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High-Intensity Focused Ultrasound: A Review of Mechanisms and Clinical Applications

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Abstract

High Intensity Focused Ultrasound (HIFU) is an emerging and increasingly useful modality in the treatment of cancer and other diseases. Although traditional use of ultrasound at lower frequencies has primarily been for diagnostic imaging purposes, the development of HIFU has allowed this particular modality to expand into therapeutic use. This non-invasive and acoustic method involves the use of a piezoelectric transducer to deliver high-energy pulses in a spatially coordinated manner, while minimizing damage to tissue outside the target area. This review describes the history of the development of diagnostic and therapeutic ultrasound and explores the biomedical applications utilizing HIFU technology including thermally ablative treatment, therapeutic delivery mechanisms, and neuromodulatory phenomena. The application of HIFU across various tumor types in multiple organ systems is explored in depth, with particular attention to successful models of HIFU in the treatment of various medical conditions. Basic mechanisms, preclinical models, previous clinical use, and ongoing clinical trials are comparatively discussed. Recent advances in HIFU across multiple medical fields reveal the growing importance of this biomedical technology for the care of patients and for the development of possible pathways for the future use of HIFU as a commonplace treatment modality.

Keywords

Ablation; Drug Delivery; Neuromodulation; Sonoporation; Focused Ultrasound

Introduction

Ultrasound technology was first discovered in 1880 by Pierre and Jacques Curie when examining the effects of mechanical vibration on quartz crystals [86]. While early applications included underwater visualization during World War I and metal impurity testing for industrial uses, ultrasound was eventually introduced to the medical setting [87]. Since then, it has broadly grown into a fundamental clinical modality (Table 1). From fetal imaging

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and bone sonometry to echocardiograms and biopsy guidance, ultrasound technology has become a diagnostic mainstay in many medical fields [88]. Diagnostic ultrasound is usually delivered at 0.1 W/cm^2 with higher energy dose administration categorized as either high intensity (1,000 W/cm^2 - 10,000 W/cm^2) [108], medium intensity, or low intensity (< 3 W/cm^2) [79]. This review focuses on the applications of high intensity focused ultrasound (HIFU) in which acoustic waves are administered at the highest energy level and converge at a focal point.

HIFU was first therapeutically suggested in 1932 when H. Freundlich, K. Collner, and F. Rogowski discovered the medium's propensity to heat tissue [40]. In 1942, Lynn et al. explored the localized impact of targeted beams on tissue blocks and live animal organs [40]. The researchers specifically noted the method's ability to cause intense change at the energy's focal point while leaving tissue in the path of the beams unharmed [40]. In the 1960s, interest in HIFU greatly increased due to contributions by the Fry brothers, who created cortical lesions in patients with Parkinson's and other hyperkinetic disorders [18] in an effort to slow disease progression. HIFU further gained momentum as a viable treatment option in the fields of ophthalmology and neurosurgery through the later 1900s, but research was stalled due to limited imaging modalities and the temperature-monitoring software required for precision during treatment [80].

The advent of Magnetic Resonance Imaging (MRI) technology in the 1980s led to a renewed interest in high-intensity focused ultrasound due to the potential for precise spatial guidance via imaging and the development of MR-thermometry, allowing for accurate temperature tracking [30]. The first coupled MR-guided focused ultrasound machine (MRgFUS) in 2003 [80], set the stage for HIFU to become a useful treatment option with broader applications.

While HIFU is increasingly being used across disparate areas of medicine, one field of particular interest is oncology. Current strategies for treating malignant neoplasms include a combination of surgery, radiation, chemotherapy, and immunotherapy. Chemotherapy is the most widely employed systemic treatment, yet, even the most promising chemotherapies have been unable to demonstrate desired efficacy due in large part to barriers in delivery, tumor heterogeneity, and cancer resistance. In the pursuit to optimize cancer treatment, HIFU is emerging as a promising and versatile technology that presents itself as both a novel standalone treatment and also one that can enhance the effectiveness of currently available agents. Modulating the intensity of ultrasound treatment allows for its usage as either a drug delivery mechanism or ablative modality, both of which show promise as treatments for neoplasms.

HIFU Mechanism

High intensity focused ultrasound is traditionally delivered by a piezoelectric transducer with a fixed aperture and focal length. The transducer generates an ultrasound field with frequencies ranging from 1 to 7 MHz [32]. These sound waves are then converted to thermal energy and travel through the body, converging at a focal point and capable of causing coagulative necrosis. Similar to general ultrasound, there are two categories of treatment effects on tissue: thermal and mechanical.

Thermal effects include the physical heating of targeted tissue due to absorption of ultrasound waves. At lower deposited energy doses (< 55 °C), the induced hyperthermia can lead to increased cellular permeability, better facilitating the delivery of nanoparticles [47]. This can be advantageous in tandem with thermally modulated carrier molecules. At higher deposited energy doses (> 55 °C), a state of cell death is induced by coagulative necrosis [22]. This level is characteristic of tumor ablative therapies where the lesioned area is mapped using diagnostic ultrasound (USgFUS) or preferably MR imaging (MRgFUS). The precision of HIFU delivery allows the distance between ablated and normal tissue to be minimal. Yu-Feng reported an almost imperceptible margin between affected and unaffected myocytes, even providing images depicting histological differences across a single cell soon after ablation; the half that was within lesion boundaries demonstrated dramatic subcellular fragmentation while the other half of the cell outside the margins remained intact [85]. ter Haar et al reported this distance to be approximately 10 cells (250-300 microns) when ablating hepatocytes [23]. Even accounting for tissue variability, HIFU ablation results in a very thin boundary between affected and unaffected regions [85].

The mechanical effects of HIFU include radiation force, increased pressure, and most importantly, acoustic cavitation. Acoustic cavitation describes the process by which pressure field differences in the targeted tissue lead to the formation, oscillation, and collapse of microbubbles. While ultrasound administered at a low intensity causes sheer stress on nearby structures, ultrasound administered at high intensity leads to the formation of jet streams and shock waves. This increased frequency fosters the creation of transient pores in the plasma membrane, increasing cellular permeability - a process known as sonoporation [47]. Sonoporation (Figure 1) is useful from a drug delivery standpoint, as the pores allow for increased particle uptake in target tissues and the crossing of intercellular and intracellular barriers.

Applications

Focused Ultrasound and Ablation

Due to its heating effects, the most commonly explored utilization of HIFU is thermal ablation (Figure 1) [94]. The idea was first introduced by Lynn et al. in the 1940s when exploring inducible hyperthermia[108], and further expanded upon in the 1980s when Wang et al. correlated the scope of ablative injury with wave intensity and irradiation time in porcine liver tissue [74]. Since its first application, ablation has become a popular therapeutic option for treatment in the bone, liver, pancreas, breast, and kidney [15].

To adequately ablate an area with high-intensity focused ultrasound, certain parameters are determined including the treatment zone, safety margins, radiation dose, and duration of ablation. The treatment zone is the most variable and includes both the target tumor volume and a surrounding perimeter of normal tissue as a safety margin, which is similar to the surgical excising approach [13]. Lesion depth is taken into account as well; deeper structures (>10 cm) result in more attenuation of the acoustic waves as they pass through the body and are less effective at depositing the set energy dose [13]. Reflective interfaces between tissues and dense structure obstruction may lead to under-treatment of the target region. In

addition, the delivery path should avoid gas-filled organs due to their muffling of HIFU effects through focal point displacement and sound wave modulation [27].

Monitoring lesion formation during ablative pulses is of the utmost importance from an efficacy and safety standpoint. Transducer dose deposition is actively adjusted to control temperature fluctuations, allowing those delivering care to optimize ablative impact within safety limits. Because of its ability to monitor lesion formation and tissue temperature in real time, MRI and thermometry is preferred over diagnostic ultrasound. For accurate delivery, anxiolytic, analgesic, and antispasmodic medications are administered to decrease movement during the procedure and temporarily block digestive peristaltic motion [83].

Focused Ultrasound and Drug Delivery

Though traditionally used in an ablative setting, HIFU has more recently been explored as an adjunct to drug delivery due to its effect on membrane permeability. Specifically, there are two leading justifications for nanoparticles to be utilized in conjunction with ultrasound. First, nanoparticles can serve as nucleation sites, lowering the cavitation threshold during the formation of microbubbles; this potentiates the mechanical effects of HIFU and results in more efficient treatment applications. A 2019 study by Khirallah et al. demonstrated the increased capacity of perfluorohexane nanoparticles in reducing the cavitation threshold during ablation of tissue phantoms contained red blood cells [33]. Second, carrier particles themselves can be loaded with drug molecules and ablated at the appropriate delivery site by selectively applying HIFU to the region. Thus, externally triggered drug release can be accomplished with spatiotemporal control, with HIFU “activating” select particles via thermal and/or mechanical effects [1]. A description of select nanoparticles used with HIFU for cancer therapy shown in Table 2.

To rely on the thermal effects of HIFU, particles must be temperature-sensitive such that above or below a certain heat or energy threshold, drug is released. Dromi et al. explored the use of thermo-sensitive liposomes [12]; *in vitro* and *in vivo* mouse models demonstrated a more rapid and concentrated release of doxorubicin following administration of HIFU pulses and injection of low temperature-sensitive liposomes. In contrast, Liang et al. demonstrated that high temperature-sensitive cerasomes underwent a burst-release of drug molecules over a 5 °C temperature increase in their target region when administered to treat adenocarcinoma of the breast in mice [38].

The study of inducible characteristics relying on the mechanical effects of HIFU has centered on nanoparticles; this is due to their capacity to present as additional nucleation sites and also act as carrier molecules, allowing for increased drug unloading via sonoporation at the site of HIFU application. These nanoparticles can be organic, such as lipid- or polymer-based, or they can be inorganic, such as metallic, or they can be a hybrid combination. You et al. explored the use of a metal oxide conjugated polymeric nanoparticle to unload perfluorohexane and treat hepatocellular carcinoma in a xenograft rabbit model. In addition to demonstrating *in vitro* efficacy, the nanoparticle + HIFU experimental group demonstrated a significantly ($p < 0.05$) lower tumor proliferative index than the HIFU alone control group [82]. Along with its efficacy in rabbit liver tumor xenograft tissue, nanoparticles in combination with HIFU has also been successfully utilized in mouse

models. For example, researchers have demonstrated that pulsed HIFU (administered across burst intervals) effectively synergized with glycol chitosan nanoparticles in murine models [84]. Furthermore, in a study by You et al, specific HIFU pulsed dosing of 10, 20, and 50 W resulted in leaky murine femoral vasculature, demonstrated by increased fluorescence signals as compared to untreated tissue [81]. HIFU treatment has increasingly been shown to increased extravasation of drug-loaded carrier nanoparticles, overcoming tissue penetration, one of the critical obstacles to nanoparticle use.

Limitations of HIFU in facilitating drug delivery include its short duration of effect and variable drug uptake. In clinical practice, solid tumors benefit from sustained release of chemotherapeutic agents to most fully penetrate the mass. Because the delivery mechanism of HIFU has inherent limitations in the number of pulses per session due to safety, large tumors may require longer and more complicated treatment protocols [55]. Additionally, the delivery of nanoparticles depends on transport through extracellular barriers to reach the target area. With variance within heterogenous tumors as well as from patient to patient, there can be dramatic differences in drug penetration and uptake based on tumor type, treatment area, and other biological characteristics.

Focused Ultrasound and Neuromodulation

In addition to ablative and drug delivery applications, focused ultrasound techniques have the potential to be used in neuromodulation therapies especially when administered at a lower intensity. Neuromodulation (Figure 1, Figure 2) refers to the alteration of neuronal activity by a therapeutic agent, including electrical stimulation and pharmacologic chemicals [95]. With the FDA having only recently approved therapeutic ultrasound, neuromodulatory treatments are a newly emerging target of investigation with limited current literature. In contrast with the ablation caused by high intensity focused ultrasound (HIFU), low intensity focused ultrasound (LIFU) has been theorized to play a useful role in neuromodulation [14]. Mechanistically, LIFU creates a nonthermal mechanical disturbance in voltage-gated ion channels, affecting electrical signaling across membranes and therefore impacting neuronal activity [14]. In order for neuromodulation to occur as opposed to thermal ablation, ultrasound must be delivered at lower energy (< 3 W/cm^2) and provide marginally enough stimulation to modify channels short of causing mechanical damage [79]. The reversibility of this mechanism, as first demonstrated by the Fry brothers [17], provided the basis for the investigation of ultrasound for neuromodulation. Furthermore, the resulting changes in neuronal activity are not limited to the duration of the LIFU therapy and can last for hours to days [14,25]. HIFU, conversely, is believed to not function through this neuromodulation mechanism, given its overt thermal destruction of tissue at higher frequencies [3,14].

Preclinical animal studies have repeatedly suggested the relative safety and efficacy of LIFU for neuromodulation. A study by Deffieux and colleagues in 2017 investigated LIFU as a tool to modulate prefrontal cortex activity, specifically visuomotor actions, in awake macaque rhesus monkeys [11]. By training the monkeys to initiate specific saccade movements based on a stimulus, they found that this behavior could be modified through the application of LIFU, suggesting potential for similar behavior-modifying capacity in humans [11]. A study by Dallapiazza et al. in 2018 explored the use of LIFU to modulate the swine sensory

thalamus as a means of noninvasively mapping the brain [9]. The authors found success in inhibiting specific thalamic nuclei without affecting neighboring nuclei, creating any tissue damage, or inducing any thermal effects, affirming the safety and specificity of delivered ultrasound signals and opening the possibility of developing neuromodulation as a brain-mapping tool pending future investigation in patients [9]. A setup and analysis of FU-guided neuromodulation is exemplified in Figure 2, in which Airan et al. in 2017 demonstrated that sonication can safely deliver seizure-silencing nanoparticles without brain parenchymal damage in a rat model[1].

Several studies have investigated the use of ultrasound for neuromodulation in patients. A recent study by Sanguinetti and colleagues demonstrated the application of transcranial focused ultrasound to the right prefrontal cortex in healthy patients through a randomized, placebo-controlled, double-blind study; the authors found that this ultrasound use improved mood and affected the connectivity of neural networks related to emotional regulation [61]. These results provide a positive projection for future studies that may investigate the potential use of LIFU as a psychiatric neuromodulation treatment in patients suffering from mood disorders. An active clinical trial (NCT04197921), is examining LIFU as an adjunctive treatment in opioid use disorder. As researchers further develop an understanding of the mechanisms of LIFU as a neuromodulator, these studies will shed light on both the utilities of neuromodulation with LIFU and the impact this therapeutic modality could have on the treatment of various neurologic disorders.

HIFU Clinical Trials

Uterine Leiomyomas/Myomas and Adenomyosis

One of the most established applications of HIFU is in the female reproductive system. HIFU is FDA-approved for treatment of uterine leiomyomas and currently in the clinical trial stage for treatment of uterine adenomyosis [96]. Adenomyosis occurs when the inner endometrial lining of the uterus grows into the muscular wall and leads to a thickening of the organ. Though the cause has not been fully elucidated, it results in painful menstrual cramps and abnormal bleeding in many affected women. There are several current treatment protocols for adenomyosis include hysteroscopic resection, focal excision, uterine artery ligation, and myometrial electrocoagulation [70]. Yet, many of these procedures have not gained widespread acceptance due to negative side effects and serious contraindications in certain populations.

Studies on the treatment of adenomyosis with HIFU have yielded positive results but still indicated the need to standardize protocols and optimize parameters. In a 2016 study, Gong et al. investigated factors affecting HIFU ablative efficiency in 245 patients diagnosed with adenomyosis. Increased abdominal wall thickness, distance from skin to lesion, richer blood supply, and high T2 signals on MRI scans were all found to be predictive factors for lower HIFU ablative efficiency [20]. Marques et al. released a meta-analysis of all English language studies examining HIFU-treatment of adenomyotic lesions between 2010 and 2020 [45]. Results indicated that uterine volume and dysmenorrhea significantly decreased with a standard mean difference of 0.85 and 2.37 respectively at the 12 month-interval. Patients further reported a significant improvement in quality of life at both the 3 month

and 12 month mark [45]. Still, comparative studies have not been conducted to evaluate HIFU treatment against more traditional standards of care [45], indicating a need to assess direct impacts of treatment protocols prior to adjusting clinical decisions.

In 2004, HIFU was approved by the Food and Drug Administration (FDA) for the treatment of leiomyomas, otherwise known as uterine fibroids [106]. Uterine leiomyomas are benign monoclonal tumors arising from smooth muscle cells of the myometrium. They are the most prevalent pelvic tumors in premenopausal females, currently affecting 11 million females in the United States [46]. Treatments for uterine fibroids include hysterectomy, myomectomy, endometrial ablation, myolysis, and MRgHIFU [59]. Compared to more traditional treatments, MRgHIFU has been theorized to be more safe and effective due to its noninvasiveness, rapid recovery time, and ability to spare the uterus [97]. In 2015 Shui et al. evaluated the long-term improvement of clinical symptoms of adenomyosis after USgHIFU. 224 patients were followed for two years (Figure 3)[65]. All patients completed HIFU ablation without severe postoperative complications. Dysmenorrhea significantly decreased after treatment ($P< 0.001$) and the relief rate was 84.7%, 84.7%, and 82.3%, respectively at 3 months, 1 year, and 2 years after treatment. The menstrual volume in 109 patients with menorrhagia was also significantly improved after treatment ($P< 0.001$) with a relief rate of 79.8%, 80.7%, and 78.9%, respectively at 3 months, 1 year, and 2 years after HIFU treatment. This clinical follow up study determined that HIFU was a safe and effective treatment for adenomyosis.

A retrospective observational trial published by Li et al. in 2020 analyzed long-term reintervention rates among their cohort of patients with uterine fibroids who were treated with ultrasound-guided HIFU [37]. With an overall reintervention rate of 20.7% and 86.4% of patients reporting relief from distressing symptoms, HIFU was concluded to be an effective treatment for leiomyomas [37]. Similarly, Wang et al. collected data on 245 women who were treated with ultrasound-guided HIFU for their uterine fibroids and 129 women who underwent uterus-sparing surgery for symptomatic fibroids [73]. The treatment resulted in reduced procedural complications and significantly higher symptom relief ($p < 0.05$). Furthermore, long-term clinical outcomes were reported to be better in the group that was administered HIFU as compared to the uterus-sparing surgical group [73]. While these studies are promising, larger-scale clinical trials should also be conducted to further validate these findings.

There are two completed or currently active clinical trials examining the treatment effects of HIFU [98] on adenomyosis and 13 on uterine leiomyomas [99]. The vast majority of these trials are focused on HIFU as an ablative treatment in comparison with previously mentioned protocols such as uterine artery ligation, myomectomy, etc. The results of these ongoing trials will help to further elucidate the long-term effects of HIFU in the context of uterine leiomyomas/adenomyosis and aide in protocol optimization.

HIFU and Prostate Cancer

Prostate cancer is the second most common cancer in men and a major cause of mortality due to its high recurrence rates, necessitating extensive research into various potential tumor treatments to render affected patients disease-free [57]. HIFU has been examined and

employed for several years as a treatment method for ablation of prostate cancer [69]. A multi-center study published in 2018 by Guillaumier and colleagues investigated 625 patients with nonmetastatic prostate cancer treated with HIFU between 2006 and 2015 [21]. They found that at the five-year mark, metastasis-free survival was 98%, cancer-specific survival levels were 100%, and morbidities were low as compared to whole-gland radical prostatectomy and radical radiotherapy, which are interventions that though extremely successful are commonly known to have urinary, sexual function, and bowel side effects. The authors concluded that though long-term data is unavailable, HIFU is an advantageous therapy for prostate cancer care, lacking the morbidities of more aggressive and invasive therapies, and can be offered as a treatment to certain patients with nonmetastatic disease [21]. Glybochko et al. found similarly low morbidity rates in their 35-case retrospective study on patients who received HIFU hemiablation of the prostate cancer and too noted that HIFU shows promise as a low-risk and feasible procedure [19] (Figure 4).

Due to the high likelihood of recurrence of prostate cancer, the use of HIFU in prostate cancer has also been proposed and investigated as a salvage therapy after traditional therapy fails to prevent local recurrences. A study in 2017 by Crouzet and colleagues examined 418 patients with locally recurrent prostate cancer across several institutions treated with external beam radiotherapy followed by HIFU. The authors found that 7-year survival rates increased with the utilization of salvage HIFU [8]. Furthermore, a study the next year by von Hardenburg et al. examined 24 patients who underwent MRI and transrectal ultrasound (TRUS) guided HIFU (nineteen patients with focal HIFU and five with zonal HIFU) as an ablative therapy for prostate cancer. The study found that though HIFU was capable of achieving successful local tumor ablation, 40% of patients actually had a positive biopsy at short-term follow-up [26], indicating a current need for a more robust treatment regimen as well as further investigation and development in the use of this technology before it can become a standalone therapy.

A search of clinicaltrials.gov provides a robust list of over 30 completed or active clinical trials investigating the use of HIFU in the treatment of prostate cancer, particularly regarding different guidance techniques and the utility of PET scans for prostate cancer identification and HIFU ablation. A few such trials include NCT03350529, investigating MRI guided transurethral ultrasound in prostate cancer and benign prostatic hyperplasia, and NCT03927521 and NCT04461509, both investigating using PET-MRI as a selection tool for HIFU treatment. No current trials exist regarding enhancement of drug delivery with the use of HIFU in prostate cancer, but this is would be an interesting are to explore in future studies in the prostatic cancer care field.

HIFU and Breast Cancer

HIFU has undergone extensive examination in multiple cancer types as a technique for cancer ablation and drug delivery, and results from these studies provide encouragement for further exploration. One such cancer investigated is breast cancer, which is the most common cancer in women (276,480 new cases/yr and 42,170 deaths/yr) [100]; Although it has a high survival rate (5-year survival of 89% between 2005 and 2011) [58], there remains a significant population who suffer from more aggressive disease refractory to standard

surgical intervention, radiation, and chemotherapy protocols, demanding the exploration of advanced techniques, including HIFU.

Several studies have examined the use of HIFU as a method of ablation for breast cancer treatment. One of the earliest published results came from Wu et al. in 2003, who examined a cohort of 48 women with biopsy-proven breast cancer staged at T_{1-2}, N_{0-2}, M0 [77]. The patients were randomized to either the control group, who received modified radical mastectomy, or the treatment group, who received ultrasound-guided HIFU and modified radical mastectomy within 1-2 weeks of ablation. The authors found that HIFU left no severe short-term side effects and that cells treated with HIFU underwent severe damage, achieving complete coagulative necrosis and losing the ability to proliferate and metastasize, indicating its worth as a potential noninvasive treatment of breast cancer [77]. Wu and colleagues further explored this technique in 2007, affirming its ability to achieve wide local ablation in localized breast cancer [76,78].

Other studies since have reinforced the value of HIFU as an ablative technique for breast cancer treatment [56]. In 2016, Knuttel et al. examined the histopathological changes of MR-guided HIFU versus that of traditional radiofrequency ablation (RFA) [34]. The authors found that there were several distinctions between histopathologic changes in HIFU and RFA. For HIFU, there were more necrotic-type changes *in vivo* that were more subtle *ex vivo*, whereas for RFA, *in vivo* and *ex vivo* histopathologic changes were similar in character, with hyper-eosinophilic stroma and elongated nuclei. Further, RFA created large transition zones, while HIFU created smaller ones, suggesting a more defined area of effect with HIFU [34]. Several ongoing clinical trials (NCT02407613, NCT03560102, NCT03342625, and NCT00008437) are continuing to examine both short- and long-term effects of HIFU as a method of noninvasive tumor ablation and will continue to guide clinical practice as their results are determined in the coming years.

HIFU has also been examined as a method to enhance drug delivery in breast cancer. Based on prior research indicating that pulsed HIFU could enhance systemic delivery of various drugs, Frenkel and colleagues in 2006 performed one of the earliest experiments by examining the delivery of liposome-encapsulated doxorubicin in a murine breast cancer model using pulsed HIFU. These authors injected a cell suspension of either a mouse mammary adenocarcinoma or squamous cell carcinoma into the bilateral flanks of their mice, and unilaterally treated with pulsed HIFU and/or doxorubicin as compared to a saline control on day 21 of tumor growth via tail-vein injection. Their aim was to use HIFU to enhance uptake, but not specifically through hyperthermia. The results from this study indicated that HIFU did not sensitize tissue to doxorubicin delivery [16]. Although such results were not immediately promising, other tumor types investigated have shown HIFU to be a viable method of enhancing doxorubicin delivery via induction of hyperthermia in rabbits with a unilateral Vx2 tumor in the thigh. The rabbits were treated at 11-13 days after inoculation with the tumor, with thermosensitive liposomal doxorubicin via ear-vein injection. For rabbits receiving the hyperthermia variable, this was injected once the HIFU created a mild hyperthermia state of 40-43°C, with a target mean of 42°C. The rabbits who underwent hyperthermia-focused HIFU treatment had better uptake of doxorubicin into their tumors and longer survival times. [2,67] An ongoing clinical trial (NCT03749850) is

taking place to further examine how MR-guided HIFU can enhance doxorubicin delivery in breast cancer. Another mechanism by which HIFU may enhance drug delivery is through the disruption of microbubbles; a study by Lee and colleagues found that HIFU burst chemically-generated microbubbles containing the chemotherapeutic drug methotrexate, allowing for highly targeted local delivery [35]. A final mechanism by which HIFU may augment drug delivery is through enhancing antigen presentation. Specifically, HIFU can cause in situ tumor emulsification, facilitating an increased breakdown of antigenic proteins and stimulating an inflammatory response. This response upregulates chemoattractants and allows for local delivery of exogenous drug-carrier molecules [44]. A current trial (NCT03237572) is examining the mechanisms behind this therapeutic regimen, specific to pembrolizumab therapy in patients with metastatic breast cancer. With careful titration and examination, HIFU may become a useful tactic to enhance drug delivery to treat multiple types of solid tumors.

HIFU and CNS Diseases/Tumors

With neurological disorders a major cause of death and disability globally, dysfunction in the central nervous system (CNS) is associated with serious consequences [71]. Comprising the brain and spinal cord, the CNS is responsible for sensory integration, response coordination, and motor output. High intensity focused ultrasound was first applied to the human CNS when the Fry brothers discovered its ability to treat neurological disorders in the early 1950s [30]. Since then, it has been utilized to treat essential tremor (ET), neuropathic pain, and CNS tumors. HIFU has also been used as a technique to transiently make the brain more accessible for the delivery of systemically administered agents.

Essential Tremor—In 2016, focused ultrasound was approved in the United States as a treatment for essential tremor (ET) by the FDA[109]. In this treatment, the ventral intermediate nucleus of the thalamus is ablated, selectively creating brain lesions at the focal point of soundwave convergence. With structures in the wave path largely unaffected, HIFU is relatively safe for non-targeted regions and results in lower risk of thrombosis and lower risk of infection as compared to traditional ET treatments such as deep brain stimulation and radiofrequency ablation [24,36,60]. A study by Ito et al. explored long-term clinical outcomes of MRgFUS in patients with medication-refractory ET [29]. Focal left-sided thalamotomy resulted in a 60% reduction of clinical rating scale for tremor scores (CRST) in the right hand. Though patients reported significant symptoms including headache during treatment and sensory disturbances post-treatment, the study validated MRgFUS unilateral thalamotomy as a viable choice for refractory ET [29]. Furthermore, Park et al. demonstrated sustained clinical mitigation of refractory ET by unilateral MRgFUS thalamotomy 4 years after initial treatment [54]. Current clinical trials include NCT04112381 in which scientists are examining the effect of bilateral thalamotomies on left and right-sided tremors [101]. NCT03465761 is another similar prospective single-arm trial, studying outcomes of bilateral focused ultrasound ablative treatment to treat drug-refractory ET [102]. These larger-scale studies will set the stage for further treatment optimization of HIFU technology.

Neuropathic Pain—Neuropathic pain is generally caused by abnormalities in the somatosensory system and impacts 7-10% of the population [7]. Dealing with a chronic issue,

those affected report a lower quality of life due to persistent symptoms and limited treatment options. Primary central neuropathic pain is frequently a result of injury to the spinal cord whereas peripheral neuralgias can be due to an array of disease states including diabetes, inherited disorders, autoimmune diseases, etc [103]. Conventional methods to treat neuropathic pain include medications, nerve blocks, and invasive surgery, yet many patients are unable to find long-term relief.

Focused ultrasound was first theorized to have an effect on neuropathic pain in 1996 [10]. A prospective clinical trial released in 2012 followed 12 patients who suffered from treatment-resistant chronic neuropathic pain. MRgFUS was utilized to perform central lateral thalamotomies, with patients reporting a mean pain relief score of 57% at the 1-year follow-up interval [31]. In a 2020 study, Ma et al. further concluded the high potential of HIFU to become a non-invasive treatment modality for primary trigeminal neuralgia [42]. There are currently 8 clinical trials underway to examine the short- and long-term effects of focused ultrasound on neuropathic pain, including trigeminal neuralgia (NCT04579692), phantom limb pain (NCT03111277), and craniofacial neuralgias (NCT04202783). Though preliminary studies have speculated the ability of HIFU to relieve neuropathic pain, the results of these trials will dictate its potential to become a mainstay treatment in the field.

CNS Tumors and the Blood-Brain Barrier—In 2020, approximately 23,890 malignant tumors of the brain and spinal cord will be diagnosed [66]. Current strategies for treating brain tumors include a combination of surgery, radiation, and chemotherapy. Yet, the most promising chemotherapies have been unable to demonstrate as much success in the central nervous system as they have in other systemic locations [75]. This is due to the blood-brain barrier (BBB), which is a tight layer of cells lining vessels in the brain that serve to protect the brain from potentially harmful substances in the circulation. In addition to functioning in an ablative capacity, HIFU has been shown to open this endothelial barrier in a safe, minimally invasive, and regional manner by means of cavitation and other physical mechanisms [104]. The ability to non-destructively penetrate the blood-brain barrier in a targeted manner and deliver appropriate concentrations of select drugs has the potential to revolutionize the way we treat some of our most vulnerable patients.

The utilization of focused ultrasound to transiently and reversibly open the blood-brain barrier poses several advantages over traditional delivery methods. Transcranial application eradicates the need for invasive procedures, reducing mechanical shift of brain tissue and infection risk. Tandem MRI use would allow for focal application of FUS, increasing the precision of treatment. And furthermore, current research has indicated no long-term deficits in blood-brain barrier function [4].

Proof of concept has been shown in multiple *in vivo* trials, demonstrating targeted delivery of nanoparticles to selective brain regions in animal models [6,39,72]. Recently, human trials are emerging evaluating the feasibility of focused ultrasound applications in this regard. A clinical trial published by Mainprize et al. reported a 15-50% transient contrast enhancement in five patients who were administrated chemotherapy after MRgFUS pulses for high-grade glioma [43]. Barrier function reportedly returned to normal within 20 hours, affirming the transient and reversible nature of the treatment modality. Sattiraju et al. further posited on

the compounded treatment effects of focused ultrasound to bypass the blood-brain barrier and surpass the efficacy of therapeutic drugs [62]. Chan et al. delivered varying sizes of Cy5-DNA-Au nanoparticles across the BBB using focused ultrasound and showed smaller NPs were delivered 6 times more efficiently than the largest ones tested, even though the difference in diameter between the particles was < 5nm), suggesting that optimizing NPs for intracranial delivery needs to be precisely fine-tuned (Figure 5)[6]. To establish translational data and substantiate theorized efficacy in humans, there are currently four clinical trials examining the effect of focused ultrasound on blood-brain barrier disruptions. One trial (NCT02343991) is examining the potential of MRgFUS to facilitate doxorubicin accumulation in the brain tumors of ten patients. Another prospective, single arm, non-randomized trial (NCT03714243) will evaluate focused ultrasound as a tool to intentionally disrupt the blood-brain barrier in a transient and targeted manner in patients with breast cancer and brain metastases. The larger goal of both trials is to examine and determine safety factors in order to provide quantitative parameters when assessing treatment efficacy in the future.

As evidenced throughout this discussion, the application of HIFU in a therapeutic rather than diagnostic method has invigorated the medical community in recent years. Though published literature on HIFU as a treatment modality on humans is limited, several clinical trials are underway in the hopes to introduce HIFU into common practice (Table 3). Promising preliminary results from a number of these trials indicate that HIFU will become a valuable therapeutic tool in the years to come.

High-intensity focused ultrasound is an emerging treatment modality with ground-breaking potential. Since its integration with imaging software in the early 2000s, HIFU's applicability has increased as both an ablative treatment and technique to improve drug delivery of multiple agents. Significant applications of HIFU have been demonstrated clinically for CNS disorders, pain, and cancer. For oncological diseases in particular, including uterine leiomyomas, adenomyosis, breast, prostate, and CNS cancers, the field has significantly advanced over the last decade and has great promise. Despite these gains, larger clinical trials are still needed to further substantiate results and increase the therapeutic options to best utilize this innovative modality.

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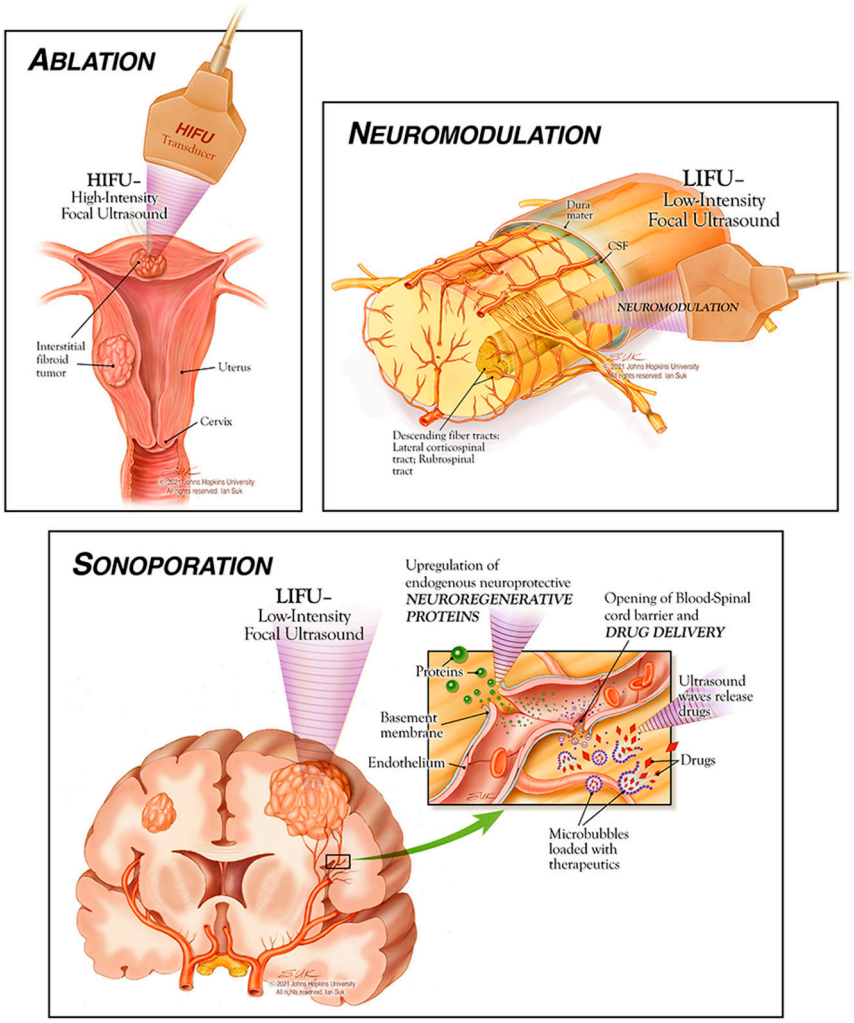

Figure 1:
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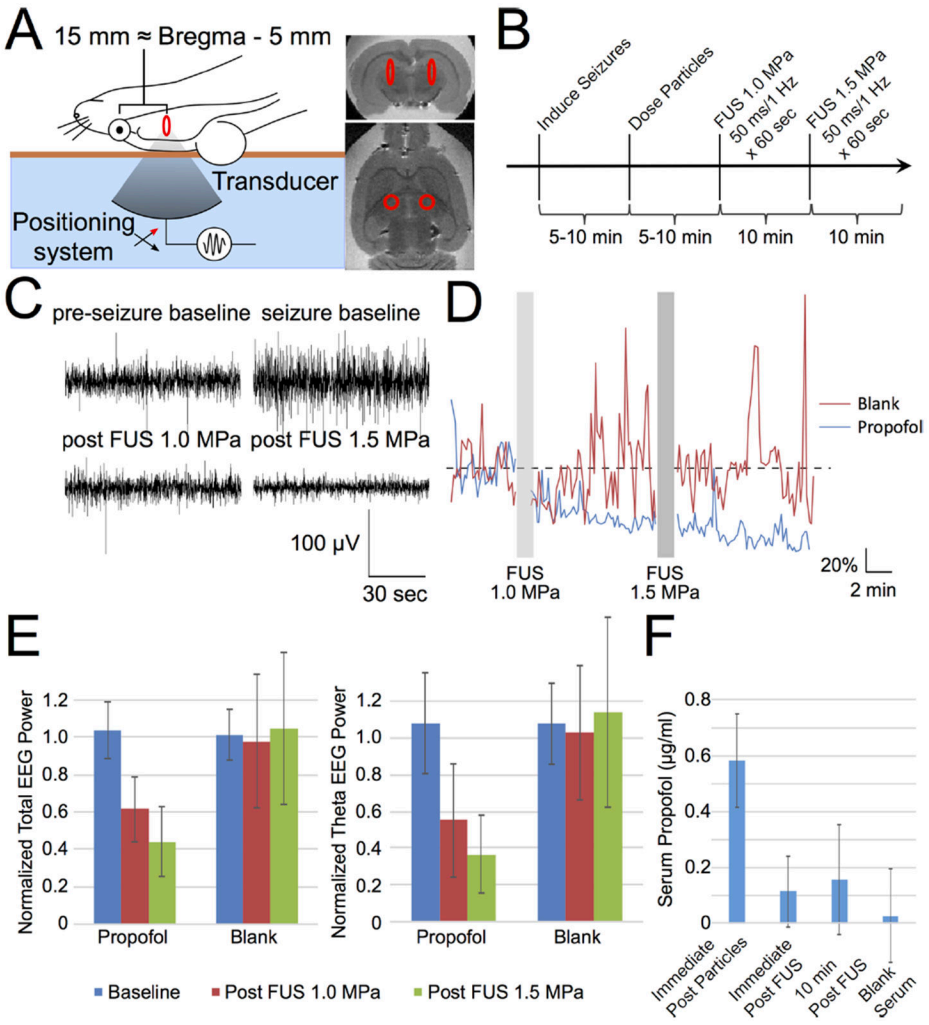

Figure 2.

Focused ultrasound-gated propofol release is potent enough to silence seizure activity. (A) Schematic of rat positioning for this demonstration of in vivo efficacy. Rats were placed supine on the bed of a focused ultrasound transducer and underwent seizure induction, coupled to the transducer via degassed water (light blue), a Kapton membrane filled with degassed water (orange-brown), and ultrasound gel (not pictured). Expected location of the two sonication foci are overlaid onto ex vivo MRI images with the red ellipse indicating the fwhm of the sonication focus, located ~5 mm caudal to bregma. (B) Schematic of experiment timing for seizure induction, particle administration, and FUS application. (C) Sample traces of EEG voltage from one rat receiving propofol-loaded particles before and after seizure-induction and focused ultrasound application at the indicated pressures. (D) Total EEG power normalized by baseline averaged across rats receiving particles loaded with either propofol (blue) or no drug (blank, red) across experiment time (N = 7 propofol, 5 blank). Gray bars indicate time of FUS application. (E) Mean ± SD of normalized total (left) and theta band (right) EEG power in the indicated time period across rats receiving propofol-loaded particles or blank particles (N = 7 propofol, 5 blank). (F) Mean ± SD of the HPLC-quantified serum propofol concentration of samples from N = 4 rats taken

immediately after propofol-loaded particle administration, immediately after sonication, and 10 min post sonication, compared to a blank serum sample. There was no appreciable serum propofol peak for the post sonication samples.

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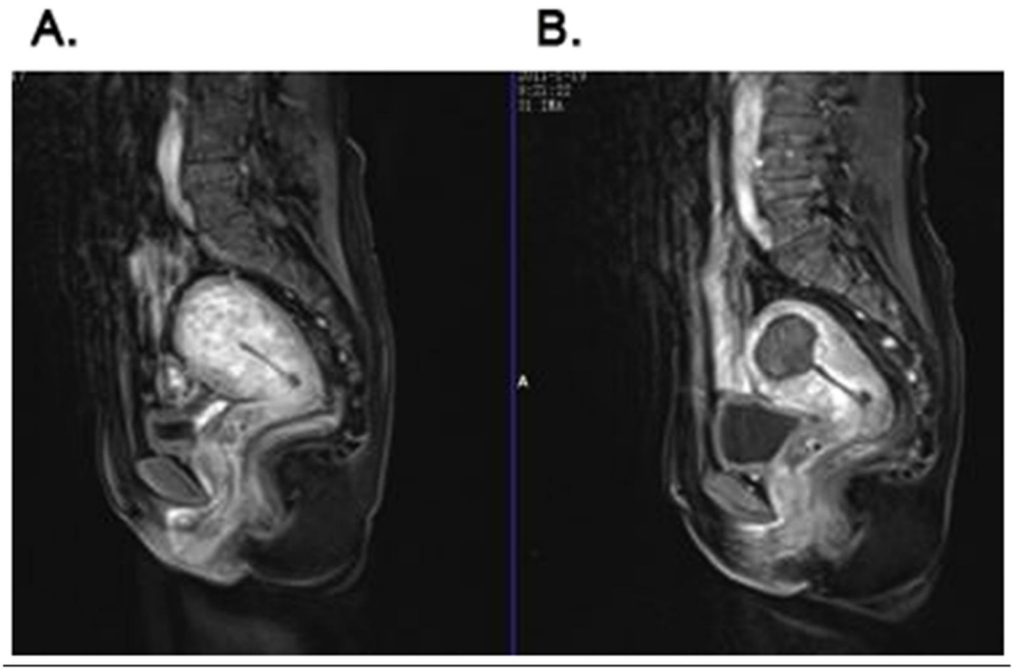

Figure 3.

Preoperative and postoperative enhanced MRI. (A) Enhanced MRI of adenomyosis before treatment which shows the thickening of the myometrium in fundus of uterus and rich blood supply. (B) Enhanced MRI from a patient with adenomyosis 1 day after HIFU treatment, which shows non-perfused area in the lesion. Reprinted from Ultrasonics Sonochemistry, Vol. 27, Shui L, Mao S, Wu Q, et al. High-intensity focused ultrasound (HIFU) for adenomyosis: Two-year follow-up results, Pages 677-681 (2015) with permission from Elsevier[65].

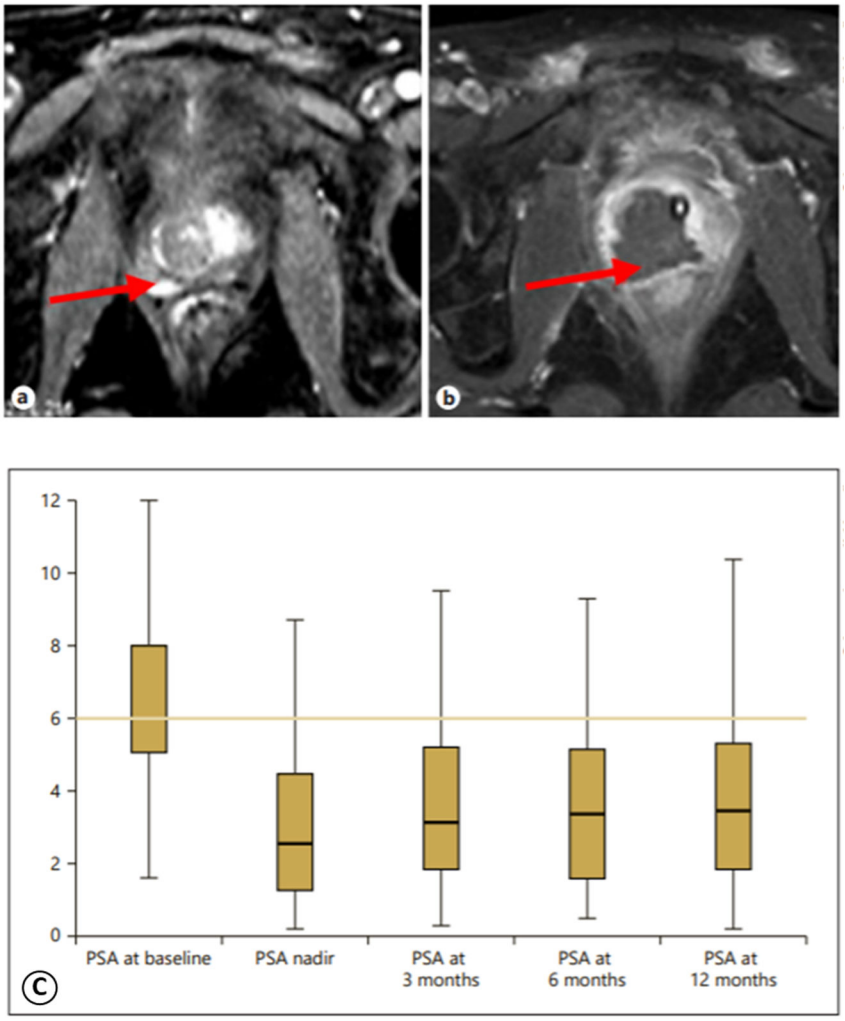

Figure 4.

Preoperative ultrasound shear wave elastography and prostate histoscanning and dynamics of prostate-specific antigen (PSA) before and after hemiablation. Representative MRI control findings of the pathological focus (arrows) before HIFU hemiablation (a) and its disappearance 3 months after the procedure (b). (C) demonstrates a box plot showing changes in PSA level before and after HIFU hemiablation (n=35), The line indicated the mean, the box indicated the interquartile range, and whiskers indicate the maximum and minimum values. The final, published version of this article is available at https://www.karger.com/Article/Fulltext/499739 [19].

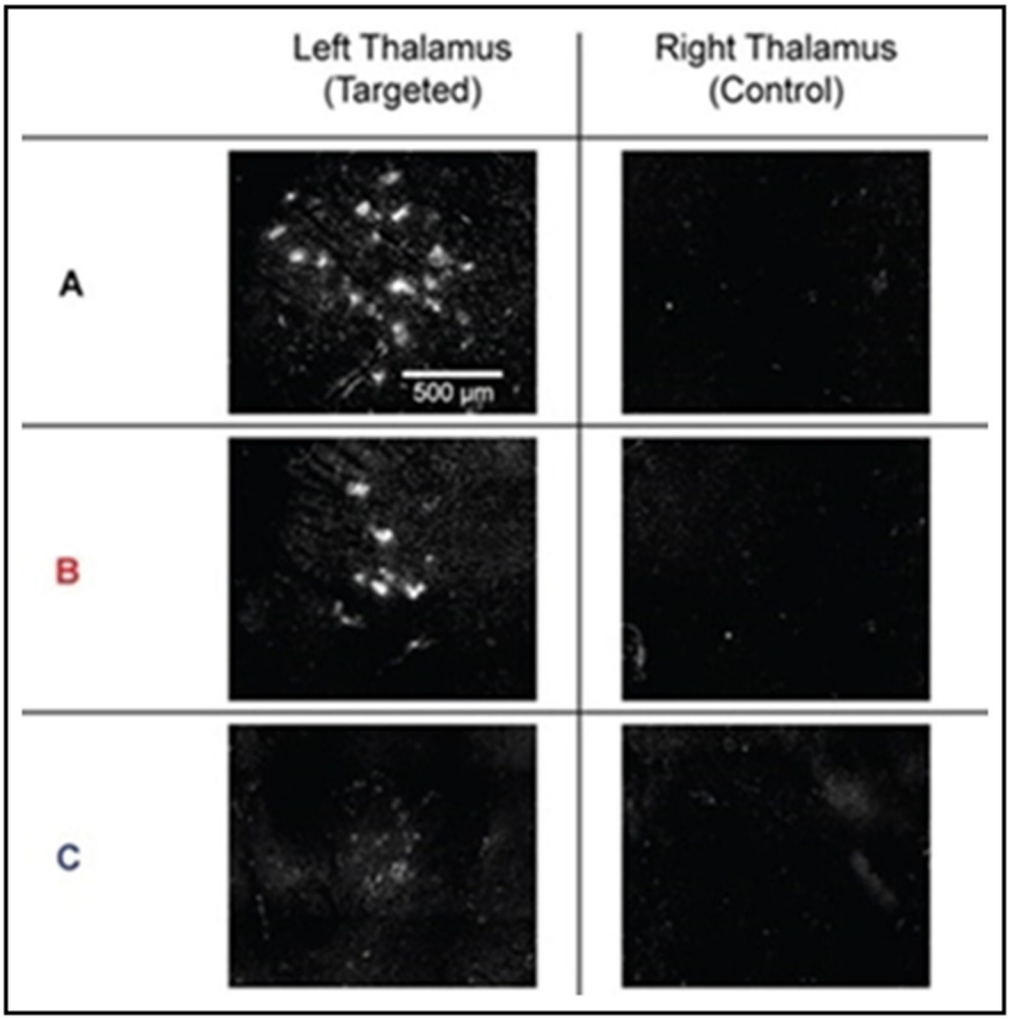

Figure 5.

Fluorescence images from the delivery of Cy5-DNA-Au NPs across the BBB using focused ultrasound. There is a size-dependency associated with the delivery of Cy5-DNA-Au NPs across the BBB using focused ultrasound, with the smallest NPs tested in this study (A) delivered across the BBB six times more efficiently than the larger/largest NPs tested (B/C). A spot-like distribution of fluorescence was observed in the left thalamus, while no fluorescence signal is detected in the right thalamus. Reprinted with permission from John Wiley and Sons [6].

Table 1:

Milestone table of notable advancements in ultrasound technology.

1880	Jacques and Pierre Curie discover piezoelectricity; ultrasound technology discovered [86]
1927	Effects of ultrasound on biological tissue investigated [107]
1932	Ultrasound first suggested in a therapeutic context [68]
1942	HIFU effects in animals (Lynn et al.) – first focused ultrasound device and first tissue lesion [40]
1944	First preclinical ultrasound study (Lynn and Putcham) [89]
1950-1969	Molecular study on HIFU effects (Fry brother) [30]
1951-1960	Radiofrequency generator and electrode developments [48]
1955	Fry brothers use focused ultrasound to perform partial ablation of basal ganglia after craniotomy [30]
1962	Focused ultrasound is explored as a treatment for multiple brain pathologies, including Parkinson's Disease [51]
1964	First cancer application of FU (M. Oka reported treatment of thyroid and breast cancer) [90]
1968	First brain cancer treated using FU (Dr. Robert Heimberger) [30]
1980s-present	MRI technology
1988	First FDA approval for Sonocare CST-100 Therapeutic Ultrasound System (to treat glaucoma) [50]
1994	First commercial HIFU machine receives FDA approval, approved for benign prostatic hyperplasia (BPH) (Sonablate 200) [52]
1996	First blood-brain barrier (BBB) opening moderate-intensity FU application, monitored by MRI [28]
2004	The FDA approved INSIGHTEC's Exablate 2000 to treat uterine fibroids; first FDA approval of integrated MRgFUS machine [91]
2009	First ultrasound to treat neuropathic pain [92]
2014	Focused ultrasound for bone cancer pain [64]
2016	Ultrasound approved to treat essential tremor (ET) [109]
2018	First clinical trial conveying local drug delivery published in Lancet Oncology [41]. BBB clinical trials begin at University of Maryland in brain tumor patients [93]

Table 2.

Select nanoparticles used with HIFU for cancer therapy

HIFU Effect	Particle Type	Particle	*In Vitro*	*In Vivo*	Model	Ref.
Thermal	Conjugated Polymer	HMME+PFP/PLGA-Ab (liquid fluorocarbon)	X	X	Breast cancer	84
	Liposome	Low temperature-sensitive liposomes	X	X	Mammary adenocarcinoma	12
		High temperature-sensitive liposomal cerasomes	X		Breast adenocarcinoma	38
Mechanical	Metallic	Gold		X	Colon cancer	63
		Porous Silicon	X	X	Laryngeal cancer	53
		Titanium Dioxide	X		Oral squamous cell carcinoma	49
		Magnetite (Fe_3O_2)	X		Breast cancer	5
	Conjugated Polymer	Fe3O4-PFH/PLGA	X	X	Hepatocellular carcinoma	82

Table 3.

Current active ongoing HIFU clinical trials described at clinicaltrials.gov (last updated on 04/11/2021) [105]

Disease	N	Primary Outcome	ClinicalTrials.gov Identifier
Uterine Adenomyosis	10	Perceived symptom change after HIFU treatment based on menstrual pain score	NCT02954757
Uterine Leiomyoma	40	Post-treatment myoma stiffness and ablathermy efficiency	NCT04345003
	50	Temperature elevation, non-perfused volume (NPV) of fibroid, adverse events related to potential damage to tissue outside the treatment zone, and over treatment volume	NCT03323905
Uterine Adenomyosis + Leiomyoma	500	Technical efficacy of HIFU for treatment of uterine fibroids as assessed by a change in the symptom severity	NCT02914704
Prostate Cancer	40	Feasibility to use the PET-MRI imaging for focal-HIFU guidance	NCT03927521
	170	Patient proportion with controlled disease, treatment efficacy (percentage of positive biopsies in the treated lobe at 12 months after inclusion)	NCT03568188
	250	Number of patients without clinically significant prostate cancer, functional results, patients who need repeated focal treatment, disease-free survival, treatment-free survival, overall survival, metastasis-free survival, patients who need radical (surgery or radiation), or palliative treatment (hormone therapy)	NCT04549688
	146	Patient proportion who needed to seek further radical treatment	NCT03531099
	10	Positron emission tomography (PET) based of Assessment of Local Therapeutic Response	NCT03949517
	117	Absence of biochemical failure (defined as achieving a PSA nadir of ≤ 0.5 ng/mL within 12 months of treatment)	NCT00772317
	4022	Recurrence-free survival	NCT04307056
	130	Recurrence free survival after focal therapy, pathological persistence after prostate cancer focal therapy	NCT03255135
	20	Absence of prostate cancer on Biopsy	NCT03927924
	200	Treatment failure	NCT03668652
	354	Conversion to radical therapy and/or requiring systemic therapy and/or developing metastases and/or dying of prostate cancer	NCT01194648
	70	Targeting accuracy of HIFU ablation and volume of HIFU ablation separately in each study arm/group, radiologically and histopathologically determined treatment accuracy, safety of MRI-guided transurethral HIFU ablation in various prostate diseases	NCT03350529
	200	Prostate biopsy Gleason grade	NCT03492424
	2450	Progression-free survival (PFS) rates of focal therapy alone compared to radical therapy, Failure-Free-Survival (FFS) rates of focal therapy alone compared to focal therapy combined with other therapies	NCT04049747
	10	Micro-wave ablation area	NCT04831905
	918	Post-standard of care prostate biopsy, safety, progression-free survival	NCT03763253
Breast Cancer	10	Amount of ablated tissue at histopathological examination, presence of non-perfused volumes on DCE-MRI	NCT02407613
	15	Change in tumor infiltrating lymphocytes	NCT03237572
	10	Accuracy of MRI as method for assessment of quantitative/qualitative treatment success (correlation with results of the histopathological analysis performed as reference method	NCT03560102
	15	Efficacy of HIFU for the treatment of breast tumors based on histological criteria	NCT03342625
	12	Safety and tolerability of the study treatment, logistical MR thermometry and administration	NCT03749850

Disease	N	Primary Outcome	ClinicalTrials.gov Identifier
	32	Incidence and severity of adverse events and incidence of dose-limiting toxicities, proportion of patients with increased CD8+ T cell infiltration of spot-treated metastasis.	NCT04116320
Essential Tremor	50	Change in QUEST Score, patient-based Assessment of Utility	NCT04501484
CNS Tumor	10	Incidence of Treatment-Emergent Adverse Events Safety and Tolerability, Measurement of Tumor Volume	NCT03028246
CNS Blood-Brain Barrier Disruption	10	To evaluate the incidence and severity of adverse events associated with the ExAblate transcranial treatment	NCT02343991
	10	Rate of adverse events following each treatment through end of study	NCT03714243