Chapter 7
The Use of High-Intensity Focused Ultrasound in Prostate Cancer

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Introduction

The use of ultrasonic waves for medical purposes was first investigated in the 1950s,[1] and high-intensity focused ultrasound (HIFU) for focal tissue destruction was established in 1955.[2] One of the first clinical applications of HIFU was for the treatment of neurological disorders by the production of small lesions deep inside the cerebral cortex. Routine use of the technique, however, was limited by the need for a large cranial bone flap and by the lack of an appropriate imaging device. Exploration of the use of HIFU for the irradiation of tumors started in 1956,[3] continued during the late 1970s and early 1980s,[4,5] and by the mid-1980s, the technique was being used to treat ocular cancers and glaucoma.[6] The use of HIFU in the treatment of prostate disorders began in the early 1990s with clinical trials of HIFU in the treatment of benign prostatic hyperplasia (BPH)[7,8] and the treatment of organ-confined prostate cancer.[9]

Mechanism of Action

HIFU can be delivered as a pulsed or a continuous beam. Continuous beam processes include solar waves, microwaves, and radar technology, while medical HIFU and extracorporeal shock wave lithotripsy (ESWL) involve pulsed HIFU. HIFU destroys tissues via two mechanisms, acoustic cavitation (similar to bubble formation during boiling) and internal friction; these mechanisms result in the generation of sufficient heat within the tissues to create a necrotic lesion.

In the treatment of prostate cancer with HIFU, ultrasound waves are generated by the high-frequency vibration (0.5–10 MHz) of a piezoelectric or piezoceramic transducer within a probe introduced into the rectum. *The ultrasound waves penetrate the rectal wall with only slight absorption and reflection and therefore, no tissue damage*, but as they are focused (by an acoustic lens or parabolic reflectors) onto a small area (the focal point) in the prostate, the power density increases. At the focal point, bubbles form inside the cells due to the negative pressure of the ultrasound wave. The bubbles increase in size to the point at which resonance is achieved; this triggers their sudden collapse, creating high pressure (20,000–30,000 bars) which damages cells and generates heat (Fig. 7.1). The increase in temperature is determined by the absorption coefficient of the tissue, as well as the size, shape, and thermal response of the heated region. The biological changes that are induced by the rise in temperature depend on the thermal dose, that is, the temperature reached and the length of time that the tissue is exposed to the elevated temperature. A steep temperature gradient exists between the tissue at the focal point and the surrounding tissue; a sharp demarcation between the necrotic lesion and the normal cells can be seen in histological samples (Fig. 7.2). A number of factors affect the extent of the lesion and the process has to be carefully controlled. Treatment parameters important for effective tissue coagulation using HIFU include:

- The power setting (W)
- The piezoelectric frequency (MHz)
- The shot duration
- The delay between shots (this is necessary to avoid accumulation of cavitation bubbles in adjacent lesions)
- The number of shots per prostate volume (dose)

Pros and Cons of Different Commercial Systems

Two commercially available HIFU systems are currently in use: the Ablatherm® (EDAP SA, Lyon, France) and the Sonablate® (Focus Surgery, Inc., Indianapolis, IN, USA). The two systems are similar in TRUS imaging, and treatment is possible with both using a probe encased in a degassed, fluid-filled balloon that cools the rectum. The two systems differ in terms of positioning of the patient, the ultrasound frequencies used during treatment and planning, shoot, and delay times, the treatment mode within the prostate, and the safety measures available to protect the rectal wall.

O. Ukimura and I.S. Gill (eds.), *Contemporary Interventional Ultrasonography in Urology,*
DOI: 10.1007/978-1-84800-217-3_7,

Fact Sheet

- The use of ultrasound for medical purposes started in the 1950s for the treatment of neurological disorders
- The use of ultrasound for tumor ablation started in 1956, but it was not until the 1990s that ultrasound was used to treat prostate cancer
- Medical HIFU involves a pulsed ultrasound beam
- HIFU destroys tissues by generating heat sufficient to cause necrosis
- When treating prostate cancer, ultrasound waves are generated by a transducer within a probe introduced into the rectum
- The ultrasound waves penetrate the rectal wall with only slight absorption and reflection, but are focused onto a small area (the focal point) in the prostate to generate a lesion
- The HIFU process has to be carefully controlled, and a variety of treatment parameters are important

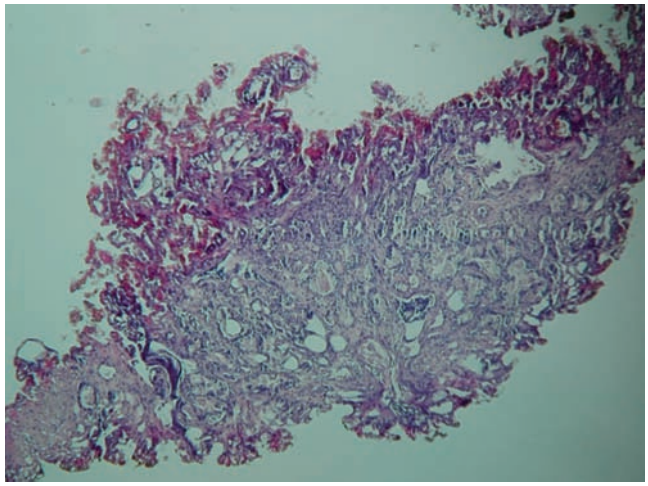

Fig. 7.2. Histological section of the prostate following treatment with high-intensity focused ultrasound

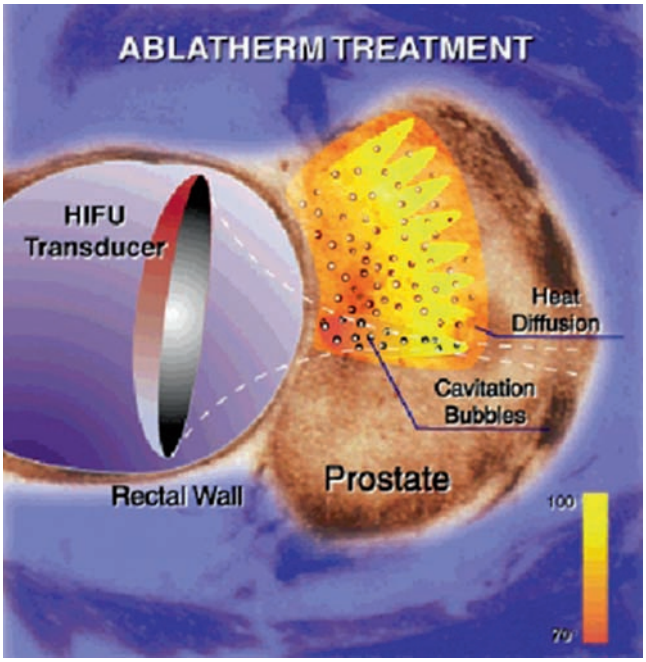

Fig. 7.1. Ultrasound waves generated by the high-intensity focused ultrasound (HIFU) transducer are focused on the tumor lesion within the prostate

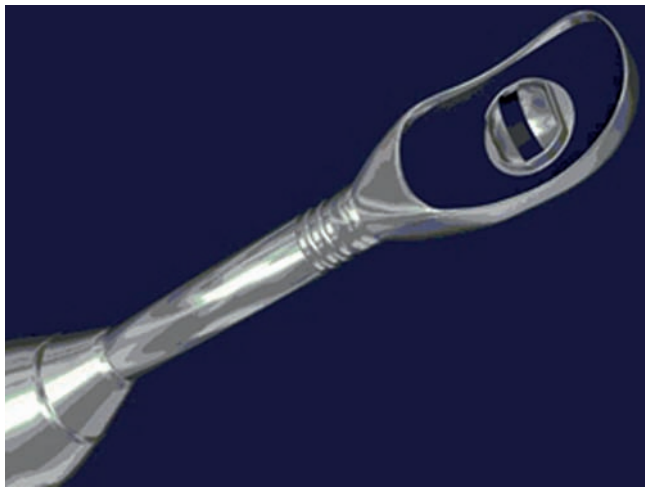

Fig. 7.3. Ablatherm® piezoelectric probe

The Ablatherm® system includes a treatment bed, an endorectal probe, and probe positioning system, an ultrasound power generator, a cooling system for preservation of the rectal wall, and a control module. The endorectal probe (Fig. 7.3) incorporates a two-dimensional imaging probe working at 7.5 MHz and a treatment transducer focused at a maximum of 45 mm and working at 3 MHz. *Thus a single probe fits all prostate sizes and undertakes both imaging and treatment functions*. Variable focusing of the transducer is shown in Fig. 7.4. Real-time rectal wall control is provided by automatic adjustment of the probe toward the rectal wall, and multiple security circuits are in place to prevent accidental focusing on the rectal wall, thereby avoiding rectal injury. In 2005, modifications were made to the Ablatherm® system to allow integrated imaging. The features of the two models (the pre-2005 Ablatherm® Maxis and the post-2005 Ablatherm® device with integrated imaging) are outlined in Table 7.1. *The Ablatherm® system can be used for primary HIFU treatment, HIFU retreatment, and salvage therapy in patients who have previously received radiotherapy*.

The Sonablate® system does not have a dedicated treatment bed; instead, treatment is performed with the patient in the dorsal position under general anesthetic. Furthermore, rather than the single, dual-frequency probe used for gland

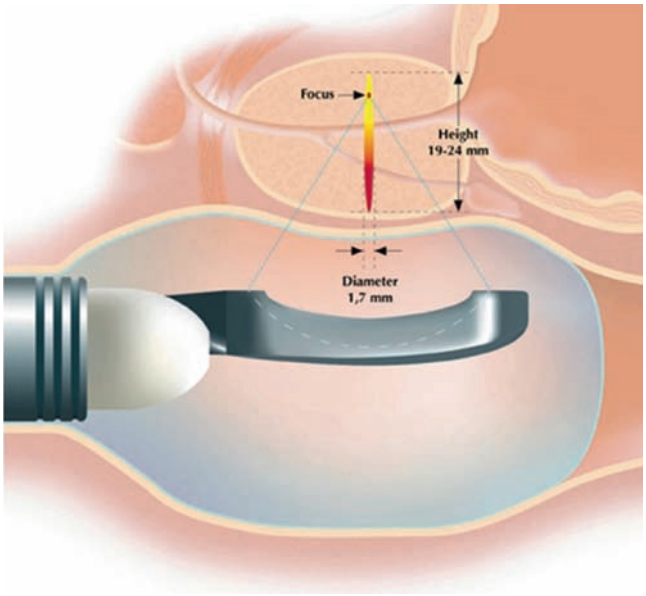

FIG. 7.4. The Ablatherm® transducer demonstrating variable focusing

imaging and treatment used in the Ablatherm® system, *the Sonablate®system uses a range of treatment probes*. Probe selection is determined by the size of the lesion required; a 25- or 45-mm focal length probe results in a lesion that is 10 mm in length and 2 mm in diameter, and a 30-, 35-, or 40-mm focal length probe used with a split beam results in a lesion that is 10 mm in length and 3 mm in diameter. Prostate size also has to be taken into account, and larger glands require probes with a longer focal length. Treatment is usually conducted in three consecutive coronal layers, starting from the anterior prostate and moving from the apex to the base. At least one probe change is required during the treatment process. *No automatic, real-time, rectal wall distance control is present, which means that the operator has to perform manually guided, rectal-wall-orientated HIFU treatment in the peripheral zone (which is the predominant location of a prostate tumor*). The limitations of the Sonablate® system mean that the indications for this system are restricted to T1–2 prostate cancer; the system cannot be used for salvage or palliative HIFU.

Fact Sheet

- Two commercially available HIFU systems are currently in use – the Ablatherm® system and the Sonablate® system
- Both systems provide simultaneous imaging and treatment using an endorectal probe
- The main differences between the systems are in patient positioning, the ultrasound frequencies used during treatment and planning, shoot and delay times, the treatment mode within the prostate, the measures available to protect the rectal wall, and treatment indications
- Overall, the Sonablate® system has limitations, while the Ablatherm® system provides a number of treatment and safety benefits

Patient Selection: Indications and Contraindications

Indications

HIFU is indicated for patients with localized prostate cancer (stage T1–T2 N0M0 Gleason score [GS] 1–3) who are not candidates for surgery due to their age, general health status or a prohibiting comorbidity, or who would prefer not to undergo a radical prostatectomy. However, the indications have been expanded based on clinical experience to include: partial therapy in unilateral low volume, low GS tumors (T1–2a Nx/0M0, GS1–2, prostate-specific antigen [PSA] < 20 ng ml^{-1}); salvage therapy in recurrent prostate cancer after radical prostatectomy, radiotherapy, or hormone ablation (all T Nx/0M0, all GS/PSA); and advanced prostate cancer as a debulking process (T3–4 Nx/0M0, all GS/PSA). *While other nonsurgical treatment options for localized prostate cancer (e.g., cryotherapy or brachytherapy) cannot generally be repeated in cases of local recurrence, HIFU can be repeated, and can also be used as a salvage therapy*.

TABLE 7.1. Distinguishing features of the two generations of the Ablatherm® high-intensity focused ultrasound device.

Ablatherm® integrated imaging	Ablatherm® maxis
• Electronic applicator with integrated 7.5-MHz real-time TRUS	• Electromechanical applicator with inserted 7-MHz alternating TRUS
• Excellent TRUS resolution by a new diagnostic ultrasound unit	• No real-time control
• Fast and highly precise planning by computerized scanning procedure	• High TRUS resolution with a standard diagnostic ultrasound unit
• Virtual prostate reconstruction	• Manual therapy planning
• Real-time TRUS control	• Real-time TRUS control
• Electronic picture and data storage	• Electronic picture and data storage
• Ablaview® "blackbox"	• Learning curve: 30 treatments
• Treatment time reduced by 25%	
• Learning curve: ten treatments (new users); five treatments (Ablatherm® users)	

TRUS, transrectal ultrasound

Contraindications

Contraindications for the use of HIFU in prostate cancer include a gland size larger than 40 ml (due to the focal length of HIFU). Larger glands can be reduced in size using transurethral resection of the prostate (TURP) and/or hormonal therapy with a luteinizing hormone-releasing agonist (LHRHa) prior to HIFU. Other contraindications include conditions where the rectal wall is damaged or rendered more susceptible to damage (e.g., rectal fistula or conditions when there is a reduced blood supply), following radiotherapy, or when there is active local infection. HIFU is not suitable for patients with rectal stenosis or rectal amputation, as these conditions mean that the probe cannot be placed in the rectum.

Fact Sheet

Ablatherm = A Sonablate = S

- HIFU is indicated:
  - For localized prostate cancer (stages T1–T2 N0M0 Gleason score 1–3) (A + S)
  - For partial therapy in unilateral low-volume, low Gleason score tumors (A + S)
  - For salvage therapy in recurrent prostate cancer after radical prostatectomy, radiotherapy, or hormone ablation (A)
  - For advanced prostate cancer as a debulking process (A)
- HIFU is contraindicated:
  - For gland sizes larger than 40 ml (larger glands can be reduced in size prior to HIFU) (S)
  - In conditions where the rectal wall is damaged or rendered more susceptible to damage (A + S)
  - Following radiotherapy (S)
  - When there is active local infection (A + S)
  - In cases of rectal stenosis or rectal amputation (A + S)

Transurethral Resection of the Prostate Plus HIFU

For prostate gland sizes greater than 40 ml, TURP is conducted 1 month prior to HIFU For prostate sizes less than 40 ml, TURP is carried out at the same time as HIFU. In salvage HIFU, the use of TURP is limited or unnecessary. TURP prior to HIFU can reduce gland size, remove calcification, abscesses, and large adenomas, reduce significantly postoperative side effects, allow more patients to meet the inclusion criteria for HIFU, and help achieve greater efficacy with HIFU. TURP results in the generation of a cavity, which is subsequently compressed by the rectal balloon, increasing the accessibility of the remaining gland to HIFU waves. TURP prior to HIFU should remove the ventral region of the gland, leaving intact a large area of the gland at the bladder neck. This reduces the risk of stenosis of the neck of the bladder as a result of prostate gland shrinkage during HIFU. The rectal balloon that covers the HIFU probe is then able to "squeeze" the gland, fixing it into position. TURP before HIFU has been used as a standard procedure in the Munich clinic since 2000. *TURP carried out at the same time as HIFU also has the benefit of stopping TURP-related prostatic bleeding due to necrotic coagulation and prostate edema.*

Fact Sheet

- TURP before HIFU reduces gland size, improves HIFU efficacy, and expands the indication for the procedure
- TURP carried out at the same time as HIFU reduces TURP-related prostatic bleeding

The HIFU Procedure: Ablatherm®

The Key Steps in the Ablatherm®

HIFU procedure is shown in Table 7.2.

Preoperative Preparation

Approximately 2 h before the procedure, an enema should be given to cleanse the rectum. At the start of treatment, prophylactic antibiotics are administered and a urethral catheter is put into place. Antibiotic prophylaxis is used to avoid urinary tract infections following HIFU, as necrotic tissue provides a good substrate for bacterial growth. Antibiotics should continue for about 1 week or until the catheter is removed. Urethral catheterization is needed during and after treatment to control bladder filling and bleeding, and to avoid patient movement as a result of bladder irritation. Both suprapubic and urethral catheters can be used. Suprapubic catheters tend to be used if TURP and HIFU are performed in the same treatment session. The use of a suprapubic catheter prevents the TURP syndrome and any inflow of cells, and helps continuous bladder washing during the procedure. The urethral catheter can be withdrawn the day following the procedure, and the patient can be discharged with a urine collection bag attached to the suprapubic catheter.

TABLE 7.2. The key steps in the Ablatherm® high-intensity focused ultrasound procedure.

1. *Preoperative preparation*
2. Anesthesia
3. Positioning the patient and keeping him warm
4. Device preparation
5. Introducing the transrectal probe
6. Transrectal ultrasound simulation
7. Treatment planning
8. Robotic treatment
9. The perioperative phase
10. *Follow up*

Anesthesia

While HIFU can be performed using spinal or general anesthesia, spinal anesthesia with analgesic sedation is the preferred anesthetic method in the Munich clinic. *If general anesthesia is used, muscle relaxation should be maintained until the rectal probe has been removed at the end of the procedure, as waking the patient early can lead to spontaneous, uncontrolled movements that can result in rectal perforation by the probe*.

Positioning the Patient and External Warming

It is important that the patient remains perfectly still throughout the procedure. As the treatment time is around 95 min (30–150 min), making sure that the patient is comfortable helps him to stay still, and ensures precise and rapid treatment. The patient is positioned on his right side on the treatment table, with restraints and cushions to support the feet, knees, back and left arm, as appropriate. *Special attention should be paid to the comfortable positioning of the right arm and shoulder, as most disturbances at the end of the HIFU treatment are due to patient movement because of discomfort of the right shoulder*. External warming should be applied to counteract the internal cooling of the rectum that will occur during the procedure. *The patient should be kept warm by keeping the treatment room warm and by draping blankets over him* (Fig. 7.5).

Device Preparation

The endorectal probe containing the transducer is covered with a balloon, which is inserted into the rectum via the anus and then filled with 150 ml degassed transmitter fluid (Ablasonic®) (Fig. 7.6). Device preparation is important; the balloon should be fixed using tape to avoid dilatation of the anus, and inflation of the balloon should be minimal prior to positioning.

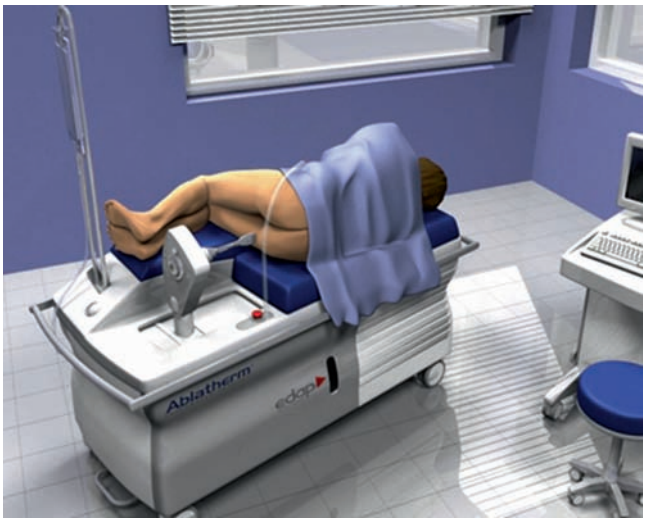

Fig. 7.5. Positioning of the patient in the Ablatherm® table; patient should be kept warm

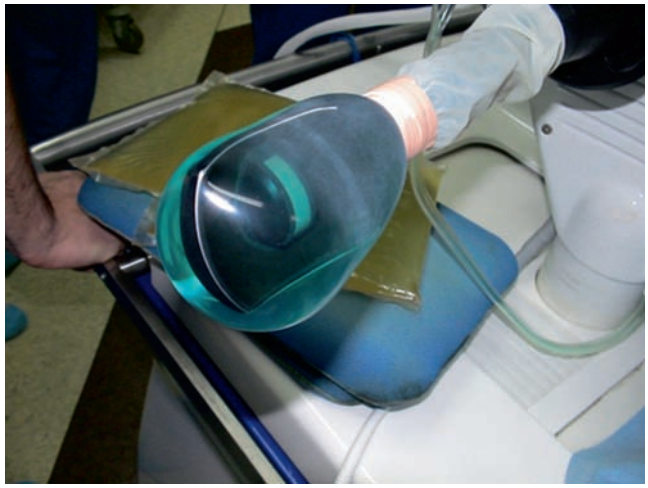

Fig. 7.6. Ablatherm® probe covered with fluid-filled balloon

Introducing the Probe

The balloon-covered probe should be covered with ultrasound gel before it is inserted into the rectum; this is to ensure close, smooth contact between the balloon and the rectal mucosa. Ultrasound gel should not be introduced directly into the rectum. Digital rectal examination using anal dilatation with up to two fingers may be needed to allow smooth introduction of the probe. An absence of feces is important at this point. *Dilatation using more than two fingers can result in the balloon "popping out" during treatment, which can lead to delays*. The presence of hemorrhoids is not a problem – a small amount of bleeding of the anal mucosa due to dilatation is not a cause for concern. *Introduction of the probe is made easier by lifting the patient's left buttock and making small lateral movements with the probe*.

Once the probe is positioned in the rectum, the balloon should be filled with the Ablasonic® liquid. This blue, anti-cavitation coupling and cooling fluid prevents the acoustic cavitation of bubbles within the cooling circuit and in front of the probe. This fluid is cooled to limit the heat damage to the rectal wall by creating a temperature gradient between the rectal mucosa and the prostatic capsule. *It is important that all the liquid supplied is used, as this ensures sufficient dilatation of the rectal ampulla, good contact and compression of the rectal wall, and optimum HIFU treatment and cooling while preventing the passage of feces or air. The rectum cannot be damaged by overfilling the balloon*. A roller pump circulates the liquid slowly through the balloon into a cooling unit and back to the rectum at a temperature of 15°C.

Transrectal Ultrasound Simulation

The prostate is scanned automatically by the integral 7.5 MHz TRUS, from the apex to the base, to generate a high-definition, two-dimensional image of the gland. A three-dimensional

TRUS simulation is generated; this allows accurate treatment planning to be performed, including calculation of the prostate volume and clear definition of the base and apex of the gland (Fig. 7.7).

Treatment Planning

The TRUS image is used to plan a treatment that generates a series of lesions that includes the whole of the prostate, including the seminal vesicles if appropriate. Apex definition is one of the most important aspects of treatment planning; this allows an appropriate balance to be made between the preservation of continence and effective treatment. Planning takes into account starting HIFU treatment 5 mm from the apex, moving toward the bladder, and treating the left lobe followed by the right lobe of the prostate. Treatment of the seminal vesicles is optional and depends on the anatomy of the patient, seminal vesicle length, and location of the tumor. Treatment of the seminal vesicles is desirable if the tumor is located on the base of the prostate, but in small individuals, this can be difficult. Lateral or ventral tissue remaining untreated can be a reason for persistently elevated PSA levels and prostate cancer recurrence.

FIG. 7.7. Mapping of the prostate during high-intensity focused ultrasound treatment using transrectal ultrasound simulation

During planning, the prostate is divided ("sliced") into 1.6-mm transverse sections, each representing a single lesion to be generated during active treatment. The length and the diameter of the lesions are defined by the operator on the control screen, tailored to fit the anatomy of the prostate of the individual being treated. Up to 800 lesions may be defined, depending on the size of the prostate.

Tissue type is also taken into consideration, specifically untreated, HIFU pretreated, or irradiated prostate tissue. Three power settings are available, involving the application of different energy levels suited to the three different tissue types. The different power settings used by the Maxis system (pre-2005) and the Integrated imaging system (post-2005) are provided in Table 7.3. Power and shot duration are lower for patients who have received radiotherapy than for those receiving primary HIFU treatment or HIFU retreatment because irradiated prostate tissue has a higher uptake of HIFU energy,[11] so a lower level is used to reduce the risk of rectal wall injury. It is important that the correct software setting is selected from "Standard," "HIFU retreatment," and "Salvage." Failure to select the correct setting can result in side effects such as rectourethral fistula. The actual plan of how the HIFU will be delivered is then generated by the computer software.

Active Treatment

To achieve accurate lesions, it is important that the patient remains perfectly still throughout the procedure. The treatment time is around 95 (30–150) min, and the actual treatment carried out is recorded and can be reviewed after the procedure. For optimal efficacy, the entire prostate is normally treated. Treatment is divided into sequences lasting approximately 30 min; these are referred to as treatment "blocks." The larger the prostate, the more blocks have to be performed. As a rough guide, a standard resection is likely to need four blocks and a local recurrence is likely to need one block. *Before delivering HIFU to the prostate, the urethral catheter should be withdrawn 5 cm into the urethra to prevent the reflection of ultrasound waves*.

Treatment automatically follows the computerized instructions generated during the planning phase. The probe generates a series of pulsed HIFU beams that destroy a small slice of the prostate with intense, localized heat. The zone destroyed by each pulse creates a lesion that is 1.6 mm deep, with a

TABLE 7.3. Power settings used during high-intensity focused ultrasound (HIFU); standard, re-treatment and radiation failure cases depicted.

	MHz		Power (%)		Shot duration (s)		Delay duration (s)	
	M	ii	M	ii	M	ii	M	ii
Standard	3.0	3.0	100	100	5	6	5	4
HIFU retreatment	3.0	3.0	100	100	4.5	5	5	4
Radiation failure	3.0	3.0	90	95	4	5	7	5

M, maxis; ii, integrated imaging

height and a width that match the anatomy of the prostate at that particular point (Fig. 7.8). The whole gland is treated in this way. In most cases, the only adjustments that the operator needs to make during the procedure are small manual corrections to the inflow or the outflow of fluid to the rectal balloon, or readjustment of the external movement detector. Very rarely, electronic or mechanical disturbances stop treatment and necessitate restarting.

To maximize safety and efficacy, the Ablatherm® system incorporates a number of safety features, including alarm screens, an external movement detector, the Ablaview® function and real-time imaging with post-2005 equipment. Red and yellow alarm screens indicate problems during treatment. If a red alarm occurs, treatment should be stopped; these alarms seldom occur. Yellow alarms indicate the need for small adjustments by the operator. An external movement detector provides an additional warning if the patient moves. *Changing the position of the probe to treat the right prostate almost always triggers this alarm due to movement of the pelvis as the probe is adjusted.*

The Ablaview® function registers and retains all planning and treatment sequences. This enables previously untreated areas to be easily distinguished if treatment is restarted or if there has to be a change of operators for any reason. This function also provides the ability to check whether all areas of a prostate have been treated correctly. The endorectal probe is held away from the rectal wall by means of the balloon filled with Ablasonic® fluid. This anticavitation coupling and cooling fluid prevents the formation of acoustic cavitation bubbles within the cooling circuit and in front of the probe. This fluid is cooled to limit the heat damage to the rectal wall by creating a temperature gradient between the rectal mucosa and the prostatic capsule.

The Ablatherm® Integrated Imaging system has real-time imaging as a result of improvements to the piezoelectric probe. Less local movement has also been achieved through fixation of the HIFU probe (Fig. 7.9) allowing greater accuracy in the delivery of HIFU. The device also has inbuilt controls which detect when the probe is too close to the rectal wall and allows the device to "fire" with an accuracy of ±1 mm.

The Perioperative Phase

Following HIFU treatment, the prostate swells immediately due to inflammation and edema. This effect can compress the urethra, hence the need for a urethral catheter. The inflammation and the edema usually resolve over the following 3–8 days. TURP carried out at the same time as HIFU often reduces the level of urethral compression and the need for a urinary catheter. Perioperative morbidity is low following HIFU; significant bleeding is unusual, the need for blood transfusions or intensive care, and the occurrence of thrombo-

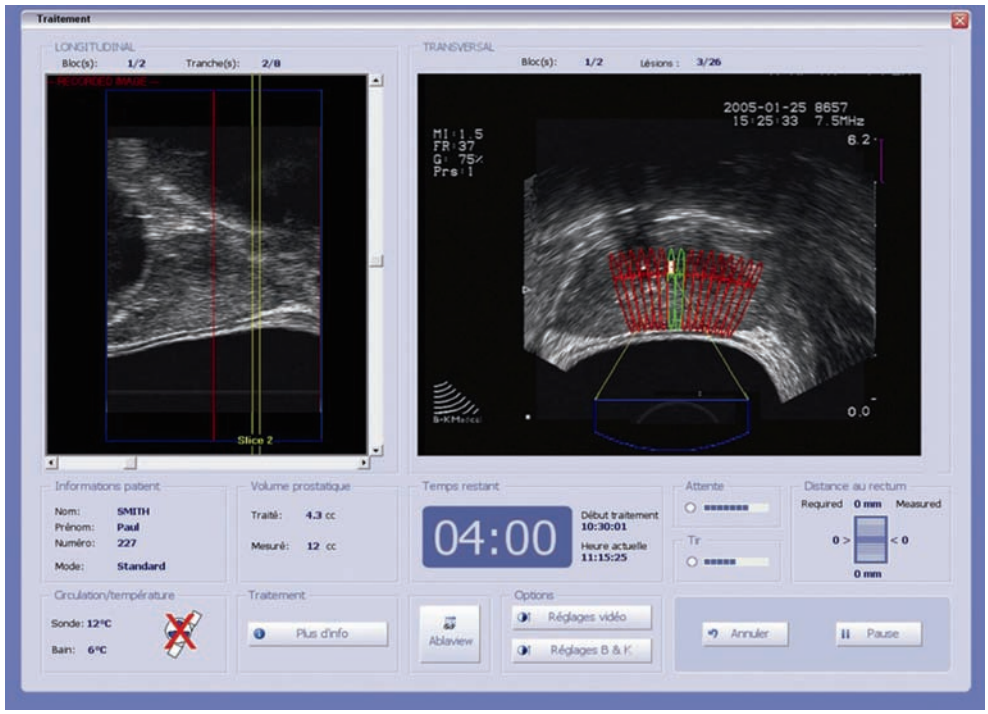

FIG. 7.8. Treatment of the prostate with high-intensity focused ultrasound; transrectal ultrasound image overlaid with lesions being generated

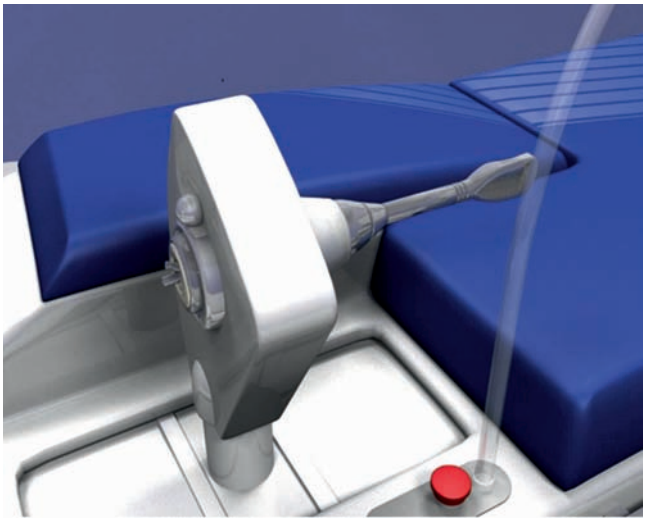

FIG. 7.9. Fixation of the high-intensity focused ultrasound probe

sis or pulmonary embolism is uncommon. Usually there is minimal postoperative pain for the patient making analgesic medication unnecessary. *Should pain occur following spinal anesthesia, it is likely to be in the lower left abdomen; this can be managed using intravenous analgesics*. Antibiotic prophylaxis is usually continued until removal of the suprapubic catheter at about 1 week following the procedure.

Follow up

PSA levels should be measured every 3 months for all patients. Other follow-up activities depend on whether the goal of treatment is curative or palliative. In cases where HIFU constitutes curative treatment, biopsies are necessary if the PSA velocity increases above a rate of 0.5 ng $ml^{-1}yr^{-1}$; such biopsies will identify small residual tumor volumes that may require retreatment with HIFU. Complete remission is indicated by negative biopsies, low PSA levels, and a PSA velocity that

Fact Sheet

1. *Preoperative preparation*: Preoperative preparation for HIFU includes the administration of an enema, prophylactic antibiotics, and catheter placement
2. *Anesthesia*: Spinal or general anesthesia can be used for HIFU; spinal anesthesia with sedation is recommended
3. *Positioning the patient and keeping him warm*: It is important to position the patient carefully in a comfortable position and to keep him warm
4. *Device preparation*: Correct preparation of the endorectal probe and its balloon cover is essential for speed, safety, and efficacy
5. *Introducing the probe*: A number of things can be done to make introduction of the endorectal probe easier; using all the supplied Ablasonic® liquid is important for efficacy and safety
6. *Transrectal ultrasound (TRUS) simulation*: Automatic TRUS simulation allows accurate treatment planning, including calculation of the prostate volume and clear definition of the base and apex of the gland
7. *Treatment planning*: Based on the TRUS simulation, treatment is planned to generate a series of lesions tailored to fit the anatomy of the prostate being treated and to include the whole gland
8. *Treatment*: Treatment automatically follows the computerized instructions generated during the planning phase to generate a series of pulsed HIFU beams that produce lesions that are 1.6 mm deep, with a height and a width that match the anatomy of the gland (robotic treatment)
   - Treatment is divided into sequences lasting approximately 30 min; these are referred to as treatment "blocks"; the larger the prostate, the more blocks have to be performed
   - Safety and efficacy are maximized by a number of safety features, including alarm screens, an external movement detector, the Ablaview® function, and real-time imaging with post-2005 equipment
9. *The perioperative phase*: In the perioperative phase, the prostate immediately swells due to inflammation and edema, necessitating the use of a urethral catheter; these symptoms tend to resolve over 3–8 days
   - Other perioperative morbidity is low following HIFU; it is unusual for there to be significant pain, bleeding, the need for blood transfusions or intensive care, and the occurrence of thrombosis or pulmonary embolism is uncommon
10. *Follow up*: Follow up should include measurement of PSA levels every 3 months for all patients; other follow-up activities depend on whether the goal of treatment is curative or palliative
    - In cases where HIFU constitutes curative treatment, biopsies are necessary if the PSA velocity increases above a rate of 0.5 ng ml−1 yr−1; such biopsies will identify small residual tumor volumes that may require HIFU retreatment
    - In cases where HIFU constitutes palliative therapy, biopsies should be done only if a local treatment could provide a benefit

remains stable below 0.2 ng $ml^{-1}yr^{-1}$. In cases where HIFU constitutes adjuvant palliative therapy, biopsies should be done only if a local treatment could provide a benefit.

Specific Measures to Avoid and Manage Complications

Clinically significant complications that can occur with HIFU include incontinence and erectile dysfunction (ED). Specific measures can be taken to avoid ED, while the incidence of incontinence is rare.

Incontinence

HIFU can result in urinary obstruction, and fibrosis or tissue shrinkage of the urethra, although incontinence is often due to TURP or the combination of TURP and HIFU. Grade 1 and 2 incontinence after primary HIFU is rare and can be managed using pelvic floor training. Grade 3 incontinence is very rare and can only be managed by invasive treatment (Table 7.4).

ED

ED following HIFU is caused by heat-induced nerve damage. Potency protection relies on preservation of neurovascular bundles within the prostate. *If the tumor is unilateral, low grade, and low volume, sparing the nerves by leaving a 5-mm margin of subcapsular tissue is possible and can protect potency in 80% of cases*. If ED does occur, patients can be advised that this often decreases over time following the procedure. Oral pharmacological therapy (e.g., sildenafil) can be helpful in the management of ED following HIFU.

Fact Sheet

- Clinically significant complications that can occur with HIFU include incontinence and ED
- In the rare cases where incontinence occurs, it is due to TURP or the combination of TURP and HIFU; little can be done to avoid the occurrence of this complication
- Specific measures can be taken to avoid ED; if the tumor is unilateral, low grade, and low volume, it is possible to spare the nerves by leaving a 5-mm margin of subcapsular tissue and protect potency in 80% of cases

Outcome: Munich Database

HIFU has been in use in the Munich Clinic for over 10 years, and during this time much research has gone into the optimization of the procedure.[12–14] A registration of all patients treated in the Munich Clinic was started in 1996, and this database records all relevant information on each patient, including treatment parameters, outcome, and side effects. Up to 2007 there were over 1,350 patients registered on the database.[15–19] Patients were categorized into the following risk groups: low risk: T1–T2a, PSA ≤10 ng ml^{-1}, GS < 7; intermediate risk: T2b or PSA 10 ng ml^{-1} to ≤ 20 ng ml^{-1} or GS 7; high risk: T2c or PSA > 20 ng ml^{-1} or GS > 7. *Outcome in 1,000 patients treated between 1996 and 2004* with a median follow-up time of 2.5 years (max: 6.5 years) is shown in Table 7.4. *As can be observed, a high negative biopsy rate of 93.7% at a mean of 9 months and a zero PSA nadir at 3 months have been achieved in patients with localized cancer who have low- or medium-risk disease*. PSA velocity was also very low in this group and PSA stability, defined according to the ASTRO criteria, was recorded in 81%. *At the other end of the spectrum, in the metastatic patient, a negative biopsy rate of 60–66% was achieved, which is very high for this group of patients*. Considering that this patient group comprised patients with GS 9

Table 7.4. The Munich database of patients treated with high-intensity focused ultrasound.

Prostate cancer risk group	Negative biopsy (%)	Median PSA nadir (ng ml^{-1})	PSA velocity (ng yr^{-1})	PSA stability (%)	Additional PCa therapy (%)	Stress incontinence Grades II-III (%)	Potency preservation (%)
Localized Low + medium risk (n = 400)	93.7	0	0.11	81	4.9	1.6	36
Localized high risk (n = 332)	87.6	0	0.15	73	14.7	2.7	27
Locally advanced (n = 209)	79.4	0.1	0.78	23	28.2	2.3	20
Metastatic $N+$ (n = 26)	60	0.1	0.62	NR	42.9	3.6	0
Metastatic $M+$ (n = 33)	66	0.15	16.9	NR	100	2.9	0

PSA, prostate-specific antigen; PCa, prostate cancer; NR, not recorded

Fact Sheet

- A total of 1,350 patients have been entered into a database of patients treated with HIFU at the Munich center between 1996 and 2007; low-, intermediate-, and high-risk patients have been treated
- Outcome in 1,000 patients indicates a 93.7% negative biopsy rate at a mean of 9 months and a zero PSA nadir at 3 months in patients with localized, low/medium-risk prostate cancer. In patients with metastatic disease, the equivalent negative biopsy rate was 60–66%
- The incidence of severe complications was low in this patient series, and preservation of potency was high, particularly in patients with localized cancer at low and medium risk

and 10, the PSA nadir values recorded were very promising. The objective of treating these patients was not to obtain cure but to reduce local morbidity and increase survival time by delaying metastasis from the primary tumor. *The incidence of severe complications was low in this patient series* and preservation of potency was high, particularly in patients with localized cancer at low and medium risk.

Future Directions

Promising advances in HIFU include the formulation of new treatment strategies for specific patient groups, and improvements in the visualization and assessment of HIFU lesions.

New Treatment Strategies

In the case of a unilateral tumor and where potency is an important issue for the patient, rather than treating the entire prostate, the contralateral lobe/capsule and neurovascular bundle could be excluded. This would be achieved by excluding 5 mm of tissue on the contralateral lobe and treating only 90% of the prostate. This approach might be appropriate in young patients, with small, low GS, unlilateral tumors. Patients requesting this approach would need to be advised of the risk of tumor recurrence in the untreated area and the requirement for good compliance with follow up.

Improvements in the Visualization and Assessment of HIFU Lesions

The application and the continued development of a variety of imaging techniques are likely to provide improvements in the visualization and assessment of HIFU lesions in the near future. Magnetic resonance imaging (MRI) is the gold-standard technique used for assessing the efficacy of HIFU treatment, and the extent of necrosis can be clearly visualized on gadolinium-enhanced T1-weighted images.[20] MRI has also been used to guide HIFU treatment by monitoring temperature changes within the tissues.[20,21] Magnetic resonance elastography (MRE) may also provide a means of assessing the effects of thermal tissue ablation by measuring the mechanical properties of the lesion.[22] HIFU-induced lesions are visible using standard ultrasound,[23] although there are limitations to the accuracy of this approach. Other ultrasound-based techniques that might prove useful for assessing the extent of HIFU-induced lesions include MRE,24 contrast-enhanced power Doppler,[25] and other techniques that characterize the acoustic properties of tissues.

Fact Sheet

Promising advances in HIFU include the formulation of new treatment strategies for specific patient groups, and improvements in the visualization and assessment of HIFU lesions

- New treatment strategies include partial treatment of the prostate gland in selected patients; this approach does carry an increased risk of tumor recurrence
- A variety of imaging techniques are likely to provide improvements in the visualization and assessment of HIFU lesions in the near future

Conclusions

HIFU is an effective standard treatment for prostate cancer, with a broad range of indications in all tumor stages. Specifically, HIFU is indicated for localized prostate cancer (stage T1–T2 N0M0 Gleason score 1–3), partial therapy in unilateral low-volume, low Gleason score tumors, salvage therapy in recurrent prostate cancer after radical prostatectomy, radiotherapy, or hormone ablation, and as a debulking approach in advanced prostate cancer. HIFU destroys carefully selected tissue by generating heat sufficient to cause necrosis, while leaving surrounding tissue unharmed. Of the two commercially available HIFU systems, the Ablatherm® system provides well-defined, computer-controlled treatment planning and execution, supported by a variety of safety measures to maximize efficacy and safety. While other nonsurgical treatment options for localized prostate cancer (e.g., cryotherapy or brachytherapy) cannot generally be repeated in cases of local recurrence, HIFU can be repeated and can also be used as a salvage therapy. Postoperative morbidity is low. Clinically significant complications that can occur with HIFU include incontinence and ED, and specific measures can be taken to avoid the latter. HIFU is a highly effective treatment of patients with localized prostate cancer and can also be considered for patients with metastatic disease. Promising advances in HIFU include the formulation of new treatment strategies for specific patient groups, and improvements in the visualization and assessment of HIFU lesions

Overview

HIFU is an effective standard treatment for prostate cancer, with a broad range of indications in all tumor stages, including:

- Localized prostate cancer (stage T1–T2 N0M0 Gleason score 1–3)
- Partial therapy in unilateral low-volume, low Gleason score tumors
- Salvage therapy in recurrent prostate cancer after radical prostatectomy, radiotherapy, or hormone ablation
- For advanced prostate cancer as a debulking process

The contraindications for HIFU are well defined and include:

- Gland sizes larger than 40 ml (larger glands can be reduced in size prior to HIFU by TURP)
- Conditions where the rectal wall is damaged or rendered more susceptible to damage (e.g., following radiotherapy or when there is active local infection)
- In cases of rectal stenosis or rectal amputation

When treating prostate cancer using HIFU, ultrasound waves are generated by a transducer within a probe introduced into the rectum. The ultrasound waves penetrate the rectal wall with only slight absorption and reflection, but are focused onto a small area (the focal point) in the prostate to generate a lesion by generating heat sufficient to cause necrosis.

Two commercially available HIFU systems are currently in use – the Ablatherm® system and the Sonablate® system. Both systems provide TRUS imaging and treatment using an endorectal probe. The main differences between the systems are in the indications that can be treated, patient positioning, the ultrasound frequencies used during treatment and planning, shoot and delay times, the treatment mode within the prostate, and the range of safety measures available. Overall, the Sonablate® system has a number of limitations, while the Ablatherm® system provides features that maximize treatment efficacy and safety.

While other nonsurgical treatment options for localized prostate cancer (e.g., cryotherapy or brachytherapy) cannot generally be repeated in cases of local recurrence, HIFU can be repeated and can also be used as a salvage therapy. HIFU utilizes information available from prostate biopsies and TURP and can be combined with TURP for large volume tumors.

The steps in the Ablatherm® HIFU procedure are well defined and can be thought of as follows:

1. Preoperative preparation
2. Anesthesia
3. Patient positioning and external warming
4. Device preparation
5. Introducing the probe
6. TRUS simulation
7. Treatment planning
8. Robotic treatment
9. The perioperative phase
10. Follow up

Practical tips and tricks refine the procedure further and improve the speed and ease with which the treatment can be conducted.

Apart from immediate swelling of the prostate which tends to resolve over 3–8 days, perioperative morbidity is low following HIFU; significant pain, bleeding, the need for blood transfusions, or intensive care are unusual, and the occurrence of thrombosis or pulmonary embolism is uncommon. Clinically significant complications that can occur with HIFU include incontinence and ED. Specific measures can be taken to avoid ED, such as leaving a 5-mm margin of subcapsular tissue to spare the nerves if the tumor is unilateral, low grade and low volume; this approach protects potency in 80% of cases.

A total of 1,350 patients have been entered into a database of patients treated with HIFU at the Munich center between 1996 and 2007. Patients treated include those with low-, intermediate-, and high-risk disease. Outcome in 1,000 patients treated up until 2004 with a median follow-up of 2.5 years has been analyzed. Data indicate a 93.7% negative biopsy rate at a mean of 9 months and a zero PSA nadir at 3 months in patients with localized, low/medium-risk prostate cancer. In patients with metastatic disease, the equivalent negative biopsy rate was 60–66%. The incidence of severe complications was low in this patient series and preservation of potency was high, particularly in patients with localized disease at low and medium risk.

Advances promising to improve HIFU further in the near future include:

- New treatment strategies such as partial treatment of the prostate gland in selected patients (although this approach does carry an increased risk of tumor recurrence).
- The application and the continued development of a variety of imaging techniques are likely to provide improvements in the visualization and assessment of HIFU lesions in the near future.

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