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Outcome prediction in intracranial tumor surgery: the National Surgical Quality Improvement Program 2005-2010

Kimon Bekelis, M.D.^{1,*}, Samuel F. Bakhoun, Ph.D.^{2,*}, Atman Desai, M.D.¹, Todd A. MacKenzie, Ph.D.³, and David W. Roberts, M.D.^{1,2,4}

¹Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH

²Geisel School of Medicine at Dartmouth, Hanover, NH

³Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH

⁴Department of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Abstract

Background—Accurate knowledge of individualized risks is crucial for decision-making in the surgical management of patients with brain tumors. Precise delineation of those risks remains a topic of debate. We attempted to create a predictive model of outcomes in patients undergoing craniotomies for tumor resection (CTR).

Methods—We performed a retrospective cohort study involving patients who underwent CTR from 2005-2010 and were registered in the American College of Surgeons National Quality Improvement Project (NSQIP) database. A model for outcome prediction based on individual patient characteristics was developed.

Results—Of the 1,834 patients, 457 had meningiomas (24.9%) and 1377 had non-meningioma tumors (75.1%). The respective 30-day postoperative risks were 2.1% for stroke, 1.3% for MI, 2.7% for death, 2.4% for deep surgical site infection, and 6.6% for return to the OR. Multivariate analysis demonstrated that pre-operative tumor-related neurologic deficit, stroke, altered mental status, and weight loss, were independently associated with most outcomes, including post-operative MI, death, and deep surgical site infection. An additive effect of the variables on the risk of all outcomes was observed. A validated model for outcome prediction based on individual patient characteristics was developed. The accuracy of the model was estimated by the area under the receiver operating characteristic (ROC) curve, which was 0.687, 0.929, 0.749, 0.746, and 0.679 for postoperative risk of stroke, MI, death, infection, and return to the OR, respectively.

Conclusions—Our model can provide individualized estimates of the risks of post-operative complications based on pre-operative conditions, and can potentially be utilized as an adjunct in the decision-making for surgical intervention in brain tumor patients.

Corresponding Author: Kimon Bekelis, M.D. Dartmouth-Hitchcock Medical Center One Medical Center Dr. Lebanon, NH 03756
kbekelis@gmail.com T: 603-650-5110 F: 603-650-4547.

*These authors contributed equally to this work and co-primary authors

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Keywords

brain tumor; craniotomy; risk prediction; NSQIP; meningioma

Introduction

There is a national trend for accountable care and rationalization of the decision making process in all areas of medicine¹. Neurosurgery, as a high risk and high cost specialty, is among those clinical areas receiving particular attention. Craniotomy for brain tumor resection is one of the most commonly performed neurosurgical interventions². Although several risks of the procedure are recognized by practicing surgeons², the justification of the decision making process on individual patient characteristics is frequently arbitrary. In this environment, the need for benchmarking of the outcomes of craniotomies for tumor resection (CTR) and identification of modifiable patient level risk factors for complications is obvious.

There have been several studies attempting to identify such modifiable risk factors. Most of these have been retrospective analyses of single institution experiences³⁻¹³, demonstrating results with limited generalization given their inherent selection bias. The interpretation of other multi-center studies is equally limited given their focus on regional^{14,15} or subgroup data^{2,16}, and administrative registries¹⁷⁻¹⁹. The latter have been heavily criticized for not been independently validated and underreporting patient comorbidities and procedural complications.

These limitations are largely addressed by the American College of Surgeons' National Quality Improvement Program (NSQIP) database, which contains prospectively collected data from more than 180 private and academic hospitals across the country. It allows for the unrestricted study of the patient population in question, through high quality and reliable data sets²⁰. Using this database, preoperative co-morbidities associated with postoperative stroke, MI, death, wound infection, and return to the OR in patients undergoing craniotomies for tumor resection were identified. Based on these data, a risk factor-based predictive model for negative outcomes in CTR was developed.

Methods

National Surgical Quality Improvement Program (NSQIP) Database

All patients undergoing craniotomies for tumor resection in the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Database between 2005 and 2010 were included in the analysis. ACS-NSQIP is a prospective database with over 180 academic and private centers participating. The ACS-NSQIP prospectively collects data on over 200 variables pertaining to patient characteristics, co-morbid conditions, operative details, and 30-day postoperative outcomes for a variety of surgical procedures. The latest inter-rater reliability audit for participating sites has revealed an overall disagreement rate of 1.99%. More information about ACS NSQIP is available at <http://www.acsnsqip.org>.

Cohort Definition

In order to establish the cohort of patients, we used CPT codes 61510 (craniotomy for resection of supratentorial tumor, not meningioma), 61512 (craniotomy for resection of supratentorial tumor, meningioma), 61518 (craniotomy for resection of infratentorial tumor, not meningioma), 61519 (craniotomy for resection of infratentorial tumor, meningioma), and 61520, 61526, 61530 (craniotomy for resection of cerebellopontine angle tumor, multiple approaches) to identify patients in the registry who underwent CTR between 2005 and 2010 (Figure 1).

Variables

The primary outcome variable was the 30-day postoperative risks of stroke, MI, death, deep surgical site infection, and return to the OR for patients registered in NSQIP-ACS undergoing CTR. The effect on the CTR outcomes of the pertinent exposure variables was examined in a multivariate analysis. The variables were continuous for age and body mass index (BMI). Gender, diabetes mellitus (DM), smoking, alcohol consumption, chronic obstructive pulmonary disease (COPD), hypertension, peripheral vascular disease (PVD), dialysis, history of transient ischemic attack (TIA), metastatic cancer, bleeding disorder, weight loss, abnormal preoperative sodium level, meningioma on tumor histology, history of heart disease with prior intervention (coronary artery bypass graft, coronary angioplasty), history of heart disease without prior intervention, altered mental status at presentation, tumor-related neurological deficit (motor deficit associated with the tumor), and history of stroke were categorical variables.

Statistical analysis

The multivariate logistic regression parameter values were used to construct a predictive model for post-operative complications. The probability (p) of a given postoperative complication was determined by the following relationship:

$$p = \frac{1}{1 + e^{-(\alpha + \sum_{i=1}^n \beta_i X_i)}}$$

where α is the model intercept, n is the number of variables, β is the model parameter, which is the natural logarithm of the Odds Ratio $\ln(\text{OR})$, for a given variable, and X is either 0 or 1 for qualitative variables, or the value of a quantitative variable.

Logistic regression was used to develop a multivariable model for the prediction of the combined outcome. The C-index (area under the receiver operating characteristic curve) was used to measure discriminatory ability. A value of 0.5 indicates a model of no discriminatory ability at all (not better than chance). A C-index corrected for overfitting bias was calculated using leave-out cross-validation (i.e. leave 4% out, repeated 1000 times, as well as bootstrap validation, repeated 1000 times). The Hosmer-Lemeshow test was used to assess calibration of the model. Interactions were tested but none were significant at the threshold (0.001) we set to correct for multiple testing ($20 \times 19/2 = 190$ interactions in all) and further none

improved the C-index by more than 0.002. Non-linear functions of the continuous characteristics (age and BMI) were explored using regression splines but none improved the model. Statistical analyses were performed using the XLSTAT version 2011.2.01 (adinsoft) and R (version 2.15.1).

Results

Demographics and Clinical Characteristics

In the selected study period there were 1,834 CTR patients (mean age was 55.7 years, with 52% males) registered in NSQIP (Figure 1), of whom 457 had meningiomas (24.9%) and 1377 had non-meningioma tumors (75.1%). The two groups demonstrated significant differences in the prevalence of the following patient characteristics: gender, diabetes mellitus, smoking, COPD, disseminated cancer, weight loss, altered mental status (Table 1).

Clinical Outcomes

The 30-day incidence of stroke, MI, death, infection, and return to the OR was 2.1%, 1.3%, 2.7%, 2.4%, and 6.6% respectively (Table 2). Patients with meningiomas demonstrated a significantly lower incidence of postoperative MI and death.

Multivariate analysis of 30-day postoperative outcomes (Supplementary Tables)

Death—Risk factors independently associated (Figure 2A) with a higher risk of postoperative death within 30 days were: altered mental status at presentation (OR 4.330, 95% CI, 2.199, 8.527, $P<0.0001$), tumor-related neurologic deficit (OR 2.667, 95% CI, 1.330, 5.349, $P=0.006$), heart disease with prior intervention (OR 3.671, 95% CI, 1.445, 9.326, $P=0.006$), and history of stroke (OR 2.794, 95% CI, 1.080, 7.227, $P=0.034$). No such association was identified with older age ($P=0.104$).

Myocardial infarction—Postoperative myocardial infarction within 30 days (Figure 2B) was independently associated with disseminated cancer ($P=0.006$), weight loss ($P=0.007$), altered mental status at presentation ($P=0.003$), and history of stroke ($P=0.002$). No such association was identified with history of heart disease. There was a trend for an association of postoperative MI with older age ($P=0.061$) and hypertension ($P=0.057$), which did not reach statistical significance.

Deep surgical site infection—The following risk factors were independently associated (Figure 2C) with a higher risk of the deep surgical site infection within 30 days: disseminated cancer (OR 2.284, 95% CI, 1.119, 4.662, $P=0.023$), weight loss (OR 3.379, 95% CI, 1.241, 9.201, $P=0.017$), tumor-related neurologic deficit (OR 2.343, 95% CI, 1.071, 5.129, $P=0.033$), and history of stroke (OR 4.244, 95% CI, 1.749, 10.297, $P=0.001$).

Return to the OR—The following risk factors were independently associated (Figure 2D) with a higher risk of return to the OR within 30 days: smoking (OR 1.696, 95% CI, 1.094, 2.629, $P=0.018$), hypertension (OR 1.761, 95% CI, 1.140, 2.719, $P=0.011$), tumor-related neurologic deficit (OR 1.715, 95% CI, 1.049, 2.803, $P=0.031$), history of stroke (OR 2.561, 95% CI, 1.400, 4.684, $P=0.002$).

Stroke—Postoperative stroke within 30 days (Figure 2E) was independently associated with older age only (OR 1.031, 95% CI, 1.006, 1.057, $P=0.015$). No such association was identified with history of stroke ($P=0.359$) or TIA ($P=0.913$).

Predictive model application

The predicted risk for infection, MI, return to the OR, and death was calculated for the most individual variables, as well as their combinations (Table 3). An additive effect of the variables was observed on the risk of all four outcomes. Patients with history of weight loss, tumor related neurologic deficits, and prior history of stroke had a four times higher risk of infection in comparison to similar patients without prior stroke. History of smoking, hypertension, and the presence of a tumor related neurologic deficit increased the possibility of return to the OR almost by five times. In patients with history of stroke and weight loss, presentation with altered mental status is associated with a significantly higher (4.83% versus 1.02%) risk of MI. Finally, the addition of altered mental status at presentation in the risk factors of patients with prior stroke and heart disease treated with intervention triples their postoperative risk of death bringing it close to 30%.

Interestingly, based on this model there was no independent effect of age on the risk of infection, MI, return to the OR, and death. In addition tumor type (meningioma or non-meningioma) was not found to be independently associated with any 30-day postoperative complications.

Accuracy of the model

The Area Under Curve (AUC) or c statistic of the Receiver Operating Characteristic (ROC) was used to estimate the accuracy of the model (Supplementary Figure). That was calculated to be 0.687, 0.929, 0.749, 0.746, and 0.679 for postoperative risk of stroke, MI, death, infection, and return to the OR, respectively, demonstrating good discrimination. Our validated c-statistics yielded similar values. The bootstrap validated C-index was 0.676 (SE=0.027), 0.93 (SE=0.03), 0.743 (SE=0.025), 0.739 (SE of 0.028), and 0.673 (SE=0.026) for postoperative stroke, MI, death, and combined risks, respectively. The cross-validated C-index was 0.652 (SE=0.03), 0.924 (SE=0.019), 0.726 (SE=0.033), 0.72 (SE of 0.038), and 0.656 (SE=0.027) for postoperative risk of stroke, MI, death, infection, and return to the OR, respectively. In addition to the AUC, we performed the Hosmer-Lemeshow test and found that our models for the 30-day postoperative risk of stroke ($P=0.161$), MI ($P=0.510$), death ($P=0.847$), infection ($P=0.615$), and return to the OR ($P=0.608$) demonstrated good calibration (elevated P-values indicate that the model and data are not significantly different).

Discussion

The identification of modifiable risk factors associated with poor prognosis as well as the development of predictive models for outcomes are the cornerstones of defining quality in surgical healthcare delivery¹. Accountable care will be based on such benchmarks¹. The NSQIP, as a high quality prospectively collected database can be very helpful for that purpose²⁰. Although its results are not strictly representative of the US population at large,

the quality of the data from a broad range of academic and private institutions performing craniotomies for tumor resection, allows for reliable risk factor identification and modeling.

In the present analysis altered mental status at presentation, tumor related neurologic deficit, heart disease with prior intervention, and history of stroke were the only risk factors independently associated with increased postoperative mortality in CTR patients. The common denominator of these variables is their association with reduced patient mobility and lower chance of independent function, leading to higher risk of medical complications. In addition, they point toward more symptomatic tumors (larger or located in eloquent areas), possibly resulting in longer and more complicated operative interventions. The reported 30-day postoperative mortality of 2.7% is in accordance with the relevant literature^{6,16,21-26} with rates ranging from 1.7% to 3.4%. We did not observe an independent effect of tumor type (meningioma versus non meningioma) on postoperative mortality.

Interestingly, in the current report there was only a non-significant trend of higher mortality with older age. It is possible that this study is merely underpowered to detect differences in mortality. In several analyses of the Nationwide Inpatient Sample¹⁷⁻¹⁹, an administrative database, older age was found to be associated with higher in-hospital mortality in patients undergoing CTR. This effect, however, may have been the result of an increased prevalence of comorbidities in the elderly. The authors focused their multivariate analysis on center and provider characteristics, and not on patient level risk factors, creating this confounder. In addition, in a retrospective analysis¹⁶ of the VA patients registered in NSQIP before 2006, patients over 70 years old undergoing craniotomies for meningioma resection were found to have 3 times higher mortality than younger patients. However, the generalizability of these results is limited to the VA patient population. Moreover, the rapid evolution of anesthetic and neurosurgical care is making the interpretation of their conclusions in the modern setting difficult, given that some of the patients were operated on 15 years ago. Besides these national level studies, there are several single institution or regional analyses with conflicting results on the effect of increasing age on mortality^{2,3,10,14,22,26}. Our analysis supports offering surgical intervention as a first-line option to carefully selected elderly patients.

Morbidity immediately related to the surgical intervention was also investigated. Postoperative deep surgical site infection (2.3%) was slightly higher than what is reported in the literature, possibly secondary to the reporting bias of individual center case series. Risk factors resulting in compromised patient mobility (prior stroke, neurologic deficits) and relative immunosuppression (disseminated cancer, weight loss) were independently associated with a higher risk of postoperative infection. In addition, there appears to be a high incidence of return to the OR (6.6%) for patients undergoing CTR. History of smoking, hypertension, prior stroke and neurologic deficits at presentation increased the risk of this outcome. These variables may be associated with an increased risk of postoperative hematoma (HTN) or deep surgical site infection (prior stroke, neurologic deficit) requiring repeat surgical intervention, or with larger tumors (neurologic deficit) with an increased risk of residual tumor, necessitating reoperation.

Finally, general surgical morbidity measures were examined. Myocardial infarction, although an important risk of every operation, is generally underreported in the CTR literature^{2,3,16-18}. Factors associated with a higher burden of atherosclerotic disease (prior stroke), with limited patient mobility (prior stroke, altered mental status at presentation), or disseminated cancer result in increased risk of postoperative MI. Prior heart disease does not appear to be independently associated with perioperative MI, probably due to the very strict definition of MI by NSQIP in the perioperative period, which is expected to be different from what was deemed as heart disease in the clinical history of the patient. In addition, no factors other than increased age appear to predispose patients to an increased risk of perioperative stroke during CTR.

The proposed predictive model for all outcomes was validated and demonstrates good accuracy and discrimination. This model will need to be tested in future studies for further validation. It may provide a useful tool for patient counseling and informed decision-making in the preoperative evaluation of patients with brain tumors. If the risk of morbidity and mortality remains unacceptably high, after optimizing any modifiable risk factors, alternative treatments (radiotherapy or observation) should be considered if appropriate. However, given the fact that we were unable to investigate important factors such as surgeon volume and tumor location, the application of this model in the clinical setting should be done with caution.

The present study has several limitations. The hospitals participating were not a random sample from the United States but were rather motivated to improve the quality of surgical care, although individual surgeons are unaware of the inclusion of their patients in the NSQIP database preoperatively. Hospitals participating in NSQIP are expected to be larger and more likely to have an academic affiliation than the average US hospital. However, the hospitals included were still diverse with respect to size, region, and academic status, supporting the generalizability of our findings. In addition, the current analysis contains the largest cohort of NSQIP patients investigated to date.

On the other hand, the diagnosis of postoperative stroke is not necessarily based on postoperative exam by an independent neurologist certified on the NIH Stroke Scale, and there is no mention of Rankin scores. Therefore the diagnosis might vary among providers. However, this is most likely representative of a real world experience, where a stroke might be diagnosed by the provider performing the procedure (i.e. a neurosurgeon).

Conclusions

The National Surgical Quality Improvement Program (NSQIP) database is a prospective database, appropriate for benchmarking in the quality of national healthcare delivery. By using it, we identified independent risk factors associated with stroke, MI, death, infection, and return to the OR in patients after craniotomy for tumor resection. Interestingly, there is no observed correlation of increased age and the risk of death. The patient's tumor type (meningioma versus non meningioma) was not found to be significantly associated with any of the complications. Based on the results of the multivariate analysis a risk factor based predictive model of all the outcomes was devised and validated. Although the generalization of these predictions should be done with caution, the model can potentially assist with risk

stratification and tailoring of surgical decision-making in individualized patients. This model will also need to be tested in future studies for further validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cohort selection for the study. ACS-NSQIP=American College of Surgeons-National Surgical Quality Improvement Program, CPT=Common Procedural Terminology

Figure 2.

Multivariate analysis of the 30-day risk of death (A), myocardial infarction (B), wound infection (C), return to the OR (D), and stroke (E) after craniotomy for tumor resection. The odds ratios for the significant variables are represented with forest plots on the right side of each table. Plegia= tumor related neurologic deficit, HTN = hypertension, AMS = altered mental status, TCD = treated (with intervention) cardiac disease, Dca= disseminated cancer

Table 1
Demographics of patients undergoing craniotomy for tumor resection in the NSQIP database 2005-2010

		All Patients		Non-Meningioma		Meningioma		P-Value
		N	%	N	%	N	%	
Gender	F	954	52.02	654	47.49	300	65.65	
	M	880	47.98	723	52.51	157	34.35	<0.0001
Diabetes Mellitus	-	1617	88.17	1232	89.47	385	84.25	
	+	217	11.83	145	10.53	72	15.75	0.003
Smoking	-	1425	77.70	1043	75.74	382	83.59	
	+	409	22.30	334	24.26	75	16.41	0.001
Alcohol consumption	-	1771	96.56	1325	96.22	446	97.59	
	+	63	3.44	52	3.78	11	2.41	0.168
COPD	-	1739	94.82	1291	93.75	448	98.03	
	+	95	5.18	86	6.25	9	1.97	0.000
Hypertension	-	1079	58.83	822	59.69	257	56.24	
	+	755	41.17	555	40.31	200	43.76	0.193
Peripheral Vascular Disease	-	1818	99.13	1363	98.98	455	99.56	
	+	16	0.87	14	1.02	2	0.44	0.248
Dialysis	-	1830	99.78	1374	99.78	456	99.78	
	+	4	0.22	3	0.22	1	0.22	0.990
Transient Ischemic Attack	-	1799	98.09	1353	98.26	446	97.59	
	+	35	1.91	24	1.74	11	2.41	0.368
Disseminated cancer	-	1490	81.24	1046	75.96	444	97.16	
	+	344	18.76	331	24.04	13	2.84	<0.0001
Bleeding disorder	-	1783	97.22	1342	97.46	441	96.50	
	+	51	2.78	35	2.54	16	3.50	0.294
Weight loss	-	1783	97.22	1332	96.73	451	98.69	
	+	51	2.78	45	3.27	6	1.31	0.028
Abnormal preoperative Na level	-	1471	80.21	1092	79.30	379	82.93	
	+	363	19.79	285	20.70	78	17.07	0.092

		All Patients		Non-Meningioma		Meningioma		P-Value
		N	%	N	%	N	%	
Heart disease with prior intervention	-	1720	93.78	1292	93.83	428	93.65	
	+	114	6.22	85	6.17	29	6.35	0.896
Altered mental status	-	1658	90.40	1227	89.11	431	94.31	
	+	176	9.60	150	10.89	26	5.69	0.001
Tumor-related neurologic deficit	-	1591	86.75	1183	85.91	408	89.28	
	+	243	13.25	194	14.09	49	10.72	0.066
Stroke	-	1723	93.95	1295	94.05	428	93.65	
	+	111	6.05	82	5.95	29	6.35	0.762
Heart disease without prior intervention	-	1815	98.96	1364	99.06	451	98.69	
	+	19	1.04	13	0.94	6	1.31	0.500

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30-day postoperative outcomes of patients undergoing craniotomy for tumor resection in the NSQIP database 2005-2010

Table 2

	Non-Meningioma		Meningioma		P-value
	N	%	N	%	
Stroke	25	1.82	13	2.84	0.187
Infection	36	2.61	7	1.53	0.215
RTOR	98	7.12	23	5.03	0.129
MI	23	1.67	1	0.22	0.016
Death	45	3.27	4	0.88	0.004

Chi-square test was used to compute p-values.

Table 3
Predictive model application

Deep surgical site infection		Return to the OR (absolute risk (%) $\pm$ C.I.)	
No factors	0.90	No Risk	3.79
WL	2.97	Smoking	6.26
Plegia+WL	6.70	HTN+Smoking	10.53
Stroke+Plegia+WL	23.37	Plegia+HTN+Smoking	16.79
All Significant Factors	41.05	All Significant Factors	34.06
Myocardial infarction (absolute risk (%) $\pm$ C.I.)		Death (absolute risk $\pm$ C.I.)	
No Risk	0.03	No Risk	0.91
Stroke	0.19	TCD	3.25
WL+Stroke	1.02	Stroke+TCD	8.58
AMS+WL+Stroke	4.83	AMS+Stroke+TCD	28.89
All Significant Factors	17.39	All Significant Factors	52.01

WL= weight loss

Plegia= tumor related neurologic deficit

HTN = hypertension

AMS = altered mental status

TCD = treated (with intervention) cardiac disease