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Survival improvement in patients with glioblastoma multiforme during the last 20 years in a single tertiary-care center

Barbara Fazeny-Dörner[1], Anwar Gyries[1], Karl Rössler[2], Karl Ungersböck[2], Thomas Czech[2], Alexandra Budinsky[1], Monika Killer[2], Karin Dieckmann[3], Maria Piribauer[1], Gerhart Baumgartner[4], Daniela Prayer[5], Mario Veitl[6], Manfred Muhm[7], and **Christine Marosi[1]**

[1] Clinical Division of Oncology & Ludwig Boltzmann Intitute for Clinical Experimental Oncology, Department of Medicine I, [2] Department of Neurosurgery, [3] Department for Radiooncology, University of Vienna, [4] 5th Medical Department, Hospital Lainz, Vienna, [5] Department of Neuroradiology, [6] Clinical Institute for Medical and Chemical Laboratory Diagnostics, and [7] Department of Anesthesiology and University of Vienna, Vienna, Austria

Überlebensverlängerung von Patienten mit Glioblastoma multiforme während der letzten 20 Jahre in einem tertiären Versorgungszentrum

Zusammenfassung. *Studienziel:* Ziel der retrospektiven Analyse war es, die Überlebensdauer und einen eventuellen Fortschritt von 357 konsekutiven Patienten mit Glioblastoma multiforme (GBM) innerhalb von 3 Gruppen aus unterschiedlichen Diagnose-Zeiträumen (Gruppe A: 1982–1984, B: 1994/1995; C: 1996–1998), die während der letzten 20 Jahre an unserem tertiärem Zentrum behandelt wurden, zu untersuchen.

Patienten und Methoden: Patienten der Gruppe A (n = 100) wurden zwischen 1982 und 1984 diagnostiziert und dienten als historische Kontrolle. Patienten der Gruppe B (n = 93) wurden 1994/1995 und Patienten der Gruppe C (n = 164) zwischen 1996 und 1998 diagnostiziert.

Die Überlebens-Analyse wurde durchgeführt in Bezug auf die drei Patientengruppen (A versus B versus C), in Bezug auf die applizierten Therapiemodalitäten nach neurochirurgischer Intervention (keine spezifische Therapie versus Radiotherapie versus kombinierte Radio-/Chemotherapie), in Bezug auf die unterschiedlichen first-line Chemotherapien, in Bezug auf Alter, Geschlecht und Tumorlokalisation. Die non-parametrische Kaplan-Meier Methode wurde angewandt. Ein p-Wert < 0,05 wurde als statistisch signifikant angesehen.

Patienten der Gruppen A und B erhielten Radio- und/oder Chemotherapie in einem unterschiedlichen Ausmaß (Radiotherapie: Gruppe A: 22%, Gruppe B: 62%; Chemotherapie: Gruppe A: 6%, Gruppe B: 33%). Die Chemotherapie wurde in beiden Gruppen nach Abschluss der Radiotherapie appliziert. In Gruppe C erhielten 96% der Patienten eine kombinierte Radio-/Chemotherapie innerhalb von 3 Wochen nach der neurochriurgischen Intervention.

Ergebnisse: Das mediane Überleben betrug in Gruppe A 5,2 Monate, in Gruppe B 5,1 Monate und in Gruppe C 14,5 Monate (p < 0,0001). Länger als 18 Monate lebten 9% der Patienten in Gruppe A, 10% der Patienten in Gruppe B und 25% der Patienten in Gruppe C (p < 0,05).

Schlussfolgerung: Die Überlebenszeitverbesserung in Gruppe C ist auf die frühzeitige und kombinierte Applikation von Radio-/Chemotherapie zurückzuführen. Die Therapie wurde ambulant durchgeführt; dies wurde durch ein interdisziplinäres neuro-onkologisches Team ermöglicht. Die Nebenwirkungen waren mild und die Akzeptanz bei den Patienten hervorragend.

Schlüsselwörter: Glioblastoma multiforme, Erwachsene, Neurochirurgie, Stereotaktische Biopsie, Radiotherapy, Chemotherapy, Nitrosourea, Fotemustine, Dacarbazine.

Summary. *Methodology:* The survival of 357 consecutive patients with newly diagnosed glioblastoma multiforme (GBM) in three treatment groups reflecting different time-periods of diagnosis (A: 1982–1984; B: 1994/1995; C: 1996–1998) was analysed to assess the impact and the potential improvement of changing treatment strategies in our tertiary-care center.

Patients and methods: Group A (n = 100) included all consecutive patients diagnosed from 1982 to 1984 and served as the historical control. Group B (n = 93) included all consecutive patients diagnosed in 1994/1995 and group C (n = 164) those diagnosed from 1996 to 1998. Survival in the three treatment groups (A vs. B vs. C) was analysed according to treatment given after neurosurgical intervention (i.e. no specific therapy versus radiotherapy versus combined radio-/chemotherapy), and according to first-line chemotherapy, age (< 40, 40–60, > 60), sex, and tumor location (hemispheric versus bilateral or multifocal tumors, and tumors involving eloquent brain areas). Survival was analysed using Kaplan-Meier's non-parametric method. A p-value < 0.05 was considered statistically significant.

Results: Patients in groups A and B received radio- and/or chemotherapy to a varying extent (radiotherapy: group A: 22%, group B: 62%; chemotherapy: group A: 6%, group B: 33%). Chemotherapy was administered after termination of radiotherapy in both groups. In group

C, 96% of patients received combined radio-/chemotherapy which was administered concomitantly and started within three weeks after surgery.

Median survival was 5.2 months in group A, 5.1 months in group B and 14.5 months in C ($p < 0.0001$). Nine patients in group A (9%), 9 in group B (10%) and 40 in group C (25%) survived more than 18 months ($p < 0.05$).

Conclusions: Survival improvement in group C might be attributable to the early start of combined radio-/chemotherapy. Therapy was administered on a complete outpatient basis, enabled by a dedicated interdisciplinary neuro-oncologic team caring for group C. Toxicity was mild and patients' acceptance excellent.

Key words: Glioblastoma multiforme, adult, neurosurgery, stereotactic biopsy, radiotherapy, concomitant chemotherapy, nitrosourea, fotemustine, dacarbazine.

Introduction

The majority of papers dealing with high-grade gliomas still begin by stating the unchanged fatal outcome and the persisting futility of efforts to treat these tumors [1–13]. However, an increasing number of studies report prolongation of survival associated with refined microsurgical dissection techniques and use of radiotherapy [14–17]. Further, the benefit of chemotherapy in addition to postoperative radiotherapy has been re-demonstrated in a recent meta-analysis [18]. Nevertheless, chemotherapy has still not gained common acceptance as an integral part of up-front standard treatment. The use and exact timing of chemotherapy are still discussed controversially [7, 19–22]. Common arguments raised against the use of chemotherapy in malignant gliomas are, among others, the high inherent drug resistance, the low concentrations of chemotherapeutic agents in brain tissue as a consequence of the blood-brain barrier, the toxicity of chemotherapy and, moreover, the low response rates of malignant gliomas to chemotherapy [4, 6, 11, 20, 23–31]. In addition, the interpretation of several studies of malignant gliomas is impeded by the inclusion of patients with heterogeneous histologic and clinical characteristics and by difficulties in using clinical features and radiodiagnostic imaging to evaluate response.

Following changing treatment strategies during the last two decades, we analysed survival of three groups of consecutive patients in three different periods of diagnosis (groups A, B, and C) according to treatment and first-line chemotherapies, and according to age, sex, and tumor location, in order to evaluate a potential improvement in survival of patients with newly diagnosed glioblastoma multiforme in our tertiary-care centre.

Patients and methods

Eligibility criteria and patients groups

A total of 357 consecutive adult patients (≥18 years) suffering from newly diagnosed and histologically proven supratentorial glioblastoma multiforme (GBM) were enrolled in this retrospective study. For analysis, patients were divided into three groups (A, B, and C) consisting of consecutive patients diagnosed within particular time periods. Group A consisted of 100 consecutive patients diagnosed between 1982 and 1984. They served as the historical control. Group B consisted of 93 consecutive patients diagnosed between January 1994 and De-

Table 1. Patients' characteristics

	Group A	Group B	Group C
Year of diagnosis	1982–1984	1994/1995	1996–1998
Number of patients	100	93	164
Age in years: median (range)	57 (18–77)	58 (21–78)	55 (23–83)
Karnofsky score: median (range)	70 (60–100)	70 (60–100)	80 (60–100)
Female/male	50/50	48/45	51/113
Neurosurgical procedures			
Gross total resection	78	32	62
Subtotal resection	22	21	67
Stereotactic biopsy only	0	40	35
Specific therapy after neurosurgical intervention			
Radiotherapy	22 (22%)	58 (62%)	158 (96%)
Chemotherapy	6 (6%)	31 (33%)	162 (99%)
Combined radio-/chemotherapy	0	0	158 (96%)
First-line chemotherapy			
German-Austrian Trial	6	17	0
Lomustine	0	0	122
Carboplatinum/etoposide	0	14	0
Dacarbazine/fotemustine	0	0	40
Repeat neurosurgical resection			
At relapse	38 (38%)	5 (5%)	22 (13%)
Second-line chemotherapy	0	2 (2%)	33 (34%)

cember 1995. Group C consisted of 164 consecutive patients diagnosed between January 1996 and December 1998.

Patients in group C were prospectively recorded, whereas data from patients in groups A and B were based on retrospective evaluation of the records.

Neuropathological assessment

Tumor histology had to meet the WHO criteria for glioblastoma multiforme [32–34]. For patients in groups A and B, the histology of GBM was verified by central neuropathologic re-evaluation by one neuropathologist. In none of the patients treatment decisions based on imaging only.

Patients' characteristics and the treatments given are summarised in Table 1.

Study end-points

The study end-points were median survival of patients in the three time periods of diagnosis according to treatment given following neurosurgical intervention, according to first-line chemotherapies, and to age, sex, and tumor location, as well as the evaluation of 18-months survival.

Treatment modalities

Neurosurgical procedures

In group A, neurosurgical procedures were carried out without a microscope or magnifying glasses. In groups B and C, neurosurgical procedures were performed using state-of-the-art microneurosurgery with an operation microscope (Contraves, Zeiss, Oberkochen, Germany) and since 1995 with a pointer-device neuronavigation system (Easy Guide Neuro, Philips, Netherlands) or with a stereotactic microscope (MKM, Zeiss, Germany) for tumor targeting and resection guidance [35].

Gross total resection was defined as resection of 95% or more of the radiologically visible tumor. Subtotal resection was defined as removal of less than 95% of the radiologically visible tumor. For evaluation of the extent of residual tumor, postoperative CT or MRT scans were performed routinely within 72 h after surgical intervention in groups B and C. In group A, CT scans were not performed routinely within 72 h after neurosurgical intervention in all patients. Determination of the extent of resection based on the individual neurosurgeon's assessment and was documented in the operation records.

Repeat neurosurgery at tumor relapse or tumor progression was not routine and was based on individual decision.

Radio-oncologic treatment

Patients in group A received whole-brain radiotherapy with a dose of 50 Gy in a conventional fractionation scheme with 1.8–2.0 Gy per day. The dose was applied with two lateral opposing fields with cobalt 60 units.

For groups B and C a 3-D treatment-planning system based on CT and MRI sectional imaging was used. The target volume, i.e. the tumor volume plus a security margin of 2 cm, was defined by the radio-oncologist and was based on preoperative radiographic data. A radiation dose of 53 Gy (3 Gy/day) or 66 Gy (2 Gy/day) was delivered to the target volume using a conventional multileaf collimator.

Chemotherapeutic treatment

The different chemotherapeutic regimens administered to patients are detailed in Table 2.

Table 2. First-line chemotherapeutic regimens

1. German-Austrian Trial (n = 23; before 1996):

Day 0–3: Hyaluronidase 50.000 IE i.v. continuous infusion
Day 1: CCNU 80 mg/m², orally, q 6 weeks
Methotrexate 120 mg/m², i.v., q 28 days
5-Fluorouracil 750 mg/m² i.v., q 28 days
Day 2 + 3: Cisplatinum 25 mg/m² i.v., q 28 days
Etoposide 80 mg/m² i.v., q 28 days
Day 3: Leucovorine 120 mg/m², i.v., day 3

2. Carboplatinum/Etoposide (n = 14; before 1996):

Hyaluronidase 200.000 IE i.v.;
Carboplatinum 250 mg/m² day 1+2 i.v.;
Etoposide 150 mg/m² i.v., day 1; q 28 days

3. CCNU orally (n = 122):

80–120 mg/m² , orally; repeated every 6–8 weeks for one year at maximum

4. Dacarbazine/Fotemustine (n = 40):

Fotemustine 100 mg/m², i.v.
Dacarbazine 200 mg/m² i.v.; q 21 days

In groups A and B chemotherapy was started after termination of radiotherapy**.** In group C chemotherapy was started within three weeks after initial diagnosis and was administered with concomitant radiotherapy.

Before the start of chemotherapy a written informed consent was mandatory and patients had to fulfil the following eligibility criteria: patients were required to be older than 18 years and to have a Karnofsky index ≥ 60, adequate liver function (SGOT, SGPT, and alkaline phosphatase levels below twice the normal range; bilirubin in serum below 1.5 mg/dl), renal function (creatinine level below 1.5 times the normal range) and bone marrow function (leukocyte count > 3.000/µl, haemoglobin > 10 g/dl, platelet count > 100 000/µl). Pregnant or breast-feeding women and patients with acute infections were not eligible. Adequate contraception was mandatory.

Second line chemotherapies were not routinely used in patients with progressive disease. Patients eligible and warranting further chemotherapy were given either intravenous dacarbazine/fotemustine (n = 7) [36] or oral temozolomide (n = 28) [37], in a dose of 150 mg/m² on days 1–5, only if they had a Karnofsky performance score ≥ 60. Eight patients beyond first relapse were treated with the antiangiogenic agent thalidomide 100–200 mg/day orally for compassionate reasons [38].

Antiemetic prophylaxis in group A consisted of metoclopramide intravenously, up to a maximum of 2 mg/kg every 2 hours. In groups B and C, 5-HT3 receptor-antagonists were prophylactically administered. Dexamethasone 4 mg twice daily was given when clinically indicated in all three groups.

Toxicity evaluation

Toxicity was evaluated according to the World Health Organization (WHO) criteria [39].

Response evaluation

Response evaluation was based on MacDonald's criteria [40]: complete response (CR) was defined as the disappearance of all measurable disease with improved neurology in the ab-

sence of corticoid therapy. Partial response (PR) was a ≥ 50% decrease in tumor size with an improved or stable neurology on stable or decreased dexamethasone dose. Stable disease (SD) was a less than 50% decrease, or less than 25% increase of the tumor size with an improved or stable neurology on stable or decreased dexamethasone dose. Progressive disease (PD) was a greater than 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 T-2-weighted MRI images or of the hypodense region on CT scans were used.

In group A, CT scans of patients were re-evaluated retrospectively.

Statistical considerations

All analyses were done by intention to treat.

The reference point for median survival and 18-months survival was the date of neuropathologic diagnosis, and the endpoint was survival until death, including deaths from causes not related to the disease.

Survival of patients in the three periods of diagnosis (A, B, and C) was analysed according to treatment (no specific therapy versus radiotherapy versus combined chemo-/radiotherapy), to first-line chemotherapies (Table 2), and according to age, sex, and tumor location (hemispheric versus bilateral or multifocal tumors and tumors involving eloquent brain areas).

Survival curves were constructed using Kaplan Meier's non-parametric method, and medians (and their respective 95% confidence intervals) were calculated from the Kaplan-Meier estimates [41, 42]. The GraphPadPRISM program (version 3.00) was used.

A p-value ≤ 0.05 was considered statistically significant.

Results

Survival

Survival of patients in the three groups reflecting the time-periods of diagnosis is shown in Fig. 1 and did not differ between group A (5.2 months) and group B (5.1 months) but increased to 14.5 months in group C ($p < 0.0001$).

Early death, i.e. death within 10 weeks after diagnosis, occurred in 19 patients in group A (19%), in 24 patients in group B (26%) and in 7 patients in group C (4%) ($p < 0.003$).

Long-term survival beyond 18 months was better in group A than group B and was attributed to three long-term survivors being between 18 and 25 years at initial diagnosis.

Survival according to treatment given after neurosurgical intervention is shown in Fig. 2. After neurosurgical resection (gross total and partial resection), median survival was 15.9 months in patients receiving concomitant radio-/chemotherapy and 10.8 months in patients receiving radiotherapy alone ($p < 0.03$). After stereotactic biopsy, median survival was 7.1 months in patients receiving

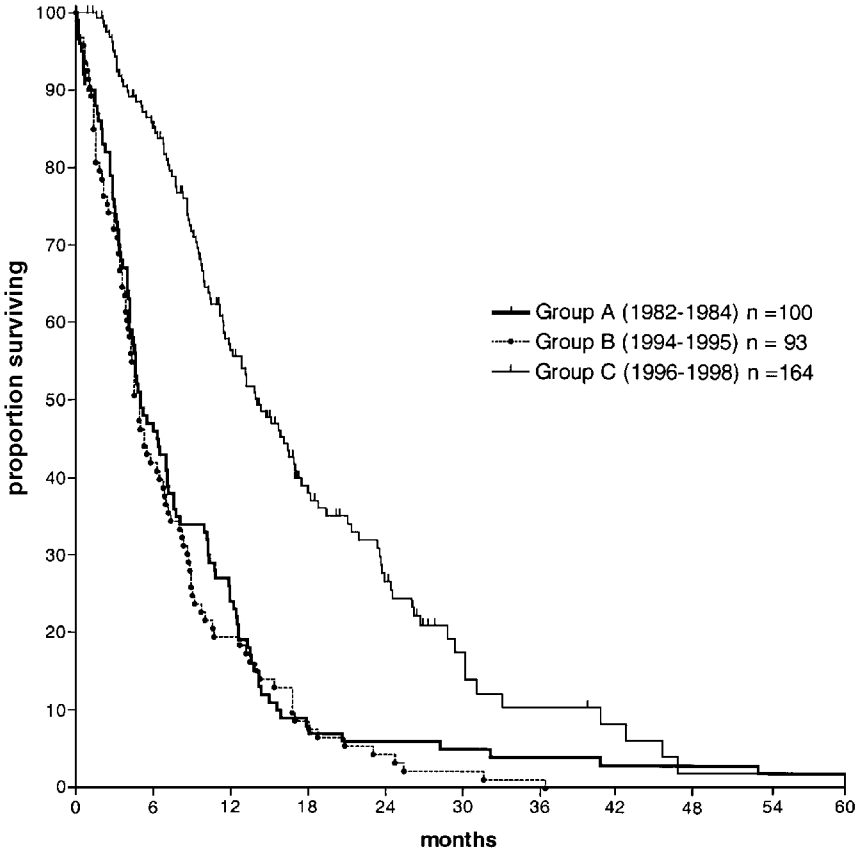

Fig. 1. Survival of three groups of patients with glioblastoma multiforme (A, B, C) according to time-period of diagnosis. Group A vs. group C ($p < 0.0001$); Group B vs. group C ($p < 0.0001$)

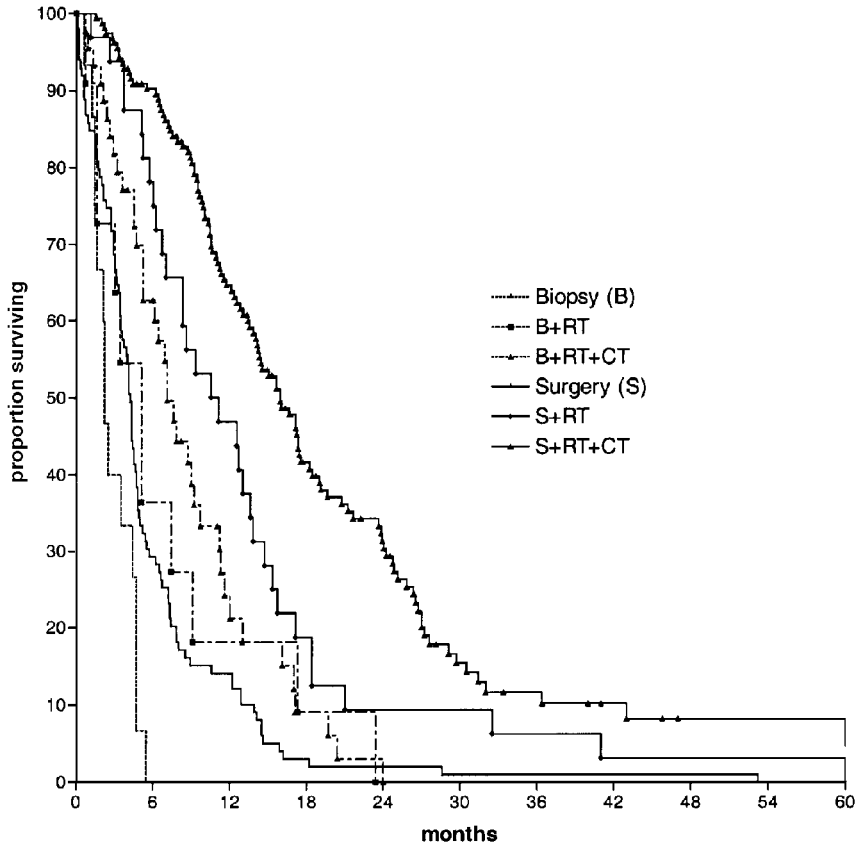

Fig. 2. Survival of patients with glioblastoma multiforme according to the treatment received after neurosurgical intervetion. B: stereotactic biopsy (n = 15); B + RT: stereotactic biopsy + radiotherapy (n = 11); B + RT + CT: stereotactic biopsy + radiotherapy + chemotherapy (n = 44); OP + RT: total gross / subtotal resection + radiotherapy (n = 27); OP + RT + CT: total gross / subtotal resection + radiotherapy + chemotherapy (n = 88); B versus B + RT + CT: $p < 0.0001$; OP + RT versus OP + RT + CT: $p < 0.0035$

combined radio-/chemotherapy and 2.2 months in those without any specific therapy ($p < 0.001$).

Fifty patients (32%) receiving combined radio-/chemotherapy reached 18 months survival, whereas only four patients (3%) of those not receiving any chemotherapy survived longer than 18 months ($p < 0.003$).

Survival according to first-line chemotherapy is shown in Fig. 3.

Median survival after oral lomustine was 13.6 months and 20 months after dacarbazine/fotemustine ($p < 0.02$).

Survival according to age is shown in Fig. 4.

In patients older than 60 years median survival was 5.1 months, in patients aged between 40 and 60 years 10.3 months, and in patients under 40 years 17.1 months ($p < 0.0001$).

Survival according to tumor location or sex was not statistically significant.

Toxicity of chemotherapy

The toxicities of the four chemotherapy regimens are shown in Table 3.

Drugs used in the German-Austrian Trial and the combination of carboplatinum/etoposide, both administered before 1996, resulted partly in severe toxicity. Severe hematotoxicity, severe nausea/emesis and severe stomatitis were observed. Because of these severe side-effects, obviously reducing patients' quality of life, both regimens were abandoned in the early trial phase in our institution.

In contrast, oral lomustine resulted in mild to moderate asymptomatic thrombocytopenia, requiring at most a delay of further therapy. The toxicity profile of dacarbazine/fotemustine was similar to that of lomustine, but thrombocytopenia occured earlier and resulted either in therapy delays (4/40 patients) or in exclusion from further therapy (3/40 patients). Pneumonia with pulmonary obstruction occurred in three young patients but was completely reversed after antibiotic treatment. In one patient, dacarbazine/fotemustine therapy was stopped after the first administration because the patient experienced a whole-body erythema within hours; however, this was reversible within a short period.

Lung fibrosis was not observed, neither with lomustine nor with fotemustine.

One febrile neutropenia and five cases of infections requiring antibiotics and/or antiviral therapy were observed in group C (4 pneumonia, 1 herpes zoster) but were uncomplicated and completely reversible within a short period.

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

Discussion

Our study documents improvement in the survival of patients treated since 1996 (group C) compared with patients treated earlier (groups A and B). Patients with GBM do much better in the late 90s if treated by a specialized interdisciplinary team applying multimodal therapy including microsurgical gross total resection, standard radiotherapy and potentially chemotherapy.

The changes in neurosurgical techniques – from aggressive neurosurgical resection to microscopic gross total resection – have contributed to improvement of patients' outcome without impairment of quality of life [14]. In particular, the preservation of the patient's quality of life within a few days after surgery is a necessary prerequisite for early initiation of radio-/chemotherapy. Another expla-

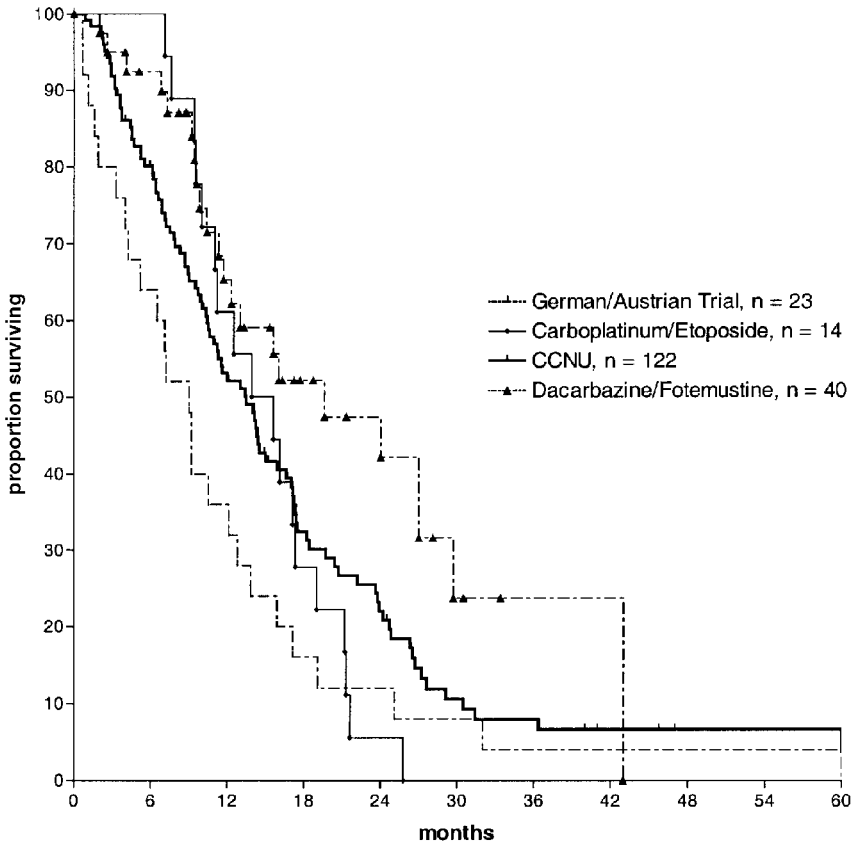

Fig. 3. Survival of patients with glioblastoma multiforme according to first-line chemotherapy. German-Austrian Trial: n = 23; Carboplatinum / Etoposide: n = 14; CCNU orally: n = 122; Dacarbazine / Fotemustine: n = 40; CCNU versus Dacarbazine / Fotemustine: $p < 0.02$

Table 3. Toxicity of chemotherapeutic regimens

	German-Austrian Trial	Carboplatinum/Etoposide	Lomustine	Dacarbazine/Fotemustine
Number of patients	23	14	122	40
WHO-Toxicity Grade	III–IV	III–IV	III–IV	III–V
Leukopenia	11 / (48%)	4 / (29%)	9 / (7%)	1 / (3%)
Thrombocytopenia	13 / (56%)	2 / (14%)	5 / (4%)	4 / (10%)
Anemia	7 / (30%)	2 / (14%)	5 / (4%)	1 / (3%)
Nausea/emesis	14 / (60%)	4 / (29%)	0	0
Stomatitis	3 / (13%)	0	0	0
Dry skin	0	0	0	1 (3%)*
Alopecia	16 / (69%)	10 / (71%)	0	0

* Whole-body erythema within hours after the first dose of dacarbazine/fotemustine.

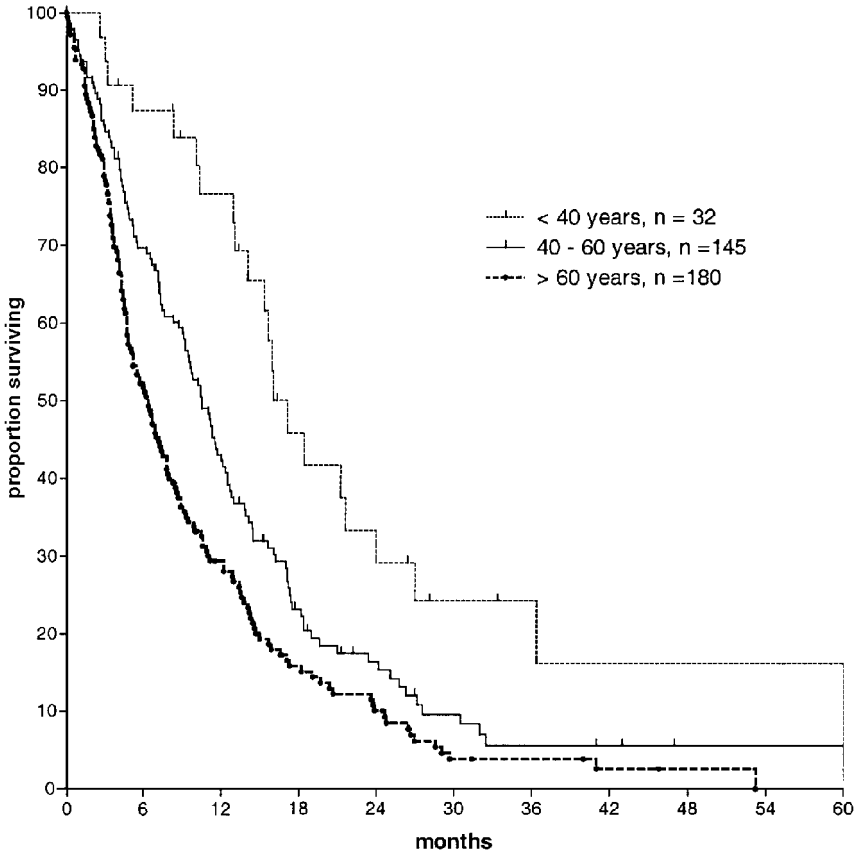

Fig. 4. Survival of patients with glioblastoma multiforme according to age. < 40 years (n = 32); 40–60 years (n = 145); > 60 years (n = 180); < 40 years vs. 40–60 years: ($p < 0.0001$)

nation for the better outcome of group C is that 96% of these patients received combined radio-/chemotherapy starting within three weeks after neurosurgical intervention. The concept of early combined radio-/chemotherapy may be especially important in this rapidly growing tumor and has been shown to improve survival of patients with high-grade gliomas in several recent studies [18, 36, 43, 44]. Late commencement of or no radiotherapy at all is known to worsen prognosis in malignant glioma.

However, an uncontrolled bias cannot be formally excluded, as this is not a controlled comparative study. In addition, the extent of the impact of chemotherapy alone on survival cannot be defined, owing to the retrospective study design. Nevertheless, the recent meta-analysis of the Glioma Meta-analysis Trialists Group [18] has demonstrated the beneficial effect of adjuvant chemotherapy on survival, independently from age, sex, performance status and histology (WHO III and IV tumors). In addition, prospective brain-tumor trials are known to favour the inclusion of selected patients with better prognostic criteria [40, 45]: patients older than 70 years are rarely included in prospective trials, although they constitute a substantial number of patients suffering from high-grade glioma [20, 22]. In our study, all consecutive patients diagnosed during the defined periods were unselectedly enrolled into analysis and a considerable proportion of patients were older than 70 years. Even so, the survival outcome of patients in group C is comparable to outcome in other recent studies [3, 4, 6, 9, 12, 13, 18, 20, 22, 36, 44, 46].

The toxicity of combined radio-/chemotherapy, in particular of oral lomustine and the combination of dacarbazine and fotemustine, was acceptable and consisted mainly of mild asymptomatic thrombocytopenia and was without substantial burden for the patient. The complete outpatient administration of combined radio-/chemotherapy in group C was supported by the continuous care provided by a dedicated interdisciplinary neuro-oncologic team, founded in 1995 in our institution, and resulted in excellent patients' acceptance. This is in accordance with the multicenter CRC phase II trial of temozolomide [37, 47], which unequivocally demonstrates that chemotherapy is not necessarily synonymous with impairment of quality of life. In contrast to the mild toxicity of oral lomustine and the combination of dacarbazine/fotemustine in group C, both the chemotherapies used before 1996 (the drugs in the German-Austrian trial and the combination of carboplatinum/etoposide) were abandoned within a short period because of severe side-effects. The combination of dacarbazine/fotemustine has been successfully incorporated into first-line as well as second-line chemotherapy of a substantial number of patients with GBM in our institution [36, 44].

In conclusion, in accordance with recent prospective chemotherapy trials and the review of the Glioma Meta-analysis Trialists Group [18], the addition of chemothera-

py to radiotherapy and the early commencement of both seems to have a beneficial influence on both median and long-term survival, i.e. 18-months survival without impairment of quality of life [14, 37, 47]. The results of these studies are in contrast to the widespread fears of referring physicians who are still hesitating to suggest such treatments to their patients. All these studies together with our own experience, gained by analysing the outcome of patients with GBM treated in our tertiary care center during the last two decades, should encourage clinicians to offer early combined radio-/chemotherapy to all patients suffering from GBM.

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Correspondence: Christine Marosi, MD, Department of Medicine I/Oncology, University of Vienna, Währinger Gürtel 18–20, A-1090 Wien, Austria,
E-mail: christine.marosi@akh-wien.ac.at

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