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HIFU: Local Treatment of Prostate Cancer

*H. Azzouz *, J.J.M.C.H. de la Rosette*

Academic Medical Center, Amsterdam, The Netherlands

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Abstract

Objective: Treatment of carcinoma of the prostate (CaP) begs some complex questions. Different disease stages call for different treatment modalities and no universally 'gold standard' treatment has yet been agreed upon. In the present work we will present the results, indications and limitations of HIFU in the treatment of CaP.

Methods: Relevant information on HIFU treatment was identified through a literature search of published studies and review articles.

Results: HIFU can be considered for patients with (recurrent) localized CaP and a prostate volume of 40 cc or failure after radiotherapy. Treatment outcome is evaluated with PSA measurements and prostate biopsies. Mid-term follow up (2–5 years) reveals a PSA of 0.15 ng/ml and in 85% of cases the PSA level remains at the post HIFU nadir. The negative control biopsies are found in 90% of patients. A combination with a TURP reduces the treatment related morbidity.

Conclusions: HIFU has proven mid-term high local and biochemical efficacy in patients with local confined prostate cancer. A HIFU also shows promising results in local recurrence of prostate cancer after external beam radiation.

* Corresponding author. Department of Urology (G4-236), Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5666030; fax: +31 20 5669585.
E-mail address: H.Azzouz@westfriesgasthuis.nl (H. Azzouz).

1. Introduction

At the time of diagnosis, prostate cancer is organ confined in 70% of the cases. Approximately a quarter of these patients undergo local therapy: surgery or external beam radiation. The rest of the remaining patients are subjected to watchful waiting or hormonal ablation or a combination of the above mentioned. Because patients often do not fit these treatments, the quest continues for a reliable and minimally invasive alternative to open surgery or external beam radiation (Fig. 1).

Several treatment modalities have faced the surface in the armamentarium of the management of localised prostate cancer: brachytherapy, cryotherapy and HIFU. The latter is the new kid on the block with very attractive features and promising initial results. HIFU destroys prostate cells by coagulative necrosis of the tissue [1] without damaging the intervening structures passed by HIFU

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Fig. 1 – Patient positioned on treatment table and physician behind operating module.

and without an increase in metastasis formation [2]. In addition to being a primary therapy to combat prostate cancer, HIFU can also be considered as a salvage treatment for radiation and brachytherapy failures. And, as experience and improving techniques will become available in the future, even high and locally advanced stages of prostate cancer may be treated with HIFU [0]as a palliative approach to improve patients QOL and reduce disease progression rate. High intensity focused ultrasound has the potential to provide the clinician with another truly non-invasive, targeted treatment option in targeting local prostate cancer.

2. History and background

The initial work on ultrasound in the treatment of the benign prostatic hyperplasia (BPH) began in the early 1990s, but already during the 1950s, the Fry brothers imagined the first medical application of ultrasonic waves [3]. Their first works were related to the extra-corporeal treatment of neurological disorders such as Parkinson disease. Using a set of ultrasound transducers focused on the area to be treated, they could realize tiny biological lesions located deep inside the cerebral cortex [4,5]. But the lack of an imaging device with adequate performance and accuracy stopped the development of this type of therapies[0]. By 1956, Burov had suggested that high intensity ultrasound could be used for the treatment of cancer [6]. At the end of the 80s, studies using HIFU to irradiate experimental tumours followed [7,8]. The main purpose of this work was to develop applications to treat malignant tumours, and after this the role HIFU for treating prostate cancer was picked up.

3. Procedure

HIFU relies on the same principles as conventional ultrasound. It can propagate harmlessly through living tissue, but if the ultrasound beam carries sufficient energy and is brought into a tight focus, the energy within the focal volume can cause a local rise in temperature of 80 to 90 degrees Celsius or more in two or three seconds [9], which is lethal to prostate cancer tissue. There is a steep temperature gradient between the focus and neighbouring tissue, which is demonstrated by the sharp demarcation between the volume of necrotic lesion and normal surrounding cells on histology [10]. The lesion extension is about 3/4 in front of the transducer focus and 1/4 beyond. The lesion dimension is related to the firing duration: the lesion starts at the transducer focus and progresses toward the transducer during the firing sequence. 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 and allowing the treatment to be applied multiple times without increased risk. The ability to cause cell death in a volume of tissue distant from the ultrasound source makes HIFU an attractive option for development as a non-invasive surgical tool. Depending on which device is used, the patient is either placed on his back with legs elevated in the dorsal lithotomy position or on his right side. The HIFU probe is placed into the rectum and multiple gland images are taken. The transrectal non-invasive approach avoids the percutaneous treatment that HIFU requires in other diseases. Ultrasound and MRI have made real-time monitoring of the procedure possible. The major advantage of HIFU is its extra corporal approach for destruction of deep tissues without making an incision in the skin. Then, at the HIFU control panel, all of the images are reviewed, and the treatment zones are defined and logged into the treatment computer. Not every prostate can be treated all at once, so the prostate is divided into zones, but a 40 g prostate can be entirely treated in one session.

The entire procedure can take between 1 to 3 hours, depending on the size of the gland. The procedure is performed on an outpatient basis under epidural or general anaesthesia. Due to oedema secondary to the thermal effects a urethral Foley or a suprapubic catheter is placed into the bladder for 2 weeks on average after the procedure, but 2 to 3 days

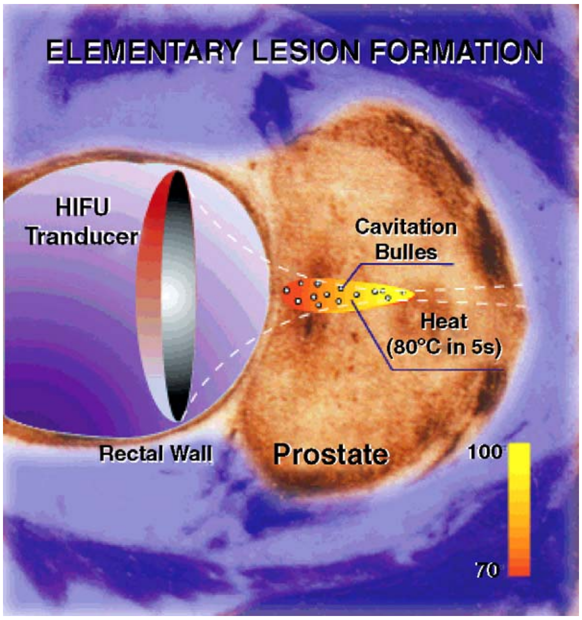

Fig. 2 – Basic concept of HIFU treatment.

only when TURP performed prior to the HIFU treatment (Fig. 2).

4. HIFU devices

As for now, the Ablatherm® and the Sonablate® are the only used machines in the world to treat prostate cancer. There are certainly differences in technologies between these two devices. The Ablatherm® machine (EDAP TMS SA, Vaulx-en Velin, France) has electronical lesion length adaptation, real time rectal wall control, automatic applicator adjustment towards the rectal wall and multiple security circuits to avoid accidental focussing on the rectal wall. One applicator fits all and includes 7,5 MHz localisation and 3 MHz therapy frequency.

The Sonablate® device (Focus Surgery Inc., Indianapolis IN) requests the necessity of an intraoperative applicator change to enable a sufficient HIFU penetration depth. A compromise was chosen: 4 MHz for localisation as well as for therapy. At the same time there is no real time rectal wall distance control, so it is difficult to perform a highly precise, rectal wall orientated HIFU treatment in the peripheral zone of the prostate: the zone where PCa is located in most cases. This different technology of the Sonablate® led to the restricted indication range for only T1-2 prostate cancer Sonablate® does not propose salvage HIFU or palliative HIFU as treatment option.

Furthermore the Ablatherm® treatment module consists of the following parts: a bed for the patient, the positioning system for the probe, the ultraound power generator, the cooling system for the rectal wall and the ultrasound scanner which is used during the treatment localization phase. The Sonablate® system is slightly different: several treatment probes are available and there is no bed with the machine. The treatment is performed in a dorsal position, only under general anesthesia. Furthermore, the treatment is made in three layers: starting from the anterior part of the prostate and moving to the posterior part.

As stated before in this article, rectal injury during HIFU therapy has been reduced greatly these days. This affect can be attributed to numerous safety features especially in the Ablatherm® machine: a safety ring that prevents the rectal wall from moving with the transducer movements, the distance between the therapy transducer and the rectal wall is constantly monitored and it comes with a patient motion detector that stops the treatment if the patient moves during the firing sequence. During the procedure the patient is in lateral position (Fig. 3).

5. Indications

In general HIFU is recommended for patients with localized prostate cancer (stage T1-T2 N0M0) who are not candidates for a radical prostatectomy (because of their age, their general state of being or an associated disease) or patients who prefer an alternative to surgery. Brachytherapy and cryotherapy are other alternative non-surgical options,

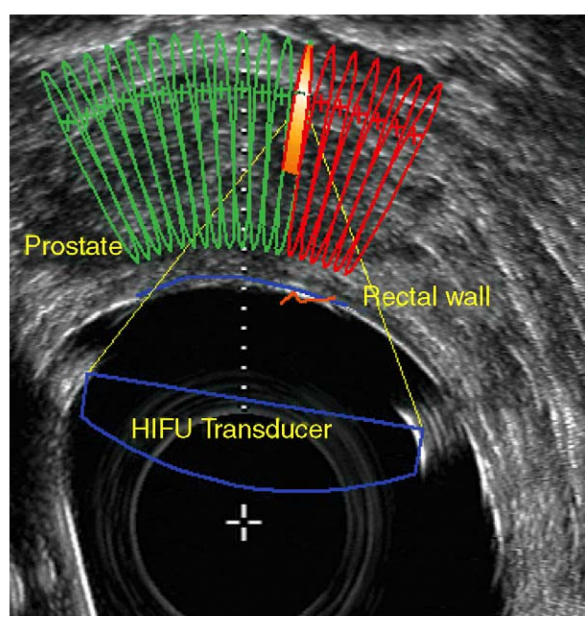

Fig. 3 – HIFU transducer in position delivering treatment with identification of Rectal Wall and Prostate.

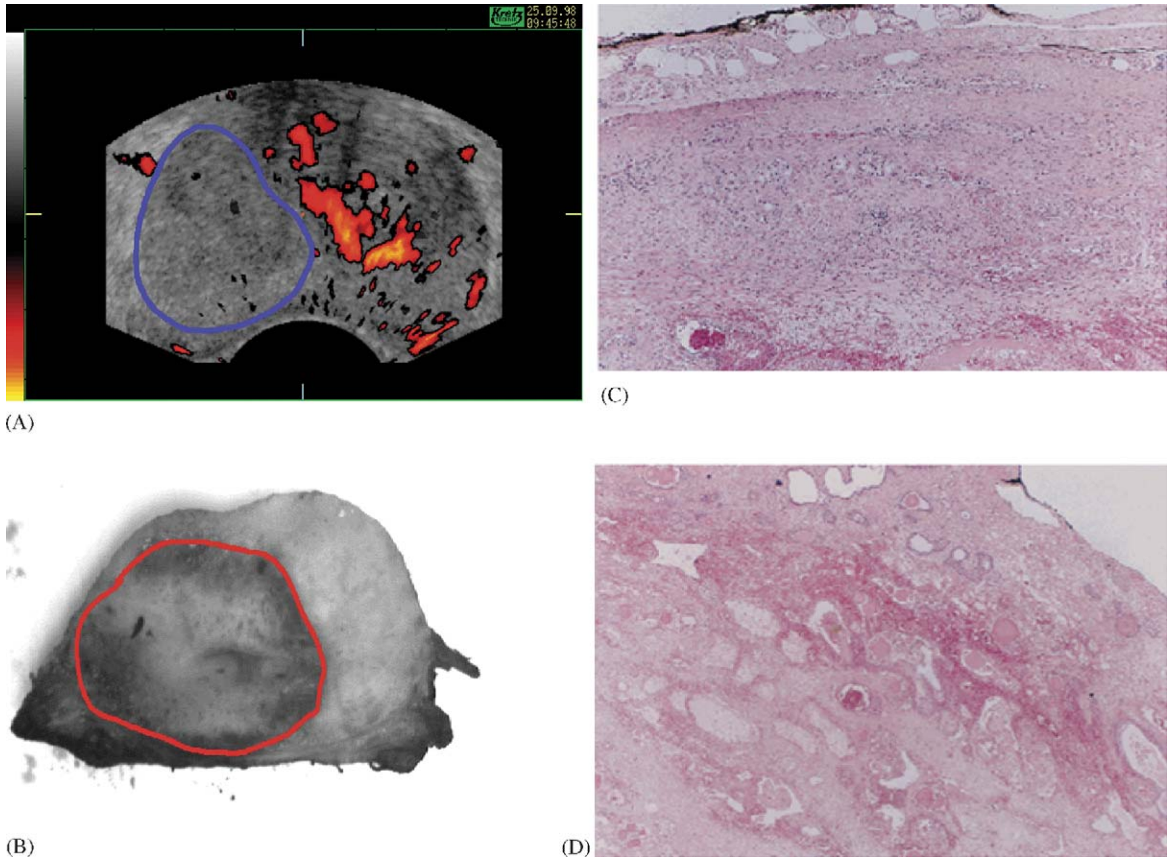

Fig. 4 – (A) Colour Flow Doppler study post HIFU treatment demonstrating absence of blood flow in treated area. (B) Radical Prostatectomy Specimen in patient who had HIFU treatment 2 weeks prior to surgery. Within the targeted area a complete necrosis was achieved (C) Vital prostate tumor (D) Necrosis following HIFU.

receiving increasing interest as well. One major drawback of all of these techniques mentioned is that treatment cannot generally be repeated in cases of local recurrence, whereas HIFU can even be repeated after previous HIFU treatment or following failed surgery. Aside from the primary therapy, HIFU can be used as a salvage therapy in patients who have local recurrence after external radiotherapy, and since brachytherapy seeds do not interfere with the energy transfer it is also useful after unsuccessful brachytherapy. There is however one notable difference between the Ablatherm® device and the Sonablate®: the indications for brachytherapy comply only in 50% of the cases with Ablatherm® (T1/T2, Gleason<7, N0, M0, no obstruction, no TURP), while when operating the Sonablate® the indication for HIFU and brachytherapy are nearly identical (Fig. 4).

6. Contraindications

There are a few contraindications in performing HIFU in prostate cancer. Prostate gland size must be less than 40 cc, because of the limited focal length of HIFU. If the gland is larger, downsizing is suggested with LHRH agonist, performing a TURP will also downsize the gland and can be useful in treating patients who suffer from calcifications or abscesses. A history of rectal fistula is a current contraindication, because the possibility of a not completely healed fistula at the time the HIFU treatment. Also, the damaged tissue may have less vascular reserve and be more susceptible to injury than normal tissue. In addition if a rectal stenosis or rectal amputation does not allow the probe to be placed in the rectum, HIFU cannot be used. Bleeding problems or anticoagulation is not an absolute contraindication. Usually it is recommended that all anti coagulant medication should be stopped 10 days in advance, because there may be some minor rectal bleeding from the stretching caused by the rectal probe.

7. Outcome data

In 1995 Madersbacher et al. first reported the ability to destroy entire tumours in human prostate successfully [11]. The rates of local control have increased dramatically from 50% at 8 months in early studies to approaching 90% in the latest reports [12,13]. Early on, HIFU was mainly used as an additive tool in the treatment of CaP prior to hormonal ablation [14]. From that moment on techniques progressed from local to global treatment of the gland, mainly because treatment time was reduced [15,16], and with experience results improved [16,17]. Longer term follow-up data come from papers by Chaussy and Thüroff [18] and Gelet et al. [19], and the most recent European data (including over 2000 patients) were reported by Chaussy in 2002 [20]. In their overall case series, they have observed negative biopsy rates in 87.2% of patients, and prostate specific antigen (PSA) values remained at their post HIFU nadir in 84.1% at 1 year. Blana et al. [21] reported on their 5-years results with HIFU in localised prostate cancer: 146 patients with biopsy proven T1-T2N0M0 prostate cancer had a PSA nadir 3 months after treatment of 0,07 ng/ml, after 22 months average (up to 5 years) a PSA of 0,15 ng/ml was reported. 87% of the patients had a constant PSA level of less than 1 ng/ml.; 93.4% of all patients had negative control biopsies. A detailed account of the complications encountered during 3 years' experience (315 treatments) is provided by Thüroff and Chaussy, and the most recent data describe stress incontinence in 13% (but only 1% Grade III), erectile dysfunction in 22% and urinary tract infection in only 5% if HIFU is preceded by a limited TURP. Pre-HIFU TURP is indeed now standard for treatment in Europe. It serves to reduce the prostate volume prior to HIFU and has also been shown to reduce post-HIFU rates of urinary tract infection and acute retention of urine. A total treatment time of 2–3 hours is reported for the combined procedure. Chaussy et al. [22] evaluated the effects of combining HIFU with a TURP. 96 patients were treated with HIFU alone (criteria localised prostate cancer, no previous treatment before) and 175 patients received a HIFU treatment and a TURP. A statistically significant impact was observed on catheter time (40 days vs. 7 in median), incontinence (15.4% vs. 6.9%), urinary infection (47.9% vs. 11.4%) and post treatment IPSS (8.91 vs. 3.37) in favour of the TURP plus HIFU group. There was, however, no peri-operative mortality, no requirement for blood transfusion and no instance of urgent surgical revision. So, the combination of a TURP and HIFU treatment reduces the treatment related morbidity significantly and postoperative per course of patients treated with TURP and HIFU showed to be identical to that of a classical TURP.

Finally, Gelet et al. evaluated the efficacy of HIFU for locally recurrent prostate cancer after external beam radiotherapy in a total of 71 patients [23]. Before HIFU the mean PSA level was 7.7 ng/ml, the mean age was 67 years and the mean prostate volume was 21 ml. All pre-HIFU biopsies were positive, with a Gleason score of 2 to 6 in 24 patients, 7 in 13 patients, and 8 to 10 in 34 patients. After HIFU treatment 57 of the 71 patients had negative biopsies and 43 of 71 had a nadir PSA level of less than 0.5 ng/ml. At the last follow-up (mean 14.8 months) 44% of the patients had no evidence of disease progression.

8. Side effects and complications

Concerning side effects (therapy immanent) and complications (unexpected problems) the following can be said. After HIFU, urinary retention is a known side effect and will always occur, caused by a swollen gland. Often, there will be necrosis (slough) because of the coagulated adenoma. Most of the patients will pass the debris without any problem, but sometimes a resection by cystoscope is needed. Thuroff et al. [24] described the side effects in 315 patients treated with HIFU from 1996 to 1999. As a major adverse event they reported stress incontinence grade 1 in 6 cases. After repeated treatments with HIFU, 5 patients suffered from rectourethtral fistulas as a complication of the treatment, stress incontinence grade 1 was seen in 6 patients, grade 2 in 1 patient and grade 3 in 2 patients. Post-HIFU rectal mucosa burn decreased from 15% in 1996 to 0 within recent years. Due to additional safety features (like control of the rectum wall position with respect to the transducer) and treatment parameters adjustment according to the patient history (retreatment, radiotherapy failure), rectal injury dropped dramatically since 2002. But in case of HIFU treatment following radiation failure, the risk of rectal injury is obviously higher due to the surrounding tissue effects of radiation. Obstruction, due to gland swelling, was avoided in all treatment by suprapubic urinary diversion. Furthermore, all patients undergoing HIFU treatment will have no ejaculation with climax and they will be infertile. Impotence is a side effect that can occur, mainly because potency preservation treatment is not recommended in high risk or locally advanced prostate cancer. Table 1 presents the treatment side effects and complications of HIFU and compares them with three other leading treatments injury.

Table 1 – Data Table comparing Treatment side effects

	Fistula	Urgency	Bleeding	Diarrhea	Incontinence	Impotence
Radical Prostatectomy	<0.5–4%	6–16%	1–3%	6–19%	7–52%	14–96%
External Beam Radiation		19–43%	13–17%	12–42%	0–15%	50–61%
Brachytherapy	0–3%		4–11%		0–19%	14–66%
Cryoablation	0–0,5%				1–7%	47–95%
HIFU	<0,5–5%				0–2%	28–30%

[27].

9. Considerations

To date, HIFU has been assessed for its potential role in the treatment of organ-confined disease in patients who would otherwise not have been offered surgery, and of local recurrence following failed surgery or radiation. As stated before, the Ablatherm® and the Sonablate® do play a different role in each of those indications. It is clear that further long-term follow-up is required to support early findings and randomized controlled trials will be needed if clinicians are to be convinced, but the technology has been well studied and developed to a point that it is a real alternative to surgery or radiation therapy. To prevent obstruction after the procedure many European centres nowadays perform prostate incisions or TURP prior to the procedure in an attempt to alleviate this problem and other adverse effects of the treatment. However, it certainly appears as though HIFU already has a valuable niche to fill in an otherwise problematic group, and we seem to be approaching the stage where HIFU could be proposed more widely as a primary therapy of localised prostate cancer. In addition, the use of HIFU (the Ablatherm® device) in high and locally advanced stages of prostate cancer is currently being studied. More scientific evidence is needed to prove it is a real alternative to other treatments in this group of patients. A nerve sparing approach is another appealing option in the primary treatment of localized prostate cancer that deserves to be studied. Obviously HIFU is the treatment modality with many attractive features and potentials that deserve to be studied more extensively. The future of HIFU in the treatment armamentarium of CaP is beyond discussion very promising (Figs. 5 and 6).

10. Future perspectives of HIFU treatment

HIFU has been used since 2000 on a clinically routine basis in local treatment of prostate cancer. In this regard Europe clearly has taken the lead. HIFU treatment of other organs is still in an experimental phase: HIFU in bladder cancer, for instance, was abandoned due to its poor outcomes in clinical studies [25]. HIFU as a non-invasive treatment in kidney tumours is still at an early stage of development [26]. Due to the continuing device developments and improvements in imaging techniques, HIFU will increasingly provide improving results in prostate cancer while reducing side effects and complications. To monitor the efficacy of HIFU treatment, today the MRI is considered the golden standard [27]. On gadolinium-enhanced T1 weighted images hyposignal zones can be shown. Because it is sensitive to temperature changes in tissue, MRI is an effective method for guiding and controlling ultrasound pulses. MRI guided HIFU treatment has thus been used to monitor temperature changes within tissue. MRE (magnetic resonance elastography), by measuring the mechanical properties of the lesion, has also been proposed in assessing the effects of thermal tissue ablation [28]. This is currently a field of extensive experiment, research and development. The HIFU Urobot for example, is an expirimental robotic

Fig. 5 – Sonablate device.

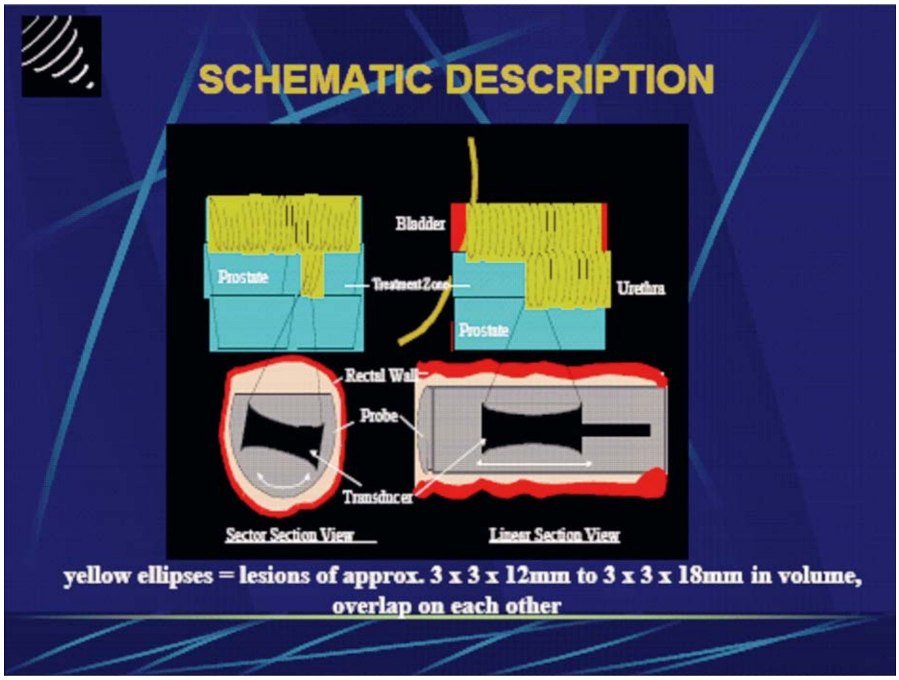

Fig. 6 – Sonablate, Focus Surgery, USA.

system that houses the transrectal ultrasound probe and the HIFU transducer [29]. Pre –operatively slices of MRS prostate images of the patient are stored into the imaging processing/path planning module in the computer. The robot then develops a 3D model of the prostate by using ultrasound images delivered by the TRUS. This model is than mapped with a similar model obtained from the earlier MRS images. The surgeon than defines target position within the prostate where he wants the HIFU transducer to focus, with knowledge of the cancerous sites. After the target has been defined, the computer commands the robot to manipulate the HIFU transducer such that its focus point coincides with the defined target. The image guidance therefore provides the surgeon more accuracy and requires less skill from the practitioner. Might contrast-enhanced 3-D ultrasound of the prostate be the future tool to visualise HIFU- induced lesions, since the extent of the lesions is not always accurate on standard ultrasound. Sedelaar et al. [30] already reported in 2000 that 3-D contrast-enhanced ultrasound is a promising method to determine the size of the defect of HIFU ablative therapy. For now HIFU already offers a reliable treatment for organ confined prostate cancer and showed reassuring results as a salvage therapy after external beam radiotherapy. If HIFU can deliver in other urological fields as it has in prostate cancer, HIFU might justifiably be coined as the new surgical tool.

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CME questions

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1. What makes high intensity ultrasound treatment well suited for cancer treatment?
   A. Ultrasound is by far the most harmless way to attack malignancies.
   B. It is a reliable alternative for those patients who don't fit other invasive treatments.
   C. Other treatments cause too many side effects.
   D. The ability to cause core cell death in distant organs by way of an ultrasound source makes it an alternative in cancer treatment, especially in localised prostate cancer.

2. The transrectal approach is:
   A. The main reason why HIFU therapy can be repeated after previous HIFU treatments.
   B. A major advantage in this therapy because of its non-invasiveness.
   C. The only way to the prostate.
   D. The least preferable procedure due to high occurrence of complications.

3. TURP prior to HIFU treatment
   A. Reduces side effects after HIFU treatment.
   B. Increases penetration depth in larger prostates.

C. Suits patients with BPH and localised prostate cancer.
D. Can be used for other prostate problems such as calcifications and abcesses as well, and improves the results in this group.

4. What is the difference between the Ablatherm® and the Sonablate® device in treating localised prostate cancer?
A. There is no difference, both the Ablatherm® and the Sonablate® can be used for all different indications in treating localised prostate cancer.
B. The Sonablate is® not suitable for salvage therapy.
C. The Sonablate® device consists of a 4 MHz probe that makes it suitable for highly precise treatment in the peripheral zone of the prostate.
D. The Ablatherm® device has rectal wall control.

5. Rectal fistulas are:
A. Side effects caused by HIFU treatment in localised prostate cancer.
B. Complications after HIFU treatment in localised prostate cancer.
C. A normal occurrence in HIFU treatment.
D. A contra indication to perform HIFU therapy because of persistence of the fistula. and bad quality of the surrounding tissue.

6. HIFU treatment in localised prostate cancer
A. Is more popular in the USA than it is in Europe.
B. Is as successful in treating prostate cancer as it is in treating other forms of urologic cancer.
C. Will be improved in the future due to experiments to monitor the temperature gradient with ultrasound and MRI.
D. Is currently the most reliable form of treatment for prostate cancer.