# Randomized Study of Postoperative Radiotherapy and Simultaneous Temozolomide without Adjuvant Chemotherapy for Glioblastoma

Martin Kocher[1], Peter Frommolt[2], Sigrid Klara Borberg[3], Ursula Rühl[4], Maria Steingräber[5], Markus Niewald[6], Susanne Staar[7], Martin Stuschke[8], Gerd Becker[9], Arnt-René Fischedick[10], Klaus Herfarth[11], Hermann Grauthoff[12], Rolf-Peter Müller[1]

**Purpose:** To evaluate the efficacy of simultaneous postoperative temozolomide radiochemotherapy in glioblastoma patients.
**Patients and Methods:** From February 2002 to July 2004, n = 65 patients from 11 German centers with macroscopic complete tumor resection were randomized to receive either postoperative radiotherapy alone (RT, n = 35) or postoperative radiotherapy with simultaneous temozolomide (RT + TMZ, n = 30). Patients were stratified according to age (≤/>50 years) and WHO performance score (0–1 vs. 2). RT consisted of 60 Gy in 30 fractions. In the RT + TMZ arm, oral TMZ was administered daily at a dose of 75 mg/m$^2$ including weekends (40–42 doses). Adjuvant treatment was not given, but in both arms, patients with recurrent tumors and in good condition (WHO 0–2) were scheduled for salvage chemotherapy with TMZ.
**Results:** The trial was stopped early due to the results of EORTC-study 26981-22981 that showed a survival benefit for the combination of concomitant and adjuvant TMZ compared to radiotherapy alone. In total, 62/65 patients were evaluable. Stratification variables were well balanced (≤ 50 years 26% vs. 20%, WHO 0–1 91% vs. 100%). Neither overall survival (median 17 vs. 15 months) nor progression-free survival (median 7 vs. 6 months) differed significantly between the two arms. In the RT (RT + TMZ) arm, 76% (62%) of the progressing patients received salvage chemotherapy with TMZ, 36% (50%) had a second resection. There was a time-constant trend for increased general quality of life (EORTC questionnaire QLQ C30) and brain-specific quality of life (EORTC questionnaire B20) in the combined arm. Lymphopenia G3–4 was more frequent (33 vs. 6%) in the RT + TMZ arm.
**Conclusion:** After early closure of this trial, a benefit for progression-free survival for simultaneous TMZ radiochemotherapy alone could not be demonstrated. In both arms, salvage therapies were frequently used and probably had a major effect on overall survival.

**Key Words:** Malignant glioma · Glioblastoma · Irradiation · Radiochemotherapy · Temozolomide · Quality of life

Strahlenther Onkol 2008;184:572–9
DOI 10.1007/s00066-008-1897-0

**Randomisierte Studie zur alleinigen postoperativen simultanen Radiochemotherapie mit Temozolomid ohne adjuvante Chemotherapie beim Glioblastom**

**Ziel:** Bestimmung der Effektivität einer alleinigen simultanen, postoperativen Radiochemotherapie mit Temozolomid bei Patienten mit Glioblastom.
**Patienten und Methodik:** Von Februar 2002 bis Juli 2004 wurden n = 65 Patienten aus 11 Zentren nach makroskopischer Tumorresektion randomisiert und erhielten entweder eine postoperative lokale Strahlenbehandlung (RT, n = 35) oder eine simultane Radiochemotherapie mit Temozolomid (RT + TMZ, n = 30). Die Stratifizierung erfolgte anhand des Alters (≤/>50 Jahre) und des

[1] Department of Radiotherapy, University Hospital, Cologne, Germany,
[2] Institute for Biostatistics, Informatics, and Epidemiology, University Hospital, Cologne, Germany,
[3] Gemeinschaftspraxis for Radiation Oncology and Radiotherapy, Hannover, Germany,
[4] Department of Radiotherapy, Vivantes Klinikum im Friedrichshain, Berlin, Germany
[5] Department of Radiotherapy, Vivantes Klinikum Neukölln, Berlin, Germany,
[6] Department of Radiotherapy, University Hospital Homburg/Saar, Germany,
[7] Department of Radiotherapy, Zentralkrankenhaus St.-Jürgen-Str., Bremen,
[8] Department of Radiotherapy, University Hospital Essen, Germany,
[9] Department of Radiotherapy, Klinik am Eichert, Göppingen, Germany,
[10] Department of Radiotherapy, Clemens-Hospital, Münster, Germany,
[11] Department of Radiotherapy, University Hospital, Heidelberg, Germany
[12] Department of Radiotherapy, Lukaskrankenhaus Neuss, Germany.

Received: April 20, 2008; accepted: September 9, 2008

Allgemeinzustands (AZ) nach WHO (0–1 vs. 2). Die Bestrahlung wurde mit 60 Gy in 30 Fraktionen durchgeführt. Im RT + TMZ-Arm wurde TMZ oral in einer täglichen Dosis von 75 mg/m$^2$ an allen Bestrahlungstagen und am Wochenende verabreicht (40–42 Dosen). Eine adjuvante Therapie mit TMZ erfolgte nicht, stattdessen war für die Patienten in gutem AZ (WHO 0–2) im Falle einer Tumorprogression in beiden Armen eine Rezidiv-Chemotherapie mit TMZ vorgesehen.

**Ergebnisse:** Die Studie wurde vorzeitig nach der Veröffentlichung der EORTC-Studie 26981-22981 abgebrochen, die eine Verlängerung der Überlebenszeit durch eine simultane und adjuvante Radiochemotherapie mit TMZ gezeigt hatte. Insgesamt waren 62/65 Patienten auswertbar. Die Arme (RT vs. RT + TMZ) waren bezüglich der Stratifikationsvariablen ausgeglichen (≤ 50 Jahre 26% vs. 20%, WHO 0–1 91% vs. 100%). Weder das Gesamtüberleben (Median 17 vs. 15 Monate) noch das progressionsfreie Überleben (Median 7 vs. 6 Monate) unterschieden sich signifikant. In dem RT-(RT + TMZ-)Arm erhielten 76% (62%) der progredienten Patienten eine Rezidiv-Chemotherapie mit Temodal, 36% (50%) wurden nochmals operiert. Für die allgemeine und hirnfunktionsbezogene Lebensqualität (EORTC-Fragebögen QLQ C30 und BN20) zeigte sich in dem RT + TMZ-Arm ein zeitkonstanter Trend für bessere Werte. Im RT + TMZ-Arm war die Häufigkeit einer Lymphopenie Grad 3–4 erhöht (33% vs. 6%).

**Schlussfolgerung:** Nach dem vorzeitigen Abbruch der Studie konnte ein Vorteil bezüglich des progressionsfreien Überlebens für die alleinige simultane Radiochemotherapie mit Temozolomid nicht gezeigt werden. In beiden Armen wurden Rezidivtherapien häufig eingesetzt, diese hatten wahrscheinlich einen erheblichen Einfluss auf das Gesamtüberleben.

**Schlüsselwörter:** Maligne Gliome · Glioblastom · Radiochemotherapie · Bestrahlung · Temozolomid · Lebensqualität

## Introduction

In 2005, the EORTC published the results of a randomized trial that induced a major change in the treatment of grade IV gliomas [24]. The authors showed that, compared to postoperative irradiation alone, radiotherapy (RT) combined with simultaneous and adjuvant temozolomide (TMZ) improved both progression-free and overall survival in patients with glioblastoma. Unfortunately, due to the design of this trial and the preceeding phase II study [23], it was not possible to analyse the two possible effects of simultaneous TMZ (potential for radiosenzitation) and adjuvant TMZ separately.

Therefore, we initiated a randomized phase III study to evaluate the effect of simultaneous radiochemotherapy in patients with glioblastoma as compared to radiation alone. The study was based on promising results of a phase I/II study [14]. The use of TMZ apart from RT was intended only for tumor progression in which case it was offered to all patients in good condition. In consequence, progression-free survival (PFS) was chosen as the primary endpoint. After the results of the EORTC-study 26981-22981 were published, the study was stopped early after the recruitment of 65 out of 500 patients because it seemed unethical to withhold patients TMZ until tumor progression.

## Patients and Methods

### Study Design

The study was planned to detect an increase of PFS (primary endpoint) for glioblastoma patients with macroscopic tumor resection who received postoperative simultaneous radiochemotherapy with TMZ as compared to RT alone. As it was expected that patients with macroscopic complete tumor resection would benefit most from the combined radiochemotherapy, only these patients were included.

The trial was initiated by the Department of Radiotherapy, University of Cologne, Germany. Data management according to GMP guidelines and analysis was done by the local KKSK (Koordinationszentrum fuer Klinische Studien, Koeln). ESSEX Pharma®, Munich, Germany provided financial support for data analysis and supplied TMZ for the simultaneous therapy. The protocol was approved by the local ethics committee and by all responsible ethic committees of the participants. Before randomization, informed consent was obtained from every patient. Neither patients nor physicians were blinded to the mode of therapy. Placebo medication was not used.

For calculation of the patient number needed, an absolute increase of 10% in PFS at 9 months was assumed (equivalent to a hazard ratio of 0.75). The accrural time was estimated to last 3 years, the minimal follow-up-time was 1 year. A drop-out rate of 5% was expected. Choosing the usual error bounds of $\alpha = 0.05$ and $\beta = 0.2$, a sample size of $n = 500$ patients was needed. A one-sided generalized, nonparametric log-rank test (BRESLOW) was used for comparison of the 2 arms, both for PFS and overall survival. Patients were stratified according to age (≤/> 50years) and WHO performance score (0–1 vs. 2).

Adjuvant treatment was not given; instead, patients with recurrent tumors and in good health condition (WHO 0–2) were scheduled for salvage chemotherapy with TMZ in both arms. Secondary endpoints were overall survival and quality of life. Permittance to use the EORTC quality of life questionnaires was granted by the EORTC Quality of Life Unit, Brussels, Belgium.

### Inclusion Criteria

Patients had to fullfill all the criteria shown in Table 1 to be included and were excluded in presence of at least one of the exclusion criteria also shown in Table 1. Patients were randomized after surgery and were only included if macroscopic tumor resection was assured. Macroscopic resection was assumed if no visible tumor remained during the operative pro-

cedure and in the early postoperative computed tomography (CT) scan.

### Radiotherapy

In all cases, megavoltage equipment, mask fixation and CT-based treatment planning was used for irradiation. Planning target volumes (PTV) included the contrast-enhancing regions in the postoperative CT (postoperative blood brain barrier damage) and/or the resection cavity with a margin of 1.5–2.5 cm. PTV delineation on fused magnetic resonance (MR) images was allowed, but not recommended [16]. A dose of 60.0 Gy in 2.0 Gy daily fractions, 5 fractions per week, was applied.

### Simultaneous Chemotherapy with Temozolomide

TMZ was applied as a single daily oral dose of 75 mg/m$^2$ 1–2 hours before each radiotherapy fraction and also on weekends; treatment with TMZ should be interrupted in case of leucopenia (< 2000/µl until recovery to 3000/µl), neutropenia (< 1000/µl until recovery to 1500/µl), thrombopenia (< 50000/µl until recovery to 100000/µl) or any in case of a severe adverse event. Chemotherapy had to be stopped if leucocytes dropped below 1000/µl, neutrophils below 500/µl, thrombocytes below 25000/µl, in case of severe viral or bacterial infection, or when the performance score fell below WHO 2 for more than 1 week. In both arms, primary therapy was to be stopped in case of tumor progression during therapy, if the performance score persisted below WHO 2 or whenever the patient developed new, severe neurologic symptoms or signs of increased intracranial pressure. Prophylactic antibiotics were not used.

### Follow-up

During radiochemotherapy, blood cell counts and determination of GOT, GPT and γ-GT were done once weekly or more frequently if necessary. Six weeks after radiochemotherapy and every 3 months afterwards, patients were re-evaluated by physical and neurological examination, determination of WHO performance score, CCT (cranial CT) and/or magnetic resonance tomography (MRT) of the brain and assessment of Quality of Life by means of the EORTC QLQ-C30 (general) and QLQ-B20 (brain module) questionnaires.

Progression of the disease was assumed in case of any of the following situations: newly diagnosed or progressive (> 25%) contrast-enhancing lesions in the CT or MRT scans, deterioration of the performance score below WHO 2 without other possible explanations, or new neurological symptoms such as pareses, seizures, and signs of increased intracranial pressure lasting more than 2 weeks under antiedematous therapy. Progression-free and overall survival times were computed according to the Kaplan-Maier method for censored observations, using the date of surgery as the reference timepoint. Patients were also grouped according to the RPA (Recursive Partitioning Analysis) classes as adapted by the EORTC [18] using the WHO performance status and the age at randomization as parameters.

### Salvage Therapy

Patients with recurrent tumors and in good health condition (WHO 0–2) were scheduled for salvage chemotherapy with TMZ in both arms. In the RT arm, a dose of 200 mg/m$^2$ for 5 days every 4 weeks was recommended, in the pretreated patients of the RT + TMZ arm, TMZ was to be applied using 150 mg/m$^2$ for 5 days every 4 weeks.

## Results

From 2/2002 to 7/2004, a total of n = 65 patients from 11 German centers were randomized, see Appendix. A total of 3 patients from 2 centers were lost to follow-up (2 patients immediately after randomisation and 1 patient at the beginning of primary therapy) and were thus not evaluable. Thus, 33 patients in the RT arm and 29 patients in the RT + TMZ arm were evaluable for progression free and overall survival.

**Table 1.** Inclusion and exclusion criteria.

**Tabelle 1.** Einschluss- und Ausschlusskriterien.

**Inclusion criteria**

- Age 18–70 years
- Unifocal glioblastoma
- Macroscopic complete tumor resection (no residual tumor mass after surgery as assessed by the surgeon and on early postoperative CCT/MRT)
- Performance status after surgery 0–2 (WHO)
- Sufficient bone marrow function (leucocytes > 3000/µl, thrombocytes > 100000/µl)
- Sufficient renal function (creatinin normal according to local normal values)
- Sufficient liver function (GOT < 30 U/l, GPT < 40 U/l, γ-GT < 50 U/l according to standard normal values). As these enzyme activities may increase due to halogenated inhalative anesthetics and after anticonvulsive therapy, patients in which any of these factors seemed responsible for increased values above the mentioned limits were also included.

**Exclusion criteria**

- Recurrent glioblastoma
- History of prior brain irradiation
- History of prior chemotherapy
- Cardiac insufficiency
- Major lung or metabolic disease
- Local or systemic infection
- HIV-infection, active Hepatitis B/C infection
- Pregnancy, lactation, insufficient contraception
- Major neurologic or psychiatric symptoms or diseases, either caused by the brain tumor or due to an independant reason
- Regular medication by immunosuppressive or antibiotic drugs
- Any disease preventing intake of oral medication
- Preexistant malignant disease other than R0-resected in-situ carcinoma of the cervix

Analysis was based on the intent-to treat principle. Patients characteristics, allocation to treatment arms and stratification factors were well balanced, see Table 2.

**Table 2.** Characteristics and stratification of evaluable patients (median and range unless otherwise stated). [a]: data of 1 patient missing; [b]: according to EORTC adaptation. RT: radiotherapy; TMZ: temozolomide.

**Tabelle 2.** Charakteristika und Stratifizierung der auswertbaren Patienten (Median und Spannbreite, soweit nicht anders dargestellt). [a]: Daten von 1 Patienten fehlen; [b]: gemäß EORTC-Adaptation. RT: Radiotherapie; TMZ: Temozolomid.

| | RT | RT + TMZ |
|---|---|---|
| Total number of patients | 33 | 29 |
| Age (years) | 58 (37– 69 ) | 59 (34–67) |
| Gender (male/female) | 26/7 (79%/21%) | 15/14 (52%/48%) |
| Tumor size (maximal diameter, cm) | 4.0 (0.7–7.5) | 4.6 (1.1–8.0) |
| Tumor location | | |
| cerebral lobes | 31 | 29 |
| basal ganglia | 1 | 0 |
| cerebellum | 1 | 0 |
| Time interval surgery-radiotherapy (d) | 28 (17–52) | 28 (19–49) |
| Radiation dose (Gy, average (range)) | 58.3 (4.0–61.0) | 59.8 (55.9–60.0)[a] |
| On steroids at primary therapy | 16 of 33 (48%) | 14 of 28 (50%)[a] |
| On anticonvulsants at primary therapy | 16 of 33 (48%) | 9 of 28 (32%)[a] |
| Stratification | | |
| WHO 0–1, age $\leq 50$ | 8 | 6 |
| WHO 2, age $\leq 50$ | 0 | 0 |
| WHO 0–1, age $> 50$ | 23 | 23 |
| WHO 2, age $> 50$ | 2 | 0 |
| RPA class 3[b] | 16 | 16 |
| RPA class 4[b] | 17 | 13 |

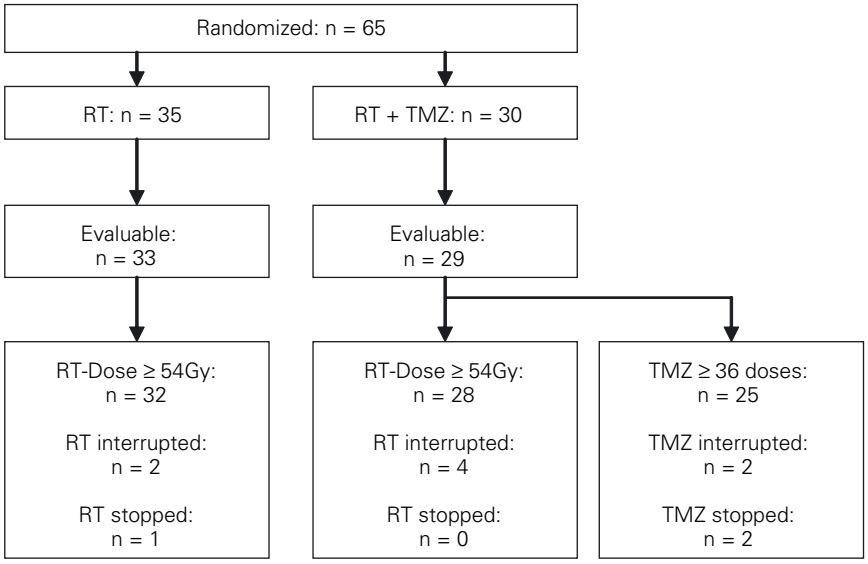



**Figure 1.** Patient randomization, treatment allocation and compliance to treatment. RT: radiotherapy; TMZ: temozolomide.

**Abbildung 1.** Randomisation, Therapie und Compliance der Patienten. RT: Radiotherapie; TMZ: Temozolomid.

### Compliance

Compliance to the allocated treatment scheme is shown in Figure 1. Especially, the number of patients receiving at least 90% of the prescribed radiation dose (= 54 Gy) and at least 90% of the planned minimum TMZ doses ($0.90 \times 40 = 36$ doses) is depicted.

In the RT arm, in 2 pts. radiotherapy was interrupted due to tumor progression and stopped early in 1 of them. In the RT + TMZ arm, the median number of daily TMZ doses during radiochemotherapy was 42 (range 31–49) doses. RT was interrupted in 4 cases because of seizures, toxicity of temodal, gastroenteritis and tumor progression, respectively (see Figure 1). TMZ was interrupted simultaneously with RT in two of these patients and stopped in another 2 patients due to infection and myasthenia.

### Toxicity

The participants were asked to report the following toxicities and adverse events occuring during primary therapy according to the NCIC CTCG Expanded Common Toxicity Criteria: Headache, somnolence, pareses, disturbances of sensitivity and mood, nausea, vomiting, diarrhea, fever, infection, thrombosis, leucopenia, lymphopenia, thrombopenia, bleeding, anemia, elevation of liver enzymes (GPT, GOT, γ-GT and other toxicities if present. As shown in Table 3, significant differences between the two arms were only found for the occurrence of nausea, lymphopenia and elevated levels of liver enzymes which were all more frequent in the RT + TMZ arm. In both arms, a maximum of 1–2 patients were affected by grade 3 or 4 other than the above mentioned toxicities. Also during follow-up and salvage therapy (see below), a maximum of 1–2 patients in both arms had grade 3 or 4 toxicities in any category.

Serious adverse events in the RT arm were observed in 2 patients. They included hospitalization due to a cyst of the cerebrospinal fluid and one death of pulmonary embolism. In the RT + TMZ arm, 4 patients were hospitalized because of seizures, and 4 patients because of pulmonary embolism after surgery for recur-

rence, meningoencephalitis, myasthenia and somnolence. One patient committed suicide and one died from laryngeal edema.

### Progression-free Survival and Therapy in Case of Progression

The primary endpoint was PFS. PFS curves are shown in Figure 2a. In the RT arm, median PFS time was 7.6 (95% confidence interval 6.8–8.4) months. As shown in Table 4, in both arms, the dominant type of progression was tumor growth documented in the follow-up CT/MRT scans. In the RT + TMZ arm, median PFS time amounted to 6.3 (5.1–7.5) months which was not significantly different (p = 0.801) from the RT arm.

Most patients were in good condition (WHO 0-2) at recurrence (Table 4) and received multimodal salvage therapy including TMZ in 76% (RT arm) and 62% (RT + TMZ arm). In the RT arm, a median number of 4 cycles of TMZ (range 1-25) was given, in the RT + TMZ arm 3 cycles of TMZ (1–13) were applied. In both arms, a substantial number of patients (36% vs. 50%) also had a second tumor resection.

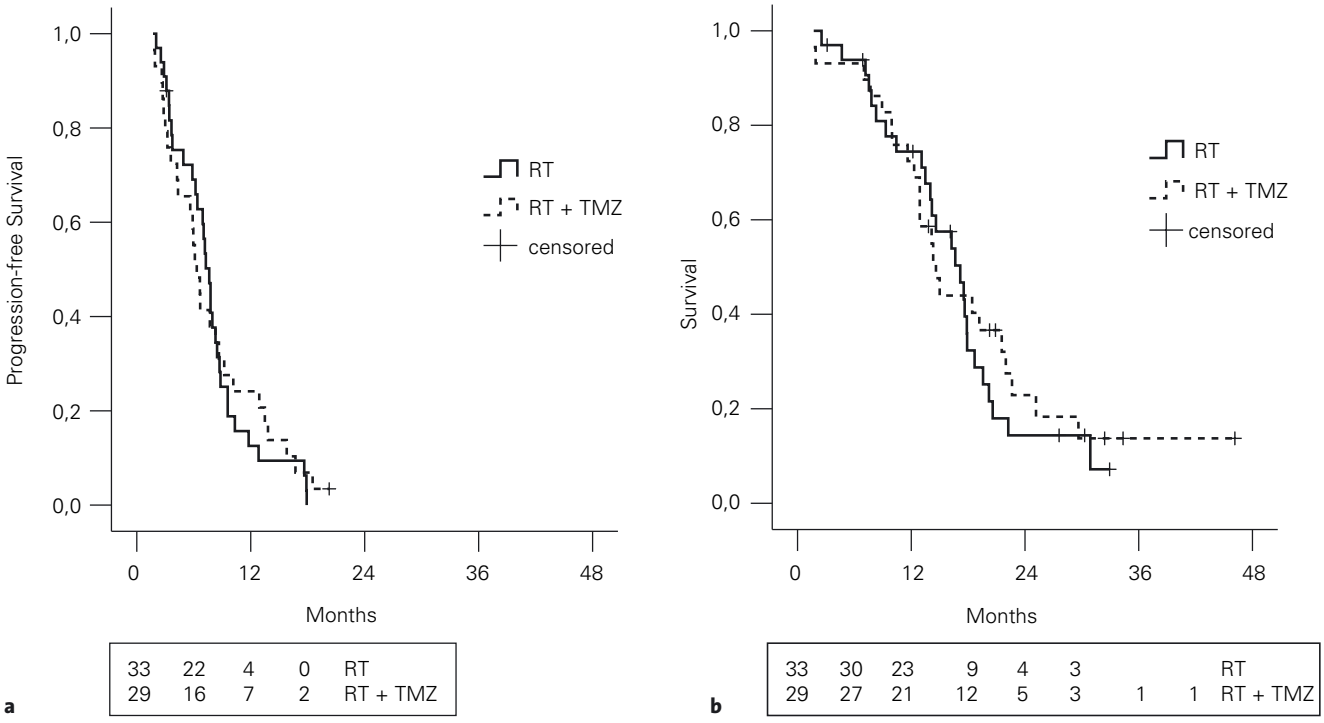
**Table 3.** Toxicity during primary therapy, percentages of patients affected are shown. Only events differing significantly between treatment arms are depicted. *: p < 0.05 using chi-square test; RT: radiotherapy; TMZ: temozolomide.

**Tabelle 3.** Toxizität während der Primärtherapie. Gezeigt ist der prozentuale Anteil der Patienten für diejenigen Ereignisse, die in den beiden Behandlungsarmen signifikant verschieden häufig auftraten. *: p < 0,05, Chi-square-Test. RT: Radiotherapie; TMZ: Temozolomid.

| | RT (n = 33) Grade | | | | RT + TMZ (n = 28) Grade | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Nausea (%) | 0 | 0 | 3 | 0 | 21 | 7 | 4 | 0* |
| Lymphopenia (%) | 12 | 3 | 3 | 3 | 14 | 11 | 29 | 4* |
| GPT (%) | 12 | 0 | 0 | 3 | 36 | 14 | 7 | 0* |
| GOT (%) | 3 | 0 | 0 | 0 | 32 | 4 | 4 | 0* |

### Overall Survival

In the RT arm, 25 of 33 patients died from glioblastoma, 7 were alive at time of analysis. In the RT + TMZ arm, 21 of 29 died from glioblastoma, 6 were alive. Overall survival is shown in Figure 2b. Median survival amounted to 17.1 (13.5–20.8) months in the RT arm and 14.6 (12.0–17.2) months in the RT + TMZ arm without significant difference (p = 0.668) between the treatment arms. The RPA-class 3 patients had a median survival time of 16.6 (12.0–21.3) months, the class 4 patients one of 14.6 (11.3-18.0) months. Differences between the




**Figures 2a and 2b.** Progression-free (a) and overall (b) survival in glioblastoma patients initially treated with surgery and postoperative radiotherapy alone (RT) or surgery and postoperative simultaneous radiochemotherapy with temozolomide (75 mg/m²/day, RT + TMZ). Numbers of patients at risk are shown in the number rows.

**Abbildungen 2a und 2b.** Progressionsfreies Überleben (a) und Gesamtüberleben (b) bei Patienten mit Glioblastom nach Resektion und postoperativer Bestrahlung (RT) oder Resektion und postoperativer Radiochemotherapie mit Temozolomid (75 mg/m²/Tag, RT + TMZ). Die Anzahl der „patients at risk" steht in den Zahlenreihen.

RPA classes and between the treatment arms within each RPA class were not significantly different (p = 0.479 and 0.672).

### Quality of Life

For the analysis of quality of life, in both groups questionnaires stemming from up to 7 follow-up visits were evaluated. For general quality of life, a mean score from all items of the questionnaire QLQ-C30 was built, resulting in a number ranging from 1.0 to 4.0. The same procedure was used for determination of the quality of life as related to the cerebral disease using the QLQ-B20 questionnaire. All together, 52 of 127 (41%) expected forms in the RT arm, and 59 of 122 (48%) expected forms in the RT + TMZ arm were available. For both general and brain-related quality of life, better scores were observed at nearly all points of time in the RT + TMZ group; before therapy, the scores were similar in both groups (Figures 3a and 3b).

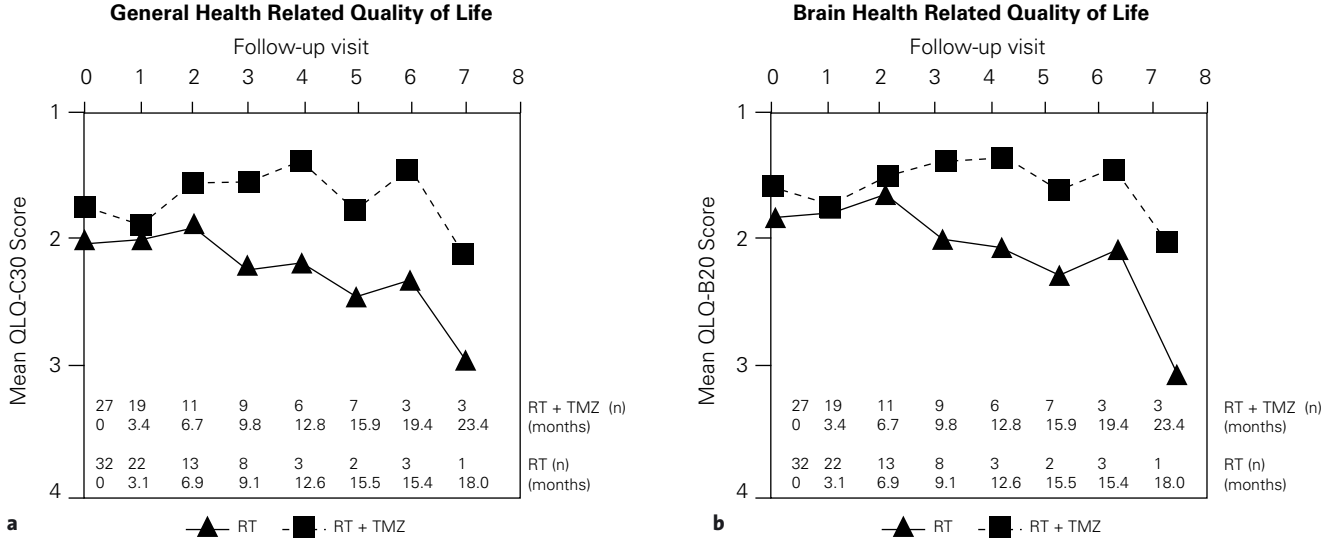
**Table 4.** Patterns of failure and salvage treatment. RT: radiotherapy; TMZ: temozolomide.
**Tabelle 4.** Rezidivmuster und Rezidivtherapie. RT: Radiotherapie; TMZ: Temozolomid.

| | | RT (n = 33) | RT + TMZ (n = 29) |
|---|---|---|---|
| Progression documented | | 28 | 26 |
| Tumor growth in MRT/ CT scans | | 27 | 23 |
| Neurologic deterioration | | 1 | 0 |
| Drop of performance ccore | | 0 | 3 |
| WHO performance status at recurrence | 0–2 | 25 | 24 |
| | 3–4 | 3 | 2 |
| Therapy at recurrence included | | | |
| TMZ | | 19/28 (76%) | 16/26 (62%) |
| Number of cycles: median (range) | | 4 (1–25) | 3 (1–13) |
| Dose: mg/m², median (range) | | 186 (70–200) | 192 (100–200) |
| Chemotherapy other than TMZ | | 4/28 (14%) | 7/26 (27%) |
| Second surgery | | 10/28 (36%) | 13/26 (50%) |
| Re-Irradiation | | 4/28 (14%) | 3/26 (12%) |
| No therapy at all | | 3/28 (11%) | 5/26 (19%) |

## Discussion

The EORTC study [24] showed that a combination of simultaneous and adjuvant TMZ with postoperative RT prolonged overall survival compared to RT alone. The survival benefit was most pronounced in younger patients in good condition (RPA-class 3) [12, 18] and lasted over more than 2 years, resulting in a substantial amount of long-term survivors [22]. These results were confirmed in a smaller randomized trial from Greece [1] and also in some retrospective studies [17, 27].

The present study was designed to clarify whether this advantage can be attributed to the simultaneous part of the chemotherapy. There were no dif-




**Figures 3a und 3b.** General (a) and Brain-Related (b) quality of live after initial surgery and radiotherapy (RT, lower curves and number rows) compared to postoperative radiochemotherapy with temozolomide (RT + TMZ, upper curves and rows) as measured by the EORTC Quality of Life Questionnaires QLQ-C30 and QLQ-B20. The numbers in the row depict the number (n) of patients who filled in the questionnaires and the median time interval in months for the respective follow-up visits. Score 1 refers to good, score 4 to bad Quality of life.

**Abbildungen 3a und 3b.** Allgemeine (a) und hirnbezogene (b) Lebensqualität nach Resektion und Bestrahlung (RT, untere Kurven und untere Zahlenreihen) im Vergleich zur postoperativen Radiochemotherapie (RT + Temozolomid, obere Kurven und Zahlenreihen), gemessen mit den EORTC-Lebensqualitäts-Fragebögen QLQ-C30 und QLQ-B20. Die Zahlen in den Reihen geben die Anzahl der Patienten (n), die die Fragebögen ausgefüllt haben, und das zu dem Nachsorgebesuch gehörende mediane Intervall an. Ein Score von 1 bedeutet gute, ein Score von 4 schlechte Lebensqualität.

ferences regarding tumor size, timing and extent of surgery and RT between the two arms. We found no significant difference in progression-free or overall survival between the two treatment arms. As progression was detected in radiological examinations mainly performed by radiologists not directly involved in the study, these results were probably not biased although neither patients nor physicians were blinded. Probably, the negative result is a consequence of the small sample size due to early closure of the study, but the possibility that the simultaneous part of TMZ chemotherapy has a lesser impact on survival than the adjuvant part can not be ruled out.

Various schedules of combined radiochemotherapy with temodal in glioblastoma have been tested in small, non-randomized studies [20]. In two studies, treatment arms differed in the use of concomitant TMZ. De Sanctis et al. [10] treated 64 patients in two sequential phase II trials with either RT and both concomitant and adjuvant TMZ or with RT and adjuvant TMZ alone. Median survival times of 18 months did not differ between the two arms. The same arms were used by Corsa et al., also from Italy, who investigated the use of RT and adjuvant TMZ in 64 patients with high grade gliomas [9]. In one of the two groups, simultaneous TMZ was added, but survival times did not improve.

Thus, these small studies regarding the concomitant use of TMZ were negative. These findings contrast with the results from experimental models where a marked radiosensitizing effect of TMZ in human glioblastoma cell cultures [7, 29] was observed and with the clinical observation that a substantial number of patients develop complete tumor necrosis after concurrent RT and TMZ [8].

The reason for these conflicting results may stem from the numerous factors that influence the response of malignant glioma cells to TMZ. The most dominant factor probably is the methylguanine methyl transferase status [12], which was not determined in the present trial. Any imbalances in this factor could explain the negative result. Several other factors, including chromosomal aberrations such as deletion of 9p and 10q [30] or loss of heterozygosity of 1p and 19q [13] and alterations in other enzyme activities such as MSH6 [4] determine the cellular response which itself is characterised by a number of events such as induction of hypoxia-inducible factor-1 (HIF-1), and vascular endothelial growth factor (VEGF)-production [11]. Also, the response to radiation is not uniform [19, 21]. In addition, many factors will probably change during the course of the disease.

Therefore, the optimal treatment schedule including neoadjuvant [2, 6], metronomic [15] or dose-intensified TMZ [31] application can only be determined in large, randomized trials such as those which have been performed for anaplastic oligodendrogliomas [5, 28]. As a consequence, a 4-arm trial in anaplastic astrocytoma which will allow to separate the effects of adjuvant and concurrent TMZ has been started (EORTC 26503, CATNON-trial), and a 2-arm trial in glioblastoma (RTOG trial 0525) that examines the effect of dose-intensified adjuvant TMZ has been performed.

In the present trial, progression was mainly diagnosed by radiological findings. Therefore, the possibility that so called "pseudoprogression" [3] observed after combined radiochemotherapy in gliomas was present in these cases cannot be excluded, but 23 of 54 recurrences (42%) were confirmed by second surgery.

In both arms, salvage therapies including second surgery, chemotherapy and re-irradiation [26] were frequently used. The median time between initial therapy and recurrence (about 7 months) was much smaller than the time between recurrence and death (about 10 months). Compared to the EORTC study, overall survival for both the RPA class 3 and 4 patients (17 months and 15 months) was in between the range observed for the EORTC radiotherapy only and combined arm (class 3: 15/21 months, class 4: 13/16 months) [18]. In another small, non randomized Italian study where TMZ was applied both neoadjuvant and adjuvant to RT compared to TMZ only at first relapse, time to progression was prolonged but survival was not different [9]. Thus, it seems that salvage therapy can, at least in part, compensate for the missing adjuvant chemotherapy and has an important impact on final outcome and should be carefully recorded in all trials for malignant glioma.

Regarding quality of life, we observed a trend in both general health-related and brain-specific quality of life, favouring the concurrent radiochemotherapy arm. Due to the amount of missing forms, these data have to be interpreted with caution. However, our findings are in concordance with the EORTC 26981-22981 study where TMZ had no negative effect on quality of life [25].

In conclusion, this early-stopped study was not able to demonstrate a benefit for progression-free or overall survival for RT plus concurrent TMZ without adjuvant TMZ compared to RT alone. In both arms, salvage therapies were frequently used and probably had a major effect on overall survival. Further trials will identify the optimal schedule for combining treatment modalities during primary and salvage therapy in glioblastoma patients.

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**Address for Correspondence**
Prof. Dr. Martin Kocher
University Hospital
Department of Radiotherapy
Joseph-Stelzmann-Str. 9
50924 Köln
Germany
Phone (+49/221) 478-5449, Fax -6158
E-mail: martin.kocher@uk-koeln.de


## Appendix

**Participating Centers / Teilnehmende Zentren**

| Institution | Site | Patients |
|---|---|---|
| University Hospital, Dept. of Radiotherapy | Köln | 16 |
| Gemeinschaftspraxis for Radiation Oncology and Radiotherapy | Hannover | 9 |
| Vivantes Klinikum im Friedrichshain, Dept. of Radiotherapy | Berlin | 8 |
| Vivantes Klinikum Neukölln, Dept. of Radiotherapy | Berlin | 7 |
| University Hospital, Dept. of Radiotherapy | Homburg/ Saar | 6 |
| Zentralkrankenhaus St.-Jürgen-Str., Dept. of Radiotherapy | Bremen | 6 |
| University Hospital, Dept. of Radiotherapy | Essen | 5 |
| Klinik am Eichert, Dept. of Radiotherapy | Göppingen | 3 |
| Clemens-Hospital, Dept. of Radiotherapy | Münster | 2 |
| University Hospital, Dept. of Radiotherapy | Heidelberg | 2 |
| Lukas-Krankenhaus, Dept. of Radiotherapy | Neuss | 1 |