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REVIEW OPEN ACCESS

Chemotherapy for Spinal Cord Intramedullary Pediatric Low-Grade Glioma—A Systematic Literature Review

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ABSTRACT

Pediatric intramedullary low-grade gliomas (PIMLGGs) are rare neoplasms that present unique clinical and management challenges. Although surgery remains the primary tool for tissue diagnosis and decompression, complete gross-total resection is frequently unfeasible due to the infiltrative nature of these lesions. To define the role of chemotherapy, we conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-based systematic review of 21 studies published between 2000 and 2025, comprising 98 patients who started chemotherapy at a median age of 3.9 years (ranging from 3 months to 17.7 years). In half of the cases, chemotherapy was used as primary therapy in cases of incomplete resection or biopsy, and half of the patients received salvage chemotherapy in cases of progressive tumor or recurrence. A platinum-based regimen was used in most of the patients. Complete response was achieved in 9% of cases, 9% had an incomplete response, and 42% had stable disease. Disease progression occurred in 26% of patients, and 15% died, most commonly due to disease progression. Median follow-up was 5 years (ranging from 3 months to 18 years).

1 | Introduction

Primary spinal cord tumors in children are rare, with an estimated incidence of approximately 0.09–0.26 cases per 1 million children per year [1]. The majority of pediatric intramedullary spinal cord tumors (IMSCTs) are astroglial [1, 2], including entities such as pilocytic astrocytoma, as well as ganglioglioma and oligodendroglioma [1, 3].

In high-grade lesions, overall prognosis remains poor in most cases, despite intensive surgical and oncological treatment [4].

Abbreviations: BRAF, B-rapidly accelerating fibrosarcoma, proto-oncogene (also called v-raf murine sarcoma viral oncogene homolog B1); CDKN2A, cyclin-dependent kinase inhibitor 2A; CNS, central nervous system; CR, complete response; CSF, cerebrospinal fluid; EFS, event-free survival—measured from the primary surgery/diagnosis and counts the initiation of any chemotherapy/radiotherapy as an event; GTR, gross-total resection; IMSCT, intramedullary spinal cord tumor; IR, incomplete response; KIAA1549 Part, Contributes the 5′ portion of the fusion, originating from chromosome 7q34, a gene of largely unknown function; LGG, low-grade glioma; MAPK/ERK kinase, mitogen-activated protein kinase/extracellular signal-regulated kinase; MEK, MAPK/ERK kinase; MRI, magnetic resonance imaging; OS, Overall survival; PD, Progressive disease; PFS, progression-free survival—measured from the first day of chemotherapy/radiotherapy to evaluate the true stabilizing power of that specific adjuvant treatment; PIMLGG, pediatric intramedullary low-grade glioma; PR, Partial resection; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RAS-MAPK, rat sarcoma and mitogen-activated protein kinase; SD, stable disease; STR, subtotal resection; V600E, amino acid valine (V) at position 600 changed to glutamic acid (E); WHO, World Health Organization.

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For pediatric intramedullary low-grade gliomas (PIMLGGs), standard treatment recommendations typically include safe maximal resection [5]. Radiotherapy (RT) in PIMLGGs has been associated with long-term risks, including spinal column effects, myelopathy, malignant transformation, and late toxicity [6, 7].

As maximal resection and RT in these tumors may both be associated with significant morbidity, there is an increased interest in exploring chemotherapy-based approaches and biologically targeted treatments. Although the use of targeted biological therapies in PIMLGGs represents a critical evolution in neuro-oncology, it remains beyond the immediate scope of this systematic review, which focuses on cytotoxic chemotherapy.

Although chemotherapy has shown promising results in selected cases, its precise role in PIMLGGs remains insufficiently defined. We therefore aimed to systematically review the literature on this topic. This manuscript evaluates the current evidence regarding the role of chemotherapy in the treatment paradigm for pediatric spinal cord tumors, with particular emphasis on intramedullary low-grade gliomas (LGGs).

2 | Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We conducted a systematic literature search in the following electronic databases and trial registers: MEDLINE, Cochrane Library, and ClinicalTrials.gov.

The search was limited to studies published between January 2000 and January 2025. This time frame was selected because it corresponds to the implementation of modern multi-agent chemotherapy protocols since the 1990s. Contemporary regimens, particularly vincristine- and carboplatin-based therapies, have largely replaced older, more toxic treatment approaches.

Eligible studies included pediatric patients with low-grade (World Health Organization [WHO] Grades I and II) IMSCTs who received chemotherapy as part of their treatment. Eligible histologies included pilocytic astrocytoma, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, diffuse (fibrillary) astrocytoma WHO Grade II, ganglioglioma, and oligoastrocytoma.

To identify eligible studies, we used a combination of Medical Subject Headings (MeSH) and free-text keywords, using combinations of the following: "spinal cord neoplasms," "intramedullary spinal cord tumor," "spinal glioma," "low grade glioma," "astrocytoma," "child," "pediatric," "children," "chemotherapy," and "adjuvant therapy." Two researchers independently manually reviewed the bibliographies of identified articles.

Studies were excluded if they involved adult populations, non-spinal tumors, high-grade tumors (WHO Grades III and IV), non-glial histologies, ependymomas, or mixed cohorts in which relevant data could not be disaggregated for the predefined population or tumor characteristics.

We grouped the extracted variables into the following domains. *Demographic and study characteristics* included the number of pediatric patients with intramedullary low-grade spinal cord tumors who received chemotherapy and the age at initiation of chemotherapy. *Tumor histology* (e.g., pilocytic astrocytoma and ganglioglioma), previous or concomitant treatment (including the type of surgery, extent of surgical resection, and RT), type of chemotherapy, toxicity if reported, follow-up length in years after chemotherapy, and results of treatment are included. Extent of resection was categorized as gross-total resection (GTR), subtotal resection (STR), partial resection (PR), or biopsy.

Outcome measures included radiological response on magnetic resonance imaging (MRI), changes in tumor size following chemotherapy, progression-free survival (PFS), overall survival (OS), and event-free survival (EFS), when reported. Radiological response was classified as complete response (CR), defined as complete disappearance of the tumor; incomplete response (IR), defined as a reduction in tumor size; stable disease (SD); or progressive disease (PD). Because response criteria varied across the included studies, reported minor, partial, and major radiographic responses were pooled as "incomplete response" for descriptive analysis; no retrospective RAPNO reclassification was attempted [8].

Mortality and morbidity data included overall mortality rates and, when available, the specific causes of death. Causes were categorized as tumor progression, metastatic dissemination (including leptomeningeal spread), treatment-related complications, or neurological and respiratory deterioration.

3 | Results

Database and registry searches identified 2592 records (Figure 1). After removal of duplicates and clearly irrelevant publications based on titles, as well as studies published before 2000, 488 abstracts were screened for relevance. Of these, 342 records were excluded, for example, reviews and meta-analyses, animal and experimental studies, expert opinions, book chapters, and articles deemed off topic based on abstract screening.

A total of 146 full-text articles were assessed for eligibility. Out of the total, 120 papers were further excluded because they reported mixed cohorts by age, histology, or tumor location, in which data specific to the population of interest could not be disaggregated—specifically, the number of pediatric patients with intramedullary LGGs who received chemotherapy (Figure 1).

A total of 21 studies published between 2000 and 2025 were included in the main cohort, comprising 98 patients [9–29]. Moreover, we separately analyzed four studies that included mixed populations (children and adults) and/or mixed tumor locations (cranial and spinal) and grades (low- and high-grade). These studies provided some extractable information relevant to our investigation's focus. Table 2 presents data from 74 patients reported in 4 mixed-cohort studies [30–33].

We identified 21 focused studies, comprising 98 pediatric patients with low-grade intramedullary tumors treated with chemotherapy (Table 1). All tumors were LGGs, predominantly pilocytic

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TABLE 1 | Summary of chemotherapy use in the management of pediatric low-grade intramedullary spinal cord tumor: focused papers, including case reports and case series.

Reference	Study type	Age at the time of CT initiation (year)	Histology	Treatment before CT	Chemotherapy	Follow-up (year)	Results
Perwein et al. [9]	PS	4.2 (0.7–15.6)	35 LGG 27 PA 2 DG Grade II 2 GG 4 others	13 BX 16 PR 3 STR 2 GTR	Reason: 9 initial treatment and 26 salvage treatment Regimen: 35 vincristine/carboplatin → 4 etoposide	8 (0–21)	7 IR or CR 17 SD 4 PD 7 DOD
Scheinemann et al. [10]	RS	1.4	9 LGG (most LGA)	STR	Reason: initial treatment Regimen: vincristine/carboplatin	11	PD
		6.5		PR→	Reason: salvage treatment Regimen: vincristine/carboplatin	4.6	SD
		1.5		PR	Reason: initial treatment Regimen: vincristine/carboplatin → salvage CT	2.8	SD
		1.6		STR	Reason: initial treatment Regimen: vincristine/carboplatin → salvage CT	5.9	SD
		8.1		PR, RT → STR →	Reason: salvage treatment Regimen: vincristine/carboplatin → salvage CT (with STR) → salvage CT (with GTR)	8.2	SD
		10.8		STR → STR →	Reason: salvage treatment Regimen: thioguanine/procarbazine/lomustine/vincristine	4.9	SD
		5.4		STR →	Reason: salvage treatment Regimen: vincristine/carboplatin → salvage CT	3.7	PD
		9.4		STR →	Reason: salvage treatment Regimen: carboplatin	2.2	SD
		11.2		BX	Reason: initial treatment Regimen: vincristine/carboplatin	0.4	PD
Carey et al. [11]	RS	0.9	ACT	STR	Reason: initial treatment Regimen: platinum-based	18.2	PD
		2.3	PA	GTR	Reason: initial treatment Regimen: platinum-based	11.5	CR
		1.1	PA (V600E)	PR	Reason: initial treatment Regimen: platinum-based	9.6	PD, DOD
		0.6	PA (BRAF duplication)	BX	Reason: initial treatment Regimen: platinum-based	6.5	SD
		2.5	PA (BRAF duplication)	STR	Reason: initial treatment Regimen: platinum-based	4.7	PD
		0.6	PA	BX	Reason: initial treatment Regimen: platinum-based	3.2	SD
		3.2	PA	BX	Reason: initial treatment Regimen: platinum-based	3	IR

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TABLE 1 | (Continued)

Reference	Study type	Age at the time of CT initiation (year)	Histology	Treatment before CT	Chemotherapy	Follow-up (year)	Results
14.9	Oligoast-rocytoma	BX	Reason: initial treatment Regimen: platinum-based	0.6	DOD		
Silva et al. [12]	RS	Children	6 LGG (most ACT)	4 STR, 1 NTR, and 1 GTR → 2 RT →	Reason: 5 initial therapy and 1 salvage treatment Regimen: vincristine/carboplatin	6 (1–16)	3 SD 3 PD
Merchant et al. [13]	RS	6.7 (0.8–17)	Oligoast-rocytoma	STR → STR → GTR→	Reason: salvage treatment Regimen: cyclophosphamide/vincristine/etoposide/cisplatin	5	CR
			LGA	BX → RT → STR→	Reason: salvage treatment Regimen: cisplatin/vincristine/actinomycin/bleomycin		SD
			LGA	STR → RT	Reason: salvage treatment Regimen: cyclophosphamide/vincristine/etoposide/cisplatin/carboplatin /ifosfamide		CR
			PXA	STR → RT→	Reason: salvage treatment Regimen: cyclophosphamide		PD, DOD
			GG	STR → RT	Reason: salvage treatment Regimen: etoposide/cisplatin		SD, death
Mora et al. [14]	RS	1.9	ACT Grade II	BX	Reason: initial Regimen: carboplatin and vincristine → cisplatin/irinotecan	7	IR
		1	ACT Grade II	BX	Reason: initial Regimen: carboplatin and vincristine → cisplatin/irinotecan	7	SD
		5.9	PA	BX	Reason: initial Regimen: cisplatin/irinotecan	6	SD
		5.2	ACT Grade II	PR	Reason: initial Regimen: cisplatin/irinotecan	5.7	SD
Crawford et al. [15]	RS	9	Fibrillary astrocytoma	STR	Reason: initial or salvage Regimen: NA	NA	PD, death
		1.5	Fibrillary astrocytoma	STR			PD
		1.5	PA	STR			PD
		17	PA	STR			SD, death
Townsend et al. [16]	RS	Children	4 LGA	4 PR or STR	Reason: initial treatment Regimen: vincristine/carboplatin	4 (0.8–4.5)	1 IR 2 SD 1 PD
Hassall et al. [17]	RS	3.6	GG	PR	Reason: salvage treatment Regimen: carboplatin	1.5	SD
		3.9	PA	STR		2.2	IR

(Continues)

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TABLE 1 | (Continued)

Reference	Study type	Age at the time of CT initiation (year)	Histology	Treatment before CT	Chemotherapy	Follow-up (year)	Results
2	PA	PR	0.5	CR			
Khaw et al. [18]	RS	7.3	All LGA	BX	Reason: salvage treatment Regimen: carboplatin → temozolomide	3	CR
		3.4		Resection		2.3	IR
		6.7		Resection		2.1	PD
Schneider et al. [19]	RS	4	PA	PR	Reason: initial treatment Regimen: NA	5	PD
		Child	PA	GTR	Reason: salvage treatment Regimen: NA	5	PD
		3	WHO II astrocytoma	PR	Reason: initial treatment Regimen: NA	7	PD, DOD
Choi et al. [20]	RS	6	PA	STR	Reason: initial treatment Regimen: NA	6	PD
		10	WHO II astrocytoma	PR + RT		0.7	DOD
Hung et al. [21]	RS	1.9	WHO II astrocytoma	BX	Reason: initial treatment Regimen: cisplatin/etoposide	3	SD
		0.9	Astrocytoma	PR		6	PD
Chamoun et al. [22]	CS	14	LGA	STR → re-resection + RT	Reason: salvage treatment Regimen: temozolomide	8	SD
		12	LGA	STR → re-resection + RT		3	SD
Mora et al. [23]	CS	1.5	Fibrillary Grade II astrocytoma	PR	Reason: initial treatment Regimen: vincristine/carboplatin → irinotecan/cisplatin	1.5	CR
		0.9	Fibrillary Grade II astrocytoma	PR		1	CR
Matsuzaki et al. [24]	CRep	1	PA	PR	Reason: initial treatment Regimen: cisplatin/etoposide	5.3	CR
Goyal et al. [25]	CRep	14	Grade II astrocytoma	BX + RT	Reason: salvage treatment Regimen: temozolomide	5	IR
Almubarak et al. [26]	CRep	3	PMA	PR	Reason: initial treatment Regimen: vincristine/carboplatin → etoposide/cyclophosphamide	4	PD
Dolen et al. [27]	CRep	0.9	PA	GTR	Reason: salvage treatment Regimen: vincristine/carboplatin	12	SD
Rondinelli et al. [28]	CS	5	PA	PR + RT	Reason: initial treatment Regimen: carboplatin/etoposide → vincristine/carboplatin	7.8	IR
Levenbaum et al. [29]	CS	5	GG	STR	Reason: initial treatment Regimen: vincristine/carboplatin → vinblastine	0.4	IR

Abbreviations: ACT, astrocytoma; CR, complete response; CRep, case report; CS, case series; CT, chemotherapy; DG, diffuse glioma; DOD, death of disease; GG, ganglioglioma; GTR, gross-total resection; IR, incomplete response; LGA, low grade astrocytoma; LGG, low-grade glioma; PA, pilocytic astrocytoma; PD, progressive disease; PFS, progression-free survival, PMA, pilomyxoid astrocytoma; PR, partial resection; PS, prospective study; PXA, pleomorphic xanthoastrocytoma; RS, retrospective study; RT, radiotherapy; SD, stable disease; STR, subtotal resection.

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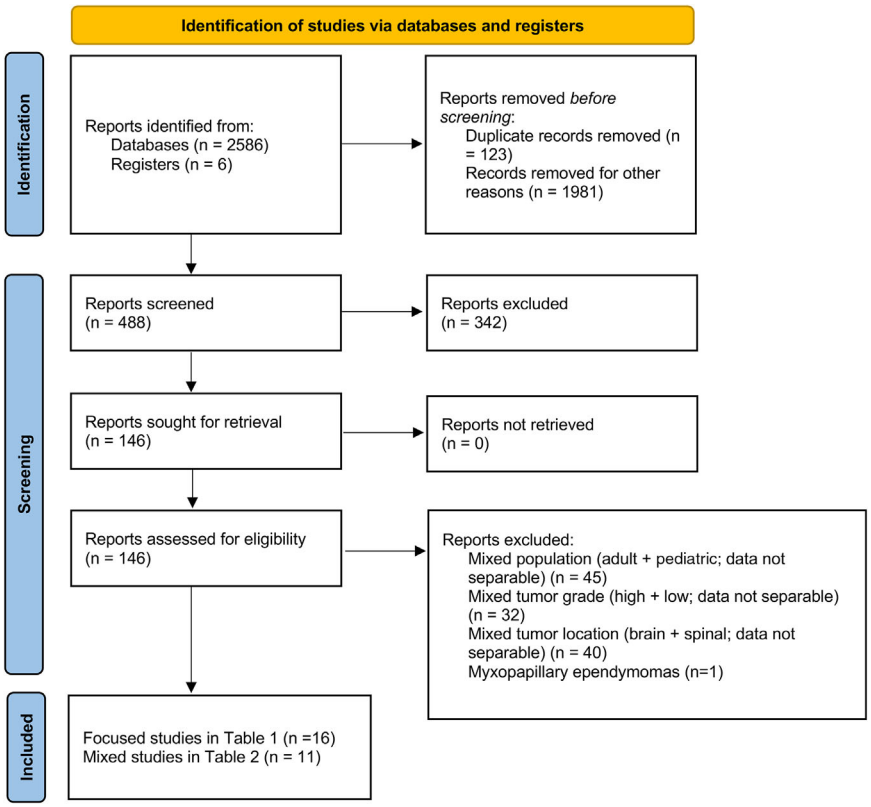


FIGURE 1 | PRISMA flow chart of the current literature review.

astrocytoma (45 cases, 46%), unspecified low-grade astrocytomas (LGA)/gliomas (31 cases, 32%), 13 astrocytomas Grade II (13%, including "diffuse," "fibrillary," and unspecified), five gangliogliomas (5%), two oligoastrocytomas (2%), one pilomyxoid astrocytoma [26], and one pleomorphic xanthoastrocytoma [13].

The median age at chemotherapy initiation was 3.9 years (ranging from 3 months to 17.7 years). This demographic profile was heavily dominated by early childhood, with the largest single series, Perwein et al. [9], reporting a median age at diagnosis of 4.2 years and over half of the patients (54%) presenting under the age of 4 years. This exceptionally young age distribution was corroborated by other prominent series, including those by Scheinemann et al. (median age 1.4 years) [10] and Carey et al. (median age 0.9 years) [11].

Incomplete resection was documented in 64 cases (65%), whereas 24 patients (24%) underwent biopsy alone. GTR before chemotherapy was achieved in seven cases (7%), and the extent of resection was not specified in three cases. Thus, prior to the initiation of chemotherapy, the vast majority of patients had residual tumor burden (90% of cases). RT was administered before or concomitantly with chemotherapy in 12 cases (12%).

Chemotherapy initiation fell into two distinct clinical categories: initial treatment (48 cases, 50%) and salvage therapy for tumor regrowth or disease progression (49 cases, 50%).

Only a single very young patient (<3 years) received initial adjuvant chemotherapy after GTR [11]. The other patient who received chemotherapy after GTR received it due to tumor recurrence.

The most commonly used regimens were platinum-based protocols, administered in 87 cases (89%), with vincristine/carboplatin-based regimens being the most frequently used, accounting for 55 cases (56%) (see Table 1).

The median follow-up after chemotherapy was 5 years (range, 4 months–18 years). CR or IR was observed in 16% of cases ($n = 16$). Disease stabilization was the most common outcome, occurring in 42% of patients ($n = 41$). Progression despite treatment was reported in 26% of cases ($n = 25$). Mortality occurred in 15% of patients ($n = 15$): 12 cases died of disease progression (including metastasis and growth), and 3 from other reasons.

3.1 | Histology

Pilocytic astrocytomas generally demonstrated more favorable survival and disease control than WHO Grade II diffuse/fibrillary astrocytomas [9, 19, 20]. Rare aggressive variants, including pilomyxoid astrocytoma [26] and pleomorphic xanthoastrocytoma [13], showed poorer outcomes, whereas gangliogliomas generally had an indolent course [13, 17]. Molecular alterations also influenced outcomes, with B-rapidly accelerating fibrosarcoma (BRAF) V600E–mutated tumors showing poorer responses to conventional chemotherapy than BRAF fusion/duplication tumors [11].

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TABLE 2 | Summary of chemotherapy use in the management of pediatric spinal low-grade gliomas: Mixed studies (cranial and spinal; children and adults; and low and high grade).

Reference	Design	General cohort	Histology	RT	CT in pediatric patients with intramedullary LGG	Follow up (year)	Results and conclusions
Ghaith et al. [30]	RS	Epidemiological study $N = 884$ Spinal low-grade gliomas only Mixed age (294 pediatrics + 590 adults) Some received CT	54 LGG (most ACT)	yes	$N = 54$ Reason: initial or salvage Regimen: NA	10	RT and CT reduce OS
Ater et al. [31]	RCS	$N = 274$ All pediatrics All received CT Mixed localization (head and spine)	9 LGA	no	$N = 9$ Reason: initial or salvage Regimen: 6 carboplatin/vincristine 3 thioguanine/procarbazine/lomustine/vincristine	5	5-year EFS 49% ± 6% 5-year OS 88% ± 4%
Ahmed et al. [32]6	RS	$N = 37$ All low-grade All pediatric All intramedullary	7 LGG (most ACT)	yes	$N = 7$ Reason: initial Regimen: NA	12 ± 1.4	5-year PFS 55% (RT + CT) 5-year PFS 36% (no RT/CT)
Zelcer et al. [33]	RS	$N = 25$ All pediatrics (<3 years old) All spinal Mixed grade	4 LGA	no	$N = 4$ Reason: initial treatment Regimen: NA	7 ± 6.5	5-year OS 93% ± 6.4%

Abbreviations: ACT, astrocytoma; CT, chemotherapy; EFS, event free survival; LGA, low grade astrocytoma; LGG, low-grade gliomas; NA, not available; OS, overall survival; PFS, progression-free survival; PS, prospective study; PSCT, pediatric spinal cord tumor; RCS, randomized controlled study; RS, retrospective study; RT, radiotherapy.

3.2 | Regimen

Carboplatin/vincristine remained the most commonly used first-line chemotherapy regimen and was primarily associated with disease stabilization and prolonged disease control. Weekly irinotecan plus cisplatin was associated with a disease control rate of 93.5% in a small cohort of patients, including complete radiological responses and clinical improvement in some patients with progressive and symptomatic disease [14, 23]. Temozolomide, administered as oral salvage chemotherapy, was also associated with disease stabilization and objective responses in a small cohort, including cases with PD after prior treatment [18, 22, 25].

3.3 | Age

Younger age, particularly infancy and early childhood, was consistently associated with higher progression rates in the main cohort (Table 1) and in the mixed cohort (see Table 2). Perwein et al. found significantly poorer EFS in younger children with spinal LGGs (regardless of CT): 10-year EFS was 27% in patients aged <5 years, 34% in those aged 5–<11 years, and 54% in those ≥11 years ($p = 0.008$); age ≥11 years was an independent favorable prognostic factor (HR 0.36) [9].

Ater et al., in the COG A9952 randomized trial (a mixed cohort that includes predominantly cranial LGGs), identified younger age as an independent predictor of poorer EFS and OS; infants <1 year had particularly unfavorable outcomes [31].

Within the Carey and Scheinemann cohorts, younger age at diagnosis serves as a major risk factor for tumor progression, as demonstrated by a 69.2% recurrence rate (9 of 13 patients) in children under 5 years compared to 31.2% (5 of 16) in older patients in the Scheinemann series ($p = 0.05$) [10] and the fact that 50% of all relapsed patients (8 of 16) in Carey's study were aged 3 or younger ($p = 0.05$) [11].

3.4 | PFS, EFS, and ES

In the Perwein et al. study, 35 patients received chemotherapy [9] with a 5-year PFS of 48% ± 9%, increasing to 62% ± 11% when patients with disseminated disease were excluded

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(10-year PFS, 49% ± 2%). OS was 80% in the chemotherapy group. Among 117 patients managed without upfront chemotherapy, 5-year EFS was 44%, and OS was 97% ± 2%. These differences likely reflect substantial confounding by indication, as chemotherapy was preferentially given to patients with aggressive, extensive, or disseminated disease.

Ahmed et al. retrospectively analyzed 37 pediatric low-grade IMSCTs [32]. Five-year PFS was 55% with adjuvant CT + RT versus 36% with surgery/observation alone, although adjuvant chemotherapy did not independently improve OS.

In the COG A9952 trial (Ater et al.) [31], nine patients with spinal LGA received chemotherapy, with a 5-year EFS of 49.6% and OS of 88.4%.

Townsend et al. reported four children with low-grade spinal astrocytoma treated with carboplatin/vincristine, with 4-year PFS of 75% and 100% OS [16].

Zelcer et al. reported 14 infants with low-grade spinal astrocytoma [33]. Of these, four received chemotherapy. Five-year OS was 93% ± 6.4%, with no significant OS benefit from adjuvant therapy; long-term recurrence/progression occurred in 72%.

Similarly, Ghaith et al. [30], using a large epidemiological database, found worse OS among patients receiving chemotherapy or RT than those treated with surgery alone; however, this was attributed to treatment selection bias rather than a harmful treatment effect (see Table 2).

3.5 | Toxicity

Carboplatin/vincristine was generally well tolerated but caused cumulative toxicities, including carboplatin hypersensitivity, vincristine neuropathy (19%), and frequent hematologic toxicity requiring treatment delays or dose modifications. TPCV had a more intensive toxicity profile, including Grades III/IV neurological events and peripheral neuropathy. Cisplatin-based regimens were associated with myelosuppression and ototoxicity, with high-frequency hearing loss. Weekly irinotecan/cisplatin was generally well tolerated, with mainly mild neutropenia and gastrointestinal toxicity and no significant long-term nephrotoxicity or ototoxicity.

Temozolomide primarily caused hematologic toxicity, particularly thrombocytopenia and neutropenia, sometimes requiring transfusions and substantial dose reductions.

4 | Discussion

Astrocytomas often exhibit an infiltrative growth pattern, leading to a poorly defined cord–tumor interface, which can make achieving GTR challenging. Following GTR for PIMLGG, 5-year EFS rates range from 80% to 90% [5, 32]. That is much higher than 5-year PFS in STR and PR (40%–45%) [12, 32]. However, GTR may be associated with significant morbidity, so in many centers a less aggressive approach is commonly adopted. *Residual tumor* frequently demonstrates progression over time; therefore, *adjuvant oncological treatments*—including RT, chemotherapy, and targeted therapies—are often considered.

Prior systematic reviews have highlighted the evolving yet still limited evidence base regarding the role of chemotherapy and RT in progressive PIMLGG. Several reviews analyze low- and high-grade tumors together, making it difficult to draw conclusions specific to PIMLGG [34, 35].

One of the most comprehensive reviews was conducted by Azad et al. [4]. They analyzed the treatment of 578 children with IMSCTs of different grades. The authors emphasized that, owing to the rarity of these lesions, the available evidence is largely retrospective and primarily focused on surgical management, particularly comparisons between GTR and STR, rather than on adjuvant therapy strategies.

The role of adjuvant RT in PIMLGGs remains highly contentious, balanced between temporary local disease control and severe, life-altering long-term toxicities. Although prospective data from the German GPOH group (Perwein et al.) reported an excellent 5-year PFS of 92% ± 8% for patients receiving RT [9], this cohort was subject to substantial treatment-selection bias. Patients selected for RT were significantly older (median age 13.5 years vs. 5.8 years for the chemotherapy group), harboring more mature spinal columns and localized, lower-risk tumors.

The pediatric spinal cord is highly sensitive, with a radiation tolerance estimated to be 10%–15% lower than that of adults [36]. Beyond myelopathy, spinal irradiation in children induces profound skeletal and endocrine morbidities [36]. Secondary spinal column deformities, primarily progressive kyphoscoliosis, develop in up to 70% of pediatric patients undergoing spinal irradiation [4, 36]. Furthermore, endocrine toxicities such as hypothyroidism are common; however, these are anatomically restricted to cases when cervical spinal fields are used [4, 36].

Modern RT modalities improve treatment precision, limiting radiation dose to adjacent normal structures. More recently, proton beam therapy has emerged as a highly attractive particle-based alternative. In the largest prospective protocol to date evaluating proton beam therapy in pediatric LGGs ($n = 174$; median follow-up 4.4 years), Indelicato et al. demonstrated that this dosimetric precision does not compromise efficacy, achieving excellent 5-year local control of 85%, PFS of 84%, and OS of 92% [37].

However, Indelicato et al. identified a critical dose-response relationship that is highly challenging for spinal lesions. To prevent severe myelotoxicity in children with brainstem or spinal cord tumors, institutional guidelines required reducing the prescription dose to a safer 50.4 Gy. This necessary dose reduction directly compromised tumor control, resulting in a significantly lower 5-year local control and PFS for spinal and brainstem tumors compared to other central nervous system (CNS) sites (62% vs. 90%, $p < 0.01$). The rate of radiologic pseudoprogression was 32.1% (mean onset at 12.1 months), and 68% of these cases were successfully managed with conservative surveillance alone.

Importantly, despite excellent visceral and systemic tissue sparing, proton beam therapy does not alter the radiation dose

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delivered directly to the involved spinal cord parenchymal tract or the surrounding vertebral bones. As a result, the risks of radiation-induced local myelopathy, vertebral growth plate arrest, and progressive postradiation kyphoscoliosis remain.

Chemotherapy is generally better tolerated in this context and is associated mainly with systemic toxicities that are often reversible. Epidemiological database studies often note a correlation between adjuvant therapy and decreased OS [30]. However, this survival paradox must be framed as a classic treatment selection bias (confounding by indication). Systemic chemotherapy is strictly reserved for patients with the worst clinical baseline: infants in whom radiation must be deferred, patients with inoperable biopsy-only disease, or those presenting with aggressive neuraxis dissemination, which independently drops 10-year OS from 97% to 68%.

Epidemiological data demonstrated that chemotherapy was more frequently administered to younger children (median 3.9 years). These numbers are significantly lower than the median age of diagnosis for the broader IMSCT population, which is typically reported between 6 and 13 years [10]. This disparity highlights that chemotherapy is frequently utilized as a *bridge or delay strategy for infants and very young children* who cannot safely receive RT due to the risk of severe neurological sequelae and permanent structural damage.

It should be noted that this group (patients under 5 years with intramedullary tumors, including LGG) also exhibited significantly worse OS. This age-stratified progression disparity, demonstrated across the Perwein (10-year EFS of 27% under 5 years) [9], Scheinemann (69.2% recurrence under 5 years) [10], and Carey (50% of relapses under 3 years) [11] cohorts, points to a distinct biological subgroup in infants. Although older children exhibit indolent disease characterized primarily by KIAA1549-BRAF fusions, very young children often harbor non-BRAF fusions (e.g., NTRK and FGFR) or atypical histologies, alongside differing telomere maintenance biology [10].

The *lower survival rates* observed in this review *for pediatric intramedullary spinal cord low-grade gliomas* compared to the 90%–95% survival typically reported for pediatric cranial LGGs, even among those who underwent incomplete resection, can be attributed to the eloquent and confined anatomy of the spinal cord and spine [11, 31]. Although the cranium has a greater capacity to accommodate slowly growing or stable masses, the very small diameter of the spinal canal and mobility (especially in the cervical region) mean that even minimal tumor growth or disease stabilization can lead to neurological failure.

Evidence from the reviewed papers supports several specific causes for this increased mortality: (1) respiratory and functional compromise in cases of high cervical or cervicomedullary tumors; respiratory paralysis, central breathing regulation disorders, and aspiration frequently caused deaths [9]; (2) tumor progression and dissemination [11]; and (3) postoperative complications (meningitis, cerebrospinal fluid [CSF] leak, etc.—less common) [15].

Malignant transformation of LGGs is exceedingly rare and is primarily associated with tumors harboring BRAF V600E mutations combined with cyclin-dependent kinase inhibitor 2A (CDKN2A) deletion. These molecular alterations are exceptionally uncommon in spinal cord LGGs, the majority of which are characterized by BRAF fusion events [38]. Current evidence suggests that BRAF fusion-driven tumors carry an extremely low, if not negligible, risk of transformation to high-grade glioma. Therefore, malignant progression is unlikely to account for the higher mortality observed in pediatric spinal low-grade gliomas compared with their intracranial counterparts.

Published experience with molecularly targeted therapy specifically in PIMLGG remains limited and has predominantly involved patients with recurrent or PD. Consequently, the optimal sequencing of conventional chemotherapy and targeted therapy in molecularly defined spinal LGG remains uncertain.

Although GTR remains the ideal neurosurgical objective, achieving a strict radiographic GTR in infiltrative spinal astrocytomas is often impossible without causing severe permanent neurological deficits. Data from the GOSH cohort suggest a highly practical clinical compromise: small-volume residual disease does not compromise PFS, yielding a 5-year PFS of >85% that behaves identically to GTR, whereas residual volumes exceeding 5% drop the 5-year PFS to <40% [12]. These findings suggest that small-volume residual disease may be oncologically acceptable when further resection would increase the risk of neurological morbidity. Experience from major treatment groups, including the German LGG consortium [9] and St. Jude Children's Research Hospital [11], and others [20], support management in centers equipped with advanced intraoperative neurophysiological monitoring (including mapping techniques) and ultrasonic aspiration technology. Such resources facilitate meticulous surgical planning and maximize the likelihood of achieving safe maximal resection while preserving neurological function.

Centralizing the currently available data is therefore crucial not only to summarize existing experience but also to encourage improved reporting by treating centers and to stimulate future collaborative multicenter research efforts. As chemotherapy is only applied sporadically across many centers, structured, comprehensive data on its use in PIMLGGs remain very limited. We therefore aimed to organize the existing evidence to support the design of prospective multicenter studies that could provide more robust and clinically useful information.

4.1 | Limitations

This study has several limitations characteristic of research on rare pediatric neoplasms. First, these include heterogeneity in the extent of surgical resection, variable use of RT and chemotherapy, and differences in chemotherapy protocols across centers. Moreover, assessing true tumor response to chemotherapy is difficult, as disease stability in these low-grade lesions may reflect the natural history rather than a treatment effect. Attribution of treatment effect is challenging: it is difficult to determine which therapy—chemotherapy or RT—contributed most to outcomes. The retrospective nature of most included studies may introduce selection bias and lead to heterogeneous reporting of clinical findings and treatment outcomes.

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Furthermore, older historical datasets largely lack standardized molecular profiling, limiting the ability to correlate clinical outcomes with modern molecular drivers. This is particularly relevant for infants, where tumors may not always appear pathologically high-grade despite harboring high-risk oncogenic alterations associated with a progressive clinical course. Consequently, the long-term efficacy and optimal sequencing of targeted agents in pediatric IMSCT management remain largely unexplored.

5 | Conclusions

PILMGGs often demonstrate a more aggressive clinical course and are associated with worse outcomes than their intracranial counterparts, despite the use of adjuvant therapies. These differences suggest that spinal LGGs should be considered a distinct clinical entity requiring dedicated treatment strategies rather than direct extrapolation from cranial LGG management paradigms.

The available literature indicates that chemotherapy remains an important component of treatment, particularly for patients with residual, progressive, or recurrent disease when further surgical resection is not feasible. In young children with unresectable, progressive, or symptomatic residual PIMLGG, cytotoxic chemotherapy remains an established treatment option and may permit deferral of RT. Treatment selection should, however, be individualized on the basis of age, tumor location, prior therapy, histology, and molecular alterations, particularly when an actionable mitogen-activated protein kinase (MAPK)-pathway alteration is identified.

In half of reported series, chemotherapy was administered following tumor progression after surgery. However, it has also been used as upfront adjuvant treatment, usually in patients with residual tumors. Future multicenter studies with standardized molecular characterization and outcome reporting are needed to define the optimal treatment algorithm for this unique patient population.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Statement

Ethical approval was not requred for this systematic review because it used only previosly published data and did not involve direct participation of human subjects or acces to identifiable personal data.

Data Availability Statement

The data that support the findings of this study are openly available in PROSPERO at https://www.crd.york.ac.uk/PROSPERO/myprospero, reference_number_CRD420261375148.

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