Analysis of Treatment Tolerance and Factors Associated with Overall Survival in Elderly Patients with Glioblastoma

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BACKGROUND: **As the population ages, the proportion of elderly patients with glioblastomas has increased. Recently, many researchers have focused on the treatments available to and prognoses in elderly patients with glioblastomas.**

METHODS: **We conducted a retrospective study of glioblastoma patients aged 60 years old or older who were treated at the Neurosurgery Center at Beijing Tiantan Hospital from 2012 to 2014. Their clinical features, immunohistochemical characteristics, treatments, and outcomes were evaluated to determine treatment tolerance and identify prognostic factors.**

RESULTS: **Among the 70 included patients, the median survival time was 15 months. In the univariate analysis, patients who underwent a gross total resection had longer overall survival times than patients who had a subtotal resection ($P < 0.05$), and patients who received postoperative adjuvant therapy had longer overall survival times than those with no postoperative adjuvant therapy ($P < 0.05$). The expression of the p53 protein significantly affected overall survival. Patients with low p53 protein expression had a median survival of 17 months, whereas those who had high p53 protein expression had a median survival of 11.50 months ($P < 0.05$). Undergoing a gross total resection, receiving postoperative adjuvant therapy and having low p53 protein expression were factors that independently contributed to longer overall survival times in multivariate analysis.**

CONCLUSIONS: **Maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide significantly prolonged overall survival times and was well tolerated in elderly patients with glioblastomas. In addition, low p53 protein expression was a significant favorable prognostic indicator in this population.**

INTRODUCTION

Glioblastoma multiforme is one of the most malignant forms of brain tumor, and patients with glioblastoma multiforme face a dismal prognosis.[1] The median age of patients at the time of diagnosis is 64 years of age. During the past several decades, the incidence of glioblastoma has increased, especially in elderly patients.[2] The most common treatment for glioblastoma includes maximal safe surgical resection followed by radiation therapy with concurrent and adjuvant temozolomide[3]; however, the results of a clinical trial of this therapy excluded elderly patients (aged 70 years old or older), and pre-existing medical comorbidities, poor physiological reserves, overall poorer prognosis, and longer recovery times after extensive resections were associated with maximum resections in this age group.[4]

Furthermore, some reports have shown that temozolomide-based radiochemotherapy is associated with an increased risk of Grade 4 adverse events in elderly patients when administered concomitantly.[5] Many clinicians have therefore questioned whether the most common treatment for glioblastoma is appropriate in this apparently weaker population.[6-8] In this study, we present data resulting from an analysis of 70 glioblastoma patients who were 60 years old or older. We evaluated their clinical features, immunohistochemical characteristics, treatments, and outcomes to identify factors that are associated with overall survival times, and we further explored whether aggressive treatment is well tolerated in this population.

Key words
- Elderly
- Glioblastoma
- Prognosis
- Treatment

Abbreviations and Acronyms
CI: Confidence interval
HR: Hazard ratio
KPS: Karnofsky Performance Score

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METHODS

Participants

This study was approved by the Beijing Tiantan Hospital of the Capital Medical University of Medicine Institutional Review Board. Glioblastoma patients ages 60 years old or older who underwent craniotomy at the Neurosurgery Center at Beijing Tiantan Hospital from 2012 to 2014 were included. Patients who underwent stereotactic biopsy were excluded.

Methods

Data Collection. Patients who met the inclusion criteria according to the medical records system of Beijing Tiantan Hospital were selected. We viewed patient medical records, including resident admission notes, progress notes, operation records, discharge records, and preoperative and postoperative imaging materials. Patient demographics, including age, sex, entering complaint, preoperative Karnofsky Performance Score (KPS), comorbidities, preoperative and postoperative neurologic examinations, tumor characteristics, whether a primary glioblastoma was identified, the extent of resection, postoperative complications, and immunohistochemical outcomes, were recorded for these patients. Adjuvant therapies and overall survival times were followed up. Overall survival was defined as the time from surgery to death or the date of the last follow-up.

Grouping Methods. The preoperative KPS was used to classify patients according to their functional status. A better functional status was associated with a more favorable KPS score. We identified the extent of resection by comparing the preoperative and postoperative imaging data. Gross total resection was defined as the complete resection of the main part of the enhanced lesions that were observed in preoperative imaging. Other results were categorized as subtotal resections. When we evaluated immunohistochemical outcomes, patients for whom we had access to complete immunohistochemical staining index data, a commonly used analysis in glioblastoma patients, were selected. We defined negative (−), suspicious positive (±), and weak positive (+) expression as low expression and moderate positive (++) and strong positive (+++) as high expression.

Statistical Analysis

The continuous variables and categorical data were expressed as medians and percentages, respectively. The Mann-Whitney *U* test or Kruskal-Wallis test was used for comparisons of continuous variables, and categorical variables were compared with χ^2 tests. Overall survival was estimated using the Kaplan-Meier method, and differences were compared between survival curves using log-rank tests. The multivariate analysis was performed with a Cox proportional hazard model, with the inclusion criteria set to 0.1. All statistical analyses were performed using the statistical analysis software package SPSS, version 19.0 (IBM Corp, Armonk, New York, USA). Statistical significance was defined as a *P* value < 0.05.

RESULTS

A total of 70 patients fit the inclusion criteria (Table 1), including 43 male patients (male/female ratio = 1.6:1). The mean age of the participants was 64.2 years old (range 60–81 years). The median overall survival time was 15 months (Figure 1). The median preoperative KPS score was 70. The majority of the tumours (54%) involved the temporal lobe, followed by the parietal (41%), frontal (40%), and occipital (23%) lobes. In all, 96% of the patients presented primary glioblastomas, and 10% of the tumors involved the corpus callosum, whereas 9% involved the thalamus or basal ganglia. Among the secondary glioblastomas, 2 were anaplastic gliomas, and 1 originally was diagnosed as an ependymocytoma.

At the date of last follow-up, 51 (72.9%) of the patients had died. Among the survivors, with the exception of 2 patients who presented with good functional status and needed no care, the patients displayed low functional status. Some were bed ridden, experienced difficulty eating or had an indwelling gastric tube, or displayed aconuresis or encopresis. These patients often required a caregiver.

The majority (89%) of the patients achieved gross total resection. Radiotherapy with concomitant temozolomide chemotherapy was used in 71% of the patients. Therapy consisting of postoperative radiotherapy with concomitant temozolomide chemotherapy followed by at least 6 cycles of adjuvant temozolomide chemotherapy was administered in 44% of the patients, radiotherapy with adjuvant chemotherapy was used in 2 patients, only radiotherapy was used in 1 patient, only chemotherapy was used in 1 patient, and no adjuvant therapy was used in 23% of the patients. Complete data for immunohistochemical staining were achieved in 33 patients for an index, including ki-67, phosphatase and tensin homolog, epidermal growth factor receptor, vascular endothelial growth factor, p53, matrix metallopeptidase-9, and O^6-methylguanine-DNA methyltransferase (Table 2). The majority of the patients were safely discharged, except for 1 patient, who experienced a brain tumor apoplexy who underwent an emergency operation. This patient entered a persistent coma after the surgery and died in hospital.

Survival Analysis

The univariate analysis showed that survival times were longer in patients who underwent a gross total resection than in those who underwent a subtotal resection (15 vs. 10.50 months, respectively; $P = 0.005$) and that significantly improved survival was observed in patients who received postoperative adjuvant therapy than in those who received no postoperative adjuvant therapy (16.50 vs. 6 months, respectively; $P < 0.001$). The expression of the p53 protein significantly affected overall survival. Patients with low p53 protein expression had a median survival of 17 months, whereas those who had high p53 protein expression had a survival of 11.50 months ($P = 0.012$) (Figures 2-4).

In the multivariate analysis, undergoing a gross total resection (hazard ratio [HR] 3.676; 95% confidence interval [95% CI] 1.072–12.609; $P = 0.038$), receiving postoperative adjuvant therapy (HR 4.179; 95% CI 1.635–10.683; $P = 0.003$), and having low p53 protein expression (HR 2.768; 95% CI 1.148–6.675; $P = 0.023$) were factors that independently contributed to longer overall survival times (Table 3).

DISCUSSION

Because the benefits of treatment are unclear in elderly patients,[9,10] many neurosurgeons are reluctant to treat elderly