Do Patients with a Poor Karnofsky Performance Status Scale Profit from Tumour Volume Reduction?

Melanie Barz (melanie.barz@tum.de)
Klinikum rechts der Isar der Technischen Universität München Neuro-Kopf-Zentrum
https://orcid.org/0000-0001-8734-9309

Julia Gerhardt
Helios Klinikum Berlin, Department of Neurosurgery

Stefanie Bette
Universitätsklinikum Augsburg, Department of neuroradiology

A. Kaywan Aftahy
Technische Universität München, Department of neurosurgery

Thomas Huber
Universitätsklinikum Mannheim: Universitätsklinikum Mannheim

Stephanie E. Combs
Technische Universität München: Technische Universität München

Yu-Mi Ryang
HELIOS Klinikum Berlin-Buch

Benedikt Wiestler
Technische Universität München: Technische Universität München

Marco Skardelly
Universitätsklinikum Tübingen: Universitätsklinikum Tübingen

Irina Gepfner-Tuma
Technische Universität München: Technische Universität München

Felix Behling
Technische Universität München: Technische Universität München

Friederike Schmidt-Graf
Technische Universität München: Technische Universität München

Bernhard Meyer
Technische Universität München: Technische Universität München

Jens Gempt
Technische Universität München: Technische Universität München

Research article
Abstract

**Purpose:** Median overall survival (OS) after diagnosis of glioblastoma (GBM) remains 15 months amongst patients receiving aggressive surgical resection, chemotherapy and irradiation. Treatment of patients with a poor preoperative Karnofsky Performance Status Scale (KPSS) is still controversial. Therefore, we retrospectively assessed the outcome after surgical treatment in patients with a KPSS of ≤ 60%.

**Methods:** We retrospectively included patients with a de-novo glioblastoma WHO °IV and preoperative KPSS ≤ 60%, who underwent surgery at two neurosurgical centres between September 2006 and March 2016. We recorded pre- and postoperative tumour volume, pre- and postoperative KPSS, OS, age and MGMT promoter status.

**Results:** 123 patients (58 females/65 males, mean age 67.4 ± 13.4 years) met the inclusion criteria. 75 of the 123 patients (61%) underwent surgical resection. 48/123 patients (39%) received a biopsy. The median preoperative and postoperative tumour volume of all patients was 33.0 ± 31.3 cm\(^3\) (IR 15.0–56.5cm\(^3\)) and 3.1 ± 23.8 cm\(^3\) (IR 0.2–15.0 cm\(^3\)), respectively. The median KPSS was 60% (range 20–60%) preoperatively and 50% (range 0–80%) postoperatively. The median OS was 123 ± 220 days (IR 52–395 days).

Age (p<0.001, HR: 1.045 [95% CI 1.022–1.068]), postoperative tumour volume (p=0.02, HR: 1.016 [95% CI 1.002–1.029]) and MGMT promoter status (p=0.016, HR: 0.473 [95% CI 0.257–0.871]) were statistically significant in multivariate analysis.

**Conclusion:** Patients with a preoperative KPSS of ≤ 60% benefit from low postoperative residual tumour volumes. Age and MGMT-methylation status were also significant prognostic parameters in this patient cohort.

Introduction

In 1949, Karnofsky and Burchena described their instrument, the Karnofsky Performance Scale (KPS) score, as a numerical scale for quantifying patients' status in relation to the degree of their independence in daily activities and self-care. Originally, it was used for patients with systemic malignancies and divided them according to their level of activity and medical requirements. Patients are scored into 11 categories from 0 to 100, where, for example, a KPSS of 70% means the patient is able to care for himself but is unable to carry out daily activities\[13\]. After it had been proven successful in patients with systemic cancer, more and more research groups started to evaluate the KPS score for brain cancer\[24, 22, 14\]. Previously published studies could show a significant correlation between the preoperative KPS score and the outcome after glioma surgery\[4, 15\]. In most studies, only patients suffering from a glioblastoma with a KPSS of ≥ 70% were included\[19, 6\]. For example, those studies analysed prognostic factors such as tumour size, GRT and adjuvant therapy modalities postoperatively. However, in our clinical daily work, patients with a noticeably lower KPSS are represented as well. It should be noticed that this can be due to
clinic symptomology as seizures, acute mental status changes or focal neurologic deficits caused by tumour size and/or location itself. Therefore, the following study intends to show whether it is worthwhile for patients with a KPSS 60% or below to achieve tumour volume reduction.

**Patients And Methods**

This retrospective, non-interventional bicentric study was approved by the local medical ethics committee (5625-12) and is in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments[9].

**Patient Population**

We retrospectively assessed 968 patients with a histologically confirmed glioblastoma WHO IV with a preoperative Karnofsky Performance Status Scale (KPSS) of ≤ 60%, who were treated surgically between September 2006 and March 2016 in two neurosurgical departments. According to interdisciplinary neuro-oncological consensus, patients were assigned to surgery with the intent of complete resection or to biopsy to confirm the histopathological diagnosis. We retrospectively reviewed pre- and postoperative KPSS, date of initial tumour diagnosis, date of death/last contact, age, sex, adjuvant treatment and histopathological findings from the patients’ medical charts. Also, we performed histopathological analysis according to the WHO criteria of 2016[17] and quantitatively assessed methylation of the O6-methylguanin-DNA-methyltransferase (MGMT) promoter status. We assessed KPSS with regards to hospital admission and five days after surgery. Then, we calculated the overall survival (OS) from the date of surgery until the date of death or censored for the date of the last patient contact. Only patients with complete magnetic resonance imaging data were included to calculate pre- and postoperative contrast-enhancing tumour volumes. Patients with recurrent tumour or incomplete data were excluded (Fig. 1).

**Imaging**

All patients received preoperative and early postoperative MRI (within 72 hours after surgery). In centre A, we performed imaging using three different 3 T MRI scanners: Philips Achieva; Philips Ingenia (Philips Medical Systems, The Netherlands B.V.); and Siemens Verio (Siemens Healthcare, Erlangen, Germany). Images included T1w sequences with and without contrast agent, FLAIR (Fluid attenuated inversion recovery) sequences, T2 gradient echo sequences, diffusion-weighted imaging or diffusion-tensor imaging, whereas we calculated isotropic diffusion-weighted images and apparent diffusion coefficient (ADC) maps automatically. Tumour volumes of the contrast-enhancing tumour on pre- and early postoperative MR images using iPlannet® Cranial 3.0.1 were manually segmented by two neurosurgeons (5 and 10 years of experience) and two neuroradiologists (3 years and 6 years of experience).

In centre B, we conducted MR imaging with a 3.0 T MRI scanner (Biograph mMR, Siemens Healthcare, Erlangen, Germany). One neurosurgeon (14 years of experience) and one medical student assessed the volumes of the contrast-enhancing tumour through manual segmentation via iPlannet® Cranial 3.0.1
(iPlannet® 3.0 cranial planning software, Brainlab AG, Munich, Germany). The postoperative tumour volumes of patients who underwent biopsies were considered identical to the preoperative tumour volumes.

Statistical Evaluation

We conducted our data analysis using IBM SPSS Statistics Version 24.0 (SPSS Inc., IBM Corp., Armonk, NY, USA). In the descriptive data analysis, we show non-normally distributed data as median and interquartile range (IR), normally distributed variables as mean and standard deviation.

We compared the OS distributions using the Kaplan-Meier estimates (log-rank) and a Cox regression model for multivariate survival analysis. We considered differences with an error probability of less than 0.05 to be statistically significant.

Results

Patients and Clinical Data

123/968 patients (58 females/65 males) with a mean age of 67.4 ± 13.4 years; (range 21–90 years) met our inclusion criteria: surgical treatment for glioblastoma, preoperative KPSS of ≤ 60%, preoperative and early postoperative MRI, complete medical documentations with date of initial tumour diagnosis, date of death/last contact, age, sex, adjuvant treatment and histopathological findings (Table 1). The median preoperative tumour volume of all patients was 33.0 ± 31.3 cm³ (IR 15.0–56.5 cm³) and the median postoperative tumor volume was 3.1 ± 23.8 cm³ (IR 0.2–15.0 cm³) postoperatively. Complete resection of contrast-enhancing tumours on postoperative MRI was achieved in 24 (19.5%) of all patients. MGMT-methylation status was available in 80 patients (65%), of whom 26 (32.5%) presented with a methylated MGMT-promotor status.

Surgical resection with intent for maximum/complete resection was performed in 75/123 patients (61%) (34/75 females and 41/75 males; mean age 64.4 ± 13.7 years (21–87 years). The median tumour volume was 35.2 ± 31.3 cm³ (IR 19.7–65.3 cm³) preoperatively and 0.5 ± 2.8 cm³ (IR 0–2.3 cm³) postoperatively. Complete resection of the contrast-enhancing tumour on postoperative MR imaging was seen in 24 (32%). In this group, we assessed MGMT-methylation status in 52/75 patients (69.3%). We observed methylation of MGMT in 19/52 patients (36.5%) and no methylation of MGMT in 33/52 patients (63.5%).

Fifty-eight of 75 (77.3%) patients underwent postoperative adjuvant treatment; three of 58 patients (5.1%) underwent monotherapy with temozolomide, 27/58 (46.6%) received radiation therapy only and 28/58 (48.3%) received a combined therapy according to the Stupp regime. The remaining 48 patients (38.7%) (23/48 females, 25/48 males) with a mean age of 72.1 ± 11.6 years (34–90 years) underwent biopsy for tumour histopathological diagnosis. The median tumour volume in these patients was 26.3 ± 30.9 cm³ (IR 8.1–51.7 cm³). MGMT-methylation status was available in 28 patients (58.3%) with 21/28 (75%)
unmethylated MGMT promotor status. After confirming histopathological diagnosis of glioblastoma via biopsy, 8/48 (16.7%) received combined radio-/chemotherapy, 3/48 (6.3%) received chemotherapy with temozolomide only, 21/48 (43.7%) received radiotherapy alone and 16/48 (33.3%) did not receive any adjuvant therapy.

**Karnofsky Performance Status Scale (KPSS)**

The median KPSS of the entire patient cohort was 60% (20–60%) preoperatively and 50% (0–80%) postoperatively. Seventeen patients (22.67%) who had undergone surgical tumour resection had an improved KPSS at time of discharge from the hospital, 25 patients (33.3%) remained unchanged and 33 patients (44.0%) worsened. There was no difference in the median KPSS between patients receiving surgical resection compared to patients receiving biopsy only. In the biopsied group, we recorded a median preoperative KPSS of 60% (range 40–60%) and median postoperative KPSS of 50% (range 0–70%). Patients who were treated by surgical resection showed a median preoperative KPSS of 60% (range 20–60%) and 50% (range 0–80%) postoperatively.

**Overall Survival (OS)**

Median OS was 123 days (IR 52–395 days). At the time of the study, 102/123 patients (82.9%) had died, and 21/123 (17.1%) were still alive or censored for their last date of contact. In-hospital mortality was seen in 3/123 (2.4%). Two of these patients received biopsy and one surgical tumour resection. Patients who received a biopsy showed a median OS of 90 days (IR 41.5–173.8 days), whereas patients who underwent surgical resection showed a median OS of 193 days (IR 80–475 days).

**Univariate Model**

Surgical resection compared against biopsy (p < 0.001) and complete resection of contrast enhancement (p = 0.03) showed a significant impact on OS in the univariate analysis using Kaplan-Meier estimates (Figs. 2–5).

**Multivariate Model**

Cox regression, including all treated patients, showed age at the time of surgery (p < 0.001, HR: 1.045 [95% CI 1.022–1.068]), postoperative tumour volume (p = 0.02, HR: 1.016 [95% CI 1.002–1.029]) and methylation status (p = 0.016 HR: 0.473 [95% CI 0.257–0.871]) as statistical significant predictors of OS. Preoperative tumour volume (p = 0.996, HR: 1.000 [95% CI 0.992–1.009]), preoperative KPSS (p = 0.068 HR: 1.023 [95% CI 0.998–1.049]) and postoperative KPSS (p = 0.237 HR: 0.987 [95% CI 0.965–1.009]) were not significant in the multivariate analysis.

**Discussion**

In this cohort of GBM patients with a preoperative KPS ≤ 60%, postoperative tumour volume, age at the time of surgery and MGMT-methylation status were significant predictors of OS in the multivariate analysis. In contrast, preoperative tumour volume and KPSS had no significant impact on OS.
Nevertheless, as already understood from other studies, we could also show that extent of resection is an important factor in OS in patients with glioblastoma[16, 10, 3, 2].

In general, patients with poor preoperative KPSS usually do not receive aggressive surgical therapy. Therefore, data on these patients are very limited. In our cohort, 56/123 (45.5%) showed an improved or unchanged postoperative KPSS with a median of 50%. Adjuvant treatment such as radiation therapy or chemotherapy is usually only offered to patients with a KPSS ≥ 70%[20, 12]. Consequently, these patients are usually considered ineligible for adjuvant oncological treatment even after tumour resection. Malakhov et al. could show that 51.2% of the patients presenting with KPSS < 60 and receiving chemoradiation had improved survival compared to RT alone[18]. However, the majority of our patient cohort (77.6%) who underwent surgical resection received adjuvant therapy. Considering the early postoperative assessment of KPSS in this study, secondary improvement is to be expected. Patients undergoing a biopsy were older and had smaller preoperative tumour volumes than patients, who were selected for surgical tumour resection. Only 16.7% of the patients who received a biopsy underwent adjuvant treatment regimes.

Reduced preoperative KPSS is an important prognostic factor in patients with glioblastoma[21, 23]. Age, comorbidities and neurological deficits have an impact on KPSS and, in conclusion, on OS[1, 5, 23]. Postoperative deterioration of the performance status scale is usually multifactorial, with the reasons being edema, haemorrhage, postoperative delirium, ischemic events or direct surgical lesions of eloquent brain structures[8].

In our opinion, the KPSS does not offer sufficient information about quality of life and therefore should not be overrated concerning the selection of patients undergoing surgery. For example, patients with preoperative neurological deficits such as hemiparesis due to surrounding edema might have a KPSS of 60% or below and might therefore not be selected for surgical therapy. However, as we know today, the surrounding edema will disappear a few days after surgery, and the patients are able to recover for adjuvant treatment. The KPSS should therefore be considered with care.

The decision for or against aggressive surgical therapy should be made individually by experienced neurosurgeons within the framework of an interdisciplinary neuro-oncology board.

**Limitations of the Study**

This study has limitations. First, the retrospective non-randomized design is the main limitation. Second, molecular status was not available for all patients in our cohort study, as the MGMT-methylation status of patients with glioblastoma is known to be one of the strongest predictors concerning survival prognosis[7, 11].

**Conclusion**
Even glioblastoma patients with a poor preoperative KPSS seem to profit from low postoperative residual tumour volumes. Age at the time of surgery and MGMT-methylation status had a significant influence on OS in our series. We therefore suggest considering surgical resection even in patients with a KPSS of $\leq 60\%$ after careful selection based on an interdisciplinary neuro-oncological board decision and counselling of patients and their relatives.

Declarations

Author contributions:

Conceptualization: Jens Gempt, Melanie Barz, Julia Gerhardt, Marco Scardelly

Methodology: Melanie Barz, Stefanie Bette

Formal analysis and investigation: Melanie Barz, Julia Gerhardt, A. Kaywan Aftahy, Felix Behling, Irina Gepfner-Tuma

Writing- original draft preparation: Melanie Barz, Julia Gerhardt

Writing- review and editing: Insa Janssen, Yu-Mi Ryang, Jens Gempt, Bernhard Meyer, Friederike Schmidt-Graf, Benedikt Wiestler, Thomas Huber

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Resources: no other resources

Supervision: Bernhard Meyer, Jens Gempt, Stephanie E. Combs

ETHICAL STATEMENT

Funding

There was no funding

Conflict of Interest

JG, BM and SB work as consultants for Brainlab (Brainlab AG, Feldkirchen).

YMR receives financial research grants from BrainLAB, Carl Zeiss Medical, DepuySynthes, Icotec, Medtronic, Silony, Spineart and Ulrich Medical. Furthermore, YMR works as a consultant for BrainLAB and Icotec.

TH worked as a medical consultant for Brainlab AG (Munich, Germany) until 2016 and is head of scientific collaborations at Smart Reporting GmbH (Munich, Germany)—all unrelated to the present study.
In addition, BM works as a consultant for Medtronic, Spineart, Icotec, Relievant and Depuy/Synthes. In these firms, BM acts as a member of the advisory board. Furthermore, BM reports a financial relationship with Medtronic, Ulrich Medical, Brainlab, Spineart, Icotec, Relievant and Depuy/Synthes. He received personal fees and research grants for clinical studies from Medtronic, Ulrich Medical, Brainlab, Icotec and Relievant. All this occurred independently of the submitted work. BM holds the royalties/patent for Spineart.

All named potential conflicts of interest are unrelated to this study.

Ethical Approval

This retrospective, non-interventional bicentric study was approved by the local medical ethics committee (5625-12) and is in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments[9].

Informed Consent

All patients sign a generally valid declaration of consent for participation in retrospective studies upon admission.

References


Tables

Table 1: Baseline tumour and patient characteristics; normally distributed variables shown as mean ± standard deviation, non-normally distributed as median (interquartile range); KPSS (Karnofsky Performance Status Scale)
### Demographic data

<table>
<thead>
<tr>
<th>Demographic data</th>
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<tbody>
<tr>
<td>Age</td>
<td>67.4 ± 13.4 years, range 21-90 years</td>
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<tr>
<td>Female</td>
<td>58/123 (47.2%)</td>
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<tr>
<td>Male</td>
<td>65/123 (52.85%)</td>
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### Surgical data & tumor burden

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<tr>
<td>Biopsy</td>
<td>48/123 (39%)</td>
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<tr>
<td>- Median preoperative tumor volume</td>
<td>26.3 ± 30.9 cm³ (IR 8.1-51.7 cm³)</td>
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<tr>
<td>- Median postoperative tumor volume</td>
<td>26.3 ± 30.9 cm³ (IR 8.1-51.7 cm³)</td>
</tr>
<tr>
<td>Resection</td>
<td>75/123 (61%)</td>
</tr>
<tr>
<td>- Median preoperative tumor volume</td>
<td>35.2 ± 31.3 cm³ (IR 19.7-65.3 cm³)</td>
</tr>
<tr>
<td>- Median postoperative tumor volume</td>
<td>0.5 ± 2.8 cm³ (IR 0-2.3 cm³)</td>
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### Karnofsky Performance Status Scale

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<thead>
<tr>
<th>Karnofsky Performance Status Scale</th>
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<tr>
<td>Median preoperative KPSS</td>
<td>60% (20-60%)</td>
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<tr>
<td>Median postoperative KPSS</td>
<td>50% (0-80%)</td>
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### Overall survival

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<th>Overall survival</th>
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<tr>
<td>Median overall survival</td>
<td>123 ± 219.9 days (IR 52-395 days)</td>
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<tr>
<td>Median overall survival after biopsy</td>
<td>90 ± 141 days (IR 41.5-173.8 days)</td>
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<tr>
<td>Median overall survival after surgery</td>
<td>193 ± 340.2 days (IR 80-475 days)</td>
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### MGMT-methylation status

<table>
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<tr>
<td>MGMT- methylation status available</td>
<td>81/123 (65.9%)</td>
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<tr>
<td>MGMT-methylated</td>
<td>26/81 (32.1%)</td>
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<tr>
<td>MGMT-unmethylated</td>
<td>55/81 (67.9%)</td>
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