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Re-irradiation for Paediatric Tumours

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Abstract

Despite best available therapy, many children with cancer develop recurrence after multimodal treatment, including initial radiation therapy. Re-irradiation is defined as the use of a second course of radiation therapy with a retreatment volume that overlaps substantially with that of a previously delivered course of radiation therapy. Re-irradiation is an important part of salvage treatment for patients with recurrent ependymoma, diffuse intrinsic pontine glioma, medulloblastoma and germinoma. In patients with ependymoma, conventionally fractionated re-irradiation (1.8 Gy/day) can provide long-term disease control with low rates of high-grade toxicity. For children with progressive diffuse intrinsic pontine glioma, re-irradiation provides effective palliation of symptoms and a survival gain as compared with those treated without re-irradiation. Repeat radiation therapy that includes craniospinal irradiation, if safe to deliver, may provide long-term tumour control in patients with medulloblastoma. Patients with recurrent intracranial germinoma can be effectively salvaged with re-irradiation that includes craniospinal irradiation. Finally, the emerging role of re-irradiation in non-brainstem high-grade glioma and extracranial solid tumours requires further study regarding its efficacy and safety. When given, re-irradiation should be delivered with care so that doses to organs at risk are minimised. In all cases, re-irradiation should be considered as an option alongside, or concurrently with, other salvage treatments, including surgery or systemic therapy, to maximise the likelihood of durable disease control.

Key words: Brainstem neoplasms; brain tumour; ependymoma; germinoma; medulloblastoma; re-irradiation; recurrent

Introduction

Radiation therapy is an important component of the primary management of most paediatric brain tumours [1] and extracranial solid tumours [2]. Despite best available multimodal treatment, which often includes surgery, chemotherapy and initial radiation therapy, many children with malignancies develop disease recurrence requiring salvage therapy. In this setting, repeat irradiation can play an important role in curative-intent salvage treatment or palliation. In this review, re-irradiation is defined as a second course of radiation therapy that is delivered to a volume that substantially overlaps with a previously delivered course of radiation therapy.

Re-irradiation is indicated for many types of recurrent paediatric cancer as an effective and safe salvage treatment. Recurrence is a particular problem with high-grade gliomas (HGGs), which are not curable with current therapy. A large minority of patients with ependymoma and medulloblastoma also develop disease recurrence with time, in which re-irradiation plays an important role in selected patients. Germ cell tumours, particularly germinoma, have a high rate of cure, but because of the low intensity of initial radiation therapy, repeat irradiation can often be safe, feasible and effective as a salvage treatment. Finally, the role of repeat irradiation for extracranial solid tumours is briefly discussed.

Repeat irradiation is always approached with caution because of incomplete repair and recovery of normal tissue tolerance after a course of radiation therapy [3]. Tissues in the central nervous system have the ability to undergo recovery beyond traditional tolerance doses, depending on the time between first and second irradiation, and whether toxicity has already occurred with the first irradiation [3]. Dose tolerance has been best studied in the spinal cord, where recovery of 60% is estimated based on animal models

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[4]. Repeat irradiation of the spinal cord is known to be feasible and safe, particularly with greater time intervals between first and second radiation therapy [5]. Other tissues have been less well studied, but similar care to spinal cord re-irradiation is required with repeat irradiation of serial organs, such as the brainstem, peripheral nerve plexuses and luminal gastrointestinal organs.

In this review, we will discuss the evidence surrounding the use of re-irradiation in children with cancer. Most of the data pertain to the use of re-irradiation for intracranial central nervous system tumours (ependymoma, diffuse intrinsic pontine glioma [DIPG], medulloblastoma and germinoma), although the role of re-irradiation for some other tumours (supratentorial HGG and extracranial solid tumours) is also briefly discussed.

Ependymoma

Rationale

The standard of care for localised, grade 2–3 ependymoma is a maximum safe resection (ideally, a gross total resection) followed by focal radiation therapy to a total dose of 59.4 Gy [6–8]. Most children with ependymoma have a primary tumour site located in the fourth ventricle within the posterior fossa [6], making the brainstem an important organ at risk during radiation therapy. Despite treatment, at least 20% of children treated with gross total resection and focal adjuvant radiation therapy develop recurrence of their ependymoma [6], requiring salvage therapy.

Evidence

Selected contemporary studies of re-irradiation in paediatric patients with ependymoma are listed in Table 1. An important, early paper was reported by St Jude Children's Research Hospital in 2008 [9]; the data were updated in 2018 and represent the largest single-institution series of patients treated with fractionated re-irradiation for this disease (101 patients) [10]. In this study, all but one patient had resection of recurrent disease. Fifty-six had local failure and 46 of those received focal re-irradiation, whereas those with any component of distant failure received craniospinal irradiation (CSI) followed by boost re-irradiation to all sites of resected or *in situ* disease. Children with distant-only failure and treated with CSI had the best 5-year overall survival (76%) and freedom from progression (49%).

Lobón *et al.* [11] reported on 32 patients retreated with a variety of hypofractionated and fractionated regimens for recurrent ependymoma. In this study, three of 11 patients who received ≥3 Gy/day of re-irradiation developed radiological radiation necrosis (crude rate, 21%), whereas two of 21 patients who received ≤2.5 Gy/day developed necrosis (crude rate, 10%). The median progression-free survival (PFS) for the entire cohort was 1.2 years, whereas it was 6.8 years for those treated with CSI for distant failure, affirming the St Jude data, which found that those with

Table 1
Selected published studies of re-irradiation for paediatric ependymoma

Reference	*n*	First radiation therapy dose	Re-irradiation dose	PFS or FFP from re-irradiation	Overall survival from re-irradiation	Radiation necrosis
Fractionated re-irradiation						
[10]	101	59.4 Gy	54 Gy (focal) 36–39.6 Gy (CSI)	5-year FFP 37%	5-year 57%	Grade ≥ 3 7.9% (actuarial, 10 years)
[11]	32	54 Gy	Up to 54 Gy*	2-year PFS 70%†	2-year 38%†	5 total (4 asymptomatic; 1 resolved with steroids)
[12]	24	n/a	n/a	n/a	5-year 16%	n/a
[13]	20	55.8 GyE	50.4 GyE	3-year PFS 28%	3-year 79%	Grade ≥ 3 5% (crude)
[14]	19	n/a	n/a	n/a	2-year 45%†	n/a
[15]	18	54–59.4 Gy	54–59.4 Gy (focal) 36 Gy (CSI)	3-year PFS 56%	3-year 81%	No cases§
[16]	7	50 Gy	36 Gy	5-year 60%	5-year 50%	No cases
Hypofractionated re-irradiation						
[17]	21 (32 tumours)	52.2 Gy	9–22 Gy (SRS)	3-year 20%‡	3-year 23%	2 total (1 asymptomatic, 1 resolved with steroids)
[18]	12	54–59.4 Gy	24 Gy in 3 fractions	67% (crude)	2-year 71%	Grade ≥ 3 25% (crude)
[19]	8	44–60 Gy	20 Gy in 2 fractions; 21 Gy in 3 fractions; 25 Gy in 5 fractions	3-year 21%	3-year 38%	No cases
[20]	6	55.8–59.4 Gy	24 Gy in 3 fractions	2-year 100%	2-year 100%	3 total (all asymptomatic)

CSI, craniospinal irradiation; FFP, freedom from progression; GyE, gray equivalent; PFS, progression-free survival; SRS, stereotactic radiosurgery.

* Some patients were treated with hypofractionated regimens of up to 5 Gy/day.

† Estimated from published Kaplan–Meier survival plots.

‡ Probability of being free from distant tumour relapse.

§ In an updated series with 27 patients (published in abstract form only), four cases of necrosis were observed (crude rate, 15%; grade of toxicity not specified) [21].

distant failure have a favourable long-term outcome after re-irradiation.

Bouffet *et al.* [15] published a series of 18 patients treated with re-irradiation for recurrent ependymoma. They compared this group with an institutional cohort of patients who were not selected to receive re-irradiation and found a survival difference (re-irradiation versus not, 3-year overall survival 7% versus 81%, $P < 0.0001$). This series was updated in abstract form [21], with a total of 27 patients treated with re-irradiation. In the updated dataset, those with local failure who received CSI had a 3-year PFS of 75% versus 36% for those who received focal re-irradiation alone (not significant). This provocative data suggest that CSI may play an important role even in patients with local recurrence of ependymoma.

There are fewer data with respect to the safety and efficacy of hypofractionated re-irradiation or stereotactic radiosurgery (SRS). There may be an increased risk of imaging changes or necrosis with hypofractionated courses of repeat radiation therapy because the α/β ratio of brain is low [22]. In the studies by Hoffman *et al.* [18] and Liu *et al.* [20], which both used $\geq$24 Gy in three fractions, 50% developed any imaging evidence of radiation necrosis (as compared with 27% with fractionated radiation therapy [10]). Therefore, the risk of toxicity may be greater with larger doses per fraction [23]. Use of highly conformal re-irradiation (SRS) may be relatively well tolerated [17]; however, patients treated with SRS remain at high risk of subsequent ependymoma recurrence [9,17,24].

Summary

Children with recurrent ependymoma should be offered repeat surgery (if possible), followed by re-irradiation. Those with distant recurrence should receive 36 Gy CSI followed by fractionated boost radiation therapy. Those with local recurrence may be treated with focal re-irradiation or CSI; CSI may improve outcomes in these patients. Our preferred approach is to give fractionated re-irradiation with daily fraction sizes of 1.8 Gy (rather than hypofractionated re-irradiation) to reduce the risk of necrosis; focal doses of up to 54 Gy appear safe. The brainstem should not receive any dose exceeding the re-irradiation prescription dose. The risk of toxicity may be increased with a short interval between the first and second radiation [9]; therefore, a delay of at least 9 months between the first radiation therapy and re-irradiation is recommended [10].

Diffuse Intrinsic Pontine Glioma

Rationale

DIPG is a devastating disease of childhood and has a uniformly terminal prognosis [25]. Radiation is the primary treatment for this tumour, to a total dose of 54 Gy (1.8 Gy/day) [25]. Recent work has found that 70–90% of DIPGs carry a K27M mutation in histone 3.1 or 3.3 (H3.3 K27M or H3.1 K27M, forming the basis for the new pathological diagnosis of 'diffuse midline glioma, H3 K27M–mutant') [25–27]; however, as of yet, this discovery has not yet translated into a therapeutic target. Therefore, re-irradiation may be offered as a salvage treatment for DIPG at recurrence, notwithstanding traditional brainstem tolerance doses [28,29].

Evidence

Selected contemporary series of re-irradiation for DIPG are listed in Table 2. The largest series was published by Janssens *et al.* [30], on behalf of the SIOP-E-HGG/DIPG working group. In this matched cohort study, 31 patients who underwent re-irradiation, with at least 3 months required between the first radiation therapy and re-irradiation, were compared with 39 patients who were not selected for re-irradiation. Twenty-nine per cent of re-irradiated patients had received a hypofractionated course of first radiation therapy. When counting survival from initial diagnosis, an overall survival benefit was observed with re-irradiation (13.7 versus 10.3 months, $P = 0.04$). Patients with a greater time interval from initial diagnosis to first radiation therapy had greater benefit with re-irradiation. This analysis did not use a time-dependent covariate to account for immortal time bias [31–33].

Lassaletta *et al.* [34] published a pan-Canadian series of 16 patients who had undergone re-irradiation for recurrent DIPG. The median time from diagnosis to first progression was 10.5 months. When compared with patients who were not selected for re-irradiation, the median survival from progression to death was 92 days (no re-irradiation) versus 218 days (re-irradiation, $P = 0.0001$).

In addition to the aforementioned literature, other studies have made comparisons between patients with recurrent DIPG who were selected for re-irradiation versus not. Although these comparisons are subject to selection

Table 2
Selected published studies of re-irradiation for diffuse intrinsic pontine glioma

Reference	*n*	First radiation therapy dose	Re-irradiation dose	Clinical response	Median survival from progression or re-irradiation	Absolute median survival gain with re-irradiation
[30]	31	n/a	19.8–30 Gy	77% (crude)	n/a*	3.4 months
[34]	16	n/a	21.6–36 Gy	81% (crude)	6.5 months	4.1 months
[35]	14	n/a	n/a	n/a	7 months	3.5 months
[36]	11	54 Gy	19.8 Gy	91% (crude)	6 months	2.7 months (n.s.)
[37]	5	54–55.8 Gy	18–20 Gy	80% (crude)	5 months	n/a

* Study reported survival from diagnosis, not progression.

bias, most studies showed a statistically significant median survival benefit after re-irradiation for recurrent DIPG, ranging from 3 to 4 months [35–37].

Although re-irradiation after hypofractionated radiation therapy has been reported in a few cases [30], the risk of toxicity in this setting may be increased due to the low α/β of brain tissue [22]. Care to minimise dosimetric hot spots and perhaps use of a lower total re-irradiation dose (in 1.8 Gy daily fractions) in these patients may be warranted. Hypofractionated re-irradiation is not recommended and may cause brainstem toxicity [34].

Summary

The existing data suggest a clinically important symptomatic and survival benefit after re-irradiation in children with DIPG. The maximum doses reported in the literature ranged from 30 to 36 Gy (1.8 Gy/day). Our current practice is to offer repeat irradiation as standard of care palliation for patients who develop progression more than 6 months after first radiation therapy, as these are the patients who would probably benefit from re-irradiation [30]. These individuals also would have had sufficient time since their first radiation therapy to permit some recovery of brainstem tolerance.

The dose is guided by time to recurrence:

(i) if re-irradiation is given between 6 and 12 months from first radiation therapy, then 30.6 Gy in 17 fractions is prescribed;
(ii) if re-irradiation is given more than 12 months from first radiation therapy, then 36 Gy in 20 fractions is prescribed.

High-grade Glioma

Patients with non-brainstem HGG experience somewhat improved prognoses as compared with DIPG, but long-term (3-year) PFS and overall survival remain poor, at 22% and 28%, respectively [38]. Re-irradiation is one of the treatment options in patients with recurrent HGG [39]. Its role is better established in adult patients with HGG, with numerous retrospective single-institution series [40], as well as ongoing prospective studies (RTOG 1205, NCT01730950) in support of its use in selected patients. However, a systematic review by Kline *et al.* [39] only identified two studies of re-irradiation in children with HGG, one of which included patients with DIPG.

The sole study that evaluated re-irradiation for recurrent, non-brainstem HGG in children was published by Müller *et al.* [41], using data from the German HIT-HGG study group. Eight patients, including patients with symptomatic or asymptomatic recurrences, were reported. The first radiation therapy had been delivered to a dose of 54–60 Gy. Re-irradiation was given to a dose of 30.6–55.8 Gy (among those who received fractionated re-irradiation). Three patients (38%) experienced clinical and radiological improvement. The median survival from initial progression was 11 months, whereas the median survival from re-irradiation was 4.6 months. There are no known data on neurocognitive function or quality of life after re-irradiation for HGG in children; this should be an area of future study [42].

Summary

Our institutional approach has been to offer salvage systemic therapy for patients with recurrent non-brainstem HGG. For those who develop further progression, are symptomatic and have exhausted systemic therapy or clinical trial options, full-dose, in-field re-irradiation is offered to up to 54 Gy (1.8 Gy/day).

Medulloblastoma

Rationale

Patients with newly diagnosed medulloblastoma are curable, with a 5-year event-free survival of 81% for patients with average-risk disease [43] and 70% for those with high-risk disease [44]. Standard treatment includes maximum safe resection [45], CSI to 23.4 Gy (average-risk) or 36 Gy (high-risk) followed by focal tumour boost [46] and chemotherapy. Despite therapy, patients with recurrence require salvage treatment, for which re-irradiation plays an important role.

Evidence

Wetmore *et al.* [47] published a detailed series of patients from St Jude with recurrent medulloblastoma treated with ($n = 14$) or without re-irradiation ($n = 24$). Patients were aggressively treated for disease recurrence, with six of 14 (43%) undergoing repeat surgery prior to re-irradiation and eight of 14 (57%) undergoing CSI as a component of re-irradiation. Among standard-risk patients (at diagnosis), 10-year overall survival was 45% of those who were re-irradiated, as compared with 0% of those who were not selected for re-irradiation ($P = 0.036$). A similar overall survival benefit was seen for high-risk patients at diagnosis ($P = 0.003$), but that analysis was limited by small patient numbers. Patients who did not receive re-irradiation also did not get surgery for their recurrence. Both survival comparisons were counted from diagnosis, not recurrence, which does lead to an immortal time bias in favour of those who were re-irradiated. The patients re-irradiated also represent a highly selected population who were suitable for aggressive surgical debulking and salvage treatment, and the favourable results may not be broadly generalisable. Nonetheless, among the available reports from the literature (Table 3), the approach by Wetmore *et al.* [47] resulted in the longest median survival.

A series of 13 patients re-irradiated for recurrent medulloblastoma was reported by Bakst *et al.* [49]. The median fraction size was 1.5 Gy/day (range 1.0–1.8 Gy) to reduce the incidence of toxicity. Most patients received large field radiation therapy, but none received CSI. The median survival

Table 3
Selected published studies of re-irradiation for medulloblastoma

Reference	*n*	Radiation therapy details	Median survival from re-irradiation	Radiation necrosis
[48]	20	Total dose: median 24.5 Gy (in 4 fractions) or SRS, median 15 Gy (range 10–18 Gy)	1 year 65% 3 years 25%	None (grade > 2)
[14]	20	n/a	8.4 months	n/a
[47]	14	Total dose: median 36 Gy (18–54 Gy) CSI (57%) Spine (21%)	65 months† (standard-risk) 59 months† (high-risk)	64% (crude, grade 1–2, 'subclinical' necrosis)
[49]	13	Total dose: 19.8–45 Gy Posterior fossa (46%), other large field* (64%)	37 months	7.7% (crude; asymptomatic)
[50]	12	30 Gy in 6 fractions	29 months	7% (crude)

CSI, craniospinal irradiation; SRS, stereotactic radiosurgery.
* 31% whole brain or supratentorial brain, 23% spine, 8% posterior fossa and spine.
† Counted from first recurrence, not re-irradiation. The median time from first recurrence to re-irradiation was 3.1 months.

from re-irradiation was 37 months. Those without gross disease at re-irradiation had the best outcomes, with 83% having no evidence of disease, as compared with 14% of those with gross disease at the time of re-irradiation. Again, this corroborates data from St Jude that an aggressive, combined surgical and re-irradiation approach may lead to improved outcomes.

Three other series of patients are available; these were largely treated with focal approaches. Saran *et al.* [50] published a series of 12 patients treated with hypofractionated stereotactic re-irradiation for adults and children with locally recurrent medulloblastoma. Although adult patients have biologically distinct disease from children and are typically treated without chemotherapy at diagnosis, this study did show reasonable local disease control after a short course of re-irradiation and only one case of radiation necrosis. Gururangan *et al.* [51] reported patients with recurrent medulloblastoma who were salvaged with a variety of different approaches; in their overall cohort were five patients who were re-irradiated (four focal, one CSI). Based on tabular data presented in their manuscript, the median survival among those who received re-irradiation was 12 months versus 9 months for those who did not receive re-irradiation. Milker-Zabel *et al.* [48] treated 20 patients with hypofractionated, focal re-irradiation or SRS; long-term survival after re-irradiation was not achieved in most patients (1-, 3- and 5-year overall survival of 65%, 25% and 17%).

Several studies combined different tumour histologies in analysing re-irradiation in children with brain tumours [14,52,53]. Rao *et al.* [14] assembled a multi-institutional cohort of 67 re-irradiated children with any primary brain tumour. Twenty patients had medulloblastoma; the median survival was 8.4 months after re-irradiation. In a report by Chojnacka *et al.* [53], eight patients with recurrent brain tumours were reported, six of whom had medulloblastoma and two had germ cell tumours. 40 Gy in 20 fractions was given focally to those with medulloblastoma; the median PFS and overall survival from re-irradiation was 6.5 and 17.5 months, respectively, for the entire cohort of eight patients. No late toxicities were observed.

Summary

Re-irradiation for children with recurrent medulloblastoma may achieve long-term disease control. Patients most suitable for an aggressive approach are those who previously had standard-risk disease and were initially treated with reduced-dose CSI (23.4 Gy). These patients who develop a localised recurrence may be treated with salvage surgery, followed by comprehensive neuraxis re-irradiation (repeat CSI) to eradicate micrometastatic disease. Patients with no gross residual disease probably have the best outcomes [49]. Unfortunately, patients with recurrence after high-dose CSI (36 Gy) have limited re-irradiation options because of an inability to comprehensively retreat the neuraxis with a meaningful dose of CSI. These patients may benefit from focal or limited-field re-irradiation as a palliative measure to achieve durable local control; the optimal dose and fractionation in this setting has not been defined. Conventionally fractionated (1.8 Gy/day) or hypofractionated re-irradiation, which may be more convenient for patients, are both reasonable options. Overall, further study is needed to better select patients most suitable for repeat irradiation.

Germinoma

Children with germinoma have good long-term outcomes [54], with disease-free survival probabilities in excess of 85–90% [55,56]. Patients can be treated upfront with focal radiation therapy, ventricular radiation therapy or CSI [57]. However, recurrences can occur, requiring salvage treatment, where re-irradiation, typically CSI, plays an important role [57,58].

Hu *et al.* [58] carried out an institutional review of 14 Taiwanese patients with recurrent germinoma initially treated with radiation therapy (median 40 Gy). This institutional series was pooled with 88 patients from the literature, including 25 patients from Kamoshima *et al.* [57], to create a combined global cohort of 102 patients. Salvage treatments included CSI in 55%, focal radiation therapy,

whole brain radiation therapy or ventricular radiation therapy. Patients who had salvage CSI, non-CSI radiation therapy or no radiation therapy experienced 5-year overall survival probabilities of 93%, 60% and 36%, respectively ($P = 0.001$). In a multivariable analysis, use of any re-irradiation was associated with an overall survival benefit. More specifically, CSI appeared to provide better overall survival rates than non-CSI radiation therapy, although this comparison was not statistically significant. The study recommended low-dose CSI as an important component of salvage therapy for recurrent germinoma.

Summary

For patients with recurrent germinoma we suggest administering 20–25 Gy in daily fractions of 1.5–1.8 Gy per day to the entire neuraxis (CSI). Salvage chemotherapy may also be considered, but requires further study.

Extracranial Solid Tumours

There are very few published reports of re-irradiation for extracranial solid tumours in children. The most common solid tumours are neuroblastoma, Wilms' tumour, Ewing sarcoma, rhabdomyosarcoma and soft tissue sarcomas [59]. However, most of these tumours tend to undergo systemic dissemination; although local failures do occur, this is often combined with concurrent distant failure. In the setting of progression after radiation therapy, surgery or chemotherapy are reasonable first-line options, with re-irradiation reserved for persistent disease. This approach balances the need for local control against concerns of late toxicities after retreatment.

Taunk *et al.* [60] reported on a patient who received salvage stereotactic body radiotherapy (27 Gy/three fractions) for in-field, persistent neuroblastoma mass after conventionally fractionated radiation therapy (21 Gy in 14 fractions), with severe grade 3 myositis occurring as a complication. Brown *et al.* [61] reported on a case of grade 3 sacral plexopathy after 60 Gy/10 fraction re-irradiation to a region that had previously received 59.4 Gy in 33 fractions for Ewing sarcoma. Gultekin *et al.* [52] reported on four patients retreated with hypofractionated stereotactic radiation therapy for various extracranial solid tumours, but it was unclear whether the retreated region was in-field to prior radiation therapy or not.

Summary

Re-irradiation for extracranial solid tumours should be reserved as a last resort in patients with persistent, localised disease recurrence. Patient selection and the total dose of re-irradiation depends on many factors, including patient prognosis, distant disease control, prior radiation therapy dose and volume, and nearby organs at risk, especially spinal cord, peripheral nerves and luminal gastrointestinal organs. Other options for local control, such as surgery or chemotherapy, should be explored prior to re-irradiation.

Conclusions

Re-irradiation plays an important role in the salvage treatment of paediatric tumours. The greatest body of evidence exists in the retreatment of intracranial neoplasms, particularly ependymoma, DIPG, medulloblastoma and germinoma. CSI is a critical component of curative-intent salvage treatment of tumours with a propensity for neuraxial spread, such as in recurrent ependymoma and germinoma, especially for patients with distant sites of recurrence. CSI may also be important in children with recurrent medulloblastoma. In DIPG, focal re-irradiation provides effective symptom control and prolongation of life. In patients with recurrent HGGs and extracranial solid tumours, there is less evidence to support or refute re-irradiation. Therefore, in these settings, re-irradiation can be carefully considered, alongside alternative salvage therapies such as surgery, systemic therapy or clinical trial options. In all cases, suitability of re-irradiation should be discussed in a multidisciplinary setting. If re-irradiation is recommended, it should be delivered with attention to minimising the risks of toxicity, harm and decreased quality of life in a child's final months or years. Families need to clearly understand the risks of retreatment, with appropriate documentation of informed consent. Conventionally fractionated re-irradiation (1.8 Gy/day) is a reasonable option, as hypofractionation may increase the risk of treatment toxicity, especially for patients with recurrent ependymoma. Doses to organs at risk should be controlled and minimised. Ideally, prospective documentation of functional and survival outcomes is essential for radiation and paediatric oncologists to better understand how re-irradiation fits into the armamentarium of salvage therapies against recurrent paediatric cancer.

Conflict of interest

The authors declare no conflict of interest.

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