

## Reviews in Endourology

# Transrectal High-Intensity Focused Ultrasound Devices: A Critical Appraisal of the Available Evidence

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### ABSTRACT

Developments in the technology applied to the field of minimally invasive surgery have led to the exploration of high-intensity focused ultrasound (HIFU) for the treatment of localized prostate cancer. Extensive research and continuous evolution have resulted in two commercially available HIFU devices: the Ablatherm<sup>®</sup> and the Sonablate500<sup>®</sup>. These devices are conceptually the same; however, specific technical differences exist. This paper reviews the clinical outcomes obtained with these devices, evaluates the quality of the evidence from the individual trials, and provides the results of a head-to-head comparison in terms of oncologic outcomes and complication rates.

### INTRODUCTION

ADVANCES IN TECHNOLOGY and their implementation in medicine have increased the treatment options in oncologic urology. Established options for patients with prostate cancer include watchful waiting, radical prostatectomy, brachytherapy, external-beam radiation, and hormonal therapy. Lately, however, the armamentarium for localized prostate cancer has expanded to include minimally invasive options such as cryotherapy and high-intensity focused ultrasound (HIFU). The goal of these methods is to provide similar rates of cure with fewer side effects. Purely noninvasive treatment, by means of tissue penetration, is provided by HIFU, with promising initial results.

Several authors have reviewed the application and effectiveness of HIFU in prostate cancer treatment.<sup>1-6</sup> However, no head-to-head comparison of the available devices has been done yet. The authors' intention is not to present HIFU treatment in detail but rather to compare the available devices according to the existing evidence in terms of technical features and clinical outcome differences.

### PRINCIPLE OF HIFU TREATMENT

High-intensity focused ultrasound destroys prostate cells by coagulative necrosis of the tissue without damaging the struc-

tures intervening between the transrectal probe and the target tissue.<sup>7</sup> The principle of HIFU is based on the physical effect of ultrasound on tissue. When ultrasound waves of high intensity are focused on a single point, the focal-area temperature will rise, causing damage to a discrete volume of tissue.<sup>8</sup> The lesion is caused by elevated tissue temperatures, which lead to melting of lipid membranes and to protein denaturation. Additionally, there is a cavitation effect (gas microbubbles) secondary to alternations of large positive and negative acoustical pressures, which indirectly increases the temperature.<sup>9</sup> Each pulse of energy causes ablation of a small volume of tissue. Each volume is an ellipsoid with a size that is a function of the crystal geometry used in the transrectal probe.

The procedure can be performed on a day-care basis under spinal or general anesthesia.<sup>1</sup> The entire procedure takes 1 to 3 hours, depending on the size of the prostate gland. Because of edema secondary to the thermal effects, a transurethral or suprapubic catheter is placed for 2 weeks on average after the procedure. When a transurethral resection of the prostate (TURP) is performed prior to the procedure, the catheterization period decreases to 2 or 3 days. In general, HIFU is recommended for patients with prostate cancer stage T<sub>1c</sub> to T<sub>3</sub> who are not candidates for a radical prostatectomy because of age or associated disease or patients who prefer an alternative to surgery. It can be used either as primary treatment, as salvage therapy after local recurrence, after external radiotherapy, or after unsuccessful brachytherapy. In addition, HIFU can be repeated after a

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previous HIFU treatment failure or can be used for palliative therapy, debulking large tumors that are causing pain, bleeding, and obstruction.

### EARLY EXPERIENCES AND AVAILABLE DEVICES

The feasibility of HIFU for the treatment of localized prostate cancer was initially confirmed by studies on cancerous prostates several days before radical prostatectomy.<sup>10,11</sup> Delineated areas of coagulative necrosis in the treated areas were revealed in both studies. Investigators used different HIFU devices (Ablatherm<sup>®</sup> and Sonablate200<sup>®</sup>). Early experience with the use of HIFU for the treatment of prostate cancer was reported in 1996.<sup>12</sup> In this study, 14 men who had stage T<sub>1</sub> or T<sub>2</sub> disease and were unsuitable for radical surgery were treated with HIFU (Ablatherm). Half of the patients achieved a serum prostate specific antigen (PSA) concentration <4 ng/mL and negative biopsies. However, complications were reported in 9 of the 14 patients in this pilot trial (61%), with 3 rectal burns.

Since those initial experiences, the devices have evolved, and modifications are being made continually, aiming to improve treatment accuracy, easiness of use, and safety. There currently are two commercially available HIFU technologies. The first device was the Ablatherm (Edap-Technomed, Lyon, France), with initial clinical results published in 1996.<sup>12</sup> Subsequently, Focus Surgery (Indianapolis, IN, USA) introduced a system called the Sonablate500<sup>®</sup>, and the preliminary results from its use in prostate cancer treatment were published in 2002.<sup>13</sup>

### TECHNICAL CHARACTERISTICS OF AND DIFFERENCES BETWEEN HIFU DEVICES

Even though the fundamental HIFU features of both systems are identical, there are several technical differences between the two devices, with modifications evolving continually (Table 1). The Ablatherm uses separate crystals for imaging (7.5 MHz) and treatment (3 MHz), but since 2005, in the latest-generation device, the two types of transducer have been integrated into the same probe<sup>14</sup> that has a focal point 45 mm from the crystal. The 3.0-MHz treatment crystal creates an ablation area with a volume ranging from 24 mm (anterior to posterior) × 1.7 × 1.7 mm (total volume 36 mm<sup>3</sup>) to 19 × 1.7 × 1.7 mm (total

volume 29 mm<sup>3</sup>). There are three treatment algorithms available for the Ablatherm, each designed for a specific application: HIFU as a primary treatment, HIFU following failed radiation therapy, and HIFU re-treatment.<sup>14</sup> This is critical, because the thermal properties of tissue are not the same in every condition; thus, a prostate that has never undergone treatment is vastly different from one that has. Although real-time imaging is available with the Ablatherm, this is not usually employed to detect patient movement; this process relies on an automated internal A-mode ultrasound detection system that, together with the external ultrasound scanner used during the treatment localization phase, measures the distance from the rectal wall and ensures that the patient has not moved.<sup>15</sup> This automated real-time safety monitoring eliminates the risk of coagulating the rectal wall and makes the procedure less operator dependent.

The Sonablate uses a single crystal for both imaging and treatment and has four crystals that are selected by the operator according to the size of the elementary lesion: 10 mm in length × 2 mm in diameter for a single beam performing with 25-mm or 45-mm focal-length probes or 10 mm in length × 3 mm in diameter for a split beam performing with 30-, 35-, or 40-mm focal-length probes.<sup>6</sup> The Sonablate device accomplishes this by having two probes that contain four crystals placed back to back. An operating frequency of 4 MHz has been determined to provide both sufficient image quality and effective treatment. The 4-MHz resolution probe provides detailed imaging of the anterior part of the prostate but has lower resolution and image quality in the posterior margin of the gland and the rectal wall in comparison with higher-frequency ultrasound probes. The Sonablate uses different algorithms for each crystal. The device has no real-time imaging, but alternating the therapy and imaging modes creates an image overlay, which is used to detect patient movement.<sup>6</sup> This is done by placing the planned treatment map over real-time images of the prostate taken during the procedure. If the images consistently line up during the procedure, this is an indication that no patient movement has occurred.

The two technologies use different patient positions during treatment.<sup>1</sup> The lithotomy or supine position utilized during treatment with the Sonablate permits classical access. However, if bubbles are present in the fluid surrounding the treatment crystal or are created during treatment, they will rise and end up between the crystal and the prostate, which can compromise the treatment quality (both ablation and targeting), as air sharply

TABLE 1. TECHNOLOGICAL DIFFERENCES IN HIFU DEVICES

	<i>Ablatherm</i> <sup>®</sup>	<i>Sonablate 500</i> <sup>®</sup>
Patient position	Right lateral decubitus	Lithotomy or supine
Crystals	Integrated (imaging 7.5 MHz; treatment 3 MHz)	Four single (both imaging and treatment 4 MHz)
Focal point	45 mm from crystal	25–40 mm from crystal in 10-mm steps
Ablation volume	29–36 mm <sup>3</sup>	21–47 mm <sup>3</sup>
Treatment algorithms	Three (primary treatment, after failed radiotherapy, HIFU pretreatment)	One algorithm for each crystal
Additional safety features	Automated movement detection Permanent A-mode distance detector	Alternating image overlying Reflectivity measurement

reflects ultrasound waves. Treatment with the Ablatherm is performed with the patient in a right lateral decubitus position (lying on his right side). This is done as a safety precaution. If there are any bubbles in the fluid surrounding the treatment probe, they will rise upward out of the treatment field. With the patient on his side and the treatment aimed laterally, bubbles will not end up between the HIFU treatment crystal and the prostate.

The Sonablate incorporates an additional safety feature: reflectivity measurement.<sup>14</sup> Analyzing reflected ultrasound signals and comparing them with images taken prior to commencement of therapy can detect tissue changes resulting from higher temperature. As the temperature increases, the reflectivity index (ratio of the two signals) changes. This provides real-time feedback indicating that an excessive build-up of thermal energy may be imminent. If significant reflectivity index changes are observed in a region, the device will automatically pause until sufficient energy has dissipated before the therapy resumes.

## COMPARISON OF CLINICAL OUTCOMES

Given that the available HIFU devices have the same fundamental design with considerable technical differences, differences might exist in their clinical outcomes when used for the treatment of prostate cancer. Clinical outcomes can be divided into primary and secondary. The primary outcomes are the short- and longer-term oncologic results, whereas treatment-related complications are secondary outcomes.

### *Materials and Methods*

A MEDLINE search was conducted using the terms "HIFU" and "prostate cancer." Only original articles were included; review articles, articles not written in English, and letters were excluded. An extra and more selective search was then performed to identify the largest case series reported from each medical center in order to eliminate population overlapping. Studies that provide clinical outcomes or treatment-related complications were sought for this review.

Methodology of comparison was based on different criteria for each category of outcomes and also depended on the available evidence. Criteria for short-term primary outcomes were PSA nadir and negative biopsy rate (%), whereas the criteria used for longer-term outcomes were the overall biochemical disease-free survival (BDFS) or long-term cancer-specific survival rates. Finally, each study was scored independently for its technical quality and evidence level according to the criteria of the Oxford Centre for Evidence Based Medicine.<sup>16</sup>

### *Results*

Clinical data from the use of HIFU in the treatment of prostate cancer are derived mainly from studies conducted in Europe, as U.S. Food and Drug Administration-approved clinical trials are currently still in progress. The Ablatherm device has been utilized in more centers for a longer period of time, providing more clinical information regarding its effects. The results from a European multicenter study were published in

2003, and large case series from different countries have provided some longer-term outcome data. On the other hand, the Sonablate device has been tested mainly in Japan and, just lately, in the U.K. The three sources of clinical data on its application come from a multicenter study in Japan published in 2005,<sup>25</sup> the case series from Uchida's group,<sup>26</sup> and short-term results from visually directed HIFU treatment published by Illing and collaborators in the U.K.<sup>27</sup> Table 1 summarizes the largest clinical series reported and the outcomes for both HIFU devices, mainly for the primary treatment of localized prostate cancer.

There are no randomized controlled trials comparing the clinical efficacy of the two HIFU devices directly, and all existing evidence is based on case series, including two nonrandomized controlled studies showing the effectiveness of combined HIFU + TURP treatment, and two multicenter studies, one for each device (all studies provide evidence of level 4). Our MEDLINE search revealed, in total, nine observational studies that provide data on short- and longer-term oncologic outcomes (Table 2). Six of these studies also review secondary outcomes according to our definitions and, together with two studies specifically reporting treatment-related complications, were used to create Table 3. Our MEDLINE search did not reveal any data for overall or long-term cancer-specific survival rates, as the endpoint in most series is BDFS.

**Primary outcomes.** Comparisons of mean PSA nadirs as a short-term measure of treatment success is not feasible, as PSA nadir is not reported in the larger studies with the Sonablate device. In a recent publication that presented the device profile of the Sonablate,<sup>6</sup> the authors included a study of 63 patients by Uchida's group that achieved a mean PSA nadir of 1.38 ng/mL.<sup>28</sup> We did not include this study in our Table 1 because of overlapping populations, as the same year, the same group of investigators published their long-term results in 181 patients, among whom were the previously mentioned group.

Comparisons of the negative-biopsy rates provide a more objective measure of short-term treatment success because the rate of false-positive results is practically zero. The negative-biopsy rates reported from the largest studies with both devices are given in Figure 1. The range of negative-biopsy rates for patients treated with the Ablatherm device is 75% to 87.7%, whereas 68% was reported in the multicenter study from Japan. These rates show a small trend in favor of the Ablatherm device in short-term treatment success. However, drawing an inference from this comparison should be precluded, as this comparison is done with only one representative study using the Sonablate device, and statistical comparison is not possible. In the previously mentioned study of 63 patients by Uchida's group,<sup>28</sup> the reported negative-biopsy rate was 87%, providing a similar range of values for both devices. It therefore is evident that more studies are needed with the use of the Sonablate device to draw safe conclusions about short-term treatment success.

In order to compare the biochemical control outcomes, it is necessary to have the same definition of BDFS and similar follow-up. Studies that have 5-year biochemical control outcomes are the ones in Figure 2. Three of these studies use the ASTRO definition of biochemical failure, whereas the other one defines biochemical relapse as PSA nadir + 2 ng/mL. On the other

TABLE 2. OUTCOMES OF PROSTATE CANCER TREATMENT BY HIFU<sup>a</sup>

	Thuroff et al (2003) <sup>21</sup> (multi-center)		Poissonnier et al (2007) <sup>21</sup>		Chaussy et al (2003) <sup>24</sup>		Uchida et al (2005) <sup>25</sup> (multi-center)		Uchida et al (2006) <sup>26</sup>		Illing et al (2006) <sup>27</sup>	
	Ablatherm	HIFU only	Ablatherm	HIFU only	Ablatherm	HIFU only	Ablatherm	HIFU only	Ablatherm	HIFU only	Ablatherm	HIFU only
Device	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm
No. of patients	402	52	463	102	140	96	175	72	181	9	25	25
No. of sessions	1.47	1.4	—	1.7	—	1.25	0.4	1.2	1.2	—	—	—
Criteria <sup>b</sup>	T <sub>1</sub> -T <sub>2</sub>	T <sub>1</sub> -T <sub>2</sub> PSA <20 GS <8	T <sub>1</sub> -T <sub>2</sub> PSA ≤15 GS <8	T <sub>1</sub> -T <sub>2</sub> PSA <20	T <sub>1</sub> -T <sub>2</sub> PSA <15 GS <8	T <sub>1</sub> -T <sub>2</sub> PSA <20	T <sub>1</sub> -T <sub>2</sub> PSA <20	T <sub>1c</sub> -T <sub>2</sub> PSA <20	T <sub>1c</sub> -T <sub>2</sub>	T <sub>1</sub> -T <sub>2</sub> PSA <15 GS <8	T <sub>1</sub> -T <sub>2</sub> PSA <15	Visually directed
Follow-up (mos)	13.5 (0-51)	27 (12-121)	23 (± 16)	19 (3-76)	76 (± 13)	18.7	10.9	14 (2-24)	18 (4-68)	≥3 months	≥3 months	≥3 months
PSA nadir	1.8 (mean) 0.6 (median)	0.33 (mean) 0.10 (median)	0.10 (median)	0.57 (mean)	0.16 (median)	0.48 (mean)	0.26 (mean)	—	—	1.51 at 3 mos	1.51 at 3 mos	0.15 at 3 mos
Biochemical disease-free survival rate <sup>c</sup> (%)	—	—	64 (4-year)	66 (5-year)	73 (5-year) 69 (6-year) PSA nadir + 2	84	80	76 (2-year)	78 (5-year)	—	—	—
Five-year disease-free survival rate <sup>c</sup> (%)	—	58	—	—	—	—	—	—	—	—	—	—
% negative biopsy	87.2	86	84.5	75	86.4	87.7	81.6	68	—	—	—	—

<sup>a</sup>Oxford level of evidence was 4 for all studies.

<sup>b</sup>PSA = prostate specific antigen (ng/mL); GS = Gleason score.

<sup>c</sup>By ASTRO criteria unless otherwise specified.

TABLE 3. COMPLICATIONS OF HIFU TREATMENT OF PROSTATE CANCER<sup>a</sup>

	<i>Thuroff et al</i> (2003) <sup>21</sup> (multicenter)	<i>Poissonnier et al</i> (2007) <sup>20</sup>	<i>Thuroff et al</i> (2006) <sup>19</sup> (primary) single treatment)	<i>Gelet et al</i> (2001) <sup>22</sup>	<i>Blana et al</i> (2006) <sup>23</sup> (single treatment)	<i>Uchida et al</i> (2005) <sup>25</sup> (multicenter)	<i>Uchida et al</i> (2006) <sup>26</sup>	<i>Illing et al</i> (2006) <sup>27</sup>
Device	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Ablatherm	Sonablate	Sonablate	Sonablate
No. of patients	402	227	1078	102	223	72	181	34
Urinary retention (sloughing) (%)	8.6	9	5	5	—	—	—	—
UTI (%)	13.8	2 (acute)	9.5	8 (acute)	1.4 (acute)	—	—	8.8
Urethrorectal fistula (%)	1.2	—	0.2	1	0.7	—	1	—
Stenosis (urethra, bladder neck) (%)	3.6	12	—	17	19.7	18	22	20.6
Urinary incontinence (any degree) (%)	14.6	13	1.7 (>3 mos)	23	7.6	1.4	0.6	—
Chronic perineal pain (%)	—	3	—	2	0.9	—	—	—
Impotence (%)	—	35.8	55	61	49.8	39	20	—
Epididymitis (%)	—	—	—	—	—	8.3	6	2.9
Prostatitis (%)	—	—	—	—	—	5.5	—	—
Nephrotic syndrome (%)	—	—	—	—	—	1.4	—	—
Balanoposthitis (%)	—	—	—	—	—	1.4	—	—
Fecal incontinence (%)	—	—	—	—	—	1.4	—	—
Retrograde ejaculation (%)	—	—	—	—	—	1.4	9	—

<sup>a</sup>Oxford level of evidence was 4 for all studies.

hand, the study by Poissonier and colleagues<sup>20</sup> provides disease-free survival (DFS) rates, which additionally include pathology reports from biopsy results, whereas the other studies express only BDFS. These different definitions make statistical comparison between the two technologies impossible, and the small trend observed in favor of the Sonablate device in long-term oncologic outcomes should not be interpreted as an advantage over the Ablatherm.

**Secondary outcomes.** The series reporting complications from primary HIFU treatment for prostate cancer are presented in Table 2. These studies represent a heterogeneous population, which makes the attempt to compare treatment-related morbidities difficult. Parameters of heterogeneity that influence secondary outcomes are antibiotic use, coexisting pathologies, synchronous TURP, undefined previous specific status, and different definitions of complications. In addition, the time effect (mainly

for the Ablatherm) with the continuous evolution of technology results in different-generation HIFU devices in the various reported series. This also occurs within the same series, in which two different-generation devices sometimes have been used.

The main complications to HIFU treatment of prostate cancer are postoperative stenosis (either urethral or bladder neck), some degree of urinary incontinence, erectile impotence, and urethrorectal fistulas. Urethrorectal fistulas occurred more often with the initial devices, but the introduction of rectal cooling and rectal safety margins with automatic detection-driven alarms have reduced the incidence (around 1% for both devices and <0.1% when treating stage T<sub>1c</sub> cancers). Attempting to compare the incidences of urinary incontinence is not feasible because there is no standard definition of incontinence in the various studies and previous continence status is not defined. Incontinence possibly is an underreported complication, and

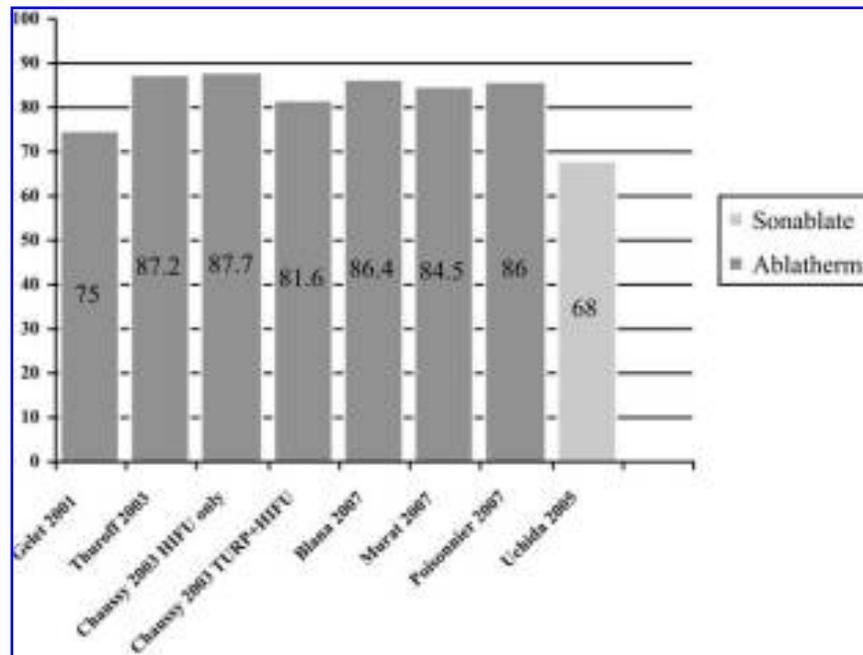


FIG. 1. Comparison of negative-biopsy rates (%).

preoperative or postoperative urodynamic evaluation is absent in most of the series. The two complications most often reported with both HIFU devices are stenosis and impotence. When looking at them (Figs. 3 and 4), it seems that there is a slight trend for more urethral or bladder-neck strictures with the Sonablate device, whereas the Ablatherm-treated patients appear to have a slightly higher impotence rate. However, it is unclear if a true

statistical difference exists, and the previously mentioned limitations in comparisons should be kept in mind.

Among the minor complications reported with both devices is urinary-tract infection (UTI). However, inconsistency in the definition of UTI makes even a trend observation impossible, because some authors report only the acute cases, and there is difference in chemoprophylaxis schemes. Moreover, the pa-

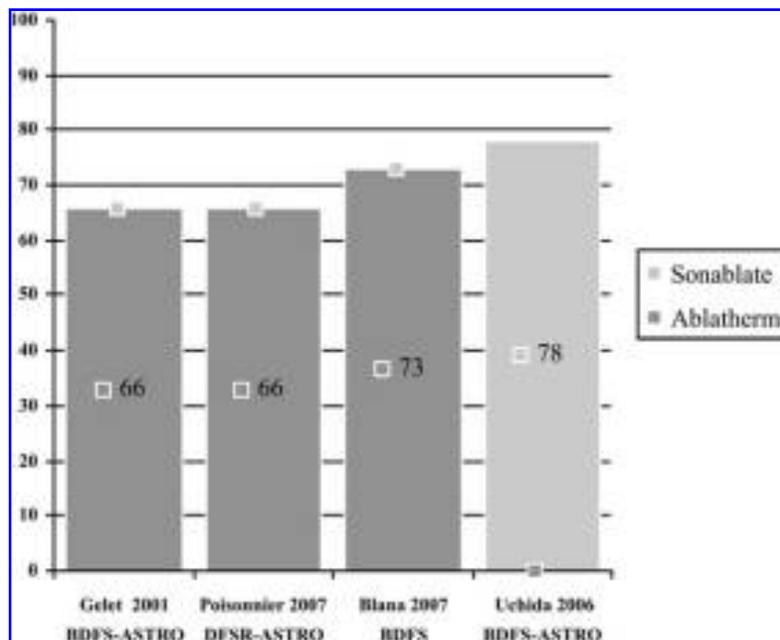


FIG. 2. Five-year outcome results (% values). DFS = disease-free survival; BDFS = biochemical disease-free survival.

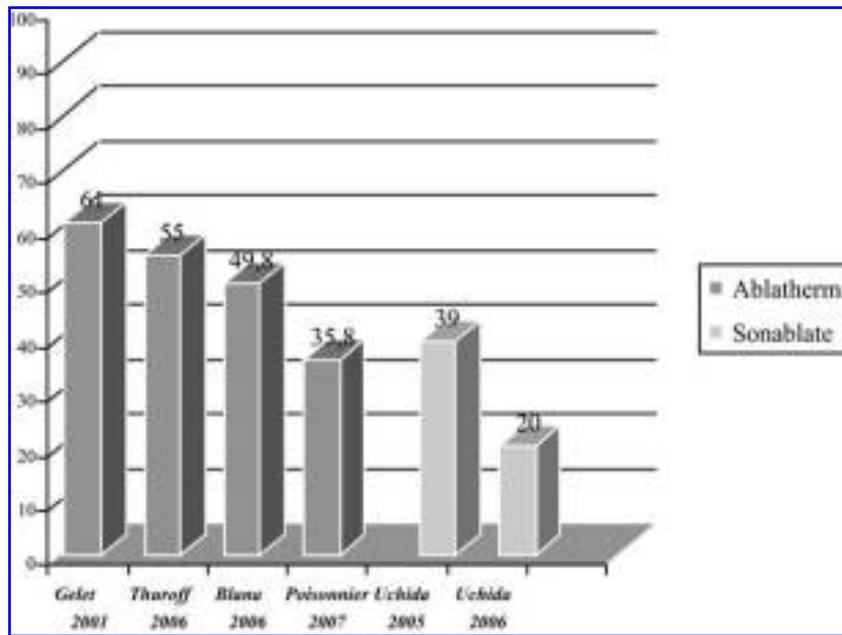


FIG. 3. Reported impotence rate after HIFU.

tients' clinical characteristics such as coexisting pathologies and pretreatment urinary culture results are not mentioned. Chronic perineal pain and urinary retention secondary to tissue sloughing have been reported only with the use of the Ablatherm device, whereas only the Sonablate groups have reported epididymitis, prostatitis, nephritic syndrome, balanoposthitis, fecal incontinence, and retrograde ejaculation.

**DISCUSSION AND CONCLUSIONS**

On a theoretical basis, the ideal HIFU device should consist of a single probe for both adequate imaging and effective cancer treatment, with optimum safety features to stop energy delivery if there is any patient movement and to protect the external sphincter and rectal wall. Treatment of prostate cancer

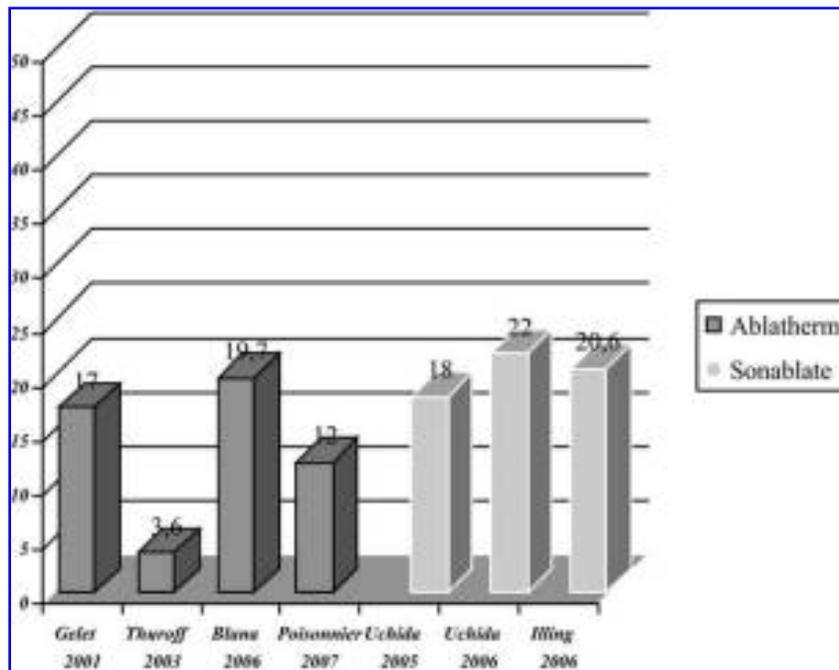


FIG. 4. Reported rate of stenosis of urethra or bladder neck after HIFU.

by HIFU should be oncologically safe, ablating the whole prostate gland with the peripheral zone and apex while preventing complications. Technology has been rapid in the development of HIFU devices. The Ablatherm has been available in the market for a longer period of time and has undergone more modifications and technical improvements since it was first produced. Improvements were made in the applied software programs for optimizing treatment planning and scanning of the target organ and in the development of safety features, leading to the implementation of the rectal cooling system and automated movement detector, and in producing a single probe for both imaging and treatment. This has resulted in a significant reduction of the observed complication rates between the initial prototype device and the latest-generation Ablatherm device. The initial Sonablate 200 was likewise followed by the improved Sonablate 500®. In addition, the performance of concomitant TURP with HIFU has significantly reduced postoperative obstruction, while higher energy doses (HIFU dose) per treatment result in better cancer-free rates and PSA nadirs.

In trying to identify which device is better, it is significant that both of the currently available devices for HIFU treatment of prostate cancer share a fundamental concept with several technical differences. When applied to patient treatment, however, direct comparison of outcomes and complications is not feasible, because outcome data from randomized controlled trials are not available. A statistical comparison between different case series of the two devices is not possible, as this can be done only when looking at large studies with identical patient populations, the same length of follow-up, and the same study endpoints. In addition, the Ablatherm device has been in the market for a longer time, and it has been used in more centers, whereas the Sonablate device has been introduced recently, and results from its use are still limited in terms of the number of patients treated. The median follow-up time in the available case series is short and unequal, and the definition of the available biochemical progression-free survival rate and reported complications (i.e., degree of urinary incontinence, UTIs, urinary retention) differs greatly among studies. However, it should be mentioned that the availability of more short- and long-term oncologic outcomes with the Ablatherm device creates less uncertainty about the actual efficacy of the device-specific treatment. Regarding treatment-related complications, there does not seem to be a significant difference.

In summary, HIFU has been used effectively in the treatment of prostate cancer. The constant evolution of the technology has led to the development of devices that today have differences with regard to technical characteristics, but their overall outcomes seem to be similar.

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#### ABBREVIATIONS USED

ASTRO = American Society for Therapeutic Radiology and Oncology; BDFS = biochemical disease-free survival; HIFU = high-intensity focused ultrasound; PSA = prostate specific antigen; TURP = transurethral resection of the prostate; UTI = urinary-tract infection.



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