Quantitative assessment of residual tumor is a strong and independent predictor of survival in methylated glioblastoma following radiochemotherapy with CCNU/TMZ

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Abstract

Background Maximum tumor resection improves overall survival (OS) in patients with glioblastoma. The extent of resection (EOR) is historically dichotomized. The RANO resect group recently proposed criteria for volumetry-based EOR assessment in patients that were treated according to Stupp´s protocol. The purpose of this study was (1) to investigate the prognostic value of EOR in patients receiving combined chemotherapy with lomustine (CCNU)/temozolomide (TMZ), and (2) to analyse the prognostic performance of binary EOR assessment compared to volumetric assessment.

Methods 78 patients with newly diagnosed MGMT-methylated GBM undergoing tumor resection followed by radiochemotherapy with CCNU/TMZ were included in this study. Residual contrast-enhancing (CE) tumor volume after the first resection was measured and its influence on OS and PFS was analysed using uni- and multivariable Cox regression analysis as well as two-sided log rank test. Patients were divided into RTV ≤1 cm^3, >1 cm^3 - ≤5 cm^3 and >5 cm^3 following the proposed criteria of the RANO resect group.

Results Prolonged OS was associated with age <60 years, low RTV, and gross total resection (GTR). Residual tumor volume (RTV) had a superior prognostic value compared to binary EOR assessment. Patients with total or near total resection of CE tumor (≤1 cm^3 RTV) showed prolonged OS (median 54.4 months, 95% CI 46.94-not reached), with a 5-year survival rate of 49%.

Conclusion Low RTV is associated with increased survival in glioblastoma patients undergoing radiochemotherapy with CCNU/TMZ. This study demonstrates the applicability of the recently proposed RANO resect criteria in this subgroup of patients.

Keywords: glioblastoma, MGMT-promotor, residual tumor volume, extend of resection

Keypoints

- Residual CE tumor volume ≤1 cm³ in combination with adjuvant therapy according to the CeTeG protocol in MGMT-methylated GBM conveys prolonged survival with a 5-year survival rate of around 50%
- Volumetric assessment of residual CE tumor has superior prognostic value to binary EOR assessment
- The recently proposed RANO resect criteria are applicable to the subgroup of MGMT-methylated patients undergoing adjuvant treatment with CCNU/TMZ

Importance of the study

Maximum safe tumor resection in GBM patients favors outcome and historically, the assessment of EOR was dichotomized (GTR vs PR). This ensured a better comparibility of GBM patients in clinical trials. However, a dichotomized concept cannot provide precise information on tumor mass reduction. Therefore, the RANO resect group recently proposed new criteria for EOR assessment in GBM patients undergoing adjuvant radiochemotherapy with temozolomide. Measurement of residual tumor volume (RTV) is the basis for these criteria.

The current study provides evidence that assessment of RTV in MGMT-methylated GBM is valuable for survival prognosis and is superior to binary EOR assessment. Patients with few or no CE residual tumor (≤1 cm³) that subsequently undergo radiotherapy + lomustine/temzolomide have prolonged overall survival (Median survival in this subgroup 4.5 years). Apart from that, the study shows that the proposed RANO resect criteria are suitable for the investigated subgroup of GBM patients.

Introduction

Glioblastomas (GBM) are highly malignant central nervous system neoplasms and are the most common malignant primary brain tumors in adults[1]. Therapy is based on maximum safe surgical resection, radiotherapy, and chemotherapy. Nevertheless, it is considered an incurable disease due to its diffusely infiltrating growth pattern and its capability of developing treatment resistance, making it very difficult to treat[2]. There are well-defined factors that correlate with survival, including age, O^6-Methylguanine DNA Methyltransferase (MGMT) promotor methylation status, and general condition of the patient (e.g., according to the Karnofsky Performance Score (KPS))[3].

Since 2005, temozolomide (TMZ) is the standard chemotherapy for GBM patients[4]. In particular, patients with MGMT promotor hypermethylation can expect a survival benefit from TMZ therapy[5]. However, the CeTeG/NOA-09-study[6] showed that these patients, under certain conditions, can also be offered a combined chemotherapy with lomustine (CCNU) and TMZ that can prolong survival without serious additional toxicity[7, 8]. In clinical practice, this treatment is frequently used in German neuro-oncology centers[9, 10].

The initiation of radiochemotherapy requires tissue sampling of the suspected tumor lesion and unequivocal histological evidence of GBM. Whenever possible and safe, complete resection of the visible tumor (contrast-enhancing (CE) and non-enhancing lesions) is aimed for. If successful, this gross total resection (GTR) is widely known to be an important factor for prolonging overall survival (OS) and progression-free survival (PFS) when compared to partial resection (PR) or biopsy only[11]. Various studies have subsequently demonstrated the prognostic benefit of a high extent of resection (EOR), generally including patients treated according to the Stupp protocol[12-14]. The favourable prognostic effect of high EOR is also maintained with a combination of Stupp´s protocol and bevacizumab, as well as with a combination of Stupp´s protocol and vorinostat[15]. However, there are no published data on the importance of EOR in patients undergoing CCNU/TMZ treatment.

For the evaluation of EOR, an early postoperative MRI (conducted about 48 hours after surgery) is recommended[16]. A reliable and standardized cut-off for significant residual tumor volume (RTV) does not exist, previous studies identified cut-offs from 1.5 cm^3 - 8 cm^3 as being relevant[17-19]. A recent report from the RANO resect group[20] was able to demonstrate the high prognostic value of low residual tumor burden in GBM patients following standard radiochemotherapy with TMZ. Notably, they defined a new classification system for EOR, proposing that patients can be stratified into several groups based on RTV and percentual tumor mass reduction. Historically,

and still widely used in clinical practice, the assessment of EOR after tumor resection is binary, defining the two groups of GTR and PR[21-23]. However, a volumetric (three-dimensional) quantitative assessment seems to be more meaningful because it allows a more precise statement on the amount of the residual tumor and therefore conveys an adequate evaluation of residual disease burden that must be addressed by subsequent medical therapies. In addition, investigator-identified EOR remains subjective and is known to be highly variable between institutions and investigators[24]. RTV in GBM patients is usually defined as the volume of persistent CE tumor after cytoreductive surgery, although Karschnia et al. demonstrated an additional prognostic benefit of the resection of non-CE tumor tissue[20].

The purpose of this study was to, for the first time, identify the significance of RTV and EOR for OS and PFS in glioblastoma patients receiving adjuvant radiochemotherapy with CCNU/TMZ. We hypothesized that the amount of persisting CE tumor tissue (referred to in the following as RTV) has a higher prognostic value than the radiological classification of the EOR in GTR or PR.

Methods

Patient selection

A total of 127 patients diagnosed with MGMT-methylated glioblastoma (WHO classification 2021) who underwent surgery and radiochemotherapy and received CCNU/TMZ as first-line chemotherapy were screened for this retrospective study. Patients were recruited from the CCNU/TMZ arm of the modified intention-to-treat (mITT) trial cohort of the CeTeG / NOA-09 trial (n=66, recruited 2011-2014) and from a monocentric off study cohort that received CCNU/TMZ in 2014-2024 (Neurooncology Center Bonn, n=61). Patients with an IDH mutation or an undefined IDH status (n=21) were excluded. Patients who underwent biopsy only were excluded from the analysis (n=15), as the assessment of RTV is not meaningful in these patients. Twelve patients had no or unevaluable postoperative MRI images. To achieve homogenization of the two cohorts, we excluded patients from the off-study cohort that did not fit the inclusion criteria of the CeTeG trial (age 18 - 75 years at the time of diagnosis, KPS ≥70, adequate haematological, hepatic, renal, and coagulation function). Ultimately, 78 patients (43 patients from CeTeG/NOA-09 and 35 patients from the off study cohort) were included in this analysis. A flowchart illustrating patient selection is provided in figure 1.

Within 22-35 days after surgery, all patients initiated standard involved-field radiotherapy (RT) (59.4-60 Gy). At the same time, CCNU/TMZ chemotherapy was started with CCNU 100 mg/m^2 d1, TMZ 100 mg/m^2 d2-6, and repeated for up to 6 six-week courses. TMZ dose was increased up to 200 mg/m^2 if no relevant hematological side effects occurred, as described previously[6].

MRI and progression assessment

Postoperative MRI scans (1.5T or 3T) were obtained 24-72 hours after surgery. The slice thickness of the MRI images was 2-5 mm. The binary assessment of EOR (GTR vs. PR) was performed by an independent and experienced neuroradiologist (at least 3 years of experience in the assessment of brain MRIs in neuro-oncology). PR was defined as evidence of significant residual CE tumor volume in early postoperative MRI. The assessment of RTV was performed by TZ and LB under supervision of DP (>5 years of experience in the assessment of brain MRIs in neuro-oncology). For segmentation and volumetric assessment, the Medical Imaging Interaction Toolkit software (MITK, Workbench and Toolkit 2016.11, provided by the German Cancer Research Center (DKFZ)) was used. Based on a manual outline of the resection cavity and CE tumor, a computer-assisted three-dimensional representation of the contours could be generated. For this purpose, preferably axial pre- and post-contrast T_1- weighted MRI scans were used. Tumor-associated FLAIR/T2 hyperintensities were contoured using the same scheme.

Figure 2 provides an illustration of the RTV assessment. First, the region of interest (1) (*ROI(1)*) was determined on native T_1 scans. For this, the resection cavity, including hyperintense structures, was clearly delineated on the native T1- weighted scans (correlate of the post-surgical MRI changes). Second, the *ROI(2)* was determined by measuring the resection cavity and additionally all parts of hyperintense structures on CE scans (post-surgical MRI changes + any residual tumor). Next, the RTV was calculated using the following formula: RTV= *ROI(2) – ROI(1)*. The postoperative FLAIR volume was calculated using the following formula*: ROI(3)* (equals local FLAIR/T2 hyperintensities) – *ROI(2)*. In addition to volumetric assessment, tumor contact with the subventricular zone (defined as contact of T_1-enhancement lesion to the ventricular-subventricular zone) was assessed.

Following the recommendation of the RANO resect group, patients were grouped into three classes[20]:

1.) RTV ≤1cm³ = "*total resection or near total resection of residual CE tumor*"

2.) RTV >1cm³ - ≤5cm³ = "*subtotal resection of residual CE tumor*"

3.) RTV >5cm³ = "*partial resection of residual CE tumor*"

Of note, deviating from the original RANO resect classification, patients with total resection and near total resection were combined into one group as our assessment method of RTV does not allow to define a group with "zero" residual tumor. Apart from that, reduction of tumor mass in percent and residual non-CE tumor volume, as provided in the RANO resect paper, was not considered as measurement of preoperative CE and non-CE tumor volume was not performed.

Assessment of tumor progression was performed according to the modified response assessment in neuro-oncology (RANO) criteria as described previously[6]. These criteria require that up to 12 weeks after the completion of radiotherapy, disease progression can only be considered for new enhancing lesions outside the radiation field (beyond the 80% isodose) or unequivocal histological demonstration of proliferating tumor. Disease progression 12 to 24 weeks after completion of radiotherapy can only be diagnosed if another MRI showing further progression confirmed it 4–6 weeks afterwards.

Statistical analysis

Statistical analyses were performed using SPSS Version 27 (IBM software) and R (R core team, version 4.2.1). The distribution of characteristics in relation to residual tumor volume was assessed by two-sided Chi-Square test for categorical and Kruskal-Wallis tests for metric variables. The distribution of the factor age was analysed with an ANOVA test. Univariable Cox regression analysis was performed for OS and PFS. Variables associated with survival ($p<0.1$) in the univariable Cox model were considered to be potentially prognostic and were subsequently included in multivariable analyses. Redundant variables were excluded to avoid multicollinearity. Therefore, multivariable Cox regression models including EOR or RTV were constructed separately, and the resulting models were compared using Akaike's information criterion (AIC).

We performed stepwise comparisons of different cut-off values of RTV applying univariable Cox regressions and two-sided log-rank tests. To account for multiple testing, the p-value was adjusted to <0.005 following the Bonferroni method. A plot of the derived p-values is given in figure 4.For all statistical analyses, p-values <0.05 were regarded as statistically significant. In the figures, significant results are marked as *=<0.05, **=<0.005. In selected cases, the p-values are shown within the figure; otherwise, they can be found in the figure legend or manuscript text.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Helsinki Declaration and its later amendments and the Guidelines for Good Clinical Practice. The CeTeG/NOA-09 study was approved by the Ethics committees of all participating centers. Collection of data from the off-study cohort was approved by the Ethics committee Bonn (number 09/22).

Results

Patient cohort and therapy for recurrence

Among the 78 patients included in the study, the median age at the time of initial diagnosis was 59 (range 28-74) years. The sex distribution was approximately 2:1 (55 male patients and 23 female patients). Approximately 80% had a postoperative KPS of 90% or 100%. 51 (65.4%) patients had GTR (following binary radiological assessment). The median RTV was 2.7 cm^3 (IQR 0.96-4.79). Half of the patients had subependymal tumor infiltration, and the median postoperative FLAIR volume was 37.2 cm^3 (IQR 20.9-68.7) (Supplemental table 1).

To verify the absence of selection bias, patients were grouped according to RTV in strata following the RANO resect classification (≤1 cm^3 vs. >1 cm^3 - ≤5 cm^3 vs. >5 cm^3). We hypothesized that the distribution of the aforementioned characteristics is independent of RTV and considered this an important requirement for further analysis of RTV and its influence on OS and PFS. As shown in Table 1, there were no relevant differences in age, sex, KPS, ependymal infiltration, and postoperative FLAIR volume (continuous variable) between the RTV groups (all $p \geq 0.2$).

Therapy for recurrence was performed in 66.6% of patients with total or near total resection, and 55.6% of patients with subtotal or partial resection, respectively (p=0.5). Most frequent salvage therapy was chemotherapy with TMZ. Supplemental table 2 provides more details on salvage therapies. Laser interstitial thermal therapy (LITT) was not used for second-line therapy in this cohort. Therapy with tumor treating fields (TTF) was applied in two patients during first-line therapy and discontinued after first progression.

Prognostic factors for OS and PFS

The median OS in the patient cohort was 38.7 months (27.95- 49.38) with a 12-month OS rate of 85.9% (Supplemental figure 1A). The median PFS was 13.4 months (8.7-18.2), and 52.6% of the patients had a PFS longer than 12 months (Supplemental figure 1B).

In the univariable Cox analysis, younger age (<60 years; p= 0.048), low RTV (p <0.001) and GTR (p= 0.027) were significantly associated with increased OS, while KPS ≥ 90% showed a trend (p=0.063). The other investigated factors, including sex, postoperative FLAIR volume, and ependymal infiltration, showed no significant association with OS (Table 2). Interestingly, none of the above-mentioned factors showed a significant association with increased PFS, although there was a trend for RTV (p=0.051).

Factors that showed an association (p<0.1) with OS were included in subsequent multivariable Cox analyses to identify independent predictors of OS. Due to multicollinearity between the variables as described above, separate multivariable analyses were performed for RTV and EOR, both adjusted for age and KPS. The association between RTV and OS remained highly significant in the multivariable analyses (Table 3.1; p<0.001). EOR also showed a significant association (Table 3.3; p=0.007). The multivariable Cox regression model including RTV was superior to the model including EOR, with an AIC of 347.7 (RTV) and 355.7 (EOR), where lower values indicate a better model performance.

Until recently, reliable and standardized cut-offs for the interpretation of RTV did not exist and previous studies investigating EOR have attempted to define a binary cut-off for RTV as described above[17-19]. However, the RANO resect classification defines more subgroups and stratifies patients into subgroups of total resection (no residual CE tumor), near total resection (≤1cm³), subtotal resection (>1cm³ - ≤5cm³) and partial resection (>5cm³). Applying this RANO resect classification[20], the derived Kaplan-Meier curve illustrates the significant impact of low residual tumor burden on OS (figure 3, log-rank test, p=0.01). While patients with total or near total resection (RTV ≤1cm³) had a median OS of 54.4 months (95% CI 46.9-not reached), patients with subtotal resection (RTV >1cm³-≤5cm³) had a median OS of 33 months (95% CI 19.3-46.7) and patients with partial resection (RTV >5cm³) had a median OS of 29.3 months (95% CI 8-49.4). The 5-year survival rate of patients with RTV ≤1 cm³ was 49%.

We stepwise tested RTV values (1 step = 1 cm³) and compared OS in univariable Cox models and two-sided log-rank tests (Supplemental table 3). As expected, OS showed an inverse association with RTV. While patients with an RTV <1.0 cm³ had a median OS of 54.4 months,

those with an RTV >10 cm³ showed a median OS of 11.9 months. After Bonferroni adjustment for multiple testing, the median OS between groups differed significantly at a cut-off value of 6cm³ and 10 cm³, respectively (HR 0.4 (CI 0.21-0.76), p= 0.004; HR 0.225 (CI 0.009-0.6), p=0.001). However, the difference between p-values (log-rank test) of the associated cut-off values are marginal (figure 4), indicating that it is not useful to define a binary cut-off for survival prediction.

Comparing the influence of postoperative FLAIR volume on survival in dichotomized analysis (above vs. below the median value), results convey an impact on overall survival that does not reach statistical significance (supplemental figure 2, p=0.07, log-rank).

Discussion

Investigating a cohort of MGMT-methylated GBM patients undergoing CCNU/TMZ radiochemotherapy, we showed that (1) low RTV and GTR are associated with longer OS, and especially patients with very low CE tumor burden (RTV ≤1 cm³) achieve a prolonged survival of >5 years in almost 50% of cases. (2) Quantitative volumetric assessment conveys a better OS prediction performance than binary assessment, and (3) the EOR classification criteria recently proposed by the RANO resect group[20] are applicable to the subgroup of MGMT-methylated GBM that undergo combined radiochemotherapy with CCNU/TMZ.

The investigated cohort represents patients that are typically selected for combined chemotherapy with CCNU/TMZ as they are relatively young (Median age 59 years) and in a good clinical condition (median KPS 90%). Patients with IDH mutations or undefined IDH mutation status were excluded from this analysis, which sets this study apart from previous studies. This is important as patients with IDH mutation show a significantly prolonged OS compared to IDH wildtype patients, conveying a potential bias in survival analysis[25, 26]. The postoperative FLAIR volume and the frequency of subependymal tumor infiltration were not significantly different between the groups, although patients with an RTV >5 cm^3 tended to have a larger postoperative FLAIR volume.

Univariable Cox regression analysis revealed that long OS was accompanied by young age, low RTV, and GTR. High KPS tended to be associated with longer OS (p=0.06) which might be explained due to low sample size and consecutively reduced statistic power. However, high KPS is constantly described as a favourable prognostic factor in literature[27-29]. The influence of

ependymal infiltration on survival is controversially discussed[30-32]. Interestingly, none of the mentioned predictors showed a significant association with PFS with only RTV reaching a trend (p=0.051). This is surprising, as the investigated prognostic factors were shown to be strong predictors of PFS in multiple studies (especially younger age[28, 32]) and as PFS and OS generally showed a positive correlation. A possible explanation for the discrepancy between the correlation with OS but not PFS might be the progression assessment according to the modified RANO criteria in this patient group. As recently described, there is evidence that in patients receiving CCNU/TMZ, a remarkably short PFS is seen especially in patients with very long OS, raising the possibility of a relevant amount of undetected pseudoprogressions in this patient group[33].

Multivariable Cox analysis revealed a strong association of RTV and EOR with OS (p<0.001 and p=0.007, respectively). However, in multivariable analysis, radiological EOR was accompanied by a high KPS (radiological EOR p=0.007; KPS p=0.018). For comparing the prediction performance of RTV and EOR, the AIC was calculated for each Cox regression model and revealed better performance of the RTV-based model (RTV: 347.7; EOR 355.7). As suggested, an explanation might be the more precise information on the actual amount of residual tumor which goes in line with previous data from Gabrowski et al[34]. As these results demonstrate the independent prognostic value of quantitative assessment of residual CE tumor compared to binary EOR assessment, a comprehensive transfer to clinical routine would be desirable. While the required personal and timely resources represent a challenge, artificial intelligence-based algorithms might be an approach to overcome this issue[35].

Patients with RTV ≤1 cm³ had a median OS that was 2 years longer than that of patients with RTV >5 cm^3. This reveals a reliable prognostic impact of the EOR classification system that was recently proposed by Karschnia et al. also in GBM patients with MGMT methylation undergoing combined radiochemotherapy with CCNU/TMZ. The analysis of different cut-off values confirms the applicability of this classification system and is therefore more meaningful than identifying a binary RTV cut-off. Rather, surgically achievable further decrease of residual tumor volume without introducing neurological deficits represents an additional survival benefit for the respective patients. Of note, patients with an RTV of ≤1 cm³ had a 5-year survival rate of almost 50%, which is remarkable for a GBM cohort.

Following this, neurosurgeons try to determine if additional resection of non-CE tumor might be even more favourable. This approach is based on the assumption that hyperintense FLAIR volume is often infiltrated with a considerable amount of tumor cells, which might play a role in the development of local tumor recurrence[36]. The concept of supramarginal resection aims at

additionally resecting FLAIR/T2 hyperintensities and therefore achieving an even higher amount of cytoreduction. Several recent studies (including the work of the RANO group and UCSF) showed an additional OS and PFS benefit of supramarginal resection, including the resection of non-CE tumor[20, 37, 38, 39]. In our cohort, the analysis of postoperative FLAIR volume suggests some beneficial impact of lower FLAIR volumes on survival that did not reach statistical significance (supplemental figure 2). However, although the dichotomized analysis reveals a trend for survival benefit, it should be mentioned here that the postoperative FLAIR volume includes residual non-CE tumor, but also perifocal edema and resection-induced local MRI changes (incl. local ischemia or contusion), possibly reducing its prognostic value compared to non-CE tumor volumetry based on both pre- and post-operative assessments. Given the compelling evidence supporting the additional benefit of non-CE tumor resection, prospective studies, including the randomized-controlled ATLAS trial and the SUPRAMAX study, are currently underway[40, 41].

Conclusion

We confirmed dichotomized and volumetric assessments of resection extent and RTV as independent prognostic factors in newly diagnosed MGMT-methylated glioblastoma patients receiving CCNU/TMZ and validated the applicability of the RANO resect EOR classification in this subgroup of patients. Volumetric assessments should be implemented in clinical practice, as they allow for a more precise survival prognosis in glioblastoma, and AI-based methods might support this by reducing the associated time and effort.

Statement and Declarations

Funding

The CeTeG/NOA-09 trial was funded by the German Ministry for Education and Research.

Conflicts of Interest

CSei reports Grants from Seagen and Amgen (provided for a Lab project in brain metastases), Consulting fees from Seagen, honoraria from Seagen, Novocure, Oncovis, Mitteldeutsche Studiengruppe and Zuckschwerdt-Verlag.

DP reports Grants from Bonfor (UNTWIST), Deutsche Forschungsgemeinschaft (DFG) (project number: 445704496) and EKFS (EKES.33), Consulting fees from Guerbet and honoraria from Siemens Healthcare.

EG reports honoraria and support for attending meetings from Astra Zeneca, Novocure and IntraOp.

EH reports honoraria from Ely Lilly.

GT reports the following support for the present manuscript: Adolf-Leuze-Stiftung, Medical Faculty Tübingen, Else Kröner Forschungskolleg 2019_Kolleg_14, DFG Germany´s Excellence Strategy, EXC2180. GT further reports consulting fees from Bayer, Boehringer Ingelheim and Curevac, honoraria from Novocure and Servier, travel grants from Novocure and Servier, participation on an advisory board for Bayer, Boehringer Ingelheim, CureVac, Miltenyi Biomedicine and Novocure. GT further reports fiduciary role in Steering committee ONTRK, Bayer and Steering committee TIGER, Novocure.

JSt reports consulting fees from Glaxo-Smith Kline, Boehringer, Servier, Novocure, Seagen and Roche, and honoraria from Med-Update.

LN reports honoraria for talks from Merck, Novartis GmbH and Alexion and travel grants from CSL Behring.

MG reports consulting fees from Roche, Novartis, Daiichi Sankyo, Novocure, Bayer, Janssen-Cilag, Servier and Oncomagnetix, honoraria from Novartis, Merck, Novocure, Medac and Kyowa Kirin, travel grants from Novocure. MG further reports participation on an advisory board from Zeiss.

NG reports honoraria from Blue Earth Diagnostics for lectures, participation on advisory boards for Telix and the following memberships: Head of the PET/RANO group, Co-Chair Publishing Activity Committee.

PH reports Grants from Deutsche Krebshilfe, DFG, Wilhelm Sander-Stiftung and Bayrisches Zentrum für Krebsforschung, consulting fees from Novocure, Glaxo Smith Kline and Seagen, honoraria from Novocure and Seagen. PH further reports participation on an advisory board for Glaxo Smith Kline and the following memberships: Neuroonkologische Arbeitsgemenschaft in der

deutschen Krebsgesellschaft, Kommission Neuroonkologie in der Deutschen Gesellschaft für Neurologie, Steering Board Brain tumor group of EORTC.

RG reports participation on an advisory board for CAR T-cell study on glioblastoma and the following memberships: President of the German Society of Neurosurgery, Vice president of the German Society of Surgery.

UH reports consulting fees from Medac, Oncomagnetics, Servier and Bayer and honoraria from Medac and Bayer.

All other authors report no conflicts of interest.

Authorship

TZ, CSch, DP and UH designed the analysis. LB, TZ and JW analyzed the data. LB and TZ wrote the first draft of the manuscript. CSch, DP, JW and UH supervised the work. All authors contributed to data acquisition, commented on previous versions and read and approved the final manuscript.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author (TZ) on reasonable request.

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Figure legends

Figure 1 shows the selection of patients according to the given inclusion and exclusion criteria, as described in the main text. Abbreviations: NA: not available; GBM-O: Glioblastoma with oligodendroglial component.

Figure 2 illustrates the volumetric assessment of residual CE tumor. As described in the main text, ROI1 (resection cavity and precontrast hyperintensities) and ROI2 (also including CE residual tumor on postcontrast T_1) were determined. RTV was calculated using the following formula: ROI(2)-ROI(1).

Table 1 shows age, sex, KPS, ependymal infiltration and perifocal edema in the three patient groups according to RTV (group 1: ≤1 cm^3; group 2: >1 - ≤5 cm^3; group 3: >5 cm^3). The p-value of each group comparison is given. [a] ANOVA variance analysis; [b] two- sided Chi- Square- Test; [c] Kruskal- Wallis- Test. Abbreviations: SD standard deviation; n number of patients; KPS Karnowsky performance score; EOR extent of resection, PR partial resection, GTR gross total resection; IQR interquartile range.

Table 2 shows univariable COX analysis of the variables age, sex, KPS, EOR, ependymal infiltration, perifocal edema, and RTV and their correlation with OS and PFS, respectively. Abbreviations: KPS, Karnofsky performance score; EOR, extent of resection; GTR, gross total resection, PR, partial resection; RTV, residual tumor volume.

Table 3. Multivariable COX regression models for overall survival adjusted for age and KPS. Multivariable regression was performed separately for RTV and EOR. Abbreviations: KPS, Karnofsky performance score; EOR, extent of resection; GTR, gross total resection, PR, partial resection; RTV, residual tumor volume.

Figure 3 (A) shows OS in Kaplan- Meier plots with stratification according to RTV as proposed by the RANO resect group. (B) shows median OS in groups and 12-months, as well as 5 year survival rates, respectively. [a]Log-rank test over all three groups.

Figure 4. Association of stepwise defined RTV cut-offs from 1 cm^3 - 10 cm^3 with overall survival. For each cut-off value the significance level (p-value of log-rank test) for dichotomous survival prediction is shown. Red line indicates significance level of p=0.05. All cut-offs, except one (2 cm^2), have a p-value of <0.05, and difference of all p-values is marginal (range 0.001-0.055) indicating that defining of a single binary cut-off for survival prediction is not useful.

Tables

Table 1

variables		RTV (cm^3) ≤ 1.0	RTV (cm^3) >1.0-≤5.0	RTV (cm^3) > 5.0	p- value
patients (n=78)		24	36	18	
Age	<60	11	18	12	0.37[b]
n	≥60	13	18	6	
	Mean (SD)	58.3 (±8.3)	58.7 (±7.8)	54.3 (±10.4)	0.2[a]
Sex	male	14	28	13	0.27[b]
n	female	10	8	5	
KPS	70-80	5	9	3	0.78[b]
n	90-100	19	27	15	
Ependymal infiltration	yes	13	17	11	0.62[b]
	no	11	19	7	
Postoperative FLAIR volume (cm^3)	median (IQR)	24.4 (13.6-68.0)	37.79 (20.9-70.0)	40.86 (30.6-47.0)	0.27[c]

Table 2

	Overall survival		Progression free survival	
Characteristics	Hazard ratio (95% CI)	P- value	Hazard ratio (95% CI)	P- value
Age (years)	**1.04 (1.00-1.07)**	**0.039***	1.02 (0.99- 1.04)	0.184
<60 vs ≥60 (ref)	**0.56 (0.32-0.99)**	**0.048***	0.75 (0.46- 1.21)	0.238
Sex male (ref) vs. female	0.61 (0.32-1.17)	0.139	0.90 (0.53-1.54)	0.699
KPS 90-100 vs 70-80 (ref)	0.53 (0.28- 1.03)	0.063	0.68 (0.38-1.22)	0.199
RTV (cm³)	**1.11 (1.05- 1.18)**	**<0.001****	1.05 (1.00-1.11)	0.051
≤2.5 vs. >2.5 (ref)	**0.557 (0.31-0.99)**	**0.045***	1.015 (0.63- 1.64)	0.953
EOR GTR vs. PR (ref)	**0.52 (0.29- 0.93)**	**0.027***	0.74 (0.45- 1.22)	0.235
Postoperative FLAIR volume (cm³)	1.01 (0.99- 1.01)	0.246	0.99 (0.99- 1.00)	0.438
ependymal infiltration no vs. yes (ref)	0.82 (0.46- 1.45)	0.490	0.95 (0.58- 1.54)	0.824

Table 3

Table 3.1 Multivariable analysis of prognostic factors for overall survival.			
Variable	Hazard Ratio	95% CI	p- value
Age (years) <60 vs. ≥60 (ref)	0.54	0.30- 1.00	0.05
KPS 90-100 vs. 70-80 (ref)	0.61	0.30- 1.21	0.157
RTV (cm^3)	1.13	1.06- 1.21	**< 0.001****

Table 3.2 Multivariable analysis of prognostic factors for overall survival.			
Variable	Hazard Ratio	95% CI	p- value
Age (years) <60vs. ≥60 (ref)	0.60	0.34- 1.06	0.079
KPS 90-100 vs. 70-80 (ref)	0.47	0.26- 0.88	**0.018***
EOR PR (ref) vs. GTR	0.46	0.26- 0.81	**0.007***

Figure 1

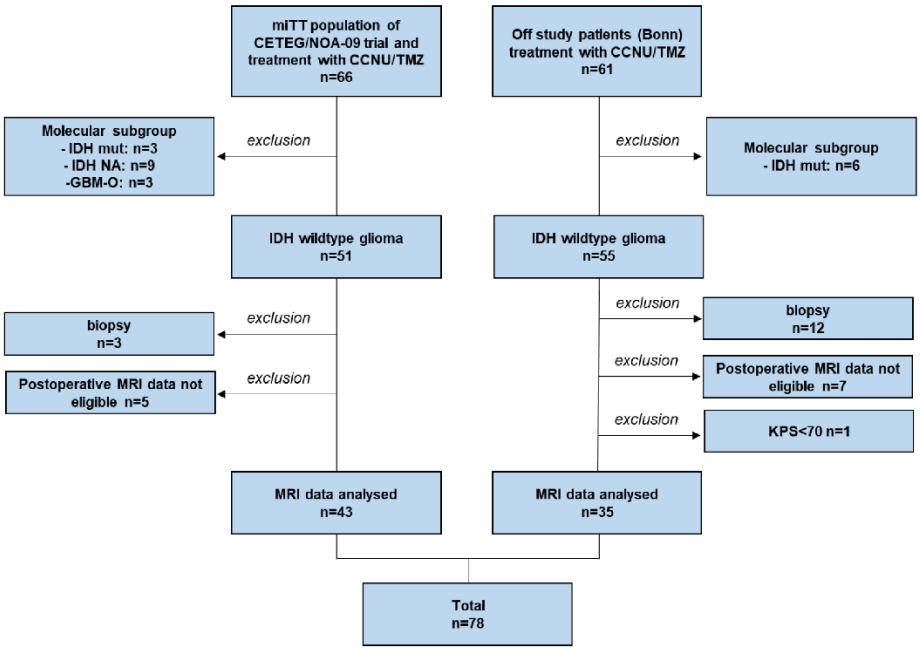

Figure 2

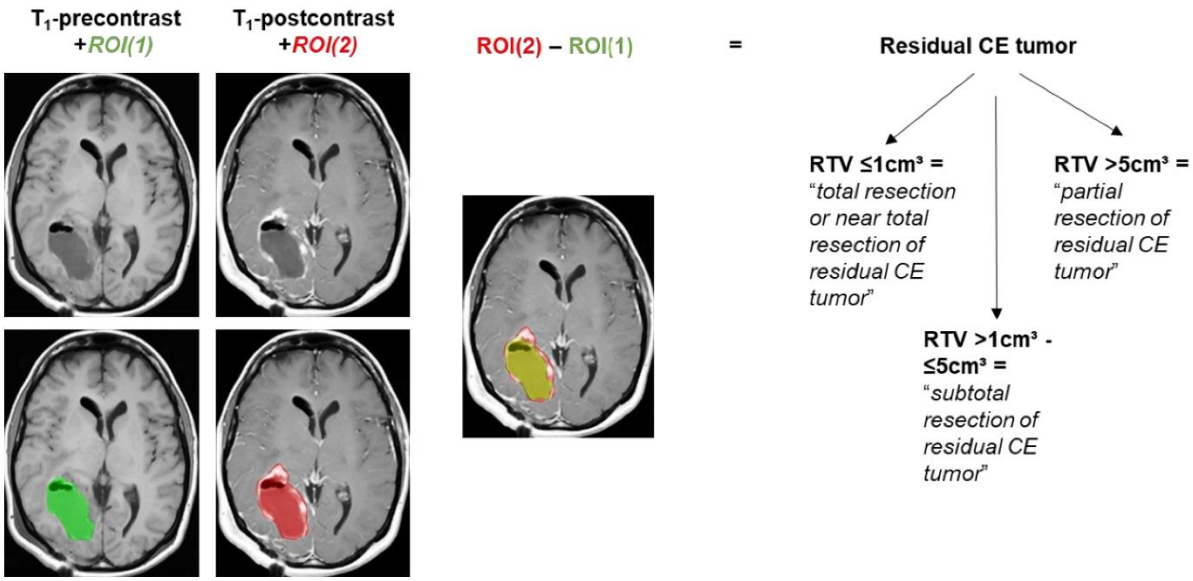

Figure 3

A

	RTV <=1cm³	RTV 1-<=5cm³	RTV >5cm³	P-value (log-rank-test)
Median (months)	54.4	33.0	29.3	0.01*[a]
95%CI	46.9-not reached	19.3-46.7	8-49.4	-
12-months survival rate	96%	89%	78%	-
5-year survival rate	49%	23%	0%	-

B

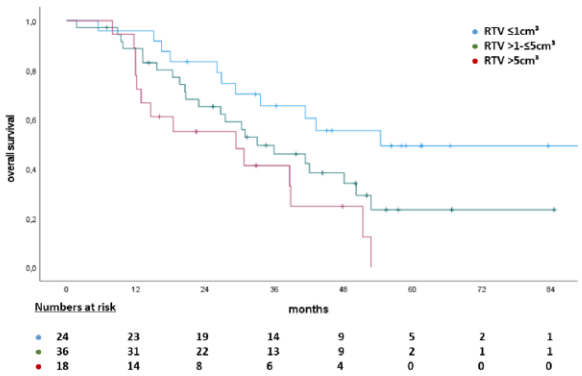

Figure 4