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Treatment results and outcome in elderly patients with glioblastoma multiforme – A retrospective single institution analysis

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ABSTRACT

Objective: Although glioblastoma multiforme is more common in patients older than 65 years, the elderly population is often excluded from clinical studies. Decision making in this subgroup can be challenging due to the lack of evidence for different neurosurgical and adjuvant treatment strategies.
Methods: In this retrospective study, we evaluated clinical, treatment and survival data of 124 consecutive patients over 65 years of age with supratentorial glioblastoma multiforme.
Results: Median OS was 6.0 months (std. error 0.783, 95% CI 4.456–7.535). Mean OS was 9.7 months (std. error 0.830, 95% CI 8.073–11.327). In univariate regression analysis, low KPS was of negative prognostic value ($p < 0.006$ for KPS ≤ 80), while greater advanced age did not have any impact on survival ($p = 0.591$ for differences between groups). Gross total resection and subtotal resection led to significantly improved overall survival (median 15.0 and 11.0 months; $p < 0.02$) compared to partial resection or biopsy (both 4.0 months), but complications were more common in subtotal and partial resections. The last observation did not reach statistical significance ($p = 0.06$). Combinations of irradiation and Temozolomide chemotherapy proved to be more effective than other adjuvant therapies. Extent of resection (gross total resection vs. all others) and form of adjuvant treatment were the only factors of independent prognostic value in multivariate analysis ($p = 0.031$ and $p < 0.001$, respectively).
Conclusions: It appears that more aggressive treatment regimens can lead to longer overall survival in elderly glioblastoma multiforme patients. Gross total resection should be offered whenever safely possible; otherwise, biopsy may be preferred. Non-surgical treatment should consist of postoperative radiotherapy and concomitant and/or adjuvant chemotherapy. Possibly higher rates of hematological side effects in concomitant chemotherapy need to be further investigated.

1. Introduction

Although primary brain tumors are rare [52], increased population aging leads to an increase in tumor frequency among the elderly [21,83], especially regarding glioblastoma multiforme (GBM) [32]. With the introduction of the "Stupp-protocol", the median survival of glioblastoma multiforme (GBM) patients was prolonged to 14.6 months [72]. While this study excluded patients over 70 years, other studies confirmed that surgery with adjuvant radiochemotherapy is also efficient in elderly patient cohorts [7,21,49,55].

Most clinical trials on GBM therapy do not include patients >65 or 70 years, as age itself is considered to be an independent negative prognostic factor [1,3,15,19,24,29,34,39,46,47,50,60,64,69,70,72,75,89,91,92]. It is not until 2007 that Keime-Guibert et al. have shown that radiotherapy is more effective than supportive care in GBM patients over 70 years [33]. Although recent multicenter randomized controlled trials (RCTs) like NOA-08 and NORDIC have helped to improve decision-making in elderly glioma patients, they mainly focused on the impact of different radiochemotherapy regimens [46,85]. The role of surgery, especially extent of resection (EOR), still remains a matter of discussion. In younger trial population groups, there is strong evidence that an EOR around 80–98% is independently prognostic [39]. Some

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Table 1
Major presenting symptoms.

	No.	%
Hemiparesis	37	29.8
Mental status change	22	17.7
Seizure	17	13.7
Speech impairment	14	11.3
Cephalea	13	10.5
Vertigo	8	6.5
Gait disturbance	7	5.6
Visual impairment	4	3.2
Incidental finding	2	1.6

retrospective analyses – none of these including patients treated later than 2008 – support the role of cytoreductive surgery in elderly patients [3,12,19,29,47,64].

We present a comprehensive data analysis of patients older than 65 years with GBM treated at the University Hospital Graz from 2005 to 2012 and provide an up-to-date overview regarding the influence of surgical and non-surgical treatments on overall survival (OS).

2. Materials and methods

The medical charts of 124 patients aged ≥65 years with glioblastoma multiforme treated between 2005 and 2012 were systematically reviewed. Patients were identified using a prospective database. Patients aged ≥65 years with diagnosis of glioma but without histological verification were excluded as well as patients with diagnoses of more favorable prognosis, i.e. Astrocytoma WHO II and III, Oligoastrocytoma or Gliosarcoma. The Follow-up protocol used in clinical routine consists of immediate post-operative MRI (within 48 h), MRI control studies after adjuvant radiochemotherapy or no later than three months postoperatively followed by MRI studies every three months or in any case of clinical deterioration. Clinical data like Karnofsky Performance Status (KPS), age, complications related to surgery and side effects of adjuvant treatment were collected along with treatment data in categorical form. Except for 19 patients, survival data was either directly available or updated from the Austrian Death Records.

Tumor locations and major presenting symptoms were categorized as shown in Tables 1 and 2. For cox regression analysis, tumor locations were grouped in frontal vs. all other locations and in central (basal ganglia, corpus callosum, multilocular) vs. all other locations.

OS was correlated with patient age as a linear variable and as a categorical variable after stratification into 4 age groups (65–70, 70–75, 75–80, >80 years).

EOR was categorized in gross total resection (GTR, removal of complete or at least 95% of the contrast enhancing tumor portion), subtotal resection (STR, removal of 80–95%), partial resection (PR, removal of ≤80%) and stereotactic Biopsy (B). EOR was assessed according to the Macdonald criteria on early postoperative MRI (within 48 h after surgery) [44]. For cox regression analysis, EOR was also grouped in GTR vs. all other locations.

Neurosurgical complications were categorized in "permanent neurological deficit" (focal neurological deficits significantly interfering with activities of daily living), "lethal neurological complication" (brain infarction, secondary bleeding or brain edema leading to death during post-op hospitalization, i.e. within a period of 1 week postoperatively), "transient medical complication" (deep vein thrombosis, pulmonary artery embolism, pneumonia or myocardial infarction), "lethal medical complication" (same as transient medical complication, but leading to death during hospitalization) and "infection, impaired wound healing, secondary bleeding or cerebrospinal fluid fistula". Categories of (radio-)chemotherapy side effects were: "no severe side effects", "fatigue", "thrombopenia" and "infection". The side effects were graded according to CTCAE v3.0.

Patients were stratified into 6 groups of adjuvant treatment: (1) "none": Patients who received no further treatment other than surgery. (2) "radiochemotherapy only": At least 4 weeks of combined radiochemotherapy with 75 mg Temozolomide per square meter of body-surface area (mg/m^2) per day, 7 days per week from the first to the last day of radiotherapy (fractionated, 40–60 Gy). (3) "Stupp-protocol": fractionated radiotherapy (60 Gy) plus continuous daily 75 mg/m^2 Temozolomide, followed by six (at least 3 actually administered) cycles of adjuvant Temozolomide (150 mg/m^2 for 5 days during each 28-day cycle) [72]. (4) "radiotherapy only": Postoperative irradiation (fractionated focal irradiation, 40–60 Gy). (5) "chemotherapy only": at least 3 cycles of adjuvant Temozolomide chemotherapy (150 mg/m^2 for 5 days during each 28-day cycle) without irradiation. (6) "radiotherapy followed by chemotherapy": postoperative irradiation followed by at least 3 cycles of adjuvant Temozolomide chemotherapy (150 mg/m^2 for 5 days during each 28-day cycle).

Information about date of death was not available in 19 cases. Therefore, we corrected their survival data by presuming that patients with severely reduced overall performance at the last follow-up visit (KPS ≤40) would most likely die within one month. This correction did not influence the statistically significant results.

Progression-free survival is not presented, as inconsistencies regarding follow-up intervals seemed prevalent in this patient cohort. That data would have been prone to misinterpretation.

Statistical analysis was performed using SPSS® (IBM Corporation) Version 20.0. Categorical data for KPS and EOR were correlated with categorical data for surgical complications using Pearson Chi Square cross tabulations. We used Kaplan–Meier plots and tested for equality of OS distribution for Age, tumor location, KPS, EOR and form of adjuvant treatment categories using Log Rank (Mantel–Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware tests. Age as a linear parameter was correlated with OS using the Pearson product-moment correlation coefficient while using one way ANOVA and cox regression when defining age as a categorical parameter. We performed univariate cox regression analyses and pairwise comparisons providing differences in OS and Hazard Ratios (HR) for all categorical factors. For multivariate regression analysis, we used a cox regression model and the forward: conditional method. In all applied tests, a p-value of less than 0.05 was used as level of significance.

The study protocol was approved by the local ethics committee of the Medical University of Graz (ID: 25-2812 ex 12/13).

3. Results

Data from 124 patients were analyzed. 51 women and 73 men with a mean age of 71.0 years (min. 65, max. 84) were included. The major presenting symptoms, i.e. the reasons why imaging was performed, are outlined in Table 1.

At the time of analysis, 93 patients had died, 14 were in progressive, 9 in stable disease status and 8 patients were lost to follow-up.

Median OS was 6.0 months (std. error 0.783, 95% CI 4.456–7.535). Mean OS was 9.7 months (std. error 0.830, 95% CI 8.073–11.327).

3.1. Location

Tumor locations were distributed as shown in Table 2. Survival analysis, one-way ANOVA and univariate cox-regression did not depict significant differences in OS between the location groups.