Therapeutic Ultrasound and Prostate Cancer

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Abstract

Therapeutic ultrasound approaches including high-intensity focused ultrasound (HIFU) are emerging as popular minimally invasive alternative treatments for localized, low-to-intermediate risk prostate cancer. FDA approval was recently granted for two ultrasound-guided HIFU devices. Clinical trials for devices using MRI guidance are ongoing. The current level of evidence for whole-gland ultrasound ablation suggests that its clinical efficacy and adverse event rates including erectile dysfunction and urinary incontinence are similar to current definitive therapies such as radical prostatectomy and external-beam radiotherapy. Short-term data suggest that more focal therapy could reduce the rates of adverse events.

Keywords

- high-intensity focused ultrasound
- prostate cancer
- therapeutic ultrasound
- high-intensity directional ultrasound

Objectives: Upon completion of this article, the reader will be able to (1) describe the rationale for minimally invasive treatment of localized prostate cancer with therapeutic ultrasound; (2) describe different available therapeutic ultrasound options; and (3) discuss the current level of evidence behind prostate HIFU and controversies associated with it.

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Prostate Cancer: Epidemiology, Current Practices, and Need for Minimally Invasive Technologies

Prostate cancer (PCa) is the second most common cancer in American men (after skin cancer) and the second most common cause of cancer-related death (behind lung cancer).[1] However, PCa represents a spectrum of diseases ranging from those that are low risk and indolent to those that are aggressive and lethal.[2] Most patients with localized PCa do not die from it. The traditional prostate cancer screening, diagnosis, and treatment options comprising of prostate-specific antigen (PSA) testing, random transrectal ultrasound (TRUS) biopsy, and prostatectomy/radiation have significant limitations.

PSA is a nonspecific test, which is elevated in many benign situations.[3] The American Cancer Society's estimates of 180,890 new cases of PCa in the United States[4] in 2016 is a significantly lower number than that of 2015, mostly due to the United States Preventative Services Taskforce (USPTF) recommendations against routine PSA testing.[5] Random TRUS biopsy is notorious for the conundrum of overdiagnosis of low-risk PCa and underdetection of high-risk PCa. Random biopsy of the prostate to diagnose or exclude cancer is performed nearly 1,000,000 times annually in the United States, most frequently as a result of elevated PSA. Less than one-third of these are positive.[6] Both prostatectomy and radiation are associated with high risks of incontinence and impotence. Many patients with low- and intermediate-risk disease unnecessarily undergo these aggressive treatment options.

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There is considerable ongoing effort to improve the deficiencies in the diagnostic and treatment approaches for patients with low-to-intermediate risk PCa. For example, better screening methodologies are being developed, including strategies on how to incorporate prostate magnetic resonance imaging (MRI) into the screening algorithm. The improvement in prostate MRI techniques and advent of targeted biopsy techniques has enabled physicians to actually see and target the risk driving "index" lesion. In the treatment realm, a wide range of minimally invasive modalities has been tested for whole-gland, partial-gland, and focal treatments.[7] Therapeutic ultrasound is a popular FDA-approved, nonsurgical, "no-needle" ablative therapy that does not use ionizing radiation. Theoretically, therapeutic ultrasound has the potential to markedly reduce treatment-related complications that affect urinary and sexual function.[7] However, there is a critical need to understand the technology including its limitations and the current data supporting its use to properly drive its adoption for the appropriate PCa population.

Principles of Therapeutic Ultrasound

High-intensity focused ultrasound (HIFU) incorporates ultrasound beams produced by multiple piezoelectric and piezoceramic elements directed into a small three-dimensional (3D) focal point. For PCa treatment, this is largely done using a transrectal approach. There are two main effects of HIFU on tissues—mechanical and thermal.[8] Heat generation occurs due to absorption of focused acoustic energy with the temperature rising rapidly to 60°C or higher, causing coagulation necrosis in a short period of time. These thermal effects of HIFU form the basis of most clinical tumor ablation devices available currently (►**Fig. 1**).[9]

There is a relatively new approach of therapeutic ultrasound in the prostate ablation realm—high-intensity directional ultrasound (HIDU).[10] A transurethral prostate transducer emits a HIDU beam, resulting in a well-collimated flame-shaped region of heating in the prostate (►**Fig. 1**). The base of the flame-shaped region next to the urethra is the hottest, reaching up to 95°C, whereas the temperature at the edge of the flame at the prostate capsule can be controlled with MR thermometry feedback to 55°C with the temperature dropping to nonablative ranges beyond the prostate capsule.

Available Prostate HIFU Devices

Research on HIFU treatment of PCa began in the 1990s and has since incorporated the latest advances in engineering and imaging. Using a multitude of devices (►**Table 1**) and their previous iterations, more than 50,000 men worldwide have been treated with HIFU.[11] Within the last year, the FDA has approved two devices (Sonablate and Ablatherm) which use ultrasound-guided HIFU for prostate tissue ablation. Clinical trials for devices using MRI guidance are ongoing (►**Table 2**). Since approval, many U.S. men have undergone the procedure. We provide a summary of current available and upcoming therapeutic ultrasound devices and their capabilities (►**Table 1**) along with a more detailed explanation below. A composite picture of the devices can be seen in ►**Fig. 2**.

1. Sonablate (SonaCare Medical LLC, Charlotte, NC)—The FDA-approved device consists of a console, two motorized probes, and SonaChill, a module for circulating degassed chilled water for rectal cooling and transducer coupling. Each probe contains a two-sided transducer assembly, with each side consisting of a 6.5-MHz imaging and a 4.0-MHz therapy crystal. The two sides vary in the focal distance of the therapy crystal: a 4-cm focal distance creating a 12 × 3 × 3 mm lesion and a 3-cm focal distance creating a 10 × 3 × 3 mm lesion. The patient is positioned in a lithotomy position. The device allows the physician to modify and adjust power levels (total acoustic power or TAP) based on monitoring visual tissue changes and using an ultrasound-processing algorithm called tissue change monitoring (TCM)[12] that estimates the relative amount of tissue change during sonication

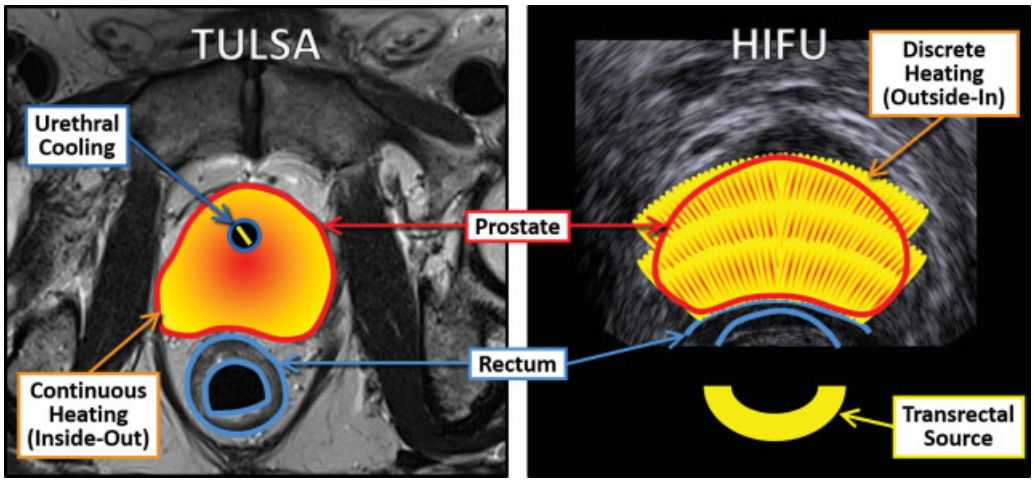

Fig. 1 Representation of transurethral and transrectal whole-gland ablation approaches. The transurethral approach, referred to as TULSA, uses continuous heating, whereas the transrectal approach treats the whole gland by targeting discrete lesions encompassing the prostate volume. (Image used with permission from Profound Inc.)

Table 1 Summary of specifications of currently available devices

Device	Manufacturer (location)	Patient positioning	Method	Transducers	Focal length/Lesion size	Size or volume limitations	Calcification, cysts, rectal wall thickness requirements	Preventive precautions	Monitoring
Sonoblate 500	Sonacare Medical LLC (Charlotte, NC, USA)	Lithotomy	Transrectal	4 total (2 for imaging and 2 for treatment	Dual focal lengths of 4 and 3 cm/12 × 3 × 3 mm or 10 × 3 × 3 mm	up to 37 mm (AP dimension + rectal wall thickness)	Any significant calcification or cyst (not defined)	Suprapubic catheter	TCM estimates relative tissue change and RIM assesses heat build up
Ablatherm II	EDAP TMS (Vaulx-en-Velin, France)	Right lateral	Transrectal	2 total (1 for imaging and 1 for treatment)	4.5 cm/1.7 mm in thickness, 17–24 mm AP in mm increments	up to 24 mm AP dimension	Calcifications in treatment volume do not matter; cysts >10 mL; rectal wall thickness >6 mm	TURP	Visual gray scale changes, 3 pre-fixed energy levels depending on presence or absence of prior treatment
Focal-One	EDAP TMS (Vaulx-en-Velin, France)	Right lateral	Transrectal	Imaging transducer and annular array with 16 individual concentric rings	4.5 cm, 5–40 mm AP	up to 40 mm AP dimension	Calcifications in treatment volume do not matter; cysts >10 mL; rectal wall thickness >6 mm	Suprapubic catheter, TURP	As above and also contrast-enhanced ultrasound with Sonovue for posttreatment imaging
TULSA-PRO	Profound Medical, Inc. (Toronto, Canada)	Lithotomy	Transurethral (with endorectal cooling coil)	Linear array of 10 independent transducers	Directional: 3 cm from urethra in all axial dimensions	5 cm sagittal × 6 cm axial (3 cm from urethra); volume <90 mL,	Calcifications and cysts >1 cm	Suprapubic catheter	Real-time MR imaging with thermometry
Exablate	INSIGHTEC (Haifa, Israel)	Lithotomy	Transrectal	Endorectal phased-array transducer (990 elements)	Up to 4 cm from rectal wall (6 cm from transducer), used only for focal therapy/ 2 × 8 mm	Volume <70 mL	Calcification ≥2 mm in the ultrasound beam path and <5 mm from rectal wall; multiple cysts	Foley catheter usually (focal treatment only)	Real-time MR imaging with thermometry

Abbreviations: AP, anteroposterior; TURP, transurethral resection of the prostate; RIM, reflectivity index monitoring; TCM, tissue change monitoring.

Table 2 Current clinical trials

Name (trial number)	Sponsor	Phase	Oncologic eligibility	Primary outcome
Intervention trial evaluating focal therapy using HIFU for the treatment of prostate cancer (NCT02265159)	University of Zurich, Switzerland	II and III	• Age >40 y, stage T1–T2cN0M0, PSA <15 ng/mL • Unilateral Gleason score ≤4 + 3 • Bilateral disease: clinically significant cancer in both sides (Gleason score ≤4 + 3) OR insignificant disease with >50% of biopsy cores OR bilateral clinically insignificant disease with <50% of biopsy cores positive	• To determine the proportion of men who are free of clinically significant PCa in the treated area AND are free of clinically significant PCa in the untreated area 36 mo after focal therapy using HIFU
Focal therapy using HIFU for localized prostate cancer (NCT02016040)	Jewish General Hospital, Montréal, Canada	II	• Age >50 y, stage T1c or T2a, PSA <10 ng/mL • Gleason ≤7 (3 + 4)	• Rate of patients without cancer (6 mo) using MRI, biopsy, PSA
Focal MR-guided focused ultrasound treatment of localized low-intermediate risk prostate cancer (NCT01226576)	InSightec, USA	II	• Age 55–80 y, stage T1–T2b, PSA <20 ng/mL, PV <60 mL • Gleason score 6 or 7 on targeted biopsy • Low-intermediate risk, organ-confined prostate cancer • ≤2 lesions, each ≤10 mm	• Safety: incidence and severity of device-related adverse events from treatment and up to 6-mo follow-up • Evaluating initial effectiveness of MRgFUS to achieve adequate tumor control in low-risk organ-confined PCa patients, based on 6-mo transperineal mapping biopsy findings
Pivotal study of MRI-guided transurethral US ablation to treat localized prostate cancer (NCT02766543)	Profound Medical, Inc, Toronto, Canada	II	• Age 45–80 y, Gleason score ≤ 3 + 4, PSA ≤15 ng/mL • Eligible for MRI and general anesthesia • Clinical stage ≤ T2b; biopsy-confirmed adenocarcinoma of the prostate. Biopsy (minimum 10 cores) obtained ≥6 wk and ≤6 mo before treatment	• Incidence of treatment-emergent adverse events within 1 y
Evaluation of focal treatments of localized prostate cancers with HIFU using the Focal One Device (NCT02662673)	Hospices Civils de Lyon, France	N/A	• Age 50–80 y, stage T1 or T2, PSA ≤ 10 ng/mL • Gleason score of 6 and biopsy invasion length >5 mm OR Gleason score of 6 and corresponding focal lesion of MRI with a PIRADS score ≥4 or 5 and a diameter ≥5 mm OR Gleason score of 7 (3 + 4) regardless of biopsy invasion length OR MRI results	• Negative biopsy rate in the treated area between 6 and 12 mo after treatment
Sonablate HIFU Registry	Multiple U.S. sites	N/A	N/A (probable start January 2017)	N/A

Abbreviations: MRI, magnetic resonance imaging; PCa, prostate cancer; PSA, prostate-specific antigen; PV, prostate volume.

Fig. 2 Currently available therapeutic ultrasound devices. (**a**) Sonasource with Sonablate and Sonachill. (**b**) Ablatherm II. (**c**) Focal One. (**d**) TULSA-PRO. (**e**) Exablate. (Images provided by respective manufacturers.)

based on differences in real-time pre- and post-sonication pulse-echo back-scattered scans.[13] A reflectivity index monitor (RIM) assesses heat buildup in the rectal wall and is used to adjust TAP and pause during the course of treatment. The current version supports MR–ultrasound fusion technology for focal treatment (►**Fig. 3**). Doppler images are available for neurovascular bundle visualization. Prostate size requirement is that the anterior-posterior (AP) dimension plus rectal wall thickness should be less than 37 mm. The Sonablate user manual does not currently specify an apical safety margin because the current lesion size and planning capability does not limit the energy delivery to the apex zone, but some practitioners may choose a safety margin at the apex to spare the external sphincter. As with any ultrasound technology, significant changes in tissue density such as calcifications and/or cysts (depending on size) may have an effect on ultrasound attenuation and overall energy and may impact the patient's suitability for treatment. For safety, rectal wall monitoring and distance calculations are built in, and the physician can compare real-time images with reference images to access for motion. The treatment is done in one to three "horizontal" zones that can overlap, allowing a lesion AP distance to vary from 10 to 37 mm. Posttreatment, patients are typically discharged with a suprapubic catheter or Foley catheter that is removed as soon as patient is able to void on his own[14] (machine cost —$450,000.00. Disposable kit cost—$2400.00 [cost decreases depending on number of disposable kits bought]).

2. Ablatherm II (EDAP TMS, Vaulx-en-Velin, France)—This FDA-approved transrectal device integrates both the imaging transducer (7.5 MHz) and therapeutic transducer (3 MHz). The probe, which is mounted on a robotic arm, is covered with a latex condom filled with proprietary coupling and cooling gel. The system consists of a special bed, which enables lateral positioning (►**Fig. 2b**). The therapeutic transducer has a 45-mm focal length and can create ellipsoid lesions 1.7 mm in diameter and heights ranging from 17 to 24 mm in millimeter increments. The maximum treatable AP dimension of the prostate is 24 mm. Lesions are placed approximately 4 mm from the external sphincter, allowing for conductively transferred heat to ablate the prostatic apex. The rectal wall thickness needs to be less than 6 mm. For larger prostates, volumetric reduction techniques like transurethral resection of the prostate (TURP) are required. In addition to cytoreduction, TURP is also useful in reducing postprocedure urinary symptoms. The system has three treatment modes with fixed power—treatment naïve, previously sonicated, and previously radiated prostate tissues. The difference between the treatment modes is largely to allow for appropriate cooling intervals in between sonications for previously treated tissues. The operator defines the target area and the computer generates a treatment plan in multiple phases ablating at a rate of 25 to 30 mL/hour. With real-time imaging, the treated lesions appear as hyperechoic areas. Calcifications in the treatment volume do not matter. Cysts greater than 10 mL are a contraindication. Patient's motion detection is monitored with an infrared detector and image recognition software determines the location of the rectal wall prior to each shot and the device robotically adjusts the probe

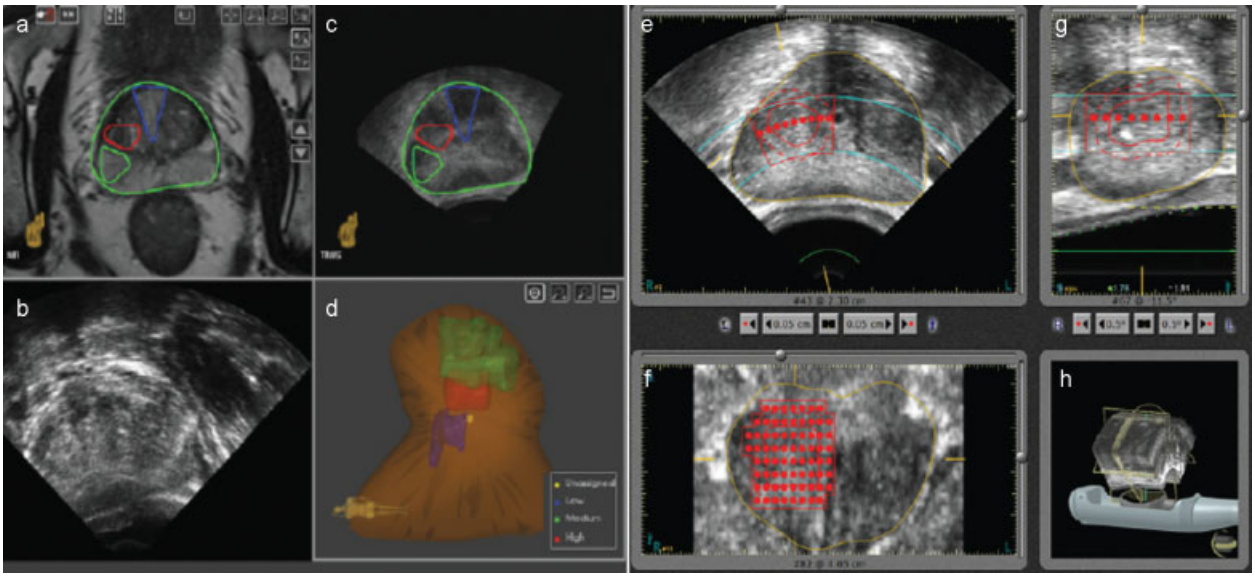

Fig. 3 Representative focal treatment using the Sonoblate 500 system. (**a**) Representative MR image showing three lesions in the contoured prostate, with the red lesion representing clinically significant cancer. (**b**) TRUS image. (**c**) Fused MR–ultrasound image with lesions superimposed in the ultrasound volume. (**d**) 3D representation of prostate volume and lesion volumes. (**e**) Treatment planning images. Blue lines represent the longer focal length transducer (4 cm), which creates lesions of 12 × 3 × 3 mm. The red dots represent the center of 12 mm AP ablation lesions that encompass the high-risk lesion and extend beyond the lesion margin to provide adequate treatment margins. (**f**) Coronal image showing the red dots encompassing the entire craniocaudal length of the lesion and to the determined safety margin. (**g**) Green dotted line representing the rectal wall, which is constantly monitored during treatment. (**h**) Diagram demonstrating energy application from the transducer to the predetermined treatment area. (Image created by combining images provided by Sonacare Medical LLC.)

position to ensure safety[14] (machine cost—$500,000.00; disposable kit cost—$800.00).

3. Focal-One (EDAP TMS, Vaulx-en-Velin, France)—This is a system by EDAP that is CE approved and currently submitted to the FDA for approval. The patient is placed in the right lateral position without the requirement of a special bed. The imaging transducer is the same as the Ablatherm II device, but the HIFU transducer consists of an annular array with 16 individual concentric rings. This array enables electronic steering of the focal point that enables more conformal treatment and lesions of AP dimension ranging from 5 to 40 mm. It also offers MR–ultrasound fusion capabilities for focal therapy. Another improvement from Ablatherm is that the target area can be modified in real time. Additionally, that maximum AP dimension that can be targeted has increased from 24 mm to 40 mm. Contrast-enhanced ultrasound with Sonovue (Bracco Imaging, Switzerland) is available at the end of the procedure to check nonperfused volume and retarget if necessary.[15]
4. TULSA-PRO (Profound Medical Inc., Toronto, Canada)—This device has a CE mark. This device uses a transurethral ultrasound applicator and real-time MRI-guided closed-loop temperature feedback control algorithm to modulate the intensity, frequency, and rotational rate of the ultrasound to deliver precise therapy to individual prostate anatomy. This approach uses HIDU in direct contact with the prostate, instead of HIFU through the rectal wall. Fluid flow through the transurethral ultrasound device as well as a rectal cooling device thermally protects the urethra and rectum, respectively (►**Fig. 4**). By conducting the procedure within an MRI scanner (Phillips and Siemens), high-resolution planning images allow precise delineation of the prostate, which are registered naturally to real-time quantitative thermometry images acquired during

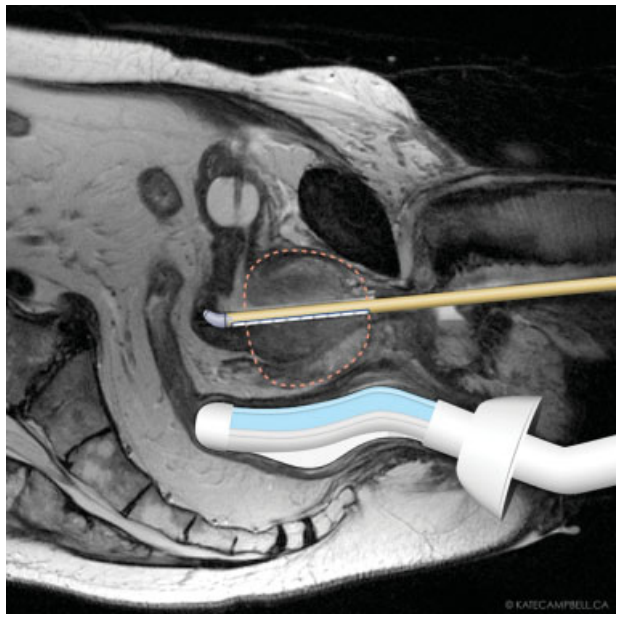

Fig. 4 Representative sagittal MRI image demonstrating placement of the transurethral ultrasound applicator and the endorectal-cooling device which are a part of the TULSA-PRO system. (Image used with permission from Profound Inc.)

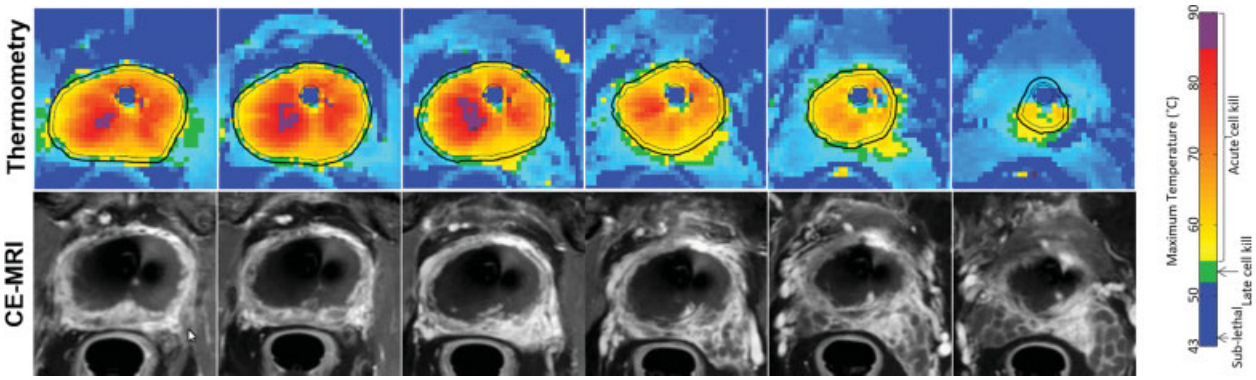

Fig. 5 Thermometry and contrast-enhanced MRI from TULSA-PRO treatment. *Top-row:* MR thermometry images acquired after treatment completion using the TULSA-PRO device demonstrating the T_{max} reached in every voxel. Please note the urethral cooling as seen by low temperatures around the transurethral device (blue voxels). The temperatures are hottest around the urethra. *Bottom-row:* Posttreatment gadolinium-enhanced T1W MR images demonstrating the nonperfused volume which is congruent with the temperature maps on the top row.

ultrasound treatment delivery. Maximum temperature occurs a few millimeters from the urethra and can reach up to 95°C, whereas temperature at the edge of the target tissue is controlled via feedback to not exceed around 55°C to prevent significant heating outside the prostate (►**Figs. 5** and **6**). This device is CE marked and currently being evaluated in an FDA-approved pivotal trial of 110 low- and intermediate-risk prostate cancer patients. Prostate size limitations are 90 mL total volume, 5-cm sagittal length, and 6 cm in axial diameter (the ablation zone can extend 3 cm from the urethra in all directions). Owing to urethral cooling, any tumor within 3 mm of the urethra may not be completely ablated. At the prostate apex, there is a safety margin of 3 mm. Cysts and calcifications greater than 1 cm in size and an obstructive median lobe are contraindications. General anesthesia is used. A suprapubic catheter is placed preprocedurally for continuous bladder drainage and left in place for around 2 weeks. MRI with contrast after treatment is used to visualize the nonperfused volume and confirm the conformal ablation

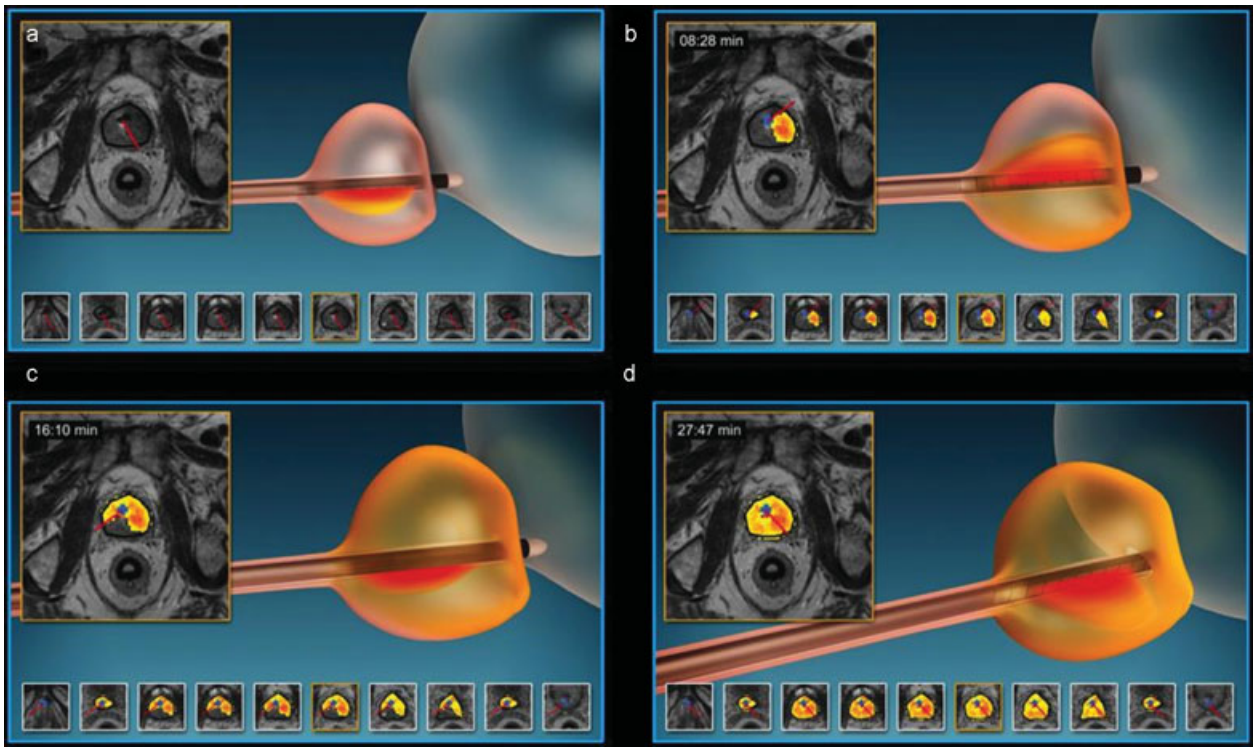

Fig. 6 Diagrammatic representation of the functionality of the TULSA-PRO device. Inlaid MR images on the top-left corners demonstrate the directional ultrasound beam (represented by the solid red line) extending to the prostate capsule (solid black line). Image (**a**) demonstrates that treatment starts at 5 o'clock and rotated counter clockwise after delivering the required heat as measured by PRF thermometry in images **b, c,** and **d**. The color overlay represents Tmax reached in every voxel. The bottom row in each image demonstrates how heating is progressing at other axial slices in the prostate (right to left—base to apex) reaching up to 90°C (purple voxels). Also, we can see that temperatures at the capsule are controlled to 55°C (green voxels). (Image used with permission from Profound Inc.)

(►**Fig. 5**) (machine cost—unavailable; disposable kit cost—unavailable).

5. ExAblate Prostate (INSIGHTEC, Haifa, Israel)—This is a transrectal MRI-guided device, which has not yet been FDA or CE approved and is for focal treatment only. The endorectal phased-array transducer (990 elements/2.3 MHz) enables beam steering to the tumor location in the prostate based on anatomic MR images on which the prostate gland, tumor, and critical structures like rectal wall, neurovascular bundle (NVB), bladder wall, and urethra are contoured. The transducer is housed inside a single-use endorectal balloon with continuous circulating cold degassed water. The patient is in the lithotomy position on a special MRI-compatible tabletop which has the transducer system installed on it. Currently, the device works only with GE MR scanners, but InSightec recently entered into an agreement with Siemens to develop interoperability for ExAblate devices and Siemens scanners. While ultrasound energy is delivered, MRI provides real-time temperature feedback of the targeted region. This device has been shown to do focal or sector ablations. Whole-gland ablations have also been reported anecdotally, but no published data are available. The treatment software automatically generates the treatment plan, optimizing the required energy level at a frequency of 2.3 MHz and power of 30 W, the number of sonications, and the sonication area morphology. The typical focal spot size has a cylinder shape of 2-mm diameter and 8-mm AP. Other spot sizes are also possible by microsteering of the beam. Studies have included a 5-mm margin around the visible lesion limited by surrounding critical structures. Treatment is considered successful if temperature in the sonicated volume is greater than 65°C. Retreatment can be done if needed after cooling periods. General anesthesia has been performed most commonly. Prostate gland volume limitation is 70 mL and lesion distance of up to 4 cm from the rectal wall (6 cm from the transducer—when the transducer is inserted in the rectum, it is ~2 cm from the rectal wall). Calcifications 2 mm or greater in the ultrasound beam path and less than 5 mm from the rectal wall and presence of multiple cysts are contraindications. A urinary catheter, usually a Foley, is left in place for continuous bladder drainage. MRI with contrast after treatment is used to visualize nonperfused volume to confirm adequacy (machine cost—unavailable; disposable kit cost—unavailable).

Indications and Outcomes

Currently, high-intensity ultrasound is used to treat patients in three different contexts: (1) primary treatment for localized, low-to-intermediate risk PCa; (2) salvage therapy after failure of definitive treatment strategies; and (3) as a repeat treatment. Currently, there is no defined role for therapeutic ultrasound in high-risk, localized PCa or metastatic disease, although many patients with high-risk localized PCa have been treated with HIFU.[16] Primary treatment for localized PCa can further be divided into whole-gland, hemiablation, and focal therapies.[7,17] Most long-term data are from whole-gland treatments with some short-term data from focal strategies. Most common complications are related to urinary and sexual dysfunction along with rectal injury.[18]

Inclusion and Exclusion Criteria

Treatment inclusion varies by device (see above for description) with differences in prostate size, tumor location, rectal wall thickness, calcifications, and cysts (►**Table 1**). Most commonly, the patient population has low-to-intermediate risk disease. People with underlying contraindications to anesthesia and MRI (in cases where MRI guidance is used) are usually not good candidates. Patients with underlying rectal problems, nearby implants, and serious urinary problems are also usually excluded.

Primary Treatment for Localized PCa

There have been many publications about efficacy of whole-gland HIFU from Europe, but there has been lack of data from prospective, multi-armed controlled studies. Additionally, the diversity of devices, the heterogeneity of oncologic efficacy, and side-effect statistical analyses among various studies make comparisons difficult.

A retrospective single-center study on 538 consecutive patients treated with Ablatherm devices (Ganzer, Germany) demonstrated biochemical disease-free survival (BDFS) of 71, 63, and 32% in low-, intermediate-, and high-risk patients at 10 years, respectively.[19] Bladder outlet obstruction (BOO) was 28.3%, urinary incontinence (Grades 1, 2, and 3) was 16.9%, and rectourethral fistula rate was 0.7%. Preserved potency was 25.4% in previously potent patients. Approximately 13 to 39% of patients received more than 1 HIFU session depending on risk level of original disease, while 18% of patients received salvage treatments.[20] Crouzet et al recently published data from a prospective single arm single-institution cohort study using multiple iterations of the Ablatherm device in 1,002 patients.[21] The 8-year biochemical-free survival rates based on the Phoenix criteria[22] for low-, intermediate-, and high-risk patients were 76, 63, and 57%, respectively. Approximately 40% of patients received multiple HIFU sessions, while 37.1% of patients received salvage therapy.[21] Potency was preserved in 42.3% of patients with baseline International Index of Erectile Function (IIEF) score of ≥17. Fistula rate was 0.4%, urethral stenosis was 9%, BOO was 16.6%, and urinary incontinence was 23.7%.[21] Dickinson et al recently published medium-term outcomes (5 years) from a UK multi-institutional, whole-gland HIFU treatment of low-to-high risk, localized PCa using Sonablate 500 in 569 patients.[16] Results demonstrated that composite failure-free survival (which was defined as no transition to local salvage therapy, systemic therapy, metastases, or prostate cancer–specific mortality) at 5 years after first HIFU for 569 patients was 70% (95% confidence interval [CI]: 64–74). This was 87% (95% CI: 78–93), 63% (95% CI: 56–70), and 58% (95% CI: 32–77) for National Comprehensive Cancer Network defined[23] low-, intermediate-, and high-risk groups, respectively.[16] Approximately 29% of patients required re-do HIFU (permitted as part of the trial), 30%

required endoscopic interventions for lower urinary tract symptoms, 0.17% developed fistulas, and 12% of previously continent patients developed incontinence. Additionally 39% of patients who had good erectile function at baseline subsequently maintained function.

Complications decrease and efficacy increases with increasing operator experience and improvements in device design. Studies by Uchida et al (Sonablate) and Thüroff et al (Ablatherm) have shown improved efficacy and decreased complications with advancements in device capabilities.[24,25]

A phase II trial of whole-gland ablation with transurethral MR-guided ultrasound ablation device is currently ongoing at multiple sites in United States, Canada, and Europe (►**Table 2**). The phase I trial of 30 patients demonstrated no rectal injuries, no change in erectile function, and a pad-free continence rate of 100% at 12 months.[26] Positive biopsies showed 61% reduction in total cancer length, clinically significant disease in 9 of 29 patients, and any disease in 16 of 29 patients. However, given that 10% of juxta-capsular prostate parenchyma was not treated (3 mm safety margin), better understanding about this device's oncologic efficacy and side-effect profile will be available after the phase II trial.[26]

Clinical trials with the Exablate prostate device are ongoing with preliminary data available from a small number of patients. Overall, the device has shown to be safe.[27,28] Please note that this device has been used mostly for focal therapy and not for whole-gland therapy. In cases of MR-invisible cancer, sector ablations have been performed based on results of mapping biopsy.

Salvage Therapy after Failure of Definitive Treatment Strategies

Studies have examined HIFU as a salvage first-line treatment for palpable, TRUS-evidenced, biopsy-proven locally recurrent PCa after radical prostatectomy (RP). Results suggest a degree of short- and midterm control of PCa but with 10 of 19 (52.6%) failures at 48 months.[29] Gelet et al in 2004,[30] Chaussy et al in 2006,[31] Poissonnier et al in 2008,[32] and Murat et al in 2009[33] used HIFU as local treatment of biopsy-proven recurrence after external beam radiotherapy (EBRT), with a short-term negative biopsy rate of 80, 60–74, 80, and 73%, respectively. The best results were in patients with initial low- or intermediate-risk group characteristics. Patient selection is particularly important in the setting of HIFU after EBRT or brachytherapy, because complication rate is significant, as fistula rate reaches an incidence of 7% and incontinence rate grows up to 50%, with multiple cases of grade 3 stress incontinence.[34] The fistula rate reported as part of the Sonablate FDA data in a post-EBRT population was 5%.

Repeated HIFU Treatments

In contrast to radiotherapy approaches, HIFU treatments can be repeated. Some studies have shown that a repeat HIFU session may improve control of localized disease, but the effects diminish beyond two sessions. Re-do rates for trials described above range from 29 to 40%. Complication rates, especially urinary, of re-do treatments are higher.[35]

Comparison of Different Approaches for Prostate Tissue Targeting with Therapeutic Ultrasound

Focal versus Whole-Gland Therapy

A recent study with 10-year follow-up demonstrated no survival benefit between active surveillance, radiation, and prostatectomy for the management of localized disease, although disease progression and metastasis rates were higher in the active surveillance (AS) cohort.[36] This study reiterates the need for alternative therapies, which can offer disease control and metastasis-free survival while avoiding complications associated with aggressive whole-gland treatment strategies.

When discovered, more than 90% of prostate cancers present with multifocal lesions throughout the prostate.[7] Unilateral disease is thought to be present only in 20 to 40% of patients.[7] A single index lesion, which represents the bulk of PCa tissue, often predicts cancer outcomes, as most metastatic prostate cancers arise from the cell clone of the index lesions.[7,9] This raises the possibility that treatment of the index lesion alone is enough to provide long-term control of PCa. A dichotomy now exists of whether focal therapy targeting the index lesions (aided by minimally invasive techniques) or whole-gland strategies (encompassing minimally invasive techniques, EBRT, and RP) is necessary. Evidence concerning whole-gland therapy is discussed above.

In 2015, an expert consensus panel recommended use of focal therapy in men with intermediate-risk prostate cancer recognizing that patients with low-risk and very low-risk PCa can be adequately managed with active surveillance.[37] Furthermore, it was recommended[37] that a suitable candidate for focal therapy must have a life expectancy greater than 5 years and a WHO performance status of 0 or 1. Focal therapy may allow for preservation of a large majority of normal tissue, including the neurovascular bundle, which should improve adverse events such as sexual dysfunction and urinary incontinence.[7] Aided by the advances in multiparametric magnetic resonance imaging (mpMRI) in accurately defining target lesions, focal therapy can be as specific as targeting the index lesion, broadly targeting the prostate hemisphere, where the lesion in located (hemiablation), and hockey stick configuration, where the hemiablation is extended to include the contralateral posterior or anterior compartment from where the index lesion is located.[7] If the primary lesion is not well visualized (up to 20% of mostly intermediate-risk lesions may be invisible on current MRI sequences[38]), approaches such as sector ablation after mapping biopsy are available, as this is the strategy being used in the InSightec trial. Early data from clinical trials suggest the focal therapy strategy may avoid adverse outcomes compared with whole-gland approaches, but longer-term data are needed. For example, Ahmed et al in 2012 published data from a prospective trial of focal therapy for localized unifocal and multifocal PCa.[39] Analysis of 41 men treated with HIFU using the Sonablate 500 device demonstrated histological negative tumor in 30 of 39 patients at 6 months and 39 of 41 patients having no evidence of disease on mpMRI at 12

months. In terms of sexual function, 31 out of 35 men with good baseline erectile function had erection sufficient for penetration. In terms of urinary incontinency, all 38 men who were pad free at baseline remained pad free at 12 months. Overall, 26 (84%) patients achieved the trifecta of being pad free, erections sufficient for intercourse, and no evidence of clinically significant disease on mpMRI at 12 months.[39]

In 2015, Ahmed et al analyzed data from 56 patients with mpMRI and biopsy-proven multifocal PCa treated with Sonoblate 500 on the index lesion only. At 12 months, 48 of 56 had no measurable PCa by biopsy and/or mpMRI. A composite of patients with leak-free, pad-free continence, and erections sufficient for penetration decreased from baseline frequency of 40 out of 56 (71.4%) to 33 out of 56 (58.9%) patients in the same time period.[40] Cordeiro et al recently published data from 67 patients treated with HIFU hemiablation for unilateral organ-confined PCa using the Ablatherm HIFU system.[41] At the median follow-up of 12 months, negative biopsy was confirmed in 50 of 67 patients (83.6%) with 10 of 67 patients having positive biopsies in the treated lobe, 6 of 67 patients in the contralateral lobe, and 1 of 67 patients with positive biopsies in bilateral lobes. PSA values decreased to 1.5 $\pm$ 1.3 ng/mL. In terms of functional outcomes, continence and urinary symptoms were not significantly adversely affected, but there was significant impact on erection as measured by the IIEF questionnaires.[41] This study was followed by a more recent multicenter hemiablation trial of 111 patients with mpMRI and biopsy-proven unilateral PCa using the Ablatherm Integrated Imaging medical device. At 12 months, 95% demonstrated absence of clinically significant PCa. Radical treatment-free survival at 24 months (radical interventions include RP, radiotherapies, and radical HIFU) was 89%. At 12 months, continence was preserved in 97% of patients and erectile functions in 78% of patients.[42]

MR versus Ultrasound Imaging Guidance for Therapeutic Ultrasound

Ultrasound-guided procedures are usually easier to do as compared with MRI-guided procedures. An ultrasound device does not require a special room and can usually be operated independently by the physician performing the ablation. MRI guidance, on the other hand, requires use of specialized, MRI-compatible equipment, and stringent observance of MRI safety practices along with use of a MRI scanner room including the services of a technologist. MRI is more sensitive to artifacts from motion and small air bubbles, and requires longer time to re-plan the treatment in case organ or patient motion necessitates it.

Compared with ultrasound, MRI offers the chance to directly visualize the target lesion. Both the Sonablate 500 and Focal One devices offer the ability to use MR–ultrasound fusion to target MR visible lesions under ultrasound imaging using registration of MR images to the ultrasound images (►**Fig. 3**). Fusion algorithms can have a co-registration error of up to 3 mm for small lesions.[43] Many studies have shown great performance of MR–ultrasound fusion biopsy systems in diagnosing PCa. Due the possibility of co-registration errors, practitioners must plan for adequate safety margins (►**Fig. 3**). Overall, MRI has greater spatial and contrast resolution than ultrasound, making visualization of prostate boundaries and periprostatic structures such as neurovascular bundles easier.

MRI allows for real-time monitoring of temperature and thermal dose using temperature-sensitive sequences. A commonly used technique is the proton resonance frequency shift method that measures chemical shifts in continuously acquired, 2D phase-sensitive images.[9,10,44] Information is displayed in a color-coded thermal map. With time information, thermal dose can be calculated and also displayed. Motion, metallic artifacts, and problems at the tissue/fat interface limit MR thermometry. Ultrasound-guided HIFU can only check for secondary signs of temperature elevation in the tissues such as gray scale changes and radiofrequency-based measurement of tissue back-scattering power (as used in the Sonoblate 500 device), which are not a very accurate indicator of thermal dose and tissue damage when compared with quantitative MR thermometry. Please see ►**Table 3** for a summary comparing MR versus ultrasound for imaging guidance.

After treatment, both contrast-enhanced MRI (CE-MRI) with gadolinium (►**Fig. 5**) and contrast-enhanced ultrasound (CE-US) with microbubbles can be performed to

Table 3 MR versus ultrasound imaging guidance during therapeutic ultrasound

	MRI	Ultrasound
Advantages	• Greater spatial and contrast resolution • Real-time monitoring of temperature and thermal dose • Better visualization of prostate boundaries and periprostatic structures • Direct visualization of tumor • Complexity due to equipment and personnel	• Relative familiarity and ease of use • MR–ultrasound fusion available (however, small chance of registration) • Ability to retreat perfused areas after post-treatment microbubble-enhanced scans
Disadvantages	• Sensitivity to artifacts caused by motion and small air bubbles • Inability to retreat after post–gadolinium injection • Hip prostheses can preclude MRI guidance	• Secondary signs of temperature changes based on greyscale changes and RF pulse-echo backscatter are not true estimates of heat deposition

evaluate the true extent of thermal damage. Currently, after gadolinium administration, there cannot be retreatment of any enhancing areas due to concerns about gadolinium stability.[45] Therefore, as gadolinium agents have intravascular half-life of 90 minutes, it will not be feasible to retreat perfused areas in the same session. However, ex vivo experiments do suggest stability and it has been used just prior to treatment in Japan. A more recent concern about gadolinium is that it can cause error in MR thermometry.[46] On the other hand, CE-US with microbubble posttreatment is readily available with Focal One. Retreatment of enhancing areas can be done without any detrimental effects.

Transrectal versus Transurethral Approach

As described earlier, all HIFU prostate devices deliver therapeutic ultrasound transrectally (►**Table 1**). Urologists do many transrectal prostate biopsies and are very familiar with the transrectal approach. However, even with precautions such as rectal wall monitoring and cooling, there remains a small risk of rectal injury with this approach. The use of a HIDU transurethral approach with the urethral cooling and endorectal-cooling device (TULSA-PRO), in contrast to the transrectal HIFU approach, may reduce risk of damage to periprostatic structures such as the rectum, urinary sphincter, neurovascular bundles, and pelvic bone. Further data will become available as phase II trials are underway.

Current FDA Approval Controversy and Guidelines

Prior to the 2015 FDA approval for prostate tissue ablation, devices failed to win approval for localized prostate cancer treatment due to lack of substantial clinical efficacy.[47] The first application by EDAP TMS (July 2014) failed to win approval for Ablatherm Integrated Imaging HIFU System due to lack of clinical benefit. A nonrandomized controlled trial compared efficacy of their device to cryotherapy for low-risk PCa. The trial, which began in 2006, was terminated in 2010 due to inability to enroll enough patients, particularly in the cryotherapy arm. EDAP then conducted a meta-analysis of HIFU and cryotherapy results in the literature, plus a review of comparisons of a European HIFU registry with surgery in U.S. VA study PIVOT. FDA did not approve the device due to deficiencies and potential safety concerns including a 28% cumulative positive biopsy rate 2 years after HIFU treatment among individuals in the nonrandomized trial.[48] SonaCare Medical tried to win FDA approval for the Sonablate 450 HIFU System based on an interim analysis on a multicenter, single-arm trial from the first 100 patients (200 planned) with recurrent PCa following EBRT who underwent whole-gland HIFU ablation compared with surgery or cryotherapy in the same postradiation setting. Assessment was made of BFS and NBR after 12 months and showed similar safety profile to surgery but was deemed too early to demonstrate any clinical advantage and the FDA committee advised the company to wait for trial completion.[49]

Then in 2015, FDA approved Sonablate under a de novo pathway for tissue ablation, without specification of an indication for PCa. The de novo pathway was introduced in 1997 with the FDA Modernization Act and is an alternative to a lengthy and costly premarket approval process that requires stringent clinical data (that were lacking during the two prior applications for a specific prostate cancer indication). De novo clearance is predicated on three conditions: (1) a novel device or new intended use of an existing device; (2) a low- or moderate-risk profile; (3) no predicate (i.e., legally marketed device). Subsequently, Ablatherm then obtained 510K FDA clearance. FDA commented, "Clinicians, in consultation with their patients, should decide how best to use this tool."[11]

Despite some encouraging data, current European guidelines set forth by EAU-ESTRO-SIOG suggest HIFU use in nonmetastatic PCa as part of a clinical trial only.[50] The American Urological Association (AUA) guidelines from 2007 (updated in 2011) made no suggestion of HIFU treatment for localized PCA due to the minimal amount of data available. Until longer-term follow-up studies occur or randomized control trials directly testing standard treatments to high-intensity ultrasound approaches, guidelines are unlikely to change.[51]

Comparing HIFU with other Standard and Minimally Invasive Approaches

For whole-gland therapeutic strategies, urinary incontinence and sexual dysfunction are the major complications associated with treatment. These adverse events are routinely measured using validated questionnaires such as the International Prostate Symptom Score, IIEF 15 items, and The University of California, Los Angeles-Expanded Prostate Cancer Index Composite Urinary Continence domain. This allows for some standardization of adverse outcomes as comparisons are made between therapies and trials.

A Comparison of HIFU with Active Surveillance, Radical Prostatectomy, and Radiation Treatment

In terms of oncological outcomes, a recent UK meta-analysis looked at data from 4,000 patients who received HIFU across 21 studies (1 NRCS and 20 case series). Evidence suggests statistically significant biochemical recurrence (BCR) and disease-free survival (DFS) rates were higher at 1 year when using HIFU than when using EBRT but were no longer statistically significant at 5 and 3 years, respectively. The biochemical result was in contrast to overall survival at 4 years, which was higher when using HIFU. There was no evidence of a difference between cancer-specific outcomes for HIFU versus RP. Limited data comparing outcomes in people who had HIFU versus AS suggested no evidence of significant difference in overall survival at 4 years.[18]

In terms of complications, the same meta-analysis demonstrated a numerically increased risk of incontinence for HIFU compared with EBRT at 1 year, but this was not statistically significant. When compared with RP, HIFU showed a statistically significant decrease in risk of incontinence at 1 year. At 5 years, the risk of incontinence was larger for HIFU, but was not statistically significant. In terms

of erectile dysfunction, meta-analysis from two studies showed a numerical reduction in rates of erectile dysfunction following HIFU compared with RP at 1 year. In terms of rectourethral fistula, the recent meta-analysis suggests fistula occurrence was low with median reported rate from three studies of 1%.[18] Limited data comparing outcomes in people who had HIFU versus AS suggested no evidence of significant difference in erectile dysfunction at 1 year.[18]

There are short-term complications associated with procedural use of HIFU including urinary retention, infections (e.g., urinary tract or epididymo-orchitis), dysuria, urethral sloughing, stricture formation, and bladder spasms. When making comparisons to EBRT or RP, differences in short-term complications were broadly similar.

Other Ablative Technologies

Along with therapeutic ultrasound, there are many competing minimally invasive technologies available for PCa treatment, including *cryoablation, laser ablation, radio-frequency ablation, targeted brachytherapy, photodynamic therapy (PDT), and irreversible electroporation (IRE).* All approaches have been shown to be safe, but cryotherapy and HIFU are the two most widely used methodologies.[52] A comprehensive discussion about pros and cons of each approach is beyond the scope of this article. A recent review has provided an excellent comparison of focal ablation strategies.[7] Many clinical trials are ongoing for evaluation of various approaches. Below, we present data from a few comparative studies.

Primary whole-gland cryoablation and HIFU demonstrated good oncological outcomes for localized prostate cancer. The HIFU patients experienced better urinary function improvement and more possible sexual function preservation than the cryoablation patients.[53]

Barret et al compared three groups of patients undergoing cryotherapy, HIFU, or photodynamic therapy and identified no difference in postoperative IIEF scores between treatment groups and no difference in pad-free rates or change in IPSS scores at 12-month follow-up assessment.[54] No significant difference in efficacy or complications of different types of energies used for focal ablation has been demonstrated. Oncologic effectiveness of focal therapy in the long term needs to be further evaluated.[55] Some groups have suggested an "a-la-carte" approach with focal therapy consisting of using HIFU for posterior tumors, transperineal/transrectal needle ablation for anterior tumors in large glands, and nonthermal treatment of tumors near critical structures, for example, at the apex (IRE, PDT, brachytherapy).

Detection of Recurrence after Treatment and Options after Focal and Whole-Gland HIFU Failure

For patients with localized PCa undergoing initial definitive therapy such as RP, biochemical failure (BCF) is defined as failure of PSA to fall to undetectable levels or undetectable PSA after RP with subsequent detectable PSA on two or more determinations.[23] To date, there is no universal consensus on the definition of BCF in patients treated with therapeutic ultrasound. Multiple studies have suggested a PSA nadir, which usually reached in 3 months, of 0 to 0.2 ng/mL had a lower clinical failure rate than patients with PSA nadir greater than 0.21 ng/mL after HIFU treatment. However, PSA nadirs often vary depending on the type of treatment. For example, patients undergoing focal therapy may have a higher PSA nadir than those with whole-gland ablations due to the remaining functional prostatic parenchyma. Even with whole-gland treatment, there is some prostate parenchyma that is spared, usually at the apex. More recently, the American Society for Therapeutic Radiology and Oncology (ASTRO) adopted the Stuttgart criteria (PSA nadir + increase > 1.2 ng/mL)[22] or the less stringent Phoenix criteria (PSA nadir + increase > 2 ng/mL)[56] for failure after EBRT. These criteria have been applied to patients treated with HIFU by multiple clinical trials. PSAs are routinely monitored at 3, 6, and 12 months posttreatment and then yearly afterward.

Beyond PSA, mpMRI and prostate biopsy are routinely performed at 1 year posttreatment or sooner if PSA values become concerning. mpMRI is of increasing importance after focal therapy.[57,58] The most effective sequence in determining remnant tumor is dynamic contrast-enhanced imaging, given the propensity of T2 and diffusion-weighted images to be affected and confounded significantly by treatment. Residual disease is sometimes encountered in biopsy. An international panel of experts recently agreed that cancer in the treatment zone from focal ablations of Gleason grade 3 + 3 with a cancer core length of 3 mm is clinically acceptable but only if this represents a decrease in the original cancer burden. Basically, the original cancer lesion should be of a higher grade or higher volume than the cancer that remains in the treatment field. Gleason grade 3 + 4 or 4 + 3 is never clinically acceptable. Based on clinical trial design, a decision is made of whether a patient should undergo re-do HIFU treatment, definitive therapy with RP, or continued surveillance.[37] Overall, the lack of a universal definition of BCF leads to challenges in interpreting oncologic efficacy.[59]

Costs

Therapeutic ultrasound for localized PCa represents a "bleeding edge" technology with a degree of risk to patients and early adopters in terms of complications and costs associated with treatment. Recent efforts have tried to understand time-driven activity-based costing for currently approved competing treatments of low-risk PCa.[60] Calculated costs, which takes into account each phase of care from the initial urological visit through 12 years of follow-up, suggests AS is more cost-effective than low-dose brachytherapy, cryotherapy, high-dose brachytherapy, robotic-assisted laparoscopic prostatectomy (RALP), and intensity-modulated radiation therapy (IMRT) in ascending order.[59] Strategies such as brachytherapy and RALP take approximately 7 to 10 years to become cost equivalent to AS. Ramsay et al determined that HIFU was the most cost-effective whole-gland ablative therapy (compared with cryotherapy and brachytherapy).[18] Based on current device costs, treatment

times, and estimated costs of treating complications of HIFU including conversion to definite therapy such as RP, an estimated numerical cost of partial prostate gland HIFU could exceed RALP within 2 years but remain more cost-effective compared with IMRT.[11] True focal therapies cost analyses have yet to be performed.

Conclusion

PCa diagnosis and treatment strategies are evolving because of increasing adoption of prostate MRI, targeted fusion biopsy, and new ablative techniques. Given the significant side effects associated with whole-gland treatment, strategies are shifting toward focal treatment of the index lesion. Therapeutic ultrasound has a potential to be a nonaggressive, successful treatment option for localized disease. Critics of HIFU point to lack of large multicenter trials demonstrating its efficacy and significant side effects of whole-gland treatment. Supporters of HIFU point toward its potential for focal therapy that is just now being studied. This underlines the need for comparative studies, registries, and proper patient selection to demonstrate clinical efficacy and reduced complications. Additionally, more long-term information on cancer-specific and overall survival is needed before therapeutic ultrasound can truly challenge the current standards of care including RP and AS. Many trials are ongoing (►**Table 2**) and recent FDA approval for prostate tissue ablation will likely enable further trials for efficacy testing and hopefully lead to more options for patients with localized PCa, especially in the United States.

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