



A novel online calculator predicting short-term postoperative outcomes in patients with metastatic brain tumors

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Received: 28 June 2020 / Accepted: 16 September 2020
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Abstract

Purpose Establishing predictors of hospital length of stay (LOS), discharge disposition, and total hospital charges is essential to providing high-quality, value-based care. Though previous research has investigated these outcomes for patients with metastatic brain tumors, there are currently no tools that synthesize such research findings and allow for prediction of these outcomes on a patient-by-patient basis. The present study sought to develop a prediction calculator that uses patient demographic and clinical information to predict extended hospital length of stay, non-routine discharge disposition, and high total hospital charges for patients with metastatic brain tumors.

Methods Patients undergoing surgery for metastatic brain tumors at a single academic institution were analyzed (2017–2019). Multivariate logistic regression was used to identify independent predictors of extended LOS (> 7 days), non-routine discharge, and high total hospital charges (> \$ 46,082.63). $p < 0.05$ was considered statistically significant. C-statistics and the Hosmer–Lemeshow test were used to assess model discrimination and calibration, respectively.

Results A total of 235 patients were included in our analysis, with a mean age of 62.74 years. The majority of patients were female (52.3%) and Caucasian (76.6%). Our models predicting extended LOS, non-routine discharge, and high hospital charges had optimism-corrected c-statistics > 0.7, and all three models demonstrated adequate calibration ($p > 0.05$). The final models are available as an online calculator (https://neurooncsurgery.shinyapps.io/brain_mets_calculator/).

Conclusions Our models predicting postoperative outcomes allow for individualized risk-estimation for patients following surgery for metastatic brain tumors. Our results may be useful in helping clinicians to provide resource-conscious, high-value care.

Keywords Brain tumor · Neuro-oncology · Outcomes

Introduction

Metastatic tumors are the most common cancerous lesions in the brain, with approximately 20–40% of all cancer patients developing brain metastases [1]. Aside from a poor clinical prognosis, patients who develop metastatic brain tumors also often face the additional burden of high cost of care [1, 2]. Value-based care aims to lower healthcare costs associated with metastatic brain tumor management [4]. Important metrics used to gauge the effectiveness of value-based care approaches include minimizing hospital length of stay,

optimizing discharge disposition, and reducing costs [5, 6]. While statistical models that predict these value-based outcomes have been developed within various medical specialties, there is a lack of generalizability of these models for practical use in the metastatic brain tumor population [11, 12]. Additionally, the importance optimizing healthcare resource utilization has become increasingly evident during the ongoing COVID-19 pandemic [13, 14]. Our tool may be useful in aiding healthcare systems to more effectively allocate scarce healthcare resources before, during, and after similar times of high future demand.

The present study developed and validated three predictive models that can be used to predict extended length of stay, nonroutine discharge disposition, and high total hospital charges among patients undergoing metastatic brain tumor resection. We provide access to the predictive models through a web-based calculator application that has the

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potential to directly aid in accurately predicting postoperative outcomes and secondarily increasing the provision of high-value healthcare.

Methods

Patient selection and recorded variables

The present study utilized data from a consecutive series of 356 adult patients (age ≥ 18 -years-old) who were operated on for metastatic brain tumors at a single institution between January 1, 2017 and December 31, 2019. Our Institutional Review Board (IRB) approved the waiver of informed consent for this study (IRB00209855). The following variables were collected by the Center for Clinical Data Analysis at our institution using International Statistical Classification of Diseases and Related Health Problems 9th (ICD-9) and 10th revision (ICD-10) codes: patient age, sex, race, ethnicity, marital status, medical comorbidity data, total hospital LOS (in days), total hospital charges (in U.S. dollars), and incidence of postoperative complications. Patient insurance status, admission source, primary cancer site, number of metastatic brain tumors, tumor size (cm^3), tumor location (supratentorial, infratentorial, or both), presence of additional extracranial metastases, history of prior radiation therapy, Karnofsky Performance Status (KPS) score, surgery duration (in min), and discharge disposition were verified using manual chart review of electronic medical records. Due to a low number of African-American, Asian, and Other race patients, race was analyzed as binary categorical variable (Caucasian and non-Caucasian). Tumor size was determined using magnetic resonance images (MRIs) and was measured using tumor dimensions in the axial (x), coronal (y), and sagittal (z) planes via the following formula: $\frac{x \cdot y \cdot z}{2}$. “Additional extracranial metastases” was defined as a metastasis from the tumor’s primary site to a location other than the brain. For each patient, we calculated a 5-factor modified frailty index (mFI-5) score [15]. Patients received one point for each of the following comorbidities: hypertension, diabetes, heart failure, chronic obstructive pulmonary disease, and functional status. Functional status was defined as requiring assistance with activities of daily living.

After excluding repeat surgeries and patients for whom we were missing any of the aforementioned data, our final cohort consisted of 235 patients who underwent a craniotomy for tumor resection ($n=234$, 99.6%) or received a stereotactic biopsy ($n=1$, 0.4%). In the present study, extended hospital LOS was defined as > 7 days, as 7 days was the cutoff for the upper quartile of hospital LOS in our patient cohort. High total hospital charges were defined as charges exceeding \$ 46,082.63, which was the upper quartile for hospital charges in our cohort. This methodology of using

the upper quartile to define extended LOS and high healthcare charges has been previously described [16–19]. Routine discharge disposition was defined as discharge to home (self-care) or home with healthcare service assistance. Nonroutine discharge disposition was defined as discharge to any other location (i.e. rehabilitation facility, skilled nursing facility).

Statistical analysis

Data were collected using Microsoft Excel (version 2016, Microsoft Corp.). Statistical analyses were conducted using R statistical software and RStudio (3.3.2, r-project.org). The Shapiro–Wilk test was used to test for normality. In bivariate analyses, categorical variables were analyzed using Fisher’s exact test, and the Mann–Whitney U test was used to analyze continuous variables due to violation of the normality assumption. Multivariate analyses were conducted using logistic regression models. Variables that demonstrated an association with extended LOS, discharge disposition, or high total hospital charges at a significance level of $p < 0.05$ were included as covariates in three separate multivariate logistic regression models examining each of these outcomes individually. The final models were chosen by selecting the combination of covariates that minimized the Akaike information criterion (AIC) [20, 21]. Variance inflation factors (VIFs) were calculated for each model covariate, with a $VIF > 5$ indicating collinearity [22]. Model discrimination was assessed using the c-statistic. In the present study, a c-statistic cutoff of ≥ 0.7 defined a model with clinically-useful predictive ability [23, 24]. A naïve c-statistic was calculated by fitting our model to the entire dataset, and 2000 bootstrap samples were used to calculate an optimism-corrected c-statistic [25]. The Hosmer–Lemeshow test was used to assess model calibration, with a test result of $p > 0.05$ indicating adequate model calibration. Values of $p < 0.05$ were considered statistically significant, and p-values were reported as two-sided.

Results

Patient demographic and clinical characteristics

The characteristics of our patient cohort are summarized in Table 1. Our patients had a mean age of 62.74 years and were majority female (52.3%), Caucasian (76.6%), and not of Hispanic/Latino origin (98.7%). There was no significant difference between the racial proportions of patients who were excluded due to missing data (84 Caucasian patients, 25 African-American patients, 7 Other race patients, and 5 Asian patients) when compared to the racial proportions of patients included in our analysis ($p=0.093$ by Fisher’s exact test). Most patients were married (62.6%), had private

Table 1 Patient demographics and clinical characteristics for overall cohort (n = 235)

Characteristic	n (%)
Mean age in years (\pm SD)	62.74 \pm 11.35
Sex	
Female	123 (52.3)
Male	112 (47.7)
Race	
Caucasian	180 (76.6)
African-American	44 (18.7)
Asian	8 (3.4)
Other	3 (1.3)
Ethnicity	
Not hispanic latino	232 (98.7)
Hispanic/latino	3 (1.3)
Marital status	
Married	147 (62.6)
Not married	88 (37.4)
Insurance	
Medicare	98 (41.7)
Private	119 (50.6)
Medicaid	18 (7.7)
Admission source	
Home	175 (74.5)
Non-home	60 (25.5)
Primary cancer type	
Lung	71 (30.2)
Unknown primary site	52 (22.1)
Skin	33 (14.0)
Breast	32 (13.6)
Gastrointestinal	21 (8.9)
Other specific site*	17 (7.2)
Renal	9 (3.8)
Number of metastatic brain tumors	
> 1	110 (46.8)
1	125 (53.2)
Mean tumor size \pm SD**	15.49 \pm 19.53
Tumor location	
Supratentorial	163 (69.4)
Infratentorial	30 (12.8)
Both	42 (17.9)
Additional extracranial metastases	
Yes	100 (42.6)
No	135 (57.4)
History of prior radiation therapy	
Yes	64 (27.2)
No	171 (72.8)
Mean KPS \pm SD	80.06 \pm 14.33
Mean mFI-5 \pm SD	1.00 \pm 0.90
Medical comorbidities comprising the mFI-5	
Hypertension	131 (55.7)
Chronic obstructive pulmonary disease	35 (14.9)

Table 1 (continued)

Characteristic	n (%)
Diabetes	42 (17.9)
Functional status†	17 (7.2)
Heart failure	9 (3.8)
Mean surgery duration in minutes (\pm SD)	141.77 \pm 72.23
Mean length of stay \pm SD	6.17 \pm 6.41
\leq 7 days	176 (74.9)
> 7 days	59 (25.1)
Discharge disposition	
Routine	182 (77.4)
Non-routine	53 (22.6)
Mean total hospital charges (\pm SD; \$)	40,172.65 \pm 22,505.77
\leq 46,082.63	176 (74.9)
> \$46,082.63	59 (25.1)

*Other specific metastases sites: 5 patients with prostate metastases, 4 with gynecological metastasis, 3 with thyroid metastases, 2 with bladder metastases, 1 with parotid salivary duct metastases, 1 with olfactory neuroepithelial metastasis, and 1 with testicular metastases. KPS karnofsky performance status, mFI-5 5-factor modified frailty index, SD standard deviation. **For patients with more than 1 tumor, all tumor volumes were measured and summed. †Functional status was defined as requiring assistance with activities of daily living

health insurance (50.6%), and were admitted to the hospital from home (74.5%). The three most common primary cancer types were brain metastases originating from the lung (30.2%), from an unknown primary site (22.1%), and from the skin (14.0%). A total of 110 (46.8%) patients had more than 1 metastatic brain tumor. The mean tumor size (\pm standard deviation) of our patient cohort was 15.49 (\pm 19.53), and a majority of patients (69.4%) had supratentorial tumors.

Within our patient cohort, a total of 100 (42.6%) patients had metastases to sites besides the brain. The extracranial metastases noted within our cohort were as follows: 30 (12.8%) patients had extracranial metastases to the lungs, 26 (11.1%) to bone; 2 (0.9%) to the liver; 2 (0.9%) to the prostate; 2 (0.9%) to the thyroid; 2 (0.9%) to the kidney; 1 (0.4%) to the spleen, and 1 (0.4%) to the colon. The remaining 34 (34.0%) patients had metastases to two or more sites besides the brain. The average KPS score, mFI-5 score, surgery duration, LOS, and total hospital charges for our cohort were 80.06, 1.00, 141.77 min, 6.17 days, and \$40,172.65 dollars, respectively. Within our cohort, 59 (25.1%) patients had a LOS > 7 days, 53 (22.6%) patients had a nonroutine discharge disposition, and 59 (25.1%) patients had hospital charges greater than \$46,082.63.

In line with previous neurosurgical oncology health disparities research efforts, we sought to explore differences specifically between Caucasian (n = 180) and African-American (n = 44) patients regarding the following preoperative variables: age, sex, marital status, insurance, admission

source, known versus unknown cancer primary site, number of metastatic brain tumors, tumor size, tumor location, presence of additional extracranial metastases, history of prior radiation therapy, KPS score, and mFI-5 score [26, 27]. African-American patients were significantly more likely to be female rather than male compared to Caucasian patients (OR = 2.84, $p=0.0041$), and were also significantly more likely to be unmarried rather than married compared to Caucasian patients (OR = 3.10, $p=0.0015$). Regarding insurance status, African-American patients were significantly more likely to be insured through Medicaid (OR = 3.86, $p=0.015$) rather than private insurance when compared to Caucasian patients. African-American patients were also significantly more likely to present with metastatic brain tumors in both supratentorial and infratentorial locations (relative to supratentorial location only; OR = 2.41, $p=0.043$) when compared to Caucasian patients. No other preoperative variables were significantly different between these two patient cohorts.

In our study, a total of 86 (36.6%) patients experienced at least one postoperative complication. The following types of complications were noted within our patient cohort: 38 (16.2%) patients experienced an intracranial injury (including concussions, lacerations, contusions, intracranial hemorrhages, or unspecified intracranial injuries), 27 (11.5%) experienced a thromboembolic event, 18 (7.7%) had a fracture or dislocation, 7 (3.0%) had sepsis, 4 (1.7%) had physiological and metabolic derangement, 4 (1.7%) had respiratory failure, 3 (1.3%) had a cerebrospinal fluid leak, 2 (0.9%) experienced diabetic ketoacidosis, and 2 (0.9%) developed a wound infection.

Metastatic tumor primary site subset analysis and bivariate analysis

Demographic and clinical characteristics for patients with either known ($n=183$) or unknown ($n=52$) primary cancer sites were recorded. Overall, there were no significant differences in admission source, KPS scores, mFI-5 scores, surgery duration, LOS, discharge disposition, or hospital charges between these two patient cohorts.

Bivariate analyses were performed comparing patient characteristics with the following outcomes: routine versus extended (> 7 days) LOS, routine versus nonroutine discharge disposition, and low or average versus high total hospital charges (> \$46,082.63). Variables significantly associated with extended LOS included non-Caucasian race ($p=0.013$), non-home admission source ($p<0.0001$), lower KPS score ($p<0.0001$) and higher mFI-5 score ($p<0.0001$). Older patient age ($p<0.0001$), non-Caucasian race ($p=0.026$), unmarried status ($p=0.024$), non-home admission source ($p<0.001$), lower KPS score ($p<0.0001$), and higher mFI-5 score ($p<0.0001$) were all significantly

associated with nonroutine discharge disposition. Variables significantly associated with higher costs included non-Caucasian race ($p=0.0022$), non-home admission source ($p<0.0001$), lower KPS score ($p<0.001$), higher mFI-5 score ($p=0.0024$), and longer surgery duration ($p<0.001$). No other variables were significantly associated with extended LOS, discharge disposition, or high total hospital charges. Further, incidence of at least one postoperative complication was not significantly associated with extended LOS ($p=0.21$), nonroutine discharge disposition ($p=0.26$), or high hospital charges ($p=0.12$).

Multivariate analysis and model predictive performance metrics

Tables 2, 3, 4 display the AIC-optimized models for our high-value care outcomes. Independent predictors of extended LOS included non-Caucasian race (OR = 3.24, $p=0.0037$), non-home admission source (OR = 6.64, $p<0.0001$), KPS score (OR = 0.96, $p=0.0032$), and mFI-5 score (OR = 1.79, $p=0.0028$). For nonroutine discharge disposition, independent predictors included patient age (OR = 1.07, $p=0.0035$), non-Caucasian race (OR = 3.61, $p=0.0055$), non-home admission source (OR = 3.76, $p=0.0015$), and mFI-5 score (OR = 1.61, $p=0.035$). Unmarried status approached but did not attain a statistically significant association with discharge disposition in multivariate analysis (OR = 1.93, $p=0.098$). Finally, independent predictors of high hospital charges included non-Caucasian race (OR = 4.18, $p<0.001$), non-home admission source (OR = 5.25, $p<0.0001$), KPS score (OR = 0.97, $p=0.0071$), mFI-5 score (OR = 1.58, $p=0.021$), and longer surgery duration (OR = 1.01, $p<0.001$). The VIFs for all covariates in our three models were below 2, suggesting an absence of

Table 2 Multivariate analysis of length of stay > 7 days ($n=235$)

Variable	Odds ratio	95% confidence interval	p-value	VIF
Race				
Caucasian	Ref	–	–	–
Non-caucasian	3.24	1.47–7.24	0.0037*	1.09
Admission source				
Home	Ref	–	–	–
Non-home	6.64	3.19–14.29	<0.0001*	1.08
KPS (per 1 point increase)	0.96	0.94–0.99	0.0032*	1.02
mFI-5 (per 1 point increase)	1.79	1.23–2.66	0.0028*	1.02

Asterisks, bold, and italics indicate statistical significance ($p < 0.05$)
KPS karnofsky performance status score, *mFI-5* 5-factor modified frailty index, *VIF* variance inflation factor

Table 3 Multivariate analysis of nonroutine discharge disposition (n = 235)

Variable	Odds ratio	95% confidence interval	p-value	VIF
Age (per 1 year increase)	1.07	1.02–1.11	0.0035*	1.23
Race				
Caucasian	Ref	–	–	–
Non-caucasian	3.61	1.47–9.13	0.0055*	1.19
Marital status				
Married	Ref	–	–	–
Not married	1.93	0.89–4.27	0.098	1.06
Admission source				
Home	Ref	–	–	–
Non-home	3.76	1.67–8.67	0.0015*	1.08
KPS (per 1 point increase)	0.94	0.91–0.96	<0.0001*	1.05
mFI-5 (per 1 point increase)	1.61	1.04–2.52	0.035*	1.11

Asterisks, bold, and italics indicate statistical significance ($p < 0.05$)
KPS karnofsky performance status score, *mFI-5* 5-factor modified frailty index, *VIF* variance inflation factor

significant collinearity. We also analyzed the associations between LOS, discharge disposition, and hospital charges within our patient cohort. Patients who had an extended LOS were significantly more likely to have a nonroutine discharge disposition (OR = 19.03, $p < 0.0001$) and were also significantly more likely to incur high hospital charges (OR = 62.90, $p < 0.0001$). Further, patients who incurred high hospital charges were also significantly more likely to have a nonroutine discharge disposition (OR = 14.39, $p < 0.0001$).

Naïve c-statistics for our extended LOS, nonroutine discharge, and high hospital charges models were 0.824, 0.870,

and 0.833, respectively. Optimism-corrected c-statistics for LOS (0.810), nonroutine discharge (0.851), and high hospital charges models (0.817) indicated that our three models all had clinically-useful discrimination [23, 24]. Our LOS, nonroutine discharge, and high hospital charges models had Hosmer–Lemeshow test p-values of 0.97, 0.70, and 0.64, respectively, indicating adequate model calibration ($p > 0.05$). Our three models have been deployed as an online calculator, available at the following web link: https://neurooncsurgery.shinyapps.io/brain_mets_calculator/.

Discussion

The present study developed models predicting risk for extended length of stay, nonroutine discharge disposition, and high total hospital charges among metastatic brain tumor patients. Independent predictors of these postoperative outcomes included KPS score, mFI-5 score, non-Caucasian race, patient age, non-home admissions source, and surgery duration.

Our results demonstrate a significant, independent association between KPS score and LOS, discharge disposition, and hospital charges. While research has shown KPS to be strongly associated with overall and progress-free survival among metastatic brain tumor patients, there has been limited research into how well KPS can prognosticate high-value care outcomes [28, 29]. To our knowledge, the present study is the first to utilize KPS to predict individualized risk of high-value care outcomes specifically among patients undergoing surgical treatment of metastatic brain tumors.

Our study also established mFI-5 score as a novel independent predictor of LOS, nonroutine discharge disposition, and high total hospital charges for metastatic brain tumor patients. The mFI-5 was recently developed as a means to addressing the shortcomings of previous indices such as

Table 4 Multivariate analysis of total hospital charges > \$46,082.63 (n = 235)

Variable	Odds ratio	95% confidence interval	p-value	VIF
Race				
Caucasian	Ref	–	–	–
Non-caucasian	4.18	1.91–9.40	<0.001	1.11
Admission source				
Home	Ref	–	–	–
Non-home	5.25	2.46–11.53	<0.0001*	1.10
KPS (per 1 point increase)	0.97	0.94–0.99	0.0071	1.07
mFI-5 (per 1 point increase)	1.58	1.08–2.35	0.021	1.04
Surgery duration (per min increase)	1.01	1.01–1.02	<0.001	1.05

Asterisks, bold, and italics indicate statistical significance ($p < 0.05$)

KPS karnofsky performance status score, *mFI-5* 5-factor modified frailty index, *VIF* variance inflation factor

the Charlson Comorbidity Index (CCI) and the 11-factor modified frailty index (mFI-11) [30, 31]. Recent work has established the mFI-5 as both an effective predictor of outcomes such as 90-day mortality, LOS, complications, hospital charges, and successful postoperative day 1 discharge among brain tumor patients [31–33]. Using a tool such as the mFI-5 to create an integrated treatment plan cognizant of medical comorbidities is a promising avenue for optimizing quality of care [34–36]. For instance, a subset of patients with high frailty and poor estimated short-term outcomes from surgery may be counseled to consider non-invasive treatments, including potentially upfront stereotactic radiosurgery (SRS) [37].

The independent predictive value of non-Caucasian race on extended LOS, nonroutine discharge disposition, and high total hospital charges are in line with previous research findings [27, 38, 39]. Nuno et al. found that, even after controlling for risk factors such as insurance status and medical comorbidities, African-American patients undergoing craniotomy for brain metastases still had poorer postoperative outcomes compared to Caucasian counterparts [26]. Additionally, Sheppard et al. found that African-American patients undergoing craniotomy for tumor resection had prolonged LOS relative to Caucasian counterparts, even after controlling for insurance status [40]. As discussed by Mukherjee et al., findings associating patient race with adverse outcomes likely arise as a result of larger structural factors such as health literacy and unequal access to care among patients who identify as racial minorities [27]. Notably, insurance status may represent a potentially modifiable risk factor that can be influenced through targeted policy initiatives and which may reduce racial disparities in adverse postoperative outcomes. It is also important to note that while our study cohort is 18.7% African-American, the population of Baltimore City, Maryland is 62.5% African-American [41]. This difference is likely also due to unequal access to care, in line with previous research by Mukherjee et al. demonstrating that both African-American patients with brain tumors were significantly less likely than white patients to be admitted to high-volume hospitals [42]. Our study therefore also highlights persistent barriers to neuro-oncologic care for racial minorities.

As an independent predictor for nonroutine discharge disposition, greater patient age is also an important factor to consider during management of brain tumor metastases. Older age has been independently associated with a non-home discharge for many procedures, including craniotomy for brain tumor, shoulder arthroplasty, and anterior cervical discectomy and fusion [19, 43, 44]. Our results also demonstrate that non-home admission source in an independent risk factor for extended LOS, nonroutine discharge disposition, and high total hospital charges in metastatic brain tumor patients. Previous research suggests

that patients who are admitted to the hospital from sites other than home experience a greater association with other adverse outcomes such as postoperative mortality [45, 46]. Special consideration should be taken to provide the highest-quality healthcare for older metastatic brain tumor patients and those from a non-home admission source. Evaluation of baseline health status and comorbid conditions should help guide surgical decision making and the consideration of possible non-operative management in frail older patients [47, 48]. Our study also established surgery duration as an independent predictor for increased total hospital costs among metastatic brain tumor patients. Individualizing surgical approaches and investigating the efficacy of existing surgical practice patterns can potentially help increase operative efficiency and subsequently decrease operative duration [28, 49, 50].

While our online calculator has the potential to be easily incorporated into clinical workflows, it is important to clarify that the purpose of our models is to serve as an adjunct to the clinical acumen of an experienced clinician. The models should only be considered a single facet among many factors determining a patient's treatment plan. If utilized to help guide decision-making within an established patient-provider relationship, our calculator may aid clinicians in proactively providing high-value care to patients with metastatic brain tumors.

Limitations

This study is retrospective and therefore we cannot comment on causal relationships between the variables examined in our study. Additionally, the administrative dataset we utilized to determine hospital charges may not have captured all charges associated with care, such as that incurred by molecular analysis of tumor tissue. Third, it is possible that postoperative complications not captured in our dataset (i.e. postoperative cognitive deficits) may demonstrate a significant association with LOS, discharge disposition, or cost, in contrast to our present findings. Fourth, our database did not contain the data elements necessary to fully examine why non-Caucasian patients incurred higher hospital charges, and more specifically the extent to which LOS contributed to higher cost relative to other factors. This may serve as a promising avenue for future research. Fifth, our patients were all treated at a single, academic institution during a restricted time period and therefore the generalizability of our models must be established by external validation before clinical use. Sixth, our online calculator has not been validated for patients treated using only chemotherapy, radiation, and other non-surgical approaches.

Conclusion

Our study developed three models predicting length of stay, nonroutine discharge disposition, and high total hospital charges among patients undergoing surgery for metastatic brain tumors and incorporated these models into an online calculator. Our calculator may be useful for individualizing risk-estimation and in aiding clinicians to provide high-value care.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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