Distance to the Neurooncological Center: A Negative Prognostic Factor in Patients with Glioblastoma Multiforme. An Epidemiological Study

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Abstract. Background: Regardless of current multimodal treatment strategies, the prognosis of patients harboring glioblastoma multiforme (GBM) is still dismal. The introduction of concomitant radiochemotherapy and adjuvant cyclic temozolomide has significantly improved the overall survival, compared to postoperative radiotherapy-alone. Furthermore this regimen shows a lower toxicity profile compared to previous nitrosourea-based chemotherapy and can easily be applied on an outpatient basis, thus potentially facilitating chemotherapy in rural and more remote areas. The distance to the oncological center has been shown to be a negative prognostic parameter in other types of cancer. Therefore, we aimed to investigate whether the introduction of temozolomide as the standard regimen in the treatment of GBM has influenced the administration of chemotherapy and the prognosis of patients depending on the distance to our neurooncological center. Patients and Methods: A total of 208 patients diagnosed with GBM (M:F=1.4:1), surgically resected between 1990 and 2009, thus covering the pre-temozolomide and the temozolomide-era, were included retrospectively in this analysis. The distance from the patients’ residences to the neurooncological center was determined and statistical analysis was performed to assess its influence on overall survival and administration of adjuvant treatment (radiotherapy-only, nitrosourea-based chemotherapy and adjuvant temozolomide). Results: Overall, 41.3% of the cohort underwent subtotal surgical resection, whereas a gross total resection was accomplished in 57.2%. The median distance to the neurooncological center was 75 km (range=1-870 km). Postoperatively, 68 patients (32.7%) received concomitant and adjuvant radiochemotherapy with temozolomide, 31 (14.9%) were treated with nitrosourea other than the Procarbazin, Lomustin, Vincristin (PCV), 34 (16.3%) with PCV, and 71 patients (34.1%) had radiotherapy-alone. The distance to the neurooncological center had a significant influence on overall survival for the whole cohort (p=0.027) and patients with increasing distances, were significantly less often treated with chemotherapy (p=0.05). With the introduction of temozolomide this relation was lost (overall survival, temozolomide and other agents: p=0.685/p=0.007; administration of adjuvant chemotherapy in the temozolomide-era/whole cohort: p=0.612/p=0.05). Conclusion: The distance to the neurooncological center negatively-influenced the prognosis of patients with GBM. Patients were less often treated with adjuvant chemotherapy in the pre-temozolomide era with increasing distance to the neurooncological center. Although the introduction of temozolomide as the standard chemotherapeutic agent in GBM treatment changed this fact, the influence of the distance to the specialized center should be kept in mind as a prognostic factor for this disease.

Glioblastoma multiforme (GBM) is the most frequent primary malignant brain tumor in adults (1). Until 2005, adjuvant radiotherapy was the standard treatment regimen and chemotherapy was added mostly for cases of recurrence (2). Since the introduction of concomitant radiochemotherapy and adjuvant temozolomide following surgery or stereotactic biopsy according to Stupp et al., overall survival (OS) has improved significantly (3). Several studies have been performed for other malignancies (e.g. breast cancer) investigating whether the distance to the caring center influences the outcome [OS and progression-free survival (PFS)] (4), but so far this factor has not been investigated for the treatment of malignant glioma (5-8).

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In the treatment of patients with GBM it was demonstrated that temozolomide causes less toxicity and side-effects (9-11) compared to pre-existing chemotherapies such as Procarbazin, Lomustin, Vincristin (PCV) or other nitrosourea-based drugs, even in prolonged administration (12-14). As a result, temozolomide should be more easily applied on an outpatient basis, which may particularly have a benefit for patients living in rural areas, remote from the caring neurooncological center.

Therefore, this monocentric retrospective cohort study aimed to investigate the influence of the distance from the neurooncological center on OS and the frequency of adjuvant treatment and the influence of temozolomide-introduction into therapy.

**Patients and Methods**

**Patient population.** More than 500 patients with GBM have been operated on in our Department between 1990 and 2009. For this retrospective analysis, a subpopulation of patients was selected according to predefined criteria: histopathologically-confirmed GBM (WHO grade IV), older than 18 years of age, surgical resection (subtotal or macroscopically complete), sufficient follow-up and sufficient availability of data. A total of 208 patients (M:F=1.4:1) aged between 21 and 83 (median=55.5 years) were eligible using a patient database. Patients diagnosed by biopsy were excluded.

The distance between the patients’ homes and our center, ranging from less than 1 km to 870 km (mean 75 km) was calculated using a standard route planner (Google Maps®; Mountain View, CA, USA). Patients included in this study all lived in Tyrol, Austria or in adjacent countries (e.g. northern Italy) and completed at least three regularly documented postoperative visits at our Department. Tyrol, with a population of about 710,000 people, has a size of 12,647 square kilometers and a west-east extension of about 220 km, but due to its geographical characteristics, only 15% of the area is inhabited.

**Study design.** The study was performed as a retrospective monocentric cohort study. Date of operation, histopathological confirmation of the diagnosis and date of death were collected from the patients’ files, for all patients operated on an intracranial glioblastoma between 1990 and 2009 at the Department of Neurosurgery at the Innsbruck Medical University. The baseline examination included imaging by the means of postoperative computed tomography (CT) or magnetic resonance imaging (MRI) to determine whether a macroscopically total resection was accomplished or not. Due to the extended time range some patients underwent postoperative CT only.

Overall, 165 patients (79.3%) underwent postoperative radiotherapy, 71 (34.1%) of them with a radiation dose of less than 50 Gy and 94 (45.2%) patients with doses of 50 Gy or more. Adjuvant chemotherapy was performed in 133 patients (63.9%): 34 PCV (16.3%), 31 nitrosourea (14.9%) other than PCV, 68 concomitant and adjuvant temozolomide (32.7%).

Patients treated with concomitant and adjuvant temozolomide received 75 mg/m² body surface concomitant and 150-200 mg/m² body surface for adjuvant cycles (3). In stable disease, a prolonged cyclic temozolomide administration until progression or occurrence of side-effects was performed.

The primary goal of this study was to analyze the correlation between OS of patients with GBM and the distance to the neurooncological center. The secondary goal of the study was to analyze the influence of the distance to the neurooncological center on administration of adjuvant treatment other than radiotherapy-alone.

**Statistical analysis.** Descriptive statistics are given as means, standard deviations, ranges and frequencies.

For statistical analysis we used the logarithm of the distance to the center, as this variable would not have a normal distribution. The association between logarithmic distance to center and survival time was based on Pearson correlation co-efficients. Group comparisons were made using one-way analysis of variance. Group differences and correlations between variables were considered significant at a p-value below 0.05. Statistical analysis was performed using SPSS 11.0 (SPSS Inc, IBM, NY, USA).

**Results**

From 1990 until 2009, a subpopulation of 208 patients out of the total number of patients treated for GBM were eligible for medical record review for this study. A subtotal surgical resection was accomplished in 86 patients (41.3%), in 119 patients (57.2%) a macroscopically total resection was achieved. Postoperative adjuvant therapy consisted of either radiation, chemotherapy or both (Table I).

Before the establishment of concomitant radiochemotherapy and adjuvant temozolomide in 2005 by Stupp et al. as standard therapy, 71 patients (33.9%) were treated by surgery followed by radiation-only. A total of 34 patients (16.3%) received chemotherapy with PCV, 31 patients (14.9%) with nitrosourea-based chemotherapeutics other than PCV and 68 (32.7%) patients were treated according to the scheme of Stupp et al.

Distribution of gender (M:F=1:4:1) was well-balanced. The median distance between the patients’ homes and our center was 75 km (range=1 to 870 km) (Figure 1).

The median OS was 12 months, with a range from less than one month to 123 months. According to the therapy subgroup, the median OS showed a significant benefit for patients treated with concomitant radiochemotherapy and adjuvant temozolomide [median survival in the temozolomide-treated group=16 (range=1-123) months; median survival with other adjuvant treatments=12 (less than one–107) months].

There was a statistically significant advantage in OS for patients living closer to the neurooncological center (p=0.027) (Figure 2). Divided according to the different treatment subgroups, further analysis showed a strong negative influence of the distance to the neurooncological center for GBM patients treated with radiation therapy-alone, PCV chemotherapy or nitrosourea-based chemotherapy other than PCV (p=0.007). In the subgroup of patients treated with concomitant radiochemotherapy and adjuvant cyclic temozolomide, the distance to the center showed no statistically significant disadvantage (p=0.685).
With increasing distance to the center, adjuvant treatment other than radiotherapy was significantly less often administered ($p=0.05$). In patients treated with concomitant and adjuvant temozolomide, there was no such correlation ($p=0.612$).

**Discussion**

This retrospective analysis of more than 200 patients treated for GBM over a period of two decades demonstrated, to our knowledge for the first time, that there was an impact of the distance from the patient’s residence to the neurooncological center in the pre-temozolomide era, which was lost thereafter.

In patients with newly-diagnosed GBM concomitant radiochemotherapy according to Stupp *et al.* has been established as the standard adjuvant treatment following surgery, leading to a significant survival benefit compared to radiation therapy only (3). With the advent of temozolomide in the treatment of GBM, the incidence of side-effects was significantly reduced even in cases of prolonged administration (12, 14). The toxicity profile of temozolomide is lower compared to previously administered chemotherapy such as PCV and other nitrosourea agents. According to existing literature up to 46% of patients experience severe side-effects when treated adjuvantly with PCV–chemotherapy (15). Most frequently, hematopoetic disturbances (16-18), but also neurotoxic effects, cognitive deficits or cerebral atrophy on MRI have been reported (19).

Hematopoetic side effects of Common Toxicity Criteria (CTC) grade 3-4 are rare in patients treated with temozolomide (32% for PCV compared to 5% for temozolomide, respectively) (20). Neurotoxicity [described for nitrosourea-based chemotherapeutics (5, 19)] is not discussed as a relevant problem in patients receiving temozolomide chemotherapy. For patients treated by PCV or other nitrosourea-based drugs, the diagnosis and treatment of chemotherapy-related side-effects might therefore be a challenge, especially in areas not well-serviced. The finding that patients living more distant from a specialized center were less often treated with adjuvant therapy other than radiation therapy in the pre-temozolomide era might be explained by this fact. Additionally, the general attitude of a more rural population to severe and deadly disease might be different.

Temozolomide treatment, in contrast, has already been proven to be effective and safely administerable. In addition, regular follow-ups concerning the most common side-effects (neutropenia and thrombopenia) (21) can be handled by general practitioners, as they are preponderantly CTC grade 1 and 2. Thus, there is no need for weekly examinations at a specialized center. Simple laboratory investigations in an outpatient setting provide adequate surveillance of most of the side-effects associated with temozolomide treatment.

The findings of this study demonstrate that in the temozolomide era, the distance to the neurooncological center is no longer a factor of deferring adjuvant chemotherapy ($p=0.041$ for PCV and other chemotherapeutics vs. $p=0.612$ for temozolomide therapy).
In previous studies including socioeconomic prognostic parameters (4-8, 20), it has been shown that in addition to classical prognostic parameters (Karnofsky performance index, age, gender, general medical condition), the distance to the caring neurooncological center seems to have a strong influence on the outcome of patients with all sorts of brain malignancies. Retrospective studies performed in patients with glioma in the United Kingdom (8) or in patients with medulloblastoma in Greece (6) and larger epidemiological studies of all types of brain malignancies in the United States (5, 7), have already suggested that patients living in rural areas more distant from an oncological center have a less favorable prognosis. However, an analysis of this interdependence is lacking for the subgroup of GBM. The explanation for this may be that patients living in distance from a specialized center might have hindered access to follow-up examinations and inconsistent monitoring of therapy-associated side-effects.

This study on more than 200 patients operated on at the same Neurosurgical Department, demonstrates a direct correlation between survival and the distance to the specialized neurooncological center. Patients living closer to our center have an OS benefit, with a significance level of \( p = 0.027 \) in univariate analysis. In a more differentiated analysis regarding patients treated with concomitant radiochemotherapy and adjuvant temozolomide, this correlation was lost \( (p = 0.685) \).

Obviously, from our data it cannot be concluded that the adjuvant chemotherapeutic treatment of patients suffering from GBM should be solely managed by a general practitioner. But with the introduction of temozolomide administration on an outpatient basis, de-centralization of neurooncolgical treatment is possible and increases the administration of chemotherapy even in rural areas, in distance from the specialized center.

**Conclusion**

This retrospective analysis demonstrates that the distance to the neurooncological center influenced the prognosis of patients with GBM in the pre-temozolomide era; with increasing distance to the neurooncological center, patients were less often treated with adjuvant chemotherapy. Although the introduction of temozolomide as the standard chemotherapeutic agent in treatment of GBM changed this, the influence of the distance from the specialized center should be kept in mind as a prognostic factor in these patients.

**Conflicts of Interest**

We declare that we have no conflicts of interest.

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**References**


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