Review

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Surgical outcomes of glioblastoma multiforme in low and middle-income countries: current state and future directions

Muili Abdulbasit Opeyemi, MBBS[a], Nicholas Aderinto, MBBS[a], Ayodeji Akinmeji, MBBS[c], Fatihi Bamigbola Mustapha, MBBS[d], Jolayemi Mustapha Mubarak, MBBS[d], Ayodele Yusuf Joshua, MBBS[b], Piel Panther Kuol, MBChB[e,*], Adeyemo Rebecca Opeyemi, MBBS[a], Kehinde Alare, MBBS[a], Gbolahan Olatunji, MBBS[d], Kokori Emmanuel, MBBS[d]

Abstract

Glioblastoma (GBM) is a highly aggressive and deadly brain tumor. The challenges in managing GBM in low- and middle-income countries (LMICs) have been underexplored. This review provides a review of surgical management techniques, challenges, outcomes, and future directions for GBM treatment in LMICs. A search of academic databases yielded studies from various LMICs, focusing on surgical management techniques and their outcomes. The data were analyzed in the context of socio-economic, cultural, and infrastructural factors. Comparative analyses were performed to highlight disparities between LMICs and high-income countries. GBM management in LMICs faces multi-faceted challenges, including healthcare infrastructure deficiencies, delayed diagnosis, high treatment costs, cultural beliefs, and limited research funding. This adversely affects patient outcomes and survival rates. Surgical excision followed by radiation and chemotherapy remains the standard of care, but LMICs have not significantly benefited from recent advancements in GBM management. Intraoperative neurosurgery ultrasound is identified as an affordable and practical alternative for LMICs. Patient outcomes following GBM surgery in LMICs vary widely, making early detection challenging. Cultural sensitivity and ethical considerations are crucial factors in improving healthcare practices. Surgical management of GBM in LMICs is hindered by complex challenges that require multi-faceted interventions. By addressing socio-economic, cultural, and infrastructural factors, LMICs can improve GBM care and outcomes. Raising awareness and advocating for change are crucial steps in this process.

Keywords: challenges, glioblastoma, surgery

Introduction

Glioblastoma multiforme (GBM), a grade IV astrocytoma, represents one of the most aggressive and prevalent primary brain tumors in adults[1]. Despite considerable progress in medicine, GBM patients continue to face a grim prognosis, with a median survival time of merely 12–15 months, even when provided with the most advanced treatments available[2]. While extensive studies have been conducted on the surgical management and outcomes of GBM in high-income countries, there is a notable gap in the literature regarding addressing this critical topic in low- and middle-income countries (LMICs)[3].

The incidence of GBM exhibits significant global variation, with Caucasians displaying a notably higher prevalence compared to African Americans[4]. Contributing factors include the

HIGHLIGHTS

- Glioblastoma (GBM) is a highly aggressive and deadly brain tumor.
- GBM management in low- and middle-income countries (LMICs) faces multi-faceted challenges, including healthcare infrastructure deficiencies, delayed diagnosis, high treatment costs, cultural beliefs, and limited research funding. This adversely affects patient outcomes and survival rates.
- Surgical excision followed by radiation and chemotherapy remains the standard of care, but LMICs have not significantly benefited from recent advancements in GBM management. Intraoperative neurosurgery ultrasound is identified as an affordable and practical alternative for LMICs.

Departments of [a]Medicine, [b]Anatomy, Ladoke Akintola University of Technology, Ogbomoso, [c]Department of Medicine and Surgery, Olabisi Onabanjo University, Ago Iwoye, [d]Department of Medicine and Surgery, University of Ilorin, Ilorin, Nigeria and [e]Department of Medicine and Surgery, Moi University School of Medicine, Eldoret, Kenya

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**Corresponding author. Address: Moi University School of Medicine, Eldoret, Rift Valley Kenya. Tel.: +254 700 559 644. E-mail: jokpiel003@gmail.com (P. P. Kuol).*

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absence of tumor registries, instances of preoperative mortality due to cultural and religious beliefs hindering medical intervention, and a shortage of neuropathologists or general pathologists experienced in diagnosing the condition[5]. Also, there is limited knowledge on the incidence and prevalence of GBM in low and middle-income countries due to limited advancement in neurosurgical research and technology in these regions[6,7].

A possible reason for the seemingly low prevalence of GBM in LMICs is the underreporting of recognized risk factors, such as exposure to radioactive substances, and the inadequate documentation of familial syndromes like Lynch and Li-Fraumeni disorders[8]. In Morocco, a study highlights the under-researched nature of GBM survival due to the absence of a national tumor registry and limited qualitative epidemiological data, even though regional research projects indicate that GBM constitutes a significant portion of intracranial tumor malignancies[9,10]. The varying incidence of GBM across populations may be attributed to previously undiscovered genetic susceptibilities, environmental influences, and cultural practices[11]. Recent research suggests that the high incidence of consanguinity in Jordan may be responsible for a significant proportion of high-grade GBM in infants[11]. Additionally, higher socio-economic status is linked to a greater prevalence of GBM when comparing high-income and low- and middle-income nations on a national and international scale[12]. These variations are often attributed to increased access to diagnostic and healthcare services.

However, healthcare delivery systems in LMICs face unique challenges, including limited access to advanced medical facilities, shortages of skilled healthcare professionals, economic constraints, and social disparities, all of which complicate GBM diagnosis and treatment[13]. Therefore, it is crucial to explore the surgical management of GBM in LMICs and compare their outcomes with those in high-income countries.

This review aims to analyze the surgical outcomes of GBM in LMICs by reviewing the current surgical practice used for GBM in LMICs by analyzing their positive and negative outcomes in the management of the condition.

Methodology

This narrative review aimed to provide a review of the surgical outcomes of GBM in LMICs. The review focused on studies published in English between 2008 and October 2023 that investigated surgical approaches and outcomes for GBM patients in LMICs.

Literature search strategy: We conducted an extensive search using PubMed, Scopus, Web of Science, and Google Scholar. Search terms included "glioblastoma," "surgical management," "outcomes," and "low- and middle-income countries."Boolean operators (AND, OR) were employed to refine the search. Additionally, we explored reference lists of relevant articles for any potential sources. A supplementary hand search was performed Using the Google and Microsoft Bing search engines (Google Inc., Mountain View, California, USA) to identify relevant Gray literature.

Study selection: Initial screening of titles and abstracts was conducted by two independent reviewers to identify relevant articles. A full-text review of selected articles followed, ensuring that they met the inclusion criteria. Inclusion criteria were studies published in English between 2008 and October 2023 that investigated

(1) surgical approaches used in the management of glioblastoma multiformes in LMICs
(2) survival rates, and factors in surgical outcomes for GBM patients in LMICs.

Exclusion criteria were studies published as reviews or conference papers. Any discrepancies between reviewers were resolved through consensus or consultation with a third reviewer.

Data extraction, synthesis, and analysis: Using a standardized data extraction form, important data from the selected studies was drafted in a tabular form. A narrative synthesis approach was also utilized to organize and analyze the collected data. Studies were grouped by common themes with findings presented descriptively, emphasizing identifying trends and variations among studies that were exclusively analyzed.

Results

A total of 300 articles were found through the literature search. Out of these, 200 articles were screened at the title and abstract level for eligibility. At this stage, 100 articles were excluded. Furthermore, 100 articles underwent a full-text article screen. Out of these, only 24 articles were found suitable for the final qualitative data synthesis (Fig. 1).

Surgical techniques

In pursuing effective GBM treatment, several surgical approaches have yielded diverse outcomes and insights from different regions. See Table 1. Faustino *et al.*[14] conducted Maximal Surgical Resection, utilizing surgical resection as a local treatment method for eight patients, with univariate analysis highlighting its significant association with improved overall survival. Meanwhile, He *et al.*[15] adopted surgical resection with fluorescence-guided surgery, achieving complete resection in 82.76% of patients. The employed fluorescence material exhibited a sensitivity of 94.44% and specificity of 88.24%, facilitating accurate tumor identification.

Touati *et al.*[16] explored Large resections, Partial resections, and Biopsy techniques, revealing varying mean overall survival times: 39.6 months for biopsies, 40.5 months for large resections, and 53.2 months for partial resections. In a case report from Brock *et al.*[17], Surgical Resection yielded a positive outcome as, after one year, no evidence of residual or recurrent tumors was detected. However, complications arose during resection, resulting in unexpected bleeding, lesion growth, and edema, resembling an arteriovenous malformation. Elsakka and colleagues reported positive results with Awake Craniotomy and Subtotal Tumor Resection, with no documented negative treatment outcomes. On the other hand, Uche *et al.*[19] explored microsurgical resections, biopsies, and cerebrospinal fluid (CSF) Diversion techniques, noting a decline in overall survival rates over time. Wu *et al.*[20] employed Surgical Resections and Craniotomy, reporting no negative treatment outcomes. Kanmounye *et al.*[21] utilized External Cystic Drainage, resulting in significant recovery in the patient's movement and speech, with no reported negative treatment outcomes in this case.

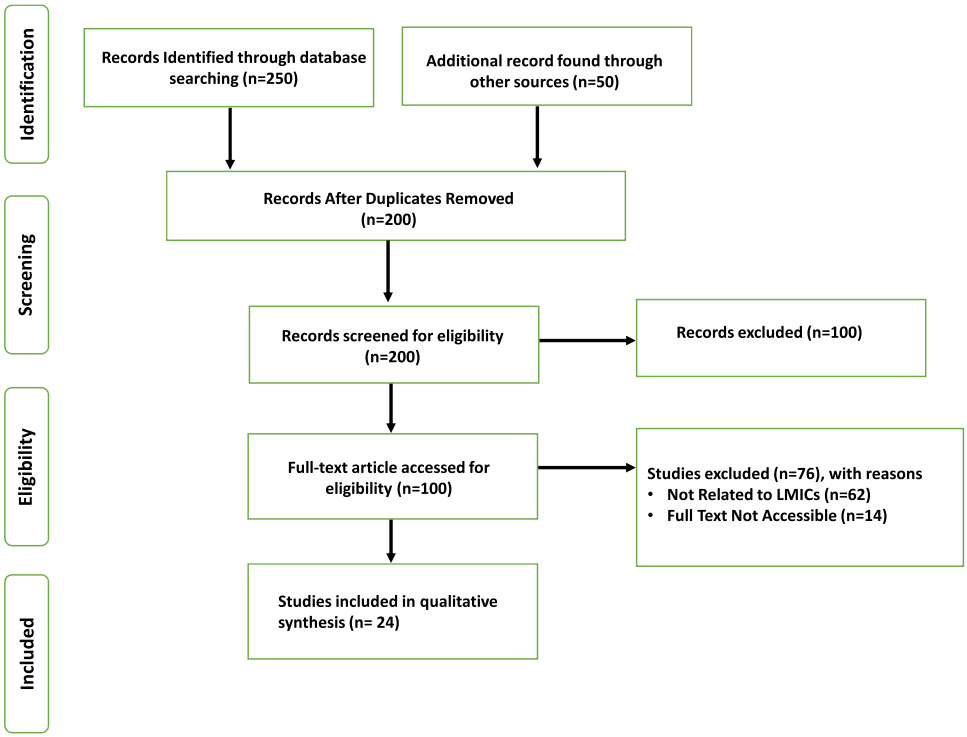

Figure 1. Surgical outcomes of Glioblastoma Multiforme in low and middle-income countries: current state and. future directions: Search Strategy using preferred reporting item for systematic review and meta-analysis. LMICs, low- and middle-income countries.

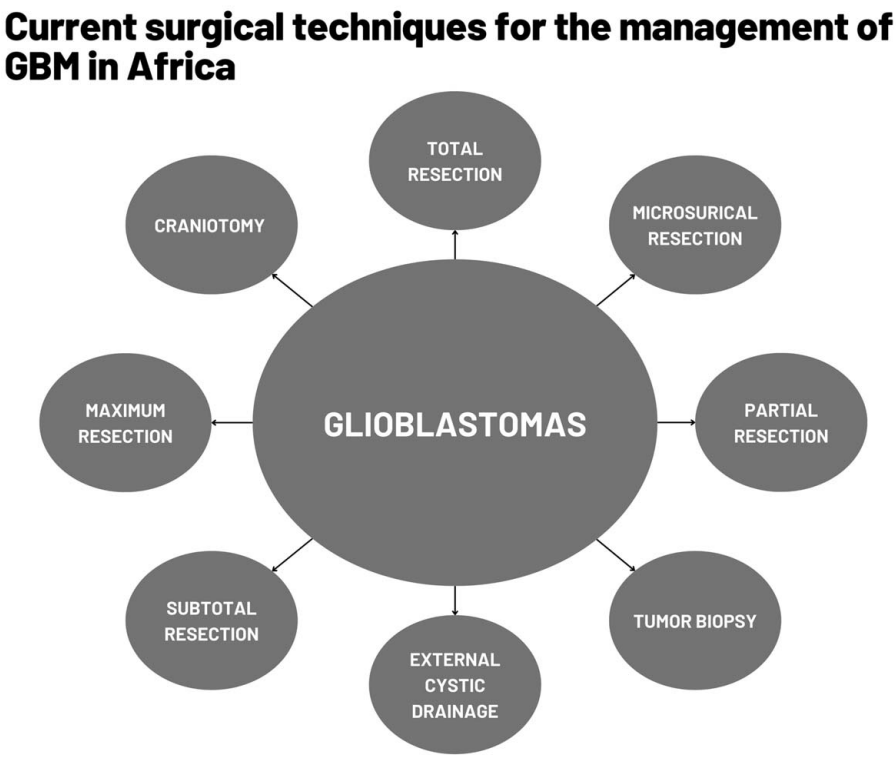

Figure 2. The current surgical techniques for the management of glioblastoma multiform in Africa.

Table 1

Study characteristics.

Authors	Publication year	Study design	Patients population	Surgical procedures	Positive treatment outcomes	Negative treatment outcomes
Faustino *et al.*[14]	2020	Retrospective cohort study	50	Maximal surgical resection	Surgical resection served as mean for local treatment in 8 patients and univariate analysis revealed it to be significantly associated with better Overall survival	Nil
He *et al.*[15]	2020	Clinical trial	29	Surgical resection with fluorescence-guided surgery	Complete resection was achieved in 82.76% of patients. The sensitivity and specificity of the fluorescence material used were 94.44% and 88.24%, respectively, which will help in the proper identification of the tumors	14 patients died during the trial and were not able to follow-up on their treatment
Touati *et al.*[16]	2020	Retrospective study	183	Large resection, partial resection and biopsy	The mean Overall survival for patients who underwent a biopsy was 39.6 months, that of large resection was 40.5 months and 53.2 months for those who had a partial resection	Nil
Brock *et al.*[17]	2017	Case report	1	Surgical resection	After a year of surgery, no evidence of residual or recurrent tumor was seen in the patient	During the resection process, unexpected bleeding started to occur with associated lesion growth and edema, resembling an Arteriovenous Malformation
Elsakka *et al.*[18]	2018	Case report	1	Awake craniotomy with subtotal tumor resection	Nil	Nil
Uche *et al.*[19]	2015	Retrospective cohort study	NS	Microsurgical resections, biopsies and CSF diversion	Nil	The overall survival rates were low and it decreases with time
Wu *et al.*[20]	2020	Retrospective study	259	Surgical resections and craniotomy	Nil	Nil
Kanmounye S.U[21]	2021	Case report	1	External cystic drainage	Maximum recovery was recorded in the movement and speech of the patient	Nil
Rajabpour *et al.*[22]	2017	Retrospective study	123	Tumor biopsy, partial or complete tumor resection	High survival rates were recorded few months post-surgery	However, the overall survival rates decreased with time
Hur *et al.*[23]	2008	Case study	1	Gross total resection	Symptoms and neurologic signs gradually improved post operation and no recurrence of the tumor was recorded after 1 year	Nil
Ma *et al.*[24]	2009	Retrospective study	205	Radical and partial Surgery	Survival rate was high in the first 6 months for both radical (89%) and partial surgery (70%)	However, the overall survival rates decreased with time
Mwita *et al.*[25]	2019	Prospective study	31	Gross total tumor resection, subtotal resection and biopsy	Nil	Systemic surgical complications occurred in 2 (6.5%) patients while 12 (38.7%) had regional surgical complications
Labuschagne and Chetty[26]	2019	Case report	1	Craniotomy and stereotactic radiosurgery	Nil	18 months after the surgery the patient presented at the hospital with a seizure
Kumar *et al.*[27]	2012	Case report	1	Surgical excision and craniotomy	No recurrence few years postoperative	The patient developed seizure 20 years after his first presentation and diagnosis showed left frontal cystic recurrence
Ndoumbe *et al.*[28]	2018	Retrospective study	19	Biopsy, partial resection and total resection	Nil	The outcome was poor with 46.43% of patients dying before 2 years after diagnosis
Khan *et al.*[29]	2016	Retrospective case series	**6**	Awake craniotomy	High Karnofsky Performance Status score were noted in the patients post-surgery and this technique was effective in maintaining postoperative functionality of the patient	Mild facial weakness were noticed in one of the patients post operation

Table 1

(Continued)

Authors	Publication year	Study design	Patients population	Surgical procedures	Positive treatment outcomes	Negative treatment outcomes
Ji *et al.*[30]	2019	Cohort study	502	Fluorescence surgery	Glioblastoma patients showed positive fluorescence in 96% of cases including strong intensity in 85.6%. Additionally, complete resection could be achieved in 89.6% of cases showing fluorescence positive , but only 75.0% of fluorescence negative cases succeeded in complete resection	Nil
Li *et al.*[31]	2018	Cohort study	14	Fluorescence-guided surgery	The fluorescent material used was of high sensitivity and sensitivity. This helped in improving the extent of resection and progression-free survival (PFS) at 6 months	Nil

CSF, cerebrospinal fluid.

Positive outcomes

Rajabpour *et al.*[22] reported high survival rates among patients who had undergone tumor biopsy, and partial, or complete tumor resection, with particularly promising results observed in the months following the surgery. Meanwhile, Hur *et al.*[29] noted significant improvements in symptoms and neurologic signs following gross total resection, with no tumor recurrence detected even after 1 year. In another study, Khan *et al.*[24] found that patients post-surgery exhibited high Karnofsky Performance Status scores, and the awake craniotomy technique effectively preserved postoperative functionality in these patients. Ji *et al.*[30] conducted a study on glioblastoma patients, where an impressive 96% of cases exhibited positive fluorescence, with 85.6% showing strong intensity. This fluorescence-guided approach allowed for complete resection in a notable 89.6% of cases with positive fluorescence, although only 75.0% of cases with negative fluorescence achieved the same result[30]. Additionally, in China, Li *et al.*[31] utilized a fluorescent material in fluorescence-guided surgery characterized by its high sensitivity and specificity, resulting in an enhanced extent of resection and improved progression-free survival at the 6-month mark.

Negative outcomes

In the clinical trial of surgical resection with fluorescence-guided surgery, 14 patients tragically lost their lives during the trial and were unable to continue their treatment[15]. Brock and colleagues reported complications in the case of Surgical Resection, where unexpected bleeding occurred during the resection process, leading to associated lesion growth and edema, resembling an arteriovenous malformation. This unforeseen development highlighted the potential risks associated with this surgical approach[17]. Additionally, time played a significant role in the outcomes of certain surgical procedures. Ma *et al.*[24] noted a decrease in overall survival rates over time for patients who underwent radical and partial surgery. Similarly, Uche *et al.*[19] found that the overall survival rates declined over time for patients who had microsurgical resections, biopsies, and CSF diversion.

Mwita *et al.*[25] reported systemic surgical complications in 2 (6.5%) patients and regional surgical complications in 12 (38.7%) patients who underwent gross total tumor resection, subtotal resection, and biopsy. These complications raised concerns about the safety and efficacy of these surgical techniques. In the case of Labuschagne and Chetty[26], a patient presented at the hospital with a seizure 18 months after undergoing craniotomy and stereotactic radiosurgery. This unexpected development pointed to potential postoperative complications associated with these procedures. Kumar *et al.*[27] documented a patient who developed seizures 20 years after their initial presentation following surgical excision and craniotomy. The diagnosis revealed left frontal cystic recurrence, highlighting the long-term challenges that can arise after these surgical interventions.

Furthermore, the study by Ndoumbe *et al.*[28] indicated a poor outcome for patients who underwent biopsy, partial resection, and total resection, with 46.43% of patients succumbing to the disease within two years after diagnosis. This unfortunate outcome underscored the need for more effective treatment strategies. Mild facial weakness was observed in one of the patients

following Awake Craniotomy, signifying potential postoperative complications associated with this technique[29].

Discussion

Challenges with surgical management of GBM in LMICs

Surgical management of GBM in LMICs presents a complex web of challenges deeply intertwined with the broader healthcare landscape in these regions. The fundamental obstacle lies in the lack of an efficient healthcare framework within LMICs. Healthcare systems, already burdened by the challenges of poverty and economic constraints, struggle to provide effective GBM management from diagnosis to treatment. This inefficiency manifests as heightened morbidity and mortality rates, leading to unfavorable outcomes for GBM patients.

One key issue is the absence of clearly defined research, diagnostic, and treatment protocols tailored to the unique conditions of LMICs. The lack of a structured approach to GBM management directly impacts the prognosis of patients, relegating them to a less favorable position compared to their counterparts in developed countries. The insufficiency of facilities for radiotherapy exacerbates this situation. Radiotherapy is a critical component of GBM treatment, but its availability in LMICs is limited. Even if facilities exist, the challenge of affordability arises due to poor health insurance systems, making access to specialist care elusive for many impoverished citizens.

Public healthcare facilities, though more affordable, often lack the resources they need to provide quality GBM care. Inadequate funding translates to insufficient diagnostic capabilities, hospital bed space, research opportunities, and specialist intervention. In contrast, private facilities, while better funded, are often too expensive for a significant portion of the population, further marginalizing access to proper surgical management.

Compounding these issues are logistical challenges. Increased waiting times, primarily in public facilities, present hurdles for patients in urgent need of care. Poorly maintained roads contribute to longer transit times, reducing the ability to access quick care during emergencies. The scarcity of efficient ambulance facilities and inadequate health coverage only further complicate the process. Delayed presentations of GBM patients in LMICs constitute another significant challenge. Poor socio-economic conditions mean that seeking medical assistance, especially tertiary care, becomes a last resort for many, given the financial burden. Consequently, patients often present at advanced stages of the disease, diminishing the prospects for successful surgical interventions.

The diagnostic process itself is hindered by reduced knowledge of GBM pathophysiology and limited expertise in disease management. These factors lead to delayed diagnosis and can significantly impact the effectiveness of surgical procedures. Inadequate imaging technology in resource-poor regions serves as a further significant hindrance to timely and accurate GBM diagnosis. Without access to advanced imaging, healthcare professionals face challenges in identifying and understanding the extent of the disease. Moreover, the high and continually rising costs of anti-cancer agents, such as Temozolomide, and intensity-modulated radiotherapy pose a substantial threat to GBM management in LMICs. These costs are often beyond the means of a significant portion of the population, necessitating external intervention or support. Despite several clinical trials aiming to find more effective GBM treatments, none have succeeded in substantially improving the median prognosis. GBM remains a deadly disease, characterized by intra and inter-tumoral heterogeneity and the presence of highly resistant GBM cells, making it an even more formidable challenge in LMICs due to the associated costs of disease management.

Limited capacity and technology for brain cancer research further compound these challenges. Inadequate funding for research projects in LMICs results in a lack of the required knowledge for optimal therapeutic interventions. The increasing burden of GBM is met with a deficit in research efforts, particularly in regions like South-East Asia where the disease's prevalence is on the rise. Traditional beliefs and attitudes toward illness also impact GBM management in LMICs. Some communities hold the view that diseases like GBM are trials from a higher power, and there is nothing that can be done to alter such divine decrees. Seeking the help of shamans and fortune tellers for medical illnesses is not uncommon, further affecting the prognosis of GBM in these regions.

Future directions and recommendations

This study has shed light on the surgical management techniques employed in LMICs (Fig. 2) while considering socio-economic, cultural, and infrastructural factors. The comparative analysis of survival rates and quality of life among GBM patients in LMICs and high-income countries has exposed significant disparities. LMICs confront unique challenges in managing GBM, including limited access to advanced medical facilities, shortages of skilled healthcare professionals, economic constraints, and social disparities. These challenges collectively hinder the effective management of glioblastomas in LMICs and result in poor outcomes for patients in resource-limited settings.

The standard of care for GBM treatment globally involves surgical excision followed by radiation and chemotherapy. However, the translation of these advancements into LMICs remains limited due to multi-faceted challenges. The shortage of radiation facilities and neurosurgical expertise in LMICs restricts their ability to provide effective GBM treatment. Given the prevalence of GBMs as the most common invasive brain tumors, health authorities must prioritize and enhance GBM management in LMICs.

In high-income countries, neuronavigation technologies guide surgeons during GBM surgery. However, in LMICs, financial constraints often necessitate the reliance on neurosurgeons' knowledge of neuroanatomy and preoperative imaging for guidance. An affordable and practical alternative for LMICs is the use of intraoperative neurosurgery ultrasound, which offers real-time visual guidance during surgery without the high costs associated with advanced neuronavigation devices.

Patient outcomes, survival rates, and long-term follow-up data following GBM surgery in LMICs predominantly involve maximal surgical resection followed by concomitant chemoradiation, a standard established in 2005 after a clinical trial. The combination of surgery, radiotherapy, and chemotherapy has demonstrated higher 2-year survival rates compared to maximal surgical resection alone. A clinical trial in China that utilizes fluorescence-guided surgery (FGS) with IRDye800-BBN for GBM has shown an impressive 82.76% complete resection rate. Nonetheless, patients exhibit varying overall survival (OS) and progression-

free survival (PFS) times, emphasizing the need for tailored treatment approaches.

Prediction models for characterizing gliomas using multiple variables have yielded inconsistent results, with some studies revealing differences in survival rates between complete and partial resection. Studies from Kenya and Cameroon have highlighted poorer outcomes in GBM surgeries, while case reports from other LMICs have presented conflicting results. Notably, there is no current screening tool for detecting GBM before clinical symptoms manifest, and MRI remains the gold standard for imaging studies. This variability in patient outcomes and survival rates in LMICs underscores the complexity of GBM management and the need for region-specific approaches.

The variable patient outcomes and survival rates, the lack of early detection tools, and the influence of cultural sensitivity on patient care underscore the complexity of GBM management in LMICs. Bridging these gaps will necessitate multi-faceted interventions. This includes improving healthcare infrastructure, promoting early diagnosis, reducing treatment costs, addressing cultural and ethical aspects, and expanding research funding. Standardized data collection and reporting protocols will also play a crucial role in advancing GBM care in LMICs.

It is imperative to address cultural sensitivity and ethical considerations in GBM surgeries in LMICs. These factors wield a substantial impact on patient outcomes, informed consent, and healthcare practices in these regions. Emerging issues, such as the de-anonymization of patients' health information, are a source of concern. This has hindered the confidentiality of patients among health professionals, which can lead to future errors and misunderstandings in treatment plans. Therefore, future efforts should prioritize cultural competency and ethical guidelines to ensure improved healthcare practices and outcomes for GBM patients in LMICs.

Limitations and strengths of review

This review, while comprehensive and informative, has limitations that need to be considered. The studies included exhibit heterogeneity in their study design, patient populations, and methodologies, which can make direct comparisons and generalizations challenging. Language bias is also a limitation, as the review may be confined to studies published in specific languages, potentially excluding valuable data from other sources. On the positive side, this review has notable strengths. It inclusively examines a wide range of studies from diverse LMICs, providing a comprehensive perspective on GBM surgical management challenges and outcomes. The comparative analysis between LMICs and high-income countries highlights disparities and challenges specific to resource-limited settings.

Conclusion

This comprehensive review has shed light on the intricate web of issues that hinder effective GBM treatment in LMICs, revealing a stark contrast to the standards observed in high-income countries. The disparities in healthcare infrastructure, delayed diagnosis, high treatment costs, cultural beliefs, and limited research funding collectively contribute to the poor outcomes for GBM patients in LMICs. In addition, standard GBM management protocols such as surgical excision followed by radiation and chemotherapy have not been readily adopted due to resource limitations. However, this review identifies an alternative in the form of intraoperative neurosurgery ultrasound, offering an affordable and practical solution for LMICs.

As this review highlights the intricate challenges faced by LMICs in managing GBM, it also emphasizes the urgency of change. Raising awareness, advocating for improvements, and channeling resources toward addressing the unique needs of LMICs are crucial steps toward enhancing the surgical management of GBM and ultimately improving the lives of GBM patients in these resource-limited regions. The path forward requires collaborative efforts on a global scale, involving healthcare professionals, policymakers, researchers, and advocacy groups to create a more equitable landscape for GBM treatment in LMICs.

Ethical approval

Ethics approval was not required for this review.

Consent

Informed consent was not required for this review.

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Author contribution

Conceptualization: A.O.M. Writing—original draft: A.O.M.; P. P.K.; Y.J.A.; M.J.M.; A.R.O.; N.A.; M.F.B.; A.A.; K.E.; O.D. Writing—review and editing: A.O.M.; P.P.K.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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