# Survival and prognostic factors of patients with unresectable glioblastoma multiforme

Barbara Fazeny-Dörner[a], Catharina Wenzel[a], Mario Veitl[b], Maria Piribauer[a], Karl Rössler[c], Karin Dieckmann[d], Karl Ungersböck[c] and Christine Marosi[a]

**The aim of this study was to assess survival and prognostic factors of 98 consecutive patients with unresectable glioblastoma multiforme (GBM) after stereotactic biopsy. Patients were diagnosed between 1993 and 1998, and the treatment modality subsequent to stereotactic biopsy was determined by the year of diagnosis. Before 1995, patients did not receive further specific therapy after stereotactic biopsy ($n=36$). In 1996, patients were administered radiotherapy starting within 6 weeks after stereotactic biopsy ($n=24$). From 1997 to 1998, patients received combined radio-/chemotherapy (RCT; CCNU orally) starting within 2 weeks after stereotactic biopsy ($n=38$). Patients' age ranged from 21 to 84 (median 64) years and their median Karnofsky performance score 2 weeks after stereotactic biopsy was 80 (range 60–100). Survival and prognostic factors were analyzed with respect to administered treatment modalities (without specific therapy versus radiotherapy versus combined RCT), with respect to age ($>/\leq 50$ years), gender, Karnofsky performance score ($\geq/<80$), tumor location (frontal, parieto-temporal, central, occipital) and tumor size ($>/\leq 5$ cm; tumor multiplicity was considered as diameter >5 cm) by the Kaplan–Meier method, by log-rank test and multivariate Cox regression analysis. Post-biopsy treatment modality was the strongest predictor for survival. Median (range) survival was 9 (3–47) weeks in those without specific therapy, 13 (5–54) weeks in patients receiving radiotherapy and 31 (11–101) weeks in patients receiving combined RCT ($p\leq 0.001$). Age $\leq 50$ years ($p\leq 0.05$) in addition to tumor size in multivariate Cox analysis were found to be of significant influence onto survival, too. Combined RCT could be performed on a complete outpatient basis. Toxicity consisted of mild asymptomatic thrombocytopenia. We conclude that the administration of combined RCT within a minimum interval after stereotactic biopsy yielded a significant increase in survival. Patients' acceptance was excellent. These results encourage us to treat even patients with unresectable GBM with combined RCT. *Anti-Cancer Drugs* 14:305–312**


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[a]Clinical Division of Oncology & Ludwig Boltzmann Institute for Clinical Experimental Oncology, Department of Medicine I, [b]Clinical Institute for Medical and Chemical Laboratory Diagnostics, Clinical Chemistry, [c]Department of Neurosurgery and [d]Department of Radiooncology, University of Vienna, Vienna, Austria.

Correspondence to B. Fazeny-Dörner, Department of Medicine I/Oncology, Ludwig Boltzmann Institute for Clinical Experimental Oncology, University of Vienna, Währinger Gürtel 18–20, 1090 Wien, Austria.
Tel: +43 1 40400 4457; fax: +43 1 2198963;
e-mail: barbara.doerner@chello.at

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## Introduction

Glioblastoma multiforme (GBM) can be neurosurgically resected in the majority of patients. However, surgical resection may not be the appropriate treatment for all patients. In patients with tumors in eloquent or deep areas, with midline tumors, or in those with extensive tumors and/or multifocal tumors, or in patients with heavily reduced performance status, stereotactic biopsy might appear as the most appropriate neurosurgical intervention in the individual case. Consequently, these patients are supplied with stereotactic biopsy in order to gain material for neuropathologic diagnosis for further treatment decision. Among all patients with GBM, those with unresectable tumors are considered to have the worst prognosis. The treatment strategy for patients with unresectable GBM is poorly documented in the literature, even though this subgroup of patients can represent up to 35–40% of all GBM patients. Some information concerning the patient subgroup with unresectable GBM can be found in a recent meta-analysis of the Glioma Meta-analysis Trialists Group [1]. An absolute increase in 1- and 2-year survival was associated with chemotherapy regardless of the extent of resection, age, sex, histology or performance status. Additionally, in several studies, the administration of adjuvant nitrosourea resulted in an increase in long-term survival regardless of any prognostic factor [2–5].

Another important reason to investigate this specific patient subgroup in more detail is the fact that the effect of radio- and/or chemotherapy can be demonstrated without the confounding factor of surgery. Frenay *et al.* [6] analyzed up-front chemotherapy in 33 non-removable glioblastomas and yielded a median survival of 10 months with a combination of fotemustine/cisplatin/etoposide. Coffey *et al.* [7] assessed the outcome of 64 patients with unresectable GBM. Unfortunately, the results of this

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study are limited because a significant number of patients had undergone tumor resection after radiotherapy.

Considering the frequency of unresectable GBM in clinical neuro-oncology, physicians may feel deprived of guidelines for patient management. Therefore, we addressed this subject and reviewed our institution's experience of patients with unresectable GBM in the period from 1993 to 1998. Outcome of patients was analyzed according to post-biopsy treatment modalities, according to age, gender, Karnofsky performance status, tumor location, as well as tumor size. The treatment modality subsequent to stereotactic biopsy was determined by the year of diagnosis and reflects the institution's process of transformation from therapeutic nihilism to the standardized treatment with combined radio-/chemotherapy (RCT) even in patients with unresectable GBM.

## Methods

### Inclusion criteria

This retrospective analysis presents our institution's experience of all consecutive patients ($n = 98$) with unresectable GBM diagnosed between 1993 and 1998. Unresectable GBM represented between 23 and 38% of the whole GBM diagnosed during the study period (total number of GBM diagnosed from 1993–1998: 334; percentage of unresectable GBM: 1993 and 1994: 23% each; 1995: 26%; 1996: 38%; 1997: 35%; 1998: 32%). Neurosurgical resection was contraindicated in all these patients. Stereotactic biopsy was performed in order to achieve material for neuropathologic diagnosis as well as for further treatment decisions. The indication for stereotactic biopsy was made under the following circumstances: (i) when surgery was suspected to pose high risks to result in severe neurological deficits due to involvement of eloquent areas, (ii) in patients with inaccessible areas of the brain where surgical exposure poses undue risks of new neurological deficits, (iii) in patients with multifocal and extensive tumors, and (iv) in patients with heavily reduced performance status (Karnofsky performance status $< 70$). Stereotactic biopsy was not institutionally preferred over neurosurgical resection. Thus, all 98 patients had stereotactic biopsy as the only neurosurgery. No treatment decisions were based on imaging only.

Tumor histology had to meet the WHO criteria for GBM [8,9]. The histology of GBM was verified by central neuropathologic re-evaluation.

Written informed consent was obtained from all patients.

### Neurosurgical procedure

Stereotactic biopsy was performed by using the BRW or CRW stereotactic frame (Radionics, Oberkochen, Germany) [10].

### Treatment modalities

The administered treatment modality subsequent to biopsy was determined by the year of diagnosis. Before 1996, patients did not receive further specific therapy after stereotactic biopsy ($n = 36$). In 1996, all patients with unresectable GBM received radiotherapy within 6 weeks after stereotactic biopsy ($n = 24$). From 1997 until 1998, patients systematically received combined RCT, both starting within 10–14 days after stereotactic biopsy.

### Patients characteristics

The characteristics of the three patient groups according to post-biopsy treatment modality are summarized in Table 1.

Patients in the three groups are comparable with respect to median age, median Karnofsky index (KI), as well as the number of patients having a tumor size $< / \geq 5$ cm and tumor multiplicity.

Tumor location and tumor size [(greatest single diameter on contrast enhanced computed tomography (CT) or magnetic resonance tomography (MRT)] were determined by pre- and post-biopsy (within 72 h) contrast-enhanced CT and/or MRT.

### Radiotherapy

Radiotherapy was planned by using a three-dimensional treatment planning system based on contrast-enhanced CT and/or MRT sectional imaging. The planning target volume, i.e. the tumor volume including a security margin of 2 cm, was defined by the radiooncologist based on pre- and post-biopsy imagining data. Immobilization masks were used for patient fixation to ensure a reproducible set-up. A radiation dose of 66 Gy (2.0 Gy/day) was delivered to the target volume using a multiple field technique with individually designed shielding blocks or standard multileaf collimators. The radiation dose was

**Table 1 Characteristics of the three patient groups according to the year of diagnosis and treatment subsequent to stereotactic biopsy (BX)**

| | BX | BX + radiotherapy | BX + radiotherapy + chemotherapy |
|---|---|---|---|
| Year of diagnosis | 1993–1995 | 1996 | 1997–1998 |
| No. patients | 36 | 24 | 38 |
| Median age | 65 | 61.5 | 61 |
| Median KI | 80 | 80 | 90 |
| Tumor diameter [no. patients (%)] | | | |
| $<5$ cm | 15 (42) | 8 (33) | 16 (42) |
| $\geq 5$ cm | 21 (58) | 16 (67) | 22 (58) |
| Tumor location | | | |
| frontal | 12 | 5 | 10 |
| parieto-temporal | 7 | 4 | 6 |
| central | 14 | 12 | 17 |
| occipital | 3 | 3 | 5 |
| Tumor multiplicity (no. patients) | 4 | 3 | 3 |

administered over a period of 6–7 weeks starting within 6 weeks after stereotactic biopsy in the radiotherapy group (treated in 1996) and within 2 weeks in the group receiving combined RCT (patients treated from 1997 until 1998).

### Chemotherapy

Chemotherapy was administered on an outpatient basis and consisted of the oral nitrosourea lomustine (CCNU 100 mg/m$^2$) in 6–8 weekly intervals. Lomustine application was started within 2 weeks after stereotactic biopsy. Lomustine was administered until documented disease progression by neuroimaging or until death.

Eligibility criteria for chemotherapy were: Patients were required to be older than 18 years and to have a KI $\geq$ 60. Adequate liver function (with SGOT, SGPT and alkaline phosphatase levels $<$ 2 times the normal range; bilirubin in serum $<$ 1.5 mg/dl) as well as renal function (with creatinine level $<$ 1.5 times of the normal range) and bone marrow function (leukocyte count $>$ 3000/$\mu$l, hemoglobin $>$ 10 g/dl, platelet count $>$ 100 000/$\mu$l) were required. Pregnant or nursing women as well as patients with acute infections were not eligible. Adequate contraception was mandatory.

Before start of chemotherapy a written informed consent was mandatory.

For antiemetic prophylaxis, all patients receiving oral lomustine were given either granisetron or tropisetrone orally from day 1–3.

Toxicity evaluation of chemotherapy side effects was performed according to WHO criteria [11].

### Treatment of therapy failures

After disease progression, further treatment was individualized and consisted of the administration of second-line chemotherapy with i.v. fotemustine/dacarbazine in two patients [12]. Repeat neurosurgical procedures were not performed in any patient after disease progression.

### Dexamethasone

In view of the fact that the dexamethasone dosage was not administered according to a standardized protocol during the three different treatment periods, dexamethasone was not considered a reliable prognostic factor and therefore was not further assessed. The administered dosage of dexamethasone ranged from 4 to 12 mg/day and was given over a period of 3–101 weeks.

### Anti-convulsants

The majority of patients were administered anti-epileptic drugs (phenytoin) for either a single epileptic seizure or it was started immediately after neurosurgical procedure.

### Response evaluation

Response evaluation was based on MacDonald's criteria [13]. Complete response (CR) was defined as the disappearance of all measurable disease with improved neurology in the absence of corticoid therapy. Partial response (PR) was a $\geq$ 50% decrease in tumor size with an improved or stable neurology on stable or decreased dexamethasone dose. Stable disease (SD) was a $<$ 50% decrease or $<$ 25% increase of the tumor size with an improved or stable neurology on stable or decreased dexamethasone dose. Progressive disease (PD) was a $>$ 25% increase in tumor size or the appearance of new lesions. Tumor evaluation was based on the product of the two largest perpendicular diameters of the contrasting lesion. If the tumor did not enhance, the diameters of the hyperintense signal on T2-weighted magnetic resonance imaging (MRI) images or of the hypodense region on CT scans were used.

Patients were monitored with either cranial CT or MRI scan after 2, 4, 6 and 8 cycles of therapy in the case of clinical and neurological stability, and immediately when disease progression was suspected clinically.

### Analysis and statistics

All analyses were done by intention to treat.

The study endpoint was survival until death. Survival was defined as the time from neuropathologic diagnosis until death (from any cause).

Six factors were considered for statistical analysis (Table 2): post-biopsy treatment modalities (no specific therapy versus radiotherapy versus combined RCT), patient's age at stereotactic biopsy ($>/\leq$ 50 years), gender, Karnofsky performance score 1 week after stereotactic biopsy ($\geq/<$ 80), tumor location (frontal, parieto-temporal, central, occipital) and tumor size expressed by the largest measurable diameter on contrast enhanced CT or MRT ($>/\leq$ 5 cm; tumor multiplicity was considered as tumors having a diameter $>$ 5 cm).

Survival curves were constructed using the Kaplan–Meier non-parametric method. Medians (and their respective 95% confidence intervals) were calculated from the Kaplan–Meier estimates [14,15]. The log-rank test was used to test differences in survival time between subgroups of patients [15].

Hazard ratios for the time-to-event-endpoint were estimated using the multivariate Cox regression analysis in a forward stepwise method to evaluate the effect of multiple independent prognostic factors on survival outcome (age, Karnofsky performance status, tumor location and post-biopsy treatment modality) [15].

Statistical evaluations were performed with SPSS version 10.0.7 program package. A $p$ value $\leq 0.05$ was considered statistically significant.

## Results

All patients had complete follow-up until death.

Patients' survival data (Kaplan–Meier) and the statistic significance according to the six factors (log-rank) considered for statistical analysis are detailed in Table 2.

Patients' median age was 64 (range 21–84) years. The median Karnofsky performance score 1 week after stereotactic biopsy was 80 (range 60–100).

A total of 71 (range 1–6; median 4) cycles of oral lomustine were administered in the RCT group with a median cumulative dose of 640 mg.

### Response

Two PRs (5%) lasting for 2 and 3 months, respectively, have been observed in the group treated with combined RCT. Twenty-six patients (68%) showed SD. A CR has not been observed with combined RCT.

### Survival

Median survival time in all patients (Fig. 1) was 17 (range 3–101) weeks with a 95% confidence interval of 12.2–21.9 weeks. Six-month survival was 37% and 12-month survival 12%. Three patients (3%; 32, 63 and 72 years of age) survived 18 months. One patient (1%; 50 years of age) survived 24 months.

In univariate analysis post-biopsy treatment modalities revealed to be of prognostic importance were patients receiving combined RCT survived significantly longer (median: 31; range 11–101 weeks) than patients receiving radiotherapy (median: 13 ; range 5–54 weeks) and patients without any specific therapy (median: 9; range 3–47 weeks) ($p < 0.001$; Fig. 2).

Patients aged $\leq 50$ years yielded a significant better median survival of 22 (range 10–104) weeks as compared to those $>50$ years with a median survival of 16 (range 3–72) weeks ($p \leq 0.05$; Fig. 3).

Occipital tumor location was associated with longer survival (median: 34; range 5–101 weeks) as compared to the other tumor locations, but did not reach statistic significance.

Karnofsky performance score, gender and tumor size were not significantly related to survival in univariate analysis.

### Toxicity of chemotherapy

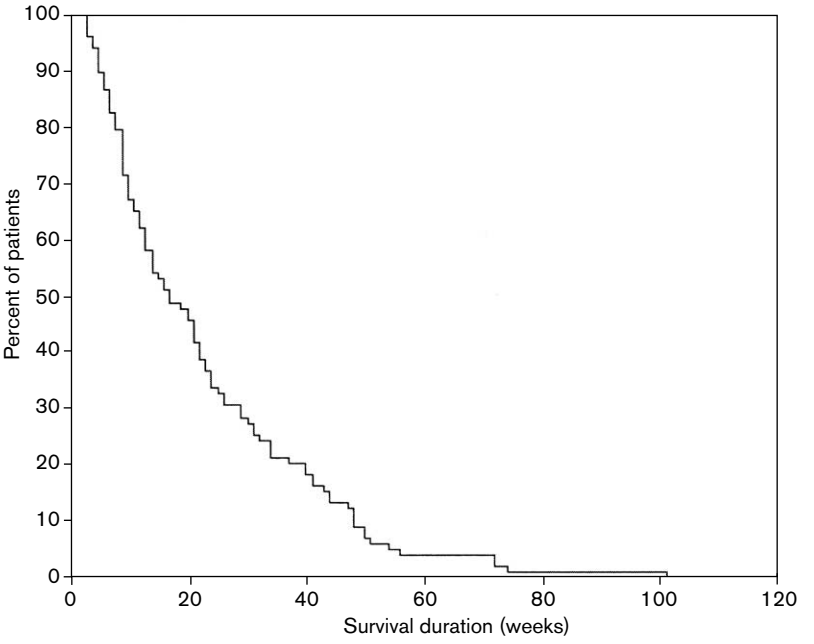
Orally administered CCNU resulted in mild to moderate asymptomatic thrombocytopenia and mainly occurred after 3–5 cycles of therapy. Seven patients showed thrombocytopenia of WHO grade III. Consequently, further therapy administration was postponed up to 3 weeks at maximum, otherwise the dosage of CCNU was reduced from 100 to 75 mg/m$^2$ ($n = 4$ patients). Neither bleeding complications nor lung fibrosis were observed.

Under standardized prophylactic antiemetics patients did not suffer from gastrointestinal toxicity.

**Table 2 Characteristics of 98 patients with unresectable GBM eligible for stereotactic biopsy only and the association of the six covariates with median survival**

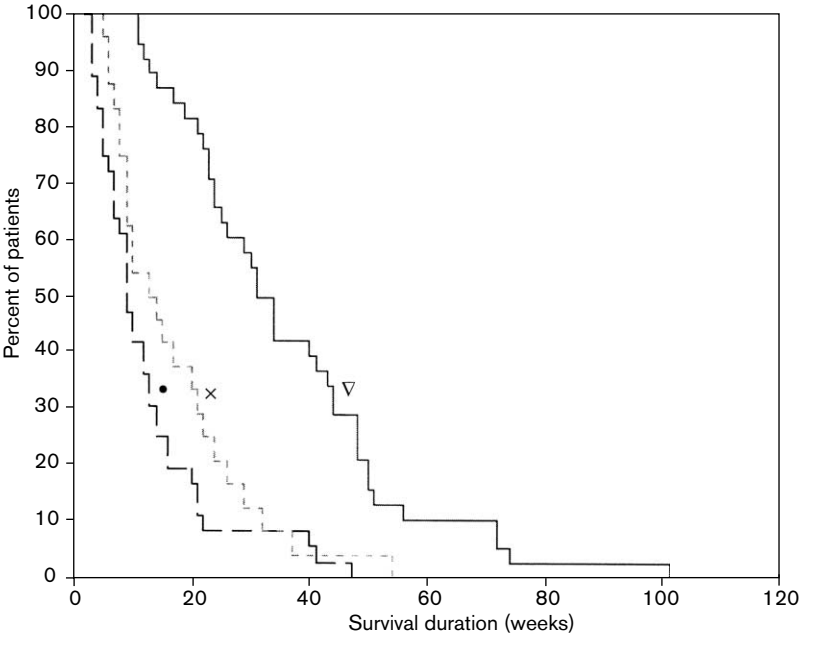
| Characteristics | No. of patients | Median survival [weeks (range)] | $p$ |
|---|---|---|---|
| Age at stereotactic biopsy | | | |
| >50 years | 87 | 16 (3–72) | |
| ≤50 years | 11 | 22 (10–101) | ≤0.05 |
| Treatment modality | | | |
| stereotactic biopsy without any specific therapy | 36 | 9 (3–47) | |
| stereotactic biopsy plus radiotherapy | 24 | 13 (5–54) | |
| stereotactic biopsy plus combined RCT | 38 | 31 (11–101) | ≤0.001 |
| Gender | | | |
| male | 60 | 14 (3–101) | |
| female | 38 | 14 (3–54) | NS |
| Tumor location | | | |
| frontal | 28 | 12 (3–72) | |
| parieto-temporal | 17 | 14 (3–48) | |
| central | 41 | 19 (4–72) | |
| occipital | 12 | 34 (5–101) | NS |
| Largest measurable diameter on CT/MRT after stereotactic biopsy | | | |
| <5 cm | 39 | 20 (3–74) | |
| ≥5 cm (including tumor multiplicity) | 59 | 14 (3–101) | NS |
| KI 1 week after stereotactic biopsy | | | |
| ≥80 | 72 | 17 (3–101) | |
| <80 | 26 | 17 (3–56) | NS |

**Fig. 1**




Survival of 98 patients with unresectable GBM.

**Fig. 2**



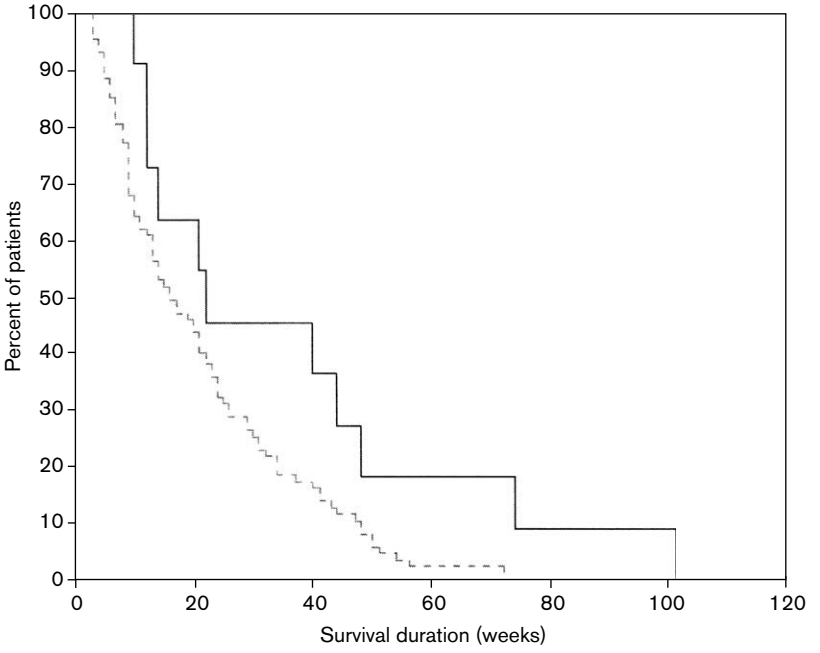

Survival of 98 patients with unresectable GBM according to the treatment modalities: (circle) survival of patients without any specific therapy ($n=36$), (cross) survival of patients receiving radiotherapy ($n=24$) and (triangle) survival of patients receiving combined RCT ($n=38$). $p<0.001$.

The main complaints of patients concerned side effects from chronic glucocortic intake, primarily the cushingoid appearance, myopathy and vulnerability of the skin.

### Prognostic factors

Post-biopsy treatment modality revealed to be the most significant predictor for survival using the multivariate Cox regression model, including post-biopsy treatment

**Fig. 3**




Survival of 98 patients with unresectable GBM according to patient age at diagnosis: (solid line) age $\leq$50 years ($n$=11) and (dotted line) age >50 years ($n$=87). $p \leq 0.05$.

**Table 3 Coefficients of the multivariate Cox regression analysis**

| | β | SD of β | *p* | Exp. (β) |
|---|---|---|---|---|
| Treatment modality | 0.794 | 0.138 | 0.001 | 2.213 |
| Tumor location | 0.119 | 0.095 | 0.208 | 1.127 |
| KI | 0.096 | 0.241 | 0.691 | 1.101 |
| Tumor diameter | 0.012 | 0.232 | 0.958 | 1.012 |
| Age | 0.598 | 0.363 | 0.099 | 1.818 |

**Table 4 Coefficients of the multivariate Cox regression analysis after exclusion of post-biopsy treatment modality and Karnofsky performance score**

| | β | SD of β | *p* | Exp. (β) |
|---|---|---|---|---|
| Tumor location | 0.102 | 0.093 | 0.274 | 1.107 |
| Tumor diameter | 0.444 | 0.217 | 0.040 | 1.559 |
| Age | 0.686 | 0.357 | 0.055 | 1.986 |

modality, tumor location, Karnofsky performance score, age and tumor size ($p \leq 0.001$; Table 3).

Tumor size was of prognostic significance after exclusion of post-biopsy treatment modality and of Karnofsky performance score ($p \leq 0.05$; Table 4).

## Discussion

The main findings of this study are, on the one hand, that GBM patients without surgical resection do very poorly and, on the other hand, that a significant prolongation of survival was associated with combined RCT administered within a minimum interval subsequent to stereotactic biopsy.

The survival benefit of combined RCT may have several explanations. (i) Early onset of combined RCT subsequent to stereotactic biopsy seems to have contributed to survival prolongation. The early initiation of combined RCT may be an important point, especially in these rapidly growing tumors. The missing survival benefit in patients who received radiotherapy only is to be related to its late onset, starting with an interval of 5–6 weeks after stereotactic biopsy. Late onset of radiotherapy is known to worsen prognosis in GBM. (ii) The survival benefit may also be attributed to an effect of chemotherapy, although the extent of the exclusive impact of chemotherapy on survival cannot be defined exactly due to the retrospective study design. However, randomized trials have demonstrated the exclusive impact of chemotherapy, independent of the extent of tumor resection, age, sex and performance status [1].

In this particular subgroup, the treatment effects of chemotherapy and radiotherapy can be best evaluated

because results are not confounded by the factor of surgery. Frenay *et al.* [6] reached a median survival of 10 months with a polydrug regimen of cisplatin, etoposide and fotemustine in unremoveable GBM. In contrast, monotherapy with oral temozolomide resulted in median survival ranging from 3 to 7.7 months in glioblastoma at first relapse [16–18]. In comparison to Frenay's data [6], we attributed the shorter median survival of 7 months in our study to monotherapy with lomustine. Therefore, in our institution, the combination of dacarbazine and fotemustine has been introduced into second-line therapy of GBM [12]. After it has shown an encouraging survival of 10 months, the combination could be successfully introduced into first-line therapy [19]. (iii) The effect of combined treatment may also be explained by an uncontrolled bias, which cannot be formally excluded, considering it is not a controlled comparative study.

Despite the retrospective character of our study, the distribution of the major prognostic factors—age, Karnofsky performance score and tumor size—were comparable across the three groups. In particular, the prognostic factors of the patient group treated with combined RCT were not superior as compared to the other two groups.

A high Karnofsky performance score has often been expected to be associated with a favorable outcome [20,21]. In our study, the Karnofsky performance score was revealed to be a weak prognostic parameter; consequently, the exclusion in the stepwise Cox analysis was indicated. The GMT Group's results also showed no evidence that performance status influenced the effect of combined RCT [1].

A further result of our analysis revealed age $\leq 50$ years to be of positive prognostic importance in this specific subgroup. Additionally, tumor size was of prognostic importance in multivariate Cox analysis including age, tumor size and tumor location. In the literature, the roles of postoperative tumor size and cytoreductive surgery, particularly as they are related to survival, still remain unclear. Several studies demonstrated that postoperative tumor size was correlated with longer survival [22–25], whereas others did not [26–29].

The administration of oral CCNU concomitantly to radiotherapy was well tolerated by patients. The asymptomatic thrombocytopenia could not be associated with the anti-epileptic valproate as our patients were administered phenytoin [30]. However, the thrombocytopenia was without substantial burden for the patients. The complete outpatient administration of combined RCT even in patients with unresectable GBM was supported by gapless patient care provided by a dedicated interdisciplinary neuro-oncologic team and resulted in excellent patient acceptance.

The results of our study might help to contribute to counterbalance the contemporary trend in neuro-oncology to restrict adjuvant chemotherapy to young patients with excellent prognostic factors only [2,24,31]. Prospectively randomized trials are known to favor the inclusion of selected patients with better prognostic patterns [32]. In particular, patients $>70$ years are rarely included into randomized trials, although they constitute a substantial number of patients suffering from high-grade gliomas [33,34].

Especially in view of the fact that unresectable GBM can represent up to 40% of all GBM, patient management guidelines seem to be urgently needed. Our results might help to encourage physicians to treat these poor prognosis patients with concomitant RCT. In the meanwhile, it seems to be the most challenging task for physicians to continue looking for the best treatment strategy for this large number of poor prognosis patients.

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