Impact of Extent of Resection on Incidence of Postoperative Complications in Patients With Glioblastoma

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BACKGROUND: Extent of resection (EOR) is well established as correlating with overall survival in patients with glioblastoma (GBM). The impact of EOR on reported quality metrics such as patient safety indicators (PSIs) and hospital-acquired conditions (HACs) is unknown.

OBJECTIVE: To perform a retrospective study to evaluate possible associations between EOR and the incidence of PSIs and HACs.

METHODS: We queried all patients diagnosed with GBM who underwent surgical resection at our institution between January 2011 and May 2017. Pre- and postoperative magnetic resonance images were analyzed for EOR. Each chart was reviewed to determine the incidence of PSIs and HACs.

RESULTS: A total of 284 patients met the inclusion criteria. EOR ranged from 39.00 to 100%, with a median of 99.84% and a mean of 95.7%. There were 16 PSI, and 13 HAC, events. There were no significant differences in the rates of PSIs or HACs when compared between patients stratified by gross total resection (EOR $\geq$ 95%) and subtotal resection (EOR $<$ 95%). The odds of encountering a PSI or HAC were 2.5 times more likely in the subtotal resection group compared to the gross total resection group ($P = .58$). After adjusting for confounders, the odds of encountering a PSI or HAC in the subtotal resection group were 3.9 times greater than for the gross total resection group ($P < .05$).

CONCLUSION: Gross total resection of GBM is associated with a decreased incidence of PSIs and HACs, as compared to subtotal resection.

KEY WORDS: Glioblastoma, Quality metrics, Extent of resection, Glioma, High-grade glioma, Postoperative complications, Patient safety indicators, Hospital-acquired conditions

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Increasing extent of resection (EOR) for patients with glioblastoma (GBM) is associated with significantly improved survival.[1-3] Numerous retrospective studies have demonstrated that EOR is positively associated with overall and progression free survival.[4-7] Therefore, all treatment for GBM starts with a discussion of the feasibility of achieving a maximal and safe resection. Several technologies have also been developed to improve the likelihood of an aggressive resection, such as tumor fluorescence and intraoperative magnetic resonance imaging (MRI).[8-11]

The aim for maximal resection must be tempered by the risk of causing a postoperative complication, which diminishes quality of life and also impacts overall survival.[5] Patients who sustain a surgical complication following glioma resection may be up to 4.4 times more likely to die during their hospital stay.[12] The most prevalent complications are iatrogenic stroke and postoperative hemorrhage.[12] The introduction of postoperative language or motor deficits

ABBREVIATIONS: CNS, central nervous system; **DVT,** deep venous thrombosis; **EOR,** extent of resection; **GBM,** glioblastoma; **GPS,** generalized propensity score; **GTR,** gross total resection; **HAC,** hospital-acquired condition; **IRB,** Institutional Review Board; **KPS,** Karnofsky Performance Score; **MRI,** magnetic resonance imaging; **PS,** propensity score; **PSI,** patient safety indicator; **REDCap,** Research Electronic Data Capture; **SD,** standard deviation; **STR,** subtotal resection

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has been shown to negatively impact overall survival.[13] Moreover, a new permanent neurological deficit after resection of a newly diagnosed GBM significantly reduces survival compared to patients with only temporary deficits or no deficits.[5]

Neurological complications are meaningful for patients and providers. However, regulatory agencies track complications that allow for comparison across healthcare institutions and most of these complications are not neurological complications. The Agency of Healthcare Research and Quality and the Center for Medicare and Medicaid Services have created a list of events termed patient safety indicators[15] (PSIs) and hospital-acquired conditions (HACs) that are intended to represent quality metrics that can be used as a point of comparison between healthcare providers and between hospitals. Examples of PSIs and HACs include central venous line-related blood stream infection, deep vein thrombosis and pulmonary embolism, sepsis, retained foreign object, and catheter-associated urinary tract infection.[14,15] These metrics are becoming increasingly important for rating quality of care and reimbursement. Therefore, they are often the focus of strategies to reduce complications. The impact of EOR on these reported quality metrics is unknown. Our objective was to determine the impact of EOR in patients with GBM on the incidence of PSIs and HACs in the postoperative period.

METHODS

Patient Selection

After obtaining approval by our Institutional Review Board (IRB), we searched the billing database for the records of patients who had a craniotomy for a supratentorial GBM, between January 1, 2011 and May 17, 2017. This study caused no risk to the study population, and therefore, IRB approval was granted without need for obtaining patient consent. Patients less than 18 yr of age were excluded from this study. All patients who underwent craniotomy for resection of pathology-proven GBM, with postoperative cranial imaging within 72 h of surgery, were included in this study.

Data Acquisition

Patient data were collated in REDCap (Research Electronic Data Capture)—a secure, web-based online database. Patient charts were reviewed from initial presentation, until up to 3 mo following surgical resection, including outpatient clinic visits. Data collected included patient demographics, comorbid medical conditions, and use of antiepileptic drugs, steroids, and anticoagulants. Radiographic parameters measured from preoperative and postoperative scans were also collected. Preoperative MRIs were analyzed to define tumors located near eloquent locations. Tumor eloquence was defined as those tumors located in the motor cortex, sensory cortex, language cortex, visual cortex, basal ganglia, or brainstem. In the absence of preoperative functional MRI, left hemispheric dominance for language was assumed. Postoperative periods were screened for the following 23 PSIs: misplaced trach tube, adverse effects of central nervous system (CNS) depressants/anesthetics, poisoning by other CNS depressants/anesthetics, pressure ulcer, foreign body retained postoperatively, iatrogenic pneumothorax, central venous line infection, postoperative hip fracture, secondary diabetes with ketoacidosis, diabetes with hyperosmolarity, diabetes with other coma, postoperative hemorrhage, acute respiratory failure, mechanical ventilation for more than 96 h, mechanical ventilation, reintubation, deep venous thrombosis (DVT), pulmonary embolism, postoperative wound dehiscence, accidental puncture or laceration, and transfusion reaction. Postoperative periods were also screened for the following 15 HACs: foreign body retained postoperatively, air embolism, blood incompatibility, pressure ulcer stages III and IV, fracture, dislocation, intracranial injury, crushing injury, burn, other injuries, and catheter-associated urinary tract infection. We excluded HACs that were not applicable such as mediastinitis following coronary artery bypass graft, surgical site infection following certain orthopedic procedures, surgical site infection following bariatric surgery, and DVT/pulmonary embolism following certain orthopedic procedures.

Methods for volumetric analysis have been published elsewhere with demonstration of adequate interobserver reliability.[5] Patient preoperative and postoperative imaging results were reviewed by 4 of the authors, and tumor volumes were manually measured with the Eclipse (Varian, Palo Alto, California) treatment planning system. The enhancing region on T1 postcontrast MRI was contoured. The contours were then copied to a MATLAB (MathWorks, Natick, Massachusetts) script that summed the pixels inside each contoured region, yielding an area of interest per slice. These areas were normalized to the pixel resolution width of each slice, and then summed per region of interest.

Statistical Analysis

Summary statistics are provided as means with standard deviations, medians with ranges/interquartile ranges, or percentages. The Wilcoxon rank sum test was used to compare distributions of observed EORs between patient groups defined by the presence/absence of each PSI or HAC. The likelihood ratio chi-square test and the Fisher exact test were used to compare PSI/HAC occurrence rates between patient groups defined by resection status: gross total resection (GTR; EOR $\geq$ 95%) or subtotal resection (STR; EOR $<$ 95%). We estimated the STR: GTR odds ratio for "any PSI/HAC" risk that our study sample size could detect with adequate statistical power. Assuming the study sample size of 250 used for effect estimation, a GTR prevalence of 72%, and a rate of 5.6% for "any PSI/HAC" events in GTR patients, an odds ratio of 3.44 could be detected with 80% powder at a 2-sided significance level of .05.

Demographics, comorbidities, and anatomical features were also compared between GTR and STR patient groups using the same tests.

Mixed effect logistic regression was used to model either the numeric level of EOR exposure or stratified GTR/STR exposure as a predictor of the log-odds of a patient experiencing at least one PSI or HAC. Between-surgeon variability in the outcome was assessed in each model by considering surgeon as a random effect.[16] To adjust for confounding, a generalized propensity score (GPS) model predicting the numeric level of continuous EOR exposure (mixed effect linear regression) and a standard propensity score (PS) model predicting the likelihood of GTR exposure were developed from a set of potential confounders using stepwise selection and bootstrap validation of the selection procedure to avoid model overfitting.[16-19] Potential confounders included demographics, individual comorbidities, and tumor anatomic features. Surgeon was modeled as a random effect in both the GPS and PS models. EOR scores from the final GPS model were converted to inverse GPS weights, and the PSI/HAC outcome model with numeric EOR exposure was refitted using inverse GPS weighting, yielding an EOR odds ratio adjusted for the

TABLE 1. Covariate Balance Achieved by the STR Propensity Score Model

Predictor	Unadjusted	Inverse propensity score weighting		
	GTR	STR	GTR	STR
Hyperlipidemia	20%	25.70%	20.90%	22.30%
Other neurological disorder	20.60%	31.40%	23.80%	23.80%
Use of antiepileptic drugs	76.10%	88.60%	79.50%	81.60%
Use of anticoagulant	19.40%	12.90%	18%	19.10%
Tumor crossing midline	8.90%	14.30%	10.30%	9.60%
Parietal location	23.30%	34.30%	25.80%	25.80%
Midline shift	45.00%	50.00%	46.90%	49.80%
Eloquent location	27.60%	35.70%	28.80%	25.90%
KPS (mean)	72.60%	75.30%	73.40%	74.50%
Mean tumor volume (ccs)	46	40	44.5	44.6

confounders from the final GPS model. Similarly, GTR scores from the final PS model were converted to PS weights, and the PSI/HAC outcome model with binary STR/GTR exposure was refitted using inverse PS weighting, yielding a GTR: STR odds ratio adjusted for confounders from the final PS model.

The effectiveness of inverse GPS score weighting was assessed by comparing mean-weighted EOR between the strata of each confounder selected in the final GPS model. The impact of inverse PS score weighting on covariate balance between GTR and STR strata was assessed by contrasting unadjusted and weighted summary statistics of each confounder between GTR/STR strata (Table 1). In both the PS and outcome models, a mixture chi-square test was used to determine if the surgeon random effect variance component exceeded zero.[20] Odds ratios from logistic regression model fits are presented with 95% CI intervals and Wald test *P* values for difference from an odds ratio of 1. All $P < .05$ were considered statistically significant. All computations were carried out using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patient Demographics

A total of 284 patients met the inclusion criteria for this study. The baseline patient characteristics are shown in Table 2. The majority of patients were male (n = 161, 57%). The average age at diagnosis was 53.4 (standard deviation [SD] 15.5). The median preoperative Karnofsky Performance Score (KPS) was 80 (range 20-100). The average preoperative tumor volume was 42.1 cm^3 (SD 33.9), with a residual volume of 1.6 cm^3 (SD 3.0), resulting in a median EOR of 99.8% (range 39.0-100%). Residual tumor volume was significantly greater in patients who received STR (4.94 cm^3), as compared to GTR (0.38 cm^3) ($P < .0001$). The most common comorbid presenting variables were hypertension (n = 108, 38%), former smoking status (n = 70, 25%), other neurological disorders (ie, dementia and unrelated seizure disorder) (n = 66, 23%), hyperlipidemia (n = 58, 21%), and current smoking status (n = 58, 20%). The majority of patients had radiographic evidence of vasogenic edema at the time of initial imaging (n = 214, 79%), and 120 (45%) had evidence of midline shift. Tumor location in decreasing frequency was as follows: frontal (n = 146, 51%), temporal (n = 112, 39%), parietal (n = 73, 26%), occipital (n = 28, 10%), and insular (n = 13, 5%). For patients who underwent GTR, 33.7% of tumors were

TABLE 2. Baseline Patient Characteristics (N = 284 Patients)

Variable	Mean (SD), median (range) or %
Mean age in years (SD)	53.4 (15.5)
Male	56.7%
Median preop KPS score (range)	80 (20-100)
Peritumoral edema	79.0%
Midline shift	44.9%
Tumor location	
Crossing midline	11.1%
Frontal	51.4%
Temporal	39.4%
Parietal	25.7%
Occipital	9.9%
Insular	4.6%
Comorbidities	
Hypertension	38.2%
Ex-smoker	24.7%
Other neuro	23.3%
Hyperlipidemia	20.6%
Smoker	20.4%
Cancer	15.2%
Gastrointestinal disease	13.1%
Diabetes mellitus	12.5%
Endocrine disorder	9.9%
Lung disease	8.9%
Coronary artery disease	8.1%
Renal disease	6.4%
Previous venous thromboembolism	2.1%
Congestive heart failure	1.1%
Volumetrics	
Mean enhanced tumor volume in cm^3 (SD)	42.1 (33.9)
Median EOR in % (range)	99.8 (39.0-100.0)
Mean RV in cm^3 (SD)	1.6 (3.0)

TABLE 3. Frequency of PSIs and HACs (N = 284 Patients)

PSI/HAC	N	%
Deep vein thrombosis	4	1.4
Pulmonary embolism	4	1.4
Postoperative wound dehiscence	4	1.4
Sepsis	3	1.1
Mechanical ventilation (<96 h)	1	0.4
Catheter-associated UTI	13	4.6
One PSI only	8	2.8
At least one PSI	12	4.2
At least one HAC	13	4.6
At least one PSI or HAC	22	7.8

located in eloquent cortex, and for those who underwent STR, 36% were located in eloquent cortex ($P = .71$) (**Table**, **Supplemental Digital Content 1**). The percentage of patients with a preoperative neurological deficit at baseline did not differ in patients who received GTR vs STR (45.2% vs 36%, $P = .17$) (**Table**, **Supplemental Digital Content 2**).

Incidence of PSI and HAC

At least one PSI was encountered in 4.2% (n = 12) of our patient population (Table 3). The most common PSIs in glioma patients undergoing resection of tumor were DVT (n = 4, 1.4%), pulmonary embolus (n = 4, 1.4%), postoperative wound dehiscence (n = 4, 1.4%), sepsis (n = 3, 1.1%), and mechanical ventilation for less than 96 h (n = 1, 0.4%). No other PSI categories were encountered. An HAC occurred in 4.6% (n = 13) of our patient population, with all 13 patients experiencing a catheter-associated urinary tract infection. Overall, 22 patients experienced at least one PSI or HAC, accounting for 7.75% of our patient population. Surgeon variance did not significantly affect the rate of PSI or HAC when considered alone, or in conjunction with GTR/STR status included as a random effect.

Simple comparison of EOR rank sums between patient groups defined by the presence/absence of each PSI or HAC revealed no significant shift in the distribution of observed EORs between PSI/HAC and non-PSI/HAC strata (Table 4). When EOR was considered as a continuous linear predictor of the log-odds of a patient experiencing at least one PSI or HAC in the subset of 250 patients with nonmissing data for all confounders, no significant association was observed (Table 5). The absence of an association persisted when the effect of continuous EOR was adjusted for confounding via inverse PS weighting. Covariates in the EOR PS model included current smoker, hyperlipidemia, use of antiepileptic drugs, use of anticoagulants, KPS, tumor crossing midline, eloquent tumor location, parietal tumor location, presence of midline shift, and preoperative tumor volume.

There were 209 patients who had GTR of malignant glioma (EOR ≥ 95%) and 75 patients who had STR (EOR < 95%). PSI and HAC rates of occurrence did not differ significantly between

TABLE 4. Median Extent of Resection in Patient Groups Defined by PSIs and HACs (N = 284 Patients)

PSI/HAC	Group	N	Median EOR	Interquartile range	P
Mechanical ventilation	No	281	99.9	94.5-100	.25
	Yes	1	93.0	93.0-93.0	
DVT	No	280	99.8	94.3-100	.34
	Yes	4	100.0	97.3-100	
Pulmonary embolism	No	280	99.8	94.6-100	.99
	Yes	4	97.3	94.4-100	
Sepsis	No	281	99.9	94.9-100	.36
	Yes	3	93.0	88.8-100	
Postoperative wound dehiscence	No	280	99.8	94.4-100	.95
	Yes	4	98.2	93.1-100	
Catheter-associated urinary tract infection	No	271	99.9	94.9-100	.28
	Yes	13	96.1	92.9-100	
At least one PSI	No	272	99.8	94.9-100	.83
	Yes	12	98.2	93.6-100	
At least one PSI/HAC	No	262	99.9	95.0-100	.53
	Yes	22	98.1	93.8-100	

TABLE 5. Linear Association Between EOR and the Odds of Encountering at Least One PSI or HAC (N = 250 Patients With Nonmissing Data for all Confounders)

Confounder adjustment	Odds ratio (95% CI) per 5% decrease in EOR	P
No adjustment	1.09 (0.86-1.38)	.49
Inverse propensity score weighting	1.02 (0.83-1.26)	.82

TABLE 6. Frequency of PSIs and HACs in GTR and STR Patient Groups (N = 284 Patients)

PSI/HAC	GTR, N (%)	STR, N (%)	P
Mechanical ventilation	0 (0%)	1 (1.3%)	.26
DVT	3 (1.4%)	1 (1.3%)	1
Pulmonary embolism	2 (1.0%)	2 (2.7%)	.28
Sepsis	1 (0.5%)	2 (2.7%)	.17
Postoperative wound dehiscence	3 (1.4%)	1 (1.3%)	1
Catheter-associated urinary tract infection	7 (3.4%)	6 (8.0%)	.11
At least one PSI	7 (3.4%)	6 (8.0%)	.11
At least one PSI or HAC	13 (6.2%)	9 (12.0%)	.12

GTR and STR patient groups on direct comparison (Table 6). Logistic regression modeling of resection status (GTR/STR) as a predictor of the log-odds of encountering at least one PSI or HAC in the 250 patients with nonmissing confounder data revealed that the odds of developing a PSI or HAC were

TABLE 7. Change in the Odds of Encountering at Least One PSI or HAC in STR Relative to GTR (N = 250 Patients With Nonmissing Data for All Confounders)

Confounder adjustment	STR:GTR odds ratio (95% CI)	*P*
No adjustment	2.51 (0.97-6.50)	.058
Inverse propensity score weighting	3.86 (1.43-10.37)	.008

2.5 times greater in STR patients relative to GTR patients ($P = .058$) (Table 7). The STR: GTR odds ratio increased to 3.9 when the effect of resection status was adjusted for confounding via inverse PS weighting ($P = .008$) (Table 7). Covariates in the GTR/STR PS model included hyperlipidemia, presence of other neurological disorders, use of antiepileptic drugs, use of anticoagulants, tumor crossing midline, tumor location, midline shift, KPS, and preoperative tumor volume (Table 1).

Overall, the results demonstrate that when EOR is considered as a continuous linear predictor, it is not associated with the likelihood of developing a PSI or HAC. However, when the study population is stratified into STR (EOR < 95%) and GTR (EOR ≥ 95%) patient groups, GTR is strongly associated with a decreased likelihood of experiencing a PSI or HAC after adjustment for confounding.

DISCUSSION

PSIs and HACs have become increasingly important given their impact on reimbursement and quality ratings for hospitals. These metrics are imperfect measures of patient outcomes as they are mostly utilized to determine quality of care delivered at hospitals. Because of the reporting on these metrics to regulatory agencies, postoperative complication avoidance has become a topic of interest for neurosurgeons delivering care to complex brain tumor patients. The literature now supports aggressive surgical management of GBM as a method to improve overall survival. Therefore, understanding the correlation of EOR with reportable quality metrics will be important to neurosurgeons as they are compared to other healthcare providers.

PSIs and HACs are associated with overall worse outcomes. Nuno et al[21] have shown that patients undergoing intervention for an intracranial tumor are almost 8 times more likely to die in the hospital if they experienced a PSI. However, overall the rates of PSI and HACs are low. Congruent with previously published data, our results demonstrate that less than 5% of patients experienced a PSI, slightly less than the 7.4% of brain tumor patients in prior reports.[21,22] Additionally, less than 5% of patients in our population developed an HAC. Other studies have shown that irrespective of admission diagnosis, the most commonly identified PSIs, in descending order, were deep vein thrombosis, postoperative respiratory failure, and postoperative hemorrhage or hematoma.[23] These findings are similar to the data presented here.

The data presented here demonstrate that maximizing resection for newly diagnosed GBM is not associated with an increase in reportable quality metrics and may be associated with fewer events in the postoperative period. The association of increased PSIs/HACs with STR is mostly related to complications such as venous thromboembolism and sepsis. Therefore, the higher incidence of having a PSI/HAC in patients with STR may be related to tumor burden as they are treated with chemotherapy and radiation. Our analysis corrected for confounders using PS weighting, and therefore, the differences are unlikely to be related to patient comorbidities.

Limitations

The limitations of this study include a retrospective study design, patients from a single institution, and low frequency of PSIs and HACs. We attempted to minimize the impact of these factors through thoughtful statistical design. Because of the infrequencies of the events, these data cannot be generalized to individual patients undergoing surgery for GBM. Furthermore, the incidence of postoperative deficits in patients with STR was not significantly greater than those patients in which GTR was achieved; as such, the development of new or worsening postoperative neurological deficit does not explain the increased incidence of PSIs/HACs in patients for whom STR was achieved.

Overall, increasing EOR is associated with improved overall survival and does not seem to correlate with an increased risk of postoperative reportable quality metrics such as PSIs or HACs. Therefore, neurosurgeons should continue to attempt to maximize safe, aggressive resection for patients with GBM. This strategy, in our analysis, is not associated with an increased risk of causing PSIs or HACs.

CONCLUSION

The odds of encountering a PSI or HAC are less in GBM patients who underwent a GTR as compared to STR. In the future, large, prospective studies with rigorous coding of PSIs and HACs may provide more precise estimates of the prevalence of adverse events in this population.

Disclosures

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Supplemental Digital Content 1. Table. Comparison of postoperative neurological deficit rates by tumor feature location.

Supplemental Digital Content 2. Table. Influence of postoperative deficit on any PSI/HAC.