The oncological role of resection in newly diagnosed diffuse adult-type glioma defined by the WHO 2021 classification: a Review by the RANO resect group

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Glioma resection is associated with prolonged survival, but neuro-oncological trials have frequently refrained from quantifying the extent of resection. The Response Assessment in Neuro-Oncology (RANO) resect group is an international, multidisciplinary group that aims to standardise research practice by delineating the oncological role of surgery in diffuse adult-type gliomas as defined per WHO 2021 classification. Favourable survival effects of more extensive resection unfold over months to decades depending on the molecular tumour profile. In tumours with a more aggressive natural history, supramaximal resection might correlate with additional survival benefit. Weighing the expected survival benefits of resection as dictated by molecular tumour profiles against clinical factors, including the introduction of neurological deficits, we propose an algorithm to estimate the oncological effects of surgery for newly diagnosed gliomas. The algorithm serves to select patients who might benefit most from extensive resection and to emphasise the relevance of quantifying the extent of resection in clinical trials.

Introduction

Diffuse gliomas represent the most frequent primary parenchymal brain tumours in adults,[1] and surgical resection is recommended as initial management for newly diagnosed disease.[2,3] The resected tissue allows a neuropathological diagnosis, and resection translates into increased survival in patients with tumours that have historically been denoted as low-grade or high-grade gliomas.[4,5] The assumption for an oncological role of resection is supported by beneficial associations between a greater extent of resection and more favourable survival,[6,7] regardless of whether residual tumour remains due to its proximity to crucial brain regions.[8] Supramaximal resection beyond the tumour margins that are visible on imaging has emerged as a promising approach (figure 1A),[6,9] but a salient point of discussion remains on how to identify patients who might benefit from such a resection. Although maximal resection is the goal for surgery,[10] nuanced weighing of the oncological benefits against the risk for clinical deterioration is paramount for appropriate patient selection given that the introduction of neurological deficits might negate the benefits of more extensive resection.[11–14]

Despite the evidence for an oncological role for glioma surgery, interventional trials have frequently refrained from quantifying the extent of resection that might result in prognostic imbalances between study groups. A comparison between different studies might be further hampered by inconsistent terminology used to describe the extent of resection,[15] with residual postoperative tumour volume representing the most surgically relevant oncological measurement.[6]

In turn, the inconsistent acknowledgment of the extent of resection in trials hinders the interpretation of the oncological effects of surgery across glioma types. The ill-defined oncological value of resection is becoming more problematic as the WHO 2021 classification necessitates the use of molecular features in addition to histopathological diagnostics to establish an integrated histomolecular diagnosis of the specific glioma type,[16] moving beyond the colloquial terminology of low-grade and high-grade tumours. An integrated molecular diagnosis serves to guide medical management,[2] and evidence has emerged suggesting that the effects of resection might differ between distinct molecular glioma types.

Based on a thorough review of the pertinent literature, our international and multi-disciplinary Response Assessment in Neuro-Oncology (RANO) resect working group delineates the oncological role of surgery in newly diagnosed, diffuse adult-type gliomas defined by the WHO 2021 classification. The data from the literature are compiled into an algorithm to estimate the oncological effects of surgery by weighing the expected survival benefit of more extensive resection against other clinical factors within the framework of the molecular tumour profile.

The oncological role of resection in molecularly defined gliomas

IDH-wildtype glioblastoma, CNS WHO grade 4

Glioblastomas represent the most frequently encountered glioma with an incidence of approximately 60% among diffuse gliomas and with a poor median overall survival of 12–17 months.[1,17] Pivotal prospective data supporting extensive resection comes from a phase 3 randomised controlled trial by Stummer and colleagues who assigned patients with suspected glioblastoma to undergo fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) or conventional microsurgery with white light at first resection (table 1).[5] Patients randomly assigned to the 5-ALA group had higher rates of complete resection of

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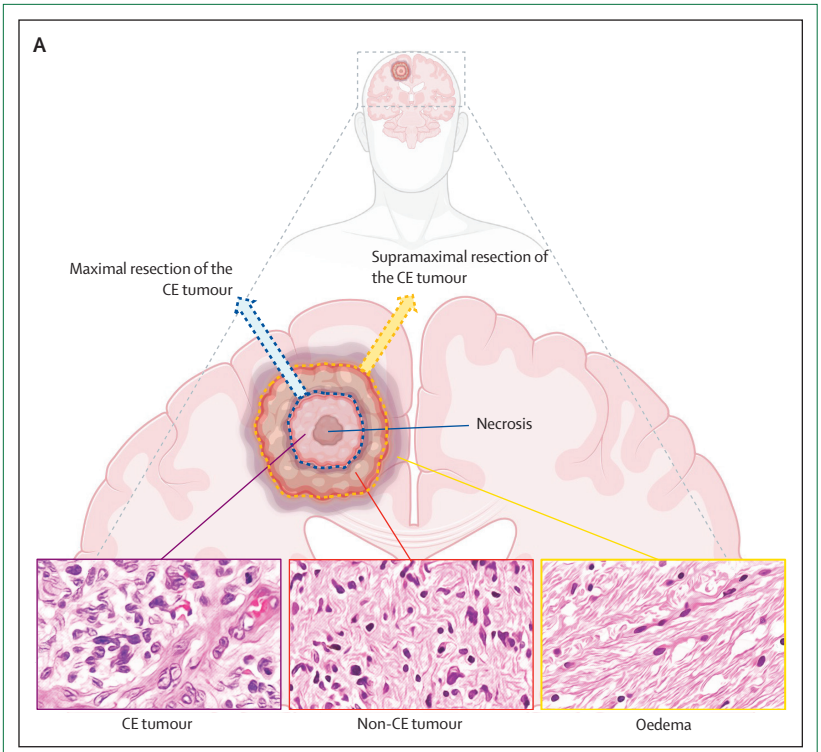
the contrast-enhancing tumour, and had reduced risk for progression or death at 6 months (hazard ratio [HR] 0·73, 95% CI 0·6–0·9, p=0·01). Post-hoc analysis correcting for clinical confounders yielded associations between residual contrast-enhancing tumours and overall survival,[5,23] and these findings were recently confirmed in another randomised controlled study on the use of 5-ALA and in large retrospective cohorts.[19,44] In the study by Stummer and colleagues, 237 (87·8%) of 270 patients were diagnosed as glioblastoma based on histopathological features alone, as per WHO 2000 classification.[45] Although the current WHO 2021 classification restricts the diagnosis of glioblastoma to isocitrate dehydrogenase (IDH)-wildtype tumours,[16] only 5–10% of tumours with glioblastoma-like histology have IDH mutations.[30,46] The median outcomes of cohorts on histological glioblastoma before 2021 might therefore be reasonably extrapolated to cohorts of IDH-wildtype glioblastoma. A recent prospective, parallel cohort study by Roder and colleagues compared intraoperative MRI with 5-ALA for achieving more complete resections in newly diagnosed histological glioblastoma at 11 German centres.[18] Although the primary endpoint testing for superiority of intraoperative MRI in achieving smaller tumour remnants was not shown, a pooled analysis of 256 patients from both groups showed that the presence of a postoperative contrast-enhancing tumour was prognostic for a median decline in overall survival of 8·5 months (HR 1·59, 95% CI 1·0–2·5, p=0·048). The finding was corroborated by inferior progression-free survival (HR 1·77, 95% CI 1·3–2·4, p<0·01), and the overall survival curves of patients with 0 cm³ residual tumour size compared with those greater than 0 cm³ began to separate 3 months after resection. As expected, only a small proportion of 30 (10·8%) individuals from 277 patients in the as-treated analysis had IDH-mutations or unknown IDH-status. The retrospective multicentre GLIOMAP study used propensity-score matching to mimic a randomised trial design to analyse patients with eloquent glioblastoma undergoing either awake or asleep resection.[30] With smaller contrast-enhancing remnants in the awake group and lower rates of postoperative deficits, overall survival was longer following awake resection in the matched population of 536 patients (17 *vs* 14 months, p<0·001) and in clinically important subgroups.[27,30] The role of *MGMT* promotor methylation on the effects of resection is unclear as the survival benefits of lower residual tumour volumes were uniformly shown across studies of unmethylated tumours, including the trial by Roder and colleagues (>0 cm³ residual tumour: HR 2·35, 95% CI 1·3–4·4, p=0·006), whereas conflicting results exist for methylated tumours.[6,9,18,30,31] We speculate that the less pronounced associations between residual tumour and survival in methylated tumours could be due to methylated glioblastomas being more responsive to alkylating chemotherapy.[2]

Given that randomised trials that include a group that intentionally leaves tumour remnants cannot be ethically justified due to a perceived lack of equipoise, analyses on the tumour proportion that needs to be removed for a survival benefit rest upon retrospective cohorts. Generally, volumetric analyses rather than two-dimensional measurements of postoperative tumour volume are used.[6,9,30] Older studies reported a contrast enhancement reduction of about 70–90% or about 5 cm³ residual enhancement as being prognostic.[6,41,42] Importantly, clinically well characterised retrospective cohorts suggest an exponential relationship between residual contrast enhancement and risk for death: Molinaro and colleagues assessed 761 glioblastomas treated at the University of California between 1997 and 2017, and found that the relative death rate (normalised for resections of 75–80%) considerably decreased with high extent of resection (>80% resection) and substantially increased for low (<40% resection) extent of resection.[9] Associations between resection and outcome were observed in an IDH-wildtype subgroup of



B RANO categories for the extent of resection in glioblastoma

Class 1: supramaximal CE resection	Class 2: maximal CE resection	Class 3: submaximal CE resection	Class 4: biopsy
0 cm³ CE + ≤5 cm³ non-CE	≤1 cm³ CE and/or >5 cm³ non-CE	>1 cm³ CE	No reduction of tumour volume

Figure 1: **Surgical resection in diffuse gliomas**
(A) Extents of resection designated according to the removed tumour portion. (B) RANO classification based on tumour remnants. CE=contrast-enhancing. RANO=Response Assessment in Neuro-Oncology. Figure created with BioRender.com.

	Design	Population	Intervention (resection)	Key results
Prospective patient cohorts				
Roder et al (2023)[18]	Non-randomised controlled clinical trial	Glioblastoma* (n=277)	ioMRI guided resection versus 5-ALA guided resection	No difference in complete resection rate between ioMRI versus 5-ALA (81% *vs* 78%, OR 1·09, 95% CI 0·57–2·08, p=0·79)†; no difference in OS between ioMRI versus 5-ALA (HR 1·00, 95% CI 0·64–1·55, p=0·99), nor in PFS (HR 0·91, 95% CI 0·69–1·20), p=0·50)‡; complete resection was associated with higher median OS of 27·9 (95% CI 18·1–37·7) months versus 19·4 (16·7–22·1) months (HR 1·59, 95% CI 1·0–2·5, p=0·48)‡; and complete resection was associated with higher median PFS of 6·9 (95% CI 5·0–8·9) months versus 3·8 (95% CI 3·5–4·1) months (HR 1·77, 95% CI 1·3–2·4, p=0·001)§
Picart et al (2023)[19]	Randomised controlled trial	Glioblastoma* (n=171)	5-ALA guided versus conventional white-light guided	Higher rate of complete resection of the CE tumours in the 5-ALA group, 79% versus 48% (absolute difference 29%, 95% CI 17–40, p<0·0001)†; complete resection was associated with higher OS (HR 0·65, 95% CI 0·42–1·01, p=0·05)‡; and complete resection was associated with higher PFS (HR 0·56, 0·36–0·86, p=0·0080)‡
Beiko et al (2014)[20]	Prospective cohort study	Astrocytoma grade 3* (n=128) and glioblastoma* (n=207)	Complete versus subtotal resection of CE tumours	For overall cohort, complete resection was associated with higher median OS 19·6 (95% CI NA) months versus 10·7 (95% CI NA) months (p=NA); for subgroup analysis: complete resection was associated with higher median OS in the subgroup that received chemoradiation with complete resection, 22·4 (95% CI 15·7–29·1) months versus 13·2 (95% CI 8·5–18·0) months (p=NA); and IDHmt gliomas were more amenable to complete resection versus IDHwt (93% *vs* 67%, p<0·001)
Kreth et al (2013)[21]	Prospective cohort study	Glioblastoma* (n=273)	Complete versus subtotal resection of CE tumours	Complete resection was associated with higher median OS: 17·1 (95% CI 12·6–21·5) months versus 11·7 (10·0–13·5) months (p=0·001)
Senft et al (2011)[22]	Randomised controlled trial	Anaplastic astrocytoma* (n=1), anaplastic oligodendroglioma* (n=1), and glioblastoma* (n=46)	ioMRI guided versus conventional resection	Complete resection more frequent with ioMRI guided resection as compared with conventional resection (96% *vs* 68%, p=0·023)†; higher 6-month PFS with ioMRI guided resection as compared with conventional resection (67% *vs* 34%, OR 0·28, 95% CI 0·09–0·91, p=0·046)‡; and postoperative rates of new neurological deficits did not differ (13% in ioMRI *vs* 8% in the conventional group, p=1·0)‡
Stummer et al (2008)[23]	Post-hoc analysis of the trial by Stummer et al (2006)[5]	Glioblastoma* (n=243) from per-protocol cohort	Complete versus subtotal resection of CE tumours	Complete resection was associated with higher median OS 16·7 (95% CI 13·4–19·0) months versus 11·8 (95% CI 10·4–13·7, p< 0·0001) months (HR 1·75, 95% CI 1·26–2·44, p=0·0004)
Pichlmeier et al (2008)[24]	Post-hoc analysis of the trial by Stummer et al (2006)[5]	Glioblastoma* (n=243) from per-protocol cohort	Complete versus subtotal resection of CE tumours	For the overall cohort, complete resection was associated with higher median OS 16·7 (95% CI 4·3–19·0) months versus 11·8 (95% CI 10·4–13·7) months (p<0·0001); and for subgroup analysis, complete resection was associated with higher median OS in the RTOG-RPA cohort IV and V: (IV) 17·7 (95% CI 14·3–22·5) versus 12·9 (95% CI 10·3–14·7) and (V) 13·7 (95% CI 8·3–17·6) versus 10·4 (95% CI 8·1–11·5) months (p=0·0007)
Stummer et al (2006)[5]	Randomised controlled trial	Glioblastoma* (n=270) in full-analysis cohort	5-ALA guided versus conventional white-light guided	Higher rate of complete resection of the CE tumours in the 5-ALA group, 65% *vs* 36% (absolute difference 29%, 95% CI 17–40, p<0·0001)†; and 6-months PFS higher in 5-ALA group, 41·0% (95% CI 32·8–49·2) versus 21·1% (95% CI 14·0–28·2) with an absolute difference of 19·9% (95% CI 9·1–30·7, p=0·0003)‡
Retrospective patient cohorts				
Park et al (2024)[25]	Retrospective cohort study	Oligodendroglioma grade 2–3§ (n=183), astrocytoma grade 2–4§ (n=211), and glioblastoma§ (n=799)	Complete versus near total versus subtotal resection of CE tumours	For oligodendroglioma grade 2–3, complete resection of CE tumours was associated with higher OS (HR 0·16, 95% CI 0·05–0·56, p=0·004), but complete resection of non-CE tumours was not (HR 0·56, 95% CI 0·22–1·43, p=0·22); for astrocytoma grade 2–4: complete resection of CE tumour (HR 0·27, 95% CI 0·10–0·70, p=0·008), and non-CE tumours (HR 0·030, 95% CI 0·16–0·59, p<0·001) were associated with higher OS; and for glioblastoma: complete resection of CE tumour (HR 0·78, 95% CI 0·63–0·98, p=0·030) and non-CE tumours (HR 0·53, 95% CI 0·42–0·68, p<0·001) were associated with higher OS
Mendoza Mireles et al (2023)[26]	Retrospective cohort study	Glioblastoma* (n=1657)	Complete versus subtotal resection of CE tumours	Complete resection was associated with higher median OS 16·1 (95% CI 15·1–17·5) months versus 10·8 (95% CI 8·8–10·8, p<0·001) months, and for non-GTR (HR 1·68, 95% CI 1·47–1·92, p<0·001)
Gerritsen et al (2023)[27]	Retrospective cohort study with propensity score matching	Glioblastoma§ (n=1047)	Complete versus near total versus subtotal resection of CE tumours	For overall cohort, complete resection was associated with higher median OS 19·0 (95% CI 17·0–27·5) months versus 18·0 (95% CI 14·0–21·5, 0·2–1·0 ml RTV) months versus 16·0 (95% CI 12·0–22·0, 1·0–2·0 mL RTV) months versus 12·5 (95% CI 12·0–14·5, >2·0 ml RTV, p<0·0001) months (HR 0·58, 95% CI 0·39–0·86, p=0·0070); for overall cohort, complete resection was associated with higher median PFS 9·5 (95% CI 8·0–11·0) months versus 8·5 (95% CI 6·0–11·0) months versus 6·0 (95% CI 4·8–10·0) months versus 7·0 (95% CI 6·0–8·5) months (p=0·0029); for subgroup analyses, complete resection was associated with higher OS and PFS in the subgroups of IDHwt, MGMT methylated, age <70 years, and preoperative NIHSS 0–1, irrespective of preoperative KPS; and complete resection with preservation of neurological function was associated with the highest median OS of 30·5 (95% CI 22·0–38·5) months versus 15·5 (95% CI 14·0–18·0) months (p<0·001), and PFS of 22·0 (95% CI 16·5–35·5) months versus 14·0 (95% CI 12·5–16·0) months (p<0·0001)
Karschnia et al (2023)[28]	Retrospective cohort study	Glioblastoma§ (n=1008)	Supramaximal versus complete versus subtotal resection of CE tumours	Supramaximal resection was associated with higher median OS 24 (95% CI 20–41) months versus complete resection 19 (95% CI 17–20) months versus subtotal resection 15 (95% CI 12–17) months; supramaximal resection was associated with higher median PFS 11 (95% CI 9–13) versus complete resection 9 (95% CI 8–10) versus subtotal resection 8 (95% CI 7–9) months; and in comparison to supramaximal resection, complete resection was associated with lower OS (HR 1·58, 95% CI 1·1–2·3, p=0·004), as was subtotal resection (HR 1·89, 95% CI 1·2–2·9, p=0·003)

(Table 1 continues on next page)

	Design	Population	Intervention (resection)	Key results
(Continued from previous page)				
Drexler et al (2023)[29]	Retrospective cohort study	Glioblastoma§ (n=345)	Complete versus near complete versus partial resection or biopsy of CE tumours	For overall cohort, complete resection was associated with higher median OS 24·0 (95% CI 17·9–30·1) months (reference for HR) versus near complete resection 17·0 (95% CI 13·6–24·0) months (HR 0·97, 95% CI 0·6–1·5) versus partial resection or biopsy 10·0 (95% CI 7·9–12·1) months (HR 2·18, 95% CI 1·5–3·2, p<0·01); and for DNA methylation subclass analysis, associations of complete resection with favourable outcome retained in receptor tyrosine kinase subclass I and II, but not in the mesenchymal subclass
Gerritsen et al (2022)[30]	Retrospective cohort study with propensity score matching	Glioblastoma§ (n=1047)	Awake craniotomy versus conventional resection	For the overall cohort, awake craniotomy was associated with lower mean RTV 1·9 (SD 5·6) mL versus 5·9 (SD 11·0) mL, fewer neurological deficits at 3 months (22% *vs* 33%, p=0·019), 6 months (26% *vs* 41%, p=0·0048), higher median OS 17·0 (95% CI 15·0–24·0) months versus 14·0 (95% CI 13·0–16·0) months (p=0·0054), and higher median PFS 9·0 (95% CI 8·0–11·0) months versus 7·3 (95% CI 6·0–8·8) month, (p=0·0060) compared with conventional surgery; and for subgroup analyses: awake craniotomy resulted in less RTV and less neurological deficits in all subgroups irrespective of age, preoperative neurological status, or KPS, but only improved OS and PFS in younger patients (<70 years), with no to minimal preoperative neurological morbidity (NIHSS 0–1) or excellent preoperative KPS (90–100)
Aabedi et al (2022)[14]	Retrospective cohort study	Glioblastoma§ (n=228)	Complete versus subtotal resection of CE tumours	Complete resection was associated with higher median OS 28·4 (95% CI 21·5–37·2) months versus subtotal resection 17·6 (95% CI 15·8–20·4) months (HR 1·79, 95% CI 1·25–2·56, p=0·001); no significant association was found between new neurological postoperative deficits and the extent of resection of CE tumour (OR 1·02, 95% CI 0·99–1·1, p=0·18) or non-CE tumour (OR 0·99, 95% CI 0·98–1·00, p=0·17)
Molinaro et al (2020)[9]	Retrospective cohort study	Glioblastoma§ (n=761)	Supramaximal versus complete versus subtotal resection of CE tumours	Supramaximal resection was associated with higher median OS: 31·7 (95% CI 22·2–56·2) months versus complete resection 17·9 (95% CI 16·4–19·7) months versus subtotal resection 11·6 (95% CI 10·6–13·2) months, (HR 1·45, 95% CI 1·15–1·83, p=0·001); and residual non-CE tumour volume of 5·4 mL was found to be the significant cutoff value for OS to differentiate between supramaximal resection versus complete resection
Incekara et al (2020)[31]	Retrospective cohort study	Glioblastoma§ (n=326)	Maximal resection (>97%) versus subtotal resection versus biopsy of CE tumours	For the overall cohort, maximal resection was associated with longer OS on univariate (HR 0·51, 95% CI 0·36–0·72, p<0·0001) and multivariate analysis (HR 0·58, 95% CI 0·39–0·87, p=0·009); the association between maximal resection and favourable OS retained in patients with (p=0·014) and without (p=0·004) MGMT promotor methylation compared with patients with subtotal resection; and the association between submaximal resection and favourable OS retained in patients with (p=0·018), but not in patients without (p=0·560) MGMT promotor methylation compared with patients who had a biopsy
Xing et al (2018)[32]	Retrospective cohort study	Glioblastoma* (n=292)	Supramaximal versus complete versus subtotal resection of CE tumours	Complete resection was associated with higher median OS 17·6 (95% CI 13·7–19·1) months versus 12·9 (95% CI 10·3–15·9) months (p=NA); and subtotal resection was associated with lower PFS (HR 1·16, 95% CI 1·00–1·34, p=0·033), but not with OS (HR 1·12, 95% CI 0·97–1·30, p=0·22)
Mampre et al (2018)[33]	Retrospective cohort study	Glioblastoma* (n=245)	Supramaximal versus complete versus subtotal resection of CE tumours	Subtotal resection was associated with lower OS (HR 1·03, 95% CI 1·01–1·03, p=0·001); subtotal resection was associated with lower PFS (HR 1·03, 95% CI 1·01–1·05, p=0·01); and supramaximal resection was not associated with OS (HR 1·00, 95% CI 1·00–1·01, p=0·61) or PFS (HR 1·01, 95% CI 1·00–1·01, p=0·54)
Carroll et al (2018)[34]	Retrospective cohort study	Astrocytoma grade 3* (n=1429) and glioblastoma* (n=12 537)	Complete versus subtotal resection of CE tumours	For astrocytoma grade 3, complete resection was associated with higher OS in frontal tumours (HR 0·51, 95% CI 0·36–0·73, p<0·001) in general, in patients <50 years with frontal tumours (HR 0·27, 95% CI 0·17–0·47, p<0·001), and in patients <50 years with non-frontal tumours (HR 0·54, 95% CI 0·32–0·91, p=0·021); not in non-frontal tumours (HR 0·79, 95% CI 0·58–1·08, p=0·143) in general, in patients ≥50 years with frontal tumours (HR 0·97, 95% CI 0·59–1·60, p=0·90), or in patients ≥50 years with non-frontal tumours (HR 0·98, 95% CI 0·67–1·43, p=0·90); and for glioblastoma, complete resection was associated with higher OS in frontal tumours (HR 0·73, 95% CI 0·67–0·79, p<0·001), and non-frontal tumours (HR 0·79, 95% CI 0·74–0·84, p<0·001)
Pessina et al (2017)[35]	Retrospective cohort study	Glioblastoma* (n=282)	Supramaximal versus complete versus subtotal resection of CE tumours	Supramaximal resection was associated with higher median OS: 28·6 (95% CI 18·4–38·9) months versus complete resection 16·2 (95% CI 13·9–18·6) months versus subtotal resection 13·8 (95% CI 12·2–15·4) months (p<0·001); and FLAIR resection of ≥45% improved median OS 24·5 (95% CI 18·9–30·1) months versus 15·7 (95% CI 14·2–17·2) months (p<0·001) as compared with <45% FLAIR resection
Jiang et al (2017)[36]	Retrospective cohort study with propensity score matching	Glioblastoma* (n=416)	Complete versus subtotal resection of CE tumours	Complete resection was associated with higher median OS 20·5 (95% CI NA) months versus 16·0 (95% CI NA) months (HR 0·46, 95% CI 0·36–0·58, p<0·001); and complete resection was associated with higher median PFS: 12·0 (95% CI NA) versus 9·0 (95% CI NA) months (HR 0·55, 95% CI 0·44–0·68, p<0·001)
Padwal et al (2016)[37]	Retrospective cohort study	Astrocytoma* grade 3 (n=2755) and glioblastoma* (n=21 962)	Complete versus subtotal resection of CE tumours	For astrocytoma grade 3, complete resection was associated with higher OS (HR 0·60, 95% CI 0·49–0·74, p<0·0001); for glioblastoma, complete resection was associated with higher OS (HR 0·76, 95% CI 0·73–0·80, p<0·0001)
Li et al (2016)[38]	Retrospective cohort study	Glioblastoma* (n=1229)	Complete versus subtotal resection of CE tumours (78–100%)	Complete resection was associated with higher median OS 15·2 (95% CI 14·1–16·3) months versus 9·8 (95% CI 8·8–10·8, p<0·001) months (HR for non-GTR 1·53, 95% CI 1·33–1·77, p<0·001); and FLAIR resection of ≥53·21% was associated with the highest median OS 23·2 (95% CI 17·8–28·6) months versus 18·7 (95% CI 16·9–20·5) months as compared with <53·21% FLAIR resection

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	Design	Population	Intervention (resection)	Key results
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Noorbakhsh et al (2014)[39]	Retrospective cohort study	Glioblastoma* (n=20 705)	Complete versus subtotal resection of CE tumours	Complete resection was associated with higher OS in patients age 18–44 years (HR 1·70, 95% CI 1·39–2·08, p<0·001), age 45–59 years (HR 0·82, 95% CI 0·77–0·89, p<0·001), age 60–74 years (HR 0·79, 95% CI 0·74–0·84, p<0·001), and age ≥75 years (HR 0·78, 95% CI 0·70–0·86, p<0·001)
Marko et al (2014)[40]	Retrospective cohort study	Glioblastoma* (n=721)	Maximal safe resection	Higher EOR was associated with higher OS (HR for continuous variable 1·14, SE 0·26, p<0·001); there was an OS advantage associated with any degree of resection
Chaichana et al (2014)[41]	Retrospective cohort study	Glioblastoma* (n=292)	Complete versus subtotal resection of CE tumours	Complete resection was associated with higher median OS (HR 1·11, 95% CI 1·03–1·19, p=0·006) and median PFS (HR 1·09, 95% CI 1·01–1·18, p=0·01); residual tumour volume of <2 cm^3 yielded greatest OS risk reduction
Sanai et al (2011)[42]	Retrospective cohort study	Glioblastoma* (n=500)	Complete versus subtotal resection of CE tumours	Higher EOR was associated with higher OS (HR for continuous variable 0·99, 95% CI 0·98–0·99, p=0·004); EOR of >78% was a significant cutoff for OS risk reductions
McGirt et al (2009)[43]	Retrospective cohort study	Astrocytoma grade 3* (n=249) and glioblastoma* (n=700)	Complete versus near total versus subtotal resection of CE tumours	For glioblastoma subgroup, complete resection (HR 0·45, 95% CI NA, p=0·001) and near total resection (HR 0·61, 95% CI NA, p=0·002) were associated with higher OS in comparison with subtotal resection; and for grade 3 subgroup, complete resection was associated with higher OS (HR 0·59, 95% CI NA, p=0·048), but not near total resection (HR 0·65, 95% CI NA, p=0·070) compared with subtotal resection

PubMed was searched for prospective cohorts or retrospective cohorts of more than 200 patients with newly diagnosed glioblastoma. Only papers published after 2005 (following the introduction of the EORTC 26981/22981-protocol for concomitant chemoradiotherapy) with data on the extent of resection were included. Study names, design, population, intervention, and key results are indicated. Database closure was Jan 1, 2024. 5-ALA=5-aminolevulinic acid. Please note that for simplification, arabic numerals are indicated independent of the WHO classification used. CE=contrast enhancement. EOR=extent of resection. FLAIR=fluid-attenuated inversion recovery. HR=hazard ratio. IDHwt=isocitrate dehydrogenase wildtype. IDHmt=isocitrate dehydrogenase mutant. ioMRI=intraoperative MRI. KPS=Karnofsky Performance Score. MGMT=06-methylguanine-DNA-methyltransferase. NA=not available. NIHSS=National Institute of Health Stroke Scale. OR=odds ratio. OS=overall survival. PFS=progression-free survival. RPA=recursive partitioning analysis. RTOG=Radiation Therapy Oncology Group. RTV=residual tumour volume. SD=standard deviation. SE=standard error. *Pathological diagnosis based on histology. †Primary outcomes. ‡Secondary outcomes. §Pathological diagnosis based on WHO 2021 criteria.

Table 1: **Key papers evaluating the extent of resection in newly diagnosed glioblastoma**

478 individuals, and in an external validation dataset of 206 individuals from the Mayo Clinic and the Ohio Brain Tumor Study. Ratifying the increased risk of death with higher contrast-enhancing remnants analysing 744 IDH-wildtype glioblastomas,[6] the RANO resect group postulated a classification system to standardise the terminology for the extent of resection, which was recently validated in an external Norwegian cohort (figure 1B).[47] The RANO classification will be incorporated into trial protocols of the National Clinical Trials Network to reduce disparities between study groups. Of note, patients with submaximal resection had more favourable median overall survival than patients who underwent biopsy (15 *vs* 10 months, p=0·001) despite smaller preoperative tumours in patients who had biopsies.[6] This finding might be due to substantially lower postoperative tumour volumes after submaximal resection (and more beneficial clinical properties), contradicting previous interpretations that only maximal resection results in detectable survival differences.[21] A meta-analysis of 41 117 glioblastomas supports the notion that more extensive resection is superior to subtotal resection in improving survival, with patients who had biopsies exhibiting the worst prognosis.[48]

IDH-mutant astrocytoma, CNS WHO grade 2–3

IDH-mutant astrocytomas represent about 15–20% of diffuse gliomas.[1] Although these tumours exhibit a longer-term disease course compared with glioblastomas with a median overall survival of 7–11 years for grade 2–3 tumours, affected patients are diagnosed at a median age of 35–40 years that causes a large absolute number of life-years lost given that recurrence inevitably occurs.[17] Whether the distinction between WHO grade 2 and 3 in molecularly defined IDH-mutant astrocytomas is prognostically relevant is the subject of debates,[49] but grade 2 tumours without contrast enhancement have a better outcome.[17,50] Most notions on the associations between early resection and outcome rest upon astrocytomas grade 2 (table 2): Jakola and colleagues reported on 61 patients with IDH-mutant astrocytomas who presented to one of two Norwegian neuro–oncological centres, with region A preferring a biopsy-only approach and region B a resection strategy in the newly diagnosed setting at a time of uncertainty of which strategy to pursue.[4,61,64] Both cohorts were balanced with respect to demographical and clinical confounders, supporting the quasi-randomised study design. With a median overall survival of 5·6 years in region A, patients undergoing open resection due to presentation in region B had a longer survival of 10·2 years. The survival curves start to split after 4 years.

While information on the extent of resection was not available to Jakola and colleagues, a first volumetrically and molecularly well-annotated retrospective study from Rotterdam dichotomised 112 IDH-mutant astrocytomas according to the residual non-contrast-enhancing tumour volume and found inferior survival times with an estimated increase in the HR for death by 1·01 (95% CI 1·0–1·1) per cm^3 remnant (p=0·016).[57] This finding was supported by larger cohorts of 154 and

202 IDH-mutant astrocytomas provided in retrospective studies from Kavouridis and colleagues and Hervey-Jumper and colleagues, respectivley.[7,56] Making use of recursive partitioning analyses, Hervey-Jumper and colleagues showed that a postoperative tumour volume larger than 4·6 cm³ was associated with a worse survival of 9·0 years compared with smaller tumour remnants. Median overall survival in the cohort with smaller tumour remnants ranged from 19·9 years for tumours treated with chemotherapy (HR 0·31, 95% CI 0·2–0.6, p<0·001) or was not reached when immediate chemotherapy was not deemed necessary (HR 0·13,

	Design	Population	Intervention (resection)	Key results
Prospective patient cohorts				
Shaw et al (2008)[51]	Prospective cohort study	Astrocytoma* grade 2 (n=61); and grade 2 oligodendroglioma* (n=50)	Complete versus subtotal resection of CE tumours	Residual tumour volume ≥1 cm was predictive for PFS (HR 3·54, 95% CI 1·83–6·84, p=0·0002)
Retrospective patient cohorts				
Hervey-Jumper et al (2023)[7]	Retrospective cohort study with propensity score matching	Astrocytoma IDHmt† (n=202); oligodendroglioma IDHmt, 1p/19q-codeleted† (n=190)	Supramaximal versus complete versus subtotal resection of CE tumours	For astrocytoma IDHmt, supramaximal resection was significantly associated with higher median OS: NA (95% CI 14·7–NA) years versus complete resection 16·2 (95% CI 9–NA) years versus subtotal resection 11·4 (95% CI 9·4–16, p<0·001) years; for oligodendroglioma IDHmt 1p/19q-codeleted, supramaximal resection was significantly associated with higher median OS: NA (95% CI 18·3–NA) years versus complete resection NA (95% CI NA) years versus subtotal resection 22·2 (95% CI 19·9–NA, p=0·04) years; and for residual CE tumour volume of 4·6 cm³ and EOR of ≥75% were the significant cutoff values for OS to differentiate complete resection versus subtotal resection
Rossi et al (2021)[52]	Retrospective cohort study with propensity score matching	Astrocytoma*‡ grade 2 (n=130); and oligodendroglioma*‡ grade 2 (n=189)	Supramaximal versus complete versus subtotal resection of CE tumours	Supramaximal resection was significantly associated with higher OS (HR 0·01, 95% CI 0·00–0·08, p<0·001); and supramaximal resection was significantly associated with higher PFS (HR 0·03, 95% CI 0·01–0·13, p<0·001)
Ius et al (2022)[53]	Retrospective cohort study	Astrocytoma IDHmt*‡ (n=83); astrocytoma IDHwt*‡ (n=34); and oligodendroglioma*‡ (n=115)	Supramaximal versus complete versus subtotal resection of CE tumours	Complete resection of the CE tumour was not associated with higher OS (HR for subtotal resection 2·93, 95% CI 1·00–8·60, p=0·050), nor with higher PFS (HR 0·95, 95% CI 0·63–1·43, p=0·8); and residual CE tumour volume was not associated with higher OS (HR for continuous variable 1·03, 95% CI 1·00–1·06, p=0·083), nor with higher PFS (HR 1·02, 95% CI 1·0–1·05, p=0·074)
Garton et al (2020)[54]	Retrospective cohort study	Oligodendroglioma* grade 2 (n=1677); and grade 3 oligodendroglioma* (n=837)	Complete versus subtotal resection of CE tumours	For oligodendroglioma grade 2, complete resection was not associated with higher OS (HR 0·83, 95% CI 0·56–1·23, p=0·36); and for oligodendroglioma grade 3, complete resection was associated with higher OS (HR 0·57, 95% CI 0·36–0·90, p=0·02)
Kinslow et al (2019)[55]	Retrospective cohort study	Oligodendroglioma* grade 2 (n=2186); and oligodendroglioma* grade 3 (n=949)	Complete versus subtotal resection of CE tumours	For oligodendroglioma grade 2, complete resection was associated with higher OS (HR 0·74, 95% CI 0·58–0·95, p=0·02); and for oligodendroglioma grade 3, complete resection was associated with higher OS (HR 0·60, 95% CI 0·44–0·82, p=0·001)
Kavouridis et al (2019)[56]	Retrospective cohort study	Astrocytoma* grade 2 (n=154); and oligodendroglioma grade 2 (n=140)	Complete versus subtotal resection of CE tumours	Residual CE tumour volume was associated with lower OS (HR per cm³ increase 1·02, 95% CI 1·0–1·03, p=0·004)
Wijnenga et al (2018)[57]	Retrospective cohort study	Grade 2 astrocytoma* (n=112); grade 2 oligodendroglioma* (n=86); and mixed oligoastrocytoma* (n=30)	Complete versus subtotal resection of CE tumours	Residual CE tumour volume was associated with a lower OS (HR per cm³ increase 1·01, 95% CI 1·00–1·02, p=0·016); post-hoc analysis: in astrocytoma grade 2, any residual tumour volume was associated with a lower OS, but such a cutoff point for oligodendroglioma grade 2 could not be defined
Ding et al (2018)[58]	Retrospective cohort study	Glioma*‡ grade 2 (n=614); glioma*‡ grade 3 (n=358); and glioblastoma* (n=206)	Complete versus subtotal resection of CE tumours	Complete resection was associated with OS (HR 1·24, 95% CI 0·94–1·64, p=0·13) and PFS (HR 1·49, 95% CI 1·17–1·90, p=0·001); higher EOR improved median OS (HR for continuous variable 1·55, 95% CI 1·03–2·31, p=0·03); and for subgroup analysis: complete resection was not associated with OS in the oligodendroglioma subgroup (HR 1·33, 95% CI 0·79–2·21, p=0·28), nor was EOR in general (HR 1·54, 95% CI 0·78–3·05, p=0·21)
Alattar et al (2018)[59]	Retrospective cohort study	Oligodendroglioma* grade 2 (n=2378); and oligodendroglioma grade 3 (n=1028)	Complete versus subtotal resection of CE tumours	For oligodendroglioma grade 2, complete resection was not associated with higher OS (HR 1·06, 95% CI 0·73–1·53, p=0·75); and for oligodendroglioma grade 3, complete resection was not associated with higher OS (HR 1·18, 95% CI 0·80–1·72, p=0·40)
Schupper et al (2017)[60]	Retrospective cohort study	Astrocytoma* grade 2 (n=4113)	Complete versus subtotal resection of CE tumours	For overall cohort, complete resection was associated with higher median OS (>120, 95% CI 103–120+ months, p=NA; HR 0·72, 95% CI 0·60–0·85, p<0·0001); for subgroup analysis, complete resection was associated with higher OS in patients' age <50 years (HR 0·74, 95% CI 0·57–0·97, p=0·028), age ≥50 years (HR 0·66, 95% CI 0·53–0·83, p<0·0001), in the pre-temozolomide era (HR 0·77, 95% CI 0·61–0·97, p=0·027), and in the post-temozolomide era (HR 0·64, 95% CI 0·49–0·84, p=0·001)
Jakola et al (2017)[4]	Retrospective cohort study	Astrocytoma* grade 2 (n=117); oligodendroglioma* grade 2 (n=22); and oligoastrocytoma* grade 2 (n=14)	Resection versus biopsy and watchful waiting	For overall cohort, resection was associated with higher median OS 14·4 (95% CI 10·4–18·5) versus 5·9 (95% CI 4·5–7·2) years (p=0·005); HR for biopsy and watchful waiting 1·8 (95% CI 1·2–2·9, p=NA); and for subgroup analysis, resection was associated with higher median OS in the IDHmt non-co-deleted subgroup 10·2 (95% CI 6·9–13·4) years versus 5·6 (95% CI 3·5–7·6) years (p=NA) and the IDHwt subgroup 5·3 (95% CI 0·0–20·0) versus 1·4 (95% CI 0·6–2·2) years (p=NA)

(Table 2 continues on next page)

	Design	Population	Intervention (resection)	Key results
(Continued from previous page)				
Jakola et al (2012)[61]	Retrospective cohort study	Astrocytoma* grade 2 (n=117); oligodendroglioma* grade 2 (n=22); and oligoastrocytoma* grade 2 (n=14)	Resection versus biopsy and watchful waiting	For overall cohort, resection was associated with higher median OS not reached versus 5·9 (95% CI 4·5–7·3) years (p=0·01); HR for biopsy and watchful waiting 1·8 (95% CI 1·1–2·9, p=0·03); for subgroup analysis, resection was associated with higher median OS in astrocytoma grade 2 9·7 (95% CI 7·5–11·9) years versus 5·6 (95% CI 3·5–7·6) years (p=0·05)
Smith et al (2008)[62]	Retrospective cohort study	Astrocytoma* grade 2 (n=93); oligodendroglioma* grade 2 (n=91); and mixed oligoastrocytoma* (n=32)	Complete versus subtotal resection of CE tumours	Residual CE tumour volume was associated with lower OS (HR for continuous variable 1·010, 95% CI 1·001–1·019, p=0·03) and PFS (HR 1·007, 95% CI 1·001–1·014, p=0·035); and complete resection of fluid-attenuated inversion recovery abnormalities was associated with higher OS (HR 0·094, 95% CI 0·023–0·39, p=0·001)
Sanai et al (2008)[63]	Retrospective cohort study	Gliomas*‡ grade 2 (n=184); gliomas*‡ grade 3 (n=55); and glioblastoma* (n=71)	Maximal safe resection with awake mapping	Complete resection in 51·6% of grade 2, 65·5% of grade 3, and 69·0% in glioblastoma with overall 3·2% permanent neurological morbidity

PubMed was searched for prospective cohorts or retrospective cohorts of more than 200 patients with newly diagnosed astrocytomas grade 2–4 and oligodendrogliomas grade 2–3. Only papers published after 2005 (following the introduction of the EORTC 26981/22981 protocol for concomitant chemoradiotherapy in glioblastoma) with data on extent of resection were included. Study names, design, population, intervention, and key results are indicated. Two studies by Jakola and colleagues[4,61] did not meet formal inclusion criteria, but were included as those studies are considered landmark papers. Database closure was Jan 1, 2024. Please note that for simplification, arabic numerals are indicated independent of the WHO classification used. 5-ALA=5-aminolevulinic acid. CE=contrast enhancing. EOR=extent of resection. HR=hazard ratio. IDHwt=isocitrate dehydrogenase wildtype. IDHmt=isocitrate dehydrogenase mutant. KPS=Karnofsky Performance Score. NA=not available. OS=overall survival. PFS=progression-free survival. *Pathological diagnosis based on histology. †Pathological diagnosis based on WHO 2021 criteria. ‡Pathological diagnosis not further specified.

Table 2: **Key papers evaluating extent of resection in newly diagnosed IDH-mutant astrocytoma grade 2–4 and oligodendroglioma grade 2–3**

95% CI 0·1–0·3, p<0·001). These survival differences took between 3–7 years to materialise with fewer than ten deaths in the first 3 years after initial surgery. An external cohort of 193 IDH-mutant astrocytomas from Norway and Boston (MA, USA) validated the associations of residual tumour volume with outcome, and propensity-score matching was used to minimise confounders.[7] A stepwise log-rank analyses of the matched cohort showed decreasing HRs for both overall and progression-free survival with increasing extent of resection.

For IDH-mutant astrocytoma grade 3, Beiko and colleagues in a retrospective study reported that resection of contrast-enhancing disease in 113 IDH-mutant astrocytomas—of which 86 tumours (76·1%) had grade 3 histology and 27 tumours (23·9%) had grade 4 histology—translated to a favourable outcome.[20] The fact that additional reduction of the non-contrast-enhancing disease provided a complementary survival benefit (HR per cm³ 1·04, 95% CI 1·0–1·1, p=0·006), gives rise to the hypothesis that the non-contrast-enhancing tumour prognostically matters in IDH-mutant astrocytoma grade 3. Other retrospective studies or population-based register analyses support this assumption.[37,52] The effects on outcome are seen around 4 years after resection (ie, earlier than in grade 2 tumours) while the absolute difference in survival between varying degrees of resection appear to be somewhat less than in grade 2 tumours, presumably due to a more aggressive biology of grade 3 tumours. Prospective data with standardised imaging would help clarify differences in surgical effects between tumour grades, but unfortunately, the post-hoc volumetric analysis of previous studies with a long follow-up period required for adequately powered statistics is hampered by a lack of digitised imaging available for segmentation. This absence of imaging was exemplified by the CATNON trial[65] where communication with the corresponding authors revealed that imaging data could not be provided due to lack of availability as recruitment started in 2007.

IDH-mutant astrocytoma, CNS WHO grade 4

Molinaro and colleagues performed a subgroup analysis on 36 (7·0%) IDH-mutant astrocytomas grade 4 from a cohort of 514 glioblastomas with known IDH-mutation status.[9] Here, reduction of contrast-enhancing tumour (HR per percent 0·95, 95% CI 0·9–1·0, p=0·02) and non-contrast-enhancing tumour (HR per percent 0·96, 95% CI 0·9–1·0, p=0·02) was associated with improved survival. Interpretation of other historic studies assessing the outcome in relation to surgery is complex for grade 4 IDH-mutant astrocytomas as cohorts with malignant histological features (defining glioblastoma before the WHO 2021 classification)[16] have only a small fraction of patients with IDH-mutation,[30,46] and detection of a homozygous *CDKN2A/B*-deletion now allows the diagnosis of a IDH-mutant astrocytoma grade 4 even in the absence of grade 4 histological features.[2] Moreover, studies that histologically designated IDH-mutant astrocytomas grade 4 as glioblastoma, such as the retrospective trial by Beiko (which included 27 individuals with IDH-mutation and grade 4 histology) focused only on contrast enhancement.[20] Here, favourable outcomes seemed to be associated with greater extents of resection as residual contrast-enhancing tumour volume was of prognostic significance, also when statistically adjusting for histological tumour grade. Acknowledging a median overall survival of 2–5 years for patients with IDH-mutant astrocytoma grade 4,[46,49] considerable effects of surgery on survival might be presumed as survival differences were seen within that limited time window. It should be noted that scarce prospective data do not allow

reliable conclusions as to whether it is the contrast-enhancing tumour or the total tumour volume (including non-contrast-enhancing disease) that dictates outcome in astrocytomas grade 4. The view that total tumour volume dictates the outcome of patients with astrocytoma grade 4 is corroborated by data regarding grade 2–3 tumours (as it would be paradoxical that non-contrast-enhancing disease exclusively matters in astrocytomas grade 2–3),[7,20] and also by the study by Molinaro and colleagues.[9]

IDH-mutant and 1p/19q-codeleted oligodendroglioma, CNS WHO grade 2–3

Compared with astrocytic tumours, 1p/19q-codeleted and IDH-mutant oligodendroglioma are characterised by a long-term natural history as illustrated by a median overall survival of more than 15 years for grade 2 tumours and more than 10 years for grade 3 tumours.[17,66,67] Given the low rate of patients who die in the first years after diagnosis even in the absence of treatment, long follow-up and large cohorts are necessary to reveal the benefits of surgery. Accordingly, survival curves from 43 patients with oligodendroglioma grade 2 derived from the Norwegian study by Jakola and colleagues split after 6 years in favour of patients presenting to region B, which preferred open resection, but median survival was not reached, while median overall survival in region A was 16·7 years.[4,68] Also, in the studies by Wijnenga and colleagues and Kavouridis and colleagues,[56,67] a trend towards better survival with more extensive resection was observed in oligodendrogliomas grade 2 after about 5–6 years, but median survival was not reached at a median follow-up of 5–6 years. Notably, in both studies the favourable effects of no detectable tumour over small remnants were less pronounced than in comparable patients with IDH-mutant astrocytomas. The study by Hervey-Jumper and colleagues had a long median follow-up time of 11·7 years for 190 oligodendrogliomas grade 2,[7] and showed that residual non-contrast-enhancing tumours larger than 4·6 cm³ were associated with a survival of 19·9 years compared with an even better median survival (not reached, HR 0·32, 95% CI 0·2–0·7, p=0·003) in smaller remnants. This effect favouring smaller remnants was also seen in the larger cohort (including patients from the Norway and USA validation datasets) of 362 oligodendrogliomas, with a dichotomisation cutoff of less than 9·75 cm³ residual tumour and malignant progression-free survival as the endpoint (12·0 years *vs* not reached).[7] Selected population-based studies[55] or prospective trials (including EORTC 26951)[69] on non-surgical treatments for oligodendroglioma grade 2 stratified according to the extent of resection and found a better outcome for more extensive resection. However, the associations between larger tumour remnants and survival appear to be mitigated by smaller sample sizes or restricted follow-up periods,[57,70] confounding a clear conclusion on the effects of extent of resection.

Accordingly, the beneficial effects of more extensive resection in oligodendroglioma WHO grade 3 are seen in large population-based studies,[37,55] but less so in smaller institutional series that might indicate a limited effect size of resection.[71] The CODEL trial currently recruits, and randomly assigns newly diagnosed patients with oligodendrogliomas grade 3 to receive radiotherapy combined with temozolomide or procarbazine, lomustine, and vincristine.[72] The balance between the groups will be controlled with respect to the extent of resection, and CODEL offers the exciting opportunity to volumetrically analyse the effects of more extensive surgery in a prospective setting once data are mature.

Supramaximal resection and resection beyond imaging-defined tumour borders

In contrast-enhancing tumours, resection of the surrounding non-contrast-enhancing tissue was denoted by the term supramaximal resection.[15] Three large retrospective studies reported on 101, 253, and 356 patients with IDH-wildtype glioblastoma who underwent complete or near-complete resection of the contrast enhancement and subsequent chemotherapy.[6,9,73] These studies showed remarkable associations between the additional removal of the non-contrast-enhancing tumour and overall survival (HR 0·52, 95% CI 0·3–0·8, p<0·01;[73] HR 0·56, 95% CI 0·4–0·8, p=0·005;[9] and HR 0·62, 95% CI 0·5–0·8, p=0·003).[6] In another study on 98 patients with IDH-wildtype glioblastoma without contrast-enhancement—62 (63·3%) patients lacked histopathological glioblastoma-like features—a steep increase in the HRs for death with higher residual tumour volumes was observed (HR per cm³ 1·02, 95% CI 1·0–1·1, p=0·001)[28] supporting the relevance of non-contrast-enhancing tumours in glioblastoma. Comparison of a prospective study on 30 patients combining intraoperative MRI with 5-ALA to resect newly diagnosed glioblastoma with an institutional historic cohort of 75 individuals operated on exclusively using intraoperative MRI, found that longer survival was attained with the combined approach (18·5 *vs* 14·0 months, HR 0·45, 95% CI 0·3–0·7, p<0·001). The findings were attributed to more extensive resection of the infiltration zone;[73] however, a formal volumetric analysis of the tumour remnants was not provided. Four prospective, controlled trials are recruiting to assess the removal of a pre-defined volume beyond the contrast enhancement (table 3). Cautiously, only resection of the mass-like non-enhancing regions appears to provide a survival benefit rather than resection of all T2-fluid attenuated inversion recovery (FLAIR)-hyperintense abnormalities (including oedema with scattered tumour cells).[6,75] Areas of higher tumour densities correlate with metabolic hotspots, which seem prognostic of outcome when the postoperative metabolic activity was quantified by ^{18}FET-PET.[76] Criteria to distinguish non-contrast-enhancing tumours from oedema on MRI were proposed in a joint effort of four

RANO groups,[77] and the imaging features await prospective evaluation.

The concept of supramaximal resection is increasingly adopted into the management of tumours without contrast enhancement, but generalisability is hampered given that uniform definitions do not exist as exact quantification of the tissue removed beyond the T2-FLAIR-hyperintense tumour does not appear to be feasible. In the study by Hervey-Jumper and colleagues,[7] median overall survival was not reached for 26 patients with IDH-mutant astrocytoma in which resection beyond the borders was applied but was 16·2 years in individuals who had complete resection of the imaging abnormalities (p<0·001). The promising findings on

	Study name	Study design	Study population and location	Estimated enrolment (n)	Study question	Intervention	Outcome measures	Status
Newly diagnosed glioma studies evaluating extents of resection								
NCT06146738	The PALSUR-study: Palliative Care Versus Surgery in High-grade Glioma Patients (ENCRAM 2203, PALSUR)	Observational, multicentre, prospective, non-randomised controlled, and open label	Suspected and newly diagnosed high-grade glioma; ENCRAM Consortium (USA, western Europe, and Japan)	1015	Effect of palliative care versus biopsy versus resection on OS and adjuvant therapies	Best supportive care versus biopsy versus resection	Primary: OS and proportion of adjuvant therapies; secondary: PFS, neurological morbidity, quality of life, and serious adverse events	Recruiting
NCT06146725	The RESBIOP-study: Resection Versus Biopsy in High-grade Glioma Patients (ENCRAM 2202, RESBIOP)	Observational, multicentre, prospective, non-randomised controlled, and open label	Adults and older patients (18–90 years), suspected, and newly diagnosed high-grade glioma; ENCRAM Consortium (USA, western Europe, and Japan)	564	Effects of biopsy versus resection on OS and adjuvant therapies	Biopsy only versus maximal safe resection	Primary: OS and proportion of adjuvant therapies; secondary: PFS, neurological morbidity, quality of life, and serious adverse events	Recruiting
NCT06118723	The SUPRAMAX Study: Supramaximal Resection Versus Maximal Resection for High-Grade Glioma Patients (ENCRAM 2201, SUPRAMAX)	Observational, multicentre, prospective, non-randomised controlled, and open label	Suspected and newly diagnosed high-grade glioma; ENCRAM Consortium (USA, western Europe, and Japan)	640	Efficacy and safety of supramaximal resection with and without mapping techniques	Supramaximal resection (CE and non-CE tumour) versus maximal safe resection (CE tumour)	Primary: OS and neurological morbidity; secondary: PFS, EOR, onco-functional outcome, quality of life, and serious adverse events	Recruiting
NCT05735171	Supramarginal Resection in Glioblastoma Guided by Artificial Intelligence (SupraGlio-AI)	Interventional, multicentre, prospective, non-randomised, and open label	Suspected and newly diagnosed high-grade glioma in non-eloquent areas; Spain	60	Feasibility of artificial intelligence-guided supramarginal resection	Resection of CE tumour versus supramarginal resection using artificial intelligence-guided recurrence probability maps (CE tumour and high-risk non-CE areas)	Primary: feasibility (eligibility); secondary: OS, PFS, neurological function, global disability, EOR, and complications	Recruiting
NCT04737577	Glioma Supra Marginal Incision Trial (G-SUMIT)	Interventional, multicentre, prospective, randomised controlled, and double blind	Suspected newly diagnosed CE high-grade glioma and safe anatomical localisation; North America	72	Feasibility of supra-marginal resection	Total resection (CE tumour) versus supra-marginal resection (CE tumour and 1 cm or nearest non-CE sulcal boundary)	Primary: enrolment; secondary: feasibility, efficacy, safety, and radiological volumetrics	Recruiting
NCT04243005	Supramarginal Resection in Glioblastoma	Interventional, multicentre, prospective, randomised controlled, and double blind	Suspected and newly diagnosed supratentorial high-grade glioma; Scandinavia and Austria	90	Effect of supramarginal resection on OS	Supramarginal resection (CE tumour and 1 cm or non-CE tumour) versus maximal safe resection (CE tumour)	Primary: OS; secondary: neurological function, neurocognition, quality of life, and EOR	Recruiting
NCT03997136	Prognostic Impact of Surgical Resection Extent for Supratentorial High Grade Gliomas	Observational, single centre, prospective cohort, and open label	Suspected and newly diagnosed supratentorial high-grade glioma; Egypt	28	Compare clinical outcomes depending on EOR	Different categories of extent of resection	Primary: disability score; secondary: progression after 3 months	Unknown
NCT02676687	Supratotal Resection for Gliomas Within Noneloquent Areas: a Single Center Prospective Randomized Controlled Clinical Trial	Interventional, single centre, prospective, randomised controlled, and double blind	Suspected newly diagnosed and untreated glioma in non-eloquent areas (1 cm margin to eloquent areas or subcortical tracts); China	120	Efficacy of supramaximal resection on PFS	Total (CE and non-CE tumour) versus supratotal resection (CE and non-CE tumour with 1 cm margin)	Primary: PFS at 2 years; secondary: volume of resection and KPS	Unknown

(Table 3 continues on next page)

	Study name	Study design	Study population and location	Estimated enrolment (n)	Study question	Intervention	Outcome measures	Status
(Continued from previous page)								
Newly diagnosed glioma studies evaluating monitoring or imaging techniques for tumour resection								
NCT04708171	The PROGRAM-study: Awake Mapping Versus Asleep Mapping Versus No Mapping for Glioblastoma Resections (PROGRAM)	Observational multicentre, prospective, cohort, and open label	Suspected and newly diagnosed high-grade glioma in (near) eloquent areas; ENCRAM Consortium (USA, western Europe, and Japan)	453	Effect of intraoperative mapping techniques on EOR and morbidity	Resection with awake mapping versus asleep mapping versus no mapping	Primary: EOR and neurological morbidity; secondary: OS, PFS, onco-functional outcome, serious adverse events, and motor function	Recruiting
NCT03861299	The SAFE-Trial: Awake Craniotomy Versus Surgery Under General Anesthesia for Glioblastoma Patients (SAFE)	Interventional, multicentre, prospective, randomised, and open label	Suspected and newly diagnosed glioblastoma in (near) eloquent areas; Netherlands and Belgium	246	Effect of awake tumour resection with intraoperative neuromonitoring on EOR and surgical morbidity	Awake tumour resection with intraoperative stimulation and brain mapping versus tumour resection under general anaesthesia	Primary: neurological morbidity and gross total resection rate; secondary: quality of life, OS, PFS, and serious adverse events	Recruiting
NCT05475522	Intraoperative Sonographically Versus Fluorescence-guided Resection of Contrast-enhancing Gliomas and Brain Metastases	Interventional, single centre, randomised controlled, and non-inferiority	Suspected newly diagnosed CE high-grade glioma or brain metastases in safe anatomical localisations; Russia	134	Effect of intraoperative ultrasound guided versus fluorescence-guided surgery on gross total resection rates	Ultrasound-guided brain tumour resection versus 5-aminolevulinic acid fluorescence-guided brain tumour resection	Primary: gross total resection rates; secondary: EOR, motor and speech function, KPS, and complications	Recruiting
NCT05474573	Concurrent Fluorescence and Sonographically Guided Eradication of Contrast-enhancing Gliomas and Metastases (CONFLUENSE)	Interventional, single centre, prospective, and randomised controlled	Suspected newly diagnosed CE high-grade glioma or brain metastases; Russia	52	Effect of intraoperative ultrasound and fluorescence-guided surgery on EOR	Combined ultrasound and fluorescence-guided brain tumour resection versus fluorescence-guided brain tumour resection	Primary: gross total resection rates; secondary: EOR, motor and speech function, KPS, and complications	Recruiting
NCT05470374	Intraoperative Sonographically Guided Resection of Non-enhancing Gliomas (SONOGLIO)	Interventional, single centre, prospective, and randomised controlled	Suspected and newly diagnosed glioma without CE; Russia	96	Effect of intraoperative ultrasound on EOR	Tumour resection with versus without intraoperative ultrasound	Primary: EOR; secondary: gross total resection rates, motor and speech function, KPS, and complications	Recruiting
NCT05399524	Functional and Ultrasound Guided Resection of Glioblastoma (FUTURE-GB)	Interventional, multicentre, prospective, randomised controlled, and double blind	Suspected and newly diagnosed high-grade glioma; UK	357	Effect of additional imaging (DTI) and intraoperative ultrasound on outcome	Neuronavigation and fluorescence-guided resection (standard of care) versus standard of care with DTI and intraoperative ultrasound	Primary: feasibility and deterioration-free survival; secondary: OS, PFS, EOR, complications, functional outcome, and quality of life	Recruiting
NCT04745156	A Study Using Brain Stimulation and Behavioral Therapy to Increase Extent of Resection in Low-Grade Gliomas	Interventional, single centre, open-label, and device-feasibility study	Suspected and newly diagnosed low-grade glioma invading the primary motor cortex in the non-dominant hemisphere; USA	3	Inducing remapping of functional cortex to enable a greater EOR of invasive gliomas	After subtotal resection, device system implantation for deficit-inducing cortical stimulation with targeted physiotherapy to improve EOR during second surgery	Primary: EOR and motor function	Not yet recruiting
NCT03291977	Interest of Fluorescein in Fluorescence-guided Resection of Gliomas (FLEGME)	Interventional, single centre, prospective, randomised controlled, and open label	Suspected and newly diagnosed high-grade glioma; France	51	Effect of fluorescein-guided resection on gross total resection rates	Fluorescein versus white-light microscopy	Primary: gross total resection rates; secondary: EOR and neurological deficits	Completed
NCT02150564	3D Ultra Sound for Resection of Brain Tumors (SonoRCT)	Interventional, single centre, prospective, randomised controlled, and open label	Suspected and newly diagnosed glioma; India	72	Effect of intraoperative 3D ultrasound on gross total resection rates	Tumour resection using neuronavigation versus tumour resection using intraoperative three-dimensional ultrasound	Primary: gross total resection rates; secondary: accuracy of ultrasound, OS, and PFS	Completed

(Table 3 continues on next page)

	Study name	Study design	Study population and location	Estimated enrolment (n)	Study question	Intervention	Outcome measures	Status
(Continued from previous page)								
NCT01502280	Fluorescence-guided Surgery for Low- and High-grade Gliomas (BALANCE)	Interventional, single centre, prospective, randomised controlled, and open label	Suspected and newly diagnosed high-grade glioma; USA	127	Effects of 5-aminolevulinic acid on EOR	5-aminolevulinic acid versus placebo	Primary: EOR; secondary: OS, PFS, and National Institutes of Health Stroke Scale	Completed
NCT01351337	Functional Monitoring for Motor Pathway in Brain Tumor Surgery Within Eloquent Area	Interventional, single centre, prospective, and open label	Suspected and newly diagnosed glioma; China	58	Effect of DTI-based tractography for pyramidal tract mapping on EOR	Diffusion tensor tractography neuronavigation and intraoperative subcortical stimulation	Primary: EOR; secondary: motor function and long-term functional status	Completed
Recurrent glioma studies evaluating extents of resection								
NCT04838782	Role of Repeat Resection in Recurrent Glioblastoma	Interventional, single centre, prospective, randomised, and open label	Recurrent and previously resected glioblastoma; Canada	250	Effect of re-resection on OS and hospitalisation in recurrent glioblastoma	Re-resection versus non-surgical management in recurrent glioblastoma	Primary: OS; secondary: length of hospitalisation or palliative care and nursing home	Recruiting
NCT02394626	Surgery for Recurrent Glioblastoma (RESURGE)	Interventional, multicentre, prospective, randomised, and open label	Recurrent and previously resected glioblastoma; Europe	120	Effect of re-resection on OS and hospitalisation in recurrent glioblastoma	Re-resection with adjuvant second-line therapy versus non-surgical second-line therapy alone in recurrent glioblastoma	Primary: OS; secondary: recruitment rate, PFS, morbidity, and hospitalisation	Recruiting

Clinicaltrials.gov was searched for recently completed trials, currently active trials, and planned trials evaluating the surgical management for primary or recurrent glioma in adults. The following search terms were used: conditions and diseases—ie, glioma, gliomas, glial tumour, glial tumours, glial cell tumours, and glioblastoma; and interventions and treatments—ie, resection, extent of resection, residual, residual volume, residual tumour, removal, and tumour removal. Terminated or withdrawn studies were excluded. 359 studies were screened and 21 included. Study names, design, population, intervention, and outcome measurements are indicated. The database was searched up to Jan 1, 2024. CE=contrast enhancing. DTI=diffusion tensor imaging. EOR=extent of resection. KPS=Karnofsky Performance Score. OS=overall survival. PFS=progression free survival.

Table 3: **Current clinical trials evaluating the effects of surgical approaches in diffuse gliomas**

supramaximal resection for IDH-mutant astrocytoma are corroborated by uncontrolled studies by Rossi and colleagues and Duffau and colleagues (albeit the Duffau group provided no molecular data), describing median survival times ranging well beyond 10 years.[51,78] While there is conflicting evidence for similar effects of supramaximal resection among 1p/19q-codeleted oligodendroglioma,[7,79] it is unclear whether this is due to low efficacy or due to restricted follow-ups for such a novel surgical approach in a slow growing tumour with excellent outcome after complete (but less than supramaximal) resection.

Clinical predictors of outcome interacting with the oncological benefits of resection

Postoperative neurological deficits

Although sophisticated technical tools continuously evolve to increase intraoperative safety,[10,63] the oncological value of ever-increasing extents of resection reach an asymptote when surgery results in diminished functional outcome. In glioblastomas, the induction of substantial neurological deficits completely negates the benefits of more extensive resection.[12–14] This notion is exemplified by the GLIOMAP study cohort, where 242 (25·1%) of 965 patients with eloquent glioblastoma had functional deterioration 6 weeks after surgery, characterised by at least one National Institutes of Health Stroke Score point decline, which was a negative predictor of outcome (HR 1·41, 95% CI 1·2–1·7, p=0·001), while complete resection of the contrast enhancement tumour was a positive predictor of comparable statistical strength (HR 0·58, 95% CI 0·4–0·9, p=0·007).[27,30] This result was caused by the detrimental effect of neurological deterioration on functioning as it was the most important predictor for Karnofsky Performance Scale deterioration (HR 7·46, 95% CI 5·0–11·1, p<0·001). Given that IDH-mutant tumours with or without 1p/19q-codeletion are characterised by slower growth than IDH-wildtype tumours, postoperative deficits might have less effect on survival (albeit the quality of life might be affected upon) given that the interval to initiate medical therapy is longer (allowing for recovery from surgery). Accordingly, the presence of a surgically induced neurological deficit in seven of 49 patients with glioma grade 2 (14·3%; including three transient deficits) did not change the notion that open surgery was associated with more favourable survival compared with a biopsy-only approach (in which none of 77 patients showed postoperative deteriorations).[80] It is worth mentioning that major deficits occur less commonly in specialised centres,[53,62] although routine reporting and grading

remain suboptimal and are warranted to capture the true incidence. Meticulous clinical scoring tools need to be applied prospectively to distinguish deficits resulting in worse outcome (eg, decreased consciousness) from minor, prognostically not relevant deficits (eg, quadrantanopia).[81]

Patient characteristics

Age as a continuous variable represents an independent prognostic marker for patients with IDH-wildtype, and to a lesser extent, IDH-mutant tumours with or without 1p/19q-codeletion.[6,82] With increasing age, the (absolute) effects of surgery are oncologically less pronounced given the limited overall prognosis and higher frailty that prohibits patients from undergoing further non-surgical therapy. This finding is exemplified by the prospective, controlled ANOCEF trial for which 107 patients with glioblastoma over the age of 70 years were randomly assigned to undergo open resection or biopsy.[83] Although surgery did not cause increased morbidity, no differences in survival were detected (HR 0·79, 95% CI 0·5–1·2, p=0·28). Volumetric analyses were absent and beneficial surgical effects might have been counteracted by low extents of resection. The study enrolled selected patients from nine centres over 11 years, showing a peculiar fraction of patients where randomisation was deemed acceptable; thus, generalisability of the results from the ANOCEF trial might be hampered. Although the authors interpreted the study to be in support of resection given that there was less deterioration in repetitive measurements of quality of life and clinical performance, ANOCEF highlights the inconclusive oncological effects in older patients. In IDH-mutant tumours, median age of diagnosis is in patients about the age of 40 years and older patients are rarely encountered in the newly diagnosed setting.[1,49] Other factors that might adversely affect the outcome include preoperative Karnofsky Performance Scale,[6,30] functional tumour localisation,[6,57] ethnicity (with non-Hispanic White people displaying the least favourable outcome),[84,85] and socioeconomic background.[86]

Interaction of surgical effects with non-surgical therapies

Radiotherapy (with concomitant chemotherapy for glioblastomas) followed by maintenance chemotherapy constitutes the postoperative standard for IDH-wildtype glioblastomas and IDH-mutant gliomas grade 3–4, and those approaches consolidate any surgical success.[2] Postoperative neurological deficits prohibiting patients from undergoing such therapy almost certainly negates the effects of resection. In patients with IDH-mutant gliomas grade 2, radiotherapy might be deferred to preserve cognitive function; and the randomised, controlled phase 3 INDIGO trial showed that the mutant IDH-inhibitor vorasidenib might augment the effects of resection in delaying progression.[87]

Summary: the RANO algorithm for oncological effects of surgery

For accurate estimations of the oncological effects of surgery (compared with patients managed with biopsy), the RANO algorithm weighs the achieved extent of resection against neurological function (figure 2). Severe deficits decrease survival, while moderate deficits that ameliorate within months but delay non-surgical therapy might be less devastating depending on the molecular tumour profile. Clinical risk factors including age, baseline function, and tumour localisation influence the potential benefits of more extensive resection as patients with a more favourable risk profile might experience the unfolding benefits of greater resection.[7,9,27,30]

In IDH-wildtype glioblastomas grade 4, the effects of more extensive resection on survival become evident within weeks to months, but patients living for more than 5 years after diagnosis (long-term survivors) are rare.[11] The gains in median survival time from more extensive resection compared with biopsy might be extrapolated to be in the range of several months to a year, acknowledging that tumours handled with a biopsy-only strategy, due to non-resectable localisations or comorbidities, often identify with an inherently worse prognosis. Even moderate deficits prohibiting patients to undergo chemoradiotherapy within 6 postoperative weeks almost certainly turn the effects of resection to negative as progression inevitably occurs within months.

In IDH-mutant astrocytomas grade 2, oncological benefits of resection are seen after 3–7 years. The gain in survival time increases impressively to a median difference of up to 10 years between patients with aggressive resections compared with patients initially managed by biopsy. This finding is exemplified by the fact that virtually no progression occurs in the first decade following complete resection.[7,52,57] Although moderate postoperative deficits might affect progression-free survival as an endpoint by delaying radiotherapy or chemotherapy, it is tempting to speculate that the effects on the survival endpoint might be less influenced given that the timing of non-surgical therapy is of less importance than in IDH-wildtype gliomas.[2] With higher WHO grades of IDH-mutant astrocytomas, the priority shifts towards the avoidance of new deficits depending on the estimated urgency for postoperative radiotherapy.

In IDH-mutant and 1p/19q-codeleted oligodendrogliomas grade 2, the effects of resection on survival are expected after more than 6 postoperative years. While a median survival difference of several years might be measured after a decade, exact quantification has yet not been possible given the rather favourable natural disease course with low death rates. Acknowledging the effects of the available medical therapies and indolent natural course observed in most patients, new moderate deficits might offset the effects of surgery, at least for low extents of resection. In grade 3 oligodendrogliomas, the surgical priority somewhat

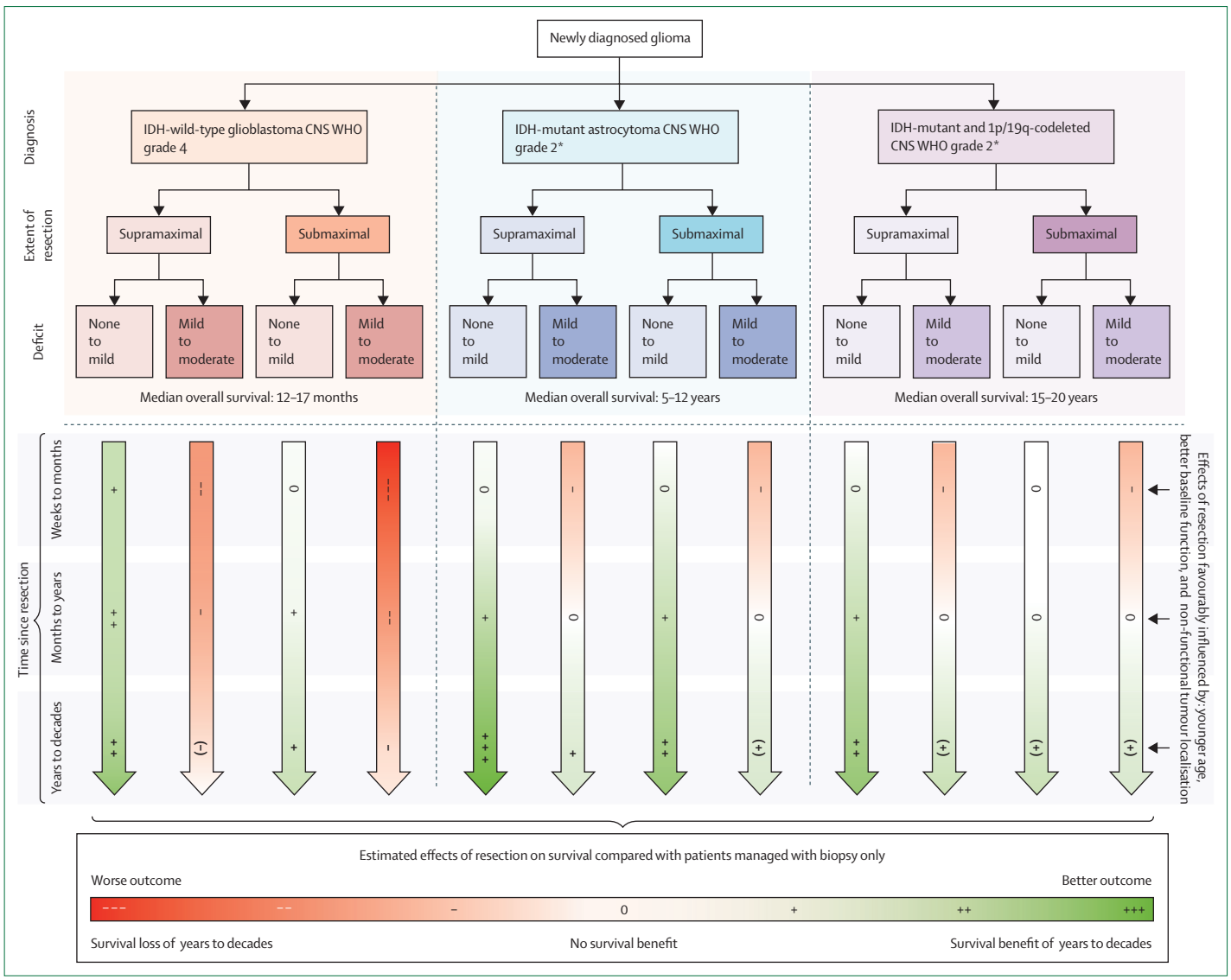

Figure 2: **RANO algorithm for oncological effects of resection**
Estimated effects on survival outcome over time based on WHO 2021[16] tumour type and grade, extent of resection, and neurological function. Deficits can be mild (transient within weeks without delaying medical therapy) or moderate (partly transient within months with potential delay in medical therapy). Brackets indicate potential effects for which only scarce evidence exists. IDH=isocitrate dehydrogenase. RANO=Response Assessment in Neuro-Oncology. *With higher WHO grade in IDH-mutant tumours, the effects of resection on outcome progressively shift towards the effects of resection estimated for IDH-wildtype glioblastomas.

shifts towards the avoidance of deficits as radiotherapy is warranted, but substantial recovery time might still be granted given the slow-growing biology of the tumour.

Precision surgery in neuro-oncology

The RANO algorithm serves as a framework to inform clinical trials about the relevance to control for the extent of resection in clinical trials to reduce imbalance between study groups, and might aid judicious selection of individuals benefiting most from extensive resection by estimating the effects of resection on survival over time. In such patients, it might appear germane to prioritise the extent of resection over transient deficits, and early re-resection strategies for unplanned tumour remnants need to be assessed. Also, survival analysis in prospective trials should stratify patients according to the extent of resection, including patients with supramaximal resection. In turn, the algorithm helps to select individuals in which biopsy constitutes the oncological default setting, such as in older patients with slow growing tumours and otherwise restricted life expectancy. The value of resection for recurrent gliomas needs to be addressed once data from recruiting randomised trials are mature (NCT02394626 and NCT04838782), as previous retrospective studies might be biased given that patients with an inherently

Search strategy and selection criteria

References were identified by searching the PubMed database using combinations of the following search terms: "contrast enhancing", "extent of resection", "FLAIR", "glioma", "glioblastoma", "IDH", "molecular", "mutant", "non-contrast enhancing", "outcome", "prognostic", "resection", "residual", "surgery", "survival", "tumor", "volume", "WHO classification", "WHO 2021", and "wildtype". The Cochrane Library, Google Scholar, the registry for clinical trials of the US National Library of Medicine ClinicalTrials.gov, references from relevant articles, and the authors' own files were also searched. Only studies published in English language journals between Jan 1, 2000 and Jan 15, 2024 were included. Uncertainties in publications were clarified by personal communication with the corresponding authors. The final reference list was generated based on originality and relevance to the topics covered in the present Review.

long-term disease course are more likely to undergo re-resection.[11] Helpfully, the recent RANO 2.0 update established a single set of standard response criteria for both newly diagnosed and recurrent IDH-wildtype and IDH-mutant gliomas, therefore replacing previous modifications such as mRANO or iRANO that can be used for all studies regardless of the treatment modalities being assessed with both two-dimensional or volumetric measurements used (while it remains to be shown whether two-dimensional measurements of postoperative tumours have a prognostic value similar to volumetric analyses).[88,89] With the molecular tumour diagnosis dictating the gains to be expected from resection, real-time diagnostics could guide neurosurgeons to balance aggressive resection against the risk for functional deterioration during crucial operative steps.[10] Neural networks analysing data from methylation profiles or label-free optical imaging methods yield an intraoperative diagnosis with an accuracy of 70–95% within a few minutes.[90,91] Optical imaging methods that preserve the cytoarchitecture were developed to detect tumour cells within the infiltration zone in real-time,[92] and techniques such as hyperspectral imaging might be seamlessly integrated into the surgical workflow for tissue differentiation.[93] Such approaches might eventually allow tailoring of supramaximal resection according to the intraoperative tissue-based delineation of the expansive tumour. Quantification of tumour burden beyond the surgical target or epigenetic tumour subtyping using intraoperative tissue-analysis tools might distinguish localised from gliomatosis-like growth patterns, thus selecting patients with confined disease who could benefit the most from extensive resections (akin to a concept of minimal residual disease).[12,29] Tissue might also be retrieved from a stereotactic biopsy before open resection, which heralds the introduction of surgery into advanced treatment concepts, including window-of-opportunity or phase 0 trials;[94] thereby maximising the level of information derived from resection. With novel diagnostic methods and study designs on the horizon, we are being ushered into an era of precision surgical neuro-oncology.

Contributors

PK and J-CT were responsible for study concept and design. PK, JKWG, NTe, GR, and J-CT did the data collection. Data analysis and interpretation was performed by PK, JKWG, NTe, DPC, ASJ, MvdB, MW, OS, EOV-K, NTh, AJPEV, MMK, GR, SMC, SLH-J, MSB, and J-CT. PK and J-CT drafted the manuscript. The manuscript was revised by PK, JKWG, NTe, DPC, ASJ, MvdB, MW, OS, EOV-K, NTh, AJPEV, MMK, GR, SMC, SLH-J, MSB, and J-CT.

Declaration of interests

DPC serves on advisory boards for Lilly, GlaxoSmithKline, Incephalo, Boston Pharmaceuticals, Servier, Boston Scientific, and Pyramid Biosciences; receives consultant fees from the USA National Institutes of Health and Department of Defense; and fees from lectures for Merck. MvdB receives consultant fees from Celgene, Bristol Myers Squibb, Agios, Boehringer, AbbVie, Bayer, Carthera, Nerviano, and Genenta. MW receives fees for honoraria or advisory board participation and consulting from Bayer, CureVac, Medac, Novartis, Novocure, Orbus, and Philogen; and research grants from Quercis and Versameb. MMK receives consultant fees from Blue Earth Diagnostics, and research grants from EpicentRx and Blue Earth Diagnostics. J-CT receives research grants from Novocure and Munich Surgical Imaging; serves on an advisory board for AAA Novartis; and receives royalties from Springer. All other authors declare no competing interests.

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