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Prognostic evaluation of re-resection for recurrent glioblastoma using the novel RANO classification for extent of resection: A report of the RANO *resect* group

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Abstract

Background. The value of re-resection in recurrent glioblastoma remains controversial as a randomized trial that specifies intentional incomplete resection cannot be justified ethically. Here, we aimed to (1) explore the prognostic role of extent of re-resection using the previously proposed Response Assessment in Neuro-Oncology (RANO) classification (based upon residual contrast-enhancing (CE) and non-CE tumor), and to (2) define factors consolidating the surgical effects on outcome.

Methods. The RANO *resect* group retrospectively compiled an 8-center cohort of patients with first recurrence from previously resected glioblastomas. The associations of re-resection and other clinical factors with outcome were analyzed. Propensity score-matched analyses were constructed to minimize confounding effects when comparing the different RANO classes.

Results. We studied 681 patients with first recurrence of Isocitrate Dehydrogenase (IDH) wild-type glioblastomas, including 310 patients who underwent re-resection. Re-resection was associated with prolonged survival even when stratifying for molecular and clinical confounders on multivariate analysis; ≤1 cm^3 residual CE tumor was associated with longer survival than non-surgical management. Accordingly, "maximal resection" (class 2) had superior survival compared to "submaximal resection" (class 3). Administration of (radio-)chemotherapy in the absence of postoperative deficits augmented the survival associations of smaller residual CE tumors. Conversely, "supramaximal resection" of non-CE tumor (class 1) was not associated with prolonged survival but was frequently accompanied by postoperative deficits. The prognostic role of residual CE tumor was confirmed in propensity score analyses.

Conclusions. The RANO *resect* classification serves to stratify patients with re-resection of glioblastoma. Complete resection according to RANO *resect* classes 1 and 2 is prognostic.

Key Points

- Residual contrast-enhancing tumor ≤1 cm^3 is associated with favorable outcomes after re-resection.
- The RANO *resect* classification serves for prognostic stratification according to residual tumor.
- (Radio-)chemotherapy may consolidate the beneficial effects of re-resection.

Importance of the Study

The value of re-resection for recurrent glioblastoma has been the subject of debate. We, therefore, studied a molecularly and clinically well-defined cohort of 681 patients with first recurrence of a IDH wild-type glioblastoma. Based on this cohort from 8 high-volume centers in the United States and Europe, we provided evidence that re-resection is associated with favorable outcomes when a post-operative volume of less than 1 cm^3 residual contrast-enhancing (CE) tumor can be surgically achieved. Accordingly, the RANO *resect* classification served to prognostically stratify patients according to extent of resection. This notion was confirmed using propensity score-matched analyses to minimize effects of confounders. The use of (radio-)chemotherapy following re-resection was strongly associated with increased survival and particularly pronounced in patients in whom at least "maximal CE resection" was achieved. Surgery plays an important role in the treatment of recurrent glioblastoma, and the RANO *resect* classification serves as a stratification tool also in recurrent glioblastoma.

In glioblastoma, microsurgical resection followed by concomitant radiochemotherapy and maintenance chemotherapy represents the standard of care.[1,2] Despite such intensive first-line therapy, progression inevitably occurs and is often characterized by an aggressive disease course and poor prognosis.[3] Therapeutic considerations for recurrent glioblastoma remain controversial as no treatment has shown convincing improvement in post-recurrence survival in a randomized controlled trial.[4,5]

Whereas some studies have failed to demonstrate favorable effects of surgical resection at tumor progression,[3,6] the use of re-resection has more recently been associated with improved outcomes.[7–9] However, such notions were predominantly established in molecularly ill-defined cohorts prior to the World Health Organization (WHO) classification 2021.[10] Also, patients deemed suitable for re-resection might have a favorable clinical profile and less extensive, non-eloquent disease.[11] As such, it is unclear whether this outcome benefit is rather selection bias or indeed the extent of resection per se which contributes to a potential association between re-resection and outcome in retrospective cohorts. A prospective randomized controlled trial excluding potentially resectable tumors from surgery is difficult to conduct and the only currently active trial (NCT02394626) is still recruiting since more than five years. Accordingly, various retrospective studies reported a range of resection thresholds that may translate into a survival benefit.[7,8,12] In this context, the value of "supramaximal" resection, which emerged for newly diagnosed glioblastoma, remains unanswered for recurrent tumors as potential benefits need to be carefully weighed against increased risks of post-operative deficits.[13,14]

These comparative analyses of previous reports are further complicated by the terminology to describe extent of resection which has been inconsistently applied and often refers to the relative tumor reduction (in percentage).[7] Given that the absolute residual tumor (in cm^3) might be prognostically more important than the relative extent of resection,[15] we recently established the "RANO classification for extent of resection" based upon the residual contrast-enhancing (CE) and non-CE tumor to standardize terminology.[14,16] In the current study, we made use of this classification system to analyze the associations of re-resection with outcome in a well-annotated multicenter cohort of patients with first recurrence from previously resected glioblastoma per WHO 2021 classification.[17] Here, we first examined the prognostic relevance of re-resection when controlling for residual tumor volume and clinical confounders. We then explored the associations of different residual tumor volumes with outcome, including approaches involving "supramaximal" resection beyond CE tumor borders as determined by the RANO classification. Next, the interrelations of non-surgical therapies with the associations between re-resection and outcome were analyzed. To minimize such and other confounding effects on our estimation of the true biological effects of residual tumor defined by the RANO classification, we constructed propensity score-matched analyses comparing varying volumes of residual tumor.

Methods

At each participating center, clinical data were collected with institutional Institutional Review Board (IRB) approval. Coded data were sent for analysis and storage to the main study center at the Ludwig-Maximilians-University in Munich, Germany. The study protocol was approved by the IRB of the Ludwig-Maximilians-University (AZ 21-0996).

Study Population

The RANO *resect* group searched the institutional databases of 8 neuro-oncological centers in Europe and the United States for patients with first relapse of a previously resected glioblastoma (Figure 1A). Patients were selected based on the following criteria: (1) first radiographic recurrence of a previously resected IDH wild-type glioblastoma per WHO 2021 classification,[10] (2) information on treatment and outcome following first recurrence available for review, and (3) pre-and post-operative magnetic resonance imaging (MRI) (including contrast-enhanced T1- and T2/ fluid-attenuated inversion recovery [FLAIR]-sequences) available for review when patients underwent re-resection. In patients meeting those criteria, a standardized set of demographic, clinical, therapeutic, and volumetric information was extracted from the databases by each center.

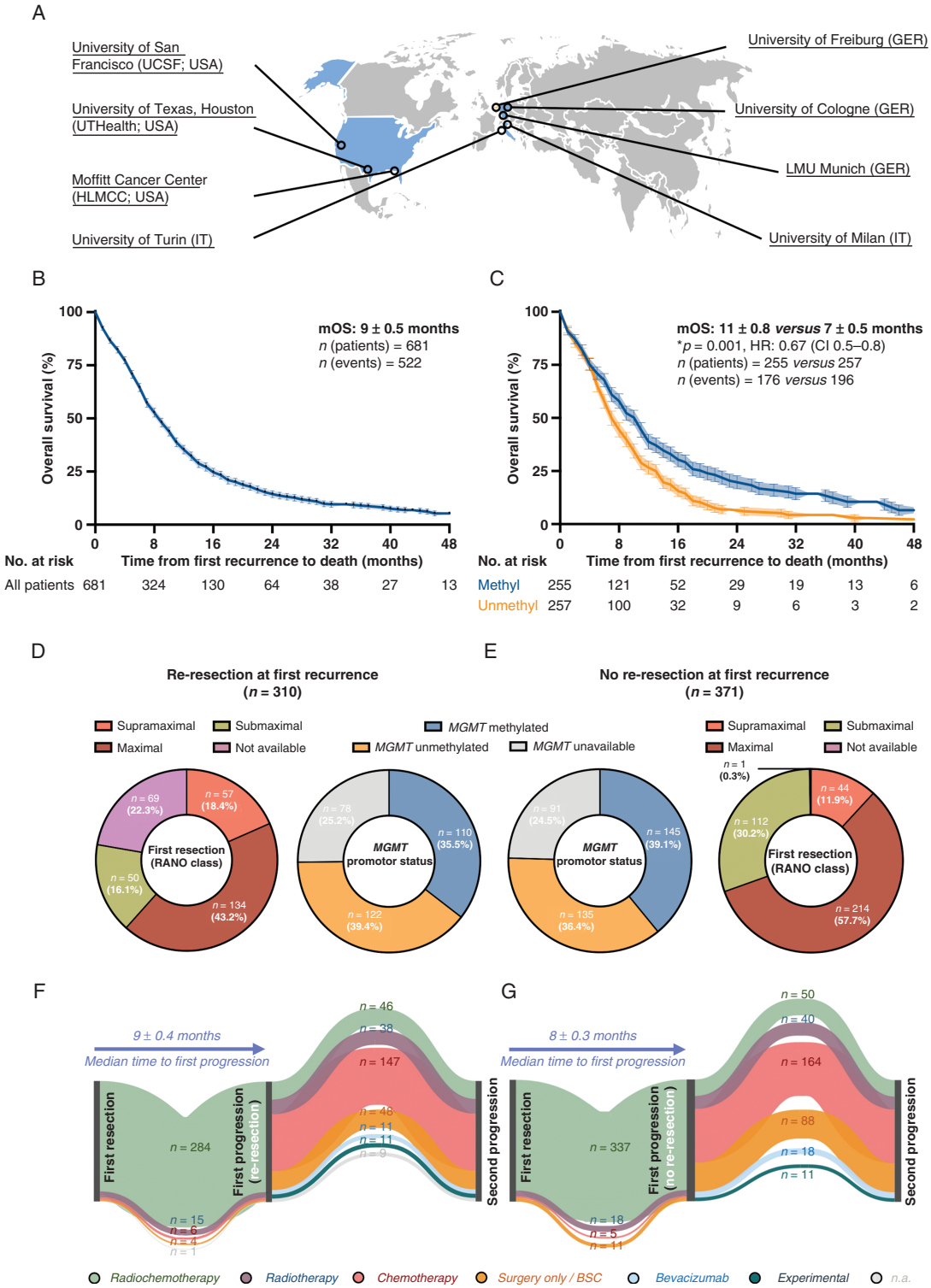

Figure 1. Baseline characteristics of patients with first recurrence of a previously resected glioblastoma. (A) Schematic representation of the 8 neuro-oncological centers participating in the study. (B, C) Kaplan–Meier estimates of overall survival after first recurrence for the entire study cohort (B; *n* = 681) and for patients with *MGMT* promotor status available (C; *n* = 512). Points indicate deceased or censored patients, light shading indicates standard error of the mean (SEM). (D, E) Distribution of residual tumor following first resection (measured according to the RANO classification) and *MGMT* promotor methylation status across patients with re-resection (D; *n* = 310) and patients managed without re-resection (E; *n* = 371) at first recurrence. (F, G) Therapeutic approaches following diagnosis and first recurrence among patients with re-resection (F; *n* = 310) and patients managed without re-resection (G; *n* = 371) at first recurrence. Nodes of the Sankey plots represent time points in the disease course (new diagnosis, first recurrence, second recurrence); and time to first progression is indicated. Therapeutic approaches are color-coded and arc thickness corresponds to patient numbers.

Measurement of Tumor Volumetrics and Patient Stratification

Tumor volumes were manually delineated on pre- and postoperative MRI scans (obtained within 72 hours following resection whenever possible)[18] as previously described.[14] Volumes were quantified using the preferred institutional software (BrainLab Smartbrush, Philips IntelliSpace Discovery, 3D Slicer) by by institutional raters, and results were cross-checked with the radiologic reports. Total CE tumor was measured on contrast-enhanced T1-sequences, and non-CE tumor was measured on FLAIR (or if not available: T2)-sequences. Raters were advised to ensure that FLAIR/T2-abnormalities were not therapy-related changes by reviewing pre-operative imaging and post-operative sequences (particularly including diffusion-weighted imaging [DWI]); and non-CE tumor was identified based upon disruption of the anatomical architecture as well as its FLAIR/T2-signal intensity compared to CSF and physiological white matter. Discrepancies were resolved by consensus with another rater at the individual institution. Multifocal disease was quantified separately at each focus and summed together. Absolute tumor volumes (in cm^3) were recorded; and individual patients were then stratified based on the residual tumor volumes following the recently proposed "RANO classification system"[14,16]:

- "supramaximal CE resection" (class 1): 0 cm^3 CE tumor + ≤5 cm^3 non-CE tumor.
- "maximal CE resection" (class 2): 0–1 cm^3 CE tumor ± >5 cm^3 non-CE tumor.
- "submaximal CE resection" (class 3): >1 cm^3 CE tumor.

Definition of Endpoints

Patients were followed until death or day of database closure (February 1, 2023). Patients lost to follow-up were censored on the day of last follow-up. Date of diagnosis was defined as date of first tumor resection. Date of first recurrence was set as date of MRI showing disease progression per RANO criteria.[19] Progression-free survival after recurrence was defined as the interval from date of first recurrence to next radiographic progression or death from any cause; and overall survival after recurrence was defined as the interval from date of first recurrence to death from any cause.

Statistics

Continuous variables were assessed for normal distribution and equal variance using the D'Agostino-Pearson test. For parametric data, differences between 2 groups were tested by the unpaired Student's *t*-test and between multiple groups by one-way Analysis of Variance (ANOVA). For non-parametric data, the Mann–Whitney U-test was used for 2 groups and the Kruskal–Wallis test for multiple groups. The interaction between pre- and post-operative tumor volumes was estimated using Pearson's correlation coefficient (*r*), and prediction models were constructed using simple linear regression. Data are expressed as mean ± SEM if not indicated otherwise, and range is given. The relationship between categorical variables was analyzed using the χ^2-test, and categorical variables are described in absolute numbers and percentages.

For univariate survival analysis stratifying to a binary variable, Kaplan–Meier survival estimates and log-rank tests were calculated. The reverse Kaplan–Meier method was applied for calculation of median follow-up. For univariate survival analysis of outcomes depending on a continuous variable, Cox proportional hazard regression models were constructed to compute hazard ratios (HR) and 95%-confidence intervals (CI). Similarly, Cox proportional hazard regression models were calculated for multivariate survival analysis. For this purpose, markers were first assessed on univariate analysis; and if of significance forwarded into the multivariate model. Assumptions of proportional hazards and linearity were confirmed using scaled Schoenfeld residuals (vs. time) and deviance residuals.

To minimize confounding effects when comparing various residual tumor volumes translating into different RANO classes, we made use of propensity score-based nearest neighbor matching. Matching was based on demographic and clinical markers (age, pre- and post-operative Karnofsky performance status (KPS), presence of a new post-operative deficit), tumor properties (anatomic localization, O^6-methylguanine DNA methyltransferase [*MGMT*] promotor methylation status, pre-operative CE tumor volume), and second-line therapies. The resulting distilled associations of the residual tumor volume between the matched data sets with outcome were assessed using Kaplan–Meier survival estimates and log-rank tests.

All statistical analyses were performed using Prism (v9.5.0; GraphPad Software Inc., San Diego, CA) and Stata statistical software (v17.0; StataCorp LLC., College Station, TX). The significance level was set at $P \leq .05$. Coded data can be accessed upon qualified request from the authors.

Results

Baseline Patient Characteristics

Data from 681 glioblastoma patients at first tumor recurrence diagnosed between 2003 and 2022 were collected (Table 1). All tumors met the definition of IDH wild-type glioblastoma WHO grade 4 as defined by the WHO 2021 classification.[10] *MGMT* promotor status was methylated in 255 patients (37.5%), unmethylated in 257 patients (37.7%), and not available in 169 patients (24.8%). Each patient underwent microsurgical tumor resection at diagnosis, and the vast majority of patients had concomitant radiochemotherapy (621 patients; 91.2%) per current standard of care.[1] Median time until recurrence was 8 ± 0.2 months. Following diagnosis of recurrence (and re-resection in a subset of patients), chemotherapy (311 patients; 45.7%; including predominantly lomustine, temozolomide, and fotemustine), radiochemotherapy (96 patients; 14.1%), or re-irradiation (78 patients; 11.5%) were the most commonly provided non-surgical second-line treatments. At the time of database closure, 588 patients had experienced a second recurrence (86.3%), 159 patients

Table 1. Characteristics for the Study Cohort of Patients With First Recurrence From a Previously Resected Glioblastoma WHO Grade 4

Surgical second-line therapy		Re-resection at first recurrence	No re-resection at first recurrence	Total	*P*-value
Overall		***n*** = 310	***n*** = 371	***n*** = 681	
IDH status (*n*, %)	*wild-type*	310 (100%)	371 (100%)	**681 (100%)**	*1.000*
	mutated	0	0	**0**	
MGMT promotor (*n*, %)	*methylated*	110 (35.5%)	145 (39.1%)	**255 (37.5%)**	*.605*
	non-methylated	122 (39.4%)	135 (36.4%)	**257 (37.7%)**	
	n.a.	78 (25.2%)	91 (24.5%)	**169 (24.8%)**	
TERT promotor (*n*, %)	*wild-type*	21 (6.8%)	35 (9.4%)	**56 (8.2%)**	*.093*
	mutated	118 (38.1%)	161 (43.4%)	**279 (41.0%)**	
	n.a.	171 (55.2%)	175 (47.2%)	**346 (50.8%)**	
Demographics	*Age at first diagnosis (years)*	57.1 ± 1	60.2 ± 1	**58.8 ± 0.5**	***.001***
	M:F-ratio	1:0.6	1:0.7	**1:0.7**	*.171*
Localization at diagnosis (*n*, %)	*(sub-)cortical*	268 (86.5%)	272 (73.3%)	**540 (79.3%)**	***.001***
	deep-seated	21 (6.8%)	48 (12.9%)	**69 (10.1%)**	
	multifocal	18 (5.8%)	50 (13.5%)	**68 (10.0%)**	
	n.a.	3 (1.0%)	1 (0.3%)	**4 (0.6%)**	
	dominant	148 (47.7%)	188 (50.7%)	**336 (49.3%)**	*.158*
RANO class after first resection	*RANO 1 ("supramaximal")*	57 (18.4%)	44 (11.9%)	**101 (14.8%)**	***.001***
	RANO 2 ("maximal")	134 (43.2%)	214 (57.7%)	**348 (51.1%)**	
	RANO 3 ("submaximal")	50 (16.1%)	112 (30.2%)	**162 (23.8%)**	
	RANO 4 ("biopsy")	0	0	**0**	
	n.a.	69 (22.3%)	1 (0.3%)	**70 (10.3%)**	
First-line therapy (*n*, %)	*Radiochemotherapy*	284 (91.6%)	337 (90.8%)	**621 (91.2%)**	*.445*
	Radiotherapy alone	15 (4.8%)	18 (4.9%)	**33 (4.9%)**	
	Chemotherapy alone	6 (1.9%)	5 (1.4%)	**11 (1.6%)**	
	Resection alone	4 (1.3%)	11 (3.0%)	**15 (2.2%)**	
	n.a.	1 (0.3%)	0	**1 (0.2%)**	
Time to first recurrence	*PFS (months)*	9 ± 0.4	8 ± 0.3	**8 ± 0.2**	***.001***
Clinical markers at recurrence	*KPS at recurrence (median, range)*	80 (30–100)	80 (30–100)	**80 (30–100)**	***.001***
	Post-OP KPS (median, range)	80 (20–100)	n. appl.	**80 (20–100)**	
	New post-operative deficit (n, %)	59 (19.0%)	n. appl.	**59 (19.0%)**	
Second-line therapy (*n*, %)	*Chemotherapy alone*	147 (47.4%)	164 (44.2%)	**311 (45.7%)**	***.006***
	Radiotherapy alone	38 (12.3%)	40 (10.8%)	**78 (11.5%)**	
	Radiochemotherapy	46 (14.8%)	50 (13.5%)	**96 (14.1%)**	
	Surgery only or BSC	48 (15.5%)	88 (23.7%)	**136 (20.0%)**	
	Bevacizumab	11 (3.6%)	18 (4.9%)	**29 (4.3%)**	
	Experimental agents	11 (3.6%)	11 (3.0%)	**22 (3.2%)**	
	n.a.	9 (2.9%)	0	**9 (1.3%)**	
Outcome after first recurrence	*PFS (months)*	5 ± 0.4	4 ± 0.4	**5 ± 0.2**	*.272*
	OS (months)	11 ± 0.7	7 ± 0.5	**9 ± 0.5**	***.001***

Characteristics are given for patients with first recurrence from a previously resected IDH wild-type glioblastoma WHO grade 4 (total; *n* = 681). Patients were stratified according to whether they underwent re-resection at first recurrence (*n* = 310) or were managed with non-surgical approaches (*n* = 371). Differences between the groups were analyzed 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 performed for survival analyses. *P*-values are given in italic letters, and asterisks and bold letter indicate $P \leq .05$.
Abbreviations: BSC, best supportive care. F, female. IDH, Isocitrate dehydrogenase. KPS, Karnofsky performance status. M, male. MGMT, O^6-methylguanine DNA methyltransferase. n.a., not available for review. n. appl., not applicable. OS, overall survival. PFS, progression-free survival. TERT, telomerase reverse transcriptase.

were alive at last follow-up (23.3%) including 115 patients who were lost to follow-up (not seen for ≥12 months), and 522 patients (76.7%) were deceased. Median time from first to second recurrence was 5 ± 0.2 months, and median time from first recurrence to death was 9 ± 0.5 months (Figure 1B). Among patients with *MGMT* promotor status being reported, methylation was strongly associated with prolonged survival after first recurrence (Figure 1C).

310 patients (45.5%) received re-resection for first glioblastoma recurrence (Figure 1D), and 371 patients (54.5%) were managed with non-surgical approaches (Figure 1E). There was no distinct molecular profile (ie, *MGMT* promotor status) of tumors that were scheduled for re-resection; but these tumors were anatomically often characterized by superficial localization. Patients with re-resected tumors had frequently received "supramaximal" or "maximal" resection of CE tumor (defined as RANO class 1 or 2) at diagnosis. Clinically, patients undergoing re-resection had more favorable clinical features such as younger age and higher KPS at recurrence. There were no striking clinically meaningful differences in time from diagnosis to recurrence or second-line medical therapies beyond surgery which were administered to patients with or without re-resection (Figure 1F, G).

Prognostic Role of Re-resection When Controlling for Clinical Confounders and Residual Tumor Volume

Surgical re-resection for first recurrence was associated with favorable outcomes in the unadjusted patient cohort (Figure 2A). Patients undergoing re-resection had a median overall survival of 11 ± 0.7 months after recurrence compared to 7 ± 0.5 months among patients who were managed with non-surgical approaches (HR: 0.69, CI: 0.6–0.8; $P = .001$). A survival difference was seen in both patients harboring tumors with (HR: 0.60, CI: 0.4–0.8; $P = .001$) and without (HR: 0.54, CI: 0.4–0.7; $P = .001$) *MGMT* promotor methylation (Figure 2B, C). Since clinical factors differentially distributed among patients selected for re-resection versus non-surgical second-line therapies were associated with survival on univariate analysis (Supplementary Table 1), we aimed to control for any confounding effects from these variables on the association of re-resection and outcome. The prognostic value of re-resection was retained in the multivariate analysis (HR: 0.65, CI: 0.5–0.8; $P = .001$) after stratifying for such potential clinical confounders (Figure 2D). There was no difference in the favorable outcome of re-resected patients when stratified according to whether re-resection was provided within 6 months of first diagnosis ($n = 87$) or after 6 months ($n = 223$; HR for within 6 months: 0.91, CI 0.7–1.2; $P = .518$).

To study the associations of residual tumor with outcome in detail, we volumetrically assessed the post-operative tumor volume in patients undergoing re-resection. Sufficient volumetric information was available in 307 patients (307/310 patients, 99.0%) with a median pre-operative CE tumor of 9.77 ± 0.9 cm^3 (0–92 cm^3). No residual CE tumor was detected on postoperative imaging in most patients, resulting in a median residual CE tumor of 0 ± 0.2 cm^3 (0–31 cm^3). There were no differences in pre- and post-operative tumor volumes or rate of new deficits between patients presenting at the different study centers (although the pre- and post-operative clinical performance status was different between the study centers). There was a strong correlation between pre- and post-operative CE tumors ($r = 0.543$; $P = 0.001$) with a predicted increment in residual CE tumor of 0.14 cm^3 per each cm^3 of pre-operative CE tumor volume (β_1: 0.14). When we grouped patients into intervals according to their post-operative CE tumor, we found that only a residual CE volume of ≤1 cm^3 was associated with improved outcomes whereas patients with >1 cm^3 residual CE tumor had no superior survival compared to patients without re-resection (Figure 2E).

Exploring the Prognostic Implication of CE and Non-CE Tumor Using the RANO Classification System

We also delineated the non-CE tumor volume (Figure 3A). Based on the information of CE and non-CE tumor volumes, patients were allocated following the "RANO classification for extent of resection" into one of 3 categories[14]: "supramaximal CE resection" beyond the CE tumor borders (RANO class 1; 60/307 patients, 19.5%), "maximal CE resection" (RANO class 2; 157/307 patients, 51.1%), and "submaximal CE resection" (RANO class 3; 90/307 patients, 29.3%) (Figure 3B; Supplementary Table 2). No differences in the interval between MRI demonstrating first progression and re-resection were detected between the 3 RANO classes, but patients in RANO class 3 had more often local recurrence adjacent to the original resection cavity. Given that a prognostic cutoff of ≤1 cm^3 residual CE tumor was identified to be linked to better outcomes with re-resection, this provides another rationale to summarize patients with post-operative tumor volumes of >1 cm^3 CE tumor as RANO class 3 ("submaximal CE resection") as previously defined. Accordingly, the outcome of patients in RANO class 3 was comparable to patients without re-resection (Figure 3C). In turn, an exponential decrease in hazard ratio for death after first recurrence was noted for each cm^3 less of residual CE tumor as predicted by univariate Cox proportional hazard regression modeling (Figure 3D). Patients designated as RANO class 1 or 2 ("supramaximal CE resection" or "maximal CE resection") had *per definitionem* a residual CE tumor of ≤1 cm^3; and superior survival was found in these patients compared to RANO class 3 (12 ± 0.8 versus 9 ± 0.9 months, HR: 0.57, CI: 0.4-0.8; $P = 0.001$) (Figure 3E).

We then aimed to explore the prognostic relevance of non-CE tumors. In patients with no residual CE tumor, median pre-operative non-CE tumor volume was 28.60 ± 3.0 cm^3 (0–275 cm^3) and post-operative non-CE tumor was 17.03 ± 2.4 cm^3 (0–226 cm^3). Again, a considerable correlation between pre- and post-operative tumor volumes was found ($r = 0.850$, β_1: 0.69; $P = .001$). There was no association between residual non-CE tumor and hazard ratio for death using a Cox proportional hazard regression model in patients with no residual CE tumor ($n = 155$) (Figure 3F). As such, there was no difference in overall survival between patients with "supramaximal CE resection"

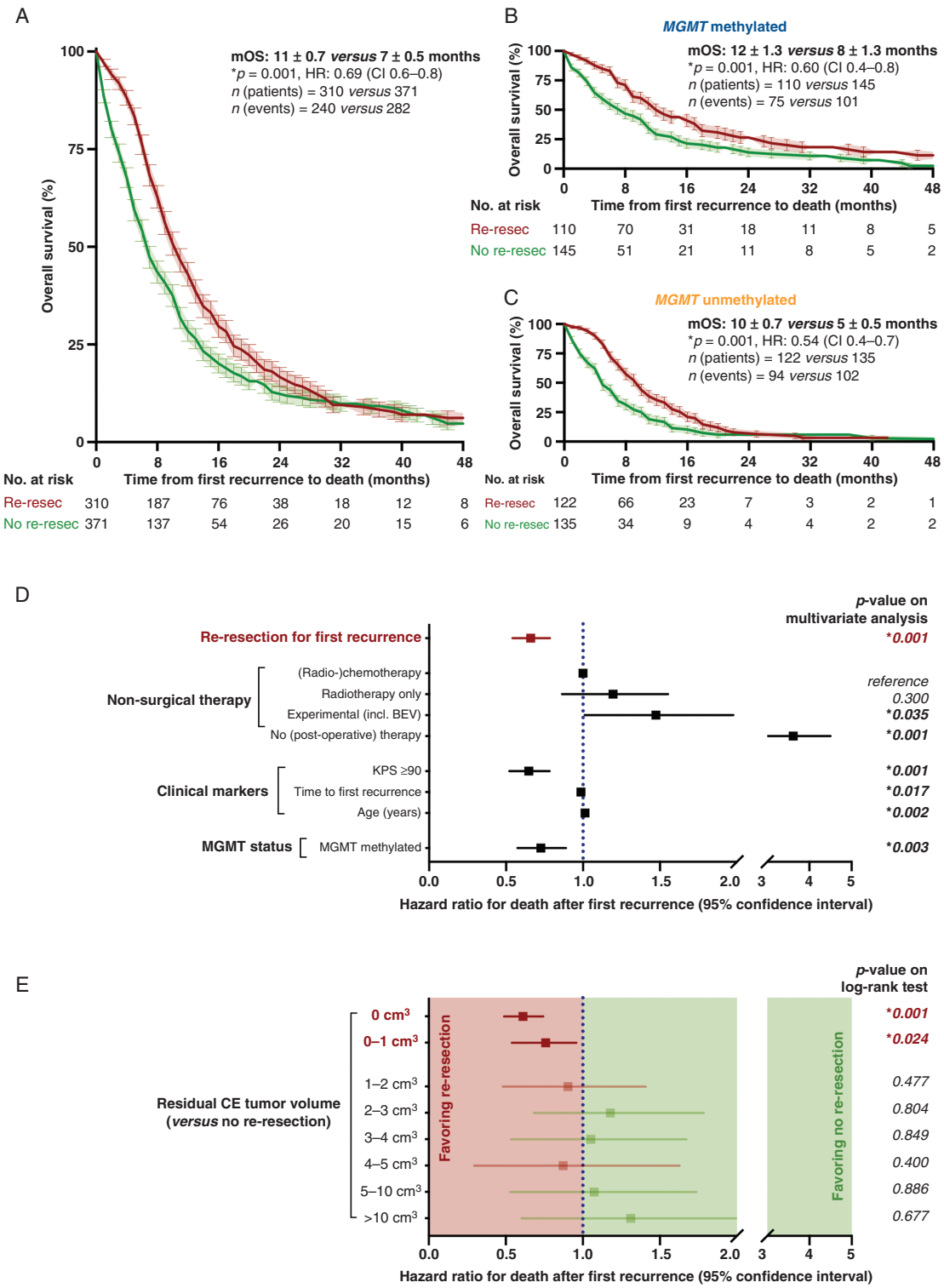

Figure 2. Prognostic role of re-resection compared to non-surgically managed patients. (A–C): Kaplan–Meier estimates of overall survival after first recurrence for the entire study cohort (A; *n* = 681) and for patients with *MGMT* promotor status being methylated (B; *n* = 255) or unmethylated (C; *n* = 257). Patients were stratified according to whether re-resection was provided at first recurrence. Points indicate deceased or censored patients, light shading indicates SEM. (D) Multivariate analysis using a Cox proportional hazard regression model estimating the hazard ratio for death after first recurrence. All included variables were of significance on univariate analysis. BEV: Bevacizumab. Hazard ratio ± 95% confidence interval. (E) Univariate analysis using log-rank tests comparing patients with different amounts of residual contrast-enhancing (CE) tumor volumes following re-resection to non-surgically managed patients. Note that an association favoring re-resection was only observed for residual CE tumor volumes of ≤1 cm³. Hazard ratio ± 95% confidence interval.

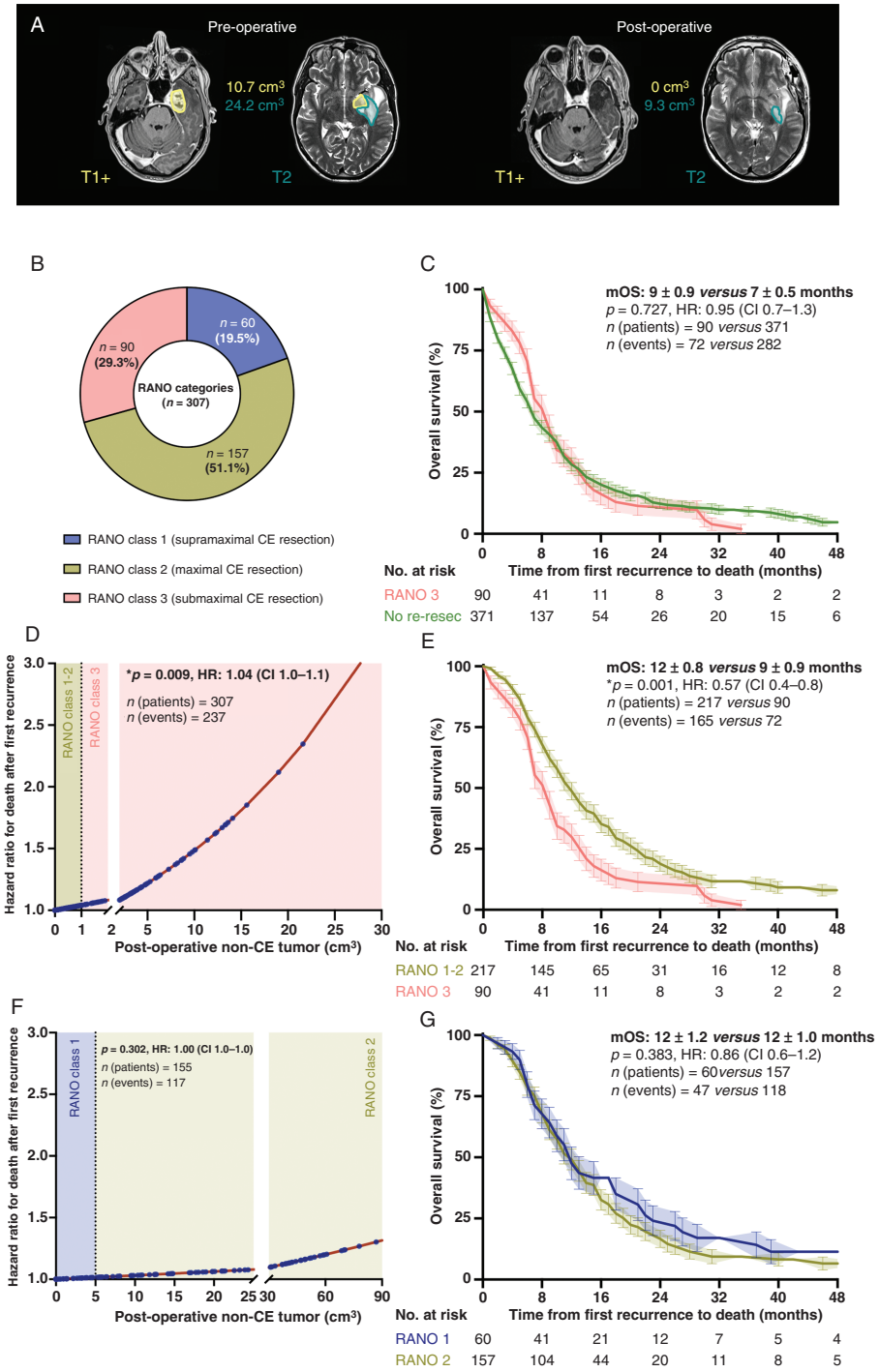

Figure 3. Implications of the stratification per RANO classification by residual contrast-enhancing (CE) and non-CE tumor volumes on outcome. (A) Axial brain MRI with contrast-enhanced T1- (left on each panel) and T2-weighted (right on each panel) sequences demonstrating a left temporo-mesial glioblastoma. The CE (yellow) and non-CE tumor (blue) is delineated. On post-operative imaging, complete CE resection becomes apparent. Note the residual non-CE tumor being surrounded by edema. (B) Stratification of all patients undergoing re-resection with pre- and post-operative volumetrics available for review ($n = 307$) according to the previously proposed RANO classification. (C) Kaplan–Meier estimates of overall survival after first recurrence for patients stratified to RANO class 3 ($n = 90$) compared to non-surgically managed patients ($n = 371$). No differences were observed. (D) Hazard ratios for death after first recurrence calculated for each individual residual CE tumor volume among patients undergoing re-resection ($n = 307$). An exponential hazard increase can be seen for higher residual CE volumes. (E) Kaplan–Meier estimates of overall survival after first recurrence for patients stratified to RANO class 1/2 (corresponding to ≤1 cm³ residual CE tumor; $n = 217$) compared to RANO class 3 ($n = 90$). A significant survival difference is calculated. (F) Hazard ratios for death after first recurrence calculated for each individual residual non-CE tumor volume among patients without any residual CE tumor ($n = 155$). Only a minimal hazard ratio increase can be seen for large residual non-CE volumes. (G) Kaplan–Meier estimates of overall survival after first recurrence for patients stratified to RANO class 1 (corresponding to ≤5 cm³ residual non-CE tumor; $n = 60$) compared to RANO class 2 ($n = 157$). No benefit of non-CE tumor resection was detected. Points indicate deceased or censored patients, light shading indicates SEM.

compared to patients with "maximal CE resection" (RANO 1 vs. RANO 2: 12 ± 1.2 vs. 12 ± 1.0 months, HR: 0.86, CI: 0.6–1.2; P = .383) (Figure 3G). It remains to be noted that the rate of post-operative neurologic deficits was higher among patients with "supramaximal CE resection" and such patients numerically received less often further therapies compared to patients with "maximal CE resection" (new deficits: 20.0% vs. 17.2%, p = 0.631; no further therapies: 16.7% vs. 12.1%, P = .377). There was no difference between patients in RANO class 1 and RANO class 2 regarding the fraction of deficits that were transient within 3 months following re-resection. Survival among patients with "supramaximal CE resection" tended to be longer when no post-operative deficit was encountered (15 ± 2.5 (n = 48) versus 8 ± 1.7 months (n = 12); HR: 0.45, CI: 0.2–1.0; p = 0.057); however, no distinct outcome was observed when only patients without deficits in RANO class 1 and RANO class 2 were compared. Only 4 of the 12 patients (33.3%) with a new deficit (with 2 of them being transient in nature) and "supramaximal CE resection" had intraoperative neuromonitoring during re-resection. Findings on outcome also held true when limited to patients who were homogenously treated as per EORTC-26981/22981-protocol (TMZ/RT→TMZ) as first-line therapy or when overall survival was defined as time from surgical resection (rather than date of MRI showing progression) to death.

Interactions of Non-surgical Therapies With Re-resection of CE Tumor

We explored interactions of further non-surgical therapies with re-resection by additionally stratifying patients according to their non-surgical second-line approaches. As we did not find outcome differences between patients treated with radiochemotherapy and chemotherapy following re-resection, we grouped patients according to whether they have received (radio-)chemotherapy, radiotherapy alone, or only re-resection (or experimental therapy) after second surgery (Figure 4A). Here, the use of (radio-)chemotherapy was associated with substantially longer survival following re-resection (Figure 4B), and this finding was conserved when stratifying for *MGMT* promotor methylation status (but particularly pronounced when methylation was present). This finding was also true when extent of resection measured per RANO classification was considered (Figure 4C): Patients with at least "maximal CE resection" (RANO class 1–2) had superior survival when (radio-)chemotherapy was provided compared to patients receiving radiotherapy alone in the post-operative setting and to patients in whom experimental (including bevacizumab) or no therapy was administered (15 ± 1.3 vs. 9 ± 1.2 vs. 9 ± 0.8 months; P = .001). Similar findings were made when analyzing post-operative therapies among patients with "submaximal CE resection" (RANO class 3) ([radio-]chemotherapy vs. irradiation versus no [or experimental] further therapy: 10 ± 1.2 vs. 8 ± 2.2 vs. 7 ± 1.1 months; P = .005). Notably, the rates of new post-operative deficits were substantially higher with up to 40% among individuals who subsequently received no further treatments; suggesting that decreased clinical status might have prevented patients from receiving further therapies. Also, other clinical parameters indicative of less favorable clinical status in patients without (radio-)chemotherapy were present (Figure 4D).

Confirming the Prognostic Relevance of the RANO Classification by Propensity Score-Matched Analyses

To confirm our findings on the associations between RANO classes and outcome, we matched cohorts to balance covariates between the different RANO classes by identifying nearest neighbors based on propensity score calculations (Figure 5A). Here, we accounted for demographic, clinical, tumor, and therapeutic markers; and achieved excellent covariate balance (Figure 5B, D). Using this approach, we verified the superior outcome of patients who received at least "maximal CE resection" compared to "submaximal CE resection" (RANO 1/2 vs. RANO 3: 12 ± 0.8 vs. 8 ± 0.5 months, HR: 0.59, CI: 0.5–0.8; P = .001) (Figure 5C). Also, we again did not find evidence of distinct outcome favoring the resection of non-CE tumors as there was comparable survival between patients with "supramaximal CE resection" (RANO class 1) or "maximal CE resection" (RANO class 2; 12 ± 1.2 vs. 16 ± 1.1 months, HR: 1.39, CI: 0.9–2.2; P = .140) (Figure 5E).

Discussion

The value of re-resection for recurrent glioblastoma has been the subject of debate. Based on a molecularly well-defined glioblastoma cohort facing treatment for first recurrence, we delineate the important association of residual tumor volume with outcome, propose a prognostic stratification tool to denominate patients accordingly, and provide hypothesis-generating evidence for further non-surgical therapy. These results provide major implications for the design of clinical trials and potentially also for clinical patient management.

We have provided the strongest evidence to date that re-resection is associated with favorable outcomes when a post-operative volume of less than 1 cm^3 residual CE tumor can be surgically achieved. We ruled out that the prognostic associations of re-resection were induced by the presence of clinical or molecular confounders including *MGMT* promotor methylation status or timing of re-resection with respect to initial surgery, and a HR of 0.65 was estimated on multivariate analysis compared to patients without re-resection. Our encouraging findings corroborate prior findings of a secondary analysis of the prospective DIRECTOR trial (which assessed dose-intensified temozolomide rechallenge in progressive glioblastoma) reporting that patients without residual CE tumor experience substantially longer survival following re-resection.[8] In the modern era of neurosurgery, maximal resection of recurrent CE tumors might be frequently achieved in patients deemed to be surgical candidates: 217 of 307 patients (70.7%) in our cohort had less than 1 cm^3 residual CE tumor; and similar numbers might also be extrapolated from other studies.[7,8,20] Conversely, re-resection,

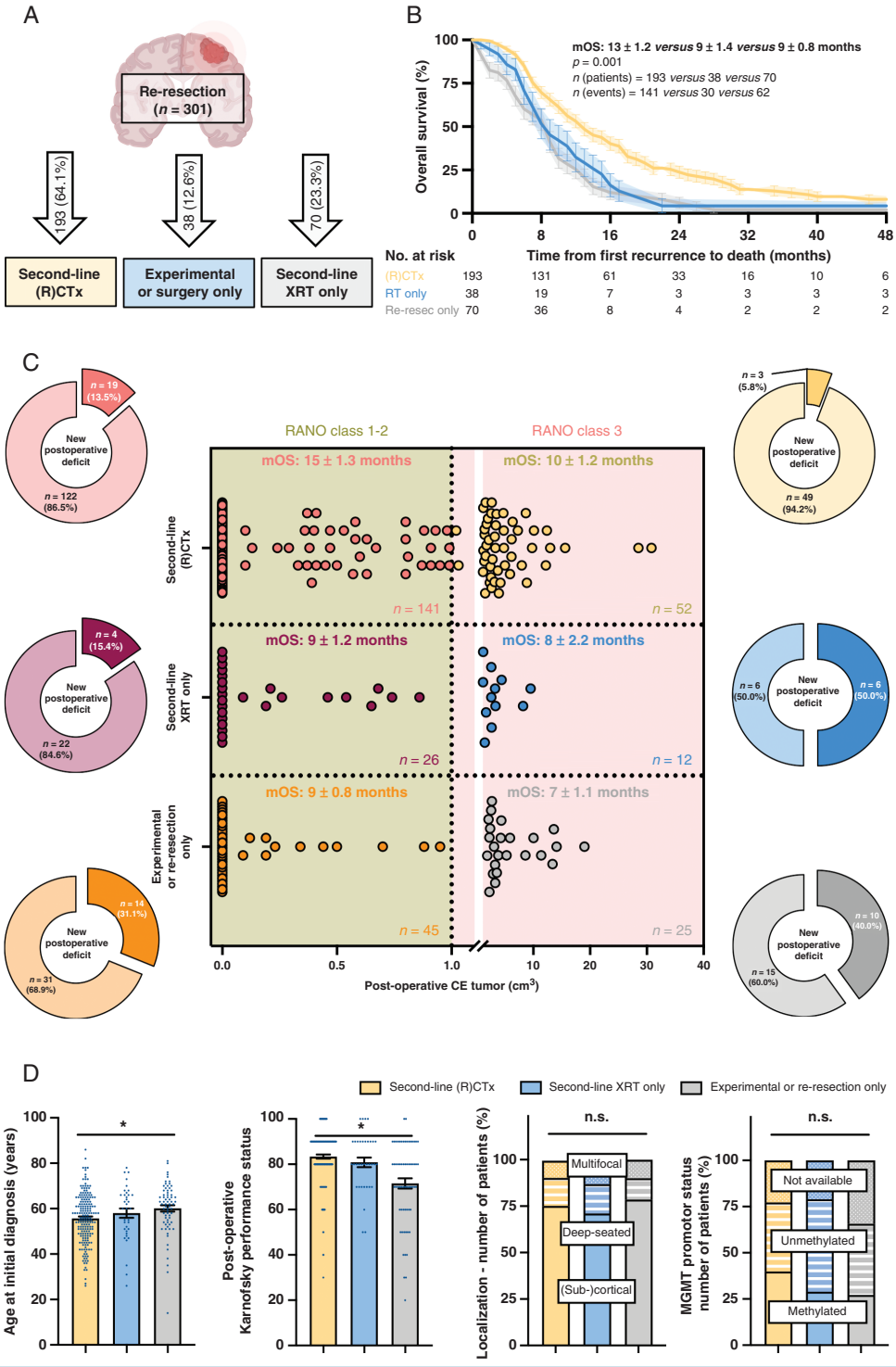

Figure 4. Associations of medical therapies on outcome following re-resection. (A) Overview on the non-surgical approaches provided after re-resection (n = 301). (B) Kaplan–Meier estimates of overall survival after first recurrence for patients with re-resection stratified for (radio-) chemotherapy ((R)CTx; n = 193), radiotherapy (XRT; n = 38), and re-resection (or experimental) therapy only (n = 70). Points indicate deceased or censored patients, light shading indicates SEM. (C) Contingency table stratifying patients to residual contrast-enhancing (CE) tumor (x-axis; yellow: RANO class 1/2, pink: RANO class 3) and further medical management (y-axis). Each dot represents one individual patient, the median survival of the respective patient subgroup is indicated, and the rate of new post-operative deficits is indicated by a pie chart next to each patient subgroup. Darker colors in each pie charts indicate individuals with post-operative deficits. (D) Distribution of age (left panel), post-operative Karnofsky performance status (KPS; second to left), tumor localization (second to right panel), and *MGMT* promotor methylation status (right panel) across the different therapy subgroups. Asterisks indicate $P \leq .05$ and n.s. indicates "not significant" when all 3 groups were tested together using a Kruskal–Wallis test (for continuous data) or a χ^2-test (for categorical variables). Mean ± SEM for continuous data.

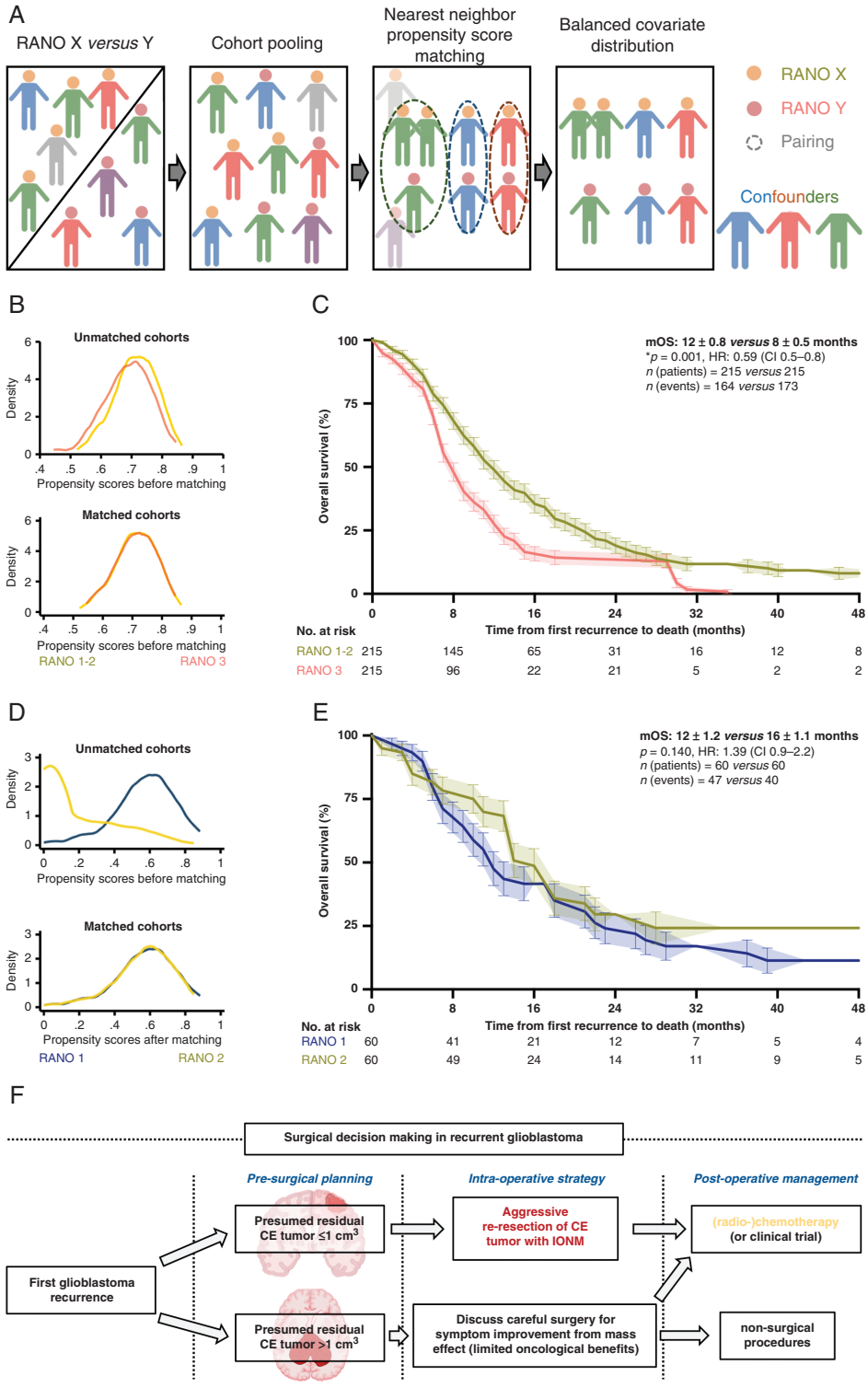

Figure 5. Prognostic confirmation of the RANO classification using propensity score-matched analyses. (A) Schematic representation of the principals of propensity-scored based matching. Nearest neighbor matching for multiple covariates results in 2 comparable cohorts who only differ for the variable of interest. (B–E) Kernel density estimates before and after propensity score-based matching (B, D) and Kaplan–Meier estimates for survival after first recurrence (C, E). Patients stratified to RANO class 1/2 (corresponding to ≤1 cm^3 residual contrast-enhancing (CE) tumor; $n = 215$) were matched to controls selected from RANO class 3 ($n = 215$) (B, C); and patients stratified to RANO class 1 (corresponding to ≤5 cm^3 residual non-CE tumor; $n = 60$) were matched to controls selected from RANO class 2 ($n = 60$) (D, E). Note that survival differences were only observed for the comparison based on CE tumor, but not for non-CE tumor. Points indicate deceased or censored patients, light shading indicates SEM. (F) Proposed strategy for surgical decision-making in patients with recurrent glioblastoma. Importantly, the optimal therapy beyond surgery warrants prospective evaluation as the current study is only hypothesis-generating in this regard.

therefore, needs to be critically discussed from an oncological standpoint when pre-surgical planning yields that a residual CE tumor much above 1 cm^3 must be expected; although surgery for improvement of mass effect-related symptoms or inclusion into phase 0 trials might still be reasonable in selected cases (Figure 5F).[21]

In turn, we detected an exponential increase in risk for death with each cm^3 residual CE tumor left behind among patients undergoing re-resection. These results strongly argue for dedicated intraoperative efforts to reduce CE tumors as much as safely possible once the decision for re-resection has been made. This finding is in line with retrospective observations from the SN1 study group on a multicenter glioblastoma cohort but also from others,[7,22] outlining that a higher relative tumor reduction results in longer survival following re-resection. Our data, therefore, contradict prior reports suggesting that patients with recurrent glioblastoma do not benefit from re-resection,[3,6] but indicate that any effect critically depends upon the surgical success as measured by residual CE tumor volume. Unlike in newly diagnosed glioblastoma,[13,14,23] we did not find evidence for a benefit from "supramaximal" resection of non-CE tumor. A considerable rate of post-operative deficits might have counteracted the oncological effects of re-resection in patients designated as RANO class 1. Notably, the majority of cases with a new post-operative deficit in this group were operated on without functional monitoring or stimulation. Hence, the use of sophisticated (stimulation) mapping strategies is recommended when resection beyond CE tumor is provided as preventing deficits should be prioritized,[24–26] although vascular injuries might not be preventable using stimulating mapping. As no standardized mapping strategies have been utilized in our current dataset, only limited conclusions can be drawn on the impact of supramaximal CE resection.

We verified that the "RANO classification system" represents a prognostic stratification tool for patients with recurrent glioblastoma. Patients assigned to a RANO class reflecting lower residual CE tumor had more favorable outcomes, and this was convincingly confirmed by propensity score-matched analyses.[14] This easy-to-use classification may therefore serve for patient stratification during clinical trials not only in the primary setting,[14] but also for recurrent glioblastoma. Here, it adds valuable granularity to the clinical description of re-resection. It is tempting to speculate that previous studies might have avoided the risk of missing important associations by using such a stratification system.[3,6] A large number of "RANO class 3" patients may shift the results towards a negative conclusion regarding the role of re-resection effects for outcome; and vice versa. With continuous improvement in intraoperative visualization and monitoring tools,[24–26] the rate of patients undergoing re-resection for recurrent glioblastoma with residual CE tumor volumes below the critical threshold of 1 cm^3 might have increased in the last years. In line with this assumption, more recent studies also found a benefit from re-resection even when not controlling for volumetrics.[27–30]

Utilizing propensity score-based matching,[31] we made it unlikely that our findings on the prognostic role of the RANO categories were confounded by molecular or clinical factors (which have in part been inconsistently distributed across the contributing study centers). Also, neither dominant nor superficial tumor localization predisposed to lower residual CE tumor volumes. Thus, the observed associations between lower CE tumor volumes and more favorable outcomes cannot be solely explained by the assumption that a larger post-operative tumor is a surrogate marker for tumors with an inherently worse prognosis due to growth closer to critical brain regions. On a cautionary note, pre- and post-operative CE volumes were linearly correlated indicating that extensive resection might have been limited due to invasion of eloquent areas in large tumors.[3,14]This might be further aggravated by the difficulties to dissect in a heavily pretreated tissue, particularly close to functional areas. As such, patients with "submaximal CE resection" (RANO class 3) had less extensive resection at first surgery and more often localized recurrence adjacent to the original resection cavity. This may further point towards eloquent structures hampering resection, and surgery might have been scheduled in those patients for symptoms due to mass effect despite pre-operative planning yielding a high probability of incomplete resection. However, we have no detailed information on whether re-resection was provided for mass effect symptoms or for oncological purposes; and it is reasonable to speculate that a higher number of patients in RANO class 3 had surgery for mass effect which might have contributed to their less favorable outcome.

In our cohort, the use of (sequential or concomitant) (radio-)chemotherapy was strongly associated with increased survival and particularly pronounced in patients in whom at least "maximal CE resection" (RANO class 1/2) was achieved, irrespective of *MGMT* promoter status. We hypothesize that chemotherapy may therefore consolidate the beneficial effects of re-resection (or re-resection the effects of chemotherapy); and our assumption is consistent with the report from the SN1 study group concluding that chemotherapy positively influenced survival following re-resection.[7] Our patients in RANO class 1/2 treated with (radio-)chemotherapy had an overall survival of 15 months, which has been recently postulated to represent the outcome goal for single-arm phase II trials to convincingly demonstrate antitumor activity.[32] Notably, the use of (radio-)chemotherapy reflected a favorable clinical profile (ie, younger age, higher KPS, and less post-operative deficits) in our cohort which might represent a confounding factor. In this respect, it is noteworthy that not only re-resection but also chemotherapy has not been shown to improve survival compared with any control intervention in a randomized trial.[33] Conversely, also irradiation was accompanied by such favorable clinical markers but no compelling evidence for improved outcome was noted. Whether the prognostic role of chemotherapy (and the exact regimen used) will finally hold true in prospective clinical trials with pre-specified sample size statistics and regardless of *MGMT* promotor status warrants evaluation. Although prospective trials in this regard are yet missing, omitting therapy after re-resection should be only used with caution as this may jeopardize the beneficial effects of re-resection.

Our results are derived from well-annotated glioblastoma cohorts treated consecutively at large neuro-oncological centers. It remains to be noted that the distribution of

patients who underwent re-resection compared to non-surgically managed patients might not depict the surgical landscape which is being offered across Europe and the United States; particularly as all of our centers are (inter-) national referral centers. It is therefore unclear whether our findings might be generalizable to smaller centers or lower- and middle-income countries; particularly as we cannot fully exclude some selection bias as the clinical performance status was inconsistently distributed across the centers translating into different outcomes when comparing the individual centers. Also, the value of re-resection early after initial surgery (and, thus, during or shortly after [radio-]chemotherapy) warrants particular evaluation in future study as we were unable to retrieve the exact dates of when last medical or radiotherapeutic treatment was received. Volumetric information on the recurrent tumors of non-surgically managed patients were not available for review due to the retrospective nature of our study. Therefore, it was not possible to reliably utilize propensity score-matched analysis also for a comparison between patients with and without re-resection. Moreover, we did not control for inter-rater variability in delineation of the tumors, but we previously found high agreement for CE tumor volumetrics.[14] However, inter-rater variability for non-CE tumors might appear considerably higher, particularly as treatment effects additionally hamper volumetric analysis in the recurrent situation. Both T2/FLAIR but also CE changes can be mistakenly interpreted as active disease in the post-treatment setting. Thus, our data are in support of centralized imaging reviews and advanced imaging techniques for future studies on supramaximal resection of non-CE tumor in recurrent glioblastoma.

Collectively, we provide further evidence that re-resection translates into improved outcomes when maximal safe resection with minimal residual CE tumor is achieved. The proposed RANO *resect* classification may allow stratifying patients accordingly in the setting of clinical trials. While the optimal therapy at recurrence awaits to be evaluated, our study supports complete resection according to RANO *resect* class 1 and 2 to be beneficial and (radio-)chemotherapy might consolidate the effects of re-resection.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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classification | extent of resection | glioblastoma recurrence | outcome | surgical re-resection

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MW - Research grants: Quercis, Versameb. Honoraria or advisory board participation and consulting: Bayer, CureVac, Medac, Novartis, Orbus, Philogen. M.vdB. - Consultant: Celgene, BMS, Agios, Boehringer, Abbvie, Bayer, Carthera, Nerviano, Genenta. N. T**a**-Research grant: Medtronic. Founder: BrainDynamics; Advisory Board: Nervonik, BrainGrade. RR - Honoraria, advisory board, and consulting: UCB, Bayer, Novocure, Genenta, Servier. MAV - Indirect equity and patent royalty interests: Infuseon Therapeutics. Honoraria: Chimerix, Midatech. Research grants: DeNovo Pharma, Oncosynergy, Infuseon, Chimerix. JCT -Research grants: Novocure, Munich Surgical Imaging. Advisory board: AAA Novartis. Royalties: Springer Publisher. PK, AD, JSY, STJ, N. Te, LH, TS, CYM, FB, LN, RAM, AFH, JB, SHJ, AMM, LB, OS, SJG, SMC, MSB, and YE - None.

Authorship statement

Study concept and design: PK, MW, and JCT. Data collection: PK, AD, JSY, STJ, N. Te, LH, TS, CYM, FB, LN, RAM, and AFH. Data analysis and interpretation: PK, AD, JSY, LH, MW, AMM, RR, MAV, LB, OS, SJG, SMC, MSB, YE, and JCT. Statistics: PK, AMM, JCT. Manuscript drafting: PK, JCT. Manuscript revising: PK, AD, JSY, STJ, N. Te, LH, TS, CYM, FB, LN, RAM, AFH, MW, MvdB, JB, SHJ, AMM, N. Ta, RR, MAV, LB, OS, SJG, SMC, MSB, and JCT.

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