*White paper*

# History of MR guided Focused Ultrasound: *A literature review*

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The history of ultrasound as a therapeutic modality dates back to the early 20th century, much earlier than when ultrasound was first used as a diagnostic tool. The use of high intensity focused ultrasound has long intrigued scientists and has been the subject of extensive clinical research.

MR guided focused ultrasound surgery (MRgFUS) extends the capabilities of FUS and represents a new treatment paradigm, a new form of surgery, as it were. It is not only non-invasive. Its use of real time MR guidance, monitoring and control provides closed loop feedback. At the end of the procedure the physician knows exactly what was treated, how it was treated, and what the results were, a level of detail which has generally not been available.

This paper reviews the long history of research and development of the use of focused ultrasound for medical applications, and, with the emergence of Magnetic Resonance Imaging, the extensive benefits this new technology adds in combination with FUS.

## PIONEERS OF FOCUSED ULTRASOUND

The ability of high intensity ultrasound to induce biological effects in tissue was first observed and studied in unicellular organisms, frogs, and fish by Wood and Loomis in 1926 [1]. Eight years later in 1935, Gruetzmacher placed a concave surface to a piezoelectric generator and discovered that ultrasound could be focused [2]. In 1942, Lynn *et al* [3] pioneered the use of focused ultrasound (FUS) for therapeutic effects. They produced FUS lesions deep in bovine liver without damaging surrounding tissue.

Also in 1942, Fry *et al.* [4] developed a FUS device that mechanically aligned four focused ultrasound generators which produced focal lesions in cat brain. Research of using FUS to destroy central nervous system (CNS) tissue for therapeutic purposes was advanced in the 1950s [5]. In animal models, Fry *et al.* described results in which focused ultrasound beams were used to thermally ablate localized regions in the central nervous system of cats. This technique demonstrated the non-invasive nature of FUS treatment: i.e. no requirement for cutting of brain tissue; no disturbance to the blood vessels; and no opening of the dura mater [6].

By 1957, single and multiple element focused ultrasound transducers were constructed to deliver focused ultrasonic beams [7]. Human clinical studies began in 1959 after animal testing proved aiming and localized necrosis was possible using these transducers. In this study, FUS was used to produce lesions in the pallidofugal and nigral complexes in the brains of patients with hyperkinetic and hypertonic disorders [8]. Several cases of Parkinson's disease were treated successfully with FUS, but the study was halted due to difficulties in imaging and targeting of treatment sites in the brain. The introduction of L-dopa drug treatment at that time also reduced the popularity of FUS due to the simplicity of taking a drug versus surgery.

## FUS FROM 1950s THROUGH 1980s

FUS was thought to be a useful modality for cancer treatment, however, shortly after the Wood and Loomis experiments, ultrasound was reported to have no effect on Ehrlich's carcinoma [9]. Twenty years would pass until the investigation of FUS for cancer treatment recommenced. Burov and Andreevskaya used high-intensity pulsed ultrasound for treating tumors implanted in rabbit testes, and cutaneous melanoma in humans [10]. In the 1960s and 70s, Oka reported using FUS to treat thyroid and breast cancers [11, 12].

Research in the 1970s with animal tumor models continued to indicate that FUS had significant promise for cancer treatment. FUS was effective in treatment of murine gliomas implanted in abdominal walls [13], medulloblastomas in hamster flank [14], and liver tumors [15]. In-depth experiments testing dosimetry and lesion formation thresholds were also performed during this time [16-18].

Research in the application of FUS in the central nervous system also continued [19-21]. Expanding on the clinical use potential by describing non-neurological applications of thermal ablation procedures using focused ultrasound technology in animals, Lele, in 1975, provided a comprehensive review of the technology of focused ultrasound used in both diagnostic and thermal ablation purposes. Characterized as "the ideal surgery," and thus setting the standard for future technology developments, Lele described focused ultrasound as better suited for deep lesions than other forms of energy, including focused infrared or laser beams, due to the relatively higher permeability of sound waves through soft tissue.

"*Focused ultrasound technology meets the requirements of an ideal surgical tool. It has the demonstrated ability to destroy pre-selected targets located deep within tissue without any damage to the tissue in the path or surrounding the lesions.*" [22]

Furthermore, Lele concluded that for FUS to be truly an ideal surgery, the inflicted lesions should be (a) predictable, reproducible and controllable in size, (b) non-hemorrhagic, (c) sharply demarcated from surrounding unaffected structures, (d) instantaneous in development, (e) devoid of delayed effects as seen with X-rays or other forms of radiation, (f) the technique should lend itself to using sub-lethal dosages to produce transient alterations of function, which can be used to assist in target localization and (g) the surgeon should have the capability to verify the completeness of the treatment by localizing the energy delivery and monitoring the cell destruction as it happens and after the treatment is completed.

There were also promising results in the 1980s from experiments using FUS for ophthalmological applications: for treating glaucoma and retinal detachment, and for sealing traumatic capsular tears [23-25]. However, FUS did not gain much clinical acceptance for this until the 1990s.

The late 1980s saw a surge in research devoted to FUS, along with the advancement in technology and its emergence in clinical use. In 1987, Hynynen *et al.* studied temperature elevation at the muscle-bone interface during FUS using a scanned four transducer FUS system [26, 27]. Ter Haar and colleagues in the UK [28] demonstrated that focal lesions could be induced in porcine liver *in vitro*. In the early 1990s, Yang, *et al.* also investigated the use of FUS for ablating liver tissue. The group initially used FUS with a rat hepatoma model and showed improved survival rates in FUS treated animals [29]. Later, FUS was used to treat subcutaneous murine neuroblastoma in mice and showed reduced tumor growth [30].

A group in Lyon, France (INSERM) examined the effects of FUS treatment of liver tumors and showed significant tumor size reduction [31, 32]. This group, led by Gelet and Chapelon, also proved that irreversible FUS lesions in prostate tissue can be created through the rectal wall [33].

## FUS IN THE EARLY 1990s

### Clinical trials of FUS

Gelet's counterparts in Paris, led by Vallancien, conducted a feasibility study that used extracorporeal FUS for treating benign prostatic hyperplasia, and kidney and liver metastases in human patients. It was shown that precise focal ablations were possible, but with a side effect of skin burn [34]. They called their technique "extracorporeal pyrotherapy" to distinguish it from various techniques of local, regional or systemic hyperthermia, in which tissue temperatures, although elevated, remain much lower than FUS treated tissue. Their tissue effect (pyrotherapy) is based on the phenomena of marked and rapid temperature rise and cavitation (the collapse of microbubbles). Their focused ultrasound technology was able to induce necrosis in the focal zone, and heat diffusion to surrounding structures was virtually non-existent because of the brief sonication duration.

The Vallencien study was designed to evaluate the ergonomic features of the treatment table, the quality of detection using ultrasound, the quality of displacement of the firing head in all planes, the choice of dose (number of sonications and their duration), as well as the actual effects on the target tissues by endoscopic or operative examination and subsequent histology. In addition, the overall safety of the system was evaluated by monitoring the local, regional and systemic toxicity of the technique.

Twenty-eight patients with benign prostatic hyperplasia were treated as well as twelve patients with superficial bladder tumors. In addition, eight patients underwent the same treatment to the kidney and two were treated for liver metastases. Histological examination of the target organs demonstrated severe tissue lacerations followed by necrosis, corresponding to the dimensions of the focal area. The authors concluded that the technique of focused extracorporeal pyrotherapy could be performed at the cost of moderate side effects. Those included a transient rise in serum creatine phosphokinase with longer sonication durations, and skin burns. The authors concluded that these side effects could be avoided by determining the relationship between sonication durations, and the distance from the skin to the focal point.

### MR guided FUS emerges

In the mid-1990s, animal studies continued showing that FUS effectively produces lesions in the kidney, liver and prostate [35-38]. However, the FUS experiments up until this point were guided by B-mode ultrasound or by visual means. These methods lacked precision and did not provide thermal feedback to FUS treatment. In 1993, Hynynen proposed the use of non-invasive focused ultrasound surgery in a magnet using magnetic resonance imaging (MRI) to guide and monitor tissue damage [39]. Hynynen *et al.* described the significant potential of this technology combination, and supported their theory with results obtained from animal testing.

The first study using a clinically working prototype (which would eventually become the ExAblate system) using MR-guided focused ultrasound surgery (MRgFUS) for tumor ablation in rabbit skeletal muscle was performed in 1995 by Cline and Jolesz *et al.* [40]. This prototype differs from the current ExAblate in that it used a single element FUS transducer instead of a phased array. The authors concluded that MR imaging provided accurate target definition and control for thermal therapy in a variety of tissues with variable perfusion rates, as well as good thermal imaging feedback.

As the use of MRgFUS became more and more attractive for tumor ablation, shortcomings of the prototype were realized during treatment of larger tumor volumes. The single element transducer used would be inconvenient for treatment of larger volumes because of the required cool-down time between sonications, resulting in lengthy procedures. An effective way to reduce the treatment time was pointed out by Jolesz and Hynynen *et al.*, who proposed an increase in acoustic focal volume to decrease the number of required sonications. This was accomplished using a phased array transducer, developed by InSightec. This is a transducer comprised of many individual ultrasonic elements that are individually excited using a timing scheme to achieve the desired focusing. In addition, this technology offers the flexibility to electrically move the focal spot without physically moving the transducer [41].

## FUS RESEARCH LATE 1990s - PRESENT

FUS is currently in clinical use for the treatment of prostate cancer and benign prostatic hyperplasia [42-47]. Building on continuous clinical and life science studies in the early nineties, along with further technology improvements, Sanghvi and coworkers developed and implemented a clinical protocol for FUS treatment of benign prostatic hyperplasia (BPH), a benign tumor of the prostate [47]. Their device involves an ultrasound transducer that switches between imaging and therapy, both at 4 MHz. Transrectal ultrasound probes with differing focal depths are designed to treat varying sizes and shapes of tumors. This multicenter study involved sixty-two patients, enrolled at seven sites (5 US, 1 Canada, 1 Japan). Efficacy was evaluated by measuring changes in urinary peak flow rate, quality of life and International Prostate Symptoms Score. Efficacy and safety results were both considered a success by the authors. ter Haar's group is leading clinical trials in a variety of stage 4 primary and metastatic cancer tumors of the kidney, liver, and ovaries in humans [48]. Kidney ablation using FUS, for the purpose of treating renal carcinoma, is being studied in the US [49] and Germany [50]. FUS is also being evaluated as an alternative to vasectomy. Canine vas deferens and epididymis were treated with FUS and occluded [51-53].

A group in Chongqing, China, led by Wu *et al.*, has shown FUS treatment to be safe, effective and feasible in 164 patients with liver cancer, breast cancer, malignant bone tumor, and soft tissue sarcoma [54]. Cessation of blood flow in tumor vessels was also shown after treatment [55]. Dr. Wu's group has in all, treated thousands of patients using FUS, perhaps the most widespread use of FUS for tumor treatment. Other groups in China are using FUS for treating bone, liver, pancreas and other malignant tumors in patients [56-59].

Jolesz and Hynynen *et al.* investigated the use of MRgFUS for ablating tumors in the brain using a rabbit model [60, 61] using the ExAblate. Their group also investigated the use of using gas bubbles at the FUS focus to enhance ultrasound absorption, which resulted in larger lesions [62].

## MR guided FUS Studies

### ExAblate Animal Studies

Studies using the first prototypes of the ExAblate date back over more than ten years. In the late 1980's, the capability of MR imaging to visualize and later quantify thermal changes *in vivo* was first described [63]. The cross-sectional anatomic imaging and quantitative thermal maps possible with MR combined with the non-invasive heat source of FUS was a logical combination. Cline and coworkers at GE conducted the very first animal study designed to evaluate the performance characteristics of a FUS system combined with magnetic resonance image as an integrated system capable of MR guided tumor ablation to provide a closed loop therapy. These researchers constructed the first prototype of a clinically useful magnetic resonance guided focused ultrasound surgery (MRgFUS) system, which would later become the ExAblate. They reported the results from tests on *in vivo* rabbit skeletal muscle, and other potential medical applications [40]. The findings were important in that post-treatment pathology evaluations confirmed that the region heated by the focused ultrasound beam was within 1 mm of that observed on temperature-sensitive MR images. MR imaging proved to provide the long awaited capability for target definition and guidance feedback for this type of non-invasive thermal therapy in living tissue.

Jolesz and Hynynen and coworkers have spent most of the last 2 decades in research efforts to find a true non-invasive surgical technique aimed at destroying soft-tissue, for the benefit of patients and with a goal of significantly reducing cost for these types of procedures. Their findings and reflections were summarized in an article published in 1996 [64]. They discussed FUS-induced thermal effect and their contribution to tissue necrosis, as well as the technical and clinical aspects of MRI thermometry. Further testing proved that the thermal mechanisms of focused ultrasound were much better understood and predictable compared to systems that relied on cavitation (collapse of gas bubbles in tissue that produced mechanical damage) to produce the treatment effects. Therefore, thermal effects are preferred in FUS treatments until the cavitation effects will be controllable, repeatable, and predictable.

Unrelated to the development of focused ultrasound as an energy source, the Sapareto and Dewey equations were developed to relate dose to a probability for complete cell necrosis [65]. Thermal effects are quantified by calculating the thermal 'dose' (time and temperature history) to a volume of tissue, and comparing this to a 'threshold' to allow the prediction of thermal necrosis of the volume.

The tissue damage induced in the rabbit thigh was found to be consistent with previous predictive models, and to also correlate well with the MR imaging-derived temperature and thermal dose measurements (and not with sonication energy). Tissue damage occurred at all locations with temperatures exceeding 54ºC, and thermal doses greater than 31.2 equivalent minutes at 43ºC. No tissue damage occurred when the temperature was below 47.2ºC and the thermal dose was below 4.3 equivalent minutes. These findings offered insight into energy levels required for target volume coagulation [67].

Treatment of cancer by using minimally or non-invasive surgical techniques has regained interest largely for reasons of health care economics. When considering MRgFUS for the non-invasive thermal ablation of cancerous tumors, complete tumor removal is of critical importance. Recent animal studies have been conducted to investigate the use of MRgFUS as a non-invasive alternative to surgery in the local control of soft-tissue tumors by ablating prescribed volumes of VX2 rabbit tumors and comparing the results with the ablation of normal tissue volumes [32].

Detailed pathology and histology of the treated tissue was correlated with lesion size predictions, *in vivo* temperature imaging, and post-therapy MRI. The results supported the conclusion that FUS is an effective technique for treating tumors *in vivo,* especially when MR temperature feedback is available during the procedure [68].

### ExAblate Clinical Trials

In 1988, temperature-sensitive MRI techniques became available to monitor thermal ablations [63]. Together with Jolesz and Hynynen at Brigham and Women's Hospital (Harvard Medical School, Boston, MA) and Cline (GE), InSightec pioneered and gradually perfected the use of magnetic resonance-guided focused ultrasound (MRgFUS) for a number of clinical applications.

Jolesz and Hynynen published the results of a study investigating the feasibility of treating benign fibroadenomas of the breast with non-invasive MRgFUS in 2001 [69]. Researchers used temperature-sensitive phase-difference-based MR-imaging to monitor focus localization and off-line calculation of temperature changes. Eleven fibroadenomas were treated in nine patients under local anesthesia. The treatment was successful in 8 out of 11 fibroadenomas, as demonstrated by complete or partial lack of contrast material uptake on post treatment MR contrast imaging. This lack of uptake is indicative of tumor perfusion destruction, producing a dark spot on the image in the region where the tumor was previously localized. The authors concluded that MRgFUS could be performed safely to non-invasively coagulate benign breast fibroadenomas. Although fibroadenomas of the breast represent clinically meaningful targets for non-invasive therapy, the final outcome of the treatment is not as critical as in a case of breast cancer. The authors pointed out that the objective of this feasibility study was therefore to establish the safety and effectiveness of this treatment modality and to ultimately use the knowledge gained for the non-invasive treatment of malignant breast tumors.

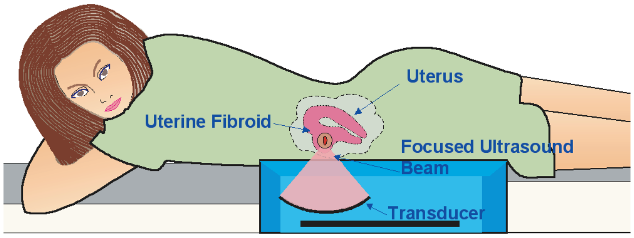

**Figure 1:** *Illustration of patient being treated by MRgFUS for uterine fibroids. Patient lies prone on patient table above water bath with energy generating transducer. Focused ultrasound energy focuses on a specific point in the uterine fibroid without affecting surrounding tissue.*

One year later, researchers at Brigham and Women's Hospital and at St. Luc Hospital in Montreal, Canada, headed by David Gianfelice, MD, conducted a feasibility study including twelve patients with invasive breast carcinomas using the ExAblate system. All patients were treated with MRgFUS before undergoing tumor resection, and the resected masses as well as the surrounding tissue were analyzed histopathologically [70]. Thermal ablation efficacy was determined from the histopathology findings.

Efficacy results differed depending on which of two FUS systems was used: a single element transducer equipped system with a fixed focal point, or a phased-array transducer equipped system with 3D planning and monitoring capabilities, which allowed the operator to vary the depth and size of focus in real time. The phased array system was more efficacious. Residual tumor was mostly located in the periphery of the tumor mass, indicating a need to include a margin around the tumor to the treatment field. The authors concluded that this initial experience using MRgFUS was a promising, well tolerated thermal ablation modality demonstrating high safety and efficacy.

Based on the findings of the feasibility study using MRgFUS for the treatment of fibroadenomas of the breast, the first clinical trial of MRgFUS surgery for uterine leiomyomas was undertaken using ExAblate [71]. Nine fibroids were included and MR images and hysterectomy specimens were pathologically evaluated. Results of the study show that this non-invasive method for thermal ablation of uterine leiomyomas using MRgFUS surgery was both feasible and safe and the value of the MR system in a clinical setting was underscored.

The most important feature of MR imaging when used in conjunction with FUS is its ability to localize focal sonications and to provide real-time thermal dose feedback to the physician, which allows for closed-loop therapy. The closed loop capability was developed by InSightec and integrated into the ExAblate system.

Six leiomyomas received full therapeutic doses and 98.5 % of the sonications were visualized. Sonications and temperature history were visualized and confirmed using MR thermal images. All focal necrotic lesions were seen using MR and five were pathologically confirmed. Contrast-enhanced T1-weighted images showed focal areas that were partially or completely lacking contrast material uptake, implying devascularization and tissue necrosis and indicating a technically successful treatment.

During 2001 a separate multi-center study was completed including fifty-five women with clinically significant uterine leiomyomas, treated non-invasively with MRgFUS [72]. Pain and complications were assessed prospectively and MRI was used to determine the treatment effects. In three of the five centers, patients underwent planned hysterectomy following treatment, providing a pathological correlation of treatment. All MRgFUS treatments were conducted in an outpatient setting. Subjects only suffered from minimal discomfort and no major complications were reported. Pathologic examination of uterine fibroids after hysterectomy showed that MRgFUS provided safe and accurate delivery of effective levels of energy to the intended regions. This study showed that MRgFUS was a well tolerated procedure for the treatment of uterine leiomyomas [72].

In October 2004 the FDA approved the ExAblate 2000 for treatment of uterine fibroids. The approval was based on a prospective, multicenter non-randomized clinical study of 109 patients who were treated with MRgFUS for symptomatic uterine fibroids.

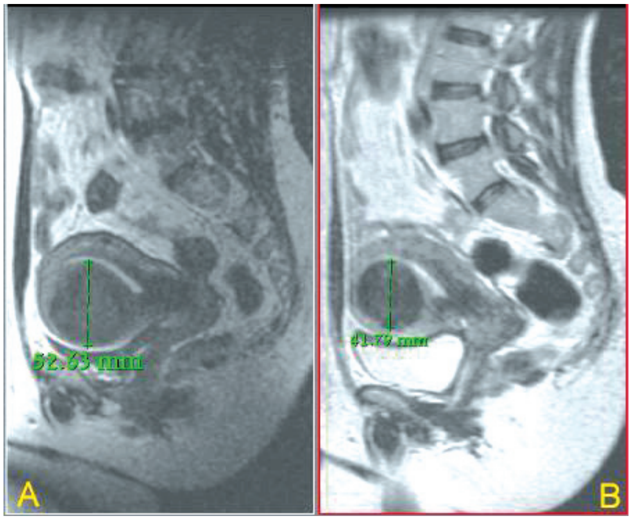

**Figure 2:** *T2w sagittal images of 105cc uterine fibroid before treatment (A), and after six months (B) with fibroid shrinkage of 57% and significant symptom relief.*

After six months, 70.6 percent of the women reported a significant improvement in fibroid related symptoms. The study compared the results of ExAblate treatment with total abdominal hysterectomy. Patients treated with the ExAblate missed 1.4 working days, on average compared to an average of 18 days for the hysterectomy group. They returned to normal activity in less than three days, compared to 17 days for the hysterectomy group.

In a talk paper issued by the FDA it stated that it "expedited review of the device because it offers significant advantages over existing treatments for uterine fibroids." [73]

Researchers involved in the clinical trials summarized their view of MR guided focused ultrasound therapy as follows: "we believe that MRI-guided focused ultrasound therapy provides a potentially important new noninvasive and effective treatment for uterine fibroids, particularly in women who wish to avoid invasive or painful therapies. In particular, the total lack of invasiveness of MRI-guided focused ultrasound therapy compared with all other fibroid procedures and the fact the procedure make it particularly attractive for patients. We also believe that MRI-guided focused ultrasound therapy for fibroids may prove to be an important model for the spread of this noninvasive, precise, controlled, tissue-destructive technology to other disorders in a variety of organs." [74]

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