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Intraoperative Imaging for High-Grade Glioma Surgery

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Intraoperative imaging

Intraoperative imaging, by acquiring and displaying timely information during surgery, provides a beneficial adjunct to glioma surgery. Gliomas can be difficult to differentiate from surrounding tissue making intraoperative estimates of residual tumor inaccurate. During surgical resection, brain shift of as much as 1 cm can occur after craniotomy and dural opening¹ due to CSF egress, diminished mass effect, osmotic diuresis, edema, lesion resection, or intraoperative pneumocephalus^{2,3} These changes render preoperatively acquired images increasingly inaccurate as the surgery proceeds, limiting their usefulness in guiding intraoperative decision-making.

Intraoperative imaging allows visualization of brain shift and other changes which have occurred during tumor resection providing an updated set of images to guide additional tumor resection. The opportunity to perform additional resection reduces the need for return to OR, as residual tumor can be taken after the intraoperative scan and before closure⁴. Intraoperative imaging can also identify intraoperative complications such as hematoma so that these can be promptly managed while the patient is still in OR^{2,4}. Through real time monitoring, intraoperative imaging has led to the development of novel interventions for gliomas including laser interstitial thermal therapy (LITT) and focused ultrasound blood brain barrier disruption (FUS BBBB).

While beneficial, intraoperative imaging and intraoperative MRI (iMRI) in particular also presents several clinical challenges. Between patient set up, scanning time, moving the MRI into and out of the operating room, instrument counts, and safety protocol procedures, iMRI can add over 2 hours to craniotomy². Solutions to some of these inherent problems have been mitigated by establishing iMRI workflows and newer methods that shorten scanning

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times². As newer technology becomes available such as 5-ALA⁵ further studies are needed to establish the relative benefit costs of different intraoperative adjuncts.

Intraoperative Ultrasound (iUS)

The first report of iUS for brain tumors was by Ballantine et al. in 1950.⁶ Original ultrasound techniques were first developed using 2D B-mode. This technology is based on pulsed acoustic waves that are reflected off the tissue of interest and detected at transducers to display their properties based on time and scattering. Most neurosurgical transducers operate within 1-25MHz and provide up to 10cm of depth penetration. A basic principle is that the higher the frequency, the better the resolution closer to the probe, however, higher frequencies have less penetration and hence less ability to image deeper structures (ex. 25MHz can provide maximum resolutions only a few centimeters from the emitting source).⁷ Most often, the transducer type is determined by tumor size, craniotomy, anatomy of interest, and surgeon preference. iUS has significant advantages in that it has a lower cost of purchase and upkeep, takes up less OR space, is less disruptive to workflow, and may be available in settings in which intra-operative MR imaging is not available.⁸

Integration with Neuronavigation and Brain Shift

iUS has been an effective tool in maximizing resection of brain tumors⁹⁻¹¹ (Figure 1). Advances in technology have revitalized the use of iUS. Most US systems used in neurosurgical operating rooms use 2D B-mode ultrasound. One method of reconstructing a 3D image is to acquire a “sweep” of 2D images while tracking the probe with neuronavigation and rebuilding these into a 3-D dataset. This technique has provided powerful volumetric data that is typically collected by freehand sweeps, mechanical sweeps or a phased array transducer.¹² 3D ultrasound data can then be integrated and fused with pre-operative MRI scans for neuronavigation¹³⁻¹⁷. Research groups have developed 3D US/MRI fusion-based neuronavigation and this approach has been commercialized recently.

Because intraoperative ultrasound offers real-time imaging, it can help by giving updated information regarding brain shift. There are a variety of techniques which have been applied to compensate for brain shift including rigid registration using hyperechoic structures¹⁸, automated non-rigid registration¹⁹⁻²¹, a “pseudo-US” technique²², and vessel registration²³. iUS is often compared to iMRI as both can provide updated imaging in the operating room. There are no randomized controlled trials, comparing iUS to iMRI, but there are mixed reviews showing less sensitivity in detecting small residual tumor volumes.^{10,11,24,25}

Artifacts in intraoperative US

Although iUS usefulness improves with surgeon experience, there are conditions present during surgery such as blood products that can make interpretation variable and challenging. For instance, sound waves transmit through air at 330 m/s, saline at 1,480m/s, and brain tissue around 1,550 m/s.²⁶ This can produce errors in location of approximately 1.6mm, 10cm from the transducer. A clinically significant problem is that there is an artifactual hyperechoic signal due to changes in impedance at the margin of the fluid filled resection cavity and the surrounding parenchyma which makes interpretation of the images

particularly challenging in the area of greatest clinical concern. Recently, a promising acoustic coupling fluid has been developed to reduce this artifact, and is currently in phase 1 clinical studies ²⁷.

Advanced iUS Modalities

There are a number of advanced ultrasound modalities currently in development. One promising well-studied technique, ²⁸ is contrast enhanced ultrasound (CEUS). CEUS utilizes a microbubble based contrast, similar to that used in echocardiography, which can outline gliomas, differentiate between tumor/edematous brain, provide grading information, show dynamic arterial/venous phases of the lesion, and be integrated to navigation systems as described above ^{29,30}. A recent review from our group, highlights the current state of the art. ³¹

Intraoperative MRI (iMRI)

Intraoperative MRI (iMRI) in neurosurgery started at Brigham & Women's Hospital (BWH) in Boston, MA in 1994 (Figure 2) ^{2,32,33}. Between 1995 and 2007, over 1,000 craniotomies using iMRI were completed ⁴. General Electric working closely with BWH in the early 1990's developed an open-configuration iMRI consisting of two vertically oriented superconducting magnets with separate communicating cryocoolers in a "double-donut" conformation ^{3,4}. The General Electric Signa System 0.5-T field machine allowed for the patient's head to be placed in the vertical gap between the coils, as close as possible to the magnet isocenter ³, minimizing spatial distortion and signal loss ³⁴ while allowing for access to the patient by the surgeon and assistants. The system had the option of docking the operating table into the magnet sideways or lengthwise, depending on what configuration would maximize patient access ³. The patient was fixed, and the MRI was also fixed; one did not need to move either to acquire iMRI. The main disadvantages of this early system were low field strength, which limited image resolution and the need for all surgical instruments and personnel to be MRI compatible³.

In later iMRI systems, the MRI was fixed, but the patient had to be rotated into the MRI machine, which was placed at a 160 degree angle to the operating room table ^{35,36}. Other open-configuration iMRIs included the Siemens systems, including one with a table that could rotate into and out of a 1.5-T closed-bore magnet, and the Medtronic PoleStar system (Medtronic, Minneapolis, MN) ³. The advantage of these systems was that minimal modifications to OR suites had to be made, unlike the original iMRI. The major disadvantage was again the relatively low field strength ³²

A significant development in iMRIs was the modification of diagnostic closed-configuration MRI scanners for intraoperative use. One system (IMRIS, Deerfield Imaging, Minnetonka, MN) is a rail-mounted system which moves the MRI instrument to the patient allowing for minimal patient movement ^{37,38}. Launched commercially in 2005 and first launched in Europe in 2010 ³⁵, over 60 such systems have been installed worldwide to date ³². A major advantage of iMRI with machines in or adjacent to ORs are that the patient does not need to be moved; therefore, IV lines, catheters, and endotracheal tubes are at less risk of dislodging ³⁵.

To reduce scanning time, which prolongs overall surgical time, iMRI sequences can be tailored to particular types of tumors or lesions². There is no universal iMRI protocol; rather, image sequences are obtained and reformatted into imaging planes and- if further resection is required-merged with stereotactic surgical navigation systems³⁴. The standard sequences obtained during iMRI for glioma resections may include T1 (gadolinium enhanced or non-enhanced) T2, and fluid attenuated inversion recovery (FLAIR) as well as diffusion images³⁹.

Glioblastoma (GBM) and Extent of Resection

Maximal safe surgical resection of GBM is a key part of treatment. There are numerous studies showing a survival benefit with gross total resection of enhancing tumor⁴⁰⁻⁴². iMRI can play a significant role in aiding the surgeon during the resection of GBMs including identifying incomplete resections (Figure 3) and updating the neuronavigation dataset. In a prospective randomized control study, Senft et al. showed that iMRI had more complete resections of the enhancing tumor than controls (96%) and a longer progression-free survival (226 days vs 98 days).⁴³ Another study identified 47% of patients who underwent additional resection because of residual disease identified on the intraoperative scan.⁴⁴ Napolitano et al. also showed in a non-randomized study that patients who underwent iMRI had a 17% improved quality of resection with 9% more gross total resection (GTR) without additional morbidity. iMRI may have an increasingly important role in the future as there is increasing emphasis on maximizing the extent of resection for particular molecular subtypes of GBMs^{45,46}.

iMRI-guided biopsies

iMRI-guided frameless stereotactic brain biopsy can confirm intraoperatively that the biopsy needle has reached its target location and converts a blind procedure into a visualized procedure with high histologic yield^{47,48}. A prospective analysis (June 2009 to April 2011) showed that frameless stereotactic iMRI-guided tumor biopsy increased diagnostic effectiveness and safety and decreased cost⁴⁹. Several systems for iMRI-guided biopsies currently exist. Neurogate (Daum GmbH, Germany) is an MR-compatible device for stereotactic biopsy of lesions⁵⁰. A study of 28 patients between 1997 and 2000 with intracranial metastatic tumors or gliomas who underwent biopsy with Neurogate established stereotaxy in the open MRI as safe and accurate for intracranial biopsies⁵⁰. Other available MRI-compatible biopsy systems include the Magnetic VisiOn (Magnetic VisiOn GmbH, Switzerland), the Heidelberger Interventions-Trajektor (Pilling Weck Chirurgische Produkte GmbH, Karlstein, Germany) and the Navigus trajectory guide (Image-Guided Neurologics, Inc., Melbourne, FL, USA)⁵⁰.

The Clearpoint Smartframe system (MRIInterventions, California, USA) is an MRI-compatible stereotactic tripod system originally developed for MRI-guided placement of deep brain stimulating electrode which can also be used for intracranial biopsies. The system consists of three circular fiducials and a cannula filled with gadolinium contrast⁵¹. It is typically mounted on the scalp through screws that pierce skin and penetrate the outer cranium table, or the frame can be mounted directly on the skull⁵². It provides submillimeter accuracy for stereotaxy⁵¹. Another option is Hall and Truwit's "prospective

stereotaxis” system which uses iMRI to target the lesion, monitor needle advancement, and track progress in real time at one to three images per second, and the needle can be advanced manually or via remote control^{39,53,54}

Laser Interstitial Thermal Therapy (LITT)

The advent of MR thermometry allowed the controlled delivery of laser energy to the brain with near real time monitoring of heating. Thermal therapy emerged from an observation in 1891 that an inoperable sarcoma went into remission after a patient had a febrile strep infection^{55,56}. Treatment of cancer by thermal methods was bypassed in favor of radiation and chemotherapy until its resurgence in 1967, when Cavaliere et al.⁵⁷ proposed that cancer cells may be preferentially vulnerable to heat^{56,57}. LITT was first used to ablate treatment-resistant focal metastatic intracranial tumors, and was then approved by the FDA for use of soft tissue ablation in neurosurgery (Figures 4a and 4b)^{58,59}. Its use was later expanded to glioma surgery.

In a first clinical study of LITT in gliomas, median survival of 16 patients with supratentorial GBM who underwent LITT after first relapse increased from 9.4 to 11.2 months (vs. a natural history of survival <5 months or after temozolomide chemotherapy 5.4-7.1 months)⁶⁰. LITT has been used to ablate newly diagnosed and recurrent GBMs. In a study of 8 patients with newly diagnosed and 13 patients with recurrent GBMs, LITT extended median survival from 2 to 8 months in newly diagnosed GBM; median survival of patients with recurrent GBMs who underwent LITT was 7 months, suggesting LITT may be an effective salvage therapy⁶¹. LITT can also be used in cases of radiographic progression, especially when patients have few other salvage treatment options⁶².

MR-guided LITT is a major advancement because it allows for monitoring of ablation in real time with MRI⁶³. Without MRI guidance, LITT harbored an unacceptably high risk of thermal damage to the surrounding healthy brain⁶³. The Visualase System by Medtronic is an MRI-guided laser ablation system used in the US since 2007. It gained CE approval in March 2018^{64,65}. The Neuroblate System by Monteris is currently the only robotic LITT system⁶⁶. iMRI-guided LITT may be a safer alternative to patients in whom GBM is not accessible by surgery or in patients who are not surgical candidates due to medical comorbidities or other risks⁶⁷.

Intraoperative computed tomography (iCT)

iCT for glioma surgery was first described in the 1980s.⁶⁸ The initial limitations were image quality and hardware artifact⁶⁹. Current systems available include a multidetector CT which provides high resolution images of the soft tissue, or the cone-beam CT which provides better bony resolution with decreased cost and radiation exposure⁷⁰. Although the imaging quality when compared to iMRI of intra-axial malignant tumors is poor, there is a significant advantage in terms of acquisition time, cost, maintenance, workflow and avoidance of room logistics such as magnetic shielding.

Because iCT offers the ability to image with the patient’s head fixed in pins, it can be used to update neuronavigation, accommodate for brain shift, and obtain vascular imaging.⁷¹

This has also paved the way for automated registration techniques using a low-dose CT scan to reduce mean target registration errors to under 1mm.⁷² One study showed the workflow interruption to obtaining an intraoperative scan is around 10-15 minutes with one of their 7 glioma patients needing further resection after the intraoperative scan.⁶⁹

Conclusion

Intraoperative imaging is a useful adjunct to achieving a maximally safe resection during high-grade glioma surgery. There are a variety of modalities available including iMRI, iUS, iCT all of which aim to give the surgeon more information, address brain shift, identify residual tumor, and increase the extent of surgical resection.

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Synopsis:

This chapter includes intraoperative imaging techniques used during high-grade glioma surgery. Intraoperative imaging helps to alleviate problems encountered during glioma surgery such as brain shift and residual tumor. The chapter starts with a brief introduction followed by a review with the latest advances in intraoperative ultrasound, intraoperative MRI, and intraoperative CT.

Key Points:

Intraoperative imaging allows accommodation of brain shift, identifies residual tumor and increases extent of resection. Intraoperative imaging techniques include ultrasound, MRI and CT.

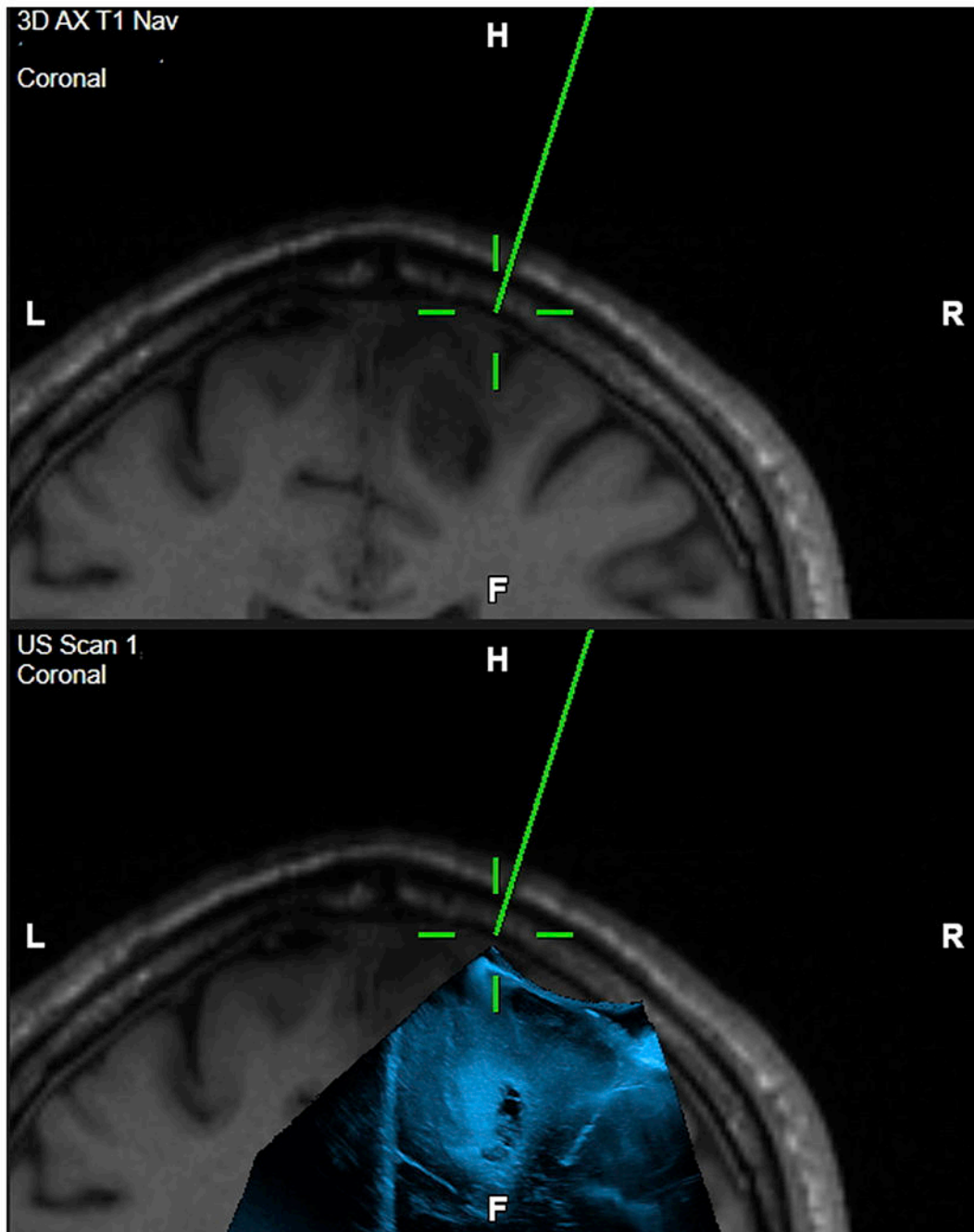


Fig. 1. Navigated iUS fused to a preoperative T1-weighted MRI image of a glioma. Navigated iUS allows for accommodation of brain shift showing shift of the hyperechoic tumor relative to the registered preoperative MRI.



Fig. 2.
The AMIGO suite for image-guided surgery at Brigham and Women's Hospital.

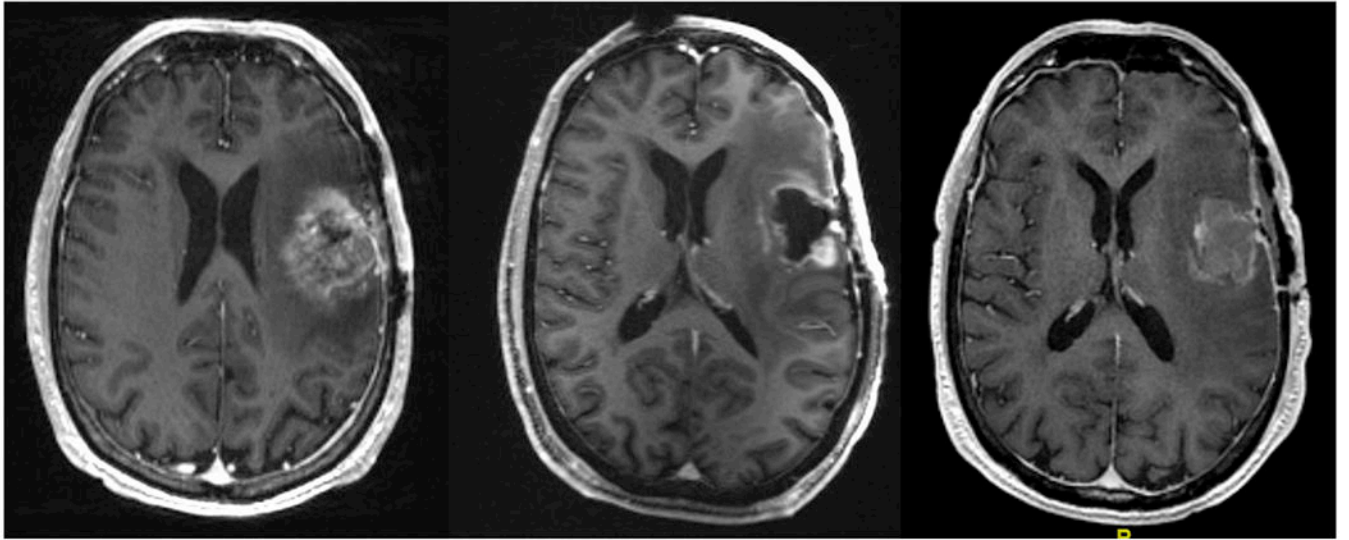


Fig. 3. Preoperative contrast-enhanced T1-weighted MRI of a recurrent GBM (*left*), intraoperative contrast-enhanced T1-weighted MRI showing residual tumor under the lip of the resection edge (*middle*), postoperative T1-weighted contrasted MRI showing gross total resection of enhancing tumor (*right*).

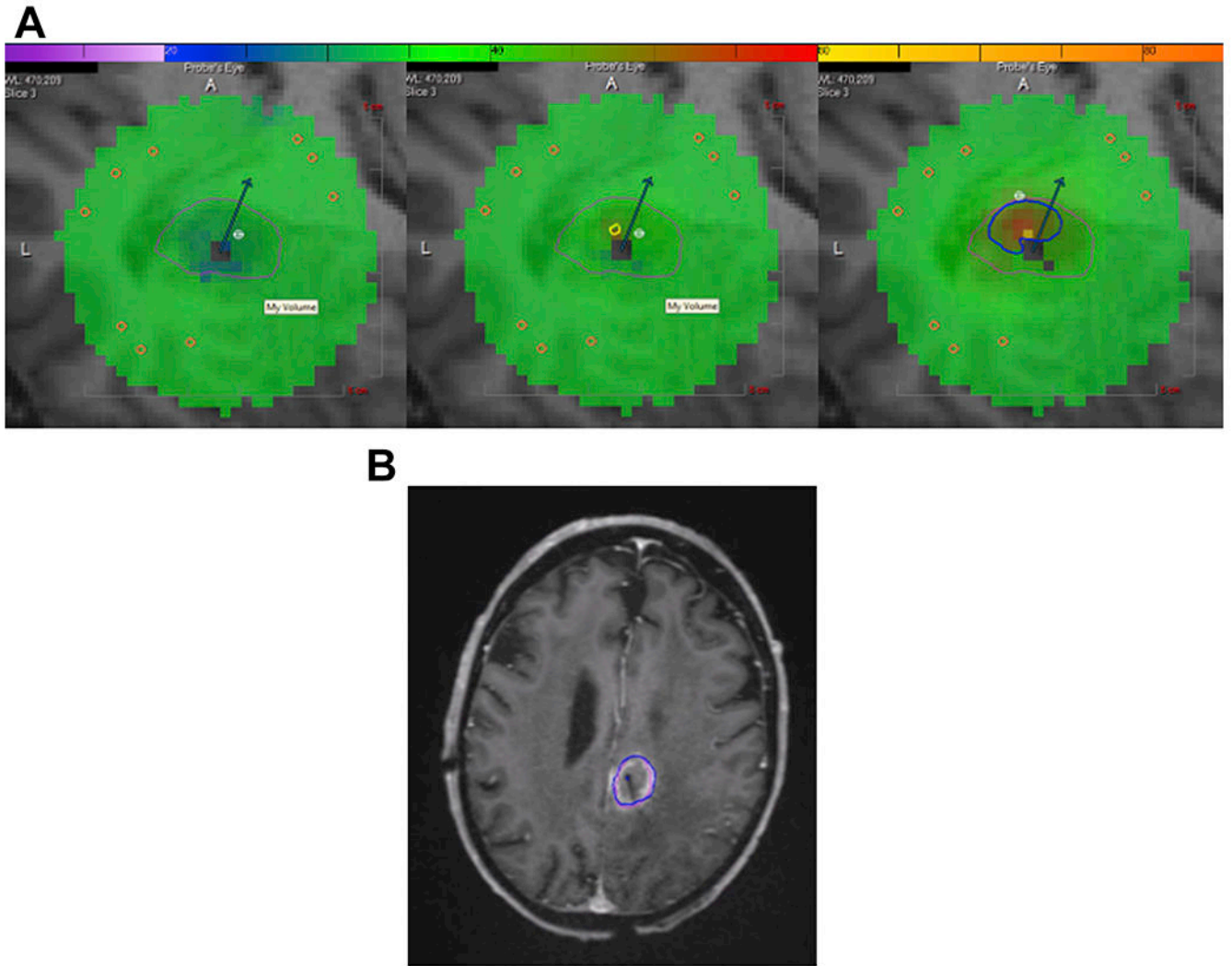


Fig. 4. (A) Magnetic resonance thermometry allows the operator to assess relative temperature maps in real-time. The three panels are the same slice taken at different time points in the ablation. (Left) The tumor (pink outline) preablation with a cooler center (bluish hue) as cooled CO₂ is sent around the catheter tip. (Middle) The same slice midablation with a relative warming up of the center of the catheter (greenish hue) and the beginnings of the thermal damage estimate beginning to appear (yellow). (Right) Further warming (reddish hue) and larger thermal damage estimate. (B) LITT ablation procedure performed in iMRI using magnetic resonance thermometry sequences to derive thermal damage estimates.

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