A hand-held intraoperative focused ultrasound device to open the blood-brain barrier (BBB)

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Background

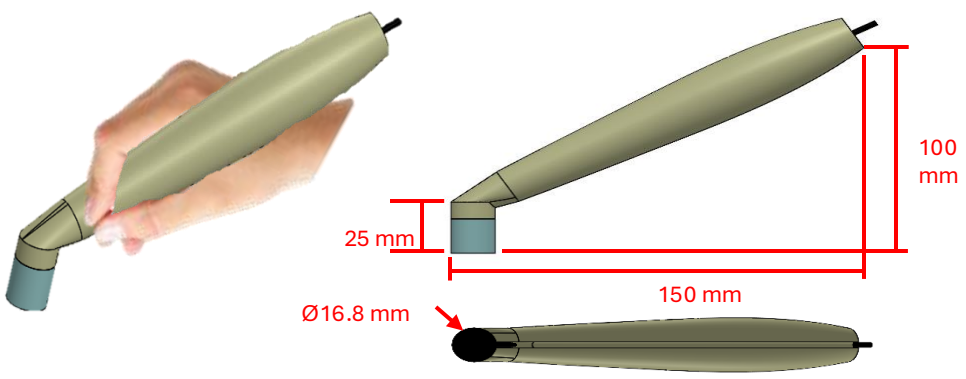
- Incidence of glioblastoma (GBM) ranges from 0.59 – 4 per 100,000.
- Median survival rate is 14 – 16 months.
- GBMs are difficult to treat because:
  - Profoundly immunosuppressive tumor microenvironment (TME), few infiltrating immune cells, limited neoantigen presentation.
  - Blood-brain barrier (BBB) prevents transport of therapies into the tumor and surrounding tissue.
- New tools to change and study the TME during tumor resection can advance the understanding of GBM.

Hypothesis

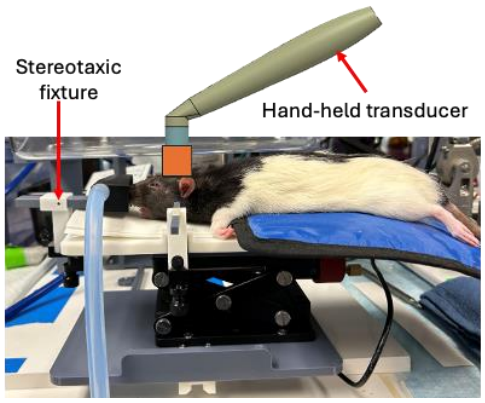
- A hand-held focused ultrasound (FUS) transducer will enable a new technique to study the GBM TME:
  - Focused ultrasound with the hand-held device can be applied while a patient with GBM is undergoing surgical resection.
  - Tumor (roughly corresponding to the contrast-enhanced areas) and peritumoral tissue is exposed.
  - BBB can be opened with the hand-held device in these areas by applying the ultrasound directly to tissue.
  - Drugs that typically do not cross BBB can be administered and TME changes can be observed/measured during the time of resection (approximately 4 hours).
    - Pre- and post-sonication tissue samples can be analyzed and compared.

Preliminary study

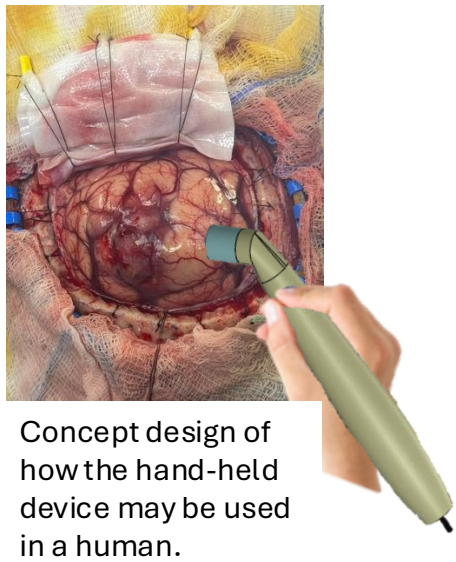
- A single element high frequency transducer was used to open the BBB intraoperatively with microbubbles (Lumason®) in healthy rodents by placing the transducer directly on brain tissue following a craniotomy.



Concept design of the intraoperative handheld FUS transducer.



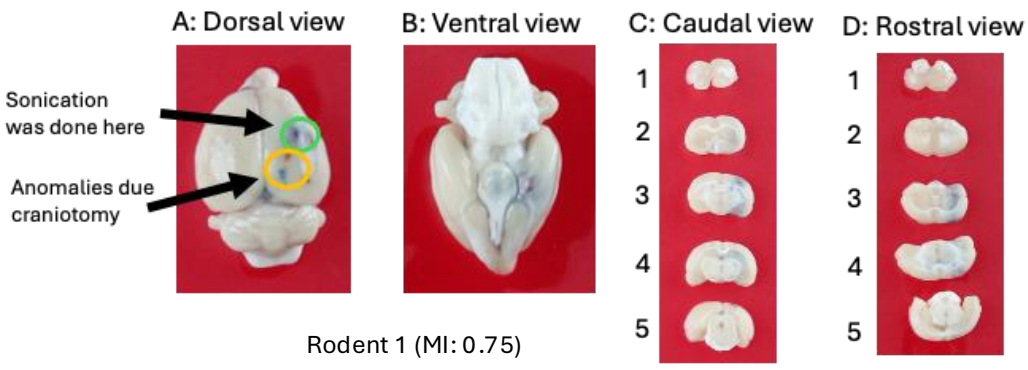
The single element transducer was used intraoperatively by placing it directly on brain tissue. The handle was not used for this study.



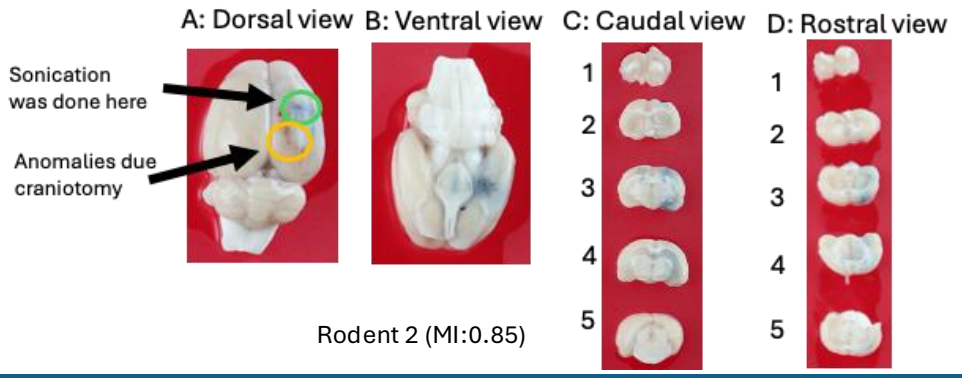
Concept design of how the hand-held device may be used in a human.

- Specifications: 1.6 MHz, 17mm diameter, pulse length of 10 ms, pulse repetition rate of 1 Hz, treatment duration of 180s, acoustic pressures ranged from 0.75 MPa – 1.2 MPa.

Results



Rodent 1 (MI: 0.75)



Rodent 2 (MI:0.85)

Conclusions

- BBB opening with a hand-held transducer format in an intraoperative procedure is feasible as evidenced on rodents.
- This novel technique can allow (1) study of the TME in GBM (2) allow delivery of drugs at the time of surgery at inoperable sites (3) allow liquid biopsy of sites that are not accessible or inoperable during surgery.

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