A prognostic classification system for extent of resection in *IDH*-mutant grade 2 glioma: an international, multicentre, retrospective cohort study with external validation by the RANO resect group

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Summary

Background The efficacy of resection in *IDH*-mutant grade 2 gliomas remain controversial since terminology for the extent of resection has been inconsistently applied across studies. We aimed to establish a standardised classification for the extent of resection and assess the association between supramaximal resection and survival across molecular subtypes.

Methods In this international, multicentre, retrospective study, patients aged 18 years and older with newly diagnosed grade 2 *IDH*-mutant glioma were identified from institutional databases across 16 centres in the USA, Europe, and Asia between between Sept 1, 1993, and May 10, 2024. We used Cox proportional hazard regressions to analyse the associations between residual tumour and progression-free survival and overall survival. Patients were stratified according to a previously postulated classification system based on residual tumour volume. A cohort of patients from UCSF diagnosed between Feb 16, 1998, and Nov 14, 2017, was used for geographically and institutionally independent external validation.

Findings We identified 1391 patients with newly diagnosed *IDH*-mutant grade 2 gliomas, with a median follow-up of 81 months (95% CI 78–85). 728 patients (379 with astrocytoma and 349 with oligodendroglioma) received no first-line treatment beyond surgery, allowing us to study the isolated effects of resection. Patients with maximal T2-fluid attenuated inversion recovery (T2-FLAIR) resection (class 2; 0–5 cm³ remnant) had superior progression-free and overall survival compared with submaximal T2-FLAIR resection (class 3; 5–25 cm³ remnant) or minimal T2-FLAIR resection (class 4; >25 cm³ remnant), with 10-year survival rates of 82% (95% CI 76–87) versus 75% (62–84) versus 48% (29–65; p<0·0001) and 5-year progression-free survival rates of 44% (38–50) versus 25% (16–34) versus 12% (4–24; p<0·0001), respectively. Resection beyond T2-FLAIR borders (class 1) provided survival benefits, with a 10-year survival rate of 98% (95% CI 92–99) and a 5-year progression-free survival rate of 83% (76–88) for supramaximal T2-FLAIR resection (class 1). Associations between survival and extensive resection were evident after 3 years in astrocytomas, whereas survival curves separated after 6–8 years in oligodendrogliomas. The prognostic relevance of the four-tier classification was conserved in multivariable analyses, in 625 patients receiving first-line chemotherapy or radiotherapy (with or without chemotherapy), and in the external UCSF cohort of 381 patients with *IDH*-mutant grade 2 gliomas.

Interpretation The proposed RANO classification for extent of resection could serve as a tool for prognostic stratification. Although associations between survival and extensive surgery are evident sooner in patients with astrocytoma, supramaximal resection also translates into survival benefits for patients with oligodendrogliomas.

Funding None.

Introduction

Maximal safe resection is recommended as initial management for newly diagnosed *IDH*-mutant WHO grade 2 glioma.[1–3] In both astrocytomas and oligodendrogliomas,[4] previous studies showed that extensive resection of T2-fluid attenuated inversion recovery (FLAIR)-hyperintense tumours is associated with favourable outcomes.[5–9] With nuanced weighting of

Research in context

Evidence before this study

Since 2021, the WHO classification for glioma has necessitated the use of molecular features to achieve an integrated histomolecular diagnosis. We searched PubMed between Jan 1, 2000, and Dec 31, 2024, with various combinations of the following search terms, without language restrictions: 'contrast enhancing', 'extent of resection', 'FLAIR', 'glioma', 'IDH', 'molecular', 'mutant', 'non-contrast enhancing', 'outcome', 'prognostic', 'resection', 'residual', 'surgery', 'survival', 'tumor', 'volume', 'WHO classification', and 'WHO 2021'. Our search revealed that retrospective single-centre studies have established maximal safe resection as initial management for newly diagnosed *IDH*-mutant grade 2 gliomas. However, whether patients with any molecular subgroups of *IDH*-mutant gliomas benefit from extensive resection remains a point of discussion. In this context, interpretation of previous reports is further hampered by the inconsistent terminology applied to describe the extent of resection.

Added value of this study

The international and multicentre RANO resect group assessed the interactive effects of residual tumour volume and other prognostic factors (including age, clinical function, and 1p19q-codeletion) in a cohort of 1391 patients with newly diagnosed *IDH*-mutant grade 2 glioma. Smaller post-operative tumour volumes were associated with more favourable outcomes, and supramaximal resection beyond the imaging-defined tumour border translated into an additional survival benefit. Although effects of resection on survival were evident in patients with *IDH*-mutant astrocytomas, patients with 1p19q-codeleted oligodendrogliomas also had longer survival with increased extents of resection (including supramaximal resection). Building on the observed prognostic relevance of residual tumour volume, a four-tier classification system for extent of resection was developed, which identified four distinct risk categories. The prognostic value of the novel classification system was verified in a multivariable analysis, in subgroups of patients with astrocytomas or oligodendrogliomas, and in an external validation cohort of 381 patients with *IDH*-mutant grade 2 gliomas. Residual tumour volume, as characterised by the novel classification system, was the strongest predictor of outcome if good clinical functioning was retained following resection, particularly in patients managed without further non-surgical first-line therapy or with only chemotherapy.

Implications of all the available evidence

While a substantial oncological role of resection can be assumed for all molecular subgroups of *IDH*-mutant grade 2 gliomas, the associations between residual tumour volume and outcome can vary depending on the presence of a 1p19q-codeletion. As such, more aggressive surgery might be particularly helpful in prolonging survival in most patients with astrocytomas. As the value of ever-increasing extents of resection reaches a limit when surgery results in diminished functional outcome, it might be appropriate to pursue a less aggressive surgical approach in patients with smaller-sized oligodendrogliomas located in surgical high-risk areas, to not jeopardise potential good outcomes. Consequently, our study provides neurosurgeons with evidence for judicious surgical decision making in individual patients with *IDH*-mutant grade 2 gliomas. Based on the importance of residual tumour, the proposed RANO classification system could serve as a novel tool to standardise terminology when describing surgical results to reduce prognostic imbalances between study groups in clinical trials.

potential oncological benefits of resection against the risk for post-surgical clinical deterioration being paramount for patient selection,[10] the effectiveness of so-called supramaximal resection beyond the imaging-defined tumour borders is currently under debate for grade 2 glioma.[7,10,11] Whether oligodendrogliomas might derive a less pronounced outcome benefit from (supramaximal) resection than astrocytomas given their prolonged natural history and good response to chemoradiation is unclear.[5,6,8] The ill-defined prognostic value of resection across molecular glioma subtypes is complicated by studies from the pre-molecular era that use the colloquial terminology of low-grade and high-grade tumours.[4,9] Comparative analysis between different reports is further hampered by the inconsistent terminology applied to describe extent of resection.[12,13] Although we have previously proposed an evidence-based classification system to standardise terminology for the extent of resection in gliomas,[14] our classification system has not been evaluated in *IDH*-mutant grade 2 glioma.

In the current study, we explored the oncological role of resection, as defined by residual tumour volume in a well-annotated, international, multicentre cohort of newly patients diagnosed with *IDH*-mutant grade 2 glioma.

Methods

Study design and participants

In this international, multicentre, retrospective study, patients aged 18 years and older with newly diagnosed *IDH*-mutant grade 2 gliomas diagnosed between Sept 1, 1993, and May 10, 2024, were identified in the institutional databases of 16 centres participating in the RANO resect group in the USA, Europe, and Asia (appendix p 6). Patients were selected based on the following criteria: tissue-based diagnosis of a previously untreated *IDH*-mutant grade 2 glioma meeting the diagnostic criteria of the WHO 2021 classification;[4] information on 1p19q codeletion status or evidence of *ATRX* loss for astrocytomas; pre-operative and post-operative MRI (including contrast-enhanced T1 and

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T2-FLAIR sequences) available for calculation of volumetrics as previously described;[12,15,16] and follow-up of at least 6 months after diagnosis of *IDH*-mutant grade 2 glioma. Patients who received upfront treatment before surgical tissue diagnosis based on imaging alone were excluded. An additional cohort of patients with *IDH*-mutant grade 2 gliomas diagnosed between Feb 16, 1998, and Nov 14, 2017, at UCSF (San Francisco, CA, USA) has previously been reported[5] and served as a geographically and institutionally independent external validation. There was no patient or public involvement in the design, conduct, or reporting of this study.

The study protocol was approved by local institutional review boards (Friedrich-Alexander-University Erlangen-Nuremberg AZ-24-495-Bn; Ludwig-Maximilians-University Munich AZ-21-0996). The TRIPOD-AI recommendations for clinical prediction models were followed (appendix pp 1–2). Participant consent was waived by the institutional review board owing to the retrospective nature of the study.

	Astrocytoma (n=727)	Oligodendroglioma (n=664)	p value
Demographics			
Age at diagnosis, years	36·0 (30–44)	43·0 (34–51)	<0·0001
Sex			0·22
Female	310 (43%)	305 (46%)	..
Male	417 (57%)	359 (54%)	..
Clinical markers			
Preoperative seizures	433 (60%)	439 (66%)	0·041
Preoperative KPS	100 (90–100)	100 (90–100)	0·38
Postoperative KPS	90 (90–100)	90 (90–100)	0·43
Any new postoperative deficit	127 (17%)	129 (19%)	0·62
Severe new postoperative deficit	43 (6%)	49 (7%)	0·13
IDH status			1·0
Wild type	0	0	..
Mutation	727 (100%)	664 (100%)	..
1p19q-codeletion status			<0·0001
Co-deleted	0	664 (100%)	..
Intact	692 (95%)	0	..
NA	35 (5%)	0	..
Nuclear *ATRX* expression			<0·0001
Lost	338 (46%)	7 (1%)	..
Retained	122 (17%)	367 (55%)	..
NA	267 (37%)	290 (44%)	..
Localisation at diagnosis			0·47
(Sub)cortical	630 (87%)	592 (89%)	..
Deep-seated	87 (12%)	63 (9%)	..
Multifocal	8 (1%)	8 (1%)	..
NA	2 (<1%)	1 (<1%)	..
Dominant or non-dominant at diagnosis			0·097
Dominant	372 (51%)	339 (51%)	..
Non-dominant	306 (42%)	260 (39%)	..
NA	49 (7%)	65 (10%)	..
Tumour volumes, cm^3			..
Preoperative contrast-enhancing tumour	0·0 (0–0)	0·0 (0–0)	<0·0001
Preoperative non-contrast-enhancing tumour	33·9 (12·9–69·0)	32·7 (14·1–59·5)	0·42
Postoperative contrast-enhancing tumour	0·0 (0–0)	0·0 (0–0)	0·30
Postoperative non-contrast-enhancing tumour	2·0 (0–15·1)	2·8 (0–19·1)	0·34

(Table continues on next page)

Procedures

Tumour volumes (in cm^3) were calculated on pre-operative and post-operative MRI, with post-operative scans for volumetrics obtained between 4 weeks and 16 weeks after surgery to allow resolution of surgically-induced changes, including oedema. Immediate post-operative (diffusion-weighted) imaging obtained within 72 h after surgery was reviewed to estimate areas of ischaemia.[17] For manual tumour delineation by previously trained raters,[12] the preferred institutional software was applied.[12,15,16] Total contrast-enhancing tumour was measured on contrast-enhanced T1 sequences, and non-enhancing tumour was quantified on T2-FLAIR sequences. For multifocal disease, the volumes of each focus were added together.

Based on a literature review, we previously proposed a classification system that formed the basis for the initial patient stratification.[14] Patients were designated to individual categories according to the residual T2-FLAIR tumour volume, as follows: supramaximal resection—resection of non-infiltrated anatomical structures beyond the T2-FLAIR tumour borders in the absence of residual tumour; complete resection—no residual T2-FLAIR-hyperintense tumour; near total resection—5 cm^3 or less residual T2-FLAIR-hyperintense tumour; subtotal resection—25 cm^3 or less residual T2-FLAIR-hyperintense tumour; partial resection—more than 25 cm^3 residual T2-FLAIR-hyperintense tumour; and biopsy—no tumour reduction.

Outcomes

Details of analytical methods are outlined in the appendix (pp 3–5). Patients were followed up until death or date of database closure (Jan 31, 2025), whichever came first. Date of surgery was set as date of diagnosis. Date of progression was set as first MRI showing progression per RANO 2.0 criteria,[17] or per physician's judgement (in cases of clinical deterioration despite stable MRI findings). Progression-free survival was defined as the time between diagnosis and first recurrence or death from any cause, whichever occurred earlier. Overall survival was defined as the time between diagnosis and death from any cause. Patients lost to follow up were censored at time of last patient contact. No informative censoring was identified. No data on race or ethnicity were collected. Patients' sex was derived from the institutional databases, relying on the clinical information collected during patients' routine treatment.

Statistical analysis

Following testing for normal distribution and equal variance by the D'Agostino-Pearson normality test, differences in parametric data between two groups were assessed by unpaired Student's *t* test and differences between multiple groups by one-way ANOVA. For non-parametric data, we used the Mann-Whitney U test for two groups and the Kruskal-Wallis test for multiple groups. For categorical variables, differences between groups were analysed using the χ^2 test.

Time-to-event endpoints were estimated by the Kaplan-Meier method and log-rank tests. The proportional hazard assumption was confirmed by visual inspection of scaled Schoenfeld residuals and deviance residuals (data not shown). For univariable survival analysis stratifying of continuous variables, Cox proportional hazard regression models were constructed for calculation of hazard ratios (HRs) as point estimates and 95% CIs. Interaction was tested using Stata's formal test for effect×subgroup interaction, assessing the null hypothesis that all coefficients for the interaction terms are zero. Markers of prognostic significance on univariable analysis were forwarded into multivariable testing via forced entry using a Cox proportional hazard regression-model. Harrell's c indices were calculated as goodness-of-fit measurements for risk modelling using the estat concordance command in Stata.[18] Model Brier scores (at 10 years after diagnosis for overall survival; at 5 years after diagnosis for progression-free survival) and null model Brier scores were computed using the stbrier command in Stata;[19] and the index of prediction accuracy (IPA) as a complementary measure of model calibration was calculated as follows:[20] IPA=1−(model Brier score/null model Brier score).

The 95% CI for the IPA was approximated by the delta method, assuming independence between the null model Brier scores and the model Brier scores. Statistical analyses were done using Prism (version 10.3.1) and Stata (version 17.0). The significance level was set at p≤0·05. Prespecified analyses were prognostic assessment of the previously specified classification system based on residual tumour volume, refinement of this classification system based on the results of the prognostic assessment, external validation in a separate dataset, and analysis of associations between residual tumour volume and outcome among molecular glioma subgroups. Exploratory analyses included model evaluation measures as well as stratified subgroup analyses by treatment modality.

Role of the funding source

There was no funding source for this study.

Results

For the multicentre development cohort, clinical data from 1391 patients with *IDH*-mutant grade 2 gliomas diagnosed between Sept 1, 1993, and May 10, 2024, were assembled from the 16 centres in the study (table; appendix pp 7–9), including 727 (52%) patients with astrocytoma and 664 (48%) patients with 1p19q-codeleted oligodendroglioma. Although more patients with astrocytoma were treated with temozolomide-based therapy and more patients with oligodendroglioma received lomustine-based therapy, there was no statistically significant difference between astrocytomas and oligodendrogliomas in the rate of patients allocated to a wait-and-scan approach (ie, with no first-line treatment following surgery; 393 [54%] of 727 patients *vs* 355 [53%] of 664 patients; figure 1A). Baseline T2-FLAIR tumour volumetrics did not differ between astrocytomas and oligodendrogliomas, and pre-operative and post-operative T2-FLAIR tumour volumes were correlated (figure 1B).

After a median follow-up of 81 months (95% CI 78 to 85), the median progression-free survival was 67 months (63 to 73) in the overall development cohort and was shorter for astrocytomas (58 months, 95% CI 52 to 64; 393 events) than for oligodendrogliomas (82 months, 70 to 91; 312 events; p<0·0001; figure 1C). The median overall survival was not reached (95% CI not reached) in the overall development cohort. Patients with astrocytoma had a shorter median overall survival of 181 months (95% CI 141 to not reached; 152 events) than patients with oligodendroglioma (not reached; not reached to not reached; 64 events; p<0·0001; figure 1D).

The external UCSF validation cohort included 191 (50%) patients with astrocytomas and 190 (50%)

	Astrocytoma (n=727)	Oligodendroglioma (n=664)	p value
(Continued from previous page)			
First-line therapy			<0·0001
Surgery only	393 (54%)	355 (53%)	..
Radiotherapy alone	112 (15%)	41 (6%)	..
Temozolomide alone	38 (5%)	64 (10%)	..
Temozolomide plus radiotherapy, followed by temozolomide maintenance therapy	120 (17%)	61 (9%)	..
Lomustine-based chemotherapy alone	6 (1%)	48 (7%)	..
Lomustine-based chemotherapy plus radiotherapy, followed by lomustine-based maintenance chemotherapy	33 (5%)	74 (11%)	..
Experimental therapy	15 (2%)	13 (2%)	..
NA	10 (1%)	8 (1%)	..
Endpoints met			..
First progression	393 (54%)	312 (47%)	0·0084
Death	152 (21%)	64 (10%)	<0·0001
Outcome, median (95% CI)			..
Follow-up	79 (75–84)	85 (75–89)	0·75
Progression-free survival	58 (52–64)	82 (70–91)	<0·0001
Overall survival	181 (141–NR)	NR (NR–NR)	<0·0001

Data are median (IQR) or n (%), unless otherwise indicated. Characteristics for the validation cohort are in the appendix (pp 10–12). KPS=Karnofsky performance status. NA=not available for review. NR=not reached.

Table: **Characteristics of the development cohort for newly diagnosed IDH-mutant grade 2 gliomas from 16 institutions**

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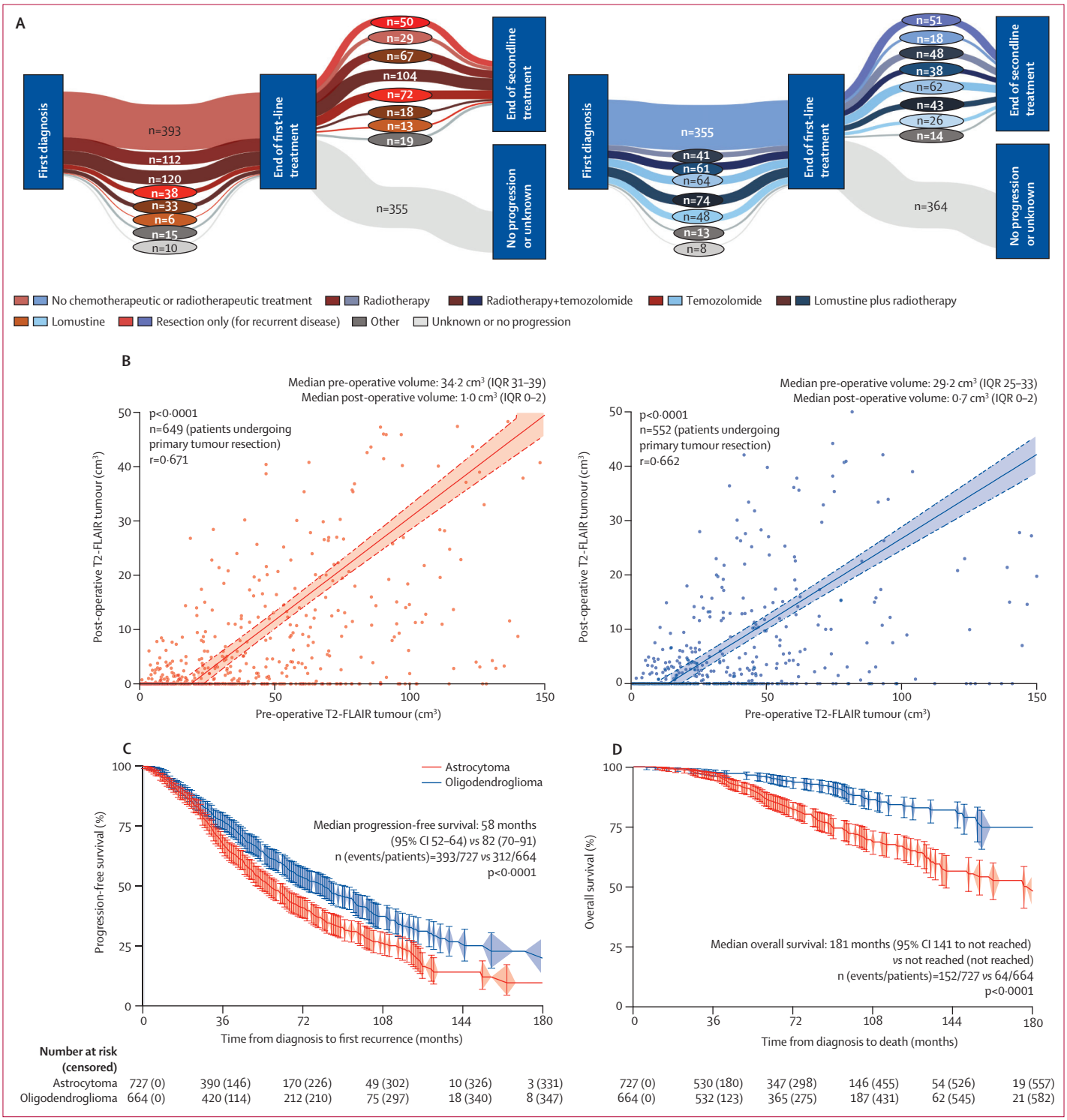


Figure 1: **Baseline characteristics of the multicentre development cohort**
(A) Therapeutic approaches following new diagnosis and first recurrence among patients with astrocytoma (left panel; n=727) and oligodendroglioma (right panel; n=664). Nodes of the Sankey plots show timepoints in the disease course (diagnosis, end of first-line treatment, end of second-line treatment). (B) Simple linear regression analyses comparing the pre-operative and post-operative T2-FLAIR tumour volumes for patients with astrocytoma (left panel) and oligodendroglioma (right panel), in those undergoing microsurgical tumour resection. Dotted lines indicate 95% CIs. Kaplan-Meier estimates of progression-free survival (C) and overall survival (D) for the entire study cohort (n=1391). Error bars and shadings around the lines show 95% CI. FLAIR=fluid attenuated inversion recovery.

patients with oligodendrogliomas diagnosed between 1998 and 2017.[5] Key baseline patient characteristics were similar between the overall development cohort and the external UCSF cohort (appendix pp 10–12). With a longer follow-up of 144 months (95% CI 136–151), the relative rate of patients who had progression or died was higher in the UCSF cohort than in the overall development cohort. 147 patients with astrocytoma and 115 patients with oligodendroglioma had disease progression and 83 patients with astrocytoma and 31 patients with oligodendroglioma died during follow-up in the UCSF cohort. Moreover, progression-free survival was longer in the UCSF cohort compared with the overall development cohort (76 months, 95% CI 66–94 *vs* 67 months, 63–73) due to longer times to progression among patients with oligodendroglioma within the UCSF cohort compared with patients with oligodendroglioma within the overall development cohort (110 months, 92–140 *vs* 82 months, 70–91). Nevertheless, median overall survival was similar between the development cohort and the validation cohort (appendix pp 13–15).

To study the associations between resection and disease natural history, we selected 728 patients (379 astrocytomas and 349 oligodendrogliomas) from the multicentre development cohort in whom no first-line treatment beyond surgery was provided and sufficient volumetric data were available (appendix p 16). In this patient subgroup, a decrease in HR for death or progression was noted for each cm³ less of residual T2-FLAIR tumour (figure 2A). The effects of each cm³ of higher tumour volumes on outcome were more pronounced in

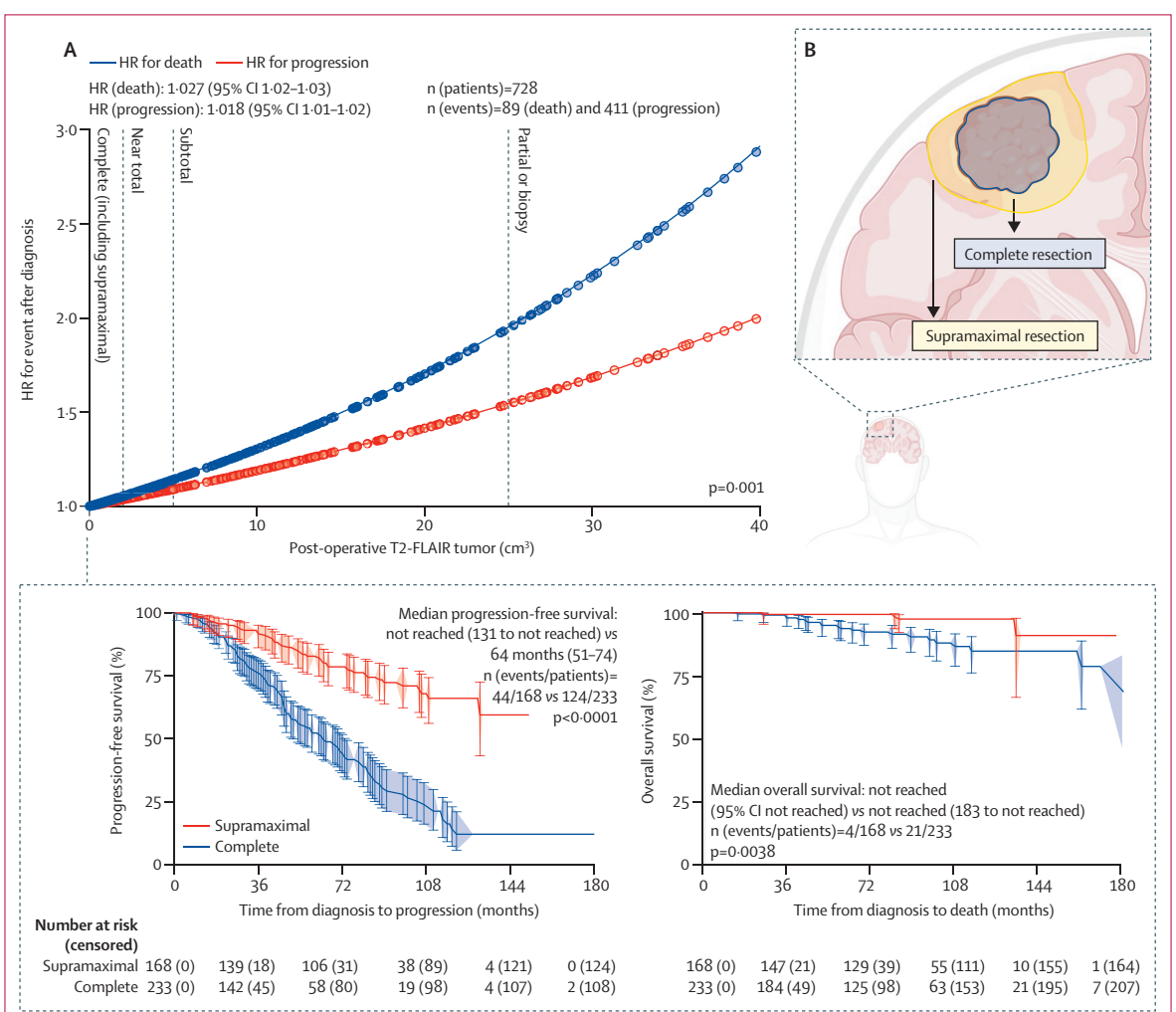


Figure 2: **Prognostic implications of residual T2-FLAIR tumour volume and supramaximal resection**
(A) HRs for death or first progression calculated for each individual residual T2-FLAIR tumour volume among patients from the surgery only development cohort. (B) Definitions of supramaximal resection based on resection of previously non-affected structures beyond the T2-FLAIR-hyperintense tumour borders. Figure created with BioRender.com. (C) Kaplan-Meier estimates of progression-free survival (left panel) and overall survival (right panel) for patients with no residual T2-FLAIR tumour volume (n=401) from the surgery only development cohort. Error bars and shadings around the lines show 95% CI. FLAIR=fluid attenuated inversion recovery. HR=hazard ratio.

astrocytomas (HR for progression 1·03, 95% CI 1·03–1·04; HR for death 1·04, 1·03–1·05; p<0·0001 for both) than in oligodendrogliomas (1·00, 0·98–1·01; p=0·71; 1·02, 1·01–1·03; p<0·0001).

Analogous to the previously proposed classification system,[14] patients from the development cohort who did not undergo first-line treatment beyond surgery were stratified based on the residual T2-FLAIR tumour volume, as follows: supramaximal resection (168 [23%] of 728 patients); complete resection (233 [32%]); near total resection (157 [22%]); subtotal resection (101 [14%]), and partial resection (27 [4%]). 42 (6%) patients underwent biopsy. Among all categories, similar proportions of patients were diagnosed with astrocytoma or oligodendroglioma. Patients who had biopsy had a 10-year survival rate of 71% (95% CI 40 to 88) and patients with partial resection had a 10-year survival rate of 45% (23 to 65) although this difference was not significant (median overall survival not reached, 95% CI 97 to not reached *vs* 114 months, 61 to not reached; p=0·059). Together with eight patients who had any post-operative contrast enhancement (10-year survival rate 44%, 95% CI 7 to 79), patients undergoing biopsy or partial resection had the least favourable outcomes. Notably, patients who had partial resection had higher post-operative volume than those who had biopsy (post-operative tumour volume 24·6 cm³, IQR 10·2 to 36·1 *vs* 33·9 cm³, 27·2 to 48·8; p=0·0038). No patients in any group received non-surgical upfront therapy before surgery or post-operative first-line treatment. Patients with subtotal resection had a 10-year survival rate of 72% (95% CI 59 to 82; median overall survival not reached, 95% CI 136 to not reached). Patients with complete resection had a 10-year survival rate of 85% (95% CI 76 to 91) and patients with near total resections had a 10-year survival rate of 81% (70 to 88; median overall survival not reached, 95% CI 183 to not reached *vs* 181 months, 151 to not reached; p=0·085 for complete resection *vs* near total resection). These findings were supported when assessing progression (5-year progression-free survival rates for complete *vs* near total *vs* subtotal *vs* partial *vs* biopsy: 52%, 95% CI 45 to 59 *vs* 32%, 24 to 40 *vs* 19%, 11 to 28 *vs* 13%, 3 to 30 *vs* 33%, 19 to 48; p<0·0001 for all groups).

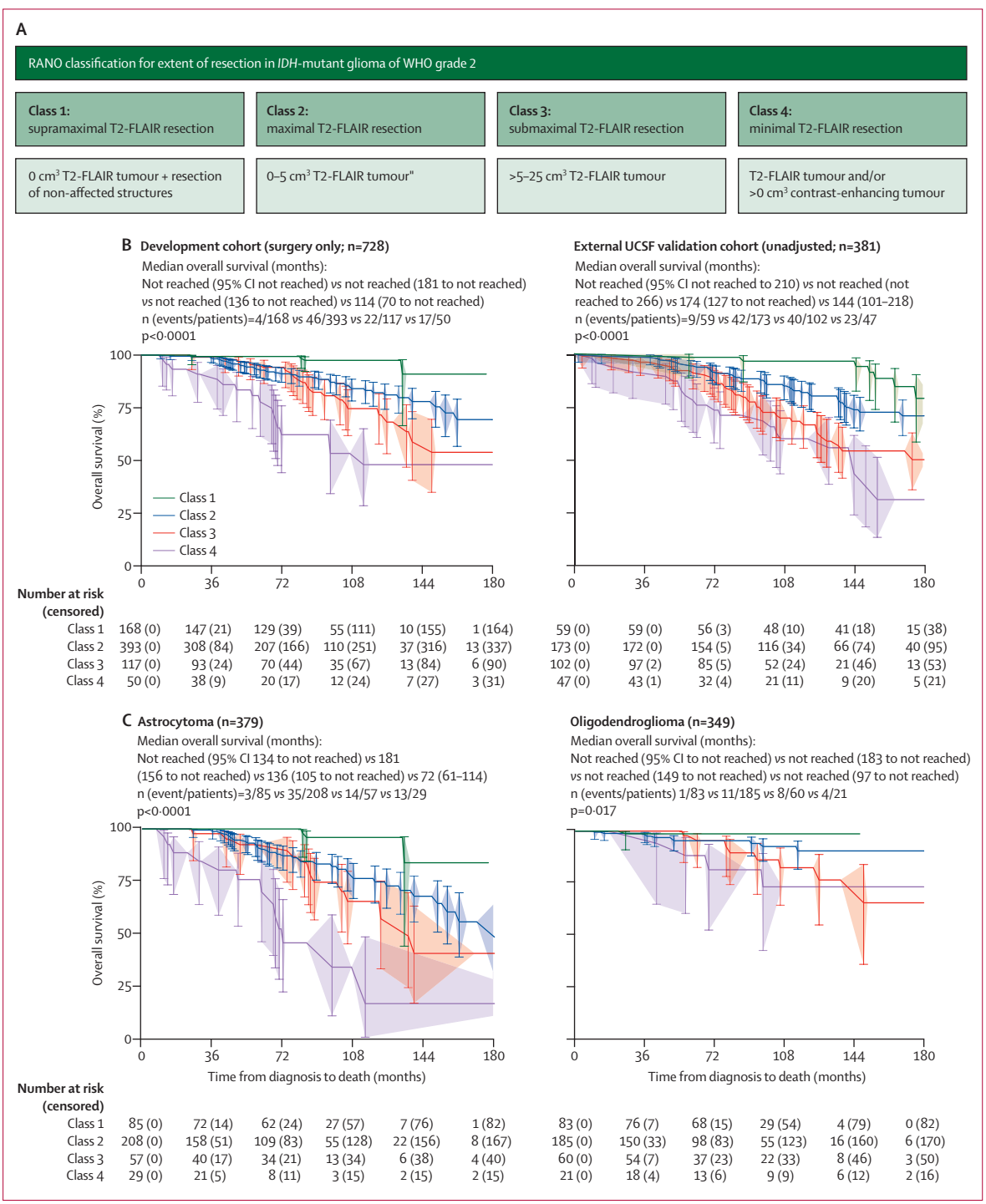
Patients with supramaximal resection of previously non-infiltrated structures (figure 2B) had a 10-year survival rate of 97·5% (95% CI 92–99) and a 5-year progression free-survival rate of 82·8% (76–88), which was significantly better than with patients with complete resection only (HR for overall survival 0·24, 95% CI 0·11–0·53); p=0·0038; HR for progression free-survival 0·29, 0·21–0·39; p<0·0001; figure 2C). Besides slightly younger age among patients undergoing supramaximal resection, there were no substantial differences in relevant baseline characteristics between patients with supramaximal resection or complete resection (appendix p 17). Our findings on an association between supramaximal resection and more favourable outcome than complete resection remained when assessed in subgroups of patients with astrocytoma (HR for overall survival 0·26, 95% CI 0·10–0·69; p=0·023; HR for progression-free survival 0·37, 0·25–0·55; p<0·0001) and oligodendroglioma (0·27, 0·06–1·22; p=0·090; 0·22, 0·14–0·34; p<0·0001).

Applied to the prespecified classification, the C-index was 0·696 (95% CI 0·639 to 0·753) for overall survival and 0·697 (0·670 to 0·724) for progression-free survival. IPA values for the prespecified classification were 4·1% (95% CI –21·1 to 29·2) for overall survival and 16·9% (9·9 to 24·0) for progression-free survival.

We aimed to refine the classification system for simplicity. Acknowledging similar outcomes for complete and near total resection and for partial resection and biopsy, these categories were summarised as maximal resection (for complete or near total resection) or minimal resection (for partial resection). Although rarely encountered, patients with residual post-operative contrast enhancement were assigned to minimal resection. As biopsy per se was not associated with poorer outcomes than in the partial resection group, patients who underwent biopsy were stratified according to their individual post-operative tumour volume. The resulting classification system was termed RANO classification for extent of resection in *IDH*-mutant grade 2 glioma (figure 3A). When applying the refined RANO classification system to our multicentre development cohort (figure 3B), the respective classes reflected distinct survival outcomes (C-index for overall survival 0·686, 95% CI 0·632 to 0·739, with an IPA of 6·0%, 95% CI –18·8 to 30·8; C-index for progression-free survival 0·682, 0·656 to 0·708, with an IPA of 18·2%, 11·2 to 25·1; appendix p 18). Patients assigned to supramaximal resection (class 1) had superior outcomes compared with patients with maximal resection (class 2), whereas the patients with maximal resection had superior outcomes to patients with submaximal resection (class 3), and patients with minimal resection (class 4) had least the favourable overall survival (10-year survival rates: 98%, 95% CI 92–99 *vs* 82%, 76–87 *vs* 75%, 62–84 *vs* 48%, 29–65; p<0·0001) and progression-free survival (5-year progression-free survival rates 83%, 95% CI 76–88 *vs* 44%, 38–50 *vs* 25%, 16–34 *vs* 12%, 4–24; p<0·0001). No differences were found in the incidence for neurological deficits or tumour subtypes between the classes (appendix pp 19–21).

When the prognostic relevance of the RANO classification was tested in molecular subgroups, a stepwise increase in overall survival with lower residual tumour volumes was observed for astrocytomas and oligodendrogliomas from the multicentre development cohort (figure 3C). Associations between lower residual tumour volumes (as characterised by lower RANO classes) and overall survival of extensive resection

became apparent after 3 years in astrocytomas, whereas survival curves separated after 6–8 years in oligodendrogliomas. Nevertheless, the absolute differences between the survival curves were less pronounced in oligodendrogliomas compared with astrocytomas throughout the observation period. No significant interaction between RANO classes and 1p19q-codeletion-based subgroups for overall survival was observed (formal test for effect×subgroup interaction: p>0·70). The finding of an association between RANO classes and outcome was retained when assessed in a stratified Cox model (with centre as a stratum), and when RANO



(Figure 3 continues on next page)

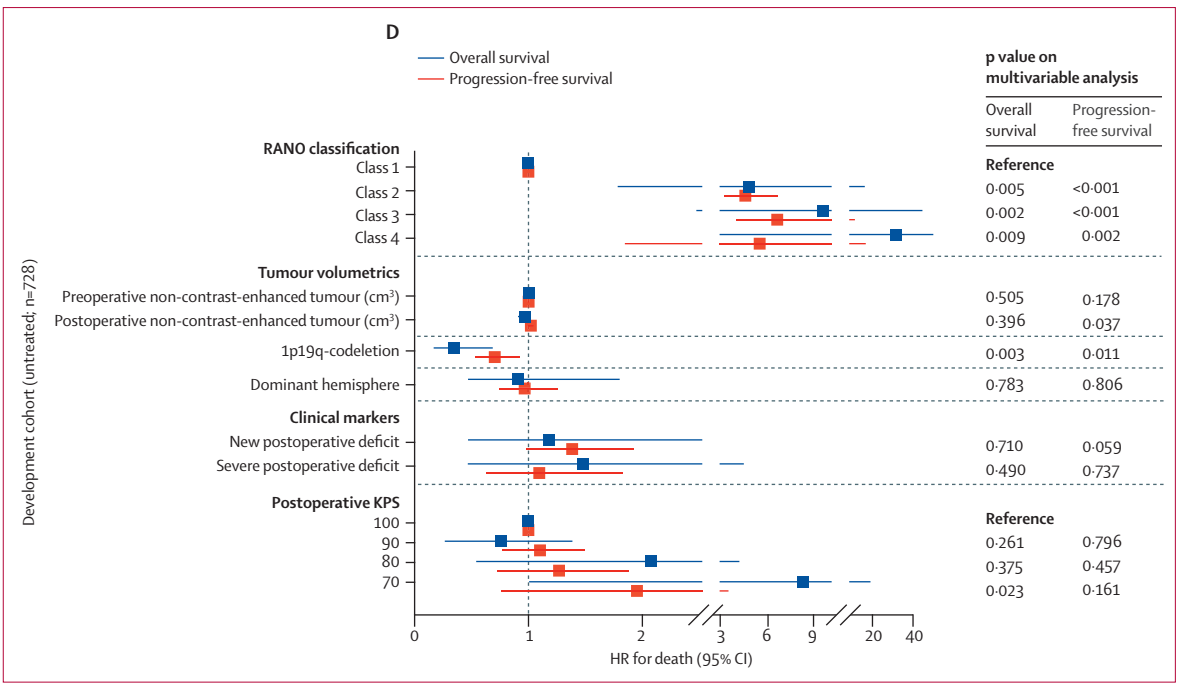


Figure 3: **Validation of the novel RANO classification system for grade 2 gliomas**
(A) Refined RANO classification for extent of resection in *IDH*-mutant grade 2 glioma. Kaplan-Meier estimates of overall survival for patients in the development cohort with no first-line treatment beyond surgery (B; left panel; n=728) and the external validation cohort (B; right panel; n=381), and for patients with astrocytoma (C; left panel; n=379) or oligodendroglioma (C; right panel; n=349) from the exploratory development cohort. Error bars and shadings around the lines show 95% CI. (D) Multivariable analysis using a Cox proportional hazard regression model to estimate the HR for death (blue) and first progression (red) of numerous factors that were significant on univariable analysis. KPS=Karnofsky Performance Status.

classes were tested together with centres in a multivariable model (data not shown).

In univariable models of the multicentre development cohort, novel RANO classification, pre-operative and post-operative T2-FLAIR tumour volume, presence of a 1p19q-codeletion, dominant hemisphere involvement, any new or severe post-operative deficits, and post-operative Karnofsky Performance Status (KPS) were associated with overall survival (appendix pp 22–23). The prognostic value of the RANO classification was retained when included in a multivariable model (figure 3D). When RANO class 1 was set as the reference level, decreased overall survival was confirmed across the RANO classes (class 2 HR 4·72, 95% CI 1·79–16·27; p=0·0047; class 3 9·65, 2·48–44·69; p=0·0018; class 4 31·94, 2·59–517·80; p=0·0092). The presence of a 1p19q-codeletion and higher post-operative KPS were also associated with more favourable survival.

The prognostic value of the RANO classification system was confirmed in the external validation UCSF cohort (C-index for overall survival 0·661, 95% CI 0·613 to 0·709 with an IPA of 8·7%, 95% CI –10·5 to 27·9; C-index for progression-free survival 0·584, 0·547 to 0·620 with an IPA of 2·3%, –3·8 to 8·4), with 10-year survival rates of 97% (95% CI 87 to 99) versus 82% (75 to 87) versus 66% (55–75) versus 60% (43 to 73; p<0·0001; figure 3B) and 5-year progression-free survival rates of 76% (63 to 85) versus 57% (50–64) versus 55% (50 to 64) versus 41% (27–55; p<0·0001; RANO class 1 *vs* 2 *vs* 3 *vs* 4, respectively). Although better outcomes were detected for lower RANO classes among patients with astrocytomas (10-year survival rates for classes 1–4: 96%, 95% CI 72 to 99 *vs* 68%, 56 to 77 *vs* 37%, 21 to 54 *vs* 44%, 24 to 63; p<0·0001) and oligodendrogliomas (10-year survival rates for classes 1–4: 97%, 81 to 99 *vs* 97%, 90 to 99 *vs* 88%, 74 to 94 *vs* 78%, 52 to 91; p=0·0004) in the validation cohort, there was no significant difference in overall survival between class 1 and class 2 for oligodendrogliomas in the external validation UCSF cohort.[5]

To assess the relevance of the RANO classification system across treatment-based subgroups, we combined the multicentre development cohort and the external validation UCSF cohort (n=1485 with full volumetric and treatment information) to identify 451 (30%) patients who received (chemo)radiotherapy, 174 (12%) patients who received chemotherapy, and 828 (56%) patients in whom only surgery was provided (appendix p 24). Administration of radiotherapy with or without chemotherapy was associated with longer progression-free survival compared with chemotherapy or surgery only (astrocytoma 83 months, 95% CI 70 to 100 *vs* 33 months, 26 to 51 *vs* 47 months, 43 to 53; p<0·0001; oligodendroglioma 117 months, 95 to not reached *vs* 66 months, 49 to 96 *vs* 69 months, 60 to 90; p<0·0001; figure 4A). The absence of any non-surgical

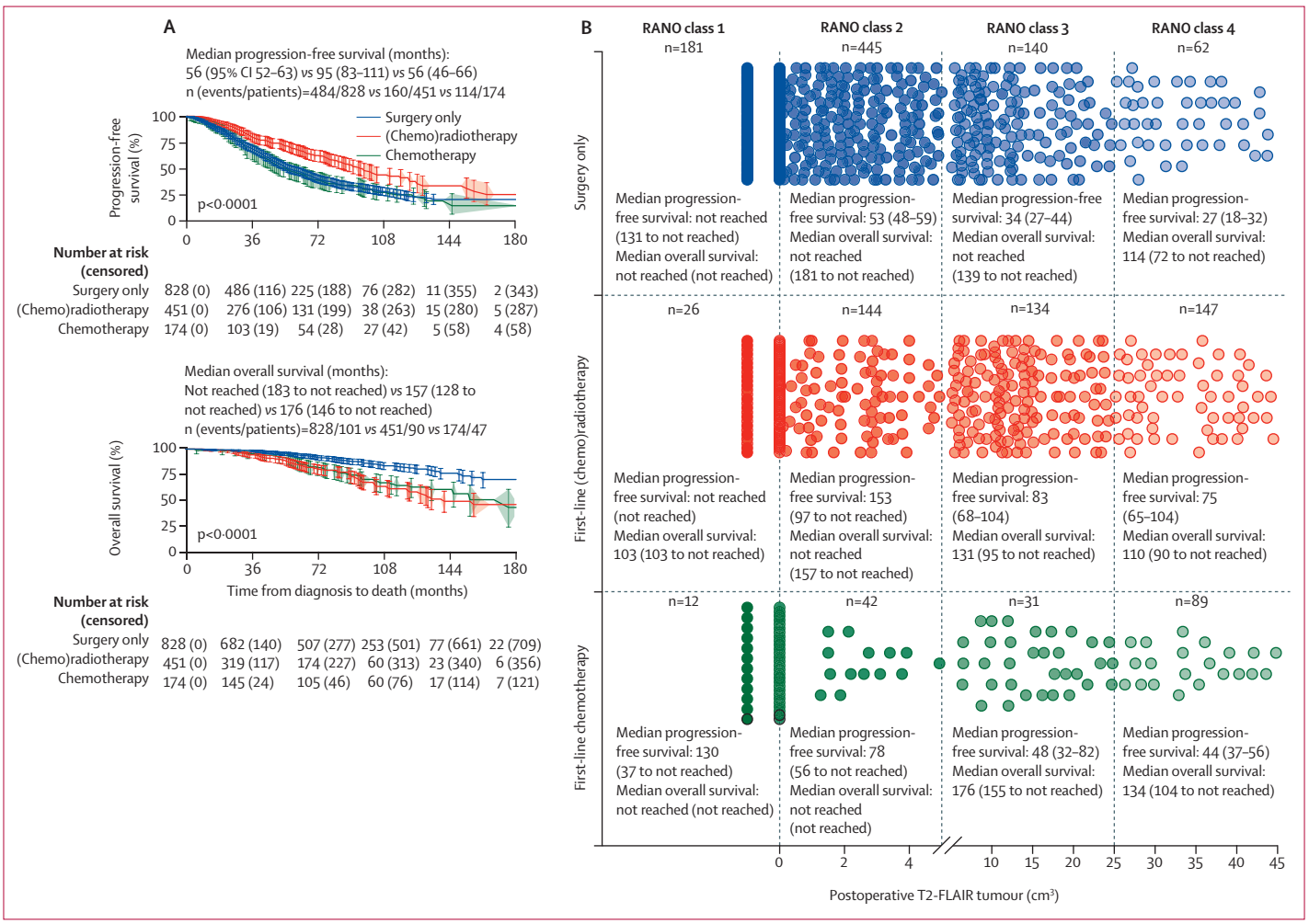


Figure 4: **Prognostic value of the RANO classification system across treatment-based subgroups**
(A) Progression-free survival (top panel) and overall survival (bottom panel) for patients stratified according to whether they underwent surgery only (n=828), (chemo)radiotherapy (n=451), or chemotherapy (n=174). Error bars and shadings around the lines show 95% CI. (B) Contingency table stratifying patients by residual T2-FLAIR tumour and first-line management beyond surgery. Each dot represents one individual patient, and the median progression-free survival and overall survival of the respective patient subgroup is indicated in months. Numbers in brackets indicate 95% CIs.

treatment was associated with the most favourable overall survival in patients with astrocytoma and oligodendroglioma. Second-line chemotherapy or radiotherapy was applied in 305 (53%) of 571 of patients with documented progression who had not previously received radiotherapy.

Among all three treatment-based subgroups, we verified that lower residual T2-FLAIR tumour volume characterised by the novel RANO classification was associated with longer progression-free survival and overall survival (figure 4B). Within each treatment-based subgroup, the range in proportion of tumours with or without a 1p19q-codeletion was similar across the four RANO classes (surgery only 89 [49%] of 181 patients to 36 [58%] of 62 patients with astrocytoma; [chemo] radiotherapy 13 [50%] of 26 patients to 90 [63%] of 144 patients with astrocytoma; chemotherapy 27 [30%] of 89 patients to four [33%] of 12 patients with astrocytoma). Although interaction testing found no interaction between RANO classes and the chemotherapy-based subgroup, there was evidence for interaction with the (chemo)radiotherapy-based subgroup for overall survival ($p<0·0001$), but no interaction effects were seen for progression-free survival ($p=0·068$; data not shown).

Discussion

We verified the prognostic value of the novel RANO classification in a multicentre development cohort of treatment-naive patients, an external validation cohort, across molecular glioma subtypes, and in treatment-based subgroups. We minimised the possibility that the prognostic relevance of the RANO classification was induced by the presence of clinical or molecular confounders, including 1p19q-codeletion or first-line treatment beyond surgery, and the four individual RANO classes were associated with distinct outcomes. In line

with previous reports,[5,21] a multivariable analysis supported that residual volumes but not preoperative tumour size affected outcome. As suggested by C-indices as goodness-of-fit measurements and supported by IPA values, a modest but consistent improvement in predictive performance compared with the Kaplan-Meier baseline model was observed and model discrimination and calibration were not worse for the RANO classification than for the (more complex) previously prespecified model.[14]

Resection of non-infiltrated structures beyond the T2-FLAIR-hyperintense tumour borders was associated with an additional survival difference, which provides a rationale to clearly designate such supramaximal resection as RANO class 1. Our findings corroborate a report by Ng and colleagues,[7] describing better survival of patients who undergo supramaximal resection in a propensity score-matched cohort of 113 patients with grade 2 gliomas. Similar observations were made in an unmatched retrospective cohort of 700 patients with grade 2 gliomas by Gallotti and colleagues,[22] who postulated that a resection cavity that extends 20% beyond the tumour borders was associated with the lowest recurrence risk. We intentionally refrained from a volumetric definition of supramaximal resection given that changes in configuration of the resection cavity are frequently encountered for months after surgery.[23] A detailed discussion on future directions for guiding resections beyond MRI-defined tumour borders and potential confounders of our analysis on supramaximal resection is given in the appendix (pp 25–27).

The designation of patients who underwent a biopsy did not add additional prognostic information compared with residual tumour volume. Biopsy in cases of smaller tumour volumes might be associated with better overall outcomes than partial resection of extensive tumours with considerably large tumour remnants. Our findings can still be interpreted to support the quasi-randomised study by Jakola and colleagues, which found open resection to be preferable to biopsy,[6,24] as it is possible that the average tumour remnants were smaller among patients scheduled to undergo resection (although tumour volumetrics were not reported by Jakola and colleagues).[24]

Depending on the presence of a 1p19q-codeletion, the associations between residual tumour volume and outcome were differently weighted. Survival curves for RANO classes were found to separate within 3 years after astrocytoma resection, whereas a marked difference between survival curves for RANO classes was not observed for 6–8 years for oligodendrogliomas. The assumption of a disease-specific role for resection is supported by the fact that a benefit of supramaximal resection can be found for astrocytomas across many previous studies,[5,7,8,22] whereas smaller cohorts (such as our external validation cohort) with shorter follow-up times might not detect beneficial effects among oligodendrogliomas.[5,8] Furthermore, the prognostic role of residual T2-FLAIR tumour volumes is more evident in patients with astrocytoma across studies.[5,8,21,25]

Although the value of ever-increasing extents of resection reaches a limit when surgery leads to diminished functional outcome, it might still be appropriate to prioritise the extent of resection over mild permanent deficits, particularly in young patients with astrocytoma. In turn, a less aggressive surgical approach might be warranted in older patients with smaller-sized oligodendrogliomas located in surgical high-risk areas. Whether the idea that the absence of a 1p19q-codeletion dictates a more substantial role (compared with patients with the presence of a 1p19q-codeletion) for resection might change due to the introduction of IDH inhibitors, which prolong time to progression in *IDH*-mutant gliomas, should be considered.[26] Particularly within treatment-based subgroups of patients receiving chemotherapy or surgery alone, a more favourable outcome was observed with lower residual tumour volume (appendix pp 25–27).

This study has several limitations. First, we only used three dimensional-based volumetric measurements to assess tumour size, as previous studies have shown better inter-rater variability and accuracy in longitudinally assessing tumour growth compared with two dimensional-based methods.[27,28] Therefore, we cannot comment on whether tumour volumetrics indeed represent a better prognostic factor than two dimensional-based tumour size in our cohort. Importantly, the presence of any contrast-enhancing tumour was associated with an outcome that was similar to that of large T2-FLAIR volumes. Whether those rare cases of post-operative contrast-enhancing tumour represent under-sampled gliomas of higher grades or show the biological significance of enhancement in grade 2 gliomas remains unclear.[29,30] The finding that the absence of any non-surgical treatment was associated with the most favourable overall survival might represent a combination of provider treatment bias due to lower residual tumour volumes in patients receiving no first-line treatment (as exemplified by the finding that 181 (83%) of 219 patients in RANO class 1 did not receive treatment beyond surgery) and that second-line (chemo)radiotherapy was applied in 305 (53%) of 571 of patients with documented progression who had not previously received radiotherapy. By contrast, less pronounced effects in patients receiving (chemo)radiotherapy together with results from interaction testing suggest that the implications of residual disease after initial surgery might to some extent be salvaged by radiotherapeutic treatment. Unfortunately, supramaximal approaches have only recently been adopted, which might skew outcome results when assessing the role of surgery in patients previously managed with different adjuvant therapies.

In conclusion, the RANO classification system retains its prognostic value across molecular and treatment-based subgroups and might serve to improve the overall design and analysis of clinical trials and risk stratification in routine clinical care.

Contributors

PK and J-CT conceived and designed the study. PK, JSY, MMJW, TS, NT, AC, AW, GY, YWP, LH, STJ, AD, FE, EEMM, NN, FB, CAT, TvdV, MR, MCN, LG, AG, and AJPEV collected the data. PK, SMC, ASJ, OS, LB, MJvdB, SHJ, MSB, and J-CT analysed and interpreted the data. PK, NT, and J-CT accessed and verified the data. PK and J-CT drafted the manuscript. All authors had access to the data and contributed to revising the manuscript.

Declaration of interests

PK reports consulting for the American Society for Clinical Oncology. MMJW reports consulting for Servier. FE reports research funding from German Cancer Aid and Accuray and honoraria and travel support from Accuray and ZAP Surgical Systems. NN reports advisory board participation and consulting for Servier and B Braun New Ventures. MW reports research grants from Novartis, Quercis, and Versameb and honoraria or advisory board participation and consulting for Anheart, Bayer, CureVac, Medac, Neurosense, Novartis, Novocure, Orbus, Philogen, Pfizer, Roche, and Servier. DPC reports advisory board participation for Lilly, GlaxoSmithKline, Incephalo, Boston Pharmaceuticals, Servier, Boston Scientific, and Pyramid Biosciences (equity interest), speaker Honoria from Merck, and clinical trial and grant review for the US National Institutes of Health and Department of Defense. RYH reports advisory board participation for Vysioneer and consulting for Nuvation Bio. MAV reports indirect equity and patent royalty interests from Infuseon Therapeutics, honoraria from Chimerix and Midatech, and research grants from DeNovo Pharma, Oncosynergy, Infuseon, and Chimerix. RR reports honoraria, advisory board participation, and consulting for UCB, Bayer, Novocure, Genenta, and Servier. JD reports consulting and advisory board participation for Amgen, Novartis and Janssen, research support from Ono Therapeutics and Novartis, and royalties from Wolters Kluwer. PYW reports research support from AstraZeneca, Black Diamond, Bristol Meyers Squibb, Chimerix, Eli Lily, Erasca, Global Coalition for Adaptive Research, Kazia, MediciNova, Merck, Novartis, Quadriga, Servier, and VBI Vaccines and advisory board participation or consulting for Anheart, AstraZeneca, Black Diamond, Celularity, Chimerix, Day One Bio, Genenta, GlaxoSmithKline, Kintara, Merck, Mundipharma, Novartis, Novocure, Prelude Therapeutics, Sagimet, Sapience, Servier, Symbio, Tango, Telix, and VBI Vaccines. MJvdB reports consulting for Celgene, Boehringer, Carthera, Nerviano, Genenta, Servier, Anheart Therapeutics, Boehringer Ingelheim, Fore Biotherapeutics, Incyte, and Symbiopharma. J-CT reports honoraria or advisory board participation and consulting for CarThera, Servier, ERCM, and Impatients. All other authors declare no competing interests.

Data sharing

The de-identified individual-level patient data and data dictionary for this study can be provided to researchers upon written request 12–36 months after publication of this Article. Please send enquiries to the corresponding author (PK). A detailed proposal for how the data will be used is required and applications will be assessed on a casebycase basis by representatives of all participating centres, and only for the purpose of individual participant data meta-analysis. No study protocol or statistical analysis plan will be shared due to study regulations and language restrictions (as the study protocol and statistical plan have been drafted in German). A data access agreement must be signed for these data to be released.

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