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High intensity focused ultrasound: The fundamentals, clinical applications and research trends

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Abstract Diagnostic ultrasound has been clinically used for decades. More recently, high intensity focused ultrasound (HIFU) has been developed for therapeutic use as a non-invasive technique for tissue ablation. HIFU is also being investigated for advanced applications at the cellular level. Under guidance by magnetic resonance or ultrasound imaging, HIFU can achieve precise biological effects in tissue with a high safety profile. In this article, we discuss the basic principles, advantages and limitations of HIFU. We will also address the food and drug administration (FDA) approved clinical applications in the United States and highlight active HIFU research with promising clinical outcomes.

Percutaneous interventions are now considered the cornerstone of interventional oncology (IO). In contrast with open surgery, image-guided tumor ablation techniques provide lower peri-procedural mortalities, shorter hospital stays, faster recoveries and a better quality of life [1,2]. The safety profile of percutaneous intervention is further enhanced through increased usage of navigation systems [3]. Thermal ablation techniques like radio frequency (RF), microwave, laser and cryoablation use special needles or probes to deliver extremes of temperature to tumor cells thus causing tissue necrosis. These techniques have been used to treat a wide range of body tumors [4,5].

High intensity focused ultrasound (HIFU) is a needleless, non-ionizing, thermal ablation tool. Though potential clinical applications of HIFU were reported as early as 1950s [6,7], precise targeting was a major issue. The first HIFU

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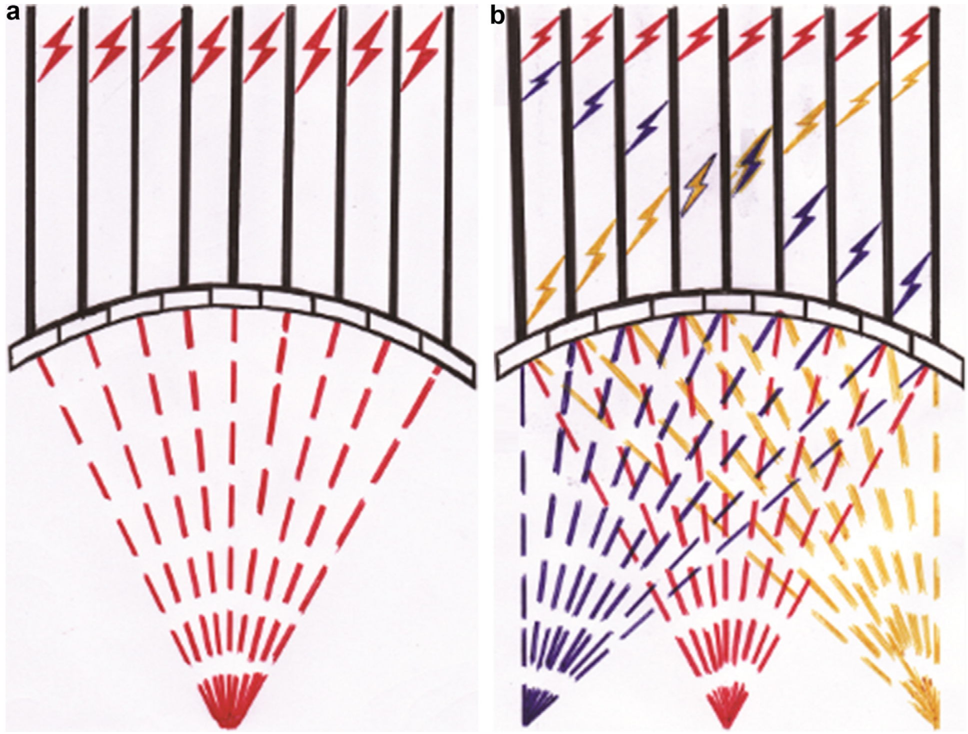

Figure 1. Electronic steering of the high intensity focused ultrasound beam. (a) Phased array transducer is composed of multiple elements, each of which has a separate excitation signal (continuous black lines) with a specific phase. Emitted ultrasonic beams follow their corresponding phase and converge at the original geometric focus. Changing the phase of the excitation signal in (b) changes the direction of the ultrasound beams causing them to converge into a new focus.

application to receive Food and Drug Administration (FDA) approval, which was magnetic resonance (MR) guided uterine fibroid ablation, was in 2004. Since that time, HIFU has attracted increased attention and significant technology improvements took place. As such, three new HIFU clinical applications received FDA approval in 5 years' time frame (2012—2016) [8]. These three applications are treatment of prostate cancer, essential tremors and pain from bone metastasis. In this article, we discuss the basic principles, advantages and limitations of HIFU. The clinical applications of HIFU will be reviewed with emphasis on the FDA approved applications. We shed light on some advanced HIFU research as well.

Basic principles of HIFU

Generation of ultrasound waves

Therapeutic ultrasound intensity range is higher than that used in diagnostic ultrasound. The intensity of diagnostic ultrasound is below 0.1 W/cm^2 [9]. Therapeutic ultrasound intensities differ depending on the intended effect. High intensity range, from 100 W/cm^2 up to 10,000 W/cm^2 or higher [10], is used for tissue ablation mainly through coagulation necrosis. Lower intensity range, from 0.125—3 W/cm^2, is used to induce mechanical effects on the cellular level. These effects can facilitate drug and gene delivery as detailed later [11].

Focusing of ultrasound waves

To achieve localized biological effects HIFU transducers are designed such that ultrasound beams are focused to converge at a focal point. Different beam focusing techniques are used for this purpose. One technique is referred to as geometric focusing. This takes advantage of the spherically/cylindrically concave surface of HIFU transducers that causes ultrasound waves to arrive at a focal point. Beam focusing using an acoustic lens is another focusing technique. In this approach, an acoustic lens is placed on the surface of the transducer, mimicking a concave surface transducer. Another technique, electronic focusing, uses phased array transducers composed of multiple piezoelectric elements. Each of the elements has a specific excitation signal. Changing the phase of the exciting signal to the transducer elements can displace the focus along the axial or the lateral direction without moving the transducer (Fig. 1) [10]. This displacement of the focal point without mechanically moving the transducer is known as electronic steering.

Interaction with tissue

Upon interaction with tissue, ultrasound energy either gets absorbed, reflected or deflected. Absorbed energy is converted to heat due to pressure fluctuations at the focus [12]. This raises temperature rapidly to 60 °C or higher, causing coagulation necrosis within a very short time. The classic individual thermal lesion has a cigar shape and size of a rice