

# Palliative Radiotherapy of Primary Glioblastoma

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**Abstract.** *Background/Aim:* Care is often palliative when patients are not fit and complete resection of glioblastomas cannot be achieved. This study aimed to identify predictors of survival after palliative radiotherapy. *Patients and Methods:* Thirty-one patients irradiated after biopsy or incomplete resection of primary glioblastoma were retrospectively analyzed. Median total dose, dose per fraction and equivalent dose in 2 Gy fractions (EQD2) were 45.0 Gy, 3.0 Gy and 46.0 Gy, respectively. Median number of fractions was 15, median treatment time 3 weeks. Ten patients received temozolomide. Six factors were evaluated for survival including location of glioblastoma, Karnofsky performance score (KPS), gender, age, EQD2 and temozolomide. *Results:* KPS  $\geq 60$  showed a trend for improved survival ( $p=0.141$ ). For other factors including EQD2, no significant association with survival was found. *Conclusion:* Patients with a KPS  $\leq 50$  have a poor survival prognosis and appear good candidates for short-course radiotherapy. Selected patients with better KPS may be considered for more aggressive treatments.

Glioblastoma represents the most common type of glioma and accounts for approximately 40% of primary tumors of the central nervous system (1). About 90% of glioblastomas are primary glioblastomas (2). Of the four grades specified in the World Health Organization classification of gliomas, glioblastomas (*i.e.* grade IV gliomas) are associated with the worst prognoses (3). Very poor prognoses have been reported for patients who are elderly, have a poor performance status and those with incomplete resection (2, 4, 5). For these

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patients, the situation is very often palliative. Instead of standard treatment including resection followed by radiochemotherapy [mainly 60 Gy of local irradiation in 30 fractions over 6 weeks plus concurrent and adjuvant chemotherapy with temozolomide (6)], many of these patients receive palliative radiotherapy alone including lower total doses and shorter overall treatment times compared to the standard regimen (1, 7-9). Patients assigned to palliative irradiation may benefit from personalized treatment programs considering their individual situation and remaining lifespan. In case of a short lifespan, the patients may be treated with a very short course of radiotherapy such as 25 Gy in 5 fractions over 1 week (9). In contrast, patients with considerably more favorable survival prognoses may be considered for a more aggressive treatment or even standard treatment with resection plus radiochemotherapy (6). Knowledge of prognostic factors associated with survival is helpful when looking for the optimal treatment for a specific patient with a glioblastoma receiving palliative radiotherapy. The primary intention of this study was to identify such factors in a cohort of glioblastoma patients irradiated with palliative doses.

## Patients and Methods

A total of 31 patients who received palliative radiotherapy after biopsy ( $n=16$ ) or incomplete resection ( $n=15$ ) of primary glioblastoma between 2006 and 2019 were included in this retrospective analysis. The study was approved by the responsible Ethics Committee (University of Lübeck, AZ 15-355A, amendment from August 17<sup>th</sup>, 2020).

In many countries, the most common dose-fractionation-regimen of radiotherapy for glioblastoma is 60 Gy given in 30 fractions of 2.0 Gy over 6 weeks. The equivalent dose in 2 Gy fractions (EQD2) of this regimen with respect to tumor cell kill (alpha-beta ratio of 10 Gy) is 60.0 Gy (10, 11). Radiotherapy is generally combined with concurrent and adjuvant chemotherapy (temozolomide).

In the present study, radiotherapy was administered as palliative treatment with a lower total dose and a shorter overall treatment time. The median total radiation dose was 45.0 Gy (range=20-51.5 Gy), the median dose per fraction 3.0 Gy (range=1.8-6.0 Gy), the median EQD2 46.0 Gy (range=8.9-53.3 Gy), the median number of fractions  $n=15$  (range=5-22 fractions), and the median overall treatment time 3 weeks (range=1-4.5 weeks) (10, 11). Treatment

was considered palliative, since complete tumor resection was not achieved and the patients had additional limitations including reduced performance status, older age and/or multi-focality or larger size of the glioblastoma. In addition to radiotherapy, only 10 patients received chemotherapy with temozolomide.

Six potential prognostic factors (for distributions, see Table I) were evaluated for associations with survival following radiotherapy. These factors included the main location of the glioblastoma (frontal vs. temporal vs. parietal +/- occipital vs. other locations), Karnofsky performance score ( $\leq 50$  vs.  $\geq 60$ ), gender (female vs. male), age at radiotherapy ( $\leq 69$  vs.  $\geq 70$  years, median age=69 years), EQD2 of palliative radiotherapy ( $\leq 46.0$  vs.  $>46.0$  Gy, median EQD2=46.0 Gy), and administration of temozolomide in addition to radiotherapy (no vs. yes). The survival analyses were performed using the Kaplan-Meier method and the log-rank test.  $p$ -Values  $< 0.15$  were considered indicating a trend, and  $p$ -values  $< 0.05$  were considered demonstrating significance.

## Results

The median follow-up time was 1 month (range=0-12 months) in both the entire series and the 24 patients who were alive at the last contact. In the survival analysis, a better performance status (Karnofsky performance score  $\geq 60$ ) showed a trend for improved survival ( $p=0.141$ , Figure 1). For the other investigated factors, including EQD2 of the administered palliative radiotherapy, no significant association with survival was found (Table II).

## Discussion

Since the majority of patients with glioblastoma have poor prognoses, a considerable number of pre-clinical studies were performed during recent years to better understand this aggressive disease and contribute to the improvement of its treatment (12-17). Another strategy to improve the outcomes of glioblastoma patients is personalization of their treatment. This strategy is particularly important for patients who are assigned to a palliative treatment approach and not the standard treatment, including neurosurgical resection plus adjuvant radiochemotherapy (6). Patients not suitable for standard treatment are mainly elderly patients and patients with a poor performance status (frail patients). The question is whether these patients should be treated with a comparably aggressive combined treatment, palliative radiotherapy plus supportive care, or with best supportive care (BSC) including corticosteroids alone. In 2007, a randomized trial compared BSC with vs. without 50 Gy of radiotherapy in patients  $\geq 70$  years of age with glioblastoma (WHO grade IV) or anaplastic astrocytoma (WHO grade III) (3, 18, 19). The trial was stopped after an interim analysis of 85 patients (81 with glioblastoma). Median survival times were 29.1 weeks in the radiotherapy group and 16.9 weeks in the BSC alone group ( $p=0.002$ ). Radiotherapy did not result in decreased quality of life or neurocognition. In an earlier retrospective study of

Table I. Factors evaluated for local control and survival.

Factor	Number of patients (%)
Main location of glioblastoma	
Frontal	6 (19.4)
Temporal	10 (32.3)
Parietal +/- occipital	7 (22.6)
Other	7 (22.6)
Not available	1 (3.2)
Karnofsky performance score	
$\leq 50$	11 (35.5)
$\geq 60$	12 (38.7)
Not available	8 (25.8)
Gender	
Female	15 (48.4)
Male	16 (51.6)
Age at radiotherapy	
$\leq 69$ Years	17 (54.8)
$\geq 70$ Years	14 (45.2)
Dose of radiotherapy (EQD2)	
$\leq 46$ Gy	16 (51.6)
$>46$ Gy	15 (48.4)
Additional chemotherapy	
No	21 (67.7)
Yes	10 (32.3)

EQD2: Equivalent dose in 2 Gy fractions.

85 patients aged  $\geq 65$  years (median age=70 years) with malignant gliomas (64 with glioblastoma), the addition of radiotherapy (60 Gy in 30 fractions) to BSC was the only independent predictor of better survival (20). Thus, radiotherapy can be considered superior to BSC alone.

Another important question addresses the optimal dose-fractionation regimen. To keep the treatment time as short as possible for elderly or frail patients, several studies have investigated shorter-course radiotherapy programs. A small prospective study compared 29 elderly glioblastoma patients ( $\geq 65$  years) receiving 30 Gy in 10 fractions to a historical control group receiving  $>50$  Gy (7). A survival benefit was found for the higher-dose regimen in patients with a KPS  $>50$ . In another study, 92 elderly and/or frail patients with high-grade gliomas receiving 30 Gy in 6 fractions over 2 weeks were matched for glioma-grade, performance score and age to patients irradiated with 60 Gy in 30 fractions over 6 weeks (control group) (21). The median survival of the control group was 2.5-4.5 months longer than the 5 months achieved by the 30 Gy group. In 2004, a randomized trial compared 60 Gy in 30 fractions to short-course irradiation with 40 Gy in 15 fractions over 3 weeks, in 100 glioblastoma patients aged  $\geq 60$  years (1). Median survival times (5.1 vs. 5.6 months) and 6-month survival rates (44.7% vs. 41.7%) were not significantly different ( $p=0.57$ ). In a subsequent randomized trial, 40 Gy in 15 fractions was compared to 25 Gy in 5 fractions in 98 elderly ( $\geq 65$  years)

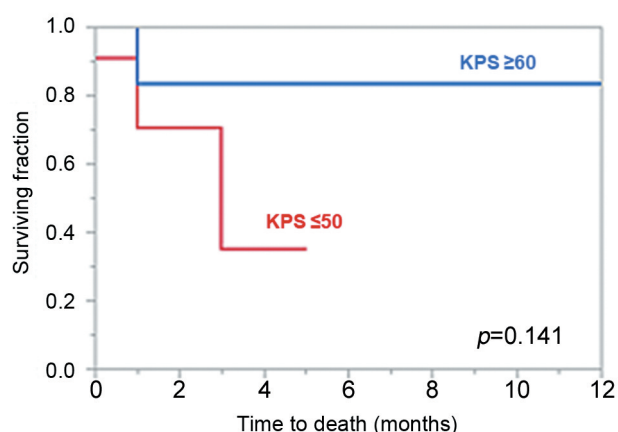


Figure 1. Kaplan–Meier curves showing the survival of patients with a Karnofsky performance score (KPS) of  $\leq 50$  and those patients with a KPS of  $\geq 60$ .

and/or frail (KPS 50–70) patients (9). Median survival times were 6.4 months and 7.9 months, respectively ( $p=0.988$ ). In another randomized trial of elderly glioblastoma patients that compared radiotherapy with 34 Gy in 10 fractions over 2 weeks to 60 Gy in 30 fractions, the short-course regimen resulted in significantly better median survival in the subset of patients older than 70 years ( $p=0.02$ ) (22). Thus, short-course palliative radiotherapy may be a reasonable option for patients with limited survival prognoses. Patients with better prognoses may benefit from more aggressive treatment programs. A retrospective study of 102 patients  $\geq 70$  years compared higher-dose radiotherapy with  $\geq 55$  Gy to palliative radiotherapy with  $\leq 40$  Gy and biopsy alone (23). In this study, gross tumor resection plus higher-dose radiotherapy was associated with the longest median survival time (17.3 months). In the entire cohort, median survival times were 7.3 months after higher dose radiotherapy and 4.5 months after lower-dose radiotherapy, respectively ( $p<0.0001$ ) (24). It was concluded, that elderly glioblastoma patients who are suitable candidates can benefit from more aggressive treatments.

When aiming to select the most appropriate regimen for a glioblastoma patient assigned to palliative treatment, the knowledge of prognostic factors of survival is helpful. Since the addition of radiotherapy to BSC improves survival in these patients, palliative treatment most commonly means palliative radiotherapy. Therefore, the present study was performed in a cohort of glioblastoma patients irradiated with palliative doses. The study aimed to identify predictors of survival to facilitate the decision whether a patient should receive a very short course of radiotherapy (e.g. 5 $\times$ 5 Gy over 1 week), shorter-course radiotherapy (e.g. 15 $\times$ 2.66 Gy over 3 weeks) or an aggressive treatment including resection, higher-dose

Table II. Survival rates at 3 and 6 months following palliative radiotherapy.

Factor	3 Months (%)	6 Months (%)	p-Value
Main location of glioblastoma			
Frontal (n=6)	83	n.a.	0.906
Temporal (n=10)	68	68	
Parietal +/- occipital (n=7)	56	56	
Other (n=7)	71	n.a.	
Karnofsky performance score			
$\leq 50$ (n=11)	35	n.a.	0.141
$\geq 60$ (n=12)	83	83	
Gender			
Female (n=15)	69	69	0.842
Male (n=16)	67	n.a.	
Age at radiotherapy			
$\leq 69$ Years (n=17)	68	68	0.952
$\geq 70$ Years (n=14)	68	68	
Dose of radiotherapy (EQD2)			
$\leq 46$ Gy (n=16)	74	74	0.443
$>46$ Gy (n=15)	70	70	
Additional chemotherapy			
No (n=21)	64	64	0.895
Yes (n=10)	78	n.a.	

n.a.: Not available; EQD2: equivalent dose in 2 Gy fractions.

radiotherapy (e.g. 30 $\times$ 2.0 Gy over 6 weeks) and chemotherapy. The KPS showed a trend for an association with survival and may be used for guidance. Since patients with a KPS  $\leq 50$  had a 3-month survival rate of only 35%, these patients appear good candidates for ultra-short-course or shorter-course radiotherapy. In contrast, in patients with a KPS  $\geq 60$ , the 6-month survival rate was 83%. Selected patients of this group may be considered for a tri-modality treatment approach as described above. The prognostic role of the performance score in patients with glioblastoma has been described in previous studies, which demonstrates consistency of the present findings (2, 4, 5, 23, 24). When considering the suggestions made above, the limitations of this study including the retrospective design, the very short median follow-up time and the small sample size need to be considered.

In summary, patients with a KPS  $\leq 50$  have a very poor survival prognosis and appear good candidates for short-course radiotherapy. Selected patients with better KPS may be considered for more aggressive treatments including neurosurgery, higher-dose radiotherapy and temozolomide. However, the results of this study need to be confirmed in a larger prospective trial.

## Conflicts of Interest

The Authors report no conflicts of interest regarding this study.

## Authors' Contributions

J.W., S.E.S. and D.R. designed this study. The data were collected by J.W. and analyzed by all Authors. The article was drafted and finally approved by all Authors.

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