Focused ultrasound therapy for brain tumours

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What is Focused Ultrasound (FUS)?

Focused ultrasound (FUS) waves can be used to create kinetic energy and vibrations that result in both mechanical and thermal damage to targeted tissue. There is increasing clinical research investigating the use of FUS for the treatment of brain tumours. FUS represents an attractive therapeutic option for difficult surgical targets (e.g. deep-set tumours), as well as for more aggressive, treatment-resistant tumours (e.g. glioblastoma (GBM)) (2,3).

The main clinical advantage of FUS is that it is an "incisionless" method of surgery. The FUS waves have the capability to reach a desired brain region without the need for general anaesthesia, or exposure of underlying skull or brain. It is potentially a repeatable outpatient 'daycase' procedure, which minimises time in hospital and allows patients more time at home with family. Additionally, the accuracy of FUS ensures damage only occurs in desired locations (i.e. tumour), and not to adjacent healthy tissue.

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There are different methods of delivering FUS.

The most clinical trial progress to date has involved the use of a helmet containing 1024 ultrasound transducers that a patient wears whilst entering a magnetic resonance imaging (MRI) machine. MRI-guided focused ultrasound (MRgFUS) allows for precise definition of the target tissue at millimetre resolution as well as real-time temperature evaluation of lesional effects during the procedure. Other methods of delivering navigated FUS trans-cranially include large-field moveable arrays, or a water-filled rubber cap embedded with ultrasound transducers. Other clinical trials have started using an implantable device that is embedded within the skull after initial brain surgery. The latter device uses less FUS energy as it bypasses the relatively thick human skull. However, the target tissue is limited to being near the site of previous surgery.

MRgFUS is already approved for use in patients with essential tremor, where FUS waves are targeted to the "tremor centre" of the brain - the thalamus. FUS-induced thermal lesioning results in a satisfactory improvement of tremor in approximately 80% of cases (1).

For brain tumours, FUS represents a useful therapeutic tool with two main applications:

1. Reversible opening of the blood-brain barrier (BBBO): which can enhance drug delivery, potentiate the release of tumour biomarkers for liquid biopsy, and induce tumour microenvironment (TME) disruption. The TME is the ecosystem of cells, molecules, and blood vessels that surround and support a tumour.
2. FUS-induced activation of sonosensitisers: which induce selective brain tumour cell death (sonodynamic therapy).

Drug Delivery

A small clinical safety trial (NCT03712293) looked at the potential for MRgFUS to increase the efficacy of the chemotherapy agent temozolomide via BBBO in six GBM patients, where the BBB was opened during the six concomitant TMZ treatments that patients receive as standard of care after radiotherapy (5). After one year of follow-up, there were no immediate or delayed complications, demonstrating that FUS-induced BBBO (to enhance intracranial uptake of temozolomide) is safe and repeatable. Other Phase 1 and 2 clinical trials using different FUS delivery devices and various chemotherapy agents are currently underway in the USA and Canada.

FUS-induced BBBO is also an attractive therapy for brain metastases (BMs), as has been demonstrated for increasing delivery of Herceptin for HER2+ breast cancer metastases (6). It is less invasive than standard therapies, doesn't involve ionizing radiation, and is a repeatable therapy. Considering this, the ongoing clinical trial NCT05317858 (LIMITLESS) is investigating the use of FUS-induced BBBO to increase the efficacy of the immunotherapeutic agent pembrolizumab for BMs secondary to non-small cell lung cancer (NSCLC) (7).

Liquid Biopsy

FUS-induced BBBO is also being trialled to facilitate liquid biopsy of brain tumours. Liquid biopsy is the sampling of blood to retrieve tumour-related gene information (circulating cell-free DNA) without invasive biopsy via craniotomy. FUS-induced BBBO would allow more of this DNA to enter the blood stream and potentially enable early detection of tumour-related gene mutations (i.e. gene profiling) and personalisation of anti-cancer therapies.

This may be particularly helpful in the treatment of BMs. Some BMs harbour actionable mutations that can be targeted with specific therapies (e.g. HER2 mutations in breast cancer, ALK rearrangements in NSCLC) (8).

FUS-facilitated liquid biopsy could also be helpful for differentiating tumour recurrence from pseudo-progression for tumours previously treated with surgery or radiotherapy.

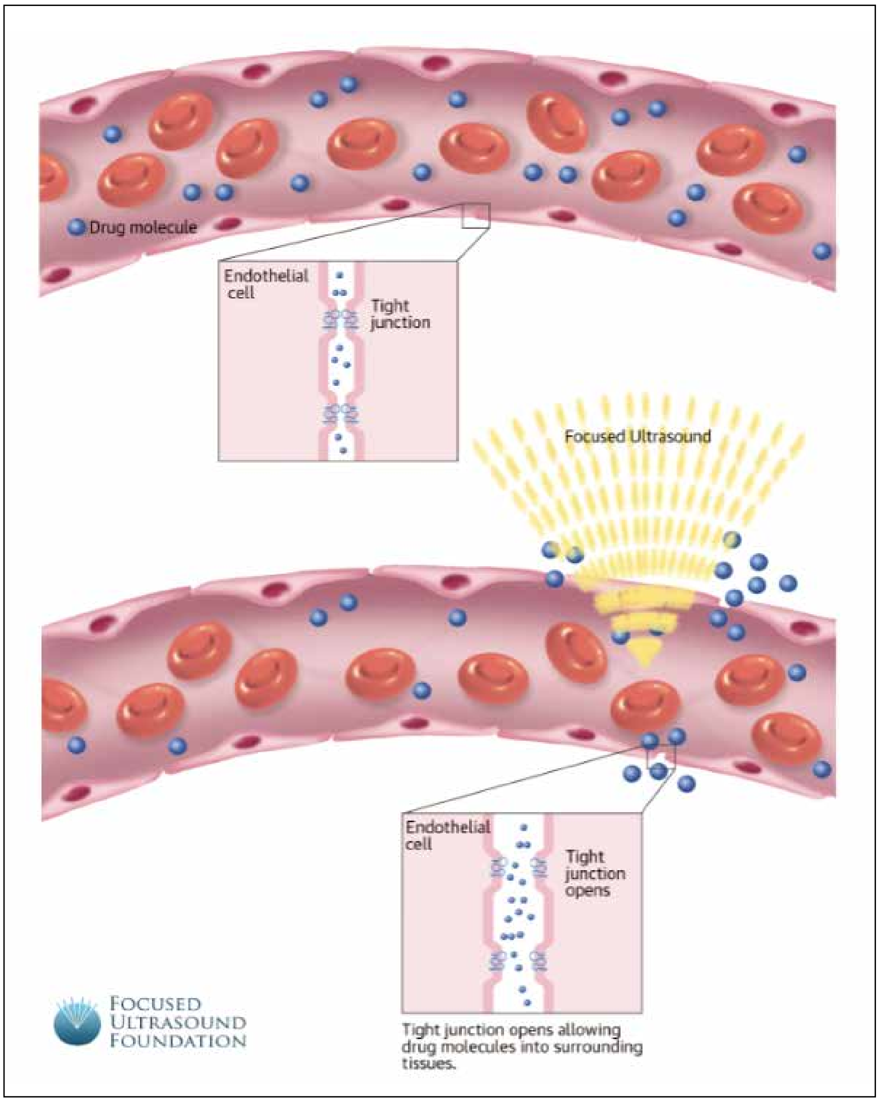

Figure 1: Blood brain barrier (BBB) opening to deliver drugs: The BBB is impermeable to most drugs. However, FUS represents a method of transiently and reproducibly opening this barrier, allowing drug molecules (indicated as blue spheres in the above figure) such as chemotherapy agents (e.g. temozolomide) to enter the brain that normally could not. Drug molecules are now able to move out from the endovascular space (the space where blood flows inside blood vessels) and into surrounding brain tissue due to FUS-induced opening of tight junctions that span between adjacent endothelial cells.

Sonodynamic Therapy (SDT)

Sonodynamic therapy (SDT) is the application of FUS in combination with a chemical agent to trigger 'apoptosis' (cell death which occurs as a normal and controlled part of an organism's growth or development). The chemical agent used is termed a 'sonosensitiser', as its anti-tumoural effect is activated by the FUS waves. Sonosensitisers are tumour-specific, meaning that they preferentially accumulate within tumour cells, whilst avoiding surrounding healthy brain tissue (Figure 2).

FUS delivery releases energy that brings the sonosensitiser to an excited state in which it releases reactive oxygen species (ROS), specifically in the tumour cells where it has accumulated. ROS are toxic, highly-reactive chemicals capable of damaging DNA and cellular membranes, as well as triggering the activation and expression of pro-apoptotic genes within target tumour cells.

Blood-brain barrier opening (BBBO)

The blood-brain barrier (BBB) is composed of endothelial cells and tight junctions which join them. The BBB also contains selective transporters that protect the brain from toxins and pathogens. Unfortunately, the BBB also represents an obstacle to the treatment of brain tumours by hindering the entry of chemotherapeutics, targeted treatments, and immunotherapies into the central nervous system.

A key attraction of FUS is that it has been shown to induce transient and reproducible BBBO and enhance drug delivery (Figure 1). Low-intensity FUS in combination with microbubble (MB) injection has now become the primary method for BBBO – whereby the previously injected MBs oscillate (expand and contract) at the frequency of the FUS waves upon passing through the sonication. This disrupts elements of the BBB for approximately 24 hours (4), which allows drugs to enter the brain or tumour

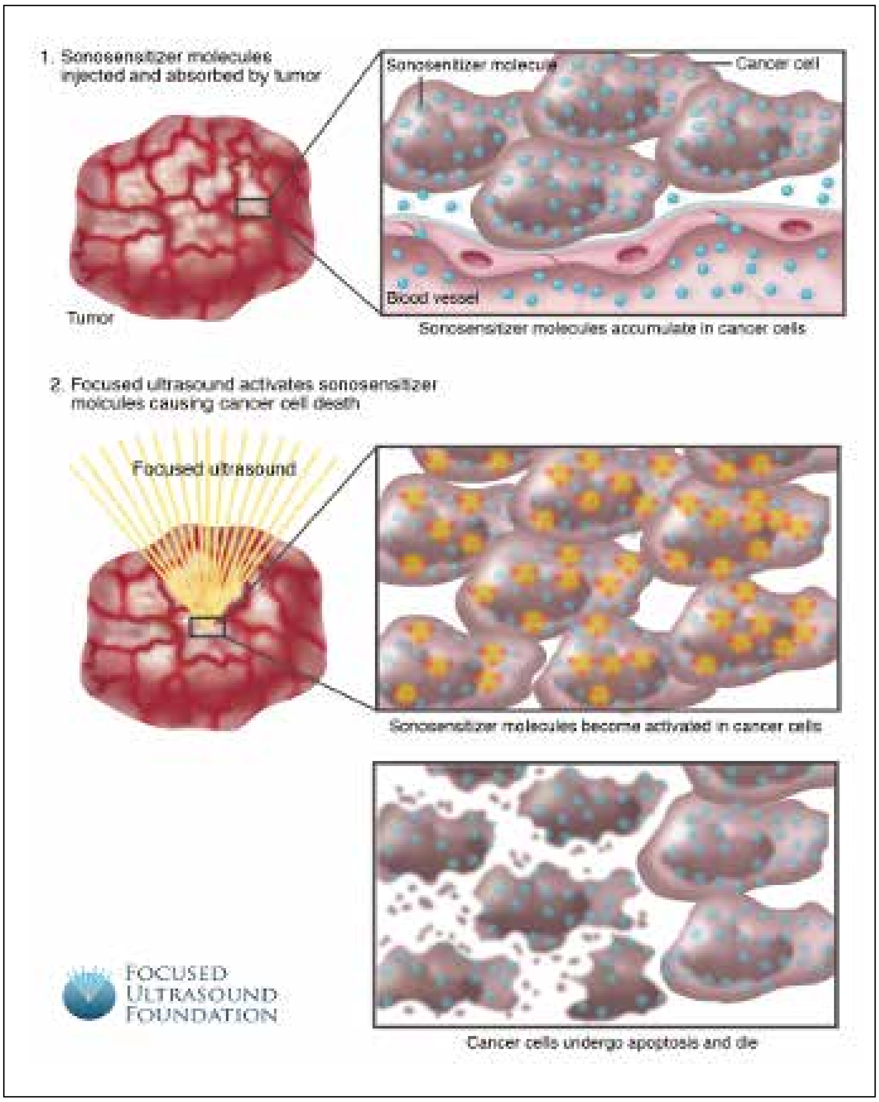

Figure 2: Sonodynamic therapy (SDT). Sonosensitiser molecules (indicated as blue spheres in the above figure) are ingested or injected and selectively absorbed by tumour cells. Subsequent exposure to FUS waves activates the sonosensitizer that has already accumulated in tumour cells – triggering tumour-specific cell death.

DNA to leave the brain and enter the circulation.

5-aminolevulinic acid sonodynamic therapy (5-ALA-SDT)

5-aminolevulinic acid (5-ALA) is a sonosensitiser approved for use in aiding surgical resection of GBM tumours. 5-ALA is readily converted by GBM cells into protoporphyrin (PpIX), which selectively accumulates within GBM cells.

The patient drinks 5-ALA prior to surgery. During surgery, shining blue light on the area of the tumour, and the edges surrounding it causes PpIX to fluoresce – making any remaining tumour cells around the resection margin appear pink (2). This visual aid allows neurosurgeons to better differentiate between normal brain and tumour. It optimises safe resection and increases the extent of tumour resection.

5-ALA-SDT is not yet approved for use in GBM patients. However, pre-clinical studies have shown that SDT-mediated PpIX activation can trigger ROS upregulation, and selective cell kill of tumour cells (9). The exact mechanism of PpIX activation is unclear; however, it is hypothesised that there could either be direct activation by the energy generated from rapid collapse of microbubble formation or the FUS waves themselves stimulate the release of a flash of blue light that activates the sonosensitiser.

Emerging clinical trials of FUS in GBM patients show promising results. This includes a recent phase 0 clinical trial (NCT04559685) of 5-ALA-SDT in recurrent high-grade glioma patients (10). Patients were given intravenous 5-ALA six to seven hours prior to low-intensity FUS. Cell death was observed within four days of a single treatment, and SDT was well-tolerated in all patients.

Following this success, a phase 2 study for progressive or recurrent GBM patients has been commenced (SDT-202, NCT05370508) (11). In Europe, a group in Milan is trialling the safety of oral ALA in newly diagnosed GBM (Sonic ALA, NCT04845919) There is hope that future trials will demonstrate increased survival rates for patients receiving SDT.

Another research group are also recruiting recurrent GBM patients to trial 5-ALA-SDT (Trial GBM 001, NCT06039709) using a frameless ultrasound delivery device (12). In this trial, patients undergo SDT one to three weeks prior to resection – as opposed to the above trials, where patients have already received previous treatment options. A commercial trial using a similar frameless device has recently reported the results of their Phase 1 study in 12 patients with recurrent high grade brain tumours. They demonstrated safety, lack of side effects and repeatability of SDT, with very encouraging progression-free and overall-survival above historic control results – a Phase 2 study is due to commence in 2025 (13).

A study of 5-ALA-SDT conducted for paediatric patients with diffuse intrinsic pontine glioma (DIPG), SDT-201 NCT05123534 is in the analysis phase but has shown SDT to be safe (14). Even with the current standard of care (conventional fractionated radiotherapy), the average survival for DIPG patients remains around nine to twelve months from diagnosis. The group recruited 15 DIPG patients following standard radiation therapy. They have reported that the first recruited patient tolerated 5-ALA-SDT well – with no adverse effects, and clinical improvement of both walking and double vision.

SDT and effects on distant tumours

It is hoped that SDT could also induce an "abscopal effect". The abscopal effect is a phenomenon where direct therapy to the primary tumour can also promote regression of distant tumours. The observation of SDT to generate an abscopal effect is still largely unexplored.

However, preclinical data suggest that localised SDT has the potential to enhance the body's overall immune recognition of tumour cells and promote immune-mediated destruction of distant tumours (15). This, therefore, makes SDT attractive for treating patients with multifocal brain tumours, or known brain metastases.

Conclusion

FUS could represent a novel progression from the current standard-of-care for GBM patients, as well as other brain tumour diagnoses. However, there is a lack of standardized parameters that provide maximal clinical efficacy, whilst avoiding potential side effects.

Before FUS is approved for clinical use, the safest FUS intensity, transducer frequency, duration and number of cycles, as well as choice and dose of sonosensitiser must be determined (7). We also need to further define eligibility criteria for FUS, including: stage of disease (i.e. primary or recurrent), patient performance status, and degree of comorbidities (medical conditions that a person has in addition their brain tumour diagnosis) (3).

Thus far, FUS has proven to be well-tolerated in patients enrolled in research studies and is associated with fewer local and systemic side-effects than radiotherapy. Additionally, in contrast to standard chemotherapeutics, sonosensitising agents are non-toxic and pharmacologically safe.

FUS represents a uniquely non-invasive and highly selective approach to directly targeting solid tumours (via sonodynamic therapy) (16), as well as increasing the efficacy of existing therapies (via BBBO). These features make FUS particularly attractive as: (i) a first-line option for patients unsuitable for surgery (or other modalities), (ii) a salvage option for patients who have failed with other treatments, and (iii) a method to enhance the effects of standard therapies. ■

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