Current Status of High-intensity Focused Ultrasound for Prostate Cancer: Technology, Clinical Outcomes, and Future

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Based on a review of recently published articles, we evaluated the current status of high-intensity focused ultrasound (HIFU) as a primary treatment option for localized prostate cancer and as a salvage therapy when radiation has failed. With mid- and long-term progression-free survival rates around 70%, negative postoperative prostate biopsies almost 90%, and an excellent morbidity profile, primary HIFU appears to be a valid alternative to active surveillance protocols in low-risk patients and standard therapies in patients with life expectancies of 10 or fewer years. Moreover, HIFU has a considerable potential for local-only recurrence after radiation failure. HIFU is a recent technology, and many improvements will undoubtedly expand its future indications and use for the management of prostate cancer.

Introduction

With the continuous efforts for early detection of prostate cancer based on prostate-specific antigen (PSA) screening, the number of men diagnosed with early-stage prostate cancer is increasing [1,2]. Indolent cancers may represent a large part of these newly diagnosed patients [3]. With the population aging and the incidence of low-grade prostate cancer increasing, the management of localized prostate cancer with surgery or radiation may not be the appropriate strategy. Adolfsson [4] demonstrated that most men can live with prostate cancer for a very long time. However, advising all men to undergo watchful waiting may be wrong, even in the elderly [5]. Therefore, there is a search for new minimally invasive alternatives to standard treatment options for the treatment of prostate cancer.

High-intensity focused ultrasound (HIFU) appears to be an attractive and promising therapy. To date, HIFU has been assessed for its potential role in both the treatment of organ-confined disease in patients who would otherwise not have been offered surgery and the treatment of local-only recurrence following failed radiation.

This report reviews current published articles concerning HIFU in prostate cancer management to define its place in the clinical practice.

High-intensity Focused Ultrasound: The Technology

Principles

Ultrasound is a vibration produced by a crystal or transducer at a frequency inaudible to human ears. Ultrasonic waves deposit energy as they travel through tissues. Ultrasound for imaging is harmless due to a low ultrasonic intensity, thus resulting in an insignificant energy deposit. With HIFU, wave intensity is increased to a sufficient level to generate a large amount of deposited energy causing tissue destruction. Moreover, the ultrasonic wave is focused, leading to a converging beam that will result in the creation of a small volume of ablation, the elementary lesion. This elementary lesion is reproducible and its size is a function of main sonication parameters (acoustic intensity, duration of exposure, crystal geometry). The destruction of large volume requires the juxtaposition of many elementary lesions.

The destructive effects of HIFU may be organized into two major mechanisms: heat and cavitation [6••]. At the focal point, the acoustic energy delivered causes a rapid and intense rise in temperature (> 85°C), resulting in irreversible damage. Cavitation is the result of ultrasound interaction with the microbubbles located in the exposed tissue. This interaction may lead to the oscillation of these microbubbles, violent collapses, and dispersion of energy

that enhances the tissue ablation. Both complementary mechanisms lead to the destruction of the exposed cells by the phenomenon of coagulative necrosis [7].

Standard ultrasound imaging demonstrates in real-time the HIFU-induced lesions as hyperechoic areas, but their occurrence and extent are not always accurately defined. Gadolinium-enhanced MRI is accurate and may be the best way to determine the tissue damage extent during post-HIFU follow-up, but cannot predict histologic results [8,9••]. Whereas HIFU treatment is now performed under transrectal ultrasound guidance, MRI with real-time temperature monitoring will be available in the future [10].

HIFU devices

Two HIFU devices are available for the treatment of prostate cancer: Sonablate 500 (Focus Surgery, Indianapolis, IN) and Ablatherm Integrated Imaging (EDAP-TMS SA, Vaulx en Velin, France). Both devices are currently used in Europe and Japan, but not yet approved by the US Food and Drug Administration for prostate cancer indications.

The technology of both devices is basically the same but there are several differences. The Ablatherm device uses two transducers for imaging (7.5 MHz) and treatment (3 MHz), whereas the Sonablate 500 has a single transducer (4 MHz) for both functions. Sonablate has multifocal length transducers, whereas the Ablatherm device has a unique focus point at 40 mm.

Depending on which device is used, patients are either placed on their backs with legs elevated in a dorsal lithotomy (Sonablate) or laid on their right side on a specific bed (Ablatherm). With the Sonablate device, the treatment is performed in two or three layers, moving from the ventral to the dorsal part of the prostate. A single treatment algorithm is used in which the power can be manually adjusted depending on B-mode ultrasonic changes observed during the procedure [11]. The surgeon's constant presence is necessary to ensure that what has been planned is performed.

With the Ablatherm device, once the prostate is ultrasound-scanned and three-dimensionally reconstructed, the surgeon plans the treatment on the screen, slice by slice, from the apex to the bladder neck. Usually the prostate is divided into two to three volume boundaries [12]. The computer-driven treatment is automatically delivered according to the planned surgeon's instructions. Three treatment algorithms have been defined according to the clinical use (primary procedure, HIFU retreatment, radiation failure).

Both devices offer real-time monitoring of the treatment using ultrasound. Both devices provide active cooling of the rectal wall during the treatment to prevent rectal complications. The Ablatherm device provides additional safety features such as a safety ring that stabilizes the rectum wall during the procedure, a permanent control of the distance between transducer and rectal wall and a patient motion detector.

Primary Procedure

Outcome measures

HIFU has been applied in most series [11–16,17••,18–22,23••] and is usually recommended [24] for patients with localized prostate cancer, with cT1-T2 Nx-0 M0 prostate cancer who are not candidates for radical prostatectomy (life expectancy ≤ 10 years), or in those who refuse to undergo surgery.

In 1995, Madersbacher et al. [25] used the Sonablate 200 in 10 patients with localized prostate cancer. In 1996, Gelet et al. [26] reported a preliminary experience with an Ablatherm prototype in almost the same indications. From these first papers to the contemporary series, several publications with both devices have confirmed the HIFU efficacy as a primary procedure in the aforementioned indications with short- and mid-term results [11–22].

End points available in these series are either biochemical, disease-free survival rates with highly variable definitions of PSA end points, thus making comparisons between series and devices hazardous; biopsy data; or a combination of both. On the basis of combined pathologic or biochemical outcomes, the estimated 5-year, disease-free survival rate was reported between 66% and 78% (Table 1).

Poissonnier et al. [17] followed up 227 patients with clinical T1-T2 prostate cancer NxM0 by serial PSA measurements and biopsy. More than one HIFU session was performed for 42% of the patients, with 38% and 4% receiving two and three or more sessions, respectively. Mean follow-up was 27.5 ± 20 months. Progression was defined as any patient with positive biopsies or a PSA less than 1 ng/mL with three consecutive rises. At 5 years, the estimated progression-free survival (PFS) rate was 66%. There was a significant inverse relationship between PFS and PSA level (90%, 57%, and 61% when PSA < 4.1 ng/mL, 4.1–10 ng/mL, and > 10 ng/mL, respectively). Regarding 137 patients treated and followed in a similar manner, another team reported a 5-year PFS rate of 64% and 44% when the biochemical progression was defined as a PSA rise greater than 0.4 ng/mL or greater than 0.2 ng/mL, respectively [14]. Uchida et al. [20] reported an estimated 5-year outcome of 78% with Sonablate based on PSA stability in a population of 181 patients, with 52% having received a hormonal therapy prior to HIFU therapy.

The first unique report on long-term outcome of up to 8 years was recently published coming from a multicenter analysis of 142 low- and intermediate-risk patients [23]. The series included patients with a minimum of 5 years of follow-up treated with prototypes or first generation of Ablatherm devices between 1997 and 2001. The mean follow-up was 6.4 ± 1.1 years. Median PSA nadir was 0.16 ng/mL achieved at a mean of 4.9 months. The estimated biochemical failure-free survival rates (SR) at 5 and 7 years were 77% and 69%, respectively, using the last PSA greater than nadir plus 2 ng/mL as the definition for biochemical progression.

Table 1. Outcomes following high-intensity focused ultrasound

Study	Device	Patients, *n*	Clinical stage	Mean pre-HIFU PSA, *ng/mL*	Mean or median follow-up, *mo*	Negative biopsies, %	Mean or media PSA nadir, *ng/mL*	DFSR, *criteria*
Uchida et al. [13]	S	63	T1c-2b N0 M0	11.2	22.3	87	0.5	75% at 3 y (ASTRO 1997)
Blana et al. [14]	A	146	T1-2 N0 M0	11.3	22.5	93.4	0.07	84% at 22 mo (PSA < 1 ng/mL)
Chaussy et al. [15]	A	271	T1-2 Nx/0 M0	8.3	14.8	84.6	0	82.1% (ASTRO 1997)
Lee et al. [16]	A	58	T1-2 Nx/0 M0	10.9	14	–	0.2	69% at 14 mo (ASTRO 97 + biopsies)
Poissonnier et al. [17••]	A	227	T1-2 Nx/0 M0	6.99	27	86	0.1	–
Vallancien et al. [18]	A	30	T1-2 Nx/0 M0	7	20	83	0.9	–
Thuroff et al. [19]	A	402	T1-2 Nx/0 M0	10.9	13.1	87.2	0.6	
Blana et al. [23]	A	140	T1-2 Nx/0 M0	7	76.8	86.4	0.16	69% at 7 y (ASTRO 2005)

A—Ablatherm Integrated Imaging (EDAP-TMS SA, Vaulx en Velin, France) ; ASTRO—The American Society for Therapeutic Radiology and Oncology; DFSR—disease-free survival rate; HIFU—high-intensity focused ultrasound; PSA—prostate-specific antigen; S—Sonablate 500 (Focus Surgery, Indianapolis, IN).

Cancer local control achieved by negative sextant biopsies in most series was observed between 83% and 93.4% (Table 1). The rates of local control have increased dramatically from 50% at 8 months in the early studies [26], approaching 90% in the most recent series [13–16,17••,18,19].

An ideal result with HIFU entails the achievement and maintenance of an undetectable PSA. Studies have shown a continuous decrease in the PSA nadir with technology evolution and device improvement. In contemporary series, a PSA nadir less than 0.5 ng/mL is usually obtained between 61% [27] and 84% [14,17••] of the cases with the Ablatherm device. It was reported to be less than 0.2 ng/mL in 32% [21] with the Sonablate, whereas it increased to 84% when a visually directed HIFU protocol was applied [11]. In most cases, the PSA nadir is reached within 6 months following the procedure, making it possible to have early feedback on treatment efficacy. Many studies have demonstrated that the PSA nadir significantly predicts HIFU success [16,21,28]. Lee et al. [16] proposed to carefully monitor those patients in whom the PSA nadir has not dropped below 0.5 ng/mL. Blana et al. [23••] reported on a long-term series a PSA nadir less than or equal to 0.5 ng/mL in 68.4% of patients and demonstrated a significant inverse relationship between the 5-year disease-free survival rate and the PSA nadir, with 83% being observed in patients achieving a PSA nadir of 0.5 ng/mL or less versus 34% when the nadir is greater than 0.5 ng/mL. Uchida et al. [21] also demonstrated unfavorable outcomes when the PSA nadir was greater than 0.2 ng/mL. In this series, a PSA nadir of greater 0.2 ng/mL was associated with four times greater risk of HIFU failure as defined by positive biopsy. These findings were recently confirmed by Ganzer et al. [27] who noticed that when the PSA nadir was under 0.2 ng/mL the treatment failure rate was 4.5% whereas it increased to 30.4% and 100% when PSA was 0.21–1 ng/mL and greater than 1 ng/mL, respectively [28]. If an adequate PSA nadir is not reached within 6 months, HIFU is probably failing and an additional HIFU session or a change in therapy should be considered.

Low-risk patients as defined by d'Amico's classification (PSA < 10 ng/mL; Gleason score < 7; and a number of sextant biopsies < 5) have been shown to be good prognostic factors [17••,19,20,29].

Contraindications

Some relative or absolute contraindications need to be excluded before considering HIFU.

Accessibility is a main contraindication of HIFU because it is applied via a transrectal approach. Pathologic or anatomic conditions impairing the probe introduction through the anus or displacement in the rectum are potential contraindications. Therefore, local rectal conditions should be carefully checked during the rectal examination if possible or at least with a transrectal ultrasound.

Major calcifications should be considered as possible contraindications unless TURP can remove them. The volume of the prostate is also a major limitation, mostly in relation with commercialized devices available, but not the technology itself. Therefore, prostate volume greater than 40 mL should be excluded. Many options are possible to reduce prostatic volume. The use of hormonal deprivation and transurethral resection of the prostate (TURP) [15] before HIFU can be helpful. Uchida et al. [22••] demonstrated that stopping the use of a neoadjuvant androgen suppression by the time of the HIFU procedure did not affect the chance of being disease free on prostate biopsies 6 months after the treatment.

Complications

Side effects following HIFU as a primary procedure have been extensively described in many articles (Table 2) [11–16,17••,18–21,22••,23,26,27.]

A common and usually transient complication is acute urinary retention in between 0.3 and 8.6% of cases. In the immediate postoperative course, edema induced by the treatment may increase the volume of the prostate up to 30% of its initial volume, thus resulting in obstructive symptoms and subsequent retention in some cases. A symptomatic treatment with recatheterization for a few days is usually enough. A TURP prior to HIFU has been shown to significantly decrease the retention rate and the catheterization period [18].

Sloughing is the passage of necrotic debris of the coagulated adenoma. When sloughing occurs (9%–14%), usually in the mid-term postoperative period, the patient experiences frequency, dysuria, and occasionally retentive symptomatology. Sloughing can be associated in some rare cases with longer-term problems such as incontinence, stricture, and calcifications of the prostatic urethra. Sloughing can be usually managed conservatively with a symptomatic treatment but in exceptional cases may require a transurethral debridement to remove necrotic debris.

Another frequent complication is bladder outlet obstruction occurring in 3.6% to 22% of patients. Without TURP, it was reported in 22% of cases and required intermittent dilatations [20]. The combination of TURP and HIFU has significantly reduced the stricture rate with the Ablatherm device [15].

Urinary infection occurred in up to 13.8% of patients and should be treated with appropriate antibiotics. Hyperleukocyturia is extremely frequent following HIFU. This issue does not need to be treated except if an associated infection is present.

Urinary incontinence was reported in 0.6% and 15.4% of patients. However, it tended to decrease with the last generations of HIFU devices due to a better definition of the prostatic apex, thus resulting in a better preservation of the urinary sphincter.

The reported impotence rate ranged from 20% to 49.8%. However, the absence of validated erectile function questionnaire use and the variable evaluation of potency between series make it almost impossible to compare both

Table 2. Adverse effects following primary procedure

Study	Urinary retention, %	Stress incontinence, % *(grade 1/2/3)*	BOO, %	UTI, %	Impotence, %	Fistula, %	Sloughing, %	Perineal pain, %
Chaussy et al. [15]	–	15.6* (9.1/6.3/0) vs 6.9 (4.6/2.3/0)	–	47.0 vs 11.4	35.9	0	–	–
Lee et al. [16]	0.3	16 (16/0/0)	0	–	–	0	14	–
Poissonnier et al. [17••]	–	13	12	2	–	0	9	3
Vallancien et al. [18]	6	3	0	10	32	0	–	0
Thuroff et al. [19]	8.6	13.1 (10.6/2.5/0)	3.6	13.8	–	1.2 (0.5†)	–	–
Uchida et al. [20]	0.6	0.6 (grade 1)	22	6	20	1	–	–
Blana et al. [23]	–	–	–	7.1	54	0	–	5.7

*High-intensity focused ultrasound (HIFU) vs HIFU + transurethral resection of the prostate.
†Since the addition of the cooling system.
BOO—bladder outlet obstruction; UTI—urinary tract infection

devices. Omitting elementary lesions on the lateral edges of the prostate to preserve an untreated area close to the neurovascular bundles and opposite the suspected cancer location has led to nerve-sparing HIFU therapy. Erections were preserved in 69% of the 26 pre-HIFU potent patients, for which a preservation was possible in the series reported by Poissonnier et al. [17••]. If nerve-sparing HIFU has shown good results in preserving potency, this decrease in erectile dysfunction rate must be balanced with a higher rate of retreatment [30,31].

Uretro–rectal fistula have significantly decreased with the improvement of devices and treatment procedures. In large series, it occurred between 0% to 1.2% of patients (Table 2). In fact, most fistula occurred in the early stage of the technique. Moreover, the addition of safety features including the cooling system and the rectal wall recognition has dramatically decreased the incidence of fistula. Thuroff et al. [19] reported a fistula rate of 1.2% and 0.5% without and with the addition of the cooling system, respectively.

The recent reported long-term results suggest an effective cancer control in patients with low- or intermediate-risk localized prostate cancer, making HIFU an ideal treatment option for patients who would not be suitable for surgery. The favorable morbidity profile should also persuade clinicians to consider more patients for this curative treatment option. However, because outcome data from randomized controlled trials are not yet available for HIFU, the assessment of its exact potential role in the management of localized prostate cancer remains difficult. For this reason we believe that patients who are offered or who elect this treatment should be clearly informed of the pros and cons of HIFU therapy. We believe this treatment should be reserved for patients with a life expectancy of 10 or fewer years and contraindicated for surgery, whatever the reasons.

Retreatment

In some cases, HIFU will have to be repeated due to an incomplete or failed treatment. The major advantage of HIFU over other treatment options is that it can be repeated with no limited number of sessions or maximal dose. Up to five sessions have been performed for a single patient [32]. The retreatment rate is reported between 1.2% and 1.47%, with no difference between devices [17••,19,20,23].

The safety of repeated sessions has recently been questioned [33]. In a series of 223 consecutive patients, Blana et al. [32] reported on single and multiple HIFU treatments with regard to side effects. The goal of this study was to determine whether it was safe to offer retreatment after a primary HIFU treatment failure. They found no increase in morbidity (urinary infection, pelvic pain, bladder outlet obstruction, uretro–rectal fistula) except for incontinence and erectile dysfunction. However, the risk of incontinence and impotence related to additional HIFU sessions remained low even if they were significantly increased by 12.2% and 55%, respectively [33].

Salvage High-intensity Focused Ultrasound

Outcome measures

After external beam radiation therapy (EBRT) or brachytherapy for localized prostate cancer, between 20% and 50% of patients may experience PSA failure [34–36]. Many will harbor occult micrometastases at the time of PSA failure, but approximately a third will have a true local recurrence that can be potentially cured with a local salvage therapy. No consensus has been reached regarding the optimal management after radiation failure. Two years between radiation and prostate biopsies in case of rising PSA are advocated. If suspected, local recurrence has to be histologically proven by biopsy and any distant metastasis have to be ruled out. The imaging workup should include at least a bone scan, a pelvic MRI, and a thorax and abdominopelvic CT. Fluorocholine positron emission tomography/CT has been shown to improve the detection of metastases [37]. Recently, the use of lymphotropic supramagnetic nanoparticles in association with pelvic MRI has demonstrated a 90% sensitivity to detect lymph node metastases and may be the future diagnostic tool in this particular situation [38].

HIFU has been reported to be a valid salvage treatment option in this particular indication. Chaussy et al. [38] treated 36 patients with biochemical relapse and a biopsy-proven local recurrence. With a mean follow-up of 13.9 months, 74% had negative post-HIFU biopsies and 65% reached a PSA nadir under 0.5 ng/mL.

A retrospective analysis of 167 patients with a local-only prostate cancer recurrence after EBRT was also presented by Murat et al. [39]. All patients had a biopsy-proven local recurrence with no detectable metastasis. The mean follow-up was 17.5 months (range, 3–121). Local control was achieved with negative control prostate biopsies in 73% of cases. The median PSA nadir reached 3 months following the procedure was 0.19 ng/mL. Disease-free survival (DFS) was defined as any patient with negative prostate biopsy and a last PSA under nadir plus 2 ng/mL and no adjuvant therapy. When using this definition, the estimated 5-year DFS rate was inversely related to the initial patient risk group as defined by D'Amico with 51%, 30% and 9% for low, intermediate and high-risk patients, respectively. The poor results obtained for high-risk patients were explained by the undiagnosed micrometastatic disease by the time of the local relapse recognition emphasizing the importance of early referral and complete imaging evaluation.

Positive prognostic factors for salvage HIFU after radiation failure included initial low- or intermediate-risk disease, whereas the pre-HIFU characteristics of the recurrence seemed to have no value [40].

Complications

Complications after salvage HIFU in post-radiation patients are as significant as with any other salvage treatment options. Moreover, morbidity after salvage HIFU is much more important than when HIFU is applied on a nonirradiated gland. In 2002, a specifically designed treatment algorithm was calculated with the Ablatherm device to reduce the complication rates. These post-radiation treatment parameters generated a 4s-shot, with 95% of the intensity taking into account the particular sensitivity to HIFU of irradiated prostate including its lesser vascularization. With this new set of post-radiation treatment parameters, the importance of most complications have decreased. In the series by Murat et al. [39], the occurrence of fistula was reported to be 0% with the specific treatment parameters and 7% with the standard parameters. Half of their patients presented with urinary incontinence, including 32% with grade 2 or 3 incontinence. The incidence of grade 3 incontinence and the subsequent artificial urinary sphincter implantation were significantly reduced with the specific post-radiation parameters when compared with standard parameters: 40% versus 28% and 20% versus 6%, respectively. Sloughing was reported in 8% of the cases.

Salvage HIFU is an effective treatment option after external beam radiotherapy failure. Salvage HIFU compares favorably with other available salvage therapies with regard to the ratio of efficacy and morbidity. Therefore, HIFU appears to be a viable treatment option for this particular indication. However, patient selection is absolutely mandatory in order to choose patients who may benefit from this salvage treatment option.

Future of High-intensity Focused Ultrasound

HIFU clearly has a role for localized prostate cancer management and is a viable therapeutic option for radiation failure. Refinements in HIFU devices and imaging will continue to advance this treatment modality.

Advances in imaging technologies will play an important role in the development of future HIFU devices. MRI-guided thermotherapy of the prostate has been successfully performed in dogs [40]. An MRI-compatible, focused prototype for endorectal prostate treatment has been recently presented [41]. It is likely that an MRI-compatible transrectal HIFU device will be available in the future allowing tumor localization just before the treatment, real-time monitoring of the delivered thermal dose with MRI thermometry, and finally evaluating the heated volume at the end of the HIFU therapy.

Exciting findings showing the synergistic effects of HIFU and chemotherapy have been reported. Paparel et al. [42] demonstrated a significant inhibition in AT2 adenocarcinoma growth in a rat model with the combination of HIFU and docetaxel that was not present when using one or the other treatment option alone [43]. If these results are confirmed in human trials, the combined therapy with *HIFU and docetaxel may be useful for patients with high-risk prostate cancer.*

The use of the Ablatherm device is being studied for high and locally advanced stages of prostate cancer. Ficarra et al. [12] reported the short-term outcome in 30 patients with high-risk prostate cancer according to D'Amico's classification treated by HIFU and adjuvant 3-year hormonal therapy with luteinizing hormone-releasing hormone (LHRH) analogue blockade. Positive sextant prostate biopsies 6 months after HIFU and a total PSA level greater than 0.3 ng/mL were considered the oncologic end points. At 1 year, three (10%) patients had a PSA level greater than 0.3 ng/mL but less than 1 ng/mL. All of them, with four additional patients, had positive biopsies 6 months after the procedure for a total of 23%. Although promising, these results are preliminary and cannot be compared with randomized trials available using external beam radiation and LHRH agonists. Moreover, a larger population with a longer follow-up is required to assess the oncologic efficacy of such a combination in locally advanced or high-risk prostate cancer.

Finally, prostate cancer has been recognized to be a multifocal disease. Advances in imaging and biopsy techniques including saturation biopsies enable a more accurate and reliable diagnosis of cancer stage and make possible future protocols for focal HIFU therapy.

Conclusions

HIFU technology is routinely used for prostate cancers and is a technologically advanced minimally invasive therapy for these indications. Promising outcomes using HIFU as a primary procedure for localized prostate *cancer in patients unsuitable for surgery or as a salvage* therapy after failed radiation combined with an excellent morbidity profile will ensure the role of HIFU in prostate cancer management. Moreover, device improvements and imaging developments may place HIFU on the front line of minimally invasive treatment options for prostate cancer management.

Disclosures

No potential conflicts of interest relevant to this article have been reported.

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