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Radiotherapy in the Management of Paediatric Low-Grade Gliomas

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Abstract

Paediatric low-grade (World Health Organization grade I–II) gliomas (LGGs) represent a spectrum of primary central nervous system tumours. Local tumour control is the cornerstone in the general management of childhood gliomas. Surgery is the primary treatment of choice in the majority. Non-surgical treatments are recommended for progressive or symptomatic inoperable disease. Although chemotherapy is increasingly used as first non-surgical treatment, radiotherapy remains standard as salvage treatment or as primary treatment in selected cases in which surrounding normal tissue can be optimally preserved. The role of targeted therapies is currently under investigation in clinical trials. Modern high-precision radiotherapy techniques, including proton therapy, have the potential to improve long-term toxicities. There is therefore an urgent need for prospective studies to compare the efficacy and safety of modern radiotherapy with systemic treatment in children with LGGs. New information on molecular genetic patterns in LGGs may also have an impact on the selection and sequencing of radiotherapy.

Key words: Low-grade gliomas; proton therapy; radiotherapy; systemic treatment

Introduction

Gliomas constitute about 50–55% of primary central nervous system tumours in children [1]. They exhibit a spectrum of histological subtypes with varying clinical behaviours and treatment approaches. For therapeutic purposes, gliomas are grouped as low-grade (grade I–II), high-grade (grade III–IV) and ependymal tumours. The treatment approaches of high-grade gliomas and ependymomas differ and have been reviewed recently [2,3].

Low-grade gliomas (LGGs) constitute 30–40% of all paediatric primary brain tumours and contribute to 7% of deaths from brain tumours [1]. There are specific variants of LGGs associated with genetic diseases, such as neurofibromatosis type I (NF-1), tuberous sclerosis and Li-Fraumeni syndrome [4]. For example, about 5–15% of patients with NF-1 have LGGs of the optic tract and the hypothalamus.

Pathology and Molecular Markers

Histologically, LGGs can be either World Health Organization grade I or II (Table 1) [5]. Most childhood tumours are grade I, such as pilocytic astrocytoma (the most common subtype, which constitutes >15% of central nervous system tumours in 0–19 year olds), subependymal giant cell astrocytoma and dysembryoplastic neuroepithelial tumour (DNET) and are radiologically well-circumscribed ('non-diffuse') lesions. Grade II are generally 'diffuse' (infiltrative growth into the surrounding parenchyma) and include pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, oligodendroglioma, oligoastrocytoma and diffuse astrocytoma.

Molecular genetic markers are increasingly investigated for better stratification and prognostication of LGGs [2,6]. Certain genetic abnormalities are common with specific histological subtypes. For example, the classical

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Table 1
2016 World Health Organization classification of low-grade (grade I–II) gliomas [5]

Diffuse astrocytic and oligodendroglial tumours
• Diffuse astrocytoma (IDH-mutant, IDH-wild type or NOS): grade II
• Oliogodendroglioma (IDH-mutant and 1p/19q-codeleted or NOS): grade II
• Oligoastrocytoma NOS: grade II
Other astrocytic tumours
• Pilocytic astrocytoma: grade I
• Subependymal giant cell astrocytoma: grade I
• Pleomorphic xanthoastrocytoma: grade II
Other gliomas
• Angiocentric glioma: grade I
• Choroid glioma of the third ventricle: grade II
• Astroblastoma: ungraded (clinical behaviour range from grade I to III)
Neuronal and mixed neuronal-glial tumours
• Gangliocytoma/ganglioglioma: grade I
• Dysembryoplastic neuroepithelial tumour: grade I
• Dysplastic cerebellar gangliocytoma (Lhermitte Duclos): grade I
• Desmoplatic infantile astrocytoma and ganglioglioma: grade I
• Rosette-forming ganglioneuronal tumour: grade I
• Neurocytoma (central and extraventricular): grade II
• Cerebellar liponeurocytoma: grade II

NOS, not otherwise specified (neither tested for specific genetic changes nor detected genetic alternations are non-specific).

KIAA1549:BRAF fusion is common in pilocytic astrocytoma, FGFR1 abnormalities in DNET and MYB/MYBL1 aberrations in diffuse gliomas. Although targeting these specific molecular pathways may allow an individualised approach to improve outcomes in the future, there are limited data on the correlation between response to radiotherapy and molecular genetic markers [7].

Clinical Features and Diagnosis

Clinical presentations of LGGs are variable and include focal neurology, features of increased intracranial pressure and non-specific, such as loss of developmental milestones in young children or changes in mood and personality in older children. Optic nerve and chiasm tumours present with decreased visual acuity or visual field loss.

Magnetic resonance imaging (MRI) is essential and LGGs show features of abnormal areas of signal intensity (increased signal on T2-weighted MRI) with varying degrees of contrast enhancement depending on the subtypes. The degree of contrast enhancement has no correlation with grade of the lesion (Figure 1).

Management

Surgery, radiotherapy and systemic therapy are the primary treatment options with the aim to improve survival and preserve or improve the functional status [8]. Recent approaches focus on systemic therapy as first-line non-surgical therapy to obviate radiation-induced late effects, particularly in children aged less than 8–10 years, whereas radiotherapy is increasingly reserved for progressive disease when chemotherapy has failed.

Surgery

Resection is the primary treatment of choice, whenever possible. Resectability depends primarily on the location and grade of tumours. Hemispheric and cerebellar LGGs are usually amenable to resection [9]. Extent of resection is associated most strongly with progression-free survival (PFS), favouring gross tumour resection (GTR) [10]. In the prospective Childhood Cancer Group (CCG) 9891 study ($n = 531$), the 8-year PFS after GTR (achieved in 65% patients) was 93% compared with only 56% for those who had a postoperative residual tumour <1.5 cm^3 and 45% for those who had a residual tumour ≥ 1.5 cm^3 ($P = 0.004$) [11,12]. The corresponding 8-year overall survival rates were 99%, 95% and 90%, respectively ($P = 0.013$). In a large retrospective series ($n = 351$), on multivariate analysis, improved PFS was significantly associated with GTR and postoperative radiotherapy [13]. In those undergoing a subtotal resection, PFS was improved with adjuvant radiotherapy, with almost the

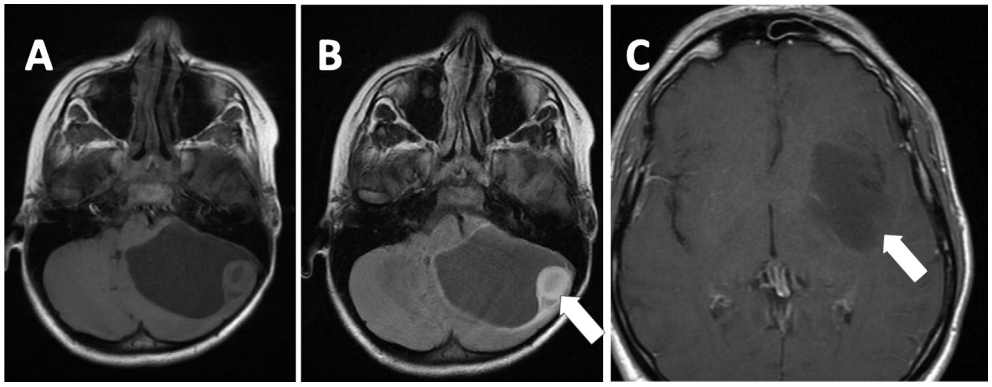

Fig 1. Cerebellar pilocytic astrocytoma (grade I) – T1-weighted magnetic resonance image showing a well-circumscribed lesion with cystic component (A) and a contrast-enhancing mural nodule (B). Grade II diffuse astrocytoma – T1-weighted gadolinium-enhanced scan showing a hypointense lesion on left side with little contrast enhancement (C).

same PFS as patients receiving complete resection. On multivariate analysis, higher overall survival was significantly associated with complete resection and pilocytic histology.

The extent of resection is also an important prognostic factor for grade II (diffuse) astrocytomas. In a series, the 5-year PFS was 79% for patients treated with GTR, 60% for those with subtotal tumour resection (STR) and 46% for those with biopsy alone. The corresponding 5-year overall survival rates were 100% after GTR, 88% for those with STR and 89% for biopsy alone [14]. However, for infiltrative tumours involving eloquent areas, biopsy alone would be feasible. Similarly, for tumours of the optic chiasm and optic nerve a resection is often not attempted, and even histological confirmation may not be necessary if course of disease and imaging are suggestive of a definitive diagnosis.

Systemic Therapy

Traditionally, chemotherapy is indicated for progressive inoperable disease in young children. More recently, upfront chemotherapy has increasingly been used as non-surgical treatment. Studies show that chemotherapy may delay or obviate the need for radiotherapy [15]. The commonly used regimens include single-agent vinblastine or a combination of vincristine and carboplatin with or without other drugs, such as thioguanine, procarbazine and lomustine [16–19]. Monotherapy with carboplatin can be equally efficient as multiagent chemotherapy [20]. Recently, SIOP-LGG 2004 reported no improvement in 5-year PFS and overall survival with the addition of etoposide to standard chemotherapy with vincristine and carboplatin; the combination of carboplatin and vincristine therefore remains the standard first-line systemic therapy [21].

It is difficult to compare the tumour response rates and ultimately long-term results reported by the various trials on childhood LGG. Characteristics of the patient population, the indication to start therapy, the criteria defining response as well as the timing of tumour response assessment vary between studies [22]. Trials may report either event-free survival (EFS) or PFS. In the COG A9952 protocol, the 5-year EFS and overall survival rates for all patients were 45% and 86%, respectively [16]. In the HIT LGG 96 trial, the 10-year PFS was 62% following radiotherapy and 44% following chemotherapy, indicating a higher efficacy for radiotherapy [22].

Most LGGs exhibit mutations involving mitogen-activated protein kinase (MAPK) pathways or BRAF pathways [6,23–25]. A recent phase I trial of MEK inhibitor, selumetinib, in paediatric patients with recurrent or refractory LGG reported a 2-year PFS of 69% with a dose of 25 mg/^{2}/dose twice daily [26]. In a study, six children with progressive pilocytic astrocytoma receiving trametinib reported two partial responses and three minor responses [27]. A number of targeted therapies are currently being investigated in prospective trials [28]. However, late toxicities of these targeted therapies are unknown and the efficacy and safety of radiotherapy after targeted agents are not prospectively evaluated. Future first-line studies on LGGs should therefore compare the relative efficacy of novel agents with high-precision radiotherapy and should have prolonged surveillance for late effects.

Radiotherapy

Radiotherapy has traditionally been the treatment of choice in non-completely resected progressive LGGs and is highly effective in tumour control and preservation or improvement in visual function [8,29,30]. PFS and overall survival are excellent with definitive radiotherapy (Table 2). For example, in the series of Merchant *et al.* [31], 5- and 10-year EFS were 87.4 and 74.3%, respectively. The corresponding overall survival rates were 98.5 and 95.9%.

Grade II (diffuse) astrocytomas constitute only 4.5–6% of LGGs in children [22,42]. It is not clear whether the outcome following radiotherapy for grade II tumours is similar to that of grade I tumours (Table 3). The reported 5-year PFS ranged from 68 to 72% for grade I tumours compared with 43–52% for grade II tumours. Other studies reported either no difference in survival or a slightly better EFS for grade I tumour, but similar overall survival [22,47].

The optimal timing (early versus delayed) of radiotherapy for incompletely resected grade II tumours in children is unknown. In adults with LGGs and oligodendroglioma, the European Organization for Research and Treatment of Cancer (EORTC) 22845 study ($n = 314$) compared 'early' radiotherapy with radiotherapy deferred until symptomatic progression ('delayed') [48]. The median overall survival of the early group was similar to that of the delayed group (7.4 years versus 7.2 years, $P = 0.872$). Although the median PFS was better for the early group, 5.3 years versus 3.4 years ($P < 0.0001$), there was no quality of life analysis and, therefore, it is not known whether time to progression reflected clinical deterioration. A recent Cochrane review also did not report improvement in overall survival with early radiotherapy in adults [49]. In a paediatric study, the 5- and 10-year PFS rates were 50 and 43%, respectively, for delayed radiotherapy compared with 61 and 43%, respectively, for the early radiotherapy group [14]. The 5- and 10-year overall survival rates were 97 and 92%, respectively, for those receiving no radiation at diagnosis as compared with 84 and 74%, respectively, for those receiving radiotherapy upon progression. In an analysis of 24 patients with grade II tumours included in the German HIT LGG 96 and 2004, outcome was poor after salvage radiotherapy for progressive disease [46]. With a median follow-up of 2.0 years, 11 patients (45.8%) experienced progression and eight patients (33.3%) died. The 3- and 5-year PFS rates were 56 and 28%, respectively, and the 5-year overall survival was only 63%.

Radiotherapy following Chemotherapy

The optimal sequencing of the various treatments in paediatric LGGs is an area of uncertainty. Following biopsy or surgery, patients are selected for observation, chemotherapy or radiotherapy, based on the burden of symptoms, age, site and extent of tumour, and institutional practice. All these modalities are with confounding factors and there are

Table 2
Results of childhood low-grade gliomas treated with modern radiotherapy techniques

Study	No. patients	Technique and dose	Follow-up	Results and comments
Debus *et al.* [32]	10 (optic glioma)	Stereotactic technique Median dose: 52.4 Gy/1.6–2.0 Gy Margin: 7 mm	12–72 months	5-year PFS: 90% 5-year OS: 100% No acute toxicities
Saran *et al.* [33]	14	Stereotactic technique Median dose: 50–55 Gy/30–33 fractions Margin: 5–10 mm	33 months	3-year PFS: 87% 3-year OS: 100% 1 relapse within GTV
Hug *et al.* [34]	27	Protons 50.4–63.0 CGE/1.8 Gy Margin: no data	3.3 years	Local control survival Hemispheric 71% 86% Diencephalon 87% 93% Brainstem 60% 60%
Marcus *et al.* [35]	81	Stereotactic technique Median dose: 52.2 Gy/1.8 Gy Margin: 2 mm	6.9 years	5-year/8-year PFS: 82.5%/65% 5-year/8-year OS: 97.8%/82% 6 local relapses All within field
Combs *et al.* [36]	15 (optic glioma)	Three-dimensional conformal radiotherapy Median dose: 52.2 Gy/1.8 Gy Margin 5 mm	97 months	3-year/5-year PFS: 92%/72% 5-year OS: 90%
Merchant *et al.* [31]	78	Three-dimensional conformal radiotherapy Median dose: 54 Gy/1.8 Gy Margin: 15 mm	89 months	5-year/10-year EFS: 87.4%/74.3% 5-year/10-year OS: 98.5%/95.9% 13 relapses (8/13 within PTV) (1/13 marginal) (4/13 CNS metastatic)
Oh *et al.* [37]	147 (29 grade II)	Three-dimensional conformal planning Median dose: 54 Gy/1.8–2 Gy Margin not available	6.4 years	7-year FFP/OS: 67%/94% 7-year FFP better after GTR (81% versus 56%, $P < 0.02$) Radiotherapy improved FFP if less than GTR (89% versus 49%, $P < 0.003$) but not OS
Gnekow *et al.* [22]	147	Three-dimensional conformal radiotherapy 50.4–54 Gy/1.8 Gy Margin: 1 cm if MRI planned, 2 cm if CT planned	–	10-year PFS 62% 9.2% progression
Paulino *et al.* [38]	39	IMRT 45–60 Gy 5–10 mm	81 months	8-year EFS/OS: 78.2%/93.7% 7/7 failures in field
Muller *et al.* [39]	75	Conventional/3D planning Median 54 Gy/1.8 Gy Margin 1–2 cm	8.4 years	Pilocytic astrocytoma 5-year/10-year PFS: 76.5% 5-year/10-year OS: 96.2% Relapse pattern: N/A
Greenberger *et al.* [40]	32 (6 grade II)	Proton therapy Median dose: 52.2 Gy_{RBE} Margin: 3–5 mm	7.6 years	8-year PFS/OS: 83%/100% Visual function stable or improved in 83.3%.
Indelicato *et al.* [41]	54	Proton therapy Median dose: 54 Gy_{RBE} Margin- N/A	2.6 years	3-year PFS/OS: 87%/95% Trend towards improved local control in grade I tumours (91% versus 76%, $P = 0.1$) and who received 54 Gy

EFS, event-free survival; PFS, progression-free survival; OS, overall survival; FFP, freedom from progression; MRI, magnetic resonance imaging; CT, computed tomography, GTV, gross tumour volume; PTV, planning target volume; CNS, central nervous system; GTR, gross tumour resection; IMRT, intensity-modulated radiotherapy.

no randomised controlled trials on sequencing of treatments. Nevertheless, a significant proportion of children receive radiotherapy following chemotherapy. It seems that this cohort of patients may have biologically more aggressive tumours and it is not clear whether prior chemotherapy renders the tumours more radiation resistant [50]. Paulino *et al.* [38] compared the outcome of nine children treated with intensity-modulated radiotherapy

Table 3
Outcome of childhood low-grade glioma according to grade

Study	No. patients	Median age	5-year PFS	5-year OS
Fouladi *et al.* [43]	Grade I: 19 Grade II: 34	7.7 years	Grade I: 68% Grade II: 52% $P < 0.05$	Grade I: 95% Grade II: 48% $P < 0.05$
Fisher *et al.* [44]	WHO grade I: 135 WHO grade II: 27	8.8 years	3-year PFS WHO grade I: 63% WHO grade II 40% $P = 0.007$	3-year OS WHO grade I: 96% WHO grade II: 48% $P < 0.001$
Stokland *et al.* [42]	Grade I: 407 Grade II: 38	6.7 years	Grade I: 71.5% Grade II: 42.6% $P < 0.001$	Grade I: 97.3% Grade II: 76.5% $P < 0.001$
Merchant *et al.* [31]	Grade I: 67 Grade II: 11	8.9 years	5- and 10-year EFS Grade I: 87% and 77% Grade II: 91% and 64% $P =$ n.s.	N/A
Jones *et al.* [45] CBTRUS 2004–2006	0–19 years: 100 20–44 years: 221	Children versus adults	n/a	WHO II only 0–19 years: 81.2% 20–44 years 39.2%
Mishra *et al.* [14]	Early radiotherapy: 52 Delayed radiotherapy: 38	9 years	Grade II only 5- and 10-year EFS Early radiotherapy: 61% and 43% Delayed radiotherapy: 50% and 43%	Grade II only 5- and 10-year OS Early radiotherapy: 84% and 74% Delayed radiotherapy: 97% and 92%
Mueller *et al.* [46]	24	2.0 years	3- and 5-year PFS: 56% and 28%	5-year OS: 63%

PFS, progression-free survival; EFS, event-free survival; OS, overall survival; n.s., not significant; WHO, World Health Organization.

following initial chemotherapy failure with 30 children with radiotherapy as first-line treatment. The 8-year PFS for children who did and did not receive prior chemotherapy was 50 and 88.4%, respectively ($P < 0.03$). Conversely, in the prospective HIT LGG 96 trial, PFS was not influenced by the use of previous chemotherapy. The 10-year PFS was 75% in 17 patients having received primary chemotherapy as compared with 77.6% in 58 patients after primary radiotherapy [39].

The issue of the sequencing of treatment modalities has also been examined in a UK cohort of 131 eligible paediatric patients treated in the LGG-1 study between 1997 and 2004. For 64 patients treated with radiotherapy at diagnosis, 3-year overall survival was 82.1% and EFS was 72.2%. For 42 receiving radiotherapy after a period of observation, 3-year overall survival was 87.5% and EFS was 71.9%. Twenty-two had radiotherapy for progression after initial chemotherapy, with 3-year overall survival 94.4% and EFS 83.6%. Eleven had radiotherapy after observation followed by chemotherapy, with 3-year overall survival 80.0% and EFS 78.8%. Patients treated at progression following observation and/or chemotherapy had a similar overall survival and EFS to those treated at diagnosis [51].

Dose–Response Effects

There are no prospective randomised studies on optimal radiotherapy dose fractionation in children. In adults with cerebral LGGs, a randomised EORTC clinical trial ($n = 379$) compared a radiotherapy dose of 45 Gy in 5 weeks with 59.4 Gy in 6.6 weeks [52]. At a median follow-up of 74 months, there was no difference in overall survival or PFS between the two arms of the trial. The patients who received a higher dose had a lower level of functioning and more symptoms (fatigue and insomnia) following radiotherapy [53]. It is difficult to extrapolate this data to paediatric practice, where the dose fractionation is often influenced by age and extent and site of tumour. The generally accepted dose prescription ranges between 45 and 54 Gy in 1.8 Gy fractions. Retrospective data, however, indicate that a dose of 50.4 Gy is equally effective as 54 Gy. In the HIT LGG 96 trial, no differences were observed with different radiotherapy doses. In a retrospective series, with ≤50.4 Gy, the 8-year PFS was 73.8% compared 90.9% after >50.4 Gy ($P = 0.37$) (Table 4) [38].

Treatment Response

Only a few series reported response after radiotherapy for LGGs in terms of tumour size and clinical symptoms [62,63]. An increase in tumour size on imaging after radiotherapy, usually within 3–9 months, may be seen and often not accompanied by clinical signs and symptoms ('pseudo-progression'). In a study of 221 children, the 10-year cumulative incidence of pseudo-progression was 29% (95% confidence interval 23–35.2) with a median time of pseudo-progression of 6.1 months [64]. Pilocytic astrocytoma has a higher incidence of pseudo-progression (10-year incidence 42.9%) and development of pseudo-progression was associated with a better 10-year EFS and overall survival. Therefore, any increase in tumour after radiotherapy should be interpreted with caution.

Table 4
Radiotherapy dose response and progression-free survival (PFS) in children and adults with low-grade glioma

Study	No. patients	Total radiotherapy dose	Fraction size	PFS (5 years)	PFS (10 years)	*P* value
Montgomery *et al.* [54]	7	≤42 Gy	N/A	Overall	N/A	N/A
	9	≥50 Gy		43%		
				100%		
Sung *et al.* [55]	13	35–45 Gy	N/A	Relapse rate: 11/13	N/A	N/A
	29	50–60 Gy		8/29		
Alvord *et al.* [56]	52	>45.0 Gy	N/A	80%	65%	N/A
	62	<45.0 Gy		65%	55%	
Flickinger *et al.* [57]	12	>45.0 Gy	Calculation according	100%	N/A	0.045
	12	<45.0 Gy	nominal standard dose	75%		
Kovalic *et al.* [58]	3	<40.0 Gy	N/A	0	0%	<0.0001
	30	>40.0 Gy		90%	79%	
Garcia *et al.* [59]	8	<40 Gy	N/A	4/8 recurred	N/A	N/A
	17	≥40 Gy		2/17 recurred		
Jenkin *et al.* [60]	19	>50.0 Gy	N/A	88%	88%	0.37
	15	<50.0 Gy		72%	57%	
Grabenbauer *et al.* [61]	9	44–45 Gy	1.6–2.0 Gy	87%	36%	0.04
	16	45.1–60 Gy		90%	85%	
Paulino *et al.* [38]	29	≤50.4 Gy	1.8 Gy	5 years	8 years	0.37
	10	>50.4 Gy		73.8%	95.2%	
				90.9%	88.9%	
Muller *et al.* [39]	13	≤50.4 Gy	1.8 Gy	77%	77%	0.941
	52	>50.4 Gy		77%	77%	

n.s., not significant; N/A, not available.

Evolution of Radiotherapy Target Volumes

Accurate delineation of target volumes is important in optimising the therapeutic ratio of radiotherapy, exploiting dosimetric advantages of particle therapy and in avoiding marginal recurrences. Fusion of planning computed tomography scan with the diagnostic and postoperative/planning T2 or FLAIR and T1 contrast MRI sequences is recommended. Postoperative residual disease or disease on diagnostic scan, if no resection carried out, is the Gross tumour volume (GTV).

Largely as a consequence of improvements in the quality and precision of neuro-imaging the geometrical margin added to derive the clinical target volume (CTV) has evolved over the last few years. Studies have shown local failure as the predominant feature in progressive or recurrent disease and the geometric margin can be reduced considerably without increasing the risk of a margin failure [10,65](Table 2). Although earlier series used a geometric margin of 1.5–2 cm in all LGGs, numerous studies have shown that a CTV margin of 5–10 mm is adequate for well-demarcated lesions [31–33,38]. Currently, most clinicians add a margin of 5 mm to the GTV. For grade II (diffuse) tumours, no detailed recommendations can be made. Due to their infiltrative growth, the CTV margin can be defined as much as 1–1.5 cm to the GTV visible on high signal T2 or FLAIR (Fluid-attenuated inversion recovery) imaging. When defining the CTV, anatomical borders and the avoidance of extending the CTV into non-target areas of the brain must be considered.

The planning target volume encompasses the CTV with an additional margin according to the precision of the treatment technique (0.1–0.3 cm if rigid head fixation and 0.5 cm if a conventional face mask/head shell is used) depending on the department's policy.

Radiotherapy in Leptomeningeal Dissemination

Leptomeningeal dissemination is seen in 4–12% of children with LGGs. Given the rarity of dissemination, the optimal treatment is unclear. Chemotherapy often leads to clinical stabilisation or improvement with overall response rates of 25% and 79% of the primary tumour and disseminated lesions, respectively [66]. Craniospinal radiotherapy (CSI) is a treatment option, especially when chemotherapy has failed [67]. Bian *et al.* [68] assessed six children with metastatic pilocytic astrocytomas. Four patients underwent CSI, one to the spine only and one to a supratentorial local field. With a median follow-up of 24 months after radiotherapy, five of six patients were alive, four with stable disease and one with progressive disease. Another study of 12 patients reported a 5-year EFS of 71% and overall survival of 70% with CSI [69]. It is possible to achieve long-term disease stability following treatment of patients with leptomeningeal metastatic disease.

Proton Therapy

Proton therapy is being increasingly used in children and it can achieve a high degree of dose conformity around the tumour with further reduction of low-dose radiation region to surrounding brain and other critical structures compared with photon therapy. In a study, 32 children received a median radiation dose of 52.2 CGE [40]. The 6- and 8-year rates of PFS were 89.7% and 82.8%, respectively, with an 8-year overall survival of 100%. Although there was no significant decline in full-scale IQ for the whole cohort, significant declines in neurocognitive outcomes were observed in young children (<7 years) and those received a dose of at least 15 GyRBE to 20% of the volume of the left temporal lobe or hippocampus ('high-risk' dose). The

incidence of endocrinopathy correlated with a mean dose ≥40 CGE to the hypothalamus, pituitary or optic chiasm. Stabilisation or improvement of visual acuity was achieved in 83.3% of patients. Another study reported a 3-year PFS of 87% and overall survival of 95% in a cohort of 54 children from the UK treated with proton therapy at the University of Florida [41]. This study suggested a trend towards a better local control in 33 patients with grade I tumours (91% versus 76%, $P = 0.1$) and those who received 54 Gy.

Specific Tumours

Optic Nerve Gliomas

Optic nerve gliomas (OPNs) constitute 3–5% of paediatric tumours and can occur anywhere in the optic path or hypothalamus [70]. They are frequently associated with NF-1 or can be sporadic. The median age at occurrence of NF-1-associated OPNs is 3–5 years and these tumours progress until 12 years before stabilising. Between 70 and 90% of sporadic tumours occur in the optic chiasm or hypothalamus and have a worse prognosis compared with those arising in the optic nerves anterior to the chiasm or in the orbit. Radiological appearance is typical. Therefore, histological confirmation is often not needed. When histology has been obtained, the common type is juvenile pilocytic astrocytoma. Asymptomatic children undergo surveillance with serial imaging.

Patients with severe visual impairment or poor prognostic tumours (sporadic, optic tract or optic radiation tumours) need treatment, which is often chemotherapy [71,72]. Chemotherapy with carboplatin and vincristine improves visual acuity in 11% and stabilises vision in two-thirds of patients [73].

Radiotherapy is often delayed to avoid the risks of vasculopathy (5% at years, increased to 12.5% if age < 5 years), second neoplasms (malignant peripheral nerve sheath tumour) and neurocognitive dysfunction [74]. However, radiotherapy is indicated for rapidly progressing and chemotherapy-resistant tumours. In a recent series of 89 patients treated with a median radiotherapy dose of 54 Gy, the 10-year EFS was 67.5% for sporadic ($n = 40$) and 61.9% for NF-1-associated ($n = 14$) OPNs. The corresponding 10-year overall survival rates were 98.4% and 92.3%, respectively [75]. In this series, the incidence of vasculopathy was 7%, with none if aged >10 years at radiotherapy. Previous studies have also reported similar excellent outcomes with radiotherapy [36,74,76].

Uncommon Low-grade Gliomas

Tectal plate gliomas are uncommon LGGs occurring predominantly in children and constitute 5% of brainstem tumours in children [77]. They often present with symptoms of raised intracranial tension. On MRI, these tumours appear typically as a well-circumscribed lesion that is isointense on T1-weighted without contrast enhancement and hyperintense on T2-weighted images. Diagnosis is often based on imaging and in view of surgical morbidities, biopsy or resection are only attempted when imaging shows atypical features or to guide targeted treatments. Cerebral spinal fluid diversion followed by close observation is the initial treatment approach. These tumours often have a prolonged natural history and in a recent review the average time to progression ranged from 3 months to 7.8 years [77]. Chemotherapy or radiotherapy are used during progression. Tumour >3 cm^2, contrast enhancement and cystic changes are associated with early progression and a worse survival. In the SIOP LGG 2004 study, there were 71 patients with tectal plate LGGs, of which 41 did not receive any tumour treatment [78]. Sixty-three (89%) patients had at least one cerebral spinal fluid diversion and the 10-year overall survival of the whole cohort was 96%. Patients with initial tumour volume ≤3 cm^3 had a significantly better 10-year EFS (56%) compared with patients with tumours > 3 cm^3 (12%, $P < 0.001$). Patients with non-contrast-enhancing tumours also had a better 10-year EFS compared with those with contrast-enhancing tumours (52% versus 23%, $P = 0.003$).

Cervicomedullary LGGs are slow-growing tumours presenting with lower brainstem symptoms or myelopathy [79]. On MRI these appear as well-defined lesions that are hypointense on T1-weighted with homogeneous contrast enhancement and hyperintense on T2-weighted. Maximal safe resection followed by surveillance is the initial treatment of choice. Radiotherapy and/or chemotherapy are effective for progressive or symptomatic inoperable disease. These tumours have a better prognosis than pontine gliomas. In a recent study the 10-year overall survival was 86.7% and treatment-free survival was 45.3% [80].

Numerous histological subtypes of paediatric LGGs are uncommon. For example, in the German HIT 96 study ($n = 1031$), 15 patients had pleomorphic xanthoastrocytoma, 92 gangliogliomas/DNET, five oligoastrocytoma, 15 oligodendroglioma ($n = 10$) and 15 subependymal giant cell astrocytoma [22]. The general management usually follows concepts used in pilocytic and grade II tumours, with surgery as the primary treatment. In the HIT 96 study, only 20 patients received either chemotherapy or radiotherapy and therefore outcome could not be meaningfully analysed. The current management of these uncommon LGGs has been recently reviewed [81].

Survival

The survival of LGGs varies with specific histological subtypes and treatments. The 10-year overall survival of pilocytic astrocytoma is >90% after GTR and >70% after STR [82,83]. With primary chemotherapy the 5-year EFS is 45–50% and overall survival 90% [16,18,21,84]. Non-comparative studies suggest that radiotherapy has a better >7-year PFS of 65–84% with overall survival 80–100% [22,31,35,37,40].

Management of Recurrence

The reported recurrence rate in paediatric LGGs ranges from 5 to 41% [85]. Most recurrences (>65%) are

asymptomatic. The modality for treating recurrence varies according to such factors as the initial modality used, age of the child at recurrence and likelihood of clinical benefit and toxicity. Two-thirds of recurrences occur within 2 years of initial treatment and 90% within 5 years. Localised recurrences are managed with further surgery, which is feasible in about 70% of cases. Inoperable recurrences are managed with systemic therapy and/or radiation/proton therapy. Although re-irradiation using fractionated stereotactic radiotherapy is reported to be effective (median survival 22 months) in teenage and young adults and adults with grade II tumours, there is no report of re-irradiation in children with LGGs [86]. Early studies indicate that MEK inhibitors are effective in patients who have recurrence after conventional treatments [26,27].

Late Effects and Survivorship

Although radiotherapy is a highly effective treatment, adverse late effects, mainly neurocognitive dysfunction, are a major concern [29,31]. However, other factors, such as tumour-induced dysfunction, the presence of NF-1, hydrocephalus, surgery, genetics and chemotherapy, also contribute to neurocognitive dysfunction [87–89]. In the series by Merchant *et al.* [31], cognitive effects following conformal radiotherapy correlated with patient age, NF-1 status, tumour location and volume, extent of resection and radiation dose. The effect of age exceeded that of radiation dose; patients younger than 5 years experienced the greatest decline in cognition. Among the cohort of 182 patients with 5-year survival, an IQ below average (<85) was associated with younger age at diagnosis, epilepsy and shunt placement, but not radiotherapy [90]. Thus, studies suggest that complex pattern of neurocognitive dysfunction caused by multiple different co-factors, among which radiotherapy is one of the contributors [90].

Growth hormone secretion abnormality was diagnosed in 24% and precocious puberty in 12% of patients before radiotherapy. After radiotherapy, the 10-year cumulative incidence of growth hormone replacement was 48.9%; thyroid hormone replacement 64.0%; glucocorticoid replacement 19.2%; gonadotropin-releasing hormone analogue therapy 34.2% [31]. Among 240 patients who survived more than 5 years, the 15-year cumulative incidence of other adverse outcomes included blindness 18%, hearing loss 22%, obesity 53% and hyperinsulinism 24%. Diencephalic location was a statistically significant independent risk factor for blindness, growth hormone deficiency, abnormal thyroid function and ACTH deficiency. Long-term results from the SEER database and a Canadian population-based study suggest that even though paediatric LGG are associated with excellent survival (20-year overall survival 87–90%), radiotherapy is a significant factor contributing to late mortality, mainly due to complications such as malignant transformation, second cancers and vasculopathy [91,92].

The physical advantage of proton therapy in reducing the integral dose to normal critical structures has the potential to reduce neurocognitive dysfunction and other late effects due to radiotherapy [93]. The early experience with proton therapy in LGG suggesting no significant decline in full-scale IQ in children >7 years and those who received a lower dose to the left temporal lobe/hippocampus is encouraging [40]. However, evaluation of the clinical benefit from proton therapy requires further clinical studies with measures of long-term physical and neurocognitive outcome measures.

Current Clinical Trials and Future Challenges

With the advances in molecular targeted agents, future trials will evaluate the relative efficacy of conventional chemotherapy with novel agents to optimise systemic therapy. For example, the proposed SIOP LOGGIC study will compare first-line treatment with vinblastine, carboplatin plus vincristine and a MEK inhibitor in children and teenage and young adults with BRAF-mutation-negative LGGs.

The techniques of radiotherapy have also advanced significantly in the last few years. The advances include improved imaging techniques for target delineation, reduction in the margin for CTV and adoption of high-precision techniques, such as intensity-modulated radiotherapy, volumetric-modulated arc-therapy, Tomotherapy® and proton therapy. Since the radiotherapy late-effects are dependent on dose-volume and integral dose distribution, the above advances, which can reduce the integral dose, have the potential to reduce the risk of late effects [31,93,94]. Brachytherapy is a valuable treatment option in selected cases, but its availability is only restricted to a few institutions [95–98]. Radiosurgery has been applied in a few cases and needs further study [99–101].

Reliable prospective data comparing systemic therapy with modern high-precision radiation/proton therapy are currently not available to guide the best evidence-based quality of care to children with LGGs. Future clinical studies, therefore, should compare the efficacy and safety of systemic treatments with proton therapy in terms of improvement in neurological functions, including visual function where appropriate, survival, late toxicities, health status and quality of life.

Conflict of interest

The authors declare no conflict of interest.

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