High Intensity Ultrasound

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High-intensity focused ultrasound (HIFU) is a technique that was first investigated in the 1940s as a method of destroying selective regions within the brain in neurosurgical research. An ultrasound beam can be brought to a tight focus at a distance from its source, and if sufficient energy is concentrated within the focus, the cells lying within this focal volume are killed, whereas those lying elsewhere are spared. This is a noninvasive method of producing selective and trackless tissue destruction in deep seated targets in the body, without damage to overlying tissues. This field, known both as HIFU and focused ultrasound surgery (FUS), is reviewed in this article.

Key words: Therapeutic ultrasound, urology, oncology, hyperthermia, thermal ablation.

Medical ultrasound is best known for its use as an imaging modality. It is often the diagnostic technique of choice in obstetrics, for example, because it is believed to be safe and not able to induce deleterious effects in the fetus or mother. The fact that it is used by physiotherapists for the treatment of soft tissue injuries shows that it is capable of inducing biological change. The main difference between diagnostic ultrasound and physiotherapy ultrasound lies in the way the sound energy is delivered, and in the acoustic power used. Ultrasound images are produced by using very short pulses (1 to 10 μs) and acoustic power levels around 200 mW. Physiotherapy uses longer pulses (10 to 100 ms) and power levels of about 1 W. The biological changes sought from physiotherapy ultrasound are usually reversible, with the aim being to facilitate function and stimulate tissue repair. If the ultrasonic power used is increased yet further (above 100 W) and pulses lasting 1 to 3 seconds are used, cell death may result. It is these high-power levels that are used in focused ultrasound surgery (FUS), a noninvasive method of inducing thermal ablation. This technique is also known as high-intensity focused ultrasound (HIFU).

Principle

Ultrasound is the term used to describe sound waves that have a frequency above the audible range (~16 kHz). For medical applications, frequencies in the low megahertz range (0.5 to 10 MHz) are commonly used. At these frequencies, the wavelength of ultrasound in tissue is short (0.15 to 3 mm). Ultrasound energy can therefore be concentrated into a small volume (focus) close to its source. This presents the possibility of using an extracorporeal source of ultrasound (a transducer) to concentrate energy on a chosen target deep within the body, thus destroying cells lying within this focal volume whilst sparing all overlying and surrounding cells (Fig 1). One such clinical device[1] uses a transducer with focal length of 15 cm to produce an ellipsoidal volume that is approximately 2 cm in length along the beam axis, and 2 mm in diameter. This focus can be swept electronically or mechanically through the target tissue in order to "paint out" the required volume. Figure 2 shows the principle diagrammatically, and figure 3 shows such an ablated volume in a porcine kidney.

Ultrasound interacts with tissue in 2 principle ways to produce cellular change. The absorption of sound energy leads to heating, and the passage of the pressure wave through tissue can give rise to acoustic cavitation.

An ultrasound beam travelling through tissue loses energy (is attenuated) by 2 main mechanisms. Some of the energy is scattered out of the main beam by tissue structures and some is absorbed. Sound scattered back towards the source may be used to form a diagnostic image. The absorbed energy goes primarily to heating the tissue. For most diagnostic ultrasound applications, the temperature rise induced is low and biologically insignificant (0.1°C to 0.2°C). How-

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1071-5517/01/0801-0009$35.00/0

doi:10.1053/slas.2001.24402

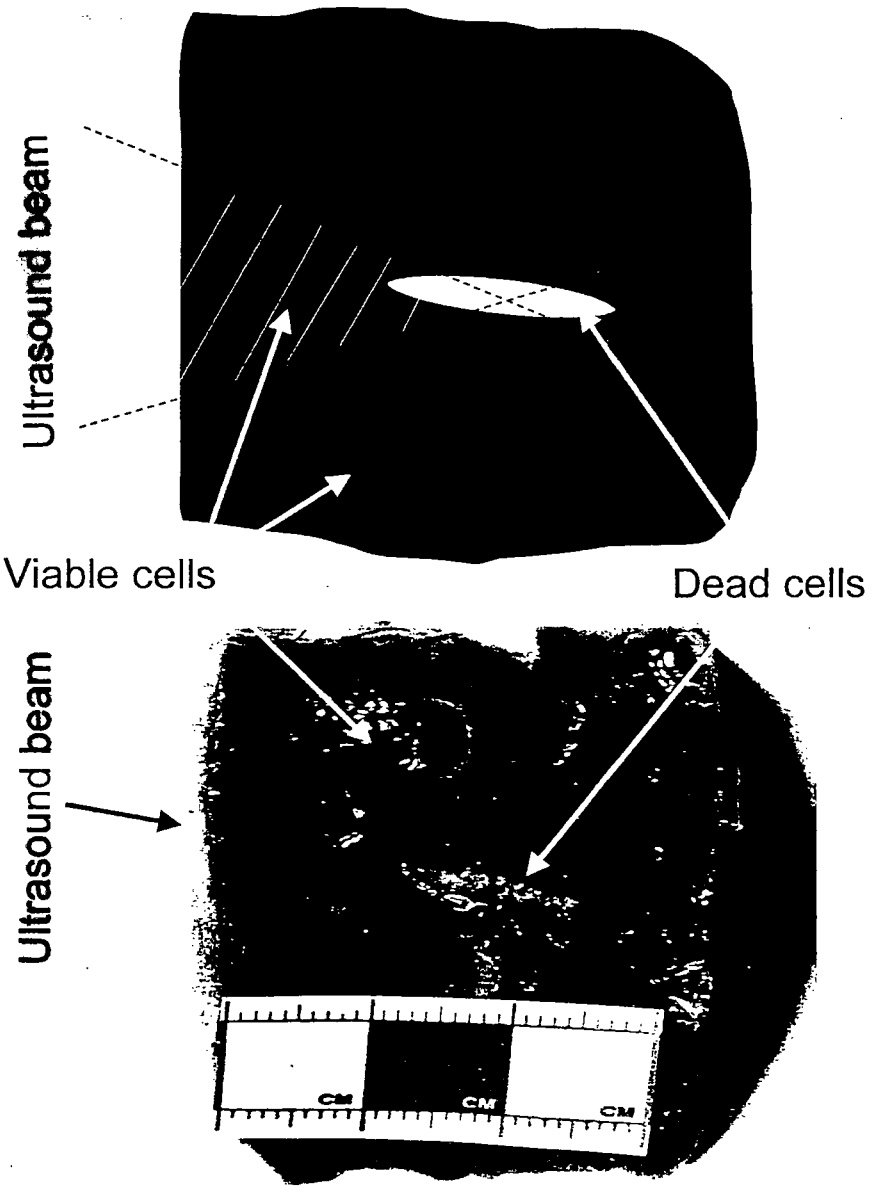

Figure 1. Schematic diagram showing the principle of focused ultrasound surgery. Only cells lying within the focal volume (in white, top;) are killed.

ever, for focused ultrasound surgery the aim is to raise the temperature to ~56°C in the target volume. Research has shown that a temperature of 56°C maintained for 1 second will cause immediate cell death. There is a well-established relationship between the temperature reached and the time for which it must be maintained to kill cells.[2] For temperatures above 43°C and for every degree drop in temperature, it is necessary to double the exposure time to get the same biological effect. In a tightly focused beam, the isotemperature contours are ellipsoidal in shape. If the lesion margins are at 56°C, the center of the focal volume has reached a temperature in excess of 70°C (Fig 4). Considerable effort has gone into predicting temperature distributions in high-intensity ultrasonic fields to facilitate treatment planning.[3]

Acoustic Cavitation is the formation and activity of gas bubbles in response to an ultrasonic field. This can give rise to destructive effects in cells. It is the negative portion of the pressure wave that draws gas out of solution in tissue, forming microscopic bubbles. The pressure variation in the sound beam causes these bubbles to vibrate, thus setting up

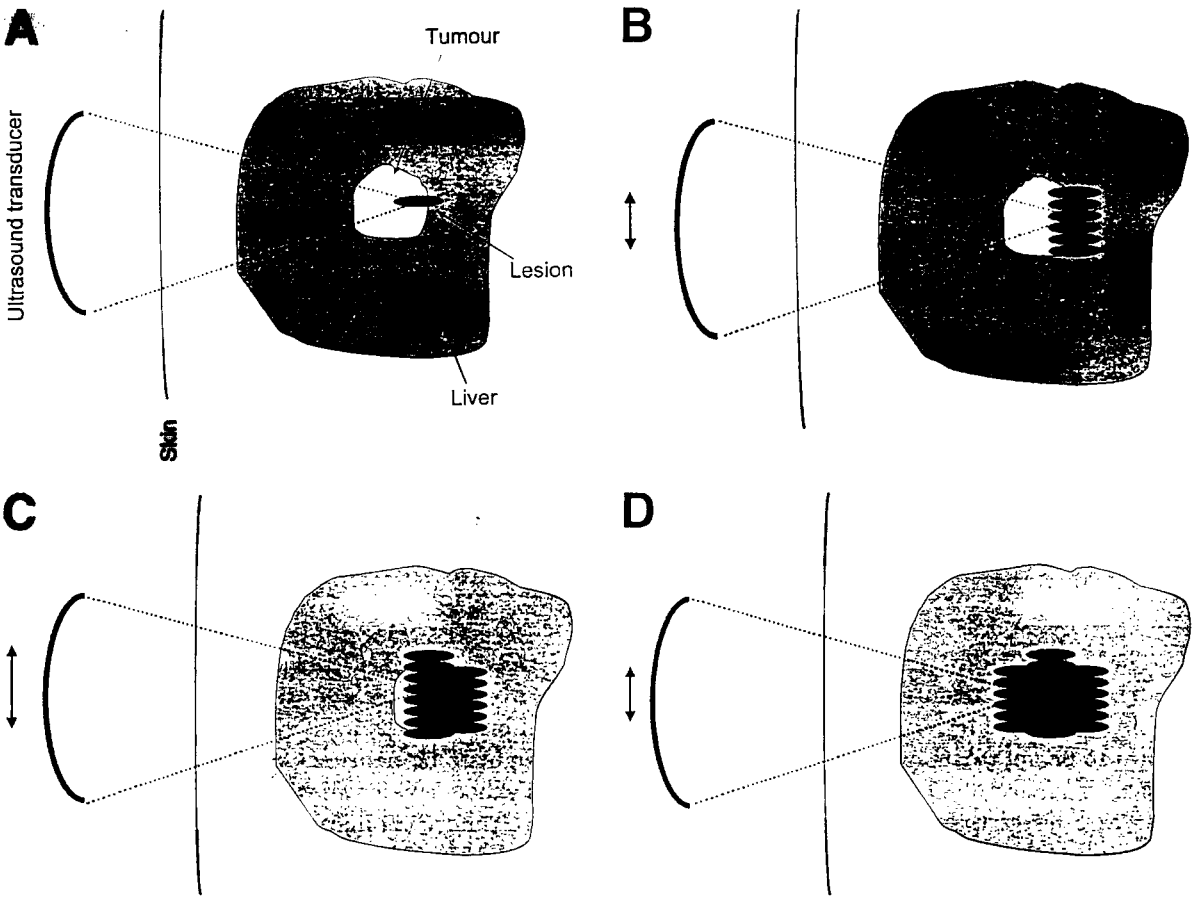

Figure 2. Schematic diagram showing the manner in which a chosen volume can be painted out. Cells at the back of the region are targeted first, because ablation of tissue changes the acoustic properties of the tissue.

local shear stresses that may, for example, alter membrane permeability and diffusion of ions across cell membranes; or, if sufficiently great, may disrupt extracellular membranes.[4] If the acoustic conditions are correct, resonance may occur, and the bubble will undergo unstable oscillations, leading to eventual collapse, which results in very high local temperatures ($\sim 10^3$K) and pressures. This is known as inertial cavitation, and results in obvious holes and tissue tears seen in histological sections. This is a threshold phenomenon, occurring only when the negative pressure exceeds the value necessary to draw gas out of solution. Whereas such bubble activity is improbable during diagnostic ultrasound exposures, it has been shown to occur in acoustic fields such as those used in high-intensity therapy ultrasound applications.

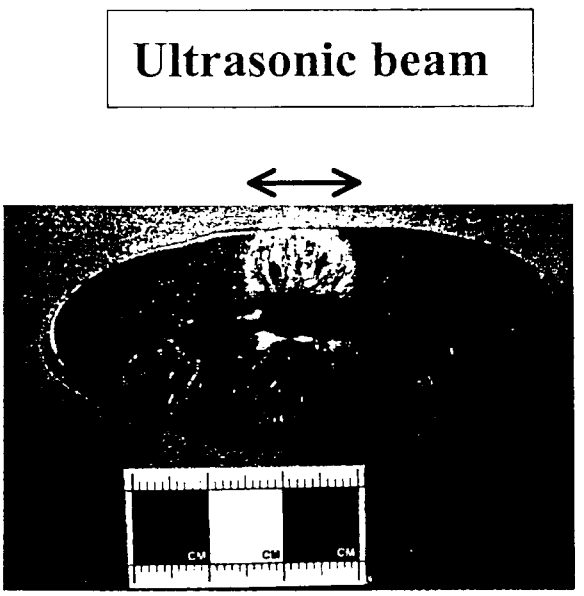

Figure 3. FUS array in porcine kidney, showing the confluent volume of cooked tissue.

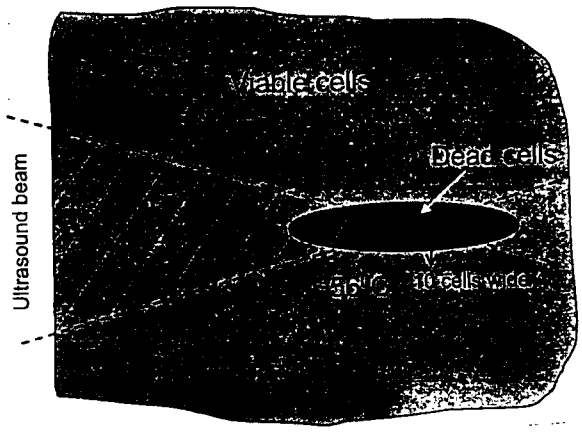

Figure 4. The temperature at the boundary of the ablated volume is 56°C, held for 1 to 3 seconds.

Histological Appearance of Tissue Damage

The most striking feature of FUS damage is the sharp demarcation between viable and non-viable cells at the lesion boundary. This has been shown to be approximately 10 cells wide.[5] This is shown in Figure 5. The microscopic appearance of an FUS lesion has been described as that of an island and moat, and is similar to that found when a wire threaded through tissue is heated.[6] This structure is shown in a lesion in a canine prostate in Figure 6. Cells within the island show coagulative necrosis.

The majority of histological studies have been performed on the brain. Vykhodtseva et al[7] used magnetic resonance (MR) thermometry techniques to attempt to correlate tissue temperature with severity of damage observed. Within the limitations of the spatial and temporal resolution inherent in the MR method, they concluded that at temperatures of 60°C to 67°C, the tissue damage seen was coagulation necrosis, followed by local hemorrhages caused by destruction of blood vessels; whereas at temperatures above 67°C, they observed total coagulation of all tissue proteins, including autolytic enzymes, and all tissue components, including blood and blood vessels. No hemorrhage was seen at these temperatures. Chen et al[8] reported neuropil vacuolation with widely separated and swollen neuronal processes in the center of brain lesions. No intact neurons could be detected, but collections of electron-dense cytoplasmic material lacking intact plasma membranes or nuclei were found. These were thought to be neuronal remnants.

Vykhodtseva et al[7] quote a threshold temperature-time combination of 53°C for 10 seconds for cell killing. Using the thermal dose concept of Sapareto and Dewey,[2] this is roughly equivalent to the lesion boundary temperature of 56°C held

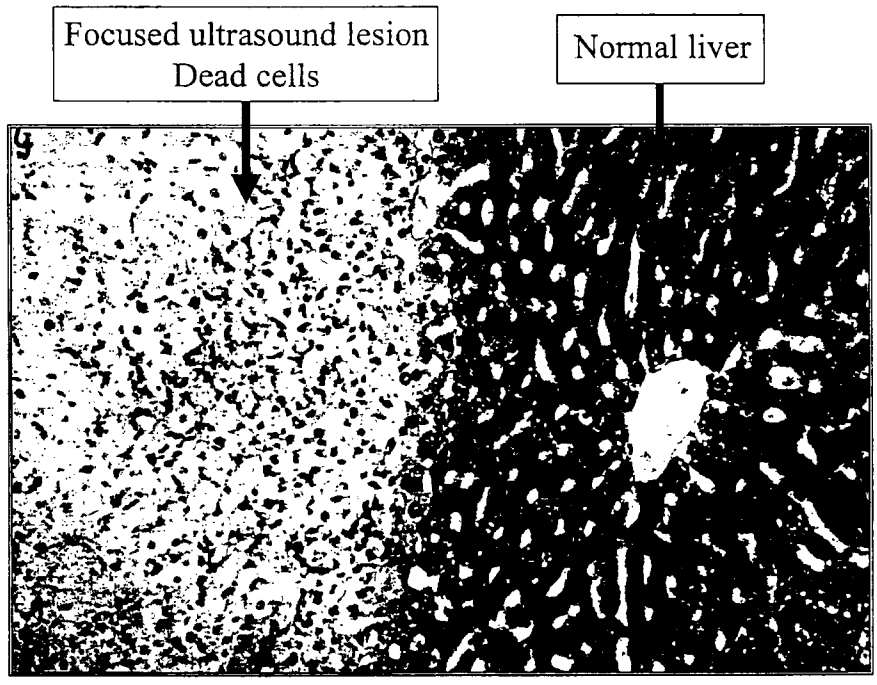

Figure 5. Histological section showing the boundary between live cells and dead cells. This has been shown to be 6 to 10 cells wide.

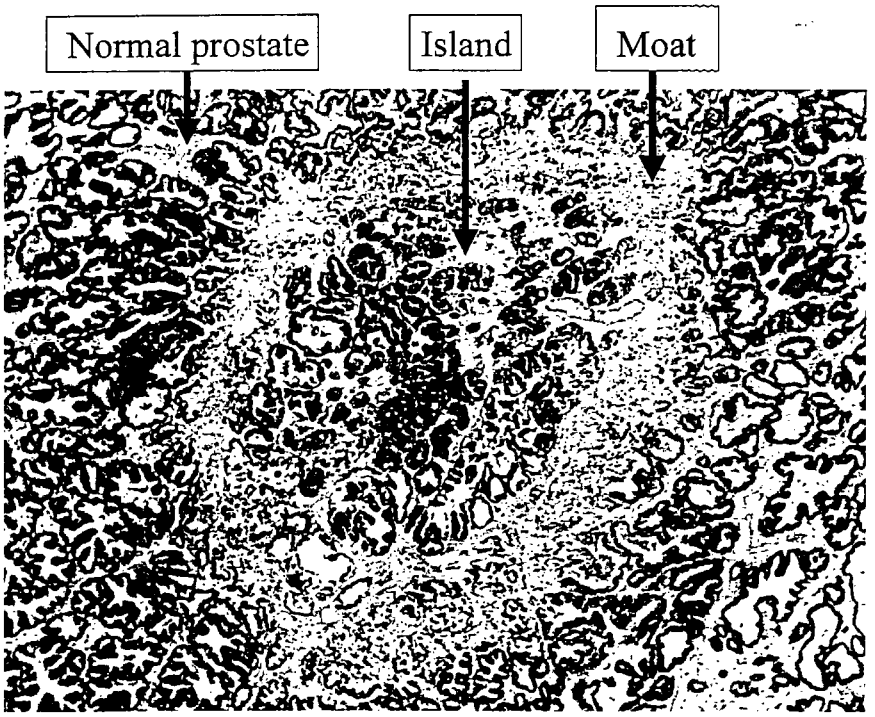

Figure 6. Transverse section of an FUS lesion in a canine prostate, showing typical island and moat structure.

for 1 second quoted by Hill et al.[9] In the brain, it appears that synapses may be the first structures to show damage, but mitochondria are also affected early.[10,11] There is a gradation of damage across the lesion cross-section that reflects the temperature. A similar distribution has been seen in the liver. Two hours after FUS exposure, the lesion boundary contained a rim of glycogen-free cells no more than 10 cells thick. The cells within this rim were dead 48 hours later.[5] Arefiev et al[12] reported that FUS lesions in the liver were characterized by parenchymal cell disruption, with total disorganization of the hepatic architecture and vascular structures.

Similar descriptions of damage are given when the target organ is the kidney. Adams et al[13] refer to the lesioned tissue as having pale eosinophilic cytoplasm, and containing cells without nuclei. Van Leenders et al[14] have studied histopathological changes after FUS treatment of localized human adenocarcinoma in the prostate. They reported that, in the center of FUS lesions, epithelium was desquamated into the gland lumina and showed homogenized eosinophilic cytoplasm. The nuclei of epithelia and stromal cells, if present, were pyknotic. At the edge of the lesioned volume, glands were lined by hyperplastic epithelium, and there was extensive hemorrhage. An immunohistochemical study of the expression of cytoskeletal proteins (pancytokeratin & cytokeratin8), PSA and Ki67, showed effects only with CK8, which was not expressed in treated tissue.[14] Electron microscopic examination of CK8-negative adenocarcinomas that looked undamaged under conventional light microscopy showed necrosis, with cells lacking extracellular and nuclear membranes and organelle structures.

Equipment

Medical ultrasound is generally produced using piezo-electric crystals. These vibrate in response to an applied oscillating voltage. At the frequencies used for therapeutic ultrasound (0.5 to 5 MHz) the wavelength in soft tissues is short, 3 mm at 0.5 MHz, 0.3 mm at 5 MHz. This means that ultrasound can be brought to a tight focus close to its source. A number of focusing techniques may be used for ultrasound surgery. The simplest to use is a spherical, curved shell of piezo-electric material. These focused bowls have been used effectively as extracorporeal sources to create FUS lesions in the brain, prostate, liver, breast, and kidney, both in experimental animals and in humans.[11,15,16] The main disadvantage of these spherical shell transducers is that the focal

volume is at a fixed distance from the source. Flexibility in focal length may be achieved by combining a plane transducer with an acoustic lens. If a set of lenses is used, a range of focal lengths may be achieved. Acoustic lenses are generally made from materials that have an acoustic impedance that is well matched to both the ultrasound transducer and water, and that have a sound velocity greater than that of water (eg, perspex). Concave lenses are therefore needed to obtain a convergent beam. The disadvantage of the transducer-lens combination is that there may be significant power loss in the lens material. More recently, phased arrays that allow electronic beam steering have been developed.[17-20] These give not only a range of focal length from a single source, but also allow different configurations of focal volume to be used.

It has generally been accepted that the only tissues that may be targeted using HIFU are those for which there is a clear acoustic path from the skin to the volume of interest, namely those that do not have bone or gas overlying them. However, it has been shown more recently that it may be possible to use phase array techniques to perform therapy through the skull bone without damaging the skull, while still maintaining the focus.[21-24] This is an exciting development that may increase the applications of FUS into neurosurgery.

Clinically, 2 types of FUS equipment have been used: transrectal devices for urological applications, and extracorporeal sources for transabdominal use. The transrectal probes incorporate both imaging and therapy elements into 1 unit, and are inserted per rectum for ablation of the prostate. In 1 design (the "Sonoblate," Focus Surgery, Indianapolis, Indiana)[25] a 4-MHz transducer is used alternately for imaging and therapy, and in another (the "Ablatherm," EDAP-Technomed, Lyon, France)[26] the therapy is performed with a 2.25-MHz source, and the imaging uses a retractable 7.5-MHz transducer.

Extracorporeal systems have 1 of 2 basic geometries. The source may either be mounted on a gantry over the patient, or may be incorporated into the bed on which the patient lies. In a modification of a commercial lithotripter, Vallancien et al[27] used a multielement 1-MHz transducer with 320-mm focal length that incorporated a 3.5-MHz imaging transducer into its center. This was mounted below the bed in a large water bath covered with a waterproof membrane, which provided coupling to the supine patient. A similar geometry is used by a system designed to be compatible with magnetic resonance imaging ("Exablate," Txsonics). In this case, a 1.5-MHz spherical bowl with a focal length of 10.3 cm lies in a water bath incorporated into the scanner couch.[28] This geometry has been used to target tumors of the kidney, breast, and uterine fibroids.

An alternative geometry, used at the Royal Marsden Hospital, London, England, uses a 10-cm diameter, 1.7 MHz 150-mm focal length spherical bowl mounted on a gantry over the patient. Acoustic coupling is achieved through a bag of degassed water placed in good contact with the skin.[1] This system has been used to target tumors of the liver, kidney, and prostate.

In general, the main problem with FUS is the small volume of tissue ablated per unit time, and vigorous attempts are being made to increase this to shorten treatment times. An original development, however, has been the miniaturization of a HIFU. In the prototype, a plane transducer working at 5 or 10 MHz has been embedded into the tip of a stainless steel tube that is 8 cm long and 3.8 mm in diameter. Rotation of the transducer on its axis results in a cylinder of tissue destruction around it.[29] This prototype has been modified for digestive endoscopy and intraductal therapy to allow its introduction into 4.2-mm accessory channels in therapeutic duodenoscopes. It has a channel for a guide-wire and is connected to a flexible shaft.

Ultrasound cannot travel significant distances through air, so it is essential that a coupling medium is present to allow transmission of the acoustic energy from the source into the body. For applications in which the transducer is held in contact with the skin, as in diagnostic imaging, this is achieved using an aqueous gel, but for other applications, a bath of degassed water is used. For transrectal applications this may be a water-filled balloon, whereas for extracorporeal devices this may be an open bag[1] or a membrane-covered bath on which the patient lies.[28]

Mode of Energy Delivery

The principle of FUS is that a very high energy pulse of ultrasound is delivered to the target very rapidly. If the pulse is sufficiently short, the temperature rise achieved is independent of the

blood supply to that tissue volume because there is not time for cooling mechanisms to have a significant influence. This makes prediction of temperature distribution more reliable and obviates the need for continuous real-time thermometry. It has been shown that if the pulses are less than 3 seconds long, the damage seen is perfusion independent.[30,31] Whereas cytotoxic temperatures are only achieved within the focal volume, tissue lying in the beam path between the source and the target may also be warmed. Because the acoustic properties, such as attenuation coefficient and cavitation threshold, are temperature dependent, it is important to allow this intervening tissue to cool between successive exposures, so that reproducible and predictable FUS damage may be achieved.[32] For this purpose, it has been shown that a regime of a 1 to 2 seconds of heating pulse followed by 60 seconds of cooling gives good results.

Ultrasonic exposures are conventionally described in terms of the beam intensity; ie, the energy crossing a specified area in a given time. The units for this are W cm^{-2}. Typically, FUS uses intensities at the focus, in tissue in situ of 1000 to 1500 W cm^{-2}.[1,33] The literature quotes several different types of intensity. Focal peak intensities are the highest values found in the field. In situ intensities are the values at a point in the tissue that have been calculated by taking the beam's attenuation by overlying tissue into account. The choice of frequency depends on the depth of target to be treated and the size of focal volume required. It ends up being a compromise between the need to keep the attenuation low to allow sufficient energy to reach the target, and the necessity of having sufficient absorption in the focal volume to ensure adequate temperature rise in the tissue of interest. Higher frequencies result in smaller focal spots and tend to be used for more superficial treatments because acoustic attenuation increases with frequency. Typically, for prostate applications, 2.25 to 4 MHz is used, and for transabdominal applications 1 to 2 MHz is used.

Applications

High-intensity focused beams were first used for selective tissue destruction in the 1940s and 1950s.[34,35] The initial intention was to provide a method of destroying specified regions of the brain to aid neurosurgical research and behavioral studies. The first reports of human applications were in 1960,[36,37] but the technique did not gain much clinical acceptance until the 1990s, probably for a number of reasons. First, it happened that for the clinical applications under consideration, successful alternative therapies were introduced at the same time. The drug, L-dopa, was brought out for the treatment of Parkinson's disease. This was a simpler solution than the lifting of the skull flap that was necessary for brain exposures with FUS. At the time that FUS for ophthalmology was being introduced, laser surgery was also becoming popular. Second, the sophisticated magnetic resonance and ultrasonic imaging techniques used today were not available. This meant that precise targeting of the focal volume and real-time monitoring of tissue ablation were not feasible. The revival of interest in the 1990s was probably caused by the introduction of thermal ablation therapies, primarily for the treatment of benign prostate disease and cancer.

Clinical applications of ultrasound that have been investigated are in the fields of neurosurgery, ophthalmology, urology, and oncology. More recently, cardiologic and gynecologic applications have also been considered.[38,39]

Benign Disease

Early attempts to place FUS lesions in the brain were not successful because the skull was left intact.[34,35] This resulted in small lesions in the brain, but profound damage to the scalp. It was not until a skull flap was raised, thus creating an acoustic window, that lesions were successfully created in the brain.[40-42] Recent research into transskull exposures may make this application more feasible.[21-24] It appears that white matter is more susceptible to damage than grey matter.

Fry et al[36] reported the treatment of 50 patients with Parkinson's disease. The procedure, which lasted 14 hours, involved craniotomy. The substantia nigra and ansa lenticularis were exposed under local anesthetic. Ballantine et al[37] reported complete pain relief in 7 patients with painful neuromata. Neither of these reports appear to have been followed up.

FUS has been used successfully to treat glaucoma,[43] retinal detachment,[44] and vitreous haem-

orrhage,[45] and to seal traumatic capsular tears.[46] Although this field achieved some measure of success, it has not found widespread application, most likely because of the apparently simpler technology of lasers.

Urological targets are particularly well suited to focused ultrasound surgery using either transrectal probes, or transabdominally (through a full bladder where necessary). Lesions have been placed in the bladder wall in experimental models,[47] and superficial bladder tumours have been treated in humans.[27,48] The kidney has also been selectively ablated in in vivo models,[49-52] but there has not been much clinical exploitation of this as yet, although renal tumors have been targeted in a phase I study.[53]

Benign Prostate Hyperplasia

The organ of most interest to urologists investigating focused ultrasound surgery is the prostate. Transrectal ultrasound imaging is often the diagnostic method of choice in the prostate, therefore it is a natural step to attempt to incorporate ultrasound diagnosis and therapy into one probe. Interest in prostate FUS started with the possibility of treating benign prostate hyperplasia (BPH) in this way. The current gold standard treatment of BPH, transurethral resection (TURP), carries with it a significant morbidity rate and usually requires a general anesthetic. It was postulated that FUS could provide a minimally invasive technique that could be conducted on an outpatient basis. Coagulative necrosis has been induced in canine prostates, and temperatures in the range of 55°C to 60°C have been recorded.[25,26] Four weeks after treatment, cystic cavities were seen lining the urothelium. In human prostates, FUS damage was seen as hemorrhagic necrosis after 1 week. Granulation tissue was seen at 10 weeks.[54]

Initial results from clinical trials[26,55,56] showed encouraging results, with increased flow rates and decreased postvoid residual volumes. However, there is some indication that these results are not maintained. Uchida et al[57] reported an average 42% increase in flow rate, and a 42% decrease in International Prostate Symptom Score (IPSS) score 12 months after treatment (n = 57) using the "Sonoblate." Madersbacher et al,[58] using the same transrectal device, found that the peak flow-rate change dropped from +30% at 12 months to +12% at 4 years. The decrease in IPSS score of 57% seen at 12 months remained approximately constant during the following 3 years. In this study of 98 men, they found that there was a 35.9% risk of needing a TURP 3 years after FUS treatment, with 43.8% of patients having had a TURP after 4 years. These investigators suggested that the need for retreatment with TURP may be attributed to 1 of 3 reasons: (1) the small volume of prostate being targeted (25% to 30%), (2) the creation of a fibrotic scar, or, most probably, (3) the fact that obstructive tissue at the bladder neck was not effectively treated. The transrectal probe that was used has been redesigned to allow for ablation of tissue from the verumontanum to 5 mm above the bladder neck.[57] In a comparative study of minimally invasive therapies for BPH and TURP, FUS was found to be of comparable efficacy to TUVP (transurethral electrovaporisation), VLAP (visual laser ablation), and TUNA (transurethral needle ablation). Whereas it might be expected that 3% to 8% of patients having TURP might have needed a second resection after 2 years, it was found that 25% of patients receiving 1 of the minimally invasive therapies needed secondary treatment within 2 years. However, the side effects of the minimally invasive techniques are considerably less than those with TURP. Although transrectal FUS was performed under spinal anaesthesia (or, more rarely, general anaesthetic) in these studies, it was free from the blood loss associated with TURP.

Tumor Ablation

FUS has been shown to be effective in treating tumors in experimental animals.[59-63] The efficacy of treatment is highly dependent on treatment planning, because the temperature drops off rapidly at the lesion edge, and with it the cytotoxic effect. This gives a very precise margin between viable and dead cells, therefore placement of successive ultrasonic exposures is crucial. However, it has been shown that, when confluent coverage of a tumor is achieved, complete tumor eradication is possible.[64,65]

The possibility of increasing metastatic spread has been considered by a number of groups. Fry and Johnson reported an increase in the rate of metastases,[59] but this has not been substantiated by other investigators.[62,63,66,67] In a more recent

study, Oosterhof et al[68] found no significant difference in the metastatic rate between FUS-exposed tumors (23%) and controls (25%) in the highly metastic AT-6 Dunning R2237 rat prostate tumor model when the tumors were subjected to clinical-type exposures from the "Ablatherm" device.

Clinical Trials in Humans

Transrectal HIFU has been used for the treatment of prostate carcinoma since 1992. Clinical trial results are now beginning to be available. In all the trials, patients with stage T1 and T2 prostatic cancer were treated mainly under spinal anaesthesia but, in a few cases, under general anaesthetia. Early results using the "Ablatherm" device showed that 50% of patients had no evidence of residual tumor at 6 months, and that the mean prostate-specific antigen (PSA) level dropped from 12.0 ± 10.0 ng/ml before treatment to 2.94 ± 3.27 ng/ml in this time.[69] Subsequent reports from this team, and others using the same equipment, show an improvement in this response, apparently caused by modifications in treatment technique.[33,70-73] Individual exposures lasting 4.5 to 5 seconds, with 5 to 12 seconds between them, are used. This allows tissue to be ablated at the rate of approximately 10 g/hour. A suprapubic catheter is inserted after treatment and remains in place for 5 days. A common finding is that successfully treated tissue shows coagulative necrosis of glandular tissue, and sometimes of periprostatic fat and the proximal part of seminal vesicles.[70] The tissue becomes necrotic within 3 months of treatment and may show an inflammatory response. Circulating prostate cells were found 30 minutes after treatment in 23% of patients who had none detected before treatment. An increase of 64% in cell numbers was measured for those patients who already had circulating cells. Patients reported the passing of necrotic debris through the urethra. Tumor response was assessed by monitoring of PSA levels and by randomized biopsy 1, 3, 6, and 12 months after treatment. The PSA level rose by more than a factor of 10 immediately after treatment, peaking at 12 hours, and then dropping rapidly.

Gelet et al[73] have divided the response into 4 groups: (1) The *complete response* group; patients who had initial prostate volumes less than 50 cc and mean initial PSA levels of 6.7 ng/ml, which dropped on average to 0.9 ng/ml over the 4 years of follow up. These patients showed no sign of residual tumor after FUS treatment (1 to 4 sessions); (2) *biochemical failures;* patients who had no evidence of residual cancer after treatment, but the mean PSA dropped only from 10.08 ng/ml before treatment to 6.02 ng/ml at the end of the study period. This group had large prostates before treatment (>50 cc). These patients were retreated when the residual cancer became obvious; (3) *biochemical control;* patients whose mean prostate volume before treatment was less than 50 cc and who had evidence of residual cancer after treatment, but their mean PSA level dropped from 8.99 to 0.9 ng/ml. The residual tumour lay anteriorly, adjacent to, and beyond the capsule. These patients were retreated when the PSA had risen to a level of 3.0 ng/ml or above; (4) *treatment failures;* patients who had initial prostate volumes of 41 ± 25 cc and initial PSA values of 18.12 ng/ml. After FUS treatment there was evidence of residual tumor, and the mean PSA level dropped to 8.96 ng/ml. These investigators have reported that 87% of their patients showed local control following transrectal FUS.[33] Local control was defined as negative biopsy, or residual cancer foci associated with a PSA level less than 4.0 ng/ml. Similar control rates have been reported by Beerlage et al.[70] Disease-free survival appears to be best predicted by a stable PSA level rather than its absolute value.[33]

The improvement in response is caused by modifications in probe design. A fixed focus device was used initially. This meant that in large glands, tissue anterior to the focal volume was not ablated. This problem has been addressed both by increasing the focal length (and thus the depth of tissue beyond the rectal wall that may be targeted) and introducing variable focusing. In addition, glandular tissue closest to the rectum remained untreated at times, because probe cooling meant that tissues closest to it did not reach toxic temperatures. This can be ameliorated by adjustment of the cooling fluid temperature, but care is necessary to ensure that the rectum is not overheated.

Few side effects have been observed with the technique. For 315 patients treated in Munich, Germany, the mean time spent in the operating theatre was 165 minutes.[74] Reported adverse events ranged from "a few hours of rectal pain" to "recto-urethral fistula" (4/315). However, in

the last 100 patients treated after technical modifications had been implemented, none of these events were recorded. The problems that remained were urinary tract infections (8%), mild stress incontinence (1%), and a decreased erection rate. As might be expected after an ablative treatment that coagulates the prostate gland, all patients suffered ejaculation problems. It has been noted that surgery is not an option after failure of FUS because the fibrosis of the posterior portion of the prostate, which persists for 3 months, makes dissection impossible.

These early results of clinical trials indicate that FUS may have a useful role to play in the treatment of prostate cancer. It may be of particular use in salvage treatments for locally recurrent disease after radiotherapy. Beerlage et al[75] compared the results obtained with cryosurgical ablation of the prostate (CSAP), brachytherapy, FUS, and radiofrequency interstitial tumour ablation (RITA). They concluded that although it was too early to make definitive conclusions about FUS and RITA, CSAP and brachytherapy give similar results to TURP. More recent FUS results indicate that it also has a similar success rate when performed with the newest treatment devices.

The only published clinical trial of treatments outside the prostate is from the Royal Marsden Hospital in the UK.[1,53] Using an extracorporeal source gantry mounted above the patient, soft tissue tumors lying 4 to 12 cm below the skin surface have been treated in fully conscious, unsedated patients. Tumors of the liver, kidney, and prostate were targeted. In this phase-I study, no significant side effects were noted. Patients reported sensations ranging from "mild heating" or a "pin prick" to "moderate pain" during the ultrasonic pulse. Treatment only had to be stopped when pulses of 3 seconds in duration were used at in situ intensities greater than 1500 W cm^{-2}. In treatment of the liver, reported pain sensations were reduced when the focus was set deeper into the organ. It was assumed that this was because the acoustic intensity at the liver capsule (where the pain sensors lie) was thereby reduced. A phase-II trial for the treatment of isolated liver metastases has shown a reduction in the carcinoembryonic antigen (CEA) tumor marker, and changes in appearance on MR or computed tomographic images.

Vascular Occlusion and Hemostasis

It has been shown that high-intensity ultrasound beams can interrupt blood flow and occlude vessels. This has been shown under several different circumstances. Hynynen et al[76,77] have shown occlusion of rabbit renal arteries, and Rivens et al[78,79] have occluded femoral vessels in the rat. Several potential applications have been suggested, including treatments of varicose veins, the occlusion of supply vessels in fetofetal transfusion syndrome, and the occlusion of tumor feeder vessels. Another application of this may lie in the treatment of hepatic injury. A high-intensity focused beam swept through the liver cauterizes the tissue through which it passes. This may act to stop bleeding. Vaezy et al[80,81] have shown that profuse bleeding in cut liver slowed to an "ooze" in less than 2 minutes, and complete hemostasis was achieved in 80% of cases in 3 minutes. This technique is also being investigated for use in the noninvasive sealing of catheter wounds.

Comparison with Other Thermal Ablation Techniques

FUS will inevitably be compared with other minimally invasive ablation methods. Laser and radiofrequency techniques bear the most similarity to FUS.[82,83] They both require the insertion of probes directly into the tissue of interest, which requires local or general anesthetic, and carries with it the risk of seeding tumor cells along the instrumentation track in cancer applications. The main advantages of these techniques are that there is no relative movement between the heating probe and the tissue, and the volume of tissue in each shot is relatively large. FUS does not require the introduction of instruments directly into the target tissue, and may be used in the fully conscious and sentient patient as an outpatient technique. However, the volume of tissue ablated per second is small. Sophisticated techniques may be necessary to track the position of the focus relative to the target volume. All of these methods may be monitored using MR imaging if the sources are made to be magnetically compatible. FUS may also be monitored with diagnostic ultrasound, with the imaging and therapy beams emanating from the same probe.

Conclusions

FUS is a novel technique that is rapidly gaining acceptance for a number of applications. It provides a noninvasive method of selective tissue destruction at depth. The treatment may be monitored in real-time using MR or ultrasonic techniques. There are still some technical improvements to be made, such as speeding up the ablation of large tissue volumes, but it is predicted that these will soon be readily available.

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