Intraoperative Magnetic Resonance Imaging (MRI)-Guided Resection of Glioblastoma: A Meta-Analysis of 1,847 Patients

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INTRODUCTION

Glioblastoma (GBM) is the most common malignant primary brain tumor with high recurrence rates and poor median overall survival of less than 2 years.[1,2] The current standard of care involves a multimodal approach, maximal safe surgical resection is the initial step in management followed by adjuvant radiation and chemotherapy.[3,4] There is a need for advancements to improve patient outcomes, as the current progress in prolonging survival has been suboptimal. Intraoperative MRI (iMRI) emerged as a valuable tool for neurosurgery, providing real-time visualization of dynamic changes that occur during surgery, and allowing for improved tumor removal.[5,6]

Aggressive resection of surgically accessible tumors has been shown to correlate with improved functional status and higher survival rates.[7-9] This is attributed to improved tumor removal which can mitigate rapid tissue infiltration. However, limitations of conventional neuronavigation (CNN), such as the inability to provide real-time intraoperative brain images and susceptibility to brain shift could negatively affect patient outcomes. To overcome these challenges, several surgical techniques have been used to improve the extent of resection while minimizing damage to healthy brain tissue.[10,11] Among these techniques, iMRI provides real-time visualization of dynamic changes during surgery, leading to enhanced tumor removal.[5,6] The available evidence discussing the effectiveness of iMRI remains limited to small studies which show conflicting results in comparison to CNN. To address this knowledge gap, we conducted the first meta-analysis to the extent of our knowledge, to evaluate the impact of iMRI in patients with GBM. The primary objective of our study is to determine the impact of iMRI on clinical outcomes, including overall survival (OS), extent of resection (EOR), gross total resection (GTR), progression-free survival (PFS), and surgical complications in GBM surgery. By analyzing the available evidence, we aim to provide valuable insights that can guide clinical decision-making in the management of GBM patients.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines were followed for this systematic review and meta-analysis.[12] All steps were done according to the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions (version 6.3).[13] The meta-analysis protocol was registered on PROSPERO on April 25, 2023, under protocol ID: CRD42023417080.

Criteria of the Included Studies

We set specific inclusion criteria to identify relevant studies for analysis. The population of interest were patients diagnosed with

Key words

- Glioblastoma
- Intraoperative MRI
- Meta-analysis
- Overall survival

Abbreviations and Acronyms

CE	Contrast-enhancing
CI	Confidence Interval
CNN	Conventional Neuronavigation
DTI	Diffuse Tensor Imaging
EOR	Extent of Resection
fMRI	Functional Magnetic Resonance Imaging
GBM	Glioblastoma
GTR	Gross Total Resection
iMRI	Intraoperative Magnetic Resonance Imaging
IONM	Intraoperative Neuromonitoring
iUS	Intraoperative Ultrasound
MD	Mean Difference
PFS	Progression-free Survival
RCT	Randomized Controlled Trial
RE	Random-effects
ROB 2	Version 2 of the Cochrane risk-of-bias tool for randomized trials tool
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions tool
RR	Risk Ratio
SMD	Standardized Mean Difference

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Citation: World Neurosurg. (2023).
https://doi.org/10.1016/j.wneu.2023.12.042

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***

either recurrent or naive glioblastoma. We included studies that compared groups utilizing iMRI either alone or in combination with other surgical modalities, while incorporating a control arm that did not employ iMRI, we excluded studies that did not meet these criteria.

We excluded studies that did not report at least one of the following outcomes of interest: OS, EOR, GTR, PFS, and surgical complications. To ensure result reliability, we limited the study design to comparative clinical trials or observational cohort studies with a minimum of 10 participants. We also excluded non-English publications, case-control studies, cross-sectional studies, systematic reviews, meta-analyses, case reports, basic science research, conference abstracts, letters to the editor, and review articles.

Literature Search Strategy

A comprehensive search of 4 electronic databases (PubMed, MEDLINE, EMBASE, and COCHRANE) from inception was performed until April 20th, 2023. Keywords and free words were used to search for *Glioblastoma*, *Intraoperative or Intrasurgical*, and *Magnetic Resonance Imaging*. The search information for each of the Databases can be found in **supplementary material 1**.

Screening of Literature Search Results

All duplicates were removed using Zotero. Initially, the retrieved references were assessed through title and abstract screening, followed by a full text review whenever needed. Two independent authors (P.P. *and* J.A.) evaluated each paper for inclusion and quality assessment, with a third author resolving any conflicts. Furthermore, references cited in the included studies were examined and included if they met the eligibility criteria.

Data Extraction

Excel spreadsheets were used to extract the following data: (1) baseline characteristics of the studied population; (2) summary of the characteristics of the included studies; (3) outcome measures; and (4) quality assessment domains.

Assessing the Risk of Bias

The quality of the included observational cohort studies was evaluated using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.[14] For the RCT, we utilized the Version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB 2) tool from the Cochrane Handbook of Systematic Reviews of Interventions 6.3.[15,16] The assessment of study quality was conducted in accordance with these established tools.

Outcome Measures

A thorough evaluation of specific outcomes was vital for assessing intervention effectiveness in this study. Overall survival (OS) and Progression-free survival (PFS) were assessed as standardized mean differences (SMDs). During the surgical resection, the MRI assessment of the residual contrast-enhancing tumor and peritumoral regions was performed based on standardized criteria in accordance with previously published literature.[17-20] EOR was evaluated as a mean percentage, accompanied by the standard deviation. Additionally, the percentage of resection was classified into gross total, near-total, and partial resection. Overall surgical complications, including hemorrhage, ischemia, infection, thrombosis, severe edema, neurologic deficits, hydrocephalus, and CSF leak, were evaluated as a percentage of occurrence.

The following outcomes were considered for our meta-analysis.

1. Overall survival (OS): The length of time from the diagnosis of GBM to the occurrence of death, regardless of the cause. The OS outcome is measured as SMD.
2. Progression-free survival (PFS): The length of time from the diagnosis of GBM to the occurrence of disease progression. PFS was represented as SMD.
3. Gross total resection (GTR): The surgical removal of the entire contrast-enhancing (CE) tumor evaluated by MRI. Percentage and total number of cases classified as GTR.
4. Extent of resection (EOR): The percentage of CE tumor that is surgically removed in relation to the tumor extent observed on preoperative imaging MRI. Represented as the percentage mean difference (MD).
5. Surgical Complications (%): Adverse events that were reported >5% as a result of GBM surgery were considered in the analysis. The reported complications included hemorrhage, ischemia, infection, thrombosis, severe edema, neurologic deficits, hydrocephalus, and CSF leak. The occurrences were classified as a percentage and the total number of cases.

Data Analysis

For dichotomous data, such as the occurrence of complications, the event frequencies and totals of each group were pooled to calculate the risk ratio (RR) with its corresponding 95% confidence interval (CI). This analysis explored the risk of experiencing complications between the groups. OS and PFS were evaluated using SMD as the measure of effect size. When necessary, SMD values along with their corresponding 95% CI were calculated.[21] This allowed for the comparison of survival outcomes between the intervention groups, considering the standardized effect size. To assess the EOR, the percentage MD and CI between the groups were calculated and pooled. This analysis showed the magnitude and direction of the difference in EOR achieved by the interventions.

The variables of interest in this study were derived from the original data reported in the included papers based on the available information. To assess the within-study variance and facilitate comparisons, a random-effects (RE) model using the DerSimonian-Laird method was employed.[22] Forest plots were utilized as a visual representation of the estimated outcomes.

Assessment of Heterogeneity

To evaluate the heterogeneity among the included studies, Cochran's Q-statistic was used, setting a significance level of $P < 0.10$. Additionally, the I^2-statistic was utilized to quantify the proportion of total variation attributable to heterogeneity, with values greater than 50% considered indicative of high heterogeneity.[23] Heterogeneity was further explored in primary outcome using subgroup analyses categorized as *multimodal* for studies that implemented more than 1 different intervention besides iMRI such as intraoperative neuromonitoring, intraoperative ultrasound, and/or intraoperative 5-ALA fluorescence. All statistical analyses, including the calculation of standardized mean difference, relative risk, and mean difference, were conducted using RevMan V.5.4.1 software.

RESULTS

A comprehensive analysis was conducted, involving 1,847 patients from the 11 selected articles that met the inclusion criteria in the meta-analysis. These articles consisted of 1 randomized controlled trial (RCT) and 10 observational cohort studies, identified from an initial pool of 771 articles.[24-34] The PRISMA flow diagram of the study selection process can be found in Figure 1.

Study Characteristics

The included studies in our analysis comprised of 1 RCT,[33] 9 retrospective cohort studies,[24-31,34] and 1 ambidirectional cohort study.[32] All studies utilized CNN and microsurgery as the standard approach. In the intervention group, the additional use of intraoperative MRI was implemented either alone or in combination with other surgical modalities. In contrast, the control arm did not incorporate iMRI in their procedures. Other intraoperative modalities used were 5-ALA, intraoperative ultrasound (iUS), intraoperative neuromonitoring (IONM), functional magnetic resonance imaging (fMRI), and diffuse tensor imaging (DTI). Subgroups comparing iMRI to non-MRI without additional surgical modalities were used whenever available. The characteristics of the included studies are summarized in Table 1. The total patient population included in our meta-analysis was 1,847 patients. Summary and baseline characteristics are shown in Table 2.

Use of Additional Surgical Techniques in Conjunction with iMRI

In the RCT, the use of iMRI was compared to the non-iMRI group, they did not use any additional intervention.[33] Regarding the

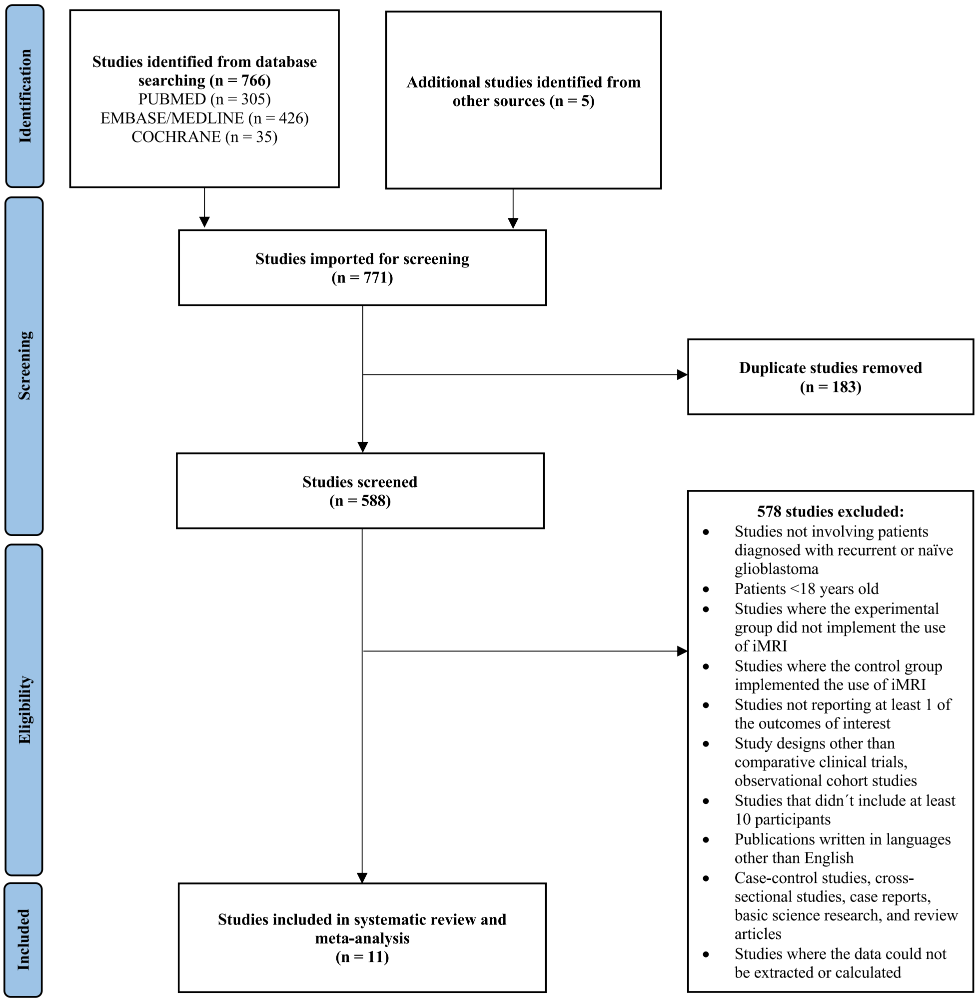


Figure 1. PRISMA Flow Diagram.

Table 1. Summary of Included Studies

Study ID	Country	Study Design	Total (Analyzed Population)	Follow up Time	Compared Interventions	Key Findings
Roder et al., 2014[25]	Germany	Retrospective Cohort	60 (27)*	2010—2012	iMRI, 5-ALA or conventional neuronavigation, with or without iUS or IONM	■ The utilization of iMRI-assisted surgery resulted in a noteworthy reduction in the mean residual tumor volume compared to both 5-ALA-guided surgery and conventional white-light surgery. This indicates that iMRI-assisted surgery was more effective in achieving complete removal of the tumor. ■ The occurrence of total resections was significantly higher in the iMRI-assisted surgery group (74%) compared to both the 5-ALA-assisted surgery group (46%, $P = 0.05$) and the white-light surgery group (13%, $P = 0.03$). ■ The use of iMRI to improve the extent of resection was safely attainable as peri- and postoperative complications were comparable among the different cohorts. ■ Notably, the increase in total resections led to a significant improvement in 6-month progression-free survival (6M-PFS) rates, rising from 32% to 45%.
Napolitano et al., 2014[26]	Belgium	Retrospective Cohort	94 (56)*	2006—2011	iMRI or conventional neuronavigation	■ In the group of patients who underwent intraoperative MRI (ioMRI), 15 individuals (26.8%) underwent an immediate second resection, resulting in an increase in the rate of gross total resection (GTR) by 10.7%, and the GTR/no residual tumor (NTR) rate by 8.9%. ■ Significant differences were observed between the use of ioMRI and the control group in terms of achieving a greater extent of resection (EOR). ■ The extent of resection (EOR) alone had a significant impact on survival outcomes. Patients who achieved GTR/NTR had a longer median overall survival of 15.26 months compared to those with a partial resection (PR) subgroup, who had a median overall survival of 10.26 months. ■ Factors such as age, sex, and adjuvant chemotherapy were identified as significant factors associated with overall survival.
Coburger et al., 2018[29]	Germany	Retrospective Cohort	70 (33)*	2008—2013	iMRI, or conventional neuronavigation, with or without IONM	■ A notable finding in the iMRI group was a significant reduction in ΔEOR (change in extent of resection) compared to other factors. ■ In a linear regression model that accounted for age, tumor volume, neurophysiologic mapping, and iMRI, only the use of iMRI had a significant impact on ΔEOR. ■ Both age and iMRI had a significant influence on overall survival, indicating that these factors played a crucial role in determining survival outcomes.

Marongiu et al., 2017[31]	Italy	Retrospective Cohort	114 (78)*	2009–2013	iMRI, or conventional neuronavigation, with or without DTI/IONM	■ In the initial lo-MRI scan, a complete gross total resection (GTR) was detected in 31 patients, while residual tumor was found in 47 patients. ■ Among these cases, 21 patients had remaining tumor located within eloquent areas. However, the use of lo-MRI with fiber tracking enabled further resection, resulting in a GTR being achieved in 12 of these patients. ■ The utilization of lo-MRI not only improved the extent of resection (EOR) but also had a positive impact on 6-month progression-free survival (6-PFS). In group A, the overall GTR rate reached 88.5% (n = 69), whereas in group B, it was 44% (n = 16). ■ The 6-PFS rates were 73% (n = 57) for group A and 38.9% (n = 14) for group B, indicating a substantial improvement in progression-free survival for patients in group A compared to group B.
Familiari et al., 2018[27]	Italy	Retrospective Cohort	129 (64)*	2009–2017	iMRI, or conventional neuronavigation, with or without fMRI/DTI	■ The mean extent of resection (EOR) showed a notable increase, from 86.23% ± 10.51% in patients belonging to group A, to 94.01% ± 7.42% in those included in group B. ■ In terms of progression-free survival (PFS), patients in group A had an average PFS of 5.38 ± 2.32 months, whereas patients in group B exhibited a longer average PFS of 7.89 ± 2.75 months. ■ For overall survival (OS), the average duration was 13.38 ± 4.06 months in group A, while patients in group B had a higher average OS of 16.43 ± 3.41 months.
Shah et al., 2020[30]	USA, Canada	Multicenter retrospective cohort	286 (176)*	1996–2019	iMRI or conventional neuronavigation	■ Out of a total of 640 cases, gross-total resection (GTR) was successfully achieved in 403 cases, accounting for a GTR rate of 63.0%. ■ Kaplan-Meier analysis, focusing on 286 cases with volumetric analysis for extent of resection (EOR), revealed that patients with 100% EOR had a longer overall survival (OS) compared to all other groups. ■ Among the 122 cases initially undergoing subtotal resection (STR), additional resection after iMRI was performed in 104 cases, resulting in an impressive 85.2% rate. This additional resection led to a mean increase in EOR of 6.3% and a mean decrease in tumor volume of 2.2 cm3. ■ Significantly higher EOR was observed in the iMRI group for both the intended GTR and STR groups. ■ Univariate analyses indicated that iMRI usage was a significant predictor of overall survival (OS). ■ Importantly, the use of iMRI did not contribute to an increased incidence of new permanent neurologic deficits, indicating its safety and efficacy in this regard.

N = total population size.

*iMRI intervention population always implemented the use of conventional neuronavigation and microsurgery.

Continues

Table 1. Continued

Study ID	Country	Study Design	Total (Analyzed Population)	Follow up Time	Compared Interventions	Key Findings
Barak et al., 2021[34]	USA	Retrospective Cohort	48 (35)*	2015–2021	iMRI, iUS, and conventional neuronavigation, or, iUS and conventional neuronavigation	■ The inclusion of intraoperative MRI (IoMRI) did not demonstrate superiority over intraoperative ultrasound (IoUS) alone in terms of overall survival (OS), Karnofsky Performance Score (KPS) at 6 weeks postoperative, or extent of resection. ■ The length of surgery (LOSx) was significantly longer in the IoMRI group compared to the IoUS group. ■ Both LOSx and hospital stay were identified as predictors of postoperative complications. ■ Higher extent of resection (gross total resection or near-total resection), receipt of postoperative adjuvant treatment, and occurrence of postoperative complications were predictive factors for overall survival (OS). ■ Patients with relatively lower preoperative KPS scores (<70) demonstrated significant improvement in their KPS scores at 6 weeks postoperative. ■ Patients who experienced postoperative complications were more likely to have lower KPS scores at 6 weeks postoperative.
Cui et al., 2022[24]	China	Retrospective Cohort	77 (56)*	2016–2020	iMRI or conventional neuronavigation, with or without IONM and fMRI/DTI	■ The multimodal approach resulted in a higher median extent of resection (EOR) and gross total resection rate compared to the conventional approach. Additionally, the multimodal group had a lower incidence of permanent motor deficits, indicating improved surgical outcomes. ■ The multimodal group exhibited longer median progression-free survival (PFS) and overall survival (OS) compared to the conventional group, suggesting that the multimodal approach may confer better long-term outcomes. ■ Postoperative language and cognitive function were similar between the 2 groups, indicating comparable functional outcomes. ■ In multivariate analysis, factors positively influencing the survival of patients with central core glioblastoma (ccGBM) included achieving a higher EOR, receiving radiotherapy, and undergoing longer cycles of temozolomide chemotherapy. ■ An optimal threshold of 92% for the extent of resection was identified, which significantly improved both PFS and OS in patients with ccGBM. This suggests that achieving an EOR above this threshold is associated with better prognosis for ccGBM patients.

Xiong et al., 2022[28]	China	Retrospective Cohort	912 (228)*	2010—2019	Multimodal interventions (≥2) or nonmultimodal intervention (<2), which included iMRI, AC and IONM	■ The multimodal group exhibited a substantially longer overall survival (OS) compared to the non-multimodal group, indicating the beneficial impact of multimodal techniques on the prognosis of glioblastoma patients. ■ The increasing popularity of multimodal approaches between the periods of 2010—2014 and 2015—2019 played a significant role in improving the prognosis of glioblastoma patients. ■ Radiologically complete tumor resection and the administration of temozolomide chemotherapy were identified as statistically significant prognostic factors in a multivariate analysis, highlighting their importance in predicting patient outcomes. ■ Significantly higher rates of complete tumor resections were observed in the group utilizing intraoperative MRI (iMRI) compared to the conventional surgery group. This suggests that iMRI is a valuable tool in increasing the extent of resection during glioblastoma surgery, leading to improved patient survival.
Senft et al., 2010[32]	Germany	Ambidirectional cohort study	43 (10)*	2004—2005	iMRI or conventional neuronavigation	■ Statistically significant prognostic factors identified in a multivariate analysis included achieving radiologically complete tumor resection and administering temozolomide chemotherapy. ■ The iMRI group exhibited a significantly higher rate of complete tumor resections compared to the conventional surgery group, indicating the efficacy of intraoperative MRI as a valuable tool in increasing the extent of resection during glioblastoma (GBM) surgery. ■ The utilization of intraoperative MRI has demonstrated its usefulness in enhancing the extent of resection in GBM surgery, ultimately leading to improved patient survival.
Kubben et al. 2014[33]	Netherlands	Randomized controlled trial	14 (6)*	2010—2012	iMRI or conventional neuronavigation	■ Median RTV in the cNN group is 6.5% with an interquartile range of 2.5—14.75%. ■ Median RTV in the iMRI group is 13% with an interquartile range of 3.75—27.75%. ■ A Mann-Whitney test showed no statistically significant difference between these groups. ■ Median survival in the cNN group is 472 days, with an interquartile range of 244—619 days. ■ Median survival in the iMRI group is 396 days, with an interquartile range of 191—599 days. ■ Clinical performance did not differ either.

N = total population size.
*iMRI intervention population always implemented the use of conventional neuronavigation and microsurgery.

Table 2. Baseline Characteristics of the Included studies' Populations

Reference	Group	N	Age (years), Mean (SD)	Multimodal	Additional Intervention	Field Strength (T)	PreOperative Tumor Voume	MGMT Methylation	Adjuvant Radiotherapy	Adjuvant Chemotherapy	Median TMZ cycles
Retrospective Cohort Studies											
Roder et al., 2014[25]	iMRI	27	52.7 (46.1)	Yes	5-ALA, iUS, IoNM	1.5	46.2	-	-	-	-
	non-iMRI	33	59.2 (44.1)		5-ALA, iUS, IoNM		38.6	-	-	-	-
Napolitano et al., 2014[26]	iMRI	56	58.1 (15.2)	No	-	3.0	-	-	45	37	-
	non iMRI	38	62.5 (10.9)		-	-	-	—	32	23	-
Coburger et al., 2018[29]	iMRI	33	62 (38.7)	Yes	IoNM	1.5	44 ± 4.2	17	37	37	-
	non-iMRI	37	57 (50.1)		IoNM	-	50 ± 5.7	6	33	33	-
Marongiu et al., 2017[31]	iMRI	78	61.7 (10.4)	Yes	IoNM/DTI	1.5	28.4 ± 16.5	-	78	78	-
	non-iMRI	36	65.4 (8.6)		IoNM/DTI		30.6 ± 14.7	-	36	36	-
Familiari et al., 2018[27]	iMRI	64	56.6 (10.4)	Yes	fMRI/DTI	1.5	26.8 ± 11.3	16	64	64	-
	non-iMRI	65	57.5 (13.5)		fMRI/DTI		27.4 ± 10.9	15	65	65	-
Shah et al., 2020[30]	iMRI	176	58.5 (11.54)	No	-	1.5 or 3	37	-	-	-	-
	non-iMRI	110	-		-	-	29	-	-	-	-
Barak et al., 2021[34]	iMRI	35	74.4 (3.3)	Yes	iUS	3	34.25	14	29	25	-
	non-iMRI	13	80.1 (5.9)		iUS	-	24.35	3	4	8	-
Cui et al., 2022[24]	iMRI	56	49.4 (14)	Yes	IoNM, fMRI/DTI	1.5	59.3 ± 40.30	22	41	-	5.5
	non-iMRI	21	49.4 (10.5)		-	-	60.40 ± 27.24	10	16	-	4
Xiong et al., 2022[28]	iMRI	228	-	Yes	AC/IoNM	-	-	-	-	-	-
	non-iMRI	684	-		AC/IoNM	-	-	-	-	-	-
Ambidirectional Cohort Studies											
Senft et al., 2010[32]	iMRI	10	60 (median)	No	-	1.5	41.95	-	30	-	
	non-iMRI	33	60.5 (median)		-	-	-	-	13	-	
Randomized Control Trials											
Kubben et al., 2014[33]	iMRI	6	61 (5)	No	-	0.15	63.16	-	-	-	
	non-iMRI	8	66 (8)		-	-	-	-	-	-	

NA, not available; iMRI: intraoperative magnetic resonance imaging, NN: neuronavigation, IoNM intraoperative neuromonitoring, fMRI: functional magnetic resonance imaging, 5-ALA: 5-aminolevulinic acid, IoUS: intraoperative ultrsonography, AC: awake craniotomy., DTI: diffusion tensor imaging.

observational cohort studies, CNN to localize the GBM in the control group was used in all of them.[24-32,34] Various additional surgical techniques were commonly employed to aid tumor resection during surgery in both the iMRI and the non-iMRI surgery groups. These techniques included intraoperative ultrasonography,[25,34] functional neuroimaging or tractography,[27,31] 5-ALA fluorescence-guided surgery,[25] awake craniotomy,[28] and intraoperative neuromonitoring.[24,25,29,31]

Overall Survival

The OS analysis showed a statistically significant SMD of 0.23 favoring the use of iMRI over the non-iMRI group (95% CI, 0.04, 0.43; $P = 0.02$), pooled studies exhibited considerable heterogeneity ($P = 0.008$, $I^2 = 65\%$). For subgroup analysis, we found a nonsignificant SMD of 0.04 for OS favoring CNN over iMRI in the nonmultimodal intervention subgroup (95% CI, −0.47, 0.38). Among the multimodal intervention subgroup, we found a statistically significant SMD of 0.31 favoring the iMRI group (95% CI, 0.09, 0.52). Regarding individual studies, the only randomized controlled trial[33] showed a nonsignificant SMD of 0.12 favoring the non-iMRI group for OS (95% CI, −1.18, 0.94). Among the observational cohort studies, only one had a not statistically significant SMD of 0.25 favoring the non-iMRI group for OS (95% CI, −0.66, 0.16).[26] The remaining observational cohort studies demonstrated a favorable SMD in the iMRI group for OS.[24,27-29,32] These findings are depicted in Figure 2.

Progression-Free Survival

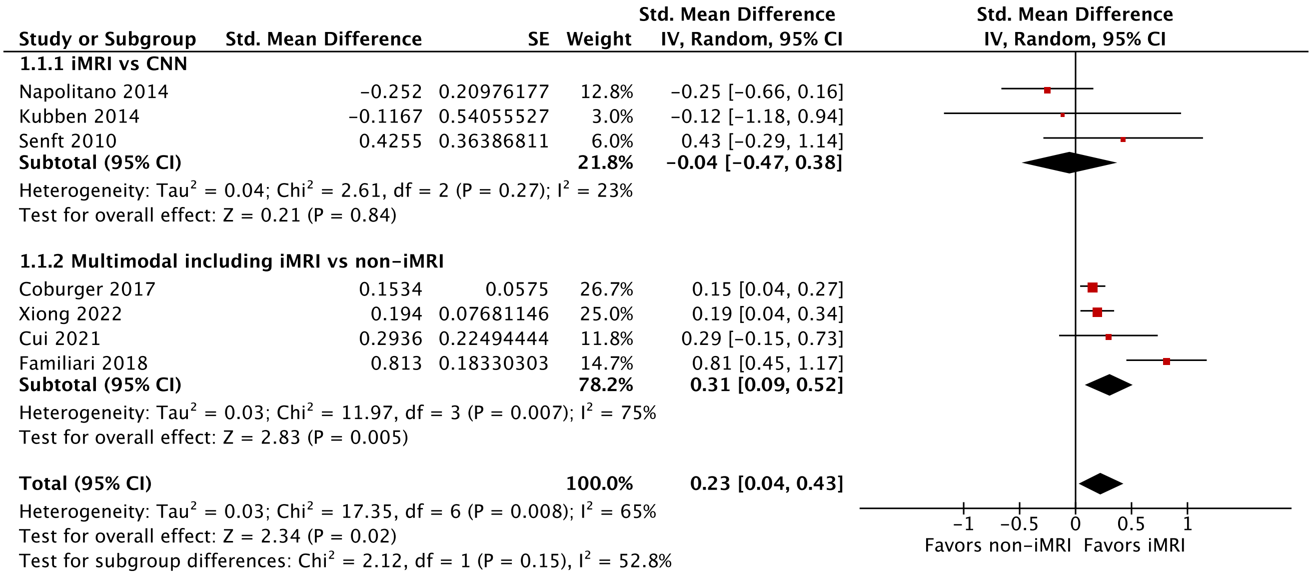
The overall PFS analysis revealed a SMD of 0.47 favoring the iMRI group over the non-iMRI group; however, this difference was nonsignificant (95% CI, −0.01, 0.52). The pooled studies exhibited significant heterogeneity ($P = 0.0003$, $I^2 = 81\%$). Since all of these 5 observational cohort studies utilized multimodal interventions, no subgroups were created.[24,25,27,29,31] These findings are depicted in Figure 3.

Gross Total Resection

The overall GTR analysis revealed a statistically significant RR of 1.57, indicating a higher likelihood of achieving GTR with the use of iMRI (95% CI, 1.21, 2.04; $P = 0.0006$), pooled studies showed substantial heterogeneity ($P = 0.0009$, $I^2 = 74\%$). In the subgroup analysis of the nonmultimodal approach, we observed a nonsignificat RR of 1.31 favoring the use of iMRI (95% CI, 0.85, 2.00). In contrast, among the multimodal intervention subgroup, a significant RR of 1.74 for GTR favoring the iMRI group was observed (95% CI, 1.43, 2.12). The analysis for GTR involved a total of 7 observational cohort studies. All of the included studies reported RR above 1, indicating a higher likelihood of achieving GTR in the iMRI group. Notably, 5 of them reached statistical significance. These findings can be found in Figure 4.

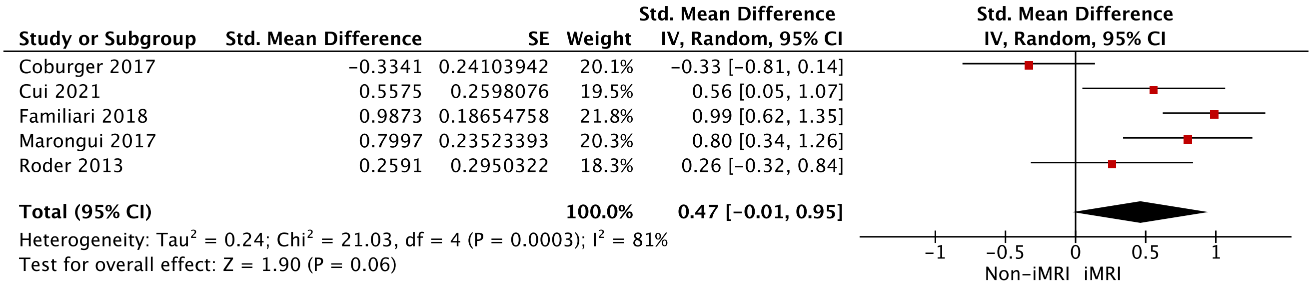
Extent of Resection

The overall EOR analysis showed a significantly higher EOR MD of 6.61% in the iMRI group (95% CI, 2.30, 10.93; $P = 0.003$). However, there was high heterogeneity among the studies ($P = 0.0001$, $I^2 = 91\%$). For this analysis, a total of 4 observational cohort studies were included. All of the studies reported an MD above 0%, in the iMRI group, indicating a higher EOR in the iMRI group. Among these studies, 3 demonstrated statistically significant differences. The detailed findings can be observed in Figure 5.



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 iMRI vs CNN				
Napolitano 2014	−0.252	0.20976177	12.8%	−0.25 [−0.66, 0.16]
Kubben 2014	−0.1167	0.54055527	3.0%	−0.12 [−1.18, 0.94]
Senft 2010	0.4255	0.36386811	6.0%	0.43 [−0.29, 1.14]
Subtotal (95% CI)			**21.8%**	**−0.04 [−0.47, 0.38]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 2.61, df = 2 (P = 0.27); I^2 = 23%				
Test for overall effect: Z = 0.21 (P = 0.84)				
1.1.2 Multimodal including iMRI vs non−iMRI				
Coburger 2017	0.1534	0.0575	26.7%	0.15 [0.04, 0.27]
Xiong 2022	0.194	0.07681146	25.0%	0.19 [0.04, 0.34]
Cui 2021	0.2936	0.22494444	11.8%	0.29 [−0.15, 0.73]
Familiari 2018	0.813	0.18330303	14.7%	0.81 [0.45, 1.17]
Subtotal (95% CI)			**78.2%**	**0.31 [0.09, 0.52]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 11.97, df = 3 (P = 0.007); I^2 = 75%				
Test for overall effect: Z = 2.83 (P = 0.005)				
Total (95% CI)			**100.0%**	**0.23 [0.04, 0.43]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 17.35, df = 6 (P = 0.008); I^2 = 65%				
Test for overall effect: Z = 2.34 (P = 0.02)				
Test for subgroup differences: Chi^2 = 2.12, df = 1 (P = 0.15), I^2 = 52.8%				

Figure 2. Overall Survival SMD Analysis.



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Coburger 2017	−0.3341	0.24103942	20.1%	−0.33 [−0.81, 0.14]
Cui 2021	0.5575	0.2598076	19.5%	0.56 [0.05, 1.07]
Familiari 2018	0.9873	0.18654758	21.8%	0.99 [0.62, 1.35]
Marongui 2017	0.7997	0.23523393	20.3%	0.80 [0.34, 1.26]
Roder 2013	0.2591	0.2950322	18.3%	0.26 [−0.32, 0.84]
Total (95% CI)			**100.0%**	**0.47 [−0.01, 0.95]**

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 21.03$, df = 4 (P = 0.0003); $I^2 = 81\%$

Test for overall effect: Z = 1.90 (P = 0.06)

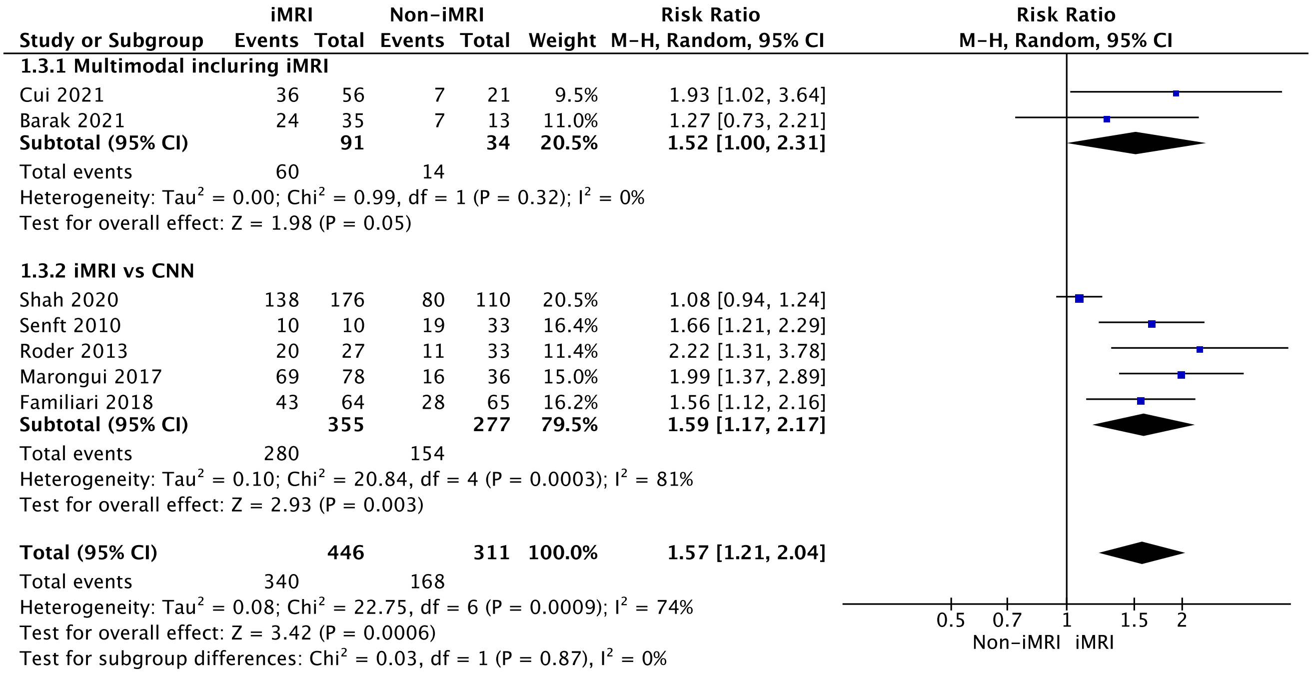
Figure 3. Progression-Free Survival SMD Analysis.

Complications

The overall complication analysis showed a nonsignificant RR of 1.32 favoring the iMRI group (95% CI, 0.77, 2.24; P = 0.31). There was some heterogeneity among the pooled studies (P = 0.20, $I^2 = 32\%$). The analysis of surgical complications included a total of 6 observational cohort studies. Four of the 6 included studies reported RR values above 1 favoring iMRI group, however only one of them reached statistical significance. These findings can be seen in Figure 6.

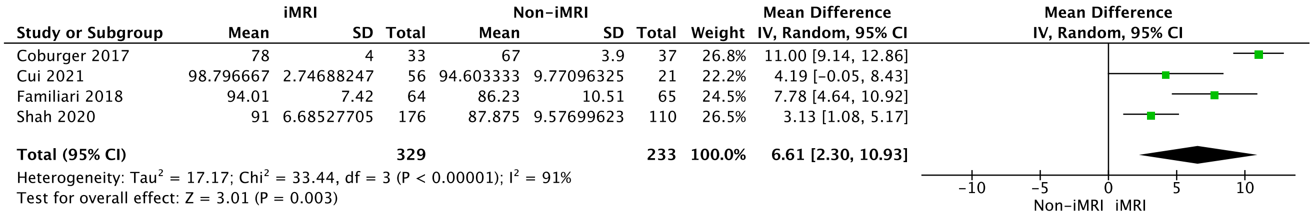
Risk of Bias Assessment

Among the 11 studies included in this analysis, risk of bias ranged from low to moderate in observational cohort studies based on ROBINS-I, and "Some concerns" for Kubben et al.,[33] the only RCT based on ROB2. While most studies mentioned that blinding surgeons to the use of iMRI was not possible, outcome assessors such as neuroradiologists and statisticians were blinded to the intervention received across the groups. Among the observational cohort studies, 9 were categorized as having a moderate risk of bias based on ROBINS-I.[24-29,31,32,34] This was mainly attributed to the observational nature of the studies, making them subject to confounding bias. To mitigate the effect of these confounders, individual studies performed subgroup analysis and adjusted for multiple variables whenever possible. However, some factors, such as the individual impact of each surgical technique apart from iMRI or the expertise of the



Study or Subgroup	iMRI Events	iMRI Total	Non−iMRI Events	Non−iMRI Total	Weight	Risk Ratio M−H, Random, 95% CI
1.3.1 Multimodal incluring iMRI						
Cui 2021	36	56	7	21	9.5%	1.93 [1.02, 3.64]
Barak 2021	24	35	7	13	11.0%	1.27 [0.73, 2.21]
Subtotal (95% CI)		**91**		**34**	**20.5%**	**1.52 [1.00, 2.31]**
Total events	60		14			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.99$, df = 1 (P = 0.32); $I^2 = 0\%$						
Test for overall effect: Z = 1.98 (P = 0.05)						
1.3.2 iMRI vs CNN						
Shah 2020	138	176	80	110	20.5%	1.08 [0.94, 1.24]
Senft 2010	10	10	19	33	16.4%	1.66 [1.21, 2.29]
Roder 2013	20	27	11	33	11.4%	2.22 [1.31, 3.78]
Marongui 2017	69	78	16	36	15.0%	1.99 [1.37, 2.89]
Familiari 2018	43	64	28	65	16.2%	1.56 [1.12, 2.16]
Subtotal (95% CI)		**355**		**277**	**79.5%**	**1.59 [1.17, 2.17]**
Total events	280		154			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 20.84$, df = 4 (P = 0.0003); $I^2 = 81\%$						
Test for overall effect: Z = 2.93 (P = 0.003)						
Total (95% CI)		**446**		**311**	**100.0%**	**1.57 [1.21, 2.04]**
Total events	340		168			
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 22.75$, df = 6 (P = 0.0009); $I^2 = 74\%$						
Test for overall effect: Z = 3.42 (P = 0.0006)						
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.87), $I^2 = 0\%$						

Figure 4. Gross Total Resection RR Analysis.



Study or Subgroup	iMRI Mean	iMRI SD	iMRI Total	Non−iMRI Mean	Non−iMRI SD	Non−iMRI Total	Weight	Mean Difference IV, Random, 95% CI
Coburger 2017	78	4	33	67	3.9	37	26.8%	11.00 [9.14, 12.86]
Cui 2021	98.796667	2.74688247	56	94.603333	9.77096325	21	22.2%	4.19 [−0.05, 8.43]
Familiari 2018	94.01	7.42	64	86.23	10.51	65	24.5%	7.78 [4.64, 10.92]
Shah 2020	91	6.68527705	176	87.875	9.57699623	110	26.5%	3.13 [1.08, 5.17]
Total (95% CI)			**329**			**233**	**100.0%**	**6.61 [2.30, 10.93]**

Heterogeneity: Tau^2 = 17.17; Chi^2 = 33.44, df = 3 (P < 0.00001); I^2 = 91%

Test for overall effect: Z = 3.01 (P = 0.003)

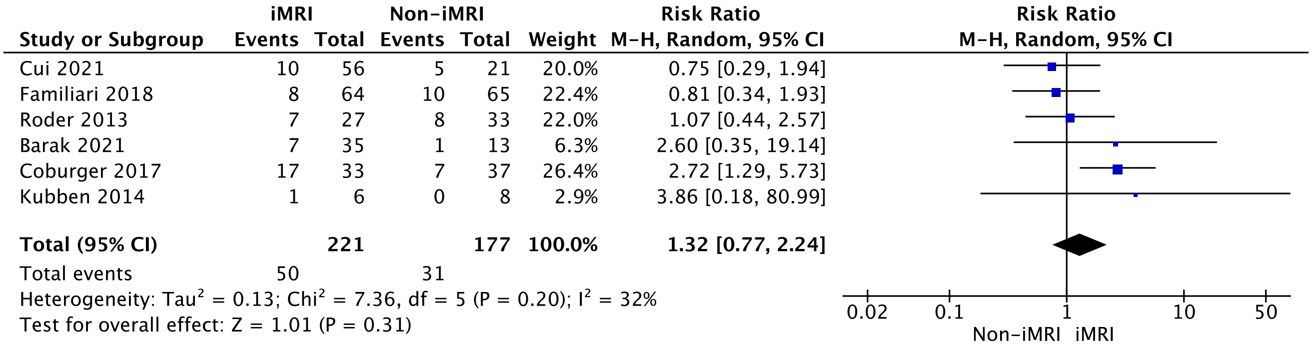
Figure 5. Extent Of Resection MD Analysis.

treating neurosurgeons may not have been adequately explored. Additionally, there was no apparent blinding of outcome assessors in 3 of the studies.[24,26,34] Shah et al.[30] was the only study in our analysis categorized as low overall risk of bias. Refer to Tables 3 and 4 for a comprehensive overview of the risk of bias assessment. A funnel plot analysis of the primary outcome showed a symmetric distribution of the studies and similar weights and point estimates which converged toward the pooled treatment effect as weight increased. These findings indicate the absence of publication bias as shown in Supplementary Figure 1.

DISCUSSION

In this study, we investigated the impact of iMRI on achieving maximal safe resection by providing real-time neuroimaging feedback to guide surgical interventions. To our knowledge, this meta-analysis represents the first comprehensive evaluation of iMRI in the context of GBM surgery to date, involving a total of 1,847 resection procedures across 11 studies. The analysis of OS indicated a marginal benefit in the iMRI group, with the majority of observational cohort studies favoring iMRI for OS. PFS analysis showed a favorable but nonsignificant effect for iMRI. Regarding GTR, all included studies reported a higher likelihood of achieving GTR in the iMRI group. The analysis of EOR demonstrated a significantly higher EOR in the iMRI group. The analysis of surgical complications did not reveal a significant difference with the use of iMRI. Overall, these findings suggest a potential benefit of iMRI in terms of OS, GTR, and EOR in GBM surgery, while maintaining a similar safety profile to conventional approach. Notably, these results have been primarily influenced by observational studies, rather than RCT. This differentiation is crucial since observational studies are subject to confounding factors. Furthermore, it is important to consider the potential effect of other variables on these findings, such as the learning curve effects and advancements in neurosurgical care over time. These factors can introduce variations in the observed outcomes and need to be carefully taken into account when interpreting the results. Future research should aim to produce high-quality RCT to obtain more robust and conclusive findings.

In recent years, there has been significant interest in the role of iMRI in glioma surgery.[35] iMRI allows for real-time assessment of tumor volume and anatomy, guiding surgeons in achieving more precise resections, and minimizing the reliance on preoperative imaging alone. While iMRI has been shown to increase the rates of GTR in glioma surgery, its impact on OS is not as straightforward.[36] Adding to previous studies, our findings suggest a slight but significant advantage in survival when iMRI was used in GBM surgery, particularly when combined with other surgical modalities. However, it is important to acknowledge the heterogeneity observed among the included studies. After performing a sensitivity analysis, we found that the study by



Study or Subgroup	iMRI Events	iMRI Total	Non−iMRI Events	Non−iMRI Total	Weight	Risk Ratio M−H, Random, 95% CI
Cui 2021	10	56	5	21	20.0%	0.75 [0.29, 1.94]
Familiari 2018	8	64	10	65	22.4%	0.81 [0.34, 1.93]
Roder 2013	7	27	8	33	22.0%	1.07 [0.44, 2.57]
Barak 2021	7	35	1	13	6.3%	2.60 [0.35, 19.14]
Coburger 2017	17	33	7	37	26.4%	2.72 [1.29, 5.73]
Kubben 2014	1	6	0	8	2.9%	3.86 [0.18, 80.99]
Total (95% CI)		**221**		**177**	**100.0%**	**1.32 [0.77, 2.24]**
Total events	50		31			

Heterogeneity: Tau^2 = 0.13; Chi^2 = 7.36, df = 5 (P = 0.20); I^2 = 32%

Test for overall effect: Z = 1.01 (P = 0.31)

Figure 6. Postoperative Complications RR Analysis.

Table 3. Risk of Bias Summary for Randomized Studies (RoB 2)

Study	Bias from Randomization Process	Bias due to Deviations from Intended Interventions	Bias due to Missing Outcome Data	Bias in Measurement of the Outcomes	Bias in Selection of the Reported Result	Overall Risk of Bias
Kubben et al. 2014[33]	Low	Some concerns	Low	Low	Low	Some concerns

Familiari et al.[27] had a notable impact on the overall heterogeneity. When removed, the heterogeneity was reduced while preserving a significant higher OS in the iMRI group ($P = 0.39$, $I^2 = 4\%$). It is important to note that Familiari et al. had distinct inclusion criteria, specifically targeting patients who had completed the Stupp protocol,[3,4] which has been shown to improve survival.

Additionally, our analysis revealed a significant improvement in GTR and EOR when iMRI was employed in GBM surgery. Both of these are key prognostic factors in high-grade glioma patients.[8,37-44] Similar to survival outcomes, GTR rates were higher when iMRI is used as part of a multimodal surgical approach. Our results demonstrate an average improvement of 6.61% in EOR when iMRI was used. These results corroborate prior research, suggesting that iMRI has substantial potential in optimizing tumor removal in glioma surgery.[36] iMRI could aid neurosurgeons to achieve precise supramaximal resection,[45] extending beyond the CE tumor area in real-time. This approach could present a promising pathway for advancements in surgical treatment. Moreover, supramaximal resection has demonstrated a positive correlation with OS and PFS, while also maintaining a reasonable postoperative safety profile.[45-48] The application of iMRI could provide critical intraoperative feedback that can influence surgical decision-making and potentially improve the precision and effectiveness of GBM interventions.

For PFS, the analysis tended to favor iMRI, but the effect size did not reach significance. This result was intriguing given the demonstrated influence of the EOR on PFS as described in the literature.[8] However, the complexity of factors affecting PFS was not extensively described in the studies. For example, O6-methylguanine-DNA-methyltransferase status in patients with GBM can predict PFS.[49] Less than half of the included studies reported the O6-methylguanine-DNA-methyltransferase status,[24,27,29,30,34] limiting our ability to comprehensively assess its impact on PFS. Future studies should aim to investigate various factors that may influence PFS when utilizing iMRI to better understand its true effects.

In terms of surgical complications, our analysis revealed no differences with the use of iMRI, indicating that the use of iMRI provides a similar safety profile in comparison to non-iMRI techniques. However, studies suggest that the length of surgery appears to be increased when utilizing iMRI.[34] For this reason, future studies should explore the cost-effectiveness of iMRI, considering the additional time required for surgical procedures.

As the use of a multimodal surgical approach in GBM surgery gains momentum,[24,25,27,31,34] it is important for future research to assess the cost-effectiveness of employing multiple simultaneous interventions. Cost reduction is becoming of significant importance in GBM treatment, particularly in the United States.[50] As we

Table 4. Risk of Bias Summary for Nonrandomized Studies (ROBINS-I)

Study	Bias due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias due to Deviations from Intended Interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall Risk of Bias Judgement
Cui et al., 2022[24]	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Roder et al., 2014[25]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Napolitano et al., 2014[26]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Familiari et al., 2018[27]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Xiong et al., 2022[28]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Coburger et al., 2018[29]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Shah et al., 2020[30]	Low	Low	Low	Low	Low	Low	Low	Low
Marongiu et al., 2017[31]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Senft et al., 2010[32]	Low	Low	Low	Moderate	Low	Low	Low	Moderate
Barak et al., 2021[34]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate

strive to optimize treatment strategies for GBM, balancing effectiveness and economic considerations becomes increasingly vital.

While this study has provided interesting findings, it is important to consider its limitations. The included studies varied in terms of their design, patient populations, surgical techniques, and outcome measures, introducing potential variability in the results. The majority of studies were observational cohorts, which are subject to biases and confounding factors. There was notable variability in MRI field strengths used and outcome reporting, with differences in units and categorization across studies, particularly OS and PFS. Furthermore, the limited number of RCT and small sample sizes in some studies may impact the statistical power and generalizability of these findings. While efforts were made to mitigate these limitations by performing subgroup and standardized statistical analyses, these restrictions highlight the need for larger, well-designed RCT with standardized approaches to provide more definitive evidence on the impact of iMRI in GBM surgery.

Our findings offer relevant information to neurosurgeons in clinical practice, providing a deeper understanding of the clinical implications associated with iMRI compared to the conventional microsurgical approach using neuronavigation.

CONCLUSION

This meta-analysis provides valuable insights on the potential of iMRI in improving surgical outcomes for patients with GBM, especially when integrated within a multimodal surgical approach. The increased OS, GTR, and EOR observed with iMRI use could translate into potential benefits for patients. While the PFS benefits were non-significant, the insights gained from this study contribute to our understanding of the relationship between iMRI use and survival outcomes. Furthermore, well-designed RCT will be essential to validate these findings and to explore potential factors contributing to heterogeneity in survival outcomes.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Pavel S. Pichardo-Rojas: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Juan Carlos Angulo-Lozano:** Conceptualization, Investigation, Methodology. **José Alfonso Alvarez-Castro:** Data curation, Validation. **Diego Vázquez-Alva:** Data curation. **Ricardo Alfonso Osuna-Lau:** Data curation. **Luz Camila Choque-Ayala:** Data curation. **Nitin Tandon:** Conceptualization, Methodology, Writing – review & editing. **Yoshua Esquenazi:** Conceptualization, Validation, Writing – review & editing.

ACKNOWLEDGMENTS

Partial results of the present study will be presented at the annual meeting of the Congress of Neurological Surgeons (CNS), in September 2023, in Washington, D.C.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 19 July 2023; accepted 7 December 2023

Citation: World Neurosurg. (2023).
https://doi.org/10.1016/j.wneu.2023.12.042

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APPENDIX: SEARCH STRATEGY

PubMed

("Glioblastoma"[MeSH Terms] OR "Glioblastoma"[MeSH Terms] OR "Glioblastoma"[All Fields] OR "glioblastomas"[All Fields] OR "GBM"[All Fields] OR "glioblast*"[All Fields] OR "glioma"[MeSH Terms] OR "glioma"[All Fields] OR "gliomas"[All Fields] OR "glioma s"[All Fields] OR "astrocyto*"[All Fields]) AND ("Magnetic Resonance Imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "Magnetic Resonance Imaging"[All Fields] OR "mri"[All Fields] OR ("Magnetic Resonance Imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "Magnetic Resonance Imaging"[All Fields]) OR "Magnetic Resonance Imaging"[MeSH Terms]) AND ("intraoperat*"[All Fields] OR "intrasurg*"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract] OR ("cohort studies"[MeSH Terms] OR "case-control studies"[MeSH Terms] OR "comparative study"[Publication Type] OR "risk factors"[MeSH Terms] OR "cohort"[Text Word] OR "compared"[Text Word] OR "groups"[Text Word] OR "case control"[Text Word] OR "multivariate"[Text Word])) AND ("Overall survival"[All Fields] OR "Progression Free Survival"[All Fields] OR "Extent of Resection"[All Fields] OR "Gross Total Resection"[All Fields]).

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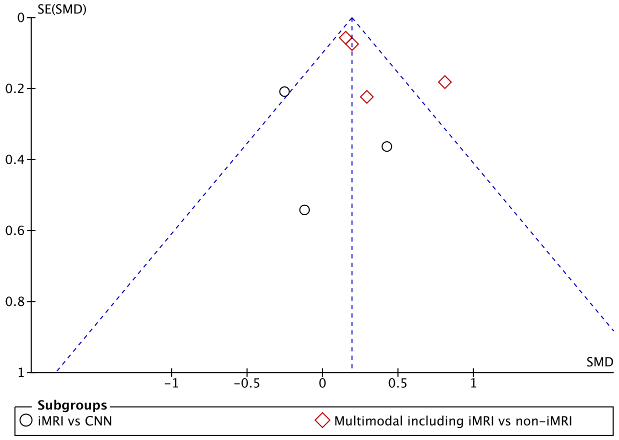
('glioblastoma'/exp OR gbm OR glioblasto* OR astrocyto* OR glioblastoma) AND ('intraoperative period'/exp OR intrasurg* OR intraop*) AND ('surgery'/exp OR surg* OR operat*) AND ('nuclear magnetic resonance'/exp OR ((magnetic AND resonance AND imaging OR mri OR magnetic) AND resonan*) OR t2 OR t1 OR flair OR dwi OR adc) AND ('clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compared':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab OR ('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk) AND ('overall survival' OR 'progression free survival' OR 'extent of resection' OR 'gross total resection').

SUPPLEMENTARY DATA



Supplementary Figure 1. Symmetric funnel plot assessing publication bias and heterogeneity.

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