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A New Survival Score for Patients Receiving Radiotherapy for Newly Diagnosed Glioblastoma Multiforme

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Abstract. *Background/Aim: In a previous study investigating radiotherapy for newly diagnosed glioblastoma multiforme (GBM), significant or almost significant associations with survival were found for performance status, upfront resection, O^6-methylguanine-DNA methyl-transferase (MGMT) promoter methylation and unifocal GBM. This study aimed to create a survival score based on these factors. Patients and Methods: Most of the 81 patients included received resection of GBM followed by radiochemotherapy (59.4 Gy/33 or 60 Gy/30 fractions). The previously identified predictors of survival were re-evaluated. Factors significantly associated with survival were used for the score. Results: All factors were significantly associated with survival. For each factor, 0 points (less favorable survival) or 1 point (more favorable survival) were assigned and added for each patient. Three groups were designed, 0-1 (n=10), 2 (n=21) and 3-4 points (n=50); 12-month survival rates were 0%, 38% and 78% (p<0.001). Conclusion: A new survival score was created for patients requiring radiotherapy for GBM that can improve treatment personalization.*

Gliomas are the most common primary tumors of the central nervous system (CNS) in adults (1, 2). The classification of the World Health Organization includes four grades (I to IV). Patients with grade IV gliomas (glioblastoma multiforme, GBM) have the worst survival prognoses (3). Since publication of the randomized trial of Stupp *et al*. in 2005, the standard treatment for GBM has changed and includes maximum possible neurosurgical resection followed by concurrent radiochemotherapy and maintenance chemotherapy (4). The dose-fractionation regimen used in the Stupp trial (EORTC 26981/22981-NCIC CE3) consisted of 60 Gy in 30 fractions (2.0 Gy per fraction on five consecutive days per week) combined with administration of 75 mg/m^2 of temozolomide (TMZ) on seven days per week (4). Concurrent radiochemotherapy was followed by six cycles of TMZ alone (150-200 mg/m^2 on five consecutive days every four weeks). This regimen resulted in a median survival of 14.6 months, which was 2.5 months longer than resection plus radiotherapy without TMZ (4). However, such a multi-modality treatment can be difficult for patients. In 2004, a randomized trial compared longer-course radiotherapy with 60 Gy in 30 fractions over six weeks to a shorter-course program, namely 40 Gy in 15 fractions of 2.66 Gy over three weeks in elderly patients (5). Median survival and survival at 6 months after randomization were similar in both groups. In this case, "elderly" was defined as ≥60 years. During the last decades, the median age of patients with GBM has increased to 64 years. Thus, 40 Gy in 15 fractions could be a reasonable option for many patients with this aggressive disease, particularly for patients with short or intermediate survival prognoses (1). More recently, Roa *et al*. presented another randomized trial that compared 40 Gy in 15 fractions over three weeks to a very short course of radiotherapy, 25 Gy in 5 fractions of 5 Gy over one week, in elderly (≥65 years) and/or frail [Karnofsky performance score (KPS) 50-70%] patients (6). They found that 25 Gy in five fractions was not inferior to 40 Gy in 15 fractions with respect to overall survival and progression-free survival. Selected patients, particularly in case of methylation of the O^6-methylguanine-DNA methyl-transferase (MGMT), may be suitable for systemic treatment with TMZ alone (7, 8).

These considerations demonstrate that it is important to be able to estimate a patient's survival prognosis prior to designing an individual treatment program. Patients with very poor prognoses may be considered for a very short

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course of radiotherapy, TMZ alone or best supportive care. Patients with intermediate prognoses appear suitable for radiotherapy with 40 Gy in 15 fractions that can be combined with TMZ (9). Patients with more favorable prognoses should receive multi-modality treatment that can lead to improved survival (4, 10). Since in patients with favorable survival prognoses late treatment-related sequelae are also important, radiotherapy with 59.4 Gy with doses per fraction of 1.8 Gy may be preferable to 60 Gy with doses per fraction of 2.0 Gy. The risk of radiation-related late complications of the normal CNS tissue increases with both total dose and dose per fraction (11, 12).

The present study aimed to develop a survival score for patients with newly diagnosed GBM who are considered candidates for radiotherapy, in order to support physicians during the process of designing a personalized treatment regimen. This new score should be based on four prognostic factors identified in a previous study, namely KPS, upfront neurosurgical resection, *MGMT* promoter methylation and number of GBM lesions (13). It is the first survival score including *MGMT* promoter methylation that does not particularly focus on elderly patients with GBM.

Patients and Methods

In a previous study of patients irradiated for newly diagnosed GBM, a significant association with improved survival was found for KPS ≥80 (*vs*. ≤70%), upfront neurosurgical resection of GBM (*vs*. no resection) and *MGMT* promoter methylation (*vs*. no methylation); borderline significance was observed for a single lesion (*vs*. multiple lesions) of GBM (13). The present study was performed to create a survival score for patients requiring radiotherapy for newly diagnosed GBM based on these four factors. The new score should particularly help estimate the survival probability at 12 months after the start of radiotherapy. The study received approval from the local Ethics Committee (University of Lübeck, *ref*. 15-355A).

This study included 81 patients irradiated between 06/2010 and 02/2020, in whom data regarding the four prognostic factors stated above were available. Twenty-eight patients (35%) were included in the previous study (13). Of the 81 patients of the present study, 30 (37%) were female and 51 (63%) were male. The median age was 59 years (range=21-81 years). The two most common sites of GBM were the temporal lobe (*n*=34) and frontal lobe (*n*=19). In 78 patients (96%), radiotherapy was combined with concurrent and adjuvant chemotherapy, which consisted of temozolomide. Fifty-nine patients (73%) received an upfront neurosurgical resection of the GBM, which was a gross total resection (GTR) in 27 patients and a subtotal resection (STR) in 30 patients.

Radiotherapy was performed as 3D-conformal radiotherapy in 5 patients (6%) and as volumetric modulated arc therapy in 76 patients (94%). Dose-fractionation regimens included 59.4 Gy in 33 fractions of 1.8 Gy over 6.5 weeks in 56 patients and 60 Gy in 30 fractions of 2.0 Gy over 6 weeks in 19 patients. In the other 6 patients, radiotherapy was given as planned in 5 patients. Four patients received 55.8 Gy in 31 fractions of 1.8 Gy and one patient 54 Gy in 30 fractions of 1.8 Gy. In one patient, radiotherapy was stopped after 57.6 Gy of the planned 59.4 Gy.

Table I. *Univariate analyses of the four prognostic factors included in the scoring system: Survival rates at 6 and 12 months after the start of radiotherapy for glioblastoma.*

Prognostic factor	6 Months (%)	12 Months (%)	*p*-Value
Number of GBM lesions			
Multiple (n=11)	64	9	**<0.001**
Single (n=70)	86	66	
Karnofsky performance score			
≤70% (n=36)	72	47	**0.039**
≥80% (n=45)	91	67	
Neurosurgical resection			
No (n=22)	55	18	**<0.001**
Yes (n=59)	93	73	
MGMT promoter methylation			
No (n=38)	76	42	**0.026**
Yes (n=43)	88	72	

GBM: Glioblastoma multiforme; MGMT: O^6-methylguanine-DNA methyl-transferase; bold *p*-values were significant.

Table II. *Prognostic factors and corresponding scoring points.*

Prognostic factor	Scoring points
Number of GBM lesions	
Multiple	0
Single	1
Karnofsky performance score	
≤70%	0
≥80%	1
Neurosurgical resection	
No	0
Yes	1
MGMT promoter methylation	
No	0
Yes	1

GBM: Glioblastoma multiforme; MGMT: O^6-methylguanine-DNA methyl-transferase.

Survival time was calculated from the first day of radiotherapy. Univariate analyses were performed with the Kaplan–Meier method. Differences between the corresponding Kaplan–Meier curves were calculated with the Wilcoxon test. *p*-Values <0.05 were considered significant and *p*-values <0.10 indicated a trend. Those factors that were significantly associated with survival were included in the scoring system.

Results

The patients were followed until death or for at least 12 months after the start of radiotherapy. The median survival time was 16 months, and the survival rates at 6 months and at 12 months were 83% and 58%, respectively. On univariate

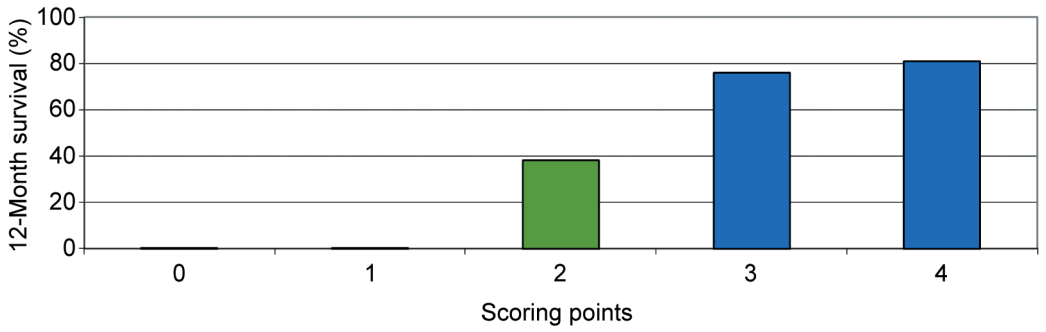

Figure 1. *The 12-month survival rates related to the scoring points calculated for each patient (patient scores).*

analyses (Table I), significant associations with better survival were found for a single lesion of GBM ($p<0.001$), upfront resection ($p<0.001$), *MGMT* promoter methylation ($p=0.026$) and KPS ≥80% ($p=0.039$).

Therefore, all four investigated factors were used for creating the scoring system. For each factor, either 0 points (less favorable survival) or 1 point (more favorable survival) were assigned (Table II). The points of the four factors were added for each patient to receive the individual scoring points (patient scores). The resulting patient scores ranged between 0 and 4 points. The corresponding 12-month survival rates were 0% (0 points), 0% (1 point), 38% (2 points), 76% (3 points) and 81% (4 points), respectively ($p<0.001$, Figure 1). Based on these survival rates, three prognostic groups were designed, namely 0-1 points ($n=10$), 2 points ($n=21$) and 3-4 points ($n=50$). Twelve-month survival rates of these groups were 0%, 38% and 78%, respectively, and median survival times were 7, 11 and 40 months, respectively ($p<0.001$, Figure 2).

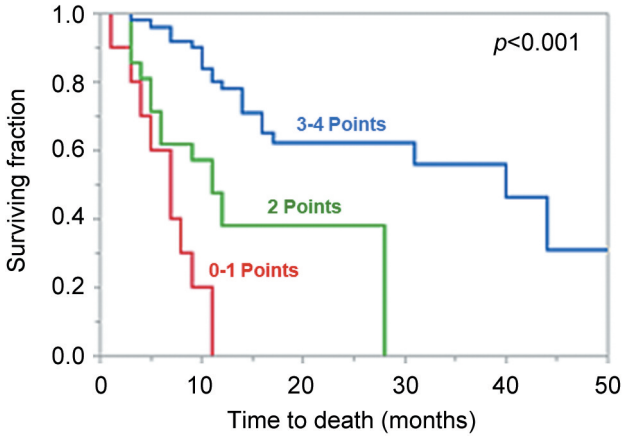

Figure 2. *Kaplan–Meier curves of the three prognostic groups 0-1 points, 2 points and 3-4 points. The p-value was calculated with the log-rank test.*

Discussion

Although considerable research has been performed during the last decade, the outcomes of the majority of patients with GBM are still poor with the 5-year survival probability of less than 10% requiring further improvement (14-19). This may be achieved with aggressive multi-modality treatment. On the other hand, if patients have a very short remaining survival time, their treatment should be as short and convenient as possible. Thus, patients with GBM will likely benefit from personalized treatments that consider their individual situation including treatment preferences, age, co-morbidities, social environment and remaining lifespan.

For almost 30 years, scoring systems have been created that aimed to predict the survival of patients irradiated for GBM. In 1993, Curran *et al*. presented a recursive partitioning analysis (RPA) of prognostic factors using data of patients with malignant gliomas from three Radiation Therapy Oncology Group trials (20). Six RPA classes and 12 subgroups (terminal nodes) were designed based on prognostic factors including performance status, age, changes in mental status, resection, total radiation dose and histology (WHO grade). Median survival times ranged between 4.3 and 58.6 months (20). However, the cohort of patients used to develop this RPA classification included different WHO grades and did not consider *MGMT* promoter methylation that was discovered to be an important predictor of survival more than 10 years later (21). In 2004, Lamborn *et al*. presented an RPA classification particularly for patients with GBM (22). Based on age, KPS, extent of resection and location of GBM, they classified patients into four risk groups, two lower risk groups (age <40 years; lowest risk with involvement of the frontal lobe only), one intermediate risk group (KPS ≥80%, resection, age 40-65 years) and one higher risk group (age >65 years, or age 40-65 years plus KPS ≤70% and/or biopsy only). Median survival times of the four groups were 132, 71, 63 and 37 weeks, respectively (22). In contrast to the previous study of Curran

et al., the classification of Lamborn *et al*. focused specifically on GBM but also did not consider the *MGMT* promoter methylation (20, 22).

After publication of the Stupp trial in 2005, the addition of TMZ to radiotherapy has become very popular for the treatment of GBM (4). In 2006, Mirimanoff *et al*. presented a study that investigated the RPA classification from 1993 (20) in the cohort of the Stupp trial (4) and found significantly different survival outcomes between RPA classes III, IV and V with median survival times of 17, 15 and 10 months, respectively (23). However, again the prognostic role of the *MGMT* promoter methylation was not investigated. In 2008, authors of the Stupp trial used the data of their trial to develop three nomograms for estimating the 2-year survival probability of patients with GBM (24). One nomogram was based on assignment to treatment (radiotherapy plus temozolomide *vs*. radiotherapy alone), age, extent of neurosurgical resection, mini-mental state examination (MMSE) score and corticosteroids at randomization. The other two nomograms were based on age, performance status and MMSE score and on *MGMT* promoter methylation, performance status and MMSE score, respectively (24). Although these nomograms can support physicians when designing an individual treatment program, they appear relatively complex. Moreover, one has to be aware that the nomograms were developed from selected patients meeting the criteria for inclusion in a randomized trial. The results obtained from these patients may likely not be generalized to other patients, who make up a considerable proportion of patients with GBM during daily routine. Furthermore, the MMSE score is generally not assessed during daily routine outside clinical trials. The easier-to-use survival score developed in the present study may be a reasonable supplement to the three previous nomograms (24).

In 2012, an additional RPA classification was presented that was limited to elderly patients (≥70 years) with GBM (24). Four RPA classes were designed: age <75.5 years and resection (class I), age ≥75.5 years and resection (class II), KPS 70-100% and biopsy only (class III), KPS<70% and biopsy only (class IV). Median survival times were 9.3, 6.4, 4.6 and 2.3 months, respectively (25). However, patients younger than 70 years and *MGMT* promoter methylation were not considered.

The most recent survival score for patients irradiated for GBM was also limited to elderly patients (≥65 years) (26). The score considered three independent predictors of survival, namely age, KPS and *MGMT* promoter methylation. It included two prognostic groups, namely 4-8 and 9-14 points, with median survival times of 2.7 and 7.8 months, respectively. In contrast to previous scores, the score of Straube *et al*. considered *MGMT* promoter methylation but was not made for patients younger than 65 years (26).

We felt that an additional survival score might be useful for patients irradiated for newly diagnosed GBM, a score that considers *MGMT* promoter methylation and can be used for unselected patients of all ages during daily routine. The new score was based on four prognostic factors identified in a previous study of patients receiving radiotherapy for GBM (13). These factors were number of GBM lesions, KPS, neurosurgical resection and *MGMT* promoter methylation. Median survival in the present cohort (16 months) was similar to the TMZ-group in the Stupp trial (14.6 months) and to patients treated after 2005 in a propensity score weighted population-base analysis (15 months) (27). Moreover, the 12-month survival rate of the present study was very similar to the rate found in the propensity score weighted population-base analysis (58% *vs*. 59%). These similarities demonstrate consistency of the data of the present study.

The four previously identified prognostic factors (13) were re-evaluated in the present study. Since they showed significant associations with survival, all four factors were considered eligible for inclusion in the survival score. Based on these factors, three groups were designed. Patients of the 0-1 points group had the worst survival outcomes. The median survival time was only 7 months, and no patient survived longer than 10 months. Therefore, these patients should be considered for treatment with a very short course of radiotherapy such as 25 Gy in five fractions over one week (6). Patients of the 2 points group with a median survival of 11 months and a 12-month survival probability of 38% represented the intermediate risk group. Since less than half of these patients lived for 12 months or longer, they might be considered for short-course radiotherapy with 40 Gy in 15 fractions over three weeks (5). Short-course radiotherapy should be supplemented by TMZ if reasonable. In a randomized trial, the addition of TMZ to radiotherapy resulted in significantly longer survival than short-course radiotherapy alone in elderly patients (≥65 years) with GBM (28). However, in a retrospective study of 112 patients aged ≥60 years a significant benefit of the addition of TMZ to shorter-course radiotherapy was not observed (29). This might be a result of the absence of the *MGMT* promoter methylation in a certain number of patients, which was not investigated in that study (29). *MGMT* promoter methylation was shown to be positively associated with outcomes after treatment with TMZ in patients with GBM (7, 8, 21).

Patients of the 3-4 points group had the most favorable survival prognoses with a median survival of 40 months and a 12-month survival rate of 78%. These patients likely benefited from multi-modality treatment including resection, longer-course radiotherapy and TMZ. Longer-course radiotherapy may be given with 60 Gy in 30 fractions of 2.0 Gy or 59.4 Gy in 33 fractions of 1.8 Gy. The latter regimen is expected to result in less late sequelae, since the equivalent doses in 2 Gy fractions (EQD2) for late complications of normal CNS tissue are 60.0 Gy for 60 Gy/30 fractions and 56.4 Gy for 59.4 Gy/33 fractions, respectively (11, 12). The EQD2 for 57.6 Gy/32 fractions and 55.8 Gy/31 fractions are 54.7 Gy and 53.0 Gy, respectively. According the quantitative analyses of normal

tissue effects in the clinic (QUANTEC), a maximum dose to the brain of <60 Gy is associated with a probability of symptomatic necrosis <3% (30, 31). Regarding the brain stem, a volume of 1-10 ml should not receive more than 59 Gy and the maximum dose should be <54 Gy to keep the risk of late complications <5% (30, 31). Regarding the optic chiasm, doses of 55-60 Gy are associated with a risk of 3-7% of optic neuropathy, and doses <55 Gy with a risk of <3%.

During the interpretation of the results of the present study, its limitations need to be considered that include the retrospective study design (risk of hidden biases) and the comparably small sample size. Moreover, the extent of resection was previously reported to be significantly associated with survival in patients with GBM (32, 33). Since our previous study showed only a trend for such an association, this factor was not included in the present score (13). A potential reason for the lack of significance in the previous study might have been the relatively small sample size. The impact of the extent of resection on survival should be re-evaluated in a larger prospective cohort of patients.

In conclusion, a survival score that considers *MGMT* promoter methylation and can be used for patients of any age was created for patients with newly diagnosed GBM requiring radiotherapy. This new score includes three prognostic groups with significantly different median survival times and 12-month survival rates. It can contribute to treatment personalization for this group and may help designing subsequent clinical studies including randomized trials.

Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

Authors' Contributions

The study was designed by all Authors. Data were collected by J.W. and analyzed by D.R. and S.E.S. The manuscript was drafted by D.R. and S.E.S. and finally approved by all Authors.

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