INTERNATIONAL JOURNAL OF ADVANCED RESEARCH
International Peer-Reviewed Research Journal
ISSN (Online): 3106-7980 | ISSN (Print): 3106-7972
Volume 3 • Issue 7 • November 2026

SURGICAL RESECTION VERSUS BIOPSY WITH ADJUVANT THERAPY FOR HIGH GRADE GLIOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OVERALL SURVIVAL, PROGRESSION-FREE SURVIVAL, AND FUNCTIONAL OUTCOMES

Ahmed Mohamed Fouad Mostafa Elshafiey[*1], Chandni Maheshwari[2], Rizwan Zaffar[3], Abdullah Salem Alsharif[4], Al-Maqdad Yahya Al Shibani[5], Noora Mohammed Ashoor[6], Syed Shahid Ahmed Shah[7], Muhammad Ali Hassan[8], Umaid Hassan Malik[9], Qasim Bushir[10]

[*1]*University of Sharjah*
[2] *People Medical University of Health Sciences, Pakistan*
[3] *Punjab Institute of Neurosciences, Pakistan*
[4]*Sheikh Shakhbout Medical City*
[5]*Royal College of Surgeons*
[6]*Dubai Medical University*
[7]*Consultant Neurosurgeon, Shifa International Hospital, Islamabad, Pakistan*
[8]*Shifa College of Medicine, Islamabad, Pakistan*
[9]*Shifa College of Medicine, Pakistan*
[10] *Shifa College of Medicine, Pakistan*

[*1]fouadahmad11@gmail.com, [2]chandnimaheshwari331@gmail.com, [3]whorizwan@gmail.com, [4]abdullah.salem1111@gmail.com, [5]almaqdadalshibani@gmail.com, [6]noora.Otaq900@gmail.com, [7]drshahidshah@gmail.com, [8]ali_hassan.scm@stmu.edu.pk, [9]umaidhassan3@gmail.com, [10]qasimbushir1@gmail.com

DOI: https://doi.org/10.5281/zenodo.24128961

Keywords
High-grade glioma, glioblastoma, surgical resection, biopsy, overall survival, progression-free survival, functional outcomes, meta-analysis.

Article History
Received: 05 August 2026
Accepted: 19 October 2026
Published: 11 November 2026

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Corresponding Author: *
Ahmed Mohamed Fouad Mostafa Elshafiey

Abstract

Background *It is difficult to differentiate the benefit of surgical resection from choice of treatment and inherent functional differences for high-grade glioma.*

Objectives *To compare overall survival (OS), progression-free survival (PFS) and functional outcome between resection and biopsy in adults with postoperative adjuvant therapy or those under consideration for postoperative adjuvant therapy.*

Methods *The searches were performed in PubMed, Europe PMC and ClinicalTrials.gov from their inception until 11 October 2026. Eligible were original studies with an accessible original PDF. The screening, extraction and appraisal were carried out using AI but not by humans. Pooled restricted maximum-likelihood random-effects models with modified Hartung–Knapp confidence intervals were used to adjust hazard ratios (HRs). Evidence was analyzed separately by random and different surgical contrasts.*

Results *267 reports were assessed with 88 reports from 82 study families included. Four cohorts of patients with glioblastoma who received*

radiotherapy (517 patients) were included in the main analysis. Any resection was associated with longer OS than biopsy (HR 0.46, 95% CI 0.32–0.66; I^2=0%). Exploratory complete-resection analyses favoured surgery for OS across 10 cohorts (HR 0.47, 95% CI 0.38–0.57; I^2=15.8%) and PFS across five cohorts (HR 0.53, 95% CI 0.31–0.89; I^2=62.3%). One randomized trial reported no OS difference, and a preference for resection for PFS. There was a wide range of functional outcomes, which were not pooled. Very low certainty of observational evidence (provisional). Evidence coverage was not possible due to 484 unretrieved reports and 19 PDF-availability exclusions.

Conclusion *Observational glioblastoma cohorts have indicated that resection is linked to longer survival, but this is confounded and retrieval limitations make it challenging to make causal inferences. The benefits and functional advantages of randomized OS are still unknown.*

INTRODUCTION

High grade gliomas are malignant tumors of the brain with poor prognosis and high neurological impairment. The treatment is typically a combination of tissue diagnosis and surgical management, systemic therapy and/or radiotherapy. However, the best surgical approach is highly variable, particularly in older patients, those with poor performance status, extensive disease and/or tumors in functionally critical brain regions [14,20,35].

Biopsy is used to diagnose the tumour, but does not significantly reduce tumour burden, while surgical resection is used to obtain diagnostic tissue and to reduce tumour burden. Observational studies have found that longer survival is associated with greater resection, even with the use of the Response Assessment in Neuro-Oncology (RANO) classification of resection extent [3,11]. But, complete resection, partial resection and biopsy are different exposures. These categories can be confusing when determining if an observed association is related to any tumour removal or to minimal residual disease. Furthermore, there are differences in surgical definitions and postoperative treatment [7,18,31] that complicate comparisons.

Another significant challenge is the selection of treatment. There may be differences between patients who have undergone resection and those who have undergone biopsy in terms of age, baseline function, tumour location, resectability and capacity to receive adjuvant treatment. Thus, differences in survival could be due to the surgical treatment as well as to the underlying prognostic factors [14,20,35]. Randomized evidence offers another point of view: The ANOCEF trial in older patients did not demonstrate an overall survival benefit for resection, but progression-free survival was in favour of resection [17].

Survival is also not enough to measure the outcomes of surgery. Patients may experience neurological deterioration, loss of independence and cognitive impairment which can impact their life and treatment. Studies have therefore been conducted to assess postoperative performance, permanent neurological deficits, cognition and functional recovery, in addition to survival [5,15,29,33]. But the different instruments used to assess, the different definitions of outcomes, and the different follow-up periods make it difficult to make direct comparisons. Other surgical complications (e.g. those that occur after surgery) should also be distinguished from the continued disability and deterioration due to disease progression.

A synthesis that dissects surgical contrasts, treatment contexts, and study designs is thus required to elucidate the available evidence. This systematic review and meta-analysis aimed to compare overall survival, progression-free survival and functional outcomes following surgical resection versus diagnostic biopsy in adults with high-grade glioma who were deemed for postoperative adjuvant therapy. When clinically appropriate, randomized evidence was reviewed

independently and adjusted observational estimates were synthesized, and functional outcomes were evaluated according to the definition of the outcomes and when they were reported.

Methods

Review design and reporting

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement [26] were followed to report this systematic review and meta-analysis. No prospective registration of the protocol was done. The eligibility criteria and analysis specifications were further refined, which were post hoc, during the review.

Eligibility criteria

Original studies were eligible if they included adults (age ≥18 years) with newly diagnosed intracranial high-grade diffuse glioma, included a surgical resection group and a group of patients undergoing a diagnostic biopsy, and included a relevant survival or functional outcome. To be eligible, there needed to be a clear statement of the adult population, an eligible age range or a separate adult sub-group.

The following were kept when applicable: historical grade III gliomas, mixed high grade populations, molecularly defined grade 4 tumours and anatomically restricted cohorts, which were separated from the primary histological-glioblastoma synthesis. The biopsy sampling during resection was not a biopsy-only comparator. A copy of the original publisher or accepted-manuscript PDF was required. Original preprints were accepted as grey literature, and were not considered to be peer-reviewed articles. Only reviews, conference abstracts, protocols without outcome data, and reports without a separable eligible population, or surgical comparison were not included.

Information sources and search strategy

The databases PubMed, Europe PMC and ClinicalTrials.gov were searched on 11 October 2026, the date of the search and of the publication or registration of the results. Records from January 1, 1900 were searched in the literature. Search for glioblastoma, high grade glioma, malignant glioma, anaplastic astrocytoma, or anaplastic oligodendroglioma and biopsy, surgical resection, debulking or surgery. In PubMed, the Medical Subject Headings and title/abstract terms were used, while in Europe PMC title/abstract terms were used for the PubMed searches.

There was no language or open-access filter used for the database queries. In the retrieval of the report and eligibility assessment, availability of PDFs was assessed. The clinical trials registrations in ClinicalTrials.gov were screened independently and connected to publications if possible. The publisher websites, repositories, PMC and identifier-based OpenAlex searches were used to retrieve, but were not added to the list of identification databases. All the queries and raw exports were stored in the supplementary search archive.

Study selection and report linkage

The selection process was done with the help of AI and is not duplicated by human reviewers. Title and metadata were screened for all unique records and abstracts were individually reviewed for selected records. All candidates who did not get resolved went on to full report retrieval. The reasons for the exclusion of full reports and unsuccessful retrieval were recorded separately.

Identification of duplicates was done by exact PubMed identifiers and normalized digital object identifiers. Instead of being automatically merged, the same types of titles were marked. Parent reports were matched with database records and if there was a match, they were counted as additional reports. Companion publications and known overlapping cohorts were linked into study families. Separate counts were made of the number of reports, study families and quantitative comparisons. An investigation contact was not made.

Data extraction and outcomes

With the help of AI, study design, population, age eligibility, cohort and analysis denominators, tumour classification, surgical definitions,

adjuvant treatment, follow-up, outcome definitions, effect estimates, confidence intervals, adjustment variables and source locations were extracted. The differences in denominators or model-reference categories were recorded.

Overall survival, progression-free survival, and functional outcomes (performance status, neurological deficits, cognition, independence, health-related quality of life) were the results. The assessment times and number of cases available were recorded. Persistent disability was differentiated from immediate complications. Time to progression and event-free survival were not considered to be progression-free survival.

Risk of bias and certainty assessment

The following factors were deemed to be confounding, treatment selection, baseline performance, resectability, tumour characteristics, postoperative treatment, missing data, outcome measurement, and selection based on survival or treatment completion: were considered for a structured AI-assisted appraisal. Randomized evidence was analyzed for post-randomization exclusions, crossover and awareness of allocation and outcome assessment.

These appraisals were not independently validated ROBINS-I or RoB 2 appraisals. Certainty judgments at the outcome level were based on design limitations, confounding, inconsistency, imprecision, applicability and availability restrictions, and were provisional.

Statistical analysis

The primary synthesis was a comparison of overall survival (OS) of clinical cohorts of adults receiving radiotherapy after any resection or biopsy of glioblastoma. Each of these study-defined groups (complete resection, partial resection, mixed-adjuvant cohorts, registry estimates, and randomized surgical-policy evidence) were analyzed separately.

The use of restricted maximum-likelihood random-effects models was used to combine hazard ratios on a log scale. The reported 95% confidence intervals were used to calculate the standard errors. Reversed comparisons were reversed and so were the confidence limits. The safeguarded modified Hartung–Knapp intervals [30] were used for pooled inference with *k*−1 degrees of freedom. Cochran's Q, I^2 and τ^2 were used to assess the heterogeneity.

One estimate was provided for each study for each synthesis. Shared-reference contrasts were combined without the use of covariance. Survival medians were not calculated and did not have hazard ratios. If definitions and/or assessment times differed, the functional risk ratios were computed from the number of events reported, and log-Wald confidence intervals were used.

Leave-one-out analyses, exclusion of an alternative complete resection definition, exclusion of selected postoperative-covariate models and inclusion of mixed-adjuvant clinical cohorts were performed as sensitivity analyses. The exploratory prediction intervals were based on a distribution of the *t* type with k−2 degrees of freedom. Funnel plots and Egger regression were only used for syntheses with 10 or more estimates. No meta-regression or trim and fill correction was done.

Python 3.12.14, NumPy 2.3.5, SciPy 1.17.0, and Matplotlib 3.10.8 were used for analyses and creating figures. The two-sided p values < 0.05 were considered statistically significant.

Results

Study selection

The full database exports found 4,156 literature records, 1,991 of which were from PubMed and 2,165 from Europe PMC. 1,744 duplicate records were removed based on PMID or DOI matching, leaving 2,412 records for screening. A total of 1,663 records were excluded due to initial title screening, abstract review (where performed) and final publication-type validation. The 749 database records that were attempted to be retrieved were not retrieved using the recorded publisher, repository and identifier-locator attempts; 484 of these records were not retrieved. Full-report assessment was conducted for the remaining 265 database reports.

Two more reports were not found in the database searches but were retrieved and evaluated, resulting in 267 reports being evaluated. Following

179 report exclusions, 88 reports were included and grouped into 82 study families. Reports were counted as separate reports and as part of their study family in the case of linked reports. There are several investigations that overlap, so family counts do not provide a completely independent participant population, and a total number of participants was not derived by adding all reports.

ClinicalTrials.gov yielded 278 registrations. 272 were excluded due to detailed screening, two programmes had outcome reports (ANOCEF and the SIND cognition programme) and four programmes had no outcome report. These registrations did not include independent outcome studies (Figure 1B).

Study Selection Counts

Table 1. Study selection counts and full-report exclusion reasons

Stage or reason	Number
Literature records after deduplication	2,412
Initial screening and metadata exclusions	1,663
Database reports sought / not retrieved	749 / 484
Database reports assessed	265
Additional unique supplied reports assessed	2
All reports assessed	267
Adjuvant treatment context not established	4
Ineligible or inseparable population or clinical stage	39
Ineligible or inseparable surgical comparator	76
No eligible surgical survival or functional outcome	36
Publication type or no original results	5
Original PDF not retrieved	19
All full-report exclusions	179
Included reports / study families	88 / 82

Selection counts and mutually exclusive full-report exclusion categories are reported in Table 1 and Figure 1A. Reports not retrieved were distinguished from assessed reports excluded for clinical ineligibility. The original-PDF availability restriction may introduce availability bias.

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PRISMA Flow Diagram

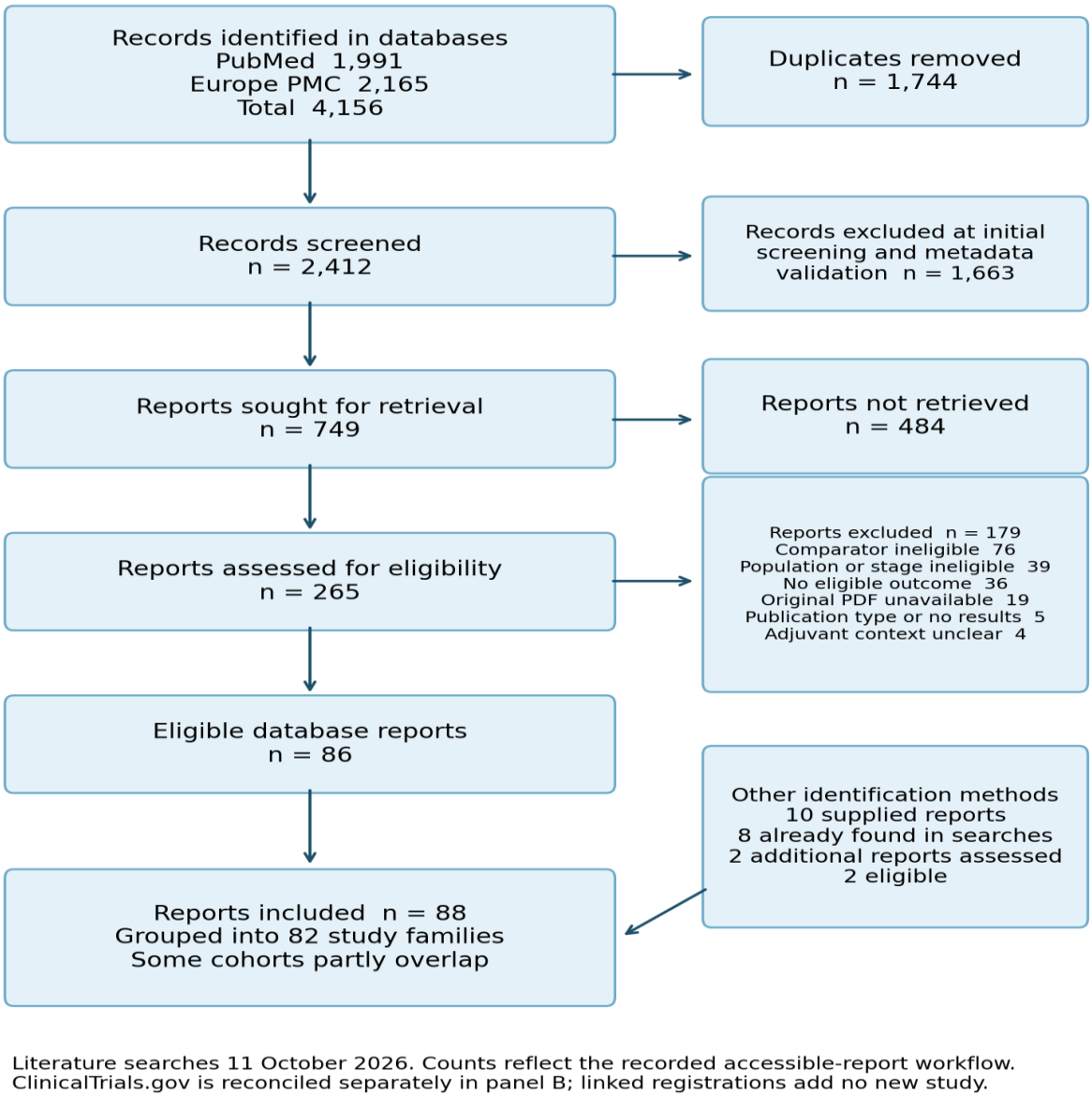
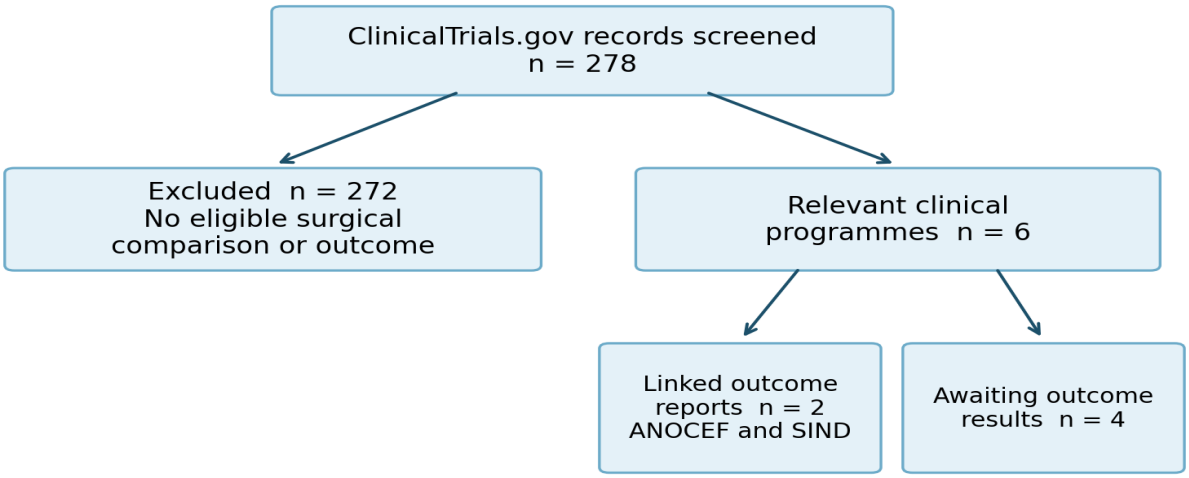


Figure 1A. PRISMA 2020 adapted literature flow. The supplied-report route contributes two additional reports after eight overlaps are removed. Counts distinguish reports, study families and pooled comparisons.

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Advanced Research

Figure 1B. ClinicalTrials.gov screening and publication linkage. Four programmes await results: NCT06146738, NCT06146725, NCT05641220 and NCT07162324. NCT04007185 has UNKNOWN registry status and a linked SIND outcome preprint; it is not labelled completed.

Study and Treatment Characteristics

The evidence covers older historical high-grade glioma series, glioblastoma series, molecularly defined tumours, anatomically restricted cohorts and elderly cohorts. The definitions of resection ranged from any debulking to complete resection as defined by MRI. When comparisons were made between histological grade III and modern molecular grade 4, between partial resection and complete resection, these were maintained. The inventory included in the report contains the identifier of the report, its DOI and the link to the study-family (Table S1).

The four clinical cohorts of glioblastoma analyzed in the primary observational analysis consisted of 104 patients from Biau et al. [2], 42 from Lim et al. [20], 104 from Glynn et al. [8] and 267 from Alnaami et al. [1] all of whom received radiotherapy with or without chemotherapy. The total number of participants in these cohorts was 517. Combined arm totals are not provided as they vary from one report to another by Alnaami. Lim's study was of thalamic glioblastoma, while the other studies involved larger clinical populations. The studies did not give a randomized estimate of the initial surgical choice, and receipt of radiotherapy alone may select fitter postoperative survivors. At least one pooled OS or PFS analysis was performed for 15 different observational cohorts; the randomized trial was analyzed separately. The 88 reports included were separate from those that were used for quantitative synthesis.

Only contrasts with a clear diagnostic-biopsy group and an effect orientation that could be verified were pooled. Ordinal extent-of-resection coefficients, merged partial-resection/biopsy comparators, odds ratios labeled as hazards, median survival ratios, and contrasts where the shared-reference covariance was not available were not replaced by binary hazard ratios.

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Overall survival

Any resection versus biopsy in radiotherapy-treated clinical cohorts

In all four cohorts (n=517), there was a lower mortality rate with any resection compared with biopsy (random-effects HR 0.46, 95% CI 0.32–0.66; modified Hartung–Knapp p=0.006). Statistical heterogeneity was not detected (I^2=0%; Q=2.33, df=3, p=0.506; REML τ^2=0.0000). Low heterogeneity does not exclude differences in treatment era, anatomical selection, baseline function or confounder adjustment. The observational association can't prove that there is a survival benefit.

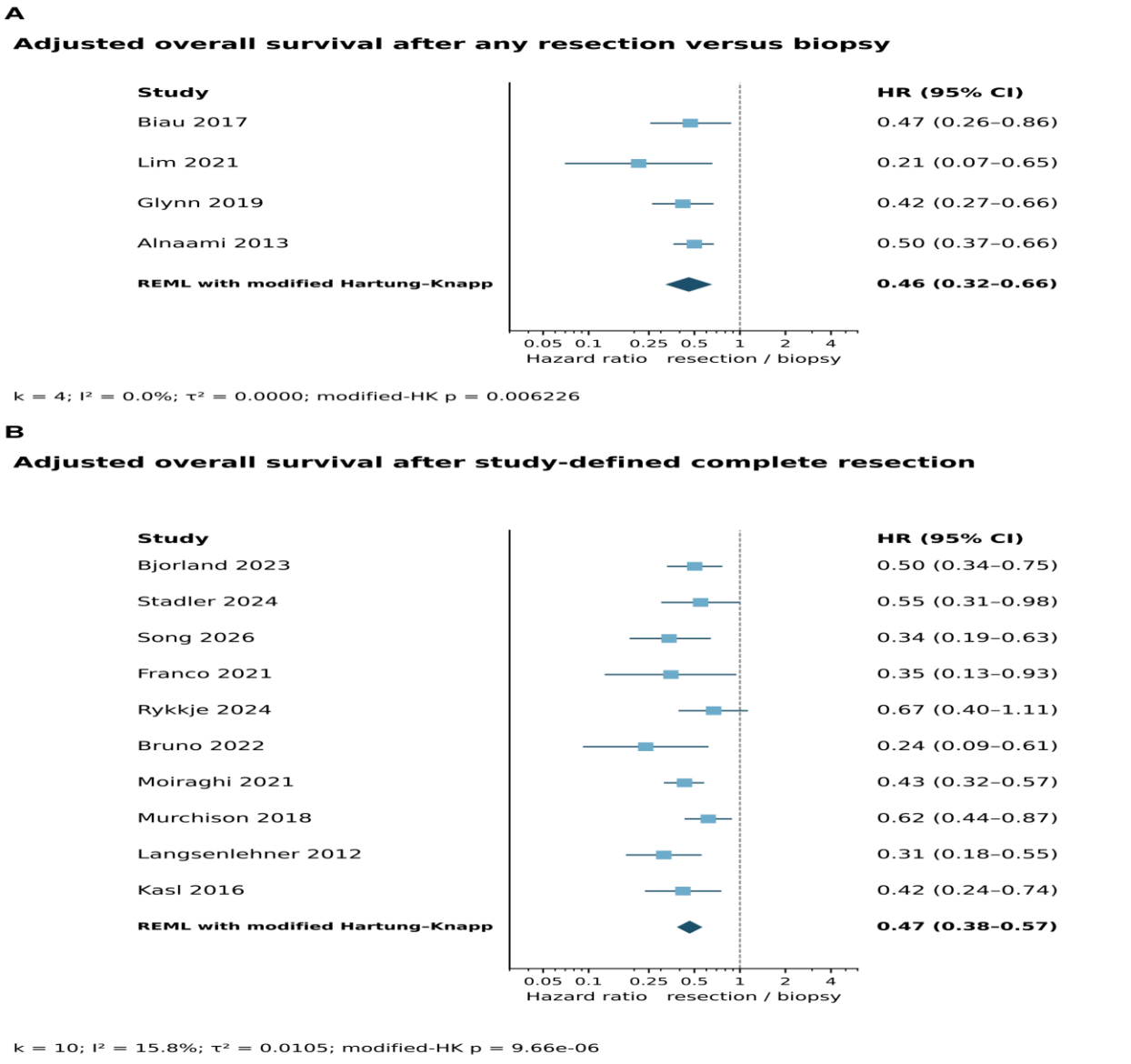


Figure 2. Adjusted overall survival after resection versus biopsy. A, Primary analysis of any resection in radiotherapy-treated clinical cohorts. B, Exploratory analysis of study-defined complete resection. Hazard ratios below 1 favour resection. Pooled estimates use REML with safeguarded modified Hartung–Knapp confidence intervals. Definitions and covariate adjustment vary between studies.

Table 2. Primary adjusted survival estimates

Study	Cohort N	Resection versus biopsy HR	Source location in original report
Biau 2017 [2]	104	0.47 (0.26–0.86)	Table 2 model 1
Lim 2021 [20]	42	0.21 (0.07–0.65)	Table 2
Glynn 2019 [8]	104	0.42 (0.27–0.66)	Table 4 full-cohort Cox model
Alnaami 2013 [1]	267	0.50 (0.37–0.66)	English abstract and Results multivariable Cox model

Adjusted models differed: Biau included clinical prognostic/treatment variables; Lim adjusted for age, preoperative KPS and Ki-67; the Irish model included age, ECOG, radiation dose, concurrent chemotherapy and radiotherapy delay; Alnaami included age, treatment regimen and radiotherapy delay. Model differences remain a limitation.

Extent specific overall survival

There were 10 adjusted cohorts in the exploratory study-defined complete-resection comparison. Complete resection was associated with lower mortality than biopsy (HR 0.47, 95% CI 0.38–0.57; p<0.001; I^2=15.8%; τ^2=0.0105). These estimates are for a more selective surgical exposure than the primary any-resection comparison and include mixed postoperative treatment. These are not to be understood as a second assessment of the same intervention.

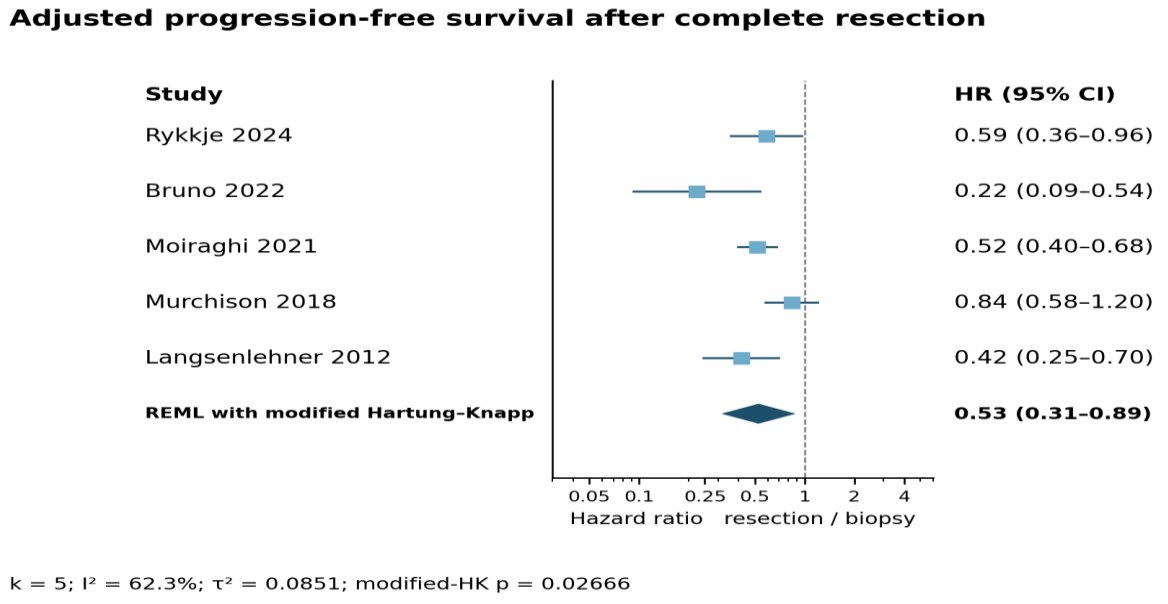


Figure 3. Exploratory adjusted progression-free survival after study-defined complete resection versus biopsy. The small number of cohorts and heterogeneous definitions limit precision and generalizability.

Extent Specific Estimates

Table 3. Extent-specific adjusted estimates

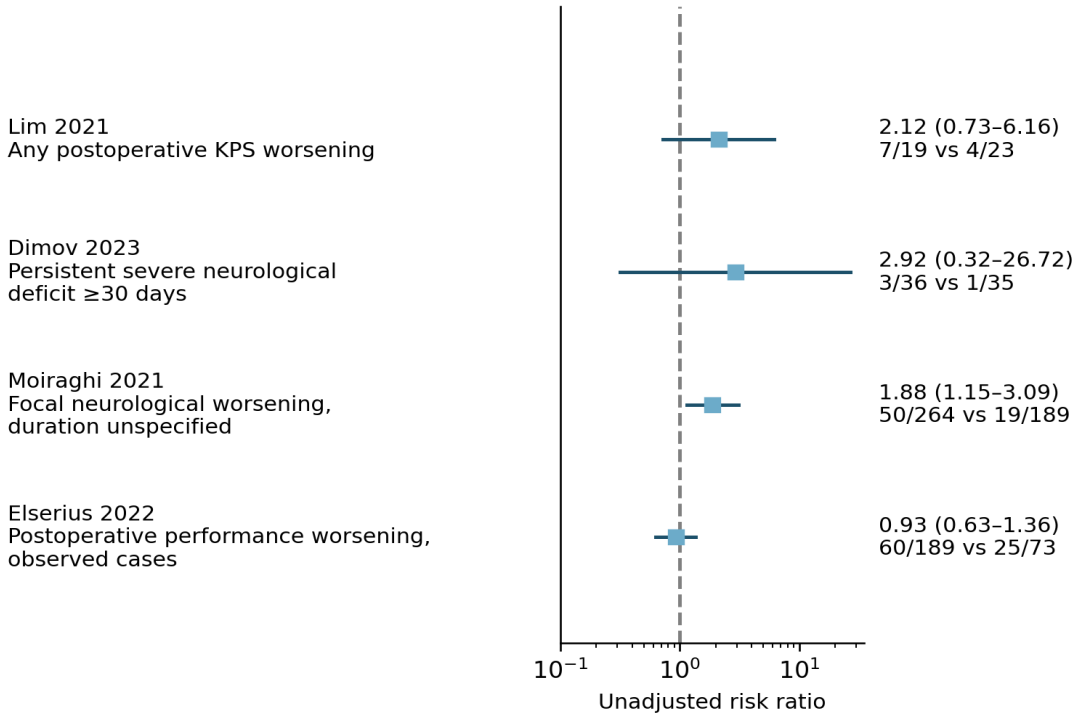
Study	OS HR (95% CI)	PFS HR (95% CI)	OS source location
Bjorland 2023 [3]	0.50 (0.34–0.75)	Not pooled	Table 3
Stadler 2024 [35]	0.55 (0.31–0.98)	Not pooled	Table 4
Song 2026 [34]	0.34 (0.19–0.63)	Not pooled	Table 2
Franco 2021 [7]	0.35 (0.13–0.93)	Not pooled	Table 6
Rykkje 2024 [31]	0.67 (0.40–1.11)	0.59 (0.36–0.96)	Table 2
Bruno 2022 [4]	0.24 (0.09–0.61)	0.22 (0.09–0.54)	Table 9
Moiraghi 2021 [24]	0.43 (0.32–0.57)	0.52 (0.40–0.68)	Table 3
Murchison 2018 [25]	0.62 (0.44–0.87)	0.84 (0.58–1.20)	Table 4
Langsenlehner 2012 [18]	0.31 (0.18–0.55)	0.42 (0.25–0.70)	Table 3; biopsy versus total inverted
Kasl 2016 [12]	0.42 (0.24–0.74)	Not pooled	Original PDF Table 2; GTR versus biopsy explicit

Franco defined gross-total removal as <5% residual enhancing tumour rather than strictly no residual tumour. Langsenlehner used the study-reported total-resection category; only a subset had no visible residual tumour on postoperative imaging. Study-specific categories were retained because they could not be harmonized to a single postoperative MRI threshold.

Progression free survival

A primary pooled PFS estimate for any-resection was not derived from compatible, verified adjusted clinical comparisons. In the separate complete-resection analysis, 5 cohorts contributed PFS estimates (HR 0.53, 95% CI 0.31–0.89; p=0.027; I^2=62.3%; τ^2=0.0851). Heterogeneity was substantial. Definitions and assessment schedules were different; time to progression and event-free-survival were separated from PFS. The exploratory 95% prediction interval was 0.18–1.54, which contained the null value.

Functional outcomes shown individually



Higher RR indicates more worsening after resection. Different definitions and assessment times prevent pooling. Intervals are calculated using the log-Wald method. Adjusted Dutch KPS results are reported in Table 4A.

Figure 4. Individual unadjusted functional risk ratios calculated from source counts. Definitions and timing differ; estimates are not pooled. Ratios are sensitive to baseline severity, treatment selection and postoperative disease progression.

Partial resection and other contrasts

The adult perfusion-MRI cohort [27] (n=135; 96 partial resections and 39 biopsies) specifically selected patients with >50% residual tumour. Its adjusted partial-resection/biopsy estimate was 1.01 (95% CI 0.61–1.67) for OS and 0.69 (0.43–1.11) for PFS. This contrast was not pooled with any resection or complete resection. The prospective mixed-grade NLR cohort [32] was also included as it represented historical grade III/IV, and adjusted for a post-treatment biomarker, with an OS HR of 0.31 (0.16–0.61).

Reports that did not have a complete set of reference categories, internally inconsistent effect estimates, or inconsistent model coding were included in the narrative synthesis but not in the appropriate quantitative analysis. Hazard ratios were not calculated for survival medians.

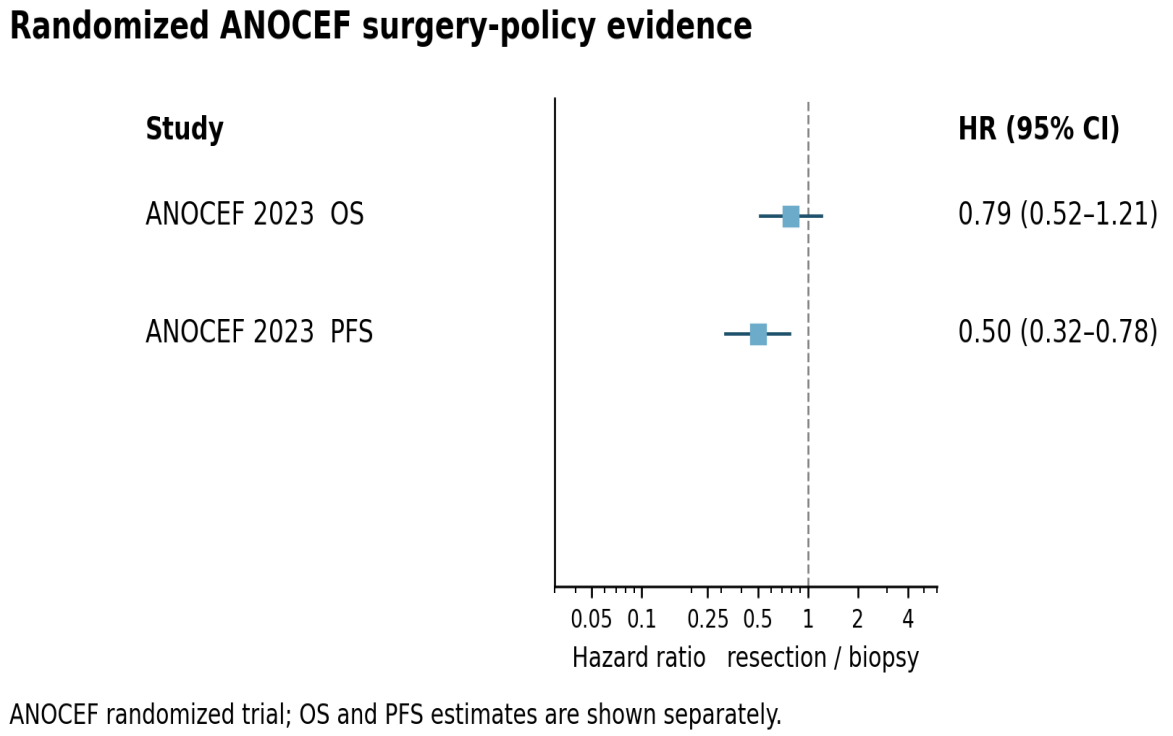


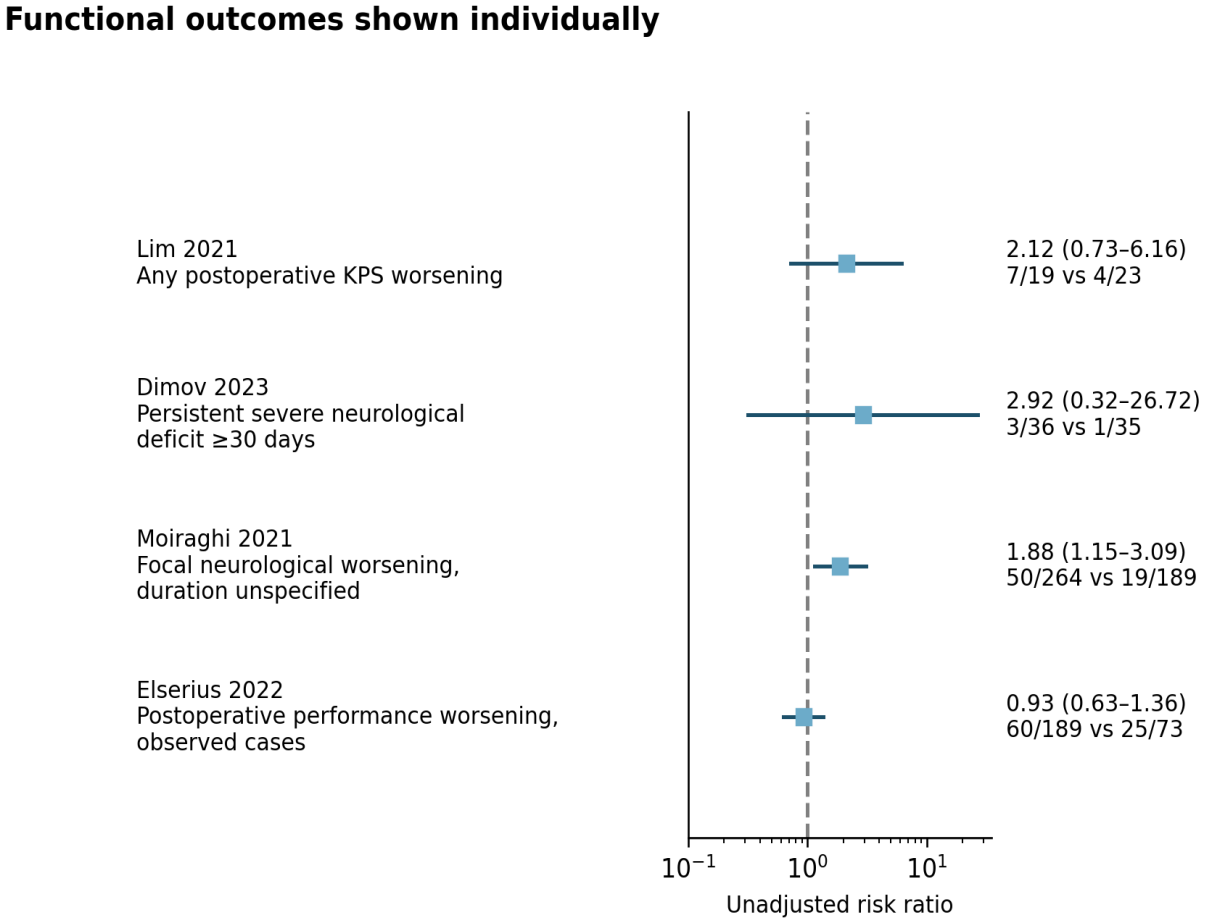
Figure 5. ANOCEF assigned surgery-policy estimates, shown separately by outcome. Overall-survival and progression-free-survival estimates from the same trial are shown separately.

Monthly KPS evolution favoured resection (time-by-treatment OR 1.19, 95% CI 1.09–1.29). The between-group MMSE slope difference was 0.22 (−0.02 to 0.46). These are longitudinal model parameters, not standardized mean differences or individual-patient event risks. Immediate motor impairment occurred in 5/50 versus 7/51; any immediate complication occurred in 16/50 versus 13/51. Complications were not equated with persistent functional disability.

Functional and Quality of Life Outcomes

Functional measures were too clinically and temporally diverse to be defensible for a common pooled effect. Postoperative KPS, ECOG, cognition, severe persistent neurological deficits, seizures, and discharge destination/health-related quality of life were evaluated at various times. Available case and survivor only denominators were used and postoperative functional status was not considered change from baseline.

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH
International Peer-Reviewed Research Journal
ISSN (Online): 3106-7980 | ISSN (Print): 3106-7972
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Higher RR indicates more worsening after resection. Different definitions and assessment times prevent pooling. Intervals are calculated using the log-Wald method. Adjusted Dutch KPS results are reported in Table 4A.

Figure 6. Individual unadjusted functional risk ratios, calculated from source counts. Definitions and timing differ, and the estimates are not pooled. These ratios are sensitive to baseline severity, treatment selection and postoperative disease progression.

Functional outcome measures

Table 4A. Additional functional comparisons retained separately

Study	Outcome and effect	Interpretation
Dutch QRNS 2021 [15]	Adjusted biopsy/resection OR 2.3 (1.9–2.7) for >10-point KPS decline at six weeks; inverse resection/biopsy OR 0.43 (0.37–0.53).	KPS data were available for 2,003 resection and 845 biopsy patients. Analyses used observed outcome denominators; early progression may contribute to decline.
Elserius 2022 [6]	Adjusted resection/biopsy OR 8.15 (1.80–37.77) for postoperative performance improvement.	Model n=262; adjustment includes preoperative performance. Improvement differs from the worsening endpoint in Figure 6.
Pöppe 2026 [29]	Table 1 KPS improvement 171 vs 57; maintained/gained independence 316 vs 114.	Available-case denominators varied, and narrative percentages differed from the table. A full-cohort risk ratio was not calculated.
Song 2026 [34]	ECOG ≥2 at three months: 17/49 vs 3/6 among assessed survivors.	The comparison used assessed survivors rather than the complete surgical groups.
Sharma 2023 [33]	Biopsy/subtotal-resection adjusted cognitive-impairment HR 2.88 (0.97–8.58).	Inverse subtotal/biopsy HR 0.35 (0.12–1.03); endpoint is MMSE-defined cognitive impairment over time.

Quality-of-life data did not provide compatible arm-level means, standard deviations and timepoints for a pooled mean difference or standardized mean difference. This absence of a pooled estimate is an outcome-reporting limitation, not evidence of functional equivalence.

Table 4B. Individual postoperative functional deterioration outcomes

Study and endpoint	Resection events / assessed	Biopsy events / assessed	Unadjusted RR (95% CI)
Lim 2021 [20] Any postoperative KPS worsening	7/19	4/23	2.12 (0.73–6.16)
Dimov 2023 [5] Persistent severe neurological deficit ≥30 days	3/36	1/35	2.92 (0.32–26.72)
Moiraghi 2021 [24] Focal neurological worsening, duration unspecified	50/264	19/189	1.88 (1.15–3.09)
Elserius 2022 [6] Postoperative performance worsening, observed cases	60/189	25/73	0.93 (0.63–1.36)

Risk ratios were calculated from reported event counts. These outcomes were not pooled because their definitions and timing differed.

Sensitivity analyses and reporting bias

Expanding the main comparison to validated clinical cohorts of mixed postoperative treatment resulted in 5 adjusted cohorts and an OS HR of 0.51 (0.33–0.79) (I^2=56.9%; τ^2=0.0554; p=0.013). This sensitivity is across treatment contexts and does not exclude patients who are treated with the same adjuvant (Figure S1).

The HRs for the exclusion of each of the main cohorts were pooled and ranged from 0.41 to 0.47, with all protected intervals below 1. HR 0.47 (0.29–0.78) was obtained when the anatomically restricted Lim cohort was excluded. These checks are based on dependence on individual estimates, not residual confounding.

OS HR 0.47 (0.38–0.58) was obtained after excluding the <5%-residual definition for Franco. Three models were excluded from the analysis because of the different extent-specific covariates used in the postoperative or salvage treatment models (Bruno, Moiraghi and Langsenlehner), resulting in HR 0.52 (0.41–0.66). Both sensitivity do not imply that other sets of covariates are unbiased.

Estimates were provided separately for the registry coded estimates. Mak reported [21] adjusted any-resection OS HR 0.59 (0.54–0.63; model n=4,282) with very limited performance status information. Lee reported [19] HR 0.50 (0.44–0.58) after excluding deaths within 90 days. The following estimates were not used in the primary pool. Overlap in the populations of the shared registries or the overlap of clinical cohorts within the same registry was not considered a separate effect in the same synthesis.

The complete-resection OS analysis (k=10) resulted in an exploratory Egger regression with p=0.197 (Figure S3). This test is not very powerful and is unable to prove the absence of publication bias. No formal asymmetry tests were performed for the four study primary analysis or the five study PFS analysis. There was no trim and fill correction or meta-regression. Those procedures are difficult to interpret due to small study numbers, heterogeneous exposures and unmeasured selection.

Table 5. Primary leave-one-out sensitivity analyses

Omitted cohort	Remaining k	Pooled HR (95% CI)	I^2
Biau 2017	3	0.46 (0.26–0.80)	14.1%
Lim 2021	3	0.47 (0.29–0.78)	0.0%
Glynn 2019	3	0.47 (0.27–0.84)	5.8%
Alnaami 2013	3	0.41 (0.19–0.86)	0.0%

Risk of bias and certainty

The structured AI-assisted appraisal highlighted important confounding issues in nonrandomized surgical comparisons, particularly baseline performance, resectability, tumour location, burden, frailty and clinician/patient selection. Postoperative treatment and salvage therapy may be mediators instead of baseline confounders. There were several reports that explicitly required survival, follow up or treatment completion to be included, which raised critical selection concerns. Estimates made with these exclusions were excluded from the primary synthesis.

The post-randomization modified population and the lack of information on exclusions were some concerns raised by the ANOCEF OS/PFS appraisal. Objective functional outcomes are more of an issue than open allocation with regards to death. Risk-of-bias judgments are one AI-assisted judgment with study-specific notes, no independent human judgment or validated formal ROBINS-I/RoB 2 judgment. Study level appraisal

summaries and provisional outcome level certainty judgments are provided in Supplementary File 1, Tables S3–S4.

Discussion

This review revealed that there was an association between surgical resection and longer overall survival in cohorts of patients treated with radiotherapy for glioblastoma. The exploratory analyses of study-defined complete resection also showed a survival benefit for surgery in overall and progression-free survival. The randomized evidence, however, did not show an overall-survival benefit and outcomes of function were too variable to be pooled. The results thus suggest a positive observation association but do not provide a measure of the magnitude of a surgical benefit.

Interpretation of survival outcomes

To avoid the confounding of any resection with complete resection comparisons, the primary analysis was intentionally conducted separately. Any tumour removal and near complete removal are two different surgical exposures, and have different needs for anatomical accessibility and patient selection. The good complete-resection rates are in line with the literature on the prognostic importance of the residual tumour burden (RANO resect classification) [11]. However, the prognostic association does not imply that extending the resection would have the same benefit for all patients. There may be systematic differences between patients who are eligible for extensive surgery and those who have biopsies.

The results are still subject to interpretation due to confounding by indication. Surgical selection and subsequent survival is influenced by baseline performance status, tumour location, multifocality, frailty and anticipated neurological risk. Measured differences can be corrected for with statistical adjustment, but not for resectability or clinical judgment. Limiting the primary synthesis to radiotherapy-treated cohorts increases the comparability of treatment context, but may lead to selection bias due to the difference in radiotherapy treatment based on postoperative survival and functional recovery. The pooled estimate is therefore not necessarily representative of the entire population of patients who might be eligible for surgery.

The lack of heterogeneity detected in the primary analysis should also be taken with a grain of salt. There is limited information on between-study variation from four cohorts and similar estimates can result from common biases. Leave-one-out analyses indicated that the association was not sensitive to any particular cohort, but this does not address residual confounding. Similarly, sensitivity analyses of the entire resection also suggest a favorable result, but not a causal one, of the numerical consistency of the available data.

Randomized evidence and progression-free survival

The observational results are complemented by the results of the ANOCEF trial. It did not show a statistically significant difference in overall-survival, but showed a statistically significant difference in progression-free survival in favour of surgery [17]. If there is no difference in overall survival, this should not be considered as evidence of equivalence: the confidence interval is still compatible with clinically relevant benefit and some harm. In addition, the trial was conducted with older patients, which restricts the applicability of the results to younger patients or other treatment environments.

The exploratory observational PFS synthesis also supported complete resection, but there was a significant amount of heterogeneity and a prediction interval that included the null value, suggesting uncertainty regarding the association in another similar setting. This may be due to the different definitions of surgery, different treatment and follow-up protocols after surgery, and different methods of assessing the progression of the disease. Therefore, PFS and overall survival should not be equated and better disease control does not necessarily mean better survival.

Functional outcomes and clinical implications

There was no consistent evidence of the advantage of either surgical approach. Performance deterioration, cognitive impairment and independence measure different aspects of recovery, and were evaluated at different time points. These differences warranted the use of individual estimates instead of calculating a pooled functional effect. The same applies to registry research, which is the case for postoperative complications versus subsequent performance decline [15].

Particular care needs to be taken with available-case and survivor only analyses. Patients who survive and are followed up may not be the same as those who are not followed up, and a postoperative score may not be a measure of change from baseline. The apparent discrepancy between functional studies might thus be due to different populations, endpoints and assessment time points, and not to conflicting surgical effects. These results provide justification to consider survival and function in tandem when considering surgical options. The review is not able to decide on the best amount of resection for a specific patient, nor can it recommend more extensive surgery, even if there is no neurological risk. Resectability, baseline independence, expected deficits, postoperative treatment options and patient preferences are all factors to consider when making decisions. Biopsy is a comparator that is important and the recipients will have a different clinical risk profile.

Strengths and limitations

One advantage of this review was the distinction of surgical contrasts, treatment contexts and study designs. Observational estimates were adjusted and synthesized separately from randomized estimates, and linked reports were separated from quantitative reports. Study-specific functional definitions were preserved, which helped to minimize the potential for a clinically misleading pooled outcome. Uncertainty due to small meta-analyses was also dealt with using modified Hartung–Knapp inference [30].

There are a number of restrictions that severely limit confidence. The majority of quantitative evidence was observational and data was not always adjusted for and may have been overlapping. Comparability with molecularly defined glioma of the modern era was restricted by historical classifications and treatment eras.Historical classifications and treatment eras restricted comparability with molecularly defined glioma of the modern era. The main analysis was restricted to four cohorts and the wider complete-resection analyses were a more selective exposure. There was also incomplete evidence retrieval: 484 database reports were not retrieved and 19 more were not retrieved due to the lack of an original PDF. These restrictions can lead to availability bias, but it is not possible to determine the direction of the bias. No human verification was performed, and screening, extraction and appraisal were performed in one workflow, assisted by AI. Assessment of risk of bias and certainty are thus provisional. The chances of review-level bias are further increased by the lack of prospective registration and post hoc refinements. Lastly, the exploratory Egger test was not significant, which does not rule out publication bias.

Implications for future research

Future studies should use reproducible postoperative imaging criteria for surgical exposures and biopsy should be reported separately from partial resection. Baseline neurological status, frailty, tumour anatomy, molecular classification and treatment should be recorded, and baseline confounders should be differentiated from postoperative mediators in prospective comparisons. Functional assessments should contain baseline measures, pre-specified follow-up time points, reasons for missing data and patient reported outcomes. Randomized studies (where possible) and well-designed prospective comparative cohorts are required to define which patients benefit from survival without unacceptable loss of function.

Conclusion

Selected observational glioblastoma cohorts suggested resection was linked to longer survival, but there was residual confounding and incomplete retrieval that precludes causal interpretation. Randomized evidence did not show an overall-survival benefit, but did show a PFS benefit for resection. The functional benefits have yet to be determined. The decision to have surgery should take into account the risk of neurological complications and the patient's preferences, as well as the possibility of controlling the disease.

REFERENCES

Alnaami, I., VanderPluym, J., Murtha, A., Walling, S., Mehta, V., Gourishankar, S., & Senthilselvan, A. (2013). The potential impact of delayed radiation therapy on patients with glioblastoma. Canadian Journal of Neurological Sciences, 40(6), 790–794. https://doi.org/10.1017/S0317167100015900

Biau, J., Chautard, E., De Schlichting, E., Dupic, G., Pereira, B., Fogli, A., Müller-Barthélémy, M., Dalloz, P., Khalil, T., Dillies, A. F., Durando, X., Godfraind, C., & Verrelle, P. (2017). Radiotherapy plus temozolomide in elderly patients with glioblastoma: A "real-life" report. Radiation Oncology, 12(1), Article 197. https://doi.org/10.1186/s13014-017-0929-2

Bjorland, L. S., Mahesparan, R., Fluge, Ø., Gilje, B., Dæhli Kurz, K., & Farbu, E. (2023). Impact of extent of resection on outcome from glioblastoma using the RANO resect group classification system: A retrospective, population-based cohort study. Neuro-Oncology Advances, 5(1), Article vdad126. https://doi.org/10.1093/noajnl/vdad126

Bruno, F., Pellerino, A., Pronello, E., Palmiero, R., Bertero, L., Mantovani, C., Bianconi, A., Melcarne, A., Garbossa, D., & Rudà, R. (2022). Elderly gliobastoma patients: The impact of surgery and adjuvant treatments on survival: A single institution experience. Brain Sciences, 12(5), Article 632. https://doi.org/10.3390/brainsci12050632

Dimov, D., Brainman, D., Berger, B., Coras, R., Grote, A., & Simon, M. (2023). The role of cytoreductive surgery in multifocal/multicentric glioblastomas. Journal of Neuro-Oncology, 164(2), 447–459. https://doi.org/10.1007/s11060-023-04410-7

Elserius, A. S. L., Hodson, J., Zisakis, A., & Ughratdar, I. (2022). Is there a limited value of cytoreductive surgery in elderly patients with malignant gliomas? Surgical Neurology International, 13, Article 320. https://doi.org/10.25259/SNI_438_2022 PubMed

Franco, P., Delev, D., Cipriani, D., Neidert, N., Kellner, E., Masalha, W., Mercas, B., Mader, I., Reinacher, P., Weyerbrock, A., Fung, C., Beck, J., Heiland, D. H., & Schnell, O. (2021). Surgery for IDH1/2 wild-type glioma invading the corpus callosum. Acta Neurochirurgica, 163(4), 937–945. https://doi.org/10.1007/s00701-020-04623-z

Glynn, A. M., Rangaswamy, G., O'Shea, J., Dunne, M., Grogan, R., MacNally, S., Fitzpatrick, D., & Faul, C. (2019). Glioblastoma multiforme in the over 70's: "To treat or not to treat with radiotherapy?" Cancer Medicine, 8(10), 4669–4677. https://doi.org/10.1002/cam4.2398

Jankovic, D., Thavarajasingam, S. G., Scurtu, D., Baby, M. V., Kramer, A., Weller, J., Stöcklein, V., Brockmann, M. A., Sommer, C., Leukel, P., Stockinger, M., Krenzlin, H., Keric, N., Ringel, F., & Kalasauskas, D. (2026). Maximal resection improves survival in MGMT methylated very elderly glioblastoma patients. Journal of Neuro-Oncology, 176(3), Article 202. https://doi.org/10.1007/s11060-025-05417-y

Johnstad, C., Reinertsen, I., Bouget, D., Rapi, O., Jakola, A. S., & Solheim, O. (2026). Population-based validation of the RANO categories for extent of resection in glioblastoma. Neuro-Oncology Advances, 8(1), Article vdag170. https://doi.org/10.1093/noajnl/vdag170

Karschnia, P., Young, J. S., Dono, A., Häni, L., Sciortino, T., Bruno, F., Juenger, S. T., Teske, N., Morshed, R. A., Haddad, A. F., Zhang, Y., Stoecklein, S., Weller, M., Vogelbaum, M. A., Beck, J., Tandon, N., Hervey-Jumper, S., Molinaro, A. M., Rudà, R., . . . Tonn, J. C. (2023). Prognostic validation of a new classification system for extent of resection in glioblastoma: A report of the RANO resect group. Neuro-Oncology, 25(5), 940–954. https://doi.org/10.1093/neuonc/noac193

Kasl, R. A., Brinson, P. R., & Chambless, L. B. (2016). Socioeconomic status does not affect prognosis in patients with glioblastoma multiforme. Surgical Neurology International, 7(Suppl. 11), S282–S290. https://doi.org/10.4103/2152-7806.181985

Keric, N., Krenzlin, H., Lange, F., Dauth, A., Freyschlag, C. F., Schnellg, O., Misch, M., von der Brelie, C., Gempt, J., Krigers, A., Wagner, A., Mielke, D., Sommer, C., Brockmann, M. A., Meyer, B., Rohde, V., Vajkoczy, P., Beck, J., Thomé, C., & Ringel, F. (2026). Treatment differences in IDH–wildtype glioma – the impact of surgery and adjuvant therapy. Journal of Neuro-Oncology, 176(2), Article 145. https://doi.org/10.1007/s11060-025-05368-4 Springer Nature Link

Klingenschmid, J., Krigers, A., Kerschbaumer, J., Thomé, C., Pinggera, D., & Freyschlag, C. F. (2022). Surgical management of malignant glioma in the elderly. Frontiers in Oncology, 12, Article 900382. https://doi.org/10.3389/fonc.2022.900382

Kommers, I., Ackermans, L., Ardon, H., van den Brink, W. A., Bouwknegt, W., Balvers, R. K., van der Gaag, N., Bosscher, L., Kloet, A., Koopmans, J., Laan, M. T., Tewarie, R. N., Robe, P. A., van der Veer, O., Wagemakers, M., Zwinderman, A. H., & De Witt Hamer, P. C. (2021). Between-hospital variation in rates of complications and decline of patient performance after glioblastoma surgery in the Dutch Quality Registry Neuro Surgery. Journal of Neuro-Oncology, 152(2), 289–298. https://doi.org/10.1007/s11060-021-03697-8

Krenzlin, H., Jankovic, D., Dauth, A., Lange, F., Wetzel, M., Schmidt, L., Janssen, I., Richter, C., Stockinger, M., Schmidberger, H., Brockmann, M. A., Sommer, C., Meyer, B., Keric, N., & Ringel, F. (2024). Multimodal treatment of glioblastoma with multiple lesions—a multi-center retrospective analysis. Journal of Neuro-Oncology, 170(3), 555–566. https://doi.org/10.1007/s11060-024-04810-3

Laigle-Donadey, F., Metellus, P., Guyotat, J., Menei, P., Proust, F., Dufour, H., Chinot, O., Honnorat, J., Faillot, T., Paquis, P., Peruzzi, P., Emery, E., Guillamo, J. S., Carpentier, A., Wager, M., Lebbah, S., Hajage, D., Delattre, J. Y., & Cornu, P. (2023). Surgery for glioblastomas in the elderly: An Association des Neuro-oncologues d'Expression Française (ANOCEF) trial. Journal of Neurosurgery, 138(5), 1199–1205. https://doi.org/10.3171/2022.8.JNS221068

Langsenlehner, T., Groll, M. J., Quehenberger, F., Payer, F., Mokry, M., & Kapp, K. S. (2012). Interdisciplinary treatment of glioblastoma: Analysis of prognostic factors and treatment results in unselected patients. Neoplasma, 59(6), 662–668. https://doi.org/10.4149/neo_2012_084 pubmed.ncbi.nlm.nih.gov

Lee, D., Lee, E., Roh, T. H., & Kim, S. H. (2024). Optimal timing of chemoradiation after resection or biopsy of glioblastomas: A nationwide population-based study. BMC Cancer, 24(1), Article 1450. https://doi.org/10.1186/s12885-024-13223-4

Lim, J., Park, Y., Ahn, J. W., Hwang, S. J., Kwon, H., Sung, K. S., & Cho, K. (2021). Maximal surgical resection and adjuvant surgical technique to prolong the survival of adult patients with thalamic glioblastoma. PLOS ONE, 16(2), Article e0244325. https://doi.org/10.1371/journal.pone.0244325 PLOS One

Mak, K. S., Agarwal, A., Qureshi, M. M., & Truong, M. T. (2017). Hypofractionated short-course radiotherapy in elderly patients with glioblastoma multiforme: An analysis of the National Cancer Database. Cancer Medicine, 6(6), 1192–1200. https://doi.org/10.1002/cam4.1070

Martín-Abreu, C., Fariña-Jerónimo, H., & Plata-Bello, J. (2024). Radiological and not clinical variables guide the surgical plan in patients with glioblastoma. Current Oncology, 31(4), 1899–1912. https://doi.org/10.3390/curroncol31040142

Mendoza Mireles, E. E., Blakstad, H., Server, A., Leske, H., Skaga, E., Aarhus, M., Brandal, P., Helseth, E., Nayak, L., Rønning, P. A., & Vik-Mo, E. O. (2026). Extent of resection and perioperative neurological status as prognostic markers in glioblastoma: A population-based study. Journal of Neuro-Oncology, 177(1), Article 15. https://doi.org/10.1007/s11060-026-05481-y Springer Nature Link

Moiraghi, A., Roux, A., Peeters, S., Pelletier, J. B., Baroud, M., Trancart, B., Oppenheim, C., Lechapt, E., Benevello, C., Parraga, E., Varlet, P., Chrétien, F., Dezamis, E., Zanello, M., & Pallud, J. (2021). Feasibility, safety and impact on overall survival of awake resection for newly diagnosed supratentorial IDH-wildtype glioblastomas in adults. Cancers, 13(12), Article 2911. https://doi.org/10.3390/cancers13122911

Murchison, S. C., Wiksyk, B., Gossman, S., Jensen, B., Sayers, D., Lesperance, M., Truong, P. T., & Alexander, A. (2018). Subventricular zone radiation dose and outcome for glioblastoma treated between 2006 and 2012. Cureus, 10(11), Article e3618. https://doi.org/10.7759/cureus.3618

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, Article n71. https://doi.org/10.1136/bmj.n71

Paik, W., Kim, H. S., Choi, C. G., & Kim, S. J. (2016). Pre-operative perfusion skewness and kurtosis are potential predictors of progression-free survival after partial resection of newly diagnosed glioblastoma. Korean Journal of Radiology, 17(1), 117–126. https://doi.org/10.3348/kjr.2016.17.1.117

Paus, S., Hoffmann, J., Roeper, J., & Griesinger, F. (2025). Real-world analysis of treatment patterns and survival outcome of glioblastoma patients in a German single-center study: Can survival rates of randomized controlled trials be achieved? Neuro-Oncology Advances, 7(1), Article vdaf009. https://doi.org/10.1093/noajnl/vdaf009

Pöppe, J. P., Buchta, M., Demetz, M., Freyschlag, C. F., Kerschbaumer, J., Thomé, C., Stefanits, H., Gahleitner, S., Gruber, A., Steinbacher, J., Machegger, L., Geroldinger, M., Zimmermann, G., Kraus, T. F. J., Sotlar, K., Korja, M., Griessenauer, C. J., & Schwartz, C. (2026). On the value of microsurgical resection compared to biopsy in elderly glioblastoma patients: A retrospective multicenter analysis and scoring system proposal. Neuro-Oncology Advances, 8(1), Article vdaf268. https://doi.org/10.1093/noajnl/vdaf268

Röver, C., Knapp, G., & Friede, T. (2015). Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. BMC Medical Research Methodology, 15, Article 99. https://doi.org/10.1186/s12874-015-0091-1

Rykkje, A. M., Carlsen, J. F., Larsen, V. A., Skjøth-Rasmussen, J., Christensen, I. J., Nielsen, M. B., Poulsen, H. S., Urup, T. H., & Hansen, A. E. (2024). Prognostic relevance of radiological findings on early postoperative MRI for 187 consecutive glioblastoma patients receiving standard therapy. Scientific Reports, 14(1), Article 10985. https://doi.org/10.1038/s41598-024-61925-3

Sharma, P., Medhi, P. P., Bhattacharyya, M., Nath, J., & Kalita, A. K. (2023). Prognostic significance of neutrophil-lymphocyte ratio in patients of high-grade glioma undergoing adjuvant chemoradiation: A prospective study. Asian Pacific Journal of Cancer Prevention, 24(10), 3487–3494. https://doi.org/10.31557/APJCP.2023.24.10.3487

Sharma, P., Medhi, P. P., Kalita, A. K., Bhattacharyya, M., Nath, J., Sarma, G., & Yanthan, Y. (2023). Factors associated with neurocognitive impairment following chemoradiotherapy in patients with high-grade glioma: Results of a prospective trial. Brain Tumor Research and Treatment, 11(3), 183–190. https://doi.org/10.14791/btrt.2023.0004

Song, R., Dapash, M., Jamshidi, P., Gondi, V., Lukas, R. V., & Khan, O. H. (2026). Survival and function in elderly patients with GBM: The role of surgical resection with contemporary multimodal therapy. Journal of Neuro-Oncology, 177(2), Article 62. https://doi.org/10.1007/s11060-026-05459-w Springer Nature Link

Stadler, C., Gramatzki, D., Le Rhun, E., Hottinger, A. F., Hundsberger, T., Roelcke, U., Läubli, H., Hofer, S., Seystahl, K., Wirsching, H. G., Weller, M., & Roth, P. (2024). Glioblastoma in the oldest old: Clinical characteristics, therapy, and outcome in patients aged 80 years and older. Neuro-Oncology Practice, 11(2), 132–141. https://doi.org/10.1093/nop/npad070