

TRANSRECTAL HIGH INTENSIVE FOCUSED ULTRASOUND (HIFU) FOR THE TREATMENT OF PROSTATE CANCER: A HISTORICAL REVIEW**Authors**

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Abstract

Prostate cancer is diagnosed 10 years earlier and men live almost 4 years longer than 30 years ago. This means that the therapeutic necessity is more than double the time than it was then. None of the classical therapies is effective enough to cover this time frame as a monotherapy without a significant risk of aggressive recurrence during these years

These changing trends in age and extent of malignancy at diagnosis have revealed limitations in conventional curative therapies for prostate cancer, including a significant risk of cancer recurrence, and the risk of long-term genitourinary morbidity and its detrimental impact on patient quality of life (QOL). Greater awareness of the limitations in radical prostatectomy, external radiotherapy and brachytherapy have prompted the search for alternative curative therapies that offer comparable rates of cancer control and less treatment-related morbidity to better preserve QOL. High intensity focused ultrasound (HIFU) possesses characteristics that make it an attractive curative therapy option. HIFU is a non-invasive approach that uses precisely delivered ultrasound energy to achieve prostate tissue necrosis without radiation or surgical excision. In current urological oncology, HIFU is used clinically in the treatment of prostate cancer, and is under experimental investigation for therapeutic use in multiple malignancies. Clinical research on HIFU therapy for localized prostate cancer began in the 1990s, and there have now been approximately 40,000 prostate cancer patients treated with HIFU. Neoadjuvant transurethral resection of the prostate (TURP) has been combined with HIFU since 2000 to reduce prostate size, facilitate tissue destruction, and to minimize side effects. Advances in imaging technologies are expected to further improve the already superior efficacy and morbidity outcomes, and ongoing investigation of HIFU as a focal therapy in salvage and palliative indications are serving to expand the role of HIFU as a highly versatile non-invasive therapy for prostate cancer.

Keywords

HIFU: High Intensity focused Ultrasound non-invasive PCa Therapy focal therapy castration resistant PCa

Introduction

Although knowledge that tissue destruction can be achieved with high-intensity focused ultrasound (HIFU) has been around since the 1930s, efforts to clinically implement this technology were delayed due to the absence of imaging technology to monitor the procedure [1]. Basic research in the urological application of HIFU began in the 1980s, when computer technology became sufficient to facilitate the control and management of this fascinating radiation free energy source. The first clinical prototypes for use in urology emerged during this period.

Clinical trials of HIFU began in the early 1990s in Europe, Japan, and the USA, with initial evaluation as a therapy for benign prostatic hyperplasia. HIFU demonstrated safety and efficacy through the precise destruction of local tissue. Also observed was the induction of a significant shrinkage process within the treated organ and resultant therapy-related side effects. Thus, HIFU was found to possess the effective attribute needed for cancer treatment of tissue destruction, but it was not effective in infravesical de-obstruction, where obstruction was increased from shrinkage and necrotic tissue. Early clinical trials of HIFU therapy for prostate cancer during the mid-late 1990s found a relationship between the coagulated prostate volume and obstruction, and analysis of prospective

studies also found a high rate of urinary tract infections in this necrotic tissue. As the result of the association between HIFU and obstruction, and consistent with the whole-gland concept of therapy, HIFU has been routinely combined with a neoadjuvant TURP since 2000 [2,3] to debulk the tumor mass and radically resect the middle lobes, calcifications, abscesses, and bladder neck [4].

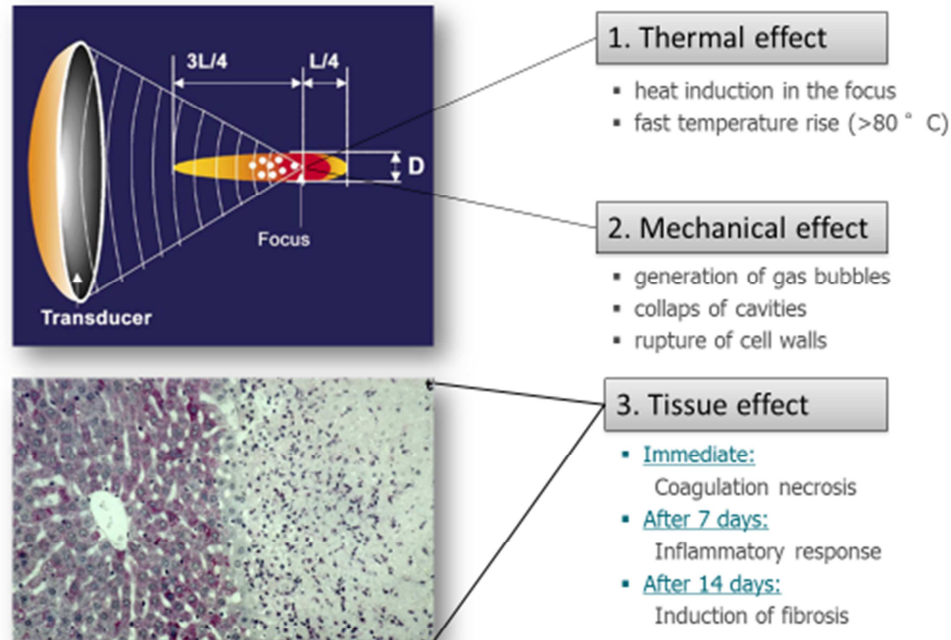
HIFU therapy has been extended to different surgical indications such as use as an extracorporeal method that allows non-invasive coagulative destruction without an open surgical procedure. The validation and international acceptance of transrectal HIFU treatment of prostate cancer has been increasing as the result of the growing clinical experience and published research on HIFU. 15-year efficacy results are available [5,6].

Material and Method

The first use of HIFU in local tissue destruction was reported in 1944 by Lynn and Putman [7]. The use of high-energy parabolic-focused ultrasound results in the mechanical alteration and changes in the biological structure of targeted volumes [1]. During the application of focused ultrasound, two different physical mechanisms account for its treatment effect: thermal and mechanical.

Figure 1: physical principle of focused energy application

High Intensity Focused Ultrasound (HIFU) Technique



The ultrasound energy produced by HIFU is absorbed by the targeted tissue and converted into heat. The extent of temperature increase in the tissue depends on the absorption coefficient of the tissue, and the size, shape and temperature sensitivity of the heated area [1]. Biological changes caused by the heating depend on the temperature level and duration of exposure. A "thermal dose", which exceeds a certain threshold, causes tissue coagulation and leads to irreversible tissue damage through coagulative necrosis [8]. The focused ultrasound waves of HIFU are capable of inducing sharp increases in temperature (around 70°C to 100°C) within a few seconds. During the clinical use of HIFU, the tissue-sensitive adjacent structures such as the rectum, external sphincter, and the neurovascular bundles

are spared from destruction due to the steep temperature gradient between focal tissue and surrounding region [8,9].

The mechanical effects of HIFU are induced by the impact of oscillating pressure of the ultrasound wave on the targeted tissue [1]. The pressure causes bubbles to form inside the targeted cells which increase in size to the point at which resonance is achieved. High pressure of 20,000–30,000 bars develops when these bubbles suddenly collapse, causing damage to nearby cells and the formation of a cavitation effect within the tissue which damages cell membranes [10]. The primary single lesions are small ($1.7 \times 19\text{--}26\text{ mm}$) and produce reproducible volumes of sharply demarcated ablation [9]. The small volume of tissue destroyed by a single

shot of ultrasound is termed “elementary” or “primary” lesion. To create larger lesions, several elementary lesions are made side by side, by adding multiple lesion targets to the algorithm

and either mechanically moving the transducer or by electronically positioning the focal point if a phased array is available [8,11-15].

Figure 2:

- a) multiple lesion application mode and
- b) volume coagulation (transducer movement algorithm)

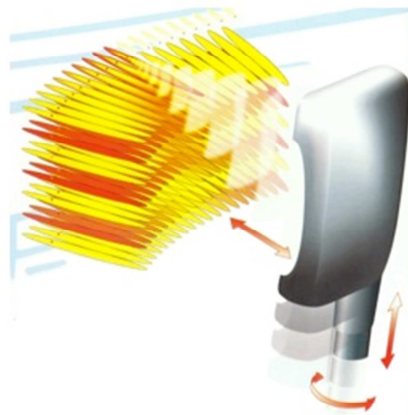


Figure 2a



Figure 2b

Experimental evaluation and clinical parameters

In vitro, in vivo, and computer simulation studies were conducted to identify and refine the ultrasound parameters required for the clinical treatment of prostatic disease. The destruction of tumors with HIFU in these studies provided the evidence that cancerous tissues can be destroyed by HIFU without inducing metastases [16],

and that prostatic tissue can effectively be targeted through transrectal delivery of HIFU [17,18].

High-intensity focused energy can be delivered as a pulsed or a continuous beam [19]. The latter process includes solar waves, microwaves and radar technology, whereas pulsed HIFU is applied as medical HIFU and extracorporeal shockwave lithotripsy. The high-frequency vibration (0.5–10

MHz) of a piezoelectric or piezoceramic transducer generates ultrasound waves, which are collected into a focal point by a concave or parabolic arrangement [10].

Essential parameters for the medical use of HIFU include the ultrasound frequency (MHz), the acoustic intensity (Watts), the duration of application (shot-time), the intervals of the pulses (delay-time), the lateral and vertical distance between elementary lesions, the longitudinal displacement of the energy source when applying multiple lesions, and the penetration depth (focal point) dependent on the applicator design [1].

These multiple technical parameters are essential in the assembly of a HIFU system with a dedicated application for specific tissue. Complex technical decisions are involved in HIFU operation, and include the selection and design of the piezoelectric energy applicator, the parameters of ultrasound treatment (MHz, Watts), the application algorithm (impulse-delay relation), the imaging system, the intraoperative target and safety features, target localization

during treatment with TRUS or MRI, and controls [1].

The ultrasonic energy transducer is characterized mainly by its operating frequency, and geometric and physical dimensions. Piezoelectric systems can be operated with sufficient energy density, reproducibility and long-term stability in accordance with the requirements of the therapy, which allow the production of geometric shapes for adaptation to changing anatomical needs [13]. Current standard urological applications use HIFU transducers with a fixed but adjustable focal point to be moved mechanically to treat a larger tissue volume [14,15].

Commercially available treatment technologies

There are two devices which differ in numerous dimensions.[**Table 1**] HIFU with Ablatherm® constitutes the majority of research involving prostate cancer therapy with HIFU.[20] Studies involving the Ablatherm® device are the major focus of this review.

Table 1: Technical Data of the Available HIFU Devices

Features	Sonablate 450/500® (by Sonacare)	Ablatherm int. imaging® (by EDAP-TMS)	Focal One® (by EDAP-TMS)
Rectal wall safety control	visual/manual	US/automatic	US/automatic
Applicators adjustment mode	Manual	Robotic (autofocus)	Robotic(autofocus)
Max. ventral prostatic HIFU penetration (mm)	30	24	40
HIFU power settings	manual	automatic	automatic
Rectal balloon pressure	low	high	flexible
TRUS frequency (MHZ)	4 / 6.3	7.5	7.5
HIFU frequency (MHZ)	4	3.5	3.5
Shot / delay mode	on/off, rhythmic	on/off, rhythmic	on / continuous
Treatment speed / 10cc	90min	60min	40min
TURP before?	obstructive or >40cc: Yes focal or <40cc: No	obstructive or >25cc: Yes focal or <25cc: No	obstructive or >50cc: Yes focal or <50cc: No
patients OR position	lithotomy	right lateral	right lateral

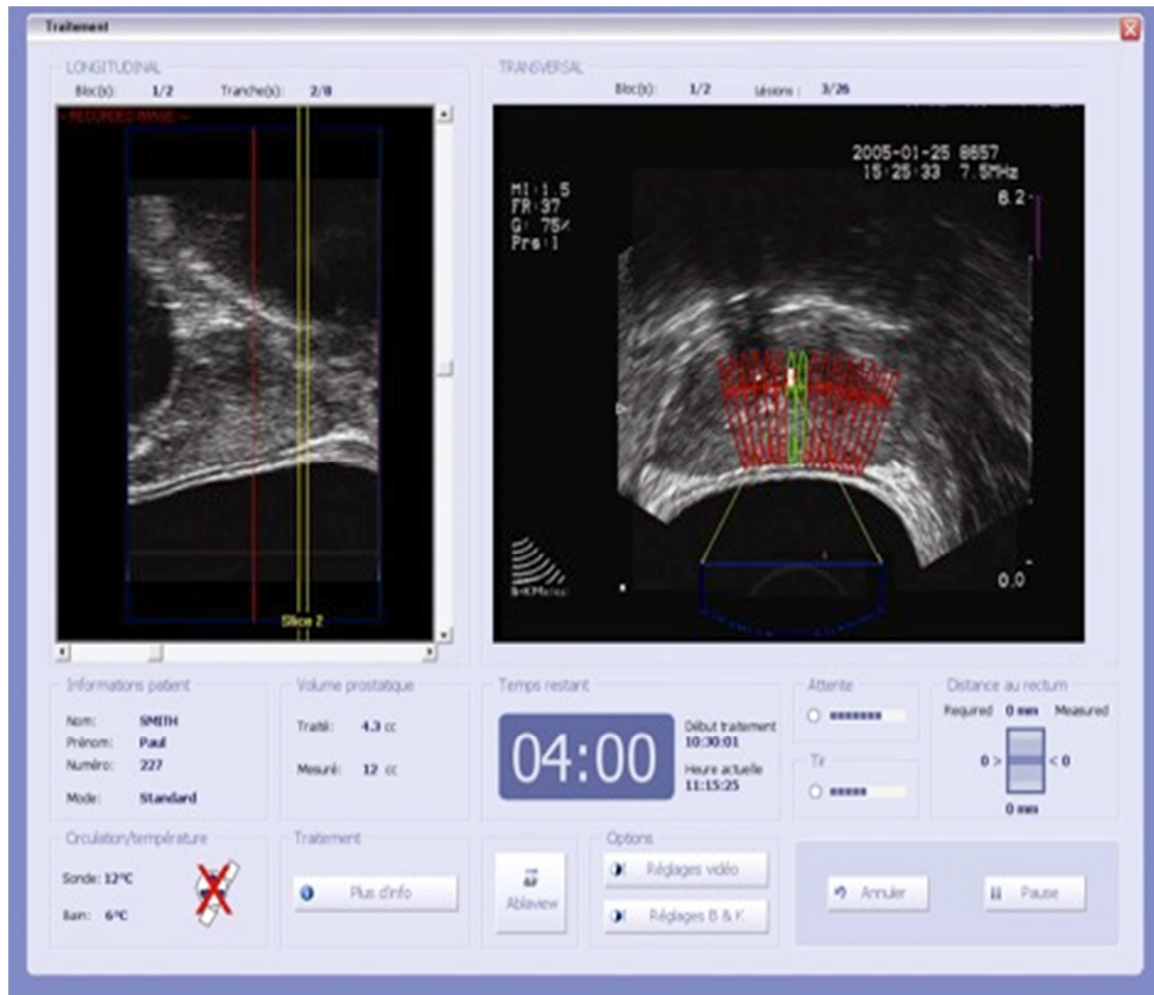
Ablatherm®

The Ablatherm® machine consists of a treatment module that includes the patient's bed, the probe positioning system, the ultrasound power generator, the cooling system for preservation of the rectal wall, and the ultrasound scanner used during the treatment localization phase. There is also a treatment and imaging endorectal probe that incorporates both an imaging probe working at 7.5 MHz and a treatment transducer focused at a maximum of 45 mm working at 3 MHz [21]. Numerous safety features have been incorporated,

starting with a safety ring that stabilizes the rectal wall mechanically during transducer movements. Consecutively a permanent control of the distance between the therapy transducer and the rectal wall, and a patient motion detector that stops treatment if the patient moves during the firing sequence have been integrated [21].

The treatment parameters are selected to optimize the size of the lesion while leaving the rectal wall and surrounding tissues intact.

Figure 3: Intraoperative, 3 dimensional, real time, transrectal ultrasound for visual treatment planning and control on control screen



The size of the elementary lesion is between 19 and 26 mm in length and 1.7 mm in diameter. Because the shape of the lesion depends on gland perfusion, treatment parameters are different according to the patient's status: 5 s treatment pulse and 5 s shot interval for

the first HIFU session in primary-care treatment; 4.5 s treatment pulse and 5 s shot interval for the second session in primary care; and 4 s treatment pulse and 7 s shot interval for local relapse after external-beam radiation therapy [21].

Figure 4a: Focal point adjustment, penetration depth (19-26 mm)

HIFU is delivered as a single-session therapy applying 100 of consecutive lesions under spinal or ITN anesthesia for a duration of 1 to 2 hours. The treatment is conducted with the patient in the lateral position. The endorectal probe containing a curved piezoelectric crystal and a transrectal ultrasound (TRUS) scanner is placed in a latex balloon filled with cooling fluid and introduced into the rectum. This probe collects emitted ultrasound beams at a focal point. Following definition of the target volume boundaries by the operator, treatment is performed from the apex to the base of the prostate. Usually 4 to 6 successive target volumes are defined in order to treat the entire prostate. During the HIFU session, a Foley-type urinary catheter or a suprapubic tube is positioned [21].

Sonablate®

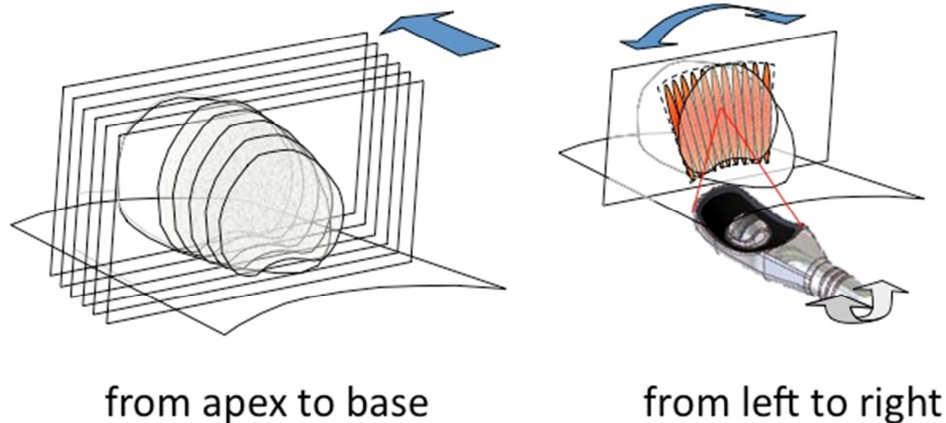
Unlike the Ablatherm® machine, the Sonablate® system has no dedicated bed. Several treatment probes are available, and are selected by the operator according to the size and intrapostatic position of the elementary lesion: 10 mm in length and 2 mm in diameter for a single beam performing with 25 mm or 45 mm focal-length probes; and 10 mm in length and 3 mm in diameter for a split beam performing with 30, 35 or 40 mm focal-length probes [20,22]. Treatment parameters vary depending on operator's choice.

Treatment is performed with the patient in a lithotomy position under general anesthesia. The probe is chosen depending on prostate size, with larger glands requiring longer focal lengths.

The treatment is usually made in three consecutive layers, starting from the anterior part of the prostate and

progressively moving to the posterior part, with at least one probe switch during the procedure [22].

Figure 4b: Focal point adjustment, latero-longitudinal (1.7 mm steps)



Tissue effects

The clinical potential of HIFU in the treatment of prostate cancer was established in a clinical trial where patients received HIFU 1 to 2 weeks before receiving radical prostatectomy, followed by histologic examination of the removed prostate. HIFU was delivered to regions of the prostate where biopsies had revealed cancer, and histologic examination found a sharp demarcation between HIFU-treated and untreated areas, with complete necrosis in all specimens [23]. Fat-saturated gadolinium-enhanced MRI has

demonstrated the extent of the tissue damage induced by HIFU. Treated areas appear as a non-enhancing hypointense zone surrounded by a peripheral rim of enhancement 3 to 5 mm thick. These abnormalities correspond to a nucleus of coagulation necrosis surrounded by a peripheral zone of inflammation. Treatment-induced abnormalities visible with MRI usually disappear in 3–5 months in a centripetal manner, and HIFU-induced tissue contraction results after about 6 months in small prostates of approximately 5- 10 cc [24].

Imaging

MRI is considered the gold-standard technique used for assessing the efficacy of HIFU treatment. The extent of necrosis can be clearly visualized on gadolinium-enhanced T1-weighted images, as hyposignal zones [25]. MRI has also been used to guide HIFU treatments [25,26], as it is possible to monitor the temperature changes within tissues with MRI during HIFU [25]. Magnetic resonance elastography has also been proposed as a method for assessing the effects of thermal tissue ablation by measuring the mechanical properties of the lesion [26]. It remains unclear whether elastographic changes are correlated with long-term tissue destruction and whether they reflect complete tissue coagulation at a cellular level [27]. HIFU-induced lesions are visible using standard ultrasound as hyperdense regions; however, the real extent of primary lesion destruction cannot be defined precisely because of variations across patients in interfering effects such as HIFU reflection (prostatic capsule, calcifications, catheters); absorption (untreated or pretreated tissue); and cooling (blood vessels, intraprostatic TURP cavity liquid) [28]. Techniques to improve characterization based on ultrasound, contrast-enhanced Doppler [29], and measurement of the acoustic behavior of tissues have been proposed to more accurately determine the extent of HIFU-induced lesions [30]. During 20 years of clinical experience with HIFU treatment of prostate cancer, transrectal ultrasound has been shown to be a safe reproducible technique even without "real time" temperature measurement. However, a "real time" technology that compensates for the limitations in tissue visualization mentioned above would be

an advantage that would help to optimize tissue ablation efficacy by minimizing the targeted volume [1].

Indications

The most widespread use of HIFU, and initially the only indication for its use, has been in patients with localized prostate cancer (T1–2N0M0; Gleason sum ≤ 6) who are not candidates for surgery because of age, general health status, a prohibiting comorbidity or a preference not to undergo a radical prostatectomy [1]. However, with the accumulation of clinical experience and expansion of research protocols these indications have broadened to include partial therapy in unilateral low-volume, low-GS tumors (T1–2aNx/0M0; PSA ≤ 20 ng/ml); salvage therapy in recurrent prostate cancer following radical prostatectomy, radiation therapy or hormone ablation (all TNx/0M0; all GS/PSA) [31]; advanced prostate cancer as an additional neoadjuvant debulking process (T3–4Nx/0M0; all GS/PSA); and in castration resistant prostate cancer (CRPCa) [32]. HIFU is used in intermediate- and high-risk patients. Most studies have used HIFU with inclusion of these patient groups with reasonable outcomes [33,34], but as with the other curative therapies, high-risk patients have a lower longterm success rate than low-risk patients. Remaining contraindications common to both HIFU devices include a missing or small rectum, and a damaged rectal wall from previous prostatic or rectal therapies [1].

The diagnosis of prostate cancer is based on the histopathological examination of biopsies in cases of suspicious PSA findings, digital rectal examination, magnetic resonance imaging, transrectal ultrasound (TRUS), or unexpected

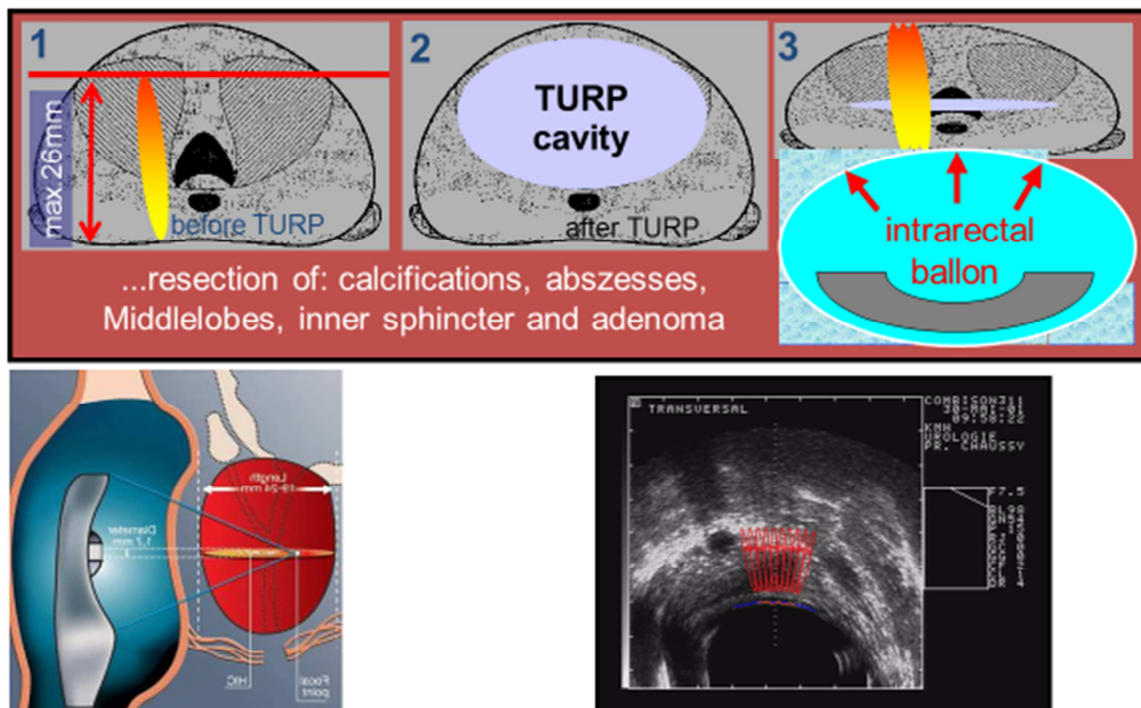
findings in resected tissue after open adenomectomy, holmium ablation, or transurethral resection [35].

TURP and HIFU

The use of TURP with HIFU became routine practice in 2000 as a means to reduce post-HIFU urethral sloughing and obstruction, and offers several other advantages over HIFU alone.

Figure 5

Compression of TUR defect by rectal balloon



The combined procedure of TURP prior to HIFU in patients with localized prostate cancer allows the instant removal of any reflecting or deviating calcifications of the transitional zone that would prevent HIFU treatment, as well as abscesses, intravesical middle lobes and large (> 40 ml) adenomas [1]. The generation of a cavity and its subsequent compression by the rectal balloon increases the accessibility of the HIFU waves to the remaining gland,

fixes the residual prostate behind the symphysis, avoids movement artefacts, and allows the complete treatment of the peripheral zone in a single HIFU session. The penetration depth of the HIFU device is 19 - 24 mm, and therefore, without a TURP, a larger gland size (> 30 ml) cannot be treated completely. TURP decreases the size of each prostate gland to approximately 25 ml to eliminate size restriction with HIFU [2,36].

Results

Localized disease

Similar to efficacy studies with external beam radiotherapy, brachytherapy, and cryoablation, biochemical markers and biopsy findings have been used as indicators of long-term cancer control with HIFU. To date there is no universal consensus on the definition of biochemical failure in patients treated with HIFU [1]. With ongoing refinements in execution and outcome measurement, the efficacy of HIFU in locally confined prostate cancer is now comparable to those of radiotherapy and radical prostatectomy, which according to the CaPSURE database are characterized by failure rates of 63% at a mean of 38 months post treatment and 30% at a mean of 34 months post treatment, respectively [37].

Early efficacy studies of HIFU defined complete response as a negative control biopsy and a PSA nadir < 4.0 ng/ml. [38,39]. Stricter criteria for treatment failure were applied by Gelet et al., with failure defined as any positive biopsy or three successive elevations in PSA with a velocity of 0.75 ng/ml/year or greater [40]. The French Urological Association guidelines in 2005 stated that biopsy was required if there were three successive elevations in PSA level over a 3-month period but not if the PSA nadir was less than 1.0 ng/ml [41]. The American Society for Therapeutic Radiology and Oncology (ASTRO) definition of disease-free status based on biochemical outcome has been applied to HIFU. PSA failure was also defined as three consecutive PSA rises after a nadir, with

the date of failure being the halfway point between the nadir date and the first rise or any rise great enough to provoke initiation of salvage therapy [34]. This definition was subsequently modified to the Phoenix definition of failure as the time at which $PSA > \text{nadir} + 2.0 \text{ ng/ml}$ was reached. A number of HIFU studies have now applied the ASTRO or Phoenix definitions.

[Table 2] provides a summary of HIFU efficacy in localized prostate cancer.

HIFU efficacy has also been reported in terms of a negative biopsy rate, which is likely to provide the best proof of definitive efficacy despite the associated sampling error. The lowest negative biopsy rate was reported by Gelet et al. in 2001 [42], which included patients treated with prototype devices. The only other series reporting a negative biopsy rate less than 80% was by Ficarra et al. [33], who included patients with high-risk prostate cancer [6]. In more recent series, negative biopsy rates have ranged from 93–96% [5,43]. Re-treatment rates have also been reported in the literature but their interpretation is confounded by the former practice of using two treatment sessions with only one prostatic lobe treated in each session. This approach was common in the studies of Gelet et al. [42] and Poissonnier et al. [6,44]. The only series that did not use this approach was the series involving high-risk patients reported by Ficarra et al. [33]. Unfortunately, the proportion of patients treated intentionally with two sessions versus those re-treated due to clinical failure was not reported in these studies.

Table 2. Robotic High-Intensity Focused Ultrasound: Efficacy Summary

Study (year)	n	Pretreatment PSA (ng/ml)	Gleason score	Stage	Median Follow-up (months)	Negative Biopsy rate (%)	Biochemical survival	Retreatment rate (%)
Chaussy et al. (2001)	184	12		T1-2 Nx		80	NR	26.1
Gelet et al. (2001)	102	8.38 (mean)	54% 2-6 46% 7-10	T1-2	19	75	66% at 5 years (ASTRO)	78.4
Poissonnier et al (2003)	120	5.67 (mean) 100% <10	64% 2-6 36% 7-10	T1-2	27	86	76.9% at 5 years (ASTRO)	1.4 Tx per patient
Thüroff et al. (2003)	402	10.9 (mean)	13.2% 2-4 77.5% 5-7 9.3% 8-10	T1-2	13	87.2	NR	36.7
Blana et al. (2004)	146	7.6 (mean)	5 ± 1.2	T1-2 NOMO	22	93.4	84% at 22 months (PSA < 1.0)	18.7
Ficarra et al. (2006)	30	18 (median)	17% 7 33% 8 37% 9 13% 10	30% T2b 70% T1-2 NOMO	6	77	90% at 1 year (PSA > 0.3)	0
Poissonnier et al (2007)	227	7.0 (mean)	67% 2-6 33% 7	T1-2	20.5	86	NR	42.7
Blana et al. (2008)	140	7.0 (mean)	5.2 ± 1.4	T1-2 NOMO	76.8 (mean)	96.4	77% at 5 years (PHOENIX)	29.3
Blana et al. (2008)	163	5 (median)	7.9 ± 3.7	T1-2 NOMO	57.6 (mean)	92.7	75% at 5 years (PHOENIX)	20.8

Blana et al. reported HIFU treatment outcomes by utilizing a large international patient series from the @-Registry [45]. Patients in the @-Registry were stratified according to D'Amico's 2003 risk group definitions [46] and Kaplan–Meier analysis was performed to determine biochemical survival, with failure defined by the Phoenix definition (PSA nadir +2 ng/mL). The overall 5-year biochemical survival rate was 85%.

In a series of 120 patients with localized prostate cancer and PSA values of <10ng/ml, cancer-free survival rates were examined [6]. The calculated cancer-free 5-year survival rate for the overall patient population was 76.9%, 85.4% in highly differentiated tumors

(Gleason score 2-6), and 61.3% in poorly-differentiated tumors (Gleason score 7–10). There were no significant differences in survival rates based on prostate volume or the number of positive biopsies. Also, PSA nadir displayed predictive relevance, with actuarial 5-year survival rates of 86% in patients with a nadir PSA <0.5 ng/ml.

A European multicenter study reported the short-term results of 402 patients with localized prostate cancer (T1-2/N0-x/M0) treated between 1995 and 1999 [48]. At 1-year follow-up, 87.2% of control biopsies were negative. When stratified by prognostic risk, the negative biopsy rate was 92.1% in low risk (Gleason < 7) patients, 86.4% in

medium risk (Gleason 7) patients, and 82.1% in high risk (Gleason > 7) patients. PSA nadir occurred 3 to 4 months after HIFU treatment, and was significantly influenced by the prostate volume in relation to the extent of completeness of the HIFU treatment.

Blana et al. [5] reported the results of 140 patients with baseline PSA ≤ 15 ng/ml and Gleason score ≤ 7 . TRUS biopsies 6 months following HIFU treatment were negative in 93.4% of patients. The mean PSA nadir was 0.07 ng/ml, with PSA values remaining stable at a mean of 0.16 ng/ml during the 22 month mean observation period. The rates of freedom from biochemical relapse at 5- and 7-year follow-ups were 77% and 69%, respectively, which are comparable to those reported in large

studies of standard curative therapies for localized prostate cancer [49-51].

A study with the longest patient follow-up was published in 2010 by Crouzet et al. [52]. The authors reported the results of a multicenter trial consisting of 803 patients followed for a mean of 42 ± 33 months. Based on the Phoenix definition, 5- and 7-year biochemical survival was achieved by 83% and 75% of low-risk patients, respectively, and by 72% and 63% of intermediate-risk patients, respectively. Negative biopsy rates for low- and intermediate-risk patients were 84.9% and 73.5%, respectively. Also observed was an 8-year overall, metastasis-free, and cancer-specific survival of 89%, 97%, and 99% respectively. Further longterm results after HIFU treatment are given in table 3.

Table 3

Longterm Results after HIFU Treatment

	Risk Group	n	Ten Year Cancer Specific Survival	Ten Year Metastases Free Survival
Ganzer 2013	Low	229	100%	100%
	Intermediate	211	96%	94%
Thüroff 2013	All localized (72% mod or high)	704	99%	95%
Crouzet 2013	Low	357	99%	99%
	Intermediate	452	98%	95%
	High	174	92%	86%

Ganzer R, BJU Int. 2013 Aug;112(3):322-9; Thüroff S, Chaussy C: J Urol. 2013 Aug;190(2):702-10. Crouzet S, Eur Urol. 2014 May;65(5):907-14.

Sonablate HIFU for PCa primary therapy

Authors retrieved seven case series assessing Sonablate HIFU as a primary therapy option in prostate cancer (Table 3) that were carried out by three study groups in the United Kingdom, Italy, and Japan [53 - 59]. Between 63 and 517 patients were treated with Sonablate HIFU who were recruited consecutively in four case series [54,56 - 58]. Both localized (T1–T2, N0, M0) as well as locally advanced (T3, N0, M0) prostate cancers were treated using the Sonablate device. Median patient age, reported in all but one study, was between 68 and 72 years [60–64].

Gleason score was 7 in most patients, and median preoperative prostate

volume was 22–33 mL; between 29% and 66% of men received neoadjuvant ADT. TURP was either not carried out or no information was provided. Patients received one to four HIFU treatments, but most (79–86%) were treated only once. A median follow-up was between 14 and 34 months; mean follow-up of 12 months was reported in one study [53]. The biochemical disease-free survival rate was given in six case series and varied between 78% and 84% at 1 year, 0–91% at 2 years, 20–86% at 3 years, and 45–84% at 5 years. The negative biopsy rate was assessed in five studies [54–58], but the time of biopsy was only presented in three of them [54–56]. The negative biopsy rate was 19–89% at 6 months and 77%–84% at 12 months.

Incidental disease in PBH

Histological examination reveals prostate cancer in up to 8% of the patients who undergo adenomectomy/holmium-laser enucleation or transurethral resection of the prostate (TURP) because of symptomatic benign prostatic hyperplasia. Consequently, some of these patients want a therapeutic approach for their prostate cancer [35].

Results have been reported on 65 patients treated with HIFU for incidental prostate cancer. Patients were 70 years in average, with a median initial PSA of 4.9 ng/mL and a prostate volume of 39 mL, of which an average of 20 g (1–95 g) had been resected. Histology showed 5% (5% to 50%) positive chips and an average Gleason scale of 5 (3–9). Patients were treated with single-session full-gland transrectal HIFU. At follow-up, a median PSA nadir of 0.07 ng/mL was achieved at 1.8 months, including 62% with PSA < 0.1 ng/mL and 81% with PSA < 0.5 ng/mL. A median PSA of 0.13 ng/mL, equivalent to a median PSA velocity of 0.01 ng/mL/y, was found after a median follow-up of 48 months

The PSA nadir of 0.07 ng/mL and the PSA velocity of 0.01 ng/mL/y indicated that HIFU can be used as a curative

therapy in patients with incidental prostate cancer.

Morbidity

The most common side effects of primary HIFU therapy include prolonged voiding dysfunction and retention caused by edema, necrosis or bladder outlet obstruction, as well as erectile dysfunction. Among patients receiving HIFU as primary therapy, Grade I stress incontinence occurs in 4–6% of patients, Grade II in 0–2%, and secondary infravesical obstruction in 5–10%. Severe incontinence (Grade III) and urethra-rectal fistulae are rare (<1%). Urinary tract infections are common (2–48%) but the incidence has greatly decreased with the introduction of TURP. Erectile dysfunction occurs at rates of 32–61%. Preservation of erectile function is directly dependent on the position of the primary lesion in relation to the neurovascular bundle. An approach to greater preserve potency involves leaving a 5-mm lateral margin on the contralateral side in men with positive biopsy results confined to one side of the prostate. Although sparing the contralateral side for neurovascular preservation can improve potency. This approach also results in a higher rate of re-treatment [4,44, 60–62]. Morbidity with HIFU is summarized in table 4.

Table 4. Summary of morbidity results following high-intensity focused ultrasound

Study (year) [Ref.]	Number	INC (%)	ED (%)	FIS (%)	S&S (%)	PR (%)	UTI (%)	CA (days)	Pain (%)
Blana et al. (2009) [45]	146	5.8	57.2	0.7	11.7	NR	4.1	SP:12.7	1.4
Thüroff et al. (2000) [61]	402	GI 10.6 GII 2.5 GIII 1.5	13	1.2	3.6	8.6	13.8	F:5 SP:34	NR
Gelet et al. (2003) [40]	102	GI 8.8 GII 9.8 GIII 3.9	61	1	17	5	NR	9.1	2
Chaussy et al. (2003) no TURP [2]	96	GI 9.1 GII 4.6 GIII 1.7	40	NR	27.1	NR	47.9	SP:45.1	NR
Chaussy et al. (2003) TURP [2]	175	GI 4.6 GII 2.3	31.8	NR	8	NR	11.4	SP:13.7	NR
Ficarra et al. (2006) [33]	30	7	NR	0	10	13	16	SP:12	NR
Lee et al. (2006) [84]	58	GI 16	NR	0	NR	3.4	NR	SP:15	NR
Poissonnier et al. (2007) [44]	227	GI 9.0 GII 3.0 GIII 1.0	39	0	12	9	2	7	3
Blana et al. (2008) Multi [5]	140	GI 5.0 GII 0.7	43.2	0	13.6		7.1	NR	5.7
Blana et al. (2008) Single	163	GI 6.1 GII 1.8	44.7	0	24.5		7.8	NR	3.7

To reduce the time of urinary diversion and postoperative morbidity (sludging, obstruction, infection), studies were undertaken to observe the effects of combining HIFU with TURP. In 30 patients with localized prostate cancer a one-stage (in the same anesthesia) combination therapy with TURP and HIFU was performed. At 6-month follow-up, the mean PIPSS (Post-treatment International Prostate Symptom Score) was 6.7 compared with a pre-treatment score of 7.5 [36]. In a study combining TURP and HIFU 96 patients were treated with HIFU monotherapy and 175 with combination therapy. The monotherapy group

required a suprapubic catheter for 40 days compared to 7 days in the combination group [2].

Chaussy and Thuroff compared the outcomes of a series of 175 patients treated with HIFU combined with TURP with those of 96 patients previously treated with HIFU alone [2]. No significant differences were found between the two treatment groups in PSA nadir or positive biopsy rate, consistent with subsequent studies finding comparable efficacy between HIFU plus TURP and HIFU alone [36,43,44]. However, the lower re-treatment rate in the HIFU/TURP group

at 4% compared with 25% in the HIFU alone group suggests a benefit of TURP prior to HIFU through the removal of calcifications of the transitional zone that would prevent optimal HIFU treatment. Also found was that the rate of urinary tract infections was significantly reduced in patients undergoing the combined TURP/HIFU procedure compared with HIFU alone (11.4% vs. 47.9%, $p \leq 0.001$). [Table 4]

Prediction of HIFU treatment outcome

The prediction of treatment outcome in patients receiving radical prostatectomy is based on the pathological features of the removed prostate gland such as tumor classification, nodal and margin status, and prostatectomy Gleason score. The absence of histological specimens following HIFU necessitates the use of surrogate parameters for treatment outcome. The pretreatment characteristics of disease stage, PSA level and GS at biopsy have been used prognostically in HIFU-treated patients. The results of a series published in 2001 involved 102 patients with T1–T2 disease. At a mean follow-up of 19 months, overall disease-free survival was 66% [42]. Differences in treatment outcome were observed between initial PSA < 10 ng/ml (73% vs. 50%; $p = 0.02$); Gleason score < 6 (81% vs. 46%; $p < 0.001$); and pretreatment sextant biopsy revealing one to four positive samples (68% vs. 40%; $p = 0.01$). Poissonier et al. studied the outcomes of 227 patients, and reported an actuarial 5-year DFSR of 66% [44]. DFSR varied when patients were stratified according to pre-treatment PSA level: The DFSR was 90% with PSA < 4 ng/ml versus 57% and 61% with pretreatment PSA of

4.1–10 ng/ml and 10.1–15 ng/ml, respectively.

Prostate-specific antigen nadir has been evaluated as a predictor of clinical failure following HIFU. In a 6-month study involving 115 patients, failure rates following HIFU were 11% (four out of 36) in patients with a PSA nadir of 0.0–0.2 ng/ml, compared with 46% (17 out of 37) in patients with a PSA nadir of 0.21–1 ng/ml, and 48% (20 out of 42) in patients with a PSA nadir > 1.0 ng/ml. In addition, PSA nadir was strongly associated with both preoperative PSA level and residual prostate volume. The predictive utility of PSA nadir in patients with longer follow-up was reported by Ganzer et al. [47]. Post-HIFU PSA nadir was shown to be significantly associated with treatment failure and DFSR; failure rates during follow-up were 4.5%, 30.4% and 100% for patients with PSA nadirs of ≤ 0.2 ng/ml, 0.21 to 1 ng/ml, and ≥ 1 ng/ml, respectively ($p \leq 0.001$). The actuarial DFSRs at 5 years were 95%, 55% and 0%, respectively, for the three PSA nadir groups ($p \leq 0.001$). These findings suggest that HIFU outcome is improved if a PSA nadir of less than 0.2 ng/ml is achieved.

Extended Indications

In contrast to most published trials of HIFU therapy that report the outcomes in patients with Stage T1-T2 disease or radiation failure, the results of a trial that enrolled 113 patients with Stage T3-T4 disease followed for a median of 4.6 years was presented [64]. The median PSA velocity of this cohort was 0.19 ng/mL/y and the cancer-specific survival was 96.4%. Another study reported the outcomes of 55 men with PSA progression and local biopsy-proven tumor recurrence during definitive

hormonal ablation therapy who received HIFU for hormonal resistant prostate cancer [65]. With a mean follow-up of 21 months, the prostate cancer-specific survival was 87.3%. The results of both studies are impressive and encouraging because this group of patients has a very poor prognosis and a short median survival.

Preliminary results of palliative treatment with HIFU in patients with advanced prostate cancer showed promising findings based on reductions in local morbidity such as rectal compression, infravesical obstruction, hydronephrosis, hematuria, and pelvic pain-syndromes. Unpublished data from several large patient groups ($n > 70$) with Stage T3 and CRPCa with follow-up of 10 years have shown a post-HIFU PSA velocity of 0.19 ng/ml/ year in T3 disease without additional hormone ablation. Local tumor ablation with HIFU has also resulted in a PSA reduction of 80% in CRPCa cases. There was also evidence of a synergistic effect with hormone ablative therapies that was reflected in the delay of onset of hormone resistance [66,10].

Salvage therapy

HIFU can be used as salvage therapy for locally recurrent disease following almost every curative prostate cancer modality, including external radiation, low-dose rate and high-dose rate brachytherapy cryoablation, primary HIFU, biochemically progressing PSA, and after combined pretreatment including radical prostatectomy. One of the factors accounting for the attractiveness of salvage HIFU is related to the very limited treatment options for men with recurrent disease following

curative therapy. According to CaPSURE data [37], 63% of the patients treated with XRT experience disease recurrence. Androgen deprivation therapy was used as salvage therapy in 93.5% of cases, and definitive local therapy in only 3.9% (salvage radical prostatectomy 0.9%, and cryoablation 3.0%). The appeal of salvage radical prostatectomy and cryoablation following local radiation failure is more theoretical in nature; in practice, their use represents a complex procedure associated with very high morbidity rates and procedural costs [9].

Radiotherapy failure

Murat et al. [67] reported the outcomes of 167 men who underwent salvage HIFU for locally radiorecurrent prostate cancer. The results indicate a 73% negative biopsy rate and a 5-year overall survival rate of 84%. Biochemical disease-free survival rates were not reported. No rectal complications were observed, but the urinary incontinence rate was 49.5%, similar to rates reported in salvage radical prostatectomy series. Berge et al. [68] reported the early results of a prospective study of salvage HIFU, and observed a biochemical failure rate of 39.1%. Significantly, the urinary incontinence rate was much lower in their cohort than in the Murat et al. study population, with 17.3% developing either grade II or grade III incontinence. One patient developed a rectourethral fistula.

Gelet et al. also reported the results of salvage HIFU in locally recurrent prostate cancer after external-beam radiotherapy [31]. Among the 71 patients, the mean time of recurrence after external beam radiotherapy was 38.5 months (range 6–120) and the mean

PSA prior to HIFU was 7.7 ng/ml (range 0.5–54 ng/ml). With a mean follow-up of 14.8 months (range 6–86), 80% of patients produced negative biopsies, corresponding to a 30-month actuarial negative biopsy rate of 73%. The actuarial disease-free rate, based on biopsy and PSA response, was 38% at 30 months.

Salvage HIFU represents a viable treatment option for men experiencing recurrence after radiation therapy. Although the tissue alteration from radiation therapy results in a higher postoperative morbidity rate than is seen in primary HIFU therapy alone [9], this does not alter the favorable risk-benefit ratio with the use of salvage HIFU treatment relative to the other available options [67].

Limited experience exists with salvage HIFU following brachytherapy, but it appears that this approach is not associated with a significant increase in complications compared to primary HIFU. It is absolutely necessary to

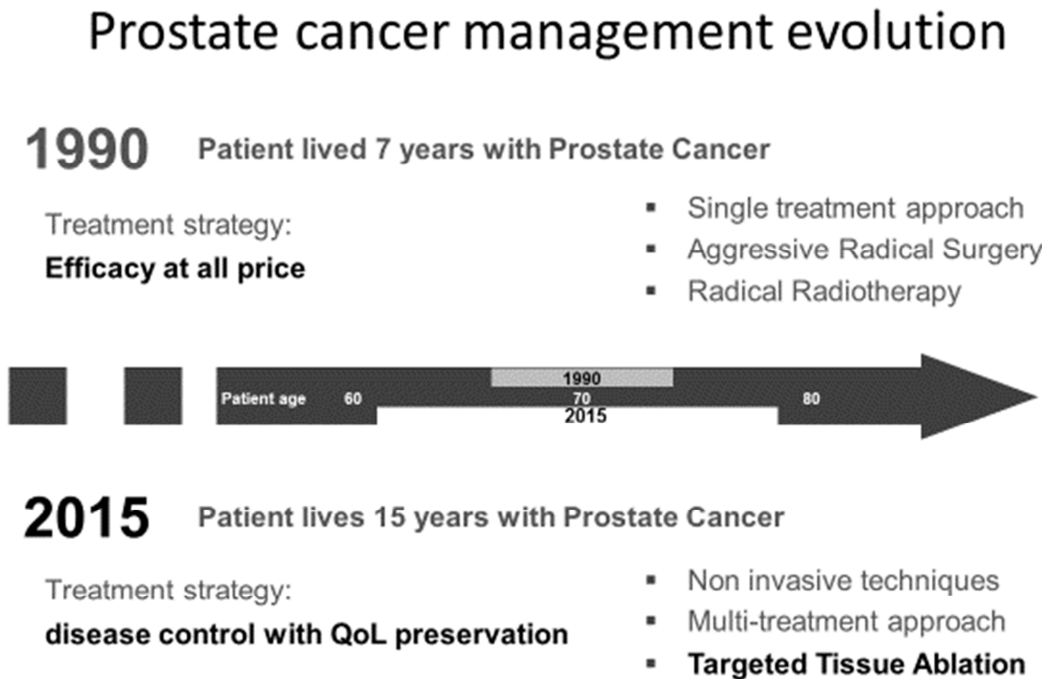
monitor the position of the seeds precisely with MRI before HIFU. There should be no seeds outside the prostate capsule, and especially between rectum and prostate as seeds in these regions would interfere with the direct entry path of the ultrasound [1].

Radical prostatectomy failure

Therapeutic options for local recurrence following radical prostatectomy are limited. HIFU offers a treatment option when local recurrence can be identified through transrectal ultrasound and verified with biopsy. After a small number of patients with post-prostatectomy failure were treated with HIFU, the treated areas showed negative biopsies in 77 % of cases. The PSA nadir averaged 0.2 ng/ml and 66 % of patients achieved a PSA Nadir <0.5 ng/ml. During follow-up of 5 years, 91% of the patients showed no biochemical progression [66,69].

[Figure 6] shows the PSA course of a patient who underwent radical prostatectomy and subsequent HIFU after 6 years.

Figure 6: Intraoperative, 3 dimensional, real time, transrectal ultrasound for visual treatment planning and control on control screen



Salvage radical prostatectomy following HIFU failure

Radical prostatectomy was performed in our institution in 7 patients experiencing failure following treatment with HIFU between 1996 and 2000. Prior treatment with HIFU created severe fibrotic adhesions between the rectum and Denovillier's fascia, and although this made salvage radical prostatectomy more technically demanding, it did not result in higher morbidity compared to a standard prostatectomy. The authors attribute these cases of HIFU failure to the incomplete treatment of larger sized prostate glands before the routine use of TURP [1].

Sonablate HIFU for PCa salvage therapy

All patients with a mean age of 65 had been diagnosed with an organ confined and histologically confirmed PCa following EBRT. Preoperative PSA level was 7.73 ng/mL. Patient follow-up was 7.4 (3–24) months. Half of the patients had a PSA level of <0.2 ng/mL at last follow-up. Three patients had metastatic disease whilst another two had only local, histologically confirmed, failure. Another four patients showed evidence of biochemical failure only. Overall, 71% had no evidence of a disease following salvage HIFU.

Side-effects included stricture or intervention for necrotic tissue in 11 of the 31 patients (36%), urinary tract infection or dysuria syndrome in eight (26%), and urinary incontinence in two (7%) patients. Recto-urethral fistula occurred in two patients.

The authors conclude that salvage HIFU is a minimally invasive procedure that can achieve low PSA nadirs and better cancer control in the short term, with comparable morbidity to other forms of salvage treatment. [70]

Focal and partial HIFU therapy

Over the past 25 years, the average life expectancy of men has increased almost 4 years while the average age of prostate cancer diagnosis has decreased 10 years [63,64]. Prostate cancer is also detected at a much earlier stage than two decades ago, with the majority of patient candidates for curative whole-prostate therapy. A sizable number of patients with small-volume monofocal tumor are being over-treated with whole-gland approaches that surgically remove or irradiate the entire prostate, and a great need exists for a focal approach to the treatment of small-volume single-lobe prostatic tumor.

The goal of focused HIFU therapy is to provide a partial treatment that is limited to the tumor and a safety margin in patients with noninvasive, monofocal, localized prostate cancer. Such an approach would preserve normal genitourinary function while treating the malignancy with sufficient efficacy [65,66]. Two focused treatment approaches with HIFU are currently being evaluated, a precise focal therapy that treats a maximum 30% of prostate volume without TURP, and a potency-

preserving partial therapy that excludes the contralateral lobe/capsule and neurovascular bundle by sparing 5 mm of tissue on the contralateral lobe and treating up to 90% of the prostate [21].

A critical issue in focused prostate cancer therapies concerns appropriate patient selection by eliminating those with bilateral multifocal tumor. Effective tumor visualization and mapping is essential in achieving this objective. Transperineal 3D mapping biopsies are more accurate than transrectal ultrasound-guided biopsies in excluding patients with clinically significant disease outside the areas to be ablated, and 3D biopsy has been found to increase Gleason scale gradings relative to conventional biopsy [67].

Tumor localization within the prostate of the so-called “index lesion” on which to focus therapy, and post-therapy monitoring is another important concern. The variable sensitivity of MRI [68,69] has prompted the investigation of other functional imaging techniques. Results suggest that vascular information from dynamic contrast-enhanced MRI or diffusion-weighted MRI combined with metabolic data from magnetic resonance spectroscopic imaging may greatly improve the accuracy in defining and staging prostate cancer especially in the ventral part of the prostate. [71,72]. There are also issues related to how best to monitor patients following treatment [21]. Despite these issues, the results of focused HIFU therapy are highly anticipated.

Immunologic response after HIFU therapy

Progress has been made in developing an effective immune strategy for treating prostate cancer. A number of

immunotherapy regimens are being studied including immunomodulatory cytokines/effectors, peptide and cellular immunization, viral vaccines, dendritic cell vaccines, and antibody therapies. Immunomodulatory agents, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), Flt3 ligand, and IL-2, have been used to stimulate the immune system to generate an antitumor response against prostate cancer. However, the encouraging early preclinical results have not been extended into the clinical setting.

Several recent studies have examined the potential of HIFU to initiate an immune response. Wu et al. studied the effect of HIFU on systemic antitumor immunity, particularly T lymphocyte-mediated immunity in cancer patients [80]. HIFU was used to treat 16 patients with solid malignancies, including osteosarcoma, hepatocellular carcinoma and renal cell carcinoma. HIFU led to a significant increase in the population of CD4+ lymphocytes and the ratio of CD4+/CD8+ in circulation. The authors concluded that HIFU could enhance a systemic anti-tumor cellular immunity in addition to local tumor destruction in patients with solid malignancies.

The same research group investigated whether tumor antigens expressed on breast cancer cells could be preserved after HIFU treatment [81]. Primary lesions in 23 patients with biopsy-proven breast cancer were treated with HIFU, then submitted to modified radical mastectomy. Breast cancer specimens were then stained for a variety of cellular molecules, including tumor antigens and heat-shock protein 70 (HSP-70). A number of tumor antigens were identified that could provide a potential

antigen source to stimulate antitumor immune response.

It has been suggested that endogenous signals from HIFU-damaged tumor cells may trigger the activation of dendritic cells, playing a critical role in a HIFU-elicited antitumor immune response. A mouse model bearing MC-38 colon adenocarcinoma tumors was treated with thermal and mechanical HIFU exposure settings. Results showed that HIFU elicited a systemic anti-tumor immune response that was related closely to dendritic cell activation, and that dendritic cell activation was more pronounced when tumor cells were mechanically lysed by HIFU. [82,83].

Conclusion

Prostate cancer is now diagnosed at an earlier disease stage in younger patients with a longer life expectancy than it was 30 years ago before widespread PSA screening. As a result, the window for curative therapy has been extended, and with patients living longer after definitive therapy, a greater emphasis is now placed on treatment-related morbidity and its impact on patient quality of life. **[Figure 6]**

Local recurrence occurs in 10–50% of patients regardless of curative approach, and the treatment of prostate cancer has evolved from a singular treatment to a multimodal, sequential approach that greatly accommodates the use of minimally invasive therapies such as HIFU. Decreasing resources for medical care are adding to the urgency for the development and clinical use of cost-effective non-invasive therapies.

Since 2000, standardized PCa therapy with CE market Ablatherm® has progressed from an experimental therapy to a therapy under long-term investigation for primary treatment of local prostate cancer and salvage therapy after radiation failure. Preliminary data suggest that HIFU may also be effective in the treatment of focal and incidental prostate cancer, as adjuvant therapy in T3/T4 disease, and in non-metastatic castration

resistant prostate cancer. This range of indications across the spectrum of prostate cancer appears to be a unique attribute of HIFU [19,31]. Additionally, HIFU can be repeated in cases of local recurrence, which is not an option with other treatment modalities for localized prostate cancer such as cryosurgery and brachytherapy.

The efficacy in cancer control of HIFU and other focal therapies will depend less on the development of therapeutic tools than on diagnostic technologies that can more accurately image and localize small but aggressive tumor lesions and multiple foci. When this goal is reached, HIFU will be the ideal therapeutic tool for focal prostate cancer treatment. To achieve this goal, several advancements in imaging technologies are being investigated for use with HIFU, including MRI, ultrasound and picture fusion of TRUS, mp MRT and fusion biopsies.

With over 20 years of clinical use in over 40,000 patients, prostate cancer is the leading application for HIFU, followed by the treatment of uterus

fibromas and myomas. Other applications for HIFU being investigated include breast cancer, brain cancer, thyroid cancer, thrombolysis and the use of HIFU as a drug delivery device.. The clinical future of HIFU will focus primarily on the treatment of soft tissue pathologies directly below the body surface with targeting volumes less than 20 cc (prostate, breast and thyroid) due to the limited penetration depth of HIFU. Drug delivery involving the accumulation of drugs in defined organ regions or genetic manipulation is anticipated to be a promising area of future HIFU research, and HIFU-provoked induction of immune response as a supportive therapy is under investigation [1].

The use of HIFU should not be viewed as a substitute or replacement for classical therapy, but instead as a therapeutic first choice in monofocal well-differentiated disease. The initial use of HIFU can help postpone the need for invasive therapies associated with greater morbidity such as surgery or radiation, allowing the patient a longer period without the risk of living with treatment-related genitourinary side effects [84]. Transrectal HIFU should be given serious consideration as a curative therapy in localized disease as well as a palliative adjuvant therapy in all other tumor stages. Ongoing improvements in imaging technologies are expected to further enhance the efficacy of HIFU. [85]

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