Focused Ultrasound: The Future of Noninvasive Surgery

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Medicine is ever changing, as is the discipline of surgery. During the last decade, surgery has experienced a technological renaissance driven primarily by the desire to provide patients less invasive surgical treatments with shorter operating times, hospital stays, and recuperative periods. Many traditional open surgical procedures are now being replaced with endoscopic and laparoscopic techniques.[1,2] As these minimally invasive techniques become sublimated in medical practice, the quest to develop truly noninvasive techniques continues in many medical specialties.

THE ACOUSTIC KNIFE

A new noninvasive approach to surgery is rapidly evolving using High-Intensity Focused Ultrasound (HIFU), which has potential for general surgical utility akin to the laser. Through the use of HIFU as an "acoustic knife," this nonionizing energy source has the ability to ablate selected tissues thermally inside the body without injuring intervening tissue. Through HIFU ablation, the surgeon may perform bloodless, noninvasive surgical treatment of solid tumors in all parts of the body with shortened operating times, lower morbidity, and shorter recovery time resulting in substantial cost savings to the healthcare system.

History

Medical use of high-intensity ultrasound is not a new concept. In fact, early studies evaluating the biologic effects of *unfocused* high-intensity ultrasound were reported by Wood and Loomis in 1927 using unicellular organisms, tissues, fish, and frogs.[3] Eight years later, Gruetzmacher discovered that the ultrasound beam could be focused with a concave lens and thus increase the energy density in the focal zone.[4] In 1942, Lynn and coworkers described the results of in vitro studies in which focal lesions were produced deep within a block of bovine liver without damaging surrounding tissue.[5] In the early 1950s Fry et al. developed a unique HIFU device that consisted of

Figure 1. Professor William Fry pictured with an early HIFU device designed to focus the energy from four separate transducers into a single focal zone. (Courtesy of the Indianapolis Center For Advanced Research, Indianapolis, Ind.)

four focused ultrasound generators (Fig. 1). These generators were mechanically aligned to produce a single focused region of high-intensity ultrasound that was used to produce discrete lesions in the cat brain. This technique was further developed and subsequently used in human studies through a craniotomy incision to produce focal lesions in the pallidofugal and nigral complexes in patients with hyperkinetic and hypertonic disorders.[6]

Researchers, realizing the potential of the acoustic knife, expanded their studies to include cancer treatment.

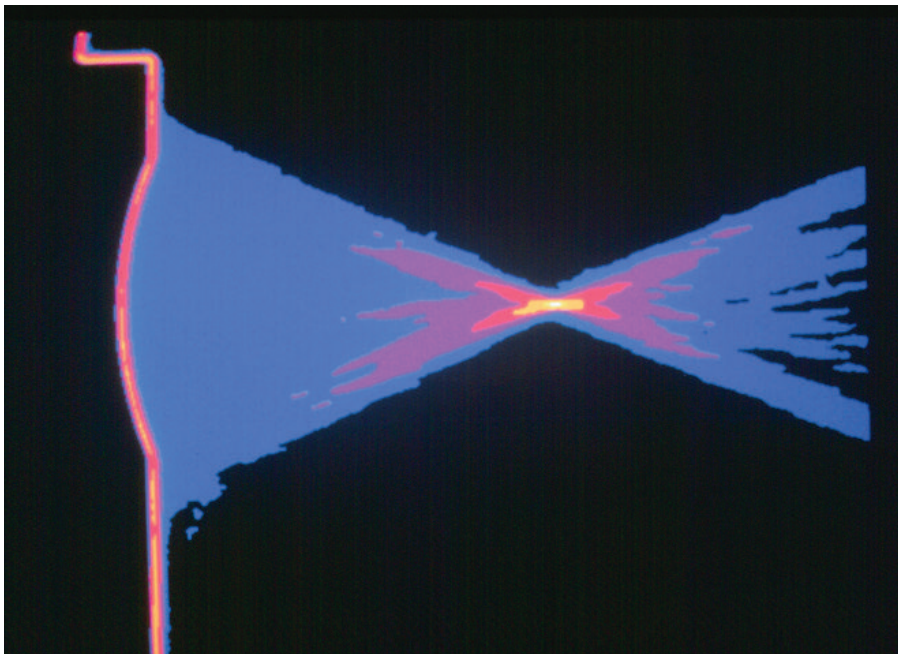

Figure 2. Color-coded Schlieren photograph demonstrates the discrete focusing ability of the HIFU transducer. Lethal zone is color-coded yellow and red. (Courtesy of Intec Research Company, Sunnyvale, Calif.)

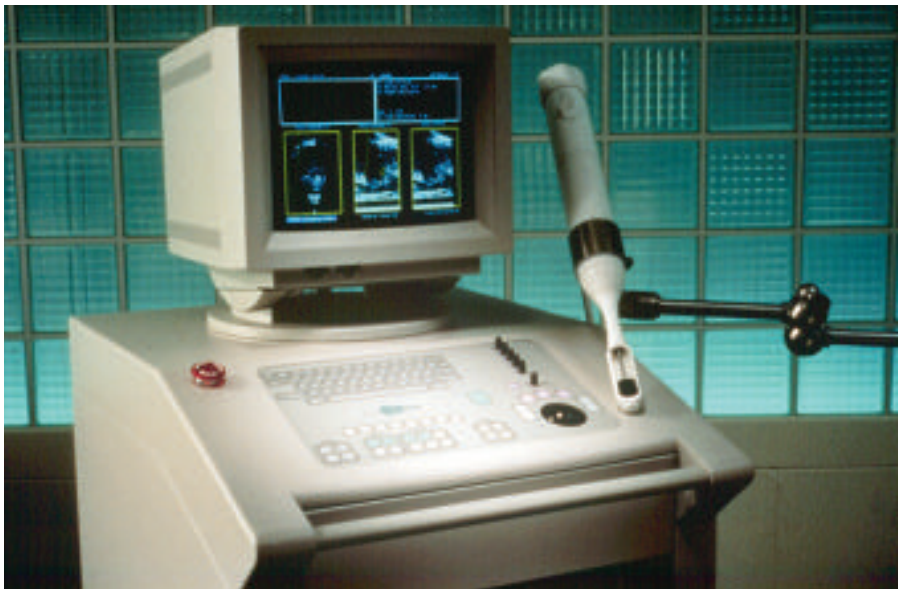

Figure 3. The Sonablate acoustic ablation system incorporates an endocavity probe that houses a dual function transducer that provides both imaging and HIFU for therapy.

Borov and Andreevskaya in 1956 reported on treating tumors implanted in rabbit testes and cutaneous melanoma in humans.[7] In 1964 and 1977, Oka reported HIFU treatment of cancers of the breast, thyroid, and lymph nodes of the supraclavicular fossa.[8,9] This was followed by Linke et al.[10] who in 1973 applied HIFU to the treatment of hepatic tumors.

A major challenge to HIFU ablative surgery was the process of accurate tissue targeting, often requiring elaborate stereotactic techniques that were exceedingly time-intensive. In the mid-1970s, a group at Indiana University Medical Center headed by Fry and Sanghvi[11] developed the first dual transducer HIFU system. The device incorporated one ultrasound transducer for low energy B-mode imaging and a second for the delivery of HIFU. This device provided the ability simultaneously to visualize diseased tissue and target the selected tissue for HIFU treatment.

In the 1980s, theoretical research was conducted at numerous sites to evaluate the interaction of high-energy sound waves with tissue. In 1985, Heimburger[12] reported on the clinical use of HIFU for the treatment of malignant brain tumors. And in the late 1980s, a unique dual function transrectal HIFU probe was developed as a joint project between The Indianapolis Center for Advanced Research (ICFAR) and the Department of Urology at Indiana University School of Medicine. This system was subsequently developed into a commercial product, the Sonablate™ (Focus Surgery, Fremont, Calif.), now being used clinically outside the U.S.A. to treat BPH.[13-15] This system is also being used experimentally for the treatment of prostate cancer,[16,17] as are several extracorporeal ablation systems for the treatment of breast cancers and fibroadenomas.

Technical Considerations and Instrumentation

The basic principle of acoustic ablation involves the interaction of mechanical vibratory energy (ultrasound) with biological tissue. When acoustic energy is propagated through a media, it loses intensity due to reflection, scattering, and/or absorption. The fact that acoustic waves behave similar to light waves and can be focused with a “lens” allows the

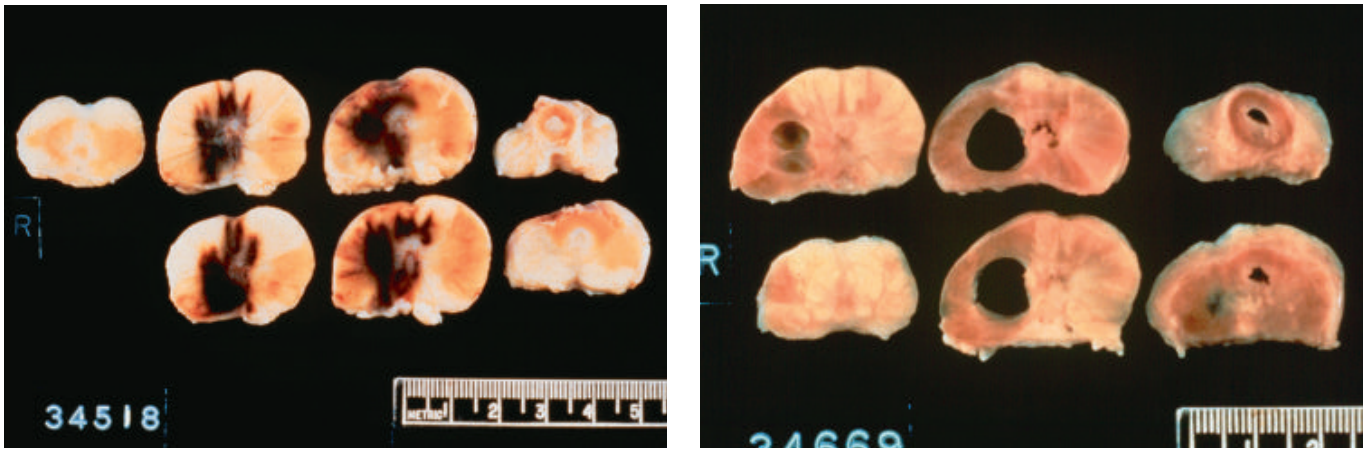

Figure 4. Canine prostate treated with HIFU shows coagulation necrosis at 72 hours posttherapy (left) and a re-epithelialized cavity at 28 days posttreatment (right). (Courtesy of Dr. R. Bihrle, Dr. R.S. Foster, Indiana University Medical Center, Indianapolis, Ind.)

potential for acoustic ablation. The "lens" in this situation is typically a specialized transducer, either physically shaped with a specific radius of curvature (Fig. 2) or electronically driven to converge upon a highly discrete focus (less than 0.5 cm^3). Given the distance of the transducer from the targeted tissue, the attenuation of that tissue, and local tissue perfusion characteristics, the acoustic power (and its rate of delivery) can be determined to assure cellular coagulative necrosis (at temperatures ranging between 65° to 100°C) within the treatment region.

Since acoustic ablation is inherently an ultrasound-based procedure, its applications are at most limited to those organs observed with conventional diagnostic ultrasound. As such, designs for various surgical ablation probes can well be expected to proceed rapidly based upon optimal designs arrived at during the history of diagnostic ultrasound. Transrectal probes for the treatment of prostatic disease are already being used clinically (as previously noted), and endovaginal probes are likely to become available in the near future. Because of the high power output required of HIFU ablation transducers, they are typically larger than standard diagnostic ultrasound transducers in order to shape their focus and thus avoid heating of adjacent tissue. Thus, new probe designs are likely to occur based on the size and geometry required to deliver the HIFU dosage required for effective ablation.

The need for substantial power amplification, a targeting/localization system, and significant safety circuitry suggests that a minimal work station is a necessary component of any acoustic ablation system. The size and complexity of the workstation can be anticipated to vary widely based upon the imaging modality used to monitor therapy. The two favored modalities, ultrasound and magnetic resonance imaging (MRI), offer distinct benefits and drawbacks.

Acoustic ablation systems utilizing ultrasound-based imaging have already been produced with an outward appearance resembling a conventional ultrasound system (Fig. 3). These systems are mobile and therefore useful in both the hospital or private clinic settings. The ablation system may be used with multiple probes designed for specific applications. In some instances a single probe may be used for both imaging and therapy which can simplify the procedure and optimize tissue targeting, treatment application, and patient monitoring during treatment.

Visualization or measurement of the tissue effect caused by HIFU presents yet another challenge. For benign conditions, echogenic response of the targeted tissue is a sufficient indicator of coagulative necrosis within the targeted region. However, at present, ultrasound-based systems have difficulty in targeting non-echogenic tumors (which may change in the future with the introduction of Albunex® or other ultrasound contrast agents). Also, the inability to quantify exactly the region of necrosis during treatment currently poses another difficulty for ultrasound-based ablation systems. Research involving color Doppler imaging (to assess differences in perfusion following acoustic ablation), ultrasonic thermal mapping, and/or the use of thermoactive markers are considered likely techniques that may provide confirmation of

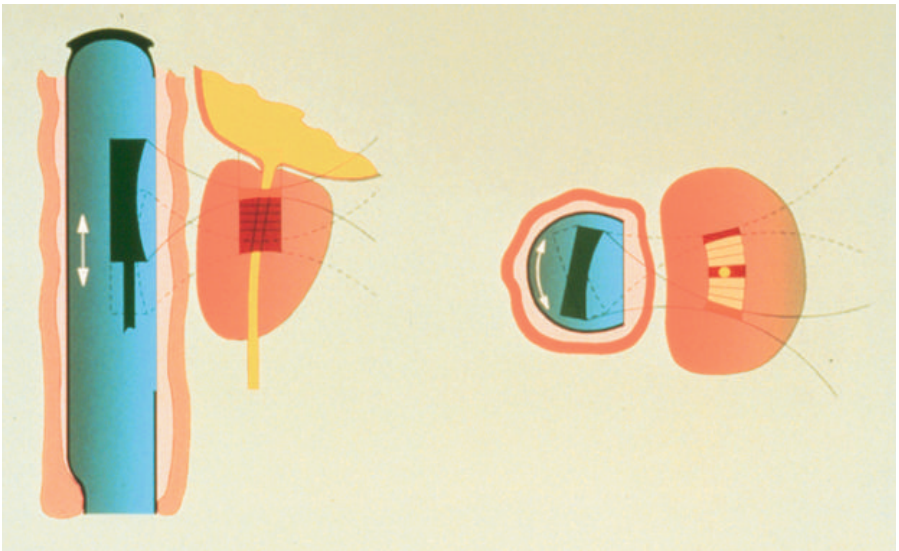

Figure 5. For BPH, the computer-controlled transducer ablates prostate tissue between the bladder neck and the verumontanum. Focal lesions are overlapped in linear rows (left) at each of the lateral sector positions (right) to create a volume lesion.

successful necrosis.

Prototype MRI-compatible acoustic ablation devices are being experimentally used for imaging and monitoring the formation and dimensions of the necrotic tissue volume. While an MRI/HIFU ablation system may be extremely expensive and require a dedicated room, it does offer several distinct advantages. MRI provides high-resolution images that are sensitive to the rise in temperature generated by HIFU. Therefore through the use of temperature maps, dosimetry can be adjusted resulting in a more precise definition of the tissue volume to be ablated.[18] MRI is also superior to ultrasound in distinguishing soft tissue lesions and is capable of detecting the edematous response of tissue following exposure to acoustic ablation. However, as with ultrasound, MRI data is not yet able to distinguish at the time of treatment between edematous tissue that is viable versus that which is not. Recent studies with thermal mapping may provide a solution to this limitation.[19] Both ultrasound-guided and MRI-guided ablation devices have advantages and disadvantages; however, it is certain that these two imaging modalities will play an important role in the future development and utility of focused ultrasound surgery.

TECHNIQUE

The three primary types of acoustic ablation treatments are extracorporeal, endocavity, and intraoperative. All are performed in generally the same manner, although intraoperative procedures require general anesthesia, a sterile environment and surgical techniques to prepare for treatment. This typically requires open resection to expose and immobilize the target organ for access to the ablation probe.

Depending upon the nature of the ablation treatment, patients are prepared by cleansing the region with which the ablation probe will make contact (including shaving or enema administration, when necessary) in order to assure optimal transmission of acoustic power. This will usually include the application of acoustic coupling gel to both the patient and the probe.

Sedation is administered according to the procedure being performed. Typically, either intravenous analgesia or epidural anesthesia are sufficient, except for patients undergoing intraoperative ablation.

The probe is then manipulated until an image of the pathologic tissue within the targeted organ is identified, and imaging confirms a lack of significant reflective obstacles (bone, air, calcifications) in the acoustic path. The physician then defines the region to be ablated (either via cursor, joystick, or light pen). The ablation system is given a signal by the physician to begin treatment and automatically steps through the various positions to assure that all areas of the targeted region are thoroughly necrosed. Updated images during treatment assure that no patient movement has occurred.

Once the procedure is completed, patients (except those having completed an intraoperative session) are typically released on the same day as treatment. Necrotic tissue is either sloughed (when connected to a lumen) or reabsorbed via phagocytosis over a three- to six-month interval.

CLINICAL APPLICATIONS

Benign Prostatic Hyperplasia (BPH)

Animal trials of the Sonablate HIFU system for treatment of BPH began in 1988 at Indiana University Medical Center.[20] The dog model was used to prove the concept of HIFU-induced coagulation necrosis followed by sloughing and reabsorption of the necrotic periurethral tissue (Fig. 4).

Human trials were initiated in Europe at the University of Vienna in June 1992 and at Indiana University in September 1992. To date, over 600 patients with symptomatic BPH have been treated worldwide at 20 medical institutions.

The patient is placed in a modified lithotomy position and administered either general, epidural, or intravenous sedation. The probe is positioned in the rectum using ultrasound guidance, and the support arm is locked to hold the probe in a fixed position. The probe is aligned so the focal zone covers the region to be ablated. For BPH therapy,

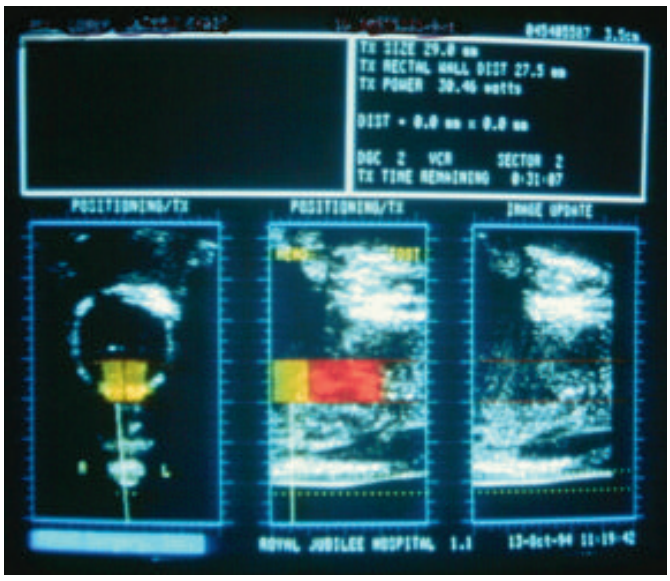

Figure 6. During HIFU therapy, the image screen shows the prostate tissue treated (red) and the region untreated (yellow). (Courtesy of Dr. P. Pommerville, Royal Jubilee Hospital, Victoria, B.C., Canada)

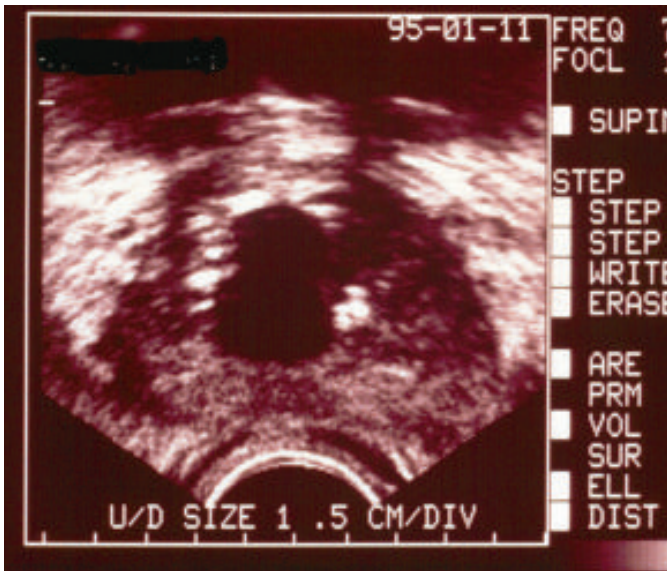

Figure 7. TRUS shows a large centrally located cavity in a human prostate at 90 days posttreatment. (Courtesy of Dr. P. Pommerville, Victoria, Canada)

the usual area of treatment is the periurethral tissue from the verumontanum to the bladder neck. The automated treatment is under computer control and follows a specific lesioning sequence to create a defined volume lesion in the prostate (Fig. 5). During therapy, ultrasound imaging provides monitoring of the treatment. The untreated area of the targeted tissue remains yellow while the treated area is color-coded red (Fig. 6). This process continues until all longitudinal positions and lateral sectors are treated, thus creating a volume lesion in the transitional zone of the prostate. In some patients a well-defined cavity can be detected with cystoscopy or transrectal ultrasound (Fig. 7) about 90 days posttreatment after the process of sloughing the necrotic tissue is complete.

Although results to date are preliminary, published results suggest that the majority of BPH patients treated with the Sonablate have experienced greater than a 50% improvement in symptom score and quality of life.[21,22] Postoperative complications have been minimal and patients can resume normal activities within days after HIFU treatment.

RESEARCH APPLICATIONS

Prostate Cancer

Prostatic adenocarcinoma is one of the most common malignancies in men. Its prevalence is highest in men older than 50 years, and its incidence increases with each subsequent decade. Since the advent of PSA, the diagnostic profile for prostate cancer is shifting to earlier detection, and it is now estimated that approximately 60% of all newly diagnosed cases will be clinically localized.[23] If prostate cancer can be detected early, proper treatment may result in an increased cure rate. At present, surgery (radical prostatectomy) and radiation therapy are the curative treatments of choice. There still remains a need for an "ideal" treatment that will cure the disease, be less invasive and well tolerated, and cause minimal or no complications or side effects. HIFU ablative surgery for localized cancer has the potential to provide such a cure. High-intensity ultrasound is now being evaluated at a number of sites worldwide for the treatment of localized prostate cancer and for palliative purposes in patients with later-stage disease.

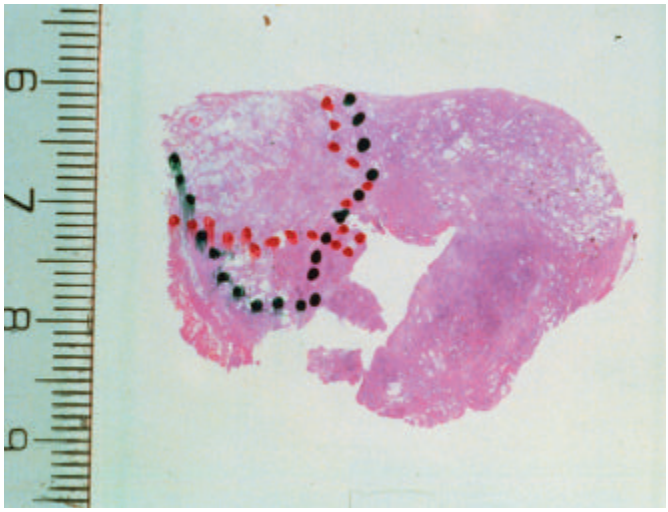

Figure 8. Postsurgical histology demonstrates the region of localized prostate cancer (red dots) and the area of HIFU-induced necrosis (green dots) from a patient who was first treated with HIFU followed by a radical prostatectomy. (Courtesy of Professor M. Marberger, University of Vienna, Austria)

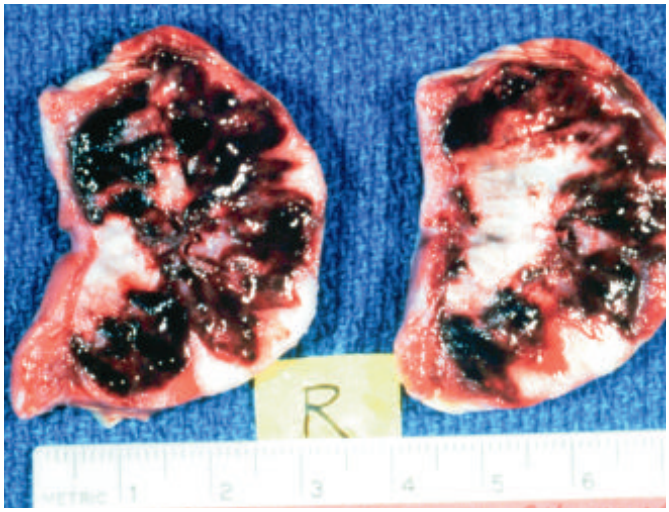

Figure 9. Canine prostate shows widespread coagulation necrosis immediately after HIFU ablation of the entire organ. (Courtesy of Dr. R. Bihrle, Dr. R.S. Foster, Indiana University Medical Center, Indianapolis, Ind.)

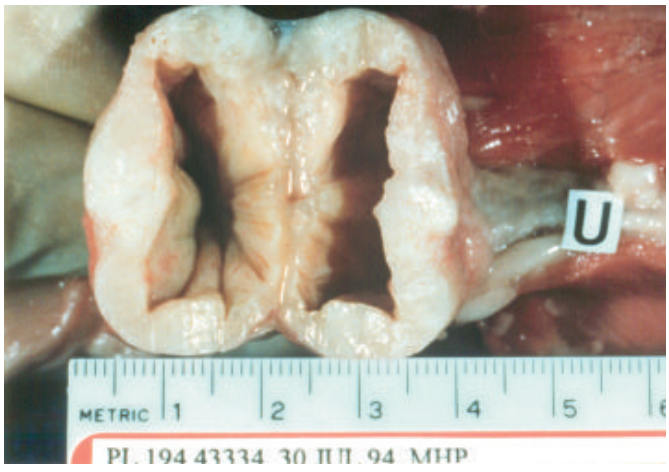

Figure 10. Ten weeks after large volume ablation with HIFU; the canine prostate shows a large central cavity surrounded by a rim of tissue. Studies are underway to ablate the entire prostate. (Courtesy of Dr. R. Bihrle, Dr. R.S. Foster, Indiana University Medical Center, Indianapolis, Ind.)

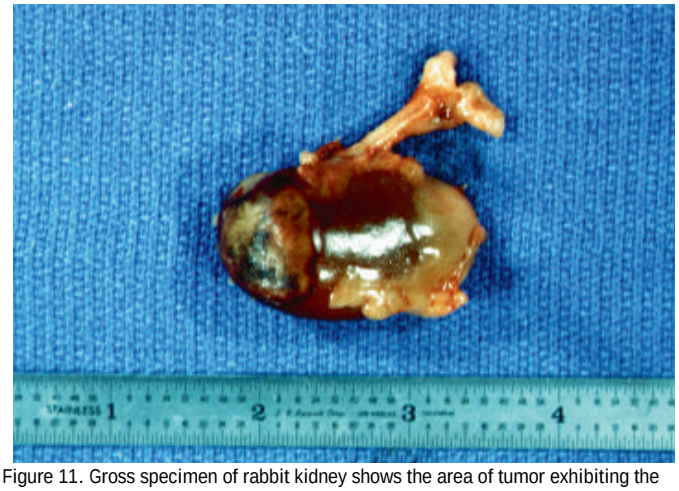

Figure 11. Gross specimen of rabbit kidney shows the area of tumor exhibiting the effects of HIFU-induced ablation.

Early-Stage Localized Prostate Cancer

Since HIFU energy can be guided to specific sites inside the prostate, localized destruction of focal tumors can be accomplished. Marberger et al. reported on the use of transrectal HIFU in the prostates of 38 patients with localized prostate cancer who subsequently underwent radical prostatectomy.[24] Postsurgical histology confirmed accurate mapping of coagulative necrosis in the region of the diseased tissue in most patients (Fig. 8). Ultrastructural analyses revealed complete necrosis of both tumor tissue and surrounding normal tissue in the HIFU targeted region.

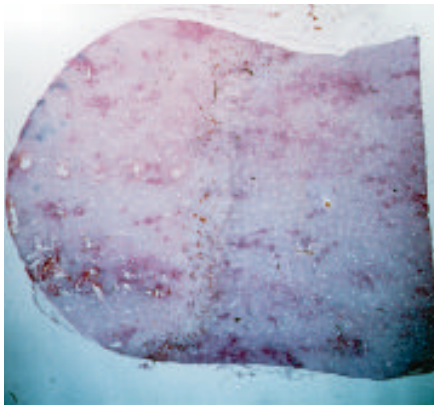

Figure 12. Low-power histologic section of rabbit kidney demonstrates the sharp demarcation between HIFU-induced necrotic tissue (left) and viable kidney tissue (right).

Additional localized prostate cancer treatments with HIFU have been reported by Marberger et al. in 10 patients with T2 cancer who were not willing to undergo radical surgery or radiotherapy. In two patients, complete destruction of the cancer was accomplished while in the remaining eight patients between 38% to 77% of the tumor volume was destroyed. These patients are being followed at three-month intervals with biopsy and PSA.

Gelet et al. reported on HIFU treatment of 14 patients with organ-confined T1 and T2 prostate cancer.[25] The entire prostate was treated in one or two sessions, performed under spinal or general anesthesia. Complete ablation and control of the cancer was demonstrated in seven patients (50%) with negative biopsies and normalization of PSA at six months posttreatment.

It appears that transrectal HIFU ablative therapy shows promise for local control of organ-confined prostate cancer. More clinical trials are required with long-term follow-up to confirm the efficacy and safety of HIFU therapy as a viable alternative to surgery for the treatment of early-stage localized prostate cancer.

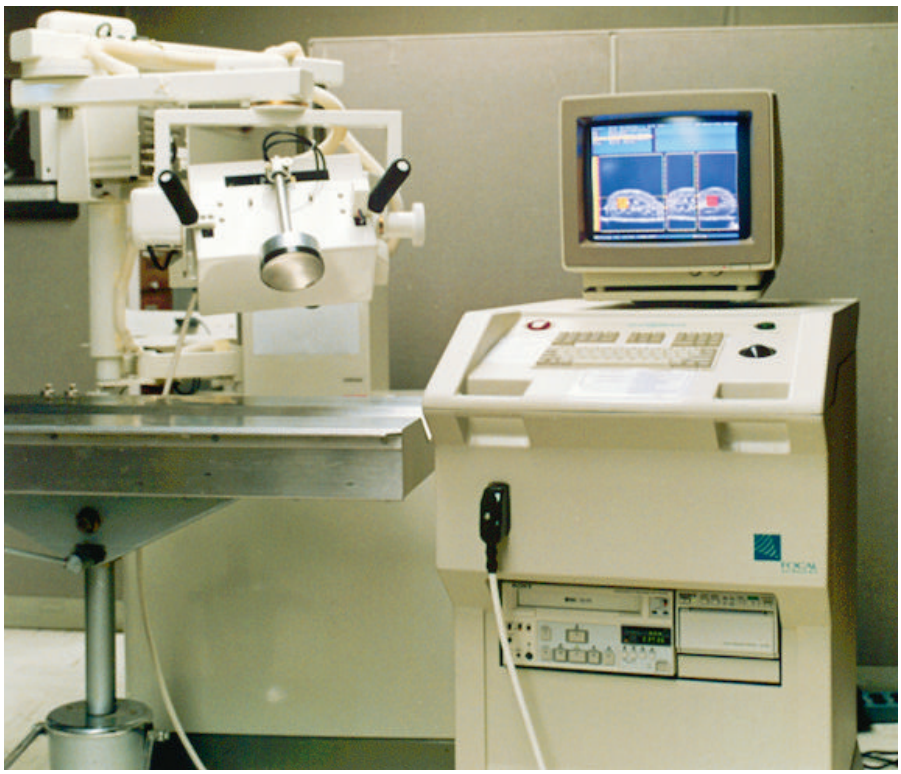

Figure 13. Prototype extracorporeal acoustic ablation device using a position-sensitive arm to accurately position the annular array imaging/therapy head. (Courtesy of the Indianapolis Center for Advanced Research, Indianapolis, Ind.)

Total Prostate Ablation

Since prostate cancer is a multifocal disease, a large percentage of patients present with multiple positive biopsies in both lobes of the prostate. These patients are typically candidates for radical prostatectomy and/or radiotherapy. If HIFU surgery can be used to ablate the entire prostate successfully, this technique has the potential to offer patients a minimally invasive alternative to radical surgery.

Bihrle et al. at Indiana University has reported on the first use of HIFU in the canine model for subtotal ablation of the prostate.[26] The Sonablate device was used, and multiple groups of sectors with different focal length probes (2.5, 3.0, 3.5 cm) were used in an attempt to ablate all prostate tissue except the extreme anterior aspect. Of the six dogs treated, the three who were sacrificed immediately after treatment showed 80% to 90% hemorrhagic/liquefactive necrosis (Fig. 9). The three dogs held for long-term follow-up showed minor complications with no rectal wall injuries or gross postoperative bleeding. At 10 weeks posttreatment, the excised canine prostates showed a large cavity (Fig. 10) with only a small rim of residual prostate tissue remaining. These canine results show promise for subtotal ablation of the prostate gland with minimal side effects. As this technique is further developed, its application to selected human prostate cancer patients can be considered. While additional technology changes are needed to provide more accurate targeting and faster treatment times of large tissues volumes, the technique holds a high level of promise as a less invasive and radiation-free alternative for the treatment of prostate cancer.

Renal Cancer

The widespread use of computerized tomography to evaluate intra-abdominal processes has led to the incidental findings of renal masses otherwise undetectable through clinical exam. In some patients, (i.e., those who have multiple small tumors; patients who, for health reasons, cannot undergo major extirpative surgery; and patients who are candidates for renal parenchyma-sparing surgery) the option of minimally invasive destruction of lesions is an exciting concept. HIFU ablative surgery has the potential to be utilized either in adjunctive therapy for surgery or as a primary

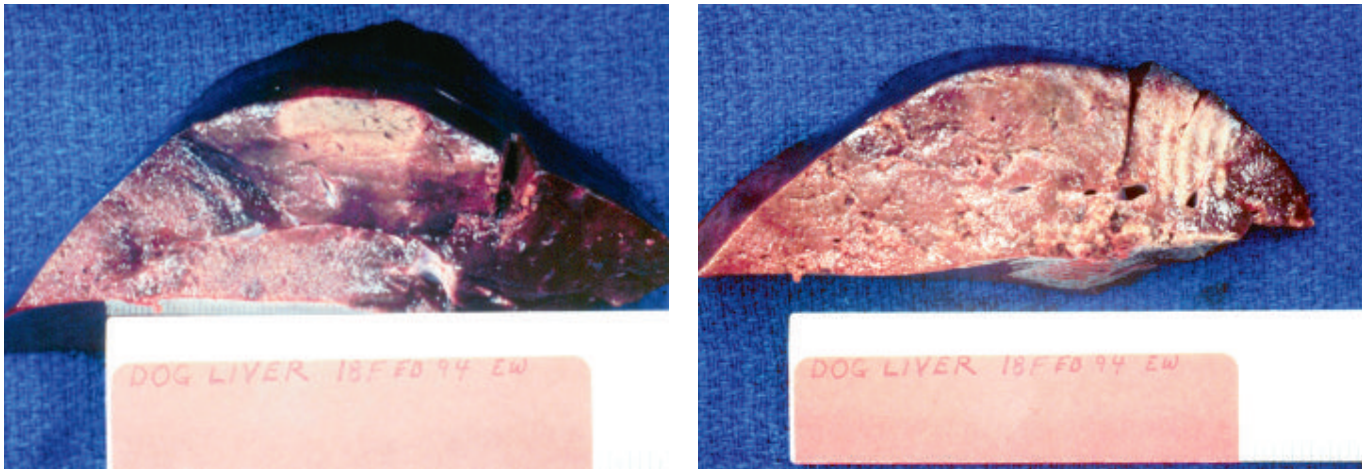

Figure 14. HIFU ablation of a freshly excised canine liver shows a well-defined necrotic lesion on the surface of the organ (left) and numerous discrete necrotic lesions deep inside the hepatic lobe. (Courtesy of Dr. R. Yang, Indiana University Medical Center, Indianapolis, Ind.)

option in selected patients. HIFU could be used either intraoperatively or transcutaneously to ablate renal tumors.

A Phase 1 animal study was designed using direct contact ablation of the kidney tumors to document histological and local field effects.[27] A VX-2 rabbit carcinoma tumor cell suspension was injected into the renal segmental artery in nine rabbits. After a two week incubation, open HIFU ablative surgery was performed with direct contact of the probe to the kidney. After a four-hour survival period, the rabbits were sacrificed and kidneys were evaluated for histopathology. The Phase 2 study attempted transcutaneous ablation of kidney tumors to evaluate sonographic visualization and destruction of renal tissue. In this Phase, the VX-2 tumor cell suspension was injected directly into the lower pole parenchyma in nine rabbits. After a two-week incubation period, transcutaneous HIFU ablation was performed, followed by a one-week survival period. Necropsy was performed to evaluate all affected subcutaneous tissues as well as the kidney.

All rabbits exhibited renal tumor growth in the Phase 1 study. After ablative surgery, there was pathologic evidence of tissue destruction in all nine animals, and seven kidneys had histologic as well as gross evidence of tumor ablation (Fig. 11). There was a sharp demarcation noted between viable and ablated tissue (Fig. 12). In the Phase 2 study, all nine rabbits exhibited nodular tumor growth. Pathologic evidence of kidney tissue ablation was seen in seven of nine animals.

The results of the rabbit studies indicate that HIFU ablation is effective at causing cell death in renal tumors as well as surrounding renal tissue. There is a sharp border found between viable kidney and ablated tissue. HIFU technology appears to offer the surgical ability to destroy small renal tumors in a localized region. However, ultrasound targeting is key to the accurate placement of the ablative energy. In addition to the above application, benign conditions of the kidney may also be treated with HIFU (e.g., complex renal cysts, symptomatic simple cysts and angiomyolipoma). More research and clinical studies are required to determine the efficacy of this procedure for renal disease.

Liver Cancer

The management of liver cancer is and continues to be a challenge in medical oncology. The liver can be the site of both primary and metastatic cancer. While primary liver cancer is one of the most common malignancies worldwide, the liver is also the most common site for the occurrence of metastatic disease. Hepatic oncologic surgery is presently very specialized and requires a highly skilled team familiar with the various techniques of hepatobiliary surgery. HIFU ablative surgery is a modality that when fully developed could become a viable noninvasive alternative to open surgery for patients with a variety of primary and metastatic tumors.

To date, a number of experimental animal studies have proven the concept that HIFU can be used to ablate both normal liver and tumor-bearing liver tissues.[28-30] Yang et al. in the early 1990s ablated small 2- to 5-mm intrahepatic Morris hepatoma tumors implanted in the liver of rats.[31] During laparotomy, the tumor-bearing hepatic lobe was exteriorized, immobilized, and intraoperatively treated with high-energy focused ultrasound. The rats were killed from 3 to 28 days after treatment. Tumor growth was significantly inhibited in the HIFU-treated group as indicated by gross pathology and histologic data.

In 1992, Yang et al. reported on extracorporeal (transcutaneous) ablation of liver tissue in the rabbit using simultaneous ultrasound imaging to target the selected tissue.[32] In 90% of the rabbits, a sharply defined region of coagulation necrosis was found with gross pathology and histology. These preliminary experiments support the concept of extracorporeal ablation of liver tumors without open surgery.

Vallancien et al. reported on the use of focused extracorporeal pyrotherapy to treat two patients with solitary liver metastases prior to surgical resection.[33] The system consists of a concave firing head, composed of multiple piezoelectric ceramics, that was submerged in a water-filled chamber mounted in a bed similar to a lithotripter. The results of these preliminary studies were disappointing as lesions were not found in the apparent target areas, most likely due to targeting errors and dosimetry inaccuracies related to the long focal distances. For more effective extracorporeal treatment, improvements in tissue visualization, targeting, and dosimetry of the acoustic energy to deeper depths is necessary to meet the challenge for successful liver ablation.

Current studies at Indiana University Medical Center using a prototype extracorporeal ablation system (Fig. 13) to study the effects on canine liver tissue incorporate a wide-aperture (10

cm) annular array transducer. When developed, this new technology will provide electronic focusing capability that will allow localized ablative surgery in a focal range from 2 to 15 cm deep in the body without damage to intervening tissue. Initial in vitro studies with an excised canine liver show well-defined necrotic regions, post-HIFU treatment (Fig. 14). An advantage of dynamic focusing is the ability to destroy selectively either superficial or deep tissue regions inside the liver with a single transducer without damage to intervening or surrounding tissues.

While preliminary studies using HIFU ablative surgery in the liver show numerous potential applications, substantial research is required to understand fully the mechanisms of action for liver destruction. In addition, further technological advancements that may combine the elements of 3-D imaging, dynamic focusing, electronic beam shaping, and computer-controlled lesion sequencing should enhance the use of HIFU ablation for intrahepatic tumors of varying sizes and locations. When this type of device is available, there is a likelihood that multifocal liver disease as well as multiple tumor nodules could be effectively treated with localized HIFU therapy instead of open surgery.

CONCLUSIONS

HIFU ablative surgery or "sonablation" holds promise as a noninvasive or minimally invasive surgical tool. Early clinical experience in a number of organs has proven the concept of regional destruction of selected tissue inside the body without damage to surrounding structures. For the acceptance and implementation of HIFU in the everyday armamentarium of surgical therapy, significant technological advances and clinical experience must be gained. These advances should include: (1) a better understanding of the biophysical mechanisms of interaction between HIFU and tissue, (2) advanced imaging techniques for precise targeting and monitoring of the therapeutic effect in tissue, (3) automated closed-loop dosimetry to assure effective localized therapy at multiple tissue depths, and (4) the development of a family of multifocus probes better to meet the needs of both extracorporeal and intracorporeal surgical applications. STI

REFERENCES

1. Ballantyne GH, Leahy PF, Motlin IM, eds. Laparoscopic Surgery.
1st ed. Philadelphia: WB Saunders; 1994.
2. Katkhouda N, Mills S. Laparoscopic surgery of the liver. In: Szabó Z, Kerstein M, Lewis JE, eds. Surgical Technology International III; 1994. p 173-9.
3. Wood RW, Loomis AL. The physical and biological effects of high-frequency soundwaves of great intensity. London J Sci 1927;4:417-36.
4. Gruetzmacher J. Piezoelektrischer Kristall mit Ultraschallkonvergenz. Z Phys 1935;96:342-9.
5. Lynn JG, Zwemer RL, Chick AJ, et al. A new method for the generation and use of focused ultrasound in experimental biology. J Gen Physiol 1942;26:179-93.
6. Meyers R, Fry WJ, Fry FJ, et al. Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. J Neurosurg 1959;16:32-54.
7. Burov AK, Andreevskaya GD. Action of high-intensity ultrasonic oscillations on malignant tumors of animals and man. Dokl Akad Nauk SSSR 1956;106:445-8.
8. Oka M. Application of intense focused ultrasound in brain surgery and other fields. Clin All-Round 1964;13:1514-23.
9. Oka M. Progress in studies of the potential use of medical ultrasonics. Wakayama Med Rep 1977;20:1-50.
10. Linke, CA, Carstensen, EL, Frizzell, LA, et al. Localized tissue destruction by high-intensity focused ultrasound. Arch Surg 1973;107:887-91.
11. Fry FJ, Sanghvi NT, Eggleton RC. Ultrasound visualization and therapeutic computer controlled system. In: White D, Barnes R, eds. Ultrasound in medicine. New York: Plenum Publication; 1976. p 481-2.
12. Heimburger RF. Ultrasound augmentation of central nervous system tumor therapy. Indiana Med 1985;78:469-76.
13. Marberger M, Madersbacher S. Treatment of benign prostatic hyperplasia with high intensity focused ultrasound: a review. Jap J Endo ESWL 1994;7(3):236-249.
14. Foster RS, Bihrle, R, Sanghvi, N, et al. High-intensity focused ultrasound for the treatment of benigh prostatic hypertrophy. Seminars in Urology 1994;12(3):200-4.
15. Nakamura K, Baba S, Deguchi N, et al. High intensity focused ultrasound for benigh prostatic hyperplasia; a 6-month follow-up. Jap J Endo ESWL 1995;8(1):36-9.
16. Marberger M, Madersbacher S, Susani S. Treatment of BPH and prostatic cancer with transrectal high-intensity focused ultrasound (HIFU). 108th meeting of the American Association of Genitourinary Surgeons. Boca Raton (FL); 1994.
17. Gelet A, Chapelon JY, Bouvier R, et al. Treatment of localized prostate cancer by high intensity focused ultrasound (HIFU) delivered by transrectal route: preliminary results. SIU Abstracts 1994;310:862.
18. Hynynen K, Damianou C, Darkazanli A, et al. On-line MRI monitored noninvasive ultrasound surgery. IEEE Pub 0-7803-0785, 1992;350-351.
19. Cline HE, Hynynen K, Watkins RD, et al. Focused US system for MR imaging-guided tumor ablation. Radiology 1995;194:731-7.
20. Sanghvi NT, Foster RS, Bihrle R, et al. Noninvasive transrectal ultrasound device for prostatic tissue visualization and tissue ablation in the focal zone using high intensity focused beam. J Ultrasound Med 1991;10:S101-4.
21. Bihrle R, Foster RS, Sanghvi N, et al. High intensity focused ultrasound for the treatment of benign prostatic hyperplasia: early United States clinical experience. J. Urology 1994;151:1271-5.
22. Madersbacher M, Susani S, Marberger M. Treatment of benign prostatic hyperplasia with high-intensity focused ultrasound: clinical and histological data. Benign Prostatic Hyperplasia. In: Kurth K, Newling DWW, eds. Recent Progress in Clincal Research and Practice. New York: I Wiley & Sons; 1994. 386: 473-8.
23. Boring CC, Squires TS, Tong T, et al. Cancer statistics. Cancer J Clin 1994;44:7-26.
24. Marberger M, Susani S, Madersbacher S, et al. Effect of high-intensity focused ultrasound on human prostate cancer. Eleventh EAU Congress. Berlin A406; 1994.
25. Gelet A, Chapelon JY, Bouvier R, et al. Treatment of organ confined prostatic cancer by high intensity focused ultrasound (HIFU) delivered by transrectal route: pilot stody. J Urology 1995;153(4):Abstract 629.
26. Bihrle R, Foster RS, Sangvhi N, et al. Transrectal high intensity focused ultrasound subtotal ablation of the prostate in the canine model. J Urology 1995;435A:Abstract 828.
27. Adams JB, Anderson JH, Moore RG, et al. High intensity focused ultrasonic ablation of renal tumors in the rabbit. J Urology 1995;403A:Abstract 699.
28. terHaar, GR, Robertson D. Tissue destruction with focused ultrasound in vivo. Eur Urol 1993;23(suppl):8-11.
29. Yang R, Sanghvi NT, Rescorla FJ, et al. Liver cancer ablation with extracorporeal high intensity focused ultrasound. Eur Urol 1993;23(suppl):17-22.
30. Schneider HT, Feigl T, Volklein BA, et al. Effects of high energy pulsed ultrasound on normal and malignant liver cells. Gastroenterology 1995;108(4):A536.
31. Yang R, Reilly CR, Rescorla FH, et al. High intensity focused ultrasound in the treatment of experimental liver cancer. Arch Surg 1991;126:1002-10.
32. Yang R, Sanghvi NT, Rescorla FJ, et al. Extracorporeal liver ablation using sonography guided high intensity focused ultrasound. Invest Radiol 1992;27:796-803.
33. Vallancien G, Harouni M, Veillon B, et al. Focused extracorporeal pyrotherapy: feasibility study in man. J Endourol 1992;6:173-81.