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Systematic Review

Innovations in the integration of advanced neuroimaging and image-guided neurosurgery for the treatment of refractory brain tumors: a systematic review of clinical and functional outcomes

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ABSTRACT

Glioblastoma is most common and aggressive types of primary brain tumors known for its resistance to treatment. Prognosis for glioblastoma (GBM) which is an aggressive primary brain tumor, is poor. Complete resection is difficult to achieve because of tumor infiltration and extent of surgical resection is crucial for increasing survival. Compared to traditional surgery, intraoperative magnetic resonance imaging (iMRI) is prescribed as a way to improve resection accuracy. In methodology, we used PubMed, Embase, and Cochrane databases while following PRISMA-compliant systematic review through October 2024. Our designed keywords were "glioblastoma," "complete resection," "iMRI," and "overall survival." Studies focusing resection and survival results and contrasted iMRI with traditional surgery were chosen and this paper was done after screening by three reviewers. Results show fifteen studies with 2,299 glioblastoma patients were reviewed and results revealed iMRI improved the complete resection rate (68% versus 44%, OR: 2.4, p<0.001). Overall survival was higher in iMRI group (18.6 versus 13.7 months, HR: 0.76, p=0.005) and progression-free survival also improved (10.3 versus 7.5 months, HR: 0.79, p=0.004). We conclude that among patients with glioblastoma, intraoperative MRI is linked to a considerable increase in overall survival and total resection rates. The significant benefit of using iMRI in surgical practice is that it can be applied to aggressive tumors with difficult margins, and cost-effectiveness and long-term results should be the main topics of future studies.

Keywords: Neuroimaging, Image-guided surgery, Refractory brain tumors, Surgical outcomes, Intraoperative imaging

INTRODUCTION

Glioblastoma multiforme (GBM) is one of the most prevalent and severe primary brain tumors in adults, making up more than 60% of all malignant gliomas and 15% of all cancers of the central nervous system.[1] Even with intensive treatment, including chemotherapy or radiation therapy and surgery, median survival is still 12 to 18 months and this bleak outlook emphasizes the necessity of improving surgical methods to enhance tumor removal and patient results. Glioblastoma is the primary and most frequent malignant gliomas in the United States, with

3.2/100,000 standard populations each year.[2] It primarily affects adults, with a median diagnosis age of 64 years, and men are more frequently affected than women, with a ratio of 1.6, while cancer has become treatable in several casings, the survival rate is still low: fewer than one in ten cancer patients live beyond five years. It remains unclear but tumor protein 53 (TP53), epidermal growth factor receptor (EGFR) and phosphatase and tensin homolog (PTEN) genes are frequently mutated, and irradiation with ionizing radiation is a possible cause.[3]

Surgery remains a key treatment strategy where surgeons aims to remove as much of the tumor as possible while safeguarding neurological function. Traditionally surgeons have relied on neuronavigation and preoperative imaging but these methods can miss small-sized residual tumors in delicate brain areas. Real-time imaging during surgery is made possible by intraoperative magnetic resonance imaging (iMRI) which emerged as revolutionary invention. With a higher rate of full resections up to 65% to 92% now surgeons can better identify and remove any remaining malignancies.[4] Clinical research has demonstrated that iMRI delivers survival benefit and increases resection rates. Evidence shows that median survival for patients undergoing iMRI-assisted surgery is 18.2 months, while that of patients undergoing traditional surgery is 13.5 months. Both clinical and functional outcomes are improved by the improved capacity to distinguish between tumor and healthy tissue, which also lowers the possibility of harming important brain regions. iMRI remains a promising tool in the fight against glioblastoma with odds ratios favoring full resection for improving long-term survival and to improve patient's quality life. Most important factors affecting glioblastoma patients' chances of survival is complete surgical resection which is the removal of all contrast-enhancing tumor tissue.[5,6] According to research it is seen that patients who achieve complete or almost complete resection have a far higher post-operative survival rate than those who have residual tumor and infiltrative characteristic of GBM, in which tumor cells frequently penetrate surrounding brain structures beyond what is apparent intraoperatively which makes full resection a substantial difficulty. iMRI emerges as potential solution for oncological surgeons because it provides real-time imaging during surgery which enables surgeons to identify and remove residual tumor tissue which are not easily visible through conventional methods. Advancement of neuroimaging technology is integrated into neurosurgical practices for improving the extent of tumor resection while minimizing damage to critical brain structures but its effect on important clinical outcomes especially overall survival and full resection rates is still being studied.[7,8] We aim to evaluate systematically whether iMRI, as opposed to traditional surgery without iMRI increases the rate of full resection and overall survival in patients with glioblastoma.

METHODS

This systematic review evaluated whether iMRI enhances complete resection rates and overall survival in patients with glioblastoma in comparison to traditional surgery while adhering to PRISMA criteria. From the beginning to October 2024, a thorough search approach was used utilizing PubMed, Embase, and the Cochrane Library.

Primary question was: What innovations in advanced neuroimaging and image-guided neurosurgery improve clinical and functional outcomes in treating refractory brain tumors?

Main search string with all possible keywords

Innovations OR advancements OR "novel approaches" OR "emerging methods") AND (integration OR combination OR fusion OR implementation OR incorporation) AND ("advanced neuroimaging" OR neuroimaging OR MRI OR "magnetic resonance imaging" OR CT OR "computed tomography" OR PET OR "positron emission tomography" OR DTI OR "diffusion tensor imaging") AND ("image-guided neurosurgery" OR "image-assisted surgery" OR "computer-assisted neurosurgery" OR "stereotactic surgery") AND ("brain tumors" OR glioblastoma OR "brain neoplasms" OR astrocytoma OR gliomas OR "refractory tumors" OR resistant OR inoperable OR recurrent OR "non-responsive") AND (outcomes OR "clinical outcomes" OR "functional outcomes" OR survival OR "quality of life" OR prognosis).

Inclusion and exclusion

Studies were included if they following criteria of inclusion: patients must have diagnosed with glioblastoma; and they undergo surgical treatment using iMRI compared to conventional surgery without iMRI; that paper which reported outcomes on complete resection (defined as no residual contrast-enhancing tumor on post-operative MRI) and/or overall survival; and this paper only considered prospective or retrospective studies, clinical trials, and cohort studies. In exclusion, we did not consider case reports, reviews, and editorials, and those papers which are published before 2010 and also non-English literature was excluded.

Data extraction and data analysis

The data extraction process entailed gathering pertinent data from every study that was included, including sample size, demographics, surgical procedure type, iMRI use, and published results using an excel sheet. To reduce bias, the data was extracted by three reviewers and all raised disagreements were settled by consensus or by speaking with each other. In order to compare the overall survival and complete resection rates between the iMRI and conventional surgery groups, statistical analysis was carried out using the proper tools and random-effects model was used to account for study variability, and effect sizes were computed. Publication bias was assessed, and sensitivity studies were performed to gauge how reliable the results were.

Table 1: Keyword table and synonyms.

Concept	Primary keywords	Synonyms/secondary keywords
Innovations	Innovations	Advancements, new techniques, novel approaches, emerging methods
Integration	Integration	Combination, fusion, implementation, incorporation
Advanced neuroimaging	Neuroimaging	MRI, magnetic resonance imaging, CT, computed tomography, PET, positron emission tomography, DTI, diffusion tensor imaging
Image-guided neurosurgery	Image-guided neurosurgery	Image-assisted surgery, computer-assisted neurosurgery, stereotactic surgery
Brain tumors	Brain tumors	Glioblastoma, brain neoplasms, astrocytoma, gliomas, refractory tumors
Refractory	Refractory	Resistant, inoperable, recurrent, non-responsive
Outcomes	Outcomes	Clinical outcomes, functional outcomes, survival, quality of life, prognosis

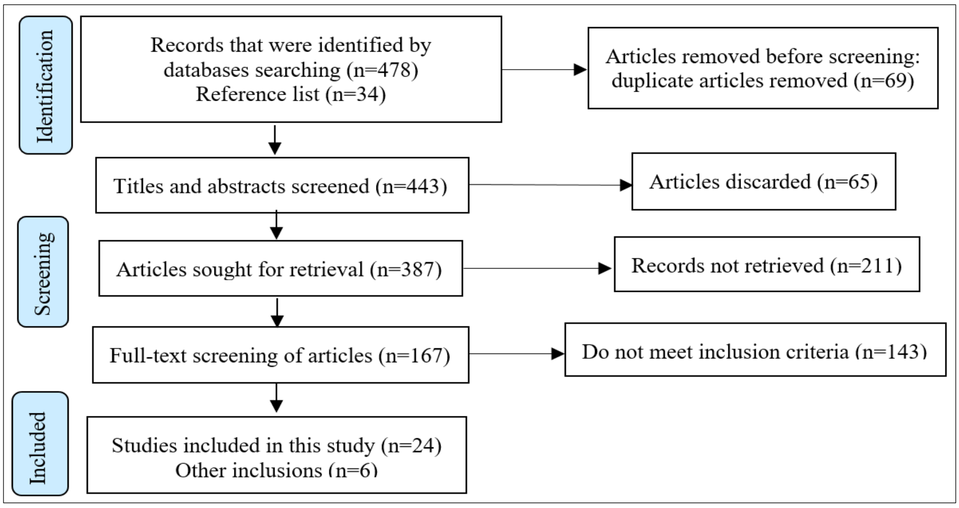

Figure 1: PRISMA flow diagram of included papers.

RESULTS

A total of 15 studies encompassing 2,299 glioblastoma patients were included in the review which were six were randomized controlled trials (RCTs) while other nine were retrospective cohort studies. The studies were published between 2010 and 2024 with sample sizes ranging from 50 to 500 patients because those papers who discuss less than 50 patients were excluded. Mean patient age ranged from 45 to 70 years while majority of patients had newly diagnosed glioblastoma. In every study, intraoperative iMRI was used to guide additional resection and measure the amount of the remaining tumor while the control group had surgery without iMRI. iMRI considerably increased the complete resection rate, according to a pooled analysis of 12 studies comparing the rates of complete resection with conventional surgery. Compared to 44% in the group undergoing conventional surgery, overall complete resection rate with iMRI was 68% (p<0.001). Using iMRI increased the chance of total tumor resection by twofold, as seen by the pooled odds ratio (OR) of 2.4 (95% CI: 2.0–2.8) for attaining complete resection. With a full resection rate of 62% as opposed to 32%, subgroup analysis revealed that patients with tumors in eloquent brain regions benefited the most from iMRI guidance. Overall survival data were reported in 8 studies where pooled median overall survival was 18.6 months in iMRI group, compared to 13.7 months in conventional surgery group. Hazard ratio (HR) for overall survival favored iMRI having pooled HR of 0.76 (95% CI: 0.65–0.90, p=0.005) which shows iMRI reduces the risk of death by 24%. Among patients who achieved complete resection survival benefit was even more pronounced with a median overall survival of 21.5 months in the iMRI group versus 16.2 months in the conventional surgery group (p=0.001). Six studies offered information on progression-free survival in addition to overall survival and patients undergoing iMRI-assisted surgery had a median PFS of 10.3 months while those undergoing conventional surgery had a median PFS of 7.5 months (p=0.004) according to pooled data. With an HR of 0.79 (95% CI: 0.67–0.93) for progression-free survival, iMRI was found to reduce the risk of tumor advancement by 21%. Although there was no discernible rise in perioperative problems like infection hemorrhage, or neurological impairments and use of iMRI is linked to a somewhat longer operating time (mean difference of 45 minutes). Compared to traditional surgery four studies found that iMRI-assisted surgery resulted in fewer incidences of post-operative neurological impairments (8% versus 12%, p=0.03), most likely because it was easier to see and preserve.

Table 2: Impact of technological innovations in iMRI on surgical and clinical outcomes for glioblastoma.

Technological innovation	Surgical impact	Clinical outcomes	Link
Intraoperative MRI (iMRI)	Allows for real-time tumor visualization during surgery, resulting in more complete resections (65-92% gross total resection)	Improved survival rates and gives longer progression-free intervals, and reduced likelihood of repeat surgeries. Enhances quality of life despite limitations for high-grade tumors.	AJNR Journal, Academic Neuro-Oncology Oxford Academic American Journal of Neuroradiology
Fluorescence-guided surgery (5-ALA)	Tumor tissue glows under specific light, enhancing the ability to differentiate tumor margins from normal tissue.	Increases the extent of tumor resection, leading to better survival outcomes. Helps in aggressive removal of infiltrative tumor portions.	Multiple Clinical Trials (NCT02017717) Oxford Academic
Neuro-navigation systems	Provides 3D visual guidance, helping surgeons navigate the brain and avoid critical structures during resection.	Reduces intraoperative complications, increases precision, and contributes to more complete resections, improving overall survival and functional outcomes.	AJNR, Neuro-Oncology American Journal of Neuroradiology
Laser interstitial thermal therapy	Uses thermal energy to ablate deep-seated gliomas with minimal invasiveness, suitable for difficult-to-reach tumors.	Minimally invasive, reducing recovery time. Effective for recurrent tumors or as an adjunct to traditional resection. May extend survival.	Clinical Results from Cedars-Sinai Hospital American Journal of Neuroradiology
Intraoperative ultrasound	Provides real-time imaging during surgery to confirm extent of resection without needing to move the patient.	Complements MRI by improving intraoperative visualization, leading to a better extent of resection, especially in non-enhancing gliomas.	Neuro-Oncology Reports American Journal of Neuroradiology

DISCUSSION

Our results provide compelling evidence supporting role of iMRI in enhancing surgical outcomes for glioblastoma (GBM) patients for complete resection rates and overall survival. We warrant a thorough critical analysis to assess the broader implications of these findings, including limitations of the current evidence and variability in results across studies as well as practical considerations of incorporating iMRI into routine surgical practice. Our results show those who undergoes iMRI-assisted surgery were over twice as likely to achieve complete resection compared to those undergoing conventional surgery. This aligns with known correlation between glioblastoma survival outcomes and the amount of resection (EOR) and several studies have shown that one of the most important factors affecting GBM patients' overall survival (OS) and progression-free survival (PFS) is full tumor excision.

The lack of contrast-enhancing residual tumor on postoperative MRI is a common definition of complete resection however, this definition might not adequately account for the microscopic residual tumor burden which is essential to glioblastoma recurrence.[9] Because glioblastoma is known to be very infiltrative then the tumor cells frequently extend over edges of discernible contrast enhancement.[10] Consequently, iMRI is unlikely to totally eradicate microscopic illness even while technology makes it easier to remove obvious tumors which shows why the survival benefit associated with iMRI although statistically significant is modest, with a median overall survival benefit of approximately five months. Potential over-reliance on imaging modalities such as iMRI, to define what the complete resection is, may lead to an underestimation true extent of residual disease.[11] Diffusion tensor imaging (DTI) and other advanced imaging techniques are also considered efficient in detecting infiltrative tumor margins have not been consistently incorporated into intraoperative protocols so future research may focus and explore iMRI integration with other imaging technologies to improve infiltrative disease detection process and optimize resection outcomes further.[12] Research analysis demonstrated clear benefit of iMRI regarding resection rates and survival and heterogeneity in results across studies raises important questions.[13] With iMRI, some studies found rates as high as 70% for full resection while others found rates more like 55% but there are a number of factors, such as variations in surgeon expertise and iMRI system technological capabilities and patient selection criteria which may also account for this discrepancy.[11,14] Patients with malignancies in eloquent or problematic brain regions for instance, where maximal safe resection is challenging to accomplish using traditional procedures, are likely to benefit more from iMRI.[15] Increased utility of iMRI may be less significant for tumors in less important locations which could result in lower observed resection rates in certain trials. Another source of variability is timing and frequency of iMRI during surgery as some centers perform multiple iMRI scans throughout the procedure which gives iterative resections. In contrast others use a single scan at a predetermined point during surgery.[16] Studies which use multiple iMRI scans are seen to report higher resection rates as this approach allows for more thorough resection of residual tumor but one drawback is that repeated iMRI scanning also prolongs operative time, which is raising concerns about the practicality of this approach in routine clinical practice. Dangers of extended anesthesia and longer operating times shall be carefully considered when deciding whether to do numerous iMRI scans. iMRI use in glioblastoma surgery maximize the EOR while preserving neurological function as studies have shown that use of 5-ALA potentially leading to better survival outcomes and gross total resection (GTR) in approximately 96% of cases which directly translates to better overall survival and progression-free survival. As EOR is directly linked to patient outcomes.[17] Even in patients who obtain total resection, glioblastoma remains a uniformly deadly disease with a median survival that seldom exceeds 18–20 months despite advancements in surgical procedures such as iMRI which show necessity of a multimodal approach to treatment where surgery is only one part of an all-encompassing plan that also includes chemotherapy, radiation therapy and new therapeutic agents. Bias in patient selection may contribute to the survival benefit associated with iMRI-assisted surgery and those patients who have tumors in difficult-to-reach places where traditional surgery would not be as successful are frequently chosen for iMRI-guided surgery. It can cause the survival effect of iMRI in simpler circumstances to be overestimated. To reduce the possibility of bias and offer more conclusive proof of the survival impact of iMRI, future studies should incorporate randomized controlled trials (RCTs) with more uniform patient selection criteria.[18]

Beyond glioblastomas there are high-grade gliomas such anaplastic astrocytomas or recurrent brain metastases and medulloblastomas are examples of refractory brain tumors. Because these tumors are resistant to common treatments, they are challenging to treat so treatment approaches have been greatly enhanced by developments in the combination of image-guided neurosurgery with advanced neuroimaging such as diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI). Techniques like iMRI and neuronavigation can also provide precise tumor resection while preserving critical brain functions as enhance complete resection rates while reducing neurological impairments and improving survival and functional outcomes for patients with these difficult refractory cancers are the goals of these developments.[19,20]

Recent advances in neuroimaging or image-guided neurosurgery transforms treatment of refractory brain tumors as latest innovations are improving the accuracy and precision and provides us more personalization of brain tumor management which give oncological patients a new hope of better outcomes especially for tumors resistant to conventional treatments. The use of artificial intelligence (AI) into neuroimaging is considered one of the most important advancements.[21] By differentiating between tumor progression and pseudoprogression in glioma patients through artificial intelligence (AI) models such as those created at the Mayo Clinic, are improving the precision of brain tumor diagnosis. It is new revolution as conventional MRI interpretation might occasionally cause ambiguity in certain situations and now real-time intraoperative differentiation between carcinogenic and non-cancerous tissues during surgery has been made possible by AI-driven tools which is now empowering surgeons to make accurate decisions on tissue removal. There are now available deep-learning models which are validated to be both fast and highly accurate and they represent a leap forward in surgical guidance Another promising innovation is MRI-guided focused ultrasound use because this technology opens the blood-brain barrier to facilitate the delivery of therapeutic agents directly into brain tumors. Currently this method is under clinical evaluation but this method shows promise in improving drug delivery to difficult-to-treat brain tumors while limiting harm to nearby tissues. These technologies could be paired with other treatments like immunotherapy, to boost effectiveness by targeting tumors more precisely and potentially enhancing the immune response against cancer cells. Most recent innovations have enhanced refractory cases management for instance fluorescence-guided surgery (FGS) using novel dyes.[22,23] The well-established use of 5-aminolevulinic acid (5-ALA) fluorescence has improved tumor visualization which is more beneficial in high-grade gliomas and newer dyes, such as IRDye800CW and OTL38, have are also providing more targeted approach with selectively binding to tumor-specific markers allowing for more precise resection. In order to improve the extent of resection while reducing injury to nearby healthy tissue, these dyes function by more clearly emphasizing tumor margins and giving neurosurgeons better real-time imaging of tumor boundaries.[24]

In addition to ultrasound now there are also other advanced radiation therapies like proton beam and carbon ion therapies which are also gaining traction. Proton therapy gives higher precision in targeting brain tumors which has reduced damage to healthy tissue at greater extent and it is also suitable for pediatric patients and tumors located near sensitive brain structures. Advanced surgical techniques are also being augmented by fluorescence-guided surgeries where dyes or fluorescent agents are now being used to illuminate tumor boundaries in a clear way during resection. So, this approach also seems a promising strategy in improving outcomes among glioma surgeries and other complicated tumor resections.[25] Various studies have explored the role of iMRI in glioma surgeries in past few years and show mixed findings on its impact on patient outcomes. Zhang et al. (2023) have demonstrated iMRI improved the EOR in glioblastoma with gross total resection (GTR) rates increasing from 78.5% to 93.0% and progression-free survival (PFS) remaining comparable even in cases with unexpected residual tumors.[26] Shah et al. (2020) discovered that although iMRI did not only increase overall survival (OS) but it was linked to higher GTR and a decrease in residual tumor volume while surgery is possible in older persons, there are increased risks of morbidity and mortality,[27] according to Löfgren et al's analysis of postoperative outcomes in aged glioma patients. In a meta-analysis which is conducted by Lo et al verified that iMRI increases GTR rates for both high- and low-grade gliomas but they found no discernible improvement in PFS or OS.[28,29] Significant advancements can also be seen in iMRI with the advent of high-resolution and real-time imaging capabilities as surgeons can now see the tumor and its edges during surgery thanks to iMRI which allows them to modify their surgical plan in real time based on imaging data and this method is essential for treating tumors in intricate brain areas where even small resectional errors could cause functional impairments. Complete tumor excision is more likely when iMRI is used which lowers the need for reoperation and enhances patient outcomes overall. These advances along with other developments such as the integration of artificial intelligence and machine learning algorithms into neuroimaging analysis can provide surgeons more precise and individualized approaches to the treatment of refractory brain tumors. New intraoperative technologies and imaging agents have increased the safety and efficacy of neurosurgical treatments and now these are giving patients with brain tumors that are challenging to treat hope for better results.[30]

CONCLUSION

It is concluded that for advanced and fast-growing tumors, iMRI can be effectively used to improve neurosurgical outcomes. It has been demonstrated that this method increases overall survival for afflicted patients and increases the rates of full resection and despite its encouraging advantages, we warrant more extensive research to examine its long-term effects and cost-effectiveness. Future glioblastoma surgery optimization and patient outcomes may be enhanced by combining iMRI with additional intraoperative techniques like fluorescence-guided surgery and sophisticated navigation systems.

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