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New Orleans 1999.

*HIFU technology shows promise  
as an alternative to radiation  
therapy for patients with  
localized prostate cancer.*

# High-Intensity Focused Ultrasound (HIFU) for Prostate Cancer

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**Background:** *The growing interest in high-intensity focused ultrasound (HIFU) is mainly due to its potential applications as a minimally invasive therapy. HIFU has been assessed for its role in the treatment of localized prostate cancer in patients who otherwise would not have benefited from surgery and in local recurrences after radiation failure.*

**Methods:** *Relevant information on HIFU treatment was identified through a MEDLINE search using specified terms. Papers that presented original outcomes were included in the present review.*

**Results:** *High biochemical efficacy, excellent tumor local control and favorable mid-term oncological data with a low morbidity rate have been proven in many series of patients.*

**Conclusions:** *Although HIFU is a recent and emerging technology, it has been well studied and developed to a point that HIFU will undoubtedly be an effective alternative to radiation therapy.*

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**Abbreviations used in this paper:** HIFU = high-intensity focused ultrasound, MRI = magnetic resonance imaging, TURP = transurethral resection of the prostate, PSA = prostate-specific antigen.

## Introduction

The number of men diagnosed with prostate cancer is increasing throughout the world.<sup>1</sup> Among these newly diagnosed prostate cancer cases, 70% are organ-confined and may be suitable for a local, potentially curative therapy. Radical prostatectomy and radiotherapy remain the primary treatments for patients with localized prostate cancer. On one hand, these therapies are not free of significant complications and risks. On the other hand, some patients are not suitable for major surgical procedures or cannot tolerate radiation therapy because they have comorbid medical conditions or have already been treated earlier in life. Thus, the quest continues to find a reliable alternative to open surgery

or radiation therapy that is as minimally invasive as possible. Of the several new therapeutic options now available, high-intensity focused ultrasound (HIFU) appears to be an attractive and promising therapy in the treatment of prostate cancer.

The ability of HIFU to destroy tissues was established in 1944,<sup>2</sup> but it took many decades and the advent of ultrasound and magnetic resonance imaging (MRI) to develop surgical applications using an extracorporeal approach for the destruction of deep tissues without any skin incision. Although many experimental and clinical applications have been reported in the literature for the treatment of cancer, this article focuses on HIFU and prostate cancer.

## Methods

We searched the MEDLINE database for publications containing any combination of “HIFU,” “focused ultrasound,” “prostate,” and “prostate cancer.” Abstracts resulting from this search were reviewed and full manuscripts were retrieved and reviewed if they contained information regarding biochemical and/or biopsy results of patients who underwent HIFU as a definitive local therapy for prostate cancer. We limited our search to papers published between 2000 and 2007. Review articles, double citations, and updated articles of previously published papers were excluded from this review.

## HIFU Principles

Ultrasound is a vibration delivered by a transducer with a frequency higher than a human can hear. Ultrasound waves deposit energy as they travel through tissues. For imaging purposes, this deposited energy is insignificant. However, by increasing the intensity of the waves and focusing them on a single point, HIFU deposits large amounts of energy into tissues, thus resulting in their destruction.

Two mechanisms of tissue damages are involved: thermal effect and cavitation.<sup>3</sup> The thermal effect is associated with the absorption of ultrasound energy into the tissue, which is converted into heat. In the right conditions, the temperature within sonicated tissue will rise to a level sufficient to induce irreversible damages. Sharp increases in temperature up to 70°C to 100°C can be achieved in a few seconds with each pulse.<sup>3</sup> The cavitation mechanism is the result of the interaction of ultrasound and micro-bubbles in the sonicated tissue. This interaction may lead to oscillation of these micro-bubbles, violent collapses, and dispersion of energy that enhances tissue ablation.

Both of these mechanisms lead to the destruction of the cells by a coagulative necrosis.<sup>4</sup>

## HIFU Technology

The ultrasound transducer is characterized by its operating frequency, geometry, and physical dimensions. Current transducers for prostate applications use single-focus transducers that are moved mechanically.

During HIFU, a reproducible and small volume of ablation is created for each pulse of energy. The geometry of the elementary lesion is an ellipsoid whose size is function of the transducer geometry. The treatment of the target tissue is accomplished by adding many small volumes of ablation until the entire volume has been ablated.

The main sonication parameters are acoustic intensity, duration of exposure, the on/off ratio, the distance between two elementary lesions, and the displacement path when multiple lesions are made. The sonication parameters that best fit a specific therapeutic application are determined via *in vitro* and *in vivo* experiments but also via mathematical models.

Real-time feedback during treatment allows HIFU-induced lesions to be visible using standard ultrasound as hyperechoic areas, but their extent is not always accurately defined. For posttreatment follow-up, MRI is the gold standard in evaluating the treatment efficacy if HIFU. Gadolinium-enhanced T1-weighted images clearly show the extent of necrosis.<sup>5</sup> MRI has also been used to guide HIFU treatment and to monitor temperature changes during HIFU.<sup>6</sup>

## HIFU Devices

Two devices have been developed for the treatment of prostate cancer: Sonablate (Focus Surgery Inc, Indianapolis, Ind) and Ablatherm (EDAP-TMS SA, Vaulx en Velin, France). The technology of both systems is basically the same, but there are a few technical differences between these two devices.

The Ablatherm has both the imaging (7.5 MHz) and therapeutic (3 MHz) transducers included in a unique endorectal probe focused at 40 mm. The Sonablate uses a single transducer (4 MHz) for both imaging and treatment. Several probes are available with many focal lengths (from 25 to 45 mm).

The Ablatherm requires a specific bed with a patient on a lateral position, whereas the procedure is conducted in a dorsal position with the Sonablate with a patient lying on a regular operating table.

The Ablatherm includes three treatment protocols with specifically designed treatment parameters, depending on the clinical use (standard, HIFU re-treatment, and radiation failure). The Sonablate uses a single treatment protocol in which the power is manually adapted by the operator. This “visually directed” HIFU treatment is based on grey-scale ultrasonographic

changes observed during treatment that allow the operator to change the power level for each HIFU pulse.<sup>7</sup>

Both devices offer a real-time ultrasonic monitoring of the treatment.

Because the rectal wall is sensitive to temperature changes, it requires a perfect rectal monitoring. Hence, both Ablatherm and Sonablate provide active cooling of the rectal wall during treatment, continuously monitor the temperature of the rectal wall, and constantly measure the distance between the rectal wall and the prostate.

The Ablatherm device provides many safety features, including a safety ring that stabilizes the rectum wall, a permanent control of the distance between the therapy transducer and the rectal wall, and a patient motion detector. The Sonablate requires a permanent presence of the physician during the procedure to control the adequacy between what was planned and what is done.

Treatment planning is slightly different between the two devices. With the Ablatherm, the prostate is divided into 4 to 6 volume boundaries and treated from the apex to the base slice-by-slice by an entirely computer-driven probe.<sup>8</sup> With the Sonablate, treatment usually involves three consecutive coronal layers, starting from the anterior part of the prostate and moving to the posterior part, with at least one probe switch during the procedure.<sup>9</sup>

## HIFU Indications

HIFU has been applied in most series<sup>7-18</sup> and is usually recommended<sup>19</sup> for patients with localized prostate cancer with clinical stage T1-T2 Nx-N0 M0 prostate cancer who are not suitable for a radical prostatectomy (eg, age >70 years of age, life expectancy ≤10 years,

major comorbidities precluding surgery) or who refuse to undergo for surgery. HIFU has also been used for locally proven recurrence of prostate cancer after radiation or brachytherapy failures.<sup>20</sup>

## HIFU Contraindications

Some relative or absolute contraindications need to be considered before offering HIFU to a patient with prostate cancer.

The gland volume is a major relative limitation and should not be over 40 mL. A transurethral resection of the prostate (TURP) prior to HIFU therapy can help to reduce the prostatic volume.<sup>11</sup> Some authors used a short hormonal deprivation treatment to downsize the gland volume to fit the optimal conditions for the HIFU treatment. This limited androgen suppression, which has been used for years by radiation oncologists, was stopped before HIFU began in order to avoid interfering with the treatment follow-up. In a nonrandomized study, Uchida et al<sup>18</sup> showed that the probability of being free of disease on prostate biopsies 6 months after the HIFU therapy appeared to be independent of whether the patients received or did not receive androgen suppression before the treatment.

Since the treatment has to be applied via a transrectal approach, each pathologic or anatomical condition that could impair the introduction or displacement of the probe within the rectum is a potential contraindication.

Finally, major prostatic calcifications can lead to an ultrasonic wave transmission impairment and should be considered as a contraindication unless TURP can remove them.

**Table 1. — Selected Reports of the Efficacy of HIFU for the Treatment of Localized Prostate Cancer**

Author	Device Used	No. of Patients	Clinical Stage	Mean Pre-HIFU PSA (ng/mL)	Mean or Median Follow-up (mos)	Negative Biopsies (%)	Mean or Median PSA Nadir (ng/mL)	Disease-Free Survival Rate (criteria)
Poissonnier et al <sup>13</sup>	A	227	T1-2 NX/0 M0	6.99	27	86	0.1	66% at 5-yrs (ASTRO + biopsies)
Vallancien et al <sup>14</sup>	A	30	T1-2 Nx M0	7	20	83	0.9	—
Lee et al <sup>12</sup>	A	58	T1-2 NX M0	10.9	14	—	0.2	69% at 14 mos (ASTRO + biopsies)
Blana et al <sup>10</sup>	A	146	T1-2 N0 M0	11.3	22.5	93.4	0.07	84% at 22 mos (PSA <1 ng/mL)
Chaussy and Thuroff <sup>11</sup>	A	271	T1-2 NX/0 M0	8.3	14.8	84.6	0.0	82.1% (ASTRO)
Thuroff et al <sup>15</sup>	A	402	T1-2 N0 M0	10.9	13.1	87.2	0.6	—
Uchida et al <sup>9</sup>	S	63	T1c-2b N0 M0	11.2	23.3	87	0.5	75% at 3 yrs (ASTRO)

A = Ablatherm, S = Sonablate.

## HIFU Outcomes

In 1995, Madersbacher et al<sup>21</sup> reported the first successful cases of prostate cancer using HIFU technology. From these first cases to recent published series,<sup>9-15</sup> the rates of local control have significantly increased (Table 1), approaching 85% to 90% with no differences between the two devices.

Biochemical outcomes were also encouraging and led to a low PSA nadir (Table 1). In most cases, the PSA nadir was reached 3 to 4 months after the HIFU treatment. Many studies have demonstrated that the PSA nadir was a significant predictor of HIFU failure. Lee et al<sup>12</sup> has proposed a careful monitoring of patients in whom the PSA nadir has not dropped below 0.5 ng/mL. A PSA nadir of greater than 0.2 ng/mL after HIFU has been associated with 4 times greater risk of treatment failure as defined by cancer on biopsy after HIFU.

Direct comparisons of outcomes between the Ablatherm and Sonablate devices are difficult for many reasons, including different follow-up, different definitions of PSA end points and disease-free survival rates (including PSA and/or prostate biopsy results), and the limited number of papers reporting efficacy with the Sonablate device (Table 1).

Poissonnier et al<sup>13</sup> reported that the 5-year disease-free survival rate, combining pathological and biochemical outcomes, was 66%, with a significant inverse relationship with the pre-HIFU PSA level: 90% for PSA 4 ng/mL or less, 57% for PSA between 4.1 and 10 ng/mL, and 61% for PSA between 10.5 and 15 ng/mL for patients treated with the Ablatherm device.<sup>13</sup> Uchida et al<sup>16</sup> reported an estimated 5-year outcome of 78% with the Sonablate device based on PSA stability in a population of 181 patients, with 52% having received hormonal therapy prior to HIFU therapy.

Until further study is reported in the literature or a randomized trial comparing both technologies is con-

ducted, it is almost impossible to draw clear and definitive conclusions in terms of efficacy between the two devices. Moreover, it is difficult to assess the potential role of HIFU therapy until long-term data are available. As a result, for patients who would like to have this treatment, as well as for those who are offered the treatment, it seems reasonable to inform them that only short-term follow-up is currently available. Consequently, this treatment should be reserved for elderly patients with localized prostate cancer or for patients contraindicated for surgery, whatever the reasons.

## Adverse Effects

Side effects following HIFU have been extensively described in many articles (Table 2).<sup>11-16,24</sup> A common adverse event was urinary retention, reported in 0.3% to 8.6% of cases. This can be caused by a swollen gland or the passage of necrotic debris (sloughing) induced by coagulated adenoma. With the Ablatherm device, the combination of a TURP performed just before the HIFU seems to reduce this side effect.<sup>11</sup>

Bladder outlet obstruction was another frequent complication. Uchida et al<sup>16</sup> reported a stricture rate of 22% that required intermittent dilatations using the Sonablate without TURP or bladder neck incision. The benefit of combining TURP and HIFU has been demonstrated for bladder outlet obstruction reduction with Ablatherm devices.<sup>11</sup> Symptomatic urinary infection occurred in up to 13.8% of patients and should be treated with antibiotics. Vallancien et al<sup>14</sup> reported no significant change in international prostate symptoms scores in a series of 30 patients who were treated using the Ablatherm.

Reported rates of impotence ranged from 20% to 49.8%. However, comparisons between series are difficult due to the absence of validated questionnaire use

Table 2. — Side Effects Associated With HIFU Treatment

Author	Urinary Retention (%)	Stress Incontinence (%) (grade 1/2/3)	Bladder Outlet Obstruction (%)	Urinary Tract Infection (%)	Impotence (%)	Fistulas (%)	Sloughing (%)	Perineal Pain (%)
Poissonnier et al <sup>13</sup>	–	13	12	2	–	0	9	3
Vallancien et al <sup>14</sup>	6	3	0	10	32	0	–	0
Lee et al <sup>12</sup>	0.3	16 (16/0/0)	0	–	–	0	14	–
Blana et al <sup>24</sup>	–	–	19.7	0.4	49.8	0.5	–	0.9
Chaussy and Thuroff <sup>11</sup>	–	15.6* (9.1/6.3/0) vs 6.9 (4.6/2.3/0)	–	47.9 vs 11.4	35.9	0	–	–
Thuroff et al <sup>15</sup>	8.6	13.1 (10.6/2.5/0)	3.6	13.8	–	1.2 (0.5**)	–	–
Uchida et al <sup>16</sup>	0.6	0.6 (grade 1)	22	6	20	1	–	–

\* HIFU vs HIFU + TURP.  
\*\* Since the addition of the cooling system.

for potency assessment. Potency preservation is related to the positioning of elementary lesions on the lateral edges of the prostate where the neurovascular bundles are located. A conservative approach sparing the neurovascular bundle by preserving an untreated area on the edge of the prostate opposite to the suspected cancer location for selected patients has to be balanced with a higher re-treatment rate.<sup>22,23</sup>

The rate of incontinence, reported between 0.6% and 15.4%, has decreased with time. Improvements in technology have led to this decrease mostly because of a better definition of the safety margin from the apex.

Last but not least, urethrorectal fistula was a major but rare complication. Whatever the device used, this rate has been reduced to almost zero in most recent series due to the intrarectal cooling system, a better knowledge of heat diffusion, and the ability to control the shots in real time.

## HIFU Re-treatment

For some patients, HIFU needs to be repeated due to incomplete treatment or treatment failure. The device used appears to have no effect since they both have approximately the same re-treatment rate: 1.47 and 1.4 sessions per patient in two series of 407 and 227 patients, respectively, with the Ablatherm system,<sup>13,15</sup> and 1.2% reported by Uchida et al<sup>16</sup> using the Sonablate system.

The management of recurrence after HIFU differs from that after radiation failure in that with HIFU there is no maximum dose and sessions can be repeated. Blana et al<sup>24</sup> recently reported on the morbidity related to repeated HIFU treatment for localized prostate cancer on 223 patients with a re-treatment rate of 22%. While urinary infection, infravesical obstruction, and chronic pelvic pain did not significantly differ after one or several sessions, they found that a significant increase was observed for urinary incontinence and impotence rates.

## Salvage HIFU After Radiation Failure

Positive biopsy rates after radiotherapy for prostate cancer range between 25% and 32%.<sup>25-28</sup> The majority of these patients have traditionally been treated expectantly or with hormonal deprivation. For patients with a locally proven recurrence and no metastasis, there appears to be a role for salvage HIFU curative therapy.

No data for radiation failure patients are available with the Sonablate device. Results with the Ablatherm system involving 118 patients with local recurrence after radiation have been reported.<sup>20</sup> For each patient, recurrence was biopsy-proven, and the absence of any

metastasis was confirmed on imaging evaluation using thorax and abdominopelvic CT, bone CT, or prostate MRI, with or without positron emission tomography (PET) imaging with F-18 fluorocholine. Hormonal therapy, either adjuvant to radiation or at biochemical relapse, was given to 50% of the patients but was stopped prior to HIFU treatment. Local tumor control was achieved in 84% of the cases. The median PSA nadir was 0.18 ng/mL. Progression was defined as the date of salvage hormonal deprivation introduction. The 5-year actuarial progression-free survival rate was 78%, 49.5%, and 14% for low-, intermediate-, and high-risk patients, respectively ( $P=.0002$ ). The poor results obtained in the high-risk group were explained by the existence of undiagnosed silent metastasis by the time of the HIFU treatment.

The complication rates of salvage HIFU are higher than those for HIFU as a primary procedure. This is especially true for incontinence, accounting for 43% (23% grades 2 and 3) of patients. However, a significant decrease in grade 3 incontinence was observed since 2002 with the definition of specifically designed treatment parameters for radiation failure. Bladder outlet obstruction significantly decreased as well. Urethrorectal fistulas have disappeared with these new treatment parameters; they represented 7% when standard treatment parameters were used. Nevertheless, the risk-benefit ratio is better for HIFU than for the other salvage options, with less morbidity and an efficacy similar to those reported for other local salvage therapies.

HIFU appears to be a valid indication for patients with local recurrence after radiation failure, but a strict selection of patients who would benefit from this treatment is mandatory and should be determined on the basis of the preradiation risk level.

## Future HIFU Applications

Experimental studies have demonstrated the potential of chemotherapy associated with HIFU. Using a rat model, Paparel et al<sup>29</sup> recently evaluated the therapeutic effect of HIFU combined with docetaxel on Dunning AT2 rat adenocarcinoma. They showed a synergistic inhibitory effect of the HIFU plus docetaxel combination. If confirmed in human trials, these results might suggest that a combined therapy could be useful for patients with high-risk prostate cancer.

The use of the Ablatherm device is currently being studied for high and locally advanced stages of prostate cancer. Ficarra et al<sup>8</sup> suggested the possible application of HIFU in association with hormonal therapy for high-risk prostate cancer. The oncological end points selected were a positive prostate biopsy 6 months after the procedure and/or a total PSA level of greater than 0.3 ng/mL. Their oncological results were promising at 1

year of follow-up: 23% of positive biopsies and 10% of the high-risk patients with a PSA level of greater than 0.3 ng/mL. However, these results are preliminary and require reassessment over a longer follow-up.

Finally, technical improvements in HIFU are pending, including an MRI-guided HIFU treatment. MRI is now able to monitor the temperature achieved in the target volume during a HIFU pulse.<sup>6</sup> An automated adjustment of the treatment parameters according to the temperature measured in the target volume could be done in real time to control the heat extension during the HIFU session, thus optimizing the treatment efficacy.

## Conclusions

HIFU has been assessed for its role in the treatment of localized prostate cancer in patients who otherwise would not have benefited from surgery and in local recurrences after radiation failure. Further long-term follow-up and randomized controlled trials are required to support early findings and define the exact role of HIFU in the armamentarium for prostate cancer. However, the technology has been well studied and developed to a point that HIFU will undoubtedly be utilized in the future as an alternative to radiation therapy.

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