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CLINICAL STUDY

Craniospinal irradiation for treatment of metastatic pediatric low-grade glioma

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Abstract Patients with disseminated pediatric low-grade glioma (LGG) initially treated with chemotherapy frequently experience disease progression, with 5-year event-free survival (EFS) of <20% and 10-year overall survival (OS) of approximately 70%. This study aimed to describe outcomes of metastatic pediatric LGG treated with craniospinal irradiation (CSI). A retrospective study was performed of all patients with metastatic pediatric LGG treated with CSI at a single institution. EFS was defined as survival without disease progression or secondary high-grade glioma. Dates were counted from the first day of irradiation. We identified 12 eligible patients; all had histologically confirmed LGG. Metastatic disease was present at initial presentation in 9 patients. The median age at CSI was 9.3 years. The 5-year EFS and OS were 71% (95% CI 33.7–89.5) and 70% (95% CI 32.9–89.2), respectively. No deaths were observed among the patients who underwent subtotal resection (STR) before radiotherapy, whereas 3 patients who had undergone biopsy died (OS log-rank $P=0.01$). EFS may be longer among patients who underwent STR before RT (EFS log-rank $P=0.03$), with a hazard ratio for biopsy of 8.4 (vs. STR; 95% CI 0.8–84.0, $P=0.07$). No patient experienced acute toxicity of grade 3 or higher. Patients with metastatic pediatric LGG treated with CSI experienced longer EFS than historical cohorts treated with chemotherapy alone, with similar OS. CSI may be considered in the management of metastatic pediatric LGG, particularly in older children experiencing progression after chemotherapy.

Keywords Craniospinal irradiation · Glioma · Pediatrics · Radiation

Introduction

Metastatic dissemination in pediatric low-grade gliomas (LGG) is uncommon, being observed in up to 5% of cases at diagnosis and up to 12% of cases at progression [1–4]. Metastasis in pediatric LGG is an adverse prognostic factor [5], but the optimal treatment approach and outcomes for metastatic pediatric LGG are not well defined because of its rarity [3, 6]. Nonetheless, it is important to initiate appropriate curative-intent treatment for these patients, because long-term survival and cure is possible [4].

Few studies have described outcomes in disseminated pediatric LGG. Historically, patients with metastatic pediatric LGG were predominantly treated with upfront chemotherapy, with few individuals receiving radiation. Subset analyses from the prospective HIT-LGG 1996 study demonstrated poor progression-free survival (PFS) and reduced overall survival (OS) in patients with disseminated disease at diagnosis. For those patients, the 5-year PFS was 6% and the 5-year OS was 73% [5]; these findings are comparable across other retrospective series [1, 2, 4]. However, the existing literature has not been sufficiently detailed about outcomes following craniospinal irradiation (CSI); few patients were treated with any type of irradiation and even

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fewer underwent CSI. Craniospinal radiation is a comprehensive neuraxis treatment that involves the complete irradiation of all subarachnoid spaces in the cranium and spine, thereby encompassing the sites of possible occult disease. This approach may provide the best chance for eradicating metastatic disease in the neuraxis, but because of the late toxicity of irradiation, the treatment is often reserved for those patients for whom systemic therapies have proved unsuccessful, or for older children where concerns about late effects are diminished [3, 4]. The purpose of this study was to document the characteristics and treatments of patients who underwent CSI for metastatic pediatric LGG and to assess the long-term cancer control and survival outcomes.

Methods

This was a retrospective study of all patients with metastatic pediatric LGG treated with craniospinal irradiation (CSI) at a single institution from 1986 to 2016. Eligible patients were aged 21 years or younger and had been diagnosed with disseminated pediatric LGG (WHO grade I or II) with intracranial involvement. Individuals with high-grade glioma (WHO grade III or IV) at diagnosis, bithalamic tumors, or diffuse infiltrating pontine gliomas were excluded. No cases of gliomatosis cerebri were identified.

Data were collected from medical charts, radiotherapy (RT) records, and the institutional picture archiving and communication system (PACS). Tumor tissue, when available, was reviewed by the institutional pathology team. Patients had follow-up clinic visits and MR imaging every 3 months for 3 years after completing RT and every 6 months through year 5. Vasculopathy was detected using MR angiography as a screening tool; abnormal findings were confirmed with CT angiogram and/or catheter angiography. Toxicities were retrospectively graded using the Common Toxicity Criteria for Adverse Events (CTCAE v4.0). Insufficient data were available to assess late neurocognitive toxicity.

Irradiation was performed using photon RT unless otherwise specified. Photon CSI used two lateral parallel opposed cranial fields matched to posteroanterior spine field(s) to cover all subarachnoid spaces in the neuraxis. The median CSI dose was 39.6 Gy. Boost irradiation of the primary tumor bed and all sites of gross residual disease was performed with a clinical target volume (CTV) margin of 0.5 cm or greater. The median boost dose for intracranial targets was 54 Gy. For boost RT planning, two-dimensional planning techniques were used for five patients, five patients received three-dimensional conformal RT (3DCRT), one patient received intensity-modulated RT, and one patient received proton therapy.

Clinical factors and baseline characteristics were reported descriptively. Event-free survival (EFS) after RT was defined as survival without true progression, diagnosis of secondary high-grade glioma on imaging or biopsy, or death; days were counted from the first day of RT. Progression-free survival after first-line chemotherapy, if given, was defined as survival without radiologic or clinical progression or death; dates were counted from the first day of chemotherapy. Survival was reported using the Kaplan–Meier method, and patients who were still alive at the last follow-up were censored. Comparisons between groups were performed using the log-rank test. Univariate comparisons were performed using Cox regression. Analyses were completed using SAS 9.4 (Cary, NC). This study was approved by the institutional review board of St. Jude Children's Research Hospital.

Results

A total of 224 patients with pediatric LGG were identified, with 12 patients treated with CSI for metastatic disease during their disease course. These 12 patients were eligible for inclusion in the study, and their characteristics and treatment details are listed in Table 1. All had received histologic confirmation of their tumor before receiving RT. Two had histologic confirmation of disease at a metastatic site; the remainder were diagnosed radiologically. Molecular testing of the tumor was performed for two patients: both had *BRAF* duplication, one had a *KIAA1549-BRAF* fusion, and neither had the *BRAF* V600E mutation. Three patients (25%) developed metastatic disease at the time of progression after initial therapy, whereas the remaining nine patients (75%) had metastatic disease at initial diagnosis. Five patients (42%) had hypothalamic primary tumors. Two patients (17%) had a large primary spinal mass, along with diffuse neuraxis and intracranial metastatic deposits. No patient had stigmata of neurofibromatosis type 1. There was a 2:1 male predominance. The median follow-up for all patients was 5.2 years (IQR, 0.8–14.2), and the median follow-up for living patients was 7.8 years (IQR 4.3–15.2).

Initial chemotherapy

The details of each patient's treatments are shown in Table 1, and the sequencing of therapies is presented in Supplementary Table 1. Nine patients (75%) received upfront first-line chemotherapy; median number of courses was 2 (range 1–3). The median PFS after first-line chemotherapy was 2.1 years (95% CI 0.3–3.5); the 1- and 2-year PFS estimates were 66.7% (95% CI 28.2–87.8) and 55.6% (95% CI 20.4–80.5), respectively (Supplementary Fig. 1). All patients who received first-line chemotherapy

Table 1 Baseline characteristics, details of treatment, and follow-up for all patients, ordered by age at first MRI of the brain

Patient #	Age at first imaging (years)	Sex	Histology	Primary site	Metastatic at diagnosis	Metastatic sites	Age at tumor surgeries (years)	Extent of surgeries before RT	Chemotherapy before RT	Age at RT start (years)
1	0.3	M	Pilocytic astrocytoma	Optic chiasm and nerves	Y	IT seeding, spinal cord (diffuse)	0.4	Bx (1°)	Carboplatin × 18 mo, then topotecan × 3 mo	3.1
2	1.7	M	Pilocytic astrocytoma	Hypothalamus and optic nerves	N	ST intraventricular deposits	1.7	STR (1°)	CV × 20 mo	6.5
3	2.1	F	Pilocytic astrocytoma	4th ventricle	Y	Diffuse brain, spinal cord (T/L)	2.1	STR (1°)	CV + tamoxifen × 22 mo, then vinblastine × 12 mo	8.6
4	3.5	M	Pilocytic astrocytoma	Hypothalamus	Y	IT seeding, spinal cord (diffuse)	3.5, 3.7	Bx (1°), Bx (1°)[a]	CV × 5 mo, then carboplatin × 5 mo, then Cy × 7 mo	11.2
5	4.6	F	Pilocytic astrocytoma	Hypothalamus	N	IT seeding, spinal cord (C/T/L)	4.6	STR (1°)	CV × 15 mo, then lenalinomide × 4 mo	8.5
6	5.7	M	Astrocytoma	Hypothalamus	Y	Diffuse neuraxis	5.7	Bx (1°)	CV × 5 mo	6.0
7	7.1	M	Low-grade glial neoplasm with piloid features	L2–4 spinal cord	Y	IT seeding, spinal cord (C/T/L)	7.1	STR (1°)	CV × 7 mo	7.5
8	8.0	M	Astrocytoma	Hypothalamus	Y	Diffuse neuraxis	8.7	STR (1°)	CV × 11 mo, then vinblastine × 5 mo	9.9
9	8.9	M	Low-grade glioneuronal neoplasm	T6–T11 spinal cord	Y	Diffuse brain, spinal cord (T)	8.9	STR (1°)	CV + TMZ × 20 mo, then vinblastine × 23 mo	15.3
10	13.3	F	Ganglioglioma	Brainstem (dorsally exophytic)	Y	Spinal cord (C/T/L)	13.3	STR (1°)	N	13.5
11	14.9	M	Pilocytic astrocytoma	Hypothalamus	Y	Spinal cord (T/L/S)	16.1	Bx (1°)	N	16.1
12	15.6	F	Central neurocytoma	Lateral ventricle	N	ST intraventricular deposits	15.6, 19.0	GTR (1°), STR (Met)	N	19.1

Table 1 (continued)

Patient #	CSI dose (cGy)	Brain boost dose	Spine boost dose	Disease progression	Site of failure	Salvage treatment	Stable disease at last follow-up	Deceased	Cause of death	Follow-up since RT start (years)
1	3600	5220	None	N			Y	N		21.4
2	3600	5400	None	N			Y	N		13.1
3	3960	5400	5040 (T8–9, L3–S3), 5400 (T12/L1)	N			Y	N		4.3
4	4140	5400	5400	N			Y	Y	Shunt infection and sepsis (*S. pneumoniae*)	0.9
5	3600	5220	5040 (C1, T8, T12), 5220 (S)	N			Y	N		0.2
6	4000	5440	4154 (C1/2)	Y	Local	None	N	Y	Necrosis and disease progression	0.8
7	3960	5400	5040	Y	Local	TMZ × 12 mo, then TPCV × 10 mo	Y	N		15.7
8	4140	5400	4680	N			Y	N		0.5
9	4140	5220	5040	N			Y	N		6.1
10	3600	5400	5040	N			Y	N		7.8
11	4480	5380	5380 (L)	Y	Local and distant	Topotecan × 3 mo, then idarubicin × 4 mo	N	Y	Disease progression with tumor hemorrhage in brainstem	3.1
12	3960	5400	None	N			Y	N		15.2

1° biopsy of primary site, *Bx* biopsy, *C* cervical, *CV* carboplatin/vincristine, *Cy* cyclophosphamide, *F* female, *IT* infratentorial, *L* lumbar, *M* male, *Met* metastatic deposit, *mo* months, *N* no, *RT* irradiation, *S* sacrum, *ST* supratentorial, *STR* subtotal resection, *T* thoracic, *TMZ* temozolomide, *TPCV* thioguanine procarbazine lomustine and vincristine, *Y* yes

[a]Biopsy was repeated to confirm diagnosis

experienced disease progression by the 5-year time point and required salvage chemotherapy or RT. The median time between the first chemotherapy treatment and the initiation of RT was 3.2 years (IQR 1.2–5.7).

Radiation

Before receiving RT, 8 patients (67%) underwent STR and 4 patients (33%) underwent a biopsy. Two patients received adjuvant RT after their first surgery; the remainder received salvage RT upon progression, either after surgery alone (one patient) or after surgery followed by chemotherapy (nine patients). The median age at the initiation of CSI and RT was 9.3 years (IQR 7.0–19.1); the youngest patient was aged 3.1 years. No patient received adjuvant chemotherapy. Salvage chemotherapy was given to two patients and resulted in long-term disease control in one patient. No patient underwent salvage surgery or re-irradiation.

Outcomes

Three patients experience disease progression on neuroimaging after undergoing CSI; one patient was successfully salvaged with chemotherapy (temozolomide followed by thioguanine-procarbazine-lomustine-vincristine). Three patients died. One of these patients had a shunt infection that developed into *Streptococcus pneumoniae* sepsis, although this individual had stable disease at the time of death. Another patient developed radiation necrosis and tumor progression 34 weeks after the initiation of RT. This patient presented with seizures, lethargy, and obtundation. Contrast-enhanced MRI demonstrated pontine enhancement located away from the primary tumor mass, as well as local tumor progression. Dexamethasone treatment was initiated, but an MRI scan performed 36 weeks after RT showed continued tumor progression and increased edema in the hypothalamic primary. The patient subsequently died 39 weeks after receiving RT. A third patient died 2.9 years after RT as a result of tumor hemorrhage in the brainstem accompanied by local and distant disease progression; this was confirmed at post-mortem examination. MR angiography 1 month prior to death did not demonstrate any evidence of radiation-induced vasculopathy, moyamoya, or aneurysm.

The EFS and OS curves are shown in Fig. 1. The 5- and 10-year EFS estimates were 71% (95% CI 33.7–89.5) and 59% (95% CI 23.4–82.5), respectively; the 5- and 10-year OS estimates were both 70% (95% CI 32.9–89.2). The timing of censoring and the small number of patients at-risk led to a 1% higher estimate of EFS than OS at the 5-year time point. Neither the median EFS nor the median OS were reached. As an exploratory analysis, EFS and OS stratified by the extent of pre-RT surgery are shown in Fig. 2. There was a statistically significant association between greater extent of surgery and improved OS and possibly EFS. The hazard ratio (HR) for OS was not reportable (because no deaths were observed in the STR group). The HR for EFS was 8.4 (95% CI 0.8–84.0, $P=0.07$). Whether or not patients received chemotherapy before RT made no difference to the EFS or OS (EFS log-rank $P=0.93$, HR for no pre-RT chemotherapy = 0.9, 95% CI 0.1–8.8; OS log-rank $P=0.99$, HR for no pre-RT chemotherapy = 1.0, 95% CI 0.1–10.9).

Four patients developed pseudoprogression in their primary tumor, defined as the growth of a tumor mass followed by subsequent stabilization (seen in one patient) or tumor shrinkage without disease progression (seen in three patients). The median time from the first day of RT to pseudoprogression was 6.1 months (range 5.7–45.8). The median time to resolution or stabilization was 5.3 months (range 1.8–36.9).

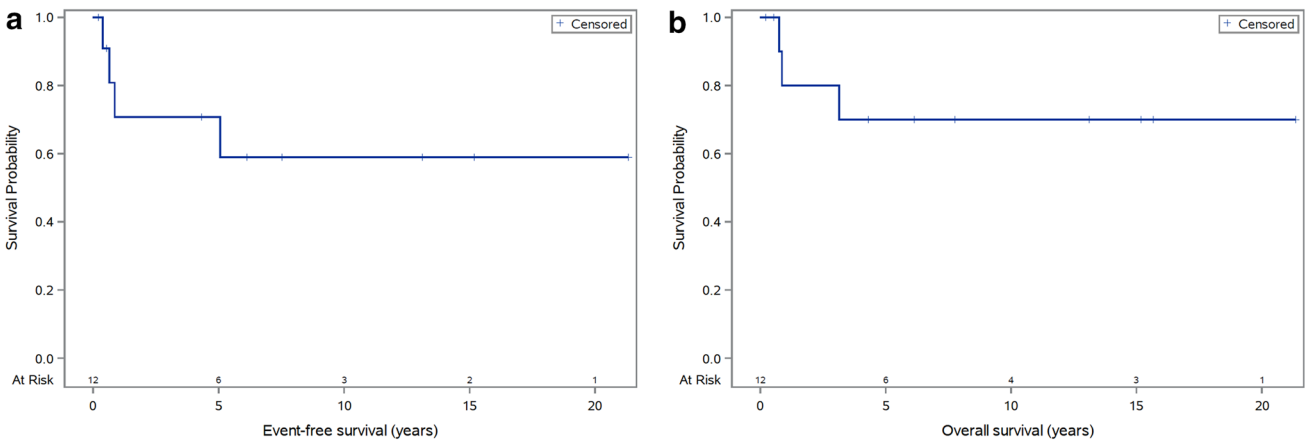

Fig. 1 Event-free (**a**) and overall survival (**b**) for all patients

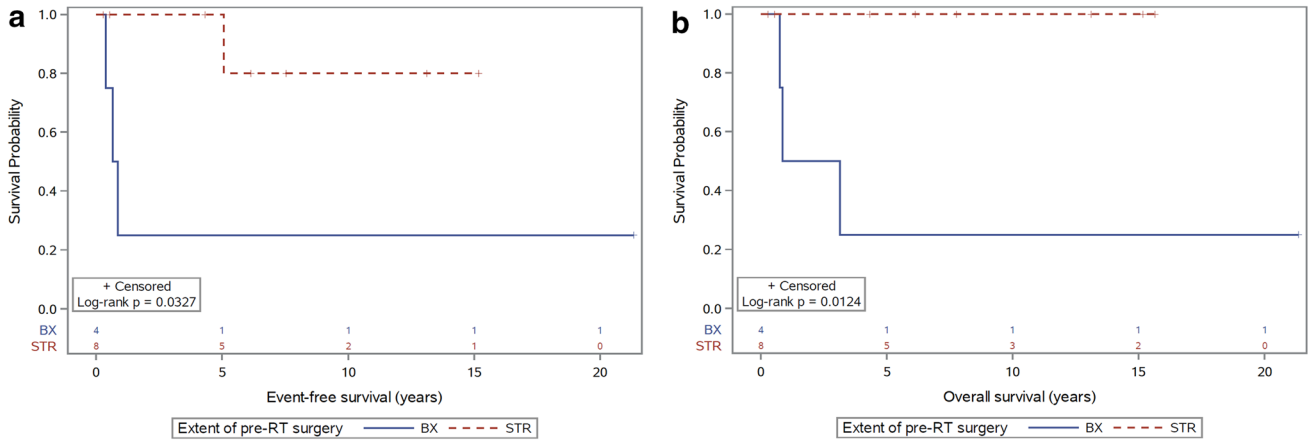

Fig. 2 Event-free (**a**) and overall survival (**b**) stratified by the extent of surgery before irradiation (*BX* biopsy, *RT* radiation, *STR* subtotal resection)

Side effects of RT

A summary of acute and late toxicities that could be attributed to treatment is presented in Table 2. There were no grade 3–5 acute toxicities; CSI was well tolerated by most patients, and none required a treatment interruption. Four patients developed a late toxicity. One patient developed radiation necrosis and tumor progression, as previously described. There were two cases of cerebral vasculopathy of grade 2 or higher that was attributable to the irradiation. One patient received CSI RT at the age of 3 years, developed moyamoya disease that was visible on MRI starting 8 months after RT, and eventually had a stroke. Another patient had a stroke 4.3 years after receiving RT. Both of these individuals recovered and are being treated with aspirin. Finally, one patient developed a pT1bN1 papillary thyroid carcinoma at the age of 28 years, 9.8 years after undergoing CSI. This individual was treated with a thyroidectomy and iodine-131 ablation; the patient remains well and free of active disease.

Table 2 Acute and late toxicities after craniospinal irradiation

Acute toxicity	Grade 1	Grade 2	Any grade[a]
Alopecia		12 (100%)	12 (100%)
Anorexia	1 (8%)	6 (50%)	7 (58%)
Diarrhea	1 (8%)		1 (8%)
Dysphagia, sore throat, or esophagitis	5 (42%)	4 (33%)	9 (75%)
External ear inflammation	4 (33%)		4 (33%)
Fatigue	7 (58%)		7 (58%)
Gastritis		1 (8%)	1 (8%)
Headache	1 (8%)	1 (8%)	2 (17%)
Lymphopenia		1 (8%)	1 (8%)
Nausea	4 (33%)	3 (25%)	7 (58%)
Radiation dermatitis	11 (92%)		11 (92%)
Vomiting	1 (8%)	2 (17%)	3 (25%)
Weight loss	1 (8%)		1 (8%)
Late toxicity	**Patient #**		**Onset from RT (years)**
Vasculopathy, grade 3	1		0.6
Vasculopathy, grade 3	3		4.3
Necrosis with tumor progression	6		0.7
Secondary neoplasm (thyroid)	12		9.8

[a]There were no grade 3–5 acute toxicities

Discussion

We have reported the outcomes of patients with metastatic pediatric LGG treated with CSI. A key finding was that long-term disease control and cure were possible, with 10-year EFS of 59% and 10-year OS of 70%. One patient (out of three) in this series who experienced progression after undergoing CSI was successfully salvaged with chemotherapy. These results suggest that comprehensive neuraxis irradiation should play a role in the treatment of disseminated pediatric LGG, particularly in older children who experience progression after receiving upfront chemotherapy.

We found an association between the extent of resection before RT and OS, and a possible association between the extent of resection before RT and EFS. One would expect optimal cytoreduction to improve disease control. An association between increased extent of resection and outcome has been observed in both prospective and retrospective studies of localized pediatric LGG [7, 8]. The findings of our present study suggest that the principle of maximal safe resection may also apply to disseminated LGG, particularly if the tumor is surgically accessible or at risk of causing obstructive hydrocephalus.

The tumor control obtained with CSI compares very favorably to that reported in other studies of disseminated LGG treatment in which upfront chemotherapy was predominantly used (Table 3). A subset analysis of patients with metastatic pediatric LGG from HIT-LGG 1996 is the largest known study, which reported outcomes for 61 patients [5]. In that study, carboplatin/vincristine was given to patients who had local disease (before dissemination). However, the radiation field was not defined in the study protocol for patients with metastatic disease, and it was unclear whether any patients received CSI. Similar to the present study, there was a male predominance in patients with metastatic LGG enrolled on HIT-LGG 1996. Chamdine et al. examined 38 patients who were treated mostly with carboplatin-based regimens [4]. Although most children included in that study experienced disease progression within 5 years, first-line treatment with chemotherapy was advocated as a way to delay CSI, particularly in younger children.

Several smaller retrospective series have also demonstrated poor PFS with upfront chemotherapy. Hukin et al. separately reported 13 patients who had leptomeningeal disease at diagnosis and 13 patients who experienced leptomeningeal progression [1, 2]. In both of those studies, the patients were generally treated with platinum-based upfront chemotherapy and few underwent CSI. The 5-year PFS was less than 20% in both patient series. Perilongo et al. compiled a brief review of 15 cases of pediatric LGG with leptomeningeal dissemination treated with RT; six of those patients received CSI [3]. Of the 15 patients, 4 died and 11 were still alive after "multiple interventions" at the time the report was prepared. A propensity for boys with hypothalamic-chiasmic tumors to develop dissemination was noted. The authors suggested that RT may be a "most effective therapeutic tool" for metastatic disease.

The tumor control outcomes in our study are particularly remarkable because most of the patients (75%) received CSI as a salvage treatment for progression after chemotherapy. One might expect these patients to represent a select subgroup with a more aggressive disease course. Nonetheless, the high levels of tumor control at 5 years with RT did not translate into increased OS as compared to OS with chemotherapy-dominant approaches (Table 3), probably as a result of the effectiveness of the salvage treatments. Thus, CSI is but one of several tools that should be considered for treating progressive metastatic pediatric LGG. In this series, the use of chemotherapy helped delay the initiation of RT by a median of 3.2 years, thereby allowing time for neurocognitive maturation prior to CSI.

This study represents one of the largest known series of patients with metastatic pediatric LGG treated with CSI. Limitations of the study include the fact that the number of patients was still quite small. There were insufficient patient numbers to analyze patient outcomes by histologic subtype, tumor location, or radiation planning technique. Molecular information was unavailable and no patient was treated with a targeted agent, such as a *BRAF* inhibitor. Thus, the role and optimal timing of targeted agents in

Table 3 Selected studies of metastatic pediatric low-grade glioma and outcomes

Study	n	Cases treated with RT (RT field)	Median follow-up (years)	5-year PFS or EFS (%)	5-year OS (%)	10-year OS (%)
Present study	12	12 (all CSI)	7.8	71	70	70
von Hornstein et al. [5]	61	4 (unclear)	5.7	6	73	73
Chamdine et al. [4]	38	7 (5 CSI, 2 focal)	6.7	8	81	63
Hukin et al. [2]	13	10 (2 CSI, 8 focal)	6.0	15	87	68
Hukin et al. [1]	13	4 (3 CSI, 1 focal)	Not reported	17	Not reported	Not reported

EFS event-free survival, *OS* overall survival, *PFS* progression-free survival

relation to cytotoxic chemotherapy and RT in metastatic patients remains unclear [9].

To better elucidate the role and optimal timing of CSI in treating metastatic pediatric LGG, the trial SIOP-LGG 2004 (ClinicalTrials.gov identifier NCT00276640) is prospectively examining the role of CSI in treating disseminated disease. In the clinical trial protocol, CSI is considered for use in patients with metastatic disease who are younger than 8 years (after chemotherapy options are exhausted) and for those aged 8 years or older (at progression, during or after chemotherapy). The recommended CSI dose is 35.2 Gy (1.6 Gy per day). The results of this prospective study are eagerly awaited.

Conclusions

The outcomes in 12 patients with metastatic pediatric low-grade glioma treated with CSI are reported. The 5-year was 71%, which compares favorably with the EFS seen in historical cohorts treated with upfront chemotherapy. The 5- and 10-year OS were both 70%, which is similar to the OS in patients treated with chemotherapy-first approaches. Patients who undergo subtotal resection of their tumor before being treated with radiation may have better outcomes than those who undergo only a biopsy. Craniospinal irradiation should be considered for treatment of metastatic pediatric LGG, particularly in older children who are less susceptible to late effects, and in children who experience disease progression after receiving chemotherapy. Prospective studies are needed to better elucidate the role and optimal timing of irradiation in treating disseminated pediatric LGG and to identify subgroups of patients who will benefit most from CSI.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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