

A Review of High Intensity Focused Ultrasound Focal Therapy Results Using the MRI Ultrasound Fusion

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Article Info

Journal of Biomedical and Sustainable Healthcare Applications (<http://anapub.co.ke/journals/jbsha/jbsha.html>)

Doi: <https://doi.org/10.53759/0088/JBSHA202202014>

Received 12 May 2021; Revised from 02 November 2021; Accepted 30 November 2021.

Available online 05 July 2022.

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Abstract – To provide its therapeutic effects, High-Intensity Focused Ultrasound (HIFU) treatment makes use of ultrasonic waves that are transmitted through tissue medium. This non-invasive technology shows capacity for a variety of medical applications, including tumor ablation, vascular coagulation, and gene and drug delivery. Nonetheless, there are many problems that can arise from using this technology. The goal of this research was to examine the effectiveness of focused HIFU treatment for prostate cancer by employing an MRI-US fusion platform to pinpoint the precise location of the tumor and administer the therapy. Focal HIFU treatment for locally advanced prostate cancer is a prospective case series employed in this article. There must not be a Gleason 5 signal on the prostatic biopsy and the focal lesion must be less than 20 mm in size on multiparametric Magnetic Resonance Imaging (MRI) for inclusion. The first half of the series were treated with traditional HIFU focused treatment, whereas the second half were treated using an MRI-US fusion platform. Requirement for salvage treatment was used as the major outcome measure of treatment efficacy. Results of supplementary interest were Prostate Specific Antigen (PSA) change, intraoperative morbidity, postoperative clinical outcome, and tumor resurgence in follow-up biopsies.

Keywords – Ultrasound (US), High-Intensity Focused Ultrasound (HIFU), Magnetic Resonance Imaging (MRI), Focused Ultrasound Surgery (FUS)

I. INTRODUCTION

In order to heat or ablate tissue, High-Intensity Focused Ultrasound (HIFU) [1] employs ultrasonic pulses that do not produce ionizing radiation. Through thermal and mechanical principles, HIFU may be used to improve the flow of lymph or blood, or to destroy tissues such as tumours. There has been much study of HIFU because of the widespread availability and inexpensive cost of ultrasonography. The idea behind HIFU is that it considered a cost-effective and non-invasive treatment that may, at the very least, provide results comparable to those of the gold standard. Similar to ultrasonic imaging, the method uses low-frequency, continuous waves rather than pulses to provide the required thermal dosages. Nonetheless, if mechanical damage rather than thermodynamic damage is needed, pulsed pulses may be employed instead. It is common practice to use acoustic lenses in order to focus the required intensity on the tumor tissues without causing damage to the adjacent tissue. Using a magnifier to concentrate sunlight is similar, in that just the spot where the light is focused is very bright. Although lenses have been the standard up until recently, phased arrays are quickly replacing them because of how readily the focal position can be adjusted.

High-Intensity Focused Ultrasound (HIFU) is often used in tandem with other imaging modalities like medical ultrasonography or magnetic resonance imaging for the purposes of therapy guiding and patient monitoring. One common experiment for children is using a magnifying glass to concentrate the sun's beams on a tiny area, in the hopes of sparking a fire. Using Ultrasound (US) rather than sunlight, HIFU treatment is a similar technology. To raise temperature or induce

other biological interactions, HIFU treatment may transmit energy as a US wave through tissues that intervene to a certain body organ location. If the ultrasound energy is directed and concentrated where it is needed, it will not have any substantial adverse biological impacts on the intermediate tissue. International medical professionals, researchers, and businesses are taking an interest in this non-invasive technology as a potential game-changer in the delivery of safe, effective treatment with minimal side effects.

Historically, therapeutic US has preceded its diagnostic usage. By 1927, HIFU's biological effects were well-established. Untargeted, low-intensity US has been used in physical therapy since the 1930s. Focusing US, as shown by Tierney, Field, Selvakumar, and Hayes [2] in 1942, has the ability to induce very targeted biological effects. According to Quinn, Chin, and Walbridge [3]. Drs. Fry used focused US for the first time to treat the brain via a soft tissue window; they were attempting to treat Parkinson's disease. This therapeutic use, however, was eclipsed by the creation of L-dopa, which was widely hailed as a triumph at the time. The last decade or so has seen a comeback in the use of this tool in clinical care, after a long time of significant inactivity. Research done by Hertwig [4] evaluated the medical application of HIFI on the prostate cancer, and since then, several further clinical studies have been conducted on its applicability to a wide range of bodily organs. Differences between HIFU and other therapeutic ultrasound methods are not universally agreed upon. HIFU is often used to describe high-energy applications like ablation and cavitation in the scientific literature, but it is also mostly employed to illustrate application with a lower intensity such as OT and PT. To heat deep tissue without making an incision, HIFU is employed. **Table 1** summarizes the most common uses. Another use of ultrasonography in a physiotherapy context is the therapy of musculoskeletal problems and disorders.

Table 1. Medical application of HIFU

Neurological disorders	Therapy of Parkinson's illness in the 1940s was among the first uses of HIFU. While HIFU's ability to lesion, pathology was not yet realized, it showed promise. Essential tremors, neuropathic, and Parkinson's tremor may now be treated using a focused ultrasound system that has received regulatory approval in Russia, Korea, Europe, Canada, and Israel. This method allows for brain therapy without the need for surgery or radiation. While Insightec's Exablate technology has shown promise in treating Parkinson's illness, it remains in the pre-marketing phase. Additional thalamocortical dysrhythmias and mental disorders are being studied as potential treatment targets.
Cancers	Because of its non-invasive nature, HIFU is a promising therapeutic modality for tumors in inaccessible or unresectable sites. Cancers of the brain and intestines are of special concern. Whether or whether HIFU is an appropriate therapy option must be determined in conjunction with other methods (supposing commercialized statements).
Prostate cancer	Research on the effectiveness of HIFU for treating prostate cancer is now being conducted in male patients. The FDA (Food and Drug Administration) issued a warning to the Sonacare company, stating that if their product is indeed a medical device, they must complete the 501(k) process and submit multiple safety medical data before the FDA will classify their product as a class 2 clinical device (which does not require registration or authorization). Even yet, it seemed to have been registered by a commercial publication.
Liver cancer	There has been much research on the efficacy of HIFU for liver cancer, with encouraging results.
Abscopal effect	Immune responses in off-target areas have been shown during HIFU therapy for metastatic liver cancer. Histotripsy is believed to cause this systemic reaction by releasing tumor antigens that preserve their immunogenicity.
Palliative care	Some patients report feeling better after receiving HIFU, suggesting it may have palliative benefits. Palliative therapy for bone metastases has been granted CE certification. In animal studies, patients with advanced pancreatic cancer had some relief.
Prostate enlargement	Transrectal HIFU treatment for prostatic hyperplasia benign (prostate hypertrophy) has failed thus far. Through the prostate, via the urinary bladder, HIFU has been made available in various nations outside the United States. It's 2019 and we still don't have any proof. NICE (National Institute for Health and Care Excellence) deemed the technique "not advised" in 2018.

Numerous malignant and benign illnesses, including fibroids, thyroid disease, and breast malignancies, have been studied as potential candidates for therapy with High-Intensity Focused Ultrasound (HIFU). In 1996, Singh et al. [5] reported their first attempts at using HIFU for prostate cancer treatment, and earlier the tool was used to ablation of the whole gland, especially in instances where patients were either unwilling or unable to undergo radical prostatectomy. Recent thinking has shifted toward using HIFU for focused therapy, with the goal of striking a healthy balance between brain metastases control and a low side-effect profile. Such localized therapy has progressed from its first analysis as a salvage therapeutic analysis for focussed recurrences after radiations to its present form as a standardized form of therapy to the local prostate cancers.

The therapy of prostate cancers, mostly in males, varies dramatically from one patient to the next. If a man's prostate cancer is in the low-risk category, which is composed mostly of grade 1 illness, he should be regularly observed utilizing an active surveillance method. Men having intermediate-risk (i.e., grading group 2 or 3) cancer have therapy options that

target the whole gland, despite substantial diversity in cancer volume, localization, and other health conditions within this group. Ten percent of men may suffer from long-term stress urine incontinence, and more than half of those who have radical prostatectomy or radiation, with or without systemic treatment, report significant sexual dysfunction.

Focal treatment, opposed to whole-gland techniques, entails removing just the malignant areas of the prostate that are visible and verified by a biopsy, while preserving the healthy sections of the prostate and the margins and surrounding structures unharmed. One strategy for lowering the likelihood of metastases and maintaining quality of life involves treating just the index tumor. With the advent of multiparametric MRI and ultrasound-magnetic resonance fusion systems for MRI-targeted prostate biopsies, the concept of an organ-sparing focused therapeutic method has become theoretically possible.

Innovations and inventions that are able to perform targeted ablation use both thermal as well as non-thermal sources of energy. High-intensity focused ultrasound has been found to safely and successfully thermally ablate cancerous prostate tissue in animal experiments and retrospective series. However, most ultrasound-guided high-intensity focused ultrasound trials to date have been done in isolated sites, have only involved patients with low-risk prostate, and have precluded direct monitoring of treatment zones. After 1 year, 65% of patients in a new study employing MRI-guided transurethral ultrasonography whole-gland ablation showed no signs of malignancy. Males with low-risk and intermediate prostate cancers were involved in this research. Our study used a transrectal acoustic transducer for energy delivery, pelvic MRI for tumor visualization, magnetic resonance thermometry for in-process temperature monitoring and control, and immediate assessment of the ablated tissue. Results from a phase 2b, multidisciplinary intervention are presented that used MRI-guided focussed ultrasound for the regional therapy of intermediate-risk prostate.

Because to mpMRI, the prostate cancer detection process has been transformed. Validation studies have shown that MRI-ultrasound (US) guided prostate biopsy enhances the identification degree of medically important tumors while decreasing the overdiagnosis of medically inconsequential malignancies. While the MRI-US fusion technology has increased the accuracy of prostate biopsies, it has not been integrated into the standard practice of delivering focused treatment by precisely targeting the affected area. Transrectal ultrasonography has traditionally been used alone for HIFU focused treatment. MRI-US synthesis application has previously been integrated into the platform of HIFU focused therapies in an effort to improve the accuracy of the therapy.

The purpose of this research was to report on the outcomes of focused HIFU treatment using MRI and US in conjunction. In that regard, this article has been organized as follows: Section II presents a methodology employed in the research to draw the required findings. Section III reviews the relevant literature texts associated with the study. Section IV focusses on an empirical review of the study where High-Intensity Focused Ultrasound (HIFI) early adoption and HIFU treatment aspects are discussed. Section V presents a critical analysis of the results while a discussion of the findings is presented in Section VI. In Section VII, final remarks regarding the research are drawn, including future research directions.

II. METHODOLOGY

There were twenty patients that had HIFU focused ablation. On average, HIFU procedures performed using a combined MRI/US platform took longer than those performed using more traditional methods. When comparing the average ablation volume to the average lesion volume, neither group performed better. In the conventional group, the percentage increase in PSA from baseline to 6 months is much higher. Six-month follow-up mpMRI scans on all 20 patients revealed no worrisome lesions. After a follow-up biopsy revealed out-of-field recurrences of medically fundamental prostate cancers in two individuals, one from each group, they both received drastic therapy.

The individuals with localized prostate cancers who obtained the treatment of HIFU between April and September 202 were included in prospective observational research. Candidates for HIFU focused treatment were men aged 40 to 80 with prostate cancer who matched the following criteria: medically tumour phase T2, visible index lesions onto the multiple parametric MRI 20 millimetres in size, locations of tumours 40 millimetres from the rectum onto the MRI, deficiency of Gleason 5 patterns onto the prostate biopsy, and the PSA 20 ng per millimetres. Individuals who were taking anticoagulants, had a history of bleeding disorders, or were otherwise deemed medically unsuitable to undergo a contrast-enhanced multiparametric MRI were not included in the research. All procedures followed what were outlined in the study's protocol and were considered ethical by the regional ethical review department. Before any participant was enrolled in the research, they all provided written informed consent.

All of the research participants had previous prostate mpMRI. The two most common methods for diagnosing prostate cancer are MRI-based US fusion biopsy and pattern systematic biopsy. Whenever an individual has been recruited and found to meet the aforementioned exclusions and inclusions methodology, he or she will be considered based on these evaluations: Ransrectal Ultrasonography to see whether there is calcification around the lesion that may impede HIFU energy delivery; International Prostate Symptom Score (IPSS) [6]; Overactive Bladder Symptom Score (OABSS) [7]; Prostate Specific Antigen (PSA) [8]; 12-items brief Survey Forms (SF-12); and International Erectile Function Index (IIEF-5) [9].

III. LITERATURE REVIEW

According to Wei et al. [10] tumours of various sorts may benefit from local ablation treatment utilizing HIFU (i.e., ISA from 100 to 10,000 Watt per square centimetre) during focused ultrasound surgery. FUS is caused by two basic mechanisms: mechanical implications integrated thermal implication in part, stimulated by sonic cavitations, and the

thermal impacts stimulated by the absorption of US. Traditional methods have made advantage of the thermal effect through absorption due to its predictability and, by extension, its manageability. This makes the treatment feasible despite the fact that thermal ablation through the standard approach of FUS often requires a lengthy surgical period for practical application. Because of its ability to increase ablation size while decreasing procedure-time, cavitation has shown promise as a means of enhancing the effectiveness of this kind of treatment. However, these benefits may come with a greater risk of complications and a longer cooling time.

As can be seen in **Fig 1** (a) and (b), a traditional thermal lesion created by a standard therapeutic 1.5 MHz HIFU beam has the form of a cigar and is around 1.5-2 mm wide and approximately 1.5-2 cm long. When compared to the size of most tumors seen in clinical practice, this hydrothermal lesion is quite tiny. A suitable ablation zone is formed by stacking the various thermal lesions without leaving intermediate viable tissue to cover the tumor and the safety margin. While tissue perfusion may impact thermal lesion size, tissue homogeneity determines lesion form. Adjusting the ultrasound frequency improves surgical circumstances by minimizing sonic attenuation (a benefit of low frequency) and concentrating energy precisely enough for precise targeting (merits of higher frequency).

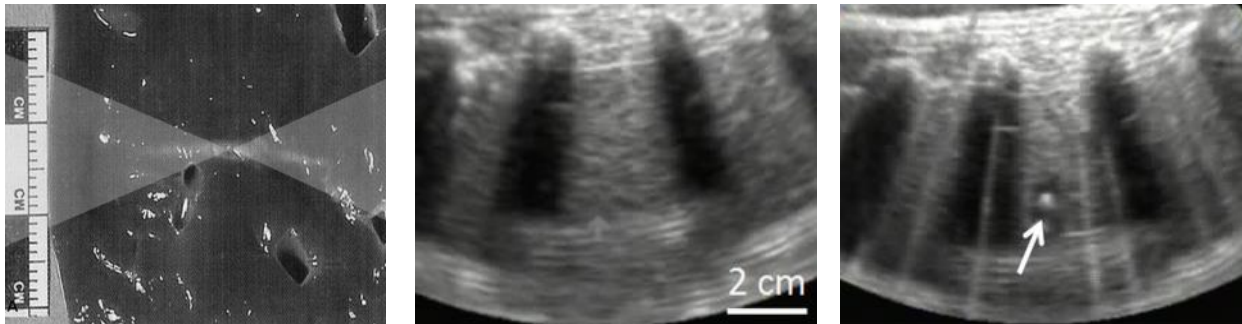


Fig 1. Using focused ultrasound (US absorbance exclusively), surgeons were able to create a conventional thermal lesion in a pig liver biopsy. At the focus region of the US waveform channel (two overlapping triangles), a cigar-shaped temperature lesion form after a solitary HIFU treatment.

(a) This pre-treatment transcostal B-mode ultrasonography picture shows the liver of a pig. The ultrasonography signal is reflected and attenuated by the ribs, creating a shadow beneath the ribs.

(b) Hepatic sonic bubbles cloud (arrow) and adjacent hypoechoic volatilized area are shown in this ultrasonography image obtained after histotripsy treatment.

According to Tsukiyama et al. [11], the impact of FUS on tissue structure has been investigated. The tumor supplying vasculature is completely destroyed by coagulation necrosis in one place ("island"), and a rim-like area ("moat") formed by glycogenic injured cells, which typically get destroyed within two days after US absorption surrounds the island. After granulation tissue and fibroblast infiltrates, retraction and scar formation take place. In addition to mechanical tearing, acoustic cavitation also results in coagulation necrosis. Under a microscope, holes or implosion cysts reveal themselves as a consequence of mechanical tearing brought on by tissue boiling and the mechanical impacts of sonic cavitation.

According to Marra et al. [12], Hemostasis using HIFU therapy was first utilized to heal battlefield wounds right away. Ultrasound of higher intensity (ISA from 500 to 3,000 Watt per square centimetre) is often used to achieve hemostasis. Animal models have been used frequently, and results have been positive, for studies of both solid organ and vascular damage. In order to prevent excessive bleeding, the heat effect is crucial. In order to explain how it works, we propose the following mechanisms. When an organ is heated to a high enough temperature, its parenchyma deforms, causing the small blood vessels and sinusoids to burst. A fibrin clot forms when the adventitia of the vessels coagulates due to the increased temperature. It seems that the mechanical action of sonic cavitation may also affect hemostasis to some degree. As a consequence of microstreaming, a cellular homogenization is formed, which acts as a barrier and causes the production of coagulation cascade. Blood treated to HIFU at frequencies up to 2,000 Watt per square centimeter shows no clinically important hemolytic anemia or changes in the amount of white blood cells or thrombocytopenia.

Potential benefits of ultrasound in thrombolysis are discussed by Vetrano et al. [13]. Ultrasound (US) with or without a thrombolytic medication has been shown to have a positive effect on thrombolysis. Thrombolysis may be facilitated by non-thermal mechanisms that are activated by US with low intensity (ISA from 0.5 to 1 Watt per square centimetre). Holes and channels in cell membranes are opened as a consequence of the strong mechanical force created by the microstreaming induced by sonic cavitation. Therefore, thrombolytic medicines applied directly to a thrombus's surface have a higher chance of being successful. The United States may use its own radiation force to help deliver the medication to the lesion ("push effect"). Changes to the fibrin mesh may be caused by mechanical forces, with or without microstreaming. Thrombolysis is believed to be induced by a combination of the aforementioned processes.

According to Rathbun and Zweig [14], there are now two ultrasound delivery methods that may be used to treat vascular thrombosis. The usage of a third-party gadget is one viable alternative. There is still a chance for problems and treatment failure with this noninvasive method because of the existence of intermediary organs and the need for increased US energy to offset for dilution through an intermediary tissue. When combined with a tumor necrosis factor activator, endovascular lower frequencies US (including intracranial Sonic US) has demonstrated encouraging outcomes in clinical studies for the therapy of brain hypoxia. There is the possibility that a small transducer linked to the tip of an arterial

catheter might be used to administer a thrombolytic drug. Some products that are part of this minimally invasive system are the EKOS® EndoWave® Peripheral Infusion Device and the EKOS® NeuroWave® Catheter (both manufactured by the EKOS® Co. in Bothell, WA).

Since ultrasound-assisted thrombolysis is a subset of the larger field of targeted medicine delivery systems, it was left out of the prior discussion. Ultrasound-guided targeted drug-delivery and gene therapy both rely on microbubbles as an integral part of their respective systems. Microbubbles may be used to transport drugs or plasmid DNA (deoxyribonucleic acid). Using ultrasound (intensity of sound attenuation, or ISA from 0.5 to 1 Watt per square centimetre), these precisely controlled microbubbles may be guided through blood vessel pathways to a specific target. Microbubbles containing drugs or genes are released when US waves burst them. By serving as cavitation nucleus, the microbubbles spread and intensify the constructive interference. In addition to facilitating sonoporation (the temporary modification of cell membrane systems as a result of a mechanical US intensity) and the "push effect" (the insertion of drugs or genes into cells via physical force), the complex microstreaming generated by the disintegration of microbubbles also aids in "microencapsulation" of the drugs or genes. However, there are limitations to the conventional viral vector-based gene treatments, such as the risk of negative systemic immune responses. The possibility of this happening is reduced if gene therapy is enhanced in the United States. Increasing the therapeutic concentration at the site of sickness with localized medication delivery may lower the likelihood of systemic adverse effects.

According to PiñeroCes et al. [15], there are two different ways that ultrasonography may be used to give medication. As an example, ultrasonography (US) may be used to help get drugs through the skin and other similar biological barriers. When acoustic cavitation and microstreaming are combined, the outermost layer of skin (the stratum corneum) temporarily becomes weaker and more porous. This method has shown to be quite useful in the clinic for the topical administration of insulin to diabetics. Medications that are photosensitive or sonosensitive may be activated by ultrasound (US) in a technique known as sonodynamic therapy. Though the precise mechanism is unknown, it is believed to include the sonoluminescence phenomenon resulting from sonic cavitation.

According to Jacobson-Kram [16], radiologists who only have experience with diagnostic ultrasound frequencies between 3 and 12 MHz might get the wrong conclusion that ultrasound is unable to penetrate through bones. Because bone has a considerably higher attenuation coefficient, it absorbs and reflects US waves to a much larger amount than the surrounding soft tissues, giving it a far higher acoustic impedance. The thickness of bone determines the percentage of incident ultrasound that may be transmitted through it; for the skull, this means frequencies below 1 MHz. This causes the skull to overheat during transcranial ultrasound therapy, which is a major drawback of the technique. There is also the problem of US waves drastically deviating from their intended course during transcranial ultrasound therapy. Ultrasound beams, in particular, lose accuracy due to the skull's irregular thickness and the bone's high speed of sound. Today, in order to solve this inefficient problem, a transducer with many high-energy sources is used. In an attempt to cool the scalp, scientists have developed an external cooling device that uses a stream of cold water.

According to Edla, Deguchi, and Lim [17], a piezoelectric component arrangement with a hemispherical design is employed to supply heat in an even form. One potential remedy to such a defocussing issue is to employ digitized multi-channel array transducers. To concentrate the ultrasound on a small, precisely defined region, the computer-calculated locus of the beams from transducers are centred on the CT-based sets of data onto the thickness of the skull for every relevant location. Scientists and engineers have developed a drive model and 512-channel transducers for use in a healthy brain in vivo. Concentrated US may selectively breach the BBB (Blood Brain Barrier) without destroying nearby healthy neurons. This opens the door for enhanced medication delivery by US to the afflicted brain regions. Each form of application has had vital therapeutic impact since conventional therapies like surgery have such limited value.

IV. EMPIRICAL REVIEW

High-Intensity Focused Ultrasound Early Application

Sharma et al. [18] discussed the first applications of HIFU ablation, which occurred in the early 1940s. In the 1960s, Indian inventor Sanghvi and University of Illinois professor Fry accomplished a lot of commercial work using HIFU sensors. The 12 significant industrial patents held by Sanghvi are testament to the success of his inventions. Stereotactic High Intensity ultrasound combined with Cincinnati's precision tool permitted for accurate brain tumour ablation. While ultrasonic heating has been used extensively for research into hyperthermia, HIFU for ablation has only lately begun to get therapeutic attention. The therapeutic complexity and the issues facing non-invasive targets on the beam might have contributed to this.

According to Bhan and Prasad [19], Sanghvi's first piece of commercial HIFU equipment, the Sonablate 200, was released in 1994 by Focus Surgery, issuing the first clinical methodology to HIFU with no clearance from the FDA. Several studies indicated that medical professionals employing the device anticipated therapeutic benefits in terms of eliminating prostatic material without the traumatic risk of blood loss and adverse repercussions often associated with such procedures. Diagnosis with Ablatherm (EDAP TMS Lyon) gradually improved progression-free survivorship for intermediate- or low- risk clients with chronic prostate cancer (70percent and 50percent respectively, according to subsequent studies on metastatic prostate cancer by Schoen et al. [20]).

It is not currently legal in the United States to use HIFU to treat prostate cancer, although this technique has been given the green light in Europe, South Korea, Canada, and Australia. Private Charlotte, North Carolina-based company

Sonablate has been bought and sold many times by a Chinese investment entity and its Chinese CEO. A rebranding was recently implemented due to the fact that the name "Sonablade" is already being used by another pornographic website. In 1992, a patent was issued referencing the use of focused ultrasound guided by magnetic resonance. Eventually, in 1998, the technology made its way to InSighTec in Israel.

HIFU Treatment

Based on glands volume, location, and tumor volume treatments were performed using either localized lesion ablation or a quadrant approach by means of the Sonablate® 500 tool for HIFU therapy. Since there were no Gleason 6 lesions bigger than 3 mm in the untreated area, only the index lesion was ablated with HIFU targeted therapy in patients with multifocal illness. Traditional HIFU ablation depended on cognitive recognition of lesion location; however, in the second part of the series, the Sonafuse™-MIM Symphony™ platform was employed to fuse US and MRI data for localization of lesion during the treatment of HIFU. MRI scans were placed in advance on the Sonafuse™-MIM Symphony™ platform, and the gland and index lesions were contoured thereafter, similar to the fusion procedure utilized in bkFusion™ for prostate biopsy. Possible constraints on the fusion platform stem from the fact that it uses a stiff fusion mode rather of an elastic fusion mode. Treatment plan with a 7 mm ablation safety margin. Complete treatment was given with the patient unconscious and monitored with real-time ultrasonography. The placement of a urethral catheter occurred either before, after and during the process, based on the lesion's location.

Seven days and six months after surgery, participants had mpMRI examinations. After 6 months, the patient was scheduled to have another MRI and subsequent biopsies. OsiriX MD 12.0 was used to recreate the prostatectomy, the lesion, and the ablation region. At three and six months, we checked in with a cognitive evaluation as well as PSA. Salvage therapy rates were used as the primary indicator of treatment success or failure. PSA shift, perioperative complications, postoperative functional outcomes, and tumor recurrence in follow-up biopsies were secondary outcomes of interest. Quantitative processing and analysis were done in SPSS 26.0. The t-test was used to evaluate whether or not there were statistically significant differences in the levels of a continuum variable between pre- and post-operative individuals. One-way repetitive measurements Analysis of Variances (ANOVA) was used to evaluate three or even more parameters, as well as the test of Pearson correlations was used to examine regression assessment. The significance threshold for the findings was set at the 0.05 level.

V. RESULTS

Twenty prostate cancer patients were treated with HIFU focal therapy, with a total of twenty-two index lesions being addressed. Across all patients, the median PSA level was 8.70 ng/ml. Six people were diagnosed with cancer through transrectal biopsy, and 14 men with a presumptive cancer diagnosis had transperineal prostate biopsies under just local anesthesia to confirm their cancer diagnosis. The mpMRI results before surgery confirmed the presence of all lesions. Discrete targeted biopsies utilizing an 18 to 24 core pattern revealed Gleason 4 + 4 cancer in both individuals with ISUP grade four illness. Ten of the twelve patients who were diagnosed with ISUP grade 1 lesions had tumor volumes higher than 0.5 cm³ on MRI. Two more patients, both of whom had tumors measuring less than half a centimeter in volume, opted for targeted HIFU treatment rather than active monitoring. Most of the destruction occurred in the perimeter.

All patients had either a focal or quadrant ablation. The gland was neither completely nor partially ablated. How near a lesion is to the urethra determines whether or not a urethral catheter should be left in place during HIFU therapy. Of these twenty patients, ten received conventional HIFU focused treatment and the other ten received fusion-guided MRI and US. On average, patients who needed a fusion platform spent 124.2 minutes in surgery, whereas those who didn't spent 107.1 minutes in surgery. There was no discernible difference between the two methods in terms of the proportion of ablation volume to lesion volume. On day one after surgery, the first six individuals had their urethral catheters withdrawn. As a result, four individuals apparently did not begin self-voiding on day 1 or were transferred back for urinary delay and catheters reinstallation on the same day. Our group settled on a catheterization duration of one week for the remaining patients. It was necessary to try removing the catheter a second time from three of the remaining fourteen patients on day seven since they had not yet urinated. Three patients with Clavien-Dindo grade 1 problems had urinary retention severe enough to need readmission, and one patient with haematuria was conservatively managed.

Ablation zones were seen on mpMRI scans over the whole region of interest in all patients by 1-week post-HIFU. The fusion group had a lower PSA decrease at 6 months (44.6 percent vs. 63 percent for the conventional group). Twenty patients received 6-month follow-up mpMRIs, and not a single one of them had any concerning lesions. More biopsies were taken from 12 people. Out-of-field relapse was seen in two individuals with medically relevant prostate; one individual had it after hybrid HIFU on a tumor in the peripheral region, while the other individual had it after regular HIFU on a tumor in the transition region. There was a critical need for medical attention for these two patients, and it was met (one with radiation and the other through robotic prostatectomy). Cancer showed GS 4 + 5 in the unilateral ectomy material, taking up just 5 percent of the prostatic region, which is compatible with a pT2-aN0 stage of disease. Two further patients with clinically modest illness had out-of-field recurrence of prostate cancer (ISUP grading group 1). The median PSA at 6 months was 4.3 3.2 for the group that did not have a recurrence, and 3.4 1.4 for the group that did. Both groups' pre-treatment median PSA ranged from 3.6-2.4, whereas the control group's ranged from 3.4-5.2.

Seven days following surgery, prostate volume was considerably greater than preoperatively (54.5 +/-20.1 cm³ vs. 39.5 +/- 14.9 cm³). After 6 months, however, the average volume of the prostate did not alter from its initial value (38.5 +/-

21.80 cm³) (see Fig 2). The median postoperative PSA level was under 4 ng/ml 6 months after treatment. In the third month following HIFU, the mean IPSS was considerably lower than it had been at baseline (11.2 +/-5.8 vs. 8.4 +/-5.1). Thirteen patients with lower urinary tract issues used alpha blockers before surgery. Eight of the initial thirteen participants were able to discontinue use of alpha antagonists after Six months. There was no substantial improvement in SF-12, EPIC-26, or uroflowmetry scores between the pre / post periods. From baseline to 3 months, there was a substantial increase in the mean IIEF-5 score for erectile function (11.7+/-8.5 vs. 15.1+/-6.5), however this trend was not evident at 6 months (13.7 7.6 vs. 15.1+/-6.5). At the start of therapy, no patients were taking a PDE5-I; by the middle of treatment, three patients were; and at the conclusion of treatment, six patients were.

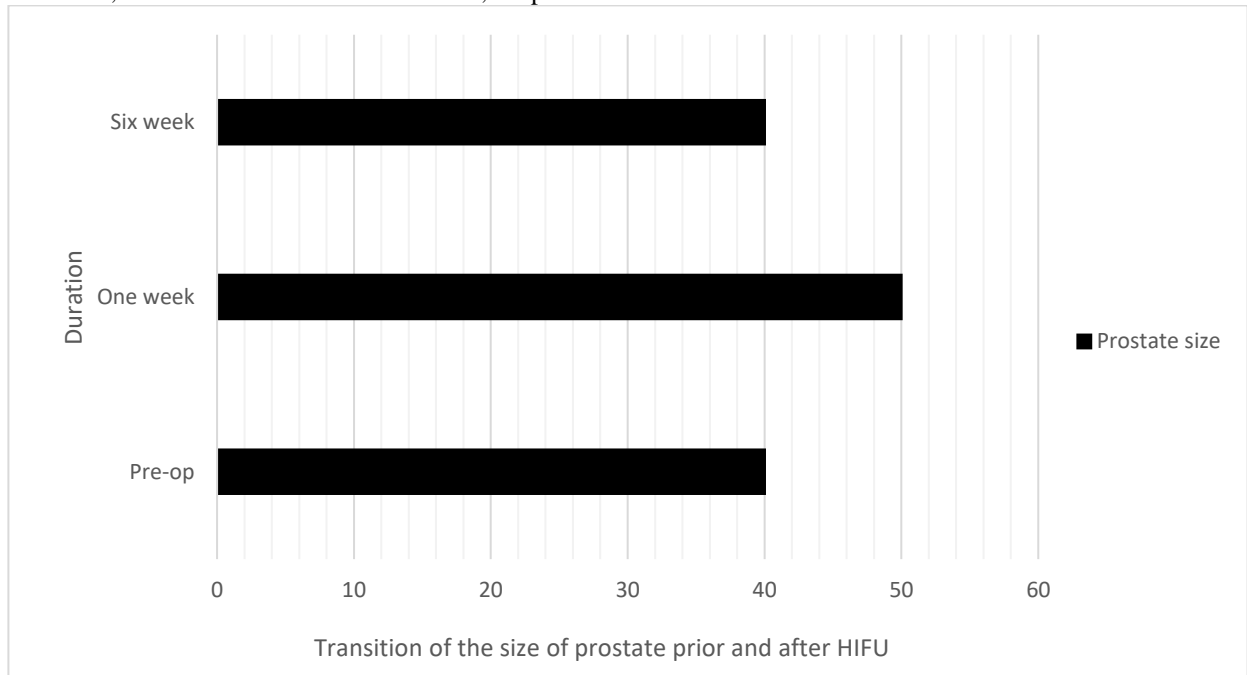


Fig 2. Quantitative analysis of the prostate shrinkage caused by HIFU therapy.

The t-test was utilized to contrast pre-op value to the current one, and the resulting P value reflects this analysis. Examining the connection between total energy delivered, ablation region size, and PSA variation provided insight into the technical side of HIFU's use. The patient's PSA density was shown to be strongly linked with their energy consumption per volume (see Fig 3). Although overall energy consumption did not correspond with changes in PSA (or the percentage of change in PSA), we did find a correlation with the PSA change. There was no fundamental variation in the average zone dimension to the volume of lesion between the instances receiving HIFU focused treatment with and without fusion support (62.8 and 66.4). Between baseline and 6 months, conventional group PSA % changes were more noticeable than fusion group PSA percentage changes (44.6 vs. 63.3).

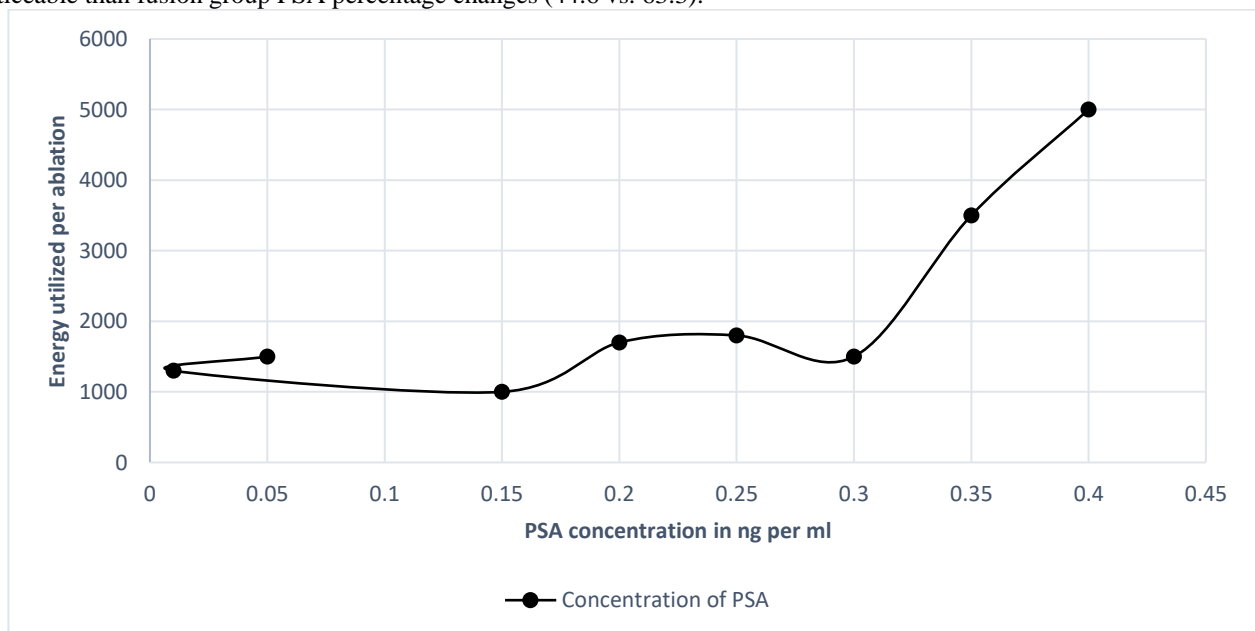


Fig 3. PSA concentration of the prostate correlates with the energy used per unit volume in the ablation region.

VI. DISCUSSION

Prostate tissue might be effectively ablated in the first High-Intensity Focused Ultrasound (HIFU) prostate cancer clinical studies, which were concluded in the mid-1990s [21]. This discovery sparked a flurry of new research, and within a decade, HIFU was being used in clinics all over the globe. HIFU was first utilized for prostate cancer whole-gland ablation procedures. Despite the positive results of this application, there was growing concern about the potential negative effects of treating prostate cancer. The phrase "focal therapy" is used to describe this kind of treatment. The purpose of focused treatment is to target the most aggressive tumor while sparing the surrounding healthy tissue in the prostate. In the case of other cancers, this strategy has gained widespread acceptance. Most kidney cancers are treated by removing or ablating the tumor while leaving the healthy kidney tissue alone. The index lesion is the prostate cancer that will be treated. When many tumors exist in a prostate, this is often the biggest and most aggressive one. Treatment of the index lesion alone with targeted treatment may result in excellent overall cancer control with fewer side effects in these circumstances since it is thought that the index lesion dictates the behavior of the prostate cancer.

Focused Ultrasound Surgery (FUS) [22] is widely used as an ablative therapy in the treatment of many disorders. Both sonographic and MRI (Magnetic Resonance Imaging) guiding systems may be used for this procedure. Many different devices may be used to do HIFU, however the most frequent ones are extracorporeal and transrectal. Using a longer ultrasonic focal length and MRI guidance, extracorporeal devices are more suited for treating abdominal malignancies, although they are bulkier than transrectal alternatives. The HIFU system has a single-element, piezo-ceramic crystal that is 12 centimeters in diameter and is protected by an acoustic lens with adjustable focus lengths. It may be powered at frequencies between 0.80 and 1.60 MHz. The transrectal devices used to treat prostate cancer are more portable than their extracorporeal counterparts, with lower focal lengths (about 3–4 cm) and operating frequencies. Prototypes, endoscopic and laparoscopic instruments, and portable probes are a few additional examples.

The usage of HIFU in the past has been extensive, and it has been used to many different disorders. Nowadays, however, HIFU is most often used to treat solid tumors in the abdomen, breast, bone, brain, soft tissue, etc. Research on the efficacy and safety of HIFU in the evaluation of malignant bone tumors included 25 patients who were monitored both before and after treatment. In this study, 21 patients reported total pain reduction with HIFU, while another 24 reported considerable improvement. Overall, 75.0% of patients who had a primary bone tumor responded well to treatment, with 6 patients experiencing a full response, 5 patients experiencing a partial response, 1 experiencing a moderate response, and 1 experiencing increasing illness. Based on the results of this research, it seems that HIFU may be used to successfully treat primary bone tumors by ablating them and alleviating associated pain.

Roehrborn et al. [23] studied enlisted 25 individuals with a mean age of 67 in order to determine the safety and efficacy of HIFU for benign prostatic hypertrophy. The Sonablate HIFU instruments were used to operate each one. Before and after therapy, symptoms were documented. Apparently, the swollen gland and high failure rate caused five participants to be removed from the research. There were no negative side effects from the medication among the remaining 20 patients. No serious adverse events were reported during HIFU therapy for BPH, leading researchers to conclude that the procedure is both effective and safe. Twenty-three breast cancer patients were engaged in research on the pathologic effects of HIFU in 2006. All of these instances were confirmed by biopsies, and all of the patients had mastectomies following HIFU therapy. The exposed tissue showed signs of coagulation necrosis under the microscope.

As a result of the thermal effects of HIFU, it was determined that heat fixing occurred at the location of the ablated tumor. Transarterial chemoembolization (TACE) [24] and High-Intensity Focused Ultrasound (HIFU) were used with no serious adverse effects. Images taken following HIFU treatment showed that the targeted lesion no longer existed and that its blood supply had decreased. Studies with a clinical, experimental, or case report focus are the most common types of articles published on HIFU. Many of the studies were international collaborations that tracked patients in many locations. A comprehensive literature search revealed little evidence supporting the use of HIFU in any number of therapeutic settings. This systematic evaluation of the literature suggests that HIFU a viable selection for the treatment of a wide variety of disorders with little risk of adverse effects. It seems that the majority of patient problems were documented in studies conducted shortly after the introduction of HIFU. In addition, this research tends to indicate that advances in HIFU technology have led to fewer patient problems.

HIFU ablation Focal therapy has shown promising short- to medium-term benefits in the diagnosis of cancer [25]. In addition to oncological factors, the size of the prostate gland is a major factor in the treatment's success or failure. In addition, the transurethral channel of energy delivery by the HIFU probes could impede access to proximal lesion, a common occurrence after surgery after HIFU treatment. Due to the significant decrease in prostatic size that results after HIFU surgery, transcatheter excision of the prostatectomy has been adopted by several facilities either as a precursor to or in combination with the procedure. Patients undergo HIFU while under general anesthesia. When the patient is unconscious, a specialized ultrasonic probe is included in the rectum. No needles or incisions are required. The ultrasonic probe serves two purposes: imaging and therapy for the prostate. After setting up the equipment and making any necessary plans, therapy may begin. In only a few seconds, HIFU can destroy a rice-sized chunk of tissue. By repeatedly administering treatments to the same location of the prostate, an ablation zone may be formed using imaging and biopsy data. The surgeon may evaluate the quality and effectiveness of ablation in real time thanks to real-time imaging and treatment factors including temperature measurements and estimated tissue changes. The time required for the operation ranges from about two hours to more, depending on the size of the target region.

Prostate enlargement and movement have been described as a consequence of both whole-gland and partial gland HIFU ablations, as reported by Olaoluwa et al. [26]. Using the OsiriX MD software, we also analyzed the variation in prostate size during surgery for focused HIFU ablation of prostate cancer. There was a statistically noteworthy increase in prostate volume 7 days after surgery; this volume returned to preoperative values 6 months later (see **Fig. 2**). Because of this, neither the IPSS nor the OABSS nor the EPIC-26 LUTS score nor the uroflowmetry variables changed between the three-month nor the six-month follow-ups. Using MRI-US guidance, prostate biopsies have been able to pinpoint the exact location of tumors. Due to this, targeted HIFU therapy is now being considered alongside traditional whole-gland and hemiablation approaches. Therefore, there is a need for improved lesion localisation during HIFU procedures. The MRI-US fusion technology for HIFU operations allows the operator to design the therapy zone while maintaining the tumor in view, reducing the probability of making an error when identifying the precise location of the index lesion. In the current HIFU series, a rigid MRI-US fusion system was used. When comparing elastic and dynamic registrations for MRI-TRUS fusion-guided biopsies, Jacewicz et al. [27] concluded that there was no change in significant clinical malignancy identification. However, Rudoy [28] discovered no distinction in recognition errors among inflexible and flexible registrations. Rigid registration decreased identification inaccuracy of target at the prostatic edge, that could be a typical location of tumour for HIFU treatment. Therefore, we introduced a fixed MRI-US fusion platform into the current investigation.

With the fusion platform, we saw an overall tendency toward a longer operating time without a corresponding rise in ablation time in our series. Possible causes include the need for more time during treatment for mapping, fusion, and planning. We want to determine whether a more focused ablation can be achieved with the help of an MRI-US fusion platform in HIFU therapy by comparing the volume of the tumor to the volume of the ablation at the end of the procedure. Although the difference between the conventional and radiofrequency groups in terms of PSA decline is not yet statistically significant, we did find that the latter group had a larger average ablation volume to the ratio of the lesion volume. It may be explained by the fact that when the exact site of a tumor is unknown, doctors are more likely to ablate a wider region in order to reduce the risk of missing any lesions. Consequently, it increases the PSA decline and ablation volume after HIFU therapy. For their study, scholars in [29] looked back at their HIFU patients treated with either the Focal-One® (with a fusion system) or Ablatherm® (without a fusion system). Perioperative problems were similar across groups, nonetheless there was a vital variation in the leakage of urine at three months in favor of those who had had fusion. No patient in our study had incontinence problems with either method. The effectiveness of MRI-US fusion HIFU therapy has to be confirmed by more research.

For better definition of the ablation zone after HIFU, Oh, Ha, and Cho [30] have suggested using contrast-enhanced ultrasonography. It is also possible to use MRI immediately after surgery to achieve the same goal. Patients treated with HIFU often had hypointense centers surrounded by a halo of enhancement anywhere from postoperative second day to the fourteenth day. Therefore, on day 7, MRI was performed in our research to evaluate the ablation zone. After primary treatment, PSA testing is routinely done to monitor for recurrence. The Phoenix ASTRO definition has been applied by certain series to record biochemical repetition. But Tsukamoto, Nakahara, Nakahara, and Furue [31] discovered that PSA criteria for ruling out or detecting failure following focused HIFU treatment show substantial diversity in performance characteristics.

PSA's diagnostic performance also shows a broad spectrum of accuracy measures throughout time. In our research, patients who had HIFU focused treatment were followed up with a combination of PSA testing, MRI, and biopsy. Our research revealed no evidence of in-field resurgence, which is consistent with the results observed by Rouvière et al. [32]. Conversely, Wu et al. [33] revealed that, of twenty participants who had 12-month diagnostics, 8 had a positive diagnostic within the ablation region. In the series, PSA and MRI were not sufficient to detect the two major prostate tumors detected by follow-up biopsy until late in the observation period. Baba et al. [34] showed in their series that posttreatment MRI had low sensitivity for detecting prostate cancer that was clinically significant. One-year biopsies by Xu et al. [35] found prostate cancer in 38.4% of participants, of whom 61.8% received further treatment. The value of regular biopsy for assessing recurrence following focused treatment in prostate cancer needs further research.

High-Intensity Focused Ultrasound (HIFU) causes tissue damage due to heat and mechanical impacts. Tissue damage is caused by cavitation and radiation force from ultrasound, while hyperthermia is caused by pressure changes within the tissue. It is the acoustic pressure, the exposure period, and the properties of the tissue that determine the size of the coagulative necrosis caused by HIFU energy deposition, which is known as the Biological Focal Region (BFR). Our data showed that the amount of coagulative necrosis detected by MRI was positively correlated with the overall energy used during sonication. Additionally, preoperative PSA density is observed to be linked with the energy used per volume of coagulative necrosis. This finding might be explained by the fact that tissues react differently to HIFU radiation in various situations. Ultrasound imaging of the intraprostatic acoustic pattern alterations, such as the "popcorn effect" as induced by the bursting of gas bubbles, is utilized to continuously monitor the thermal effects during an HIFU focused treatment session.

As we found that the popcorn effect varied in intensity from case to case, and that not all tumor ablations produced a popcorn-like acoustic appearance on ultrasound, we hypothesized that the amount of HIFU energy needed to destroy typical tissues against the tumour lesion and among various tumours would vary. The surgeon monitors the tissue's reaction during the HIFU procedure and makes adjustments to the energy's delivery amount as needed. Prostate Specific

Antigen (PSA) density differences across prostate cancer patients may indicate fundamental differences in tumor architecture. In contrast to popular belief, prostate tumour cells never produce more PSA; other than that, enhanced levels of blood PSA result from cellular structural disturbance inside the prostate gland, which is caused by the disease itself. Prostate bioimpedance research shows that when gland architecture is distorted, bioimpedance rises. Different PSA densities may indicate distinct tissue properties, calling for different amounts of HIFU energy to provide the same audible and visible ultrasonic feedback.

The scope of our investigation is limited. Only 60% of our patients in the HIFU study had the twelve-month follow-up biopsies. Despite the fact that our findings regarding MRI, Prostate Health Index (PHI), PSA established the initial profile of results of the HIFU treatment, a more detailed histological assessment of the group at twelve months is necessary. Patients often fought against submitting to a follow-up biopsy unless there was evidence of increased PSA or remaining illness on MRI. Only 37 percent to 52 percent patients in the largest published series of focused HIFU treatment had a follow-up biopsy. Not randomly comparing the outcomes of the traditional HIFU platform with the MRI-US fusion HIFU platform is another caveat of our research. Our prospectively compiled case series data may provide the foundation for a randomized controlled study to further examine the efficacy of the fusion HIFU platform in patient care.

VII. CONCLUSION AND FUTURE RESEARCH

In experimental review of this paper, the Prostate Specific Antigen (PSA) and Prostate Health Index (PHI) levels of individuals with prostate cancer who had High-Intensity Focused Ultrasound (HIFU) therapy dropped significantly, and Magnetic Resonance Imaging (MRI) evaluation showed early tumor removal. There is a favorable correlation between ablation size and material characteristics as expressed by PSA density, both of which contribute to the total amount of energy used during HIFU treatment. Further research is required to validate the advantages the HIFU therapy of the fusion between Ultrasound (US) and MRI, even though it is probably that MRI and US fusion platforms for HIFU will generate lesion visibility during ablation and planning.

Compared to other interventional treatment interventions, HIFU therapy may have a very low degradation rate due to its total non-invasiveness and crisp, tailorable therapeutic margins. There are, however, a number of problems that have been linked to HIFU treatment. These are often caused by high-energy US signals rebounded off gaseous or skeletal formations. Inadequate acoustic connection between the epidermis and the treatment window (due to factors such as poor shaving or a recent surgical scar) may lead to skin-burn. When the liver needs therapy, ultrasound waves reflected off the ribs might cause injury to the skin and other surrounding soft tissues. The similar mechanism of action is at work in gas-containing bowel loops, which may lead to thermal damage of the intestinal wall. There have also been reports of sciatic nerve damage after HIFU treatment for uterine leiomyoma. Both direct and indirect effects of increased pelvic bone temperature after US treatment are blamed for this problem. There is a risk of direct thermal harm to the underlying skin if the target zone is shallow, as is the situation with breast cancer. The same is true for internal organs that are immediately to the anterior or posterior of the focus zone.

In addition to these side effects, HIFU treatment has shown various additional drawbacks that are impeding its successful usage in clinical practice at the time this publication was written. There are a number of drawbacks to this technique that should be taken into account before committing to it, such as the length of time it takes to perform the procedure, the challenges involved monitoring and targeting mobile organs, the sonic shadowing influenced by the gas or the bones in the bowel, and the relatively higher costs. Recent technical developments, however, are anticipated to address these issues. The novel MR-assisted HIFU device is one such example; it uses a multispiral focal point trajectory and the concepts of proportionality, integration, and differentiation to provide automated on-line, spatial and temporal temperature regulation. Under real-time thermal monitoring, this technique is said to be capable of defining and establishing thermal lesion more quickly and steadily in organs that are in motion than current methods.

Data Availability

No data was used to support this study.

Conflicts of Interests

The author(s) declare(s) that they have no conflicts of interest.

Funding

No funding was received to assist with the preparation of this manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Competing Interests

There are no competing interests.

References

- [1]. A. Wiggermann, M. Beldoch, F. Hoellen, and P. Hunold, “MR-guided high-intensity focused ultrasound treatment of uterine fibroids,” *Res. Rep. Focus. Ultrasound*, vol. 4, pp. 9–14, 2016.
- [2]. T. Tierney, W. Field, T. Selvakumar, and M. Hayes, “Treating patients with movement disorders using MRI-guided focused ultrasound: recent developments and challenges,” *Res. Rep. Focus. Ultrasound*, p. 5, 2015.
- [3]. S. Quinn, W. Chin, and J. Walbridge, “MR-guided focused ultrasound for the treatment of adenomyosis: current insights,” *Res. Rep. Focus. Ultrasound*, p. 1, 2015.
- [4]. K. Hertwig, “The ESPRIT project HIFI medical application,” in *Designing User Interfaces for Hypermedia*, Berlin, Heidelberg: Springer Berlin Heidelberg, 1995, pp. 225–235.
- [5]. S. Singh, K. K. M. Nair, J. S. Koruth, A. d’Avila, and A. Danon, “The role of high-intensity focused ultrasound in ablation of atrial fibrillation and other cardiac arrhythmias,” *Res. Rep. Focus. Ultrasound*, p. 11, 2015.
- [6]. A. Gul, S. Coban, A. R. Turkoglu, M. Guzelsoy, M. Ozturk, and N. A. Kankilic, “Comparative efficacy and safety profile of 4 vs 8 mg of silodosin once daily usage in patients with benign prostatic hyperplasia-related lower urinary tract symptoms divided into subgroups according to International Prostate Symptom Score severity,” *Prostate Int.*, vol. 8, no. 4, pp. 152–157, 2020.
- [7]. M. Song, J.-Y. Chun, D. S. Yoo, J.-Y. Han, and M.-S. Choo, “Correlation of the overactive bladder symptom score, and the voiding diary and urodynamic parameters in patients with overactive bladder syndrome,” *Low. Urin. Tract Symptoms*, vol. 6, no. 3, pp. 180–184, 2014.
- [8]. P. M. Arlen et al., “Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time,” *J. Urol.*, vol. 179, no. 6, pp. 2181–5; discussion 2185–6, 2008.
- [9]. S. Ahmed Memon, M. Adil, F. Raja Khan, S. Ullah, S. Rehmat, and N. Zad Gul, “Association between erectile dysfunction, cardiovascular risk factors, and coronary artery disease: Role of exercise stress testing and International Index of Erectile Function (IIEF-5) questionnaire,” *Int. J. Cardiol. Heart Vasc.*, vol. 40, no. 101033, p. 101033, 2022.
- [10]. C. Wei et al., “The predictive value of conventional MRI combined with radiomics in the immediate ablation rate of HIFU treatment for uterine fibroids,” *Int. J. Hyperthermia*, vol. 39, no. 1, pp. 475–484, 2022.
- [11]. Y. T. Tsukiyama et al., “P1064The impact of P2Y12 reaction unit during percutaneous coronary intervention on intra-stent tissues and Peri-procedural myocardial injury in stable angina pectoris; From MECHANISM-elective study,” *Eur. Heart J.*, vol. 38, no. suppl_1, 2017.
- [12]. G. Marra, P. Dell’oglio, M. Baghdadi, X. Cathelineau, R. Sanchez-Salas, and EvaluationN of HIFU Hemiablation and short-term AndrogenN deprivation therapy Combination to Enhance prostate cancer control (ENHANCE) Study, “Multimodal treatment in focal therapy for localized prostate cancer using concomitant short-term androgen deprivation therapy: the ENHANCE prospective pilot study,” *Minerva Urol. Nefrol.*, vol. 71, no. 5, pp. 544–548, 2019.
- [13]. I. G. Vetrano et al., “Contrast-enhanced ultrasound assisted surgery of intramedullary spinal cord tumors: Analysis of technical benefits and intra-operative microbubble distribution characteristics,” *Ultrasound Med. Biol.*, vol. 47, no. 3, pp. 398–407, 2021.
- [14]. K. M. Rathbun and A. Zweig, “An affordable and easily recreated ultrasound phantom for deep vein thrombosis,” *J. Vasc. Ultrasound*, vol. 45, no. 2, pp. 64–66, 2021.
- [15]. A. PiñeroCes, M. Bande Rodriguez, M. Rodriguez Blanco, L. Peña Madrid, M. J. Lopez Valladares, and M. J. Blanco Teijeiro, “Very high-frequency ultrasonography signs in bilateral acute choroidal effusion associated with systemic sulphonamide medications: 2 cases,” *Case Rep. Ophthalmol.*, vol. 13, no. 1, pp. 64–69, 2022.
- [16]. D. Jacobson-Kram, “The effects of diagnostic ultrasound on sister chromatid exchange frequencies: a review of the recent literature,” *J. Clin. Ultrasound*, vol. 12, no. 1, pp. 5–10, 1984.
- [17]. M. Edla, M. Deguchi, and Y. Y. Lim, “A self-powered H-Bridge joule theory circuit for piezoelectric energy harvesting systems,” *Power Electronic Devices and Components*, vol. 3, no. 100015, p. 100015, 2022.
- [18]. K. V. Sharma et al., “Magnetic resonance imaging-guided high-intensity focused ultrasound applications in pediatrics: Early experience at children’s national medical center,” *Top. Magn. Reson. Imaging*, vol. 27, no. 1, pp. 45–51, 2018.
- [19]. S. Z. Bhan and S. V. A. V. Prasad, “Scope of improvement of design of major components for focused ultrasound equipment by employing the state-of-the-art active elements in coordination with artificial intelligence,” in *Data Driven Approach Towards Disruptive Technologies*, Singapore: Springer Singapore, 2021, pp. 573–582.
- [20]. M. W. Schoen et al., “Survival of veterans treated with enzalutamide and abiraterone for metastatic castrate resistant prostate cancer based on comorbid diseases,” *Prostate Cancer Prostatic Dis.*, 2022.
- [21]. M. A. Bakarev, V. P. Levin, I. V. Kachesov, and A. I. Neimark, “Morphological changes in tumor and nontumor tissue in the treatment of prostate adenocarcinoma with high-intensity focused ultrasound in combination with androgen deprivation,” *Arkh. Patol.*, vol. 80, no. 3, pp. 26–33, 2018.
- [22]. M. Finotti, M. Romano, M. Brizzolari, M. Scopelliti, and G. Zanus, “Comment on: ‘A review on radiofrequency, microwave and high-intensity focused ultrasound ablations for hepatocellular carcinoma with cirrhosis,’” *Hepatobiliary Surg. Nutr.*, vol. 11, no. 4, pp. 640–642, 2022.
- [23]. C. G. Roehrborn, M. E. Spann, S. L. Myers, C. R. Serviss, L. Hu, and Y. Jin, “Estrogen receptor beta agonist LY500307 fails to improve symptoms in men with enlarged prostate secondary to benign prostatic hypertrophy,” *Prostate Cancer Prostatic Dis.*, vol. 18, no. 1, pp. 43–48, 2015.
- [24]. N. Li, P. Yang, and J. Fang, “Transarterial chemoembolization (TACE) plus apatinib vs. TACE alone for hepatocellular carcinoma,” *Clin. Res. Hepatol. Gastroenterol.*, vol. 46, no. 9, p. 102022, 2022.
- [25]. H. Rakova, “Efficiency of combination therapy of high focal ultrasounds HIFU with cold laser 635 nm on adipose tissue,” *J. Obes. Weight Loss Ther.*, vol. 03, no. 02, 2013.
- [26]. S. Olaoluwa ONIGBINDE, C. Mopelola ASALEYE, A. Ayo SALAKO, B. Michael IDOWU, A. Olumayowa ONIGBINDE, and A. Laoye, “The effect of systemic hypertension on prostatic artery resistive indices in patients with benign prostate enlargement,” *Prostate Int.*, 2022.
- [27]. M. Jacewicz, E. Rud, K. F. Galtung, D. Noor, and E. Baco, “Cancer detection rates in targeted transperineal MRI-TRUS elastic fusion-guided prostate biopsies performed under local anesthesia,” *Anticancer Res.*, vol. 41, no. 9, pp. 4395–4400, 2021.
- [28]. G. I. Rudoy, “Analysis of the stability of nonlinear regression models to errors in measured data,” *Pattern Recognit. Image Anal.*, vol. 26, no. 3, pp. 608–616, 2016.
- [29]. Experts from the RATIONAL study (ALK testing in Chinese advanced non-small cell lung cancer patients: a national-wide multicenter prospective real world data study) and Molecular Pathology Committee of Chinese Society of Pathology, “Expert consensus on clinical practice of ALK fusion detection in non-small cell lung cancer in China,” *Zhonghua Bing Li Xue Za Zhi*, vol. 48, no. 12, pp. 913–920, 2019.
- [30]. S. Oh, J. Y. Ha, and Y. J. Cho, “Contrast-enhanced voiding ultrasonography to detect intrarenal reflux in children: comparison with 99mTc-DMSA renal scans,” *Ultrasonography*, vol. 41, no. 3, pp. 502–510, 2022.
- [31]. K. Tsukamoto, M. Nakahara, T. Nakahara, and M. Furue, “A young man with skin disorder and pancytopenia due to excessive oral methotrexate during treatment of rheumatoid arthritis,” *Nishi Nihon hifuka*, vol. 83, no. 4, pp. 317–320, 2021.
- [32]. O. Rouvière et al., “Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study,” *Lancet Oncol.*, vol. 20, no. 1, pp. 100–109, 2019.

- [33]. B. P. Wu, D. Grits, V. Foorsov, J. Xu, P. Tankha, and R. B. Bolash, “Cooled and traditional thermal radiofrequency ablation of genicular nerves in patients with chronic knee pain: a comparative outcomes analysis,” *Reg. Anesth. Pain Med.*, vol. 47, no. 11, pp. 685–690, 2022.
- [34]. A. Baba, R. Kurokawa, E. Rawie, M. Kurokawa, Y. Ota, and A. Srinivasan, “Normalized parameters of dynamic contrast-enhanced perfusion MRI and DWI-ADC for differentiation between posttreatment changes and recurrence in head and neck cancer,” *AJNR Am. J. Neuroradiol.*, vol. 43, no. 8, pp. 1184–1189, 2022.
- [35]. J. Xu et al., “Inherited risk assessment and its clinical utility for predicting prostate cancer from diagnostic prostate biopsies,” *Prostate Cancer Prostatic Dis.*, vol. 25, no. 3, pp. 422–430, 2022.