Frailty in Geriatric Glioblastoma Patients: A Predictor of Operative Morbidity and Outcome

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■ BACKGROUND: **Frailty is an emerging means of assessing overall health status and guiding management for geriatric patients. Frailty is associated with outcomes for many surgical indications in this age group. While half of all glioblastoma patients are 65 years old or older, frailty has not been examined in relation to surgery for glioblastoma.**

■ METHODS: **We performed a retrospective study of patients age 65 years and older with pathologically confirmed glioblastoma at Columbia Presbyterian Hospital from 2000 to 2012; 319 patients were identified, 243 of whom underwent craniotomy for lobar lesions. Frailty was quantified using the Canadian Study of Health and Aging Modified Frailty Index. Postoperative complications were classified according the Glioma Outcomes Project system. Systemic, regional, neurologic, and overall complications were examined in relation to age, Karnofsky performance status, frailty, comorbid disease burden, cardiovascular risk, and tumor sidedness.**

■ RESULTS: **Frailer patients were less likely to undergo surgical resection ($P = 0.0002$; odds ratio [OR], 0.15; 95% confidence interval [CI], 0.05–0.40) as opposed to biopsy, had longer hospital stays (log-rank test for trend, $P = 0.0061$), an increased overall risk of complications ($P = 0.0123$; OR, 1.40; 95% CI, 1.08–1.83), and decreased overall survival (Log rank test for trend, $P = 0.0028$).**

■ CONCLUSIONS: **Frailer patients with glioblastoma receive less aggressive intervention, have longer hospital stays, and experience more complications. Frailty may be an underused metric for the preoperative risk assessment of geriatric glioblastoma patients.**

INTRODUCTION

The growing geriatric population in the developed world is an expanding challenge for all physicians, including neurosurgeons. Recent estimates suggest that by 2040, the number of Americans aged 65 and older will increase more than twofold.[1] The higher risk of adverse outcomes in older patients complicates treatment decisions, particularly regarding the invasive procedures at the heart of neurosurgery.

Glioblastoma is the most common primary brain tumor. The median age of glioblastoma diagnosis is 64 years,[2] and epidemiological studies have shown that the risk of developing glioblastoma increases exponentially with age.[3] Indeed, approximately half of all glioblastoma cases occur in geriatric patients (age $\geq$ 65 years),[4] and that proportion is likely to increase with the aging of the population.

Frailty has emerged as a tool to estimate overall health status and risk of adverse events, particularly in geriatric patients.[5-8] Frailty has been defined as a physiologic vulnerability to adverse events,[6,7] and is thought to result from an accumulation of deficits with aging.[9] Many scores have been developed to measure frailty. The Canadian Study on Health and Aging Modified Frailty Index (mFI) is one such score that is well validated for use with retrospective data, and has previously been shown to be

Key words
- Complications
- Craniotomy
- Frail
- Frailty
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- Glioblastoma

Abbreviations and Acronyms
CI: Confidence interval
KPS: Karnofsky performance status
mFI: Canadian Study on Health and Aging Modified Frailty Index
OR: Odds ratio

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associated with postoperative complications for multiple types of nonneurologic surgeries.[10-12]

Surgical debulking has been shown on a randomized trial to increase overall survival nearly threefold for glioma patients older than 65 years.[13] However, it is unlikely that aggressive surgical resection will be beneficial for all geriatric patients. Frailty may prove useful for identifying patients who are at risk of worse outcomes, and some investigators already speculate that frailty affects patient selection for craniotomy.[14]

Nevertheless, the clinical literature on frailty among glioblastoma patients focuses on radiotherapy or chemotherapy rather than craniotomy.[15,16] Furthermore, existing studies use age,[17] functional status,[15] provider impression,[18] or a combination of these factors to classify patients as frail,[16,19-21] rather than using a validated frailty index. Frailty indices have been examined in numerous other surgical disciplines, and are predictive of outcomes in many studies.[10-12] However, to our knowledge, the use of frailty to predict outcomes following surgical intervention has not been explored for patients undergoing craniotomy.

We previously reported a series of 319 geriatric patients who underwent resection of glioblastoma, including reoperation for recurrent disease.[22] Selection factors were not clearly identified in that study. In the present study, we observed associations between mFI score and the decision to forego surgical resection, the rate of postoperative complications, length of hospital stay, and overall mortality. While previous studies have used age or Karnofsky performance status (KPS) rather than a validated frailty score, we show that the mFI frailty score is associated with outcomes independent of these variables, and thus might be useful for surgical risk assessment in geriatric patients, and for interpreting surgical series that include geriatric patients.

METHODS

Our study included all patients age 65 years and older with pathologically confirmed glioblastoma at Columbia University Medical Center New York Presbyterian Hospital from 2000 to 2012. Patients with a history of lower grade glioma or with recurrent disease at the time of presentation to our center were excluded from analysis. Only patients with lobar glioblastoma who underwent craniotomy were included for calculating complication rates, length of hospitalization, and overall survival. Data were gathered using retrospective chart review. Complication data from this cohort has been reported previously.[22]

Frailty was quantified using the mFI.[11,12] This scale accounts for eleven variables, and one point is given for each variable present: difficulty with activities of daily living; history of diabetes mellitus; lung or respiratory disease; congestive heart failure; myocardial infarction; other cardiac disease; arterial hypertension; clouding, delirium, or cognitive impairment; history of transient ischemic attack; history of stroke; and peripheral vascular disease. Comorbid disease burden was measured using the Charlson Comorbidity Index.[23,24] Postoperative complications were classified according to the Glioma Outcomes Project system.[25] Neurologic complications were defined as new or worsened neurologic deficits in the immediate postoperative period, including expected or transient deficits. Cardiovascular risk was measured using the Simplified Cardiac Risk Index.[26] Length of hospitalization and systemic, regional, neurologic, and overall complications were examined in relation to age, KPS, frailty, tumor sidedness, cardiovascular risk, year of surgery, and comorbid disease burden.

Patients who underwent craniotomy for resection were stratified by mFI score for proportional hazards analysis as described elsewhere.[8] Patients were distributed into quintiles, with adjustments made for the number of patients with a given mFI score. Length of stay and overall survival were analyzed using these stratified groups.

Statistical Analysis

Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA). Kaplan-Meier plots were generated with Prism version 6.0b (GraphPad Software, La Jolla, California, USA). Descriptive statistics, *t* tests, analysis of variance, χ^2 tests, simple logistic regression, multiple logistic regressions, Mantel−Cox statistics (log-rank statistics), and log-rank tests for trend were used as appropriate.

Variables associated with $P \leq 0.20$ on simple regression analysis were included for multiple regression analysis. Regarding complication rates, a Bonferroni correction for multiple comparisons was used with $\alpha = 0.05$.

RESULTS

Patient Population

Three hundred nineteen patients age 65 years and older were identified, of whom 59 underwent biopsy only and 260 underwent craniotomy for resection. Of the patients undergoing craniotomy, 17 patients with nonlobar glioblastoma were excluded from analysis. Of the 243 patients with lobar glioblastoma who underwent craniotomy, 28 underwent a second resection for recurrent disease, and 3 underwent a third resection, for a total of 274 craniotomies. Figure 1 shows the distribution of frailty scores among the 243 lobar glioblastoma patients who underwent craniotomy. Of these patients, 45 were categorized in the least-frail quintile (18.5%; mFI score = 0), 47 patients were categorized into the frailest quintile (19.3%; mFI score $\geq$ 3), and 151 were categorized in the moderately frail quintiles (62.1%; mFI score = 1 or 2). The mean age, KPS, mFI score, Charlson comorbidity score, and cardiac risk were significantly different between groups (Table 1).

Frailty and Cardiovascular Risk Correlated With Decision to Perform Craniotomy

Frailer patients ($P = 0.0002$; odds ratio [OR], 0.15; 95% confidence interval [CI], 0.05−0.40) and patients with higher cardiovascular risk ($P < 0.0001$; OR, 0.16; 95% CI, 0.09−0.28) were significantly less likely to undergo surgical resection on multiple regression analysis. Patients with higher cardiovascular risk were also significantly less likely to undergo reoperation for recurrent disease on multiple regression analysis ($P = 0.0049$; OR, 0.17; 95% CI, 0.05−0.58). No other variables were associated with the decision to perform craniotomy on single variable or multiple regression.

Frailty Correlates With Complication Rates Following Surgery

The overall complication rate after initial surgery was 21.4%, comparable to other series that have used the same reporting method (Table 2).[22,25,27,28] The overall complication rates for the