Histotripsy: The Next Generation of High-Intensity Focused Ultrasound for Focal Prostate Cancer Therapy

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This article reviews the most current methods and technological aspects of high-intensity focused ultrasound (HIFU), which is termed histotripsy. The rationale for focal therapy for prostate carcinoma rather than prostatectomy, which is being used extensively throughout Europe and Asia, is presented, and an argument for why HIFU is the modality of choice for primary therapy and recurrent disease is offered. The article presents a review of the technical advances including higher ultrasound beam energy than current thermal HIFU which allows for more accurate tissue targeting, less collateral tissue damage, and faster treatment times. Finally, the article presents a discussion about the advantage of ultrasound guidance for histotripsy in preference to magnetic resonance imaging guidance primarily based on cost, ease of application, and portability.

Key Words—focal therapy; high-intensity focused ultrasound; prostate cancer

As male life expectancy has increased over the last 25 years, the age at which prostate cancer is detected has decreased on average by 10 years.[1] Prostate carcinoma is the most common malignant neoplasm in men.[2,3] These trends have exposed the limitations in the conventional treatment of prostate carcinoma, including a considerable risk of recurrence and long-term genitourinary morbidity,[4,5] which have a substantial detrimental impact on the quality of life.[6–8] The development of multiparametric magnetic resonance (MR) imaging[9] and MR-ultrasound (US) fusion-guided biopsies[10–12] has substantially improved the patient selection process.

Numerous publications have emerged this year reporting a wide array of patient selection criteria, MR guidance alone, and neural networks. Kim et al[13] found that it was possible to substitute fusion biopsy for systemic biopsy to find substantial prostate carcinoma. Marra et al[14] concluded that transperineal biopsy instead of transrectal guidance would avoid infection. Haskins et al[15] found that registration between US and MR images was improved by neural networking. However, Bonekamp et al[16] recently found that up to 18% of substantial cancers were missed by multiparametric MR mapping. Hwang et al[17] found that fusion biopsy improved the detection rate of carcinoma in patients with prostate-specific antigen levels of less than 10 ng/mL. All of these methods allow patients to choose focal therapy combined with active surveillance rather than higher-risk invasive surgical or radiation therapy procedures for low- to intermediate-risk carcinomas that are contained within the prostate capsule.[18–20]

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Abbreviations
HIFU, high-intensity focused ultrasound; MR, magnetic resonance; US, ultrasound

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It is now commonly believed that the index lesion, defined as the largest lesion detected at imaging, is the one that will be responsible for disease progression.[21–24] To avoid overtreatment of these lesions[25] and reduce costs,[26] alternative curative therapies that offer rates of cancer control equivalent or better to radical prostatectomy and external radiotherapy are being attempted with greater frequency, particularly in Europe. Such alternative focal therapy treatments offer the advantage of decreased morbidity and therefore an improved quality of life.[27,28] At least 7 different energy sources[29] have been used for focal prostate therapy, including cryoablation,[30] brachytherapy, high-intensity focused ultrasound (HIFU) ablation,[31,32] focal laser ablation,[33] irreversible electroporation, vascular-targeted photodynamic therapy,[34] and stereotactic ablative radiotherapy.[35]

Research into the use of HIFU has been ongoing since the 1990s, and at this time, more than 65,000 patients with prostate cancer have been treated with HIFU in Europe.[1,36] Compared to the other modalities, HIFU ablation offers advantages over other therapies, especially the lack of substantial injury to tissues outside the treatment zone.[37] A major advantage is that HIFU is completely noninvasive and does not require the insertion of probes into the target tissue.[38] High-intensity focused US procedures are performed transperineally or via a transrectal approach (Figure 1). Transurethral HIFU has been described, but this procedure is not performed routinely (Figure 2). The literature suggests that HIFU is superior to other methods because there is less posttreatment morbidity after HIFU in comparison to the other techniques.[39,40]

Figure 1. Diagram of a transrectal US-guided HIFU system.

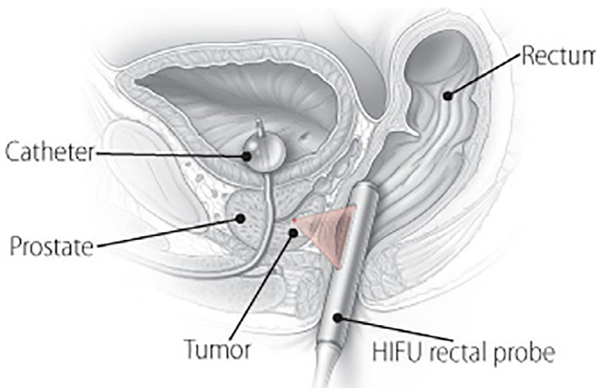
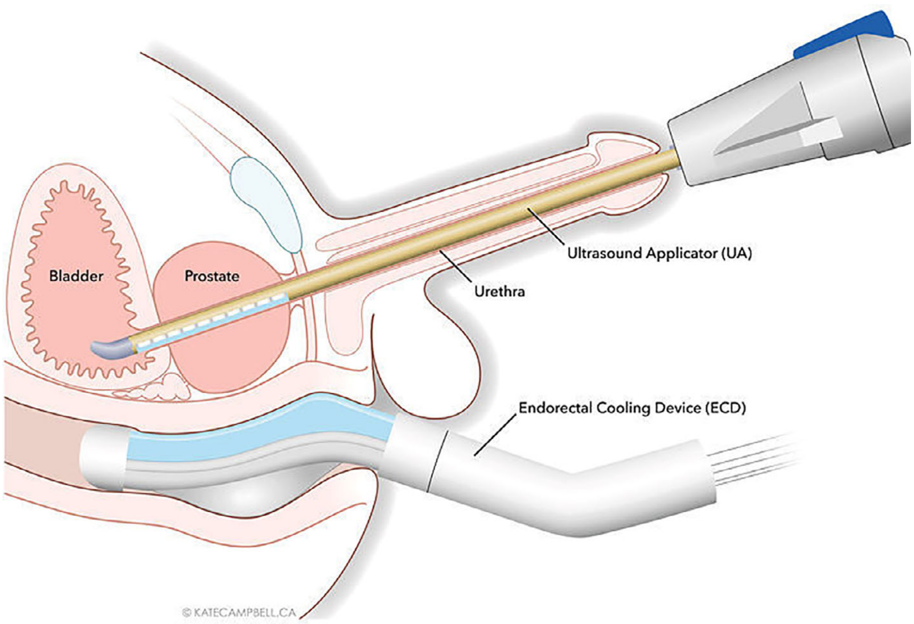


Figure 2. Diagram of a transurethral US-guided HIFU system.



Thermal Versus Mechanical HIFU

High-intensity focused US can produce thermal and mechanical effects on tissues, depending on the treatment parameters.[41] Thermal HIFU ablation is the only method implemented clinically currently. Mechanical ablation is still being developed and is experimental at this time, although it shows great promise. Thermal ablation by HIFU works by absorption of continuous US waves. In current clinical applications (HIFU), tissue is destroyed by heating a small focal area between 60°C and 80°C for 1 second or longer, which results in coagulative necrosis at that spot. All current clinical HIFU devices for prostate ablation (Focal One [EDAP, Lyon, France], Sonablate [Sonacare, Charlotte, NC], and TULSA-Pro [Profound Medical, Toronto, Ontario, Canada]) rely on these thermal effects to achieve ablation. Formation of vapor and cavitation bubbles in thermally denatured tissue typically accompanies such treatments and represents a useful, although indirect, way of visualizing the treated area on US imaging. All current clinical HIFU devices for prostate thermal ablation are miniaturized to be endoluminal, and the treatment is administered either transrectally (Focal One and Sonablate) or transurethrally (TULSA-Pro), under US and MR guidance, correspondingly. These devices are illustrated in Figure 1.

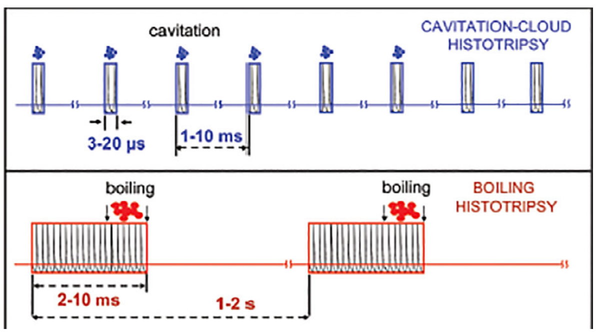
Mechanical ablation of tissue is a more recently discovered regimen of HIFU and is termed histotripsy.[42] Histotripsy uses short (microseconds- to milliseconds-long), infrequent, high-amplitude bursts of HIFU waves that induce bubble activity at the HIFU focus to fractionate tissue down to subcellular components.[42] The intensity of each pulse in these sequences is higher than what is used in thermal HIFU ablation, whereas the time-averaged intensity is lower because the bursts are delivered at a low pulse repetition frequency.[43] The bubble activity may be initiated in 1 of 2 ways: by vapor bubble formation or by cavitation cloud formation at the focus, with the corresponding techniques termed boiling histotripsy and shock wave scattering histotripsy. The major difference in the techniques is the intensity and duration of HIFU bursts. In boiling histotripsy, the pulses are emitted for a duration of 1 to 10 milliseconds every 0.1 to 1 seconds (1.0–10 Hz), whereas in cavitation cloud histotripsy, the pulses are 3 to 20 microseconds in duration, higher in amplitude, and repeated every 1 to 10 milliseconds (100–1000 Hz; Figure 3).[44,45]

Both techniques rely on nonlinear distortion of the sound waves and the subsequent formation of US shock waves at the HIFU focus to destroy tissue. Specifically, in boiling histotripsy, every millisecond-long pulse of HIFU superheats the tissue at the focal point, producing a millimeter-sized vapor bubble cloud in several milliseconds.[46] The interaction of the vapor cavity with the remainder of the HIFU pulse fractionates the tissue.[47] In mechanical histotripsy, a dense cavitation bubble cloud is formed during each HIFU pulse, and its collapse fractionates tissue at the focus.[36] Although the physical mechanisms of achieving bubble activity are different,[48] the outcome of both histotripsy techniques is the same: tissue fractionation.[41]

One of the key advantages of histotripsy techniques over thermal ablation that has been demonstrated in a number of studies is tissue selectivity, with cells being more sensitive to histotripsy damage than extracellular matrix and connective tissue structures (eg, blood vessels and ducts).[49] Furthermore, because it is being nonthermal in nature, histotripsy treatment is not affected by heat sink effects[50] and perfusion, a substantial problem for thermal ablation methods.[51]

Currently, mechanical HIFU technology, as applied to prostate ablation, is predominately at the phase of preclinical animal studies.[52–55] In the very first study in humans, prostate hypertrophy was treated by the cavitation histotripsy technique in 25 patients with an extracorporeal HIFU device (Vortx Rx [Histosonics, Inc, Ann Arbor, MI]).[56] A transient improvement in symptoms was observed in that study, and no intraoperative

Figure 3. Schematic showing the pulse periodic timing for cavitation and boiling histotripsy (reprinted with permission from *Acoustics Today*; https://acousticstoday.org/issues/2012AT/Oct2012/index.html#?page=28).



complications and only 1 case of urinary retention occurred.[56] The treatment effect was less dramatic than expected because of a limited acoustic window and challenges in targeting the prostate by the device in the extracorporeal setting.

High-Intensity Focused US as a Primary Treatment Option

At this point in time, no preference has been found in the United States regarding the safety and effectiveness of primary whole- or partial-gland HIFU or patient preferences related to the safety and effectiveness of outcomes from HIFU therapy.[57,58] Appropriate patient selection is essential for successful focal therapy.[42,45,47,59] Patients with localized prostate carcinoma[60,61] with low- to intermediate-risk disease,[62] particularly those with lower pre-HIFU prostate-specific antigen levels, and favorable Gleason scores seem to have better outcomes.[63] Noninvasive treatment options with HIFU vary from focal ablation to hemiablation to entire prostate ablation. High-intensity focused US has been investigated in each of these roles in numerous studies outside the United States. Capogrosso et al[64] reported that in patients older than 70 years, whole-gland HIFU was a feasible alternative for treatment in elderly men with local intermediate-risk prostate carcinoma who were unfit for surgery. In a direct comparison of partial-gland ablation versus radical prostatectomy with robot assistance in low- to intermediate-risk prostate carcinoma, Garcia-Barreras et al[65] concluded that when confined to the prostate, partial-gland ablation offered good oncologic control with fewer adverse effects compared to radical prostatectomy. In a study of 55 men undergoing hemiablation, Albisinni et al[53] found that HIFU was associated with faster recovery of continence, and the risk of erectile dysfunction was significantly lower. van Velthoven et al[52] had similar results in 50 patients. In a study of 67 patients, Feijoo et al[66] concluded HIFU hemiablation of unilateral organ-confined prostate cancer was satisfactory for cancer control. In a meta-analysis of 167 articles comprising 366 patients, Albisinni et al[67] found that salvage treatment-free survival, reported potency, and continence were all higher with HIFU hemiablation therapy then prostatectomy.

Long-term data are still not available for evaluation of HIFU therapy.[68,69] However, in the largest study to date with 569 patients and 5-year follow-up, Dickinson et al[37] indicated that HIFU was a reasonable choice for the treatment of nonmetastatic prostate cancer. Heterogeneity in patient selection and insufficient evidence are the major limitations at this time for concluding that focal treatment therapy with HIFU is as effective as more-traditional invasive therapy, although as more studies emerge, it is clear that focal HIFU therapy in the appropriate circumstances is very promising.[70,71]

Comparison With Other Focal Therapies

Multiple direct comparisons have also been performed between HIFU and other focal therapy modalities for the primary treatment of prostate cancer. Donis Canet et al[72] found that in reviewing 14 studies from the literature with a total of 350 patients treated with cryotherapy and 1107 treated with HIFU, both provided comparable functional results, although the oncologic results were poorer with cryotherapy. In their review of the literature, Ganzer et al[35] concluded that posterior prostate lesions were most amenable to focal therapy using HIFU; cryotherapy was better for anterior tumors; and apical lesions were best treated with focal brachytherapy. The major competitor to the use of HIFU is active surveillance: in other words, watching and waiting rather than treating.[73,74] Barayan et al[75] found that active surveillance of unfavorable disease features in patients with localized low- to intermediate-risk prostate carcinoma would prevent unnecessary treatment, including HIFU hemiablation. Although no definitive study exists to prove which is the best therapy, HIFU is the only one that is truly noninvasive, not requiring the placement of probes into the patient.

Combined Therapy

Fewer articles have investigated the combined use of varying modalities for local prostate cancer. Baumunk and Schostak[76] found that primary whole-gland HIFU resulted in similar oncologic efficacy and side effects compared to radical prostatectomy combined with radiotherapy or brachytherapy. Bakarev et al[77] reported that in 32 patients, neoadjuvant hormone therapy enhanced the efficacy of HIFU for the treatment of prostate carcinoma. Chiang compared radical prostatectomy, high-dose brachytherapy, cryoablation, and HIFU for localized prostate carcinoma and concluded that whereas oncologic outcomes were similar, the HIFU group had better urinary function, better sexual function, and an improved quality of life. High-intensity focused US–induced hyperthermia has also been investigated in preclinical studies to trigger the release of chemotherapeutic drugs from temperature-sensitive liposomes.[78–80] In general, various forms of focal therapy are all very similar in efficacy. The differences between them seem to be related more to morbidity and invasiveness.

High-Intensity Focused US in the Treatment of Recurrence

Patients with biochemical evidence of recurrence, which can occur in up to one-third of men treated primarily with surgery or radiation therapy,[81–83] are problematic, and treatment strategies in such patients can include androgen deprivation therapy (although this is associated with substantial side effects), radiotherapy, brachytherapy,[84] proton therapy,[85] and HIFU.[86,87] All salvage treatments are more toxic to the patient than the primary treatment.[88] Numerous strategies have been used to treat recurrent disease. Chapelon et al[89] reported that salvage HIFU therapy after field external beam radiation therapy was increasing, and outcomes were similar to those achieved at surgery, with the advantage of fewer adverse effects,[90] including urinary tract infections, bladder neck strictures, rectourethral fistulas, and osteitis pubis.[82] Jones et al[91] had similar results using whole-gland HIFU. In a study of 49 patients using a posttreatment prostate-specific antigen nadir of 0.2 ng/mL as a cutoff value to define biochemical recurrence, Fomkin et al[92] recommended that external beam radiation therapy could be used for salvage therapy after HIFU.

Crouzet et al[93] reported that for locally recurrent prostate carcinoma after field external beam radiation therapy, salvage HIFU should be initiated early because of high rates of cancer-specific and metastasis-free survival rates. Golbari and Katz[94] concluded that there did not appear to be any significant difference in overall survival for more-invasive salvage radical prostatectomy compared to minimally invasive treatment of recurrent carcinoma. A consensus on a trial design to study focal salvage therapy has been published,[95] but to date, no authoritative recommendations can be made regarding the treatment of focal recurrent disease because of the absence of randomized data and protocols.[96] Regardless, HIFU has to be considered as a leading option for the treatment of recurrent disease.

Magnetic Resonance Versus US Guidance for HIFU

Magnetic resonance imaging and thermometry are used to guide most forms of HIFU used in clinical practice currently because temperature the elevation to date cannot be visualized with US.[74,97,98] Magnetic resonance thermometry does image the treatment area much better for this type of HIFU. Magnetic resonance guidance[99,100] has advantages over US, particularly superior depiction of anatomic detail.[101] Magnetic resonance thermometry[102] depicts the changes that occur within hydrogen atoms when they are subjected to heat. These changes can be recorded with phase shift imaging,[103] chemical shift imaging,[104] diffusion,[105] spectroscopy,[106] or even contrast agents added to the tissues.[107]

Ultrasound guidance has been used for a longer time than MR guidance. In a study involving 30 patients, Burtnyk et al[108] found that with MR thermometry, a high degree of spatial resolution control to within 1.3 mm could be achieved. No intraoperative complications occurred in this study, and there were no cases of urinary incontinence, fistulas, or rectal injury. Complications from transurethral MR-guided HIFU did include hematuria, urinary tract infections, epididymitis, and acute urinary retention. Normal micturation function returned in all cases by 6 months.[108] Bonekamp et al[109] performed a review in 30 patients undergoing MR-guided US ablation of the prostate and found that immediate posttreatment contrast MR imaging underrepresented the entire thermal ablation volume compared to that seen 12 months after the procedure. Burtnyk et al[108] found 0.9-mm accuracy and precision at necropsy in 8 patients undergoing transurethral prostate ablation using MR thermographic guidance. Chin et al[110] concluded that MR-guided transurethral ablation for localized prostate carcinoma was feasible, safe, and technically precise for whole-gland ablation. Ramsay et al[111] found that MR-guided HIFU could treat up to a 70-cm^3 volume of tissue. Robotic systems have been developed for MR-guided HIFU treatment.[112]

The major advantages of real-time US guidance[113] over MR is that the HIFU units can be smaller, portable, and less expensive and can allow for treatment of larger and multiple tumors, since the patient does not have to hold still as much as with MR guidance, and greater tissue selectivity.[50,114] Operator dependence and the absence of clear feedback on the completeness of ablation beyond echogenicity changes that may or may not be accurate are limitations of US-guided HIFU. Sophisticated mathematical techniques[115,116] as well as advanced US technology such as that reported by Lyka et al,[117] in which prostate motion registration optimizes targeting, have been used for the performance of fused and transrectal US examinations at biopsies and could be applied to HIFU monitoring as well. Algorithms have been produced that are clinically available, such as the Tissue Change Monitoring system on the Sonoblate system, which allows real-time US imaging to monitor HIFU treatment.[118,119] It has been noted that during treatment of prostate cancer with HIFU, the resulting edema causes the prostate to enlarge, which changes the targeting of the treatment zone. Endorectal compression of the prostate under US guidance appears to improve whole-gland and lesion-targeted therapy.[120] Automated segmentation has been developed for US-guided HIFU treatments.[121]

As opposed to thermal HIFU, the bubble activity during histotripsy can be seen with B-mode US as a hyperechoic region, obviating the need for MR guidance.[50] Furthermore, the loss of the tissue structure in the liquefied region can also be observed with B-mode US as a hypoechoic region and therefore facilitates feedback on ablation completeness. Visualization can be enhanced with color Doppler imaging to produce twinkle artifacts.[122,123] Combined with the preferential tissue selectivity mentioned earlier, histotripsy ablation of the prostate appears very promising. An important consideration of such treatment is the limited acoustic window, if applied extracorporeally, and the need to miniaturize the HIFU transducer for transrectal applications. Whether it is possible to attain the HIFU intensity needed for histotripsy with such a miniature transducer has been an open question until recently. Recent developments in transducer design indicate that such a system can be designed, and these studies are currently under way.[124]

Conclusions

Improvements in technology, particularly histotripsy, allow HIFU to be monitored under US guidance, which would have substantial advantages over MR guidance, particularly related to cost and portability. High-intensity focused US and histotripsy have been shown to be beneficial for the treatment of focal prostate lesions and to have fewer side effects and complications, and overall, the patients have a better quality of life then patients undergoing more-invasive treatments such as radical prostatectomy. However, no randomized clinical studies in humans have been performed as of this time. Further refinements in power production, beam steering, and acoustic beam resolution will continue to make US-guided HIFU more feasible, safe, and technically precise for both primary and salvage therapy. Much of the published literature concludes that further research including prospective randomized trials would be necessary to investigate potential advantages of focal therapy including HIFU for the treatment of prostate carcinoma,[125–129] and longer-term data are needed to evaluate the oncologic efficacy and functional outcomes.[130] However, it is clear that the future of prostate therapy will continue to be directed toward focal therapy, and at this time, HIFU appears to be the most promising modality on the horizon.

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