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Thirty-Day Outcomes After Craniotomy for Primary Malignant Brain Tumors: A National Surgical Quality Improvement Program Analysis

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BACKGROUND: Despite improved perioperative management, the rate of postoperative morbidity and mortality after brain tumor resection remains considerably high.
OBJECTIVE: To assess the rates, causes, timing, and predictors of major complication, extended length of stay (>10 d), reoperation, readmission, and death within 30 d after craniotomy for primary malignant brain tumors.
METHODS: Patients were extracted from the National Surgical Quality Improvement Program registry (2005-2015) and analyzed using multivariable logistic regression.
RESULTS: A total of 7376 patients were identified, of which 948 (12.9%) experienced a major complication. The most common major complications were reoperation (5.1%), venous thromboembolism (3.5%), and death (2.6%). Furthermore, 15.6% stayed longer than 10 d, and 11.5% were readmitted within 30 d after surgery. The most common reasons for reoperation and readmission were intracranial hemorrhage (18.5%) and wound-related complications (11.9%), respectively. Multivariable analysis identified older age, higher body mass index, higher American Society of Anesthesiologists (ASA) classification, dependent functional status, elevated preoperative white blood cell count (white blood cell count [WBC], >12 000 cells/mm^3), and longer operative time as predictors of major complication (all $P < .001$). Higher ASA classification, dependent functional status, elevated WBC, and ventilator dependence were predictors of extended length of stay (all $P < .001$). Higher ASA classification and elevated WBC were predictors of reoperation (both $P < .001$). Higher ASA classification and dependent functional status were predictors of readmission (both $P < .001$). Older age, higher ASA classification, and dependent functional status were predictors of death (all $P < .001$).
CONCLUSION: This study provides a descriptive analysis and identifies predictors for short-term complications, including death, after craniotomy for primary malignant brain tumors.

KEY WORDS: Complications, Craniotomy, Length of stay, Primary malignant brain tumor, Reoperation, Readmission, Mortality

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Despite improvements in the treatment of primary malignant brain tumors, these invasive cancers continue to result in significant morbidity and mortality. The estimated median survival is as short as 15 mo for patients with a glioblastoma, the most common and deadliest type of primary malignant brain tumor.[1]

Currently, the standard of care for newly diagnosed primary malignant brain tumors is safe maximal resection of the tumor, typically followed by adjuvant chemotherapy and radiation.[2] Balancing between maximal resection and preservation of neurological functioning can be challenging due to the infiltrative nature of these tumors, and the short-term postoperative course is frequently complicated by major adverse events, often resulting in extended length of stay, reoperation, and readmission.[3]

Identifying the most predominant patient demographics and procedural related factors associated with morbidity and mortality for primary malignant brain tumor resection would be beneficial in identifying patients at high risk for postoperative complications, thereby improving patient selection and tailoring

postoperative management to a patient's individual risk profile. Although many multicenter studies have reported on short-term outcomes after craniotomy for brain tumors,[4-14] only few have focused on patients with a primary malignant brain tumor.[10-12,15] These studies provide valuable but limited insight into the direct postoperative course because they often assess a specific subset of outcome measures only and use varying inclusion criteria.

The current study aims to provide an overall picture of the postoperative course of this patient population by assessing the rates, causes, timing, and predictors of major short-term outcomes after craniotomy for primary malignant brain tumors. For this purpose, the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database was reviewed to investigate the occurrence of major complication, extended length of stay, reoperation, readmission, and death in the first 30 d after surgery. The findings of the current multicenter study can aid to optimize postoperative management of patients who are operated for a primary malignant brain tumor.

METHODS

Data Source

Data was extracted from the NSQIP registry (2005-2015). This validated registry tracks patients prospectively for 30 d after their surgery and includes data from over 600 hospitals across the United States.[16] Data on patient characteristics and associated postoperative outcomes are collected by trained surgical clinical reviewers at each site, and inter-rater reliability audits are performed to ensure data reliability.[17] Previous studies have used the NSQIP to analyze outcomes after neurosurgical interventions.[6,8,17-27] Our institutional review board has exempted this study from review. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used in this study.

Inclusion Criteria

All adult patients were included that underwent craniotomy for brain tumor resection (Current Procedural Terminology [CPT]: 61500, 61510, 61512, 61518, 61519, 61520, 61521, 61526, and 61530) and had a histopathologically confirmed diagnosis of a primary malignant brain tumor (International Classification of Diseases Ninth Revision [ICD-9]: 191.x). CPT codes are medical codes maintained by the American Medical Association to communicate uniform information and billing on medical, surgical, and diagnostic procedures. Similarly, ICD-9 codes are also used for uniform communication; however, ICD-9 codes refer to diagnoses, whereas CPT codes refer to medical services.

Covariates

Covariates were extracted and analyzed as follows. Age at time of surgery, body mass index (BMI), and surgery time were examined continuously in years, kg/m^2, and minutes, respectively. American Society of Anesthesiologists (ASA) classification was examined categorically (I-II, III, IV-V). Other evaluated preoperative patient characteristics included gender, race, smoking status during the past year, dyspnea, chronic obstructive pulmonary disease, hypertension requiring medication, bleeding disorders, diabetes mellitus (insulin dependent vs noninsulin dependent), steroid usage, recent congestive heart failure, preoperative functional status (dependent vs independent), and systemic sepsis. Preoperative laboratory values were also extracted and categorized according to standard reference ranges and clinical significance. When "elevated" or "decreased" laboratory groups consisted of a very low number of cases or when its association with the independent variables did not significantly differ from the normal group, this category was deemed to be clinically nonsignificant and merged with the "normal" group. This reduces the degrees of freedom and preserves statistical power, resulting in the following categories: creatinine ($<$1.4 mg/dL vs $\geq$1.4 mg/dL), hematocrit ($<$36% vs $\geq$36%), platelet count (100 000-450 000/μL vs $<$100 000/μL or $>$450 000/μL), sodium (135-145 mEq/L vs $<$135 mEq/L or $>$145 mEq/L), and white blood cell count (WBC; $\leq$12 000/μL vs $>$12 000/μL). Covariates present in less than 1% of cases or with more than 10% missing data were not included in the multivariable analysis. Cases were dropped if they had missing values in one of the variables included in the multivariable model.

Outcomes

Major complications, extended length of stay, reoperations and readmission with related reasons, and mortality within 30 d were extracted as primary endpoints. Major complication was defined as cardiovascular accident, cardiac arrest, myocardial infarction, deep venous thrombosis, pulmonary embolism, unplanned intubation, failure to wean from ventilator, acute renal failure, sepsis, septic shock, deep incisional or organ space surgical site infection, return to the operating room, or death.[28] Extended length of stay was defined as a total hospital stay of more than 10 d. Unplanned reoperation data have been collected by NSQIP since its inception in 2005, but unplanned readmission data has been collected since 2011 regardless of the hospital to which the patient was readmitted. Associated procedures for reoperation, based on CPT codes, and reasons for readmission, based on ICD-9 codes, have been collected since 2012. Nonroutine discharge was defined as discharge to another acute care facility, skilled nursing facility, or rehabilitation center.

Statistical Analysis

R 3.3.3 was used for the statistical analyses. Descriptive statistics were performed on baseline demographics after categorization, together with univariable analysis for each of the primary endpoints by means of logistic regression. Multivariable logistic regression models were constructed using variables screened by univariable analysis for occurrence of major complication, extended length of stay, reoperation, readmission, and death. All potential predictors ($P < .05$ in the univariable analysis) were included in the multivariable analysis, but age and gender were included automatically. Variables were excluded if they were multicollinear or had a small contribution to model fit. Due to the relatively large sample size of the study population, a $P < .0015$ was considered as significant, to decrease the chance of type I (false-positive) error. This critical value was based on a Bonferroni correction for multiple testing with 33 degrees of freedom ($0.05/33 = 0.0015$). To investigate whether missingness altered the results significantly, an additional analysis was performed for all final models including missing values as a supplementary covariate group. The β-estimates of continuous covariates were scaled to reflect the odds ratios and confidence intervals of clinically significant intervals. This resulted in age per 10 yr increase, BMI per 5 kg/m^2 increase, and surgery time per 60 min increase.

RESULTS

Outcomes

In total, 7376 patients met the inclusion criteria. Patient characteristics separated by the occurrence of a major complication are summarized in Table 1. A total of 16.4% of patients experienced any complication, and 12.9% of patients developed a major complication within 30 d after surgery (Table 2). The most common major complications were reoperation (5.1%), venous thromboembolism (3.5%), and death (2.6%). Most major complications occurred within the first 2 weeks postoperatively (median time to major complication: 9 d), and 82.3% occurred during hospitalization. The median hospital stay was 4 d (interquartile range 3-8 d), and 15.6% of patients stayed longer than 10 d. During the initial 30 d after surgery, 5.1% of patients required reoperation at a median of 12 d postoperatively. The most common reasons for reoperation were intracranial hemorrhage (ICH, 18.5%), hydrocephalus (17.8%), and resection of residual tumor tissue (16.4%). Readmission occurred in 11.5% of cases, at a median of 12 d after discharge. The most common reasons for readmission were wound-related complications (11.9%), seizures (8.8%), and venous thromboembolism (7.4%; Figure 1). Death within 30 d after surgery occurred in 2.6% of cases, of which 37.9% occurred during the initial hospital stay. The incidence of major complications, extended length of stay, reoperation, and death remained fairly consistent from 2009 to 2015 (Figure 2). After an initial drop in 2012, the readmission rate also remains fairly consistent; however, no readmission data was available for patients operated on before 2011.

Multivariable Analysis of Primary Endpoints

Multivariable logistic regression identified older age, higher BMI, higher ASA classification, dependent functional status, elevated WBC, and longer operative times as independent predictors of major complication (all $P < .001$, Table 3). Older age, higher ASA classification, dependent functional status, elevated WBC, low hematocrit, and ventilator dependence were predictors of hospital stay beyond 10 d (all $P < .001$). Higher ASA classification and elevated WBC were predictors of reoperation within 30 d (both $P < .001$; Table 4). Higher ASA classification and dependent functional status were predictors of readmission (both $P < .001$). Older age, higher ASA classification, and dependent functional status were predictors of 30-d mortality (all $P < .001$; Table 5). Missingness ranged between 6.2% and 10.6% depending on the specific outcome measure studied. Including missingness as an additional group did not significantly alter the results.

DISCUSSION

Despite improved perioperative management, the overall rate of short-term postoperative major complications, extended length of stay, reoperation, readmission, and mortality for patients treated with a craniotomy for primary malignant brain tumors remains considerably high. This multicenter registry study provides a descriptive analysis and identifies predictors of 30-d postoperative outcomes after craniotomy for these lesions.

The patients in the current study were identified using ICD-9 codes indicative for a primary malignant brain tumor. Because this population represents predominantly glioma patients,[1] the findings of this study should be interpreted in the context of previous studies on glioma patients. Many multicenter studies have reported on postoperative outcomes after craniotomy for brain tumors;[4-14] however, few have specifically analyzed primary malignant brain tumor or glioma patients.[10-12,14,15] Previous multicenter studies found similar length of stay, readmission rate, and mortality rate in glioma patients[10-12,15] and brain tumor patients overall, including primary benign brain tumors, metastases, meningiomas, and cranial nerve tumors.[7,9,13,29] The rates of overall and major complications in the current study were similar to other studies analyzing glioma patients,[11,14] but fall in the upper range of studies that analyzed all brain tumor patients.[7,13] This suggests that the postoperative course of glioma patients is more frequently complicated by adverse events compared to other types of brain tumors. Additionally, the reoperation rate in glioma patients has not been described in previous multicenter studies. Multicenter studies including brain tumor patients in general demonstrated similar rates of reoperation.[6,13,30]

Single-center or single-surgeon studies have reported a wide range of complication rates (4.3%-14%) and mortality rates (0%-3.7%) after craniotomy for resection of primary malignant brain tumors.[15,31-34] Despite the 30-d timeframe used, the values of complication and mortality rates determined in this multicenter study (12.9% and 2.6%, respectively) fall into the upper ends of the results from observational studies that used a longer follow-up. Although these single-institutional observational studies provide valuable insight, they can be less generalizable due to their retrospective nature, small sample sizes, and single surgeon or single-institutional experience. Because observational studies are often from academic tertiary centers with more specific expertise, the actual rates of postoperative morbidity and mortality may be underestimated in these observational studies. Two studies have previously demonstrated that low-hospital volume is associated with postoperative complications, extended length of stay, and inpatient mortality after surgery for primary brain tumors.[12,14] The high number of participating hospitals in the current study increases the generalizability of our findings to both academic and nonacademic hospitals. Therefore, our results suggest a higher rate of postoperative major complications and mortality after craniotomy for a glioma than previous observational studies have suggested.[15,31-34]

To further investigate the generalizability of the current study, the demographics of our patient population were compared with those of the Central Brain Tumor Registry of the United States (CBTRUS) report on primary brain tumors (2009-2013) by

TABLE 1. Demographics and Preoperative Comorbidities of NSQIP Patients Undergoing Craniotomy for Primary Malignant Brain Tumors, Compared by Major Complication Occurrence

Characteristic (%)	Definition	Total percentage (n = 7376)	Major complication (n = 948)	No complication (n = 6428)	Odds ratio	95% CI	*P* value
Mean age[a]	Years ± SD	54.5 ± 15.6	57.3 ± 15.5	54.1 ± 15.6	1.15[d]	1.10-1.20	**<.001**
Sex[a]	Female	42.3	41.5	42.5	Ref.	–	–
	Male	57.7	58.5	57.5	1.04	0.91-1.20	.56
Race[b]	White	91.8	91.3	91.9	Ref.	–	–
	Black	4.7	5.6	4.6	1.22	0.86-1.69	.25
	Asian	2.9	2.7	3.0	0.90	0.54-1.41	.66
	Other	0.5	0.4	0.5	0.83	0.20-2.36	.75
ASA classification[c]	I-II	27.7	16.6	29.4	Ref.	–	–
	III	59.2	62.8	58.7	1.90	1.58-2.28	**<.001**
	IV-V	13.0	20.6	11.9	3.05	2.43-3.84	**<.001**
Mean BMI[c]	kg/m^2 ± SD	28.4 ± 6.2	29.2 ± 6.5	28.3 ± 6.1	1.26[e]	1.13-1.40	**<.001**
History of CHF		0.2[d]	0.3	0.2	1.36	0.39-4.70	.63
Hypertension		35.4	44.4	34.1	1.55	1.35-1.77	**<.001**
Smoking		17.1	15.7	17.3	0.89	0.74-1.07	.21
Emergency case		6.5	10.2	6.0	1.78	1.40-2.24	**<.001**
Admitted not from home[c]		18.1	25.1	17.2	1.61	1.37-1.89	**<.001**
History of COPD		2.4	3.8	2.1	1.80	1.24-2.61	.002
Ventilator dependent		1.1	4.2	0.7	6.39	4.14-9.86	**<.001**
Dialysis		0.1[d]	0.3	0.1	2.91	0.75-11.3	.11
Renal failure		0.1[d]	0.3	0.1	5.10	1.14-22.8	.02
Weight loss		1.7	3.1	1.5	2.12	1.39-3.24	**.001**
Transfusion		0.2[d]	0.5	0.2	3.09	1.07-8.92	.03
Bleeding disorder		2.2	4.3	1.9	2.37	1.66-3.41	**<.001**
Dyspnea		2.6	4.2	2.3	1.86	1.30-2.65	**.001**
Insulin-dependent diabetes		3.9	6.4	3.5	1.91	1.42-2.54	**<.001**
Preoperative steroid usage		16.6	20.9	16.0	1.38	1.17-1.64	**<.001**
Dependent functional status[a]		5.1	10.1	4.4	2.41	1.88-3.07	**<.001**
Preoperative sodium[c]	135-145 mEq/L	89.9	86.7	90.4	Ref.	–	–
	<135 mEq/L	9.1	11.6	8.7	1.38	1.10-1.72	.004
	>145 mEq/L	1.0	1.7	0.9	1.94	1.07-3.31	.02
Preoperative creatinine[c]	≥1.4 mg/dL	4.4	6.2	4.3	1.45	1.08-1.95	.01
Preoperative WBC[c]	>12 000/μL	24.8	33.3	23.5	1.63	1.40-1.89	**<.001**
Preoperative hematocrit[c]	<36%	11.9	14.3	11.1	1.31	1.07-1.60	.007
Platelets[c]	100-450	97.5	96.1	97.7	Ref.	–	–
	< 00	1.3	2.4	1.1	2.12	1.28-3.39	.002
	>450	1.2	1.5	1.1	1.33	0.72- 2.30	.33
Median operative time[a]	Minutes (IQR)	179 (123-250)	187 (130-258)	178 (122-197)	1.19[f]	1.03-1.37	**<.001**
No general anesthesia[a]		5.9	5.2	6.0	0.85	0.62-1.14	.30

ASA = American Society of Anesthesiologists; BMI = body mass index; CHF = chronic heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; μL = microliter; SD = standard deviation; WBC = white blood cell count.
For all tests, $P < .0015$ was considered significant (in bold).
[a]Independent variable with <1% missing data.
[b]Independent variable with >10% missing data.
[c]Independent variable with 1% to 10% missing data.
[d]Inflated β-coefficients to odds ratio per 10 yr increase.
[e]Inflated β-coefficients to odds ratio per 5 kg/m^2 increase.
[f]Inflated β-coefficients to odds ratio per 60 min increase.

TABLE 2. Complication Incidence Rates and Time-to-Event Data Within 30 d After Craniotomy for Primary Malignant Brain Tumors

Complication	Thirty-day cumulative incidence (%)	Median time-to-event in days (IQR)	Occurrence during initial hospitalization (%)
Major Complication[a]	12.9	9.0 (2.0-18.0)	82.3
Any Complication	16.4	9.0 (2.0-18.0)	76.3
Length of stay	–	4.0 (3.0-8.0)	–
Length of stay > 10 d	15.6	–	–
Death within 30 d	2.6	16.5 (10.0-23.25)	37.9
Reoperation	5.1	12.0 (3.0-20.25)	51.6
Readmission	11.5	16.0 (10.0-23.0)	–
Nonroutine hospital Discharge	31.1	5 (3.0-9.0)	–
Neurological complications			
Cardiovascular accident	1.4	2.0 (1.0-8.5)	73.3
Cardiovascular complications	0.5	9.5 (2.0-17.5)	63.2
Cardiac arrest	0.3	10.5 (3.25-17.0)	66.7
Myocardial infarction	0.2	6.5 (1.25-18.0)	56.3
Hematologic complications	3.7	14.5 (8.0-22.0)	33.5
Deep venous thrombosis	2.6	13.0 (7.0-21.0)	39.6
Blood transfusion	0.2	NA	NA
Pulmonary embolism	1.5	17.0 (9.0-23.0)	27.1
Pulmonary complications	3.0	3.0 (2.0-9.0)	78.2
Unplanned intubation	2.1	5.0 (1.0-12.5)	71.2
Failure to wean from ventilator	1.9	3.0 (2.0-6.0)	91.5
Renal complications			
Renal failure	0.1	12.0 (10.0-15.0)	40.0
Infectious complications	6.3	11.0 (6.0-18.0)	43.1
Surgical site infection	2.2	15.5 (11.0-21.0)	20.1
Pneumonia	1.6	8.0 (4.0-16.5)	65.3
Urine tract infection	2.3	10.0 (7.0-15.0)	48.5
Sepsis/septic shock	2.1	11.0 (7.0-18.0)	46.8

IQR = interquartile range, NA = not available.

[a]Defined as cardiovascular accident, cardiac arrest, myocardial infarction, deep venous thrombosis, pulmonary embolism, unplanned intubation, failure to wean from ventilator, acute renal failure, sepsis, septic shock, deep incisional or organ space surgical site infection, return to the operating room, or death within 30 d.

Ostrom et al.[1] Both conclude that the incidence of primary malignant brain tumors is slightly higher among males compared to females (55% vs 45%). The median age at diagnosis was 64 yr for glioblastoma patients but lower in lower grade gliomas. This parallels the age distribution in our study. Lastly, the proportion of black individuals in our study is lower compared to that in the overall US population; however, the CBTRUS confirms that the incidence of gliomas is twice as high in white individuals as compared to black individuals. These demographic similarities suggest that the study population of the current investigation is representative for primary malignant brain tumor patients across the US.[1]

Older age, comorbidity, and dependent functional status have previously been identified as predictors of postoperative complications in glioma patients,[14,35,36] and higher BMI as an additional predictor in brain tumor patients overall.[7] With regard to extended length of stay, older age and comorbidity have been identified as predictors in glioma patients,[12,14] and higher ASA classification and dependent functional status as additional predictors in brain tumor patients in general.[8] For reoperations, higher BMI has been identified as a predictor in brain tumor patients.[7] For readmission, higher BMI, higher ASA classification, dependent functional status, and steroid usage have been identified as predictors in brain tumor patients.[4,7,30] For mortality, older age and comorbidity have been identified as predictors in glioma patients,[11,12,14] and higher ASA classification, dependent functional status, steroid usage, emergency status, and longer operative time as additional predictors in brain tumor patients overall.[7]

To the best of our knowledge, this is the first study that uses the NSQIP registry to provide a comprehensive overview of the incidences and predictors of all clinically significant short-term outcomes after craniotomy focusing on the specific group primary malignant brain tumor patients. Additionally, it provides a time-to-event analysis for all complications, visualizes trends in complication rates over a 7-yr time period, and investigates reasons for reoperation and readmission. Lastly,

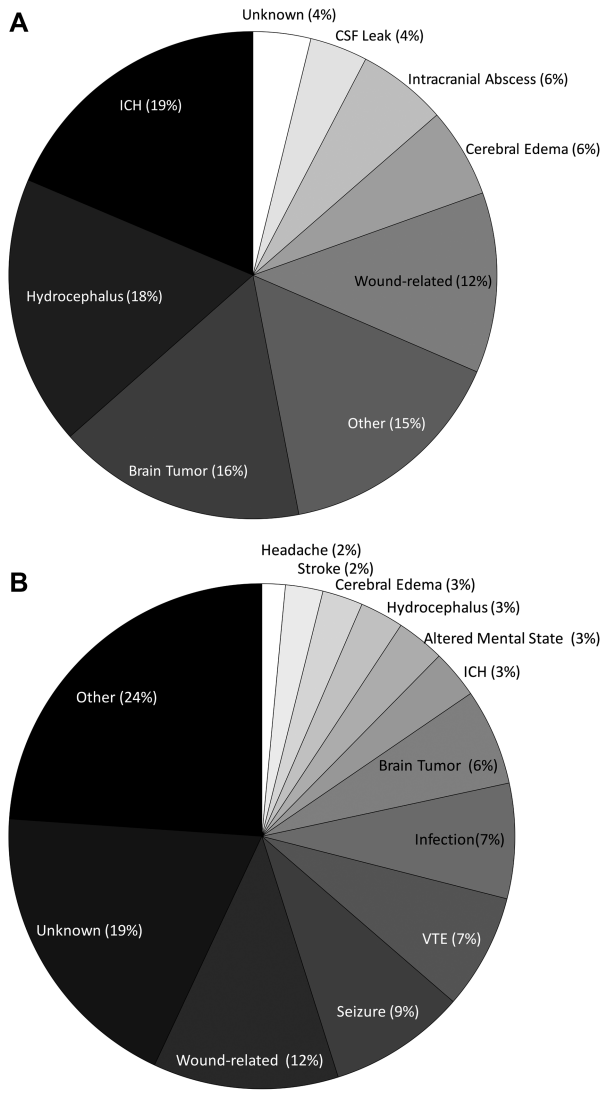

FIGURE 1. *Reasons for* **A**, *reoperation and* **B**, *readmission among NSQIP-reported patients undergoing resection of a primary malignant brain tumor. Abbreviations: CSF = cerebrospinal fluid; ICH = intracranial hemorrhage; VTE = venous thromboembolism.*

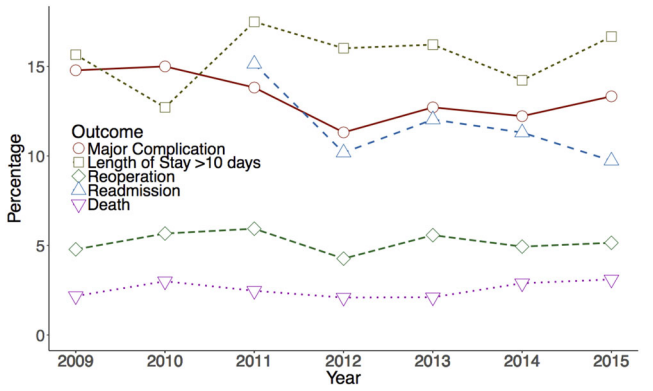

FIGURE 2. *Complication rates per year. Incidence rates for 2005 to 2008 were not included in this figure due to the low number of patients (n < 100 per year). Readmission data was collected since 2011.*

this study identifies novel predictors for short-term major complications (higher ASA classification, higher BMI, elevated WBC, and longer operative time), increased length of stay (higher ASA classification, dependent functional status, elevated WBC, low hematocrit, and ventilator dependence), reoperation (higher ASA classification and elevated WBC), readmission (higher ASA classification and dependent functional status), and mortality (higher ASA classification and dependent functional status).

Implications

Possible reasons for poorer prognosis in elderly patients likely include medical comorbidities and a lower overall fitness level.[35,36] Increased BMI also corresponds to a lower overall fitness level and has been demonstrated to be a risk factor of postoperative morbidity and mortality in other surgical specialties too.[37] ASA classification is based on comorbidity of patients before surgery.[38] Although the relationship between comorbidity and postoperative complications is intuitive, the current study validates ASA classification as a meaningful way to risk stratify glioma patients before surgery. Both ASA class III and ASA class IV-V were predictive for almost all outcome measures. A linear association between ASA classification and postoperative unfavorable outcomes is suggested because the odds ratios were generally higher for ASA class IV-V compared to ASA class III. The strongest association was found between ASA class IV-V and death within 30 d (odds ratio 5.95). Functional dependence is often associated with underlying comorbidity or motor deficits, but it is also associated with poor rehabilitation after surgery; therefore, functional outcome impacts postoperative morbidity and even long-term survival.[39] After ASA classification, functional dependence was the most frequent and strongest predictor of postoperative morbidity and mortality. For all outcome measures except reoperation, the odds were twice as high among functionally dependent patients. Increased WBC can indicate infection, inflammation, and malignancy.[40,41] In the current study, an association was found between elevated WBC and preoperative steroid usage ($P < .001$). Longer operative time results in a longer exposure to anesthesia and intraoperative risks; however, longer operative time also corresponds to surgical complexity, surgeon's experience, and other patient factors.[42] Although many of these factors have been described in previous literature as predictors of worse clinical outcomes in brain tumor or cancer patients in general, the current study also identifies

TABLE 3. Multivariable Logistic Regression Identifying Predictors of a Major Complication and Extended Length of Stay

		Major complication			Hospital stay > 10 d		
Predictor	**Definition**	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Age	Per 10 yr increase	1.09[a]	1.04-1.15	**<.001**	1.12[a]	1.07-1.17	**<.001**
Gender	Female	Ref.	–	–	Ref.	–	–
	Male	1.05	0.90-1.22	.52	0.96	0.84-1.10	.56
BMI	Per 5 kg/m^2 increase	1.11[b]	1.05-1.17	**<.001**	–	–	–
ASA classification	I-II	Ref.	–	–	Ref.	–	–
	III	1.59	1.30-1.94	**<.001**	2.09	1.73-2.55	**<.001**
	IV-V	2.42	1.90-3.13	**<.001**	3.46	2.74-4.39	**<.001**
Functional status	Independent	Ref.	–	–	Ref.	–	–
	Dependent	2.09	1.60-2.71	**<.001**	2.48	1.96-3.13	**<.001**
White blood cell count	≤12 000/μL	Ref.	–	–	Ref.	–	–
	>12 000/μL	1.52	1.29-1.78	**<.001**	1.59	1.38-1.84	**<.001**
Hematocrit	≥36%	–	–	–	Ref.	–	–
	<36%	–	–	–	1.53	1.26-1.84	**<.001**
Ventilator dependence	No	–	–	–	Ref.	–	–
	Yes	–	–	–	3.77	2.23-6.40	**<.001**
Operative time	Per 60 min increase	1.13[c]	1.09-1.17	**<.001**	–	–	–
Model fit							
	AUC	0.64	0.62-0.66	**<.001**	0.68	0.66-0.70	**<.001**

ASA = American Society of Anesthesiologists; AUC = area under the curve; BMI = body mass index; CI = confidence interval. For all tests, $P < .0015$ was considered significant (in bold).

[a]Inflated β-coefficients to odds ratio per 10 yr increase.

[b]Inflated β-coefficients to odds ratio per 5 kg/m^2 increase.

[c]Inflated β-coefficients to odds ratio per 60 min increase.

them as predictors of short-term morbidity and mortality among patients operated on for a primary malignant brain tumor.

Most predictors are nonmodifiable by surgeons; however, these results can help neurosurgeons and their multidisciplinary teams to identify high-risk patients for unfavorable outcomes after surgery. This may enable surgeons to tailor perioperative management to the needs of the individual patient. This is important because prophylactic treatment for one complication can increase the risk of other complications. For example, thromboprophylactic anticoagulation can increase the risk of ICH. Optimizing the safety and efficacy of prophylactic strategies based on a patient's risk profile can drastically reduce the rate of complications in the total population. Furthermore, targeting postoperative management can also reduce unnecessary healthcare costs.

Reoperation

Reoperation also qualifies as a major complication and was the most common major complication in this study.[28] Reoperation is an important indicator of worse clinical outcome recorded in NSQIP and inherently involves increased costs and risks to patients. In this study, ICH was found to be the primary reason for reoperation (18.5%). Postoperative hemorrhage is one of the most serious complications of any operation on the brain, and is associated with significant morbidity and mortality in addition to that from the original operation for the patient's primary malignant brain tumor.[43,44] ICH is difficult to define and may include bleeding following craniotomy at the operative site or remotely, though this is rare.[45-47] The rates of postoperative ICH following intracranial operations vary greatly throughout the existing literature (0.8%-50%).[43,48,49] Hypertension and decreased factor XIII have been identified as factors associated with ICH after brain tumor surgery.[50,51] Interestingly, resection of residual tumor tissue was identified as the third most common cause of reoperation. Improving the extent of resection has gained more attention in recent years, and many complex modalities have been developed and applied intraoperatively to guide and monitor surgical resection, such as stereotactic navigation, intraoperative MRI, ultrasound, functional mapping, and fluorescence guided surgery.[52] The use of these modalities is highly dependent on their availability and the surgeon's preference; however, they can potentially reduce the rate of short-term reoperations as they find their way to standard clinical practice.

Readmission

Readmission is a major driver of cost and re-exposes patients to associated risks of long hospital stays.[53,54] The most common causes for readmission following craniotomy for glioma resection were found to be wound related, occurring in

TABLE 4. Multivariable Logistic Regression Identifying Predictors of Reoperation and Readmission

		Reoperation			Readmission		
Predictor	**Definition**	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Age	Per 10 yr increase	0.92[a]	0.86-0.99	.03	1.03[a]	0.98-1.09	.22
Gender	Female	Ref.	–	–	Ref.	–	–
	Male	1.10	0.88-1.38	.38	0.97	0.83-1.14	.76
BMI	Per 5 kg/m^2 increase	1.09[b]	1.01-1.19	.03	1.05[b]	0.99-1.11	.13
ASA classification	I-II	Ref.	–	–	Ref.	–	–
	III	1.87	1.38-2.54	**<.001**	1.45	1.19-1.77	**<.001**
	IV-V	2.91	1.99-4.24	**<.001**	1.12	0.83-1.51	.43
Functional status	Independent	–	–	–	Ref.	–	–
	Dependent	–	–	–	2.04	1.48-2.76	**<.001**
White blood cell count	≤12 000/μL	Ref.	–	–	–	–	–
	>12 000/μL	1.54	1.22-1.94	**<.001**	–	–	–
Model fit							
	AUC	0.62	0.59-0.65	**<.001**	0.57	0.55-0.59	**<.001**

ASA = American Society of Anesthesiologists; AUC = area under the curve; BMI = body mass index; CI = confidence interval. For all tests, $P < .0015$ was considered.
[a]Inflated β-coefficients to odds ratio per 10 yr increase.
[b]Inflated β-coefficients to odds ratio per 5 kg/m^2 increase.

TABLE 5. Multivariable Logistic Regression Identifying Predictors of Death Within 30 d After Surgery

		Death		
Predictor	**Definition**	**Odds ratio**	**95% CI**	***P* value**
Age	Per 10 yr change	1.54[a]	1.35-1.75	**<.001**
Gender	Female	Ref.	–	–
	Male	1.01	0.79-1.54	.56
BMI	Per 5 kg/m^2 change	0.96[b]	0.83-1.09	.52
ASA classification	I-II	Ref.	–	–
	III	2.70	1.49-5.40	.002
	IV-V	5.95	3.11-12.37	**<.001**
Functional status	Independent	Ref.	–	–
	Dependent	2.46	1.52-3.83	**<.001**
White blood cell count	≤12 000/μL	Ref.	–	–
	>12 000/μL	1.58	1.12-2.21	.008
Model fit				
	AUC	0.76	0.72-0.80	**<.001**

ASA = American Society of Anesthesiologists; AUC = Area under the curve; BMI = body mass index; CI = confidence interval. For all tests, $P < .0015$ was considered significant (in bold).
[a]Inflated β-coefficients to odds ratio per 10 yr increase.
[b]Inflated β-coefficients to odds ratio per 5 kg/m^2 increase.

11.9% of readmitted patients. Issues with wound healing, including infection, are known and commonly reported complications of brain tumor resections.[11,15,55,56] Risk factors for wound-related complications include having previously undergone additional craniotomies, additional radiosurgery, or having been treated with the anti-angiogenic factor bevacizumab.[55,57,58]

Limitations

Limitations of this study are primarily a result of variables not included in the NSQIP dataset, potentially causing underestimation of the total complication and mortality rates for craniotomies. Tumor and surgery-specific information, such as histology, grading, size, and location of the tumor as well as the extent of resection have an enormous impact on both short

and long-term outcomes; however, these are not available in the NSQIP registry. This can cause uncontrollable confounding, as is also demonstrated in a previous study.[59] Underestimation in this case might also be caused by under-reporting and selection bias as participating hospitals are not obliged to contribute all consecutive cases; however, data are collected on randomly assigned patients by trained surgical reviewers, and inter-rater reliability audits are performed to ensure data reliability. Complications after the 30-d limit used by the database are also unaccounted for in this study. The breadth of multicenter data from NSQIP used in the current study is more representative than most single-center reports; however, the effects of surgeon experience or center volume on postoperative outcomes cannot be accounted for in this database. All surgical studies are limited by variability in surgeon experience,[60] as well as geographical location,[1] both of which have been demonstrated to independently affect complication rates in neurosurgery.

We think that the limitations are proportionate to the strengths of this study. These findings reveal valuable knowledge about the rates, reasons, timing, and predictors of major complications, extended length of stay, reoperation, readmission, and mortality among patients who are operated for a brain tumor. Future studies should focus on building advanced prediction models for short-term outcomes after craniotomy, enabling physicians to optimize perioperative treatment to the needs of the individual patient. A national neurosurgical quality improvement registry including tumor-specific and neurosurgical variables can be essential for achieving this goal.

CONCLUSION

Among patients undergoing craniotomy for primary malignant brain tumors, 12.9% experienced a major complication within 30 d after surgery, most of which occurred during the initial hospital stay. ICH and wound-related complications were the major causes of reoperation and readmission, respectively. ASA classification and dependent functional status are primarily predictive for morbidity and mortality within 30 d after craniotomy for primary malignant brain tumors. Future inclusion of tumor- and neurosurgical-specific variables could allow for a more granular risk assessment of short-term outcomes after craniotomy, but the lack of these variables currently limits the implications of this study.

Disclosures

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COMMENTS

Using the NSQIP national database, these authors thoroughly evaluated the predictors of major complications in 7376 patients who underwent craniotomy for primary malignant brain tumors. A total of 12.9% experienced a major complication, with the most common complications reported to be reoperation (5.1%), venous thromboembolism (3.5%), and death (2.6%). Some 15.6% stayed longer than 10 days; 11.5% were readmitted within 30 days after surgery. The most common reasons for reoperation and readmission were intracranial hemorrhage (18.5%) and wound-related complications (11.9%), respectively. Multivariable analysis identified older age, higher body mass index (BMI), higher ASA classification, dependent functional status, elevated preoperative white blood cell count (WBC, $>12\ 000$ cells/mm^3), and longer operative time as predictors of major complication. This work helps to provide robust prognostic information and complication rates for malignant brain tumor patients undergoing craniotomy.

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With this review of 7376 consecutive patients undergoing craniotomy for high-grade glioma from the NSQIP database, the authors have made a significant contribution to the literature. Many of their findings will

be familiar to practicing neurosurgeons, and confirm prior literature and our collective experience. It is not surprising that older patients, patients with higher ASA classification or dependent functional status are more likely to experience postoperative complications. Due to well established limitations of national databases, they were unable to investigate such risk factors as tumor size and location.

The authors were able to identify postoperative ICH and tumor residual as common factors for prolonged admission or readmission. These findings confirm the suspicion of many experienced surgeons that a subtotal resection of a high-grade glioma is often a mistake, as swelling, bleeding, and hydrocephalus may force the surgeon to return to the operating room. Techniques that allow a more aggressive resection such as brain mapping, ultrasound, intraoperative imaging and fluorescence imaging may help reduce these complications.

It was also informative that the incidence of these complications did not decline over the study period despite national efforts to reduce postoperative bleeding, deep venous thrombosis/pulmonary embolism, wound complications, and readmission. The only factors that seem to be in the control of the surgeon are operative time and significant postoperative bleeding. These would seem to be the most appropriate targets for further local quality initiatives.

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