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‘Extra-operative’ MRI (eoMRI) for Brain Tumor Surgery – Initial Results at a Single Institution

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Abstract

Background—There is accumulating evidence that extent of resection (EOR) in intrinsic brain tumor surgery prolongs overall survival (OS) and progression-free survival (PFS). One of the strategies to increase EOR is the use of intraoperative MRI (ioMRI). However, considerable infrastructure investment is needed to establish and maintain a sophisticated ioMRI. We report the preliminary results of an extra-operative (eoMRI) protocol, with a focus on safety, feasibility and EOR in intrinsic brain tumor surgery.

Methods—Ten patients underwent an eoMRI protocol consisting of surgical resection in a conventional operating room followed by an immediate MRI in a clinical MRI scanner while the patient was still under anesthesia. If MRI suggested residual safely resectable tumor, the patient was returned to the operating room. Retrospective volumetric analysis was undertaken to investigate the percentage of tumor resected after first resection and if applicable, after further resection.

Results—6 out of 10 (60%) patients were felt to require no further resection after eoMRI. The EOR in these patients was $97.8 \pm 1.8\%$. In the 4 patients who underwent further resection, the EOR during the original surgery was $88.5 \pm 9.5\%$ ($p = 0.04$). There was an average of 10.1 % more tumor removed between the first and second surgery. In 3/4 (75%) of patients who returned for further resection, gross total resection of was achieved.

Conclusion—An eoMRI protocol appears to be a safe and practical method to ensure maximum safe resections in patients with brain tumors and can be performed readily in all centers with MRI capability.

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Keywords

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Introduction

There is growing evidence that the extent of resection (EOR) in intrinsic brain tumor surgery prolongs overall survival (OS)^{13,17} and progression-free survival (PFS); in cases of low-grade gliomas, it may even deter high-grade transformation^{3,19}. One of the strategies to increase EOR is the use of intraoperative MRI (ioMRI)^{11,12,18}. As one of the first institutions to implement ioMRI, we have had a significant experience in the use of this imaging modality to assist with surgical resections of intrinsic brain tumors⁶. However, the implementation of clinical ioMRI requires considerable investment in infrastructure and personnel⁴. This may not be practical for all centers doing brain tumor surgery especially in the current healthcare climate. Furthermore, even in centers featuring a functioning ioMRI suite, the demand to use such a suite not uncommonly exceeds the capacity of the ioMRI to accommodate all brain tumor surgeries. In this scenario, a complementary method of using MRI during surgery to assess extent of resection may be additive.

To ensure that all patients receive the benefit of immediate high quality perioperative imaging guidance for maximum EOR, we have recently implemented an 'extraoperative' MRI (eoMRI) protocol. This protocol (described below), consists of transporting patients to a nearby clinical MRI scanner after maximum safe resection was felt to have been accomplished and before extubation, if the case was done under general anesthesia, or full awakening if done under monitored anesthesia care (MAC). If during eoMRI it was felt that a greater extent of safe resection could be accomplished, patients are transported back to the operating room. Otherwise, they are awakened in the intensive care unit (ICU).

We report below preliminary results of this eoMRI protocol, with a focus on safety, feasibility and EOR in intrinsic brain tumor surgery.

Methods

The study was performed under the supervision of the Partners Health Care and Brigham and Women's Internal Review Board (IRB). Adult patients that were seen by the senior author (I.D.) and were consented for possible extraoperative MRI (eoMRI) and second resection. Intraoperatively, if the senior author felt that immediate feedback about the EOR was important, patients were included in the study. This was based upon tumor location, imaging characteristics and whether or not the intraoperative MRI (ioMRI) suite was available.

This protocol consists of patients receiving standard of care preoperative imaging and intraoperative neuronavigation, microsurgical and ultrasound-guided resection. Patients were induced in the usual fashion with the sedative, propofol 1.5- 2.5 mg/kg and vecuronium, a nondepolarizer muscle relaxant to facilitate endotracheal intubation. The anesthetic was maintained with total intravenous anesthesia (TIVA) consisting of propofol

75-200 ug/kg/min and remifentanyl 0.10 - 0.20 ug/kg/min throughout the procedure depending on the level of surgical stimulation. Neuro-monitoring was commonly employed to assess motor-evoked and somatosensory-evoked potentials if sensorimotor tract integrity was a concern. Two patients were done awake under MAC anesthesia for intraoperative language assessment.

After the surgeon has completed what is felt to be the maximum resection, the craniotomy is closed in standard manner. At the time of closure, the clinical MRI suite is alerted so as to make sure that there is no wait time between closure and imaging. The patient remains intubated or under MAC anesthesia, is ventilated with a portable ventilator if necessary, and is transported to a nearby clinical MRI suite where the patient undergoes a pre-defined MR imaging protocol (discussed later) to assess for tumor residual. We currently maintain sterility in the operating room, even after the patient leaves, in anticipation that they might return based on imaging findings, outlined below. During transport all patients are monitored with a 5 lead electrocardiogram, a pulse oximeter and invasive blood pressure measurement via a radial artery catheter. The transport general anesthetic was maintained with propofol 50-75 ug/kg/min and remifentanyl 0.1 ug/kg/min. MRI safety procedures prohibit introducing standard MRI unsafe portable ventilators and intravenous pumps into the scanner room. As such, the patient must be switched to an MR-safe ventilator before entering the MR scanner room. While it is acceptable to also switch the patient to an MRI safe IV pump before bringing the patient into the scanner room, in order to save time compared with switching the pump, in our institution the patient's IV tubing was re-routed from the portable intravenous pump outside the scanner room through wave-guides in the MR room shielding. This requires that the Henora (Henora Gainesville, FL) 360 inch coiled MRI extension intravenous set be used, which is of sufficient length and compatible in the MR homogenous field.

Using a clinical 1.5 T MRI, a variety of MRI sequences are run, depending on the original imaging characteristics of the tumor. The sequences required to decide if further resection is necessary are run first. These sequences are reviewed on the scanner console without interrupting the MRI acquisition protocol. With the aid of an attending neuroradiologist, a decision is made whether maximum safe resection has been achieved. If it is felt that there may be residual tumor that is safe for resection, the scan is stopped and the patient is returned to the operating suite for further resection (see Figure 1 for detailed flowchart). If needed, an additional navigation sequence may be acquired before the patient is removed from the scanner and is used for re-registration upon reoperation. If in the surgeon's judgment a complete resection or maximal safe resection has been achieved, the remainder of a standard post-operative MRI is completed before the patient is transferred to the ICU for extubation or full awakening.

Volumetric Analysis

Semi-automated and manual 3D volumetric analysis was done retrospectively using commercially available software (iPlan Cranial Version 3.0.3, Brainlab AG, Westchester, Ill). For tumors with a significant contrast enhancing component, the enhancing tumor volume was measured preoperatively, extraoperatively and postoperatively. For non-

enhancing tumors, the volume of tumor on FLAIR T2 weighted images was segmented manually.

Results

Between January 2012 and December 2013, 10 patients underwent eoMRI protocol. Table I summarizes the preoperative clinical characteristics of the patients.

Technically successful eoMRI was achieved in all 10 patients enrolled (Table 2). Of these patients, 4 (40%) were assessed to have residual tumor that could be safely resected after their first stage resection and were taken back to the operating suite for a completion of their resection (Table 2). In the patients deemed to have a good initial stage resection that did not warrant a second stage operation the percentage of tumor removed was $97.8 \pm 1.8\%$, while in those returning for a second stage resection the percentage of tumor removed was $88.5 \pm 9.5\%$ ($p = 0.04$) (two-tailed Student t-test) during their first stage surgery (Figures 1 and 2). All four patients who were taken for second surgery had preoperative imaging demonstrating only slight (one patient) or no (three patients) contrast enhancement on T1 enhanced imaging and hyperintensity on FLAIR T2 weighted imaging. All four of these patients had final pathology of Grade II or III glial tumors.

The average time between second incision and time of out of the room from the first surgery was 1.6 ± 0.2 hours, which includes time for transport, MRI and re-draping and prepping the patient. The average time for the second surgery was 1.7 ± 0.2 hours. For the patients that underwent further resection, there was an average of 10.1 % more tumor removed between the first and second surgery. In 3/4 (75%) of cases that returned for further resection, there was a gross total resection achieved.

Discussion

Although no class I evidence exists, there is increasing evidence that EOR correlates with survival in glioma patients^{3,13,17}; this has spurred technological advances in the past 10-20 years all in the hopes of increasing the EOR in brain tumor surgery. These technologies include improved microsurgical technique, intraoperative neuronavigation, the use of fluorescent markers and ultrasound to delineate tumor margins and advanced imaging techniques for preoperative planning and intra-operative assessment of resection extent^{2,9,20}.

Although the evidence for the use of these technologies varies in terms of strength, a central tenet is that they are used as adjuncts to help the neurosurgeon perform the maximum resection possible, with the important caveat of not leaving the patient with a new neurological deficit¹⁵. It is because of this caution that for tumors in or close to eloquent cortex, gross total resection (GTR) may not always be possible. In a retrospective study of over 500 patients with histologically confirmed glioblastoma multiforme (GBM), subtotal resections (STR) were more likely to occur for those tumors residing in presumptive Broca's and Wernicke's areas⁷.

There is a large body of literature that suggests that early postoperative imaging is the best modality the best way to accurately categorize extent of resection ²¹. There is a rather poor correlation between surgeon assessment of extent of resection and what is seen on imaging ¹. Moreover, there is evidence that waiting more than 48 hours for postoperative imaging may introduce artifact ^{5,10}. It is because of this that many institutions, including ours has adopted early post-operative imaging as a standard method for tracking extent of resection. ioMRI can be thought of as a logical extension of this requirement of post-operative imaging. One advantage of ioMRI protocols is that not only does it give the surgeon an immediate feedback of extent of resection, it allows for an immediate response to this information, as reoperation becomes more feasible.

Though the exact manifestations of ioMRI may be different between institutions, the goal of ioMRI is to provide the neurosurgeon with immediate feedback about the success of maximum safe resection. There is increasing evidence that ioMRI may be helpful in increasing EOR in brain tumor surgery ^{3,8,18}. In fact, a recent randomized control trial studying the effects of ioMRI on patients with contrast enhancing lesions worrisome for GBM suggested that patients undergoing surgical resection within an ioMRI protocol may have had greater rates of GTR and had a longer cumulative progression-free survival, although this was not statistically significant compared to a control group that did have not have ioMRI ¹⁸. Importantly, there was not a significant difference in the rates of new neurological deficits between those patients that underwent ioMRI and those that did not¹⁸.

It must be noted that a fully functional ioMRI suite requires considerable capital and human resources to establish and run. It is for this reason that there are only approximately 100 of these suites worldwide. Clearly, an ioMRI investment may not be appropriate for all centers where intrinsic brain tumor surgery is performed. Moreover, in higher volume centers, only a fraction of tumor cases can be performed in an ioMRI suite due to capacity restrictions.

Besides the costs, another frequent criticism of ioMRI is that it may cause the surgeon not to be as aggressive in the original resection if they know that they will receive immediate feedback of the extent of resection. The relatively high EOR (overall 93%) achieved in our eoMRI series suggests that we are being appropriately aggressive in attempting GTR in all cases. In light of recent evidence that there indeed seems to be a stepwise improvement in patient survival with increased resection, even in the 95-100% EOR range^{17,19}, the impetus to achieve these types of resections is high and it appears that adding an eoMRI protocol has allowed us to do this in our small cohort.

It may be that patients with low-grade gliomas or non-enhancing tumors benefit most from use of intra- or extra- operative MRIs. This is because these tumors usually do not have a clear demarcation in terms of tissue consistency during surgery, making the definition of the borders of the tumor very difficult. All the patients taken back to the operating room ultimately had tissue pathology consistent with low-grade gliomas, suggesting that this was the case in our limited series. Though our series did not include pediatric patients, it may be that pediatric patients may also benefit from such an eoMRI protocol, as these patients often require additional general anesthesia and endotracheal intubation for standard post-operative MRI and this protocol would obviate the need for this.

A criticism of these types of protocols is that they may expose the patient to an increased risk of complications of another surgery without obvious beneficial effects. However, if one closely examines the data on low grade gliomas, even the incremental benefit of increased EOR may have true positive effects for the patient. For example, Smith et al. showed that even in those patients with EOR >80%, EOR was a significant predictor of overall survival, hinting that incremental increases in EOR is beneficial to the patient¹⁹. This observation has been replicated in other subsequent studies^{9,14,16}. Though our study is neither designed nor powered to show increased survival benefit or progression-free survival in those patients undergoing eoMRI protocol, the fact that we were able to make a significant change in EOR between the first and second surgeries suggests that this protocol may have an overall benefit to these patients.

Another criticism of ioMRI protocols is the time that these protocols add to the care of patients. For our eoMRI protocol, the time transporting the patients to a nearby clinical high-field MRI, taking the appropriate scans and returning the patient for another resection if appropriate was 90 minutes, which is slightly longer to the added time that ioMRI protocols have reported⁸. This time is also comparable to the time that we have in our institution's ioMRI. Thus it appears that our protocol does not add significant time to obtaining maximum safe resection compared to an ioMRI protocol. Moreover, while re-opening an incision in a second operation in the same day may theoretically confer a higher infection risk, we have yet to note a post-operative infection in this admittedly small cohort. Importantly, none of our patients had neurological complications.

By extubating patients done under general anesthesia in the ICU and by completing the postoperative MRI before transferring the patient to the ICU for extubation, our current eoMRI protocol minimizes the economic and safety burden that such an eoMRI protocol could have. Since review and discussion of the critical images takes some time and occurs while the remainder of the post-operative MRI protocol is being acquired, in our experience completion of the full post-op MRI usually can be completed within 10-15 minutes of the decision not to operate further. This minimal delay to extubation is likely insignificant in the context of time required to transport to the ICU and extubate. This is substantially offset by the improved image quality related to the lack of motion artifacts, and the additional safety, comfort and convenience that results from not having to return to MRI from the ICU within 48 hours for an additional MRI. Also, from an operational point of view, eliminating the need for a separate post-operative MRI by completion of the post-operative scan at the time of eoMRI reduces the net burden that an eoMRI protocol may have on the MRI department for available MRI scanner time. This may be even more important to smaller institutions with only 1 or 2 MRI scanners available.

Though this particular eoMRI protocol appears to be widely transferrable to institutions with a clinical MRI, there are important requirements to make it successful. First, there must be a multi-disciplinary relationship between the neurosurgeons, the neuro-anesthesiologists and the neuroradiologists to make sure this protocol runs smoothly and provides the maximum benefit to the patient, while ensuring minimization of risk. There must be open communication between the neurosurgeon and the neuro-anesthesiologist so that it is clear when the primary surgery is over, the patient must remain sedated for the removal of the

Mayfield head holder, transport to the clinical MRI suite and possible return to the OR. There must also be a willingness to extubate the patient in the ICU if needed. The most efficient imaging series must be established so as to ensure complete information for decisions is acquired regarding return to the OR while minimizing the amount of time that patient remains in the MRI suite.

We currently block off one of our clinical MRI suites for a period of time when the surgery is predicted to be finished and we also leave the operating theater sterile in case the patient returns of repeat resection. This type of resource management may not be easily transferable to institutions where there is only one clinical MRI suite, or if operating rooms are restricted.

Though this study was not designed to compare intraoperative MRI and extraoperative MRI in brain tumor surgery, it is clear that each protocol has its own advantage and disadvantages. The ioMRI protocols have the advantage of immediate feedback for the neurosurgeon about EOR and does not involve reopening an incision. However, as our experience has shown, an ioMRI suite involves a very large capital investment and is not a realistic option for many medical centers. The eoMRI protocol, as we have implemented, does allow for very fast feedback to the neurosurgeon about EOR and allows for increasing this without incurring the risk of putting the patient through anesthesia again, though it admittedly does incur the risk of reopening a fresh surgical incision. Moreover, acquiring more than one MRI during surgical resection is likely more feasible in an ioMRI suite; we have not done multiple MRI sessions in the eoMRI protocol.

An extensive cost analysis is beyond the scope of this paper, but this extroperative protocol appears to be more cost efficient than the traditional scheme of intrinsic brain tumor surgery where patients receive an postoperative MRI within 48 hours from their index surgery, followed by a second stage surgery at a later time if necessary. The eoMRI protocol eliminates at least one or two days in the intensive care unit (ICU) reducing total length of stay, a second anesthetic and in some cases a second admission. Analysis of our billing data reveals that including all professional and facility charges, the total operative case cost of our eoMRI protocol compared to our ioMRI case cost reveal largely equivalent charges. Importantly, these calculations do not include the amortization costs associated with the capital expense of the ioMRI suite.

It must be noted that part of the reason that the sample size is small is this is a single surgeon trial and that in order to be included in the study, the primary surgeon needed to believe at the conclusion of surgery that a gross total resection was in question. This requirement of uncertainty justifying the use of the eoMRI protocol contributed to the small sample size.

While the number of patients reported in this study is small, it nevertheless provides a roadmap for how MRI can be effectively used to safely increase EOR during brain tumor surgery without need for an intraoperative MRI suite. This approach could be useful in centers with an ioMRI where the demand for imaging during surgery exceeds the capacity of the ioMRI and in centers where installing and maintaining an ioMRI suite isn't feasible.

Conclusions

In this small cohort study, we show that the application of an eoMRI protocol is safe and feasible and allows for a greater EOR in surgery for intrinsic brain tumors. As with ioMRI and other new technologies for increasing EOR, it remains to be seen whether increase in EOR will translate to longer progression-free survival and deter high grade transformation of low-grade gliomas. If so, eoMRI could be easily adopted in many centers where an intraoperative MRI (ioMRI) suite is not a practical undertaking.

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Abbreviations

eoMRI	extraoperative MRI
EOR	extent of resection
ioMRI	intraoperative MRI
MAC	monitored anesthesia care
MRI	magnetic resonance imaging
OR	operating room
OS	overall survival
PFS	progression-free survival
TIVA	total intravenous anesthesia

Figure 1.

Flowchart explaining eoMRI protocol. Patients undergo cytoreductive surgery, with current standard of care neuronavigation, microsurgery and imaging. If it is felt that patient may benefit from eoMRI, patient is taken intubated or under MAC to nearby clinical MRI. Based on the preoperative characteristics of the tumor, patients undergo tailored MRI sequences and in consultation with a neuroradiology attending physician, the decision is made whether there is residual tumor and whether or not further resection can be done safely.

Figure 2. eoMRI protocol allows for increased EOR. A) Preoperative MRI reveals left frontal non-enhancing tumor. B) Extraoperatively, it was felt that a greater resection could be made in the lateral edge of tumor (black arrow). C) After returning to operating room for another resection, it was felt that gross total resection was achieved.

Figure 3. eoMRI allows for immediate confirmation of gross total resection. A) Preoperative MRI reveals left frontal tumor that enhances with gadolinium based contrast agent. B) Extraoperatively, it was felt that gross total resection had been achieved and patient was transferred from MRI to the ICU for extubation after completion of the post-operative MRI protocol.

Table 1

Age at time of surgery, tumor location, tumor size, side, eloquence, contrast enhancement, flair signal.

Patient	Age at Surgery	Tumor Location	Tumor Size (cm ³)	Side	Eloquence	Contrast Enhancement	Flair
1*	52	Parietal	4.186	Right	Y	Y	Y
2	28	Frontal	27.242	Left	N	N	Y
3	35	Parietal	91.578	Right	N	N	Y
4	29	Frontal	164.592	Left	Y	S	Y
5*	44	Temporal	6.573	Left	Y	S	Y
6	51	Occipital	20.314	Right	Y	Y	Y
7	56	Frontal	20.935	Right	N	S	Y
8	43	Frontal	6.858	Left	Y	Y	Y
9*	52	Frontal	1.9666	Left	Y	Y	Y
10	21	Parietal	23.527	Right	N	N	Y
Mean(±SD)	42(12)		36.77(52)				

* These patients had previous debulking surgery elsewhere. Abbreviations: Y – yes, N – no, S – slight.

Table 2

Time for first surgery, time for eoMRI, eoMRI sequences, volume of residual I, % of tumor resected I, Second surgery?, Time for second surgery, volume of residual II, % of tumor resected II, pathology.

Patient Number	Time for first surgery (h:mm)	Reresection	Time for eoMRI (h:mm)	Volume of residual, I (cm ³)	% of tumor resected, I	Time for second surgery (h:mm)	Volume of residual, II (cm ³)	% of Tumor resected, II	Pathology	Complications
1	4:03	N		0.076	98				Glioblastoma	None
2	4:34	Y	1:25	6.774	75	1:58	0.00	100%	Oligoendroglioma, Grade II	None
3	6:05	Y	1:23	10.547	89	1:50	3.646	96%	Oligoendroglioma, Grade II	None
4	10:16	N		1.235	99				Anaplastic Oligoastrocytoma, Grade III	None
5	3:30	N		0.386	94				Oligoendroglioma, Grade II	None
6	4:08	N		0.271	94				Glioblastoma	None
7	4:44	Y	1:49	1.350	91	1:35	0.213	99	Anaplastic Oligoastrocytoma, Grade III	None
8	3:45	N		0.087	99				Glioblastoma	None
9	4:13	N		.042	98				Glioblastoma	None
10	3:31	Y	1:45	0.734	97	1:26	.154	99	Anaplastic Oligoastrocytoma, Grade III	None