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Associations of supramaximal resection with outcome in glioblastoma across age groups: A report of the RANO *resect* group

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Abstract

Background. The oncological role of resection in elderly patients with glioblastoma remains controversial. We evaluated the value of resection in patients ≥65 years with (1) newly diagnosed and (2) recurrent glioblastoma by comparing the prognostic relevance of extent of resection to patients <65 years.

Methods. The international RANO resect group retrospectively collected patients with newly diagnosed and recurrent IDH-wildtype glioblastoma from ten neuro-oncological centers. Associations of residual tumor with molecular and clinical markers and survival were analyzed.

Results. A total of 1260 patients with newly diagnosed glioblastoma were identified, including 512 patients ≥65 years. Lower postoperative contrast-enhancing tumor volumes were favorably associated with survival on uni- and multivariate analyses; however, the associations with outcome were more pronounced in younger patients. Only in patients <65 years, supramaximal resection was associated with more favorable survival (40 vs 20 months, P = .001). In 310 patients with first recurrence (≥65 years: 92), maximal resection of contrast-enhancing tumor was associated with favorable outcomes, particularly in younger patients. Neither older nor younger patients had favorable outcome associations of supramaximal resection in the recurrent setting. All findings were confirmed in propensity-score-matched analyses to minimize confounding effects of inherent differences in demographic and clinical markers (including second-line treatments) between older and younger patients.

Conclusions. While complete contrast-enhancing tumor resection is prognostic for favorable outcomes in older patients, associations of supramaximal resection with improved outcomes were only retained in younger patients with newly diagnosed disease. Those findings support stratified surgical approaches.

Key Points

- Residual CE tumor is prognostic in both older and younger patients.
- Supramaximal resection is associated with favorable outcomes in younger but not older patients.
- RANO *resect* classes support patient stratification across age groups in clinical trials.

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Importance of the Study

The role of resection in older patients with glioblastoma remains poorly defined, and most existing studies have focused on younger populations. Using a large, well-annotated, multi-institutional dataset, we applied the RANO *resect* classification to evaluate the prognostic value of resection in patients with newly diagnosed and recurrent glioblastoma, with direct comparison between younger and older patients. Our findings confirm the importance of reducing residual contrast-enhancing tumor in both age cohorts but highlight that the association between extent of resection and survival is attenuated in older patients. In the recurrent setting, maximal contrast-enhancing tumor resection was associated with improved outcomes in both age groups, underscoring its continued relevance beyond initial diagnosis. These results suggest that age-tailored surgical strategies are essential and support the integration of objective volumetric assessments into prospective clinical trial design for older patients with glioblastoma.

Glioblastoma represents the most common and aggressive malignant primary brain tumor in adults, with a median age at diagnosis of ~66 years.[1] In older patients, glioblastoma carries a particularly poor prognosis compared to younger cohorts, both at diagnosis and recurrence.[2-4] Definitions of "elderly" patients vary across studies; however, recent trials generally consider patients ≥65 years as elderly.[5] Maximal safe surgical resection is generally recommended for patients with newly diagnosed glioblastoma.[6,7] However, its oncological benefit in older patients remains controversial. Historically, elderly patients have been underrepresented in trials.[8,9] While the multicenter, randomized ANOCEF trial failed to demonstrate survival benefits of resection over biopsy in patients ≥70 years,[10] a large retrospective single-center study[11] and a meta-analysis[12] reported favorable survival outcomes associated with maximal safe resection even among older patients. These conflicting results are problematic, given the need for nuanced surgical decision-making in older patients.

In recent years, the concept of supramaximal resection has gained increasing attention. Rather than limiting resection to contrast-enhancing (CE) tumor, supramaximal approaches involve resection extending beyond CE margins, including non-contrast-enhancing (non-CE) tumor portions. Several studies indicated that such extended resections may be associated with improved survival in patients with newly diagnosed glioblastoma.[2,11,13,14] Whether this applies to older patients, who often demonstrate increased vulnerability to treatment-related morbidity, remains unclear. Notably, a large study suggested that supramaximal resection does not confer a significant survival benefit in patients >65 years, highlighting the need for age-adapted surgical strategies.[11] Krishna et al[15] recently analyzed the interactive effects of age and extent of resection in a large molecularly annotated glioblastoma cohort, showing that prognostic effects of resection diminished with advancing age. However, their study focused on patients with newly diagnosed glioblastoma and did not assess non-contrast-enhancing tumor volumes or outcomes after re-resection. In this study, we evaluated the oncological role of resection in older patients (≥65 years) with (1) newly diagnosed and (2) recurrent glioblastoma using the established RANO *resect* classification system to stratify patients according to extent of resection by defining 4 categories based on postoperative residual CE and non-CE tumor volumes.[2,3] We compared the prognostic impact of residual tumor volume between older and younger patients to develop individualized surgical strategies and support age-adapted trial design. Potential confounding was minimized using propensity-score matching, and resection effects on outcome among older patients were systematically analyzed.

Methods

This retrospective, multi-institutional study was conducted by the RANO *resect* group, including 10 neuro-oncological centers across Europe and the United States (Figure 1A). Institutional Review Board (IRB) approval was obtained at each center, and centralized data storage and analysis were authorized by the IRBs of the Ludwig-Maximilians-University, Munich, Germany (AZ 21-0996), and the Friedrich-Alexander-Universitaet Erlangen-Nuremberg, Erlangen, Germany (AZ 24-495-Bn).

Study Population

Patients with newly diagnosed disease were selected based on: (1) tissue-based diagnosis of previously untreated IDH-wildtype glioblastoma per CNS WHO 2021 classification[16]; (2) pre- and postoperative MRI available for review (sufficient for volumetric analyses); (3) clinical follow-up of ≥3 months after histopathological diagnosis. Datasets of 8 centers were also screened for patients with first relapse of a previously resected glioblastoma with the following inclusion criteria: (1) radiographically confirmed first recurrence of a resected IDH-wildtype glioblastoma; (2) available pre- and postoperative MRI at re-resection; (3) follow-up treatment and outcome data. The cohorts have, in part, been previously published to confirm the prognostic role of our classification system for extent of resection in glioblastoma.[3,17] Standardized demographic, clinical, therapeutic, and imaging data were collected for all eligible patients. Preoperative Karnofsky Performance Status (KPS) was reported as an immediate preoperative score; no further detail on timing was available. Postoperative KPS was uniformly assessed at hospital discharge during the same

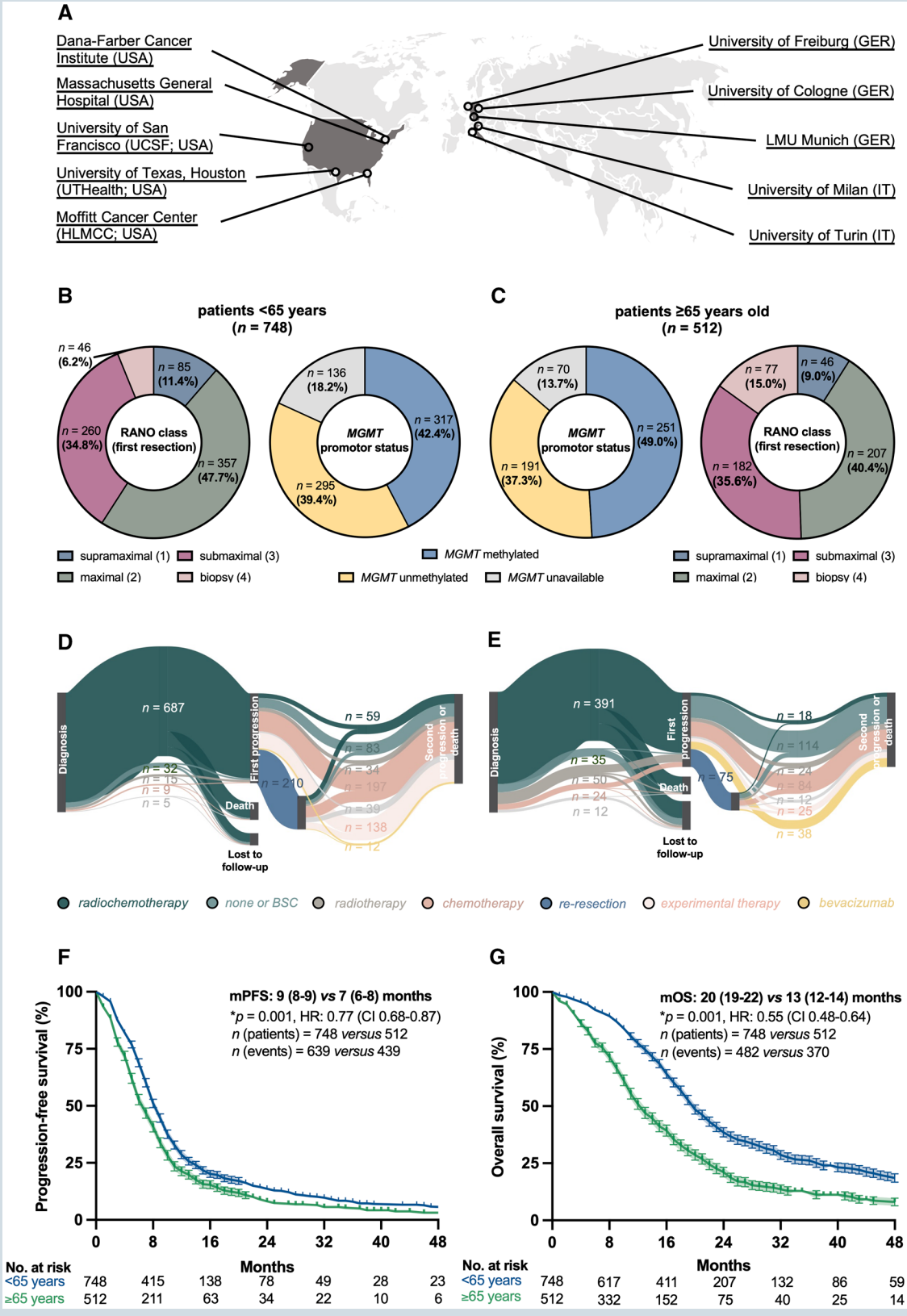

Figure 1. Baseline characteristics of patients <65 and ≥65 years of age with newly diagnosed glioblastoma (n=1260). (A) Schematic illustration of the 10 neuro-oncological centers involved in the study. (B and C) Distribution of residual tumor following resection or biopsy (according to the RANO classification) and *MGMT* promoter methylation status in patients <65 years (B; n = 748) and patients ≥65 years (C; n = 512) at first diagnosis. (D and E) Therapeutic strategies following diagnosis and first recurrence in patients <65 years (D; n = 748) and patients ≥65 years (E; n = 512). Nodes of the Sankey plots define key time points in the disease course (new diagnosis, first recurrence, second recurrence). Therapeutic strategies are

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color-coded, with arc thickness reflecting patient numbers. (F and G) Kaplan-Meier estimates of PFS (F) and overall survival (G) at first diagnosis stratified for patients <65 (n = 748) and ≥65 (n = 512) years. Points represent deceased or censored patients, while the light shading denotes the standard error of the mean (SEM).

admission. If discharge scores were missing, the earliest documented postoperative KPS within that admission was used. For patients undergoing re-resection, histopathological reports were reviewed for evidence of viable tumor, defined as any highly cellular tumor component versus predominantly treatment-related changes. Patients were stratified into cohorts of ≥65 and <65 years to evaluate the oncological role of resection in older patients.

Tumor Volumetrics and Patient Stratification

Tumor volumes were manually delineated by institutional raters using local imaging software (BrainLab Smartbrush, Philips IntelliSpace Discovery, 3D Slicer).[2,3] Pre- and postoperative CE tumor volumes were measured on contrast-enhanced T1-weighted sequences, while non-CE tumor volumes were assessed on FLAIR (if unavailable: T2) sequences. Postoperative imaging was performed within 72 h post-resection, whenever possible.[18] Raters ensured that abnormalities observed on FLAIR/T2-sequences were not treatment-related by reviewing pre- and postoperative MRI, particularly diffusion-weighted imaging (DWI). Non-CE tumor regions were identified based on disruptions in anatomical structure and differences in FLAIR/T2 signal intensity compared to cerebrospinal fluid and normal white matter.[19] Discrepancies in assessment were resolved through consensus with a second reviewer. For multifocal disease, each lesion was measured separately, and total volume was calculated as the sum of all individual foci. Absolute tumor volumes were measured in cubic centimeters (cm^3). Patients were stratified by the RANO *resect* classification system[2,3]:

- "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.
- "biopsy" (class 4): no reduction of tumor volume.

Inter-rater variance was evaluated previously and demonstrated reasonable agreement.[2]

Definition of Endpoints

Patients were followed until death or final database closure (April 1, 2023). Those lost to follow-up were censored on the day of the last follow-up. Date of first diagnosis was established as date of first tumor resection/biopsy. First recurrence was defined by MRI-confirmed disease progression per treating physicians using established clinical and radiological criteria available at the time, including timing of treatment and multimodal imaging to distinguish treatment-related changes from true progression, where applicable.[20,21]

Overall survival (OS) was defined as time from diagnosis to death from any cause, while progression-free survival (PFS) was defined as time from diagnosis to first recurrence or death from any cause.

Statistics

Normal distribution and equal variance in continuous variables were assessed utilizing the D'Agostino-Pearson-test. In parametric data, the unpaired Student's t-test was used to test differences between 2 groups, and the one-way Analysis of Variance (ANOVA) was used for multiple groups. For nonparametric data, differences between 2 groups were tested by the Mann-Whitney U-test and between multiple groups by the Kruskal-Wallis-test. Associations between 2 nonparametric continuous variables were analyzed by the Spearman correlation coefficient (ρ). Continuous data are expressed as mean ± SEM if normally distributed and as median ± interquartile range (IQR) if non-normally distributed. Categorical variables were assessed with the χ^2-test and described in absolute numbers and percentages.

Median follow-up was calculated using the reverse Kaplan-Meier method. For univariate survival analysis involving binary variables, Kaplan-Meier survival curves were calculated, and comparisons were made using log-rank tests. When analyzing survival outcomes in relation to continuous variables, Cox proportional hazard regression models were utilized to calculate hazard ratios (HR) and 95% CI. Multivariate survival analysis was conducted using Cox regression models, with variables evaluated in univariate analysis and included in the multivariate model if significant. To evaluate whether the effect of RANO resect classes on survival differed across age, we specified interaction terms between RANO class and age (continuous, centered at 65 years). Nested model comparisons were conducted using likelihood ratio tests, and global Wald tests were applied to assess overall interaction significance. To illustrate the age-dependent effects of RANO class, we derived adjusted hazard ratios at prespecified age values using linear combinations of coefficients and predictive margins. Proportional hazards and linearity assumptions were assessed using scaled Schoenfeld residuals (against time) and deviance residuals.

Propensity-score-based nearest-neighbor matching was applied to minimize confounding when comparing residual tumor volumes across RANO groups. Matching included both demographic and clinical markers (age, pre- and postoperative Karnofsky performance status [KPS]), tumor characteristics (O6-methylguanine-DNA-methyltransferase [*MGMT*] promoter methylation status, anatomic localization, preoperative CE tumor volume, RANO classes of first

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resection for analyses in the recurrent setting), and second-line treatments. The associations between residual tumor volume and outcomes in matched cohorts were evaluated using Kaplan-Meier survival estimates and log-rank tests.

All analyses were performed using Prism (v10.4.1; 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 are available upon qualified request.

Results

Baseline Patient Characteristics

Clinical information from 1260 patients with newly diagnosed IDH-wildtype glioblastoma diagnosed between 2003 and 2022 was collected: 748 patients (59.4%) <65 years and 512 patients (40.6%) ≥65 years (Table 1). All tumors met the criteria of IDH-wildtype glioblastoma, CNS WHO grade 4, according to the WHO 2021 classification.[16] Median age at diagnosis was 62 years (IR: 54-70years), male-to-female ratio 1:0.7, and median preoperative KPS 90% (IR: 70%-90%). *MGMT* promoter status was methylated in 568 patients (45.1%), unmethylated in 486 patients (38.6%), and not available in 206 patients (16.3%). Median postoperative KPS was 80% (IR: 70%-90%), and new postoperative neurological deficits occurred in 15.6% (158/1011 patients). Most patients underwent postoperative radiochemotherapy (85.6%, temozolomide ± lomustine, including 11% with additional study drugs). At database closure, 1078 patients (85.6%) had experienced a recurrence, 408 patients (32.4%) were alive at a median follow-up of 13 months (CI: 12-14 months), and 852 patients (67.6%) were deceased. Median follow-up time was 38 months (CI: 34-44 months) with a median PFS of 8 (CI: 8-8 months), and OS of 18 months (CI: 17-19 months).

While there was a statistically significant but clinically negligible difference in median postoperative KPS between patients <65 and ≥65 years (80% [IR 80%-90%] vs 80% [IR 70-90%], $P=.001$), postoperative neurological deficit rates were comparable between both groups (15.9% vs 15.3%, $P=.861$). Patients ≥65 years presented with a marginally lower preoperative KPS compared to patients <65 years (80 [CI: 70-90] vs. 90 [CI: 80-90], $P=.001$). They less frequently received a "supramaximal" (class 1) or "maximal" (class 2) resection of CE tumor compared to those <65 years (49.4 vs 59.1%), while biopsy for tissue diagnosis (class 4) was more common in older patients (15.0% vs 6.2%; Figure1 B and C). *MGMT* promoter methylation rates were similar between patients ≥65 and <65 years (49.0% vs 42.4%, $P=.118$). Following surgery, patients ≥65 years less frequently received additional investigational drugs (6.4% vs 14.0%) and more frequently received radiation or chemotherapy (Figure 1D and E). Patients ≥65 years demonstrated a shorter median PFS (7 [CI: 6-8]) vs 9 [CI: 8-9] months, $P=.001$; Figure 1F) and OS (13 [CI: 12-14] vs. 20 [CI: 19-22] months, $P=.001$; Figure 1G) compared to patients <65 years. No differences in molecular tumor characteristics or localization were observed between both groups (Table 1).

Prognostic Implication of CE and non-CE Residual Tumor

Sufficient volumetric information to assess associations of residual tumor with outcome was available in all patients. A total of 1138 patients (90.3%) underwent microsurgical tumor resection and 122 patients (9.7%) received a biopsy. Overall, median preoperative CE tumor volume was 30.2 ± 0.8 cm^3. Following biopsy or surgical resection, a median residual CE tumor volume of 4.1 ± 0.3 cm^3 was detected on postoperative MRI. Notably, pre- and postoperative CE tumors in patients undergoing resection were correlated ($P=.288$, $P=.001$). While preoperative CE tumor volumes between patients <65 and ≥65 years were similar, postoperative CE tumor residuals were higher in patients ≥65 years compared to those <65 years (5.8 ± 0.6 vs 2.9 ± 0.3 cm^3, $P=0.001$). In both groups, higher postoperative CE tumor volume was strongly associated with less favorable outcomes (HR per cm^3 tumor residual: <65 years: 1.03 [CI: 1.02-1.04], $P=.001$; ≥65 years: 1.03 [CI: 1.02-1.03], $P=.001$). This was particularly true in patients <65 years with unmethylated *MGMT* promoter status, where univariate Cox regression demonstrated a particularly exponential increase in the hazard ratio for death with each additional cm^3 residual CE tumor volume (HR per cm^3 residual tumor: 1.05 [CI: 1.02-1.09], $P=.003$; Figure 2B).

As clinical factors varied between patients <65 and ≥65 years—and were associated with survival in univariate analysis (Table S1)—we sought to account for potential confounding. After adjusting for these variables in a multivariate analysis, the prognostic significance of postoperative CE tumor volume was retained in both age groups (HR per cm^3 tumor residual:<65 years: 1.03 [CI: 1.02-1.04], $P=.001$; ≥65 years: 1.02 [CI: 1.01-1.03], $P=.001$; Figure 2A).

Next, we explored the prognostic value of residual non-CE tumor by focusing on patients undergoing resections beyond contrast-enhancing borders (Figure 2C). Thus, we selected a cohort of patients who had received complete CE tumor resection (0 cm^3 residual CE tumor volume) followed by the EORTC-26981/22981-protocol (Figure 2D). In this subgroup (300 patients), postoperative median non-CE tumor volume was 13.6 ± 1.7 cm^3. No difference in postoperative non-CE tumor volume between patients <65 (190/300 patients, 63.3%) and ≥65 years (110/300 patients, 36.7%) was found (12.9 ± 2.6 vs 15.0 ± 2.7 cm^3, $P=.201$). Although there was a trend for a continuous relation between hazard ratio for death and postoperative non-CE tumor to be found, neither patients <65 nor ≥65 years demonstrated a significant association between residual non-CE tumor and outcome (HR per cm^3 non-CE residual tumor:<65 years: 1.00 [CI: 1.00-1.01], $P=.351$; ≥65 years: 1.00 [CI: 0.99-1.01], $P=.455$; Figure 2E). Interestingly, when patients were additionally stratified into methylated and unmethylated *MGMT* promoter status, only patients <65 years with unmethylated tumors presented with a survival benefit depending on extent of postoperative non-CE tumor resection. Here, an increase in hazard ratio for death after surgery for each cm^3

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Table 1. Baseline characteristics for the entire study cohort of patients with glioblastoma, IDH-wildtype, WHO grade 4.

		<65 years	≥65 years	Total	*P* value
Overall, *n* (%)		748 (59.4%)	512 (40.6%)	1260 (100%)	
Demographics	Age, years, median (IR)	55 (49-61)	72 (68-77)	62 (54-70)	n.appl.
	Male:female ratio	1:0.6	1:0.8	1:0.7	.091
Clinical markers	Pre-operative KPS, median (IR)	90 (80-90)	80 (70-90)	90 (70-90)	***.001**
	Post-operative KPS, median (IR)	80 (80-90)	80 (70-90)	80 (70-90)	***.001**
	New post-operative deficit, *n* (%)	94 (15.9%)	64 (15.3%)	158 (15.6%)	.861
***MGMT* promotor, *n* (%)**	Methylated	317 (42.4%)	251 (49.0%)	568 (45.1%)	.118
	Non-methylated	295 (39.4%)	191 (37.3%)	486 (38.6%)	
	N.a.	136 (18.2%)	70 (13.7%)	206 (16.3%)	
***TERT* promotor, *n* (%)**	Wildtype	36 (4.8%)	19 (3.7%)	55 (4.4%)	.382
	Mutated	245 (32.8%)	174 (40.0%)	419 (33.3%)	
	N.a.	467 (62.4%)	319 (62.3%)	786 (62.4%)	
Tumor localization, *n* (%)	(Sub)-cortical	585 (78.2%)	404 (78.9%)	989 (78.5%)	.911
	Deep-seated	82 (11.0%)	52 (10.2%)	134 (10.6%)	
	Multifocal	81 (10.8%)	56 (10.9%)	137 (10.9%)	
	Dominant hemisphere	386 (52.6%)	263 (51.8%)	649 (51.5%)	.817
Tumor volumes, ml; mean ± SEM	Pre-OP CE	30.4 ± 1.1	29.9 ± 1.2	30.2 ± 0.8	.611
	Pre-OP non-CE	58.1 ± 2.2	58.2 ± 2.5	58.1 ± 1.7	.651
	Post-OP CE	2.9 ± 0.3	5.8 ± 0.6	4.1 ± 0.3	***.001**
	Post-OP non-CE	33.3 ± 1.5	38.2 ± 1.9	35.4 ± 1.2	***.018**
RANO *resect* categories of EOR, *n* (%)	RANO class 1	85 (11.4%)	46 (9.0%)	131 (10.4%)	***.001**
	RANO class 2	357 (47.7%)	207 (40.4%)	564 (44.8%)	
	RANO class 3	260 (34.8%)	182 (35.6%)	442 (35.1%)	
	RANO class 4	46 (6.2%)	77 (15.0%)	123 (9.8%)	
First-line therapy	RT alone	15 (2.0%)	50 (9.8%)	65 (5.2%)	***.001**
	TMZ/RT→TMZ	563 (75.3%)	351 (68.6%)	914 (72.5%)	
	TMZ/RT→TMZ/CCNU	19 (2.5%)	7 (1.4%)	26 (2.1%)	
	TMZ alone	9 (1.2%)	24 (4.7%)	33 (2.6%)	
	TMZ/RT→TMZ + study drug	105 (14.0%)	33 (6.4%)	138 (11.0%)	
	Best supportive care	32 (4.3%)	35 (6.8%)	67 (5.3%)	
	N.a.	5 (0.7%)	12 (2.3%)	17 (1.3%)	
Outcome, months (95% CI)	PFS	9 (8-9)	7 (6-8)	8 (8-8)	***.001**
	OS	20 (19-22)	13 (12-14)	18 (17-19)	***.001**

Characteristics are summarized for all patients with glioblastoma, IDHwt, CNS WHO grade 4 ($n = 1260$), and stratified for patients <65 years of age ($n = 748$) and patients ≥65 years of age ($n = 512$). Differences between both cohorts were analyzed using the Mann-Whitney *U*-test (for nonparametric data) or the Student's *t*-test (for parametric data) for continuous variables. 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, and asterisks indicate $P \leq .05$. Abbreviations: IR, interquartile range; KPS, Karnofsky performance status; n.a., not available for review; n. appl., not applicable; PFS, progression-free survival; RT, radiotherapy; TERT, telomerase reverse transcriptase; TMZ, temozolomide.

additional residual non-CE tumor was demonstrated by Cox regression (HR per cm^3 non-CE tumor residual: 1.02 [CI: 1.00-1.02], $P = 0.004$; Figure 3A).

Exploring the Prognostic Implication of Supramaximal Resection Utilizing the RANO Classification System

Patients were stratified according to both age (<65 and ≥65 years) and the four RANO *resect* classes based on residual CE and non-CE tumor volumes: "supramaximal CE resection," defined as resection extending beyond the CE tumor borders (class 1; 131 patients, 10.4%), "maximal CE resection" (class 2; 564 patients, 44.8%), "submaximal CE resection" (class 3; 442 patients, 35.1%), and "biopsy" (class 4; 123 patients, 9.8%). In patients undergoing resection (Figure 3B), those <65 years receiving a "supramaximal CE resection" showed a substantial survival benefit compared to patients with "maximal CE resection" (OS: 40 [CI: 22-56] vs 20 [CI: 18-21] months, HR: 0.50 [CI: 0.38-0.65], $P = .001$) or "submaximal CE resection" (OS: 40[CI: 22-56] vs 20 [CI:

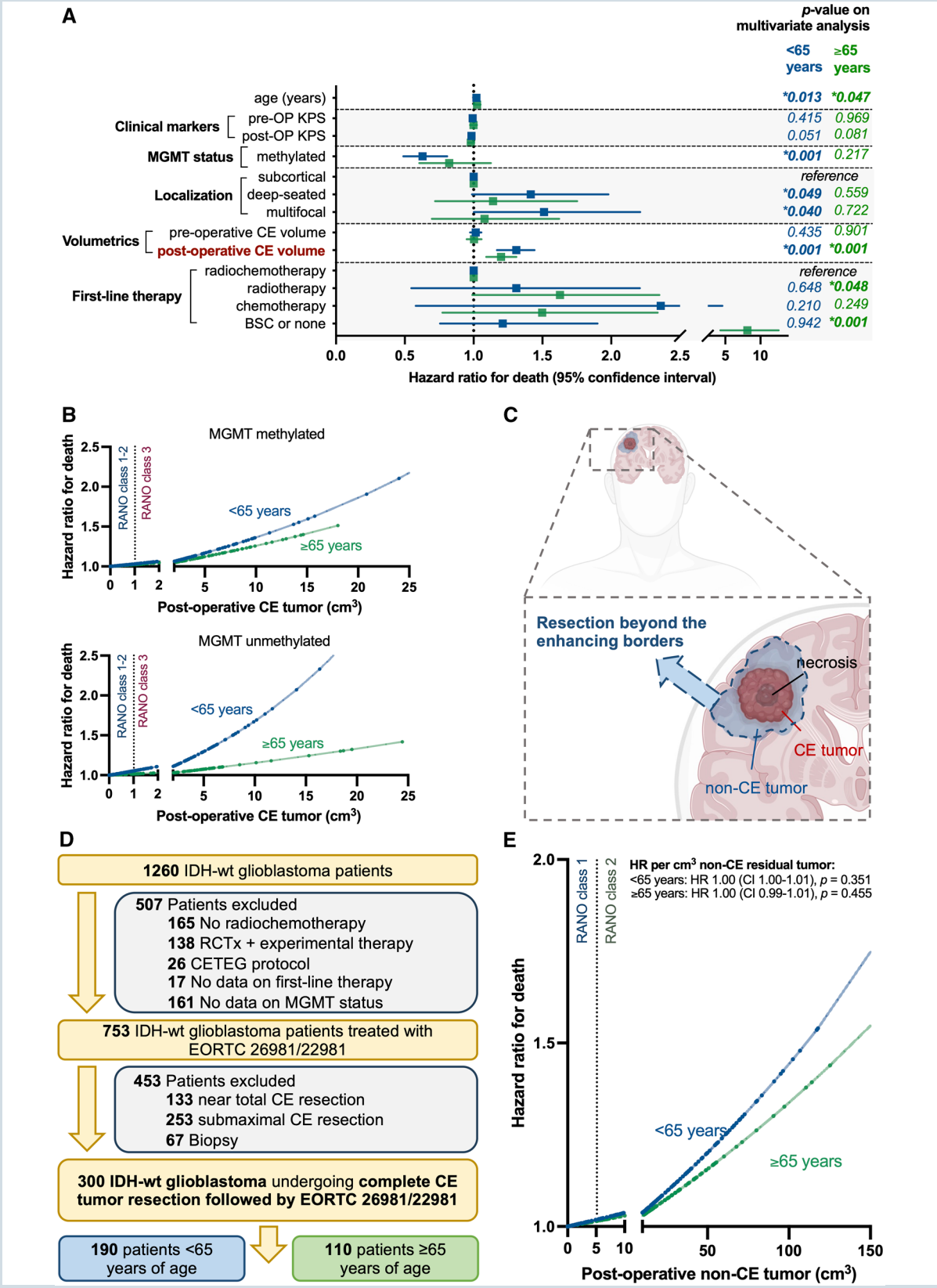

Figure 2. Prognostic implication of residual tumor volume after controlling for confounders. (A) Multivariate analysis utilizing a Cox proportional hazard regression model estimating the hazard ratio for death. All variables included were significant in the univariate analysis. Abbreviations: BSC, best supportive care; CE, contrast enhancing; KPS, Karnofsky performance status. Hazard ratios are presented with their corresponding 95% confidence intervals. (B) Hazard ratios for death were calculated for each individual residual CE tumor volume among patients undergoing resection

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stratified by age and *MGMT* promoter methylation status. Patients <65 years (n = 702) and those ≥65 years (n = 435) are displayed separately. An exponential hazard increase for higher residual CE volumes can be seen, particularly in patients <65 years with unmethylated tumors. (C) Schematic illustration of a supramaximal resection beyond the contrast-enhancing tumor borders. (D) Flow chart of the formation of a patient cohort exclusively, including IDH-wildtype glioblastomas homogenously treated with complete CE tumor resection followed by the EORTC 26981/22981 protocol (n = 300). (E) Hazard ratios for death calculated for each individual residual non-CE tumor volume among patients undergoing complete CE tumor resection stratified by age (<65 years: n = 190 vs ≥65 years: n = 110).

18-22] months, HR: 0.55[CI: 0.41-0.74], P=.001). Interestingly, no difference in outcome was seen between "maximal CE resection" and "submaximal CE resection" (OS: 20 [CI: 18-22] vs 20 [CI: 18-22] months, HR: 1.08 [CI: 0.89-1.31], P=.421) in patients <65 years, (Figure 3C). In patients ≥65 years, both "supramaximal CE resection" and "maximal CE resection" had superior survival compared to "submaximal CE resection" (class 1 vs 3; OS: 17 [CI: 11-23] vs 11 [CI: 10-12] months, HR: 0.68 [CI: 0.48-0.98], P=.050; class 2 vs 3; OS: 17 [CI: 15-19] vs 11 [CI: 10-12] months, HR: 0.66 [CI: 0.52-0.83], P=.001). Notably, no differences in outcome were seen between "supramaximal CE resection" and "maximal CE resection" (OS: 17 [CI: 11-23] vs 17 [CI: 15-19] months, HR: 1.02 [CI: 0.68-1.54], P=0.916; Figure 3D).

In Cox models including RANO *resect* class, continuous age (centered at 65 years), and their interaction, there was strong evidence for effect modification of RANO *resect* class on survival by age (Wald $\chi^2(3)$ = 21.03, P=.001; LR $\chi^2(3)$ = 21.64, P=.001). At age 65, hazards increased stepwise across classes relative to class 1: HR: 1.42 (CI: 1.08-1.86) for class 2, 1.70 (CI: 1.29-2.25) for class 3, and 2.85 (CI: 2.02-4.01) for class 4; the per-year age effect within RANO *resect* class 1 was HR: 1.03 (CI: 1.01-1.06). Comparisons of RANO resect classes at specific ages indicated an attenuation of the class 2 vs class 1 difference with advancing age, while less favorable outcome of biopsy amplified: at 75 years, HRs were 1.19 (CI: 0.78-1.81), 1.73 (CI: 1.13-2.65), and 3.65 (CI: 2.30-5.80) for class 2, 3, and 4 vs class 1, respectively; at 80 years, HRs were 1.09 (0.65-1.84), 1.74 (1.03-2.95), and 4.14 (2.34-7.30). In multivariable models, adjusting for pre- and postoperative KPS, *MGMT* promoter status, tumor localization, and first-line therapy, the interaction between RANO *resect* class and age remained significant (Wald $\chi^2(3)$ = 19.16, P=.001; LR $\chi^2(3)$ = 19.41, P=.001).

Across all patients, postoperative neurological deficit rates did not differ between those undergoing biopsy and those receiving open resection (11.2% vs 16.2%, P=.177), which held true in both patients <65 years (15.0% vs. 15.9%, P=.999) and patients ≥65 years (9.2% vs 16.7%, P=.115). Among patients undergoing resection, higher class resection was not associated with increased postoperative neurological deficit rates (class 1 vs 2 vs 3: 15.2% vs 16.2% vs 17.0%, P=.926). Postoperative KPS was even slightly higher in patients undergoing supramaximal resection (90% [IR: 80%-90%] vs 80% [IR: 80%-90%] vs 80% [IR: 70% -90%], P=.001). This finding was retained in patients ≥65 years, where both new postoperative deficit rates (14.3% vs 15.8% vs 19.0%, P=.734) and postoperative KPS (80% [IR: 70% -90%] vs 80% [IR: 80%-90%] vs 80% [IR: 70%-90%], P=.256) remained comparable across RANO classes. A similar trend was seen in patients <65 years, with no significant increase in postoperative deficits across resection groups (15.7% vs 16.5% vs 15.4%, P=.986). Although postoperative KPS was slightly lower in patients <65 years with submaximal resection, overall KPS remained high across classes (class 1 vs 2 vs 3: 90% [IR: 80% -90%] vs 90% [IR: 80%-90%] vs. 80% [IR: 70%-90%], P=.001). Postoperative neurological deficits were further stratified by type, age and RANO class (Table S2). The most frequently reported deficits included motor impairment (2.9%), visual deficits (1.7%), and aphasia (1.5%). Notably, deficits were not further specified in a considerable proportion of cases (9.7%). Given the favorable outcomes observed in patients <65 years undergoing "supramaximal CE resection" (class 1) compared to "maximal CE resection" (class 2), but the absence of a similar survival benefit in patients ≥65 years, we examined neurological outcomes in both age groups following supramaximal resection. Here, the postoperative neurological deficit rates remained similar between patients <65 and ≥65 years (15.7% vs 14.3%, P=.999). While postoperative KPS was significantly higher in patients <65 years compared to ≥65 years (90% [80%-90%] vs 80% [70%-90%], P=.025), the proportion of patients experiencing a ≥10% decline in KPS postoperatively did not differ (14.3% vs 17.8%, P=.617).

To further confirm the observed associations between "supramaximal CE resection" and outcomes both in patients <65 and ≥65 years, we adjusted for demographic, clinical, tumor, and treatment-related variables, achieving sufficient covariate balance in each age group (Figure 3E and F). Using these propensity-score-matched cohorts, we demonstrated that patients <65 years undergoing "supramaximal CE resection" had a more favorable outcome compared to "maximal CE resection" (OS: 32 [CI: 21-32] vs 19 [CI: 17-21] months, HR: 0.57 [CI: 0.45-0.73], P=.001; Figure 3E). Again, we detected no survival difference between "supramaximal CE resection" and "maximal CE resection" in patients ≥65 years (OS: 25 [CI: 14-41] vs 17 [CI: 15-20] months, HR: 0.78 [CI: 0.57-1.07], P=.104; Figure 3F).

Oncological Role of Resection in Very Elderly Patients

As optimal surgical management of glioblastomas in very elderly patients remains challenging, we examined prognostic implications of more extensive surgery in patients ≥75 years. Therefore, patients undergoing resection were stratified by age (cut-off: ≥75 years, n=142) and RANO *resect* classes: "supramaximal CE resection" (class 1; 17 patients, 12.0%), "maximal CE resection" (class 2; 67 patients, 47.2%), and "submaximal CE resection" (class 3; 58 patients, 40.8%; Figure S1A). Although the overall log-rank test was not significant (P=.063), patients ≥75 years receiving at least a "maximal CE resection" had a favorable outcome compared to patients with "submaximal CE resection" (class 1 or 2 vs

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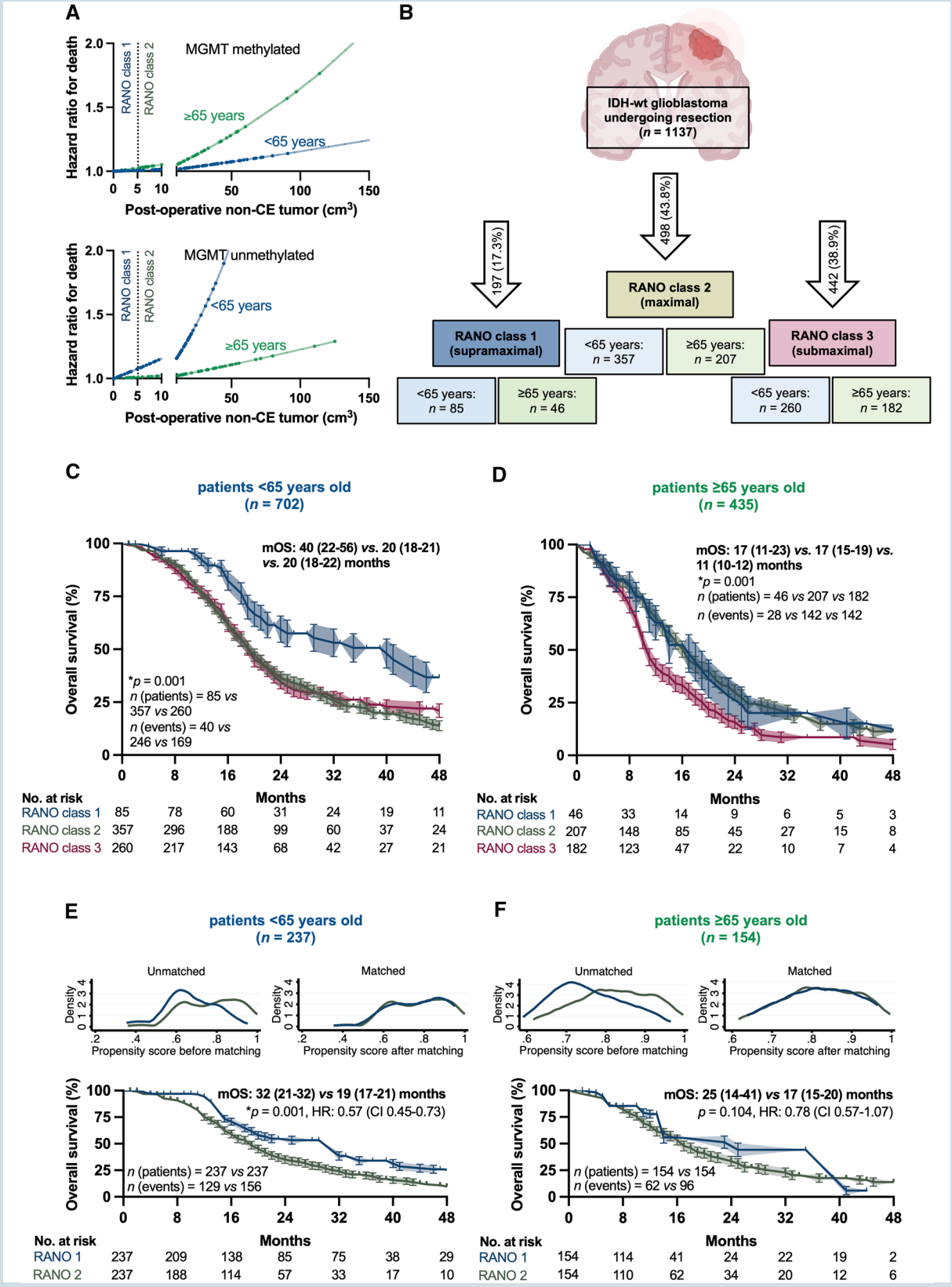

Figure 3. Associations of supramaximal resection on outcomes. (A) Hazard ratios for death calculated for each individual residual non-CE tumor volume among patients undergoing complete CE tumor resection, stratified by age (<65 years *vs.* ≥65 years) and *MGMT* promoter methylation status. Note that only patients <65 years with an unmethylated tumor demonstrated a significant association between residual non-CE tumor and outcome while an inverse, though non-significant, trend was seen in patients with *MGMT* promoter methylated tumors. (B) Flow diagram of all patients undergoing resection (n = 1137) stratified by both age and the RANO *resect* classification. (C and D) Kaplan-Meier estimates of overall

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survival stratified according to the RANO *resect* classification in patients <65 (C; *n* = 702) and ≥65 (D; *n* = 435) years undergoing resection. Points represent deceased or censored patients, while the light shading denotes the standard error of the mean (SEM). (E and F) Kernel density estimates before and after propensity-score-based matching, and Kaplan-Meier estimates for survival. Patients stratified to RANO class 1 (corresponding to ≤5 cm3 residual noncontrast-enhancing tumor) were matched to controls selected from RANO class 2 in patients <65 years (E; *n* = 237) and ≥65 years (F; *n* = 154). Note that survival differences were only observed for the comparison in patients <65 years, but not for older patients ≥65 years. Points indicate deceased or censored patients, light shading depicts SEM.

3, OS: 14 [CI: 11-18] vs 10 [CI: 8-11] months, HR: 0.66 [CI: 0.45-0.97], *P*=.016). However, similar to patients ≥65 years, survival did not differ between "supramaximal CE resection" and "maximal CE resection" (OS: 14 [CI: 5-23] vs 13 [CI: 11-19] months, HR: 1.25 [CI: 0.62-2.52], *P*=.925). Among patients ≥75 years undergoing resection, higher class resection was not associated with increased postoperative neurological deficit rates (class 1 vs 2 vs 3: 20.0% vs 12.1% vs 20.8%; *P*=.400).

To investigate where the prognostic benefit of "maximal CE resection" diminishes, we repeated the analysis in patients ≥80 years, again stratifying by age (cut-off: ≥80 years, *n*=57) and the RANO *resect* classes. Here, more extensive resection no longer conferred a survival advantage (class 1 vs 2 vs 3; OS: 14.5 [CI: 3-not reached] vs 13 [CI: 10-24] vs 9 [CI: 5-11] months, *P*=0.177; Figure S1B). Patients ≥80 years receiving at least a "maximal CE resection" showed no survival difference compared to patients with "submaximal CE resection" (class 1 or 2 vs 3, OS: 13 [CI: 10-24] vs 9 [CI: 5-11] months, HR: 1.63 [CI: 0.90-2.97], *P*=.079). In patients ≥80 years, postoperative neurological deficit rates remained comparable across RANO classes (class 1 vs 2 vs 3: 16.7% vs 13.0% vs 18.8%; *P*=.856). Postoperative neurological deficit rates in both, patients ≥75 years and ≥80 years, were similar to those observed in the ≥65-year or <65-year cohorts. Given the small sizes—particularly in the ≥80-year-old patients—these findings require cautious interpretation.

Prognostic Evaluation of Extent of re-Resection for Recurrent Glioblastoma in Older Patients

We also explored the prognostic relevance of extent of re-resection in patients <65 and ≥65 years presenting with recurrence of a previously resected glioblastoma. Here, 310 individuals (218 patients [70.3%] <65 years, 92 patients [29.7%] ≥65 years) were identified. Between patients <65 and ≥65 years, distribution of *MGMT* promoter methylation, *TERT* promoter mutation, and tumor localization at diagnosis was comparable (Table S3). Histopathological review at re-resection was available for most cases and confirmed viable tumor in 220/310 patients (71.0%). The proportion of viable tumor versus predominant treatment effect did not differ between patients ≥65 and <65 years (65.2 vs 73.4%, *P*=0.663). Among both older and younger patients, proportions were comparable across RANO *resect* classes 1-3 at re-resection (≥65 years: *P*=.412; <65 years: *P*=.586), with no evidence of class-specific differences in the recurrent setting. Interestingly, initial RANO *resect* classes at first diagnosis were similar between age groups (*P*=0.307). Radiochemotherapy was the most common first-line treatment in both groups, although patients ≥65 years more frequently received radiotherapy alone as an alternative. Median time to first recurrence was shorter in patients ≥65 years compared to those <65 years (8 [CI: 7-9] vs 9 [CI: 9-10] months, *P*=.004). Similarly, the median time from initial diagnosis to re-resection was shorter in patients ≥65 years (10 [IR: 7-15] vs 8 [IR: 5-12] months, *P*=.008). At first recurrence, patients ≥65 years demonstrated a significant, though clinically negligible, lower KPS compared to patients <65 years (preoperative: 80% [IR: 70%-90%] vs 90% [IR: 80%-90%], *P*=0.010; postoperative: 80%[IR: 70%-90%] vs 80% [IR: 80%-90%], *P*=.002). However, postoperative neurological deficit rates remained comparable between age groups (22.8% vs 17.4%, *P*=.272). Following re-resection, residual tumor volumes were similar across both age groups based on RANO resect classes (*P*=.550). Likewise, further second-line therapies were heterogeneous but distributed similarly between patients <65 and ≥65 years.

Patients were subsequently stratified by age (<65 and ≥65 years) and RANO *resect* class at re-resection: "supramaximal CE resection" (class 1; <65 years: 45/218 patients, 20.6%; ≥65years: 15/92 patients, 16.3%), "maximal CE resection" (class 2; <65 years: 111/218 patients, 50.9%; ≥65 years: 46/92 patients, 50.0%), and "submaximal CE resection" (class 3; <65 years: 62/218 patients, 28.4%;≥65 years: 31/92 patients, 33.7%). Patients <65 years receiving at least a "maximal CE resection" had a favorable outcome compared to patients with "submaximal CE resection" (class 1 or 2 vs 3; OS: 12 [CI: 10-15] vs 8 [CI: 7-9] months, HR: 0.59[CI: 0.40-0.87], *P*=.001) (Figure 4A). Contrary to the newly diagnosed setting, no difference was observed between "supramaximal CE resection" and "maximal CE resection" (OS: 11 [CI: 9-19] vs 12 [CI: 10-15] months, HR: 1.03 [CI: 0.69-1.54], *P*=.865). In patients ≥65 years (*n*=92), the overall log-rank test across groups was not significant (*P*=.100), and more extensive resection of contrast-enhancing disease only conferred a numeric but not significant survival advantage (class 1 vs 2, OS: 12 [CI: 5-17] vs 9 [CI: 7-14] months, HR: 0.60 [CI: 0.33-1.09], *P*=.102; class 1 or 2 vs 3, OS: 10 [CI: 8-14] vs 6 [CI: 3-9] months, HR: 0.70 [CI: 0.43-1.16], *P*=.112) (Figure 4B). Given the limited sample size, findings will need to be interpreted with caution.

To evaluate the effect of supramaximal CE re-resection beyond contrast-enhancing borders, propensity-score-based nearest-neighbor matching was performed to balance covariates across RANO *resect* classes 1 and 2. However, due to the limited sample size, adequate covariate balance could not be achieved, limiting interpretability of the results (see Kernel density plots; Figure 4C and E). In matched cohorts, we confirmed that "supramaximal CE resection" for patients <65 years was not associated with a convincing survival benefit compared to those with "maximal CE

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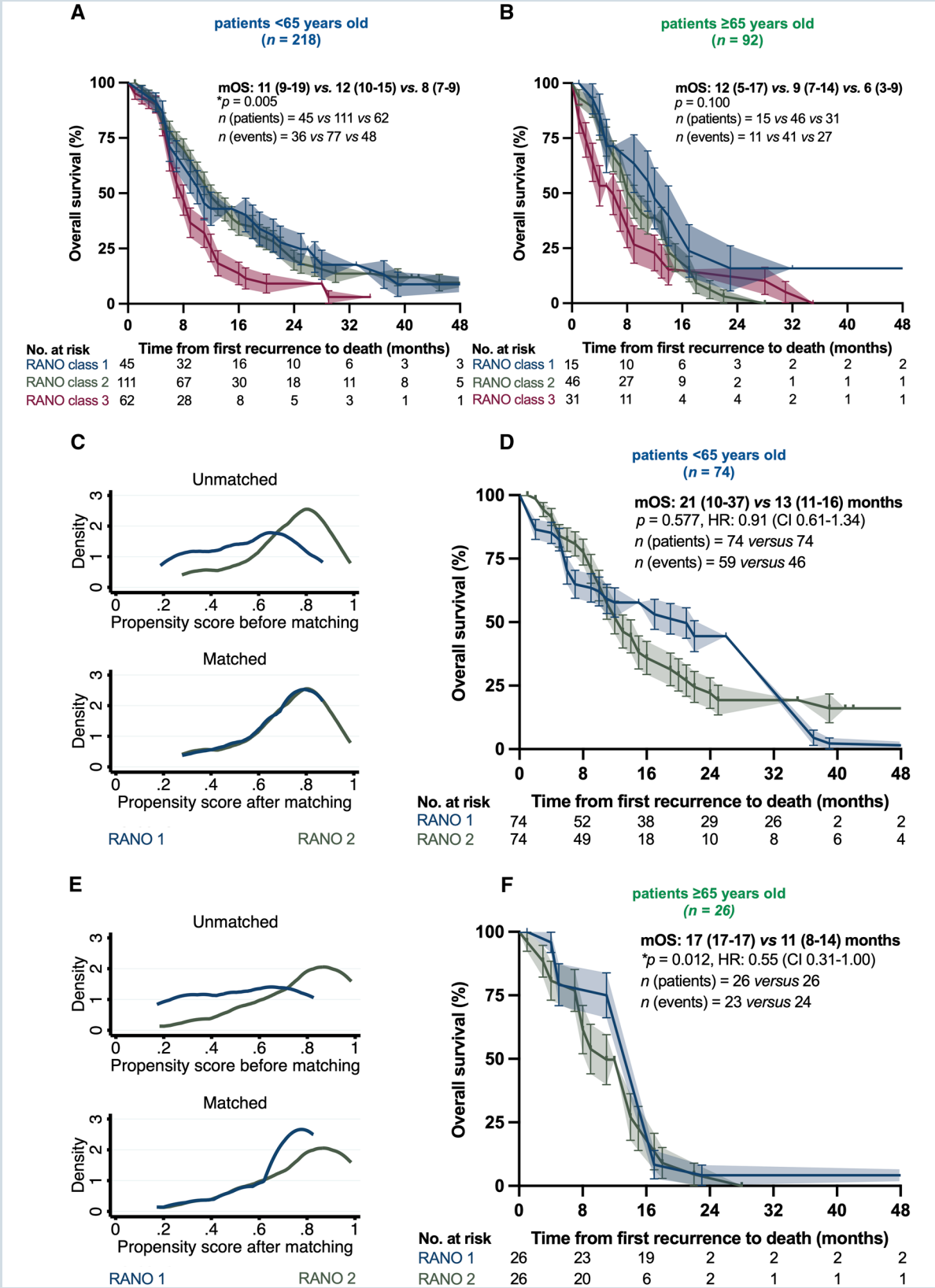

Figure 4. Prognostic evaluation of extent of re-resection for recurrent glioblastoma. (A and B) Kaplan-Meier estimates of overall survival after first recurrence stratified according to the RANO *resect* classification in patients <65 (A; $n = 218$) and ≥65 (B; $n = 92$) years undergoing resection. Points represent deceased or censored patients while the light shading denotes the standard error of the mean (SEM). (C-F) Kernel density estimates before and after propensity-score-based matching (C and E), and Kaplan-Meier estimates for survival after first recurrence (D and F). Patients stratified to RANO class 1 (corresponding to ≤5 cm^3 residual noncontrast-enhancing tumor) were matched to controls selected from RANO class

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2 in patients <65 years (C, D; $n = 74$) and ≥65 years (E, F; $n = 26$). Note that survival differences were only observed for the comparison in patients ≥65 years, where matching yielded improved yet not ideal covariate balance. Points indicate deceased or censored patients, light shading depicts SEM.

resection" (OS: 21 [CI: 10-37] vs 13 [CI: 1-16] months, HR: 0.91 [CI: 0.61-1.34], $P = .577$; Figure 4D). In patients ≥65 years, "supramaximal CE resection" seemed to have a slightly favorable association with survival (OS: 17 [CI: 17-17] vs 11 [CI: 8-14] months, HR: 0.55 [CI: 0.31-1.00], $P = .012$; Figure 4F); however, findings were substantially limited by the small sample size.

Discussion

In this retrospective multicenter cohort, we applied the RANO *resect* classification to evaluate the oncological benefit of surgical resection across older versus younger patients with glioblastoma. Consistent with prior studies,[2–4] reducing residual CE tumor burden was prognostic in both patients <65 and ≥65 years. However, an association between outcome and resection extending beyond the CE tumor borders was limited to patients <65 years. While retrospective, these results may come with implications for judicious surgical decision-making when managing older patients with glioblastoma.

Our findings support Molinaro et al. who reported that in patients ≥65 years, resection of contrast-enhancing tumor was associated with prolonged survival while resection of non-contrast-enhancing tumor did not translate into an additional survival benefit.[11] Krishna and colleagues further analyzed interactive effects and extent of resection in a large molecularly annotated dataset, showing that prognostic benefits of more extensive resection were attenuated in older patients.[15] Our study expands on these findings by evaluating extent of resection at first recurrence, quantifying non-contrast-enhancing tumor volume, and validating the RANO resect classification across subgroups including ≥75 and ≥80 years, using propensity-score-matched analyses to minimize confounding. We showed that the prognostic effect of RANO resection categories is modified by age, with the benefit of maximal over supramaximal resection attenuating in older patients, while the relative disadvantage of biopsy becomes more pronounced with advancing age. Importantly, age-dependent differences in outcomes of RANO *resect* class 1 patients might not be due to higher postoperative deficit rates in older patients. In turn, maximal safe CE tumor resection was highly prognostic of outcome; suggesting a prominent oncological role of resection also among patients ≥65 years.[11,22] Thus, decisions to pursue supramaximal resection should be individualized and carefully weighed against potential risks, particularly in older patients. On a cautionary note, postoperative deficits were assessed quantitatively, with no available data on duration or whether they were transient. Furthermore, preoperative neurological deficits were not systematically documented, and standardized neurocognitive testing was not performed. Future prospective studies should incorporate thorough neurocognitive assessments and quality-of-life metrics. Data on surgical adjuncts (eg intraoperative navigation, mapping, or fluorescence-guided resection) were not consistently available and not included in the analysis. Cause of death could not be systematically determined, limiting interpretation of survival results as competing causes of death may attenuate the observed association between extent of resection and survival. Validation of our findings in prospective cohorts with standardized follow-up protocols is warranted.

Apart from postoperative residual tumor volume, age-related differences also emerged in other prognostic factors. In patients <65 years, unmethylated *MGMT* promoter, deep-seated tumors, or multifocality remained significant negative prognostic markers, whereas in patients ≥65 years, *MGMT* promoter status and subsequent therapy emerged as dominant factors associated with outcome. These age-specific risk profiles align with current EANO guidelines, recommending standard radiochemotherapy for younger patients with good performance status (KPS ≥70), while those with reduced performance status are considered for de-escalated treatment regimens, more akin to the approach taken in older patients over 70 years, where *MGMT* promoter methylation status drives nonsurgical treatment decisions.[7] In this context, radiation dose and fractionation schedules were not considered in our stratification. Given current treatment practices, it is likely that many older patients received hypofractionated radiotherapy, which may have influenced outcomes.

While we accounted for relevant clinical and molecular confounders such as preoperative tumor volume, tumor location, and *MGMT* promoter methylation, we noted that lower residual tumor volumes were particularly associated with improved survival in younger patients with unmethylated *MGMT* promoter status. The different outcome associations of residual tumor burden by *MGMT* promoter methylation status are intriguing, and it has been postulated that in patients with *MGMT* promoter unmethylated tumors, the survival benefit of more extensive resection may be more pronounced.[4,23] Conversely, in methylated tumors, the prognostic impact of residual tumor burden may be attenuated, as temozolomide chemotherapy is much more likely to contribute to outcome and overcome the effects of less extensive resections.[24] Nonetheless, the retrospective nature introduces inherent risks for selection bias, particularly in the older patients whose overall survival exceeded that of population-based studies,[8,25,26] warranting cautious interpretation.

In line with a more pronounced oncological role of resection with lower age, not only the association between non-CE tumor but also CE tumor and survival diminished among patients above the age of 75 or 80 years. Notably, the limited number of patients in these subgroups may have precluded the detection of potential effects, leading to imprecise survival estimates, as reflected by wide

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confidence intervals. Exploratory analyses of postoperative neurological deficit rates suggested no clear excess morbidity with maximal or supramaximal resection in very elderly patients. However, given the sample sizes, results should be interpreted cautiously. These limitations highlight the importance of incorporating extent of resection into trial protocols for older patients.

Re-resection was associated with favorable outcome in both patients <65 and ≥65 years, provided at least a maximal CE resection could be achieved. Residual CE tumor burden remains a key determinant of outcome even at recurrence; contradicting prior large-population studies[27] demonstrating no survival benefit in re-resected elderly patients. Consequently, our findings corroborate studies which have discouraged utilizing age as the sole criterion for treatment de-escalation or as exclusion criterion for trials.[28] In turn, we found no definite evidence for supramaximal resection in either age group. Importantly, selection bias regarding patient suitability for re-resection must be considered at recurrence. In clinical practice, neurosurgeons may preferentially pursue extensive resections in patients with favorable tumor locations or fewer comorbidities. While we attempted to mitigate confounding through propensity-score-matched analyses, residual bias from unmeasured factors such as comorbidity burden or nuanced surgical judgment cannot be excluded. These factors limit generalizability, underscoring the need for prospective studies by multi-institutional consortia to better separate surgical selection from true oncological effects more rigorously. Finally, histopathological information at re-resection was not uniformly available, and viable tumor was not assessed in all cases. This incomplete data capture limits the strength of tissue-specific conclusions and should be interpreted with caution. Irrespective of the oncological impact of resection in patients with glioblastoma, (re-)resection for symptomatic mass effect relief should be discussed for selected patients.[3] In addition, re-resection may provide other clinical advantages, such as eligibility for window-of-opportunity trials, longitudinal evaluation of glioblastoma evolution, and enrollment in clinical trials at recurrence.[29]

Collectively, we established that the RANO *resect* classification applies to both young and elderly patients and facilitates trial stratification. While residual contrast-enhancing tumor was prognostic for outcome in both patients <65 and ≥65 years, associations of more extensive resection with outcome were less pronounced in patients ≥65 years compared to younger patients. Specifically, supramaximal resection (RANO class 1) was associated with favorable outcome in younger patients but showed no definitive survival benefit in older patients. While prognostic effects of extent of resection diminished further with increasing age, small sample sizes may have limited the ability to detect a potential impact, underscoring the importance of individualized surgical strategies. In addition, re-resection was associated with favorable outcomes when maximal resection (RANO class 2) was performed regardless. These findings emphasize the relevance of more extensive surgery, particularly in younger patients with newly diagnosed disease, while guiding surgical decision-making with special attention to patient age.

Supplementary Material

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

Keywords

extent of resection | glioblastoma | outcome | patient stratification | surgery

Author Contributions

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

Conflict of Interest Statement

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Data Availability Statement

The datasets generated for the current study are not publicly available due to institutional regulations, but are available from the corresponding author on reasonable request.

Affiliations

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