Intraoperative functional Ultrasound (fUS)-imaging during awake and anesthetized neurosurgical procedures

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Observational invasive

Summary

ID

NL-OMON55740

Source
ToetsingOnline

Brief title
fUS-Study

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system, skull and spine therapeutic procedures

Synonym
AVM, braintumor, glioma, vascular abnormality

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Imaging, Neurosurgery, Ultrasound

Outcome measures

Primary outcome

To assess the potential ability of fUS to discriminate between functional and non-functional brain areas using task-specific brain-activity during an awake neurosurgical procedure.

Secondary outcome

To assess the potential use of fUS as a means to discriminate between healthy and pathological tissue (tumor and AVMs) using CBV and/or CEUS CBV measurements to visualize vascularization differences in these tissues during both awake (tumor) and non-awake (tumor and AVM) neurosurgical procedures.

Study description

Background summary

A plethora of methods, tools and techniques have essentially contributed to our understanding of brain functioning. Today, one of the most promising techniques is ultrasound imaging. Recent advances in computing power and the ability to record raw ultrasound signals have enabled a technique called highframe-rate (HFR) ultrasound, which offers images at thousands of frames-persecond. Because of the high temporal resolution, this technique is sensitive for very small Doppler shifts (also called µDoppler), such as those caused by the moving blood inside brain vasculature. The HFR ultrasound technology to measure local increases of CBV as a result of neural activity is referred to as functional ultrasound (fUS). The clinical application of this innovative technique of fUS could have great benefits in fields such as that of neurosurgery.

On a daily basis, neurosurgeons face the difficult task to identify and distinguish pathological tissue such as brain tumors, AVMs and/or ischemic stroke tissue from functional healthy tissue, with the ultimate aim of maximizing excision of pathological tissue and minimizing postoperative

neurological damage. However, visualization of healthy functional neurological tissue, in relation to pathological tissue, both pre- and intra-operatively, remains a significant challenge and bottleneck in the treatment. With the introduction, adaptation and application of fUS to the clinical field of neurosurgery, we will be equipped with a tool that enables us to better delineate pathological from healthy tissue during surgery. Indeed, by relying on the characteristic neurovascular changes that can be specifically associated with functional or pathological neuronal tissue, fUS will allow us to make image-guided decisions during the neurosurgical dissection. With the additional use of the ultrasound contrast agent, the image quality of the vascular structure and dynamics can increase substantially. The higher signal-to-noise ratio that comes with the use of the contrast agent can increase imaging depths to reach deeper tumors, achieve higher resolution to visualize smaller vasculature, and lead to better delineation of tumor boundaries.

With the potential benefits that fUS presents, the research group aims to conduct a first, proof-of-principle study in the clinic, using fUS intra-operatively during the neurosurgical procedure of awake craniotomy for the indication of brain tumor removal.

Study objective

Firstly, to assess the ability of fUS to discriminate between functional and non-functional brain areas using task-specific brain-activity during an awake neurosurgical procedure. Secondly, to assess the ability of fUS to discriminate between healthy vs. pathological tissue such as (vascular) tumor tissue and ArterioVenous Malformations (AVMs), based on differences in microvasculature both in the awake patient group (tumor) and patients under anaesthesia (tumor and AVM). In addition we will assess cerebral blood volume (CBV) of healthy vs tumor tissue using contrast enhanced ultrasound (CEUS).

Study design

Group A: Patients undergoing awake neurosurgery for tumor removal. Based on the (extended) clinical pre-operative fMRI and functional map created by using intraoperative electrocortical stimulation mapping (ESM) (the golden standard during routine awake craniotomy surgery), we will identify and image functional and adjacent non-functional brain areas related to specific tasks using fUS. The tasks used will range from muscle movements to speaking, and will be alternated with control tasks. Additionally, we will subject patients to a post-operative fMRI to further validate the fUS-defined functional areas deeper in the brain. This will be performed in the awake patient group only. In addition we will perform fUS CBV imaging of healthy vs. tumor tissue before and after tumor resection. The fUS imaging will last a maximum of 22 minutes in total, the total scanning time in the fMRI will be max. 1,5 hour. Group B: Patients undergoing anesthetized neurosurgery for tumor or AVM removal. We

will perform healthy vs. tumor- or AVM-tissue fUS imaging before and after tumor resection. The fUS imaging will last a maximum of 22 minutes in total.
Group C: Patients undergoing anesthetized neurosurgery for tumor or AVM removal. We will perform healthy vs. tumor- or AVM-tissue fUS and CEUS imaging. The measurements will be repeated after tumor removal is completed, but before the skull is closed. The total imaging time during the surgical procedure will be a maximum of 22 minutes.

Study burden and risks

As functional mapping using ESM and Ultrasound is already an integral element of awake craniotomy surgery, the nature and extent of the burden for the patient remains limited. The patient will have no burden of the imaging process using fUS and the specific tasks we will ask the patient to perform will be very similar to the tasks already performed during ESM. The tasks together will not take longer than 22 minutes, minimizing the extra time necessary for surgery. In addition, as fUS-imaging is very similar to any type of ultrasound imaging already used in a clinical setting and during awake craniotomy surgery, there will be no additional risks associated with participation. Also, the exposure levels for the fUS imaging sequences (insonification with unfocussed beams) are well below FDA limits. For the non-awake patient group (both tumors and AVMs), a similar situation as described above applies, with the difference that patients will be subjected to tumor- or AVM-imaging only and will not be awake to consciously experience the 22 min. extension of the surgical procedure.
The ultrasound contrast agent used in CEUS, Sonovue, is safe (Sonovue - European Public Assessment Report, 2020) and registered for Doppler measurements. It is already used routinely in EMC's Cardiology department for cardiac function assessments. The most common adverse reactions in clinical trials are headache (2.3%), injection site pain (1.4%) and local injection site reactions including hematoma, warmth and paresthesia (1.7%). There is a very small chance of an allergic reaction after administration of ultrasound contrast agents (0.01%).'
If an allergic reaction occurs during the study, the anesthesiologist will treat the patient with the most suitable medication and appropriate dosage. Additional blood tests will not be required. The risks associated with participation can be considered negligible and the burden can be considered minimal.
Finally, the awake patient group is specifically asked to undergo an additional 1,5 hours of fMRI-scanning, divided over a pre- and post-operative session. As the pre-operative session is already part of the standard clinical procedure, we expect limited additional burden for the patients. For the post-operative session, the duration will be limited to max. 1 hour and the session will be planned after the surgical procedure at a moment best convenient to the patient. There are no risks associated with undergoing the fMRI-scan. The longer duration in the scanner can, however, lead to additional psychological burden/discomfort, especially if the patients is already anxious for the scan.

Taking everything into account, we expect that the extent the burden for the awake patient group (although slightly higher than the anesthetized patients), is acceptable.
Patient participation in the study will, however, lead to the benefit of further determining and increasing the potential use of fUS as a new and highly powerful intra-operative imaging tool, which has the ability to present areas of functional tissue deep inside the brain and show differences in tissue vascularity even when tumor or AVM-tissue appears similar to healthy tissue in an intraoperative setting.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

- Age > 18 years
- Mentally competent, AND
EITHER
• Undergoing awake craniotomy surgery for the indication of tumor removal with ESM already planned in the removal of their tumors
OR
• Undergoing non-awake craniotomy surgery for the indication of tumor removal
OR
• Undergoing non-awake craniotomy surgery for the indication of AVM-removal

Exclusion criteria

- Depression or an anxiety disorder
- Any contra-indication for contrast media Sonovue (Bracco International bv, Amsterdam): known allergy to Polyethylene Glycol or PEG (macrogol) in particular, or to PEG-containing products such as certain bowel preps for colonoscopy or laxatives.
- Pregnant and/or lactating women.
- Not able to provide written Informed Consent

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-10-2018
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	31-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL64082.078.17