element spherical section phased array system capable of producing "fit-to-shape" multifocus patterns, *e.g.* X, S, C, square and Q shapes, simulation and phantom experiments showed that treatment volumes could be up to 6.6 times greater in one sonication. Further, by using three-dimensional (3D) focus steering, it was feasible for other subarrays to operate if some of the elements were blocked by ribs, providing the device with the ability to avoid obstacles [27]. Advanced phased array systems with up to 20 000 elements, allowing 3D multiple foci sonication and rapid beam steering, are currently under further technological research and development.

The new transducer design has also allowed increased exploitation of mechanical effects to enhance ablation. Controlled use of cavitation can induce larger target lesions—thus achieving reduced treatment times—and research in this area is ongoing. A new approach using an endocavitary plane transducer showed that cavitation effects were induced beyond a threshold dose of acoustic intensity in *ex vivo* studies. Further, when the cavitation effect was combined with the thermal effect, it was possible to necrose cylindrical target volumes up to 31 cm^3 in 4 min [28].

Figure 2. The spherical surface of a patented array transducer with randomly distributed elements that allows multiple simultaneous foci and minimises off-target energy delivery. Reproduced with permission from IOP Publishing Ltd, from Hand et al [26].



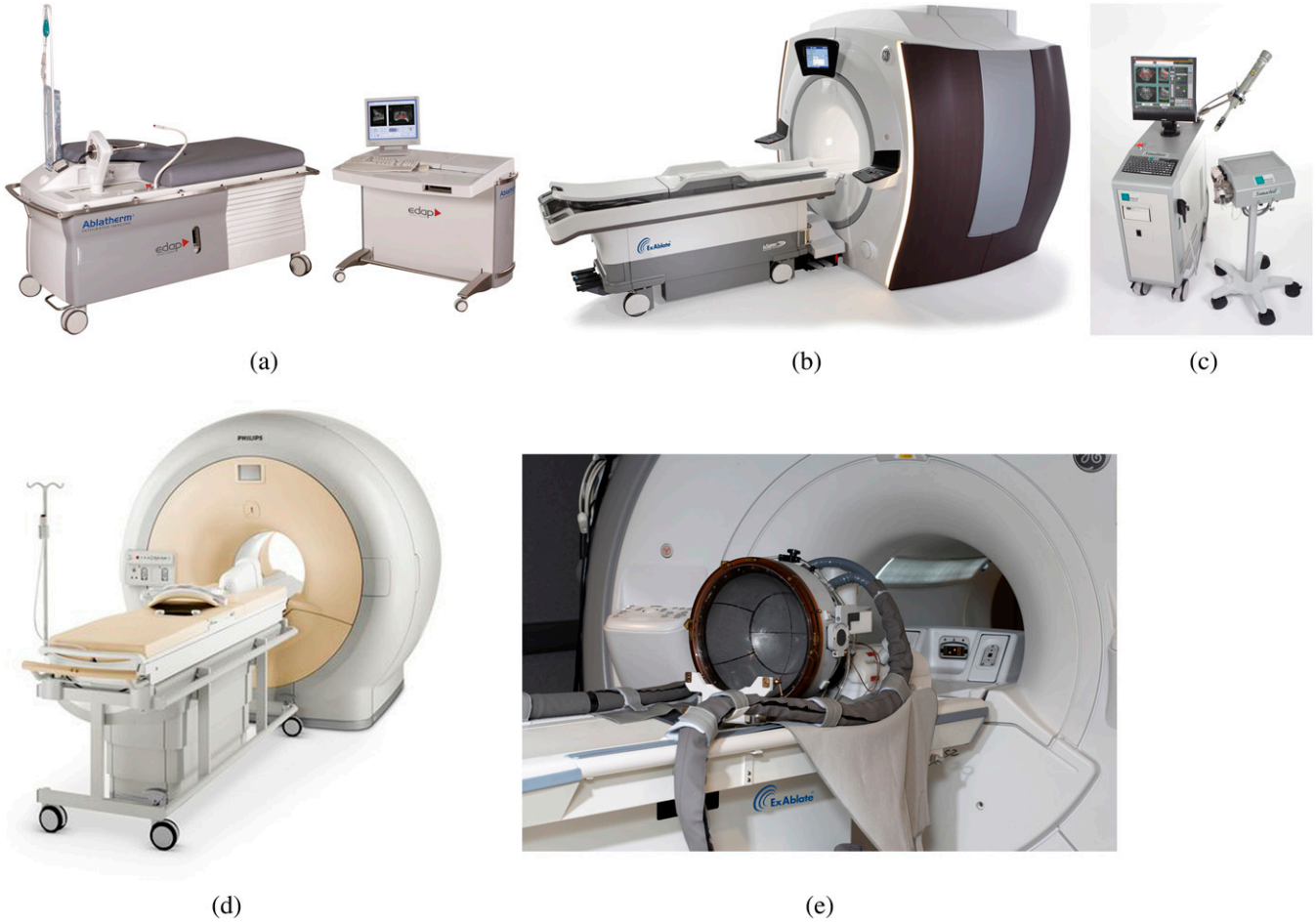
In transcranial HIFU, where skull ultrasound wave refraction can cause severe beam degradation, there have been recent important developments to improve focusing, including validation of an *in vitro* 3D CT adaptive correction method. A specifically designed 300-element spherical array therapeutic transducer was used in conjunction with CT scan acquisitions to deduce acoustic properties of the skull. Precise beam refocusing was achieved through *ex vivo* human and monkey skulls with a positioning error <0.7 mm [29]. A later development by the same group, which used MR acoustic radiation force imaging for energy-based adaptive focusing in the human cadaver head, showed greater enhancement of transcranial ultrasound beam focusing [30], paving the way for *in vivo* human trans-skull FUS.

COMMERCIAL FUS DEVICES IN CLINICAL USE

There are currently two commercially available intracavitary FUS clinical devices: the Ablatherm® (EDAP TMS, Lyon, France), which was jointly developed with the French Institute of Medical Research in the early 1990s, and Sonablate® 500 (SonaCare Medical, Charloltte, NC, previously Focus Surgery Inc., Indianapolis, IN), which was developed in the USA in 1994 (Figure 3a,c). Both use a single moveable probe, are guided by ultrasound imaging, and have been employed in trials for treating prostate cancer [31]. They also have potential application in other pelvic malignancies. Ablatherm has a robotically controlled treatment probe with dual ultrasound transducers. Sonablate 500 has a single transducer and uses a split beam technology that increases the size of the focal zone and allows near simultaneous treatment and imaging. It is more operator dependent but has the practical advantage of being fully portable.

Extracorporeal FUS devices offer a longer focal length than intracavitary devices and are more versatile overall. MRI-guided FUS (MRgFUS) extracorporeal machines include the ExAblate® system (InSightec, Haifa, Israel), which uses real-time thermometry MRI guidance (Figure 3b) and is

Figure 3. Examples of high-intensity focused ultrasound devices currently in Western clinical use or research. (a) Ablatherm® (EDAP TMS, Lyon, France), (b) ExAblate® OR (InSightec, Haifa, Israel), (c) Sonablate® 500 (SonaCare Medical, Charlotte, NC, previously Focus Surgery Inc., Indianapolis, IN), (d) Sonalleve MR-HIFU (Philips Healthcare, Guildford, UK), (e) ExAblate Neuro (InSightec). Figures are reproduced with permission from the manufacturers.



currently used worldwide to treat uterine fibroids and in Europe to treat breast cancer, adenomyosis and bone metastasis, and is being investigated in clinical trials for other uses. The Sonalleve MR-HIFU is an alternative system (Philips Healthcare, Guildford, UK), which combines an extracorporeal HIFU system and MR coil elements integrated into a patient table compatible with Philips MRI platforms (Figure 3d). A novel electronic concentric circle beam path method is used to increase ablation volumes. Sonalleve has largely been used to treat uterine fibroids in countries other than the UK but is now under investigation for oncology applications. Extracorporeal ultrasound-guided FUS (USgFUS) machines are more popular in Asia. The Model JC focused ultrasound system (Haifu Technology Co. Ltd, Chongquing, China) originated in China. It can be operated using a choice of transducers with varying focal length and has been used to treat several cancer types including liver and renal cancer [10]. Alternative USgFUS machines include the HIFU-2001 (Sumo Corporation Ltd, Kowloon, Hong Kong) machine, which has been used since 2001 to treat cancer patients in China, Hong Kong and Korea, the HIFUNIT-9000 tumour therapy system (Shanghai Aishen Technology, Shanghai, China) and the FEP-BY™ system (Yuande Biomedical Engineering Lim. Co., Beijing, China). Extracorporeal devices specifically designed for transcranial FUS include the ExAblate Neuro hemispheric phased array HIFU system, which is currently used only for neurosurgery research purposes in brain disorders (Figure 3e) [32].

CLINICAL APPLICATIONS OF HIFU IN ONCOLOGY

Prostate cancer

During the last decade, many trials have assessed intracavitary FUS as a non-invasive alternative to prostatectomy

and radiotherapy for localised prostate cancer. The UK National Institute for Health and Clinical Excellence initially supported the use of intracavitary HIFU ablation in the management of prostate cancer [33]. Although it is currently clinically used in other parts of the world, in the UK its use in the National Health Service has been recommended to be confined to clinical trials [34,35] and it is presently under interventional procedure consultation [36]. However, because of its organ-sparing and tumour control ability, retreatment potential, recent technical advances in delivery and imaging and recent promising trial results, HIFU is strengthening as a viable alternative treatment for tumour control—particularly for patients in whom localised cancer control with minimal morbidity or effective salvage are priorities [37]. For example, a review in 2009 on salvage HIFU following recurrent disease after radiotherapy reported biochemical disease-free rates, negative biopsy rates and complication rates similar to other salvage methods [38]. Similar results were reported in a 2011 study of 19 males treated with HIFU for locally recurrent prostate cancer following radical prostatectomy when good cancer control with acceptable morbidity was shown [39]. Both studies indicated better outcome for males with pre-treatment lower risk disease. A study of HIFU as salvage therapy in 22 Tokyo patients in 2011 also reported a good biochemical disease-free rate at 5 years of 52% [40]. The use of HIFU for focal salvage therapy following radiotherapy failure was also recently indicated to reduce the harms of whole-gland salvage therapies [41]. Moreover, recent encouraging results from a trial of HIFU as primary treatment in localised prostate cancer showed no histological evidence of cancer in 30 of 39 males biopsied at 6 months and a low rate of treatment-related genito-urinary side effects [42]. Non-invasive MRgFUS has also been used for prostate cancer ablation and has the advantage of improved targeting and real-time temperature monitoring, but only a few studies have been conducted with human patients [43].

Rectal tumours

Following surgery for rectal tumours, locally recurrent disease is a major concern that is often accompanied by severe pain and incapacitating complications. There is therefore an unmet clinical need for new treatments, especially for patients with residual or progressing disease in whom all current therapies have failed.

Recently, we reported the first case exploring the feasibility of intracavitary HIFU as a therapeutic option for tumour ablation in advanced rectal cancer. The patient had originally undergone surgical resection but developed recurrent local and liver metastatic disease with debilitating symptoms and was not fit for any conventional adjuvant options. Using the Sonablate 500 HIFU device, adjusted to deliver about 50% of the intensity per pulse used for prostate cancer treatment, the exophytic part of the tumour was targeted over 29 min. Symptoms improved within 24 h, there were no complications and repeat MRI at Day 7 showed tumour necrosis of the targeted area. Furthermore, the patient's overall physical condition improved to the extent that palliative radiotherapy became possible [44]. A UK Phase I/II trial has since been initiated to further investigate the feasibility and efficacy of transrectal HIFU in patients with locally advanced rectal cancer (09/H0808/43).

Liver tumours

Surgical resection or transplantation has been the gold standard treatment for both primary and metastatic liver tumours. Since the first successful HIFU liver ablation in a male in 1993 [45], extracorporeal HIFU approaches have been investigated and developed, concentrating on patients with unresectable hepatocellular carcinoma (HCC) or in whom comorbidity prevents surgery. Particular challenges include beam propagation through the ribs, respiratory movement of the liver and long ablation times owing to large tumour size and small focal volume [46, 47]. The high prevalence of HCC in China has driven HIFU technology to overcome the associated challenges, with emerging encouraging results.

A large randomised study in China in 2005 using the Model JC Haifu system in patients with stage IVA HCC reported median survival time to be significantly longer in patients who received combined HIFU and transcatheter arterial chemoembolisation (TACE) therapy (11.3 months *vs* 4 months; $p=0.004$) [48]. A 2011 Chinese study of unresectable HCC showed slightly longer median survival of 12 months after combined HIFU+TACE treatment. 45% of patients achieved complete ablation, with ablation response reported as a significant prognostic factor [49]. For HIFU treatment

alone, a report in 2011 of 49 patients from a Hong Kong cancer centre who received single HIFU treatment for unresectable HCC concluded that HIFU was an effective treatment modality with a high effectiveness rate and favourable survival outcome: complete tumour ablation was reported in 80% and local tumour control was 67% at 24 months [50]. However, serious complications have recently been reported in a minority of HCC patients, including rib fractures, diaphragmatic rupture, biliary obstruction, pleural effusion, pneumothorax and fistula formation [51]. These have arisen from unwanted thermal damage, indicating the need for caution and improved targeting of beam energy to lower risk.

Renal tumours

Many malignant renal lesions are small, so a non-invasive nephron-sparing therapeutic method is attractive. Initial studies, which used either multiple elements in a concave disc or the Storz investigational HIFU prototype device (Storz Medical, Schaffhausen, Switzerland), showed skin burns and problems with tissue ablation, inhibiting clinical use [45,52]. More contemporary extracorporeal and laparoscopic HIFU systems have produced smaller but better defined lesions and thus better results: however, they remain as investigative procedures, requiring improvements in order to compete with other ablative techniques [53]. A preliminary trial in patients with advanced renal cancers was carried out in 2003 using the Model JC Haifu device. A decrease in both flank pain (90%) and haematuria (89%) were reported with no adverse events [54]. A later study using the same device reported stable lesions in two-thirds of patients with minimal morbidity [55]. A Phase I study of laparoscopic HIFU in 2008 showed feasibility and demonstrated that this more invasive method helped to resolve the limitations caused by bowel, rib cage and abdominal wall obstruction and respiratory motion, although technological and methodological refinements were necessary to improve targeted ablation [56]. Feasibility, good tumour ablation and low morbidity with laparascopic HIFU was also shown in 2011 [57]. Methods in development, such as photoacoustic real-time monitoring [58] and respiration-induced movement correlation modelling [59], or the application of MR image guidance to monitor temperature changes for optimal heat deposition and safety [60] may improve future non-invasive renal FUS.

Pancreatic tumours

Most patients with pancreatic cancer present with inoperable disease, such that palliative treatment for local tumour control and pain relief are the main aims of treatment for which HIFU may have significant benefits. The long treatment times previously required owing to large target volumes are being addressed by the development of new multi-array devices as well as methodology harnessing mechanical tissue effects to enhance tissue ablation. Increased clinical experience is further enabling its development [16]. Early clinical studies in China supported HIFU as a primary therapy for pain relief, with no major adverse events reported [61–63]. Recent studies have confirmed pain palliation and have also indicated efficacy. A report in 2009 of all stage unresectable patients in Peking, China, treated with an FEP-BY device showed pain improvement in 80.6% of patients, an overall median survival of 8.6 months and no complications [64]. A Phase II trial in 2010 of concurrent gemcitabine and HIFU in locally advanced pancreatic cancer using a HIFUNIT-9000 system also showed promising activity, with 78% pain relief rate, 43% response rate and a median survival rate of 12.6 months [65]. In a 2011 report of mixed stage inoperable patients treated with HIFU alone, an 87.5% pain relief rate, no complications and an 8-month median survival was shown [66]. In a recent European study in 2010, all six patients with tumours in difficult to treat locations showed pain relief and full tumour ablation, with one experiencing a serious complication [67]. A minority incidence of serious complications, including third-degree burns and fistula formation, has been separately reported [51].

Breast tumours

The breast is suited to HIFU treatment as it offers a soft-tissue acoustic window and can easily be immobilised. In a 2001 feasibility study of MRgFUS of 11 breast fibroadenomas using a custom-made device, 8 lesions indicated complete or partial tissue devascularisation and necrosis [68]. In 2003, MRgFUS using ExAblate as an adjunct to tamoxifen in patients with breast carcinoma reported negative biopsies in 19 of 24 patients at 6 months [69]. A 2007 study of MRgFUS using ExAblate in Japanese females with ductal carcinoma showed only 1 case of recurrence in 21 patients over a median follow-up of 14 months [70]. Similar favourable results have been reported in China using the Model JC USgFUS device, with a 95% 5-year disease-free

survival rate [71] in one study and pathology confirming ablation in all cases in another [72]. However, limitations have included the risk of tissue damage to proximate skin, rib and lungs, which are currently being addressed by technological improvements, for example in device design [73], focal aberration correction [74] and novel contrast enhancement agents [75].

Bladder cancer

As ultrasound is commonly used as a first-line imaging method for investigation of urinary tract symptoms, HIFU offers an attractive means to visualise and treat bladder cancers at the same time. Encouraging results were reported in the first study of extracorporeal HIFU in superficial low-grade transitional cell bladder carcinoma, with no recurrence seen in 67% of treated patients [76]. However, the drawbacks of long treatment time and the need for regional anaesthesia require more research. Current interest is largely placed on ultrasound-based combination therapy [77].

Bone tumours

The first successful targeting of bone lesions using HIFU in animal models, causing necrosis of osteocytes, was reported in 2001 [78]. A key potential advantage for primary bone tumours is limb sparing. A recent study using the Model JC Haifu device showed that USgFUS was feasible and effective in primary bone malignancy. Complete tumour ablation was seen in 69 of 80 patients. Further, for patients whose tumours were completely ablated with HIFU and who completed systemic chemotherapy, the 5-year survival rate was greater than reported for other treatments [79]. Encouraging results have also been achieved for pain control of bone metastasis. MRgFUS for pain palliation in patients for whom other treatments were ineffective or not feasible showed HIFU was a safe and effective treatment option; 72% of patients reported significant pain improvement and a 67% reduction in opioid usage was recorded [80]. Supported by clinical studies, the ExAblate MRgFUS system received the European CE mark and US Food and Drug Administration approval for palliative treatment of bone metastasis in 2007 and 2012, respectively. The first UK trial testing of the Sonalleve MRgFUS system for bone metastasis is currently under way.

Brain tumours

There is great interest and potential use of HIFU in brain tumours. Enhancement of drug delivery across the blood–brain barrier (BBB) is a key active area of research, enabled by targeting BBB disruption [81,82]. However, for the development of effective and highly focused transcranial HIFU tissue ablation, physical problems caused by the skull have created significant technical hurdles (see section "Advances in transducer design and beam focus that counter limitations"). A recent pilot study in three glioblastoma patients using transcranial ExAblate showed focal heating was achieved, but greater device power was required to produce focal coagulative necrosis [83].

CONCLUSION

Non-invasive techniques that utilise HIFU to ablate tumours will enable improvements in future healthcare provision as patient morbidity can be minimised while potentially saving costs. The limitations of HIFU that have delayed its potential use in clinical practice are being overcome through advances in technology and design, ongoing research is enabling improvements and reducing risk, and experimental clinical trials for various types of tumours are showing considerable promise: for some tumour types, *e.g.* prostate and pancreatic cancer, randomised controlled trials are now required to compare FUS with standard treatments. Clinical applications of FUS are thus continuing to expand and improve and we predict that its benefits along with its increasingly clinically relevant fast treatment times will rapidly result in its adoption as a routine part of multimodal therapy for many cancers.

METHODOLOGY

A non-systematic PubMed literature search was conducted to identify relevant peer-reviewed articles published before December 2012, relating to HIFU or FUS treatment in cancer. Keywords included "high-intensity focused ultrasound", "focused ultrasound surgery", "trial", "study" and "(type) cancer" in the title and/or abstract fields, selecting only articles in English. Primary manuscripts, clinical practice guidelines and review articles were included, as were secondary references within these articles, and an assessment of their relevance to the focus of the article was performed prior to inclusion.

ACKNOWLEDGMENTS

Thanks to Dr M. Green for substantial intellectual contribution and manuscript revision.

REFERENCES

1. Wickham JE. The new surgery. Br Med J (Clin Res Ed) 1987;295: 1581–2.
2. Dubinsky TJ, Cuevas C, Dighe MK, Kolokythas O, Hwang JH. High-intensity focused ultrasound: current potential and oncologic applications. AJR Am J Roentgenol 2008; 190:191–9.
3. Zhou YF. High intensity focused ultrasound in clinical tumor ablation. World J Clin Oncol 2011;2:8–27.
4. Hill CR, ter Haar GR. Review article: high intensity focused ultrasound: potential for cancer treatment. Br J Radiol 1995;68: 1296–303.
5. Hynynen K, Lulu BA. Hyperthermia in cancer treatment. Invest Radiol 1990;25:824–34.
6. Hynynen K, Shimm D, Anhalt D, Stea B, Sykes H, Cassady JR, et al. Temperature distributions during clinical scanned, focused ultrasound hyperthermia treatments. Int J Hyperthermia 1990;6: 891–908.
7. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. Int J Radiat Oncol Biol Phys 1984;10:787–800.
8. Hynynen KH. Fundamental principles of therapeutic ultrasound. In: Jolesz FA, Hynynen KH, eds. MRI-guided focused ultrasound surgery. New York, NY: Informa Healthcare USA Inc.; 2008. pp. 5–18.
9. Kennedy JE, Ter Haar GR, Cranston D. High intensity focused ultrasound: surgery of the future? Br J Radiol 2003;76:590–9.
10. Shehata IA. Treatment with high intensity focused ultrasound: secrets revealed. Eur J Radiol 2012; 81:534–41.
11. Coleman AJ, Saunders JE, Crum LA, Dyson M. Acoustic cavitation generated by an extracorporeal shockwave lithotripter. Ultrasound Med Biol 1987;13:69–76.
12. Holland CK, Apfel RE. Thresholds for transient cavitation produced by pulsed ultrasound in a controlled nuclei environment. J Acoust Soc Am 1990;88: 2059–69.
13. Marmottant P, Hilgenfeldt S. Controlled vesicle deformation and lysis by single oscillating bubbles. Nature 2003;423:153–6.
14. Martin CJ, Pratt BM, Watmough DJ. Observations of ultrasound-induced effects in the fish Xiphophorous maculatus. Ultrasound Med Biol 1983;9:177–83.
15. Therapeutic Ultrasound Group. Non-invasive ultrasonic tissue fractionation for treatment of benign disease and cancer—histotripsy. Biomedical Engineering Department, University of Michigan [cited Jan 2013]. Available from: http://www.histotripsy.umich.edu/
16. Khokhlova TD, Hwang JH. HIFU for palliative treatment of pancreatic cancer. J Gastrointest Oncol 2011;2:175–84.
17. Gavrilov LR, Hand JW. A theoretical assessment of the relative performance of spherical phased arrays for ultrasound surgery. IEEE Trans Ultrason Ferroelectr Freq Control 2000;47:125–39.
18. Goss SA, Frizzell LA, Kouzmanoff JT, Barich JM, Yang JM. Sparse random ultrasound phased array for focal surgery. IEEE Trans Ultrason Ferroelec Freq Control 1996;43:1111–21.
19. Gavrilov LR, Hand JW. Two-dimensional phased arrays for surgery: movement of a single focus. Acoust Phys 2000;46:390–9.
20. Daum DR, Hynynen KA. A 256-element ultrasonic phased array system for the treatment of large volumes of deep seated tissue. IEEE Trans Ultrason Ferroelectr Freq Control 1999;46: 1254–68.
21. Pernot M, Aubry JF, Tanter M, Thomas JL, Fink M. High power transcranial beam steering for ultrasonic brain therapy. Phys Med Biol 2003;48:2577–89.
22. Hutchinson EB, Buchanan MT, Hynynen K. Design and optimization of an aperiodic ultrasound phased array for intracavitary prostate thermal therapies. Med Phys 1996;23:767–76.
23. Focused Ultrasound Foundation. More sites and patients join clinical trial assessing new MR-guided FUS system for prostate cancer [Updated Aug 2011; cited Jan 2013]. Available from: http://www.fusfoundation.org/Newsletter-Articles/more-sites-and-patients-join-clinical-trial-assessing-new-mr-guided-fus-system-for-prostate-cancer
24. Ellens N, Pulkkinen A, Song J, Hynynen K. The utility of sparse 2D fully electronically steerable focused ultrasound phased arrays for thermal surgery: a simulation study. Phys Med Biol 2011;56: 4913–32.
25. Raju BI, Hall CS, Seip R. Ultrasound therapy transducers with space-filling non-periodic arrays. IEEE Trans Ultrason Ferroelectr Freq Control 2011;58:944–54.

26. Hand JW, Shaw A, Sadhoo N, Rajagopal S, Dickinson RJ, Gavrilov LR. A random phased array device for delivery of high intensity focused ultrasound. Phys Med Biol 2009;54:5675–93. doi: 10.1088/0031-9155/54/19/002.
27. Mingzhu L, Xiaodong W, Mingxi W, Yi F, Feng X, Hui Z, et al. Image-guided 256-element phased-array focused ultrasound surgery. IEEE Eng Med Biol Mag 2008;27:84–90.
28. Melodelima D, Chapelon JY, Theillere Y, Cathignol D. Combination of thermal and cavitation effects to generate deep lesions with an endocavitary applicator using a plane transducer: ex vivo studies. Ultrasound Med Biol 2004;30:103–11.
29. Marquet F, Pernot M, Aubry JF, Montaldo G, Marsac L, Tanter M, et al. Non-invasive transcranial ultrasound therapy based on a 3D CT scan: protocol validation and in vitro results. Phys Med Biol 2009;54:2597–613.
30. Marsac L, Chauvet D, Larrat B, Pernot M, Robert B, Fink M, et al. MR-guided adaptive focusing of therapeutic ultrasound beams in the human head. Med Phys 2012;39:1141.
31. Gardner TA, Koch MO. Prostate cancer therapy with high-intensity focused ultrasound. Clin Genitourin Cancer 2005;4:187–92.
32. InSightec. Transcranial magnetic resonance-guided focused ultrasound surgery: current applications and progress for non-invasive neurosurgery. Tirat Carmel, Israel: InSightec; 2010 [cited Dec 2012]. Available from: http://www.insightec.com/contentManagment/uploadedFiles/fileGallery/brainwhitepapersep2.pdf
33. National Institute for Health and Clinical Excellence. High-intensity focused ultrasound for prostate cancer: guidance. IPG 118. London, UK: NICE; 2005 [cited Oct 2012]. Available from: http://www.nice.org.uk/guidance/IPG118/Guidance/pdf
34. Lukka H, Waldron T, Chin J, Mayhew L, Warde P, Winquist E, et al. High-intensity focused ultrasound for prostate cancer: a systematic review. Clin Oncol (R Coll Radiol) 2011;23:117–27.
35. National Institute for Health and Clinical Excellence. New NICE guideline on the diagnosis and treatment of prostate cancer. London, UK: NICE; 2008 [cited March 2012]. Available from: http://www.nice.org.uk/CG058
36. National Institute for Health and Clinical Excellence. Focal therapy using high-intensity focused ultrasound for localised prostate cancer—overview. IP839 London, UK: NICE; 2012 [cited Oct 2012]. Available from: http://guidance.nice.org.uk/IP/839/Overview/pdf/English
37. Uchida T, Nakano M, Hongo S, Shoji S, Nagata Y, Satoh T, et al. High-intensity focused ultrasound therapy for prostate cancer. Int J Urol 2012;19:187–201.
38. Chalasani V, Martinez CH, Lim D, Chin J. Salvage HIFU for recurrent prostate cancer after radiotherapy. Prostate Cancer Prostatic Dis 2009;12:124–9.
39. Asimakopoulos AD, Miano R, Virgili G, Vespasiani G, Finazzi Agro E. HIFU as salvage first-line treatment for palpable, TRUS-evidenced, biopsy-proven locally recurrent prostate cancer after radical prostatectomy: a pilot study. Urol Oncol 2012;30:577–83.
40. Uchida T, Shoji S, Nakano M, Hongo S, Nitta M, Usui Y, et al. High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy. BJU Int 2011;107:378–82.
41. Ahmed HU, Cathcart P, McCartan N, Kirkham A, Allen C, Freeman A, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer 2012;118:4148–55.
42. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol 2012;13:622–32.
43. Zini C, Hipp E, Thomas S, Napoli A, Catalano C, Oto A. Ultrasound- and MR-guided focused ultrasound surgery for prostate cancer. World J Radiol 2012;4:247–52.
44. Monzon L, Wasan H, Leen E, Ahmed H, Dawson PM, Harvey C, et al. Transrectal high-intensity focused ultrasonography is feasible as a new therapeutic option for advanced recurrent rectal cancer: report on the first case worldwide. Ann R Coll Surg Engl 2011;93:e119–21.
45. Vallancien G, Chartier-Kastler E, Harouni M, Chopin D, Bougaran J. Focused extracorporeal pyrotherapy: experimental study and feasibility in man. Semin Urol 1993;11:7–9.
46. Sibille A, Prat F, Chapelon JY, Abou el Fadil F, Henry L, Theillere Y, et al. Extracorporeal ablation of liver tissue by high-intensity focused ultrasound. Oncology 1993;50:375–9.

47. Fischer K, Gedroyc W, Jolesz FA. Focused ultrasound as a local therapy for liver cancer. Cancer J 2010;16:118–24.
48. Wu F, Wang ZB, Chen WZ, Zou JZ, Bai J, Zhu H, et al. Advanced hepatocellular carcinoma: treatment with high-intensity focused ultrasound ablation combined with transcatheter arterial embolization. Radiology 2005;235: 659–67.
49. Jin C, Zhu H, Wang Z, Wu F, Chen W, Li K, et al. High-intensity focused ultrasound combined with transarterial chemoembolization for unresectable hepatocellular carcinoma: long-term follow-up and clinical analysis. Eur J Radiol 2011;80:662–9.
50. Ng KK, Poon RT, Chan SC, Chok KS, Cheung TT, Tung H, et al. High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. Ann Surg 2011;253:981–7.
51. Jung SE, Cho SH, Jang JH, Han JY. High-intensity focused ultrasound ablation in hepatic and pancreatic cancer: complications. Abdom Imaging 2011;36:185–95.
52. Klatte T, Marberger M. High-intensity focused ultrasound for the treatment of renal masses: current status and future potential. Curr Opin Urol 2009;19: 188–91.
53. Nabi G, Cleves A, Shelley M. Surgical management of localised renal cell carcinoma. Cochrane Database Syst Rev 2010;3: CD006579.
54. Wu F, Wang ZB, Chen WZ, Bai J, Zhu H, Qiao TY. Preliminary experience using high intensity focused ultrasound for the treatment of patients with advanced stage renal malignancy. J Urol 2003; 170:2237–40.
55. Ritchie RW, Leslie T, Phillips R, Wu F, Illing R, ter Haar G, et al. Extracorporeal high intensity focused ultrasound for renal tumours: a 3-year follow-up. BJU Int 2010;106:1004–9.
56. Klingler HC, Susani M, Seip R, Mauermann J, Sanghvi N, Marberger MJ. A novel approach to energy ablative therapy of small renal tumours: laparoscopic high-intensity focused ultrasound. Eur Urol 2008;53:810–16; discussion 817–18.
57. Ritchie RW, Leslie TA, Turner GD, Roberts IS, D'Urso L, Collura D, et al. Laparoscopic high-intensity focused ultrasound for renal tumours: a proof of concept study. BJU Int 2011;107:1290–6.
58. Cui H, Yang X. Real-time monitoring of high-intensity focused ultrasound ablations with photoacoustic technique: an in vitro study. Med Phys 2011;38: 5345–50.
59. Abhilash RH, Chauhan S. Respiration-induced movement correlation for synchronous non-invasive renal cancer surgery. IEEE Trans Ultrason Ferroelectr Freq Control 2012;59:1478–86.
60. Grenier N, Quesson B, de Senneville BD, Trillaud H, Couillaud F, Moonen C. Molecular MR imaging and MR-guided ultrasound therapies in cancer. JBR-BTR 2009;92: 8–12.
61. Wu F, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, et al. Feasibility of US-guided high-intensity focused ultrasound treatment in patients with advanced pancreatic cancer: initial experience. Radiology 2005; 236:1034–40.
62. Xie DR, Chen D, Teng H. A multicenter nonrandomized clinical study of high intensity focused ultrasound in treating patients with local advanced pancreatic carcinoma. [In Chinese.] Chin J Clin Oncol 2003;30:630–5.
63. Wang X, Sun J. High-intensity focused ultrasound in patients with late-stage pancreatic carcinoma. Chin Med J (Engl) 2002;115: 1332–5.
64. Xiong LL, Hwang JH, Huang XB, Yao SS, He CJ, Ge XH, et al. Early clinical experience using high intensity focused ultrasound for palliation of inoperable pancreatic cancer. JOP 2009;10: 123–9.
65. Zhao H, Yang G, Wang D, Yu X, Zhang Y, Zhu J, et al. Concurrent gemcitabine and high-intensity focused ultrasound therapy in patients with locally advanced pancreatic cancer. Anticancer Drugs 2010;21: 447–52.
66. Wang K, Chen Z, Meng Z, Lin J, Zhou Z, Wang P, et al. Analgesic effect of high intensity focused ultrasound therapy for unresectable pancreatic cancer. Int J Hyperthermia 2011;27:101–7.
67. Orsi F, Zhang L, Arnone P, Orgera G, Bonomo G, Vigna PD, et al. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. AJR Am J Roentgenol 2010; 195:W245–52.
68. Hynynen K, Pomeroy O, Smith DN, Huber PE, McDannold NJ, Kettenbach J, et al. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study. Radiology 2001; 219:176–85.
69. Gianfelice D, Khiat A, Boulanger Y, Amara M, Belblidia A. Feasibility of magnetic resonance imaging-guided focused ultrasound surgery as an adjunct to tamoxifen therapy in high-risk surgical patients with

breast carcinoma. J Vasc Interv Radiol 2003;14:1275–82.
70. Furusawa H, Namba K, Nakahara H, Tanaka C, Yasuda Y, Hirabara E, et al. The evolving non-surgical ablation of breast cancer: MR guided focused ultrasound (MRgFUS). Breast Cancer 2007;14: 55–8.
71. Wu F, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, et al. Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer. Breast Cancer Res Treat 2005;92:51–60.
72. Wu F, Wang ZB, Cao YD, Zhu XQ, Zhu H, Chen WZ, et al. "Wide local ablation" of localized breast cancer using high intensity focused ultrasound. J Surg Oncol 2007;96:130–6.
73. Payne A, Merrill R, Minalga E, Vyas U, de Bever J, Todd N, et al. Design and characterization of a laterally mounted phased-array transducer breast-specific MRgHIFU device with integrated 11-channel receiver array. Med Phys 2012;39: 1552–60.
74. Mougenot C, Tillander M, Koskela J, Kohler MO, Moonen C, Ries M. High intensity focused ultrasound with large aperture transducers: a MRI based focal point correction for tissue heterogeneity. Med Phys 2012;39:1936–45.
75. Sun Y, Zheng Y, Ran H, Zhou Y, Shen H, Chen Y, et al. Superparamagnetic PLGA-iron oxide microcapsules for dual-modality US/MR imaging and high intensity focused US breast cancer ablation. Biomaterials 2012;33:5854–64.
76. Vallancien G, Harouni M, Guillonneau B, Veillon B, Bougaran J. Ablation of superficial bladder tumors with focused extracorporeal pyrotherapy. Urology 1996;47:204–7.
77. Finley DS, Pouliot F, Shuch B, Chin A, Pantuck A, Dekernion JB, et al. Ultrasound-based combination therapy: potential in urologic cancer. Expert Rev Anticancer Ther 2011;11:107–13.
78. Smith NB, Temkin JM, Shapiro F, Hynynen K. Thermal effects of focused ultrasound energy on bone tissue. Ultrasound Med Biol 2001; 27:1427–33.
79. Chen W, Zhu H, Zhang L, Li K, Su H, Jin C, et al. Primary bone malignancy: effective treatment with high-intensity focused ultrasound ablation. Radiology 2010; 255:967–78.
80. Liberman B, Gianfelice D, Inbar Y, Beck A, Rabin T, Shabshin N, et al. Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. Ann Surg Oncol 2009;16:140–6.
81. Hynynen K, McDannold N, Martin H, Jolesz FA, Vykhodtseva N. The threshold for brain damage in rabbits induced by bursts of ultrasound in the presence of an ultrasound contrast agent (Optison). Ultrasound Med Biol 2003;29: 473–81.
82. Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive opening of BBB by focused ultrasound. Acta Neurochir Suppl 2003;86:555–8.
83. McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. Neurosurgery 2010;66:323–32; discussion 332.