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Discrepancies in inter-rater agreement on resectability of recurrent glioblastoma: Complementary post-hoc analysis of the prospective, randomized DIRECTOR trial

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Abstract

Background. Tumor resection is a prerequisite in many studies of new glioblastoma therapeutics; however, no clear parameters for "resectability" exist. We evaluated inter-rater variability in assessing tumor resectability and potential associations between resectability and survival in a trial cohort of glioblastoma recurrence.

Methods. DIRECTOR (NCT00941460; 9/2009-6/2012) evaluated two dose-dense temozolomide regimens for first recurrent glioblastoma, yielding similar outcomes between arms. Re-resection was allowed before initiation of systemic therapy by institutional decision. Eleven surgical neuro-oncologists (blinded to final outcomes) rated whether a "meaningful resection" was achievable for each recurrent IDH-wildtype glioblastoma based on imaging and clinical data.

Results. MRI scans from 69 patients were available (median age: 58.2 ± 1.1 years, median survival: 10.0 months). Forty patients underwent re-resection (median age: 56.4 ± 1.7 years, median survival: 10.8 months). Surgical decision-making markedly varied between raters, ranging from 30 to 58 of 69 cases being classified as "resectable" ($\kappa = 0.405$). In patients who received re-resection, a "meaningful resection" was deemed feasible by >80% of raters in 30/40 cases (75.0%). For patients without re-resection, unanimous agreement on non-resectability occurred in only 3/29 cases (10.4%); and 5/29 tumors (17.2%) were considered resectable by >80% of raters. Knowledge of additional clinical factors virtually never changed MRI-based judgments. While patients who had a complete resection of contrast-enhancing tumor had favorable outcomes, a consensus on resectability by >80% of raters was not associated with prolonged overall survival.

Discussion. Feasibility assessment for re-resection is heterogeneous among neurosurgeons, challenging single-surgeon evaluation of "resectability." Those findings are limited by the number of surgical raters and the size of the DIRECTOR cohort.

Key Points

- Inter-rater agreement on resectability in recurrent glioblastoma is moderate among experts.
- Surgeons rely on MRI and less on clinical data for assessing resectability.
- Actual residual tumor, but not perceived resectability, is associated with survival.

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Importance of the Study

Tumor resection is a prerequisite in many studies of new therapeutics for recurrent glioblastoma; however, no objective parameters for "resectability" exist. Applying a post-hoc analysis of the prospective DIRECTOR trial, we show that perceived resectability for recurrent glioblastoma substantially varies between surgical experts despite evaluating identical imaging and clinical information. Even when an expert agreement for a surgically more accessible tumor was found for some individuals, those cases did not identify with a more favorable outcome; therefore, counteracting the assumption that previous findings on a beneficial role of re-resection are simply due to selection bias as lower tumor proximity to critical brain regions may come with an inherently better prognosis. In the present DIRECTOR cohort, only the actual postoperative contrast-enhancing tumor volume was associated with patient survival. These findings suggest that surgical judgment alone is insufficient as an inclusion criterion for trials and imply the need for standardized tools to assess resectability.

In glioblastoma, progression inevitably occurs and interventions in the recurrent setting are poorly standardized.[1] Current treatment options for recurrent disease include re-resection, re-irradiation, and chemotherapy (rechallenge), alone or in combination; or inclusion into a clinical trial whenever feasible[2,3] with patient preference and institutional practice patterns largely guiding treatment plans. No randomized controlled trial has convincingly demonstrated the superiority of one treatment modality over another.[4] In addition to previous trials,[5–7] this is also true for the DIRECTOR trial, a prospective multi-center trial that randomly assigned patients with glioblastoma at first recurrence to receive temozolomide re-challenge according to either of two dose-intensified schedules, "7-days-on/7-days-off" or "21 out of 28 days".[8] Median survival was approximately 10 months in both treatment arms, and O6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation was a powerful prognostic factor. In this trial, a high rate of re-resections in DIRECTOR was found due to the fact that *MGMT* testing of the recurrent tumor, as opposed to the primary tumor tissue, was initially required, but was no longer requested when it became clear that the *MGMT* status rarely changes in the course of disease.[9]

The use of re-resection has recently been associated with prolonged overall survival in contemporary cohorts when near-total resection of contrast-enhancing tumor can be achieved.[10,11] This interpretation rests upon a retrospective multi-center cohort of 681 patients with first recurrence of glioblastoma from the RANO *resect* group, which observed that only individuals with less than 1 cm^3 residual tumor achieved a more favorable outcome compared to patients not undergoing re-resection.[11] These findings aligned with those from a post-hoc analysis of the DIRECTOR trial, for which the 2 initial treatment arms were pooled, given that no difference in outcome for either of the 2 chemotherapy regimens was detected.[10] Despite the fact that the latter results carried limitations derived from a molecularly heterogeneous cohort preceding the WHO 2021 classification (including also isocitrate dehydrogenase [IDH]-mutant tumors),[12] it was concluded that only complete (but not incomplete) resection of the contrast enhancing tumor was associated with improved survival. However, this has not been confirmed in a randomized trial yet. Despite the relevance of the question, the RESURGE trial (NCT02394626) which started in 2015 is still enrolling patients. Here, patients with first glioblastoma recurrence are randomized to second-line therapy according to local guidelines with or without re-resection; and a sample size of 120 patients is planned.

On a cautionary note, the association between smaller tumor residual and better outcome might be explained by the assumption that larger post-operative tumor volume is simply a surrogate marker for lower resectability due to tumor proximity to critical brain regions with an inherently worse prognosis. The ill-defined role of resectability in outcome is further complicated by the fact that perceived resectability of recurrent glioblastoma may differ among surgeons[13]; however, the heterogeneity of surgeons' estimates of resectability has not yet been quantified for recurrent glioblastoma.

In this study, we performed a post-hoc analysis of patients with the first recurrence of an IDH-wildtype glioblastoma from the DIRECTOR trial. Baseline MRI imaging was evaluated by eleven neurosurgeons (all co-authors of the manuscripts) from three continents who were not involved in the surgical data analysis of the initial DIRECTOR trial to assess inter-rater variability. Potential factors influencing decision-making on resectability were analyzed, and the interrelation of perceived resectability and actual tumor residual with outcome was analyzed.

Methods

The DIRECTOR Trial: Study Cohort of the Current Post-Hoc Analysis

DIRECTOR was a prospective, open-label, randomized trial comparing two regimens of dose dense temozolomide for patients with first recurrence of glioblastoma.[8] Patients were recruited from 16 centers in Germany, Austria, and Switzerland (Figure 1A). Major inclusion criteria were (i) progression documented by MRI not earlier than 180 days after first surgery and not earlier than 90 days after radiotherapy, (ii) histological diagnosis of glioblastoma per WHO 2007 classification, (iii) prior treatment with concomitant radiochemotherapy followed by at least two cycles of maintenance temozolomide chemotherapy, (iv) age 18-80 years, (v), Karnofsky performance status (KPS) ≥50%, (vi) laboratory values allowing administration of temozolomide re-challenge, and (vii) written informed consent prior to

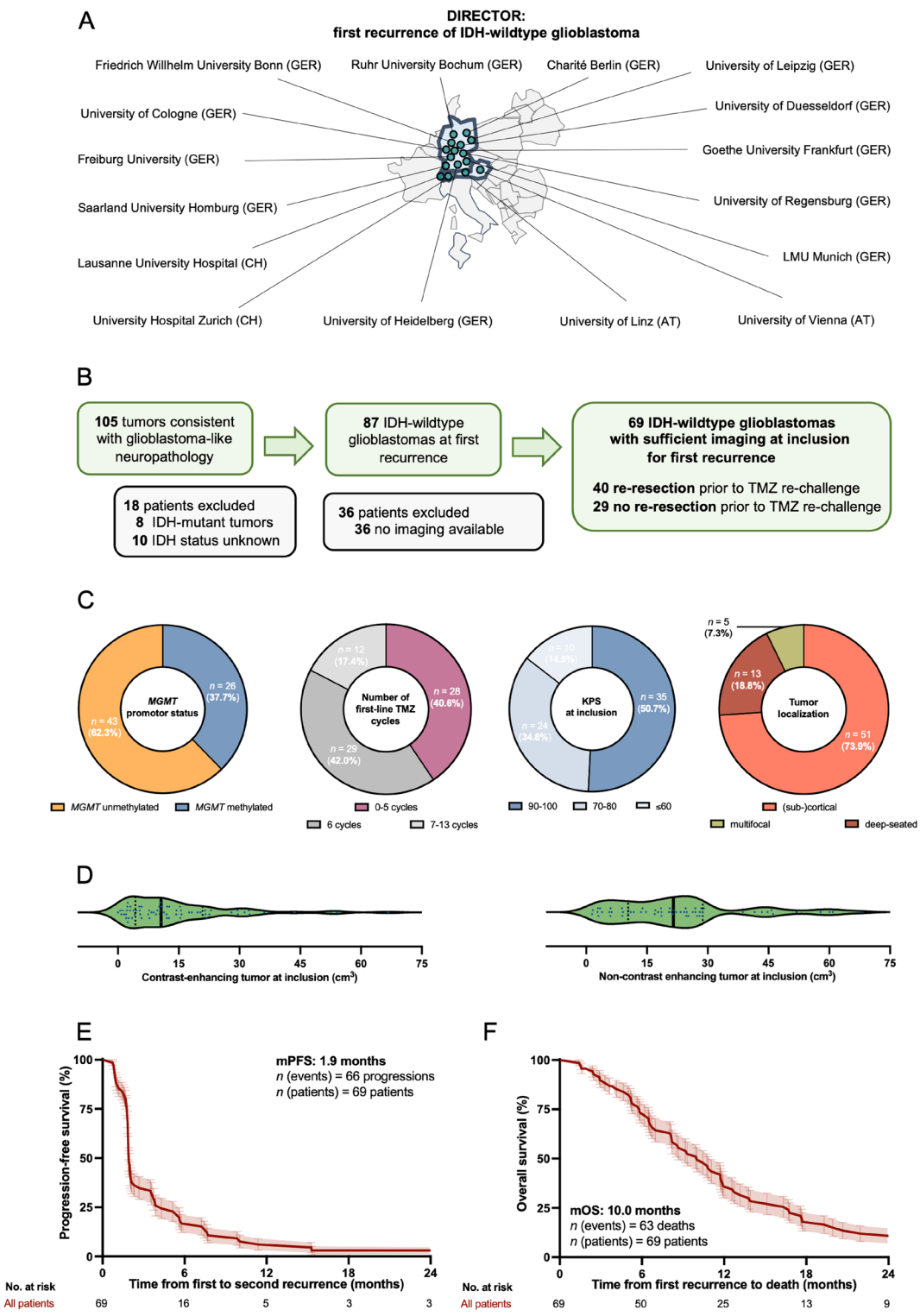

Figure 1. Baseline characteristics of patients with first recurrence of IDH-wildtype glioblastoma from the DIRECTOR trial. (A) Geographic representation of the 16 centers participating in the DIRECTOR trial. (B) Schematic representation of the subgroup of patients with first recurrence of IDH-wildtype glioblastoma with sufficient baseline imaging (n = 69). Baseline MRI confirming recurrence for study enrolment was not stored centrally in 36 patients and, therefore, not available for the current post-hoc analysis. (C) Distribution of *MGMT* promoter methylation status, number of maintenance temozolomide cycles, KPS at inclusion, and tumor localization across the study cohort. (D) Pre-operative contrast-enhancing (left) and non-contrast-enhancing tumor volume (right; in cm³) at baseline. Median ± 95%-confidence interval. (E, F) Kaplan-Meier estimates of progression-free survival after first recurrence (E) and overall survival (F) for the entire study cohort. Light shading: SEM.

inclusion. Per institutional preference, re-resection could be performed before enrolment, prior to temozolomide re-challenge. For the current post-hoc analysis, 69 patients with IDH-wildtype glioblastoma according to the WHO 2021 classification, in whom baseline MRI from the time of study enrolment was available, were selected from the originally included 105 patients (Figure 1B).[12] The DIRECTOR trial received approval from local ethical committees and competent authorities; the current post-hoc analyses were likewise reviewed and authorized by a local institutional review board (LMU: AZ 24-0740).

Assessment of Tumor Resectability

Eleven surgical neuro-oncologists from 3 continents (ASJ, CR, DPC, EOVM, KJD, LB, MAV, MLDB, MSB, OS, and YE) were invited to review the baseline MRI of each of the 69 selected patients. The 11 raters were selected based on the following criteria:

- ≥10 years of experience as a neurosurgeon specialized in glioma surgery;
- substantial scientific contributions and publications to the field of surgical neuro-oncology;
- no overlap of raters having trained or practiced at the same institution to avoid similarities in practice patterns related to education and/or training;
- no previous involvement in the surgical imaging analysis of the DIRECTOR trial to avoid bias.

Raters were blinded to whether the patients actually underwent re-resection and final survival outcomes. Coded MRIs of the 69 patients were uploaded to the IMAGYS suite by KEOSYS (St. Herblain, France), a web-based application designed for the secure management of medical imaging in clinical trials in compliance with General Data Protection Regulation (GDPR) and Health Insurance Portability and Accountability Act (HIPAA) regulations on ISO 27001-certified servers.[14] Once uploaded, images were centralized on the platform, allowing seamless central reading without the need for additional software or manual transfers. Accompanying the images, a set of pre-defined questions was displayed for each patient (Supplementary Data S1). Whether an "oncologically meaningful resection" with potential survival relevance and acceptable risk-benefit ratio might be possible was initially judged by the raters based upon MRI only, while clinical information (including age, *MGMT* promoter methylation status, time from first resection, number of maintenance temozolomide cycles; Supplementary Data S2) were provided in the following questions. This was to assess whether the raters' judgment might change when that clinical information was made accessible. Perceived resectability of the complete contrast-enhancing as well as non-contrast-enhancing tumor was interrogated.

Tumor Volumetrics

As previously described,[11] tumor volumes were manually delineated on pre- and post-operative MRI scans. Total contrast-enhancing tumor was determined on contrast-enhanced T1-sequences, and non-enhancing tumor was quantified on FLAIR (or if not available: T2)-sequences. In line with current recommendations,[15] non-enhancing tumor was identified based upon disruption of the anatomical architecture as well as its FLAIR/T2-signal intensity compared to cerebrospinal fluid and physiological white matter. Raters ensured that non-enhancing imaging abnormalities were not surgery-related by reviewing pre-operative imaging and post-operative sequences (particularly including diffusion-weighted imaging). Absolute tumor volumes (in cm^3) were collected, and multifocal disease was quantified separately at each focus and summed together. Patients were stratified based upon residual tumor volume according to the RANO *resect* classification for glioblastoma.[16]

Definition of Clinical Endpoints

Patients were followed until death or the date of database closure (April 15, 2015). Patients were monitored for disease progression with MRI every 8 weeks, and progression was assessed using the MacDonald criteria.[17] For the current post-hoc analysis, it was confirmed that all events documented as progression after inclusion into the DIRECTOR trial met the criteria for progression as defined by the RANO 2.0 criteria.[18] Progression-free survival after first recurrence (PFS-2) was defined as the time between the date of randomization until further progression or death from any cause, whichever occurred earlier. Overall survival was defined as the time between the date of first study drug administration at first recurrence (ie, enrolment in the DIRECTOR trial) and death from any cause.

Statistical Analysis

Continuous variables were assessed for normal distribution and equal variance by the D'Agostino-Pearson normality test. For parametric data, differences between groups were analyzed by the unpaired Student's *t*-test. For non-parametric data, we employed the Mann-Whitney *U*-test for two groups. Results are presented as medians if not indicated otherwise, and ranges are indicated. For categorical variables, differences between groups were evaluated using the χ^2-test, and variables are given in absolute numbers and percentages. Pearson's correlation coefficient (r) was used to explore relationships between 2 continuous variables, and simple linear regression was applied to build prediction models. Raters were treated as independent expert observers, as the primary objective of this analysis was to quantify inter-rater variability and the feasibility of consensus on resectability. Inter-rater agreement on resectability as a categorical variable was determined by Fleiss's kappa coefficient (agreement: ≤0: none; 0.01-0.20: slight; 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial, 0.81-1.00: perfect).[19] Hierarchical or mixed-effects models were not applied, as the aim was not to estimate surgeon-level decision parameters but to

evaluate whether "resectability" constitutes a reproducible construct suitable for trial inclusion criteria.

Kaplan-Meier survival curves were generated to evaluate time-to-event outcomes, and group comparisons were performed using the log-rank test. The reverse Kaplan-Meier method was applied for calculations of follow-up times. For survival analysis stratifying for continuous variables, Cox proportional hazard regression models were constructed for the computation of hazard ratios (HR) as point estimates and 95% confidence intervals (CI).

Statistical analyses were conducted using Prism statistical software (Prism 10.3.1; GraphPad Software Inc., San Diego, CA) and Stata statistical software (Stata 17.0; StataCorp LLC., College Station, TX). A *P*-value of ≤.05 was considered statistically significant.

Results

Baseline Patient Characteristics: Patients With IDH-Wildtype Glioblastoma from the DIRECTOR Trial

Clinical data and baseline imaging from 69 patients with first recurrence of an IDH-wildtype grade 4 glioblastoma were assembled from 16 centers (Table 1), including information on 40 patients (58.0%) who underwent re-resection and 29 patients (42.0%) who did not undergo re-resection prior to temozolomide re-challenge. All tumors met the criteria for glioblastoma according to the WHO 2021 classification,[12] and each patient had undergone first-line standard radiochemotherapy with a median of 6 maintenance temozolomide cycles (range: 2-13 cycles). Median time from initial surgery to randomization for the DIRECTOR trial at first recurrence was 11 months (range: 5-69 months), mean age at inclusion was 59 years (range: 52-66 years), and the median KPS at trial inclusion was 90 (range: 50-100; ie, after re-resection). *MGMT* promoter methylation status was reported as unmethylated in 43 patients (62.3%), and methylated in 29 patients (37.7%) (Figure 1C). There were no statistically significant differences for any baseline characteristics (including time to first progression) between patients managed with or without re-resection, prior to inclusion into the DIRECTOR trial.

At baseline, median contrast-enhancing tumor volume was 10.67 cm^3 (range: 0-81 cm^3), and the non-contrast-enhancing tumor volume (excluding the contrast-enhancing volume) was 21.52 cm^3 (range: 2-97 cm^3) (Figure 1D). Most tumors were located in a (sub-)cortical location in the right hemisphere. After a median follow-up of 55 months (CI: 35 months—not reached) from diagnosis, second progression was detected in 66 patients (95.7%), and 63 patients (91.3%) were deceased. The median progression-free survival after first recurrence was 1.9 months (CI: 2-2 months), and overall survival after first progression was 10.0 months (8-12 months) (Figure 1E). Re-resection was not associated with progression-free survival after first recurrence (2.0 vs 1.9 months; *P*=.075) or overall survival (10.8 vs 8.7 months; *P*=.417).

Heterogeneity in Perceived Resectability between Individual Raters

Baseline MRI of the 69 patients at first recurrence of an IDH-wildtype glioblastoma were displayed to the 11 raters (Figure 2A). While a median of 43 of 69 patients (62.3%; range: 30-58 patients) were considered as candidates for an oncologically meaningful resection by each rater, there was substantial heterogeneity in perceived resectability between the individual raters (kappa coefficient: 0.405—moderate agreement). The most conservative rater judged 30/69 tumors (43.5%) as resectable, whereas the surgically most pro-active rater deemed 58 of 69 tumors (84.1%) to be resectable (Figure 2B). For each individual patient, a median of 9 of 11 raters (81.8%) indicated that they could have provided an oncologically meaningful resection. Unanimous agreement for resectability was found in 14 patients who eventually received re-resection, and unanimous agreement against resectability was found in one patient who underwent re-resection and in 3 patients who did not undergo re-resection (Supplementary Figure S1).

Importantly, the perception that an oncologically meaningful resection would be possible was closely correlated with the perception that a complete resection of the contrast-enhancing tumor was feasible (r=0.913, *P*=.001) (Figure 2C). Understandably, the brain areas affected by the tumor might be of higher relevance for surgical decision-making than measurements of tumor volume alone. Thus, while most tumors located in (sub-)cortical areas were judged resectable by a majority of raters, tumors with deep-seated or multifocal growth patterns were less often considered amenable to resection (median agreement: 90% vs 55% vs 0%; *P*=.001). In turn, the pre-operative contrast-enhancing tumor volume did not correlate with the fraction of raters judging an individual tumor as oncologically meaningful resectable (r=–0.068; *P*=.460). Also, there was no difference in the fraction of raters judging that an oncologically meaningful resection might be possible when patients were stratified according to involvement of the left hemisphere (77.5% vs 82.0%; *P*=.280). Notably, the 11 raters indicated that there was imaging evidence for substantial non-enhancing tumor beyond the enhancing tumor borders in a median of 57 patients (82.6%; range: 23-68 patients). However, the complete resectability of non-enhancing tumor was less relevant to the raters for judging the tumor as oncologically meaningful resectable (r=0.613, *P*=.001) than the complete resectability of enhancing tumor.

Clinical Factors Influencing Perceived Tumor Resectability

For cases with clear agreement on resectability, we observed that typically more than 80% of raters agreed that an individual tumor was resectable (Figure 3A). In line with previous definitions for expert consensus,[20] a consensus is found when >80% of the raters agreed on or against resectability. There was consensus of greater than 80% of raters that the recurrence was resectable in 35 of 69 patients (50.7%), including 30 patients who were indeed re-resected and 5

Table 1. Characteristics of patients with first recurrence of IDH-wildtype glioblastoma from the DIRECTOR trial

Clinical characteristics		Re-resection	No re-resection	Total	*P*-value
Overall		*n*=40	*n*=29	*n*=69	
Demographics	Age at randomization (median; years)	55 (48-66)	61 (55-65)	**59 (52-66)**	*.052*
	M:F-ratio	1:0.48	1:0.93	**1:0.64**	*.190*
KPS at randomization	90-100 (n, %)	19 (47.5%)	16 (55.2%)	**35 (50.7%)**	*.549*
	70-80 (n, %)	16 (40.0%)	8 (27.6%)	**24 (34.8%)**	
	50-60 (n, %)	5 (12.5%)	5 (17.2%)	**10 (14.5%)**	
IDH status (*n*, %)	Wildtype	49 (100%)	20 (100%)	**69 (100%)**	*1.000*
	Mutant	0	0	**0**	
MGMT promoter methylation status (*n*, %)	Methylated	16 (40.0%)	10 (34.5%)	**26 (37.7%)**	*.640*
	Unmethylated	24 (60.0%)	19 (65.5%)	**43 (62.3%)**	
First-line treatment	Radiochemotherapy (n, %)	49 (100%)	20 (100%)	**69 (100%)**	*1.000*
	Number of maintenance TMZ cycles (median; n)	6 (2-13)	6 (2-12)	**6 (2-13)**	*.220*
	Time from diagnosis to randomization into DIRECTOR (median; months)	12 (5-69)	9 (5-49)	**11 (5-69)**	*.110*
Location at diagnosis (*n*, %)	(Sub-)cortical	32 (80.0%)	19 (65.5%)	**51 (73.9%)**	*.024*
	Deep-seated	8 (20.0%)	5 (17.2%)	**13 (18.8%)**	
	Multifocal	0	5 (17.2%)	**5 (7.3%)**	
	Dominant	18 (45.0%)	11 (37.9%)	**29 (42.0%)**	*.450*
	Non-dominant	22 (55.0%)	18 (62.1%)	**40 (58.0%)**	
Tumor volumes (median, cm^3)	Preoperative CE (range)	12.43 (1-81)	8.84 (0-32)	**10.67 (0-81)**	*.069*
	Preoperative non-CE (range)	21.52 (2-97)	21.60 (3-87)	**21.52 (2-97)**	*.900*
	Postoperative CE (range)	0 (0-47)	8.84 (0-32)	**2.50 (0-47)**	***.001***
	Postoperative non-CE (range)	0 (0-55)	21.60 (3-87)	**10.20 (0-87)**	***.001***
Endpoints met (*n*, %)	Second progression	37 (92.5%)	29 (100%)	**66 (95.7%)**	*.130*
	Death	35 (87.5%)	28 (96.6%)	**63 (91.3%)**	*.190*
Outcome (median, months)	Follow-up (95% CI)	55.03 (5-47)	34.93 (n.r.-n.r.)	**55.0 (35-n.r.)**	*.967*
	Post-progression-free survival (95% CI)	2.03 (2-3)	1.87 (2-2)	**1.9 (2-2)**	*.075*
	Post-progression overall survival (95% CI)	10.83 (8-13)	8.67 (6-13)	**10.0 (8-12)**	*.417*

Characteristics are given for patients with first recurrence of IDH-wildtype grade 4 glioblastoma (*n*=69; bold letters), stratified for patients who underwent re-resection (*n*=40), and those who did not undergo re-resection (*n*=29). Differences between the groups were assessed using the unpaired Student's *t*-test (for parametric data) or the Mann-Whitney *U*-test (for non-parametric data) for continuous variables; and categorical variables were assessed by the χ^2-test. Kaplan-Meier estimates and log-rank testing were used for survival analyses. *P*-values are given in italic letters, and asterisks with bold letters indicate $P \leq .05$.
Abbreviations: CE: contrast-enhancing tumor. F: female. IDH: isocitrate dehydrogenase. KPS: Karnofsky performance status. M: male. n.a.: not available for review. non-CE: non-contrast-enhancing tumor. n.r.: not reached. TMZ: temozolomide. 95% CI: 95% confidence interval.

patients who were not re-resected. A consensus that the recurrent tumors were not resectable was found in 12 patients (17.4%), including two patients who were re-resected and 10 patients who were not re-resected. No consensus was established in 22 patients (31.9%), including eight patients who were re-resected and 14 patients who were not.

We then assessed whether the initial judgement of the raters based upon MRI alone might be changed when imaging was contextualized by also providing clinical information on patient age, *MGMT* promoter methylation status, time from last resection, and number of maintenance first-line temozolomide cycles prior to progression. For each of the eleven raters, a median of two from the 69 cases (2.9%; range: 0-12 cases) were scored differently after providing a clinical background. The 11 raters were generally less likely to judge tumors resectable after the clinical background information was made available, as for 8 of 35 patients, no consensus was established after providing clinical background, while those tumors were originally scored as resectable by the majority of the raters based upon MRI alone

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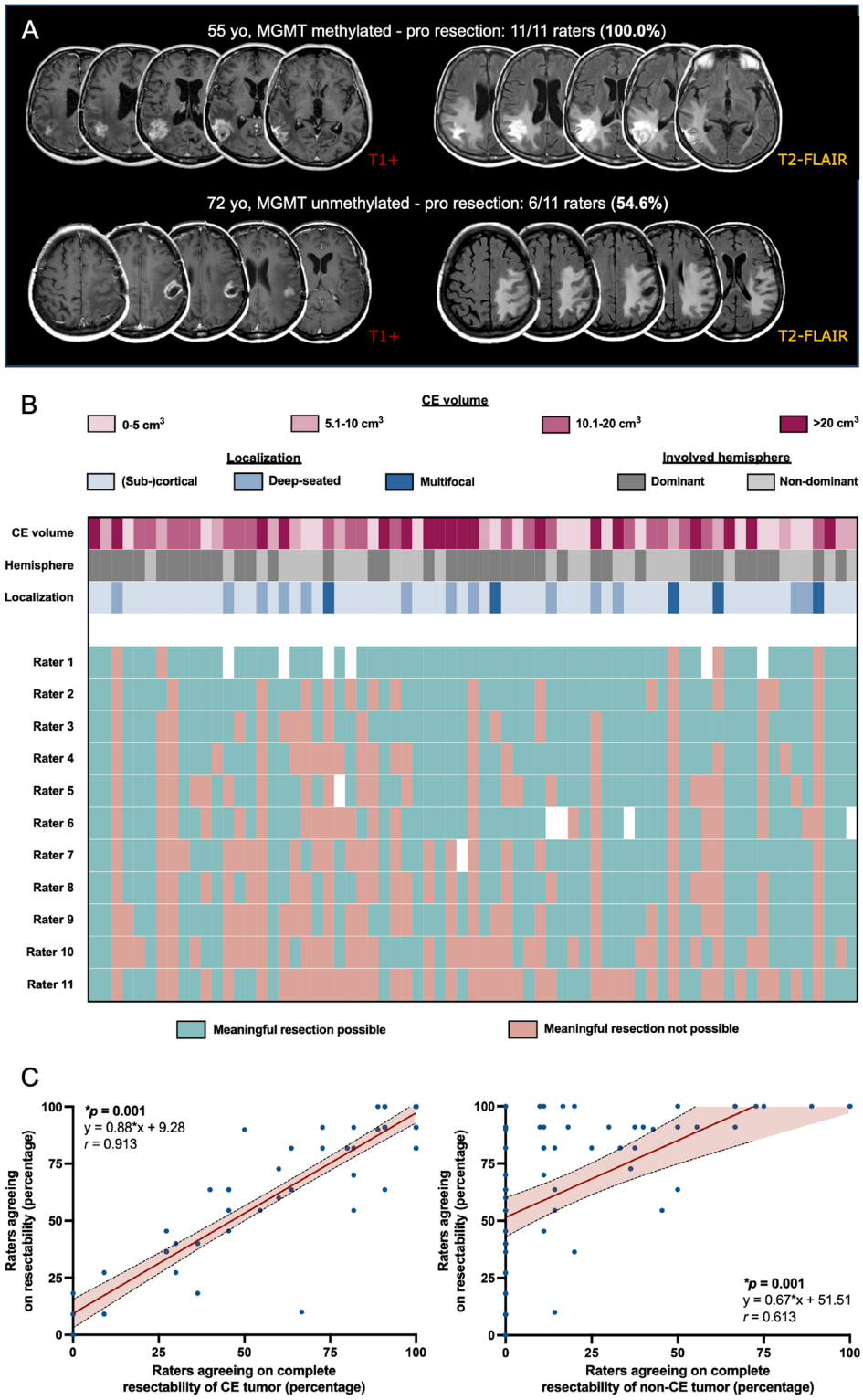

Figure 2. Assessment of resectability across raters. (A) Axial brain MRI with contrast-enhanced T1- (left on each panel) and FLAIR-weighted (right on each panel) sequences from two patients. A meaningful resection was uniformly rated as reasonable for the upper case, while ratings for the lower case were more heterogeneous. (B) Ratings of resectability based upon pre-operative MRI only. Each column represents one patient ($n = 69$), each row represents one rater ($n = 11$), and the raters' response on perceived resectability are color-coded. In the upper 3 rows, baseline imaging characteristics are indicated for each individual patient. Blank cells indicate that individual raters did not feel confident to judge the case. (C) Simple linear regression analyses comparing the raters' agreement on an oncologically meaningful re-resection against the agreement on resectability for contrast-enhancing (left) and non-contrast-enhancing tumors (right). Pearson correlation coefficients (r), calculated equations including slope β1, and P-values are given. Dotted lines indicate 95%-confidence intervals.

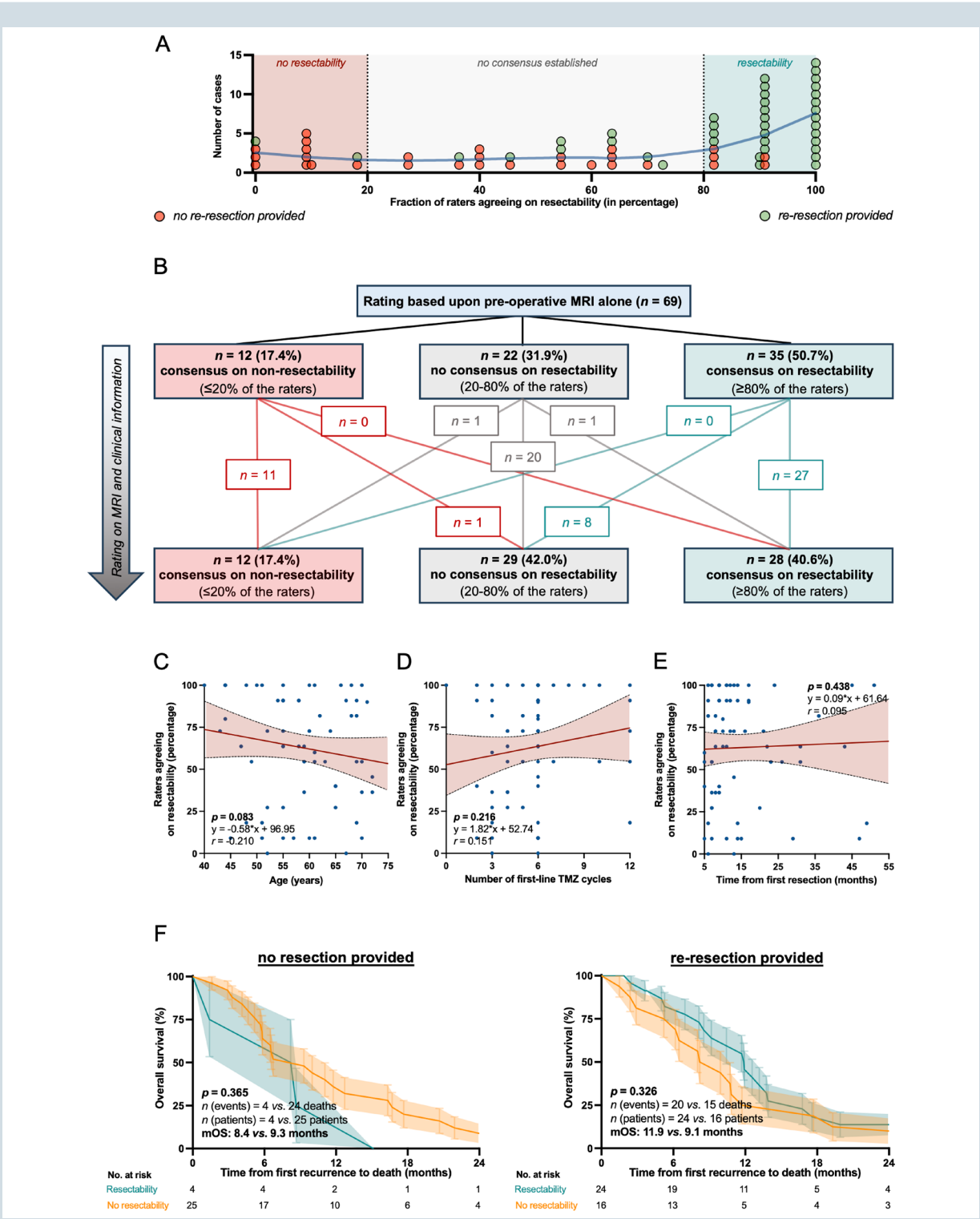

Figure 3. Clinical factors affecting perceived resectability and association with outcome. (A) Schematic representation of the fraction of raters agreeing that an oncologically meaningful re-resection could be provided. Each dot represents 1 patient, and information on whether the individual patient indeed underwent re-resection per institutional preference is color-coded. (B) Number of patients in which greater than 80% of the raters agreed for (green) or against resectability (red), or in which no consensus could be established (grey). Patients are stratified according to whether the raters' evaluation was based upon pre-operative MRI only (upper row), or also on the clinical patient background (lower row). (C-E) Simple linear regression analyses comparing the raters' agreement on an oncologically meaningful re-resection (based on MRI and clinical information) against patient age, number of first-line maintenance temozolomide cycles, and time from first resection (in months). Pearson correlation coefficients (r), calculated equations including slope β_1, and P-values are given. Dotted lines indicate 95%-confidence intervals. (F) Kaplan-Meier estimates of overall survival for patients in whom no re-resection was provided (left panel; $n = 29$) and patients in whom re-resection was provided (right panel; $n = 40$). Curves are given for patients stratified according to whether >80% of the raters evaluated that an oncologically meaningful re-resection could be achieved based upon pre-operative MRI and clinical information. Light shading: SEM.

(Figure 3B). In turn, a new consensus for or against resectability was reached in only 2 cases after clinical background was made available: one case with a consensus for resectability, the other one with a consensus against resectability.

In older patients, raters were somewhat less likely to indicate that an oncologically meaningful resection could be achieved (*r* prior to clinical background: –0.183; *r* after clinical background: –0.210). Conversely, a higher number of maintenance temozolomide cycles (*r* prior to clinical background: 0.082; *r* after clinical background: 0.151) and a longer time from diagnosis to first progression (*r* prior to clinical background: –0.041; *r* after clinical background: 0.095) influenced raters to more likely indicate that an oncologically meaningful resection could be achieved. While those trends are important to acknowledge, none of these clinical factors were significantly correlated with perceived resectability (Figure 3C-E). Also, no substantial association between *MGMT* promoter methylation status and perception for an "oncologically meaningful resectability" was found (median agreement on resectability in patients with unmethylated vs methylated tumors: 81.82% vs 63.64% prior to clinical background / 72.7% vs 63.64% after clinical background).

Associations Between Perceived Resectability, Residual Tumor Volume, and Outcome

In agreement with a previous post-hoc analysis of the DIRECTOR trial,[10] residual contrast-enhancing tumor volume prior to temozolomide re-challenge was prognostic for progression-free survival after first recurrence (HR: 1.03 with CI 1.0-1.1; *P*=.049) and overall survival (HR: 1.04 with CI 1.0-1.7; *P*=.008) in our cohort of 69 patients with first recurrence of IDH-wildtype glioblastoma (Supplementary Figure S2). An association between lower residual contrast-enhancing tumor and overall survival was retained in the subgroups of tumors with or without *MGMT* promoter methylation. When patients were classified according to the RANO *resect* classification for glioblastoma,[16] patients assigned to RANO class 1/2 had prolonged overall survival compared to patients in RANO class 3/4 (11.9 vs 8.2 months; *P*=.032). However, our limited sample size did not allow for reliable conclusions on the role of supra-maximal resection beyond the contrast-enhancing tumor borders for recurrent disease.[16]

To determine whether survival following re-resection was associated with surgically more accessible tumors (with lower proximity to eloquent structures and thus an inherently better prognosis), we explored the association between an "oncologically meaningful resectability" and outcome. However, there was no statistically significant association between the fraction of raters agreeing on resectability and overall survival, regardless of whether the raters' judgment was based on imaging only (HR for each percent of agreement on resectability: 1.03 with CI 0.5-2.2; *P*=.933) or also on clinical background (HR for each percent of agreement on resectability: 0.84 with CI 0.4-1.8; *P*=.650). Similarly, a consensus for resectability by greater than 80% of raters based upon pre-operative MRI was not associated with overall survival in either the subgroup of patients in whom re-resection was provided (10.7 vs 11.4 months, *P*=.792) nor in the subgroup of patients in whom no re-resection was provided (8.7 vs 8.0 months, *P*=.902). Also, when the consensus on resectability was based on both pre-operative MRI together and clinical background, there was no difference in overall survival in either the subgroup of patients in whom re-resection was provided (11.9 vs 9.1 months, *P*=.326) nor in the subgroup of patients in whom no re-resection was provided (8.4 vs 9.3 months, *P*=.365) (Figure 3F). Similarly, a consensus by greater than 80% of raters that an individual tumor might not be resectable was not associated with less favorable outcome; independent of whether that consensus was reached by assessing the pre-operative MRI with or without accompanying clinical information.

Discussion

Recurrence is inevitable in glioblastoma, and re-resection is common for recurrent disease, although its efficacy to extend progression-free or overall survival remains controversial.[2,3] However, the perceived resectability of recurrent glioblastomas may differ between surgeons. The potential heterogeneity in perceived resectability has implications for prospective trials: a single prospective randomized trial (RESURGE; NCT02394626) on the oncological value of re-resection includes patients for whom a central review considers complete removal of the contrast-enhancing lesion feasible without significant functional risk. Notably, complete resections are not always achieved even when this is the initial intent: in the pivotal study leading to the approval of 5-aminolaevulinic acid (5-ALA) for glioblastoma surgery,[21,22] the assumption that a complete resection of the contrast-enhancing tumor could be achieved was an inclusion criterion. However, this was only achieved in 50.7% of these patients with newly diagnosed glioblastoma (combining the white light group and the 5-ALA group). While the rate of complete resections of the enhancing tumor portion might have increased to about 80% over the last few years, as suggested by more recent prospective trials,[23] this heterogeneity may hamper the integration of re-resection into clinical trial protocols. Also, further heterogeneity might be induced by the access of operating surgeons to surgical adjuncts.[24,25] Additionally, tumors considered unresectable are often in close proximity to eloquent brain regions and may thus be associated with an inherently worse prognosis, which in combination with the aforementioned heterogeneity, may further hamper assessment of the oncological value of re-resection. Based on the clinically well-annotated, prospective cohort of patients with first recurrence of IDH-wildtype glioblastoma from the DIRECTOR trial,[8] we demonstrate that assessment of resectability is highly heterogenous even among surgical experts. While clinical background affects perceived resectability to some extent, surgical decision-making predominantly relies on evaluation of imaging. Even when evaluating our identical cohort of patients, experts made inconsistent assessments regarding oncologically meaningful tumor removal. Resectability, despite being an important criterion for inclusion in numerous neurooncological studies, is therefore not uniformly

assessed. With residual tumor volume, but no consensus on resectability from surgical experts, associated with outcome, these results might have implications for the design of clinical trials.

We provide evidence that there is only moderate agreement for resectability as well as non-resectability of recurrent glioblastoma, with no consensus by >80% of the raters on resectability for one third of cases in this study. With the surgical goal of all raters being the maximal safe resection of the contrast-enhancing tumor, the clinical practice of the raters could be interpreted to be in accordance with current evidence that complete resection of the contrast-enhancing tumor translates into favorable outcome.[11] However, the wide range for perceived resectability reported in this study more likely reflects differences in the raters' judgement as to whether the tumor can be removed without jeopardizing neurological function. These findings are corroborated by a retrospective study from Sonabend et al,[13] in which 13 surgeons rated 20 different cases of newly diagnosed glioblastoma. Here, moderate agreement with an intraclass correlation of 0.435 was computed when surgeons were asked whether to pursue a biopsy or an open resection; and, similar studies with a lower number of raters have estimated even lower agreements on whether a glioblastoma is amendable to complete resection.[26,27] Notably, none of these studies have made use of a prospective trial cohort to assess the association between resectability and survival. Considering that various prospective studies of recurrent glioblastoma (including novel study designs such as window-of-opportunity trials)[28] require resection as an inclusion criterion (eg NCT06552260 and NCT02394626), it is tempting to speculate that baseline characteristics of eligible patients differ markedly depending on the surgical team evaluating the patient. This potential selection bias is particularly problematic given the absence of a randomized control group in early phase clinical trials for recurrent disease. Standardized tools which allow a consensus-based estimation of resectability are therefore warranted to allow more objective patient stratification between trial arms in future prospective trials incorporating resection into their protocols.[29,30] Likewise, the development of such tools may identify confounding factors in retrospective studies on newly diagnosed or recurrent glioblastoma, and could also serve for benchmarking in order to compare the surgical complexity of tumor cases presenting to individual centers.

We verified that surgical decision-making is mainly based on imaging findings and surgeons' experience. In addition, clinical factors linked to a more favorable patient outcome (such as younger age or longer time to progression as a surrogate marker of less aggressive disease) encouraged raters to consider re-resection. However, providing clinical information in addition to the imaging did not result in a higher rate of consensus for resectability, but rather introduced more disagreement. While different risk scores exist to predict outcome following re-resection for recurrent glioblastoma,[31] no reliable clinical tools exist to identify patients who are likely to experience a survival benefit from re-resection. As survival benefits of lower residual tumor volumes were largely demonstrated in unmethylated (newly diagnosed) glioblastoma, and less often in studies on methylated tumors,[16,23,32–34] it remains to be seen whether future studies might add sufficient evidence that surgery is particularly valuable in unmethylated disease given the lack of benefit from alkylating chemotherapy in these patients, and contribute to surgical decision-making. In our current study, information on *MGMT* promoter methylation status was not relevant for raters when evaluating whether a patient might be a candidate for re-resection. It remains to be noted that our current cohort of patients with recurrent glioblastoma met the stringent inclusion criteria of the DIRECTOR trial, including age less than 80 years and sufficient clinical functioning to be eligible for chemotherapy re-challenge. Also, we cannot exclude the absence of significant correlations between perceived resectability and other clinical factors (such as longer time to first recurrence), which might be due to the limited sample size of our cohort. The small sample size also hampered subgroup analyses for patients in which unanimous agreement for or against resectability was reached. Future studies should consider a broader, non-clinical trial patient population with a broader range of clinical characteristics, as surgical decision-making might be guided by clinical variables to a larger extent than within the narrow inclusion criteria of a clinical trial. In this context, it must be emphasized that the induction of a new neurological deficit almost certainly negates the oncological effects of re-resection.[35] Notably, our data suggest that a deficit after surgery is the predictor of outcome rather than an eloquent tumor localization per se.

We confirmed the association of a favorable outcome with lower contrast-enhancing tumor volume prior to temozolomide re-challenge,[10] but found no evidence in the DIRECTOR cohort that tumors in more resectable locations (as judged by a higher consensus between raters based on tumor eloquence, biological aggressiveness, or surgical accessibility) had prolonged survival. This observation confirms the prognostic value of surgical results measured as tumor residual rather than disease location in accessible brain,[10,11,36] and supports the notion that perceived resectability (even when agreed upon) may not independently predict outcome. Also, submaximal resection was not associated with a more favourable outcome compared to non-surgical management as previously described.[10,11] This comes with profound clinical implications for judicious surgical decision-making: maximal safe resection of the contrast-enhancing tumor must remain a primary goal of surgery for recurrent glioblastoma. Our data support that surgeons may proceed with surgery if they are reasonably convinced they can remove the contrast-enhancing tumor without causing a new neurological deficit,[11] even when other centers have recommended differently, given that a consensus against resectability was not prognostic in our cohort. Here, it is tempting to speculate that patients treated by surgeons most experienced in performing maximal safe re-resections might also have the most favourable outcome. Perceived resectability should therefore be understood as a selection construct guiding surgical decision-making and trial eligibility, rather than as an independent determinant of outcome due to heterogeneity in intraoperative judgment, surgeon-specific aggressiveness, and institution-specific thresholds for neurological risk. The fact that a non-enhancing tumor did only marginally affect raters' judgment on resectability might reflect a surgical mindset that contrast

enhancing tumor is more relevant for survival than a non-contrast-enhancing tumor in re-resection.[11] However, we may have encountered selection bias as the DIRECTOR trial exclusively randomized patients with good clinical function, and re-resection was often provided prior to trial inclusion. Patients with poor clinical function are generally considered poor surgical candidates for re-resection.[37] We cannot comment on the number of patients with clinical deterioration due to re-resections who would have otherwise been eligible for DIRECTOR, and results from the prospective randomized RESURGE trial (NCT02394626) on the oncological role of re-resection are eagerly awaited.

This study has several limitations. First, although individual surgeons differ in operative philosophy and risk tolerance, our analysis intentionally did not model surgeon-specific effects. Our objective was to evaluate whether resectability can be assessed as a reproducible concept across experts, rather than to characterize individual decision-making concepts. Here, the term "oncologically meaningful resection" used in our study warrants careful interpretation as the oncological value of surgery is not limited to extending survival but may include tissue acquisition for molecular diagnostics, symptom relief, or prevention of neurological deterioration. With uncertainties in the definitions of the term "oncologically meaningful resection," our analyses on the association between resectability and outcome are to be considered exploratory. Second, the rater cohort consisted exclusively of senior academic neurosurgeons. While this limits generalizability, it represents a best-case scenario for consensus formation; inclusion of a broader neurosurgical population would likely further increase heterogeneity. As such, the distribution of resectability classifications across raters suggests systematic between-surgeon differences in overall thresholds (range 43.5%-84.1% resectable), consistent with differences in surgical aggressiveness. The moderate Fleiss' kappa indicates that variability is not purely random, but reflects structured differences in interpretation of identical cases. Unfortunately, our relatively small group of surgical raters also does not allow a dedicated subgroup analyses on practice variations depending on the geographical localization of the raters, the training they received, or the size of the centers the raters are practicing in. This is further complicated by the limited size of the DIRECTOR trial cohort. Third, our study deliberately evaluated resectability based on conventional MRI and limited clinical information. This does not capture the full nature of surgical decision-making, which in contemporary practice may incorporate functional MRI, diffusion tractography, awake mapping, and fluorescence-guided techniques. Accordingly, some tumors judged unresectable in this analysis might be approached surgically at experienced centers if those advanced adjuncts would be available.[24,25]

In summary, we demonstrate heterogeneity in evaluating surgical resectability for recurrent glioblastoma among experienced neurosurgeons. In our homogenously treated, prospective cohort from the DIRECTOR trial, prognostic associations with outcome were only observed for the actual residual disease burden rather than perceived resectability. Importantly, our observations are limited by the number of raters and the size of the DIRECTOR trial cohort. These findings may have implications for clinical trial design whenever resectability is an inclusion criterion and may motivate further research into how resectability is operationalized for a more standardized assessment tool.

Keywords

extent of resection | glioblastoma | heterogeneity | resectability | surgery

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Lay Summary

We asked whether neurosurgeons agree on which recurring brain tumors ("glioblastoma") can be safely removed, and whether this matters for survival. This is important because many studies require surgery, yet "resectability" is not clearly defined. We analyzed MRIs from 69 patients from a prior trial. Eleven experienced neurosurgeons independently judged if meaningful tumor removal was possible. We found that opinions varied widely, even among experts. Adding clinical details rarely changed decisions. Importantly, agreement on resectability did not predict survival, but the amount of tumor left after surgery did. This suggests we need standardized tools to guide surgical decisions and trials.

Author Contributions

Study concept & design: P.K., E.L.R., M.W., J.C.T. Data collection: P.K., N.T., E.L.R., H.G.W., A.S.J., C.R., D.P.C., E.O.V.M., M.S.B., J.S.Y., W.W., G.T., J.P.S., B.S., K.J.D., L.B., M.L.D.B., M.A.V., Y.E., O.S., M.W., J.C.T. Data analysis & interpretation: P.K., N.T., E.L.R., O.S., J.C.T. Manuscript drafting: P.K., N.T., E.L.R., O.S., J.C.T. Manuscript revising: P.K., N.T., E.L.R., H.G.W., A.S.J., C.R., D.P.C., E.O.V.M., M.S.B., J.S.Y., W.W., G.T., J.P.S., B.S., K.J.D., L.B., M.L.D.B., M.A.V., Y.E., O.S., M.W., J.C.T.

Conflict of Interest Statement

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Data Availability

De-identified individual-level patient data, along with the accompanying data dictionary and statistical protocol, will be made available to qualified researchers upon written request between 12 and 36 months after this article's publication. Requests should be directed to the corresponding author. Applicants must submit a detailed description of the intended use of the data; proposals will be reviewed individually by representatives of all participating centers and will be approved solely for projects involving individual participant data meta-analyses. Access to the data requires a signed data-use agreement.

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