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# High-Intensity Focused Ultrasound (HIFU) in Uterine Fibroid Treatment: Review Study

**Authors' Contribution:**
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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## Summary

**Background:** High-intensity focused ultrasound (HIFU) is a highly precise medical procedure used locally to heat and destroy diseased tissue through ablation. This study intended to review HIFU in uterine fibroid therapy, to evaluate the role of HIFU in the therapy of leiomyomas as well as to review the actual clinical activities in this field including efficacy and safety measures beside the published clinical literature.

**Material/Methods:** An inclusive literature review was carried out in order to review the scientific foundation, and how it resulted in the development of extracorporeal distinct devices. Studies addressing HIFU in leiomyomas were identified from a search of the Internet scientific databases. The analysis of literature was limited to journal articles written in English and published between 2000 and 2013.

**Results:** In current gynecologic oncology, HIFU is used clinically in the treatment of leiomyomas. Clinical research on HIFU therapy for leiomyomas began in the 1990s, and the majority of patients with leiomyomas were treated predominantly with HIFUNIT 9000 and prototype single focus ultrasound devices. HIFU is a non-invasive and highly effective standard treatment with a large indication range for all sizes of leiomyomas, associated with high efficacy, low operative morbidity and no systemic side effects.

**Conclusions:** Uterine fibroid treatment using HIFU was effective and safe in treating symptomatic uterine fibroids. Few studies are available in the literature regarding uterine artery embolization (UAE). HIFU provides an excellent option to treat uterine fibroids.

**MeSH Keywords:** **High-Intensity Focused Ultrasound Ablation • Leiomyoma • Uterine Artery Embolization**

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## Background

Uterine fibroid tumors (or leiomyomas) are common benign neoplasms in women of childbearing-age, and generally reported with an incidence of 20–40% among womean of reproductive age [1]. In 10–20% of women these uterine fibroids lead to symptoms, such as heavy and prolonged menstrual bleeding, pain, urinary frequency or urgency, bulk-related symptoms, and constipation [2]. Surgical intervention such as myomectomy or hysterectomy is the most common method of treatment if symptoms such as substantial bleeding or pelvic pain appear. However, hysterectomy is not accepted by women who have a strong desire for a future pregnancy. Therefore, nonsurgical treatment is the only available option for those women who want their uterus preserved [3,4].

Several minimally invasive techniques have been introduced providing local control of uterine fibroids and for preserving the uterine. One of these techniques, high-intensity focused ultrasound (HIFU) has been widely used for the treatment of solid tumors including uterine fibroids [5,6]. As a non-invasive modality, HIFU therapy is receiving increasing interest for the treatment of localized solid malignancies and benign tumors because it is capable of producing coagulative necrosis at a precise focal point within the body, without harming overlying and adjacent structures even within the path of the beam [7]. Moreover high-intensity ultrasonic beams can be focused with high accuracy using an extracorporeal transducer to thermally ablate tumors without the need to introduce needles or probes into the tumor [8].

The idea that focused ultrasound therapy might be developed as a result of controlling the local extracorporeal source of focused ultrasonic energy was introduced by Lynn et al. in 1942 [9]. Since then, therapeutic ultrasound has been tested extensively for non-invasive surgery in both animals and humans, and has been used for treatment of tumors, such as breast cancer, malignant bone tumors and liver cancer for 10 years [10,11]. Today, a rapid and ongoing technical development and clinical research on HIFU is visible. Several clinical HIFU projects have been conducted by various research groups, and substantial results indicate that HIFU treatment would be safe, effective, and feasible in clinical applications [12–14].

Due to increased patient's interest and current use of HIFU technology worldwide, this article was designed to review the techniques of HIFU in uterine fibroid therapy as well as to review the actual clinical activities in this field including efficacy and safety measures beside the published clinical literature.

## Material and Methods

An inclusive literature review was carried out in order to review the scientific foundation of HIFU in uterine fibroid treatment, and this was discussed in terms of how it resulted in the development of two extracorporeal distinct devices i.e. HIFUNIT 9000 tumor therapy system produced by Shanghai Aishen Technology (China) and a-prototype single-focus ultrasound source developed by Storz Medical AG (Switzerland). The merits and limitations of each HIFU device were addressed.

The ScienceDirect, PubMed, MEDLINE, NCBI and SAGE database were searched in February 2014 for publications containing any combination of "HIFU" and "uterine fibroids" in the title. Abstracts resulting from that search were reviewed for relevance to clinical outcomes of the procedure. Full manuscripts were retrieved and reviewed for any information regarding the evaluation the role of HIFU for the treatment of uterine fibroids as well as the technology used to perform HIFU and the published clinical literature in this field including efficacy and safety measures of the procedure used as primary treatment for uterine fibroids.

Only the papers published between 2000 and 2013 were included in the outcome analysis, and that was due to the tremendous development in this medical non-surgical therapeutic specialty at the beginning of the new millennium. There were no restrictions on the country of origin of the publications, which help to provide a wide range of opinions and experiences. Articles identified from the refined search results were further reviewed on an individual basis for content.

## Results and Discussion

### HIFU history

Around the beginning of the last century the piezoelectricity phenomenon, the potential of piezoelectric materials as sources of ultrasound, and the biological effects of high-intensity ultrasound were all reported on [15–17]. A detailed chronicle of the early work and medical applications of therapeutic ultrasound is given by Kremkau [18].

The first work to consider the potential applications of HIFU was published in 1942, and this was built upon in the 1950s, when William Fry et al. produced lesions deep in the brains of cats and monkeys [9,19]. Next, Frank Fry treated patients with Parkinson's disease and other neurological conditions [20]. Research on the use of HIFU in neurosurgery continued during the 1950s and 1960s [21–24].

In 1956, Burov suggested that high-intensity ultrasound could be used for the treatment of cancer, and in the following years, several studies looked at the effects of ultrasound on tissues [25,26]. The specific properties of focused ultrasound conduction and modes of destruction in normal tissues were investigated further during the 1970s and 1980s, and studies using HIFU to irradiate experimental tumors followed [27–31].

### HIFU effects, ablation technique and strategies

A high-intensity focused ultrasound pulse with a several-second period, generated by a piezoelectric ultrasound transducer, is the basis of the HIFU therapy. The ultrasound field is insonated via a coupling medium (e.g. Water balloon), through the skin and overlaying tissue in the targeted area. The high-intensity acoustic energy is absorbed and converted to heat at the focal point. The heat raises the temperature rapidly between 60°C and 95°C, and due to the high local concentration of acoustic energy in the focal spot, the tissue in a small volume is heated rapidly and a sharp circumscribed lesion caused by thermal coagulation will be induced. The skin and other ultrasound-penetrated tissue layers remain unaffected or show only a negligible temperature rise. Higher temperatures lead to tissue; boiling and bubble formation and can cause more undefined and less predictable lesion growth [32,33]. For HIFU, frequencies in the range of 600 kHz to 7 MHz are used depending on the application type and the penetration depth. Typical intensity and pressure values are some thousand Watts per $cm^2$ [33].

Other mechanical phenomena include acoustic cavitation and radiation forces which also contribute to the lethal effect at the focal point. Acoustic cavitation can be defined as the interaction of a sound field with microscopic gas bodies [34]. In order for cavitation to occur in tissues, the presence of gaseous nuclei which probably exist in mammalian tissues is required [35–37]. Two types of acoustic cavitation are identified: stable cavitation and inertial cavitation. Stable cavitation occurs when a bubble oscillates steadily in an ultrasonic field, thus intercepting and radiating energy to the surrounding tissues, resulting in micro streaming of fluid around the bubble. This highly localized shear stress causes cell damage [34]. Above a certain pressure amplitude threshold, the bubble oscillation becomes nonlinear and the bubbles expand and collapse vigorously resulting in localized high acoustic pressure of several thousand atmospheres that causes damage of the exposed tissues, known as inertial cavitation [38].

The nonlinear propagation of ultrasound waves through tissues causes the particles within the focal region to be under mechanical forces resulting in appreciable tissue movement causing bioeffects. This is called radiation force [34]. Radiation torque is another mechanical phenomenon associated with ultrasound propagation through tissues. Radiation torque causes rotary motion at the cellular level, resulting in spinning of the intracellular organelles causing lethal cellular bioeffects [39]. So to destroy larger structures, single lesions have to be combined without gaps until the whole target volume is covered. Between two single sonications a defined cooling time is necessary to protect adjacent healthy tissue from heat accumulation and overheating.

Special transducers designed for high-power ultrasound application are employed. Such transducers used are self-focusing piezoceramic bowls made of low-loss PZT (Lead Zirconate Titanate) or piezocomposite. Seldom used are plane piezoceramic plates with focusing lens or reflector assembly. A more expensive and technically more complex alternative is the use of phased array transducers composed of many single elements. Each element or element group is fed by separate electrical radio frequency signals (RF-signals) with defined phase shifts and amplitudes, allowing an electrical beam forming and steering of the ultrasound focus [40].

The ablation with HIFU is a time-consuming procedure. Since a single sonication generates a rather small tissue lesion, a lot of these single applications are needed with an adequate idle time in between to prevent overheating until a large tumor is ablated. To overcome this obstacle, several techniques have been developed. One possibility is to enlarge the ultrasound focus size preserving the transducer aperture and the focused characteristic of the sound field [41]. Other methods employ gas-filled micro-bubbles during insonation to enlarge the ultrasound absorption of the targeted tissue, or the defined generation of cavitation bubbles in the focal region by applying short high-intensity pulses before or at the beginning of each single ablation pulse [42,43]. Alternative techniques may include the use of a continuous, linear, circular or spiral focus motion during insonation to scan and destroy larger tissue volumes. Obstacles such as overheating of the overlying tissue, skin burns and undefined lesion developed in such a technique can be solved by the use of an online feedback Thermometry system to control the scanning process is desirable [44].

### HIFU devices in clinical use

A large number of devices have been used in experimental studies, but there are fewer devices in the current clinical use. The two main categories of the device are extracorporeal and transrectal in approach. Extracorporeal devices have been used to target many organs. They usually require a higher focal length than transrectal sources. For this reason, they tend to employ transducers of larger dimensions, which operate at lower frequencies with higher intensities than their transrectal equivalent. To our knowledge transrectal HIFU devices are used to treat focal prostate gland cancerous lesions, which is not an interest of such a review.

A prototype device was built in 1991 for extracorporeal use, which employs a spherical PZT ceramic transducer of 10 cm in diameter and 15 cm in focal length. It is driven at a frequency of 1.7 MHz and operates in a free field of spatial intensities [45]. General Electric (GE) Healthcare Medical Systems was another innovative extracorporeal device using an MRI-compatible 10-cm-diameter focused transducer with an 8-cm radius of curvature, operating at 1.5 MHz [46]. The third extracorporeal device was designed and developed in China by Chongqing HAIFU Technology Company. It uses a 12-cm diameter PZT transducer of focal length of 10-16 cm, driven at either 0.8 MHz or 1.6 MHz. It operates at higher intensities, and also has a built-in 3.5-MHz diagnostic scanner [47]. The two devices reviewed in this article are the model HIFUNIT 9000 tumor therapy system produced by Shanghai Aishen Technology (China) and prototype single-focus ultrasound source developed by Storz Medical AG (Switzerland).

A HIFUNIT 9000 tumor therapy system is guided by real-time ultrasound imaging. It is comprised of the following main components: a real-time diagnostic ultrasound device, six self-focusing acoustic different-frequency therapeutic integrated transducers, which could focus the ultrasound beam through two-time focalization and allow transducers to move along X, Y and Z planes, moving table that allows moving the patient over the therapeutic transducer for better tumor localization and targeting, computer units for automated control, an ultrasound generator for producing high-intensity ultrasounds and a degassed water circulation unit. The integrated transducers were immersed in a water bag, filled with degassed water. The water bag had an acoustic transparent membrane bottom for HIFU to transmit without obstruction, and the ultrasound coupling gel was applied to eliminate air pockets trapped between the membrane and the patient's skin. The degassed water provides acoustic coupling between the transducer and the patient, allowing the ultrasonic beam to pass directly toward the patient's body without any deflection [8].

The system can be operated by one of several transducers with focal lengths varying from 90 to 160 mm. The choice of the transducer depends on the depth of the target tumor. A transducer with a focal length of 135 mm and operating at a frequency of 0.8 MHz is the most commonly used one [8]. The focal intensity of the therapeutic transducers, which was calibrated by a radiation force assay in degassed water, was up to 3000 W/cm$^2$. The frequency of the ultrasound wave was 1.0 MHz. The focal region of the therapeutic transducers was an ellipsoid with dimensions of 8 mm along the beam axis and 3 mm in the transverse direction at a focal distance of 17 cm from each therapeutic transducer [48].

The operator console for the device has three monitors. The first monitor is used to control the therapeutic process. All the information regarding the ongoing treatment process is displayed on this monitor including the slice being treated, the focal point, the treatment mode, the acoustic intensity and exposure time. The control keys of the therapeutic transducers are also displayed on this monitor through which the position of the focal point could be adjusted to the treatment site. The second monitor is a diagnostic ultrasound monitor that monitors the echogenic changes associated with the treatment process. It has Doppler that allows real-time assessment of the vascularity of the treated area. The last monitor displays information regarding the circulation of the degassed water, allowing control of the level and temperature of the degassed water in the water reservoir [49].

Custom-made Storz Medical AG mobile HIFU unit is based on a 1.07-MHz piezoelectric source focused with a parabolic reflector. The transducer aperture and focal distance are 10 cm. The 6-dB dimension of the focal volume is 2 and 17 mm. The acoustic power emitted is regulated between 100 and 400 W. The impulse length can vary between 0.1 and 10 s. The coupling to the patient's skin is done with an inflatable cushion filled with degassed water as well. The temperature of this coupling medium is set at 16°C to give protection against accidental skin burns. It helps to cool the skin and leads to increased circulation in the subcutaneous tissues. Regulating the amount of water inside the cushion is very important to prevent cushion inflation, which will bring the transducer further away from body tissues. Deflating the cushion allows for treatment of deeper lying tissues [50,51].

For target areas lying closer to the surface, special care must be taken to prevent skin burns as local intensity peaks close to the focus might result in increased thermal effects. Theoretically, the focus can be directed into target tissues lying between 0 and 10 cm deep in the body. Therefore, the minimal applicable depth is restricted to 3 cm in practice [50,51].

#### Therapy procedure of HIFU

Therapy procedure of HIFU focuses on pre-treatment simulation, patient preparation, skin preparation, patient positioning, anesthetic considerations, treatment process, patient monitoring, after-care and follow-up. In uterine fibroids, once the patient is a candidate for HIFU treatment, pre-treatment simulation is carried out to assess the feasibility of the treatment. The patient is placed on the HIFU machine in the same position that would be used during the treatment process. Several problems are to be evaluated. The most important one is to assess whether the lesion is seen by the integrated transducer or not. If the lesion cannot be clearly visualized the patient is unsuitable for HIFU treatment as the factors that hindered visualization of the tumor will likely hinder the passage of the therapeutic ultrasound during treatment [49].

The acoustic path is also assessed during the simulation process. The focal length of the therapeutic transducer should also be evaluated. The operator must be sure that the therapeutic ultrasound can reach to the deepest layer of the uterine fibroid with a safety margin which is of great importance during the treatment. Water bags should be used to displace the bowel loops away from the acoustic pathway. For uterine fibroids, contrast-enhanced MRI is needed. Reviewing findings from this imaging modality allows proper localization of subtle small lesions during the ultrasound scanning and helps planning the HIFU therapeutic path [49]. Sensitive structures adjacent to the fibroid must be identified so that the ultrasound beam does not pass through them [52,53].

HIFU can be considered a low-risk surgical procedure as it does not involve opening the body. Patients should be assessed according to the American College of Cardiology and American Heart Association guidelines [54].

Skin preparation is a crucial step for successful HIFU treatment. Any hair, dirt or topical creams on the skin surface overlying the target tumor can cause deflection of the ultrasonic beams resulting in accidental skin burn. The skin covering the presumed course of the therapeutic ultrasound beams should be shaved and cleaned [53]. Uterine fibroid treatment is performed under intravenous conscious sedation. This allows continuous feedback from the patient. If the patient feels pain during the treatment, the acoustic path and therapeutic parameters should be rechecked [52,53,55,56].

To ensure recovery from general anesthesia, the patients are transmitted to the aftercare room, kept in a semirecumbent position and monitored for vital signs. Nonsteroidal anti-inflammatory drugs should be avoided in patients with platelet dysfunction, renal impairment or esophageal varices [55]. Skin monitoring is very important. If the skin is edematous or shows local redness or blistering, cold fermentations could be applied till the temperature reaches normal [14]. Regarding uterine fibroids, patients usually experience peri-procedural pelvic cramps, but can be discharged on the same day with oral analgesics. Fever, urinary tract infection, hematuria and back pain have been reported [57,58]. Some patients may experience increased vaginal discharge or bloody discharge which may continue for one week. Local vaginal disinfectant douches may be used to prevent secondary infection. If pain is experienced, short-acting analgesics may be used. Sexual intercourse is strictly forbidden until after the first menstruation following the treatment [49]. To assess the efficacy of the treatment, follow-up of the patients is crucial. Patient follow-up after HIFU for uterine fibroid is usually entailed and assessment of improvement in the clinical condition of the patients as well as monitoring of changes in imaging and laboratory parameters [49].

### HIFU ablation of uterine fibroids

Although uterine myomas are benign, they are far from harmless. They can cause severe menstrual bleeding and pelvic discomfort. Surgical intervention is the most common method of treatment if symptoms such as substantial bleeding or pelvic pain appear [3].

Myomectomy can be performed on patients who wish to retain their uterus, but cumulative uterine fibroid recurrence rates at 12 and 24 months after abdominal myomectomy are 12.4% and 46%, respectively [59]. The need for further surgery is high, and these surgical procedures are associated with morbidity in about 17% to 23% of cases [60]. Hysterectomy is the definitive treatment for uterine fibroids, since such benign tumors cannot recur after total uterus removal. However, this operation is unsuitable for patients wishing to remain fertile and possible sequelae, e.g., incontinence, vaginal vault prolapse, risk of premature ovarian failure, long recovery, high costs, justify serious consideration of alternative therapies such as HIFU [59,61]. Therapies such as uterine artery embolization (UAE) have been accepted as an effective alternative treatment for uterine fibroids rather than surgery, but various potential complications that may result from UAE have been reported. Major complications include uterine necrosis and infection leading to emergent hysterectomy, ovarian failure, and vaginal dryness related to nontarget embolization or overembolization [62–66].

Extracorporeal HIFU enables performance of transcutaneous tumor ablation. It provides a potential therapeutic method for precise ablation of entire tumors of different sizes and shapes without damaging overlying and surrounding vital structures. Appreciable results indicate that HIFU treatment would be effective and feasible in clinical applications [67,68]. As a noninvasive technique, HIFU is a potential treatment of choice for uterine fibroids, because these benign tumors do not require complete excision [69].

Previous research focused on studying the rate of reduction of uterine fibroid symptoms. Uterine fibroid symptoms were reduced to 53% and the degree of menstrual pain was reduced to 50% as reported by Yoon et al. [70–72]. Bulk-related and menstrual symptoms diminished in 51% of patients after 6 months of HIFU treatment [73].

Recent research has focused on measuring the fibroid volume reduction, non-perfused volume of tumor, and reduction of uterine fibroid symptoms after HIFU treatments with different follow-up periods and patient samples. After HIFU therapy, the ablated fibroid volumes decreased by 31.4% in a three-month follow up period, 31% after six months of treatment, 15% at six months after treatment, 33% at six months of follow-up, and 9.3% at 12 months after treatment [52,53,72,74,75]. It was evident that the reduction of fibroid volume was related to the non-perfused volume of the tumor immediately after the treatment. Regression of the fibroid size is expected to begin 1 month after the treatment and it becomes obvious usually after 3 months of the treatment. Fibroids in which blood supply decreased immediately after HIFU session decreased in size on follow-up [48].

### HIFU limitation in uterine fibroid treatment

Despite the wealth of research in the field of HIFU, its application as a non-invasive surgical tool is still in its infancy. The potential advantages of HIFU in ablation of uterine fibroids were discussed in previous sections. There are, however, potential limitations. Ultrasound cannot propagate through air-filled viscera such as the bowel. Ablation of fibroids lying in close proximity to the bowel, would run the risk of visceral perforation. This may therefore; introduce an anatomical restriction to the treatment of uterine fibroid by HIFU [76].

Treatment time may also appear longer than desired. In the treatment of large fibroids, where no minimally invasive option is available, longer treatment time may be justified on the grounds of a lower morbidity and mortality than in conventional surgery. In many ultrasound centers, HIFU is performed under regional anesthesia to ensure patient comfort and immobility. Movement during HIFU exposure could compromise treatment efficacy, and so an induced breath-hold during any high-intensity exposure can overcome what would otherwise be a limitation of HIFU [48].

## Conclusions

In conclusion, uterine fibroid treatment using extracorporeal HIFUNIT 9000 tumor therapy system and prototype single-focus ultrasound source was effective and safe in treating symptomatic uterine fibroids. This has been shown in numerous clinical feasibility studies on uterine fibroids. However, clinical breakthrough of HIFU may occur if HIFU conserves or improves fertility better than other treatments. Future studies will need to define whether coagulation of larger volumes can reduce symptoms caused by a fibroid and last longer. Additional studies are required to compare HIFU with other available techniques, such as UAE. HIFU provides an excellent option to treat uterine fibroids.

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