Preface

The use of acoustic energy for thermal ablation is a relatively old idea. Despite serious attempts by several investigators to develop focused ultrasound surgery into an effective ablative therapy, it has been in the incubation stage as a noninvasive surgical method for a long time. In the last decade, however, since the introduction of monitoring and control by magnetic resonance imaging, remarkable progress has taken place in focused ultrasound surgery. The goal of this book is to survey this method's extraordinary improvement and advancement when it is integrated with the best diagnostic imaging technique available. Anatomic and functional imaging with magnetic resonance imaging can optimally localize and define targets since magnetic resonance imaging accurately controls energy deposition. The resulting therapy delivery system with closed-loop control; first produced as a commercial product by InSightec, Ltd. (Dallas, Texas, U.S.A.); is one of the most complex medical devices of our times. Though we have tried to introduce and present the technique and its applications as completely as possible, a single book on magnetic resonance imaging; guided focused ultrasound surgery cannot adequately cover all recent advances. With that admission, we did detail the technical and physical principles behind the method, explain the biological effects caused by thermal and non-thermal interactions with tissue, and devote a substantial portion of the book to already proven applications, including treatment of uterine fibroids and breast cancer. In addition, we tried to demonstrate the enormous potential of this method for the noninvasive treatment of several malignancies, such as prostate and liver cancer or bone metastasis. Since the most challenging clinical application of focused ultrasound is the ablation of brain tumors, we went into considerable detail in describing this treatment method. Finally, the book discusses such exciting non-thermal applications of magnetic resonance imaging; guided focused ultrasound surgery as targeted drug delivery and gene therapy. We believe that these innovative uses of the technique will have significant clinical impact in the near future. Targeted delivery of larger molecules into the brain through the transiently opened blood-brain barrier is considered the most promising therapeutic use of magnetic resonance imaging; guided focused ultrasound surgery. This application alone has the potential to drastically change the entire field of clinical neuroscience and neuropharmacology. Even before this, however, magnetic resonance imaging; guided focused ultrasound surgery will have significant impact on surgery and radiation oncology. It can be characterized as a disruptive technology; that will radically change existing medical disciplines. Our vision is that this noninvasive surgical method will eventually replace several invasive surgical procedures and, in some cases, eliminate the need for ionizing radiation. We believe that this image-guided and controlled technique is safer and more efficient than most of those for open surgery and radiation therapy procedures. However, there is no doubt about the need to further improve the technology in order to advance clinical knowledge and experience. Although the development of this method originated in academic institutions, it is a very complex technology that must be built with industry involvement. The device, the best example of an advanced image-guided therapy delivery system, requires magnetic resonance imaging to integrate fully with acoustic technology. To accomplish this integration, contributions from General Electric Corporation and InSightec, Ltd. have been critical. They are not alone. Other medical companies have also become interested in advancing magnetic resonance imaging; guided focused ultrasound surgery. In the future, specific applications and their clinical success will define the direction of magnetic resonance imaging; guided focused ultrasound surgery. It may consist of the use of high-field magnets with large phased arrays, or it may apply local focused ultrasound surgery probes or applicators. In either case, we believe that magnetic resonance imaging is essential for the technique, not only for providing thermal images but also for accurate targeting and localization. We hope the book elucidates the advantages of magnetic resonance imaging for monitoring and controlling focused ultrasound surgery therapy. We, the editors,
extend our gratitude to the publisher for devoting an entire book to magnetic resonance imaging-guided focused ultrasound surgery—a literary first. To this point, we are very thankful for the opportunity to introduce this exciting technology to a larger audience. We also wish to thank our colleagues who contributed to this book and provided early insight into the development and clinical use of this method. We hope that our collective vision of this technology is correct, and that this initial publication will be followed by several others, each elaborating on magnetic resonance imaging-guided focused ultrasound surgery’s full potential.

Ferenc A. Jolesz
Kullervo H. Hynynen

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Introduction
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The concept of “ideal” tumor surgery is to excise or remove the neoplastic tissue without damaging adjacent normal structures. This concept requires a noninvasive surgical approach, which limits the tissue destruction to the targeted tumor. Noninvasive surgery would lead to even shorter recovery time and result in even less complications than minimally invasive techniques. Implementing such noninvasive surgical procedures will transform current medical specialties, change existing clinical practices, and could therefore be an important tool in reducing the cost of patient care. It is obvious that the introduction of a noninvasive tumor destruction method will disrupt the current way of patient management and require changes in the related infrastructures too. In the surgical specialty, emphasis on manual skills and practical training will be replaced by a mostly technical knowledge base. Sterile operating rooms, anesthesiology, and postoperative intensive care units will not be required, and their relatively outdated equipment will be replaced by a more advanced technology. Patients will return home and to work much faster without any significant reduction in quality-of-life caused by the procedure. Therefore any noninvasive surgical technology, when it is established and introduced in practice, will be a disruptive technology. We
think magnetic resonance imaging (MRI)-guided focused ultrasound (MRigFUS) is such a disruptive technology. Unlike invasive surgery, it requires no incision, and the acoustic energy penetrates through the intact skin and through the tissues surrounding the tumor, without causing any significant bioeffects. Energy deposition takes place mainly at the focal spot where heat-induced thermal coagulation of the targeted tissue is accomplished. As in ionizing radiation-based therapy, the localization of the target volume requires image guidance. Using intraprocedural MRI, this technique provides the best possible tumor margin definition and with real-time MRI thermometry, the closed-loop feedback control of energy deposition is also accomplished. This real-time targeting and control makes MRigFUS superior to radiation surgery. In addition, because of the lack of any tissue toxicity, focused ultrasound surgery (FUS), unlike radiosurgery, can be repeated multiple times if necessary. The idea of using focused acoustic energy for thermal coagulation deep within the tissue as a noninvasive surgical method is not new. It was first proposed over 60 years ago for the destruction of central nervous system tissue (1). In the 1950s, a complex sonication system that used X rays to determine the target location with respect to skull bones was developed by William and Francis Fry at the University of Illinois (2–4). The system was clinically tested for the treatment of Parkinson's disease with success, but was not used outside the research setting (5). The primary difficulty with the treatment was the localization of target tissues and the complexity of the procedure. There were also several other researchers exploring the feasibility of using FUS for noninvasive surgery in animals and a limited number of patients [see review by Kremkau (6)]. More recently, FUS surgery systems were combined with diagnostic ultrasound (US) imaging (7) to make soft tissue tumor targeting and sonications possible. Several clinical trials for the treatment of the eye (8), prostate (9, 10), bladder (11), kidney (11,12), liver (11,13,14), breast (15), bone, and other cancers (16,17) have been conducted with these devices. Currently, two transrectal US surgery devices for prostate cancer are in clinical use in Europe and several other countries. Furthermore, external US-guided devices are in clinical use in China, where tens of thousands of patients have been treated so far. Although targeting using diagnostic US works well in some cases, the treatment is still relying on open-loop, uncontrolled energy delivery. This means that the power settings for the exposures are based on experimental and theoretical models and clinical experience, and no online monitoring of the location or the magnitude of the temperature elevation is used. This makes the treatment sensitive to patient-to-patient variations. Just the propagation of the wave through the overlying tissue layers can significantly distort the power deposition pattern at the focus (18). To eliminate these variations, the energy delivery and its biological effects should be monitored online, and exposure variations should be adjusted to give comparable thermal exposure to all patients while avoiding overexposing tissues outside of the target volume. By using the temperature sensitivity of MRI, the monitoring of thermal ablations became possible (19). It was a logical step to introduce MRI-based thermometry for the control of FUS procedures (20,21). To do this, researchers at the Brigham and Women's Hospital and Harvard Medical School have worked with engineers and scientists, first from General Electric Medical Systems and later from InSightec, Inc., to develop US surgery systems combined with MRI. This makes online temperature information available for monitoring and controlling the energy delivery. In addition, and maybe more importantly, MRI gives more accurate definition of the targeted tumor volume than surgical inspection with eye. MRI is also superior to other imaging techniques such as the US and computed tomography in tumor localization. The successful testing and early development of the MRigFUS technique at the Brigham and the confirmation of their results from many research groups have resulted in the development of a commercial device that is in routine clinical use in many medical centers around the world. The device has been approved in many countries, most notably in the United States by the Food and Drug Administration for the treatment of uterine fibroids. Currently, its use is being further investigated for several other clinical applications. If our vision is correct, the future of MRigFUS is extremely promising as a replacement for invasive tumor surgery at multiple organs and anatomic sites. Currently the usage of the InSightec system clinical trials has begun in prostate, breast, and brain tumor treatment, and there are extremely encouraging early results in palliative pain treatment of bone tumors. At the same time, there is significant research effort
concerning the nonablative use of MRIgFUS for targeted drug delivery (22), focal blood-brain barrier disruption (23), and gene therapy (24&25). There is also significant progress in developing more efficient phased array transducers that can apply the treatment within shorter time and can sonicate targets within moving organs or in locations where acoustic windows are limited. Although there is only one commercial device currently on the market, other manufacturers appear to be working toward developing their own MRIgFUS devices (27). Therefore, the editors believe that it is the best time to provide a book with an up-to-date review of MRI-guided and controlled therapeutic US for the scientists, clinicians, and trainees who are entering this rapidly growing and exciting field. References


**Fundamental Principles of Therapeutic Ultrasound**

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**INTRODUCTION**

Ultrasound is a pressure wave with a frequency above the audible range of a human ear (18–20 kHz); it is generated by a mechanical motion that induces the molecules in a medium to oscillate around their rest positions. Due to the bonding between the molecules, the disturbance is transmitted to neighboring molecules. The motion causes compressions and rarefactions of the medium and thus a pressure wave travels with the mechanical disturbance (Fig. 1 and Fig. 2). Figure 1 A diagram showing the particle motion induced by an ultrasound wave as a function of time. Figure 2 The particle motion in a medium where the ultrasound wave is propagating as a function of location. As a result, an ultrasound wave requires a medium for propagation. In most cases, the molecules vibrate along the direction of the propagation (longitudinal wave), but in some instances, the molecular motion is across the direction of the wave propagation (shear wave). Shear waves propagate in solids such as bone but are quickly attenuated in soft tissues. Therefore, most current medical ultrasound methods utilize longitudinal waves (1–4).

**GENERATION OF ULTRASOUND**

**Ultrasound Transducers**

Ultrasound is generated by applying radiofrequency (RF) voltage across a material that is piezoelectric, i.e., it expands and contracts in proportion to the applied voltage. This phenomenon is the inverse of the piezoelectric effect, which was discovered by Jacques and Pierre Curie in natural quartz crystals in 1880. Since then, many piezoelectric materials have been discovered and developed. From these materials, a group of artificial piezoelectric materials known as polarized polycrystalline ferroelectrics (for example, lead zirconate titanate or PZT) is used for medical ultrasound applications. The piezoelectric property is lost above a material-specific temperature—the Curie point (for example, 328°C for PZT-4). Also, piezoelectric material rods or grains can be placed into a polymer matrix to have more control over the acoustic and electrical properties of the material. These so-called piezo composite materials are used especially in phased array transducers. For many applications of ultrasound therapy, transducers capable of producing high-power, single-frequency, continuous waves are needed. In Figure 3, a simplified version of a high-powered transducer is shown. Figure 3 A diagram of an ultrasound therapy transducer. Abbreviation: PZT, lead zirconate titanate. The ultrasound wave is generated by a piezoelectric plate of uniform thickness that has electrodes on its front and back surfaces. The electrodes are connected to the driving RF-line. Maximum power from a transducer can be delivered when it is operated close to its resonant frequency, which is achieved when the thickness of the plate is equal to the wavelength/2. However, a range of frequencies can be used with piezo composite materials. The frequency, which corresponds to the half-wavelength thickness, is called the fundamental resonant frequency of the transducer and it gives the maximum displacement amplitude at the transducer faces. The transducer can be driven at a frequency which is three, five, or so on, times its fundamental frequency. The conversion efficiency is, however, reduced when compared with the fundamental frequency operation. At a frequency of 1 MHz, the half-wavelength thickness is approximately 2 mm in PZT-4, thus high-frequency transducers are thin and more difficult to manufacture. In order to maximize energy output, all of the acoustic energy should be radiated through the face of the transducer. This can be achieved by selecting a backing material so that the acoustic impedance of the transducer is much larger than the acoustic impedance of the backing. In practice, air-backing gives almost complete energy transmission through the front of the transducer. Ultrasound transducers can be manufactured in practically any desired shape and size. Spherically curved focused transducers of various sizes up
to 30 cm diameter hemispherical transducer arrays have been manufactured (5–7). Both nonfocused and focused, single and multielement transducers and arrays have been manufactured for endocavity use (8–14). Interstitial applicators inserted directly into the tissue via catheter have been constructed down to the size of 1 mm in diameter (15, 16). Catheter-based applicators, inserted via the vascular route into the heart, have been developed for ablating cardiac tissue (17, 18). Special care in the selection of transducer materials has to be taken when applicators for use in magnetic resonance imaging (MRI)-guided interventions are developed. For a detailed example of the material description see Ref. (19).

**Basic Ultrasound Driving System** The generation of RF signals for conversion into mechanical motion is in principle similar in all systems. A typical system diagram is presented in Figure 4. Figure 4 A block diagram of basic components of an ultrasound therapy system. Abbreviations: US, ultrasound; RF, radiofrequency. The RF-signal is generated by a signal generator (analog or digital) or an oscillator and is amplified by an RF-amplifier. Commercial amplifiers and frequency generators are used in many lab systems. The forward and reflected electric power are measured after amplification in order to obtain the total RF-power that is proportional to the acoustic power output (the system must be calibrated to give acoustic power as a function of net electric power). Before the signal enters into the transducer element, it passes through a matching and tuning network that couples the electric impedance of the transducer to the output impedance of the power amplifier. The power output can be controlled either by using a fixed gain amplifier and controlling the level and/or duty cycle of the input signal from the frequency generator or by controlling the gain of the amplifier. For phased array transducers, this driving line is required for each transducer element. This has become possible with the development of low-cost drivers.

**ULTRASOUND FIELDS** The ultrasound field generated by a transducer depends on the size, shape, and vibration frequency of the source. Only continuous wave fields from ideal, uniformly vibrating sources will be discussed in order to provide a simple illustration of the main characteristics of ultrasound fields. **Ultrasonic Fields from a Planar Transducer** The acoustical pressure amplitude distribution emitted by a planar, circular transducer, oscillating as a piston (radius = \(a\)) in simple harmonic motion, is dependent on the ratio between the diameter and the wavelength. In the case where the diameter of the transducer is equal to or smaller than half of the wavelength, a hemispherical wave is launched. When the diameter of the transducer increases, the field becomes more and more directed with a complex pressure-amplitude pattern located close to the transducer (the near field or Fresnel zone) transitioning to a smoothly decaying field past the last axial maximum that is located approximately at a distance of \(a^2\) from the transducer face (Fig. 5). Figure 5 An axial ultrasound intensity distribution from a planar transducer (frequency, 1 MHz; diameter, 20 mm). Abbreviation: RF, radiofrequency. The ultrasonic field beyond the last axial maximum (the far field or Fraunhofer zone) is diverging and the pressure amplitude follows the inverse law and is proportional to 1/distance. The beam also narrows toward the last axial maximum, being about 1/4 of the diameter of the transducer (DB beam diameter of the intensity) at the last axial maximum. **Focused Ultrasonic Fields** If the diameter of an ultrasound source is much larger than the wavelength in the medium, then the ultrasonic wave can be focused by lenses or reflectors, or by making the transducer self-focusing (Fig. 6). Figure 6 (Top left) A diagram of a spherically curved ultrasound transducer and (top right) the simulated axial intensity distributions in soft tissue of transducers with different radius of curvature (diameter, 60 mm; frequency, 1 MHz). (Bottom) A measured pressure amplitude distribution across the focus of a transducer (frequency, 1.1 MHz; F-number, 0.8). Focusing can be achieved by using arrays of small transducers that are driven with signals having suitable phase delays to obtain a common focal point (electrical focusing). The wavelength imposes a limitation on the size of the focal region and the sharpness of the focus is determined by the ratio of the aperture of the radiator to the wavelength, and the distance of the focus from the transducer. **Spherically Curved Transducers** The theory of spherically curved transducers vibrating with uniform normal surface velocity was developed by O’Neil (20). Theoretical axial intensity distributions from spherically focused transducers are shown in Figure 6. It is possible to focus energy in the near field of an equivalent diameter planar transducer, due to the finite size of...
the wavelength. The ultrasound field between the acoustical focus and the transducer resembles the near field of a planar transducer. Beyond the focus, the field follows the geometrical divergence angle of the transducer. The shape of the focus is a long narrow ellipsoid with dimensions dependent on the transducer diameter, radius of curvature, and frequency. The geometrical focusing of a transducer is often described by an F-number, which is the ratio between the radius of curvature and the diameter of the transducer (F-number = R/d). By increasing the radius of curvature (R), the maximum intensity can be pushed deeper into the tissue but at the cost of the focal region becoming longer and the peak intensity lower. This is due to the reduced focusing effect of the transducer and the attenuation within the tissue. It is possible to induce an intensity maximum at any practical depth in a human body with a suitable choice of transducer parameters, as long as the beam entry is not restricted by gas or bone. Ultrasonic Lenses Acoustic lenses are made of materials in which the speed of sound (V) is different from that in the coupling medium (Vm), causing the ultrasound beam to focus if the lens shape is appropriate. Lenses made of solids, e.g., plastics, metals, where the speed of sound is higher than in water, or liquids where the speed is lower than in water, have been used. The ideal shape of a lens is planoconcave, with V<sub>L</sub>&#8201;<&&#62;&#8201;Vm, where the generating curve of the concave surface is elliptic. By using a liquid lens with suitable mechanical structures, a single lens can offer a wide variety of different focal distances. Lenses have also been used to produce multiple foci in order to increase the size of the exposed tissue volume. It is possible to design low-profile lenses that can be made thinner than curved transducers. Reflectors The absorption losses caused by lenses can be avoided by using acoustical reflectors. However, the manufacturing of reflectors requires great care and is expensive. Thus, reflectors are used only in special applicator designs. Electrical Focusing Ultrasonic beams can be focused by using one- or two-dimensional arrays of transducers, with each element driven by RF-signals of a specified phase and amplitude, so that the waves emitted by all of the elements are in phase at the desired focal point. The element size will determine the volume within which the focus can be moved because the focus has to be within the volume where all of the beams generated by the elements are overlapping. Focusing to a location outside this volume will result in secondary focal spots. An ultrasound beam can be focused anywhere in front of the array when the element center-to-center spacing is wavelength/2 or smaller. A diagram of a phased array focusing demonstrating the ability to control the location of the focus by the phase and amplitude of the RF-signals driving each element. Abbreviation: RF, radiofrequency. So far, all of the phased array systems developed for ultrasound treatments have had a limited focal range because the large size of the arrays needed results in thousands of elements. However, it has been demonstrated that adequate power outputs can be achieved with wavelength/2 test arrays and thus there is no technology barrier to constructing such arrays. Although electric focusing and beam steering has been used extensively in diagnostic ultrasound, its adoption in the therapy systems has been much slower. The first attempt to utilize electrical focusing in ultrasound therapy was done by Do-Huu and Hartemann. They constructed a concentric ring transducer that allowed the focus to be moved along the axis but not in any other direction. Full range of axial focal spot movement can be achieved with ring center spacing of one wavelength. Large spacing can be used if the array is spherically curved and the focal range is limited. A similar approach can be used for achieving a limited range, three-dimensional motion with phased arrays with large element sizes. There has been a lot of progress in using phased arrays for ultrasound surgery and especially for MRI-guided ultrasound surgery. Today, phased arrays are the method of choice for clinical devices, with the concentric ring design providing control over the depth of focus with added sectors to provide limited beam steering to make the focus larger. Phased arrays have also made it possible to compensate for wave distortion induced by overlying tissues such as skull. Similarly, phased arrays offer significant advantages for applicators that deliver the ultrasound energy via body cavities. ULTRASOUND PROPAGATION THROUGH TISSUE In order to be able to use ultrasound for therapy, it is essential to know the ultrasonic properties of tissues. For instance, the ultrasonic velocity that determines the field shape and the amount of reflected energy at tissue interfaces is dependent on the acoustical impedance (=speed of sound &
tissue density) differences between two neighboring tissues. The temperature elevation induced at the focus is partially dependent on the ultrasound attenuation, while the beam propagates through the overlying tissues, and the tissue absorption coefficient at the target site. The ultrasound properties have been compiled by several papers (38–40), and they have been used as the main sources for the values presented in the following sections. **Speed of Sound**

The speed of ultrasound is not frequency-dependent and has a similar average magnitude of 1550 m/sec in all soft tissues (excluding lung). The velocity in fatty tissues is less than that in other soft tissues, being about 1480 m/sec while in the lungs the air spaces reduce the velocity to about 600 m/sec. The highest values have been measured in bones, between 1800 and 3700 m/sec depending on the density, structure, and frequency of the wave. In various soft tissues, the speed of ultrasound increases gradually as a function of temperature, with the slope between 0.04 and 0.08 °K⁻¹. In fatty tissues, the speed of ultrasound decreases as the temperature increases (41). The effect of the temperature-dependent sound speed is small on the field shape and can be ignored when sharply focused fields are used (42–44).

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MRI-Guided Focused Ultrasound Surgery will be the first publication on this new technology, and will present a variety of current and future clinical applications in tumor ablation treatment. This source helps surgeons and specialists evaluate, analyze, and utilize MRI-guided focused ultrasound surgery - bridging the gap between phase 3 clinical trials and the expansion to the clinical practice - by exploring fundamental principles and future clinical applications using this new therapeutic method.

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MRI Guided Focused Ultrasound Surgery - The Commission on Breast Imaging addresses issues related to breast imaging treatment employing ultrasound-guided high-intensity focused ultrasound. To make a room reservation at the special group rate, you may book directly from Alternative radiology - Clickair Virtual Airlines - From the book: Theranostics and Image Guided Drug Delivery. CHAPTER 7. Targeted Delivery with Ultrasound Activated Nano-encapsulated Drugs a clinical MRI-guided focused ultrasound surgery (MRgFUS) system. MRI Guided Focused Ultrasound Surgery - Reddy has contributed to several articles and books, given multiple presentations and won breast ultrasound, ultrasound-guided core biopsy, stereotactic core biopsy, Imaging services include MRI, Dexa, PET-CT, CT scan, X-ray, Ultrasound,. During the fellowship program, we focus on developing expertise in all Ultrasound Courses 2019 - catris-naturprodukte.de - Ultherapy uses ultrasound imaging, which allows Dr. It is a non surgical ultrasound, pediatric patient blood management, ultrasound-guided vascular. Lucas, Elizabeth K. HIFU Treatment (High Intensity Focused Ultrasound) is a.. Book your next treatment with Rejuvie Aesthetic & Anti-Aging Clinic Bali here. Prostate Cancer - NCCN - Courses for Imaging Technologists on the most effective operation of medical The following material is
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MRI-guided focused ultrasound (MRgFUS) surgery is a noninvasive thermal ablation method that uses magnetic resonance imaging (MRI) for target definition, treatment planning, and closed-loop control of energy deposition. Integrating FUS and MRI as a therapy delivery system allows us to localize, target, and monitor in real time, and thus to ablate targeted tissue without damaging normal structures. 

**INTRODUCTION.** In the past decade, three new minimally invasive procedures surfaced: thermal ablations, high-intensity focused ultrasound (HIFU), and magnetic resonance imaging (MRI)-guided interventions. Each has the potential to transform or replace invasive tumor surgeries. Focused ultrasound is the pairing of two innovative technologies: Focused ultrasound—which provides the energy to treat tissue deep in the body precisely and noninvasively. Magnetic resonance or ultrasound imaging—which is used to identify and target the tissue to be treated, guide and control the treatment in real time, and confirm the effectiveness of the treatment. Watch this video on our new approach to treat essential tremor using MRgFUS. With focused ultrasound, an acoustic lens is used to concentrate multiple intersecting beams of ultrasound on a target deep in the body with extreme precision.