Prostate Cancer Therapy with High-Intensity Focused Ultrasound

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Abstract

High-intensity focused ultrasound (HIFU) has been used to ablate benign and malignant prostate tissue for several decades. This review summarizes the technology and available clinical trials to date. Continued technological advances combined with well-designed clinical trials could allow HIFU to become part of the arsenal against prostate cancer.

Introduction

Prostate cancer continues to be the most common cancer diagnosis except skin cancer and, despite a decreasing trend in mortality, remains second only to lung cancer. In 2004 alone, it was estimated that one quarter of a million men in America would be informed that they have prostate cancer.[1] Men facing this diagnosis have several viable treatment options, including watchful waiting, surgery, radiation, and thermal or hormonal therapies. Because of the unknown aggressiveness of individual prostate cancers and the known morbidities associated with current therapies, investigation of novel minimally invasive therapies for prostate cancer continues. High-intensity focus ultrasound (HIFU) is a thermal therapy initially investigated on central nervous system tumors as early as the 1950s.[2] In the 1990s, the potential of HIFU ablation of the prostate was first demonstrated in canine models[3,4] and then almost immediately translated to men with benign[5-7]or malignant[8,9] prostatic growths.

Initial investigations in the treatment of prostate diseases have resulted in the development of several centers of excellence throughout the world and 2 dominant technologies that seem to be under continual development. The goal of this review is to familiarize the reader with the evolution to the current technology, review the trials conducted in the literature, and discuss the role HIFU might play in the future management of prostate cancer.

High-Intensity Focused Ultrasound

The Technology

High-intensity focused ultrasounds use diagnostic ultrasound waves to destroy the tissue at the focal point of a transducer without injuring the intervening tissue. At the focal point of the transducer, ultrasound energy is concentrated and generates temperatures that can exceed 100°C, resulting in complete coagulative necrosis and the destruction of tissue. A focal zone is created whose size is dependent on multiple factors including focal length, wattage, frequency and time of the ultrasound, as well as tissue composition. This multitude of parameters allows for flexibility and precision of the HIFU technique. This technique was initially investigated in animals and humans in the 1940s and 1950s at Indiana University to destroy selective regions in the central nervous system.[2] It is now recognized that HIFU has the capability of transdermally/transmucosally coag-

Table 1 Attributes of HIFU Transrectal Devices[14,15]

Paramenter	Ablatherm®[14]	Sonablate® 200, 500[15]
Frequency	2.25-3 MHz	4 MHz
Focal Length	2.5 cm	2.5-4 cm
Duty Cycle, Seconds (On/Off)	4.5/12-5/5	6/12-3/6
Planning Diagnostic US	Yes	Yes
Treatment US	No	Yes
Diagnostic US During Treatment	No	Yes
Patient Movement Override	Yes	No
Reflectivity Index	No	Yes
Rectal Cooling System	Yes	Yes
Portable Device	No	Yes
Trials in BPH	Yes	Yes
Trials in Localized PCA	Yes	Yes
Trials in Recurrent PCA	Yes	Yes
Regional Anesthesia	Yes	Yes

Abbreviations: PCA = prostate cancer; US = ultrasound

ulating and destroying tissue in a variety of conditions that have medical applications including brain, prostate, spleen, liver, kidney, breast, and bone.[10-13]

Transrectal Technology Targeted Toward Prostate Gland

Diagnostic transrectal ultrasound of the prostate has been used for decades by radiologists and urologists and has provided a natural transition for development of therapeutic HIFU. Transrectal HIFU administration has been investigated for the treatment of benign and malignant growth of the prostate because of the combined attributes of being minimally invasive and potentially completely ablative. Extensive investigations in animal models led to development of a transrectal probe that exhibited ablative abilities for benign prostate hyperplasia (BPH). These early findings in BPH led to the investigation of transrectal HIFU therapy for prostate cancer.

Two companies are currently producing HIFU devices for the treatment of prostate cancer. The Ablatherm® is produced by EDAP TMS, S.A. (Lyon, France)[14] and the Sonoblate 500® is produced by Focus Surgery, Inc (Indianapolis, Indiana).[15] Each of the HIFU centers of excellence has focused its investigations on one of the devices, with the Ablatherm® being used by Gelet et al,[4,7,8,16] Chaussy and Thuroff,[17-18] Beerlage et al,[19] and Kiel et al,[20] whereas the Sonablate being used primarily by Madersbacher et al,[5,9,21,22] Uchida et al,[23-25] and Gardner et al[26] to treat BPH and/or localized prostate cancer. Table 1 illustrates the major attributes of each of these HIFU transrectal devices.[14,15]

Technical differences exist between these 2 devices, and modifications continue to evolve quickly. The Sonablate 500® operates at 4 MHz, whereas the Ablatherm® operates at 2.25-3 MHz. Higher frequencies result in higher temperatures in the same time period. The Sonoblate 500® uses a split-beam technology,[27] which increases the size of the focal zone, speeds treatment, and allows near-simultaneous imaging and treatment.

The design of the Ablatherm® device allows ultrasound preplanning of the treatment zone but not simultaneous monitoring during treatment. Safeguards in the software stop HIFU treatment if there is patient movement after planning with the Ablatherm® device. At this time, the Ablatherm® has been much more extensively studied, and therefore, there is more information about its performance in clinical trials.

Transrectal HIFU is performed under general or regional anesthesia. A high-frequency transducer probe placed in a balloon filled with room temperature or cooled degassed liquid is inserted into the rectum to serve as an acoustical interface and in some cases cool the rectal wall. There are functionally 2 transducers on these devices, low-energy transducers (3-4 MHz) for imaging and high-energy transducers for treatment. The prostate is imaged in the sagital and coronal planes, and the target treatment zone is outlined. With both systems, there is a treatment cycle in which the treatment zone is heated and then a cooling period during which the computer-controlled device moves to the next treatment zone distant from the first (5 seconds on and 5 seconds off for the Ablatherm® and 3 seconds on and 6 seconds off for the Sonoblate 500®). The Sonoblate performs diagnostic imaging during the cooling phase, which allows for real-time monitoring of treatment-related tissue changes within the treatment zone and of acoustic changes in the near field region of the rectal wall. With the Ablatherm® device, there is a single focal zone length of the treatment probe. When treatment is completed, any untreated anterior tissue can subsequently be treated after prostatic shrinkage has occurred. With the Sonoblate 500® device, 4 different probes with focal lengths ranging from 2.5 cm to 4 cm are available and are interchanged to treat different depth areas during therapy in the same session.

Transrectal High-Intensity Focused Ultrasound Approach for Benign Prostate Hyperplasia

High-intensity focused ultrasound has been studied the most in the treatment of prostatic conditions; it was initially tested in experiments in the canine prostate by Gelet et al,[4] Bihrle et al,[28] and Kincaide et al.[29] The use of the transrectal probe for the treatment of BPH in humans was first reported in the mid 1980s by the Department of Urology at Indiana University and by Madersbacher et al[5] in Vienna. Bihrle et al reported on their preliminary results with 15 patients in 1994.[6] A high-intensity focused ultrasound was used to coagulate a small region of the periurethral area of the prostate. The most common complication from HIFU treatment was transient urinary retention, which occurred in 73% of patients. Two subsequent larger studies have examined the efficacy and safety of HIFU for the treatment of symptomatic BPH.[21,30]

A multicenter clinical trial with the Sonablate 200® demonstrated sustained improvements in flow rates, symptom scores, and postvoid residuals in 70 men with 8 investigators.[26] This trial underscored the ability of many clinical investigators to obtain similar results. Trials using the Sonablate 200® targeted

Table 2 | Clinical Trial Using Various High-Intensity Focused Ultrasound Transrectal Devices[16,17,20,23-25,32,33]

Characteristic	Gelet et al[16]	Chaussy and Thuroff[17]	Kiel et al[20*]	Kiel et al[20†]	Uchida et al[23-25]	Vallancien et al[32]	European Trial[33]
Number of Patients	82	184	28	11	20	30	402
Percent Stage T1 Disease	46	NR	NR	NR	35	NR	NR
Mean Preoperative PSA (ng/mL)	8.11 ± 4.64	12	7.64 ± 5.26	6.06 ± 4.54	9.65 ± 4.43	7	10.9 ± 8.7
Mean Follow-up (Months)	17.6	6.3	15	15	13.5	20	13.3
Mean Number HIFU Treatments	1.92	1.26	1.2	1.2	1.4	1.16	1.47
Nadir PSA ≤ 0.5/1 ng/mL	NR/56	NR	NR	NR	65/90	NR/86	Average nadir, 0.6
Negative Biopsy Result	78	80	87	55	100	86	87
Negative Biopsy Result and PSA ≤ 0.5/1 ng/mL	NR	61/NR	46/71	18/36	65/90	NR/86	NR
5-Year Progression-Free Survival	68-83	0	NR	NR	88	NR	NR
Mild to Moderate Incontinence	13	0	6	–	11.4	3	14
Severe Incontinence	4	30	5	–	1	0	1.5
Impotence‡	77	0	44	–	24	32	9
Prolonged Retention	6	5	32	–	30	0	9
Rectourethral Fistula	1	10	3	–	0.5-3	0	1.2
Urethral Stenosis	17		2	–	6	0	3.6

Results are generally reported as mean ± standard deviation. Values are percentages unless otherwise indicated.
*Low risk (T1/T2, PSA < 15 ng/mL, and Gleason score of < 8).
†Moderate risk (T1-T3).
‡Percentage of patients potent before surgery.
Abbreviation: NR = not reported

small prostate volumes because of time limitations of the previous technology and explain the lack of long-term efficacy in those studies. The current and future technology has the ability to treat a greater volume of prostate tissue in the same treatment setting.

Transrectal Approach for Prostate Cancer

Feasibility Trials

Initially, a series of feasibility trials were conducted. Madersbacher et al enrolled 29 patients and applied the Sonablate 200® device (6 on/12 off) to partially ablate the prostate just before radical prostatectomy.[22] Whole-specimen mounts were compared with the preoperative HIFU-targeted ultrasound for treatment effect. This comparison revealed limited extraprostatic change to the rectum or the region of the neurovascular bundle despite the inclusion of the prostate capsule in the treatment zone. In addition to this positive short-term safety profile, well-demarcated lesions corresponding to the treatment zone could be visualized, and no immediate intraoperative periprostatic changes were visualized.

Beerlage et al reported on 14 men receiving an Ablatherm treatment to half the prostate 7-12 days before a radical prostatectomy.[19] All prostate specimens exhibited complete necrosis in the target zone with a consistent finding of viable prostate tissue in the dorsal aspect of the target zone. Four of the 14 (29%) specimens exhibited small vital tumors in the dorsal region within the treatment zone.

Gadolinium-enhanced magnetic resonance imaging (MRI) has become the standard of postthermal therapy viability in tissue regardless of thermal ablative technology used. Rouviere et al performed gadolinium-enhanced MRI 2-5 days before and after HIFU treatment in 21 men and correlated the images to post-treatment biopsy results.[31] Several critical findings were reported with the Ablatherm device: (1) HIFU results in a transient increase in prostate volume of 43-52 cm^3 by the second day, (2) the HIFU-treated area appeared as a hypointense zone surrounded by a peripheral rim of enhancement on fat-saturated gadolinium-enhanced T1-weighted images, (3) no MRI correlation was demonstrated with extent of necrosis or presence of viable tumor on biopsy; and (4) presence of targeted but untreated prostate tissue in the anterior region of the prostate.

These feasibility trials suggested HIFU could ablate prostate tissue safely but highlighted several of the challenges facing this technology. The studies by Beerlage et al and Rouviere et al demonstrate the limitations of a single focal zone.[19,31]

Clinical Trials

In reviewing the literature, it becomes clear that, although HIFU is a minimally invasive treatment modality capable of complete prostate ablation, the devices are continually evolving because of limitations on applicability to general urologic practice. Several clinical trials have used transrectal HIFU for the treatment of localized prostate cancer, locally advanced prostate cancer, and recurrent prostate cancer. The various trial designs and continual device evolution make direct comparison difficult. Table 2 shows data from various clinical trials.[16,17,20,23-25,32,33]

Madersbacher et al were the first to examine the feasibility of HIFU for the treatment of localized prostate cancer.[9] These investigators treated 29 patients with HIFU therapy before radical prostatectomy using the Sonablate-200® device, a predecessor of the currently utilized Sonoblate 500®. These investigators confirmed that HIFU resulted in a sharply demarcated lesion without injury to the rectal wall. Two of these patients had sharply demarcated cancerous lesions on ultrasound and had this area targeted with HIFU. In these patients, no heat damage was noted to the rectum or neurovascular bundle even though HIFU treatment zone extended to the prostatic capsule. Beerlage et al subsequently confirmed these findings using the Ablatherm® device.[19]

Gelet et al reported on the use of the Ablatherm® device in 82 patients with stage T1/2 prostate cancer.[8] They subsequently presented their comprehensive outcome data in 2000.[16] In the latter report, patients with stage T1/2 disease and prostate-specific antigen (PSA) levels of < 20 ng/mL were considered appropriate candidates for total prostate ablation with the Ablatherm® device. Forty-six percent of patients had stage T1 disease, 49% had stage T2, and 5% experienced local treatment failure after definitive external radiation therapy. Neoadjuvant hormonal therapy was administered in 9% of patients, which confounds the PSA results. Forty-one percent, 39%, 11%, 7%, and 1% of patients were treated with 1, 2, 3, 4, and 5 HIFU sessions, respectively.

The clinical outcomes of the trial by Gelet et al revealed 78% of patients had negative sextant biopsies at 3 and 12 months.[16] Fifty-six percent of patients had a PSA nadir of < 1 ng/mL. Forty-two men (51%) had negative biopsies and a PSA nadir < 1 ng/mL. Actuarial analysis was also performed on low-risk (PSA < 10, Gleason score of < 7) and moderate-risk (PSA < 15, Gleason score of < 8) patients, and disease-free survival rates by the criteria outlined earlier were 83% and 68%, respectively. Mean follow-up for the overall series was 17.6 months (range, 3-68.5 months). Mean postoperative catheterization time was 8.5 days. Mean time to PSA nadir was 5 months.

From 1997 to 2000, Kiel et al treated 62 patients with localized prostate cancer with the Ablatherm®.[20] In contrast to the Gelet et al study, only 1.2 sessions were administered per patient. Similarly, this study enrolled a heterogeneous population, with 5 men exhibiting treatment failure after radiation therapy, 3 men with treatment failure after radical prostatectomy, and 4 men with locally advanced disease requiring local debulking. Patients with localized disease who are comparable with other series were divided into low-risk (n = 28; stage T1/2, PSA < 15 ng/mL, Gleason score of 7) and moderate-risk (n = 11; stage T1-3, PSA and Gleason score not restricted) groups. Median follow-up was 15 months. Overall, these authors used relatively lax criteria for treatment success and defined this as negative biopsies and PSA < 4 ng/mL. Eighty-seven percent of the low-risk and 55% of the moderate-risk groups had complete responses by these lax criteria. Complete responses decreased from 87% to 71%, and 46% of the low-risk patients had a negative biopsy and a more stringent PSA nadir of < 1 ng/mL and 0.5 ng/mL, respectively.

Chaussy and Thuroff reported on a 3-year experience with HIFU using the Ablatherm® device for localized prostate cancer in 2000.[18,34] One hundred eighty-four men were treated with a total of 232 HIFU sessions (1.26 treatments per patient). These authors report an early treatment experience with 90 patients using a lower megahertz generator (2.25 MHz) and a later experience with 94 treatments using a 3-MHz generator. In addition, in the latter treatments a rectal cooling device was utilized. Entry criteria included stage T1/2 disease, PSA < 20 ng/mL, and prostate volume < 30 mL. Ninety percent of patients had a Gleason score of ≤ 7. Forty-eight percent received neoadjuvant hormonal therapy, and mean follow-up for this series was only 193 days. These investigators also noted a significant decrease in treatment-related side effects with use of the 3-MHz device and noted a decrease in rectourethral fistulae from 3% to 0.5% with these improvements. These authors also reported that one third of their patients had significant pretreatment voiding symptoms and underwent transurethral prostatic resection after the HIFU treatment.

The results of a large multicenter trial with the Ablatherm® device were reported in 2003. This report describes the results of HIFU treatment in 402 men treated across 6 sites in Europe.[33] This was an uncontrolled clinical trial in patients considered unsuitable candidates for radical prostate surgery. Thirty-five patients (9%) had undergone previous radiation therapy, and 104 patients (26%) were being treated with some form of hormonal therapy. Patients were stratified into low-, intermediate- and high-risk groups for efficacy analysis. Efficacy was assessed by sextant biopsy of the prostate and serum PSA level.

The average number of treatments per patient was 1.47, with 28% of patients requiring 2 treatment sessions. Two hundred eighty-eight patients underwent sextant biopsy after HIFU, and 87% had a negative biopsy: 92%, 86%, and 82% in the low-, intermediate-, and high-risk groups, respectively. Mean nadir PSA levels in the low-, intermediate-, and high-risk groups were 1.3 ng/mL, 1.4 ng/mL, and 3.1 ng/mL, respectively. Larger prostate volumes were predictive of treatment failure by biopsy and PSA. Transient urinary retention was the most common complication occurring in all patients and lasting for a median of 5 days. Prolonged retention was reported in 9% of patients. Although one might predict a high degree of urethral strictures and bladder neck contractures with complete urethral treatment, these were seen in only 3.6% of patients. The most serious complication of this technology was the development of a urethrorectal fistula, which occurred in 5 patients (1.2%) before the use of the rectal cooling device. Mild, moderate, or severe stress incontinence occurred in 11%, 3%, and 1.5% of patients, respectively, whereas severe incontinence requiring intervention developed in 1.5% of patients. Finally, impotence was reported in only 35 patients (9%).

The Sonoblate devices have been most extensively studied in Japan. Uchida et al are the only investigators to report an experience with the Sonoblate 200® device for the treatment of localized prostate cancer.[23] The Sonoblate 200® device uses a 4-MHz power generator that has different tissue characteristics, and it employs a rectal cooling device. Twenty patients were

treated with 28 treatments (1.4 treatments per patient). Patients all had localized disease, average PSA of 9.65 ng/mL, and all had a Gleason score of ≤ 7. Four patients (20%) received pretreatment hormonal therapy, and none received posttreatment hormonal therapy. A PSA nadir of < 0.5 ng/mL, 0.5-1 ng/mL, and 1.01-2 ng/mL was exhibited in 65%, 25%, and 10% of patients, respectively. The same center subsequently published overall 5-year biochemical disease-free rates of 67%.[25] Patients with preoperative PSA levels < 10 ng/mL demonstrated 5-year disease-free survivals of 88%. The Japanese experience with the Sonoblate 500® device now exceeds 420 patients.

The Sonoblate 500® device has just recently completed the first United States–based trial on the use of HIFU for the treatment of localized prostate cancer at Indiana University School of Medicine. This trial was structured as a feasibility trial to demonstrate the safety and, to a lesser degree, the efficacy of this technology before petitioning the Food and Drug Administration to allow Focus Surgery to conduct a multi-institutional registration trial to examine the true efficacy of this technology. The complete results of this trial will be the subject of a separate publication. Briefly, 20 patients with early-stage prostate cancer (T1/2, Gleason score of ≤ 7, and PSA ≤ 10 ng/mL) were treated with this device. Follow-up included a mandatory extended-field biopsy at 6 months after treatment. Success was defined as a negative extended-field biopsy at 12 months, and a PSA nadir < 1 ng/mL was exhibited by 58% of patients overall and in 65% of patients who underwent retreatment when indicated. Transient urinary retention occurred in all patients, and one patient developed a rectourethral fistula that healed with temporary fecal diversion. A parallel study in patients with locally recurring postradiation disease has had initial safety and efficacy outcomes, but only 3 of 20 patients have been treated to date.

Future Directions

The potential of HIFU lies in its minimally invasive image-directed tissue destruction. The use of ultrasound provides an opportunity to develop treatment algorithms based on ultrasound tissue characteristics. For example, imaging at the focal point before treatment could allow for selective ablation of tissue based on specific reflectivity. For instance, tissue with a reflectivity index suggestive of glandular tissue might require a different energy level compared with stromal tissue. Additionally, equal to providing appropriate tissue-specific energy levels to assure complete ablation of the entire prostate is the ability to use power Doppler technology to increase energy levels in regions of cancer-associated neovascularity within the confines of the prostate capsule, while attenuating the energy of the neurovascular bundles outside the prostate capsule to maximize efficacy and minimize treatment-related morbidity.

In summary, high-intensity focused ultrasound has been used to effectively ablate prostate tissue but requires further understanding and improvement of the precision and accuracy in which it is delivered to allow its general application to benign and malignant prostate disorders. The image-dependent and focal destructive capabilities of this technology should afford the urologist the opportunity of performing a neurovascular-preserving HIFU prostatectomy. To achieve this goal, continued, rigorous well-designed clinical investigations should be conducted that demonstrate therapeutic efficacy and a decreased side-effect profile equal to that of the current "gold standard" of nerve-sparing radical prostatectomy. Although these goals have been approximated in the preclinical setting,[35] significant clinical investigation and continued technical advances will be required to achieve this in patients with prostate cancer. Additionally, as more precise imaging of prostate cancer with ultrasound, MRI, or molecular probes become readily available, the urologist of the future could be detecting, targeting, and treating focal prostate cancer with such a device in a single-office setting.

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