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Original article

Independent validation of a new reirradiation risk score (RRRS) for glioma patients predicting post-recurrence survival: A multicenter DTKT/ROG analysis

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ABSTRACT

Background and purpose: Reirradiation (reRT) is a valid option with considerable efficacy in patients with recurrent high-grade glioma, but it is still not known which patients might be optimal candidates for a second course of irradiation. This study validated a newly developed prognostic score independently in an external patient cohort.

Material and methods: The reRT risk score (RRRS) is based on a linear combination of initial histology, clinical performance status, and age derived from a multivariable model of 353 patients. This score can predict post-recurrence survival (PRS) after reRT. The validation dataset consisted of 212 patients.

Results: The RRRS differentiates three prognostic groups. Discrimination and calibration were maintained in the validation group. Median PRS times in the development cohort for the good/intermediate/poor risk categories were 14.2, 9.1, and 5.3 months, respectively. The respective groups within the validation cohort displayed median PRS times of 13.8, 8.8, and 3.8 months, respectively. Uno's C for development data was 0.64 (CI: 0.60–0.69) and for validation data 0.63 (CI: 0.58–0.68).

Conclusions: The RRRS has been successfully validated in an independent patient cohort. This linear combination of three easily determined clinicopathological factors allows for a reliable classification of patients and may be used as stratification factor for future trials.

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Despite multimodal treatment for high-grade gliomas, the rate of local failure is extraordinarily high depending on several factors, such as the extent of resection, histology, molecular biology, and applied treatment line [1–4]. The treatment for recurrent high-

grade gliomas is a therapeutic challenge for the interdisciplinary team due to the invasive nature of the disease, multiple prior therapies and a frequently observed decline in patients' performance status.

Surgery, reirradiation, and systemic therapy, including either cytotoxic or immunomodulatory approaches, are among the available treatment options versus best supportive care only.

Since solid reproducible phase II–III data on the optimal management of recurrent high-grade glioma are missing, treatment

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decisions are mainly based on the available knowledge on prognostic factors. Known prognostic factors can mathematically be combined in a prognostic index to improve their predictive value. One example of such a prognostic index was published by Park and colleagues who also validated their NIH resurgery index in an independent patient cohort [5]. For reirradiation of high-grade gliomas, no successful external validation of known prognostic indices exists. One index developed by Combs et al. provided inconsistent results when validation was attempted [6]. Two external validations failed [7,8] while a third validation attempt conducted by the same authors was successful [9]. Another attempt led to a simplified version of the score [10]. In a more recent update, the aforementioned score was modified to improve its predictive value. However, the analysis was based on a similar dataset as before and not validated externally [11].

The present study included data from nine German high-volume radiotherapy centers organized within the DTK framework. The three largest centers developed a new multivariable prognostic score, and this score was validated using data from six other centers.

Material and methods

Patient selection

Patients of nine DTK centers were classified into two groups of a development cohort (Berlin, Heidelberg, Munich/LMU) and a validation cohort (Essen, Frankfurt, Dresden, Tübingen, Freiburg, Munich/TU). Data were collected retrospectively. The cohorts consisted of patients initially treated with a course of photon irradiation between 1996 and 2016. The requested initial dose range was 45.0–66.0 Gy, and only adult patients (aged ≥ 18 years) were included. Multiple prior lines of therapy were allowed. All patients were centrally registered within the RadPlanBio platform located in Heidelberg. The largest-volume centers Berlin, Heidelberg, and Munich/LMU, collected their data first and provided a new score based on these data. Likewise, the remaining centers collected their data, which were not made available before the score had been developed.

The ethics committee of each corresponding center approved the study.

Treatment schedule and outcome measure

All patients received reirradiation defined by a focal in-field radiotherapy regularly used as a high-precision fractionated treatment and, in some cases, as radiosurgery.

The primary outcome measure was post-recurrence survival (PRS) defined as survival from the first day of reirradiation to the end of follow-up or death.

Blinding for the validation data could easily be performed as data were centrally registered. The central registry (located in Heidelberg) did not offer any insight into the database, and statistical analysis was performed at another site (Munich/LMU).

Predictors and sample size

Since data over 20 years had to be retrieved, we focused on known and expected potential prognostic variables as well as physical dose only. We did not perform a correction for the biological effective dose since variation of margin concepts and fractionation schedules was considerable.

The following factors were considered for score development: initial WHO grade, age, gender, MGMT methylation status, reRT dose, planning target volume (PTV), time interval between first

and second course of radiotherapy, and clinical performance score (<70 vs ≥ 70).

A predefined sample size calculation was not performed. However, the assignment of the centers to the development and validation datasets, respectively, was done in such a way that the size of the validation dataset equals approximately 2/3 of the size of the development dataset. The cumulative number of patients was 565.

No imputation method was used for the missing data. The exclusion criteria are shown in the CONSORT diagram.

Statistical analysis

Comparison between two groups was performed using the Mann–Whitney-test or Fisher's exact test, and when it was computationally intractable using the chi-square test. Survival times were displayed as Kaplan–Meier curves. The baseline survival function (predicted survival function for a patient with RRRS = 0) was estimated non-parametrically using Efron's estimate as implemented in the R function 'survfit'. Proportional hazards Cox regression was used to assess the effects of prognostic variables on survival based on the Wald test and to derive the score. The proportional hazard assumption was tested based on the Schoenfeld residuals (with the R function 'cox.zph'). The likelihood-ratio (LR) test was used to assess global goodness of fit. Prediction error curves (as implemented in the R package 'pec') were used to represent the prediction error of Cox regression models [12].

For each of the three centers providing the development dataset, univariate Cox regression models were fitted to assess the association between PRS and each of the candidate prognostic variables. Univariate fractional polynomial regression models [13] were fitted to each metric factor to check for potential strong non-linear effects. Models with interactions interval:dose and PTV:dose were fitted to check for potential strong interaction effects. Multivariable Cox regression models including all candidate factors were fitted to each center successively. As an alternative, multivariable Cox regression models were fitted with backward variable selection using the AIC as criterion (as implemented in the R function 'stepAIC'). As sensitivity analyses, the same analyses were repeated for each of the three centers successively while excluding PTV from the set of candidate factors, thus allowing to include the many patients with missing PTV. For each fitted model, the effects of the candidate factors – in particular their signs and significance – were examined and prediction performance of the model was visualized using prediction error curves on the two remaining centers. Finally, for each center backward variable selection was repeated (with and without PTV as candidate factor) on subsamples drawn at random from the original dataset to investigate the stability of model selection as recommended in Sauerbrei et al. [14]. Prognostic factors with effect on PRS close to zero or with effects in opposite directions in the different centers or different analysis strategies were eliminated.

These analyses, combined with practical considerations, allowed to identify a set of prognostic factors that are easy to obtain in clinical practice and have a consistently strong effect on PRS over the three centers and over the different analysis strategies. Finally, a multivariable Cox model was fitted to the selected prognostic factors using the whole development dataset (Berlin, Heidelberg, Munich/LMU). This yielded a score, which was used to define risk groups. The thresholds were chosen by visual inspection of the histogram of the score for the development datasets (which was trimodal, see Results) and preferring round values.

The external validation of the score was conducted as recommended by Royston and Altman, who described a validation pipeline in form of seven steps [15]. The discrepancy between development and validation datasets was assessed by fitting a Cox model to the validation dataset using the score as well as each

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