

## **High Intensity Focused Ultrasound for Prostate Cancer: 2006 Technology and Outcome Update**

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### ***Introduction***

In the past ten years, thousands of men have had their prostate cancer treated with High Intensity Focused Ultrasound (HIFU). Most patients have been treated in Europe. 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. Despite these facts, HIFU is new to North America. It is not yet approved by the United States' FDA but the procedure is available in Canada, the Dominican Republic and Mexico. Although not reimbursed by any public or private health insurers, many men from these countries, as well as the United States, have been treated.

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. The motivation behind this update is two fold: First, there is currently a void in the literature regarding a simple explanation of what HIFU is and the thought processes used in the development of commercially available technologies. Second, there is an availability of newly published important clinical data which allows for a better clinical outcome evaluation.

## ***HIFU Fundamentals***

Sound is vibration. Vocal chords vibrate the air near you when you speak and sound waves (air vibrations) travel away from you. When these vibrations reach another person they cause their ear drum to vibrate creating a signal that is processed by the brain. Vibrations are measured in units called Hertz (Hz) which are the number of vibrations per second. Typically, the human ear can hear frequencies between about 20 and 20,000 Hz. Higher frequency sounds have a higher “pitch”. Sounds with frequencies higher than the range that humans can hear are called “ultrasound”. Medical ultrasound uses frequencies so high that they are measured in millions of hertz or “Mega Hertz” (MHz).

Ultrasound waves can be created by a special type of crystal that vibrates at a specific frequency when an electric current passes through it. The reverse is also true: the crystal will create electricity when vibrated. Both effects are important for medical ultrasound. When a pulse of electricity is passed through one of these crystals a group of sound waves is created and travels away from the crystal. As the sound passes through tissue, some of it will be reflected back to the crystal as it encounters different tissue structures. This is an “echo” and is exactly the same effect as when you yell into a canyon and some sound is bounced back. Now, when the echo comes back to the crystal 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 also important to note that air is the enemy of ultrasound imaging and causes near complete reflection of the signal destroying the ability to image. This is why a gel is put on the skin before imaging occurs. This creates 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. Air also compromises the ability to perform HIFU but that will be discussed later.

Ultrasound waves deposit energy as they travel through tissue but the amount deposited during ultrasound imaging is completely insignificant. Ultrasound imaging is harmless and is so safe that it is used to image unborn babies. The premise behind HIFU is the destruction of tissue by depositing huge amounts of energy into it. This is accomplished by doing two things: increasing the intensity of the waves (similar to turning up the volume) 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 cause irreversible tissue damage (“ablation”).

The deposit of energy during HIFU can result in two mechanisms of tissue damage. 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 the form of cavitation. Cavitation is the formation of gas bubbles within the tissue. It is difficult to create discrete ablation zones in the presence of cavitation as the gas strongly reflects sonographic waves. Thus, cavitation should be avoided during the procedure.

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 (it is shaped like a cigar), and is roughly the size of a few grains of rice stacked end to end. Treatment of cancer of the prostate is accomplished by systematically pulsing energy throughout the target volume at different locations until the entire tumor has been ablated.

**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	↓	↓		

### ***Commercially Available HIFU Technologies***

There are currently two commercially available HIFU technologies 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 HIFU technology of both systems is identical but there are several technological differences between the two machines. These differences, for the most part, arise from different schools of thought with regards to how best design the best possible 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 quality. The different approaches have resulted in the development of two commercially available HIFU devices for the treatment of prostate cancer.

The amount of energy deposited in tissue during HIFU is dependent upon both the transducer operating frequency and intensity. Increasing the intensity increases the energy incident on, and absorbed by, the tissue and therefore also increases the probability of inducing cavitation (Table I). However, 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 manage these interactions that have led to the development of different commercially available HIFU devices.

### *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 probes creating higher quality images having higher frequencies. 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 is the best frequency for treatment. 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 within a single probe. This allows not only for optimal operating frequencies 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. As with the newest Ablatherm device, there is no need to change probes between imaging and

treatment. Unfortunately, this constrains the probe to be of only one 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 although not optimal for either. 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. Pre treatment ultrasound images are captured and the user defines on them, with computer assistance, the regions to be ablated. The program then controls the ablation probe which treats exactly where the user specifies. The Sonablate uses a single treatment program in which the power can be adjusted manually. Conversely, 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 is critical 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 now 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 which could lead to rectal injury and other complications.

### *Real time monitoring*

If a patient moves during the procedure the treatment must be stopped immediately and the treatment plan must be re-checked. 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 used to detect 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 do 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 must watch the entire procedure to ensure that the images line up indicating no patient movement has occurred. If the patient does move the treatment plan is no longer valid and must be redone. This is the same for both technologies.

### *Ablation volume geometry and transducer size*

The fundamental physical constraint in the physical 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. Each pulse of a HIFU crystal will induce a discrete and consistent volume of tissue necrosis.

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 which size is adjustable from 24 mm (anterior to posterior) x 1.7 mm x 1.7 mm (total volume =  $36 \text{ mm}^3$ ) down to 19 mm x 1.7mm x 1.7 mm

(total volume = 29 mm<sup>3</sup>). 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 prostate. However, such additional treatment beyond anterior margin of the prostate will not lead to complications.

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) x 2 mm x 2 mm (total volume = 21 mm<sup>3</sup>) when operated in normal mode and 10 mm x 3 mm x 3 mm (total volume = 47 mm<sup>3</sup>) 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 extra pulses 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 10mm will be treated with the first pass. The next 10mm will then be treated with a second pass. If the prostate is greater than 20mm high a third pulse of energy would be required. This results in more treatment time which is undesirable for any treatment in which the patient is under anesthesia.

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 will 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 from 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.

### *Safety features*

#### *1. Patient position*

The two technologies use different patient positions during treatment. Several urologic procedures are performed with the patient in the lithotomy position (patient lying on their back with their feet in stirrups). 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 (lying on their right side). 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.

## *2. 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. 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:

1. active cooling of the rectal wall during treatment,
2. continuous monitoring of the temperature of the rectal wall, and,
3. 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. 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. Of note, there have been no reports in the literature of fistula formation in patients treated with the Ablatherm since 2003.

### *3. 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 reflectivity index changes are observed in a region the device will automatically pause until sufficient energy has dissipated and therapy continues.

### *Split beams:*

HIFU transducers can comprise of one or more arrays of piezoelectric crystals. 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 not 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 somewhat.

## **Efficacy comparison and update**

Several papers have been published since my last outcome review of HIFU. Specifically, an update of Dr. Uchida's patient series as well as a report from the Japanese multicenter trial is

**TableII:** Outcome observed following HIFU. Multicenter trials are marked with an asterix

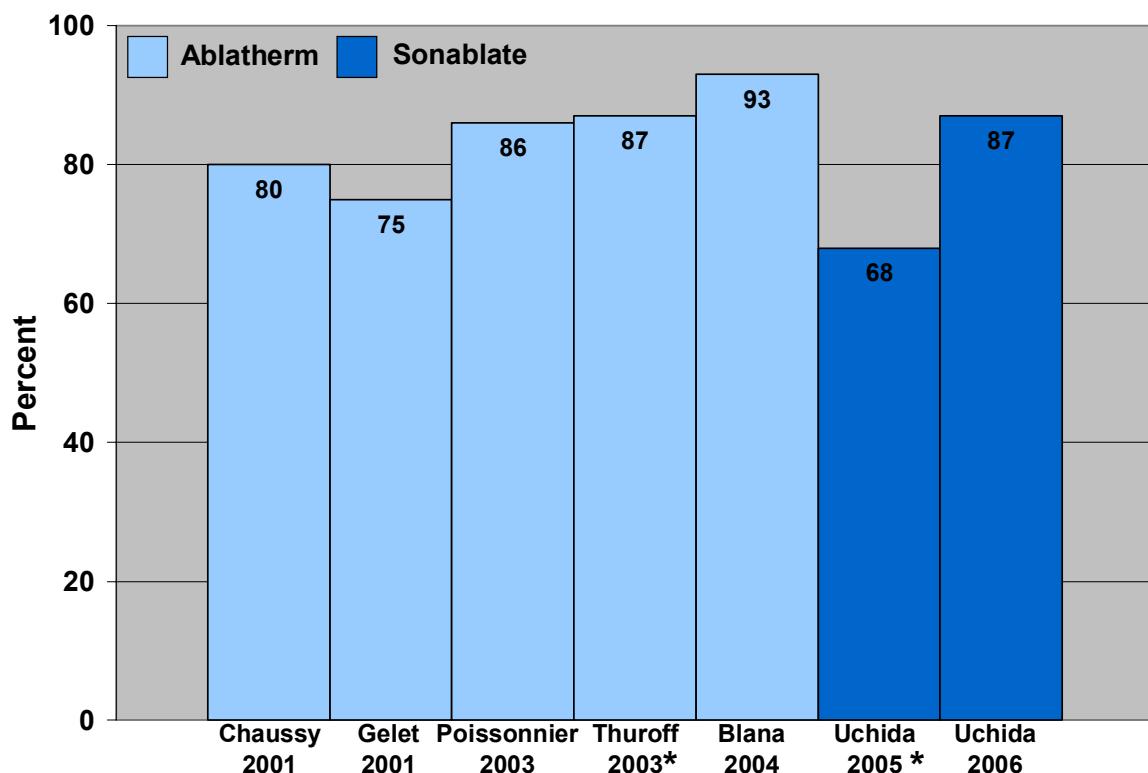
Study	Device	n	PSA (ng/ml)	Gleason	Stage	Median f/u (months)	negative biopsy	Long term efficacy (definition)
Chaussy 2001	A	184	12		T1-2 Nx		80%	
Gelet 2001	A	102	8.38 Mean	54% 2-6 46% 7-10	T1-T2	19	75%	66% @ 5 years (ASTRO)
Poissonnier 2003	A	120	5.67 Mean 100% < 10	64% 2-6 36% 7-10	T1-T2	27	86%	76.9%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

f/u = follow-up, A = Ablatherm, S = Sonablate

now available. Both of these papers report outcomes with the Sonablate. The following summary is based on all papers published in all languages in the peer reviewed medical literature from 2001 until now (the past 5 years). Only full medical journal articles are included. Conference abstracts, as they do not undergo thorough peer review to assess validity and accuracy, were not included.

Table II summarizes all papers published regarding HIFU published in the past 5 years. One paper was excluded from this table which was Uchida's 2002 report. This was done because it is replaced by his 2006 report which is an update of his personal experience with HIFU

which includes the patients from the 2002 report. The two most important studies in the table are those of Thüroff et al 2003 (Ablatherm) and Uchida et al 2005 (Sonablate). These two studies report outcomes of multi-center clinical trials utilizing the Ablatherm and Sonablate, respectfully. They both have similar patient populations and similar lengths of follow-up. They (as well as all other studies listed in table II) use negative biopsies as a fundamental endpoint. Those patients with negative biopsies show no clinical evidence of untreated or recurrent disease: a higher value indicates better cancer control. The negative biopsy rates of the two multicenter studies are quite different at 87% for the Ablatherm and 68% for the Sonablate. It is inappropriate to draw solid conclusions based solely on these two reports due to their short term follow-up. When the negative biopsy rates of all published studies are compared a different picture emerges. Figure 1 is a comparison of all negative biopsy rates.



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

Based on this comparison it appears that the efficacies of the two technologies are somewhat similar. A more definitive comparison will not be possible until more articles appear in the medical literature.

What can be concluded now is that there is less uncertainty regarding the longer term outcomes of the Ablatherm device. The Ablatherm publications have significantly more patients and the follow ups are longer.

## **Conclusions**

High intensity focused ultrasound is a technologically advanced non invasive therapy for prostate cancer. There currently exist two commercially available treatment units each with their own merits. The efficacies appear similar with longer term results available for the Ablatherm providing more certainty regarding efficacy.

## **References:**

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