Complications of ventricular entry during craniotomy for brain tumor resection

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OBJECTIVE Recent studies have demonstrated that periventricular tumor location is associated with poorer survival and that tumor location near the ventricle limits the extent of resection. This finding may relate to the perception that ventricular entry leads to further complications and thus surgeons may choose to perform less aggressive resection in these areas. However, there is little support for this view in the literature. This study seeks to determine whether ventricular entry is associated with more complications during craniotomy for brain tumor resection.

METHODS A retrospective analysis of patients who underwent craniotomy for tumor resection at Henry Ford Hospital between January 2010 and November 2012 was conducted. A total of 183 cases were reviewed with attention to operative entry into the ventricular system, postoperative use of an external ventricular drain (EVD), subdural hematoma, hydrocephalus, and symptomatic intraventricular hemorrhage (IVH).

RESULTS Patients in whom the ventricles were entered had significantly higher rates of any complication (46% vs 21%). Complications included development of subdural hygroma, subdural hematoma, intraventricular hemorrhage, subgaleal collection, wound infection, urinary tract infection/deep venous thrombosis, hydrocephalus, and ventriculoperitoneal (VP) shunt placement. Specifically, these patients had significantly higher rates of EVD placement (23% vs 1%, $p < 0.001$), hydrocephalus (6% vs 0%, $p = 0.03$), IVH (14% vs 0%, $p < 0.001$), infection (15% vs 5%, $p = 0.04$), and subgaleal collection (20% vs 4%, $p < 0.001$). It was also observed that VP shunt placement was only seen in cases of ventricular entry (11% vs 0%, $p = 0.001$) with 3 of 4 of these patients having a large ventricular entry (defined here as entry greater than a pinhole [< 3 mm] entry). Furthermore, in a subset of glioblastoma patients with and without ventricular entry, Kaplan-Meier estimates for survival demonstrated a median survival time of 329 days for ventricular entry compared with 522 days for patients with no ventricular entry (HR 1.13, 95% CI 0.65–1.96; $p = 0.67$).

CONCLUSIONS There are more complications associated with ventricular entry during brain tumor resection than in nonviolated ventricular systems. Better strategies for management of periventricular tumor resection should be actively sought to improve resection and survival for these patients.

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KEY WORDS ventricle; craniotomy; brain tumor; complication; oncology

DESPITE a paucity of Level 1 evidence, there is a growing consensus within the neurosurgical literature that a greater extent of glioblastoma (GBM) resection enhances survival.^{5,13,20,28,35,37} Furthermore, there is evidence that patients benefit from resection of recurrent GBM as well.^{2,7} Multiple surgical adjuncts, including frameless stereotaxy, intraoperative MRI, functional MRI, and diffusion tensor imaging for tractography as well as awake craniotomy for cortical and subcortical mapping, are being used with increasing frequency to optimize the

benefits of resection while driving down the risk of brain tumor resection.^{8,34,36} This is of paramount importance as contemporary studies have demonstrated that nearly all of the potential gains in survival attributable to gross-total resection of a GBM can easily be lost with any new neurological deficit incurred during an operation.^{23,38} While the benefits of these technologies on tumor resection in eloquent areas have been studied in great detail, there are comparatively few reports of surgical adjuncts for resection of periventricular GBM or the surgical limitations

ABBREVIATIONS DVT = deep venous thrombosis; EOR = extent of resection; EVD = external ventricular drain; GBM = glioblastoma; IVH = intraventricular hemorrhage; UTI = urinary tract infection; VP = ventriculoperitoneal.

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that may accompany these lesions.^{21,29} Such complications may include the development of postoperative hydrocephalus, intraventricular hemorrhage (IVH), CSF leak, or ventriculitis. Periventricular tumor location is associated with smaller resections and poorer survival.^{6,7,29} In such cases, extent of resection (EOR) is sacrificed in order to prevent ventricular entry.⁶ This finding may relate to the perception that ventricular entry leads to further complications and thus surgeons may practice avoidance of aggressive resection strategies in these areas; however, there is little support for this view in the literature. The balance between EOR and amount of ventricular entry is still poorly understood. This study seeks to determine the association of ventricular entry with perioperative complication rate and survival during craniotomy for brain tumor resection.

Methods

We performed a retrospective analysis of the electronic medical records to identify all patients who underwent craniotomy for supratentorial intraaxial tumor resection (predominantly GBM) between January 2010 and November 2012. Patients with purely intraventricular tumors were excluded from the study. Consideration was taken for intraoperative mention of ventricular entry and interventions for management of the violated ventricle (such as placement of a cellulose sponge and woven oxidized cellulose or placement of an external ventricular drain [EVD]). Careful attention was given to complications, such as hydrocephalus, subdural hematoma, and IVH. Demographic, tumor, surgical, and complication data among patients with and without ventricular entry during brain tumor resection were analyzed (Table 1). Extent of resection (subtotal vs gross-total resection) was specified in operative reports, where surgeons would mention subtotal resection due to a variety of reasons (e.g., tumor adjacent to eloquent cortex, ventricle).

Chi-square and Fisher's exact tests were used for comparisons of binary and categorical variables. A 2-sample t-test was used for comparing age, and Wilcoxon 2-sample tests were used for comparing tumor grade, length of stay, tumor size, distance from ventricle, and estimated blood loss. Tumor size was estimated as the length $\times$ width $\times$ height divided by 2. Distance from the ventricle was identified as the smallest distance from the ventricle when comparing axial, sagittal, and coronal imaging slices. Kaplan-Meier estimates were used to assess the median survival times for patients with GBMs. Cox proportional hazards regression was used to compare survival over time and compute hazard ratios with 95% confidence intervals for the GBM patients with and without an entry. The testing level was set at 0.05, and SAS (version 9.4, SAS Institute) was used for data analysis.

Results

A total of 35 patients with and 153 without ventricular entries were included in the following analyses. Table 1 contains descriptive statistics for patients who underwent tumor resection with and without ventricular entry. Tumor location with respect to ventricle and surgical and com-

plication data, along with the corresponding p values, are listed. Patients with entries were more likely to be male (77% vs 58%, $p = 0.04$). They had a higher percentage of GBM tumors (60% vs 37%, $p = 0.01$) and a lower percentage of metastatic tumors (11% vs 33%, $p = 0.01$) and higher tumor grades ($p = 0.001$). Patients in whom the ventricles were entered had significantly larger tumors (median 20.5 cm³ vs 10.6 cm³, $p = 0.002$) and a significantly shorter distance from the ventricle (median 0 mm vs 15.2 mm, $p < 0.001$). They also had a significantly higher estimated blood loss (median 150 ml vs 100 ml, $p = 0.003$). No differences were detected between the 2 groups for age, ventricle laterality, length of stay, or readmission rate. No significant difference was identified for EOR (gross-total resection vs subtotal resection). For the ventricular entry group, 34% of resections were subtotal and 66% were gross total. For the nonentry group, 25% of resections were subtotal and 75% were gross total ($p = 0.25$).

Patients in whom the ventricles were entered had significantly higher rates of any complication (46% vs 21%, $p < 0.001$), where complications included development of subdural hematoma, IVH, subgaleal collection, wound infection, urinary tract infection/deep venous thrombosis (UTI/DVT; hospital stay–related complications), hydrocephalus, and ventriculoperitoneal (VP) shunt placement. Specifically, they had significantly higher rates of EVD placement (23% vs 1%, $p < 0.001$), hydrocephalus (6% vs 0%, $p = 0.03$), IVH (14% vs 0%, $p < 0.001$), infection (15% vs 5%, $p = 0.04$), and subgaleal collection (20% vs 4%, $p < 0.001$). Of particular note, only 1 patient in the nonventricular entry group underwent EVD placement, which was done at the time of initial surgery. In the ventricular entry group, half of the patients underwent EVD placement during the first resection. Subgaleal collections were noted independent of EVD placement. It was also observed that VP shunt placement was only seen in cases of ventricular entry (11% vs 0%, $p = 0.001$), with 3 of 4 of these patients having a large ventricular entry (defined here as entry greater than a pinhole [< 3 mm]). Tumors adjacent to the ventricle were more prone to result in ventricular entry (57% vs 16%, $p < 0.001$).

Mortality data were assessed regarding ventricular entry in patients with GBM resection. In our current study, 87 of our 188 patients were found to have pathology consistent with GBM. For patients with ventricular entry, the median survival time was 329 days compared with 522 days for patients with no ventricular entry (HR 1.13, 95% CI 0.65–1.96; $p = 0.67$ [Fig. 1]).

Discussion

There is a growing body of evidence that the EOR is a key prognostic factor for patients with glioma and metastatic tumors alike.^{4,11,13,16,18,28,32,37} However, in many cases a radiographically complete resection cannot be obtained without significant risk of incurring a postoperative neurological deficit, particularly if the tumor is located in a deep or eloquent location.^{9,25,26} One of the factors shown to be predictive of subtotal resection is a tumor location near the lateral ventricles.²⁹ This is thought to be in part due to the technical complexity and greater surgical risk of

TABLE 1. Comparisons of patients with and without ventricular entry

Variable	Entry (n = 35)	No Entry (n = 149)	p Value
Age			0.53
Mean $\pm$ SD	55.3 $\pm$ 14.5	57.1 $\pm$ 15.0	
Median (range)	57 (14–81)	57 (16–94)	
Sex			0.04
Female	8 (23%)	62 (42%)	
Male	27 (77%)	87 (58%)	
Type of tumor			<0.001
GBM	21 (60%)	53 (36%)	
Gliosarcoma	1 (3%)	3 (2%)	
Oligodendroglioma	2 (6%)	19 (13%)	
Oligoastrocytoma	3 (9%)	10 (7%)	
Anaplastic astrocytoma	0 (0%)	5 (3%)	
Pilocytic astrocytoma	0 (0%)	4 (3%)	
Low-grade astrocytoma	2 (6%)	1 (1%)	
Other primary brain tumor	2 (6%)	4 (3%)	
Metastasis	4 (11%)	50 (34%)	
Tumor type			0.01
GBM	21 (60%)	53 (36%)	
Other	10 (29%)	46 (31%)	
Metastasis	4 (11%)	50 (34%)	
Metastasis			0.01
Yes	4 (11%)	50 (34%)	
No	31 (89%)	99 (66%)	
WHO Grade*			0.001
I	1 (3%)	8 (8%)	
II	3 (10%)	22 (22%)	
III	4 (13%)	14 (14%)	
IV	23 (74%)	55 (56%)	
LOS, days			0.20
Mean $\pm$ SD	11.6 $\pm$ 11.2	6.5 $\pm$ 4.3	
Median (range)	6 (2–47)	5 (2–27)	
Readmission			0.24
Yes	8 (23%)	22 (15%)	
No	27 (77%)	127 (85%)	
Total size, mm ³			0.002
Mean $\pm$ SD	37,745.9 $\pm$ 45,434.7	17,299.3 $\pm$ 18,623.8	
Median (range)	20,506 (2481–240,303)	10,699 (664–113,256)	
Distance from ventricle, mm			<0.001
Mean $\pm$ SD	8.3 $\pm$ 11.5	16.1 $\pm$ 11.8	
Median (range)	0 (0–40.1)	15.2 (0–62)	
Ventricle			0.16
4th	3 (9%)	13 (9%)	
Rt lateral	19 (54%)	68 (46%)	
Lt lateral	9 (26%)	62 (42%)	
Rt & Lt lateral	4 (11%)	6 (4%)	
Estimated blood loss			0.003
Mean $\pm$ SD	194.9 $\pm$ 197.4	133.5 $\pm$ 256.6	
Median (range)	150 (0–1000)	100 (0–2900)	

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TABLE 1. Comparisons of patients with and without ventricular entry

Variable	Entry (n = 35)	No Entry (n = 149)	p Value
Type of surgery			0.25
STR	12 (34%)	37 (25%)	
GTR	23 (66%)	112 (75%)	
EVD			<0.001
Yes	8 (23%)	1 (1%)	
No	27 (77%)	147 (99%)	
Subdural hygroma			>0.99
Yes	0 (0%)	1 (1%)	
No	35 (100%)	148 (99%)	
Subdural hematoma			>0.99
Yes	1 (3%)	4 (3%)	
No	34 (97%)	145 (97%)	
Hydrocephalus			0.03
Yes	2 (6%)	0 (0%)	
No	33 (94%)	149 (100%)	
IVH			<0.001
Yes	5 (14%)	0 (0%)	
No	30 (86%)	149 (100%)	
Infection			0.02
No	29 (85%)	142 (95%)	
Wound	5 (15%)	5 (3%)	
PNA	0 (0%)	2 (1%)	
Any infection			0.04
Yes	5 (15%)	7 (5%)	
No	29 (85%)	142 (95%)	
DVT			0.47
Yes	1 (3%)	13 (9%)	
No	34 (97%)	136 (91%)	
UTI			>0.99
Yes	1 (3%)	4 (3%)	
No	34 (97%)	145 (97%)	
PE			0.12
Yes	3 (9%)	4 (3%)	
No	32 (91%)	145 (97%)	
VP shunt placement			0.001
Yes	4 (11%)	0 (0%)	
No	31 (89%)	149 (100%)	
Subgaleal collection			0.003
Yes	7 (20%)	6 (4%)	
No	28 (80%)	143 (96%)	
Any complication			0.001
Yes	16 (46%)	32 (21%)	
No	19 (54%)	117 (79%)	

GTR = gross-total resection; LOS = length of stay; PE = pulmonary embolism; PNA = pneumonia; STR = subtotal resection.

* For nonmetastatic tumors.

approaching deep lesions.^{6,21,29} Overall survival has been shown to be lower in patients harboring a GBM close to the lateral ventricle than in patients with tumors not bordering the lateral ventricle.^{6,29} This phenomenon can be

explained in at least the following 3 ways: 1) inherent tumor biology, 2) an operative paradigm favoring subtotal resection and perceived complication avoidance by neurosurgeons leading to systematic subtotal resection of these

FIG. 1. Kaplan-Meier plot comparing patients with ventricular entry (dashed) versus patients without ventricular entry (solid). Figure is available in color online only.

lesions, and/or 3) complications associated with resection of deep, periventricular lesions, which have an impact on survival.

Tumor Biology

Evidence suggests that tumor stem cells may arise from an aberrancy in the normal process of neurogenesis in the subventricular zone (SVZ).^{3,30,33} There are a number of potential explanations for this, including the rich microenvironment within the SVZ, which is a prime location in both the embryo and adult for neurogenesis, cell communication, growth, and motility via interactions with a rich biochemical milieu comprising growth factors, chemokines, and extracellular matrix proteins not seen in other regions of brain.^{1,3,15} Activators of RTK and the Akt/mTOR/PI3K, PTEN, sonic hedgehog, notch, and wingless-type MMTV integration site family member (WNT) pathways are implicated in self-renewal and proliferation in GBM stem cells and are expressed in the SVZ.^{3,17,27} It is postulated that tumors arising in a periventricular location have a greater propensity for growth and recurrence.¹⁵ One study noted that GBMs adjacent to lateral ventricles more commonly presented with multifocal disease and noncontiguous recurrences, a known harbinger of poor prognosis.^{6,22} Another proposed the proximity to a higher density of subcortical fibers as a reason that patients are more profoundly impacted by these tumors as they progress.⁶ Regardless, to our knowledge there is only one well-controlled, retrospective observational study that demonstrates a survival disadvantage for GBM located near the lateral ventricle (8 vs 11 months).⁶ In fact, Elliott et al. demonstrated no difference in the survival of patients harboring a GBM contiguous with the ventricle over those with a noncontiguous GBM.¹⁰

Resection of Periventricular GBM

To date, there have been only 2 studies that evaluated the EOR in periventricular tumors.¹⁰ Elliott et al. reported on 51 patients with 4 potential lesion states: 1) contiguous tumor with ventricular entry, 2) contiguous tumor without ventricular entry, 3) noncontiguous tumor with ventricular entry, and 4) noncontiguous tumor without ventricular

entry. They reported no statistically significant difference in the EOR among these groups, and there was no significant difference in survival.¹⁰ Although Chaichana et al. controlled well for the rate of gross-total resection and found a survival disadvantage of 3 months associated with lateral ventricle-oriented GBM compared with nonlateral ventricle-oriented GBM, it is unclear what the EOR was in the remaining 65% of tumors in their study.⁶ Neither the relationship to the lateral ventricle nor a specific EOR beyond gross- or subtotal resection was reported in the Glioma Outcome Project.^{7,21} At this point, there is insufficient evidence to conclude that GBMs close to the lateral ventricle are more often incompletely resected.

Complications of Ventricular Entry

Ventricular entry occurred more commonly with GBM resection than with resection of metastatic tumors (27% vs 7%). This may be due to the more infiltrative nature of GBM. Often there is no distinct interface evident between brain and tumor tissue. In contrast, most metastatic lesions have a pseudocapsule that guides surgical dissection and often prevents the surgeon from deviating into adjacent structures including the ventricle. Moreover, we found that the ventricle was entered more commonly while removing higher grade glioma (Grades III and IV) than lower grade glioma (Grades I and II) (28% vs 12%, $p = 0.05$), further underscoring the role that the more infiltrative nature of higher grade gliomas can play during glioma resection.

Although not significantly different, ventricular transgression occurred less commonly when gross-total resection rather than subtotal resection was attempted (17% vs 24%; $p = 0.25$). In the majority of these cases, gross-total resection was attempted for tumors farther away from eloquent cortex and ependymal lining, as compared with subtotal resection for tissue close to eloquent cortex and ependymal lining. An EVD was left in the ventricle in 8 of 35 patients when the ependymal lining was breached. Two of 35 patients with ventricular entry developed hydrocephalus compared with none in the nonentry group; this difference was significant ($p = 0.03$).

Our literature search yielded reports with similar outcomes. Montano et al. identified 124 patients with GBM; 62 patients had ventricular entry, of whom 7 patients developed communicating hydrocephalus.²⁴ All of the patients with communicating hydrocephalus had a history of ventricular entry, and, interestingly, hydrocephalus was more common with ventricular entry in patients who underwent adjuvant chemo- and radiotherapy than in patients who did not undergo adjuvant therapies.²⁴ The proposed mechanism implicated in the development of hydrocephalus in these patients involves arachnoid granulation fibrosis coupled with increased CSF protein following ventricular entry in surgery. Fischer et al. studied 151 patients and again noted a significant association between ventricular entry and the development of communicating hydrocephalus.¹² Of those patients studied, 73% with communicating hydrocephalus also had entry into the ventricles during resection, as opposed to 17% of those without hydrocephalus. Furthermore, leptomeningeal spread was more common in the communicating hydrocephalus group (27% vs 8%). Unfortunately, neither the EOR nor survival was re-

ported.¹² Ventriculomegaly is commonly seen in GBM and can be accompanied by changes in a patient's neurological examination findings.³¹ The etiology of enlarged ventricles could be benign in nature, from parenchymal volume loss or resection, or more pathological, such as leptomeningeal/CSF spread, hemorrhage, infection, elevated CSF protein, or fibrosis of arachnoid granulations.^{24,31}

Five patients in our ventricular entry group had postoperative IVH compared with none in the control group, and this difference was significant as well ($p < 0.001$). More patients developed postoperative wound or systemic infections when the ventricle was transgressed. This was most likely due to an extended ICU stay associated with a prolonged course of an indwelling ventricular catheter, although total LOS was not different between the 2 groups. Also, a subgaleal fluid collection occurred more frequently in the patients who had ventricular entry compared with those without ventricular entry (20% vs 4%), which could have contributed to development of wound complications since CSF is toxic to tissues and impairs wound healing.¹⁹

One limitation of our study is that the CSF was not tested for tumor dissemination in cases of ventricular entry. It is possible that ventricular entry could lead to spillage of malignant glioma cells into the CSF within the ventricular system, thus opening an additional route of tumor dissemination. However, in previously described cases of ventricular entry during GBM resection, there was no difference in survival or rate of CSF dissemination when the ventricle was entered during resection, suggesting that there may be inherent factors specific to tumor biology that are more important modulators of CSF dissemination than simply access to the ventricular system.^{10,14} While our study is limited by its retrospective nature, further prospective work including continued survival analysis and functional outcome measures is currently underway.

Conclusions

To our knowledge, a limited number of published studies exist that summarize perioperative complication incidence associated with ventricular entry during resection of malignant brain tumor. In this article we demonstrate that resection of periventricular GBM is associated with an increased rate of perioperative complications, although it is still unclear whether there is an impact on survival. Complications that were statistically significant included development of subdural hematoma, IVH, subgaleal collection, wound infection, UTI/DVT, hydrocephalus, and VP shunt placement. Furthermore, survivability data suggest that patients without ventricular entry survive longer than patients in whom the ventricle was breached. Further work to determine the interplay between tumor biology, EOR, and complication rate on survival and functional status in patients with periventricular GBM is advised.

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