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Image guidance for brain metastases resection

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Abstract

The primary goal in removing a metastatic brain tumor is to maximize surgical resection while minimizing the risk of neurological injury. Intraoperative image guidance is frequently used in the resection of both primary and metastatic brain tumors. Stereotactic volumetric techniques allow for smaller craniotomies, facilitate lesion localization, and help neurosurgeons avoid eloquent structures. In turn, this leads to decreased patient morbidity and shorter hospitalizations. Image guidance is not without shortcomings, however, perhaps the most significant of which is inaccuracy of tumor resection associated with intraoperative brain shifts. The goal of this review is to expound on the uses of image guidance and discuss avoidance of technical pitfalls in the resection of cerebral metastatic lesions.

Key Words: Brain metastases, image guidance, resection

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INTRODUCTION

Brain metastases occur in 25–35% of all cancer patients, often leading to debilitating neurologic symptoms and contributing to a worse overall prognosis.[16] Lung cancer is the malignancy that most commonly metastasizes to the brain (35%), followed by breast cancer (21%), kidney cancer, gastrointestinal cancer, and melanoma.[19] Median survival after diagnosis of a brain lesion is approximately 1 year if maximal treatment measures (surgery, radiotherapy, chemotherapy) are undertaken.[19] This decreases to 6–12 months in patients with multiple metastatic lesions.[19] For multiple brain metastases, whole-brain radiation therapy (WBRT) is usually the treatment of choice; however, surgical resection of a solitary brain metastatic lesion followed by WBRT has been shown to increase the median survival to 14 months from 9 months with WBRT alone.[14,15] With new advancements in the diagnosis and treatment of various types of cancer, the reported incidence of brain metastases is likely to increase, accompanied by increasing length of patient survival.[1] This will require that neurosurgical oncologists have more techniques at their disposal for safely and effectively managing these patients. Intraoperative guidance techniques such as frameless stereotaxy using preoperative brain magnetic resonance images have been shown to prolong survival time in patients with single or multiple cerebral metastases.[19] Neuronavigation facilitates a less invasive approach to tumor resection, which is attractive in patients with metastatic disease who are often physically debilitated. In this review, we will focus on the patient selection, tumor location and selection, intraoperative technique, advantages, disadvantages, and outcomes associated with the use of image guidance in the resection of cerebral metastases.

PATIENT SELECTION

In the senior author's (RLJ) practice, patients with metastatic disease are treated with various modalities for management of their intracranial disease [Table 1]. Increasingly, stereotactic radiosurgery (SRS) has become a

Table 1: Summary of the use of image guidance in surgical cases done by the senior author for treatment of metastatic tumors during 2000–2011

	Total number of patients	Total number of procedures	Number of procedures without image guidance	Number of procedures using image guidance	Cortical mapping	IMRI	SRS	Gliasite balloon brachytherapy
Melanoma	198	316	7	69	4		236	4
Lung	110	137	7	55	1		84	
Breast	97	133	4	36	1		92	
Renal	51	79	1	19		1	59	2
Colon/rectal	10	12	3	5			3	1
Sarcoma	22	27	2	14			11	
Esophageal	7	14	3	6			3	2
Squamous cell	11	7		2			5	
Ovarian	10	15		5			10	
Endometrial	4	6		3			3	
Prostate	4	5		3			2	
Bladder	2	2	1	1		1	1	
Thyroid	9	10		2			8	
Neuroendocrine	2	3		2	1		1	
Salivary gland	2	3		1			2	
Sinonasal	1	1		1				
Seminoma	1	1		1				
Unknown	5	10		6	1		4	
Total	546	781	28	231	9	2	524	9

IMRIS: Intraoperative magnetic resonance imaging, SRS: Stereotactic radiosurgery

mainstay treatment for patients with limited intracranial disease. The outcomes from large series of patients treated with SRS, including our own, are really quite good.[4,5,9,17,18] In many ways, this has raised the bar for expectations of outcomes for treatment of intracranial brain metastasis. SRS has a high rate of local control and low complication rate. Thus, any surgical series must demonstrate similar outcomes, which neuronavigation can facilitate.

The role of surgical resection in the management of intracranial disease became widely accepted with the publication in 1990 of the seminal paper by Patchell *et al.*,[15] which demonstrated that surgery followed by WBRT was superior to WBRT alone for patients with a single brain metastasis. Although this paper focused on single metastatic brain lesions, the data from this study have provided valuable guidance regarding patient selection. First and foremost, we see that not all patients with brain metastases will benefit from surgical intervention. Traditional indications for operating on patients with cerebral metastases include young patients with surgically accessible, symptomatic lesions and a Karnofsky performance score (KPS) ≥70.[21] Other indications include patients with an undiagnosed primary tumor with the need for confirmation of tissue histology or for immediate tumor decompression due to life-threatening neurologic symptoms and likelihood of a long disease-free interval after surgical resection. Historically, patients with multiple brain metastases were thought not to be good surgical candidates because of their poor overall prognosis;[21] however, with the advent of image guidance and intraoperative neuronavigation, sick patients with multiple symptomatic lesions can benefit from smaller, more precise craniotomies and no longer need to be excluded from surgical consideration. Therefore, the decision on whether to operate for resection of a metastatic lesion should be based on patient age, KPS, number and location of metastatic lesions, symptomatology, need for tissue diagnosis, and overall prognosis.

ADVANTAGES OF IMAGE GUIDANCE

Despite initial resistance by many experienced neurosurgeons, the use of image guidance and neuronavigation has become standard in the resection of metastatic brain lesions.[6,7] This is largely because of more precise cranial localization, surgical planning, tumor identification, and accuracy, which have been shown to decrease patient morbidity as well as lead to shorter inpatient hospital stays.[13]

Dating back to the days of the eminent neurologist Paul Broca, the quest for cerebral localization has proved difficult. In more modern times, even in the hands of the most experienced neurosurgeons, finding intracranial targets can be challenging. This is especially true in smaller lesions or those near eloquent cortex, as illustrated by a simple case example. A 67-year-old man with a history of renal cell carcinoma diagnosed 4 years earlier presented to his local neurosurgeon with left arm weakness. He had known cervical spondylotic radiculopathy that had been treated with an anterior cervical discectomy and fusion 1 year earlier by the same neurosurgeon. Cervical magnetic resonance imaging (MRI) did not reveal a cause for his weakness, but a brain MRI disclosed a 1-cm right frontal lesion [Figure 1]. The neurosurgeon performed a freehand biopsy via an open craniotomy, and the tissue sample was interpreted as gliosis by the pathologist. The patient was referred to our clinic for SRS, but since no tissue diagnosis had been established, a frameless stereotactic craniotomy was performed. Preoperative images demonstrated that the actual lesion was quite remote from the location of the craniotomy [Figure 2]. The lesion was identified and was histologically consistent with renal cell carcinoma.

Precise intraoperative navigation is dependent on obtaining preoperative stereotactic MRI. The intraoperative imaging system must provide images with enough resolution to distinguish between tumor and normal brain and also between tumor and non-tumor pathologies such as peritumoral edema.[25] Functional MRI (fMRI) and cortical mapping can be used to identify eloquent cortex both before and during surgery. These surgical adjuncts increase the accuracy of tumor localization, identify tumor margins, plan the optimal surgical trajectory, and minimize the size of the craniotomy needed for lesion removal. In the series presented in Table 1, these modalities were used occasionally, although not as frequently as in the case of primary brain tumors. One explanation for this is the more defined borders and histological differences between normal brain and metastatic tumors, which enabled more precise localization; however, when a lesion was located in an area near motor or speech function and the surgical approach appeared to require traversing normal brain tissue, fMRI and intraoperative cortical mapping were applied.

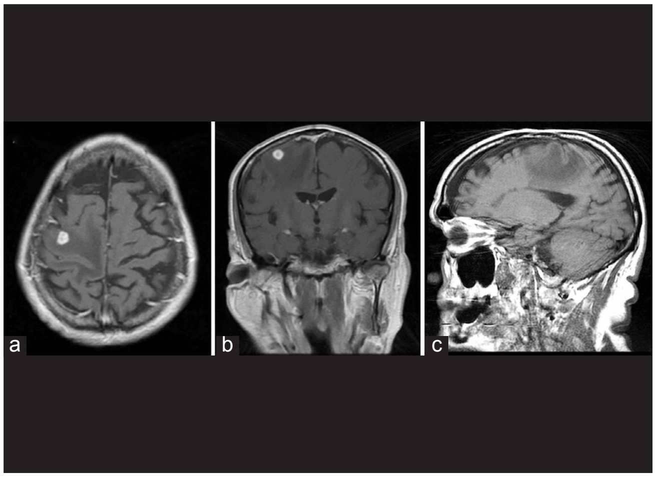

Figure 1: A 67-year-old man with a history of renal cell carcinoma diagnosed 4 years earlier presented with left arm weakness. (a) Axial, (b) coronal, and (c) sagittal T1-weighted MRIs without gadolinium enhancement demonstrate a 1-cm right frontal enhancing lesion

In a retrospective study of 150 patients with single and multiple brain metastases, Schackert *et al.*[19] showed that median survival time was prolonged in patients in whom neuronavigation was used (16 months vs. 10 months with a single metastasis, 11 months vs. 5 months with multiple lesions). Although these results were not statistically significant, the feasibility of resecting less accessible tumors in debilitated patients has increased with the use of intraoperative image guidance and neuronavigation. In our series, the overwhelming majority of cases (231/259, 89%) were performed with this surgical adjuvant [Table 1]. Because we have no control group (non–image-guided surgery) against which to compare, we have no way of determining whether this approach has impacted patient outcome including progression-free survival and overall survival.

Image guidance not only results in less surgical morbidity and greater accuracy of resection, but also in less overall cost to the patient. A British study done in 2000 showed that in patients undergoing craniotomy for meningioma resection, the use of image guidance resulted in a

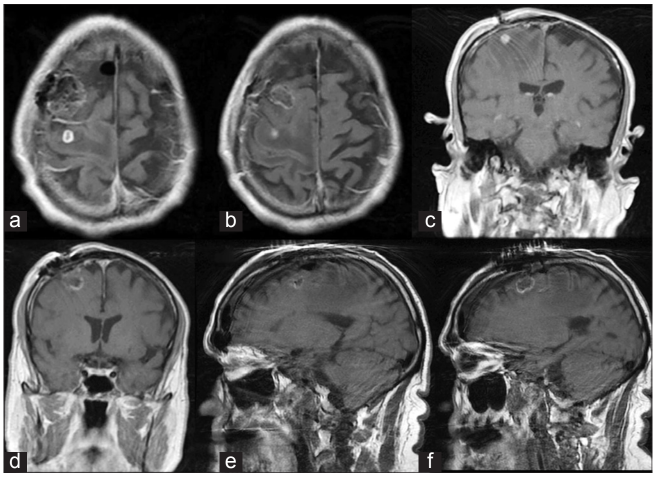

Figure 2: The patient described in Figure 1 underwent a frameless stereotactic craniotomy using intraoperative surgical navigation. Preoperative axial T1-weighted gadolinium-enhanced MRIs demonstrating actual lesion (a), with prior surgical bed visible anterior to lesion (b). Coronal T1-weighted gadolinium-enhanced MRIs demonstrating actual lesion (c), with prior surgical bed visible anterior to lesion (d). Sagittal T1-weighted nonenhanced MRIs demonstrating actual lesion with prior surgical bed visible anterior to lesion (e) and actual surgical bed (f). The lesion was identified and was histologically consistent with renal cell carcinoma

statistically significant decrease in surgical time as well as shorter duration of time in the intensive care unit (1.7 day vs. 1 day) and in overall length of hospital stay (13.5 days vs. 8.5 days).[16] Because of the added costs for prolonged hospitalization, these decreases translate to financial savings. Although we have not done a similar cost-effectiveness analysis, more accurate localization leading to complete removal of a metastatic lesion would *a priori* result in shorter time spent in the hospital and possibly decreased overall hospital costs.

DISADVANTAGES

There is a learning curve involved in employing intraoperative neuronavigation, especially for neurosurgeons trained before its development; however, contemporarily trained neurosurgical residents are well versed in the use of image-guided neurosurgery. Although improvements can be difficult to quantify in a formal randomized controlled study, neuronavigational techniques have improved over time as increasingly sophisticated neuronavigational platforms are introduced and as practitioners become more versed in the world of high-speed computing. Initially, the time required to set up the navigational systems preoperatively increased operating room time; however, although we have not specifically measured this process, we believe that this set-up time has decreased over the years of using these systems. Of course, with each software upgrade or computer operating system change, or when using a new navigation platform, these issues can return even for the experienced surgeon. Nevertheless, the time saved by precise localization of the lesion before skin incision and the decreased time spent searching for a lesion makes up for the time spent setting up the case before beginning the actual operative procedure.

Perhaps the greatest limitation of neurosurgical image-guided stereotactic lesion removal is intraoperative brain shift.[3] Brain shift can occur as a result of dural opening, the use of mannitol and hypertonic saline for brain relaxation and cerebrospinal fluid (CSF) drainage, or tumor resection itself. In fact, previous studies have shown that the brain can shift as much as 2.4 cm during tumor surgery.[10,11] This leads to inaccuracy in identifying tumor margins intraoperatively since the images used for neuronavigation are obtained prior to surgery. Other factors hypothesized to lead to intraoperative brain shift include increasing patient age (because of greater cerebral atrophy) and prior surgery or radiation (with scarring requiring increased brain manipulation).[3] Conversely, small tumor size (<30 cm^3) has been shown to correlate with the success of tumor resection using image-guided stereotactic techniques, perhaps in part due to less brain shifts with smaller lesion size.[3] Therefore, while image-guided stereotactic techniques lead to increased accuracy of tumor resection and shorter hospital stays,[13] precautions must be undertaken to minimize intraoperative brain shifts, which can lead to incomplete tumor removal.

Several techniques can be used during removal of malignant cerebral metastases to help prevent or minimize intraoperative brain shifts. These include avoiding brain contraction techniques, such as hyperventilation and mannitol administration, until the tumor is exposed and ready to be debulked. Eschewing CSF diversion whenever possible and tracing the tumor margins using neuronavigation prior to tumor resection may also help reduce the amount of brain shift, as will avoiding penetrating a tumoral cyst.[3]

One potential method for correcting for intraoperative brain shift once it occurs is the use of intraoperative MRI (IMRI), an emerging technique that allows for intraoperative imaging and reregistration of the navigational system. The newly acquired image is done in the same position as the surgical position and any brain shifting from CSF loss or tumor removal is visualized *in situ*. This technology is not widely available, and its usefulness for neurosurgical procedures has not been fully quantified. Several studies have demonstrated its usefulness in primary brain tumors, especially low- and high-grade gliomas;[8,20,24] however, the utility of this technique is not as clear for metastatic disease. We have used this technology in a limited fashion but hope to further study this in the future. In our limited use, we have this illustrative case. A 67-year-old man with 1-month history of confusion was found to have a large bifrontal mass that was thought to be a primary glioma rather than a metastatic tumor [Figure 3a]. Complete resection was obtained using intraoperative stereotactic navigation and confirmed with IMRI [Figure 3b]. A large

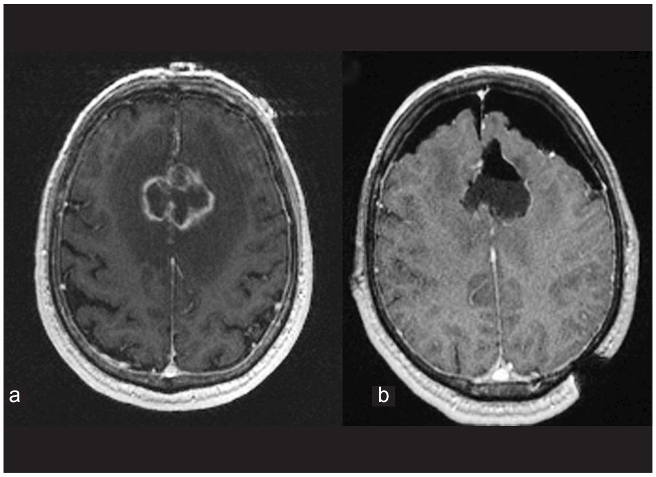

Figure 3: A 67-year-old man with 1-month history of confusion was found to have a heterogeneously enhancing mass thought to represent a primary high-grade glioma or metastatic lesion. (a) T1-weighted SPGR MRI with gadolinium enhancement. (b) Intraoperative T1-weighted SPGR MRI with gadolinium enhancement showing a noticeable amount of brain shift that would have rendered the original navigational MRI inaccurate

amount of brain shift was noted in the supine position in a bifrontal craniotomy that would have rendered the original navigational MRI inaccurate in the anterior–posterior direction. By transferring the intraoperative image to the neuronavigational system during surgery, any residual tumor would have been very straightforward to remove at that time.

TUMOR LOCATION AND SELECTION

When image guidance is used, both mean hospital stay and overall survival are similar in patients with single and multiple metastatic lesions, with no increase in perioperative complications.[12] These data imply that patients with multiple accessible tumors should no longer be excluded from surgical consideration. This is especially true in patients with symptomatic lesions with controlled systemic disease. Surgery is particularly important in patients for whom there is no identifiable primary tumor. As mentioned in the case described in Figure 1, neuronavigation is especially important when tissue diagnosis is the primary goal of the surgery. Nondiagnostic biopsies lead to more procedures with more chance for complications. An even worse scenario is a resection of tissue on the edge of the metastatic lesion that is interpreted as gliosis or low-grade astrocytoma, leading to a completely wrong treatment algorithm.

The use of neuronavigation with metastatic tumors in the posterior fossa is more controversial. Although we have used image-guided surgical techniques for many cerebellar lesions, it is somewhat less helpful in certain situations. First, given the small size of the posterior fossa and the well-defined borders of the tentorium and convexity dura, neuronavigation is not always necessary. Second, the prone position used in these surgeries can make access to external landmarks and fiducial markers more difficult than in supratentorial cases. Nevertheless, for deep-seated lesions of the posterior fossa, especially those near cerebellar nuclei, brainstem, or brachium pontis, neuronavigation may prove helpful and possibly even indispensable.

While gross total resection is desirable, many metastatic lesions have poorly defined borders and infiltrate into surrounding normal brain, so judgment must be exercised to avoid damaging the surrounding eloquent structures. Metastatic lesions, especially those treated with SRS, often show a mixture of radiation changes in the surrounding brain, necrotic tumor areas, and nests of live tumor cells. This is a situation where neuronavigation can help guide the surgeon to differentiate tumor from normal brain. This is also a situation in which IMRI may prove useful.

Neuronavigation is perhaps most useful for tumors located in eloquent cortex because critical structures can be avoided with precise lesion localization. The navigation system is indispensable in the operating room but may be even more important before the operative procedure begins. We routinely plan surgical approaches to avoid eloquent cortex using the anatomical data supplied by the preoperative MRI in the treatment planning station. Additionally, by using diffusion-weighted imaging with cortical tractography, fMRI, and positron emission tomography (PET) images loaded into the navigation system and fused to the anatomical data set, surgical plans can be made to minimize risk and maximize tumor resection. In addition, if the primary tumor is known, the surgeon should be aware of those lesions that have a high tendency to hemorrhage, including melanoma and renal cell tumors.[21] In these situations, it might be considered desirable to circumferentially dissect the tumor from the surrounding brain and disrupt blood supply to the tumor. Image guidance would allow for identification of the tumor without entering the tumor capsule and could aid in this type of surgical approach.

Along these same lines, there are reports that piecemeal resection of a supratentorial brain metastasis carries a higher risk of leptomeningeal disease (LMD) than *en bloc* resection or SRS.[22,23] Patients with LMD have also been shown to have a worse overall prognosis.[21] This concept of increased risk of LMD after piecemeal resection is largely theoretical, and how it relates to patient outcome, including progression-free and overall survival, is unknown. Nevertheless, one could make the case that neuronavigation used as a surgical adjuvant could improve a surgeon's ability to achieve an *en bloc* resection of a metastatic tumor and avoid the piecemeal approach to tumor removal.

IMAGE GUIDANCE TECHNIQUE

All patients scheduled to undergo craniotomy for resection of cerebral metastases undergo stereotactic brain imaging with fiducial markers. Since almost all metastatic tumors enhance after administration of contrast agent, a T1-weighted, three-dimensional spoiled gradient recalled (SPGR) acquisition in a steady state with gadolinium contrast is our image of choice. Stereotactic computed tomography with contrast can be used for cases in which an MRI is not possible. For patients with severe renal failure, MRI without contrast is used, but this may require acquiring both a T1-weighted SPGR without contrast and a stereotactic T2-weighted MRI. In this situation, we fuse the two images and use them to best define the tumor borders. The fiducial markers are a luxury that can reduce registration time in the operating room and theoretically improve accuracy; however, when there is a delay between acquiring the preoperative imaging and the surgical procedure, external anatomical landmarks such as the medial and lateral canthi, pinna or tragus of the ear, tip of the nose, nasion, and any prior surgical scars can all act as registration fiducials.

This imaging is then loaded onto the image guidance system either remotely through the hospital network or from a compact disc prepared by the radiology department. We routinely load the images and plan the surgical approach the evening before surgery or while the operating room is being prepared on the morning of surgery. Once in the operating room, the patient is placed in the Mayfield head holder and secured in place using three-point fixation. When we are using IMRI, a special head holder and a navigation localizer are used. The techniques for IMRI are described elsewhere and are outside the scope of this report.[8,20] Each fiducial marker, or anatomical landmark, is then registered as a surface landmark, and a non-sterile imaging probe is used to mark out the borders of the lesion to be resected to plan the surgical incision. We prefer linear incision when possible or "lazy S" or gentile curvilinear incision when required. The hair over the incision is covered with a mixture of Betadine and surgical lubricant, and the hair is parted over the planned incision; this allows for minimal or no hair removal. The planned incision is infiltrated with 1% Marcaine, and preoperative antibiotics and steroids are administered. After the craniotomy is performed, a sterile guidance probe can be traced over the dura to ensure that the correct trajectory is taken. At this point, intraoperative brain shift can be avoided by withholding the use of hypertonic saline and mannitol if the dura is not tense. The dura is usually opened in a cruciate fashion to allow for extension at this operation or in subsequent future procedures. The image guidance system is used to plan a trajectory, and once the tumor is visualized, the resection borders can be rechecked periodically using the navigation probe. Once the resection is complete, the dura is closed and the bone flap is replaced in a standard fashion. The fiducials are removed at the end of the case, and our practice is to perform an MRI with contrast enhancement on postoperative day 1 to evaluate the resection and to ensure that there are no postoperative complications.

OUTCOMES

Our experience with over 750 craniotomies using image-guided navigation, including roughly 200 for metastatic disease, has been one of improved extent of resection and less damage to surrounding eloquent structures. Others have reported similar results. In a review of 54 patients who underwent image-guided resection of malignant brain tumors (9 metastatic, 45 high-grade gliomas), 47 patients successfully underwent tumor resection.[3] Although 11/47 patients had residual tumor on MRI, in 2 of these cases the tumor was purposely left behind because of the proximity to eloquent cortex such as the motor strip, in 2 cases frozen specimen revealed radiation necrosis, and in 7 cases the tumor was deliberately left behind to conform with a gene therapy trial. In this study,[3] tumor size correlated with successful resection, as larger tumors (>30 cm^3) were less likely to be completely resected, possibly because of brain shifts causing inaccuracy with intraoperative localization. Our experience with metastatic disease suggests that especially in those patients not previously treated, larger lesions are usually fairly straightforward to completely resect. Smaller lesions, especially those of ≤ 1 cm, are the cases in which intraoperative neuronavigation is invaluable. In addition, studies have shown that patient age, prior surgery or radiation therapy, and periventricular location do not affect surgical outcomes.[3] Prior studies, however, have shown that periventricular location can lead to intraoperative brain shifts during resection because of disruption of CSF dynamics, which can result in an incomplete resection.[2] We routinely use neuronavigation to avoid entering the ventricles in an effort to maintain normal CSF pathways and avoid introducing blood into the ventricular system. Overall, the use of image guidance has shown a clear benefit as an aid in the resection of malignant brain tumors, including metastatic lesions. Metastatic lesions remain especially challenging since they often infiltrate into adjacent normal brain and can be difficult to remove without resulting in neurologic compromise. Therefore, intraoperative imaging techniques are vital to maximize resection and minimize the risk of neurologic injury.

CONCLUSION

Advances in the early diagnosis and treatment of various types of malignancies, while leading to greater life expectancy in those affected, have also resulted in a higher number of cerebral metastases. The use of intraoperative image guidance techniques enables the location and definition of cerebral metastases, leading to smaller craniotomies, less patient morbidity, and more accurate surgical resection. However, intraoperative imaging is not without pitfalls, the most significant being intraoperative brain shifts during resection, which can lead to inaccuracy in defining tumor boundaries. Future studies are needed with larger patient numbers to prospectively determine success of resection among patients with cerebral metastases using image guidance versus those in which imaging is not used. Additionally, studies that quantify the amount of brain shift intraoperatively and then correlate this shift with the extent of surgical resection would be useful to determine the exact effects of these changes on surgical outcome. Regardless, the use of image guidance is vital in the successful resection of cerebral metastases, and we recommend its use in all cases of metastatic lesion removal to maximize resection and minimize patient morbidity.

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