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Surgical management and outcome of newly diagnosed glioblastoma without contrast enhancement (*low-grade appearance*): a report of the RANO *resect* group

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Abstract

Background: Resection of the contrast-enhancing (CE) tumor represents the standard of care in newly diagnosed glioblastoma. However, some tumors ultimately diagnosed as glioblastoma lack contrast enhancement and have a '*low-grade appearance*' on imaging (non-CE glioblastoma). We aimed to (a) volumetrically define the value of non-CE tumor resection in the absence of contrast enhancement, and to (b) delineate outcome differences between glioblastoma patients with and without contrast enhancement.

Methods: The RANO *resect* group retrospectively compiled a global, eight-center cohort of patients with newly diagnosed glioblastoma per WHO 2021 classification. The associations between postoperative tumor volumes and outcome were analyzed. Propensity score-matched analyses were constructed to compare glioblastomas with and without contrast enhancement.

Results: Among 1323 newly diagnosed IDH-wildtype glioblastomas, we identified 98 patients (7.4%) without contrast enhancement. In such patients, smaller postoperative tumor volumes were associated with more favorable outcome. There was an exponential increase in risk for death with larger residual non-CE tumor. Accordingly, extensive resection was associated with improved survival compared to lesion biopsy. These findings were retained on a multivariable analysis adjusting for demographic and clinical markers. Compared to CE glioblastoma, patients with non-CE glioblastoma had a more favorable clinical profile and superior outcome as confirmed in propensity score analyses by matching the patients with non-CE glioblastoma to patients with CE glioblastoma using a large set of clinical variables.

Conclusions: The absence of contrast enhancement characterizes a less aggressive clinical phenotype of IDH-wildtype glioblastomas. Maximal resection of non-CE tumors has prognostic implications and translates into favorable outcome.

Key Points

- Postoperative residual tumor volume is highly prognostic in glioblastomas with low-grade appearance.
- Glioblastomas with low-grade appearance are characterized by a more favorable prognosis than glioblastomas with classical imaging findings.

Importance of the Study

The role of resection and the prognosis of glioblastoma patients who present without contrast enhancement on imaging ('*low-grade appearance*') are controversially debated. We, therefore, studied 98 glioblastoma patients with low-grade appearance identified from a cohort of 1323 newly diagnosed glioblastomas from eight centers in the US and Europe. Here, we provide evidence that more extensive resection and lower residual tumor volumes are associated with more favorable outcome. This notion was confirmed on a multivariate analysis adjusting for demographic and clinical markers. We then constructed a propensity score-matched analysis comparing glioblastoma patients with and without low-grade appearance and found that glioblastomas with low-grade appearance are characterized by a more favorable prognosis. Glioblastomas with low-grade appearance identify with distinct outcome, and resection plays an integral role in the treatment of such tumors.

Glioblastoma is the most frequent primary brain tumor in adults and is characterized by aggressive and infiltrative growth.[1] Microsurgical resection represents the standard of care when followed by maintenance radiochemotherapy and consolidation chemotherapy.[2,3] Maximal surgical reduction of the contrast-enhancing (CE) tumor portions has been shown to be associated with more favorable outcome.[4–6] In the setting of a supramaximal resection, large retrospective studies recently provided evidence that removal of non-CE tumor beyond the CE tumor borders might also be favorably associated with outcome.[5,7] On a cautionary note, findings of a prognostically relevant association between non-CE resection and outcome might be confounded by smaller amounts of preoperative CE tumors in glioblastoma patients amendable for a supramaximal resection. The role of non-CE resection has, therefore, been controversially debated,[8] with no prospective data on the horizon. Notably, a small proportion of glioblastoma patients present without contrast enhancement which has been previously labelled as '*low-grade appearance*'.[9] This peculiar patient population may offer the opportunity to study the role of non-CE tumor resection in glioblastoma without considering confounding CE tumor.

Tissue samples of non-CE glioblastomas frequently lack glioblastoma-like histopathological findings[9]; however, the recent WHO 2021 classification allowed the diagnosis of '*glioblastoma grade 4*' even in the absence of classical histopathological features based upon qualifying molecular features alone.[10] Whether non-CE tumors identify with a similar outcome compared to classical histopathological glioblastoma with contrast enhancement remains unclear.[9,11,12] Such a comparative analysis is further complicated by the ill-defined role of resection in glioblastoma without contrast enhancement. As such, it is unclear whether outcome similarities are due to an insufficient efficacy of surgical therapy in latter patients or indeed a comparable natural history of patients with and without (histopathological and imaging-based) glioblastoma-like morphological findings.

In the current study, we identified patients who presented without contrast enhancement from a large multicenter cohort of well-annotated IDH-wildtype glioblastomas per WHO 2021 classification.[5] Here, we explored the prognostic value of surgical resection of non-CE tumor by correlating residual volumes with outcome while adjusting for molecular and clinical confounders. We then compared the outcome of patients with and without contrast enhancement, controlling for residual tumor volume as a key confounding factor using a sophisticated propensity-score matched approach.

Methods

Clinical data were collected with institutional review board approval at eight study centers in Europe and the United States participating in the RANO *resect* group (Figure 1A). Coded data were sent for centralized analysis 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: Entire Glioblastoma Cohort

Patients were selected based upon the following criteria: (a) tissue-based diagnosis of previously untreated IDH-wildtype glioblastoma per WHO 2021 classification[10]; (b) pre- and postoperative MRI available for review (including contrast-enhanced T1- and T2/FLAIR-sequences); and (c) clinical treatment data available including a follow-up of ≥3 months after surgery yielding histopathological diagnosis of glioblastoma. IDH-status was assessed using next-generation sequencing, immunohistochemistry, or pyrosequencing per institutional preference. In patients meeting those criteria, a standardized set of demographic, clinical, and volumetric information was extracted from the databases and imaging datasets by individual centers. The association of extent of resection and outcome among patients with CE tumors has been previously reported based on selected patients from this cohort.[5]

Measurement of Tumor Volumes: Definition of Non-CE Glioblastoma

As previously described,[5] tumor volumes were manually delineated on pre- and postoperative MRI scans (which were obtained within 72 hours following resection whenever possible).[13] Total CE tumor was measured on contrast-enhanced T1-sequences and non-CE tumor was measured on FLAIR (or if not available: T2-weighted) sequences.

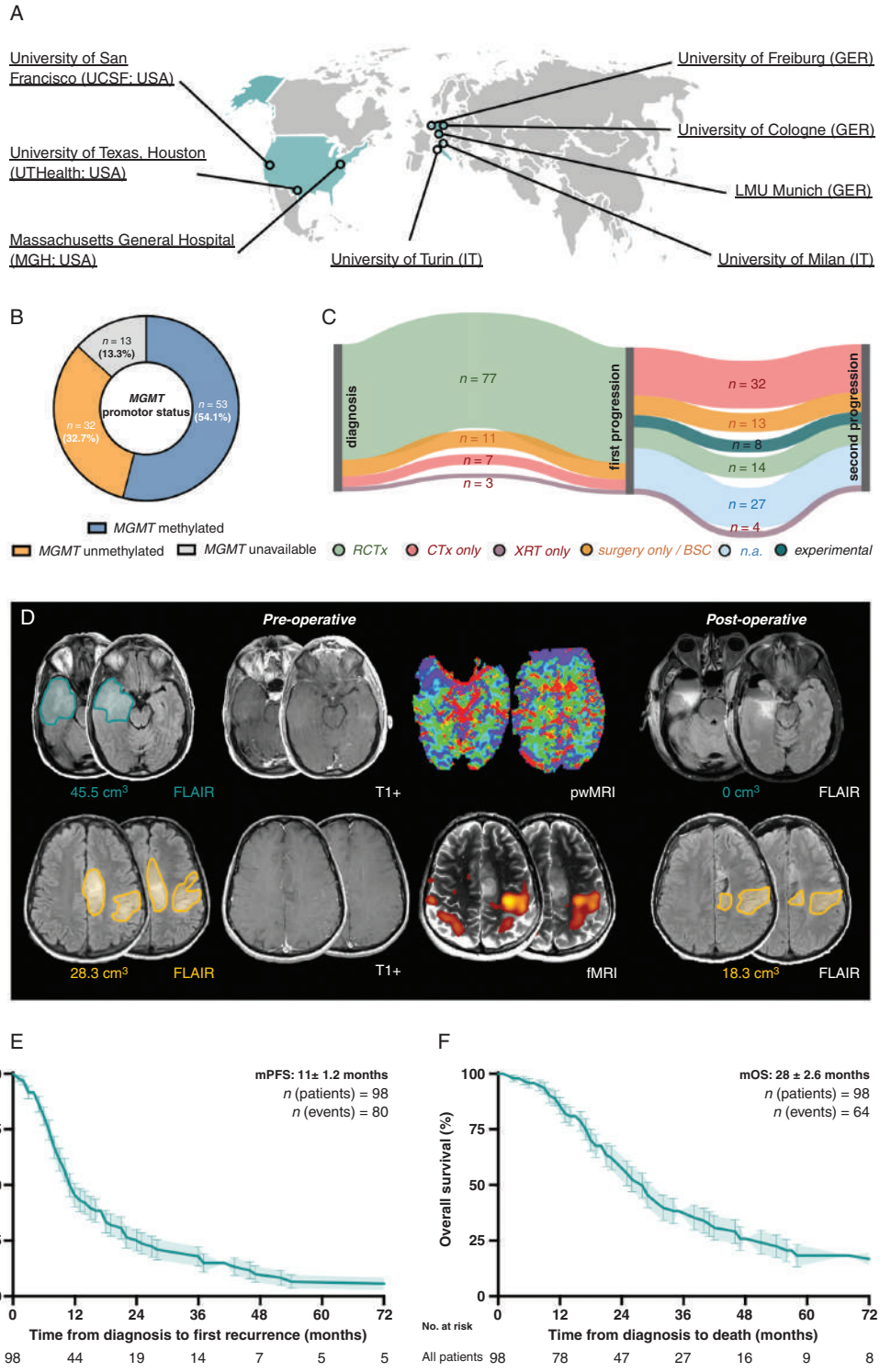

Figure 1. Baseline characteristics of patients with newly diagnosed glioblastoma without contrast enhancement ('*low-grade appearance*'). (A) Geographic representation of the eight neuro-oncological centers participating in the study. (B) Distribution of *MGMT* promotor methylation status across patients with glioblastoma without contrast enhancement ($n = 98$). (C) Therapeutic approaches following diagnosis and first recurrence among patients with glioblastoma without contrast enhancement ($n = 98$). Nodes of the Sankey plot represent time points in the disease course (diagnosis, first progression, second progression); therapeutic approaches are color-coded and arc thickness corresponds to patient numbers. (D) Axial brain MRI in the pre- (left panel) and post-operative (right panel) setting demonstrating a right temporal glioblastoma (upper panel) and a multi-focal left fronto-parietal glioblastoma (lower panel). Note that in both patients, no contrast enhancement was detected. While in the upper patient complete resection of the lesion (green) was achieved, infiltrative growth of the lesion (yellow) into the primary motor cortex as demonstrated by fMRI limited extent of resection in the lower patient. (E, F) Kaplan–Meier estimates of progression-free survival (E) and overall survival (F) for the entire cohort of patients with glioblastoma without contrast enhancement ($n = 98$). Points indicate deceased or censored patients, light shading indicates SEM.

By reviewing preoperative imaging and postoperative sequences (including diffusion-weighted sequences), raters were advised to ensure that FLAIR/T2-abnormalities were not representing surgically induced changes. Non-CE tumor was identified based upon disruption of the anatomical architecture and its FLAIR/T2-signal intensity compared to cerebrospinal fluid or physiological white matter. Multifocal disease was quantified separately at each focus and summed together. Absolute tumor volumes (in cm^3) were recorded. Patients with non-CE tumors ('*low-grade appearance*') were defined when ≤1 cm^3 contrast enhancement was found on preoperative imaging given that less than 1 cm^3 contrast enhancement is considered only measurable with some uncertainty, and no difference was previously shown for individuals with no contrast enhancement and 0–1 cm^3 contrast enhancemen when controlled for non-CE tumor.[5,6]

Individual patients were also stratified based on the *residual* tumor volumes following the recently proposed *RANO classification system*.[5,6,14,15] Here, less than 5 cm^3 residual non-CE tumor corresponds to *RANO class 1 (previously entitled: 'supramaximal CE resection')*, more than 5 cm^3 non-CE tumor to *RANO class 2 (previously entitled: 'maximal CE resection')*, and biopsy only to *RANO class 4 (previously entitled: 'biopsy')*. RANO class 3 is *per definition* reserved for patients with a substantial amount of residual CE tumor and does, therefore, not apply in patients with non-CE glioblastoma.

Definition of Endpoints

Patients were followed until death or day of database closure (April 1, 2023). Patients lost to follow-up were censored on the day of last follow-up. Date of diagnosis was defined as date of surgery (or biopsy if no open resection was provided). Date of first recurrence was set as date of MRI showing disease progression per RANO criteria.[16] Progression-free survival was defined as the interval from date of diagnosis to date of first recurrence or death from any cause, and overall survival was defined as the interval from date of diagnosis to death from any cause.

Statistics

Using the D'Agostino-Pearson test, continuous variables were analyzed for normal distribution and equal variance. In case of parametric data, differences between two groups were tested by the unpaired Student's *t*-test. In case of non-parametric data, the Mann–Whitney *U* test was applied for two groups. The interaction between pre- and postoperative tumor volumes was estimated using Pearson's correlation coefficient (*r*), and a prediction model was 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. Such 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 the calculation of median follow-up. For univariable survival analysis of outcomes depending on a continuous variable such as residual tumor volume, Cox proportional hazard regression models were constructed to calculate hazard ratios (HR) and 95% confidence intervals (CI). Similarly, Cox proportional hazard regression models were computed for multivariable survival analysis. For this purpose, markers were first assessed on univariate analysis; and if of significance forwarded into the multivariate model.

To minimize the confounding effects of residual tumor volumes and other potential confounders on a comparison between patients with and without contrast enhancement, we applied propensity score-based nearest neighbor matching. Propensity scores for matching were calculated based upon clinical variables (age, preoperative Karnofsky performance status, presence of a new postoperative deficits), tumor properties including clinical as well as molecular markers (anatomic localization, involvement of the dominant hemisphere, *MGMT* promotor methylation status), first-line treatments, and total tumor volumes both on pre- and postoperative imaging. The matched data sets were compared with respect to outcome using Kaplan–Meier survival estimates and log-rank tests, and the resulting distilled differences are assumed to represent the biological outcome difference of patients with and without contrast enhancement rather than the effect of confounders.

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 $P \leq 0.05$.

Date Availability Statement

Coded data can be accessed upon qualified request from the authors. Correspondence should be addressed to the corresponding author.

Results

Baseline Patient Characteristics: Non-CE Glioblastoma

Clinical data from 1323 newly diagnosed IDH-wildtype glioblastomas diagnosed between 2003 and 2022 were collected (Table 1). All tumors met the definition of IDH-wildtype glioblastoma per WHO 2021 classification.[10] We identified 98 patients with none to minimal contrast enhancement on preoperative imaging (non-CE glioblastoma, including 72 patients without any contrast enhancement), translating to an estimated incidence of 7.4% among all glioblastomas. Non-canonical IDH mutations were excluded per sequencing in 41 patients with non-CE glioblastoma (41.8%).

Seventy-four patients (74/98 patients, 75.5%) underwent open microsurgical tumor resection at diagnosis, and 24 patients (24.5%) had a biopsy only to allow tissue-based diagnosis. Tissue-based diagnosis rested upon the presence of histopathological features of glioblastoma together with

Table 1. Characteristics for the study cohort of patients with newly diagnosed IDH-wildtype glioblastoma with and without contrast enhancement on MRI.

Surgical second-line therapy		No contrast enhancement	Contrast enhancement	Total	*P*-value
Overall		*n* = 98	*n* = 938	*n* = 1036	
Demographics	Age at diagnosis (years)	58.7 ± 1.4	61.8 ± 0.4	61.5 ± 0.4	***0.018**
	M:F ratio	1:0.7	1:0.7	1:0.7	0.944
Clinical markers	Pre-OP KPS (median, range)	90 (60–100)	80 (20–100)	80 (20–100)	***0.001**
	Post-OP KPS (median, range)	90 (70–100)	80 (10–100)	80 (10–100)	***0.020**
	New postoperative deficit (n, %)	13 (13.3%)	145 (15.5%)	158 (15.3%)	0.837
IDH status (n, %)	Wildtype	98 (100%)	938 (100%)	1036 (100%)	1.000
	Mutated	0	0	0	
MGMT promotor (n, %)	Methylated	53 (54.1%)	420 (44.8%)	473 (45.7%)	0.148
	Non-methylated	32 (32.7%)	333 (35.5%)	365 (35.2%)	
	n.a.	13 (13.3%)	185 (19.7%)	198 (19.1%)	
TERT promotor (n, %)	Mutated	60 (61.2%)	359 (38.3%)	419 (40.4%)	***0.001**
	Wildtype	10 (10.2%)	62 (6.7%)	72 (7.0%)	
	n.a.	28 (28.6%)	517 (55.1%)	545 (52.6%)	
Histopathology (n, %)	Glioblastoma hallmarks	36 (36.7%)	937 (99.9%)	973 (93.9%)	***0.001**
Localization at diagnosis (n, %)	(Sub-)cortical	73 (74.5%)	708 (75.5%)	781 (75.4%)	0.392
	Deep-seated	16 (16.3%)	115 (12.3%)	131 (12.7%)	
	Multifocal	9 (9.2%)	115 (12.3%)	124 (12.0%)	
	Dominant	48 (49.0%)	475 (50.6%)	550 (53.1%)	***0.001**
Tumor volumes (mean; cm^3)	Pre-OP CE	0.2 ± 0.1	35.1 ± 0.9	31.8 ± 0.9	***0.001**
	Pre-OP non-CE	39.4 ± 3.6	60.0 ± 1.8	58.1 ± 1.7	***0.001**
	Post-OP CE	0.1 ± 0.1	4.4 ± 0.4	4.0 ± 0.4	***0.001**
	Post-OP non-CE	17.1 ± 2.1	38.4 ± 1.3	36.4 ± 1.2	***0.001**
First-line therapy (*n*, %)	Radiochemotherapy	77 (78.6%)	778 (82.9%)	855 (82.5%)	***0.012**
	Radiotherapy alone	3 (3.1%)	61 (6.5%)	64 (6.2%)	
	Chemotherapy alone	7 (7.1%)	26 (2.8%)	33 (3.2%)	
	Resection alone	11 (11.2%)	56 (6.0%)	67 (6.5%)	
	n.a.	0	17 (1.8%)	17 (1.6%)	
Outcome: PFS	PFS (months)	11 ± 1.2	8 ± 0.3	8 ± 0.2	***0.001**
Clinical markers at recurrence	KPS at recurrence (median, range)	90 (30–100)	80 (20-100)	80 (20–100)	***0.001**
Second-line therapy (*n*, %)	Salvage surgery	27 (27.6%)	216 (23.0%)	243 (23.5%)	0.315
	Chemotherapy alone	32 (32.7%)	233 (24.8%)	265 (25.6%)	***0.001**
	Radiotherapy alone	14 (14.3%)	55 (5.9%)	69 (6.7%)	
	Radiochemotherapy	4 (4.1%)	87 (9.3%)	91 (8.8%)	
	Surgery only or BSC	13 (13.3%)	197 (21.0%)	210 (20.3%)	
	Experimental agents	8 (8.2%)	28 (3.0%)	36 (3.5%)	
	n.a. or n. appl.	27 (27.6%)	338 (36.0%)	365 (35.2%)	
Outcome: OS	OS (months)	28 ± 2.6	16 ± 0.5	17 ± 0.5	***0.001**

Characteristics are given for patients with newly diagnosed IDH-wildtype glioblastoma WHO grade 4 (total; *n* = 1036). Patients were stratified according to whether preoperative imaging showed contrast enhancement (*n* = 938) or no contrast enhancement (*n* = 98). 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, and asterisks as well as bold letter indicate $P \leq 0.05$.

Abbreviations: BSC: best supportive care; F: female; IDH: Isocitrate dehydrogenase; KPS: Karnofsky performance status; M: male; MGMT: O^6-methylguanine-DNA methyltransferase; OS: overall survival; n.a.: not available for review; n. appl.: not applicable. OS; overall survival; PFS: progression-free survival; TERT: telomerase reverse transcriptase.

IDH-wildtype status in 36 patients (36.7%). Notably, 31 of 36 tumors (86.1%) with histopathological features of glioblastoma did not show any contrast enhancement. In the absence of classical glioblastoma-like features on histopathology, the combination of IDH-wildtype status with other qualifying markers (including TERT promotor mutations, *EGFR* amplifications, or +7/–10 genotype; most frequently TERT promotor mutation in 48 of those patients) served to establish the diagnosis in the remaining 62 patients (63.3%). *MGMT* promotor status was methylated in 53 patients (54.1%), unmethylated in 32 patients (32.7%), and not available in 13 patients (13.3%; Figure 1B). The vast majority of patients with non-CE glioblastoma received concomitant radiochemotherapy following surgery per current standard of care (77 patients; 78.6%) (Figure 1C-D).[2,3] Median time until first progression was 11 ± 1.2 months, and chemotherapy rechallenge (32 patients; 32.7%) was most often provided at first recurrence, while salvage surgery was also frequently scheduled (27 patients; 27.6%). At the time of database closure, 34 patients were noted to be as alive (34.7%) including 26 patients who were lost to follow-up (not seen for ≥12 months) and 64 patients were deceased (65.3%). At a median follow-up of 57 ± 6.9 months, the median overall survival was 28 ± 2.6 months (Figure 1E-F). Among patients with non-CE glioblastoma, there were no outcome differences when individuals were stratified according to the presence of histopathological glioblastoma-like findings (with versus without histopathological glioblastoma-like findings; overall survival: 28 ± 3.8 versus 29 ± 2.2 months, HR: 1.09, CI: 0.6–1.9; $P = 0.732$), the detection of minimal contrast enhancement ≤1 cm^3 (as opposed to the complete absence of contrast enhancement; overall survival: 29 ± 3.1 versus 26 ± 5.3 months, HR: 0.80, CI: 0.4–1.5; $P = 0.422$), or a methylated *MGMT* promotor status (as opposed to an unmethylated *MGMT* promotor status; overall survival: 28 ± 9.2 versus 32 ± 3.6 months, HR: 1.04, CI: 0.6–1.8; $P = 0.889$).

Role of Surgery in Non-CE Glioblastoma: Exploring the Prognostic Implications of Residual Tumor Volume

To study the prognostic associations of surgical resection with outcome, we delineated the pre- and postoperative tumor volumes. In patients with non-CE glioblastoma, median preoperative non-CE tumor volume was 39.4 ± 3.6 cm^3 and median postoperative non-CE tumor volume was 17.1 ± 2.1 cm^3 (which also includes patients who underwent only a biopsy; Figure 2A). There was correlation between pre- and postoperative tumor volumes among patients who underwent open microsurgical resection ($r = 0.684$; $P = 0.001$); and a regression analysis predicted an increase of 0.33 cm^3 postoperative residual non-CE volume per each cm^3 of preoperative tumor (Figure 2B). Based upon the residual tumor volumes, patients were allocated following the *RANO classification for extent of resection* into one of three categories: "supramaximal resection" (RANO class 1 with ≤5 cm^3 residual non-CE tumor; 32/98 patients, 32.7%), "maximal resection" (RANO class 2 with >5 cm^3 residual non-CE tumor; 42/98 patients, 42.9 %), and "biopsy" (RANO class 4; 24/98 patients, 24.5%) (Figure 2C). By constructing a univariate Cox proportional hazard regression model, an exponential increase of the hazard ratio for death was predicted with more residual non-CE tumor volume following surgery (HR per cm^3: 1.02, CI: 1.0–1.1; $P = 0.001$) (Figure 2D). This was also true when limiting our analysis to patients undergoing open resection. When we designated non-CE glioblastoma patients who underwent resection into intervals according to their postoperative tumor volume, we found that a residual tumor volume of ≤1 cm^3 was associated with better outcome (Figure 2E). Accordingly, there was no difference between RANO classes 2 and 4 (overall survival: 25 ± 4.4 versus 25 ± 5.6 months, HR: 1.00, CI: 0.5–1.0; $P = 0.996$) (Figure 2G). In turn, the outcome of patients in RANO class 1 was more favorable compared to patients in RANO class 2 (overall survival: 41 ± 9.7 versus 25 ± 4.4 months, HR: 0.57, CI: 0.3–1.0; $P = 0.054$) (Figure 2F). Moreover, outcome was best within subgroup of RANO class 1 patients when no residual non-CE tumor was detected at all (overall survival: 56 ± 20.9 versus 29 ± 9.7 months, HR: 0.40, CI: 0.2–1.0; $P = 0.049$). There was no difference in the frequency of new postoperative deficits between RANO class 1 and 2 (6/32 patients, 18.8% *versus* 6/42 patients, 14.3%; $P = 0.417$).

Association of Residual Non-CE Tumor and Outcome in Non-CE Glioblastoma: Adjusting for Confounders

To exclude the possibility that residual tumor volume represents only a surrogate marker for another confounder, we first identified predictors of outcome on a univariate analysis from a large list of clinical variables (Table 2). Here, residual non-CE tumor (per cm^3 residual volume; HR: 1.02, CI: 1.0–1.1; $P = 0.001$), age (per year; HR: 1.03, CI: 1.0–1.1; $P = 0.016$), and KPS at diagnosis (as continuous variable; HR: 0.97, CI: 0.9–1.0; $P = 0.027$) were associated with overall survival. Importantly, the prognostic value of residual non-CE tumor volume was retained in a multivariable analysis (HR: 1.02, CI: 1.0–1.1; $P = 0.002$) after stratifying for such potential clinical confounders (Figure 3A). Notably, the association between residual non-CE tumor volume and outcome also held true when we incorporated the use of first-line therapies into our multivariable model.

Revealing Clinical Differences Between Non-CE and CE Glioblastomas: Propensity Score-Matched Analyses

Detailed clinical and volumetric data from 938 glioblastoma patients with contrast enhancement on preoperative imaging were available for comparison against patients with non-CE glioblastoma (Table 1). There was no clear distinct molecular (ie, *MGMT* promotor status) or anatomical profile (ie, localization) of non-CE glioblastomas; however, affected patients with non-CE glioblastomas identified with a more favorable clinical profile characterized by younger age and higher KPS. Also, patients with non-CE glioblastoma had lower pre- and postoperative tumor volumes. Although somewhat less aggressive first-line therapies were provided for patients with non-CE glioblastomas,

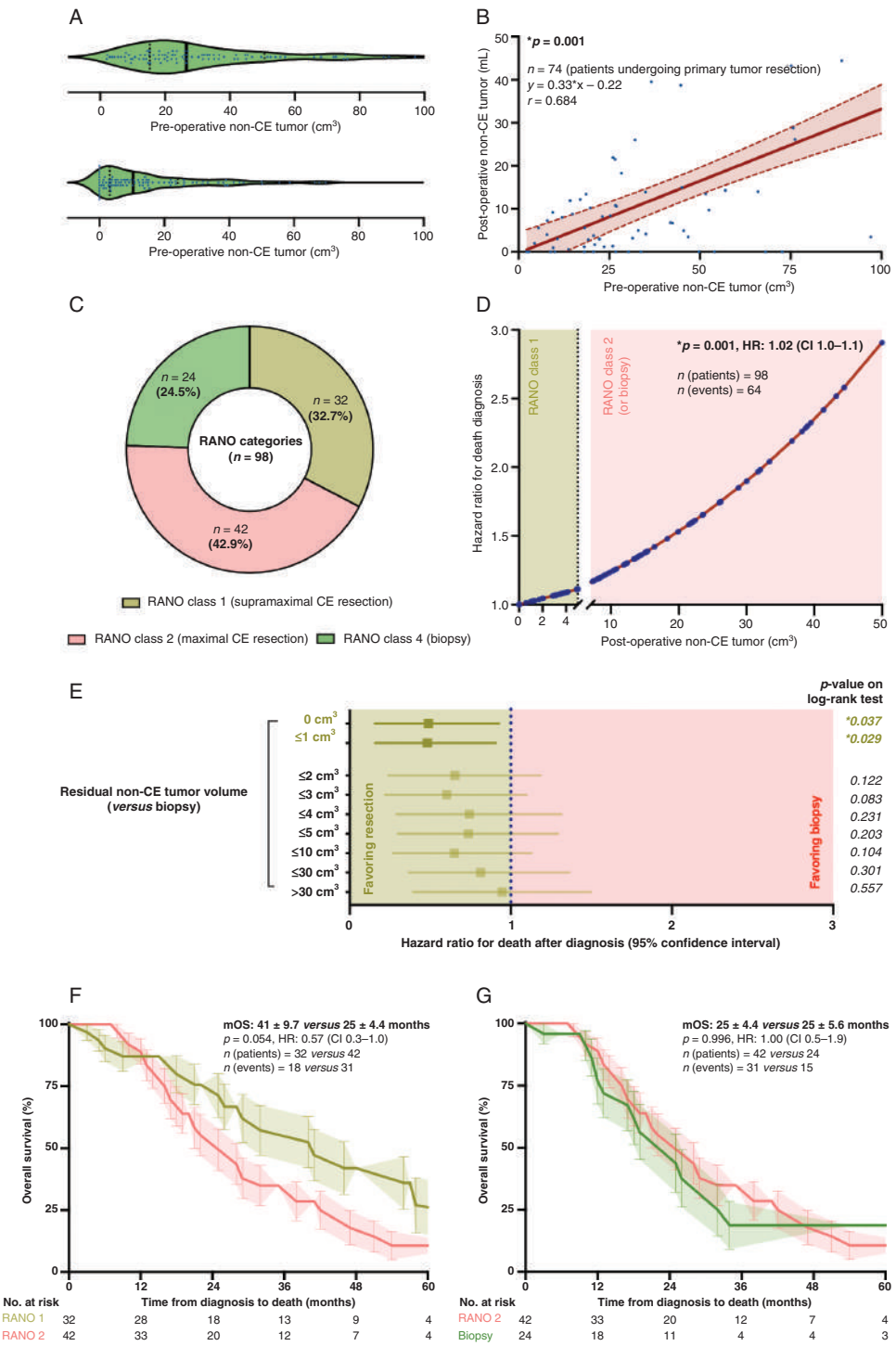

Figure 2. Prognostic associations of surgical resection of the non-CE tumor volume. (A) Pre- (upper panel) and postoperative non-CE tumor volumes (lower panel, in cm^3) after microsurgical tumor resection or biopsy ($n = 98$). Median ± 95% confidence interval. (B) Simple linear regression analysis comparing the pre- to the postoperative tumor volumes in patients undergoing microsurgical tumor resection ($n = 74$). Pearson correlation coefficients (r), calculated equations including slope β_1, and p-values are given. Dotted lines indicate 95% confidence intervals. (C) Stratification of all patients ($n = 98$) according to the previously proposed RANO *resect* classification. Note that RANO class 3 ("submaximal CE resection") refers to the amount of residual CE tumor volume and does not apply in the setting of non-CE glioblastomas. (D) Hazard ratios for death calculated for each individual residual non-CE tumor volume among patients with glioblastoma without contrast enhancement ($n = 98$). An exponential hazard increase can be seen for higher residual non-CE volumes. (E) Univariate analysis using log-rank tests comparing patients with different amounts of residual non-CE tumor volumes following resection to patients managed with biopsy. Note that an association favoring resection was only observed for residual non-CE tumor volumes of ≤1 cm^3. Hazard ratio ± 95% confidence interval. (F, G) Kaplan–Meier estimates of overall survival for patients stratified to RANO class 2 (corresponding to >5 cm^3 residual non-CE tumor; $n = 42$) compared to RANO class 1 (F; corresponding to ≤5 cm^3 residual non-CE tumor; $n = 32$) or RANO class 4 (G; corresponding to biopsy only). Points indicate deceased or censored patients, light shading indicates SEM.

Table 2. Univariate Cox proportional hazard model for patients with a newly diagnosed IDH-wildtype glioblastoma without contrast enhancement on MRI.

Variable	Type of variable	Overall survival		
		Hazard ratio	95% confidence interval	*P*-value
Tumor volumetrics				
Preoperative non-CE (cm^3)	Continuous	1.00	1.0–1.0	0.132
Postoperative non-CE (cm^3)	Continuous	1.02	1.0–1.1	***0.001**
Demographics				
Sex	Male (vs. Female)	1.03	0.6–1.7	0.915
Age (years)	Continuous	1.03	1.0–1.1	***0.016**
Clinical markers				
KPS at diagnosis	Continuous	0.97	0.9–1.0	***0.027**
New postoperative deficit	Yes (vs. No)	0.83	0.4–1.6	0.615
Tumor localization	Subcortical	0.80	0.4–2.1	0.611
	Deep-seated	1.18	0.5–3.4	0.740
	Multifocal (reference level)	-	-	-
Affected hemisphere	Dominant (vs. non-dominant)	1.08	0.6–1.9	0.792
Mode of surgery				
Biopsy only	Versus resection	1.20	0.7–2.1	0.539
Non-surgical first-line therapy				
Radiotherapy alone	Versus RCTx	0.79	0.2–2.2	0.698
Chemotherapy alone	Versus RCTx	2.29	0.8–5.3	0.081
Best supportive care	Versus RCTx	0.45	0.2–1.0	0.069
Molecular markers				
MGMT promotor status	Methylated (vs. unmethylated)	1.04	0.6–1.8	0.902

Univariate analysis testing information on non-contrast enhancing tumor volume and also demographic, clinical, and molecular markers using Cox proportional hazard models among patients with a newly diagnosed IDH-wildtype glioblastoma without contrast enhancement on MRI ($n = 98$). Hazard ratio, 95% confidence interval, and *P*-value are given for the effect of the analyzed variables on overall survival. Asterisks as well as bold letter indicate $P \leq 0.05$.
Abbreviations: KPS: Karnofsky performance status; MGMT: O6-methylguanine-DNA methyltransferase; non-CE: non-contrast enhancing; RCTx: radiochemotherapy.

time to first progression was longer in patients with non-CE glioblastomas (11 ± 1.2 versus 8 ± 0.3 months, HR: 0.58, CI: 0.5-0.7; $P = 0.001$). Such patients also had higher KPS at first recurrence, and more often underwent further antitumor therapy in the recurrent setting. Accordingly, a longer overall survival was observed among patients with non-CE glioblastoma compared to patients with CE glioblastoma (28 ± 2.6 versus 16 ± 0.5 months, HR: 0.55, CI: 0.5–0.7; $P = 0.001$). This held true when we limited our analysis to individuals who received first-line radiochemotherapy (non-CE versus CE glioblastomas: 28 ± 2.2 versus 18 ± 0.6 months, HR: 0.63, CI: 0.5–0.8; $P = 0.001$).

We aimed to assess whether the differences in outcome between non-CE and CE glioblastomas were not only related to differences in clinical properties, but perhaps also due to inherent biological differences. To test such an assumption, we matched cohorts to balance covariates and minimize the effects of confounders using the identification of nearest neighbors based on propensity score calculations (Figure 3B). We acknowledged clinical variables, tumor properties including *MGMT* promotor methylation status and anatomic localization, first-line treatments, as well as total tumor volumes on pre- and postoperative imaging. Using this approach, a sufficient balance of covariates with a reduction of the potential for confounding was achieved by selecting comparable patients with or without non-CE glioblastomas (Figure 3C and E). Here, we verified the superior outcome of non-CE glioblastoma compared to patients with CE glioblastoma (overall survival: 32 ± 3.3 versus 20 ± 1.9 months, HR: 0.56, CI: 0.4-0.9; $P = 0.008$) (Figure 3D). Such survival differences were also observed when the analysis was restricted to patients from both groups who were assigned to RANO class 1 as only minimal amounts of residual tumor volume were detected on postoperative imaging (overall survival: 56 ± 14.2 versus 19 ± 3.0 months, HR: 0.41, CI: 0.2–0.9; $P = 0.036$) (Figure 3F).

Discussion

The prognostic implications for resection of non-CE tumor in glioblastoma have been controversially discussed. Based on a contemporary multicenter cohort of

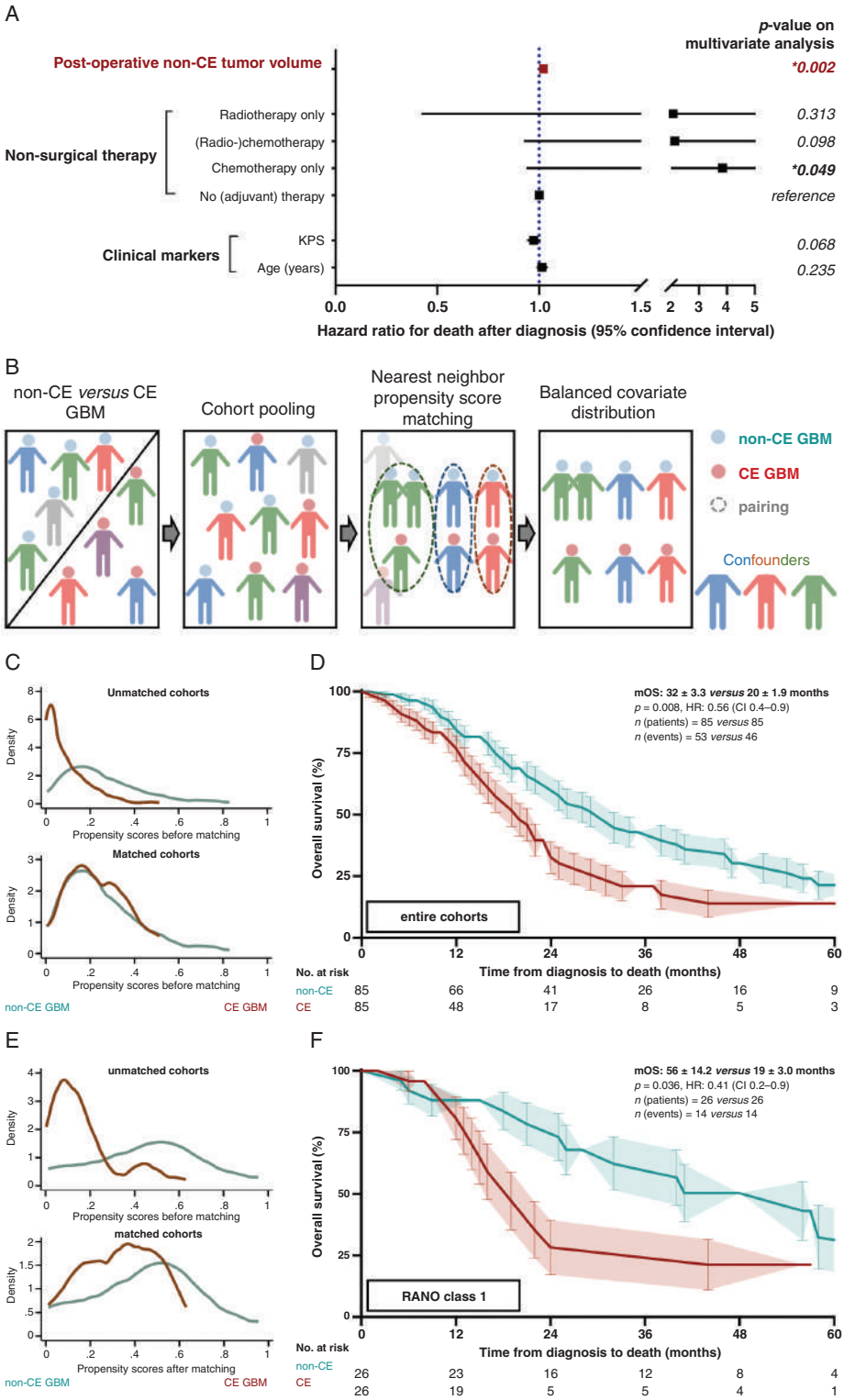

Figure 3. Outcome differences between glioblastomas with and without contrast enhancement. (A) Multivariate analysis for non-CE glioblastoma using a Cox proportional hazard regression model estimating the hazard ratio for death. All included variables were of significance on univariate analysis. KPS, Karnofsky performance status. Hazard ratio ± 95% confidence interval. (B) Principals of propensity score-matched analyses. Nearest neighbor matching using multiple covariates yields two patient cohorts who only differ for the variable of interest (ie, the presence of contrast enhancement on preoperative imaging). (C–F): Kernel density estimates before and after propensity score-based matching (C, E) and Kaplan–Meier estimates of overall survival (D, F). All patients with non-CE glioblastomas ($n = 98$ before matching; $n = 85$ after matching) were matched to controls selected from CE glioblastomas ($n = 938$ before matching; $n = 85$ after matching) (C, D); and also RANO class 1 patients with non-CE glioblastomas ($n = 32$ before matching; $n = 26$ after matching) were matched to RANO class 1 controls with CE glioblastomas ($n = 95$ before matching; $n = 26$ after matching) (E, F). Note the survival differences favoring non-CE glioblastomas. Points indicate deceased or censored patients, light shading indicates SEM.

glioblastomas presenting without contrast enhancement, we demonstrate the important associations between more extensive resection of such non-CE tumors and outcome, account for potential confounders to corroborate those findings, and highlight evidence for the rather favorable clinical course of non-CE glioblastomas compared to CE glioblastomas even in case of comparable post-resection residual tumor volume. These results potentially have substantial implications for clinical patient management and the design and analysis of clinical trials.

We provide strong evidence that resection of non-CE tumor is associated with survival in non-CE glioblastoma when extensive removal with minimal residual tumor is achieved. Using regression analysis, an increase of 1.02 in the HR for death was estimated per residual cm^3 non-CE tumor with an exponentially high risk for large remnants. Also, we verified that our results were neither confounded by first-line therapies nor other clinical factors including *MGMT* promotor methylation status or tumor localization. As such, the beneficial association between greater extent of resection and more favorable outcome cannot be solely explained by the assumption that a lower extent of resection is a surrogate marker for glioblastomas with closer proximity to highly functional brain regions and an inherently worse prognosis. Importantly, our findings on the prognostic relevance of non-CE tumor resection are further supported by large retrospective studies in glioblastomas with contrast enhancement: Molinaro et al.[7] outlined that IDH-wildtype glioblastomas with ≤5.4 cm^3 non-CE postoperative tumor (and almost no residual CE tumor) may experience a considerable survival benefit from resection. Furthermore, our RANO *resect* group has previously made similar findings highlighting the fact that resection of non-CE tumor beyond the CE tumor margins has prognostic implications in glioblastoma.[5] Together with other reports,[17] this finding argues against the conclusion derived from prior studies suggesting that glioblastomas with *low-grade appearance* (defined as none or only minimal contrast enhancement) do not benefit from resection[9,18,19]

In contrast, we only detected a clear association between resection and outcome among patients in whom ≤1 cm^3 non-CE residual tumor was surgically achieved. Although a biopsy allows tissue acquisition to guide therapy based on molecular markers, these results highlight the need for dedicated intraoperative efforts to reduce non-CE tumor as much as safely possible. Unlike previous studies,[9,18] we made use of a detailed volumetric approach which equipped our analyses with a level of granularity allowing to reveal the prognostic associations between surgery and outcome. Together with recent improvements in intraoperative monitoring and visualization tools which translated into a high rate of patients below the critical threshold of 1 cm^3 non-CE tumor,[20–23] this methodological approach may have contributed to the findings on the prognostic value of resection not observed in more historical cohorts. In the setting of future clinical trials, our findings suggest that detailed recording of non-CE residual tumor volumes may be of critical relevance for clinical trial design, patient stratification, data analyses, and interpretation. The RANO *resect* classification may serve as a tool to denominate patients accordingly and elucidate on the short- as well as the long-term benefits of surgery compared to non-surgical management.[5,6] However, the accuracy to delineate outcome differences between patients with non-CE glioblastomas according to their respective resection class might be somewhat less powerful compared to CE glioblastomas.

In our cohort, patients with non-CE glioblastoma had more favourable outcomes compared to CE glioblastoma. Not only were patients with non-CE glioblastomas of younger age, pre-operative tumor volumes were smaller, and glioblastoma-like features were frequently absent on histopathology; but the superior outcome was also retained when eliminating all those confounders utilizing a propensity score-based matching approach.[6,24] Acknowledging the considerable outcome differences as well as the clinical profile, it is tempting to speculate that non-CE glioblastomas represent classical CE glioblastomas at an earlier stage (which might also be interpreted as lead-time bias).[25,26] In line with this assumption, Berzero et al.[11] reported that the outcome of individuals without glioblastoma-like histopathological characteristics is superior to tumors with higher grade morphology even when molecular criteria allowing diagnosis of glioblastoma per WHO 2021 are fulfilled.

On a cautionary note, Tesileanu et al.[9] compared outcome between non-CE and CE glioblastomas and found no differences in overall survival. Notably, the study included a large fraction of individuals presenting with *gliomatosis cerebri* (defined as a confluent lesion in at least three lobes) and only 9%–44% of the non-CE glioblastomas underwent resection compared to 83% of CE glioblastomas. In light of our present findings regarding the prognostic value of surgery, these baseline discrepancies might have shifted outcome of non-CE glioblastoma toward the prognosis of CE glioblastoma. Whether the molecular profile in the absence of morphological glioblastoma-like characteristics is sufficient to assume a clinical course identical to CE glioblastoma, therefore, warrants further evaluation in prospective cohorts.[10,12,27] However, our analyses did not find evidence that the mere presence of glioblastoma-like features on histopathology was associated with a distinct outcome, as long as no contrast enhancement was visualized on preoperative imaging. Rather than a binary report on whether glioblastoma-like features were seen on histopathology and which diagnostic criteria have been met, such neuropathological information might need additionally to be accompanied by volumetric analyses on postoperative tumor remnants as a quantitative measurement in the setting of future clinical trials.[28]

Our patients were treated at large neuro-oncological centers in Europe and the United States, and excellent postsurgical results regarding both clinical outcome and residual tumor volumes were observed. Acknowledging a high level of surgical neuro-oncological expertise, it remains to be seen whether our findings on the associations between surgery and outcome are generalizable to centers with lower case volumes. Given the retrospective design of our study, a more detailed molecular information was not available for our review. This specifically includes differences in the number of *TERT* promotor mutations between CE and non-CE tumors, and we could, therefore, not incorporate *TERT* promotor status into our propensity score-matched analysis as such information was not

available in a sufficient number of CE glioblastomas. As such, we cannot comment on whether the prognostic role of surgery or the natural disease course varies across molecular glioblastoma variants defined by their molecular or epigenetic profile as previously postulated.[19] Larger sample size than our cohort and prospective data sampling protocols might be warranted in this regard; and case numbers of non-CE glioblastomas are expected to rise given that the WHO 2021 has only recently allowed the diagnosis of glioblastoma even in the absence of classical morphological hallmarks.[10] Such larger studies will also need to confirm the role of *MGMT* promotor status in non-CE glioblastomas among other factors, as we observed an unusually high fraction of patients with *MGMT* promotor methylation; and at the same time, we failed to detect an association between outcome and *MGMT* promotor status which is otherwise characteristically observed in classical CE IDH-wildtype glioblastomas (but less so in the absence of histopathological features).[19,29,30] More importantly, future studies will also need to apply standardized sequencing protocols to exclude non-canonical IDH-mutations among tumors which we denominated as non-CE glioblastoma. As such, standardized in-depth molecular analyses of non-CE glioblastoma which were lacking in our study are warranted.

Collectively, we provide evidence that the absence of contrast enhancement characterizes a clinically less aggressive phenotype of IDH-wildtype glioblastomas. In such glioblastoma patients with low-grade appearance on imaging, more extensive resection of non-CE tumor has prognostic value and is associated with a favorable outcome. Measurements of residual tumor volumes should, therefore, serve to stratify glioblastoma patients in the setting of clinical trials.

Keywords

contrast enhancement | extent of resection | glioblastoma | surgery | WHO 2021

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Conflict of interest

J. Dietrich: Consultant: Amgen, Unum Therapeutics, Novartis. Royalties: Wolters Kluwer. M. van den Bent: Consultant: Celgene, BMS, Agios, Boehringer, Abbvie, Bayer, Carthera, Nerviano, Genenta. M. Weller: Research grants: Quercis, Versameb. Honoraria or advisory board participation and consulting: Bayer, CureVac, Medac, Novartis, Orbus, Philogen. M.A. Vogelbaum: Indirect equity and patent royalty interests: Infuseon Therapeutics. Honoraria: Chimerix, Midatech. Research grants: DeNovo Pharma, Oncosynergy, Infuseon, Chimerix. N. Tandon: Research grant: Medtronic. Founder: BrainDynamics; Advisory Board: Nervonik, BrainGrade. R. Rudà: Honoraria, advisory board, and consulting: UCB, Bayer, Novocure, Genenta, Servier. J.-C. Tonn: Research grants: Novocure, Munich Surgical Imaging. Advisory board: AAA Novartis. Royalties: Springer Publisher. P.K., F.B., A.D., S.T.J., N.Te.., J.S.Y., T.S., L.H., R.A.M., A.F.H., A.M.M., J.B., O.S., L.B., S.H.J., N.Th., S.J.G., Y.E., S.M.C., M.S.B., D.P.C.: None.

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