Focused ultrasound: The clinical possibilities beyond ablation

By Jessica L. Foley

As our health care delivery model evolves toward optimizing population health while minimizing costs, hospitals and health care systems will need to carefully consider value-based purchasing of innovative treatment technologies, ensuring that the safety profile, patient benefit (e.g. quality of life, patient-reported outcomes) and treatment volume are worth the investment.

Focused ultrasound is an early stage, non-invasive technology that is worth watching. Currently approved in the United States for a couple of indications, focused ultrasound is poised to develop into a multipurpose platform technology using several mechanisms of action to treat a range of diseases, from neurological conditions through cancers, pain and even hypertension.

Multipurpose platform technology

Focused ultrasound is a precise tool that can be used as a stand-alone, non-invasive and non-ionizing alternative to surgery or radiation. It can also serve as a powerful adjuvant or enhancer to other treatments, including gene therapy, chemotherapy and immunotherapy. Focused ultrasound is unique amongst other ablative modalities such as radiofrequency ablation or cryoablation in that it can also produce many other non-ablative bioeffects, enabling treatment of a wide array of clinical conditions with the same therapy platform (see figure 1).

A focused ultrasound system is currently approved in the U.S.to treat symptomatic uterine fibroids and to relieve the pain of cancer that has spread to the bone. There are also two systems under review by the FDA for the treatment of early stage and salvage prostate cancer therapy. All of these

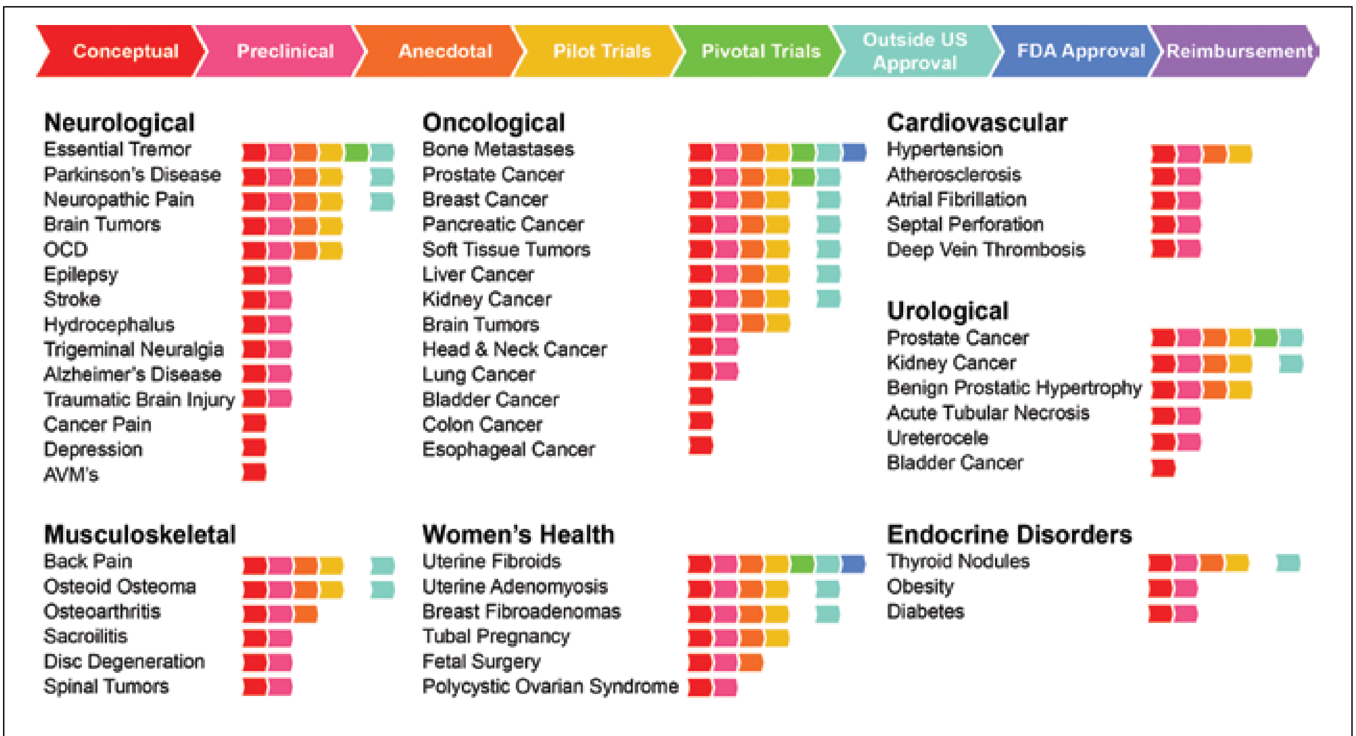


Figure 1: This chart portrays the global status of focused ultrasound. The number of indications in various states of development is increasing rapidly, but most are in the early stages of evolution.

applications utilize thermal ablation, where concentrated ultrasound energy is delivered to a small, precise location to heat and destroy tissue. Much like a magnifying glass focuses beams of light on a single point, focused ultrasound utilizes multiple intersecting beams of ultrasound energy concentrated on tissue deep in the body. At the point where the beams converge, the ultrasound energy is high enough to thermally kill the cells while avoiding damage to surrounding tissue.

Given the morbidity associated with more invasive approaches, there is particular interest in using focused ultrasound to treat the brain. The body of evidence demonstrating safe and effective focused ultrasound ablation of brain targets has grown to more than 300 patients. This non-invasive treatment option — the ExAblate magnetic resonance imaging-guided focused ultrasound (MRgFUS) system (InSightec, Haifa, Israel) — has been approved in Europe for the treatment of essential tremor, tremors associated with Parkinson's disease and neuropathic pain. Results of a pilot U.S. study on focused ultrasound for treatment of essential tremor were recently published in the New England Journal of Medicine, and a pivotal study — to obtain approval by the U.S. Food and Drug Administration (FDA) — recently completed enrollment of patients at eight sites worldwide. Clinical trials are also underway for the treatment of Parkinson's tremor, Parkinson's dyskinesia, brain tumors, and obsessive compulsive disorder. Studies are being organized for the treatment of depression, epilepsy and Alzheimer's disease.

Although thermal ablation is currently the most widely used biomechanism of focused ultrasound, there are many other biological effects that can be produced at the focus. FUS can act via thermal and mechanical mechanisms within the tissue, leading to a variety of bioeffects (see figure 2) that enable treatment of many medical conditions. Of particular significance is the ability of focused ultrasound to: (1) temporarily make the blood-brain barrier more permeable; (2) induce neuromodulation; (3) promote an immune response; and (4) enable localized drug delivery. It is important to note that research demonstrating these non-ablative effects of focused ultrasound is still early stage and consists primarily of preclinical and anecdotal clinical evidence; these represent potential high-impact areas of benefit.

Opening the blood-brain barrier

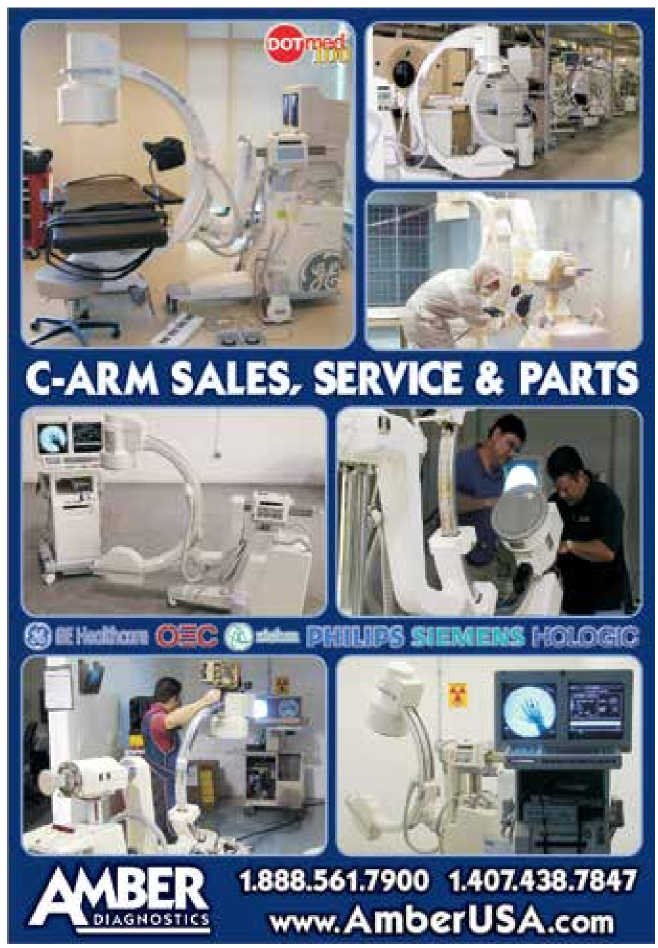
Building on the promising ablation experience, attention has begun to shift toward other ways to use focused ultrasound to treat the brain, such as its effect on the blood-brain barrier (BBB).The BBB is a dense and protective physiological barrier that separates the interior of blood vessels and the surrounding brain tissue. The BBB keeps toxins that may travel through the bloodstream out of the brain. However, this network of endothelial cells connected by tight junctions that line the vessels also significantly limits delivery of beneficial drugs and genes to their intended targets within the brain (see Figure 3).

Many classes of drugs are being developed for the treatment of serious brain disorders including malignant brain tumors, Parkinson's disease and Alzheimer's disease. Despite great promise demonstrated in preclinical studies, these agents' success in clinical trials has been limited in part by the BBB compromising their ability to reach the diseased tissue.

Clinically significant benefits often require direct injection of the compounds into the brain, which is risky and not practical for many patients, and therefore difficult to justify in the early stage of disease progression when the drugs are potentially the most effective. Researchers in academia and industry are developing drug carriers or new routes of administration, but moving drugs across the BBB remains a challenge.

Focused ultrasound can reversibly increase the permeability of the blood brain barrier, thereby temporarily allowing drugs to pass through and into the surrounding brain tissue. The mechanical effects of focused ultrasound — often enhanced and controlled by the use of microbubbles — can loosen the dense network of endothelial cells joined by tight junctions, enhancing the release of drugs from the bloodstream into the brain tissue.

The first clinical trial to investigate the ability of focused ultrasound to non-invasively open the BBB is set to begin soon in Canada, for treatment of patients with malignant brain tumors.



- Thermal ablation
- Histotripsy
- Focal drug delivery
- Immunomodulation
- Neuromodulation
- Radiation sensitization
- Drug activity enhancement
- Amplification of cancer biomarkers
- Dissolve clots: sonothrombolysis
- Coagulate blood vessels
- Vasodilation
- Vasoconstriction
- Stem cell delivery
- Sonodynamic therapy

Variety of effects, variety of disorders

Figure 2: This is a list of bioeffects that focused ultrasound can produce in tissue. These various effects enable the treatment of a wide range of clinical indications.

Activating and mapping the brain

Clinical interest is also growing for using focused ultrasound to reversibly alter neural activity in the brain for a range of potential indications. There are many diagnostic and therapeutic clinical applications that rely on precise stimulation or suppression of neural activity. Commonly used techniques include deep brain stimulation (DBS), electrical monitoring, electroporation or electromagnetic stimulation. Functional imaging modalities such as fMRI are also used to map brain activity. The U.S. Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is spurring interest and innovation in neuromodulation, via large investments (hundreds of millions) in new tools to map the circuits of the brain and/or alter their function.

These current techniques may be effective for some patients yet not for others. DBS and electrical monitoring may require invasive procedures, whereas the non-invasive options may be less precise. Focused ultrasound could offer a non-invasive and precise alternative for stimulation or suppression of neural activity, depending on the parameters of the ultrasound energy applied to the tissue. Neuromodulation can be achieved through either pulsing of the ultrasound using specific sequences to induce small mechanical perturbation of the nerve cells, or by subtly raising the temperature of the tissue.

In general, neuromodulatory effects of focused ultrasound could potentially enable a range of diagnostic and therapeutic benefits including:

1. targeting of regions in the brain for ablative procedures
2. suppressing epileptic seizures or symptoms of psychiatric disorders
3. reversible nerve blocks to treat pain
4. brain mapping

Preclinical studies have shown that the mechanical and thermal effects of focused ultrasound can reversibly suppress or stimulate the function of targeted neurons. This enables the temporary blocking or activation of neural signals from targeted locations within the brain or spinal/peripheral nerves. Such techniques hold promise in the treatment of epilepsy or chronic pain (suppression) or for precise brain mapping or treatment targeting (stimulation).

Exciting the immune system to fight cancer

The field of cancer immunotherapy is progressing rapidly with more than 25 FDA-approved drugs now available for the treatment of a range of cancers. Unfortunately, most of these therapies are effective in only around 15 to 20 percent of patients. There are many potential reasons for this modest success.

Some studies have demonstrated that immunotherapies are more effective when there is already a baseline immune response to the targeted antigen prior to treatment. What could be done to illicit this baseline response?

Ablative therapies — radiation, radiofrequency, cryo, laser, focused ultrasound — have all shown the ability to incite an immune response in preclinical and clinical studies. Ablation can awaken the tumor cells' natural defenses and increase the immunogenicity of the tumor. Some therapies such as radiation have been successful when used in combination with an immunotherapy, as a "kick start" to the immune response.

Although not yet demonstrated clinically, focused ultrasound could potentially be effective in combination with an immunotherapy. In addition to inciting the immune response, focused ultrasound could also decrease the level of immune system suppressor cells so the immune response is more robust. Focused ultrasound could be more optimal for this combination therapy than other ablative modalities given its non-invasiveness, use of non-ionizing radiation, and precision.

Furthermore, many preclinical and clinical studies have demonstrated that both the thermal and mechanical effects of focused ultrasound can illicit an immune response that in preclinical studies has led to enhanced overall survival and protection from growth of new tumors when re-challenged. This research suggests that FUS could provide benefit even as a stand-alone therapy for some patients. The recent advances in both cancer immunotherapy and focused ultrasound — whether alone or in combination — could enable powerful new approaches for the treatment of metastatic cancer. Plans are underway for a clinical trial of focused ultrasound coupled with immunotherapy for the treatment of metastatic breast cancer.

Localizing the delivery of chemotherapy

Chemotherapy plays a significant role in the treatment of cancers, extending survival and can lead to long-term remission. However, these positive outcomes are often achieved at the expense of the patient's quality of life — at least throughout the duration of the chemotherapy regimen. The systemic toxicity of chemotherapy can make it an undesirable or impractical course of treatment for many patients. Imagine a treatment modality that could enable localized chemotherapy, delivered in high concentration precisely where it is needed yet minimizing the systemic effects. Focused ultrasound has the potential to do just that.

In this process, a drug is encapsulated in or linked to carrier vehicles (e.g. microbubbles, liposomes, nanoparticles) that are sensitive to either elevated temperature or ultrasound pressure. This encapsulation prohibits the drug from interacting with its surroundings as it is injected into the bloodstream and diffuses throughout the body. During the procedure, ultrasound is focused on the target area (e.g. tumor), triggering the carriers to release the drug which is then quickly absorbed by the surrounding tissue. Triggering can be achieved by either mild thermal rise or through mechanical perturbations at the focus. Although the encapsulated drug is present throughout the entire body, the focal disruption of the carrier — the release of the drug from the carrier — enables very high drug concentration delivered to a precise location, while minimizing the systemic toxicity.

Beyond ablation

The development trajectory of focused ultrasound is broadening beyond ablation as the technology moves toward the clinic. Hospital systems who wish to maintain a competitive edge in the new environment will benefit from its potential to reduce risks by replacing traditional surgery, optimize chemotherapy and immunotherapy, increase patient treatment rates, lower costs, and ultimately help improve the overall health of the population.

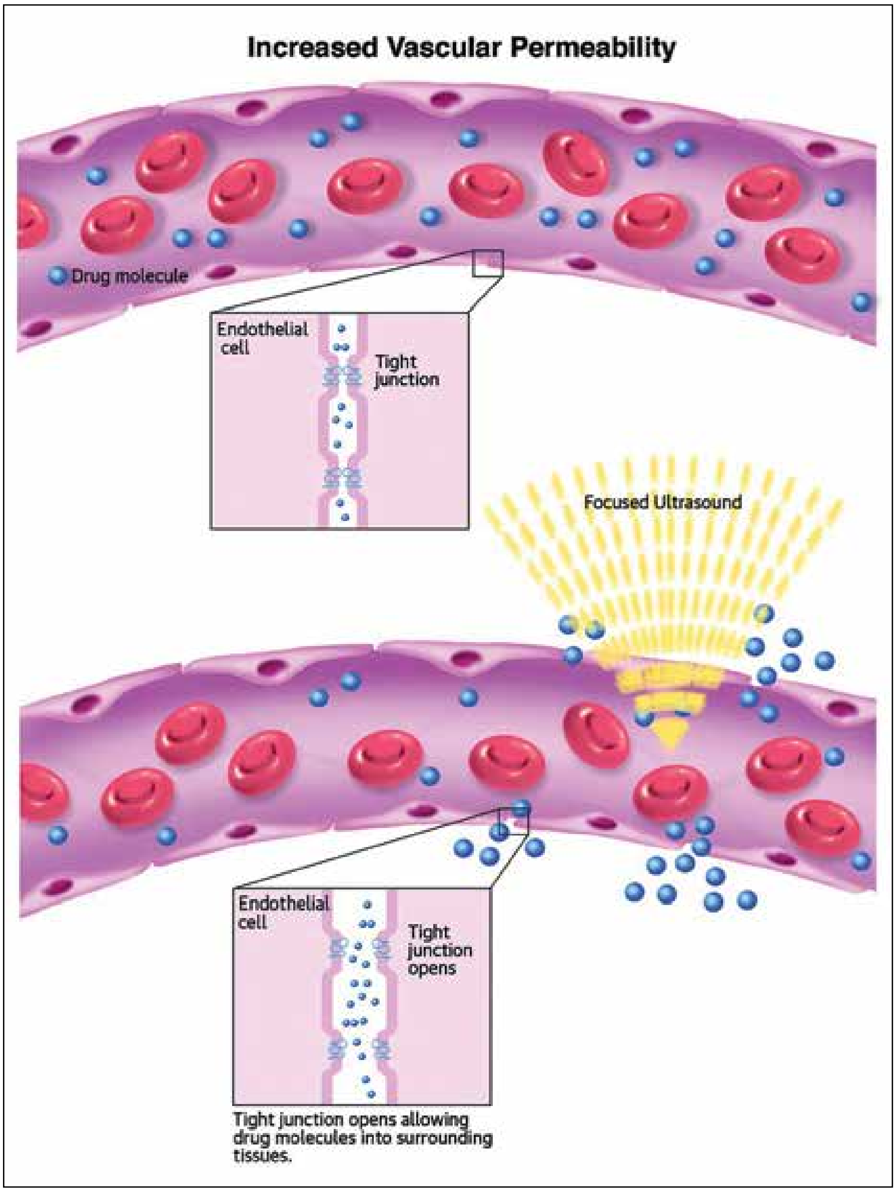


Figure 3: Focused ultrasound can loosen the dense network of endothelial cells joined by tight junctions that line the blood vessels in the brain, enhancing the release of drugs from the bloodstream into the brain tissue.

About the author: Jessica L. Foley, PhD, is the Scientific Director of the Focused Ultrasound Foundation. Dr. Foley joined the Foundation in 2012 after completing a one-year AAAS Science and Technology Policy Fellowship at the National Science Foundation. Prior to that, she was the Neuro Projects Manager and Clinical Marketing Manager at InSightec, one of the pioneering focused ultrasound medical device manufacturers. Other previous experience includes senior scientist at Medtronic. She has numerous publications, patents, and presentations at academic conferences in the field of focused ultrasound.

About the Focused Ultrasound Foundation: The Focused Ultrasound Foundation was created to improve the lives of millions of people worldwide by accelerating the development of this non-invasive technology. The Foundation works to clear the path to global adoption by coordinating and funding research, fostering collaboration, and building awareness among patients and professionals. The Foundation is dedicated to ensuring that focused ultrasound finds its place as a mainstream therapy for a range of conditions within years, not decades. Since its establishment in 2006, the Foundation has become the largest non-governmental source of funding for focused ultrasound research.

Share this story: dotmed.com/news/24828