

High Intensity Focused Ultrasound for Prostate Cancer: A Review of the Scientific Foundation, Technology and Clinical Outcomes

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High Intensity Focused Ultrasound (HIFU) is a definitive treatment for localized prostate cancer that is currently utilized most in Europe and Japan but it not yet approved by the FDA for this indication. Within the armamentarium of definitive prostate cancer therapies it is unique as it is truly non-invasive and does not involve incision or excision. The purpose of this paper is to review the scientific foundation of the technology as well as the clinical outcomes of commercially available devices. The scientific foundation of HIFU is reviewed in terms of how it has resulted in the development of commercially available equipment. MEDLINE was used to search the medical literature for publications pertaining to HIFU for prostate cancer as a primary therapy in terms of clinical outcomes. Biochemical disease free rates as well as negative biopsy rates are reviewed. Different engineering optimization strategies in the face of technicalities inherent to HIFU for prostate cancer have led to the development of two distinct commercially available devices. Each has their own merits and limitations. HIFU provides excellent biochemical and local control and results appear to be durable. Clinical outcomes are similar for the two technologies developed but are difficult to compare due to different lengths of follow-up and varying patient populations. HIFU is a technically advanced definitive local therapy for prostate cancer. Short and medium term results are encouraging and its role as a primary therapy for prostate cancer continues to be defined as more results become available.

Key words: High Intensity Focused Ultrasound; HIFU; Prostate cancer; and Local therapy.

Introduction

In the past ten years, many men have had their prostate cancer treated with High Intensity Focused Ultrasound (HIFU). Most patients have been treated in Europe and Japan. For example, the National Institute for Clinical Excellence is a government body in the United Kingdom which evaluates new treatments. It has reviewed the clinical data associated with HIFU and concluded that the evidence is sufficient and recommended its use to the UK's National Health System (1). HIFU is new to North America and it is not yet approved by the United States' FDA as a definitive treatment for prostate cancer although clinical trials are underway.

The purpose of this report is to explain, from a fundamental prospective, how HIFU works as well as to review the technologies used to perform HIFU and the published clinical literature regarding the procedure as a primary treatment for prostate cancer. The motivation behind this update is two fold: first, although there are some review papers regarding HIFU technology [*i.e.*, (2)] there is currently a void in the literature regarding a comprehensive review of the thought processes used

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in the development of commercially available technologies. Second, newly published clinical data allows for comparison of outcomes between commercially available devices.

Methods

The scientific foundation of HIFU was reviewed and it is discussed in terms of how it has resulted in the development of two distinct devices. The merits and limitations of each are addressed. The MEDLINE database was searched in February 2006 for publications containing any combination of "HIFU," "focused ultrasound," and "prostate" in the title of the report.

Abstracts resulting from this search were reviewed for relevance to the clinical outcomes from the procedure. Full manuscripts were retrieved and reviewed if they contained information regarding biochemical survival and/or biopsy results of patients who underwent HIFU as a definitive local therapy for prostate cancer. Only those papers published between 2001 and 2005 were included in the outcomes analysis.

HIFU Fundamentals

Sound is vibration. Typically, the human ear can hear frequencies between about 20 and 20,000 Hz. Sounds with frequencies higher than the range that humans can hear are termed *ultrasound*, which can be created with a piezoelectric crystal that vibrates at a characteristic frequency when an electric current passes through it. The reverse is also true: the crystal will create electricity when vibrated. When a pulse of current is passed through a piezoelectric crystal a group (or pulse) of waves is created and travels away from the crystal. As the waves pass through tissue, some of it will be reflected, or echoed, back to the crystal as it encounters tissue structures with varying ultrasound attenuations. When an echo returns it vibrates the crystal creating an electric current. By analyzing the current created by all the echoes it is possible to construct an image which leads to the most common medical application of ultrasound: imaging. It is important to note that air causes near complete reflection of the signal destroying the ability to image. During imaging a gel is put on the skin to create an air free path for the ultrasound waves to travel through. When gel is applied correctly there is no air between the ultrasound crystal and the patient and the image is readable.

Ultrasound waves deposit energy as they travel through tissue but the amount deposited during ultrasound imaging is insignificant. Ultrasound imaging is harmless and is sufficiently safe that it is routinely used to image babies in the womb (3). The premise behind HIFU is the destruction of tissue by depositing large amounts of energy into it. This is accomplished by doing two things: increasing the intensity of the waves and focusing the waves on a single point (like a

magnifying lens). If done in the right conditions it will raise the temperature of tissue to a level sufficient to induce irreversible damage in a discrete volume of tissue (4).

The deposit of energy during HIFU can result in two mechanisms of tissue damage (5). Elevation of tissue temperature leads to melting of lipid membranes and protein denaturation. This is the desired effect of HIFU. If large deposits of energy occur mechanical damage may result in gas bubble formation and/or cavitation (6). Gas can form inside tissue during HIFU as a result of several mechanisms. The first mechanism is simple boiling that will occur if the temperature of the tissue is increased beyond the boiling point of the liquids it contains. This will create air pockets that have the potential of reflecting the ultrasound signal and modify, in an uncontrollable way, the HIFU lesion. This type of gas formation is always avoided during the procedure.

The second mechanism is cavitation and can be either inertial cavitation or stable (non-inertial) cavitation. During inertial cavitation gas microbubbles form within tissue due to the negative pressure caused by HIFU. Upon subsequent collapse due to the higher pressure of the surrounding medium the temperature and pressure inside the microbubble will increase rapidly. This can lead to the dissipation of the gas into the surrounding medium in the form of a shock wave. Inertial cavitation is relatively unpredictable in terms of formation and dissipation of energy and is avoided during HIFU.

Stable cavitation is the oscillation of existing microbubbles in the tissue and it not associated with a violent collapse and dispersion of energy. Microbubble oscillations can result in sheering forces and viscous-damping heating. Although stable cavitation is currently avoided during the procedure there is some experimental evidence that stable cavitation may be able to enhance tissue ablation during HIFU and is being further investigated (7).

During HIFU a reproducible but small volume of ablation is created for each pulse of energy. The geometry of each ablation volume is an ellipsoid, and the size of the ellipsoid is a function of crystal geometry. Treatment of cancer of the prostate is accomplished by systematically pulsing energy throughout the target volume at different locations until the entire volume has been ablated (8).

Commercially Available HIFU Technologies

There are two HIFU technologies currently used for the treatment of prostate cancer, although neither one is FDA approved for the treatment of prostate cancer. The first to be available was the Ablatherm® (Edap-Technomed, Lyon, France). Subsequently, Focus Surgery (Indianapolis, IN, USA) developed a system called the Sonablate500®. The

foundation science and technology of both systems is identical but there are several technological differences between the two devices. These differences, for the most part, arise from different schools of thought with regards to how best design the optimal HIFU treatment system. Specifically, the differences arise in how the manufacturers went about choosing operating frequencies and intensities. This is an optimization based on the effects that modifying these parameters have on image quality and ablation ability.

The amount of energy deposited in tissue during HIFU is dependent upon both the transducer operating frequency and intensity (9). Increasing the intensity increases the energy incident on, and absorbed by, the tissue and, therefore, also increases the probability of inducing cavitation (Table I). Conversely, reducing the intensity reduces the temperature rise of the tissue, which results in a lower temperature increase and consequently decreased injury. Increasing the frequency increases the incidence of cavitation, increases image resolution near the ultrasound crystal, but reduces ultrasound penetration. It is the different strategies used to optimize the effect that modifying these parameters have on image quality and ablation ability that have led to the divergent paths taken in the design of commercially available HIFU devices.

Table I

Changes in cavitation probability, temperature rise, penetration, and image quality that result from changes in intensity and frequency.

Change	Effect			
	Cavitation probability	Temperature rise	Signal penetration	Image resolution
Increase the frequency	↑	↑	↓	↑
Reduce the Intensity	↓	↓		

Imaging and Treatment Probes

The Ablatherm uses separate crystals for imaging (7.5 MHz) and treatment (3 MHz). Thus, the dependence of image resolution is removed from the equation when ablation is occurring. Imaging probes for prostate applications tend to range from 5.0 MHz to 7.5 MHz with higher frequency probes creating higher quality images. The real time 7.5 MHz probe used by the Ablatherm creates a very high quality image throughout the prostate and a 3 MHz treatment probe was determined to be the best for treatment (10). Thus, optimal values are used for both imaging and treatment. Using separate imaging and treatment probes did, however, necessitate the removal of the imaging probe and insertion of a treatment probe prior to the commencement of HIFU. This is no longer an issue with the most recent Ablatherm model, which has both the imaging and treatment crystals contained back to back within a single probe that is inserted into the rectum. This allows not only for optimal operating frequen-

cies for both treatment and imaging but also allows for real time imaging during the procedure.

The Sonablate 500 uses a single crystal for both imaging and treatment, which also allows for real time imaging. This is accomplished by using a concave rectangular element cut from a spherical crystal surface that has a central 10 mm diameter segment used for imaging. There is no need to change probes between imaging and treatment. However, this constrains the probe to be of a single frequency, as probe frequency is characteristic of the crystal. An operating frequency of 4 MHz was determined to provide both sufficient image quality and effective treatment. The 4 MHz resolution probe allows for excellent imaging of the anterior part of the prostate but has decreased resolution and image quality in posterior margin of the gland and the rectal wall in comparison to higher frequency ultrasound probes.

Treatment Planning

HIFU allows for the creation of an accurate geometrical ablation volume. With both technologies treatments are planned based on the anatomy of the individual patient. Pretreatment ultrasound images are captured and the user defines on them, with computer assistance, the regions to be ablated and the regions to be preserved (for example, the external sphincter and rectal wall). The program then controls the ablation probe, which treats exactly where the user specifies. The Sonablate uses a single treatment algorithm in which the power can be adjusted manually. Specifically, the power can be reduced when treating near sensitive adjacent structures but the effect of reducing the power on the ability to ablate has not been studied. The Ablatherm uses three treatment algorithms each designed for specific applications: HIFU as a primary treatment, HIFU following failed radiation therapy, and HIFU retreatment. This was done as the thermal properties of a prostate that has never undergone a treatment is vastly different than one which has. When treating a gland that has been irradiated, care must be taken as the dissipation of energy will be slower due to decreased blood flow throughout the prostate. This is a result of radiation damage to the prostate's blood supply. The same will be true, but to a different extent, for a prostate that has previously been treated with HIFU. The reason this is important is that if not enough time is given for energy to dissipate a build up can occur that could lead to rectal injury and other complications as well as cavitation.

Real Time Monitoring

If a patient moves during the procedure the treatment must be stopped immediately and the treatment plan must be rechecked. If the movement was significant (*i.e.*, the treatment crystal is in a different position relative to the prostate) the treatment plan must be redone. The strategy used to detect

movement is different for the two technologies. Although real time imaging is available with the Ablatherm, it does not use it to detect patient movement. Rather, it relies on an automated infrared detection system to ensure that the patient has not moved. This removes human error from the equation. The real-time imaging available with the Ablatherm is, however, used to detect automatically the rectal wall position and compares this position to the one measured during treatment planning. The probe position is automatically adjusted to compensate any difference between these two measurements. The Sonablate utilizes its real time imaging to create image overlay, which in turn is used to detect patient movement. The planned treatment is placed over real time images of the prostate taken during the procedure. The physician observes entire procedure to ensure that the images line up indicating no patient movement has occurred. If the patient does move it will become visually apparent and the treatment plan is no longer valid and must be redone.

Ablation Volume Geometry and Transducer Size

The fundamental physical constraint in the design of a transducer is the fact that it must be inserted into the rectum during treatment. The physical size and shape of the ultrasound transducer determines where the energy is focused and the ablation occurs.

The Ablatherm uses a single treatment probe that has a focal point 45 mm from the crystal. The 3.0 MHz probe creates an ablation volume size that is adjustable from 24 mm (anterior to posterior) \times 1.7 mm \times 1.7 mm (total volume = 36 mm³) down to 19 mm \times 1.7 mm \times 1.7 mm (total volume = 29 mm³). The intent is that a single pulse will result in an ablation that extends the entire anterior to posterior height of the prostate. This strategy has the advantage that only one focus is needed to treat the entire height of the gland but given that prostates are not uniform in height (the base is taller than the apex) it can result in the ablation of some tissue beyond the anterior margin of the prostate.

The Sonablate probe is comprised of two different crystals with different focal lengths. This is accomplished by having two crystals placed back to back within the probe, one with a 3.0 cm focal length and the other 4.0 cm. The discrete ablation volume of both these crystals is 10 mm (anterior to posterior) \times 2 mm \times 2 mm (total volume = 21 mm³) when operated in normal mode and 10 mm \times 3 mm \times 3 mm (total volume = 47 mm³) when operated in split beam mode (see discussion on split beams below). Due to the decreased height of the focal areas a complete anterior to posterior ablation is not usually possible with a single pulse of energy, necessitating pulses on two levels to treat the whole gland. The advantage to this strategy is that the reduced ablation volume allows for better conformation of the ablation zone to the anterior margin of

the prostate. The disadvantage is time. Most every prostate has an anterior posterior height in excess of 10 mm and when this is the case multiple passes will be required. This means that to treat the prostate from top to bottom the first 10 mm will be treated with the first pass. The next 10 mm will then be treated with a second pass. If the prostate is greater than 20 mm high a third pass would be required.

That being said, both technologies are limited in their ability to treat *very* large glands. It is, however, possible to perform either a pre-treatment transurethral resection of the prostate or ablate the posterior portion of the gland then perform a subsequent HIFU treatment another day after allowing sufficient time for debulking to occur.

Treatment of the posterior margin of the gland can be difficult and unintentional ablation of the rectal wall can lead to fistula formation. Thusly, the physical proximal truncation of the discrete ablation volumes must not include any of the rectal wall. Both manufacturers, erring appropriately on the side of caution, have ablation zones that will not usually encroach the rectal wall. However, it may be the case that the posterior margin of the prostate will not be ablated due to a small rectal wall to prostate distance. To get around this with the Sonablate, additional water can be added to the condom surrounding the HIFU probe to increase its separation for the rectal wall. This facilitates full ablation of the posterior margin. The treatment crystal within the Ablatherm probe is mounted such that it can be mechanically and automatically moved in three dimensions to fine tune its position relative to the rectal wall, which is detected on the real-time images.

Split Beams

With the Sonablate a flat central element can serve dual purposes as it can be used for both imaging and treatment. Surrounding elements are utilized only for treatment. During treatment, if all arrays are incorporated and active during the therapy mode (single beam) then a sharply demarcated ablation zone will be created. By including the central element, ultrasound wave interference occurs and the resultant focal zone of ablation is approximately three times the size for the same energy and focal length. This is referred to as a split beam and has the possibility of reducing treatment time and is incorporated into the Sonablate device.

Safety Features

Patient Position: The two technologies use different patient positions during treatment. Several urologic procedures are performed with the patient in the lithotomy position. This is the position utilized during treatment with the Sonablate and allows for easy access. However, if bubbles are present in the fluid surrounding the treatment crystal or

are created during treatment they will rise and end up between the crystal and the prostate. This can compromise the treatment quality (both in terms of ablation and targeting) as air sharply reflects ultrasound. Treatment by the Ablatherm is performed with the patient in a right lateral decubitus position. This is done as a safety precaution. If there are any bubbles in the fluid surrounding the treatment probe they will rise upwards. With the patient on his side and the treatment aimed laterally bubbles will not end up between the HIFU treatment crystal and the prostate.

Rectal Wall Monitoring: During HIFU temperatures increase not only at the zones of ablation created by the deposit of sonographic energy but also throughout and adjacent to the prostate due to thermal conduction. The rectal wall is sensitive to temperature changes. Appropriately, both manufacturers recognize the need for precise rectal monitoring. To maintain acceptable temperatures throughout the rectal wall both Sonablate and Ablatherm use the following strategy:

- I. active cooling of the rectal wall during treatment;
- II. continuous monitoring of the temperature of the rectal wall and;
- III. continually measuring the distance between the rectal wall and the prostate.

Combined, these measures have reduced the occurrence of rectal fistulas with both the Ablatherm and Sonablate to essentially zero (11, 12). Additionally, the infrared system used by the Ablatherm to monitor patient position will cause the device to shut off instantly if any movement is detected.

Reflectivity Measurement: Although cavitation should not occur during HIFU due to the choice of treatment frequencies Sonablate does incorporate an additional safety measure: reflectivity measurement. Tissue changes resulting from increased temperatures can be detected by analyzing reflected ultrasound signals and comparing them to images taken prior to commencement of therapy. As the temperature increases, the reflectivity index (ratio of the two signals) changes. This allows for a real time feedback indicating that an excessive build up of thermal energy may be imminent. If significant reflectively index changes are observed in a region the device will automatically pause until sufficient energy has dissipated before therapy continues.

Clinical Outcomes

Table II summarizes all papers published regarding HIFU from 2000 through February 2006. One paper was excluded from this table, which was Uchida’s 2002 report (18). This was not included because it is replaced by a 2006 report that is an update of the same patient series. Direct comparisons of the outcomes from the two technologies are not entirely possible for several reasons, including the lack of consistency in reporting, the unique patient populations, the different lengths of follow-up, and the limited number of papers reporting efficacy with the Sonablate. Five year biochemical control outcomes are available only for patients treated with the Ablatherm with stable PSAs (according to the ASTRO definition of biochemical failure) ranging from 66-76.9%. Uchida’s 2006 paper is the longest follow-up paper reporting three year outcomes with the Sonablate observing 74% of patients to have a

Table II
Outcome observed following HIFU. Multicenter trials are marked with an asterix.

Study	Device	n	PSA (ng/ml)	Gleason	Stage	Median f/u (months)	negative biopsy	Long term efficacy (definition)
Chaussy 2001 (13)	A	184	12		T1-2 Nx		80%	
Gelet 2001 (14)	A	102	8.38 Mean	54% 2-6 46% 7-10	T1-T2	19	75%	66% @ 5 years (ASTRO)
Poissonnier 2003 (15)	A	120	5.67 Mean 100% < 10	64% 2-6 36% 7-10	T1-T2	27	86%	76.9% @ 5 years (ASTRO)
Thüroff 2003* (11)	A	402	10.9 Mean	13.2% 2-4 77.5% 5-7 9.3% 8-10	T1-T2	13	87.2%	
Blana 2004 (16)	A	146	7.6 Mean	5 ± 1.2	T1-T2 N0M0	22	93.4%	84 % @ 22 months (PSA < 1.0)
Uchida 2005* (12)	S	72	8.1 Median		T1c-T2b N0M0	14	68%	
Uchida 2006 (17)	S	63	11.2 Mean	21% 2-4 73% 5-7 15% 8-10	T1c-T2b	23.3	87%	74% @ 3 years (ASTRO)

Abbreviations: f/u, Follow-up; A, Ablatherm; and S, Sonablate

stable PSA. Although it is inappropriate to draw conclusions regarding difference in efficacy based on these biochemical control rates, the availability of longer term biochemical outcomes with the Ablatherm allows for less uncertainty in the actual efficacy of the device specific treatment.

Negative biopsy rates provide a better short term measure of treatment success as a positive biopsy definitively shows either residual or recurrent prostate cancer and is usually a trigger for the initiation of additional therapy. The range of negative biopsy rates for patients treated with the Ablatherm is 75-93.4% and 68-87% for patients treated with the Sonablate (Figure I). These ranges are similar and it is unclear if any statistical difference exists. A more pronounced difference is observed when looking at the two most important studies in Table II: Thüroff *et al.*, 2003 (11) and Uchida *et al.*, 2005 (12). These two studies report outcomes of multicenter clinical trails utilizing the Ablatherm and Sonablate, respectfully. They both have similar patient populations and similar lengths of follow-up. The negative biopsy rates of the two multicenter studies are quite different at 87% for the Ablatherm and 68% for the Sonablate.

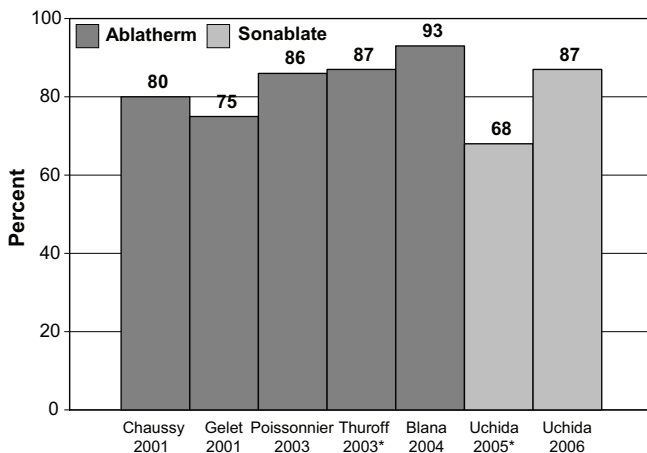


Figure 1: Comparison of negative biopsy rates between the Ablatherm and Sonablate device. Multicenter trials are marked with an asterix.

Biochemical outcomes from the two technologies appear to be similar without a discernable difference although longer term follow-up is available with the Ablatherm. Local disease control, as demonstrated with negative biopsy rates in multicenter investigational settings, appears to be higher for the Ablatherm. A more definitive comparison will not be possible until more articles appear in the medical literature or a randomized prospective trial comparing the two technologies is conducted.

Conclusions

High intensity focused ultrasound is a technologically advanced non-invasive therapy for prostate cancer. There cur-

rently exist two commercially available treatment units each with their own merits. Longer term follow-up is available with the Ablatherm device, which also has demonstrated higher local disease control in multicenter investigations. The role of HIFU will continue to be defined as more patient series are published with longer term follow-up.

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