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High intensity focused ultrasound surgery (HIFU) of the brain: A historical perspective, with modern applications

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Abstract

The field of MRI-guided high intensity focused ultrasound surgery (MRgFUS) is a rapidly evolving one with many potential applications in neurosurgery. This is the first of three articles on MRgFUS, this paper focuses on the historical development of the technology and it's potential applications to modern neurosurgery.

The evolution of MRgFUS has occurred in parallel with modern neurological surgery and the two seemingly distinct disciplines share many of the same pioneering figures. Early studies on focused ultrasound treatment in the 1940's and 1950's demonstrated the ability to perform precise lesioning in the human brain, with a favorable risk-benefit profile. However, the need for a craniotomy, as well as lack of sophisticated imaging technology resulted in limited growth of HIFU for neurosurgery. More recently, technological advances, have permitted the combination of HIFU along with MRI guidance to provide an opportunity to effectively treat a variety of CNS disorders.

Although challenges remain, HIFU-mediated neurosurgery may offer the ability to target and treat CNS conditions that were previously extremely difficult to perform. The remaining two articles in this series will focus on the physical principles of modern MRgFUS as well as current and future avenues for investigation.

Keywords

HIFU; Focused Ultrasound; Neurosurgery; MRI; Surgery; Ultrasound

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Ultrasonic Energy: The early descriptions and use

The concept of 'acoustic' energy can be dated to the times of Pythagorus, who began studying the 'pitch' of sound waves.(3) Aristotle postulated that a sound wave resonates through the motion of air, a hypothesis, which was proven correct by the architect Vitruvius, who, in the 1st century BC determined the mechanism for the propagation of sound waves, and used these ideas in the design of early theatres. (10, 20)

Galileo Galilei (1564-1642) is given credit for the modern study of sound energy. Galilei demonstrated that the pitch and frequency of sound could be related to scientific standards. (20) These early investigations set the stage for rapid expansion of the study of sound during the 17th and early 18th centuries, when the French physicist Joseph Sauveur performed detailed studies of the pitch and frequency of sound waves, and coined the term 'acoustics' for the study of sound.(45)

This pioneering work led to investigation into the mechanical effects of sound frequency. In 1880, Pierre and Jacques Curie observed that when pressure was applied to crystals of quartz or Rochelle salt, an electric charge was generated. This charge was directly proportional to the pressure applied to it, and the phenomenon was called "piezoelectricity" from the Greek root, meaning "pressure."(7) Additionally, they demonstrated the reverse piezoelectric effect that occurred when a rapidly changing electric potential was applied to the crystal that caused it to vibrate (Figure 1). These findings paved the way to the development of the modern ultrasonic transducers, which contain piezoelectric crystals that expand and contract to interconvert electric and mechanical energy. Unfortunately, the Curies' findings were ahead of their time, as the lack of electronics technology in the late 19th century limited the use of ultrasonic images.

The era of modern ultrasonics began in the early 20th century (Table 1), when the French physicist Paul Langevin, created a sandwiched quartz transducer that was designed for the purposes of submarine detection during World War I. (2, 46)

Early Medical Applications of Ultrasound and the identification of HIFU

During the interval between World War I and World War II, the initial investigations of ultrasound for medical uses began. The initial therapeutic uses of ultrasound fall into two categories-- nondestructive mechanical heating of tissue to stimulate or accelerate the normal physiological response to injury; or the selective destruction of tissue.

Study of the uses of therapeutic ultrasound started in 1938, when Raimar Pohlman (who 2 years earlier described an ultrasonic imaging method based on transmission via acoustical lenses) noted a 'therapeutic effect" when ultrasound waves were introduced into human tissues.(38) These findings introduced ultrasonic physiotherapy as a medical practice at the Charite Hospital in Berlin. These findings resulted in the marketing of the first ultrasonic device—the Sonostat, by Siemen's AG for treatment of inflammatory conditions. In 1953, Jerome Gersten a physician at at the University of Colorado reported using a similar device to successfully treat patients with inflammatory muscle disorders and rheumatoid arthritis.

(17-19) Similar data was presented by other physician groups in disorders ranging from gastric ulcers to Meniere's disease.(28, 41)

While the work on therapeutic ultrasound was ongoing, the utility of focused, lower frequency (20kHz-2MHz) ultrasound was also being investigated. The first observations of HIFU was noted by Paul Langevin, who noted changes in swimming patterns of schools of fish in the sea when placed in proximity to high intensity ultrasound.(2)

Physical Principles of HIFU

HIFU is thought to produce an effect on tissues by a variety of mechanisms including direct heating, cavitation and mechanical forces. Thermal and cavitation mechanisms have been the best described, and warrant description.

Thermal heating is caused by absorption of ultrasonic energy by the tissues. This leads to a rise in temperature of the tissues, which is dependent on the intensity of the ultrasound energy and the acoustic (ultrasound) absorption coefficient of the tissue. In HIFU, the ultrasonic intensity at the beam focus is much higher than that outside of the focus (Figure 2). This permits the generation of tissue temperature elevations of tens of degrees Celsius, in the focal zone of the beam causing tissue coagulation and denaturing tissues within seconds.(8)

When ultrasonic energy passes through a viscous medium such as human soft tissue, the intensity of the beam is attenuated. This attenuation depends on both the energy that is absorbed by the medium as well as the energy that is scattered from interfaces or inhomogeneities within the tissue. Since most of the attenuation is related to tissue absorption, it can be assumed that almost all of the energy from the primary ultrasound beam results in tissue heating.(48)

Ultrasound's nonthermal mechanisms of action are not well established but are thought to arise from cavitation and acoustic streaming. Cavitation occurs when the negative component of the acoustic wave causes liquid components to fail under tension, resulting in the formation of gas and/or vapor filled “cavities” or bubbles. These bubbles will oscillate at large displacement amplitudes if the acoustic field is continued. The mechanically driven bubbles cause damage to their surroundings, particularly if they oscillate near tissue interfaces. Cell death may occur due to acoustic cavitation if the oscillating bubble disrupts the cell membrane. Cavitation damage tends to be more random than thermally-mediated cell death because cavitation requires the existence of a nucleation site.

Histologically, cavitation-damaged tissue contains specific sites of injury, distributed within viable tissues.(26) Cavitation in tissues depends largely on ultrasound intensity and the frequency employed by the device. The higher the frequency, the higher the intensity required to initiate cavitation. For example, cavitation thresholds have been measured to be 1000 W/cm^2 for 1 MHz and 2800 W/cm^2 for 3 MHz frequencies in the dog thigh muscle.(23) Thus by operating at a higher frequency, cavitation may be avoided.

In contrast to cavitation, acoustic streaming is a circulation set up in a fluid by an acoustic field when momentum is transferred from the field onto a liquid medium by the absorption of the field. Since the velocity gradients associated with this motion may be high, (particularly in the vicinity of boundaries within the field), the shear stresses may cause biological changes or damage. Even stronger stresses are associated with the microstreaming that exists in the near field of an oscillating cavitation bubble.

Early Investigations

The first reported investigation into the use of focused ultrasound were performed by Lynn and Putnam in 1942. They noted that the high frequency and short wavelength ultrasound waves permitted them to successfully deliver high doses of targeted ultrasonic energy to specific areas of the brain with minimal disruption to the non-targeted tissue. Lynn and Punam treated 37 animals with HIFU to a wide variety of cortical and subcortical regions, resulting in both reversible and irreversible clinical deficits. All the animals were noted to have well-circumscribed lesions on pathological examination (Figure 3), an effect appeared instantaneous in contrast to radiation treatment.(37) This study, which was the first to successfully show that ultrasound waves could destroy brain tissue in animals is considered by many to be the earliest experiment demonstrating the use of HIFU application on biological tissues.

Contributions of Francis and William Fry

The most enduring contributions on the applications of HIFU in neurosurgery were performed by William and Francis Fry. William J Fry (Figure 4) was a physicist at the University of Illinois at Champaign and had a strong interest in biophysical research. During the Second World War, Fry worked on the design of piezoelectric transducers at the Naval Research Laboratory Underwater Sound Division in Washington, D.C. He then became a professor of Physics at the University of Illinois at Champaign, founding the Bioacoustics Laboratory there in 1946.(47)

Along with his brother, Francis Fry, in the early 1950's William Fry demonstrated that HIFU could be used after a craniotomy to target deep-seated areas of the basal ganglia brain in primate models.(12) The Fry's ultrasound device was complex, using a system of 4 transducers which focused high-intensity acoustic beams into an animal subject, and producing a pinpoint lesion without damage to surrounding tissue.(15)

The early successes of the Fry experiments led to the obvious question of using HIFU as a non-invasive mechanism to perform cranial surgery. In 1957, William Fry, Francis J Fry, and Reginald C Eggleton founded the lnterscience Research Institute in Champaign, Illinois. The work at the Institute had two goals: to develop and apply high-intensity ultrasound instrumentation specifically designed to treat neurological disorders, and to develop computer-based, low-intensity ultrasound instrumentation for visualization of the soft tissue. The work on the high-intensity ultrasound was very successful. In co-operation with Dr. Russell Meyers, Chief of Neurosurgery at the University of Iowa School of Medicine, this instrumentation was used to treat a number of human patients suffering from various brain pathologies, and in particular Parkinson's disease.(15) Brain sections of the few patients who died, of causes unrelated to surgery, showed well-placed lesions in the intended structures.(38) At the 1960 AIUM (American Institute of Ultrasound in Medicine) meeting they jointly presented their work in a paper entitled "Ultrasound in Neurosurgery." Fry also demonstrated a video of HIFU-mediated lesion production in the cat brain at the American Association of Neurological Surgeons (AANS) meeting in 1968.(16)

After William Fry's death in 1968, Francis Fry became Director of Research of Interscience Research Institute (IRI). In 1970 IRI became a part of the Indianapolis center For Advanced Research as a component of Indiana University School of Medicine. Here, Frank Fry worked closely with Dr. Robert Heimburger, MD Chief of Neurosurgery in the Department of Surgery of Indiana University School of Medicine, developing a complex stereotactic device which could be used in conjunction with HIFU for the purposes of targeted lesion production.(22) During the early 1970s an automated computer controlled integrated ultrasound b-mode image guided HIFU system ("The Candy machine") (Figure 5) was developed to treat brain cancer patients. The high-intensity ultrasound was found safe for the destruction of brain tumors.(21) These treatments were performed after a craniectomy, through the skin, which was placed over the ultrasound window (Figure 6). Although the safety of the procedure was established, the clinical results were mixed.

Based on the safety a second generation HIFU device was designed in 1980s using CT or MRI guidance (Figure 7). The safety and effectivness of the device was demonstrated on a canine model. The device received Investigational Device Exemption (IDE) from the FDA in 1989 and was planned to be used at M D Anderson Hospital, Houston, TX in 1990 for the treatment of astrocytoma, although this endeavor was not finished.

Evolution of Modern MR-Guided HIFU 'surgery' : The MGH Experience

The early success of the Fry brother's attracted significant amounts of national and international attention into HIFU. In 1948 Diener et al.(9), reported on a series of 3 patients, with dementia paralytica, torticollis and Parkinson's disease respectively, who had focused ultrasound to the diencephalons with ultrasound guidance. All of these patients demonstrated clinical improvement albeit with varying clinical follow-up. In 1951, Zubiani applied ultrasound cycles of between 0.6 to 1.5 Watts per centimeter to the heads of patients with various brain disorders, and "no objective neurologic signs without image guidance."(51) This study was limited however, due to lack of pathological specimens, dubious clinical indications and limited follow-up.

The early 1950's represented a time of significant in the clinical work of focused ultrasound. Padmaker ('Pat') Lele, a neurophysiologist on William Sweet's team at the Massechusettes General Hospital (MGH) studied the use of thermocouplers in conjunction with HIFU treatment, demonstrating that couplers could be used to focus energy at a target point, resulting in more precise lesioning. Lele later went on to become a Professor of Mechanical Engineering at MIT).

Dr. H. Thomas Ballantine, a neurosurgeon at the Massechusettes General Hospital, along with Lele and his associates T. F. Hueter, E. Bell, W. J. H. Nauta (one of the leading neuroanatomists of his generation), and Bernard J. Cosman performed clinical work on live animals with focused ultrasound. Hueter and Cosman had affiliations with research which was being performed at the Acoustics Laboratory at MIT and to the World War Two effort in the Underwater Research Laboratory at MIT, where sonar was developed.

These investigations led to the ability to reversibly depress spinal reflexes in the cat, as well as to accurately target the Edinger-Westphal nucleus, causing reversible pupillary dilatation (a Horsely-Clarke stereotactic apparatus was used for these studies).(1) Also noted by these investigators was the concept of a wide ‘threshold band’ which made it difficult when precisely a lesion would occur. Interestingly, Ballantine and colleagues also commented on the use of HIFU for blood brain barrier opening and the diminuation of pain responses, concepts which are as relevant to HIFU studies today as they were 50 years ago (see Part III of this series).

Significant technological advancements to ultrasound design were also performed by the MGH group. Bernard Cosman designed and built the ultrasonic generators and focusing applicators that were used by Ballantine's team at the MGH. Cosman accurately estimated that ultrasonic neurosurgery would require the production of sound intensities in the order of 1,000W/cm^2. Similar to the Fry's Cosman's lesioning apparatus consisted of a radiofrequency power oscillator, and a quartz-plate piezoelectric transducer, as well as an acoustic lens, which was used as a focusing device.(6) This system was remotely controlled using a pushbutton control pad, which connected the individual devices via a series of interconnected relays. The Cosman apparatus was used at MGH for a wide variety of applications, but most commonly mood disorders with mixed results. Cosman himself was able to achieve commercial success by developing and manufacturing several types of pulsed ultrasonic generators, which he sold to numerous clinics in the 1950s, starting a company known as Cosman and Company, which was changed to Radionics in the mid 1950s (Figure 8).

The Leksell and Lindstrom Experience: Promise and Limitations of HIFU

Petter Aron Lindstrom was one of the pioneers of HIFU-mediated lesioning in clinical neurosurgery. A Swedish-born neurosurgeon, who perhaps best remembered for being Ingrid Bergman's first husband, Lindstrom studied the use of focused ultrasound surgery on a variety of neurological disorders, including pain, psychoneuroses, anxiety, depression and epilepsy. In 1954, Lindstrom had studied the effects of HIFU-mediated lesioning as an alternative to a lobotomy procedure,(36) reporting on the pathological effects of ultrasound on human brain tissue in 25 patients with carcinomatosis and cancer-related pain. In this study, autopsies on 14 of the 15 patients who had died of cancer, had a satisfactory lobotomy procedure, with minimal disruption to the brain outside of the targeted region.

Lindstrom introduced the idea to HIFU to his associate Lars Leksell, while Leksell was living in Lund. Leksell was particularly interested in the use of HIFU for the treatment of psychiatric disorders.(42) Leksell designed a specially adapted frame and ultrasound transducer for the purposes of HIFU-lesioning (Figure 9), which he used successfully on patients for periventricular lesioning. The major limitations for Leksell however in human patients, were accuracy in targeting deep seated structures, as well as the need for a craniotomy, since ultrasound could not permit visualization through the intact skull. These limitations were compounded by the lack of reliable imaging tools to plan HIFU treatments.

The development of frame-based stereotactic radiosurgery obviated the need for a craniectomy, and also allowed for precise lesioning. As a result, Leksell decided to focus his energy on ionizing radiation, and went on to describe the principle of radiosurgery in 1951 and developed the Gamma Knife in 1967. In spite of abandoning HIFU as a lesioning device, Leksell maintained a keen interest in the potential for HIFU as a diagnostic tool, evaluating the anatomy of deep-seated cranial structures,(33) and requiring his neurosurgical team to perform ultrasonography on trauma patients in the emergency department to determine the presence of surgical mass lesion or hematoma.

Although progress had been achieved in selecting the most desirable acoustic parameters for ultrasound, during the 1950's and 1960's, it was difficult to focus the ultrasound to a precise location, thus limiting the efficacy of the procedure.

In the late 1950's Pat Lele, visited the University of Chicago and introduced the concept of tractless lesioning using ultrasound to John Jane Sr., who trained under Percival Bailey and Paul Bucy at the University of Chicago and the Illinois Psychiatric Institute. During this period, the Jane group were investigating the idea of using HIFU energy to trace anatomic white matter tracts in the tree shrew.(29) Lele's insights offered promise, as he had conducted a number of experiments using implanted thermocouples and established that ultrasound could cause tissue damage by a temperature elevation at the beam's focus.(34, 35) The Jane group attempted to elucidate the functional significance of white matter tracts using selective ablation, but their experiments were ultimately abandoned due to limited imaging capabilities and accuracy.(29)

Other limitations of focused ultrasound existed as well. This included the lack of real-time imaging during the procedure, and the need for a craniectomy operation due to beam distortion caused by an intact skull. When the skull distorts the ultrasound field, it absorbs energy, resulting in skull heating and attenuation of the ultrasound beam.

Attempts to address this problem were investigated by Fry et al. in the 1970's, as they began experimenting on the use of HIFU without a craniectomy. These studies demonstrated that focusing of the ultrasound beams were possible, but the resultant foci were severely distorted and shifted. (13, 14) This problem was solved in the 1990's with the development of phased arrays of ultrasound transducers which permitted the focusing of the ultrasound beams using a hemispheric transducer design, by correcting for the phase aberrations induced by the different pathways. The early designs required an implantable hydrophone to determine these aberrations, but more modern technology utilizes a pre-operative CT-scan, which is used to measure the skull thickness along the various acoustic pathways.(24) These measurements then permit individual transducers to emit a specific phase and amplitude to reduce phase aberration induced by the variable skull thickness.

The other major revolution in the development of modern HIFU surgery came with improvements in MR-imaging. Since the concept of an ‘ideal surgery’ requires that only the targeted tumor tissue is removed or destroyed without associated injury of the adjacent normal tissue, imaging verification of the target is vital.

The first (and most obvious) method used for guiding focused ultrasound treatment was diagnostic ultrasound. Although successful in practice, ultrasound had 2 limitations (1) it has less resolution than CT or MRI in accurately detecting the location of the lesions and (2) it's inability to detect real-time temperature changes and confirm thermally induced tissue changes (although modern ultrasound technology may permit this). MR-imaging, with its excellent sensitivity for imaging soft tissue tumors, was found preferable over other imaging modalities for localizing 3-Dimensional tumor margins and targeting tumor volumes. In addition, MRI is capable of measuring temperature changes inside the body with accuracy in the range of ±3°C at 1.5Tesla field strengths—and with even greater accuracy at higher field strengths. Because of its excellent temperature sensitivity, the HIFU focal volume can be imaged and localized well before irreversible tissue damage is induced. Moreover, MR-imaging's ability to capture the temperature change, enables the physician to delineate temperature maps and tumor volume during the procedure.(30, 31)

The development of the modern HIFU surgical device thus combined three technological advances into a single unit (Figure 10): (1) thermal ablation with high intensity focused-ultrasound (2) intraoperative guidance by MRI and temperature sensitive MR imaging (3) the use of ultrasound phased arrays to correct for skull distortion. Two commercially-available MRgFUS units are currently being marketed by Insightec (Haifa, Israel). A second model has been developed by Supersonic Imagine (Aix En Provence), but has yet to be released.

A bridge between the past and future of HIFU

Focused ultrasound holds the promise of providing multiple therapeutic functions in the field of neurolosurgical diseases through both ablative tissue disruption and non-ablative effects (delivery of therapeutic agents to a targeted volume by temporally opening of the blood brain barrier, enhanced immune response or reversible blocking of neuronal functions). These applications are discussed in considerably more detail in the following parts of this series, but are briefly reviewed below.

Tissue ablation

The success of the Fry's experiments demonstrates that successful tissue targeting is possible using HIFU treatment. Cohen et al.(5) demonstrated in a swine model with the ExAblate 2000 that the HIFU-induced thermal lesions were sharply demarcated from the surrounding brain with no anatomic or histological abnormalities outside the target. Three patients with recurrent glioblastoma multiforme after craniotomy were subsequently treated, with 2 patients experiencing survival of greater than 30 months.(39) In this experiment sharply defined lesions were observed, similar to those seen by Lynn and Fry, and MR-imaging changes were demonstrated during the treatment. A current study at the Brigham and Women's Hospital is examining the effectives of MR-guided HIFU (MRgHIFU) treatment for glioma patients without performing a craniotomy.

Regions of the brain close to the skull remain a limitation of MRgHIFU because of skull heating. This limitation may be partially circumvented by inserting ultrasound contrast agents, (preformed microbubbles) into the blood stream. These agents have been shown to enhance focal heating during sonication and may reduce the time-averaged power needed during transcranial focused ultrasound ablation.

Targeted Drug Delivery

The blood-brain barrier (BBB) is a persistent obstacle for the delivery of macromolecular therapeutic agents to the central nervous system even though many drugs have proven their potential for treating CNS diseases. It has long been recognized that ultrasound can disrupt the blood brain barrier but the prospect of creating a controlled reversible process introduces significant promise for delivering agents that currently cannot be delivered into the brain.

Hynynen et al.(25) first described a controlled, reversible, and reproducible manner of opening of the BBB while the process can be monitored by MRI. MR contrast, with a molecular weight of 928 D, was able to enter into the brain. This study has demonstrated the potential use of focused ultrasound to deliver chemotherapeutic agents, antibodies, growth factors or genes to the desired area of brain.(32, 44)

Targeting ligands that bind to receptors characteristic of various intracranial diseases can also be conjugated to microbubbles, enabling the microbubble complex to accumulate selectively in areas of interest. Once microbubbles have been targeted to the region of interest, microvessel walls can be permeabilized by destroying the microbubbles with low-frequency, high-power ultrasound. When microbubbles are destroyed, drugs or genes that are housed within them or bound to their shells can be released to the blood stream and then delivered to tissue by convective forces.(27, 31)

Nanoparticles may also be used in conjunction with HIFU for drug delivery, When nanobubbles filled with the chemotherapeutic agent doxorubicin were injected into mice, the bubbles accumulated in the tumors, where they combined to form larger structures known as “microbubbles.” When exposed to ultrasound, these bubbles create echoes, which made it possible image the tumor being targeted. Once the imaging was complete, ultrasonic energy could be focused onto the tumor, lowering the amount of energy needed to release the drug. In mice treated with this nanoparticle delivery model, the nanobubbles were more effective at blocking tumor growth than doxorubicin alone.(40) In a similar manner, gene- or drug coated thermally activated liposomes may be used as an alternative strategy to increase payload volume of drugs or genes.

Clot Lyses

Ischemic and hemorrhagic strokes have been the third most common cause of death in the US. Recent studies have demonstrated the potential of ultrasound and microbubbles in thrombolysis. The effect can be increased through the administration of microbubbles. Enhanced effects of thrombolytic agents such as urokinase and TPA with acoustic energy have been demonstrated. Recent clinical studies have demonstrated improved thrombolysis with the concomitant use of focused ultrasound and a thrombolytic agent for ischemic stroke. Ultrasound enhanced binding of tPA to fibrin and also increased activity of tPA though hyperthermia. Clot lysis followed by stereotactic needle aspiration might also be feasible in the future for hemorrhagic stroke.(11, 43)

Coagulation

Focused ultrasound has been shown to provide an effective method for hemorrhage control of blood vessels in acute animal studies.(49) The changes of the adventitia and tunica media recovered to normal appearance within 28 days. These results show that focused ultrasound can produce effective hemostasis while preserving normal blood flow and vessel wall structure. Interestingly, neointimal hyperplasia was also observed in animal studies. Post-treatment histological observations of the ultrasound-treated arteries showed disorganization of adventitia and coagulation and thinning of the tunica media. It remains to be shown whether a higher acoustic intensity can cause endothelial proliferation and thus be utilized for treatment of vascular anomalies.

Enhanced anti-tumor immunity

Except for the direct disruption of tumor tissues, creation of tumor antigens in the form of necrotic cells and the local release of a diverse array of endogenous “danger signals” from damaged tumor cells has the potential to stimulate an anti-tumor immune response.(4) An increase in CD3+ and CD4+ subsets and in the CD4+/CD8+ ratio in peripheral blood of cancer patients has been observed following focused ultrasound treatment. This effect has been suggested to go through dendritic cells activation by the signals such as ATP or hsp60.(50) A strong anti-tumor immune response may help to combat residual tumor cells at the primary treatment site and to suppress remote metastasis. This exciting potential for focused ultrasound-elicited anti-tumor immunity warrants further investigation.

Conclusions

The use of acoustic energy as a therapeutic tool is not new, and dates to the late nineteenth century. The potential of sound waves to treat disorders throughout the nervous system has also been explored, but in the past has been limited by the inability to target and monitor treatments, as well as the skull.

More recent advances in acoustic energy delivery, diagnostic imaging, and in neurosurgical techniques however, have made it possible to selectively target regions of the brain using high-intensity acoustic energy with a high degree of precision, with minimal toxicity and through the intact skull.

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Summary

High intensity focused ultrasound surgery is a rapidly evolving field which utilizes low-frequency, and high-intensity ultrasound energy to cause focused damage to tissue. Although the promise of the field relies on modern magenetic resonance (MR) imaging, the use of ultrasound in neurosurgery dates to early pioneers such as Lars Leksell, T.J. Putnum and Francis Fry, who began investigating ultrasound-mediated lesioning for neurosurgical purposes. This paper describes the early descriptions and uses of ultrasound in neurosurgery, and the evolution of modern, MR-guided focused ultrasound surgery.

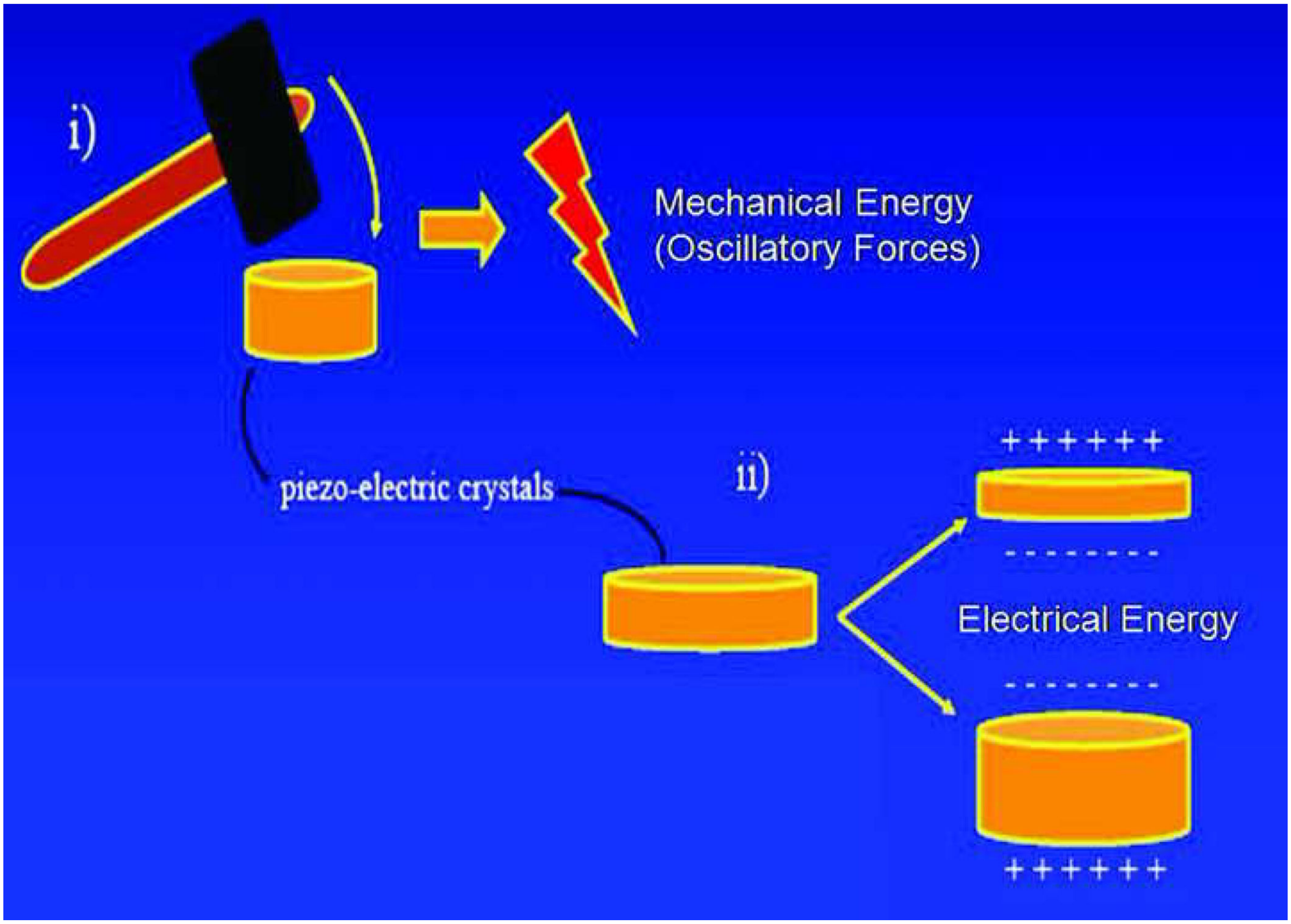

Figure 1.
The Curie brothers noted that when pressure was applied to quartz crystals, and electrical current resulted. Converesely, if the current was an alternating voltage, the crysal oscillated with a frequency that correlated with that of the drive current. This *piezoelectric* phenomenon was the foundation for studies on ultrasonic energy.

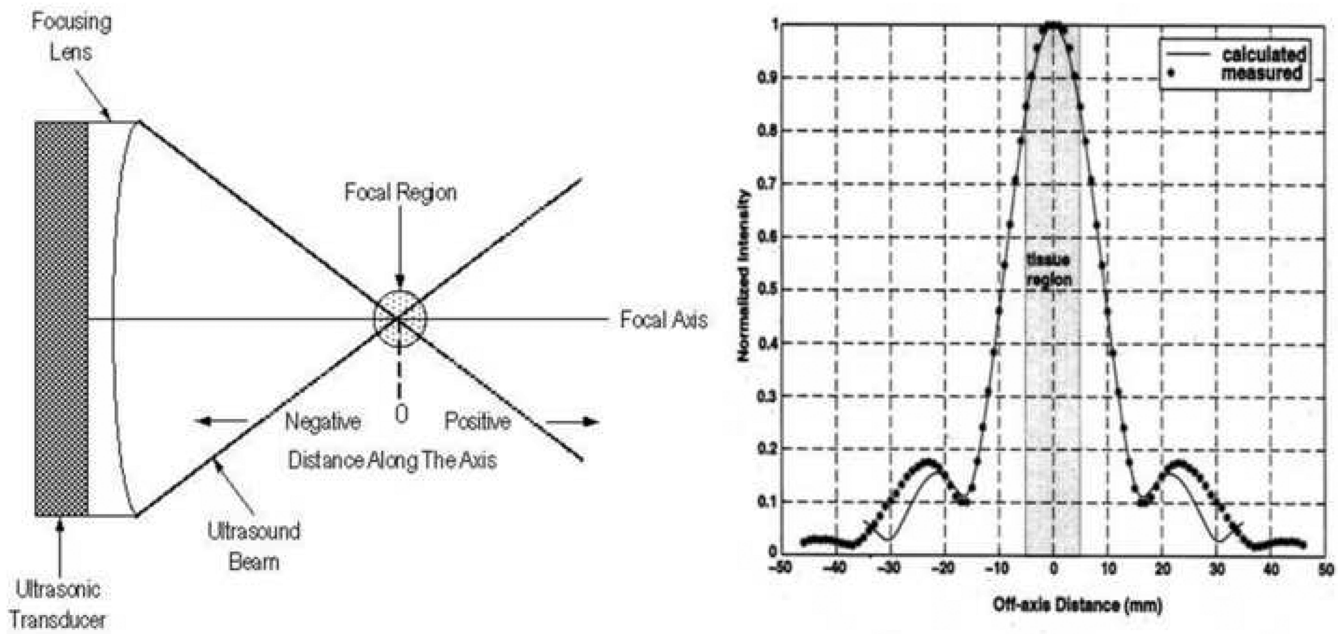

Figure 2.

Schematic demonstrating the principle of focused ultrasound-mediated tissue distruction. (*Left Panel*) The source is a planar ultrasound transducer situated outside of the tissue of interest. When the ultrasound beam is focused at the desired depth inside the tissue by a focusing body by a focusing lens, (*Right Panel*) a highly conformal dose of energy is delivered. The ultrasound beam itself can be shaped either by manipulating the lens, or by mechanical or electrical alterations to the transducers.

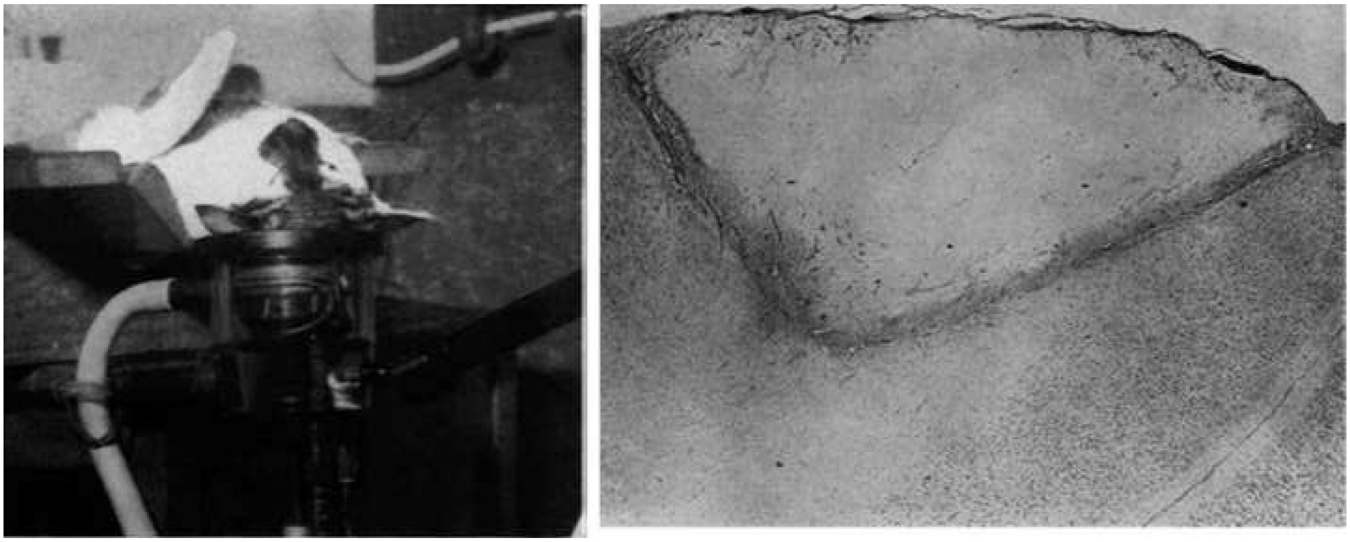

Figure 3.

(*Left Panel*) Lynn and Putnam's ultrasound generator, placed on a cat's head. (*Right Panel*) Cerebellar tissue taken after 45-seconds of focused ultrasound treatement reveals a well-demarcated, wedge-shaped region of tissue damage. *(Reproduced with permission)*(37)

Figure 4.

(Left panel) William Fry, the founder of the Bioacoustics lab at the University of Illinois, Champaign, with the early 4-beam HIFU applicator for neurosurgery circa 1960. *(Right panel)* Frank Fry receiving the Distinguished Pioneer Award from the International Society of Therapeutic Ultrasound in 2002.

Figure 5.
An early b-mode image guided HIFU system designed in the 1970's by the Fry brothers to treat brain cancer patients.

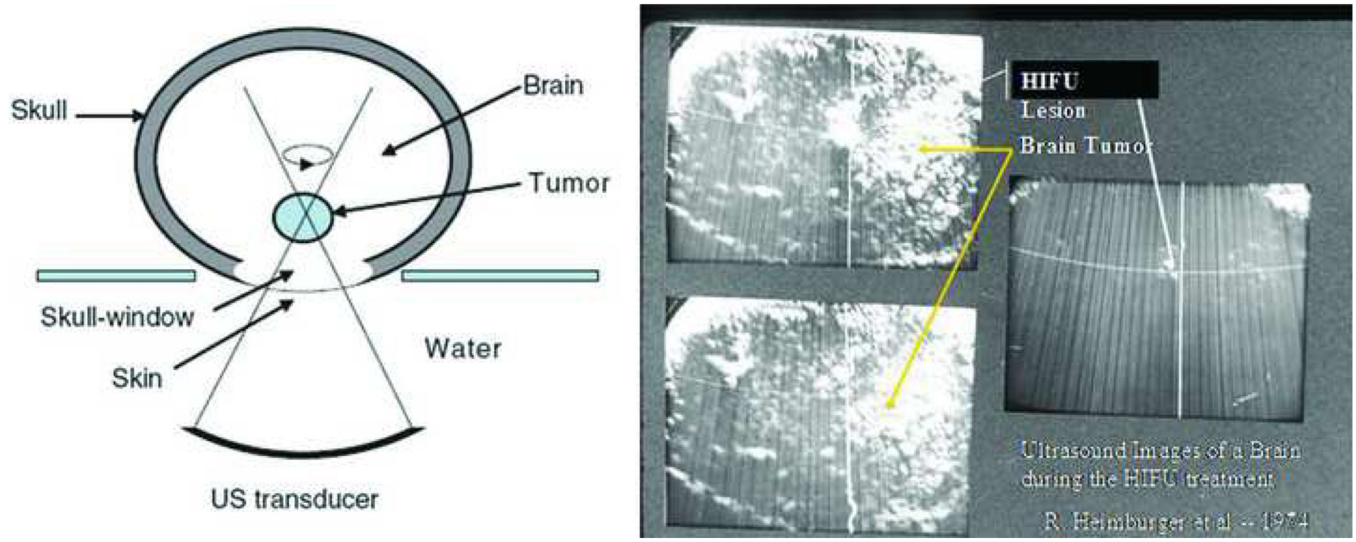

Figure 6.

Schematic (Left panel) HIFU-mediated glioma treatment after craniectomy, as described by Heimberger and Fry. (Right panel) Using real-time imaging with b-mode ultrasound guidance (a device known as the 'Candy Machine'), Heimberger and Fry were able to identify a glioma, and precisely lesion desired target. (Reproduced with Permission from Focus surgery Inc)(22)

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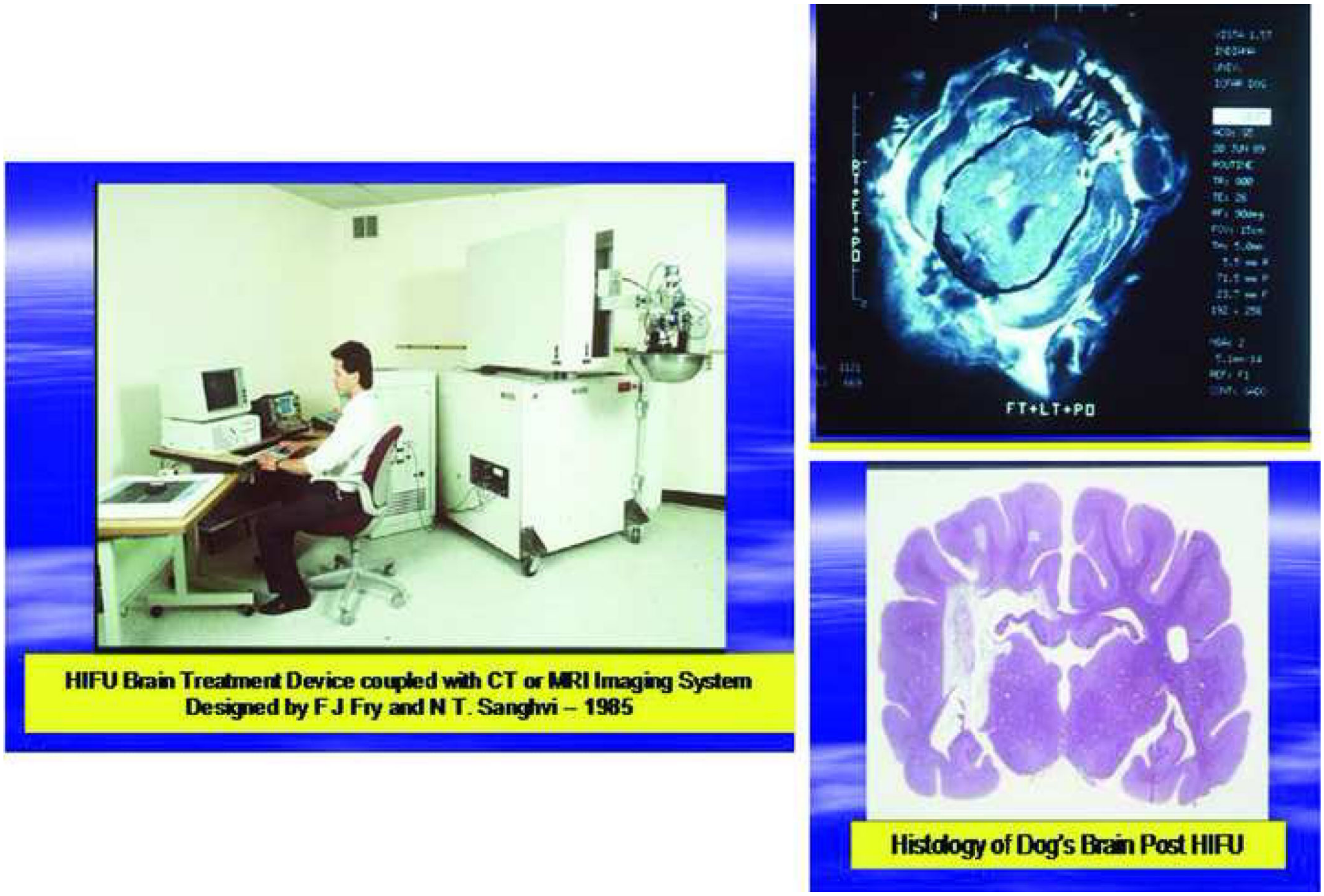

Figure 7.
(*Left panel*) The more advanced Fry HIFU apparatus introduced in the 1980's, which was coupled to CT- and later MR-guidance. (*Upper Right panel*) MR-imaging of the dog brain following HIFU-lesioning in 1989 by Fry et al. revealed 3 single lesions on the left side of the brain, and one integrated lesion on the right. (*Lower Right panel*) Histology confirmed discrete, targeted lesion formation. (*Photograph Courtesy of Narendra T. Sanghvi*)

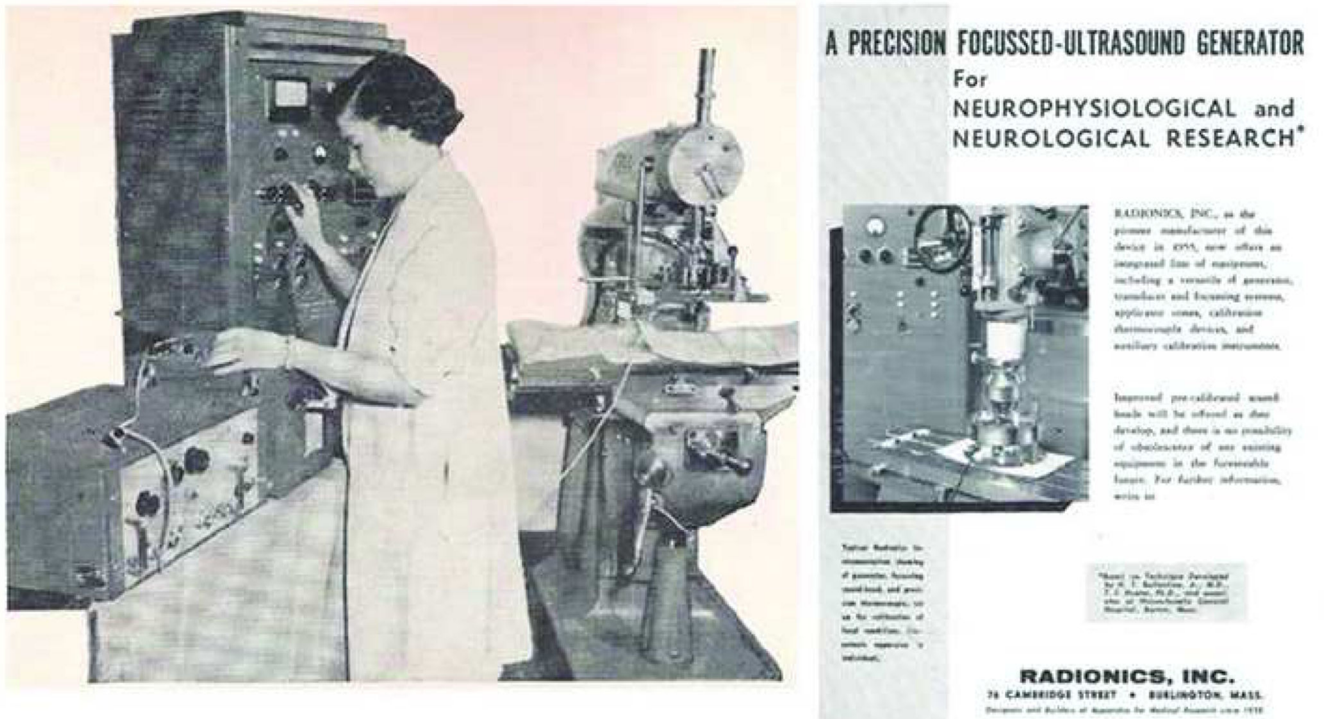

Figure 8.

(*Left Panel*) The Cosman HIFU neurosurgical machine. Note that the transducer was placed on a modified milling machine, which allowed for rigid support and accurate positioning. (Reproduced with permission)(6) (Right Panel) Radionics advertisement from the 1950's depicting the Cosman HIFU machine. (Reproduced with permission from the *JNS publishing* group)

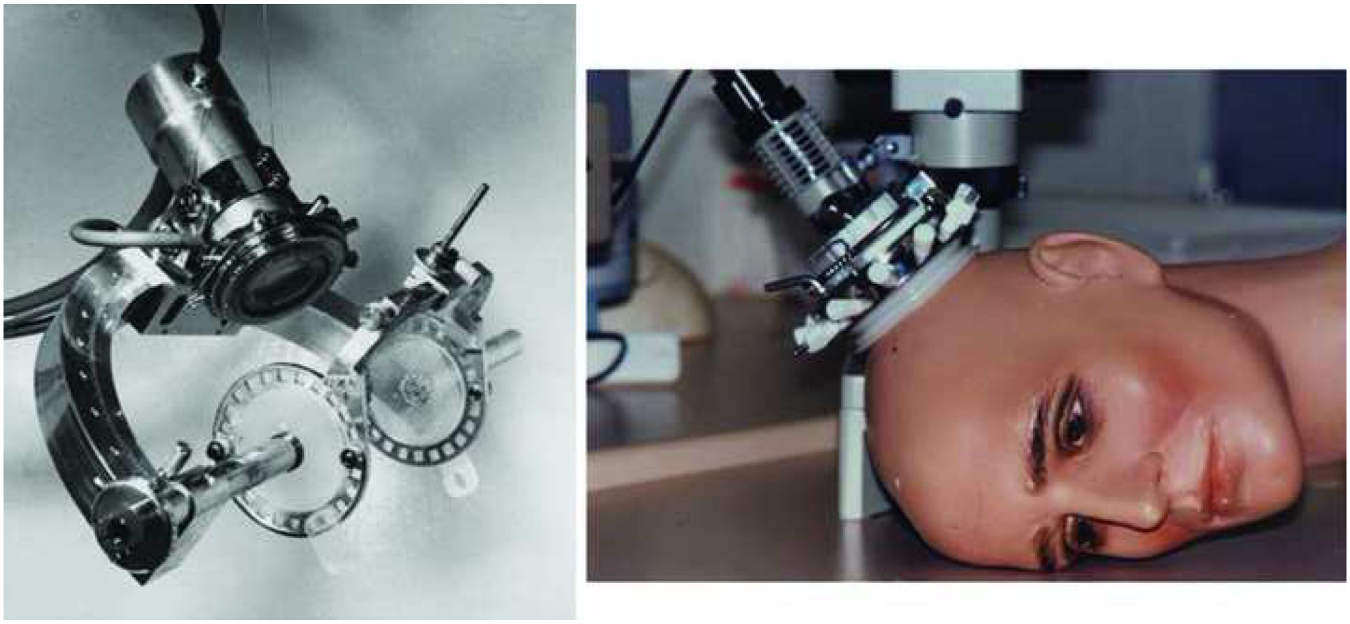

Figure 9.
(*Left panel*) the Leksell frame for HIFU treatment. (*Right panel*) The Leksell ultrasound transducer. (Photograph courtesy of Dan Leksell. Elekta Corporation)

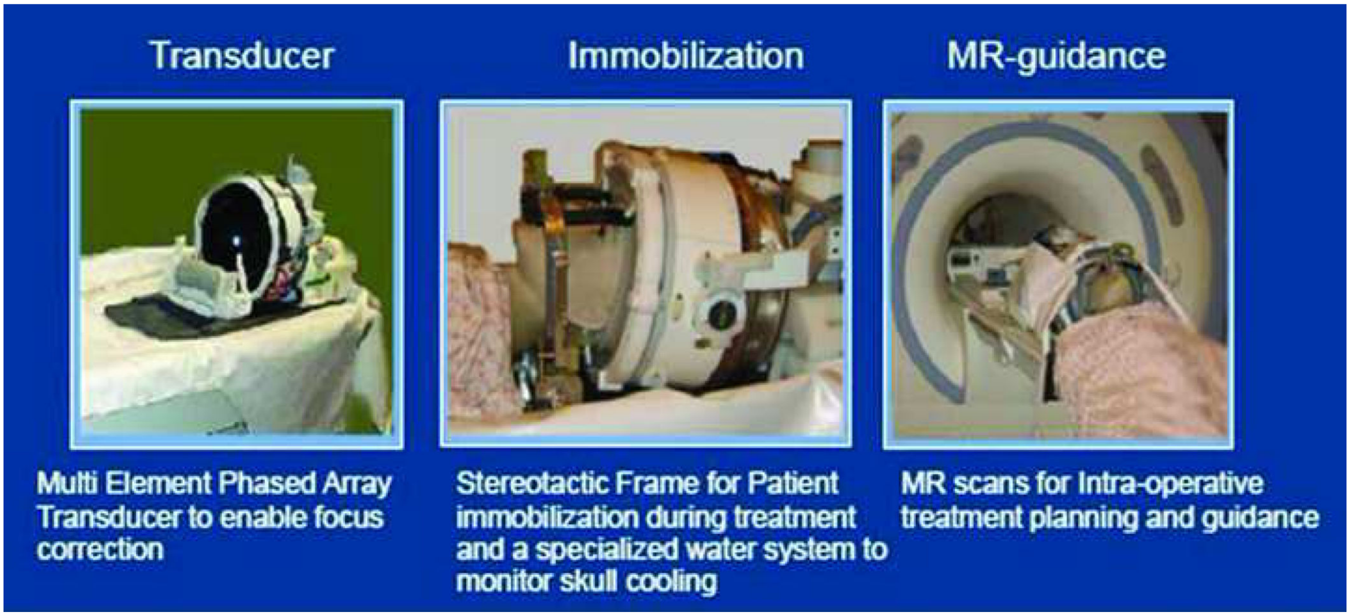

Figure 10.
Components of the Insightec 4000, MR-guided focused ultrasound device. *(Courtesy of Insightec Inc.)*

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Table 1

Timeline in the Development of HIFU technology

Date	Event
1880	Piezoelectric effect (Curie)
1907	Electronic vacuum tube (Deforest)
1918	Sonar (Langevin)
1927	Effects on biologic tissues (Looms, Wood)
1942	HIFU effects (Lynn, Putnum)
1950-1969	Molecular studies on HIFU effects (Fry)
1951-1960	Radiofrequency Generator and Electrode Development (Cosman, in light of FUS developments)
1951-1967	Radiosurgery and Gamma Knife Development (Leksell after ultrasound investigation)
1960-1980	Clinical Studies on HIFU-surgery with open skull (Fry, Heimburger)
1980's-present	MRI Technology
Early 1990's	Ultrasound Phased Arrays (Hynyen)
Mid-1990's	MR-Thermometry (Jolesz)
2001	First integrate MRgFUS Machine (Inightec)
2006	Report on MRgFUS for treatment of GBM after craniotomy (Ram)
Current	Trial on MRgFUS with skull intact (Jolesz)