Transrectal HIFU: The Next Generation?

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DOUGLAS CHINN COMPLETED HIS MEDICAL EDUCATION AT USC, AND HIS INTERNSHIP AND RESIDENCY AT LOS ANGELES COUNTY MEDICAL CENTER. HE JOINED THE GENERAL UROLOGY PRACTICE STARTED BY HIS FATHER (NOW RETIRED) AND BROTHER. A MEMBER OF THE PCRI MEDICAL ADVISORY BOARD, DR. CHINN IS A PIONEER IN CRYOSURGERY FOR KIDNEY AND PROSTATE CANCER. HE DEVELOPED THE PATENTED TEMPERATURE MONITORING TECHNOLOGY THAT IS USED TODAY IN CRYOSURGERY AND HAS PUBLISHED, LECTURED AND TRAINED PHYSICIANS IN CRYOSURGERY WORLD-WIDE. DR. CHINN FIRST STUDIED HIFU IN EUROPE THREE YEARS AGO, AND NOW FEELS THAT ITS TIME HAS COME.

What is HIFU?

HIFU, which stands for **High Intensity Focused Ultrasound**, was first developed as a treatment of benign prostatic hyperplasia (BPH) and now is also being used as a procedure for the killing of prostate cancer cells. As shown in Figure 1, this procedure utilizes transrectal ultrasound that is highly focused into a small area, creating intense heat of 80-100° C, which is lethal to prostate cancer tissue. Since ultrasound is non-ionizing (as opposed to ionizing in radiation), tissue in the entry and exit path of the HIFU beam is not injured.

The published clinical experience with HIFU for this application is limited and only extends out to 5 years, and **the procedure is not yet approved by the FDA for use in the United States**, (HIFU is approved in Europe, China, Japan, Caribbean, Mexico, and Latin America). However, HIFU offers a powerful advantage over radiation treatment: **The control and precision of HIFU allow the accomplished surgeon to accurately target the tissue to be destroyed without injuring adjacent tissue. HIFU destroys tissue by heat, rather than by cavitation or mechanical shearing forces.**

Energy pulses over 100 watts/pulse are usually required to thermally ablate tissue.[1] The predominant desired effect is thermal, as contrasted to cavitation or mechanical forces. The energy or thermal delivery dose occurs in less than 1 second, and is very controlled and well defined. The temperature immediately rises up to 70-80° C, and proceeds to thermally ablate the tissue. The surrounding tissue, which is 2 mm away from the focused lesion, is not injured. Although each lesion is small, (2 mm x 3 mm x 30 mm) sequential dosing results in a larger volume of ablated tissue.[2]

Attenuation or weakening of the HIFU by the intervening tissue can occur. The density and content of the intervening tissue can affect the HIFU power. Bone or calcification can severely attenuate and even reflect HIFU output. Air not only attenuates HIFU, but interferes with imaging as well.

Background and History

Since the 1940s, HIFU has been viewed as a potential therapeutic tool, and the initial work on its role in the treatment of the benign prostatic hypertrophy (BPH) began in the early 1990s. In what I consider a landmark study, Sanghvi et al did several safety and feasibility studies on canine prostates, utilizing HIFU and thermal mapping.[3] From 1992-93, the first group of patients was treated at Indiana University, School of Medicine, by Bihrle et al.[4] The role of HIFU for treating prostate cancer

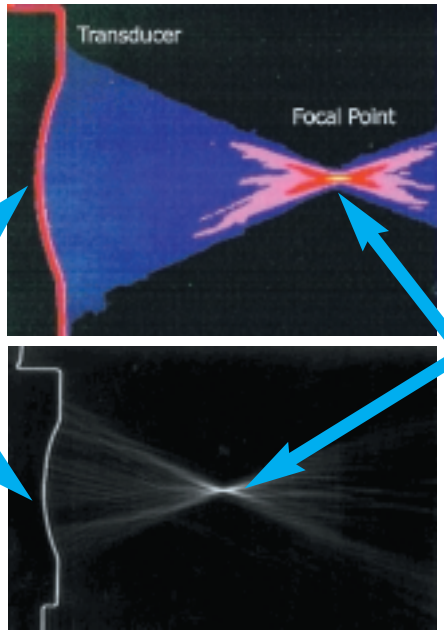
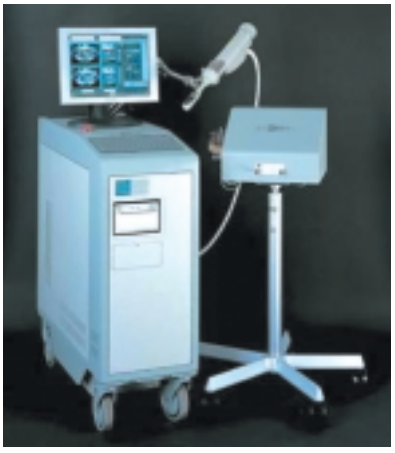


Figure 1 *Focusing of Transrectal Ultrasound to Create Lethal Heat to Malignant Tissue.*
Image above: courtesy of Focus Surgery®
Image below: courtesy of Sanghvi et al [6]

Figure 2 *Elements of the two HIFU Units.*



Sonablate 500® Unit

Ablatherm® Unit

also picked up momentum after that. Since then, several clinical outcome studies have recently been published, including a 5-year outcome study by Blana et al,[5] and a multi-center European study by Thuroff et al.[6]

Equipment

Currently, there are two companies that make HIFU units for patient use: Focus Surgery® and EDAP Technomed.® Focus Surgery® is based in the United States, and EDAP Technomed® is based in France. For both companies, the HIFU unit consists of a control console, a power generator, a cooling system, and a probe that contains a standard imaging and a high-intensity treatment ultrasound head.

Procedure

HIFU is performed as an outpatient procedure, usually under epidural anesthesia. As shown in Figure 3, the patient is either placed on his back with legs elevated in the dorsal lithotomy position (Sonablate 500®) or on his right side (Ablatherm®). The HIFU probe is placed into the rectum and multiple gland images are taken.

Then, at the HIFU control panel, all of the images are reviewed, and the treatment zones are defined and logged into the treatment computer. The entire prostate cannot be treated all at once, so the prostate is divided into treatment zones. The entire procedure can take between 2-4 hours, depending upon the gland size.

Differences Between the Sonablate 500 and the Ablatherm Units

As shown in Figure 4, the Sonablate 500 requires three treatment zones from top to bottom, and two treatment zones from side to side. The Ablatherm unit has only one treatment zone from top to bottom, but two treatments from side to side.

The Sonablate software allows the surgeon to customize each of the six treatment zones in order to safely ablate the entire gland.

As shown in Figure 5, precise HIFU lesions are overlapped side-by-side in both Sector (Transverse) and Linear (Longitudinal) planes within the prostate as defined by the doctor.

As can be seen from the real time images in Figure 6, HIFU allows the exact placement of the treatment zones up to the edge of the gland or external sphincter. If necessary, the treatment zone can extend beyond the edge of the gland to treat early extracapsular penetration, or just up to the edge of the neurovascular bundle.

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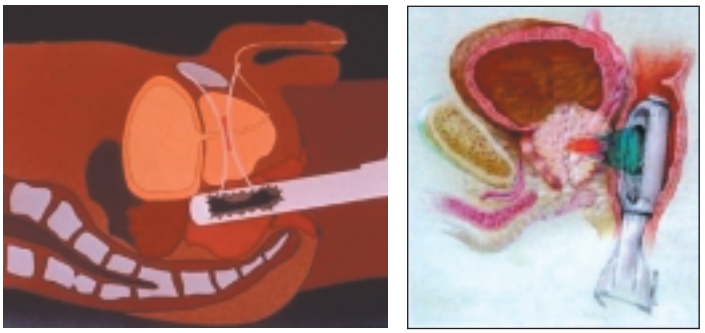


Figure 3 *Positioning of the Sonablate 500 probe (two views).* Images courtesy of Focus Surgery®

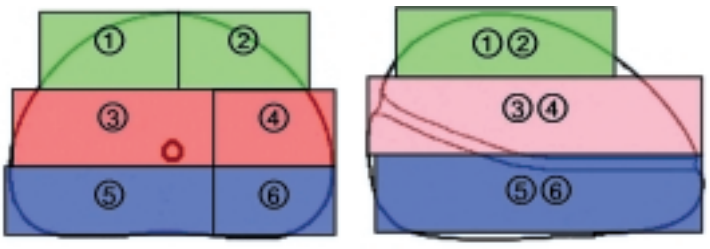


Figure 4 *Treatment Zones treated with Sonablate 500.* Courtesy of US HIFU.®

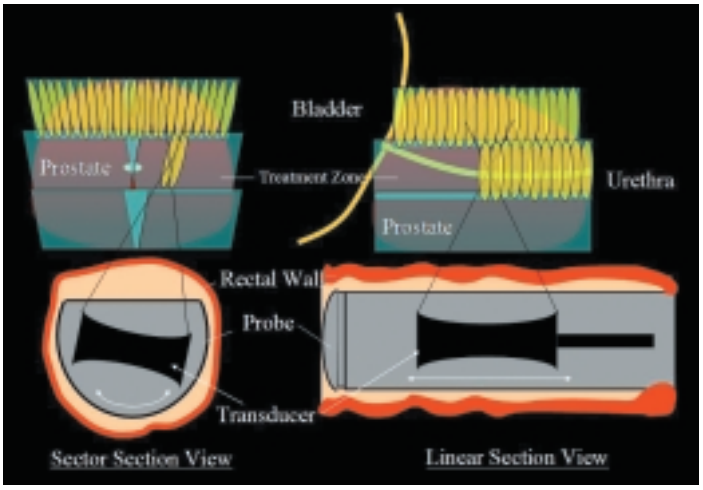


Figure 5 *The image illustrates in the Sector and Linear view, how the Sonablate® 500 HIFU beam is precisely focused and delivered into the prostate gland. Also note the multiple treatment zones required.* Courtesy of Takai Hospital Supply Co., Tokyo, Japan.

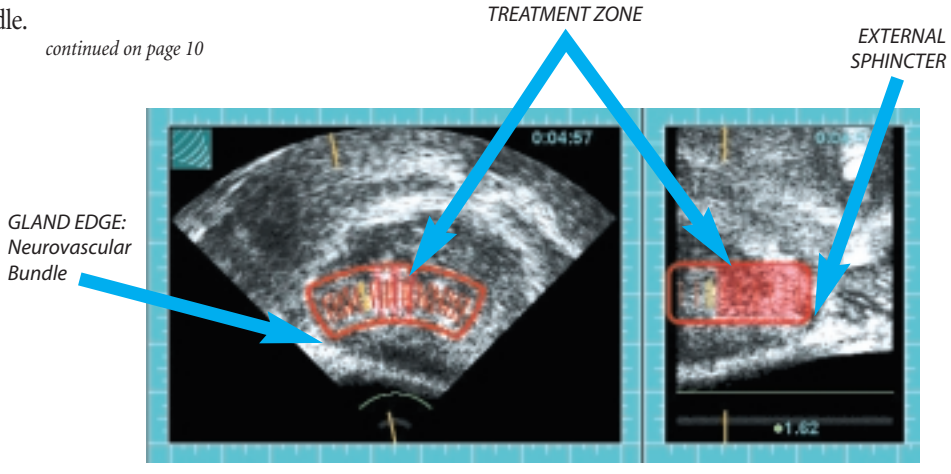


Figure 6 *Sonablate® views in the sector and linear orientation. The red box represents the planned treatment area with the vertical red lines being the exact target. The red shaded areas represent the treated areas. In the sector view, the treatment box can be accurately controlled to aim HIFU just at the lateral edge of the gland, and still avoid injuring the neurovascular bundle. In the linear view, the treatment box is controlled to end just at the apex of the prostate gland, thereby avoiding injury to the adjacent external sphincter.* Photo by D. Chinn, MD.

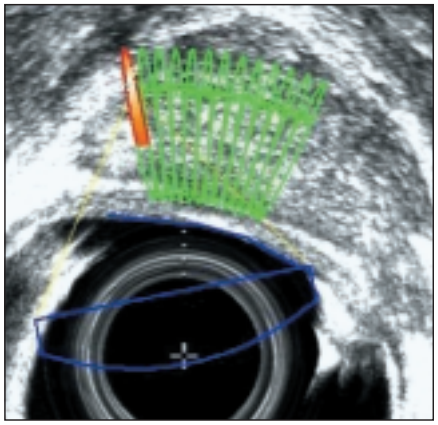


Figure 7 *Ablatherm® sector view with treatment zones mapped out. There is only a single vertical treatment zone. In this illustration, the gland is taller than the height of the treatment zone. This image is from a BPH therapy.* Courtesy of EDAP Technomed®

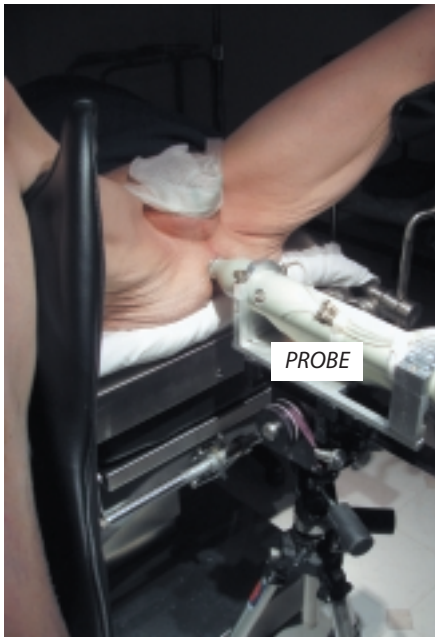
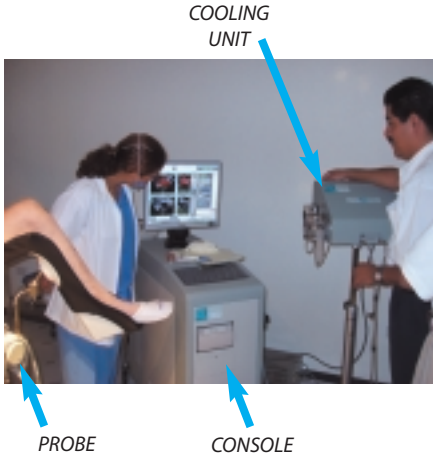


Figure 8 *(Above and below) Procedure Setup with Sonablate 500.* Photos by D. Chinn, MD.



As shown in Figure 7, the Ablatherm device uses one large treatment zone from top to bottom. It too requires multiple treatment areas from side to side.

With the Sonablate® unit, the patient is placed in the dorsal lithotomy position. (See Figure 8.) The patient is lying flat on his back, and his legs are elevated by behind-the-knee stirrups. The treatment console and cooling unit are separate. The Sonablate® unit uses a standard operating room table

With the Ablatherm® unit, the patient must lie on his right side, on a special table. (See Figure 9) The cooling unit and probe are integrated into the table. The treatment console is separate.

As shown in Figure 10, the Ablatherm® unit uses two ultrasound probes built into a single unit. The imaging probe (white) is used to record multiple images of the prostate in the transverse (end on view) and longitudinal (side view) planes. Once all of these images are recorded, they are used to plan out the treatment. Then in therapy mode, the imaging probe is retracted, and the treatment probe is moved into position in order to treat the planned zones.

The images seen during therapy with the Ablatherm are static ultrasound images, with treatment zones superimposed. There is no live ultrasound imaging during therapy. The red lines in Figure 11 represent treated tissue, the green lines tissue to be treated. The orange-filled area represents current therapy. In order to update ultrasound images, the Treatment Probe must be retracted and the Imaging Probe must be moved back into the field.

The Sonablate® 500 probe combines the Imaging and Treatment probes into the single unit shown in Figure 12. Therefore, during therapy, live ultrasound imaging can be utilized. **This allows the physician to simultaneously image and treat, thereby ensuring**

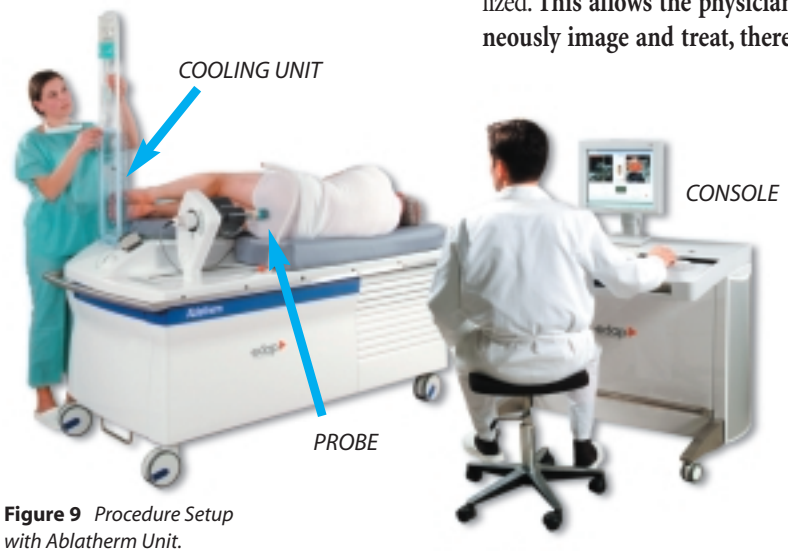
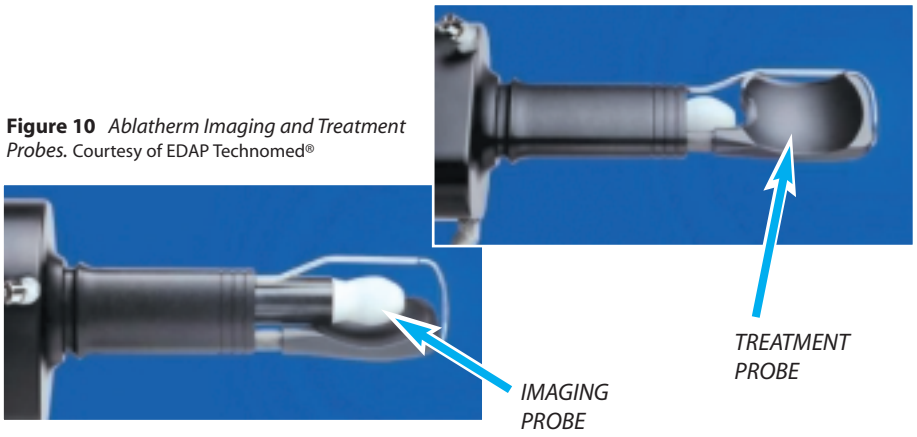


Figure 9 *Procedure Setup with Ablatherm Unit.* Courtesy of EDAP Technomed®

Figure 10 *Ablatherm Imaging and Treatment Probes.* Courtesy of EDAP Technomed®



that the treatment areas have not changed by any patient or probe movement. In fact, the tissue changes due to treatment can be seen during therapy.

In the Figure 13 image, the treatment box is outlined in red. The area shaded red represents the areas already treated; the red vertical lines without the red shading are the planned treatment areas; and the yellow vertical line represents the next treatment area. **Because of real time imaging, one can actually see the tissue changes caused by HIFU, which are the bright white spots (echoes) seen above.**

Surgery

First, the patient lies down on the operating room table and receives spinal anesthesia. The ultrasound probe is placed into the rectum and is adjusted such that all of the gland can be properly imaged. Then a series of images in the sector and linear views are captured by ultrasound, under computer control. All of the captured images are displayed on the console screen. The surgeon, using a mouse, then selects the treatment zones.

For both the Ablatherm and Sonablate units, the surgeon must make sure that the top of the gland is in the treatment zone. Depending on the extent of the cancer, the side-to-side treatment zones may extend up to the edge or beyond the prostate capsule. The surgeon must keep track of the treated zones to avoid untreated gaps occurring between the treatment zones. After one zone is treated, the probe is rotated to the untreated side of the gland. Images are recaptured, and treatment zones delineated. Treatment is then started again. Treatment ends when all of the gland has been treated.

With both units, the intensity and duration of therapy is determined by the computer, but the power can be manually adjusted by the surgeon, usually when the imaging nears the rectal wall.

After Surgery

There will be edema secondary to the thermal effects: therefore, at the end of the procedure, a urethral foley catheter is placed into the bladder. This catheter will remain for 2-4 weeks. There may be some bladder discomfort for several days, but full activities can be started the day following surgery.

Once the catheter is removed, the urinary stream may take several months to improve, as the urethra needs to heal, and the gland will take up to three months to start shrinking in size. During this time, some dead prostate tissue may pass in the urine. The rest of the gland forms scar tissue.

Indications

For the majority of patients, the goal of HIFU therapy is curative. Therefore, in my opinion, any patient with organ-confined prostate cancer may be a primary candidate. As with cryosurgery, HIFU can treat the entire prostate capsule and beyond, so **HIFU can also be used to treat prostate cancer that has begun to spread beyond the capsule.** If capsular or neurovascular bundle invasion has been detected (by DRE, Endorectal MRI, ultrasound, or biopsy) these areas can be easily and safely treated with HIFU. **More importantly, if there is no capsular invasion and the neurovascular bundles are not involved, the nerves can be spared, and potency maintained (depending upon the skill of the surgeon).**

Seminal vesicle invasion is a problem for all therapies because there is a higher incidence of occult metastatic disease with seminal vesicle involvement. Early seminal vesicle invasion can be treated with HIFU. As developers continue to improve and develop the HIFU equipment, I anticipate further seminal vesicle therapy.

Thus, the best candidates for curative intent are clinical/pathological stages T1c-T3, with an under-

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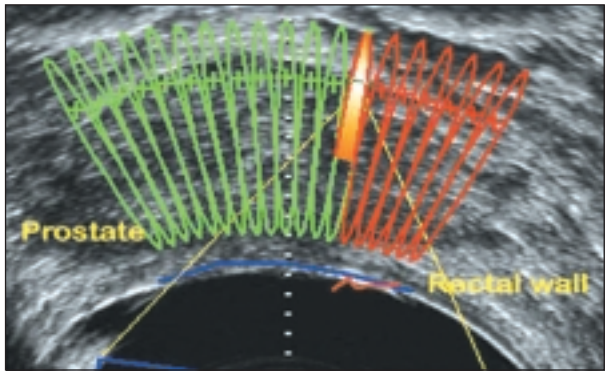

Figure 11 *Ablatherm® sector view. The treatment zone covers the gland height completely, and requires two zones to cover from side to side. Again, the HIFU beam can be precisely aimed to the lateral and posterior edges of the gland.* Courtesy of EDAP Technomed®

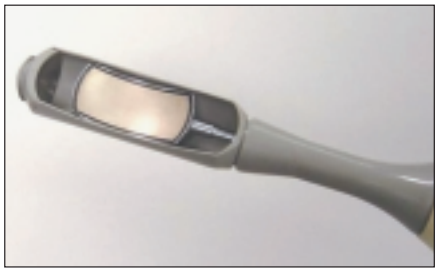

Figure 12 *Sonoblate 500 Combined Imaging and Treatment Probe.* Courtesy of Focus Surgery®

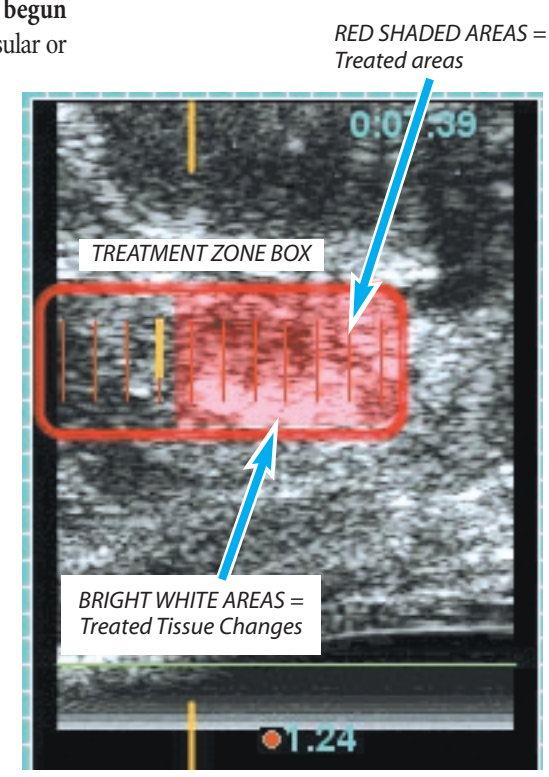

Figure 13 *Sonablate linear view demonstrating real time tissue density and image changes induced by HIFU. Treated tissue turns white, while untreated tissue remains unchanged. This allows confirmation of therapy.* Photo by D. Chinn, MD.

standing that the higher the volume/stage, the higher the risk of occult metastatic disease. As in cryosurgery, the Gleason score does not affect the lethality of HIFU.

Due to the limited focal length of HIFU, gland volume cannot be 40cc or larger. If the gland is larger, then downsizing is required with total androgen ablation using a gonadotropin-releasing hormone (GnRH) agonist, (e.g. Zoladex®) a non-steroidal anti-androgen (e.g. Eulexin® or Casodex®), and a 5-alpha reductase inhibiter (e.g. Proscar® or Avodart®). This same protocol has been utilized for preoperative downsizing for brachytherapy and cryosurgery.

Salvage Therapies

Aside from primary therapy, HIFU can be utilized as salvage therapy, primarily after radiation. With the Sonablate® unit, brachytherapy seeds do not interfere with the energy transfer. With the majority of radiation failure patients, the surrounding tissue is damaged, and the complications of incontinence, impotence, and rectal injury are increased in any form of salvage therapy (salvage radical prostatectomy or cryosurgery). **Because of the excellent control and targeting of tissue afforded by HIFU, I personally feel that HIFU will emerge as the best choice for salvage therapy.** To date, the reported incidence of incontinence and rectal injury is much less than for salvage radical prostatectomy or cryosurgery. If there is local recurrence after radical prostatectomy, and a lesion left behind can be visualized on ultrasound, then there is a chance that HIFU can be used to treat that lesion.

HIFU can also be used for palliative therapy, debulking large symptomatic tumors that are causing pain, bleeding, and obstruction. As with cryosurgery, the effectiveness is limited by the gland size.

Also as with cryosurgery, HIFU can be repeated, without any increase in risk or complications. HIFU can also be used to treat cryosurgical failures, if there is no undue calcification present. Finally, if necessary, radical prostatectomy can be performed after HIFU.

Focal Therapy

Focal therapy is a very controversial topic among urologists with the biggest concerns being the facts that: (1) prostate cancer is multi-focal; (2) there is sampling error with biopsies; and (3) there is currently no way to find all of the cancer, even with saturation biopsies. The attraction of focal therapy is a marked decrease in side effects of the procedure because not all of the gland has to be treated. This results in decreased operating room time, less post-procedural gland swelling, and reduced urinary retention. Since only a portion of the gland is treated, all side effects are greatly reduced or absent. While the validity of focal therapy is a topic for another discussion, it can be said that, while cryosurgery is the first procedure to allow focal therapy, HIFU may offer a better form of focal therapy. HIFU can truly treat just one lobe of the gland. With cryosurgery, the surgeon must drive lethal and non-lethal ice across the midline to ensure destructive ablation of one lobe. The same methodology applies to nerve-sparing procedures. With cryosurgery, in order to preserve the neurovascular bundles, the surgeon risks preserving viable prostate tissue as well. This is less of a concern with HIFU, which can focus the ultrasound beam right up to the edge of the capsule.

Contraindications

As previously stated, gland size must be less than 40cc. Also, extensive or very large calcifications will interrupt, block and reflect the HIFU beam, so these glands cannot currently be treated. If there is rectal stenosis that does not allow the probe to be placed, HIFU cannot be used. A history of rectal fistula is also a current contraindiction. If a patient had a prior rectal fistula, it may not be completely healed. Also, the damaged tissue may have less vascular reserve and be more susceptible to injury than normal tissue. Moreover, if the fistula recurs after HIFU, it might be erroneously blamed upon the procedure.

Again, as in cryosurgery, bleeding problems or anticoagulation are not absolute contraindications. It is recommended that all blood thinners be stopped 10 days in advance, because there may be some rectal bleeding from the stretching caused by the rectal probe. However, the blood thinners can be restarted 24-48 hours later. If there is a bleeding diathesis (lack of clotting factors) the corrective factors can be infused just before surgery.

Risks and Complications

Immediately after surgery, there will be urinary retention, because the gland will swell. Often, there will be necrosis (slough) of some or all of the urethra. Many patients pass this tissue without any problems, and others may require the removal of the tissue through a cystoscope (TURP). (Sloughing can also occur with cryosurgery, especially in radiation failure. Radiation necrosis of the urethra has been seen with brachytherapy, but no surgery is performed due to the high risk of problems in radiated tissue and the seeds.)

Table 1 presents the treatment side effects of HIFU and compares them with three other leading treatments. As shown, incontinence is extremely rare, especially with the Sonablate 500.® This is even more important in radiation failure patients, where the accuracy and precision in which HIFU can be delivered is very important.

Potency after HIFU can be good, again for the above mentioned reasons. Moreover, the equipment manufacturers are continuing to work on methods to improve the chances of

Table 1. Data Table Comparing Treatment Side Effects. *Courtesy of Dr. George Suarez*

	Rectal Injury				Incontinence	Impotence
	FISTULA	URGENCY	BLEEDING	DIARRHEA		
Radical Prostatectomy		6-16 % (16,17)	1-3 % (17,18)	6-19 % (16,18)	7-52 % (17,19)	14-96 % (20,21)
Beam Radiation		19-43 % (16,17)	13-17 % (17,18)	12-42 % (16,18)	0-15 % (17,18)	50-61 % (17,22)
Brachytherapy	0-3 % (23,24)		4 –11 % (25,26)		0-19 % (27)	14-66 % (27)
Cryoablation	0-0.5% (15,29)				1-7 % (15,29)	47-95 % (28,30, 33)
HIFU(Sonoblate)	<0.5-5%				0-2%	28-30%

Table 2. 5-year Outcome Data Comparison Biochemical Disease Free Survival*

	Radical	Cryo	Brachy	3DCRT	XRT	HIFU
Low	76-98%	60-92%	78-89%	76-87%	81-86%	70-71%
Moderate	37-77%	61-89%	66-82%	51-58%	26-60%	

maintaining potency after HIFU. However, as with cryosurgery or radical prostatectomy, all patients undergoing HIFU will have no ejaculation with climax, and they will be infertile.

Rectal injury appears to no longer be a significant concern for HIFU. Although early papers reported rectal fistula rates as high as 5% with earlier prototype equipment, series using the newest technology have observed rates of <0.5% (for the Sonablate 500). Hence, with the current HIFU units, the incidence should be very low. Of course, due to the surrounding tissue effects of radiation, there is still a risk of rectal injury. But, just as with cryosurgery, it depends upon the skill of the surgeon to plan and control HIFU to avoid rectal injury.

Outcome Data

When I started performing cryosurgery in 1993, there was a paucity of published data from multiple centers. Also, high-quality basic scientific studies on the technique and technology of cryosurgery, specifically for prostate, were severely lacking. It took clinicians such as myself with the support of Drs. Fred Lee Sr., Fred Lee Jr., Wilson Wong and Duke Bahn to develop the proper way to freeze the prostate gland. Until we developed the technology and technique of temperature monitoring, the excellent and consistent success of cryosurgery was unobtainable. Conversely, there have been excellent scientific and clinical publications with HIFU, notably these published journal articles by Sanghvi,[3,7] Chaussey,[8] Vallancien,[9] Gelet,[10] Blana[5] and others.[11,12,13,6] Finally, the equipment hardware and software are at a much more sophisticated level at this point than they were at this stage of started cryosurgery development.

Table 2, modified from Katz and Rewcastle,[31] compares (1) the 5-year biochemical disease-free survival rates as published since 1992 for five prostate cancer local treatments with (2) that published by Gelet et al[32] for HIFU. As can be seen, HIFU results compare well with the results of these established therapies, particularly in view of the low side-effects advantages presented in Table 1. Moreover, the results of the HIFU patient series can be considered a worst-case scenario, as the series includes the first patients ever to undergo HIFU as a therapy for prostate cancer, and many of them were treated with the original prototype HIFU.

HIFU and the FDA

HIFU has not yet been approved by the FDA for use in the United States, but it is approved for use in Europe, Latin America, the Caribbean, China, and Japan. FDA clinical phase trials I and II have been done in the United States, and plans are underway to start the final Phase III FDA clinical trials. Therefore, HIFU is not available in the United States. HIFU therapy with the Sonablate 500® is available in Santiago, Dominican Republic, Puerto Vallarta, and Los Cabos San Lucas. In Cabo, the hospital is AmeriMed, which is an American-owned hospital chain in Mexico.

Conclusion

Although HIFU is a relatively new procedure for prostate cancer treatment, it represents what may become the next generation of minimally invasive therapy for prostate cancer. While clinical experience with HIFU is still limited, the technology has been extensively studied and developed to the point that I personally believe that it is indeed ready for prime time. **The control and precision that HIFU provides truly allows the surgeon to precisely ablate the prostate gland with pinpoint accuracy and thereby preserve the adjacent structures. Furthermore, because HIFU is non-ionizing, there is no collateral tissue damage.** Despite not being FDA-approved in the U.S., HIFU remains my first choice for therapy in radiation failure, focal therapy, and potency sparing surgery. For all other cases, it is my relative first choice depending on my patients' desire.

The development of obstruction and possibly sloughing is the most common side effect of HIFU. Many European centers are performing prostate incisions or TURPs prior to HIFU in an attempt to alleviate this problem. I anticipate changes in the technique and perhaps new developments in equipment that may resolve this issue. Improvements in technology will more easily allow the surgeon to fit all of the currently rectangular treatment box into the elliptical shape of the prostate. This will undoubtedly improve our ability to totally ablate the entire prostate gland.

Of course, longer term follow-up and clinical experience is required, and as with any therapy, not everyone is going to have a local cure. However, in my opionion, HIFU should be seriously considered in the primary treatment of prostate cancer, and I feel it should be the first choice for radiation failure cases.

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Participating in a Prostate Cancer Clinical Trial

By Stanley A. Brosman, MD *Pacific Urology Institute, Pacific Clinical Research, Santa Monica, CA*

IT DOESN'T TAKE VERY LONG WHEN DISCUSSING TREATMENT OPTIONS FOR PROSTATE CANCER BEFORE WE REALIZE THAT WE DON'T HAVE THE ANSWERS TO MANY IMPORTANT QUESTIONS. Is this medication better than that one? How long is hormonal treatment necessary? Is surgery better than radiation therapy? Do seed implants work better than IMRT? The list of unanswered questions goes on because there is no way to answer them without a well-designed clinical trial.

At last year's meeting of the American Urological Association, Howard Scher, the chief of Urologic Medical Oncology at Memorial Sloan-Kettering Cancer Center made a presentation specifically addressing the pressing need for well designed clinical trials. Clearly, this is an issue that needs to be seriously addressed or we will be asking the same questions regarding treatment when our grandchildren are diagnosed with prostate cancer.

There were 25 new agents presented at this meeting that have shown promise in (1) animal studies and (2) small numbers of men with all stages of prostate cancer, particularly those with androgen-independent disease. In order to design a study to compare each of these new agents against a placebo or another agent, 980 men would be needed for each new agent in order to detect a statistically and clinically meaningful difference between the two treatment groups. **Since fewer than 5% of men currently participate in prostate cancer clinical trials**, it will take years to learn if an agent is effective and so most of these agents will never get tested.

The Purpose of Clinical Trials

A clinical trial is designed to answer specific questions. There are three phases or types of clinical trials with several subdivisions for each. Phase I trials represent the first time that an agent has been tested in humans. These are usually performed with close monitoring in hospitals or specially designed Phase I centers. Usually small numbers of people (6-12) enter these trials. Toxicity and dosing are evaluated. Phase II trials usually involve 30-50 people. Once the dosing has been determined and the toxicity carefully evaluated, the test agent is ready for Phase III. Large numbers of individuals are necessary to compare the test agent to a placebo or another standard therapy. **Of all the drugs that enter a clinical trial, only 5% successfully complete these trials and eventually enter the marketplace. This is one of the reasons our medicines cost so much.**

Clinical trials are extremely complex and difficult to perform successfully. Relatively few physicians have been trained or have the interest in organizing and conducting these studies. To understand what is involved, I have designed a simplified hypothetical clinical trial that asks a specific question: How should men be managed who have a rising PSA following surgery? We will arbitrarily select two options, radiation therapy or hormonal therapy. This seems simple enough but let's look at what is involved.

A Typical Clinical Trial

The Principal Investigator(s) who has conceived this clinical trial starts by writing a protocol that is a document detailing all aspects of the study. This includes instructions regarding how much and what type of radiation therapy, what type and doses of hormonal therapy, what tests would be needed, how often the patient should be seen, and how long a follow-up period is necessary to answer the question. The protocol stipulates who is eligible to participate and who is ineligible. For example, the protocol might stipulate that only men diagnosed with prostate cancer who have had surgery would be eligible, but those who had prior radiation therapy as treatment for their disease would be ineligible. Ordinarily, a protocol will have a list of 10-12 entry (or *inclusionary*) criteria and a similar number of *exclusionary* criteria.

The protocol is given to a bio-statistician who determines the number of men who would be needed to answer this question, or in the parlance of the statistician, what numbers are necessary to adequately power the study. To complicate matters, the two groups need to be balanced or stratified according to stage, grade, PSA, age, time between surgery and a rising PSA and any other factors that might affect the study. In order to deal with all of these factors, the bio-statistician determines that 1800 men are needed to enroll (900 in each arm) in this study in order to adequately power the study so that our question can be answered. An underpowered study ends up with either no answer or an inadequate answer. Time and money are lost and another study would need to be done.

> "Most of these agents will never get tested."

A consent form describing the study is written according to Federal regulations. This is a lengthy and often complex document. The final protocol and the consent form are submitted for review and approval by an Institutional Review Board (IRB). Revisions are often requested by the IRB, and the documents are re-submitted. Each subject participating in the study must sign the approved consent form before entering the study.

A single institution would not be able to enroll this number of men. Additional investigators are needed, and they would be recruited from a large number of sites. **If each site enrolled 50 subjects over a 3-4 year period, 600 sites would be needed.** This is a massive undertaking to answer what seemed to be a straightforward question.

Significant Time and Money

The Principal Investigator must prepare a budget in order to find the funds necessary to do this study. Money is needed to fund the research staff, the data managers, the biostatisticians, prepare all of the documents and pay for the treatments. This study would need hundreds of thousands if not millions of dollars to conduct. There is no place to compromise the budget or the study will not successfully answer the question.

When all of these steps have been completed, and it usually takes a year to do so, enrollment is ready to begin. This is where the patients come in. The patient's doctor approaches the patient about possible participation. Out of 10 men who will be asked to participate, perhaps four or five will agree and of those, only two or three will complete the study. We have a situation where we don't know which treatment, radiation or hormon-

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PCRI Welcomes Tom Kirk to the PC Community

US TOO INTERNATIONAL PROSTATE CANCER EDUCATION AND SUPPORT NETWORK HAS NAMED THOMAS KIRK AS ITS NEW PRESIDENT AND CEO. PCRI applauds Us TOO for this appointment and welcomes Mr. Kirk to the community dedicated to combating prostate cancer. He is already exploring with PCRI ways that the two organizations, working together, can better serve families facing prostate cancer issues.

Mr. Kirk traces his interest in families to his early work experience in his home state of Wisconsin where he worked for 12 years at a Family Service Association. He is well known for his work with Alzheimer's Disease. At the National Alzheimer's Association, he served as the Vice President of Patient, Family and Education Services, was the Association's first Director of Patient and Family Services, and worked in the six-state Midwestern region as a National Field Representative. For thirteen years, he helped to grow and develop the Alzheimer's Association chapter network, its programs, its educational materials and its annual conference. He is recognized for fostering strategic plans that now benefit under-served populations and for facilitating collaborations with other charitable and scientific groups.

Mr. Kirk has shared with other organizations his expertise in caring for an aging population. He previously served as the Vice President of Operations for Garden Terrace Associates, a Life Care Centers of America retirement and long-term care company headquartered in Tennessee where he managed a series of Alzheimer's Disease Centers of Excellence.

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