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Original Article

Survival Outcomes in Elderly Patients with Glioblastoma

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Abstract

Aims: Many elderly glioblastoma patients are excluded from randomised trials due to age, comorbidity or poor functional status. The purpose of this study was to describe the survival outcomes in all elderly patients with glioblastoma managed at a tertiary cancer centre.
Materials and methods: A retrospective chart review identified 235 elderly patients (age 65 years or over) with a histological diagnosis of glioblastoma between 1 December 2006 and 31 December 2013. The primary outcome of this study was overall survival by treatment type. Univariate and multivariate Cox proportional hazard models were used to explore significant prognostic variables associated with overall survival.
Results: The median survival for all patients was 6.5 months (95% confidence interval 5.3–7.7), with 1 year overall survival of 23.7% (95% confidence interval 18.8–30.0). The median survival for patients treated with radiation and chemotherapy was 11.1 months (95% confidence interval 8.1–13.7). Patients treated with radiation alone had a median survival of 6.8 months (95% confidence interval 5.6–7.9). For patients managed with comfort measures only, the median survival was 1.9 months (95% confidence interval 1.6–2.6). Univariate analysis revealed age, performance status, surgery type (biopsy, subtotal resection, gross total resection) and type of treatment received (comfort measures only, radiotherapy alone, radiotherapy and chemotherapy) to be statistically associated with overall survival. In the multivariate analysis, only two predictive factors (treatment received and surgery type) were significant.
Conclusions: Elderly patients with glioblastoma selected for treatment (surgery followed by radiation alone or radiation and chemotherapy) survive longer than patients managed with comfort measures. Prospective randomised trials will help guide management for patients eligible for therapy. Elderly patients with glioblastoma who are deemed not eligible for active therapy have very short survival.

Key words: Elderly; glioblastoma; survival

Introduction

Incidence data derived from global population-based cancer registries indicate that the age-specific rates of primary malignant brain tumours is 3.9 per 100 000 for males and 3.2 per 100 000 for females [1]. About 70% of all primary malignant brain tumours are malignant gliomas. Glioblastomas account for about 70% of malignant gliomas [2]. The mean and median age at diagnosis is 61.5 and 59 years, respectively [3,4]. In particular, there is an increasing incidence of glioblastoma in the elderly [5].

The definition of elderly patients with glioblastoma is inconsistent in the literature, but, in general, ranges from at least 60–70 years of age, with many studies using 65 years as a minimum age cut-off [6]. Advanced age is a negative prognostic factor in patients with glioblastoma [7–9], particularly among patients with a poor baseline performance status [10–12]. The management of elderly patients with glioblastoma has evolved, with options ranging from concurrent radiation therapy and temozolomide to

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monotherapy (radiation or chemotherapy alone) to comfort measures/best supportive care (BSC). However, given the poor prognosis of elderly patients with glioblastoma, the optimal management approach remains controversial.

Radiotherapy Alone

Evidence for radiation treatment of elderly patients (70 years of age or older) with glioblastoma derives from a French trial, which randomised patients to radiotherapy alone (50 Gy in 1.8 Gy fractions) versus BSC [13]. This trial was discontinued when the first planned interim analysis showed that survival was superior in patients treated with radiotherapy as compared with supportive care. Patients were eligible for this trial if their Karnofsky performance status was 70 or higher.

Dose fractionation was examined in a study by Roa *et al.* [14], which found equivalent survival between an abbreviated, hypofractionated radiotherapy course of 40 Gy in 15 fractions compared with 60 Gy in 30 fractions.

Chemotherapy versus Radiation

The NOA-08 trial [15] reported that temozolomide alone was not inferior to radiotherapy alone in elderly patients (65 years and older) with glioblastoma. Patients with methylated O^6-methylguanine-DNA methyltransferase (MGMT) had better survival with temozolomide as compared with radiation.

The Nordic trial [16] reported that for elderly patients (over 60 years) with glioblastoma, temozolomide was similar to hypofractionated (34 Gy in 10 daily fractions) radiotherapy. Survival was worse for patients treated with radiotherapy to 60 Gy in 30 daily fractions.

Concurrent Chemoradiotherapy

Randomised evidence in support of concurrent and adjuvant temozolomide was established with the European Organisation for Research and Treatment of Cancer-National Cancer Institute of Canada Clinical Trials Group (EORTC-NCIC CTG) trial, which included patients up to age 70 years. However, a subset analysis of this trial suggested a decreased benefit of concurrent temozolomide with increasing patient age [17].

The NCIC and EORTC completed accrual to a randomised trial of elderly (65 years and older) glioblastoma patients randomised to short course radiotherapy (40 Gy in 15 fractions) versus the same radiotherapy with concurrent and adjuvant temozolomide chemotherapy (CE.6, ClinicalTrials.gov NCT00482677). Published results are pending.

Despite these studies, the optimal approach for elderly patients with glioblastoma is not certain. In particular, many patients with glioblastoma are not represented in published randomised trials due to advanced age, comorbidity or poor performance status. In this retrospective review, survival for all elderly patients with glioblastoma presenting to a tertiary cancer centre are reported and compared.

Materials and Methods

A retrospective chart review was carried out for all patients age 65 years or greater with a pathological diagnosis of glioblastoma (World Health Organization grade IV) between 1 December 2006 and 31 December 2013. Cases were excluded if any radiation or chemotherapy was administered outside our institution before their first visit to the cancer centre. The database was closed on 2 May 2014 for survival analysis.

The following parameters were collected: gender, age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status at the time of initial oncology post-operative consultation, date and type of surgery, treatment received (radiation and/or chemotherapy), radiation dose fractionation, clinical trial enrolment and current status (alive/deceased). Surgical extent (biopsy, subtotal [STR] or gross total resection [GTR]) was determined by the surgeon's operative note and postoperative imaging. GTR was defined as removal of all macroscopic tumour; STR was defined as less than GTR, including tumour debulking; biopsy was defined as removal of some tumour tissue but no debulking.

MGMT methylation and isocitrate dehydrogenase 1 mutation (mIDH1) status were not routinely tested, and thus were not available. Dates of death were ascertained from the medical record, correspondence with the patient's family physician or palliative care physician, or through publicly available obituary records. The study protocol was reviewed and approved by the local hospital research ethics board.

Statistics

Overall survival was defined as the time from craniotomy to death or last follow-up. A patient alive or lost-to-follow-up was considered as censored. The actuarial median survival and 95% confidence interval were estimated by the Kaplan–Meier method. Univariate analysis of overall survival was carried out using a Cox proportional hazard model with all patients for each covariate (age, gender, ECOG performance status, surgery type and treatment received) to determine unadjusted hazard ratios and 95% confidence intervals. Kaplan–Meier survival curves were created for significant covariates related to overall survival; groups were compared using the Log-rank test. Based on the univariate analysis, we chose statistically significant covariates with $P < 0.10$ applied in backward stepwise selection to generate a multivariate Cox proportional hazard model and adjusted hazard ratios with 95% confidence intervals. A P value of < 0.05 was considered statistically significant in the final model. All analyses were conducted by Statistical Analysis Software (SAS version 9.3, Cary, NC, USA) and R package (version 2.15.2, Vienna, Austria).

Results

Patient Characteristics

In total, 235 patients meeting the eligibility criteria were identified; 121 (51%) were women; the median age at