# The Survival Effect of Repeat Surgery at Glioblastoma Recurrence and its Trend: A Systematic Review and Meta-Analysis

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**Key words**
- Glioblastoma
- Meta-analysis
- Recurrence
- Repeat surgery
- Systematic review

**Abbreviations and Acronyms**
CI: Confidence interval
EC: Effect coefficient
GBM: Glioblastoma
HR: Hazard ratio
OS: Overall survival
QoL: Quality of life
TMZ: Temozolomide

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BACKGROUND: **Glioblastoma (GBM) is a dismal disease managed in the first instance by surgical resection, temozolomide, and radiation. The role of repeat surgery at recurrence remains ill defined. This study aims to quantify the effect of repeat surgery in recurrent GBM on overall survival and determine if a trend in reported effect over time exists.**

METHODS: **Searches of 7 electronic databases from inception to January 2018 were conducted following PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. There were 2692 articles identified for screening. Prognostic hazard ratios (HRs) derived from multivariate regression analysis were extracted and analyzed using meta-analysis of proportions and linear regression.**

RESULTS: **Eight observational studies reporting prognostic HRs in 10 cohorts were included. They described 1906 recurrent GBM diagnoses, managed by surgery at primary diagnosis, with 709 (37%) undergoing further repeat surgery at recurrence. Repeat surgery was shown to confer a statistically significant survival advantage compared with no surgery at recurrence in the pooled cohort (HR, 0.722; $P < 0.001$). Newer studies trended toward a more superior prognostic advantage of repeat surgery compared with earlier studies (effect coefficient, 0.856; $P = 0.012$).**

CONCLUSIONS: **This meta-analysis of contemporary literature suggests that repeat surgery at GBM recurrence in select patients confers a significant, prognostic overall survival advantage independent of other prognostic factors. Furthermore, newer studies are significantly more likely to suggest greater benefit than are older studies. The main limitation is the selection bias inherent in the cohorts pooled for analysis. Larger prospective randomized controlled studies are needed to validate the findings of this study and provide stratification for such benefit justified by quality of life metrics.**

## INTRODUCTION

Glioblastoma (GBM) remains a devastating disease without cure. Median survival is 14 months, despite the gold standard treatment of maximal safe resection and adjuvant temozolomide (TMZ) and radiation.[1] The issue faced by clinicians is how to manage the recurrence of GBM after initial treatment, with debate existing over the usefulness of surgical resection at recurrence given its inevitable nature.[2,3] Although many studies[4-6] have shown a clear independent overall survival (OS) benefit of surgical intervention in the prognosis of the primary diagnosis, a similar consensus in GBM recurrence is lacking.[2]

At primary diagnosis, it has been shown that maximal safe resection of the GBM bulk can be associated with up to 5 months of OS benefit.[4,6] Similar benefit should also be observed at recurrence. However, there are additional morbidity concerns in assessing surgery eligibility that arise only at recurrence. These concerns include wound dehiscence and infection risks after primary immune-suppressing adjuvant therapies,[7] as well as the general risks of surgery in recurrences that are only radiologic. Furthermore, the potential quantitative extension of OS requires careful titration against subsequent quality of life (QoL) specific to each patient and their circumstances. The effect of these concerns in patient selection may bias reported results investigating OS in patients with GBM who do and do not undergo repeat surgery, dependent on other prognostic factors.

A hazard ratio (HR) is a prognostic statistic derived from regression analysis to infer the effect of a particular intervention. When obtained in a multivariate setting, it stands as an independent factor to other potential prognostic factors already defined in GBM. The aim of this study was to search the literature for HRs obtained from multivariate analyses only to investigate the independent effect of repeat surgery at GBM recurrence on OS by means of meta-analysis. Furthermore,

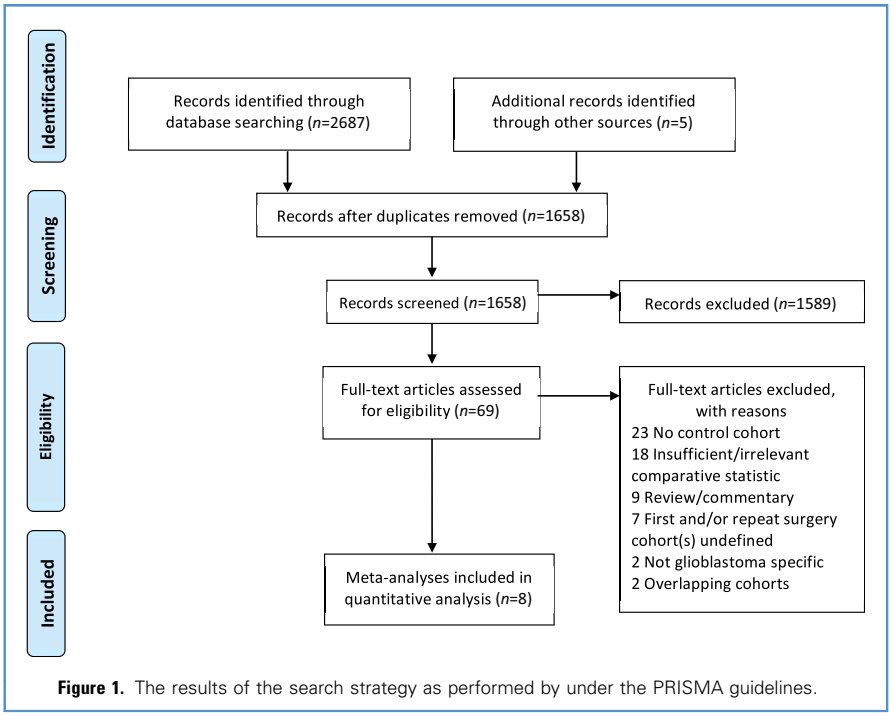


**Figure 1.** The results of the search strategy as performed by under the PRISMA guidelines.

these HRs were analyzed against year of publication to investigate if a trend existed over time that correlated with continual improvement in GBM management.

## METHODS

### Search Strategy

The strategy was designed around the PICO (Population Intervention Comparator Outcome) question format: do patients at GBM recurrence (Population) treated by surgery (Intervention) compared with those not treated by surgery (Comparator) have a superior OS (Outcome)? The present review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and recommendations.[8] Electronic searches were performed using Ovid Embase, PubMed, SCOPUS, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, and Database of Abstracts of Review of Effectiveness from their dates of inception to January 2018. The literature involving all comparative studies were searched by using the following string of MeSH (Medical Subject Heading) terms: (recurrent OR relapse) AND glioblastoma AND (surgery OR resection OR operation OR reoperation) AND survival. All identified articles were then systematically assessed against the inclusion and exclusion criteria independently by 2 investigators (V.M.L. and T.J.R.).

### Selection Criteria

The inclusion criteria used to screen all identified articles were 1) confirmed cases of recurrent GBM as per the Macdonald criteria,[9] 2) with a comparative prognostic HR statistic accompanied by estimation of error (i.e., 95% confidence interval [CI]), 3) derived from a cohort involving recurrent GBM cases managed by surgery, 4) derived from adjusted Cox multivariate regression analysis, 5) with reference to systemic therapy of chemoradiation, 6) where TMZ was included in chemotherapy management for the primary diagnosis, 7) in cohorts of patients aged >18 years. The exclusion criteria applied to all identified articles were 1) recurrent noncranial GBM, 2) no clear surgery cohort, 3) radiosurgery management, and 4) cohorts of patients <18 years. When institutions reported duplicate studies with accumulating numbers of patients or increased lengths of follow-up, and when studies reported multiple time courses of the same treated cohort, the most complete reports were included for quantitative assessment. All publications were limited to those involving human patients and in the English language. Reviews, abstracts, case reports, conference presentations, editorials, and expert opinions were excluded to minimize potential publication bias and duplication of results.

### Data Extraction and Critical Appraisal

All data were extracted from article texts, tables, and figures, with any estimates made based on the presented data and figures. These estimates include variance estimations based on established statistical methodologies when appropriate.[10-12] The clinical outcome of interest was prognostic effect of surgery at GBM recurrence as inferred by an HR and its respective 95% CI. Two investigators (V.M.L. and T.J.R.) independently reviewed each article included, with any discrepancy resolved by discussion to reach consensus. All attempts were made to contact study authors for data clarification if needed. Because quality scoring is controversial in meta-analyses of observational studies, each article included in our analysis was appraised according to a modified version of the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) criteria[13] and assessed by a modified Newcastle-Ottawa Scale.[14]

### Meta-Analysis

The HRs of each included study were pooled together by meta-analysis of proportions via a logit transformation to provide the overall summary statistic. The $I^2$ statistic was used to estimate the percentage of total variation across studies, because of heterogeneity rather than chance, with values >50% considered as substantial heterogeneity.[15] A fixed-effect model was tested, and in the case of $I^2$ >50%, a random-effect model was also tested to take into account the possible clinical diversity and methodological variation between studies. Linear regression was performed to analyze for potential modifying trend of study publication year. The effect coefficient (EC) is reported for each analysis to identify the direction of modifying trend when nonzero.

Publication bias was assessed through the generation of funnel plots for all outcomes and assessed for asymmetry. The final inclusion of any outlying study was