Journal of Neurosurgical Sciences 2025 Dec 09
DOI: 10.23736/S0390-5616.25.06656-1

REVIEW

Radiosurgical management of pathology-proven low-grade glioma: a systematic review across the pre- and post-molecular classification era

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ABSTRACT

INTRODUCTION: Low-grade gliomas (LGGs) are slow-growing heterogeneous tumors that remain challenging when complete resection is not feasible. While maximal safe resection remains standard, the evolving World Health Organization (WHO) classification emphasizing molecular characteristics has shifted perspectives on adjuvant therapies. In this context, the role of stereotactic radiosurgery (SRS) continues to be explored. This systematic review synthesizes literature on radiosurgical management of pathology-proven LGGs across pre- and post-molecular classification eras.

EVIDENCE ACQUISITION: A systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses. PubMed, Scopus, and Web of Science were searched in August 2024 for studies on pathology-proven LGGs treated with SRS. An additional search was performed to incorporate studies reporting molecular characteristics.

EVIDENCE SYNTHESIS: Of the initially included eight studies, none reported molecular characteristics required by the 2021 World Health Organization classification, and an additional search identified one study reporting molecular characteristics, which was added to the review. Nine studies with 308 patients were included. Local control rates ranged from 66% to 94%. Several studies reported superior outcomes with surgery for recurrence, adjuvant rather than salvage SRS, and no prior radiotherapy. Adverse events were predominantly mild to moderate, including headache, dizziness, nausea, and transient neurological symptoms.

CONCLUSIONS: SRS offers a non-invasive management option for selected LGGs with durable control and acceptable safety. Prognosis appears to be influenced by treatment history, including prior radiotherapy and surgical management. Lack of molecular stratification highlights the need for studies focused on IDH (isocitrate dehydrogenase)-mutant LGGs to clarify the role of SRS in the molecular era.

(*Cite this article as:* Mizutani Y, Hori YS, Harary PM, Annagiri S, Jain R, Liu J, *et al.* Radiosurgical management of pathology-proven low-grade glioma: a systematic review across the pre- and post-molecular classification era. J Neurosurg Sci 2025 Dec 09. DOI: 10.23736/S0390-5616.25.06656-1)

KEY WORDS: Glioma; Radiosurgery; Systematic review

Introduction

Low-grade gliomas (LGGs) are a heterogenous group of primary brain tumors that grow slowly and generally have a more favorable prognosis compared to high-grade gliomas. Traditionally classified as World Health Organization (WHO) Grades I and II, LGGs account for 17% to 22% of all primary brain tumors.[1-3] Despite their indolent nature, LGGs present a significant clinical challenge due to their potential for malignant transformation

and the difficulty in achieving complete surgical resection without affecting surrounding eloquent brain areas.[4] The median survival for patients with LGGs ranges between 5 and 10 years.[5]

Treatment aims to prolong survival, minimize morbidity, and thereby prevent tumor progression while preserving neurological function and quality of life.[6-8] The current standard of care for LGGs often involves maximal safe resection, followed by observation or adjuvant therapy depending on the presence of high-risk features such as patient age, tumor size, or neurological symptoms.[7, 9] However, the therapeutic landscape of LGGs has evolved with the updated WHO classification, which now incorporates molecular characteristics, particularly isocitrate dehydrogenase (IDH) mutation status, as essential diagnostic criteria.[10] This shift has refined the definition of LGGs and has significant implications for prognosis and treatment planning.

Beyond retrospective molecular characterization, several non-invasive modalities for preoperative IDH mutation prediction have gained increasing attention. Radiomics and machine learning applied to conventional CT and MRI modalities, including diffusion tensor imaging (DTI) and contrast-enhanced T1-weighted sequences, as well as PET-based analytical models, have demonstrated potential diagnostic utility.[11-14] In parallel, blood-derived biomarkers such as circulating tumor DNA analyzed by BEAMing PCR, along with liquid-biopsy based assays detecting miRNAs, exosomes, and circulating proteins, are under active investigation.[14-16] Given the important role of molecular stratification in the management of LGGs, these emerging techniques may be useful not only for diagnosing gliomas but also for predicting treatment response and supporting personalized therapeutic strategies.

In this context, the role of adjuvant therapies, including radiotherapy and chemotherapy, continues to be reevaluated, especially in cases where the tumor is surgically inaccessible or partially resected.[17] Among these adjuvant therapies, stereotactic radiosurgery (SRS) has gained attention as a potential treatment modality, offering precise, high-dose radiation while sparing healthy tissue. Although SRS is well-established in the treatment of brain metastases and high-grade gliomas, its application in the management of LGGs is less well-defined.[18-21]

In this systematic review, we aim to summarize the current literature on the radiosurgical management of pathology-proven LGGs. By incorporating both studies predating and those reflecting the molecular classification era, we highlight recent advancements, outcome data, and the evolving role of SRS in the treatment paradigm for LGGs.

Evidence acquisition

Literature search and study selection

A systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[22] We performed a comprehensive search of the PubMed, Scopus and Web of Science to identify relevant studies. Search terms used included “radiosurgery” AND “low-grade glioma”.

The search was performed in August 2024. We included studies that met the following inclusion criteria: 1) biopsy-proven LGGs treated with SRS (SRS was defined as ≤5 fractions); 2) published in English.

Studies were excluded based on the following criteria: 1) articles not reporting primary data (*i.e.* reviews, commentaries, and guidelines); 2) case reports or series with a sample size of fewer than three patients; 3) cases without a pathologically confirmed diagnosis; 4) studies published in languages other than English.

Data collection and quality assessment

Several variables were extracted from the screened literature. The quality and potential bias of each study meeting the selection criteria were evaluated using the modified Newcastle-Ottawa Scale (NOS), evaluating selection, comparability, and outcome domains.[23]

For patient characteristics, we collected data on age and the number of treated lesions. For tumor characteristics, we recorded the tumor type, gross tumor volume (GTV) and location. For SRS characteristics, we noted median marginal dose, planning target volume (PTV) and number of fractions. For outcomes, we gathered information on progression-free survival and local tumor control. Additionally, for adverse effects, we collected the number of patients with adverse effects and specific complication details.

Evidence synthesis

Search results

As depicted in the PRISMA diagram (Figure 1), the initial search identified 578 articles, with 373 remaining after duplicate removal. From these, 309 studies were excluded following title and abstract screening, while 56 were removed during full-text assessment. Ultimately, our literature search yielded 8 studies which meet the inclusion criteria.[24-31]

According to the 2021 WHO classification, a diagnosis of low-grade glioma requires the presence of specific molecular characteristics, particularly an IDH mutation.[10]

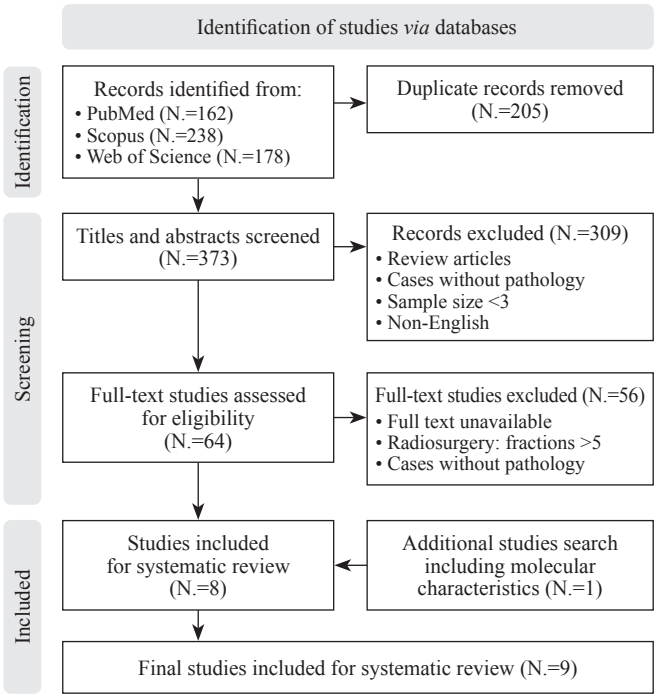

Figure 1.—PRISMA flowchart depicting study selection.

However, none of the initially included 8 studies documented molecular features. To address this limitation, we performed an additional search to identify studies that reported detailed molecular characteristics of tumors treated with SRS. As a result, we identified one relevant study (Ma *et al.*[32]), and we added it to our review.

The study by Ma *et al.* included patients with IDH-mutant astrocytoma and 1p/19q codeleted oligodendroglioma (WHO Grades II -IV) who underwent salvage therapies after radiation relapse.[32] Within this cohort, three patients, one with oligodendroglioma and two with astrocytoma, received SRS. According to the study definitions, astrocytomas were classified as gliomas with confirmed IDH mutation and either negative for 1p/19q codeletion or positive for ATRX loss. Oligodendrogliomas were defined as histological oligodendroglioma or mixed oligoastrocytoma with 1p/19q codeletion. Although some patients were treated prior to the routine implementation of IDH testing at their institution, IDH status was retrospectively determined through later tumor sample analysis. However, cases of oligodendroglioma without confirmed IDH mutation were still included, as long as they were not shown to be IDH-wildtype on next-generation sequencing. Therefore, while astrocytomas were clearly IDH-mutant, the IDH status of the oligodendroglioma case remains uncertain. Although it remains unclear whether these tumors were classified as low-grade at the time of SRS, this study was the only identified report describing the use of SRS in patients with gliomas presumed to be IDH-mutant. However, neither outcome data nor patient characteristics specific to the SRS-treated patients were reported.

Among the nine studies included in this review, Ma *et al.* was the only study providing molecular data, in which IDH status was retrospectively determined from tumor specimens rather than through preoperative, non-invasive assessment. While the present synthesis primarily focuses on the therapeutic efficacy and clinical outcomes of SRS, recent advances in non-invasive IDH prediction underscore the growing importance of molecular stratification in the management of LGGs.

All of the studies were assessed as having moderate risk bias based on NOS score. Due to the moderate heterogeneity, a meta-analysis was not performed.

Tumor and SRS procedure characteristics

Nine studies were ultimately included in this review, all of which were retrospective analyses.[24-32] These encompassed a total of 308 patients. Among the studies reporting the median age at the time of SRS, values ranged from 16 to 27 years (Table I).[24-32] Histological classifications include Grade I and II astrocytomas, pilocytic astrocytoma (PA), oligoastrocytoma and subependymal giant cell astrocytoma (SEGA).

Five of the nine included studies reported tumor location, encompassing a total of 150 lesions (Table II).[25-27, 29, 30] Tumors were most frequently located in the hemispheres, followed by the brainstem and cerebellum, with midbrain and thalamic locations also commonly reported.

Regarding SRS characteristics, the majority of studies delivered SRS in a single session (1 fraction), median marginal dose ranging from 13.0 Gy to 18 Gy. The single exception was a report by Simonová *et al.*,[28] in which the median number of fractions was five, with median prescription dose of 25 Gy.

Outcomes after treatment with SRS

Local control rates ranged from 66% to 94% (Table I). As for progression-free survival (PFS), 5-year PFS rates ranged from 41% to 88%.

Three studies compared the outcome of two groups (Table III).[24, 27, 30] Sun *et al.* reported that, in their analysis of SRS for recurrent tumors, multivariable analysis identified surgery for recurrence as a significant factor influencing PFS (17.5 *vs.* 12.0 months; HR 4.951, P=0.023).[24] Hadji-

TABLE I.—*Summary of included studies of stereotactic radiosurgery for management of low-grade gliomas.*[24-32]

Study	#patients/ #tumors	Median patient age (Years)	Tumor type	Tumor grade	Median GTV/PTV (cm^3)	Median marginal dose (Gy)	Number of fractions	PFS (%)	Local control (%)	Local control definition
Sun[24]	39/-	-	Recurrent	-	-/18.5[a]	13.0[a]	1	Median: 12.0 m	-	-
Heppner[25]	49/-	27	Primary/ residual/ recurrent	21 PA, 2 SEGA, 25 Grade II astrocytoma, 1 oligoastrocytoma	-/2.4	15	1	Median: 44 m 5y-PFS: 41	73	No radiological progression
Wang[26]	21/25	20	Primary/ residual/ recurrent	Grade I and II astrocytomas	2.4/-	14.5	1	10y-PFS: 65	67	No progression of solid component of tumor
Hadjipanayis[27]	49/-	16	Unresectable/ residual/ recurrent	37 PA,12 Grade II fibrillary astrocytomas	3.3/-	15	1	-	66	No tumor progression
Simonová[28]	70/-	17	Primary/ residual/ recurret	Grade I or II	-/4.2	Median prescription dose: 25	Median: 5	3y-PFS: 92 5y-PFS: 88	94	No tumor progression
Kihlström[29]	7/7	18	Unresectable	6 Grade II astrocytomas, 1 PA	-	18	1	-	86	No tumor progression
Hallemeier[30]	18/20	23	Primary/ residual/ recurret	PA (Grade I)	-/9.1	15	1	1y-PFS: 65 5y-PFS: 41	75	No solid tumor progression
Guo[31]	52/-	Range: 9-78	-	Grades I or II	Mean: 29.53/-	Mean: 15.67	1	-	84.3	Disappearance, reduction, and stabilization of tumors
Ma[32]	3/-	-	Recurrent	Grades II -IV glioma with IDH mutation or 1p/19q codeletion after radiation therapy (2 astrocytoma, 1 oligodendroglioma)	-	-	-	-	-	-

LGG: low-grade glioma; PA: pilocytic astrocytoma; SEGA: subependymal giant cell astrocytoma; Gy: gray; y: year; m: month; GTV: gross tumor volume; PTV: planning target volume; PFS: progression-free survival.
[a]Data represent all patients included in the study (39 low-grade gliomas and 68 high-grade gliomas).

TABLE II.— *Summary of studies reporting tumor location in low-grade gliomas.*[25-27, 29, 30]

Study	#patients/ #tumors	Tumor grade	Tumor location									
			Hemisphere	Brainstem	Cerebellum	Midbrain	Thalamus	Hypothalamus	Ventricle	Optic tract	Corpus callosum	Others
Heppner[25]	49/-	21 PA, 2 SEGA, 25 Grade II astrocytoma, 1 oligoastrocytoma	17	6	7	5 (tectum)	6	7	0	1	0	0
Wang[26]	21/25	Grade I and II astrocytomas	8	4	4	1 (tectum)	0	0	6	0	1	1 (pineal region)
Hadjipanayis[27]	49/-	37 PA, 12 Grade II fibrillary astrocytomas	12	22	4	0	6	1	1	1	1	1 (insular cortex)
Kihlström[29]	7/7	6 Grade II astrocytomas, 1 PA	0	0	0	7 (tectum)	0	0	0	0	0	0
Hallemeier[30]	18/20	PA (Grade I)	2	4	9	5	0	0	0	0	0	0
Total number of tumors for each location			39	36	24	18	12	8	7	2	2	2

PA: pilocytic astrocytoma; SEGA: subependymal giant cell astrocytoma.

panayis *et al.* analyzed a cohort of 49 patients with LGGs, including 24 who received adjuvant SRS for incompletely resected lesions and 25 who underwent SRS for recurrent disease.[27] Within this cohort, 22 tumors were located in the brainstem, with local control rates of 67% for adjuvant SRS and 50% for SRS performed for recurrence. Additionally, Hallemeier *et al.* evaluated 18 patients with pilocytic astrocytoma (WHO Grade I), comparing outcomes between those with and without prior external beam radiation therapy (EBRT).[30] The 5-year PFS was 71% in the no prior EBRT group and 20% in the prior EBRT group. Univariable analysis identified prior EBRT as significantly associated with inferior PFS (P=0.008).

Adverse events

Adverse events following SRS were reported in 7 studies (Table IV).[24-30] The majority of toxicities were mild to

TABLE III.—*Summary of selected studies comparing outcomes between two groups.*[24, 27, 30]

Study	Treatment	No. of patients (lesions) treated with SRS	Type of tumors	Local control rate	Analysis results (HR (95%CI))
Sun[24]	SRS + surgery	-	Recurrent tumors	Median PFS: 17.5 m (Median OS: 52.0 m)	Multivariable analysis for influencing factors of PFS: Surgery for recurrence 4.951 (1.245-19.696, P=0.023)
	SRS alone	-		Median PFS: 12.0 m (Median OS: 27.0 m)	Multivariable analysis for influencing factors of OS: Surgery for recurrence 8.682 (1.715-43.944, P=0.009)
Hadjipanayis[27]	SRS as an adjuvant	24[a]	Low-grade tumors	71%	-
	SRS for recurrence	25		64%	
	SRS as an adjuvant	12	Brainstem tumors	67%	-
	SRS for recurrence	10		50%	
Hallemeier[30]	No prior EBRT	8	PA (WHO Grade I)	5y-PFS: 71%	Univariable analysis for inferior PFS: Prior EBRT (P=0.008)
	Prior EBRT	10		5y-PFS: 20%	

EBRT: external beam radiation therapy; y: year; SRS: stereotactic radiosurgery; PFS: progression-free survival; OS: overall survival; PA: pilocytic astrocytoma.
[a]24 patients underwent adjuvant SRS for unresectable lesions; 16 after biopsy and 8 within 6 months post-resection for residual disease.

TABLE IV.—*Summary of studies reporting adverse effects of stereotactic radiosurgery treatment.*[24-30]

Study	Patients with adverse effects, N. (%)	Median GTV/PTV (cm^3)	Median marginal dose (Gy)	Number of fractions	SRS treatment-related toxicity
Sun[24]	5 (13)	-/18.5[a]	13.0[a]	1	Headache (Grade 1& 2), dizziness, nausea, vomiting
Heppner[25]	4 (8)	-/2.4	15	1	Neurological decline, encephalomalacia, hemiparesis
Wang *et al.*[26]	8 (40)	2.4/-	14.5	1	Mild-to-moderate AREs, mostly mild or no symptoms
Hadjipanayis[27]	3 (6)	3.3/-	15	1	Neurological decline, speech deterioration
Simonová[28]	5 (<5)	-/4.2	Median prescription dose: 25	Median: 5	Moderate-to-severe toxicity (Grade 2&3)
Kihlström[29]	6 (86)	-	18	1	Severe neurological reactions (30 Gy, 35 Gy), transient symptom aggravation with no lasting deficits (20 Gy, 18 Gy), mild transient diplopia (14Gy, 14Gy)
Hallemeier[30]	8 (44)	-/9.1	15	1	Edema, resolved with corticosteroid therapy

Gy: gray; y: year; GTV: gross tumor volume; PTV: planning target volume; SRS: stereotactic radiosurgery; AREs: adverse radiation effects.
[a]Data represent all patients included in the study (39 low-grade gliomas and 68 high-grade gliomas).

moderate, including headache, dizziness, nausea, vomiting, and transient neurological symptoms. Kihlström *et al.* reported adverse effects in 6 of 7 patients (86%) and provided a dose-specific description of toxicities, with severe neurological reactions observed at 30 & 35 Gy, transient symptom aggravation without lasting deficits at 18 & 20 Gy, and transient diplopia at 14 Gy.[29]

None of the included studies reported cognitive neurological symptoms or memory deficits secondary to SRS.

Discussion

Current therapies for management of LGGs

The management of LGGs has historically centered on surgical resection, radiation therapy (RT), and, in selected cases, chemotherapy. Surgery serves as the cornerstone of treatment, with gross total resection (GTR) being the preferred approach whenever feasible. GTR not only establishes a definitive diagnosis but also significantly reduces the risk of progression compared to subtotal resection or biopsy alone, in patients with diffuse LGG.[33] Early extensive resection has been associated with improved PFS and overall outcomes, emphasizing the importance of its prognostic significance.[34, 35]

Adjuvant RT, often initiated following surgery, has demonstrated a clear benefit in extending PFS but have showed minimal improvement in overall survival.[36, 37] Despite the benefits, long-term survivors treated with RT may experience progressive cognitive decline, especially with higher radiation doses.[38-40] Consequently, the decision to proceed with RT must balance the benefits of tumor control against the potential risks of late toxicity.

Chemotherapy has also emerged as an LGG treatment option. Buckner *et al.* reported that receiving radiation plus procarbazine, lomustine, and vincristine had significantly longer OS and PFS compared to radiation therapy alone.[41] However, there was a higher frequency and greater severity of toxic effects compared to the group that underwent radiation therapy alone. Additionally, temozolomide has been explored as an alternative, but did not show superiority over RT alone in PFS.[42]

While these traditional approaches have formed the

backbone of LGG management, SRS has emerged as a compelling alternative or adjunctive treatment. SRS offers the advantage of being minimally invasive while delivering high-dose precision radiation. This study explores the role of SRS in managing biopsy-proven LGGs, focusing on its efficacy and safety as a non-invasive treatment option.

Overall effectiveness of SRS in LGG

Our findings suggest that SRS offers favorable tumor control, with local control rates ranging from 66% to 94% and 5-year PFS rates up to 88%. Among the included studies, Sun *et al.* reported a comparatively poor median PFS of 12.0 months, which may in part be attributed to the larger median target volume of 18.5 cm^3 in their cohort.[24]

In surgically challenging locations such as the brainstem, where conventional surgery poses significant risks, SRS has shown particular advantages. Studies such as those by Hadjipanayis *et al.* reported a tumor control rate of 59% for brainstem LGGs, with improved control rates in adjuvant SRS cases (67%) compared to recurrent cases (50%).[27] These findings align with prior systematic review by Gagliardi *et al.*, which reported a 5-year OS of 97% and 5-year PFS of 92% following GKRS for brainstem LGGs.[43] This suggests that SRS serves as a viable non-invasive option in anatomically complex regions, with early adjuvant application providing enhanced tumor control.

Factors influencing SRS outcomes in LGG

The role of surgical intervention in conjunction with SRS cannot be understated. Sun *et al.* demonstrated that surgery for recurrence significantly enhanced OS and PFS (P=0.009 and P=0.023, respectively) for recurrent LGGs.[24] These results resonate with studies such as those by Ius *et al.* and Yan *et al.*, which emphasized that greater extent of resection (EOR) and smaller preoperative tumor volumes significantly improve OS and delay tumor progression. Ius et al emphasized the survival benefits of a higher EOR in incidentally discovered LGGs, showing that smaller preoperative tumor volumes (P=0.001) and higher EOR (P=0.037) were significantly associated with improved OS.[44] Similarly, Yan *et al.* identified partial tumor resection as a predictor of early tumor progression within five years (OR=1.66, P=0.031) with WHO grade II glioma, reinforcing the necessity of maximal resection when feasible.[45]

Furthermore, prior treatment history substantially influences the efficacy of SRS. Hallemeier *et al.* reported that patients with no prior EBRT achieved markedly better outcomes, with 5-year PFS of 71% compared to only 20% in those previously treated with EBRT (P=0.008).[30] This suggests that prior irradiation may make tumors more resistant to treatment, resulting in poorer local control.

Prior therapies may remodel the tumor microenvironment and select for radioresistant subclones. CD133-positive glioma stem-like cells (GSCs) can survive high-dose irradiation and serve as a source of tumor recurrence.[46, 47] These GSCs exhibit radioresistance through preferential activation of DNA damage checkpoints and enhanced DNA repair efficiency.[48] Moreover, radiation-induced hypoxia and vascular remodeling further contribute to radioresistance.[49] Tumor cells that survive irradiation can acquire hypoxia-inducible factor 1 (HIF-1) activity and migrate toward tumor vasculature, thereby leading to tumor recurrence.[50] In addition, hypoxic perinecrotic cells with altered HIF-1 signaling exhibit a radioresistant phenotype.[51] These biological alterations provide a plausible basis for the observed dependence of SRS efficacy on prior treatment exposure and sequencing.

Taken together, these findings highlight that patient selection for SRS should carefully account for surgical history, extent of resection, tumor volume, and prior radiotherapy exposure, as these factors critically shape therapeutic efficacy and long-term outcomes. Moreover, recent evidence indicates that the tumor microenvironment (TME) also plays a pivotal role in determining radiosensitivity and treatment response in gliomas. Beyond direct cytotoxicity, radiotherapy can remodel immune and stromal compartments, triggering the release of pro-inflammatory molecules and immune cell infiltration within the TME.[52] In particular, radiation has been shown to drive glioma-associated macrophages (GAMs) toward an M2-like immunosuppressive phenotype,[53] thereby attenuating antitumor immunity and promoting tumor repair and regrowth. Recognizing these microenvironmental influences could help refine radiosurgical strategies and support rational combination approaches to enhance treatment efficacy.

Considerations for SRS in LGGs

Molecular biomarkers have emerged as pivotal factors in guiding the management and prognostication of LGGs. The 2016 and subsequent 2021 WHO classifications underscored the significance of IDH mutation status and 1p/19q co-deletion in differentiating LGG subtypes, influencing both prognosis and therapeutic decisions.[2, 10] Oligodendrogliomas, typically characterized by both IDH mutations and 1p/19q co-deletions, show favorable prog-

nosis compared to other LGG subtypes, such as diffuse astrocytomas, where IDH mutations are also relevant in stratifying outcomes.

The integration of molecular markers into treatment planning for LGGs has proven critical in optimizing therapeutic outcomes, as they significantly influence treatment responses across various modalities. Surgical studies, such as that by Familiari *et al.*, demonstrate that 1p/19q co-deletion in oligodendrogliomas is associated with significantly better outcomes compared to non-deleted diffuse astrocytomas, and that the extent of resection further amplifies these differences.[54] Additionally, several studies also have reported that, even among IDH-mutant LGGs, treatment outcomes differ according to 1p/19q co-deletion status, with therapeutic efficacy varying between codeleted and non-codeleted subgroups.[42, 55, 56]

While the studies included in our review did not specifically focus on molecular characteristics as part of the tumor profile for the patients analyzed, the growing evidence highlighting the significant influence of molecular subtypes on treatment efficacy and prognosis underscores the need for incorporating molecular stratification in future research. To partially address this limitation, we conducted an additional targeted search and identified one relevant study by Ma *et al.*[32] This study included 94 patients with molecularly defined IDH-mutant gliomas, 59 with astrocytomas and 35 with 1p/19q-codeleted oligodendrogliomas, all of whom had previously received radiation therapy, with 79% receiving combined chemoradiation and 21% receiving radiation alone. After recurrence, salvage chemotherapy was administered, and 37% of the patients underwent some form of salvage re-irradiation. Within this cohort, three patients (one with oligodendroglioma and two with astrocytoma) received SRS as salvage therapy, though specific outcomes were not detailed, and SRS was infrequently used in this cohort.[32]

Given the potential of SRS technology, future studies should prioritize incorporating molecular stratification to better understand how SRS may benefit distinct molecular subgroups of LGGs, thereby refining patient selection and advancing personalized management strategies.

SRS related toxicity

Regarding safety, this review confirms the relatively low incidence of adverse events associated with SRS. Most patients experienced mild-to-moderate side effects, such as headaches or dizziness,[24, 26] with severe complications being rare.[28] This aligns with findings by Wei *et al.*, who reported a 6.8% incidence of adverse radiation effects in patients with infratentorial juvenile pilocytic astrocytomas (JPA), all managed successfully with corticosteroids.[57] Among the studies we reviewed, Wang *et al.* reported that while no procedure-related deaths occurred following GKS, mild-to-moderate AREs were observed in 40% of patients, with a higher incidence in those who had received prior cranial radiotherapy, and most symptoms were mild or absent, with no significant late complications.[26] Simonová *et al.* reported that moderate late toxicity (Grade 2) occurred in 4% of patients, and severe toxicity (Grade 3) was observed in two patients treated with single-session GKS at a minimum dose of 20 Gy.[28] Kihlström *et al.* reported that early dose selection for radiosurgery, initially based on treatments for arteriovenous malformations and metastases (30 Gy, 35 Gy), led to varying degrees of radiation-induced reactions, with higher doses causing severe or temporary neurological symptoms, while reduced doses (14 Gy) resulted in milder effects.[29]

The findings underscore the importance of dose optimization, with lower marginal doses (<15 Gy) reducing severe adverse effects while maintaining tumor control. The low rate of severe complications further supports the use of SRS. Nevertheless, careful patient selection and dose optimization remain essential to maximize therapeutic efficacy and minimize risks.

Furthermore, cognitive and memory impairment may develop following radiotherapy or radiosurgery, primarily due to unintended irradiation of memory-associated structures such as the hippocampus. Advances in radiotherapy planning have enabled hippocampal dose reduction to mitigate such neurocognitive side effects, and recent studies have explored the feasibility of these approaches in glioma. Several dosimetric analyses have demonstrated that hippocampal-sparing techniques, including hippocampal-sparing volumetric-modulated arc therapy (HS-VMAT) and multi-criteria optimization (MCO), can lower the radiation dose to the hippocampus and may help reduce the risk of cognitive decline.[58-60] Future prospective studies incorporating hippocampal dose constraints and neurocognitive assessments may help clarify the clinical value of hippocampal-sparing in glioma radiotherapy.

Limitations and future directions

Despite the promising outcomes, there are several limitations to consider in this review, including moderate heterogeneity across the included studies, which prevented a meta-analysis. Additionally, the majority of the included studies are observational, which weakens the strength of causal inferences. Importantly, most of the available data

were based on historical classifications of LGGs without molecular characterization.

Given the paradigm shift introduced by the 2021 WHO classification, future research should specifically evaluate the efficacy of SRS in IDH-mutant subgroups. Integration of molecular and genetic biomarkers into treatment planning will be essential to refine patient selection, optimize SRS protocols, and improve long-term outcomes.

Conclusions

This systematic review highlights the potential role of SRS as a non-invasive treatment option for biopsy-proven LGGs. Across the included studies, SRS achieved durable local control and PFS in selected patients, with most adverse events being mild to moderate. More favorable outcomes were observed when SRS was used as an adjuvant treatment for incompletely resected tumors, in patients who underwent surgery for recurrence, and in those without a history of prior EBRT, emphasizing the prognostic importance of treatment history. While SRS may offer a promising addition to the management strategies for LGGs, particularly in surgically challenging cases, its role should be further clarified through prospective studies incorporating molecularly stratified populations.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Yusuke S. Hori, David J. Park, and Steven D. Chang have given substantial contributions to the conception or the design of the manuscript, Yuka Mizutani, Paul M. Harary, Shreyas Annagiri to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript. All authors read and approved the final version of the manuscript.

History
Article first published online: December 9, 2025. - Manuscript accepted: October 28, 2025. - Manuscript revised: October 21, 2025. - Manuscript received: September 7, 2025.