World Journal of Clinical Oncology

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World J Clin Oncol 2024 April 24; 15(4): 482-495

DOI: 10.5306/wjco.v15.i4.482

ISSN 2218-4333 (online)

REVIEW

Focus on current and emerging treatment options for glioma: A comprehensive review

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Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Chu SH, China; Shibata Y, Japan

Received: November 22, 2023
Peer-review started: November 22, 2023
First decision: January 12, 2024
Revised: January 22, 2024
Accepted: February 28, 2024
Article in press: February 28, 2024
Published online: April 24, 2024

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Abstract

This comprehensive review delves into the current updates and challenges associated with the management of low-grade gliomas (LGG), the predominant primary tumors in the central nervous system. With a general incidence rate of 5.81 per 100000, gliomas pose a significant global concern, necessitating advancements in treatment techniques to reduce mortality and morbidity. This review places a particular focus on immunotherapies, discussing promising agents such as Zotiraciclib and Lerapolturev. Zotiraciclib, a CDK9 inhibitor, has demonstrated efficacy in glioblastoma treatment in preclinical and clinical studies, showing its potential as a therapeutic breakthrough. Lerapolturev, a viral immunotherapy, induces inflammation in glioblastoma and displays positive outcomes in both adult and pediatric patients. Exploration of immunotherapy extends to Pembrolizumab, Nivolumab, and Entrectinib, revealing the challenges and variabilities in patient responses. Despite promising preclinical data, the monoclonal antibody Depatuxizumab has proven ineffective in glioblastoma treatment, emphasizing the critical need to understand resistance mechanisms. The review also covers the success of radiation therapy in pediatric LGG, with evolving techniques, such as proton therapy, showing potential improvements in patient quality of life. Surgical treatment is discussed in the context of achieving a balance between preserving the patient's quality of life and attaining gross total resection, with the extent of surgical resection significantly influencing the survival outcomes. In addition to advancements in cancer vaccine development, this review highlights the evolving landscape of LGG treatment, emphasizing a shift toward personalized and targeted therapies. Ongoing research is essential for refining strategies and enhancing

outcomes in the management of LGG.

Key Words: Low-grade gliomas; Monoclonal antibody; Lerapolturev; Glioblastoma; CDK9 inhibitor

Core Tip: Our manuscript explores the dynamic landscape of glioma treatment, emphasizing the urgent need for innovative therapies to combat this prevalent central nervous system malignancy. We delve into the promising realm of immunotherapies, highlighting novel agents like zotiraciclib, pembrolizumab, and lerapolturev, offering insights into their mechanisms and clinical efficacy. Furthermore, we discuss the evolving role of radiation therapy, emphasizing recent advancements in reducing treatment-related toxicities while improving outcomes. Surgical strategies, including subtotal resection and intraoperative radiotherapy, are also explored, showcasing their potential to enhance survival while minimizing neurological morbidities.

Citation: Lucke-Wold B, Rangwala BS, Shafique MA, Siddiq MA, Mustafa MS, Danish F, Nasrullah RMU, Zainab N, Haseeb A. Focus on current and emerging treatment options for glioma: A comprehensive review. *World J Clin Oncol* 2024; 15(4): 482-495
URL: https://www.wjgnet.com/2218-4333/full/v15/i4/482.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i4.482

INTRODUCTION

Gliomas represent the most prevalent primary tumors in the central nervous system (CNS) across various age groups[1,2]. Gliomas have a general incidence rate of 5.81 per 100000 people, with older individuals having a threefold higher frequency than young children. Gliomas account for 29%-35% of all central nervous system tumors in the adolescent and young adult demographic (ages 15-39 years), with an incidence of 3.41 per 100000[3-5]. Gliomas continue to be a global concern, emphasizing the vital need to improve treatment techniques for lowering both mortality and morbidity, elevating it to the top of the neuro-oncology priority list[6,7].

Clinical care, therapeutic response, and outcomes differ significantly between pediatric and adult glioma patients. Children with high-grade gliomas (HGGs) have poor prognosis, with frequently limited long-term survival ranging from months to a few years after diagnosis[8,9]. In contrast, pediatric patients with low-grade gliomas (LGG) have good overall survival (OS)[10,11], despite significant tumor- and treatment-related morbidity[12] (Table 1). The increased likelihood of malignant transformation, which is extremely rare in children) adds to a less favorable prognosis in adults with low-grade gliomas[13,14].

IMMUNOTHERAPIES

Despite advancements in surgery, radiotherapy, and chemotherapy for LGG, the disease remains incurable and often progresses to secondary malignant transformation. Immunotherapeutic strategies have demonstrated success in various cancers, including lung, skin, colon, and blood-related cancers (Figure 1). Given that low-grade gliomas, particularly in younger patients, exhibit slower growth compared to high-grade gliomas, there is a suggestion that immunotherapies may be more effective due to the healthier immune systems of younger individuals, potentially leading to better treatment responses. Immunotherapies, including Zotiraciclib and Lerapolturev, exert their effects through distinct mechanism (Table 2).

Zotiraciclib

Zotiraciclib, a potent CDK9 inhibitor, exhibits efficacy against glioblastoma by suppressing transcription and disrupting cellular energy production. Preclinical studies, both in vitro and in vivo, have revealed its synergistic effect with temozolomide. In clinical trials, Zotiraciclib demonstrated the ability to cross the blood-brain barrier and suppress CDK9 activity in tumor tissues[15]. This promising mechanism, targeting multiple glioblastoma survival pathways, positions Zotiraciclib as a potential therapeutic breakthrough[16-19].

A two-stage, two-arm, randomized phase 1 clinical trial further investigated the potential of zotiraciclib in recurrent high-grade gliomas. This study included a comprehensive evaluation of pharmacokinetics, patient-reported outcomes, and a detailed examination of rapid-onset neutropenia. Despite this observed neutropenia, a thorough analysis concluded that it did not compromise patient safety, allowing the research and development of this novel CDK9 inhibitor to progress[19].

Pembrolizumab or nivolumab

Immunotherapy has garnered significant interest as a potential treatment for glioblastoma (GBM). Nevertheless, a recent

Table 1 World Health Organization classification of gliomas

Grade	Name	Description and characteristics
I	Pilocytic astrocytoma	Well-differentiated, often cystic, slow-growing, generally benign
II	Diffuse astrocytoma	Infiltrative, moderately cellular, tends to recur, can progress to higher grades
II	Oligodendroglioma	Composed of oligodendrocyte-like cells, often associated with 1p/19q co-deletion
II	Mixed oligoastrocytoma	Combination of features of oligodendroglioma and diffuse astrocytoma
III	Anaplastic astrocytoma	Higher grade astrocytoma with increased cellularity and mitotic activity
III	Anaplastic oligodendroglioma	Higher grade oligodendroglioma with increased cellularity and atypia
III	Anaplastic oligoastrocytoma	Higher grade mixed tumor with features of both anaplastic astrocytoma and anaplastic oligodendroglioma
IV	Glioblastoma	Highly aggressive, necrosis, endothelial proliferation, molecular heterogeneity

clinical study focusing on recurrent glioblastoma and employing PD-1 immune checkpoint inhibitors revealed that a minority of patients (8%) exhibited noticeable improvements in their condition[20]. The mechanistic underpinnings of the variability in response patterns remain unclear.

Enhanced T cell infiltration in the tumor microenvironment and elevated mutational burdens in various cancer types have been associated with improved responses to anti-PD-1 therapy[21-23]. However, GBM presents a more immunosuppressive tumor microenvironment and a lower burden of somatic mutations than melanomas or non-small cell lung cancer[24]. Immunosuppression in GBM is facilitated by the expression of PD-1 ligands (PD-L1/2) in tumor cells, leading to T cell exhaustion and apoptosis. The binding of PD-1 to the surface of cytotoxic T cells hampers their ability to mount an effective anti-tumor response. PD-1 inhibitor therapy disrupts this immune checkpoint, reinforcing the immune response against tumors[23].

PD-1 inhibitors, such as pembrolizumab and nivolumab, have gained attention for glioblastoma treatment. However, recent clinical studies have revealed variable responses, necessitating deeper understanding of the underlying mechanisms. Glioblastoma's immunosuppressive microenvironment and lower mutation burden compared to other cancers pose challenges. Molecular-tailored strategies hold promise for optimizing patient selection for immunotherapy, although further testing is required to validate their efficacy[25].

Lerapolturev

Lerapolturev, a viral immunotherapy, operates *via* a unique mechanism. As a polio-rhinovirus chimera, it induces persistent type-I interferon-dominant inflammation in glioblastoma, leading to polyfunctional antitumor CD8+ T-cell responses. Clinical trials involving Lerapolturev for recurrent adult glioblastoma demonstrated a 16% survival rate of at least 36 months, with a manageable safety profile[26-29].

In pediatric high-grade gliomas, Lerapolturev showed promise, with no grade 3 or 4 toxicity observed in early trials. The safety of treatment at this dose allows for further trials, including patients as young as 9 years of age. Ongoing research is crucial to understand the immunological factors influencing the efficacy of Lerapolturev in pediatric versus adult high-grade gliomas[30]. Our group's previous research in adults gained additional support from the inclusion of patients as young as 9 years old, including one individual with WHO grade 3 glioma[30]. Moreover, pediatric high-grade gliomas typically exhibit significantly different molecular profiles compared to adult high-grade gliomas[31]. However, whether immunological factors affecting viral immunotherapies, such as Lerapolturev, vary between pediatric and adult high-grade gliomas remains uncertain[30].

Depatuxizumab

Depatuxizumab (formerly ABT-806) is a humanized monoclonal antibody developed against epidermal growth factor receptor variant III (EGFRvIII) that also binds to wild-type EGFR at elevated levels[32,33]. The antibody-drug conjugate (ADC) Depatuxizumab mafodotin (formerly ABT-414) connects the depatux to the cytotoxic payload monomethyl auristatin F (MMAF or mafodotin). Upon binding to activated EGFR, ADC is internalized, degraded in acidic compartments, and releases the toxin, causing cell death. Unlike other treatments, this direct cytotoxic effect does not rely on inhibition of EGFR signaling and avoids typical toxicities[34]. Although unconjugated depatux is ineffective against GBMs, depatux-m demonstrates efficacy in GBM cell lines and models with EGFR amplification or EGFRvIII, showing effectiveness alone and in combination with radiotherapy and temozolomide[35]. ADCs, including depatux-m, show promise in various cancers[36], surpassing unconjugated monoclonal antibodies in efficacy, with numerous ADCs under investigation under diverse conditions[37].

Despite promising preclinical and early clinical data, depatux-m has proven ineffective in treating GBM. This disappointing outcome may result from the emergence of resistant clones over time, negating any overall survival benefit [38]. Limited penetration of depatux-m into large tumors and challenges in reaching intracranial tumors[39], especially in the non-enhancing tumor region, underscore crucial lessons for future studies involving large molecules[38]. Safety concerns with depatux-m were reversible, with adverse events, such as sensitivity to light and thrombocytopenia, being the most frequently observed.

Table 2 List of Immunotherapy

Ref.	Completion year	Demographics	Study phase	Identifier	Experimental drug	Sample size	Primary endpoint/outcomes	Results for primary outcome
BRAF/MEK inhibitors								
Nicolaides *et al* [107], 2020	2023	Pediatrics	Phase 2	NCT01748149 (Ongoing Trial)	Vemurafenib	40	Safety and pharmacokinetics	Not yet reported
Hargrave *et al* [108], 2019	2020	Pediatrics	Phase 1/2a	NCT01677741	Dabrafenib	32	Objective response rates and safety	Objective response rate was 44% and 91% experienced adverse effects
Kaley *et al*[109], 2018	2016	Adults	Phase 2	NCT01524978	Vemurafenib	24	Confirmed objective response rate, PFS, OS and safety	Confirmed objective response rate was 25% and median PFS was 5.5 months
FGFR inhibitors								
Lassman *et al*[110], 2022	2018	Adults	Phase 2	NCT01975701	Infigratinib	26	6-month PFS	6-month PFS rate was 16.0%
Bahleda *et al*[111], 2019	2017	Adults	Phase 1	NCT01703481	Erdafitinib	187	Safety	Most common treatment-related adverse events were hyperphosphatemia, dry mouth, and asthenia, generally grade 1/2 severity
HDAC inhibitors								
Wood *et al*[112], 2018	2018	Pediatrics	Phase 1	ACTRN12609000978268	Panobinostat	9	Safety and pharmacokinetics	2 patients experienced Grade 3-4 thrombocytopenia, 1 experienced Grade 3 anemia, and 2 experienced Grade 3 neutropenia
Imipridone								
Arrillaga-Romany *et al*[113], 2020	2023		Phase 2	NCT02525692 (Ongoing Trial)	ONC201	89	6-month PFS	Not yet reported
PI3K/mTOR inhibitors								
Wen *et al*[114], 2022	2023	Adults	Phase 2	NCT03522298	Paxalisib	32	Safety and pharmacokinetics	Well-tolerated with adverse events consistent with other PI3K inhibitors
Wen *et al*[115], 2020	2020	Adults	Phase 1	NCT01547546	GDC-0084	47	Safety and pharmacokinetics	Well-tolerated with adverse events consistent with other PI3K inhibitors
Franz *et al*[116], 2015	2014	Adults/Pediatrics	Phase 1/2	NCT00411619	Enviroximes	28	6-month change in the volume of sub ependymal giant-cell astrocytoma	Statistically significant reduction in the volume of the primary sub ependymal giant-cell astrocytoma at 6 months
NTRK/ALK inhibitors								
NCT02637687[117]	2026	Pediatrics	Phase	NCT02637687 (Ongoing	Larotrectinib	155	Objective response rates	Not yet reported

			1/2	Trial)			
NCT02576431[118]	2025	Adults/Pediatrics	Phase 2	NCT02576431 (Ongoing Trial)	Larotrectinib	204	Objective response rates, PFS, OS, Safety	Not yet reported
Desai *et al*[119], 2022	2025	Adults/Pediatrics	Phase 1/2	NCT02650401 (Ongoing Trial)	Entrectinib	69	Maximum Tolerated Dose and Objective response rates	Not yet reported
IDH inhibitors								
NCT05588141[120]	2029	Adults	Phase 1/2	NCT05588141 (Ongoing Trial)	Zotiraciclib	96	12-months PFS	Not yet reported
Mellinghoff *et al*[121], 2023	2027	Adults	Phase 3	NCT04164901	Vorasidenib	340	PFS	Significantly improved PFS
Mellinghoff *et al*[122], 2019	2024	Adults	Phase 1	NCT03343197	AG-120, AG881	49	2-hydroxyglutarate concentrationin resectedtumors	decreased tumorcell proliferationand immune cellactivation
EGFR inhibitors								
Weller *et al*[123], 2017	2016	Adults	Phase 3	NCT01480479	Rindopepimut/Temozolomide	745	OS	Median OS was 20.1 months in the Rindopepimut group versus 20.0 months in the control group
Lassman *et al*[124], 2023	2022	Adults	Phase 3	NCT02573324	Depatuxizumab mafodotin	691	OS	No OS benefit for depatux-m in treating EGFR-amp newly diagnosed GBM

PFS: Progression-free survival; OS: Overall survival.

Entrectinib

Entrectinib, approved by both the United States Food and Drug Administration and European Medicines Agency for tumors containing TRK or ROS1 fusions[40], encounters a challenge in treating brain neoplasms due to the blood-brain barrier (BBB)[35]. Effective targeted therapies for leptomeningeal disseminated tumors depend on their ability to penetrate this barrier. Although entrectinib, designed to cross the BBB, has demonstrated promise with a 79% objective response rate in various solid tumors, including CNS tumors, information on its cerebrospinal fluid penetrance in brain tumor patients is currently lacking[41].

The potential therapeutic efficacy of entrectinib, a selective pan TRK inhibitor, has been explored in patients with leptomeningeal disseminated pediatric high-grade gliomas (pHGG) harboring NTRK or ROS1 fusions[42,43]. The STARTRK-NG trial reported positive radiographic responses in four pHGG patients treated with entrectinib, indicating promise for CNS tumors[44,45]. This study investigated the in vitro sensitivity of pHGG cell models to entrectinib and suggested potential combination therapies[46]. The need for further studies to understand resistance mechanisms is emphasized, along with the generally well-tolerated nature of entrectinib. The observed CNS penetrance of entrectinib in a gliosarcoma patient has been discussed, highlighting its ability to cross the blood-brain barrier[47]. The text also considers the combination of entrectinib with radiotherapy and suggests the importance of intrathecal therapy in cases of leptomeningeal dissemination[41]. This conclusion underscores the need for comprehensive investigations and prospective clinical studies to establish the role of entrectinib and potential combination therapies in pHGG with ROS1/NTRK fusions.

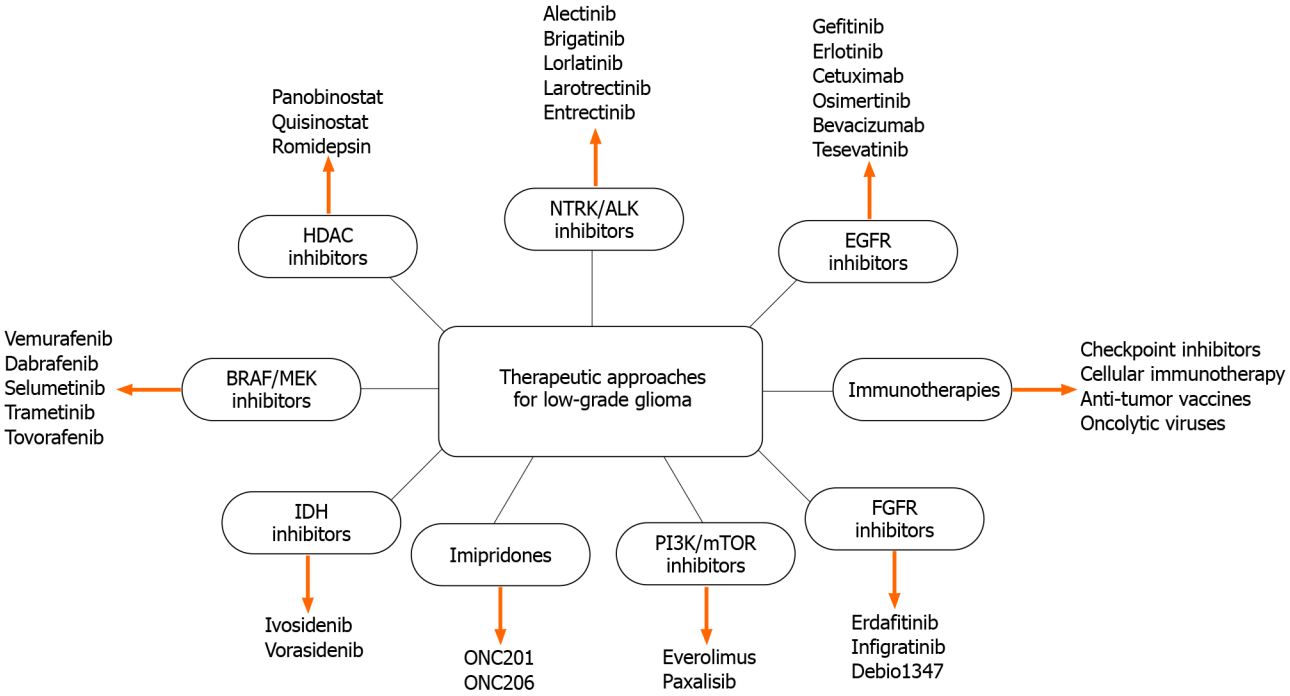

Figure 1 Illustrates a flow chart with drugs according to mutation.

ONC201 and paxalisib

ONC201, an oral small-molecule imipridone anticancer therapy, has demonstrated early clinical success in patients with diffuse intrinsic pontine glioma (DIPG)[48] and recurrent H3K27M-mutant diffuse midline gliomas[49]. Investigations across various cancer types have shown that ONC201-induced apoptosis in cancer cells, independent of p53, occurs through an atypical integrated stress response involving the expression of the antitumor protein TRAIL. This mechanism has shown promise in hematological[50], colorectal[51], breast[52], uterine cancers[53], and glioblastoma[54]. A sustained positive response was observed in a patient with secondary glioblastoma carrying an H3.3K27M mutation, prompting further exploration in patients with similar mutations, including those with DIPG[54].

Studies have discussed the therapeutic benefits of combining ONC201, a dopamine receptor D2 antagonist[55], with the blood-brain barrier-penetrant PI3K/Akt inhibitor, paxalisib, for treating DIPG. Mechanistic insights indicate that ONC201, by decreasing tyrosine hydroxylase expression, exhibits global DRD2 antagonism, with ClpP identified as a crucial target that causes mitochondrial dysfunction and oxidative stress[56]. The combination of paxalisib shows promising results in preclinical and preliminary clinical trials, leading to symptom resolution and tumor regression. Challenges related to immunologically cold tumor microenvironments in DIPG have been acknowledged, but potential changes in the epigenetic landscape and metabolic plasticity following ONC201 treatment may enhance immunogenicity [57,58]. The observed link between H3K27M mutations, metabolic changes, and the immune response highlights the complexity of DIPG treatment, presenting a potential avenue for the effective administration of therapy for glioblastoma [59].

RADIATION THERAPY

Radiation therapy (RT) is a successful management method for pediatric low-grade gliomas using both initial and salvage treatment approaches. Historically, RT was the chosen initial therapy for quickly progressing or unresectable tumors, with 10-year progression-free survival (PFS) and OS rates of 70% and 80%, respectively[60-62]. Furthermore, RT has been used as an adjuvant therapy, particularly when surgery is limited to partial resection or biopsy, particularly for tumors in the optic system, hypothalamus, deep midline tissues, and brainstem[63,64]. Adjuvant RT is suggested in cases of partial resection because PFS is greatly reduced[65,66]. However, there is a lack of agreement on its use, which is attributable in part to the paucity of randomized prospective studies[67,68].

For older children who have not responded to numerous systemic medications, RT is preferred as part of the care plan. Historically, postponing RT was motivated by concerns about RT-related toxicities such as cognitive impairment[69,70], endocrine dysfunction[71], secondary malignancies[72], vascular damage[72,73], and growth abnormalities[74]. The severity of these symptoms is directly related to the location of the tumor and the patient's age, particularly in patients under the age of 10[69,72].

An institutional evaluation covering a median follow-up of 11 years found 8-year PFS and OS rates of 83% and 100%, respectively[75]. Overall neurocognitive performance did not deteriorate in the trial; however, significant cognitive impairment was noted in young children (under 7 years old) and in patients who received high doses to the left temporal

lobe or hippocampus. Higher dosages to the hypothalamus or pituitary caused endocrine disruption, and two patients developed Moya disease. The 5-year PFS and OS rates in a recently published prospective research including 174 pediatric patients with LGG who received proton treatment were 84% and 92%, respectively, with a median follow-up of 4.4 years[76]. Four patients experienced severe late toxicities, including brainstem necrosis, symptomatic vasculopathy, radiation retinopathy, and fatal secondary cancers. While acknowledging the relevance of radiation-related damage, it is vital to emphasize that recent research has yielded promising outcomes. The extended latency of toxicity should be considered in light of the rapid developments in the field[77].

Concerns about RT-related toxicity originate mostly from long-term data collected from studies conducted during the 1970s and the 1990s using 2-dimensional RT methods that did not allow for accurate radiation dose administration. Significant technical progress has been achieved in reducing the radiation dose that reaches the normal structures surrounding the tumor. This began with the use of 3-dimensional conformal external beam RT (3D-CRT) and progressed in the 2000s with the advent of intensity-modulated RT (IMRT). Significantly, the introduction of proton therapy has reduced radiation exit dosage[78,79], contributing to its growing role in pediatric patients. Several studies have suggested that proton therapy might improve both patient quality of life and the cost-effectiveness of pediatric brain tumor treatment[80,81].

SURGICAL TREATMENT

The primary objective of glioma treatment is to strike a balance between preserving the patient's quality of life and improving PFS and OS[82,83]. The choice between oncological and surgical treatment depends on factors such as tumor size, location, and individual patient characteristics, including age and comorbidities[82,84,85]. Patients aged > 40 years at diagnosis, those with incomplete resection, and those with wild-type isocitrate dehydrogenase (IDH) status are typically considered to be at increased risk. The conventional treatment approach involves cytoreductive surgery to achieve gross total resection (GTR), followed by a combination of chemotherapy and/or radiation therapy[86,87].

The prognosis for gliomas, encompassing both LGG and HGG, is significantly influenced by the extent of surgical resection (EOSR) (Table 3). In LGG, EOSR is measured by the percentage of the FLAIR signal that is excised, whereas in HGG, it is determined by the removal of the percentage of enhancing tissue and the necrotic center. Extensive research on EOSR in LGG consistently shows that achieving GTR significantly improves survival rates, particularly among younger patients, classifying them as low-risk individuals compared to those who undergo only partial resection[82-84].

Similarly, investigations into EOSR in HGG consistently demonstrated a strong correlation between the extent of resection and survival outcomes, assuming no surgery-related neurological morbidities[88-90]. In most studies, the surgical goal is unequivocally defined as achieving GTR or complete tumor removal, typically amounting to 100% resection[91].

Recent clinical investigations have explored the concept of subtotal resection for gliomas[92]. This surgical approach aims to achieve GTR while simultaneously eliminating the FLAIR signal surrounding the necrotic and enhancing tumor mass in high-grade gliomas. Low-grade gliomas involve complete removal of the FLAIR signal along with additional radiographic extraction of the normal brain tissue adjacent to the tumor. Subtotal resection in LGG surgery was confirmed by observing that the resection cavity exceeded the initial FLAIR volume on the postoperative MRI at the three-month mark. Subtotal resection is considered justifiable when minimal neurological risks are involved, with the aim of eliminating invasive cells near the radiographic boundary[93-95]. Evidence from clinical case series of glioblastoma multiforme and HGG presents a conflicting picture, as performing supra total resection may entail an increased risk of neurological function decline, despite potential improvements in PFS and OS[92,96]. Additionally, there has been increased focus on the utilization of laser interstitial thermal (LIT) treatment for brain tumors. Recent trials investigating LIT have shown that achieving a greater level of ablation, including subtotal ablation, can lead to improved progression-free survival and overall survival outcomes in patients with HGG[97,98].

Intraoperative radiotherapy with a single high radiation dose administered following tumor resection, intraoperative radiotherapy (IORT), a novel and non-conventional form of radiotherapy, can eradicate any remaining tumor cells[99]. A wide range of cancers, including breast, pancreatic, lung, and colon cancers, have been treated with IORT[100-102]. The lack of a discernible increase in survival in IORT treatment reports for primary malignant gliomas has been ascribed to angle errors, low electrons, and small electron cones, which result in inadequate coverage of the target volume[103]. A mobile IORT unit, INTRABEAM (Zeiss, Oberkochen, Germany), can deliver an equal dose of low-energy radiation in all directions within a tumor cavity, along with spherical irradiation. According to research, IORT with low-energy X-rays increases glioblastoma patients' survival rates without causing new problems[104].

Vaccine development

Cancer vaccines targeting high-grade gliomas, predating coronavirus disease 2019, are gaining momentum. Strategies include peptide-based vaccines, dendritic cells, viral vectors, and personalized neoantigen vaccines. They are also being explored for the treatment of LGG. For IDH-mutant LGG, adjuvants such as poly (I:C) and poly-ICLC enhance immune responses, collectively reflecting a determined push for glioma immunotherapy[105]. To bolster the weak immune response in LGGs, synthetic double-stranded RNA molecules, such as polyinosinic acid homopolymers annealed to a polycytidylic acid homopolymer, have demonstrated potential[106]. They mimic viral infections and promote the release of interferon type 1 and other immune-boosting substances. Safely used as adjuvants with dendritic cells or peptide vaccines, they enhance therapeutic responses[106,107].

Table 3 Supratentorial surgical treatment options for glioma, *n* (%)

Ref.	Study origin	Study design	Total number of patients	Supratotal resection sample	Male, %	Age atresection	Permanent neurological deficits	Progression-free survival	Overall survival
Gajjar *et al* [63], 1997	United States	Cohort study	142	48 (68/142)	61	7 median (0.17-19)	Not reported	70 ± 5 at 4 years	90 ± 3 at 4 years
Fisher *et al* [67], 2008	United States	Cohort study	278	19 (52/278)	58	9.1 ± 0.3	Not reported	55 ± 3 at 5 years	87 ± 2 at 5 years
Wisoff *et al* [125], 2010	United States	Prospective trial	518	64 (332/518)	54	7.9 median (0.6-20.5)	Not reported	78 ± 2 at 8 years	96 ± 0.9 at 8 years
Yordanova *et al*[93], 2011	France	Case series	15	100.00	53.3	36.4 (24-59)	2, 13.3	73.3 at 38 months	100 at study end
Youland *et al* [11], 2013	United States	Retrospective cohort	351	67 (235/351)	55	10.9 (0.05-19.6)	Not reported	75.8 at 5 years	94.9 at 5 years
Lima *et al* [126], 2015	France	Case series	21	19.0 (4/21)	28.57	35 (18-57)	0, 0	100 at study end	100 at study end
Duffau *et al* [127], 2016	France	Cohort study	16	100.00	43.75	41.3 (26-63)	0, 0	50 relapse rate (avg 70 months)	100 at study end
Lima *et al* [92], 2017	France	Two-center prospective study	19	26.3 (5/19)	42.1	31.2 (19-51)	0, 0	100 at study end	100 at study end
Rossi *et al* [86], 2019	Italy	Case series	449	32 (145/449)	53.1	37.9 (median 36.5)	1, 0.69 (SupTR group)	Not reported	Not reported
Ng *et al* [128], 2020	France	Case series	74	28 (21/74)	41.89	35.7 (18-66)	0, 0	Not reported	100 at 5 years
Ng *et al* [129], 2020	France	Case series	47	26 (12/47)	34.04	39.2 ± 11.3	0, 0	Not reported	100 at study end
Goel *et al* [130], 2021	India	Cohort study	74	34 (25/74)	62.16	33 (21-55)	0, 0	98.7 at 2 years	100 at study end
Rossi *et al* [94], 2021	Italy	Case series	319	35 (110/319)	61.1	38.9 (18-75)	6, 1.9	94 at 92 months (SupTR group)	100 at 80 months (SupTR group)
Ius *et al* [131], 2022	United States, Canada, France, and Italy	Four center retrospective review	267	9 (24/267)	41.9	39.2 (18-71)	8, 3.1	Not reported	100 at 100 months (SupTR)

CONCLUSION

In conclusion, advancements in LGG treatment span immunotherapies, targeted therapies, radiation, surgery, and vaccine strategies. Immunotherapies like Zotiraciclib and Lerapolturev show promise, while targeted therapies such as Entrectinib and ONC201/Paxalisib combination demonstrate early success. Radiation therapy, evolving with proton therapy, remains crucial, and surgical approaches aim to achieve gross total resection. Cancer vaccines including synthetic RNA adjuvants have emerged. The evolving landscape underscores a shift toward personalized and targeted therapies, with ongoing research being essential for refining strategies and improving outcomes in LGG treatment.

FOOTNOTES

Author contributions: Shafique MA and Lucke-Wold B conceptualized the study; Danish F and Mustafa MS conducted a literature search; Drafting of the manuscript and writing was done by Nasrullah RMU, Rangwala BS, Siddiq MA, Zainab N and AH performed the editing; All authors read and agreed to the final version of the manuscript; All the authors have revised the manuscript accordingly.

Conflict-of-interest statement: All authors have no conflicts of interest to disclose.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Yuan YY

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