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Identification of Patients With Glioblastoma Who May Benefit from Hypofractionated Radiotherapy

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Abstract. *Background/Aim: Standard radiotherapy (RT) for glioblastoma lasts 6 weeks. We aimed to identify patients who would benefit from a hypofractionated approach. Patients and Methods: In 167 patients receiving standard fractionation, 10 factors were analyzed for local control (LC) and overall survival (OS). A survival score was developed and compared to a previous instrument. Results: On multivariate analysis, better LC was significantly associated with the presence of only one lesion and O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation. Better OS was associated with one lesion, better performance status, MGMT promoter methylation, and receipt of chemotherapy. Lesion diameter ≤40 mm and upfront resection were associated with improved OS on univariate analyses. Based on assigning scores to these six factors, three groups, with 32-35, 36-44 and 45-48 points, were designed with 12-month OS-rates of 0%, 56%, and 92%, respectively. Accuracy in predicting death within 12 months and survival ≥12 months was 100% and 92%, respectively, versus 67% and 83% with the previous scoring system. Conclusion: A new survival score with higher accuracy was developed for patients with glioblastoma. Our model can be utilized to individualize RT dose-fractionation recommendations for glioblastoma.*

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Radiotherapy (RT) is an integral part of the multimodal treatment of glioblastoma, which generally includes maximal safe resection followed by concurrent chemoradiation with temozolomide plus sequential maintenance chemotherapy, with or without addition of tumor-treated fields (1, 2). The standard dose-fractionation regimen of radiotherapy for glioblastoma is 60 Gy in 30 daily fractions of 2.0 Gy over a period of 6 weeks. Another regimen that is used by some centers is 59.4 Gy in 33 daily fractions of 1.8 Gy over 6.5 weeks. The rationale for this regimen is the lower dose per fraction, which is considered associated with less neurocognitive deficits (3, 4). Hypofractionated courses (including doses per fraction >2.0 Gy) have demonstrated equivalent outcomes for elderly patients and those with a poor prognosis. In a randomized trial of elderly patients with glioblastoma, hypofractionated RT with 40 Gy in 15 daily fractions of 2.66 Gy over three weeks was noninferior to standard fractionation (5). More recent studies investigated 52.5 Gy in 15 daily fractions of 3.5 Gy over 3 weeks in elderly or frail patients (6-8). The treatment was shown to be feasible and was associated with favorable outcomes when compared to historical studies. In another randomized trial of elderly (≥65 years) or frail patients, ultra-hypofractionated RT with 25 Gy in 5 daily fractions of 5.0 Gy over 1 week was noninferior to 40 Gy in 15 fractions with respect to overall survival (OS) and progression-free survival (9). Thus, elderly or frail patients may be considered for ultra-hypofractionated RT or moderately hypofractionated RT. Hypofractionated RT over 3 weeks can be combined with temozolomide (10). Patients with more favorable survival prognoses should receive multi-modality treatment including standard fractionation RT (1).

These considerations show that it is important to know a patient's survival prognosis as precisely as possible when selecting individual treatment. The judgement can be facilitated by prognostic tools. Several survival scores have already been created for patients with glioblastoma (11-17). However, most of these scores are older than 10 years, limited to elderly

Table I. *Factors analyzed for local control (LC) and overall survival (OS).*

Factor		Patients, n (%)	
		Analysis of LC	Analysis of OS
Number of glioblastoma lesions	1	133 (83)	137 (82)
	≥2	28 (17)	30 (18)
Main site of glioblastoma	Temporal/parietal	79 (49)	82 (49)
	Frontal/fronto-parietal	48 (30)	51 (31)
	Occipital/parieto-occipital	19 (12)	19 (11)
	Other sites	15 (9)	15 (9)
Maximum cumulative diameter	≤40 mm	82 (51)	86 (51)
	>40 mm	79 (49)	81 (49)
Karnofsky performance score	≤80	92 (57)	97 (58)
	≥90	69 (43)	70 (42)
Sex	Female	67 (42)	70 (42)
	Male	94 (58)	97 (58)
Age	≤60 Years	83 (52)	86 (51)
	≥61 Years	78 (48)	81 (49)
MGMT promoter methylation	No	66 (41)	67 (40)
	Yes	69 (43)	73 (44)
	Unknown	26 (16)	27 (16)
Extent of resection	GTR	55 (34)	57 (34)
	STR	68 (42)	70 (42)
	Biopsy only	38 (24)	40 (24)
Addition of chemotherapy	No	7 (4)	8 (5)
	Yes	154 (96)	159 (95)
Total radiation dose	≤54.0 Gy	8 (5)	9 (5)
	≥55.8 Gy	153 (95)	158 (95)

GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; STR: subtotal resection.

patients, or did not consider O^6-methylguanine-DNA methyltransferase (MGMT) methylation status (11-16). Compared to other existing scores, our previous tool is different, *i.e.*, it is not limited to elderly patients, is more recent, and includes the *MGMT* promoter methylation status (17). However, it was created from a small sample size of 81 patients, and its accuracy to predict survival for at least 12 months was not optimal. Therefore, we developed a new survival score for patients with glioblastoma from a larger patient cohort and compare the new score to our previous model. We also aimed to identify independent predictors of local control (LC) that may additionally contribute to individualization of RT for glioblastoma, including the identification of patients who may benefit from hypofractionated RT.

Patients and Methods

A total of 167 patients who received standard RT fractionation (5×1.8-2.0 Gy per week) for glioblastoma at the Lübeck Campus of the University Medical Center Schleswig-Holstein between 2012 (installation of new linear accelerators including volumetric-modulated arc therapy) and 2021 were retrospectively evaluated for LC and OS. The study was approved by the responsible Ethics Committee of the University of Lübeck (2022-509).

Ninety-nine patients (59.3%) received 59.4 Gy (5×1.8 Gy per week) and 49 patients (29.3%) 60.0 Gy (5×2.0 Gy per week). The other 19 patients (11.4%) received lower total doses, in 11 due to the proximity of the glioblastoma to organs at risk (*e.g.*, brain stem, optic chiasm) and in eight due to unexpected toxicity during RT or chemoradiation. In 157 patients (94.0%), RT was performed as volumetric-modulated arc therapy. Of the entire cohort, 159 patients (95.2%) received concurrent chemotherapy of temozolomide (1). Maintenance chemotherapy following RT was administered to 132 patients and consisted of six or more courses of temozolomide in 78 of them. Mainly due to toxicity, 54 patients received fewer than six courses of temozolomide, which were followed by procarbazine/lomustine or lomustine alone in eight patients. Upfront gross total resection (GTR) of the glioblastoma was performed in 57 patients (34.1%), and subtotal resection in 70 patients (41.9%). In 40 patients (24.0%), the tumor was considered unresectable and they only underwent a biopsy for histological confirmation of the diagnosis of glioblastoma.

Ten factors (Table I) were analyzed for associations with LC and OS. These factors included the number glioblastoma lesions (1 *vs.* ≥2), main site of glioblastoma (temporal/parietal *vs.* frontal/fronto-parietal *vs.* occipital/parieto-occipital *vs.* other), maximum diameter of all lesions (median=40 mm; ≤40 *vs.* >40 mm), Karnofsky performance score (KPS: median=80; ≤80 *vs.* ≥90), sex (female *vs.* male), age (median=61 years; ≤60 *vs.* ≥61 years), *MGMT* promoter methylation (no *vs.* yes), extent of resection (GTR *vs.* subtotal resection *vs.* biopsy only), addition of chemotherapy (no *vs.* yes), and total RT dose (≤54 *vs.* ≥55.8 Gy).

LC and OS were calculated from the day of resection/biopsy. Univariate analyses were performed using the Kaplan–Meier method and the log-rank test. Values of $p<0.05$ were considered significant.

Table II. *Local control rates at 6, 12 and 24 months.*

Factor		LC, %			
		6 Months	12 Months	24 Months	*p*-Value
Number of glioblastoma lesions	1	77	43	22	**<0.001**
	≥2	32	14	0	
Main site of glioblastoma	Temporal/parietal	79	49	22	0.24
	Frontal/fronto-parietal	62	27	15	
	Occipital/parieto-occipital	61	31	12	
	Other sites	46	23	15	
Maximum cumulative diameter	≤40 mm	78	40	21	0.14
	>40 mm	60	36	15	
Karnofsky performance score	≤80	61	31	10	**<0.001**
	≥90	79	46	29	
Sex	Female	69	35	10	0.12
	Male	69	40	24	
Age	≤60 Years	75	42	22	**0.038**
	≥61 Years	63	33	13	
MGMT promoter methylation	No	68	23	7	**0.002**
	Yes	69	53	30	
Extent of resection	GTR	85	44	21	**<0.001**
	STR	68	43	23	
	Biopsy only	50	20	5	
Addition of chemotherapy	No	36	36	n.a.	0.10
	Yes	70	38	18	
Total radiation dose	≤54.0 Gy	63	17	17	0.43
	≥55.8 Gy	69	39	18	

GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; n.a.: not available; STR: subtotal resection. Statistically significant *p*-values are shown in bold.

Factors found to be significant in univariate analyses were subsequently analyzed for independence using the Cox proportional hazards model. Again, values of $p<0.05$ were considered significant. Those factors that were significantly associated with OS on univariate analyses were used to develop the new survival score. For each of these factors, the 12-month OS-rates (as percentages) were divided by 10. The resulting factor scores were added for each patient to obtain the individual patient scores. Based on the 12-month OS rates for the patient scores, three groups were designed for the survival score, representing poor, intermediate and favorable survival prognoses, respectively. In addition, the new survival score was compared to a previous one (17) for accuracy in predicting death within 12 months and survival for at least 12 months, respectively. For the comparisons, we used the positive predictive values (PPVs), which were calculated with the following equations:

PPV for prediction of death within 12 months (least favorable prognostic group):

PPV=[(number of patients dying within 12 months/(no. of patients dying + number not dying within 12 months)] ×100

PPV for prediction of survival for at least 12 months (most favorable prognostic group):

PPV=[number of patients surviving ≥12 months/(number of patients surviving + number not surviving ≥12 months)] ×100

Results

Median follow-up was 16 months (range=2-98 months) for the entire cohort and 19 months (range=3-98 months) in those patients alive at the last contact. On univariate analyses of LC (Table II), improved outcomes were significantly associated with only one lesion ($p<0.001$), KPS ≥90 ($p<0.001$), age ≤60 years ($p=0.038$), *MGMT* promoter methylation ($p=0.002$), and GTR ($p<0.001$). In the multivariate analysis, the number of lesions [hazard ratio (HR)=2.60, 95% confidence interval (CI)=1.51-4.47, $p<0.001$] and *MGMT* promoter methylation (HR=0.51, 95% CI=0.35-0.75, $p<0.001$) remained significant. In contrast, KPS (HR=0.72, 95% CI=0.46-1.14, $p=0.16$), age (HR=1.38, 95% CI=0.91-2.10, $p=0.13$), and extent of resection (HR=1.20, 95% CI=0.90-1.60, $p=0.21$) were not significant in the multivariate analysis of LC.

On univariate analyses of OS (Table III), better outcomes were significantly associated with only one lesion ($p<0.001$), maximum diameter of ≤40 mm ($p=0.040$), KPS ≥90 ($p<0.001$), *MGMT* promoter methylation ($p=0.002$), GTR ($p<0.001$), and addition of chemotherapy ($p<0.001$). In the multivariate analysis, one lesion (HR=2.53, 95% CI=1.39-4.62, $p=0.002$), KPS ≥90 (HR=0.50, 95% CI=0.30-0.82, $p=0.007$),

Table III. *Overall survival (OS) rates at 6, 12 and 24 months.*

Factor		OS, %			
		6 Months	12 Months	24 Months	*p*-Value
Number of glioblastoma lesions	1	91	79	50	**<0.001**
	≥2	67	40	7	
Main site of glioblastoma	Temporal/parietal	94	77	44	0.41
	Frontal/fronto-parietal	80	70	42	
	Occipital/parieto-occipital	89	67	44	
	Other sites	67	53	40	
Maximum cumulative diameter	≤40 mm	95	79	53	**0.040**
	>40 mm	78	64	32	
Karnofsky performance score	≤80	79	63	27	**<0.001**
	≥90	97	84	63	
Sex	Female	86	71	40	0.42
	Male	88	72	44	
Age	≤60 Years	88	76	46	0.085
	≥61 Years	85	67	39	
MGMT promoter methylation	No	89	69	32	**0.002**
	Yes	89	77	56	
Extent of resection	GTR	93	82	56	**<0.001**
	TR	89	80	43	
	Biopsy only	75	43	21	
Addition of chemotherapy	No	25	13	n.a.	**<0.001**
	Yes	90	75	44	
Total radiation dose	≤54.0 Gy	56	42	28	0.073
	≥55.8 Gy	88	73	43	

GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; n.a.: not available; STR: subtotal resection; n.a.: not available. Statistically significant *p*-values are shown in bold.

MGMT promoter methylation (HR=0.53, 95% CI=0.34-0.83, $p=0.005$), and addition of chemotherapy (HR=0.17, 95% CI=0.06-0.47, $p<0.001$) remained significant. Maximum diameter (HR=1.32, 95% CI=0.83-2.08, $p=0.24$) and extent of resection (HR=1.16, 95% CI=0.83-1.63, $p=0.38$) were not significant in the multivariate analysis of OS.

For the new survival score, the six factors, namely the number of lesions, KPS, *MGMT* promoter methylation status, chemotherapy, maximum lesion diameter, and extent of resection were used. The corresponding points for each factor are shown in Table IV. After addition of the factor scores, the resulting patient scores ranged between 32 and 48 points (Figure 1). Considering the 12-month OS rates associated with the patient scores, three groups were designated, namely 32-35 points (n=6), 36-44 points (n=58), and 45-48 points (n=76). The median survival durations of these groups were 6 months, 15 months, and 30 months, respectively, and the corresponding 12-month OS rates were 0%, 56%, and 92% (Figure 2, $p<0.001$). The PPVs for correctly predicting death within 12 months and survival for at least 12 months were 100% and 92%, respectively. When applying the previous survival scoring system (17) to the patient cohort of the current study, the 12-month OS rates were 33% (poor prognosis), 74% (intermediate prognosis), and 83% (favorable prognosis), respectively. The PPVs for prediction of death within 12 months and survival for at least 12 months were 67% and 83%, respectively.

Discussion

In addition to new developments of radiotherapy and systemic therapy, outcomes of patients with glioblastoma may be improved by individualization of their treatment (17-22). Regarding RT, individualization includes selection of appropriate RT techniques and dose-fractionation regimens. Standard multi-modality treatment for glioblastoma is based on the randomized trial by Stupp *et al*. and includes maximal safe resection followed by a 6-week course of concurrent chemoradiation and sequential maintenance chemotherapy (1). To reduce the risk of late sequelae, longer-course RT may be performed with doses per fraction of 1.8 Gy up to 59.4 Gy (3, 4, 17).

A considerable number of patients with glioblastoma have poor survival prognoses. For these patients, a hypofractionated RT course over 3 weeks or an ultra-hypofractionated RT course over 1 week are treatment options. Survival models have been developed to help optimize treatment decisions in terms of RT course (11-17).

Table IV. *Prognostic factors used for the survival score, corresponding 12-month overall survival (OS) rates, and points scored for each.*

Prognostic factor		12-Month OS-rate, %	Points scored
Number of glioblastoma lesions	1	79	8
	≥2	40	4
Main site of glioblastoma	≤40 mm	79	8
	>40 mm	64	6
Karnofsky performance score	≤80	63	6
	≥90	84	8
MGMT promoter methylation	No	69	7
	Yes	77	8
Extent of resection	GTR	82	8
	STR	80	8
	Biopsy only	43	4
Addition of chemotherapy	No	13	1
	Yes	75	8

GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; STR: subtotal resection.

However, most of the models are older than 10 years and, therefore, do not incorporate the current standard of care (11-15). A more recent score published in 2020 was developed for elderly patients with glioblastoma and may not be applicable to younger patients (16). The majority of the existing scores do not incorporate *MGMT* promotor methylation status, which is now an important prognostic factor in glioblastoma (11-13, 15). Our group developed a model in 2021 that included *MGMT* promoter methylation status (17). However, that score also has significant limitations. It was developed from only 81 patients, and its accuracy in identifying patients surviving for at least 12 months was 78% and, thus, not optimal (17). As a result, we developed a new model in the current study with a larger cohort. In the present study, six predictors were identified that were significantly associated with survival on univariate analyses. These factors included the number of glioblastoma lesions, maximum cumulative diameter of the lesions, KPS, *MGMT* promoter methylation status, extent of upfront resection, and addition of chemotherapy. In comparison to our previous model (17), the new score included two additional factors (maximum cumulative diameter and chemotherapy) and provided weighted factor scores considering the 12-month survival rates (which were divided by 10). The previous system used only 0 points (worse prognosis) or 1 point (better prognosis) as factor scores and was, therefore, less differentiated (17).

The new survival score leads to three prognostic groups, with 32-35 points, 36-44 points, and 45-48 points. Corresponding 12-month survival rates were 0%, 56%, and 92%, respectively, resulting in PPVs of 100% and 92%, respectively, for correct prediction of death within 12 months and survival for at least 12 months. When using the previous score for the present cohort of patients, the corresponding PPVs were 67% and 83%, respectively (17). Thus, the new score was more precise with respect to predicting both death and survival. Considering the poor survival in the group with 32-35 points, these patients may be candidates for ultra-hypofractionated radiotherapy with 5×5 Gy over 1 week (9). Patients within the 36-44 points group should be considered for moderately hypofractionated radiotherapy, for example with 15×2.66 Gy over 3 weeks (5). In selected patients, the dose may be increased to 52.5 Gy in 15 fractions (6-8). Because of the favorable prognosis of the patients within the 45-48 points group, standard fractionation may be most appropriate (1-4). When selecting an individual treatment regimen, the risk of intracerebral progression should also be considered, which can be estimated with the independent prognostic factors of LC identified in this study. These factors, namely the number of glioblastoma lesions and *MGMT* promoter methylation, were not identified as being associated with LC in one of our previous studies, likely due to the smaller sample size of 91 patients in that study (23). However, when using these prognostic factors and the new survival score developed in this study, one should bear in mind that they are based on retrospective data and require prospective validation.

In conclusion, the new score achieved high accuracy in predicting death within 12 months and survival for at least 12 months in patients receiving multi-modality treatment including standard fractionation RT for glioblastoma. Moreover, the new score was more accurate than our previous model (17). The new survival score can be used to help individualize RT recommendations for patients with glioblastoma.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

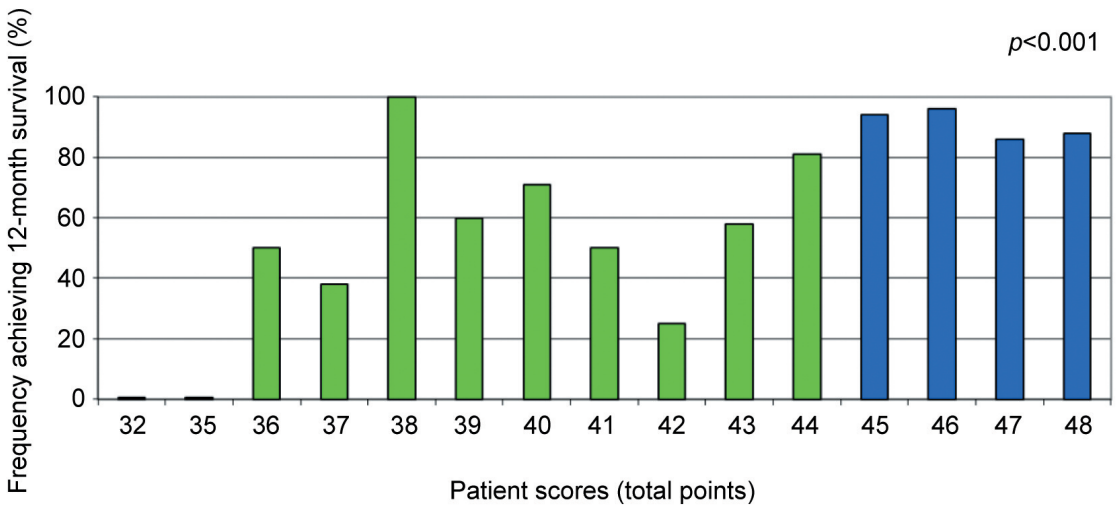

Figure 1. *The 12-month survival rates in relation to individual patient scores ranging between 32 and 48 points. No patient had 33 or 34 points, and only one patient had 38 points.*

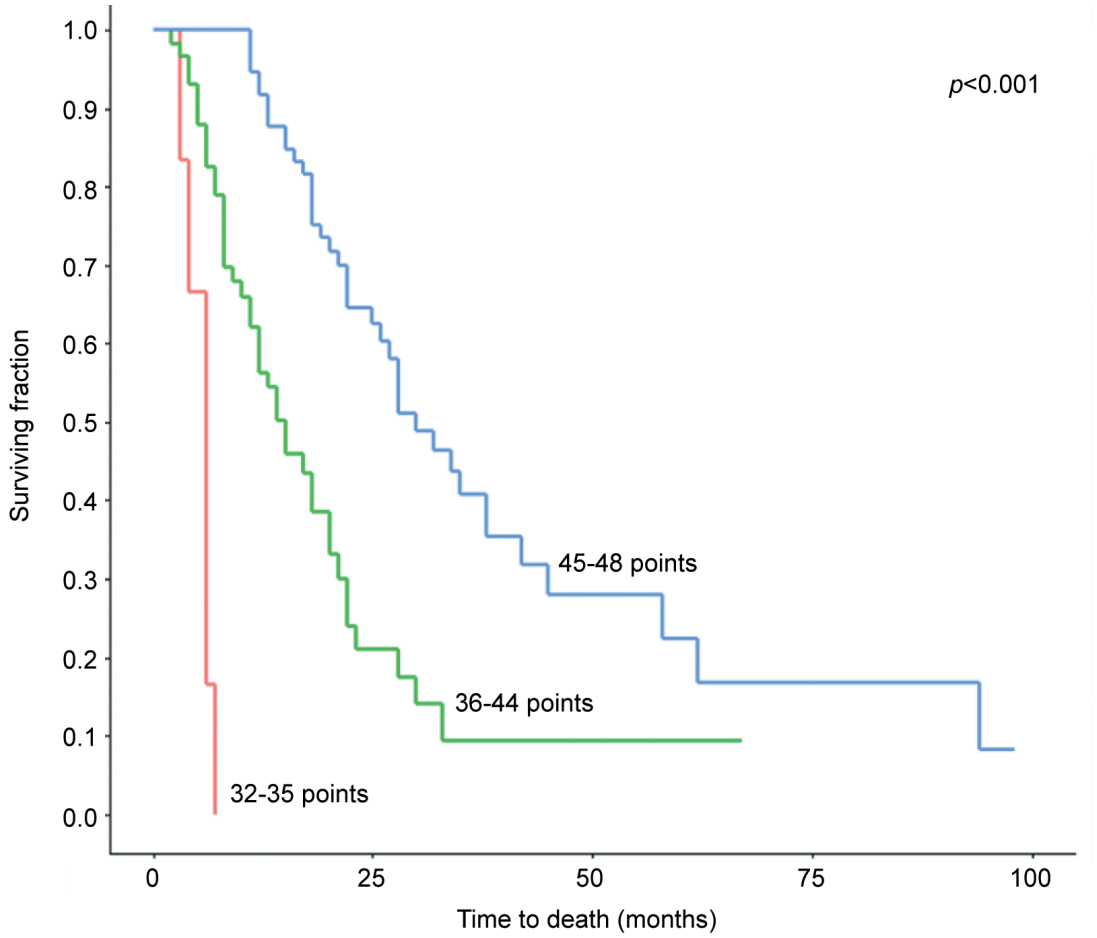

Figure 2. *Kaplan–Meier curves of the prognostic groups with 32-35 points, 36-44 points and 45-48 points (p-value obtained from log-rank test).*

Authors' Contributions

The study was designed by all Authors. Data were collected by O.Z. and D.R., and data analyses were performed by D.R. and N.Y.Y. The article was drafted by N.Y.Y. and D.R., and the final version was approved by all Authors.

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References

1 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO, European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and National Cancer Institute of Canada Clinical Trials Group: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med *352(10)*: 987-996, 2005. PMID: 15758009. DOI: 10.1056/NEJMoa043330

2 Fabian D, Guillermo Prieto Eibl MDP, Alnahhas I, Sebastian N, Giglio P, Puduvalli V, Gonzalez J and Palmer JD: Treatment of glioblastoma (GBM) with the addition of tumor-treating fields (TTF): a review. Cancers (Basel) *11(2)*: 174, 2019. PMID: 30717372. DOI: 10.3390/cancers11020174

3 Barendsen GW: Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys *8(11)*: 1981-1997, 1982. PMID: 6759484. DOI: 10.1016/0360-3016(82)90459-x

4 Joiner MC and Van der Kogel AJ: The linear-quadratic approach to fractionation and calculation of isoeffect relationships. In: Basic Clinical Radiobiology. Steel GG (ed.). New York, NY, USA, Oxford University Press, pp. 106-112, 1997.

5 Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, Fisher B, Fulton D, Gulavita S, Hao C, Husain S, Murtha A, Petruk K, Stewart D, Tai P, Urtasun R, Cairncross JG and Forsyth P: Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol *22(9)*: 1583-1588, 2004. PMID: 15051755. DOI: 10.1200/JCO.2004.06.082

6 Navarria P, Pessina F, Cozzi L, Tomatis S, Reggiori G, Simonelli M, Santoro A, Clerici E, Franzese C, Carta G, Conti Nibali M, Bello L and Scorsetti M: Phase II study of hypofractionated radiation therapy in elderly patients with newly diagnosed glioblastoma with poor prognosis. Tumori *105(1)*: 47-54, 2019. PMID: 30131010. DOI: 10.1177/0300891618792483

7 Perlow HK, Yaney A, Yang M, Klamer B, Matsui J, Raval RR, Blakaj DM, Arnett A, Beyer S, Elder JB, Ammirati M, Lonser R, Hardesty D, Ong S, Giglio P, Pillainayagam C, Goranovich J, Grecula J, Chakravarti A, Gondi V, Brown PD and Palmer JD: Dose-escalated accelerated hypofractionation for elderly or frail patients with a newly diagnosed glioblastoma. J Neurooncol *156(2)*: 399-406, 2022. PMID: 35013838. DOI: 10.1007/s11060-021-03925-1

8 Perlow HK, Prasad RN, Yang M, Klamer B, Matsui J, Marrazzo L, Detti B, Scorsetti M, Clerici E, Arnett A, Beyer S, Ammirati M, Chakravarti A, Raval RR, Brown PD, Navarria P, Scoccianti S, Grecula JC and Palmer JD: Accelerated hypofractionated radiation for elderly or frail patients with a newly diagnosed glioblastoma: A pooled analysis of patient-level data from 4 prospective trials. Cancer *128(12)*: 2367-2374, 2022. PMID: 35315512. DOI: 10.1002/cncr.34192

9 Roa W, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze D, Hentati D, Guedes de Castro D, Dyttus-Cebulok K, Drodge S, Ghosh S, Jeremić B, Rosenblatt E and Fidarova E: International atomic energy agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. J Clin Oncol *33(35)*: 4145-4150, 2015. PMID: 26392096. DOI: 10.1200/JCO.2015.62.6606

10 Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, Fay M, Nishikawa R, Cairncross JG, Roa W, Osoba D, Rossiter JP, Sahgal A, Hirte H, Laigle-Donadey F, Franceschi E, Chinot O, Golfinopoulos V, Fariselli L, Wick A, Feuvret L, Back M, Tills M, Winch C, Baumert BG, Wick W, Ding K, Mason WP and Trial Investigators: Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med *376(11)*: 1027-1037, 2017. PMID: 28296618. DOI: 10.1056/NEJMoa1611977

11 Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO and Krisch RE: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst *85(9)*: 704-710, 1993. PMID: 8478956. DOI: 10.1093/jnci/85.9.704

12 Lamborn KR, Chang SM and Prados MD: Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. Neuro Oncol *6(3)*: 227-235, 2004. PMID: 15279715. DOI: 10.1215/S1152851703000620

13 Mirimanoff RO, Gorlia T, Mason W, Van den Bent MJ, Kortmann RD, Fisher B, Reni M, Brandes AA, Curschmann J, Villa S, Cairncross G, Allgeier A, Lacombe D and Stupp R: Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. J Clin Oncol *24(16)*: 2563-2569, 2006. PMID: 16735709. DOI: 10.1200/JCO.2005.04.5963

14 Gorlia T, van den Bent MJ, Hegi ME, Mirimanoff RO, Weller M, Cairncross JG, Eisenhauer E, Belanger K, Brandes AA, Allgeier A, Lacombe D and Stupp R: Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. Lancet Oncol *9(1)*: 29-38, 2008. PMID: 18082451. DOI: 10.1016/S1470-2045(07)70384-4

15 Scott JG, Bauchet L, Fraum TJ, Nayak L, Cooper AR, Chao ST, Suh JH, Vogelbaum MA, Peereboom DM, Zouaoui S, Mathieu-Daudé H, Fabbro-Peray P, Rigau V, Taillandier L, Abrey LE, DeAngelis LM, Shih JH and Iwamoto FM: Recursive partitioning analysis of prognostic factors for glioblastoma patients aged 70 years or older. Cancer *118(22)*: 5595-5600, 2012. PMID: 22517216. DOI: 10.1002/cncr.27570

16 Straube C, Kessel KA, Antoni S, Gempt J, Meyer B, Schlegel J, Schmidt-Graf F and Combs SE: A balanced score to predict survival of elderly patients newly diagnosed with glioblastoma. Radiat Oncol *15(1)*: 97, 2020. PMID: 32375830. DOI: 10.1186/s13014-020-01549-9

17 Rades D, Witteler J, Schild SE, Trillenberg P, Bonsanto MM and Leppert J: A new survival score for patients receiving radiotherapy for newly diagnosed glioblastoma multiforme. Anticancer Res *41(1)*: 379-384, 2021. PMID: 33419834. DOI: 10.21873/anticanres.14786

18 Hama Y and Tate E: Multiparametric MRI-guided hypofractionated intensity-modulated radiation therapy with simultaneous integrated boost for glioblastoma. Anticancer Res *42(1)*: 329-334, 2022. PMID: 34969741. DOI: 10.21873/anticanres.15489

19 Witteler J, Schild SE and Rades D: Palliative radiotherapy of primary glioblastoma. In Vivo *35(1)*: 483-487, 2021. PMID: 33402500. DOI: 10.21873/invivo.12282

20 Park JH, Lee HS, Choi JW, Lim SD, Koh HK, Cho KR, Cho J, Koh YC and Yoon SY: Clinical benefit of bevacizumab and irinotecan (BEV+IRI) in patients with relapsed/refractory glioblastoma (r/rGBM) and its potential predictors. Anticancer Res *42(12)*: 6091-6098, 2022. PMID: 36456153. DOI: 10.21873/anticanres.16121

21 Rades D, Witteler J, Trillenberg P, Olbrich D, Schild SE, Tvilsted S and Kjaer TW: Increasing seizure activity during radiation treatment for high-grade gliomas – final results of a prospective interventional study. In Vivo *36(5)*: 2308-2313, 2022. PMID: 36099095. DOI: 10.21873/invivo.12961

22 Beige A, Ghiringhelli F, Lecuelle J, Truntzer C, Truc G, Vincent J, Farah W, Borsotti F, Mazilu I and Ilie SM: Efficacy of chemotherapy plus bevacizumab in recurrent glioblastoma multiform: a real-life study. Anticancer Res *42(12)*: 5847-5858, 2022. PMID: 36456149. DOI: 10.21873/anticanres.16093

23 Witteler J, Schild SE and Rades D: Prognostic factors of local control and survival in patients irradiated for glioblastoma multiforme (GBM). Anticancer Res *40(12)*: 7025-7030, 2020. PMID: 33288598. DOI: 10.21873/anticanres.14728

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