Impact of maximal extent of resection on postoperative deficits, patient functioning and survival within clinically important glioblastoma subgroups

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I confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

I confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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ABSTRACT

Background

The impact of extent of resection (EOR), residual tumor volume (RTV), and gross-total resection (GTR) in glioblastoma subgroups is currently unknown. This study aimed to analyze their impact in patient subgroups in relation to neurological and functional outcomes.

Methods

Patients with tumor resection for eloquent glioblastoma between 2010 and 2020 at four tertiary centers were recruited from a cohort of 3919 patients.

Results

One thousand and forty-seven (1047) patients were included. Higher EOR and lower RTV were significantly associated with improved OS and PFS across all subgroups, but RTV was a stronger prognostic factor. GTR based on RTV improved median OS in the overall cohort (19.0 months, $p<0.0001$), and in the subgroups with *IDH* wildtype tumors (18.5 months, $p=0.00055$), MGMT methylated tumors (35.0 months, $p<0.0001$), aged <70 (20.0 months, $p<0.0001$), NIHSS 0-1 (19.0 months, $p=0.0038$), KPS 90-100 (19.5 months, $p=0.0012$), and KPS $\leq$ 80 (17.0 months, $p=0.036$). GTR was significantly associated with improved OS in the overall cohort (HR 0.58, $p=0.0070$) and improved PFS in the NIHSS 0-1 subgroup (HR 0.47, $p=0.012$). GTR combined with preservation of neurological function (OFO 1 grade) yielded the longest survival times (median OS 22.0 months, $p <0.0001$), which was significantly more frequently achieved in the awake mapping group (50.0%) than in the asleep group (21.8%) ($p<0.0001$).

Conclusions

Maximum resection was especially beneficial in the subgroups aged <70, NIHSS 0-1, and KPS 90-100 without increasing the risk of postoperative NIHSS or KPS worsening. These findings may assist surgical decision making in individual glioblastoma patients.

Keywords

Glioblastoma; Gross-total resection; Extent of Resection; Postoperative deficits; Survival

Key points

- First study to analyze the impact of EOR, RTV and GTR in glioblastoma subgroups
- GTR was especially beneficial in the subgroups aged <70, NIHSS score 0-1 and KPS 90-100
- OFO 1 patients had the longest survival times, awake mapping helped achieving this

Importance of the study

Maximizing extent of resection (EOR) is a major surgical objective in glioblastoma surgery because previous evidence has indicated it as a strong predictor of overall survival. The term "residual tumor volume" has been introduced recently and has been suggested to be a better predictor of survival outcomes than EOR. Moreover, it seems that gross-total resection (GTR) yields the best survival outcomes in glioblastoma patients. However, since the existing evidence focuses on glioblastoma patients in general, it is currently unknown which patient subgroups benefit from such aggressive resection.

This study was the first to analyze the impact of EOR, residual tumor volume (RTV), and GTR in clinically relevant patient subgroups *in conjunction* with markers of surgical safety (neurological deficits and KPS) as cytoreduction can only be considered valuable when the patient's condition has been preserved postoperatively. This study answered the clinical question regarding which individual glioblastoma patient would benefit from aggressive surgery, which might help re-assess preoperative surgical strategies.

INTRODUCTION

Maximizing extent of resection (EOR) is often one of the main goals in glioblastoma surgery. Previous evidence strongly suggests that EOR is a strong predictor of overall survival in glioblastoma patients [1-5] including elderly patients [6-8]. Residual tumor volume has been introduced rather recently to assess volumetric tumor reduction and has been indicated to be a better predictor of survival outcomes than EOR [9,10]. Moreover, it seems that gross-total resection (GTR) of the contrast-enhancing (CE) and non-contrast-enhancing (NCE) part of the tumor yields the best survival outcomes in glioblastoma patients [10], although there is currently no consensus on the exact volumetric or percent-based threshold for assessing GTR [11]. The current evidence forms a solid foundation but a few important questions remain to be addressed adequately.

First, the association of extent of resection and residual volume has been evaluated previously in glioblastoma patients in general [1-5], in elderly patients [6-8], and in molecular subgroups (*IDH* mutation status, MGMT methylation status) [10]. However, there are currently no data available regarding the impact of EOR, GTR and residual tumor volume in clinically relevant patient subgroups based on for example preoperative neurological status or KPS which hampers objective assessment of surgical strategies. Second, studies have been focusing on the impact of these cytoreductive measures in glioblastoma patients with both eloquent and non-eloquent located tumors. Though, pursuing GTR in eloquent glioblastomas makes the patient often more susceptible to postoperative neurological deficits and functional worsening, which means that the surgeon has to balance between aggressive cytoreduction and surgical safety. This implies that tumor resection for eloquent glioblastoma differs significantly from the resection of non-eloquent tumors. Consequently, investigating the impact of EOR, residual tumor volume (RTV), and GTR in eloquent glioblastomas specifically is much needed. Third, the impact of these measures should not be evaluated by survival outcomes alone but in conjunction with markers of surgical safety, for example neurological deficits and KPS to adequately address the surgical objectives. Indeed, in glioblastoma patients, cytoreduction can only be considered valuable when the patient has not deteriorated significantly postoperatively.

With due consideration of the aforementioned scientific hiatuses, we aimed to analyze the impact of EOR, RTV and GTR on postoperative neurological deficits, postoperative KPS worsening, receipt of adjuvant therapy, overall survival and progression-free survival. All analyses were performed in subgroups of a multicenter cohort of primary, eloquently located glioblastoma patients based on age, preoperative neurological functioning and preoperative KPS. The results of this study will serve as useful objective data for potential re-assessment of surgical strategies.

METHODS

Study design and participants

The presented study was done using an international cohort of patients admitted to four tertiary neurosurgical care institutes in the Netherlands (Erasmus MC, Rotterdam and Haaglanden MC, The Hague), Belgium (UZ Leuven, Leuven) and the USA (Brigham and Women's Hospital, Boston, MA; GLIOMAP). It was approved by the ethical committee of all institutes and adhered to the Strengthening the Reporting of Observational studies in Epidemiology (known as STROBE) reporting guidelines. Patients were eligible if they were aged 18-90 years, had undergone resection, had a histopathological diagnosis of primary glioblastoma, their tumour was in an eloquent or near-eloquent location, and they had a unifocal lesion. Exclusion criteria were multifocal or midline tumour location, grade II or III gliomas with malignant transformation, recurrent glioblastomas, and incompleteness of clinical data. We only included patients with tumors in eloquent or near-eloquent locations to compare the awake and asleep technique in the appropriate setting. Whether or not the tumour was in an eloquent location was determined based on preoperative MRI images using the Brodmann areas for the eloquent areas of motor function (areas 4, 6, and 8), sensory function (areas 1, 2 and 3), language function (areas 22, 39, 40, 44, and 45) and visual function (areas 17, 18, and 19). Due to the retrospective nature of this study, written informed consent was not required from patients.

Procedures

The surgical procedures regarding awake and asleep tumour resection are described in the appendix (pp 2-3). Data were collected in the context of the GLIOMAP study [27] and included patient demographics, preoperative functioning (KPS, NIHSS), comorbidities (ASA), tumor-related factors (location by lobe, hemisphere, and eloquence), molecular factors (IDH status, MGMT status), surgical factors (intraoperative ultrasound, intraoperative fluorescence), vascular complications, adjuvant therapy, postoperative functioning (KPS and NIHSS at 6 weeks, 3 months, and 6 months), volumetric tumor data and survival data. Surgical procedures were done by neurosurgeons at each site, as per local practice. After surgery, patients were transferred to the post-anesthesia care unit, where each patient was hemodynamically and neurologically monitored for 24 h. A postoperative MRI scan was performed within 72 h after the operation to assess residual tumour volume and extent of resection. Tumor volumes were assessed both preoperatively (within 24 h before resection) and postoperatively (within 72 h after resection) with volumetric measurements on T1-weighted post-gadolinium images based on the contrast-enhancing part of the tumor, which was certified by the radiology departments at each site. Postoperative T1-weighted post-gadolinium MRIs were compared with diffusion-weighted

imaging sequences to exclude induced oedema or ischemia in the tumor volumetrics. Patients were followed up at their respective neurosurgical outpatient clinics at 1 week and 6–8 weeks after the operation and with 2–6 month intervals at the neuro-oncological outpatient clinic, with neurological examination and an MRI. Neurolinguistic follow-up was done at 3 months postoperatively, consisting of Dutch Linguistic Intraoperative Protocol (DuLIP) subset tests, shortened Token Test, verbal fluency, Comprehensive Aphasia Test, and the Montreal Cognitive Assessment.

Outcomes

The effects of extent of resection, residual tumor volume, and a wide range of other factors were assessed for their effect on five outcomes: postoperative neurological deficits (according to NIHSS score; loss of at least 1 point), postoperative KPS (loss of at least 10 points), receipt of adjuvant chemotherapy and radiotherapy, overall survival, and progression free survival. Extent of resection was calculated as ([preoperative tumor volume – postoperative tumor volume]/preoperative tumor volume) × 100%. Gross-total resection was defined as either 98-100% extent of resection, or 0.0-0.2 ml of residual tumor volume. Moreover, we analyzed the combined effect of gross-total resection based on residual volume with preservation or improvement of postoperative NIHSS (with preoperative NIHSS as reference) at both 6 weeks and 6 months. We refer to this merged outcome as the "onco-functional outcome (OFO)" which we have described more elaborately in another publication [11]. In general, OFO 1 applies to patients in which GTR are achieved, and postoperative neurological functioning is preserved or improved. OFO 2 and OFO 3 apply to patient subgroups in which one of these two goals is not achieved. OFO 2 applies to patients in which neurological functioning is preserved, but GTR is not reached, whereas OFO 3 applies to patients in which GTR is reached, but postoperative neurological deficits have occurred (1 point or more increase in NIHSS). The OFO classification can be used at 6 weeks or 6 months postoperatively.

Patients were followed-up from date of tumor resection until death, last follow-up, or October, 2021 (end of data collection, 1 year after the last patient was enrolled), whichever occurred first. Overall survival was defined as the time from date of tumor resection until death, and progression free survival was defined as the time from date of tumor resection until radiological recurrence of the tumor on T1-weighted post-gadolinium MRI.

Statistical analysis

Based on our original pre-designed study [27], patients in the awake craniotomy group from the overall (unmatched) cohort were matched (1:3) with patients from the asleep resection group (using the *matchit* package in *R* – ie, nearest neighbour propensity-score matching) on the basis of various factors, which were sex (male *vs* female), age (continuous), preoperative KPS (continuous),

preoperative NIHSS score (continuous), preoperative tumor volume (continuous), tumor location by lobe (frontal *vs* parietal *vs* temporal *vs* occipital *vs* insula), tumor location by hemisphere (right *vs* left), intraoperative fluorescence (yes *vs* no), year of surgery (continuous), study center (Rotterdam *vs* The Hague *vs* Leuven *vs* Boston, MA), and adjuvant therapy with chemotherapy and radiotherapy (yes *vs* no). Furthermore, to mimic a stratified randomization design, the original unmatched cohort was divided into six subgroups according to age (<70 *vs* ≥ 70 years), preoperative NIHSS score (0-1 *vs* ≥ 2), and preoperative KPS (90-100 vs. ≤ 80), and within these subgroups, patients in the awake craniotomy group were matched (1:3) with patients from the asleep resection group based on the aforementioned variables. These six subgroups were formed in our original study to translate clinically relevant subgroups of patients into a scientific setting as realistically as possible. Matching ratios for the overall cohort and subgroups were based on the number of patients included in the cohort and overall covariate balance based on the weighted standardized difference.

In descriptive analyses of awake craniotomy versus asleep resection, we assessed the outcomes using the following timepoints and definitions: NIHSS deterioration at 6 weeks, 3 months, and 6 months postoperatively; KPS deterioration at 6 weeks, 3 months, and 6 months postoperatively; extent of resection at less than 72 h postoperatively; residual tumor volume at less than 72 h postoperatively; OFO grade at 6 weeks postoperatively, OFO grade at 6 months postoperatively; median overall survival based on 6-week OFO grade; median overall survival based on 6-month OFO grade; median overall survival; and median progression-free survival. Receipt of adjuvant therapy was not assessed as an outcome for the descriptive analysis but was included in the Cox proportional-hazards regression because it was a variable in the propensity-score matching. We summarized demographic cohort data using standard descriptive statistics. To test for differences between the unmatched and matched cohorts for categorical variables, we used Pearson's χ^2 test. For continuous variables with two variables, we used the two tailed Student's *t* test for independent groups. For continuous variables with more than two groups, we used the one-way ANOVA test.

In the original matched cohort and matched subgroups, Kaplan-Meier survival curves were plotted for different strata of residual tumor volume or extent of resection for overall survival (OS) and progression-free survival (PFS) (*survival*, *survminer*, *dplyr and ggplot2* packages in *R*). We stratified Kaplan Meier curves for the overall matched cohort for *IDH* mutation status and MGMT methylation status. Furthermore, Kaplan-Meier curves were plotted for stratified groups based on OFO grading scale at 6 weeks and 6 months postoperatively and surgical modality (awake or asleep). Statistical significance between the survival times of different groups and subgroups was tested with the log-rank test.

In the original unmatched cohort and unmatched subgroups, we used Cox proportional-hazard regressions (hazard ratios [HRs]) to analyze the association between extent of resection and residual tumor volume (independent variables *X*) on overall survival and progression-free survival. Because including *IDH* mutation and MGMT methylation status in the matching procedure proved to be unstable as a result of missing data, we added these covariates to the Cox proportional-hazards regression model to function as covariates. For this regression analysis, we adjusted for the following potential confounders (with the exception when the factor was the outcome itself in each respective model): study center (Rotterdam *vs* The Hague *vs* Leuven *vs* Boston, MA), year of surgery (2010–15 *vs* 2016–20), sex (male *vs* female), age at diagnosis (continuous), preoperative KPS (90–100 *vs* ≤80), preoperative American Society of Anesthesiology score (score of 1 *vs* 2 *vs* 3 *vs* 4), preoperative NIHSS score (0–1 *vs* ≥ 2), tumor location by lobe (frontal *vs* parietal *vs* temporal *vs* occipital *vs* insula), tumor location by hemisphere (right *vs* left), tumor location by eloquence (motor *vs* sensory *vs* language *vs* visual), *IDH* mutation status (wildtype *vs* mutant), MGMT methylation status (methylated *vs* unmethylated), awake craniotomy (yes *vs* no), intraoperative ultrasound (yes *vs* no), intraoperative fluorescence (yes *vs* no), 6-week NIHSS deterioration (yes *vs* no), 6-week KPS deterioration (yes *vs* no), adjuvant therapy with chemotherapy and radiotherapy (yes *vs* no), postoperative vascular complications (nominal), preoperative contrast enhancing tumor volume (ordinal), postoperative contrast-enhancing tumor volume (ordinal), and extent of resection (ordinal).

RESULTS

Patients with glioblastoma surgery between 1 January 2010 and 31 October 2020 were screened for eligibility (n = 3919) **(Figure 1)**, and 1047 patients with resections for primary glioblastoma resections in eloquent areas were enrolled **(Figure 1).** Patient characteristics of the four institutional cohorts (Erasmus MC, n = 382; Haaglanden MC, n = 354; UZ Leuven, n = 111, Brigham and Women's Hospital: n = 200) (**eTable 1, appendix, pp 4-6**). Before matching, the patients in the awake group of the overall unmatched cohort (n=1047) differed significantly from patients in the asleep group for multiple perioperative factors (**Table 1**). After 1:3 matching these two groups were comparable (awake: n= 134; asleep: n= 402). Furthermore, patients in the awake and asleep groups were comparable within all matched subgroups in terms of demographic, patient-related and tumor-related factors (**eTables 2-4, appendix, pp 7-18**).

Association of extent of resection and residual tumor volume with OS and PFS

Overall survival significantly differed between residual volume strata for the overall cohort ($p < 0.0001$), *IDH* wildtype tumors ($p = 0.00055$), MGMT methylated tumors ($p < 0.0001$), <70 aged subgroup ($p < 0.0001$), NIHSS 0-1 subgroup ($p = 0.0038$), NIHSS ≥ 2 subgroup ($p = 0.0033$), KPS 90-

100 subgroup (p = 0.0012) and KPS ≤ 80 subgroup (p = 0.036) (**Figure 2; eTables 7-8, appendix, pp 23-24**).

Furthermore, overall survival was significantly longer for increasing amounts of extent of resection in the overall cohort (p = 0.00071), MGMT methylated tumors (p < 0.0001), <70 aged subgroup (p = 0.001), NIHSS 0-1 subgroup (p = 0.0020), and KPS 90-100 subgroup (p=0.0041) (e**Figure 1, appendix, pp 25-26; eTables 7-8, appendix, pp 23-24**). Progression-free survival also differed significantly between residual volume strata for the overall cohort (p = 0.0029), *IDH* wildtype tumors (p = 0.003), MGMT methylated tumors (p = 0.0011), <70 aged subgroup (p = 0.0030), NIHSS 0-1 subgroup (p = 0.037), and KPS 90-100 subgroup (p = 0.037) (**Figure 2; eTables 7-8, appendix, pp 23-24**). Furthermore, progression-free survival significantly differed between EOR strata for MGMT methylated tumors (p = 0.026) (**eFigure 2, appendix, pp 27-28; eTables 7-8, appendix, pp 23-24**).

Extent of resection versus residual volume

We observed a clearer threshold for residual volume than for EOR regarding their association with survival outcomes. OS in the overall cohort was longer in the 0.0-0.2 ml subgroup (median 19.0 months [95% CI 17.0-27.5]) than in the 0.2-1.0 ml subgroup (median 18.0 months [95% CI 14.0-21.5]) and the 1.0-2.0 ml subgroup (median 16.0 months [95% CI 12.0-22.0]), which in turn were longer than in the >2 ml subgroup (median 12.5 months [95% CI 12.0-14.5]) (**eTables 7-8, appendix, pp 23-24**). Thus, there was a significant difference in survival times for gross-total resection (maximum 0.2 ml residual volume), >2.0 ml residual volume and the "in-between" group of 0.2-2.0 ml (p < 0.0001). The same pattern could be observed within the overall cohort stratified by MGMT methylation status (MGMT methylated: p < 0.0001), stratified by *IDH* mutation status (*IDH* wildtype: p = 0.00055), and across the subgroups aged <70 (p < 0.0001), NIHSS 0-1 (p = 0.0038), NIHSS ≥ 2 (p = 0.0033), KPS 90-100 (p = 0.0012), and KPS ≤ 80 (p = 0.036) (**eTables 7-8, appendix, pp 23-24**). The association between EOR and OS was similar but less pronounced: there was no significant relationship in the overall cohort stratified by *IDH* mutation status (*IDH* wildtype: p = 0.088) and in the subgroups NIHSS ≥ 2 (p = 0.13) and KPS ≤ 80 (p = 0.20). Residual volume nor EOR were significantly associated with longer OS outcomes in the subgroup aged ≥ 70 (residual volume: p = 0.28; EOR: p = 0.29) (**eTables 7-8, appendix, pp 23-24**).

The association between residual tumor volume and PFS was also stronger than the association between EOR and PFS. Lower amounts of residual tumor volume led to improved PFS in the overall cohort (p = 0.0029), stratified by MGMT methylation status (MGMT methylated: p = 0.011), stratified by *IDH* mutation status (*IDH* wildtype: p = 0.0030), and in the subgroups aged <70 (p = 0.0030),

NIHSS 0-1 (p = 0.037), and KPS 90-100 (p = 0.037). In contrast, a higher extent of resection was only significantly associated with improved PFS in the overall cohort stratified by MGMT methylation status (MGMT methylated: p = 0.026). Residual volume nor EOR led to improved PFS in the subgroups aged ≥ 70, NIHSS ≥ 2, and and KPS ≤ 80 (**eTables 7-8, appendix, pp 23-24**).

Association of gross-total resection with OS and PFS

Gross-total resection based on residual tumor volume (0.0-0.2 ml) proved to yield superior outcomes in overall survival for the overall matched cohort (median 19.0 months [95% CI 17.0-27.5], p < 0.0001), *IDH* wildtype tumors (median 18.5 months [95% CI 17.0-27.5], p = 0.00055), MGMT methylated tumors (median 35.0 months [95% CI 30.0-NA], p < 0.0001), subgroup aged <70 (median 20.0 months [95% CI 18.0-31.0], p < 0.0001), NIHSS 0-1 subgroup (median 19.0 months [95% CI 17.0-30.5], p = 0.0038), NIHSS ≥ 2 subgroup (median 17.0 months [95% CI 15.5-31.0], p = 0.0033), KPS 90-100 subgroup (median 19.5 months [95% CI 17.0-29.5], p = 0.0012), and the KPS ≤ 80 subgroup (median 17.0 months [95% CI 13.5-36.0], p = 0.036) (**eTables 7-8, appendix, pp 23-24**).

Gross-total resection based on residual tumor volume significantly improved progression-free survival in the overall cohort (median 9.5 months [95% CI 8.0-11.0], p=0.0029), *IDH* wildtype tumors (median 9.0 months [95% CI 8.5-11.0], p = 0.0030), MGMT methylated tumors (median 13.0 months [95% CI 7.0-28.0], p = 0.011), subgroup aged <70 (median 10.0 months [95% CI 8.8-12.0], p = 0.0030), NIHSS 0-1 subgroup (median 10.0 months [95% CI 8.0-12.0], p = 0.037), and KPS 90-100 subgroup (median 10.5 months [95% CI 9.0-12.0], p = 0.037) (**eTables 7-8, appendix, pp 23-24**).

Regression analyses: survival outcomes

Gross-total resection based on residual tumor volume (0.0-0.2 ml) was significantly predictive for superior overall survival outcomes in the overall cohort (HR 0.58 [95% CI 0.39-0.86], p = 0.0070; and for progression-free survival in the NIHSS 0-1 subgroup (HR 0.47 [95% CI 0.26-0.85], p = 0.012). Gross-total resection based on extent of resection was in none of the subgroups nor in the overall cohort an independent predictor for overall survival or progression-free survival **(eTables 5-6, appendix, pp 19-22**).

Other important prognostic factors for overall survival were [1] age (overall cohort: HR 1.01 [95% CI 1.01-1.02], p = 0.0010; also significant in the subgroups aged <70 (p = 0.0060), NIHSS 0-1 (p = 0.0040), KPS 90-100 (p = 0.010), and KPS ≤ 80 (p = 0.040), [2] preoperative NIHSS score of 0-1 (overall cohort: HR 0.78 [95% CI 0.64-0.95], p = 0.014), [3] preoperative KPS score of 90-100 (overall cohort: HR 0.82 [95% CI 0.67-0.99], p = 0.044; also significant in the subgroups aged <70 (p

= 0.0060), and NIHSS ≥ 2 (p = 0.049), [3] 6-week NIHSS deterioration (overall cohort: HR 1.41 [95% CI 1.15-1.72], p = 0.0010; also significant in the subgroups aged <70 (p < 0.0001), NIHSS 0-1 (p = 0.028), NIHSS ≥ 2 (p = 0.044), and KPS ≤ 80 (p = 0.0010), [4] 6-week KPS deterioration (overall cohort: HR 1.71 [95% CI 1.41-2.07], p < 0.0001; also significant in the subgroups aged <70 (p < 0.0001), NIHSS 0-1 (p < 0.0001), NIHSS ≥ 2 (p < 0.0001), KPS 90-100 (p= 0.0010), and KPS ≤ 80 (p < 0.0001), [5] adjuvant therapy with chemotherapy and radiotherapy (overall cohort: HR 0.35 [95% CI 0.27-0.46], p < 0.0001; also significant in the subgroups aged <70 (p < 0.0001), aged ≥ 70 (p = 0.0040), NIHSS 0-1 (p < 0.0001), NIHSS ≥ 2 (p < 0.0001), KPS 90-100 (p < 0.0001), and KPS ≤ 80 (p < 0.0001), [6] *IDH* wildtype (overall cohort: HR 3.92 [95% CI 1.73-8.87], p = 0.0011; also significant in the subgroups aged <70 (p = 0.0010), NIHSS 0-1 (p = 0.0060), and KPS 90-100 (p = 0.0050); not enough data for the other subgroups), [7] use of intraoperative fluorescence (overall cohort: HR 1.53 [95% CI 1.04-2.27], p=0.033; also significant for the subgroup NIHSS ≥ 2 (p = 0.029) and KPS ≤ 80 (p = 0.0030), [8] awake craniotomy (overall cohort: HR 0.88 [95% CI 0.66-1.18], p = 0.39; but significant for the subgroup <70 (p = 0.0038) and KPS 90-100 (p = 0.016), [9] preoperative tumor volume of >100 ml (overall cohort: HR 1.86 [95% CI 1.23-2.82], p = 0.0030; also significant in the subgroups aged <70 (p = 0.029), aged ≥ 70 (p = 0.0070), NIHSS 0-1 (p = 0.0040), NIHSS ≥ 2 (p = 0.040), and KPS 90-100 (p = 0.039), [9] temporal lobe localization (overall cohort: HR 1.24 [95% CI 1.00-1.53], p = 0.049; also significant for the NIHSS ≥ 2 subgroup (p = 0.0080), and [10] ASA III classification (overall cohort: HR 1.08 [95% CI 0.78-1.50], p = 0.64; but significant in the subgroups aged ≥ 70 (p = 0.043) and NIHSS ≥ 2 (p = 0.036) **(eTable 5, appendix, pp 19-20**).

Combined impact of GTR and preservation of neurological function on OS

OFO 1 grade at 6 weeks postoperatively was achieved in 50.0% of the awake group and in 21.8% of the asleep group (p < 0.0001). Furthermore, the median OS in the OFO 1 group was 22.0 months [95% CI 17.0-32.5], which was significantly longer than the OFO 2-3 group with awake mapping (median 16.0 months [95% CI 12.5-36.0]) and the OFO 2-3 group with asleep mapping (median 14.0 months [95% CI 12.5-16.0]) (p < 0.0001) (**Table 1, Figure 4**).

OFO 1 status at 6 months postoperatively was achieved in 41.8% in the awake group and in 18.5% in the asleep group (p<0.0001). Furthermore, the median OS in the OFO 1 group was 30.5 months [95% CI 22.0-36.5], which was significantly longer than the OFO 2-3 group with awake mapping (median 16.0 months [95% CI 14.0-36.0]) and the OFO 2-3 group with asleep mapping (median 15.5 months [95% CI 14.0-18.0 (p < 0.0001) (**Table 1, Figure 4**).

DISCUSSION

A higher extent of resection and a lower residual volume significantly improved OS and PFS across all subgroups except in the subgroups with *IDH* mutant tumors, MGMT unmethylated tumors or aged ≥ 70 for OS and PFS, and NIHSS ≥ 2 and KPS ≤ 80 for PFS. Moreover, regression analyses showed that gross-total resection based on residual volume (0.0-0.2 ml) was independently associated with OS in the overall cohort, and with PFS in the NIHSS 0-1 subgroup. Residual tumor volume proved to be a better predictor for survival outcomes than extent of resection. Moreover, gross-total resection combined with preservation of neurological functioning (onco-functional outcome (OFO) grade 1) at 6 weeks and 6 months postoperatively led to significant improved survival outcomes.

Extent of resection and residual tumor volume are both important metrics to assess tumor reduction and have been associated with survival outcomes [1-10]. As described by Karschnia *et al* [14], there is currently no consensus about the definition of the concepts of partial resection, subtotal resection, near total resection, gross-total resection, and supramaximal resection. For gross-total resection, definitions in the literature range from 90-100% [15,16], 96-100% [17], 97-100% [18] to 100% [19-24], while for near-total resection most reported values were ≥ 95% EOR or ≤ 1 cm^3 (1 ml) residual volume [10, 24, 25]. Previous studies suggest that patients who had ≥ 95% EOR had better survival outcomes than patients with ≤ 95% EOR [12,17], but as Karschnia *et al* pointed out it remains virtually unknown if patients with an EOR of 95-98% experience similar or different survival outcomes from patients with EOR values above or under this range. Consequently, we addressed the question if patients with different ranges of EOR or residual volume above that "minimum threshold" would experience significantly different survival outcomes. As for minimum thresholds of EOR or residual volume that would lead to distinctly improved survival outcomes, the generally accepted values are 80% EOR or 2-5 ml residual tumor volume [4, 9, 10, 21], which we therefore used as cut-off points in the presented study. We defined gross-total resection as 0.0-0.2 ml (0.0-0.2 cm^3) residual tumor volume (which is in line with the value used by Stummer *et al* [26] in their 5-ALA trial [0.175 ml/0.175 cm^3]) or an extent of resection of 98-100%, which is comparable with values that are used in previous studies [15-24].

We restricted our cohort to primary glioblastoma resections in or near eloquent areas that were performed between 2010 and 2020 for a contemporary assessment of the impact of extent of resection and residual tumor volume. We found that in the overall cohort and across subgroups, extent of resection and residual tumor volume were strongly associated with and predictive for survival

outcomes, whereas the strongest associations were found between residual tumor volume and overall survival.

An important finding was the fact that younger patients (<70), with a preoperative NIHSS of 0-1 or KPS 90-100, or with MGMT methylated tumors, proved to have the most benefit from gross-total resection in terms of overall survival. Moreover, we found that age, adjuvant therapy with chemotherapy and radiotherapy, *IDH* mutation status, and 6-week NIHSS and KPS deterioration (except for the subgroup aged ≥ 70) were all major prognostic factors for the overall cohort and across all subgroups. However, since our data showed that the subgroup aged ≥ 70 or with MGMT unmethylated tumors did not benefit as much from gross-total resection than the other subgroups, neurosurgeons should be rather careful with pursuing gross-total resection in these patients, especially with tumors in highly eloquent areas. These results are in line with the GLIOMAP study, in which we found that three specific subgroups of patients benefit the most from awake craniotomy in terms of survival outcomes: [1] younger patients (<70), [2] patients in good to excellent preoperative condition (NIHSS of 0-1 or KPS of 90-100), and [3] patients with MGMT methylated tumors [27].

The analyses of the GLIOMAP study also showed that awake craniotomy was critical to increase the extent of resection (decrease residual tumor volume), achieve gross-total resection and improve surgical safety across all patients. Notably, we found in the GLIOMAP study that gross-total resection does not lead to a higher rate of postoperative NIHSS or KPS deterioration. Additionally, in the current study, we first found that awake craniotomy was also an independent predictive factor for survival outcomes in the subgroups aged <70, NIHSS 0-1 and KPS 90-100 (but not in the subgroups aged ≥ 70, NIHSS ≥ 2 or KPS ≤ 80), and secondly, that gross-total resection was beneficial in these clinical subgroups as well as in patients with MGMT methylated tumors. These combined findings suggest that the survival benefit of awake craniotomy in patients aged <70, with a preoperative NIHSS 0-1 or KPS 90-100, or with MGMT methylated tumors might be caused by the synergistic effect of maximum cytoreduction and adjuvant therapy with chemotherapy and radiotherapy.

This suggested synergistic effect is in line with the fact that we found residual tumor volume (absolute measurement of tumor volume) to be a better predictor for survival outcomes than extent of resection (relative measurement of tumor volume). Thus, in patients aged <70 with eloquent, MGMT methylated tumors, or with a preoperative NIHSS 0-1 or KPS 90-100, maximum tumor resection with the use of awake craniotomy should be considered to improve survival, but also to achieve optimal postoperative functioning. In contrast, according to our data, in patients aged ≥ 70, with a preoperative

NIHSS ≥ 2, KPS ≤ 80, or with MGMT unmethylated tumors, maximum tumor resection has not been demonstrated to lead to improved survival outcomes. In these patients, based on our combined results from the current study and the GLIOMAP study, neurosurgeons should be rather reserved with pursuing GTR – awake craniotomy should primarily be used to increase the safety of the resection in selected patients in order to maximize the patient's chance to undergo adjuvant therapy, since our data showed that 6-week NIHSS and KPS deterioration and receipt of adjuvant therapy are among the strongest prognostic factors.

Interestingly, the results suggest that GTR could also improve overall survival in the NIHSS ≥ 2 and KPS ≤ 80 subgroups. However, in these patients, we did not find an independent association between awake craniotomy and survival outcomes in neither the current study nor in the GLIOMAP study. The absence of a significant relationship between awake craniotomy and survival outcomes (but the presence of a significant relationship between GTR and survival outcomes) in these subgroups might be caused by the fact that awake craniotomies are performed less often in patients with NIHSS ≥ 2 or KPS ≤ 80 in general, these subgroups contain a lower absolute number of patients than the other subgroups, which may lead to insufficient power to demonstrate a potential relationship between awake craniotomy and survival outcomes. Nevertheless, our findings indicate that GTR improves overall survival in these subgroups; neurosurgeons could consider to use awake craniotomy to pursue this safely.

Last, to our knowledge, this study is the first to demonstrate the evident prognostic value of achieving OFO 1 status in glioblastoma patients: reaching GTR in combination with preservation of postoperative neurological functioning. Both OFO models at 6 weeks and 6 months postoperatively show significant longer overall survival times in the OFO 1 subgroups than in the OFO 2-3 subgroups. Besides, our data showed that it did not matter if OFO 1 status was achieved with awake or asleep mapping.

Limitations and strengths

This study was subject to several limitations. Because the presented study was observational in nature, we strived to minimize the risk of selection bias and confounding by combining propensity score matching with Cox proportional-hazards regression analyses. Moreover, we set our cut-off values for GTR at 98% for EOR and 0.2 ml for residual tumor volume. We therefore did not analyze potential differences in 98-99% and 100% extent of resection of the tumor, which might differ as reported by

Sanai *et al* [1]. Last, we did not evaluate the impact of resecting the non-contrast-enhancing (NCE) part of the tumor, which was shown by Molinaro *et al* to improve overall survival in younger patients, regardless of *IDH* or MGMT status [10]. Evaluation of the value of 100% vs. 99% vs. 98% CE tumor resection with additionally NCE tumor resection in glioblastoma patient subgroups differing in age, preoperative KPS and NIHSS scores should be the focus of future scientific efforts. Notably, major strengths of this study included the large cohort of more than 1000 eligible patients with primary eloquent glioblastomas, the patient subgroups stratified by age, preoperative NIHSS score, and preoperative KPS by; the combined analysis of the impact of EOR, RTV and GTR on survival outcomes in conjunction with functional outcomes, the analysis of the predictive value of extent of resection *vs* residual tumor volume, and the use of the onco-functional outcome in the analyses.

CONCLUSIONS

We found that a higher extent of resection and a lower residual volume improved OS and PFS the most in patients aged <70 years, with a preoperative NIHSS 0-1 or KPS 90-100, or with MGMT methylated tumors. Gross-total resection based on residual volume (0.0-0.2 ml) was independently predictive for OS in the overall cohort, and for PFS in the NIHSS 0-1 subgroup. Moreover, the achievement of OFO 1 at 6 weeks and 6 months postoperatively led to significant improved survival outcomes. To achieve OFO 1 grade, mapping techniques such as awake craniotomy can be employed by the surgeon to pursue GTR safely. The presented findings will be validated and further explored in the SAFE trial [28] and the PROGRAM study [29].

REFERENCES

1. Sanai N, Polley MY, McDermott MW et al. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg.* 2011. 115(1):3-8
2. McGirt MJ, Chaichana KL, Gathinji M et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. *J Neurosurg.* 2009. 110(1):156-62
3. Lacroix M, Abi-Said D, Fourney DR et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg.* 2001. 95(2):190-8
4. Brown TJ, Brennan MC, Li M et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. *JAMA Oncol.* 2016. 2(11):1460-9
5. Ewelt C, Goeppert M, Rapp M et al. Glioblastoma multiforme in the elderly: the prognostic effect of resection on survival. *J Neurooncol.* 2011. 103(3):611-8
6. Han Q, Liang H, Cheng P et al. Gross total vs. subtotal resection on survival outcomes in elderly patients with high-grade glioma: a systematic review and meta-analysis. *Front Oncol.* 2020. 10:151
7. Oszvald A, Guresir E, Setzmer M et al. Glioblastoma therapy in the elderly and the importance of the extent of resection regardless of age. *J Neurosurg.* 2012. 116(2):357-64
8. Noorbakhsh A, Tang Ja, Marcus LP et al. Gross-total resection outcomes in an elderly population with glioblastoma: a SEER-based analysis. *J Neurosurg.* 2014. 120(1):31-9
9. Grabowski MM, Recinos PF, Nowacki AS et al. Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. *J Neurosurg.* 2014. 121(5):1115-23
10. Molinaro AM, Hervey-Jumper S, Morshed RA et al. Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma. *JAMA Oncol.* 2020. 6(4):495-503
11. Gerritsen JKW, Zwarthoed R, Versyck G et al. A novel onco-functional (OFO) grading scale to assess extent of resection and postoperative morbidity simultaneously to compare surgical outcomes of glioblastoma subgroups: proof-of-concept. *Under review.*
12. Chaichana KL, Jusue-Torres I, Navarro-Ramirez R et al. Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. *Neuro Oncol.* 2014. 16(1):113-122.
13. Marina O, Suh JH, Reddy CA et al. Treatment outcomes for patients with glioblastoma multiforme and a low Karnofsky Performance Scale score on presentation to a tertiary care institute. Clinical article. *J Neurosurg.* 2011. 115(2):220-9

14. Karschnia P, Vogelbaum M, van den Bent M et al. Evidence-based recommendations on categories for extent of resection in diffuse glioma. *Eur J Cancer*. 2021. 149:23-33
15. Lamborn KR, Chang SM, Prados MD et al. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro Oncol.* 2004. 6(3):227-35
16. Pessina F, Navarria P, Cozzi L et al. Maximize surgical resection beyond contrast-enhancing boundaries in newly diagnosed glioblastoma multiforme: is it useful and safe? A single institution retrospective experience. *J Neuro Oncol.* 2017. 135(1):129-39
17. Bloch O, Han SJ, Cha S et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. *J Neurosurg.* 2012. 117(6):1032-8
18. Oppenlander ME, Wolf AB, Snyder LA et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. *J Neurosurg.* 2014. 120(4):846-853
19. Kreth FW, Thon N, Simon M et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. *Ann Oncol.* 2013. 24(12):3117-23
20. Beiko J, Suki D, Hess KR et al. IDH1 mutatnt malignant astrocytomas are more amenable to surgical resection and have a surgical benefit associated with maximal surgical resection. *Neuro Oncol.* 2014. 16(1):81-91
21. Li YM, Suki D, Hess K et al. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? *J Neurosurg.* 2016. 124(4):977-88
22. Suchorska B, Weller M, Tabatabai G et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. *Neuro Oncol*. 2016. 18(4):549-56
23. Al-Holou WN, Hodges TR, Everson RG et al. Perilesional resection of glioblastoma is independently associated with improved outcomes. *Neurosurgery.* 2020. 86(1):112-21
24. Marko NF, Weil RJ, Schroeder JL et al. Extent of resection of glioblastoma revisited: personalized survival modeling facilitates more accurate survival prediction and supports a maximum safe-resection approach to surgery. *J Clin Oncol.* 2014. 32(8):774-82
25. Incekara F, Smits M, van der Voort SR et al. The association between the extent of glioblastoma resection and survival in light of MGMT promotor methylation in 326 patients with newly diagnosed IDH-wildtype glioblastoma. *Front Oncol.* 2020. 10:1087
26. Stummer W, Pichlmeier U, Meinel T et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomized controlled multicentre phase III trial. *Lancet Oncol.* 7(5):392-401
27. Gerritsen JKW, Zwarthoed RH, Kilgallon JL et al. Effect of awake craniotomy in glioblastoma in eloquent areas (GLIOMAP): a propensity score-matched analysis of an international, multicentre, cohort study. *Lancet Oncol*. 2022. 22(6):802-17

28. Gerritsen JKW, Klimek M, Dirven CMF et al. The SAFE-trial: Safe surgery for glioblastoma multiforme: awake craniotomy versus surgery under general anesthesia. Study protocol for a multicenter prospective randomized controlled trial. *Contemp Clin Trials.* 2020. 88:105876
29. Gerritsen JKW, Dirven CMF, De Vleeschouwer S et al. The PROGRAM study: awake mapping versus asleep mapping versus no mapping for high-grade glioma resections: study protocol for an international multicenter prospective three-arm cohort study. *BMJ Open.* 2021. 11(7):e047306

Figure 1:

Data Flow Diagram

Figure 2:

Kaplan-Meier curves for Residual Tumor Volume strata and Overall Survival

Legend: Data are shown for the overall matched cohort (A), the overall matched cohort by IDH mutation status (B, C), by MGMT methylation status (D, E), and the matched subgroups by age (F, G), preoperative NIHSS (H, I) and preoperative KPS (J, K). Groups are described in Table 1 and in the appendix (pp 7-18). . Median survival times (95% CI's) of all strata are described in Tables 3 and 4.

KPS = Karnofsky Performance Score. NIHSS = National Institute of Health Stroke Scale

Figure 3:

Kaplan-Meier curves for Residual Tumor Volume strata and Progression-Free Survival

Legend: Data are shown for the overall matched cohort (A), the overall matched cohort by IDH mutation status (B, C), by MGMT methylation status (D, E), and the matched subgroups by age (F, G), preoperative NIHSS (H, I) and preoperative KPS (J, K). Groups are described in Table 1 and in the appendix (pp 7-18). Median survival times (95% CI's) of all strata are described in Tables 3 and 4.

KPS = Karnofsky Performance Score. NIHSS = National Institute of Health Stroke Scale.

Figure 4:

Kaplan-Meier curves stratified by Onco-Functional Outcome (OFO) grading scale

Legend: Data are shown for the overall matched cohort by OFO grade at 6 weeks (A), and by OFO grade at 6 months (B) postoperatively. Groups characteristics, median survival times (95% CI's), and proportion of patients per OFO grade at 6 weeks and 6 months postoperatively are described in Table 1. OFO = Onco-Functional Outcome.

Table 1: Patient characteristics of the unmatched and matched overall cohorts

	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
Characteristic	**Awake craniotomy (n = 140)**	**Asleep resection (n = 907)**	***p* value**	**Awake craniotomy (n = 134)**	**Asleep resection (n = 402)**	***p* value**
Center			<0.001			<0.001
Rotterdam	44/140 (31.4)	338/907 (37.3)		44/134 (32.8)	178/402 (44.3)	
The Hague	24/140 (17.1)	330/907 (36.4)		24/134 (17.9)	139/402 (34.6)	
Leuven	27/140 (19.3)	84/907 (9.3)		27/134 (20.1)	65/402 (16.2)	
Boston	45/140 (32.1)	155/907 (17.1)		39/134 (29.1)	20/402 (5.0)	
Year of surgery			0.032			<0.001
2010-2015	46/140 (32.9)	221/907 (24.4)		42/134 (31.3)	197/402 (49.0)	
2016-2020	94/140 (67.1)	686/907 (75.6)		92/134 (68.9)	205/402 (51.0)	
Gender			0.19			0.874
Male	93/140 (66.4)	550/907 (60.6)		90/134 (67.2)	265/402 (65.9)	
Female	47/140 (33.7)	357/907 (39.4)		44/134 (32.8)	137/402 (34.1)	
Age at diagnosis, years			<0.001			0.12
Mean (SD)	57.5 (13.5)	63.9 (10.8)		57.5 (12.7)	61.1 (11.2)	
Median (IQR)	59.0 (50.0-67.3)	65.0 (57.0-72.0)		59.0 (49.3-66.8)	62.0 (54.0-70.0)	
Range	22.0-87.0	20.0-90.0		22.0-87.0	20.0-87.0	
Preoperative KPS			<0.001			0.072
<60	2/140 (1.4)	19/907 (2.1)		1/134 (0.7)	0/402 (0.0)	
60	0/140 (0.0)	50/907 (5.5)		1/134 (0.7)	1/402 (0.2)	
70	6/140 (4.3)	157/907 (17.3)		6/134 (4.5)	31/402 (7.7)	
80	22/140 (15.7)	283/907 (31.2)		27/134 (20.1)	112/402 (27.9)	
90	63/140 (45.0)	313/907 (34.5)		65/134 (48.5)	191/402 (47.5)	
100	47/140 (33.6)	104/907 (11.5)		34/134 (25.4)	67/402 (16.7)	
Median preoperative KPS (IQR)	90 (80-100)	80 (80-90)		90 (80-100)	90 (80-90)	
Preoperative ASA score			0.37			0.014
I	17/123 (13.8)	89/902 (9.9)		17/119 (14.3)	61/401 (15.2)	
II	64/123 (52.0)	524/902 (58.1)		63/119 (52.9)	262/401 (65.3)	
III	40/123 (32.5)	273/902 (30.3)		39/119 (32.8)	75/401 (18.5)	
IV	1/123 (0.8)	16/902 (1.8)		0/119 (0.0)	3/401 (0.7)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-3)		2 (2-3)	2 (1-2)	
Preoperative NIHSS score			<0.001			0.31
0	63/134 (47.0)	249/903 (27.6)		63/134 (47.0)	160/402 (39.8)	
1	44/134 (32.8)	267/903 (29.6)		44/134 (32.8)	122/402 (30.3)	
2	17/134 (12.7)	188/903 (20.8)		17/134 (12.7)	72/402 (17.9)	
3	3/134 (2.2)	83/903 (9.2)		3/134 (2.2)	20/402 (5.0)	
4	4/134 (3.0)	48/903 (5.3)		4/134 (3.0)	13/402 (3.2)	
>4	3/134 (2.2)	68/903 (7.5)		3/134 (2.2)	15/402 (3.7)	
Median preoperative NIHSS score (IQR)	0 (0-1)	1 (0-2)		0 (0-1)	1 (0-2)	

Tumor location by lobe			0.012			0.055
Frontal	54/140 (38.6)	289/905 (31.9)		51/134 (38.1)	135/401 (33.7)	
Parietal	34/140 (24.3)	221/905 (24.4)		33/134 (24.6)	102/401 (25.4)	
Temporal	49/140 (35.0)	314/905 (34.7)		47/134 (35.1)	140/401 (34.9)	
Occipital	1/140 (0.7)	73/905 (8.1)		1/134 (0.7)	24/401 (6.0)	
Insula	2/140 (1.4)	8/905 (0.9)		2/134 (1.5)	0/401 (0.0)	
Tumor location by hemisphere			<0.001			0.086
Left	112/140 (80.0)	438/907 (48.3)		108/134 (80.6)	292/402 (72.6)	
Right	28/140 (20.0)	469/907 (51.7)		26/134 (19.4)	110/402 (27.4)	
Tumor location by eloquence			<0.001			<0.001
Motor	64/140 (45.7)	493/904 (54.5)		61/134 (45.5)	190/402 (47.3)	
Sensory	10/140 (7.1)	98/904 (10.8)		10/134 (7.5)	27/402 (6.7)	
Language	92/140 (65.7)	385/904 (42.6)		82/134 (61.2)	219/402 (54.5)	
Visual	3/140 (2.1)	167/904 (18.5)		3/134 (2.2)	75/402 (18.7)	
IDH status			0.52			0.68
Wildtype	107/118 (90.7)	574/621 (92.4)		101/122 (90.2)	234/254 (92.1)	
Mutant	11/118 (9.3)	47/621 (7.6)		11/122 (9.8)	20/254 (7.9)	
MGMT status			<0.001			0.070
Methylated	45/95 (47.4)	259/657 (39.4)		42/89 (47.2)	80/248 (32.3)	
Unmethylated	50/95 (52.6)	398/657 (60.5)		57/89 (64.4)	169/248 (68.3)	
Surgical adjuncts						
Intraoperative ultrasound	29/140 (20.7)	133/907 (14.7)	0.065	106/134 (79.1)	359/402 (89.3)	0.0026
Intraoperative fluorescence	27/140 (19.3)	126/907 (13.9)	0.093	105/134 (78.4)	328/402 (81.6)	0.486
Postoperative adjuvant therapy			0.013			0.279
Radiotherapy only	7/140 (5.0)	91/907 (10.0)		3/134 (2.2)	27/398 (6.7)	
Chemotherapy only	3/140 (2.1)	13/907 (1.4)		3/134 (2.2)	4/398 (1.0)	
Chemoradiotherapy	122/140 (87.1)	685/907 (75.5)		122/134 (91.0)	341/398 (85.0)	
None	8/140 (5.7)	115/907 (12.7)		6/134 (4.5)	26/398 (6.5)	
Reasons for no combined CTx + RTx			<0.001			0.693
Due to surgical deficits	1/18 (5.6)	33/219 (15.1)		1/12 (8.3)	9/57 (15.8)	
Due to rapid progression	3/18 (16.7)	30/219 (13.7)		2/12 (16.7)	6/57 (10.5)	
Pre-op already ineligible	6/18 (33.3)	113/219 (51.6)		6/12 (50.0)	28/57 (49.1)	
Patient's wish	2/18 (11.1)	26/219 (11.9)		1/12 (8.3)	10/57 (17.5)	
Due to inclusion in clinical trial	3/18 (16.7)	3/219 (1.4)		1/12 (8.3)	2/57 (3.5)	
Unknown	3/18 (16.7)	14/219 (6.4)		1/12 (8.3	2/57 (3.5)	
6-week NIHSS-status, pre-op as ref						
Deteriorated	23/128 (18.0)	219/837 (26.2)	0.046	27/125 (21.6)	99/386 (25.6)	0.36
New	12/23 (52.2)	84/219 (38.4)		12/27 (44.4)	45/99 (45.4)	
Worsened	11/23 (47.8)	135/219 (61.6)		15/27 (55.6)	54/99 (54.5)	
Transient	7/23 (30.4)	58/219 (26.5)		11/27 (40.7)	8/99 (8.1)	
Permanent	16/23 (69.6)	161/219 (73.5)		16/27 (59.3)	91/99 (91.9)	
Improved	35/128 (27.3)	267/837 (31.9)	0.30	36/125 (28.9)	115/386 (29.8)	0.83

Stable	70/128 (54.7)	351/837 (41.9)	0.0067	62/125 (49.6)	186/386 (44.6)	0.78
3-month NIHSS-status, pre-op as ref						
Deteriorated	25/128 (19.5)	202/641 (31.5)	0.0072	26/120 (21.7)	107/323 (33.1)	0.019
New	13/25 (52.0)	90/202 (42.5)		13/26 (50.0)	53/107 (49.5)	
Worsened	12/25 (48.0)	112/202 (55.4)		13/26 (50.0)	54/107 (50.5)	
Improved	39/128 (30.5)	192/641 (30.0)	0.91	36/120 (30.0)	82/323 (25.4)	0.33
Stable	64/128 (50.0)	202/641 (38.5)	<0.001	58/120 (48.3)	134/323 (41.5)	0.20
6-month NIHSS-status, pre-op as ref						
Deteriorated	30/115 (26.1)	216/575 (37.6)	0.019	30/115 (26.1)	125/305 (41.0)	0.0048
New	16/30 (53.3)	102/216 (47.2)		16/30 (53.3)	67/161 (41.6)	
Worsened	14/30 (46.7)	114/216 (52.8)		14/30 (46.7)	94/161 (58.4)	
Improved	33/115 (28.7)	166/575 (20.2)	0.97	33/115 (28.7)	71/305 (23.3)	0.36
Stable	52/115 (45.2)	193/575 (33.6)	0.017	52/115 (45.2)	109/325 (33.5)	0.025
Postoperative vascular complications						
None	134/138 (97.1)	816/864 (94.4)	0.19	103/132 (78.0)	312/392 (79.6)	0.70
Major ischemia	3/138 (2.2)	29/864 (3.4)	0.46	2/132 (1.5)	11/392 (2.8)	0.41
Postoperative (reactive) bleeding	1/138 (0.7)	19/864 (2.2)	0.25	1/132 (0.8)	7/392 (1.8)	0.40
Preoperative CE tumor volume, ml			<0.001			0.19
Mean (SD)	42.1 (50.0)	61.7 (51.9)		38.2 (46.8)	41.2 (36.6)	
Median (Q1-Q3)	26.4 (11.6-54.5)	49.4 (25.1-87.8)		22.4 (11.0-48.0)	24.5 (17.1-68.0)	
Range	0.8-208.0	0.4-396.0		0.8-208.0	0.4-334.7	
Postoperative CE tumor volume, ml			<0.001			<0.001
Mean (SD)	2.2 (6.1)	7.6 (1.6)		1.9 (5.6)	5.9 (11.0)	
Median (Q1-Q3)	0.1 (0.0-1.6)	1.8 (0.0-6.8)		0.0 (0.0-1.3)	1.5 (0.0-5.8)	
Range	0.0-41.0	00-164.0		0.0-41.0	0.0-81.7	
Extent of resection CE tumor, % by volume			<0.001			<0.001
Mean (SD)						
Median (Q1-Q3)	95.5 (8.2)	87.6 (18.2)		95.4 (8.4)	86.3 (19.3)	
Range	99.8 (94.8-100.0)	95.3 (83.6-100.0)		99.8 (94.4-100.0)	95.2 (81.3-100.0)	
	48.2-100.0	21.0-100.0		48.2-100.0	21.0-100.0	
6-week OFO grade	NA	NA				<0.001
OFO 1				58/116 (50.0)	76/349 (21.8)	
OFO 2-3				58/116 (50.0)	273/349 (78.2)	
6-month OFO grade	NA	NA				<0.001
OFO 1				46/110 (41.8)	53/287 (18.5)	
OFO 2-3				64/110 (58.2)	234/287 (81.5)	
Median progression-free survival, months (95% CI)	NA	NA				<0.001
6-week grade: OFO 1				20.0 (16.0-43.5)	22.0 (16.5-35.5)	
6-week grade: OFO 2-3				16.0 (12.5-36.0)	14.0 (12.5-16.0)	
Median overall survival, months (95% CI)	NA	NA				<0.001

6-month grade: OFO 1 6-month grade: OFO 2-3				30.0 (18.0-52.0) 16.0 (14.0-36.0)	30.5 (22.0-38.5) 15.5 (14.0-18.0)	
Median progression-free survival, months (95% CI)	9.0 (15.5-19.0)	7.0 (3.5-15.0)	0.31	9.0 (8.0-11.0)	7.3 (6.0-8.75)	0.006
Median overall survival, months (95% CI)	15.0 (10.0-30.8)	12.5 (6.0-23.5)	0.001	17.0 (15.0-24.0)	14.0 (13.0-16.0)	<0.001

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the unmatched and matched awake-asleep cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

Figure 1

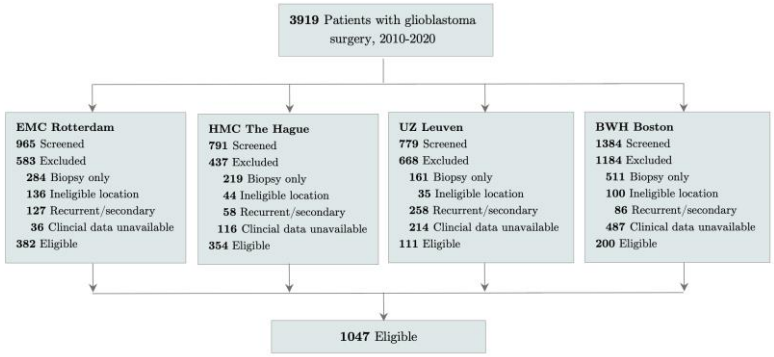

Figure 2

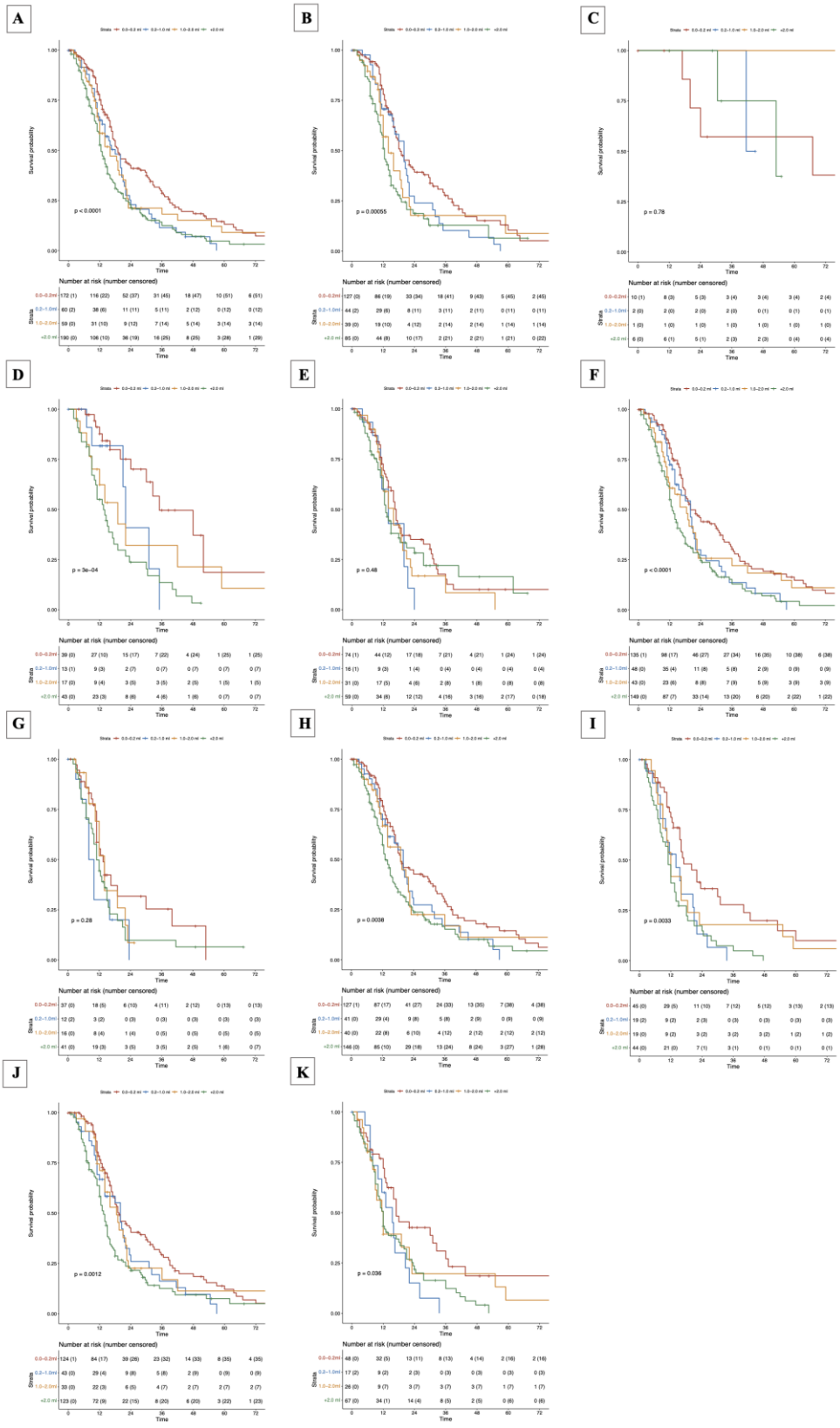

Figure 3

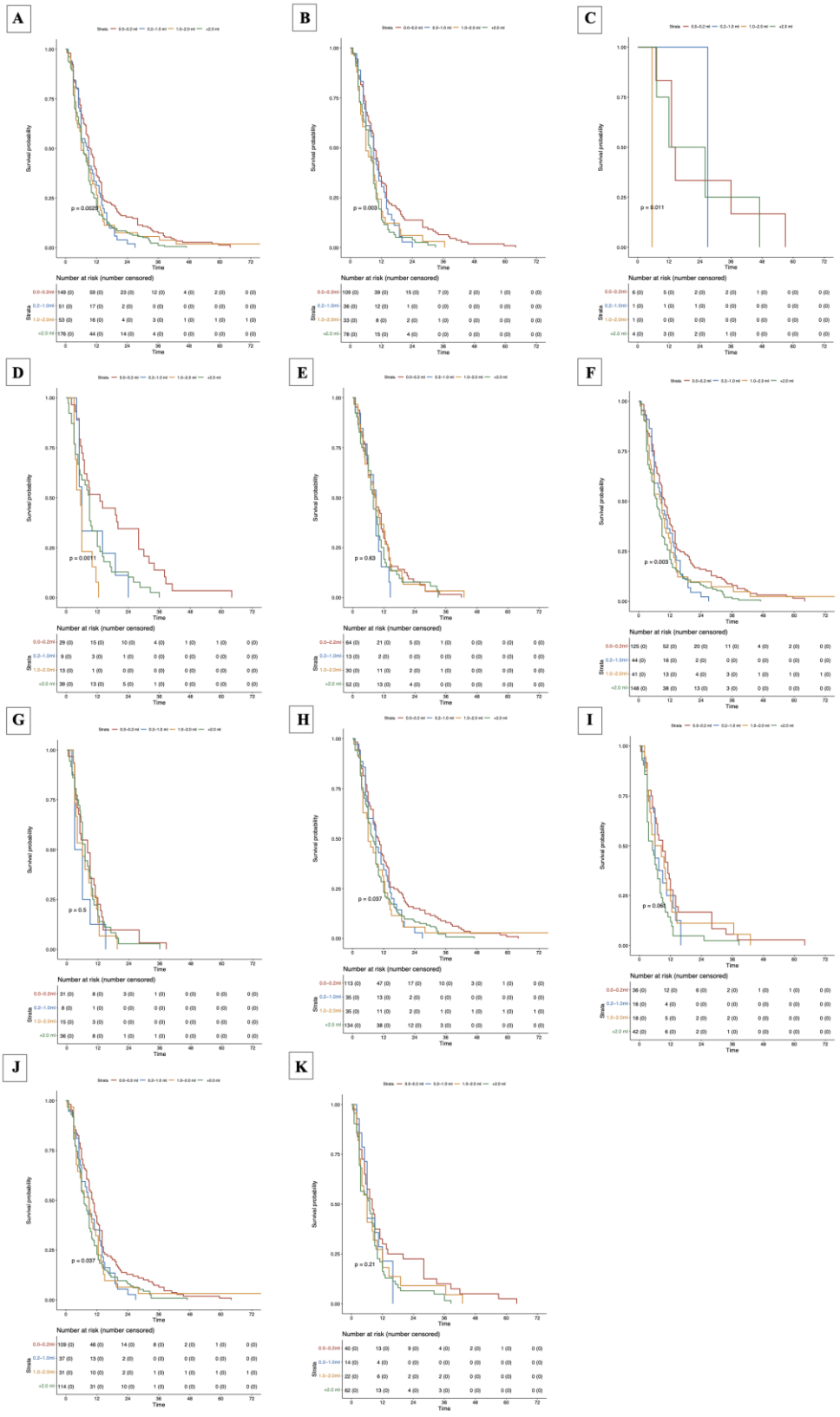

Figure 4