Physica Medica 67 (2019) 20–26

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Digital biomarkers: Importance of patient stratification for re-irradiation of glioma patients – Review of latest developments regarding scoring assessment

Kerstin A. Kessel[a,b,c,*], Stephanie E. Combs[a,b,c]

[a] Department of Radiation Oncology, Technical University of Munich (TUM), Ismaninger Straße 22, Munich, Germany
[b] Institute for Radiation Medicine (IRM), Helmholtz Zentrum München, Ingolstädter Landstraße 1, Neuherberg, Germany
[c] Deutsches Konsortium für Translationale Krebsforschung (DKTK), DKTK Partner Site Munich, Germany

ARTICLE INFO

Keywords:
High-grade glioma
Re-irradiation
Score
Patient stratification
Scoring assessment

ABSTRACT

Purpose: To review scoring assessments in re-irradiation of high-grade glioma (HGG) patients and how to use scoring for patient stratification. The next aim was to investigate the different approaches employed by the scoring systems and the way they can be applied to build homogeneous patient groups for a reliable prognosis.
Methods: We searched the Medline/Pubmed and Web of science databases for relevant articles regarding scores for re-irradiation of recurrent HGG. All references were divided into the following groups: novel score establishment (n = 5), score validation (n = 6), not relevant to this evaluation (n = 26).
Results: We identified five scoring systems. Two are modifications of an already existing score. Calculations differ immensely from easy point addition to a more complex formula with including three up to 10 individual parameters. Six validation articles were found for three of the scores; one was validated four times. Two scores were never validated.
Conclusion: For recurrent HGG, the clinical situation remains demanding. Due to the heterogeneity of data at re-irradiation, patient stratification is important. Several scoring systems have been developed to predict prognosis. As a digital biomarker, scores are of high value regarding quick patient assessment and therapy decision making. For the next generation of digital biomarkers, easy calculation, and inclusion of easily available parameters are crucial.

1. Introduction

Scoring systems are used in many oncological areas and serve as prognosis or therapy decision. Recently, scores for prognostic assessment for diagnosis such as brain metastases (recursive partitioning analysis (RPA), graded prognostic assessment GPA) [1,2], prostate [3] or gliomas [4–9] were established. The calculation strategies are very different, ranging from simple calculations with point systems, to nomograms, to complex formulas determined by statistical models. Of course, all of these factors can be used independently, however, complex calculations using models and other tools (such as mobile or web-based apps) can help quickly to calculate nomograms or other "numbers", which correlate well with outcome. Moreover, in a next step, imaging information beyond pure contrast-uptake or T2-lesions can be included, for example, information derived from radiomics of radiogenomics data [10–12]. All these digitally available, measurable values of each patient can be combined, and, again, complex calculations of independent factors can be performed; thus, "digital biomarkers" will be a stratification method of the future making use of independent factors and predicting outcome per patient based on multifactorial models [13].

To date, the use of any prognostic tool is just as different as the dataset they derive from. They serve doctors for treatment-related matters, but may also be used by patients and their relatives to get a personal impression of their health situation. Regarding the latter, in particular, the publication and availability, e.g., on the Internet, must be considered carefully.

Survival or local/distant progression rates include not only diagnosis anymore. The last decades showed for many oncological entities, the statistical impact of prognostic factors. These efforts are particularly advanced in research areas where tumors are highly aggressive, and patient survival is short. Digital biomarkers can influence survival

* Corresponding author at: Department of Radiation Oncology, Klinikum rechts der Isar, Technical University Munich (TUM), Ismaninger Straße 22, 81675 Munich, Germany.
E-mail address: kerstin.kessel@tum.de (K.A. Kessel).

https://doi.org/10.1016/j.ejmp.2019.10.021
Received 4 February 2019; Received in revised form 27 August 2019; Accepted 6 October 2019
Available online 14 October 2019

significantly.

For recurrent high-grade gliomas (HGG) recently scoring systems emerged that predict survival after re-irradiation. For this patient cohort, 6- and 12-months overall survival (OS) is about 73% and 36% [14,15]. To date, no standard therapy is established. There is an ongoing controversy about the real value of re-irradiation, the optimal time frame between first and second irradiation, limitations in tumor size and location, as well as radiation technique applied, and total dose. Generally, HGGs are treatment-resistant tumors; they seldom metastasize, however, recur locally even in areas treated with high-dose radiotherapy or after complex chemotherapy [16,17]. Due to the infiltrative nature of the disease, complete surgical resection is barely impossible, even if postoperative imaging does not show clear tumor remnants. Zones of tumor infiltration remain and require adjuvant radiotherapy, generally performed together with chemotherapy. Recurrent HGG are even more complex to treat since surgery or radiotherapy have been performed in the first place; moreover, size and location play an important role, especially for a second course of radiotherapy. Based on recent developments, in cases of HGG recurrence, many centers use adjuvant radiotherapy after resection in cases where the tumor cannot be removed completely, or in cases when neurosurgery is not possible [18,19]; however recently, re-irradiation has also emerged after complete resection of the recurrent tumor [20], and evidence is currently being generated within a prospective trial [21].

However, only a few published prospective trials exist overall focusing on re-irradiation of HGG, and most reports include only small patient numbers or very heterogeneous cohorts. Hence, clinical outcomes are also heterogeneous, and physicians search for other ways to find the ideal treatment. Especially specifying the medical indication, for which in recurrent cases there is currently no standard treatment, is difficult. Scoring assessment is a helpful tool and can predict prognosis based on given treatment and patient parameters.

Re-irradiation for HGG but also in other entities is subject of controversial debate. It gains more and more relevance in patient care. On the one hand, the techniques become more precise, and on the other hand, we have more experience and learn which concepts regarding dose and volume are of benefit. For recurrent HGG also studies with negative results exist [22], however no detailed radiotherapeutic analysis and stringent quality assurance were performed; moreover, the applied dose is today considered too low for high effectivity in this challenging clinical situation.

For daily clinical practice, therefore, precise patient stratification is an important step to predict which is the best treatment for the patient resulting in the best possible outcome. The parameters such as re-resection, the interval to re-irradiation, Karnofsky index (KI), age are prognostic factors and have been proven by several groups [23–27] (Table 1). With combining them, we built more homogenous groups with a reliable prognosis.

In the present investigation, we want to review scoring assessments in re-irradiation of HGG patients and how these can be used for patient stratification. For that, we performed a literature review on current activities in the field. We further want to discuss their different approaches. We will give an outlook on future developments and what we consider essential for the next generation of prognostic scores.

2. Methods

We searched the Medline/Pubmed and Web of science databases on January 15th, 2019 for relevant articles regarding scores for re-irradiation of recurrent HGG. We limited the search to references published in English language as a full article within the last decade. The search strategy was as follows: “(score [Title] OR scoring [Title] OR scale [Title] OR model [Title]) AND (irradiation [Title] OR radiation [Title] OR re-irradiation [Title] OR reirradiation [Title]) AND (glioblastoma [Title] OR glioma [Title] OR gliomas [Title]) AND (“2008” [Date – Publication]: “2018” [Date – Publication]) NOT animal NOT rat NOT mouse”. The queries in both databases resulted in 37 hits. All references were divided into the following groups: novel score establishment (n = 5), score validation (n = 6), not relevant to this evaluation (n = 26) (Table 2).

3. Results

We identified five scoring systems. Two are extension and modifications of an already existing score.

3.1. Score by Niyazi et al. [8]

Niyazi et al. developed a score using 353 patients. All three factors age, KI, WHO grade, showed significance in the univariate analysis. The model was calculated by a multivariate Cox Model and resulted in the reirradiation risk score (RRRS). The resulting RRRS value determines one of three risk groups. The score was tested and validated by the authors on an independent multicenter cohort with 212 patients and confirmed the significant impact on both overall (OS) and progression-free survival (PFS). A recent validation by Post et al. [36] further confirmed its significance.

3.2. Score calculation

The score is calculated by the formula: RRRS = 0.013 Age + 0.25 $\delta_{WHOgrade=IV}$ − 0.90 $\delta_{KPS\geq 70\%}$.

$\delta_{WHOgrade=IV}$ is 1 if initial primary diagnosis is WHO IV, for all other histologies it is 0. $\delta_{KPS\geq 70\%=1}$ is 1 if KI ≥ 70%, for KI < 70% it is 0. The smaller the RRRS the better the prognosis. The final risk group is shown in Table 3.

3.3. Score by Kessel et al. [7]

The score by Kessel et al. is a modification of the Combs score [4]. Latter was validated four times, twice confirming its significance; twice the score could not be confirmed. It is calculated by the addition of points that are determined for three parameters: WHO grade, age, and the interval between primary radiotherapy and re-irradiation. The latest version of the score by Kessel et al. adds three further factors: KI, tumor volume, and performed re-resection. The calculation results in four risk groups and showed a significant correlation on OS and PFS using a development cohort of 209 patients. A multicenter analysis including 565 patients validated the new scoring system. It confirmed its significant impact on OS and PFS.

3.4. Score calculation

The score is calculated by adding the prognostic values of the six factors, see Table 4. A score from 0 to 7 can be reached, the smaller, the score the better. For the final four risk groups, the score value is grouped, see Table 5.

3.5. Score by Krauze et al. [6]

Krauze et al. developed a scoring system with three sub-scores: Independent factors, target control, anticipated toxicity risk. Each of the ten parameters can have three categories rated with 1–3 points. The addition results in the score that was divided into two or three risk groups. The authors combined both sub-scores independent factors and target control to their most promising score that was significantly correlated with OS and PFS for their cohort of 31 patients. To date, no validation has been performed.

Table 1
Recent publications and the p-values of commonly tested prognostic factors for OS regarding re-irradiation of HGG. (If the factor was analyzed as a grouped variable, the threshold is in brackets).

Publication	Year	Age	Gender	KI	WHO grade	Tumor volume	Time 1. RT – 2. RT	Re-resection	MGMT	IDH	1p19q	Dose
Arvold et al. [28]	2017	0.83	0.22	0.2	–	–	0.38	0.25 (yes vs. no)	0.045*	0.14	0.74	0.27 (total dose)
Azoulay et al. [29]	2017	0.005* (65 y)	–	–	–	–	–	–	0.018*	–	–	–
Bir et al. [30]	2015	0.008* (50 y)	0.54	0.034 (70%)	–	–	–	–	–	–	–	0.143 (≤/ > 14 Gy)
Combs et al. [4]	2012	< 0.001* (50 y)	–	0.250	< 0.001* (Prim. Histo.)	0.84	< 0.001* (12 months)	–	–	–	–	–
Combs et al. [20]	2018	0.11 (50 y)	0.04*	0.08	< 0.001* (Rec. Histo.)	–	0.01 *	0.02* (extend of resection)	< 0.001*	–	–	0.025* (< 36 Gy; 38 to < 40 Gy; > 40 Gy)
Kessel et al. [7]	2017	0.002*	–	< 0.001*	< 0.001* (Prim. Histo.)	0.3 (47ml)	< 0.001* (12 months)	0.013* (yes vs. no)	< 0.001*	–	–	–
Lee et al. [26]	2016	0.498 (40 y)	–	0.03* (70%)	–	–	0.048	0.41 (yes vs. no)	0.719	–	–	0.589 (≤/ > 45 Gy)
Navarria et al. [27]	2018	< 0.001* (53 y)	–	0.004* (< 70%; 70–80%; > 80%)	< 0.01* (Prim. Histo.)	–	0.001* (12 months)	–	0.05 *	0.06 *	0.1	0.04* (BED_{10}: ≤/ > 43 Gy)
Niyazi et al. [8]	2018	< 0.001*	0.47	0.009*	< 0.001* (Prim. Histo.)	< 0.001*	0.94	–	0.036*	–	–	< 0.001*
Palmer et al. [31]	20	< 0.001*	–	0.09* (80%)	0.16 (Prim. Histo.)	0.76	–	0.02* (extend of resection)	–	–	–	–
Scholtyssek et al. [32]	2013	0.015 (50 y)	0.669	0.002 (70%)	0.009* (Prim. Histo.)	–	0.140 (12 months)	0.034* (extend of resection)	–	–	–	–
Schnell et al.	2016	–	0.5	–	< 0.001* (Prim. Histo.)	–	–	–	< 0.001*	< 0.001*	–	–
Shi et al. [33]	2018	0.07°	–	0.53° (80%)	0.46° (Rec. Histo.)	0.83° (50ml)	–	0.17° (yes vs. no)	–	–	–	–
van Linde et al. [34]	2017	0.019°	0.002°	0.124 (ECOG 0-3)	–	–	0.048*° (time 1. RT – rec. diagnosis)	–	–	–	–	–

KI: Karnofsky index; y: years; Prim: Primary; rec.: Recurrence; Histo: histology; MGMT: O-6-methylguanine-DNAmethyltransferase mythelation; IDH: isocitrate dehydrogenase; 1p19p: Chromosome codeletion; BED_{10}: biological effective dose on the tumor; *: significant value; °: Data only available for multivariate analysis.

Table 2
Relevant articles from 2008 to 2018 regarding scores for re-irradiation of recurrent HGG.

	Year	n	Used parameters	Calc.	Risk groups	Val.	Summary
Establishment							
Niyazi et al. [8]	2018	353	3: age, KI, WHO grade	+ + +	3	+	Establishment of a new re-irradiation risk score for HGG patients based on a multivariable Cox model. Validation with a separate cohort (n = 212).
Kessel et al. [7]	2017	209	6: age, WHO grade, interval between RTs, KI, re-resection, tumor size	+ +	4		Modification of the existing Combs score from 2012 [4] by adding three further parameters.
Krauze et al. [6]	2017	31	10: age, KI, WHO grade, presence of symptoms, tumor location, tumor size, presence of diffuse disease, OAR location, OAR dose distribution, disease-free interval	+ + +	2/3		Establishment of an HGG scoring system with multiple parameters resulting in three sub-scores: independent factors, target control, and toxicity risk.
Müller et al. [5]	2015	165	3: age, KI, WHO grade	+	3		Modification of an existing prognostic model for HGG based on recursive partitioning analysis by De Vleeschouwer et al. [35].
Combs et al. [4]	2012	233	3: age, WHO grade, interval between primary RT and re-irradiation	+	3		Establishment of a new re-irradiation score for HGG patients.
Validation							
Post et al. [36]	2018	124				+	Validation of the score by Niyazi et al. [8]
Combs et al. [17]	2018	565				+	Validation of the score by Kessel et al. [7]
Kessel et al. [37]	2017	199				+	Validation of the score by Combs et al. [4]
Müller el al. [38]	2015	165				+	Validation of the score by Combs et al. [4]
Niyazi et al. [39]	2014	88				–	Validation of the score by Combs et al. [4]
Scholtyssek et al. [32]	2013	64				–	Validation of the score by Combs et al. [4]

Val: Validation result, rated + = confirming and – = not confirming the significant impact; Calc.: Calculation complexity rated by the author, + = easy, + + = moderate, + + + = complex; KI: Karnofsky index; RT: Radiotherapy; HGG: High-grade glioma, OAR = Organs at risk.

Table 3
Risk groups for the Score by Niyazi et al. [8].

RRRS value	Risk group
≤ − 0.2	Good
− 0.2–0.5	Intermediate
≥ 0.5	Poor

Table 4
Scoring scheme for the Score by Kessel et al. [7].

Prognostic factor		Prognostic value
Primary histology	WHO IV	2
	WHO III	1
	WHO I/II	0
Age	≥ 50 years	1
	< 50 years	0
Time 1. RT – 2. RT	≤ 12 months	1
	> 12 months	0
Re-resection performed	No	1
	Yes	0
KI	< 80%	1
	≥ 80%	0
Tumor volume	> 47 ml	1
	≤ 47 ml	0

Table 5
Risk groups for the Score by Kessel et al. [7].

Score value	Risk group
0–1	1 (very good)
2–3	2 (good)
4–5	3 (intermediate)
6–7	4 (poor)

3.6. Score calculation

Each of the three sub-scores is calculated by adding the prognostic value of different factors (Table 6). Score 1: Independent factors includes age, KI, WHO grade, presence of symptoms; score 2: target control includes tumor size, tumor location, presence of diffuse disease; and score 3: anticipated toxicity risk includes OAR (organs at risk) location, OAR dose distribution, disease-free interval. On of three risk groups is then build according to the score value, see Table 7. The higher the score, the better. Score 1 and 2 are added as a combined score which can be categorized in one of two risk groups, see Table 7.

3.7. Score by Müller et al. [5]

Müller et al. modified an existing score by De Vleeschouwer et al. [35] and excluded the parameter for mental status. The remaining factors age, WHO grade, KI result in a grouping into three risk groups by using a recursive partitioning analysis (RPA) model. It was developed on a multicenter cohort of 165 patients and also tested with the cohort of the original score. To date, no validation has been performed.

3.8. Score calculation

The score is determined by a decision tree and results in three risk groups. The factors are divided into age < 50 and ≥50, WHO grade III and IV, and KI < 90% and ≥90% or < 70% ≥70%. Table 8 shows the combined values and the resulting three risk groups.

4. Discussion

Several prognostic scores have been developed to predict outcome in recurrent HGG. Of note, the score developed initially as one of the

Table 6
Scoring scheme for the score by Krauze et al. [6].

Prognostic factor		Prognostic value
Age	> 60 years	1
	50–60 years	2
	< 50 years	3
KI	< 50%	1
	50–70%	2
	> 70%	3
WHO grade	IV	1
	III	3
	II	3
Presence of symptoms	Documented neurological symptoms related to recurrence requiring steroid management	1
	Documented neurological symptoms related to recurrence or impending neuro symptoms	2
	No neurological symptoms related to recurrence	3
Tumor size	> 500 ml or diffuse disease/gliomatosis	1
	20–500 ml	2
	< 20 ml	3
Tumor location	< 1 cm away or completely within the original treatment field	1
	1–3 cm away	2
	> 3 cm away	3
Presence of diffuse disease	Multiple T1 gadolinium- enhancing lesions	1
	T2 FLAIR diffuse involvement	2
	None (localized recurrence only)	3
OAR location	> 1 cm away from or in the recurrence area	1
	1–3 cm away from recurrence area	2
	> 3 cm away from the recurrence area	3
OAR dose distribution	< 90% dose allowed as per Quantec dose constraints	1
	Within ± 10% of dose allowed as per Quantec constraints	2
	Exceeds > 10% over the Quantec constraints	3
Disease free interval	< 1 year	1
	1–3 years	2
	> 3 years	3

KI: Karnofsky Index; OAR = Organs at risk.

Table 7
Risk groups for the Score by Krauze et al. [6].

	Score value	Risk group
Score 1	5–6	Poor
	8–10	Intermediate
	11–12	Good
Score 2	< 6	Poor
	6	Intermediate
	> 6	Good
Score 3	< 6	Poor
	6	Intermediate
	> 6	Good
Score 1 + Score 2	≤15	Poor
	> 15	Good

Table 8
Scoring scheme for the Score by Müller et al. [5].

Combined prognostic factors	Risk group
Age < 50 and WHO III and KI ≥ 70	1 (good)
Age < 50 and WHO III and KI < 70	2 (intermediate)
Age < 50 and WHO IV and KI ≥ 90	
Age ≥ 50 and WHO III and KI ≥ 90	
Age < 50 and WHO IV and KI < 90	3 (poor)
Age ≥ 50 and WHO III and KI < 90	
Age ≥ 50 and WHO IV	

KI = Karnofsky index.

first scores remains significant over several validations and improvement stages [4,7], and with its simple approach remains practical for quick patient assessment and decision making.

Generally speaking, one can discuss the value of such scores controversially: While scientifically established prognostic scores are valuable tools to predict outcomes and seem to be of high value, each patient itself may react individually. In that respect, individual indication might also consider other personal factors, such as patients' and family's preference, for any given treatment. However, for discussions in an interdisciplinary tumor board, the results from a validated scoring system can be a helpful tool.

For re-irradiation of HGG, the clinical situation remains demanding. Based on location and tumor volume, the clinical situation varies significantly between patients. This is often due to the intricate anatomy of the central nervous system. Here, small changes in tumor volume or progressive extension into sensitive regions such as brain stem, optic chiasm, or other, complicate re-irradiation due to the limited radiation tolerance of such tissues [40].

Initially, very low doses were applied as re-irradiation with only modest survival [41]. With the advent of stereotactic techniques, treatment of recurrent HGG was improved and generally indicated for unifocal lesions at least six months form primary radiotherapy, with a diameter of maximally 4 cm. Applied doses were generally 36 Gy in 2 Gy single fractions, which can be used safely for most tumors considering a previous radiotherapy of the brain of about 60 Gy [16]. For smaller lesions, radiosurgery was performed; however, the number of patients with such small lesions remain scarce in patients with HGG [42]. Over time, different fractionation and target volume concepts developed; however, most reports only include small patient cohorts and heterogeneous dosing schemes [43]; also invasive approaches with brachytherapy or intraoperative radiotherapy were applied. Real evidence of efficacy remains scarce.

Over time, the combination of extensive surgery and re-irradiation was evaluated, and today even re-irradiation after complete neurosurgical resection is performed and currently evaluated within a prospective trial [20,21].

In general, indications remain on a very individual basis, and the search for helpful tools is still ongoing. Prognostic models and scores are one powerful asset in this context: Input parameters for scores are validated prognostic factors (Table 1), that, taken together and

weighted carefully, may help predict outcome in the sense of a "digital biomarker".

Previously, for recurrent HGG, it was shown that a simple digital biomarker including histology, time between primary radiotherapy and re-irradiation as well as patient age is reliable [4]. Over time, it was improved and sharpened and validated within the largest validation cohort of the German Oncology Consortium (DKTK) [17]. While some centers worked on scores at the same time, the score by Kessel et al. [7] includes easy to assess parameters from clinical care and provides easy handling of patient data. Lately, radiomics analyses were performed in HGG patients investigating digital imaging biomarkers for prognosis [10–12],[44]. In the future, these parameters will further extend the scoring assessment to build decision tools for the individual patient-specific radiation treatment.

5. Conclusion

As a digital biomarker, scores are of high value regarding prognosis and therapy decision. For the next generation of scores, easy calculation, and inclusion of easily available parameters are crucial.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2019.10.021.

References

[1] Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010;77(3):655–61.

[2] Nieder C, Mehta MP. Prognostic indices for brain metastases-usefulness and challenges. Radiat Oncol 2009;4(1):10.

[3] Brockman JA, Alanee S, Vickers AJ, Scardino PT, Wood DP, Kibel AS, et al. Nomogram predicting prostate cancer-specific mortality for men with biochemical recurrence after radical prostatectomy. Eur Urol 2015;67(6):1160–7.

[4] Combs SE, Edler L, Rausch R, Welzel T, Wick W, Debus J. Generation and validation of a prognostic score to predict outcome after re-irradiation of recurrent glioma. Acta Oncol 2013;52(1):147–52.

[5] Muller K, Henke G, Pietschmann S, van Gool S, De Vleeschouwer S, von Bueren AO, et al. Re-irradiation or re-operation followed by dendritic cell vaccination? Comparison of two different salvage strategies for relapsed high-grade gliomas by means of a new prognostic model. J Neurooncol 2015;124(2):325–32.

[6] Krauze AV, Peters C, Cheng J, Ning H, Mackey M, Rowe L, et al. Re-irradiation for recurrent glioma- the NCI experience in tumor control, OAR toxicity and proposal of a novel prognostic scoring system. Radiat Oncol 2017;12(1):191.

[7] Kessel KA, Hesse J, Straube C, Zimmer C, Schmidt-Graf F, Schlegel J, et al. Modification and optimization of an established prognostic score after re-irradiation of recurrent glioma. PLoS ONE 2017;12(7):e0180457.

[8] Niyazi M, Adeberg S, Kaul D, Boulesteix AL, Bougatf N, Fleischmann DF, et al. Independent validation of a new reirradiation risk score (RRRS) for glioma patients predicting post-recurrence survival: a multicenter DKTK/ROG analysis. Radiother Oncol 2018;127(1):121–7.

[9] Park JK, Hodges T, Arko L, Shen M, Dello Iacono D, McNabb A, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol 2010;28(24):3838–43.

[10] Peeken JC, Goldberg T, Pyka T, Bernhofer M, Wiestler B, Kessel KA, et al. Combining multimodal imaging and treatment features improves machine learning-based prognostic assessment in patients with glioblastoma multiforme. Cancer Med 2019;8(1):128–36.

[11] Peeken JC, Molina-Romero M, Diehl C, Menze BH, Straube C, Meyer B, et al. Deep learning derived tumor infiltration maps for personalized target definition in Glioblastoma radiotherapy. Radiother Oncol 2019;138:166–72.

[12] Peeken JC, Nusslin F, Combs SE. "Radio-oncomics": the potential of radiomics in radiation oncology. Strahlenther Onkol 2017;193(10):767–79.

[13] Straube C, Kessel KA, Zimmer C, Schmidt-Graf F, Schlegel J, Gempt J, et al. A second course of radiotherapy in patients with recurrent malignant gliomas: clinical data on re-irradiation, prognostic factors, and usefulness of digital biomarkers. Curr Treat Options Oncol 2019;20(9):71.

[14] Kazmi F, Soon YY, Leong YH, Koh WY, Vellayappan B. Re-irradiation for recurrent glioblastoma (GBM): a systematic review and meta-analysis. J Neurooncol 2019;142(1):79–90.

[15] Weller M, Cloughesy T, Perry JR, Wick W. Standards of care for treatment of recurrent glioblastoma-are we there yet? Neuro Oncol 2013;15(1):4–27.

[16] Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. J Clin Oncol 2005;23(34):8863–9.

[17] Combs SE, Niyazi M, Adeberg S, Bougatf N, Kaul D, Fleischmann DF, et al. Re-irradiation of recurrent gliomas: pooled analysis and validation of an established prognostic score-report of the Radiation Oncology Group (ROG) of the German Cancer Consortium (DKTK). Cancer Med 2018;7(5):1742–9.

[18] Ringel F, Pape H, Sabel M, Krex D, Bock HC, Misch M, et al. Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neuro Oncol 2016;18(1):96–104.

[19] Straube C, Schmidt-Graf F, Wiestler B, Zimmer C, Meyer B, Combs SE. The algorithms of adjuvant therapy in gliomas and their effect on survival. J Neurosurg Sci 2019;63(2):179–86.

[20] Combs SE, Kessel KA, Hesse J, Straube C, Zimmer C, Schmidt-Graf F, et al. Moving second courses of radiotherapy forward: early re-irradiation after surgical resection for recurrent gliomas improves efficacy with excellent tolerability. Neurosurgery 2018;83(6):1241–8.

[21] Straube C, Scherb H, Gempt J, Kirschke J, Zimmer C, Schmidt-Graf F, et al. Adjuvant stereotactic fractionated radiotherapy to the resection cavity in recurrent glioblastoma – the GlioCave study (NOA 17 – ARO 2016/3 – DKTK ROG trial). BMC Cancer 2018;18(1):15.

[22] Wick W, Fricke H, Junge K, Kobyakov G, Martens T, Heese O, et al. A phase II, randomized, study of weekly APG101 + reirradiation versus reirradiation in progressive glioblastoma. Clin Cancer Res 2014;20(24):6304–13.

[23] Minniti G, Scaringi C, De Sanctis V, Lanzetta G, Falco T, Di Stefano D, et al. Hypofractionated stereotactic radiotherapy and continuous low-dose temozolomide in patients with recurrent or progressive malignant gliomas. J Neurooncol 2013;111(2):187–94.

[24] Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001;95(2):190–8.

[25] Fogh SE, Andrews DW, Glass J, Curran W, Glass C, Champ C, et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. J Clin Oncol 2010;28(18):3048–53.

[26] Lee J, Cho J, Chang JH, Suh CO. Re-irradiation for recurrent gliomas: treatment outcomes and prognostic factors. Yonsei Med J 2016;57(4):824–30.

[27] Navarria P, Minniti G, Clerici E, Tomatis S, Pinzi V, Ciammella P, Galaverni M, Amelio D, Scartoni D, Scoccianti S, et al. Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO). J Neurooncol 2019;142(1):59–67.

[28] Arvold ND, Shi DD, Aizer AA, Norden AD, Reardon DA, Lee EQ, et al. Salvage re-irradiation for recurrent high-grade glioma and comparison to bevacizumab alone. J Neurooncol 2017;135(3):581–91.

[29] Azoulay M, Santos F, Shenouda G, Petrecca K, Oweida A, Guiot MC, et al. Benefit of re-operation and salvage therapies for recurrent glioblastoma multiforme: results from a single institution. J Neurooncol 2017;132(3):419–26.

[30] Bir SC, Connor Jr. DE, Ambekar S, Wilden JA, Nanda A. Factors predictive of improved overall survival following stereotactic radiosurgery for recurrent glioblastoma. Neurosurg Rev 2015;38(4):705–13.

[31] Palmer JD, Siglin J, Yamoah K, Dan T, Champ CE, Bar-Ad V, et al. Re-resection for recurrent high-grade glioma in the setting of re-irradiation: more is not always better. J Neurooncol 2015;124(2):215–21.

[32] Scholtyssek F, Zwiener I, Schlamann A, Seidel C, Meixensberger J, Bauer M, et al. Reirradiation in progressive high-grade gliomas: outcome, role of concurrent chemotherapy, prognostic factors and validation of a new prognostic score with an independent patient cohort. Radiat Oncol 2013;8(1):161.

[33] Shi W, Blomain ES, Siglin J, Palmer JD, Dan T, Wang Y, et al. Salvage fractionated stereotactic re-irradiation (FSRT) for patients with recurrent high grade gliomas progressed after bevacizumab treatment. J Neurooncol 2018;137(1):171–7.

[34] van Linde ME, Brahm CG, de Witt Hamer PC, Reijneveld JC, Bruynzeel AME, Vandertop WP, et al. Treatment outcome of patients with recurrent glioblastoma multiforme: a retrospective multicenter analysis. J Neurooncol 2017;135(1):183–92.

[35] De Vleeschouwer S, Ardon H, Van Calenbergh F, Sciot R, Wilms G, van Loon J, et al. Stratification according to HGG-IMMUNO RPA model predicts outcome in a large group of patients with relapsed malignant glioma treated by adjuvant postoperative dendritic cell vaccination. Cancer Immunol Immunother 2012;61(11):2105–12.

[36] Post CCB, Kramer MCA, Smid EJ, van der Weide HL, Kleynen CE, Heesters M, et al. Patterns of re-irradiation for recurrent gliomas and validation of a prognostic score. Radiother Oncol 2019;130:156–63.

[37] Kessel KA, Hesse J, Straube C, Zimmer C, Schmidt-Graf F, Schlegel J, et al. Validation of an established prognostic score after re-irradiation of recurrent glioma. Acta Oncol 2017;56(3):422–6.

[38] Muller K, Henke G, Compter I, von Bueren AO, Friedrich C, Janssens G, et al. External validation of a prognostic model estimating the survival of patients with recurrent high-grade gliomas after reirradiation. Pract Radiat Oncol 2015;5(3):e143–50.

[39] Niyazi M, Flieger M, Ganswindt U, Combs SE, Belka C. Validation of the prognostic

Heidelberg re-irradiation score in an independent mono-institutional patient cohort. Radiat Oncol 2014;9(1):128.
[40] Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21(1):109–22.
[41] Bauman GS, Sneed PK, Wara WM, Stalpers LJ, Chang SM, McDermott MW, et al. Reirradiation of primary CNS tumors. Int J Radiat Oncol Biol Phys 1996;36(2):433–41.
[42] Combs SE, Widmer V, Thilmann C, Hof H, Debus J, Schulz-Ertner D. Stereotactic radiosurgery (SRS): treatment option for recurrent glioblastoma multiforme (GBM). Cancer 2005;104(10):2168–73.
[43] Combs SE, Debus J, Schulz-Ertner D. Radiotherapeutic alternatives for previously irradiated recurrent gliomas. BMC Cancer 2007;7(1):167.
[44] Moller S, Law I, Munck AF, Rosenschold P, Costa J, Poulsen HS, et al. Prognostic value of (18)F-FET PET imaging in re-irradiation of high-grade glioma: Results of a phase I clinical trial. Radiother Oncol 2016;121(1):132–7.