MRI-guided ultrasound treatment of brain tumours

Kismet Hossain-Ibrahim, FRCS (SN), PhD
Consultant Neurosurgeon
Ninewells Hospital
Dundee

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What can we give to people with GBM when their tumour recurs after chemoRT?

A: something that will target 'a tumour', whatever its mutations

A: something that has minimal side effects

A: something that gets you home quickly
Roadmap - Neuroapplications

- Pain
- Tremor
- Parkinson’s Disease
- Epilepsy
- Brain Tumors Ablation
- Larger volume resections
- Lateral and superficial targeting
- Non-heating properties of US
- Brain Tumors Drug Delivery
- Alzheimer’s BBB
- Neuro-Modulation

- 2013
- 2016
- 2020

- Small volume treatments
- Deep central structures
Advanced Applications – MR-guided Focused Ultrasound
220kHz Investigational Transducer System
Why not ablate brain tumours?

Volume too large
Too peripheral
Risk of intracranial bleed

NB: 1st ever treatment at the Brigham resulted in collateral damage and one (out of 3 patients) died of an intraventricular haemorrhage

Since then: better thermal mapping and peri-procedure imaging has allowed 1500 treatments in essential tremor without a single stroke or serious untoward event.
Harvard trial (McDannold, 2010)

Proof of concept trial (using a mask)

Problems:

Heating of skull (1 of 3 patients in pain due to dura from brain surface heat)

Not enough power to ablate tissue

Limited to deep areas of brain
Zurich Trial (Fandino & Collucia, 2014)

25 sonications applied, with 17 sonications reaching ablative temperatures of >55°C with a maximum of 65°C.

N=3
2nd patient had recGBM 5yrs post-surgery and chemoRT
Examination showed an improvement of his pre-existing right arm paresis; the patient was able to lift the arm above shoulder level post-procedure.

Survived a further 8 mths

https://clinicaltrials.gov/ct2/show/NCT01698437
Zurich Trial (Fandino & Collucia, 2014)

Figure 1. Pre-interventional (left) contrast enhanced coronal MRI illustrating the enhancing tumor mass of a glioblastoma in the left thalami and subthalamic region. Post-sonication (right coronal MRI shows a well-circumscribed partial resolution of enhancement, indicative for ablated tumor tissue. The patient was awake and responsive during the whole intervention.
Zurich Trial: should we continue?

In one patient, an implanted catheter interfered with sonication and resulted in the inability to adequately heat the tumor target.

In another patient, an imaging artefact caused off-focus heating.

But it does not give radiotherapy and it is less invasive than Laser Interstitial therapy (which are the only similar treatments available)
Yes!

Universities of Toronto, Michigan, Zurich Sunnybrook, Virginia et al. performing preclinical research & others starting clinical trials

4 putative mechanisms:
How can MRgFUS be used in brain tumours?

1) Tumour ablation: thermal ablation or histotripsy (non-thermal microbubble-enhanced destruction/ablation) – *I am investigating at UoD with Prof Tim Hales

2) Drug delivery: focal delivery of chemotherapy agents to the brain – enhanced by FUS-induced opening of blood-brain barrier (BBB) – and reducing systemic toxicity of these agents - *lasts 6-8hrs and is reversible

3) Adjunct to immunotherapy: focal delivery of immunotherapy agents and/or stimulating the immune response

4) Treatment adjuvant: radiosensitization, activation of ultrasound sensitive agents (e.g. heat sensitive liposomes, sonodynamic agents*)
Advanced Applications – MR-guided Focused Ultrasound
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NON-THERMAL EFFECTS OF FOCUSED ULTRASOUND

- Therapeutic ultrasound agent is injected
- Low frequency (220kHz) focused ultrasound is applied
- Temporarily disrupt BBB to allow targeted delivery of therapeutic drugs

NCT03322813  N=15 recruiting Oct ’18 – June 2020       Maryland

The extent and reversibility of BBB opening will be determined by the degree of contrast enhancement seen on post-procedure MRI with contrast agent
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Sunnybrook, Toronto: Prolonged survival upon ultrasound-enhanced doxorubicin delivery in two syngenic glioblastoma mouse models

'Focused ultrasound method releases drugs millimeters from targeted brain areas'

Wang et al., Neuron Nov 2018

- Ultrasound-sensitive nanoparticles enable localized drug delivery to the brain
- Ultrasonic drug uncaging allows non-invasive and precise control of brain activity
- Drug effects are limited to the ultrasound focus and by the kinetics of the drug
Immune modulation


Magnetic resonance–guided interstitial high-intensity focused ultrasound for brain tumor ablation

J MacDonell et al.

Has an invasive HIFU probe (allows tissue sampling and no problems of skull thickness)

Describe MrgFUS effects on the immune system in other cancers
Advanced Applications – MR-guided Focused Ultrasound
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- Significant pre-clinical work on BBB disruption and delivery of drugs or other therapeutics
- First in human safety studies of focal opening of BBB have been published (GBM and Alzheimer’s)
- Phase I safety studies of delivering drugs (TMZ) to GBMs have begun
- Technology development work continues to extend ablation from deep brain structures to the cortex for epilepsy or malignant tumours
Summary:

Mechanism unknown
Efficacy unknown
Safety data very promising

Hardware is expensive but it is a potential lifeline for patients with Rec GBM and deep metastases
Developing a New and Gentler Approach to treating Malignant Brain Tumours: A Proposal to use Focused Ultrasound for Glioblastoma Multiforme in Scotland.

Fact: more young people die of brain tumours than any other cancer in the UK & current life expectancy is only 14 months with current treatments.

We, however, believe we have found a treatment to combat this appalling statistic...

Benefits with the MRI-guided focused ultrasound treatment:
- No waiting time - walk out of surgery the same day
- It kills the tumour cells
- No damage to other brain tissues
- No side-effects or radiation build up
- Importantly, our research will determine if it offers a longer life expectancy too.

Our highly specialist team at the University of Dundee and Ninewells Hospital, have a pioneering opportunity for Scotland. A technology that could transform 1000s of lives suffering from brain tumours by using focussed ultrasound waves kill tumour cells whilst the patient lies awake.

Currently surgery, then radiotherapy and chemotherapy is invasive and incredibly debilitating for the patient, requiring long periods of recovery. Malignant brain tumours spread throughout the brain, making it impossible to completely remove with current surgical methods. A very physically and emotionally tough process for patient and family with risk of stroke and weeks spent in hospital wards.

We have already reached half of our £1.2M fundraising target.
Help Scotland become the leading nation on non-invasive day case brain tumour surgery.

Please give us 10 mins of your time to discuss a charitable donation. Let's bring MRgFUS to Scotland, thank you!

Mr Kismet Hossain-Ibrahim (FRCS, PhD)
Consultant Neuroradion, Ninewells Hospital, Dundee

Oct 2018

https://www.youtube.com/watch?v=ZokRTOhZckA