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A proposed preoperative grading scheme to assess risk for surgical resection of primary and secondary intraaxial supratentorial brain tumors

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Although surgical resection of brain tumors has been performed for over a century, complications still occur with distressing frequency.

The authors propose a simple preoperative grading scheme to assess surgical risk for resection of primary and secondary intraaxial supratentorial brain tumors.

The authors retrospectively reviewed the clinical records, neuroimaging studies, and outcomes of 224 surgeries performed in 207 patients from January 1993 to December 1995 at the Cleveland Clinic Foundation Brain Tumor Center. Subsequently, they considered and statistically analyzed multiple variables related to the patients and their lesions. Surgical risk was defined as any complication occurring within 30 days postoperatively, and was divided into transient operative complications, transient medical complications, and new sustained neurological deficits. Length of stay was also recorded. The overall incidence of complications was 10.6% and the mortality rate was 2.7%, with a median hospital stay of 3 days. Patient age greater than 60 years ($p < 0.001$), preoperative Karnofsky Performance Scale scores of 50 or less ($p < 0.03$), previous irradiation ($p < 0.001$), tumor location in eloquent regions ($p < 0.03$), and depth of tumor invasion ($p < 0.001$) independently predicted complicated outcome or increased length of stay. Finally, the authors derived a simple five-tier grading scheme in which these patient risk factors are added together to obtain a grade of I to V that corresponds to outcome and length of hospital stay.

This grading scheme may be used to identify patients at higher risk and facilitate comparison of results between institutions and individual surgeons.

Key Words * glioma * brain tumor * supratentorial tumor * surgical resection * morbidity * grading system

It has been more than a century since Rickman Godlee performed the first operation for a tumor arising from the brain.[5] The patient survived the procedure but died of meningitis 1 month after surgery. Since then considerable progress in operative technique, imaging, and perioperative management has dramatically improved our ability to surgically treat primary and secondary tumors of the brain;[12,16,19,26,35] yet neurological, wound, and systemic complications occur with distressing and, often, unpredictable frequency.

The ability to accurately assess the risk of surgery for brain tumors is clearly desirable. Patients must make an informed decision based on the comparative benefit versus risk of the proposed operation. It remains difficult to compare meaningfully the results among lesion management series without knowing the breakdown of surgical risk for the patient population. Furthermore, present socioeconomic trends require a critical assessment of outcomes analysis for surgical procedures that would be potentially biased without a valid measure of surgical risk.

Spetzler and Martin[30] critically analyzed and subsequently validated a grading system of surgical risk for arteriovenous malformations that is widely accepted. Similarly, we have analyzed the relationship between clinical, neuroimaging, and historical information on patients who underwent surgical resection of supratentorial intraaxial brain tumors and neurological, wound, and systemic complications. From this information we propose a simple preoperative grading system for risk of surgical resection of supratentorial primary and metastatic brain tumors.

CLINICAL MATERIAL AND METHODS

Patient Population

The Brain Tumor Center database at Cleveland Clinic Foundation was retrospectively reviewed to identify all primary and secondary supratentorial tumors in adults treated surgically from January 1993 to December 1995. Patients younger than 18 years of age; patients with tumors arising from the pituitary gland, ependyma, and meninges; and patients who had undergone biopsies and debulking procedures were excluded. The series was confined to cases in which gross-total resection was the surgical objective. We found 224 such surgeries performed in 207 patients, with 17 patients having two operations listed in the database; these patients comprised the study population.

A comprehensive review of the medical, neuroimaging, and operative data for each patient was performed. Specific factors relating to the patient including age, sex, concurrent medical conditions, previous radiation therapy, previous open surgery on the same lesion (excluding stereotactic biopsies), and Karnofsky Performance Scale (KPS) scores were noted. Lesions were designated primary (high or low grade), recurrent, or metastatic. Primary tumors assigned a high grade included glioblastoma multiforme (GBM), anaplastic astrocytoma, anaplastic mixed glioma, anaplastic oligodendroglioma, and gliosarcoma. Factors relating to the lesion including size of tumor, depth of deepest portion, vascular territory, and location in areas of eloquent brain function were obtained from preoperative magnetic resonance (MR) images. Tumor size was determined by measuring the maximum enhancing diameter of lesions in either the axial or coronal views. The deepest portion of tumor invasion was assessed as predominantly extending into white matter parenchyma, or involving an ependymal surface or central structures such as deep gray matter and basal ganglia. Detailed characteristics of the lesions are provided in Table 1.

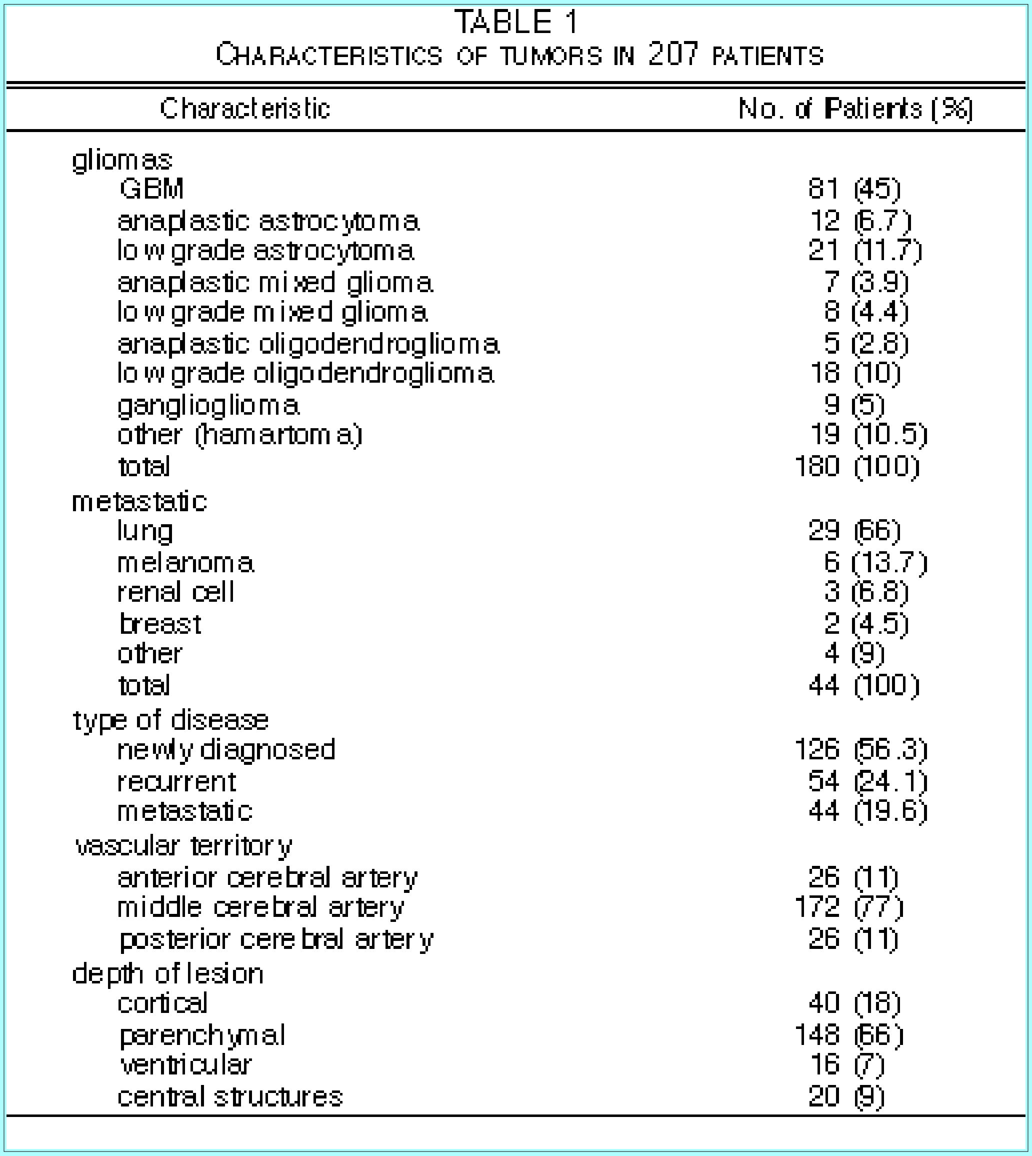

TABLE 1
CHARACTERISTICS OF TUMORS IN 207 PATIENTS

Characteristic	No. of Patients (%)
gliomas	
GBM	81 (45)
anaplastic astrocytoma	12 (6.7)
low grade astrocytoma	21 (11.7)
anaplastic mixed glioma	7 (3.9)
low grade mixed glioma	8 (4.4)
anaplastic oligodendroglioma	5 (2.8)
low grade oligodendroglioma	18 (10)
ganglioglioma	9 (5)
other (hamartoma)	19 (10.5)
total	180 (100)
metastatic	
lung	29 (66)
melanoma	6 (13.7)
renal cell	3 (6.8)
breast	2 (4.5)
other	4 (9)
total	44 (100)
type of disease	
newly diagnosed	126 (56.3)
recurrent	54 (24.1)
metastatic	44 (19.6)
vascular territory	
anterior cerebral artery	26 (11)
middle cerebral artery	172 (77)
posterior cerebral artery	26 (11)
depth of lesion	
cortical	40 (18)
parenchymal	148 (66)
ventricular	16 (7)
central structures	20 (9)

Outcome assessment was based on the incidence of any complications encountered after craniotomy up to 30 days postoperatively and on the length of hospitalization. Complications were further divided into transient operative, transient medical, and sustained neurological categories. Operative complications were defined as directly attributable to the procedure (for example, wound infection and cerebrospinal fluid [CSF] leak), whereas deep venous thrombosis, pulmonary embolism, and pneumonia were categorized as medical complications. Death or new sustained neurological deficit occurring within 30 days of surgery was recorded. Finally length of stay was calculated from the day of surgery to day of discharge.

Statistical Analysis

Analysis was performed using univariate logistic regression to examine the relationship between each variable and each outcome. Subsequently, multivariate analysis was used to compare which variables simultaneously predict outcome for tumor resection. The probability values were calculated with a chi-square test except in cases in which a patient was listed more than once in a dataset; in such cases a more computer-intensive generalized estimating equation was used for confirmation of results and to eliminate error due to dependency of data. Variables were included in the model if they were significant ($p < 0.05$) in the presence of the other variables. Finally, odds ratios with 95% confidence interval were calculated and used to construct our proposed grading scheme.

RESULTS

Details of the demographics of these patients are provided in Table 2. The mean age was 48.9 years (range 18-81 years), and the mean size of lesion was 3.5 cm (range 0.6-10 cm). A follow-up period of 30 days postoperatively was achieved in all cases. Of 224 surgeries performed, there were six deaths (2.7%), 15 new sustained neurological deficits (6.7%), 28 transient operative complications (12.5%), and 28 transient medical complications (12.5%). These outcomes were not mutually exclusive and resulted in an overall incidence of all possible complications of 10.6%. Three deaths resulted from massive cerebral edema and herniation, and one each from respiratory failure, myocardial infarction, and metastatic disease. Deep venous thrombosis accounted for 21 (75%) of the 28 medical complications as a result of which four patients developed clinically significant pulmonary embolism. Three patients developed pneumonia, two urosepsis, and one each intestinal ileus and hyperkalemia with arrhythmia. Operative complications included wound infection in 20 patients, CSF leakage in five; two patients required prolonged ventricular drainage for hydrocephalus and one required drainage of a hematoma. The mortality rate and sustained new neurological deficits did not vary significantly among patients with newly diagnosed, recurrent, or metastatic tumors. However, there was an increased incidence of transient medical and operative complications in patients with recurrent tumors, presumably the result of a higher incidence of previous radiotherapy in that patient group.

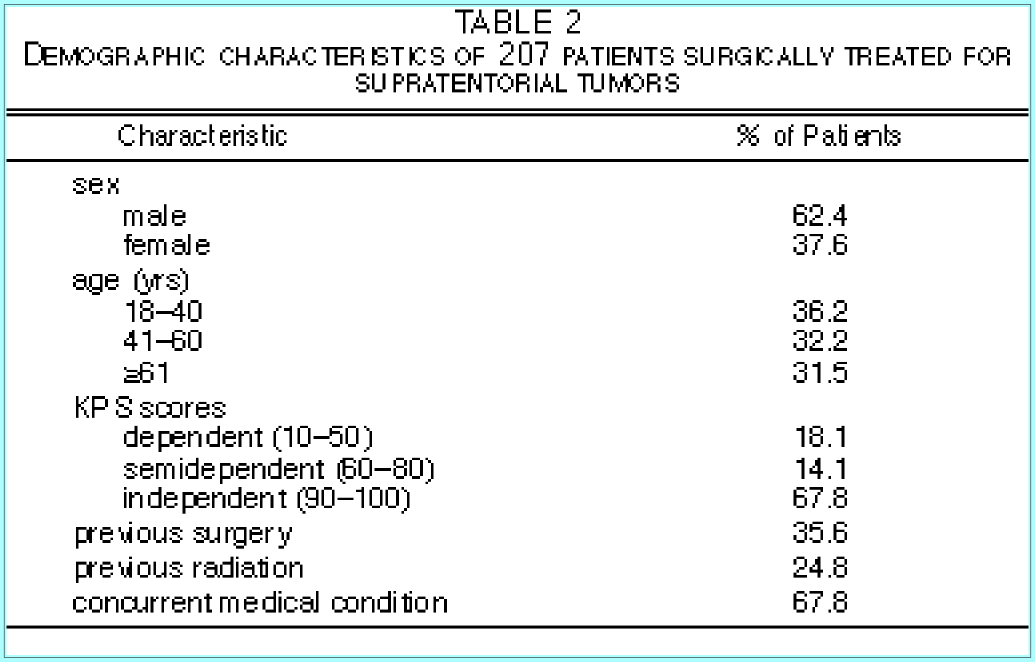

TABLE 2

DEMOGRAPHIC CHARACTERISTICS OF 207 PATIENTS SURGICALLY TREATED FOR SUPRATENTORIAL TUMORS

Characteristic	% of Patients
sex	
male	62.4
female	37.6
age (yrs)	
18–40	36.2
41–60	32.2
≥61	31.5
KPS scores	
dependent (10–50)	18.1
semidependent (60–80)	14.1
independent (90–100)	67.8
previous surgery	35.6
previous radiation	24.8
concurrent medical condition	67.8

Neurological complications are outlined in Table 3. Cortical mapping was routinely used for tumors in or near eloquent areas. All patients with new sustained neurological deficits had tumors that invaded central areas or eloquent regions. There was also a substantial number of patients who experienced improvement in preoperative neurological deficits; however, this was not part of the current study. The median length of stay was 3 days, with 81.2% of patients staying in hospital fewer than 7 days. Interestingly, 18.8% of patients accounted for 45.6% of total hospital days, confirming the significance of complications.

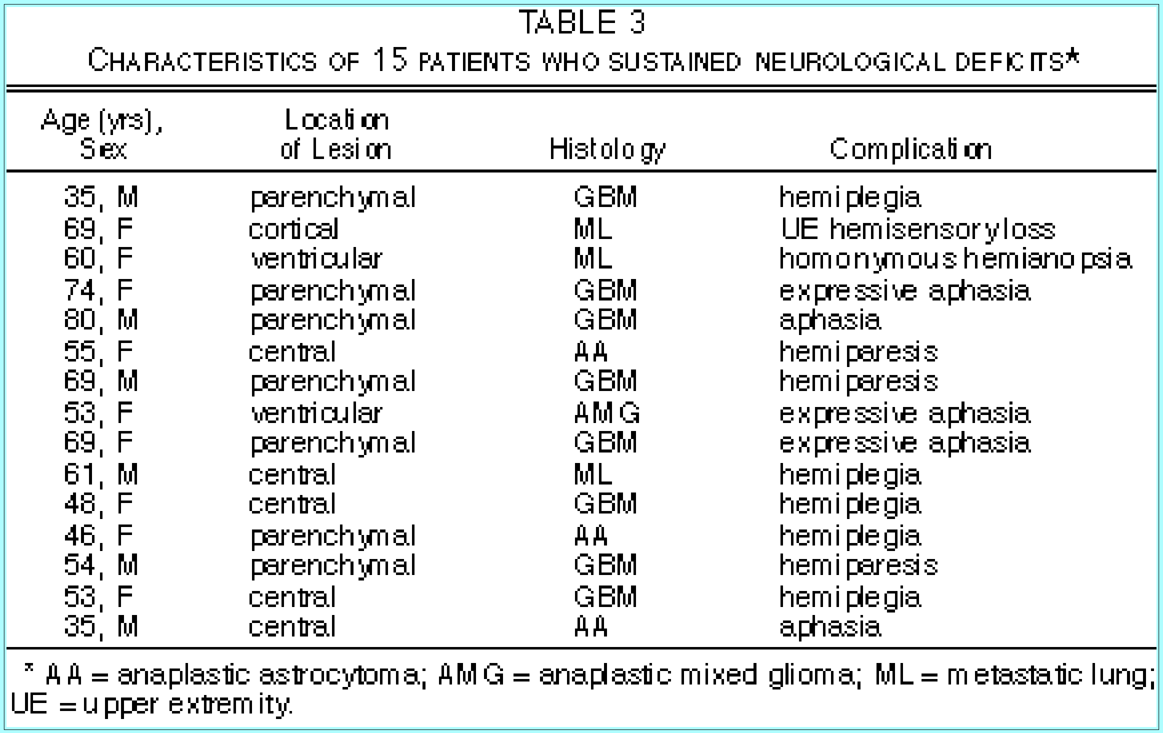

TABLE 3

Characteristics of 15 patients who sustained neurological deficits*

Age (yrs), Sex	Location of Lesion	Histology	Complication
35, M	parenchymal	GBM	hemiplegia
69, F	cortical	ML	UE hemisensory loss
60, F	ventricular	ML	homonymous hemianopsia
74, F	parenchymal	GBM	expressive aphasia
80, M	parenchymal	GBM	aphasia
55, F	central	AA	hemiparesis
69, M	parenchymal	GBM	hemiparesis
53, F	ventricular	AMG	expressive aphasia
69, F	parenchymal	GBM	expressive aphasia
61, M	central	ML	hemiplegia
48, F	central	GBM	hemiplegia
46, F	parenchymal	AA	hemiplegia
54, M	parenchymal	GBM	hemiparesis
53, F	central	GBM	hemiplegia
35, M	central	AA	aphasia

* AA = anaplastic astrocytoma; AMG = anaplastic mixed glioma; ML = metastatic lung; UE = upper extremity.

Derivation and Description of Grading System

Univariate analysis identified variables associated with all outcomes. The next step was to construct a mutivariate model excluding all probability values greater than 0.05. Older patient age, high-grade tumors, low KPS scores, and/or previous radiation therapy were associated with all complications ($p < 0.03$ for all variables). Interestingly, the size of the lesion and the histological type of tumor could not be used to predict poor outcome related to surgery. A multivariable model illustrating 95% confidence intervals is presented in Table 4. Each of these variables independently predicted poor outcome. We were unable to show any independent direct predictors of increased risk for the subset of sustained neurological deficits, but the combination of increased patient age, high tumor grade, or recurrent tumors near eloquent areas and with deep locations almost always resulted in a complicated outcome.

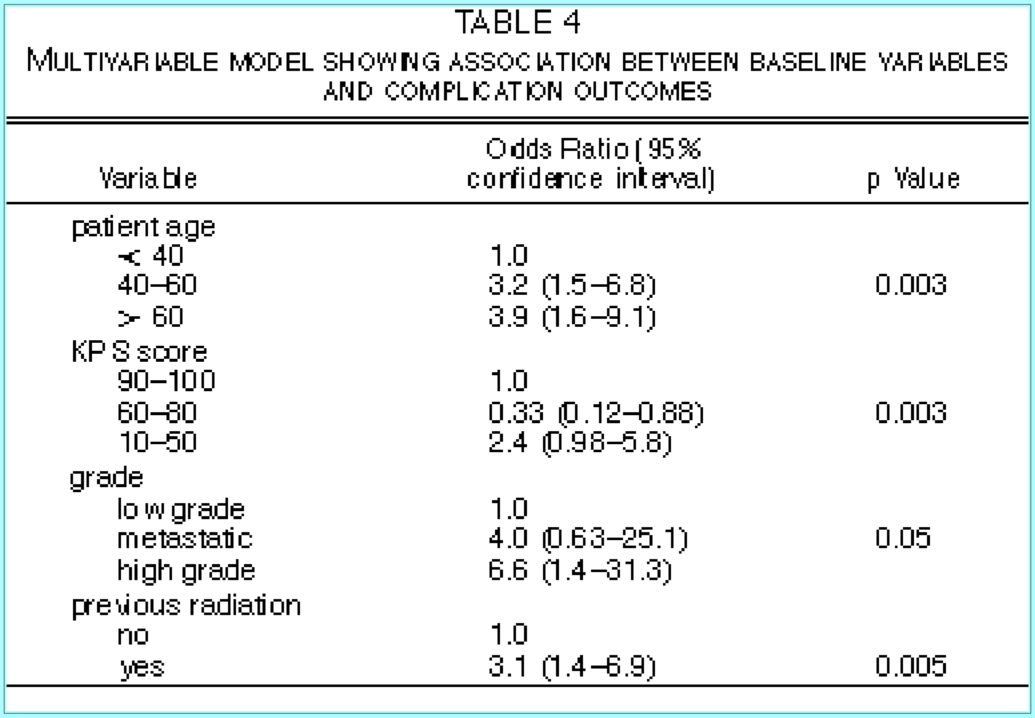

TABLE 4

Multivariable model showing association between baseline variables and complication outcomes

Variable	Odds Ratio (95% confidence interval)	p Value
patient age		
< 40	1.0	
40–60	3.2 (1.5–6.8)	0.003
> 60	3.9 (1.6–9.1)	
KPS score		
90–100	1.0	
60–80	0.33 (0.12–0.88)	0.003
10–50	2.4 (0.98–5.8)	
grade		
low grade	1.0	
metastatic	4.0 (0.63–25.1)	0.05
high grade	6.6 (1.4–31.3)	
previous radiation		
no	1.0	
yes	3.1 (1.4–6.9)	0.005

There was a strong relationship between increased patient age, previous radiation therapy, tumor location in eloquent regions, and depth of tumor invasion with length of hospital stay. Table 5 illustrates a multivariable model with hospital length of stay as an outcome measure. This may reflect neurological outcome indirectly, because patients with transient neurological deficits required a prolonged stay for physical therapy and rehabilitation.

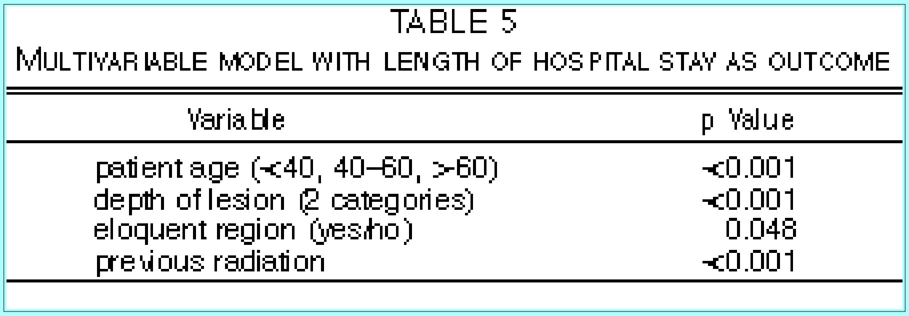

TABLE 5

MULTIVARIABLE MODEL WITH LENGTH OF HOSPITAL STAY AS OUTCOME

Variable	p Value
patient age (<40, 40–60, >60)	<0.001
depth of lesion (2 categories)	<0.001
eloquent region (yes/no)	0.048
previous radiation	<0.001

The endpoint of our analysis was to identify the variables leading to poor clinical outcome such as any complications or extended hospital stay. We combined the factors in Tables 4 and 5, excluding grade of tumor because histological results of biopsy were not always available preoperatively. Finally, a grading scheme was devised to identify patients at a high risk of surgical morbidity or prolonged hospital stay, incorporating the five most significant risk factors of age, preoperative KPS score, previous radiation therapy, depth of tumor invasion, and location in eloquent regions. A patient's grade is ascertained based on the number of risk factors (one risk factor = Grade I, two risk factors = Grade II, and so on). Each ascending grade is associated with increasing risk or prolonged hospital stay. Only one patient demonstrated all five risk factors used in our grading scheme and developed a complication in each of the three outcome categories, which necessitated a hospital stay of 55 days. Conversely, among 42 patients without any risk factors (Grade 0) only five complication events occurred in all three outcome categories combined, resulting in an incidence of 4%. A higher tumor grade, although excluded from this scheme because of a marginally significant p value and inconsistent availability of reliable histological testing before resection, contributed to risk in selected individuals. The proposed grading scheme and its correlation with complications as well as average and median lenghts of hospital stay are outlined in Tables 6 and 7.

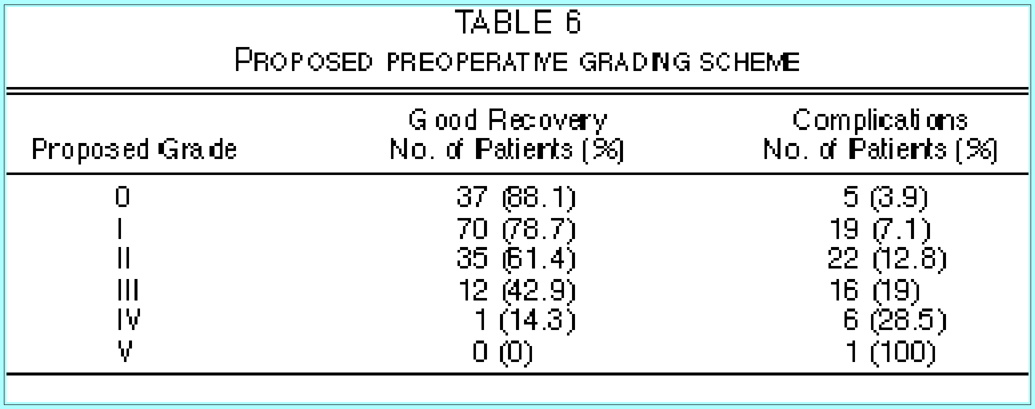

TABLE 6

PROPOSED PREOPERATIVE GRADING SCHEME

Proposed Grade	Good Recovery No. of Patients (%)	Complications No. of Patients (%)
0	37 (88.1)	5 (3.9)
I	70 (78.7)	19 (7.1)
II	35 (61.4)	22 (12.8)
III	12 (42.9)	16 (19)
IV	1 (14.3)	6 (28.5)
V	0 (0)	1 (100)

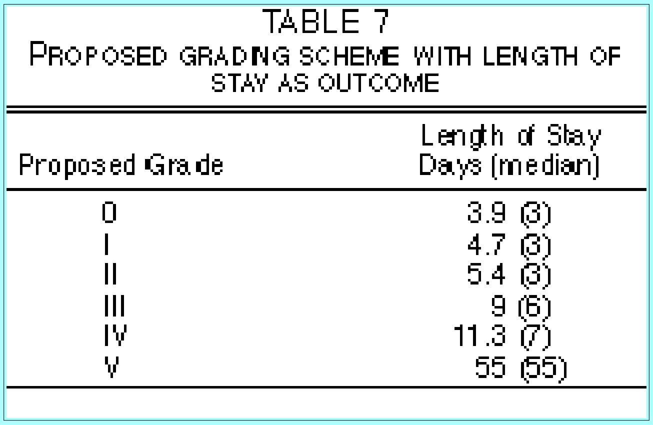

TABLE 7
PROPOSED GRADING SCHEME WITH LENGTH OF STAY AS OUTCOME

Proposed Grade	Length of Stay Days (median)
0	3.9 (3)
I	4.7 (3)
II	5.4 (3)
III	9 (6)
IV	11.3 (7)
V	55 (55)

DISCUSSION

Grading systems abound in the neurosurgical literature,[15,17,28,30] and their application in prospective studies[14,17] have proven valuable in identifying broad categories of surgical risk. The advantages of simple predictive systems are that they are meaningful and easy to remember and, as such, are most likely to be used. They do not, however, serve as a substitute for clinical judgment in the case of an individual patient.

We set out to categorize a very diverse group of patients with a spectrum of lesions. Despite a variety of radiation-based treatments, chemotherapy and immunotherapy, the vast majority of patients with brain tumors still have surgical resection as part of their treatment.[20] To achieve gross-total resection requires considerable surgical skill aided by modern technology. Our patients all received the benefit of MR image-guided computer-assisted minimally invasive stereotactic craniotomy and resection.[4] The majority of patients underwent follow-up MR imaging within 48 hours to document gross-total resection; unfortunately, some patients with poor early postoperative medical conditions were unable to undergo imaging.

Risk Factor Categories

Several factors were considered to determine the difficulty of tumor resection.

Tumor Size. We could not demonstrate a relationship between tumor size and surgical risk. Previous authors have shown a significant relationship between postoperative residual tumor volume shown on computerized tomography scans and eventual patient outcome.[2,35] We examined preoperative MR images, and the mean size (maximum diameter) of lesions in our study was 3.58 cm (mean 3.50 cm, range 0.6-10 cm). Subsequently, we analyzed these data with several statistical methods including size categories, quartiles, and graphs of continuous variables. However, none of these methods showed a significant relationship between lesion size and any of our outcome measures. We also attempted to identify a cut-off point above which complications would occur more frequently but could not. Patients with large "butterfly" tumors extending across the midline were probably excluded from this study by never being offered surgery.

Tumor Depth. Some disagreement exists in the literature regarding the metastatic consequences of an invading tumor involving an ependymal surface. Some authors believe that ventricular involvement with or without surgery increases the risk of CSF dissemination.[31] Although others disagree,[9] we chose to include it in our assessment of depth of tumor invasion. Because of the inherent difficulty of defining depth of tumor invasion in an accurate and reproducible way, we created two groups: tumors that involve central structures such as ventricles or basal ganglia and those that do not. As a whole the depth category was only marginally significant when associated with death ($p = 0.06$) and sustained neurological deficits ($p = 0.16$) but achieved strong correlation with length of stay ($p < 0.001$). This is difficult to interpret but could relate to time necessary to initiate rehabilitation and find placement for patients with new temporary neurological deficits.

Eloquent Location. The development of modern neuroimaging techniques has added a new dimension to diagnosis and localization of function in the central nervous system.[7,11,21] Consequently, the surgeon now has much more information to consider when determining the relationship of a lesion or proposed surgical trajectory to functionally eloquent areas before operation.[22] For the purpose of our grading system, we considered the following areas eloquent: sensorimotor, language and visual cortices, internal capsule, and basal ganglia. This is similar to the definition used in the familiar Spetzler-Martin grading scheme of arteriovenous malformations.[30] Their studies confirmed the significance of eloquent location as a risk factor for poor outcome. It should be noted, however, that their grading system also triggered a prolonged discussion in the literature about the relevance of designating certain areas of the cortex as "eloquent." It further raised a question about the interobserver reliability of such a definition. We chose to include this category because of its clinical relevance in guiding the surgeon and the patient when assessing surgical risk.

Type of Tumor. Different authors[1,8] have found that patients who underwent gross-total resection have fewer neurological deficits and maintain their independence longer than those with only partial resection. The predilection for local recurrence and the importance of local control have been confirmed by the Brain Tumor Cooperative Study Group in the previous decade. Some lesions may have borders that are more difficult to discern at surgery than others, and we found that high-grade tumor patients did significantly worse than those with metastatic or low-grade lesions tumors. The reason can be found in postmortem studies of GBM in which neoplastic cells have been identified at sites remote from the radiographic tumor location.[6] However, this risk factor lacks relevance in a preoperative grading scheme in which reliable histology is not always available.

Concurrent Medical Conditions. These were defined as illness requiring daily medication. We may have been able to use a narrower definition by identifying patients with specific diseases (for example, diabetes), but duration and severity of disease are difficult to quantify. Other factors such as cigarette smoking and prolonged corticosteroid use were also considered. In any event, it may be impossible to identify the relative contributions of various factors contributing to immunosuppression following neurosurgical procedures.[3] A five-tiered scheme called the American Society of Anesthesiologists Physical Status classification,[23] which defines categories of anesthesia risk, was derived from very large groups of all surgical patients and may not be applicable to the group we examined. Nevertheless, the risk of anesthesia alone is not negligible, especially in a patient with severe systemic disease with functional limitations such as congestive heart failure. We were unable to show significant correlation between our definition of concurrent medical conditions and poor outcome.

Karnofsky Performance Scale Scores. When evaluating preoperative KPS scores, we divided our patients into independent (90-100), semi-dependent (60-80), and dependent (10-50) categories in order to create three simple and functionally discrete groups. The KPS has been used extensively and shows reasonable intra- and interobserver validity, although it is occasionally difficult to assign a score in certain situations (for example, a patient with a first-ever seizure). In our evaluation, a preoperative KPS score of 50 or less proved an accurate predictor of postoperative complications or extended hospital stay.

Although performance improved after surgery in a substantial number of patients, factors associated with postoperative improvement were not a focus of this study and have been addressed elsewhere.[29]

Patient Age. Age has been shown to be the strongest predictor of outcome when treating patients with GBM.[20,34] Survival is shorter for patients older than 60 years of age[27] and in more recent reports even for patients older than 40 years of age.[24] Other contemporary series[1,8,10] have produced similar results, and one study[10] found older patients with deeper lesions to have an increased rate of early morbidity. Our results confirm this trend in the early postoperative period, showing increasing incidence of complications in all categories with increasing age ($p < 0.001$).

Previous Radiation Therapy. The value of postoperative radiation in the treatment of malignant glioma was conclusively proven by the Brain Tumor Study Group trial designed to evaluate BCNU chemotherapy.[32] Currently external beam radiation is part of our treatment protocol, and 24% of our patients had received prior radiation therapy. Late effects or radiation-induced damage to the central nervous system occurs approximately 6 months to years after irradiation.[18] Histopathological findings consist of predominantly vascular degenerative changes including endothelial atypia, vascular thickening, and telangiectasia formation.[13] These changes probably account for technical difficulty at surgery and poor wound healing, often with associated infection. In our series previous radiation therapy correlated strongly with outcome, especially operative complications ($p < 0.001$).

CONCLUSIONS

These results are consistent with postoperative outcomes achieved at other large tumor centers[24,25,33] over the last decade. This grading scheme may find application identifying patients at higher risk and facilitate comparison of results between institutions and individual surgeons. We acknowledge the possible caveat that our results were obtained at a tertiary referral center where neurosurgeons perform brain tumor operations on a daily basis, aided by the newest technology. At the Cleveland Clinic Foundation a prospective study is currently underway to validate the accuracy and relative risk predicted by this system.

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