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Technique

Correlation of factors predicting intraoperative brain shift with successful resection of malignant brain tumors using image-guided techniques

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Abstract

Background: Intraoperative brain shift may cause inaccuracy of stereotactic image guidance on the basis of preoperatively acquired imaging data. The purpose of our study was to determine whether factors predicting brain shift affect the success of image-guided resection of malignant brain tumors.

Methods: We retrospectively studied 54 patients who underwent image-guided resections of histopathologically confirmed malignant brain tumors (9 metastases, 45 high-grade gliomas). Precautions were taken during surgery to minimize brain shift, but intraoperative imaging was not performed. The following factors predictive of intraoperative brain shift were assessed: tumor size, periventricular location, patient age, prior surgery or radiation therapy, patient positioning, use of mannitol, and length of operative time. Postoperative magnetic resonance imaging was obtained in all cases within 48 hours of surgery to assess extent of resection.

Results: Perioperative mortality was 0% in our series; perioperative morbidity was 3 of 54 patients (5.5%); 1 patient required reoperation for a hematoma, and 2 had transient neurological deficits. Successful resection was accomplished in 93% of tumors less than 30 cm^3 compared with 63.6% of tumors greater than 30 cm^3 ($P = .026$, Fisher exact test). This difference was more pronounced for patients with malignant gliomas. However, other factors predictive of intraoperative brain shift were not associated with unsuccessful resection.

Conclusions: Intraoperative brain shift does not significantly affect the likelihood of successful resection of malignant brain tumors smaller than 30 cm^3. Larger tumors are less likely to be successfully resected, although factors other than brain shift can contribute to unsuccessful resection.

Keywords: Image-guided neurosurgery; Malignant gliomas; Metastases; Stereotaxy; Brain shift

1. Introduction

Malignant brain tumors, including brain metastases and high-grade gliomas, are the most common brain tumors and are significant causes of morbidity and mortality [34]. Malignant brain tumors are usually treated with multiple modalities including surgery, stereotactic radiosurgery, external beam radiation, and chemotherapy [5]. The benefits of surgery for single brain metastases are well documented [30]; the benefits of aggressive resection of high-grade gliomas are debated, but recent literature tends to support aggressive surgical intervention [1,2,16,20].

Image-guided, stereotactic volumetric techniques aid in the resection of malignant brain tumors. These techniques permit minimally invasive craniotomies, facilitate identification of tumor intraoperatively, and help surgeons avoid critical brain structures [9-12,28]. These advantages are particularly important for surgery on malignant brain tumors, including high-grade gliomas, which tend to arise near critical regions of brain and are often difficult to distinguish from normal tissue. However, there are limitations to image-guided, stereotactic volumetric techniques; the most significant may be intraoperative brain shift. Brain shift may occur as a result of patient positioning, dural opening, the use of mannitol, tumor resection, and cerebrospinal fluid (CSF) drainage by entry into cisterns or the ventricular system. Several published studies demonstrated

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and quantified intraoperative brain shift using optical techniques [15,31,32] and intraoperative magnetic resonance imaging (MRI) [21,23,25]. In these studies, the brain surface shifted up to 2.4 cm during surgery; the amount and direction of shift, and the significance of various factors in causing brain shift, varied in different studies.

Brain shift has the potential to make image-guided surgery on the basis of preoperatively acquired images inaccurate; however, it is not clear whether this inaccuracy results in worse outcomes after resection of malignant brain tumors. The purpose of this retrospective study was to test the hypothesis that factors predicting intraoperative brain shift would be correlated with unsuccessful resection of malignant brain tumors. We found that tumor size, but none of the other factors that predict brain shift, correlated with the success of tumor resection using image-guided, stereotactic volumetric techniques.

2. Methods

2.1. Patient population

This is a retrospective chart review of all patients who fulfilled the following criteria: (1) image-guided craniotomy for resection of tumor, (2) histopathologically confirmed malignant brain tumor (glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, or brain metastasis), and (3) postoperative MRI with and without gadolinium (Gd) enhancement within 48 hours of surgery. For the period of September, 1997, to February, 2003, 54 patients fulfilled these criteria: 45 patients with malignant gliomas, and 9 patients with brain metastases. This study was conducted under Mount Sinai School of Medicine Institutional Review Board guidelines.

2.2. Surgical techniques

All patients underwent placement of adhesive fiducial skin markers on the scalp on the morning of surgery, followed by Gd-enhanced MRI using a conventional frameless stereotactic protocol (2-mm-thick axial T1-weighted sections with 0-mm interval). Patients were then brought to the operating room and anesthesia induced. All patients were treated with dexamethasone, antibiotics, and anticonvulsants.

The Treon image-guided system (Medtronic SNT, Louisville, Co) was used in all cases for image guidance. Intraoperative navigation was used in all cases to determine the extent of tumor resection. When tumor was located near eloquent cortex, intraoperative electrophysiological monitoring was performed. When patients underwent reoperation for tumor after radiation therapy, frozen tissue sections were sent intraoperatively to distinguish tumor from radiation necrosis. Several techniques were used to minimize intraoperative brain shift; these techniques are listed in Table 1. No patients had intraoperative imaging or intraoperative updating of preoperatively obtained fiducial points.

Table 1
Techniques for minimizing brain shift during resection of malignant brain tumors

Hyperventilation until tumor debulking begins
Avoid mannitol and other diuretics
Avoid CSF diversion
Delineate tumor margins in 3 dimensions before debulking
Avoid penetration of tumoral cyst

2.3. Magnetic resonance imaging evaluation

We estimated tumor size using the modified ellipsoid method previously described and validated for intracerebral hematomas [8,19]. Residual enhancing tumor on postoperative MRI was defined as nodular enhancement on Gd-enhanced T1-weighted images obtained within 48 hours of surgery (Fig. 1); nodular enhancement, but not smooth linear enhancement (Fig. 2), around the tumor bed on early postoperative imaging predicts tumor regrowth in prospective studies [1,3]. Tumors were defined as periventricular when any part of the tumor touched the ventricular wall.

Successful tumor resection was defined by complete absence of nodular enhancement surrounding the tumor bed on postoperative MRI, or less than 5% of nodular enhancement deliberately left in situ by the surgeon because of information obtained intraoperatively (see "Results" section).

2.4. Statistical analysis

A statistician in the Biomathematics Department, Mt Sinai School of Medicine, New York, NY (LR), using commercially available software, conducted statistical analysis. Eleven of the 54 patients in our study underwent multiple surgeries at Mt Sinai Hospital. For these 11 patients, only outcomes from the first surgeries performed at Mt Sinai Hospital were included in our analysis, in accordance with commonly accepted statistical practice. We first analyzed all patients with malignant tumors, then analyzed the subset of patients with malignant gliomas separately. We chose to analyze patients with malignant gliomas separately because of their different surgical characteristics; specifically, malignant gliomas are more infiltrative than metastases, and are often more difficult to distinguish morphologically from normal tissue. To adjust for multiple comparisons, a significance level of $P = .025$ rather than $P = .05$ was used. We chose to analyze tumor size in bins (smaller than or greater than or equal to 30 cm^3) in part because of a bimodal distribution in our patient population, and in part to maximize the usefulness of our results in practice. In view of the generally high incidence of successful tumor resection, we used Fisher exact test rather than χ^2 test to compare qualitative independent variables. We used contingency table analyses to compare continuous variables. The independent sample t test was used to compare the ages of patients with and without successful resections. Because of a nonparametric distribution of operative times, we used the Wilcoxon W

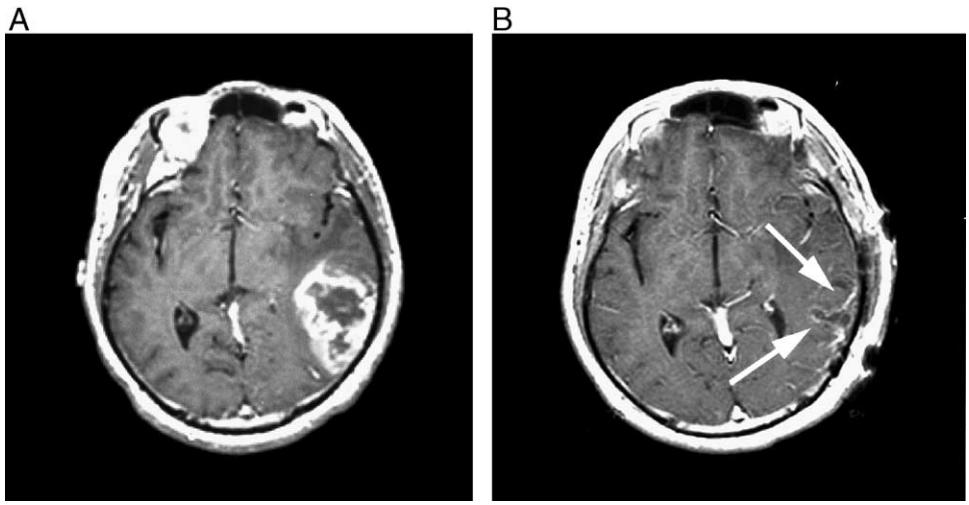

Fig. 1. Example of linear enhancement on postoperative MRI. A: Preoperative Gd-enhanced T1-weighted MRI showing enhancing tumor. B: Postoperative Gd-enhanced T1-weighted MRI showing smooth linear enhancement along the tumor bed (arrows).

test to compare the operative times of patients with and without successful resections.

3. Results

3.1. Patient and tumor characteristics and outcomes

The demographic and clinical characteristics of the patients included in this study are summarized in Table 2. The mean age of our patient population was 54.9 years (range, 33-71 years). For patients undergoing resection of high-grade gliomas, the mean age was 53.6 years (range, 33-71 years), whereas for patients undergoing resection of metastases, the mean age was 61.4 years (range, 45-78 years). Twenty-one patients were neurologically intact preoperatively, whereas 33 had deficits: 26 had hemiparesis, 6 had dysphasia, 5 had visual field deficits, 1 had hemianesthesia, and 1 had confusion. Twenty-three patients had prior surgery at other institutions; the outcomes of these surgeries were not included in our study. Seventeen patients had prior radiation therapy.

At our institution, image-guided volumetric techniques are preferentially used for patients with infiltrating gliomas rather than metastases. Reflecting this preference, 45 patients had histopathologically confirmed high-grade gliomas: 35 had glioblastoma multiforme, 6 had anaplastic oligodendrogliomas, and 4 had anaplastic oligoastrocytomas. Nine patients had brain metastases: 7 had nonsmall cell lung cancer, 1 had melanoma, and 1 had osteosarcoma. Tumor locations were as follows: 21 tumors were frontal (13 left, 8 right), 11 were temporal (6 left, 5 right), 12 were parietal (4 left, 7 right), 2 were right occipital, and 8 involved multiple lobes.

No perioperative deaths occurred. One patient with a right occipital glioblastoma multiforme developed an intraparenchymal hematoma postoperatively and required reoperation;

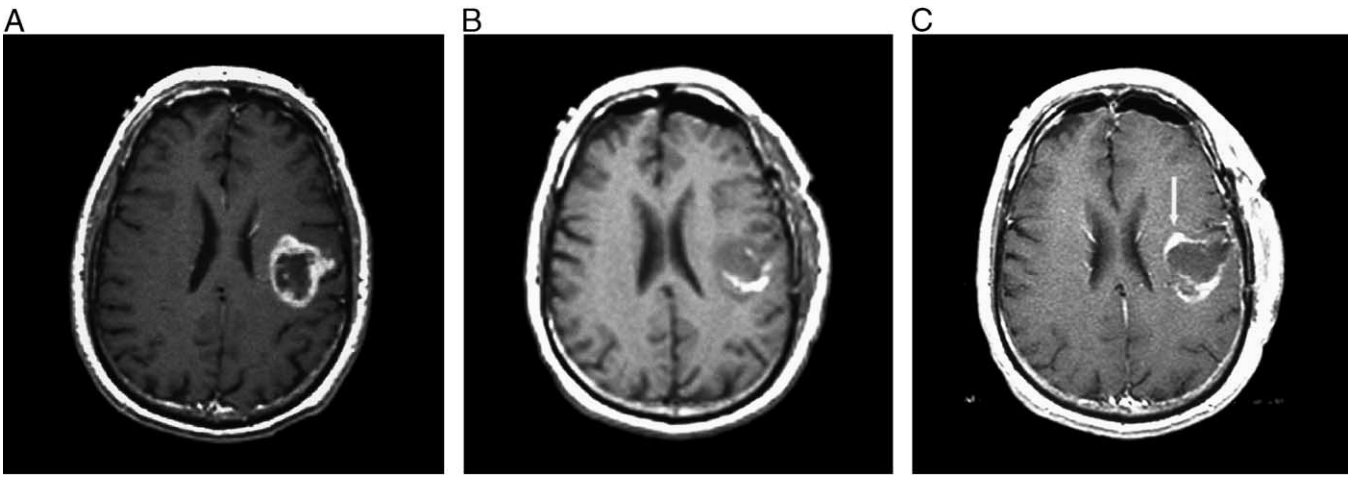

Fig. 2. Example of nodular enhancement on postoperative MRI. A: Preoperative Gd-enhanced T1-weighted MRI of another patient showing enhancing tumor. B: Postoperative, nonenhanced T1-weighted MRI showing hemorrhage in the posterior aspect of the tumor bed. C: Postoperative, Gd-enhanced T1-weighted MRI showing nodular enhancement of the anterior aspect of the tumor bed, representing residual tumor (arrow).

Table 2
Demographic and clinical characteristics of study patients

	All patients	Malignant glioma
Average age (range)	54.9 (33-71)	53.6 (33-71)
Sex (M/F)	27/27	23/22
Neurological deficit	33 (61%)	26 (58%)
Hemiparesis	26 (48%)	20 (44%)
Dysphasia	6 (11%)	6 (13%)
Visual field deficit	5 (9%)	4 (9%)
Hemianesthesia	1 (2%)	1 (2%)
Confusion	1 (2%)	1 (2%)
Prior surgery	23 (43%)	22 (49%)
Prior radiation therapy	17 (31%)	14 (31%)
Pathology		
Malignant glioma	45 (83%)	45 (100%)
Glioblastoma	35 (65%)	35 (78%)
Anaplastic oligodendroglioma	6 (11%)	6 (13%)
Anaplastic oligoastrocytoma	4 (7%)	4 (9%)
Metastasis	9 (17%)	
Nonsmall cell lung	7 (13%)	
Melanoma	1 (2%)	
Osteosarcoma	1 (2%)	
Location		
Frontal	21 (39%)	18 (40%)
Temporal	11 (20%)	11 (24%)
Parietal	12 (22%)	7 (16%)
Occipital	2 (3%)	2 (4%)
Multiple lobes	8 (15%)	7 (16%)

he recovered without new neurological deficits, and postoperative MRI revealed gross total tumor resection. One patient with a right frontal lung metastasis and contralateral hemiparesis had transient worsening of her hemiparesis postoperatively. A third patient with an osteosarcoma metastasis developed transient speech apraxia after surgery. No patients developed infections or new seizures after surgery.

Tumor resection was successful in 47 (87.0%) of 54 cases. In 11 of these 47 successful resections, postoperative MRI revealed a small amount (<5%) of enhancing tumor. In 2 cases, intraoperative cortical mapping showed that a small portion of tumor infiltrated the motor strip, and this portion of tumor was deliberately left in situ. In 7 surgeries for malignant gliomas, a small portion of enhancing tumor was deliberately left in situ to conform with the established protocol for a gene therapy trial; in 4 cases, the tumor was left adjacent to the ventricular wall, in 2 cases, the tumor was left adjacent to the sylvian fissure, and in 1 case, the tumor was left within the corpus callosum. In 2 cases, a small deep portion of enhancing material was deliberately left in situ after intraoperative frozen sections showed radiation necrosis rather than tumor.

3.2. Relationship between patient characteristics predictive of brain shift and successful resection

We hypothesized that several variables could cause brain shift and prevent successful resection of malignant brain tumors using stereotactic image-guided techniques. These variables are summarized in Tables 3 and 4. We hypothesized that increasing patient age should correlate with brain atrophy, which in turn would cause increased brain shift during surgery. We also hypothesized that prior surgery or radiation therapy would lead to changes in brain anatomy, scarring, and a greater need for brain manipulation during surgery, which in turn would cause increased brain shift and unsuccessful resection of tumors. In fact, none of these factors was correlated with unsuccessful tumor resection (Tables 3 and 4).

3.3. Relationship between tumor characteristics predictive of brain shift and successful resection

We hypothesized that surgical resection of larger tumors would cause a greater magnitude of brain shift into the tumor cavity and make successful resection less likely. In fact, we found that successful resection of larger malignant tumors was significantly less likely (Table 3). Greater size also predicted unsuccessful resection when malignant gliomas

Table 3
Relationship between qualitative factors predictive of brain shift and successful tumor resection

Variable		All patients			Malignant glioma		
		n	% Successful	*P*	n	% Successful	*P*
Volume	<30 cm^3	43	93.0	.026[a]	35	94.3	.016[b]
	≥30 cm^3	11	63.6		10	60.0	
Periventricular	Yes	27	85.2	1.00	22	81.8	.41
	No	27	88.9		23	91.3	
Prior surgery	Yes	23	87.0	1.00	22	86.4	1.00
	No	31	87.1		23	87.0	
Prior radiation	Yes	17	88.2	1.00	14	85.7	1.00
	No	37	86.5		31	87.1	
Mannitol used	Yes	8	87.5	1.00	4	75.0	.45
	No	46	87.0		41	87.8	
Supine position	Yes	45	86.7	1.00	38	86.8	1.00
	No	9	88.9		7	85.7	
Pathology	Metastasis	9	88.9	1.00			
	Glioma	45	86.7				

All *P* values are according to Fisher exact test.
[a] Borderline significance.
[b] Significance.

Table 4
Relationship between continuous variables predictive of brain shift and successful tumor resection

Variable	All patients			Malignant glioma		
			P			*P*
Age (mean ± SD)	Successful	54.6 ± 11.3	.58[a]	Successful	53.5 11.2	.90[a]
	Unsuccessful	57.1 ± 12.7		Unsuccessful	54.2 11.0	
Operative time (mean, range)	Successful	154 (86-325)	.29[b]	Successful	156 (89-325)	.30[b]
	Unsuccessful	163 (147-206)		Unsuccessful	179 (147-206)	

[a] Independent sample *t* test.
[b] Wilcoxon *W* test.

were considered separately. We also hypothesized that periventricular location would lead to unsuccessful tumor resection by increasing CSF drainage during surgery, with resulting brain shift. However, periventricular location was not associated with unsuccessful tumor resection (Table 3) Analysis of this variable was complicated by the fact that in 4 malignant glioma cases, small portions of periventricular tumor were left in situ for a gene therapy trial, to minimize seeding of viral vectors through the CSF. In these cases, great efforts were made to avoid entering the ventricle; therefore, the periventricular location of these tumors might be irrelevant for the purposes of predicting brain shift. If these 4 cases are excluded, 77% of periventricular malignant gliomas were successfully resected, compared with 91.3% of malignant gliomas that were not periventricular; the difference still did not reach statistical significance ($P = .38$ by Fisher exact test). If all malignant tumors were considered together, the results also did not reach statistical significance ($P = .69$ by Fisher exact test).

We hypothesized that malignant gliomas, because of their infiltrative nature, would require additional brain manipulation and tissue resection, leading to unsuccessful resection. However, we found that similar proportions of metastases and malignant gliomas were successfully resected (Table 3).

3.4. Relationship between surgical variables predictive of brain shift and successful resection

We hypothesized that longer surgeries would lead to greater brain shift and a higher likelihood of unsuccessful resection. However, when tested as a continuous variable, increasing length of operative time was not correlated with unsuccessful tumor resection (Table 4). For most stereotactic volumetric assisted surgeries, we avoid using mannitol whenever possible to minimize brain shift; however, in 8 cases, mannitol was used during surgery. In these cases, we hypothesized that the use of mannitol would be associated with increased brain shift and unsuccessful tumor resection. In fact, we found no significant association (Table 3). All patients underwent preoperative frameless stereotactic protocol MRI in the supine position; 45 patients underwent surgery in the supine position, and 9 underwent surgery in the lateral decubitus position. We hypothesized that difference in positioning between fiducial point acquisition and surgery would cause brain shift. We found no significant difference in the likelihood of successful resection between patients positioned in the supine and lateral decubitus positions for surgery (Table 3).

4. Discussion

Contemporary image-guided, stereotactic volumetric techniques confer many benefits for patients and surgeons, including accurate and minimally invasive surgeries, decreased morbidity rates, and shorter hospitalizations [12,29]. The accuracy of image-guided technology may be limited by intraoperative brain shift [7,15,22]. Brain shift may be minimized by taking reasonable precautions during surgery [18]. In our practice, we avoid using mannitol or other diuretics before opening the dura. Hyperventilation with end tidal CO_2 in the range of 20 to 25 torr is used during dural opening and discontinued after tumor debulking. Before beginning tumor removal, we use the frameless probe to identify the anteroposterior and mediolateral margins of the tumor and mark the tumor margins on the brain surface using a silk thread. We then insert a “picket fence” of cottonoids at the interface between the tumor and the adjacent brain, as previously described [18]. Brain shift occurs despite the use of meticulous intraoperative technique. Intraoperative imaging using MRI [13,26,27] or ultrasound [10,14,17,33] is intended to update preoperative images and enhance the accuracy of tumor resection. Drawbacks of these technologies are cost, the former, and unfamiliarity with interpreting the images, the latter. This study was conducted to indirectly address the question of whether intraoperative updating of preoperatively acquired images is necessary in all cases for successful resection of malignant brain tumors using image-guided techniques.

Elegant studies using a variety of optical and imaging techniques have proved the existence of intraoperative brain shift [15,21,23,25,31,32]. Furthermore, these studies suggested that additional tumor was identified and resected after intraoperative imaging was obtained [6,24,33]. We recently reported the results of a preliminary study of patients who underwent image-guided, stereotactic volumetric resection of high-grade gliomas. Our study suggested that 2 factors predictive of brain shift, large tumors and periventricular location, might be correlated with unsuccessful resection [4]. Our preliminary report included only patients with high-grade gliomas and only addressed tumor size, periventricular location, and patient age as predictors of brain shift.

Furthermore, multivariate analysis was not performed. In our current report, we extend our study to include patients with brain metastases. We also tested additional variables hypothesized to predict brain shift. Finally, we performed a more complete and rigorous statistical analysis; importantly, we only evaluated outcomes for one surgery per patient, in accordance with accepted statistical practice.

In our final analysis, only large tumor size was associated with unsuccessful tumor resection; other factors predictive of intraoperative brain shift had no significant effect on the likelihood of successful tumor resection. We conclude that if reasonable precautions are taken to minimize brain shift during surgery, malignant brain tumors 30 cm^3 in size or less can be accurately resected without intraoperative image updating. The likelihood of successful resection of larger tumors was significantly lower. The reasons for this are not clear. If intraoperative brain shift was the main cause of the lower likelihood of successful resection of these tumors, then we would expect other factors predictive of brain shift to also correlate with unsuccessful resection. It is more likely that brain shift is only one factor leading to unsuccessful resection of these large tumors. Other factors such as a greater degree of infiltration into adjacent parts of the brain, irregular shapes, and more difficulty visualizing tumor in the operative field may all contribute to unsuccessful resection of larger malignant brain tumors. Direct comparison of technical outcomes with and without intraoperative imaging are ongoing and will help address this question.

We acknowledge several limitations of our study. First, the study was relatively small. We performed power analysis to quantify the ability of our study to detect statistically significant differences in outcomes for periventricular and nonperiventricular gliomas, the variable coming closest to, but not reaching, statistical significance. The power of our study to detect a difference in outcomes for these patients was only 14%; a study including 440 glioma patients would be necessary to achieve 80% power. Larger multicenter collaborative studies may be helpful to address this point. Second, our study does not directly address meaningful clinical outcomes, such as progression to death or disability. Our study is intended to address a specific technical issue relevant to image-guided, stereotactic volumetric tumor resection; therefore, clinical end points are less relevant than the technical success of the operations, as assessed radiographically and by the absence of immediate complications. Third, brain shift was not measured directly during surgery; therefore, we do not know to what degree the factors hypothesized to cause brain shift really did cause brain shift during surgery. Future studies quantifying brain shift, then correlating brain shift with surgical outcomes, will be useful.

5. Conclusions

Image-guided, frameless stereotactic techniques using preoperative brain images are frequently used for the resection of malignant brain tumors. Brain shift may cause inaccuracy of these techniques. If reasonable precautions are taken during surgery to minimize brain shift, then malignant tumors 30 cm^3 in size or less can be resected successfully using image-guided techniques. Malignant tumors larger than 30 cm^3 in size are less likely to be successfully resected with image-guided techniques. Therefore, intraoperative image updating may be important when resecting larger supratentorial tumors.

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Commentary

This is an elegant clinical study that analyzes usefulness of frameless image-guided navigation in defining the margins of intraaxial brain neoplasms. Essentially, the authors found that the only variable that affected the extent of resection was the tumor size, whereas other parameters, such as location relative to the ventricle, nature of the tumor, previous radiation, and so on, did not.

The findings are somewhat counterintuitive. One may expect the brain shift to impair the surgeon's ability to use frameless navigation, particularly if the patient receives mannitol or if the patient position differs between the time of imaging and surgery. It is conceivable, therefore, that the authors' efforts in decreasing this effect of inevitable brain shift (such as insertion of cottonoid strips around the tumor perimeter in the beginning of surgery and avoiding entering tumor cysts or CSF spaces) allow them to depend less on intraoperative navigation later on during the surgery. On the other hand, the size of tumor is also an expected obstacle for its complete resection. Larger tumors worsen the shift, prolong the surgery, and may be associated with worse peritumoral edema than the smaller ones; all this, in turn, results in higher incidence of incomplete resection.

Two limitations of this paper are quite obvious. First of all, the small size of the study group may explain the lack of difference for some of the studied variables. Second, the findings of these authors reflect their practice and experience, as well as technical abilities of their image guidance system. To generalize these results and conclusions, similar findings from different settings will be required. If the results are reproduced by another group of surgeons, then other neurosurgeons will feel more comfortable in relying in image guidance at the end of intraaxial tumor resection and defining its margins.

Another limitation mentioned by the authors is the lack of the long-term follow-up. Does "complete" resection improve survival? Does it change the outcome? Can the lack of postoperative enhancement mean that some normal brain was removed together with the tumor, and the deficits that develop after the surgery arise from too aggressive tumor resection? It would be interesting to follow-up this very same patient cohort for several months, or take a step further and randomize patients to surgery with and without additional intraoperative imaging. It may be, after all, possible to reach 100% rate of "successful" resection with subsequent improvement in survival and functional outcome. Until then, however, we will be preparing patients for suboptimal resection in tumors larger than 30 cm3, and keep relying on image guidance even after the brain shifts during the operation.

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Benveniste and Germano present an interesting approach to the concept of brain shift. The extent of tumor removal, as defined on postoperative imaging controls, classified as successful resection, was compared with some factors which might influence brain shift. Only the tumor volume