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Radiotherapy Advances in Paediatric Medulloblastoma Treatment

L. Padovani *, G. Horan †, T. Ajithkumar †

* Aix-Marseille University, Oncology Radiotherapy Department, CRCM Inserm, UMR1068, CNRS UMR7258, AMU UM105, Genome Instability and Carcinogenesis, Assistance Publique des Hôpitaux de Marseille, Marseille, France
† Department of Oncology, Cambridge University Hospitals NHS Trust, Cambridge, UK

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Abstract

Radiotherapy is an essential element in the multidisciplinary management of children with medulloblastoma and postoperative craniospinal axis radiotherapy is considered to be the cornerstone of curative treatment. With modern multidisciplinary management, more than 80% of children with standard-risk medulloblastoma and up to 70% of children with high-risk medulloblastoma are long-term survivors. Current clinical trials are evaluating risk-adapted radiotherapy in standard-risk medulloblastoma to reduce long-term sequelae, whereas the research approach in high-risk medulloblastoma is to improve clinical outcome with dose-intensification of chemotherapy and the use of hyperfractionated radiotherapy regimens. Technological advances, such as tomotherapy, volumetric modulated arc therapy and proton therapy, may further improve the therapeutic ratio by reducing radiotherapy toxicities. A selected group of children with recurrent disease after treatment for standard-risk medulloblastoma may be considered for re-irradiation.

Keywords: Children; medulloblastoma; radiotherapy

Statement of Search Strategies Used and Sources of Information

We searched PubMed from January 1990 to September 2018 using the broad search terms ‘medulloblastoma’, ‘radiotherapy’ and ‘treatment’. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Introduction

In the 2016 World Health Organization classification of primary central nervous system tumours, medulloblastoma is the most common embryonal tumour [1]. Radiotherapy remains an essential element of the multidisciplinary curative treatment of paediatric medulloblastoma and currently more than 70% of children diagnosed with medulloblastoma are expected to be long-term survivors, although long survival is frequently associated with significant long-term toxicities [2]. Radiotherapy advances in the last two decades include a better target volume delineation using modern imaging and the widespread use of adaptive techniques, such as intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy and image-guided radiotherapy, and increasing use of particle beam therapy [3–5]. We review these radiotherapy advances in the management of medulloblastoma.

Initial Management of Medulloblastoma

The current standard treatment of medulloblastoma includes initial surgery followed by a combination of craniospinal irradiation (CSI) and chemotherapy. Despite advances in systemic therapy and neurosurgical techniques, CSI remains the standard radiotherapy technique. Conventionally, children with medulloblastoma are categorised post-operatively as standard-risk (66% of patients) or high-risk

Author for correspondence: T. Ajithkumar, Department of Oncology, Cambridge University Hospitals Foundation Trust, Box 193, Hills Road, Cambridge CB2 0QQ, UK. Tel.: +44-1223-274401; Fax: +44-1223-217094.
E-mail address: Thankamma.ajithkumar@addenbrookes.nhs.uk (T. Ajithkumar).

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(34% of patients). Children with >1.5 cm^2 residual disease after resection, evidence of metastases at diagnosis or with anaplastic large cell histology are considered as high-risk [6]. Patients without these criteria are categorised as standard-risk. Children younger than 3–5 years are generally managed with a chemotherapy-only approach [7–11].

Role of Radiotherapy

Standard-Risk Medulloblastoma

In earlier studies of standard-risk medulloblastoma, children were treated with maximal cytoreductive surgery followed by CSI with a conventional dose of 36 Gy to the cranial spinal axis and a boost to the posterior fossa of 18–20 Gy, delivering a total dose of 54–56 Gy. These studies reported a disease-free survival and overall survival of 55–70% at 5 years from diagnosis [12,13]. However, this approach led to significant long-term radiotherapy side-effects, such as neuropsychological, hearing, and endocrinological sequelae, particularly in very young children [14–16]. Therefore, a number of studies have evaluated the modification of radiotherapy volumes and doses, with or without chemotherapy.

Reduced-Volume Craniospinal Irradiation

One of the earliest attempts by the French SFOP M4 trial to reduce late toxicity was to exclude the supratentorial part of the brain from irradiation and reduce the total dose [17]. Unfortunately, the event-free survival (EFS) at 6 years was less than 20% and in nine of 13 cases relapse occurred supratentorially, demonstrating that CSI was necessary.

Reduced-Dose Craniospinal Irradiation

Subsequently, several studies evaluated a reduced-dose CSI. The SIOP II trial randomised 364 patients with standard-risk medulloblastoma to receive 25 or 35 Gy of CSI with or without neoadjuvant chemotherapy [18]. The study reported that patients who received adjuvant chemotherapy had a better EFS (68% versus 55%), but patients treated with 25 Gy and adjuvant chemotherapy had a worse prognosis.

The North American POG 8631/CCG 923 randomised study evaluated the role of reduced-dose CSI (23.4 Gy) [19]. The study showed that children treated with a dose of 23.4 Gy CSI reported less neurocognitive toxicity than those receiving 36 Gy. Unfortunately, the study was closed prematurely after 4 years as a higher probability of relapse was shown in the reduced-dose arm (5-year EFS 67% versus 52%, $P = 0.080$) [19,20]. This study prompted the evaluation of reduced-dose CSI with chemotherapy.

Following encouraging data from pilot studies, Packer *et al.* [21] investigated the use of a reduced CSI dose of 23.4 Gy, with a boost of 31.8 Gy to the posterior fossa followed by chemotherapy. The chemotherapy regimen was concurrent chemotherapy with vincristine followed a combination of cisplatin, vincristine and CCNU. This study reported a 3-year progression-free survival (PFS) of 86% and a 5-year PFS of 79%. In this study, 32.3% of patients (21 of 65) developed grade 3–4 ototoxicity. The following CCG A9961 phase III trial included 421 standard-risk medulloblastoma patients treated with a low dose of CSI (23.4 Gy with a posterior fossa boost to 55.8 Gy) and chemotherapy using concomitant vincristine and adjuvant lomustine or cyclophoshamide, vincristine and cisplatin [22]. Overall survival was 86% and EFS was 81% at 5 years; a recent update described 10-year overall survival of 81.3% and EFS of 75.8% [22,23]. This was the first trial to show an excellent clinical outcome with a low-dose of CSI with chemotherapy.

Reduced Posterior Cranial Fossa Boost Volume

Even though reduced-dose CSI is effective, neurocognitive dysfunction continues to be a problem. Irradiation of the whole posterior fossa leads to irradiation of 35% of the whole brain and 60% of either temporal lobe [24]. A multicentral trial (St Jude Medulloblastoma - 96 study) using three-dimensional conformal radiotherapy evaluated a reduction in the dose to the posterior fossa with a boost to the surgical cavity, in an attempt to reduce neurocognitive sequelae. The radiation treatment composed of CSI with 23.4 Gy, conformal posterior fossa radiotherapy (35.0 Gy) and primary site radiotherapy (55.8 Gy) [25]. Disease control probability was comparable with patients who received entire posterior fossa irradiation, with an EFS rate of 83% at 5 years. One other important aspect was the reduction of 13% in the posterior fossa volume receiving 55 Gy and a statistically significant reduction in temporal lobe, hypothalamus, and cochlea dose.

A French study (MSFOP 98) evaluated hyperfractionated CSI (36 Gy in 36 fractions; 1 Gy twice daily) followed by a tumour bed boost (32 Gy in 32 fractions) without chemotherapy in patients with standard-risk medulloblastoma [26]. The boost volume consisted of tumour bed with a margin of 1.5 cm. The study reported a 6-year EFS of 75% with no relapses in the posterior fossa outside the boost volume. A pooled analysis of the MSFOP 98 and MSFOP 2007 trials, which used the same tumour boost volume, did not show an increased risk of posterior fossa relapse [27]. Moreover, the mean average decline of 2 points per year for full-scale intelligence quotient score was a promising result in terms of neurocognitive late effects.

ACNS 0331 compared low-dose (18 Gy) with standard-dose (23.4 Gy) CSI for children aged 3–7 years and involved-field radiotherapy with posterior fossa radiotherapy boost in all children with standard-risk medulloblastoma [28]. Although a reduced dose of CSI was associated with worse survival, there was no difference in 5-year PFS (82% versus 80%) and 5-year overall survival (84% versus 85%) with different boost approaches. This study suggested that 23.4 Gy CSI followed by a smaller volume boost (tumour bed plus 1.5 cm margin) is an effective treatment for standard-risk medulloblastoma.

Alternative Fractionations

In Europe, for children, the radiotherapy daily dose per fraction is between 1.5 and 2 Gy, whereas in the USA it is 1.8 Gy. Over the last decades there have been a number of attempts to compare different regimens of radiotherapy

dose and dose per fraction, to reduce the possible toxicity associated with CSI.

Hyperfractionated radiotherapy (HFRT) gives a smaller dose per fraction (1 Gy), with radiotherapy treatment administered twice each day, usually 6–8 h apart. HFRT has the potential to improve the therapeutic ratio by improving cell kill and reducing normal tissue toxicities. Carrie *et al.* [29] showed that the use of HFRT with a boost only to the tumour bed produces an overall survival similar to the standard posterior fossa boost.

The prospective HIT-SIOP PNET4 trial compared conformal fractionated CSI (23.4 Gy) and boost to the whole posterior fossa (54 Gy) versus HFRT CSI (36 Gy), posterior fossa treatment (60 Gy) and boost to the tumour bed (68 Gy) with concomitant chemotherapy using vincristine and adjuvant chemotherapy with cisplatin, lomustine and vincristine in patients with standard-risk medulloblastoma [30]. After a median follow-up of 5 years there were no statistical differences between the two treatment arms in EFS (77% in standard treatment versus 78% in HFRT) and overall survival (87% versus 85%). Severe hearing loss was not significantly different between the two arms. The 10-year EFS were similar (76% versus 78%; $P = 0.81$) [31].

Summary of Treatment

Based on the above studies (Table 1), the current radiotherapy treatment for standard-risk medulloblastoma is CSI of 23.4 Gy with a boost radiotherapy of 30.6 Gy followed by adjuvant chemotherapy with cisplatin, CCNU and vincristine. The boost volume could be reduced from the whole posterior fossa to the tumour bed with a 1–2 cm margin.

High-Risk Medulloblastoma

The current standard of care for high-risk medulloblastoma is based on the data from studies of metastatic medulloblastoma and consists of a combination of surgery, chemotherapy, and radiotherapy. Radiotherapy is given to a dose of 36 Gy to the cranial spinal axis followed by a boost to the posterior fossa of 18–20 Gy for a total dose of 54–56 Gy. In the SIOP PNET3 study, patients with M2/M3 disease received two courses of etoposide, carboplatin, cyclophosphamide and vincristine followed by CSI of 35 Gy and a posterior fossa boost. This study reported a 5-year EFS of 34.7% and overall survival of 43.9% [32]. Strategies to improve clinical outcome include the use of high-dose radiotherapy, concomitant chemoradiotherapy, and high-dose chemotherapy. Recently, there has been increasing enthusiasm for HFRT.

High-Dose Craniospinal Irradiation

The POG-9031 study evaluated the role of chemotherapy before CSI in children with high-risk medulloblastoma [33]. Patients are randomised to receive three cycles of preoperative chemotherapy using cisplatin and etoposide followed by radiotherapy ($n = 112$) or radiotherapy followed by chemotherapy ($n = 112$). Patients with M0–1 disease received CSI to a dose of 35.2 Gy in 22 fractions and those with M2–3 disease received 40 Gy in 25 fractions. The posterior fossa boost was 18 Gy in 10 fractions for patients with M0–1 disease and 14.4 Gy in eight fractions for patients with M2–3 disease. The 5-year EFS (66% versus 70%, $P = 0.54$) and overall survival (73% versus 76%, $P = 0.47$) were similar in both treatment arms. In this study, the 5-year EFS for patients with M2–3 disease was >60%.

In the St Jude Medulloblastoma-96 study, children with high-risk medulloblastoma received a risk-adapted radiotherapy (M0–1, CSI of 36 Gy and M2–3, 39.6 Gy; tumour bed boost to a total of 55.8 Gy) followed by four cycles of dose-intensive chemotherapy [34]. The 5-year EFS was 70% for patients with high-risk medulloblastoma and 66% for patients with metastatic disease.

In a preliminary study, the French group evaluated, in 24 children, the feasibility and effectiveness of tandem high-dose chemotherapy with stem cell support followed by craniospinal radiotherapy (25 Gy for M0 patients to 36 Gy for M1–3 according to time period) followed by a tumour bed boost to 54 Gy [35]. The 5-year EFS and overall survival rates were, respectively, 65% (95% confidence interval 45–81%) and 74% (95% confidence interval 51–89%). A prospective study with a larger cohort is ongoing.

Concurrent Chemoradiotherapy

A phase I/II COG 99701 study evaluated the role of 36 Gy CSI with boosts of 19.8 Gy to the posterior fossa and boosts to sites of metastatic disease in combination with daily pre-radiation carboplatin in patients with metastatic medulloblastoma and supratentorial primitive neuroectodermal tumour [36]. Following radiotherapy, patients received maintenance chemotherapy for 6 months with either cyclophosphamide and vincristine (regimen A: $n = 19$) or cyclophosphamide, vincristine and cisplatin (regimen B: $n = 22$). There was no statistically significant difference in 5-year PFS (71% versus 59%, $P = 0.36$) and overall survival (82% versus 68%, $P = 0.68$) between the two regimens. The use of carboplatin as a radiosensitiser is thus considered a promising strategy for patients with high-risk medulloblastoma.

Alternative Fractionations

As demonstrated in standard-risk patients there may be a benefit with HFRT in terms of similar overall survival and PFS and reduction of toxicity compared with a standard approach. A phase II study (CCG 9931) evaluated five alternating monthly cycles of chemotherapy (cisplatin, cyclophosphamide, etoposide and vincristine alternating with carboplatin and etoposide) followed by HFRT (40 Gy CSI with tumour boost to 72 Gy delivering 1 Gy twice daily) [37]. This study reported a 5-year EFS of 43% and a 5-year overall survival of 52%.

Gandola *et al.* [38] evaluated the role of hyperfractionated accelerated radiotherapy (HART) in 33 patients with a diagnosis of metastatic medulloblastoma. The treatment regimen consisted of postoperative chemotherapy with methotrexate, etoposide, cyclophosphamide and carboplatin in a 2-month schedule followed by HART (CSI dose of 39 Gy delivered as 1.3 Gy per

Table 1
A summary of important studies in medulloblastoma

Study	No. patients and age group	Treatment approach	Results and comments
Standard risk			
POG 8631/ CCG 923 [19,20]	126 (3–21 years)	Randomised comparison of reduced-dose (23.4 Gy in 13 fractions) with standard-dose (36 Gy in 20 fractions) CSI. Total posterior fossa dose 54 Gy. No chemotherapy	• 5-year EFS 67% versus 52% ($P = 0.080$) • 8-year EFS 67% versus 52% ($P = 0.141$) Premature closure of study due to inferior outcome in reduced-dose CSI arm
Packer *et al.* [21]	65 (3–10 years)	Feasibility study: concomitant weekly vincristine with CSI 23.4 Gy plus a posterior cranial fossa boost of 31.8 Gy. Adjuvant chemotherapy with lomustine, vincristine and cisplatin	• 3-year PFS 86% and 5-year PFS 79% First study to demonstrate efficacy of low-dose CSI with chemotherapy in standard-risk medulloblastoma
CCG A9961 [22,23]	421 (3–21 years)	CSI 23.4 Gy with posterior fossa boost to 55.8 Gy with concomitant weekly vincristine followed by randomisation into eight cycles of lomustine, cisplatin and vincristine or cyclophosphamide, vincristine and cisplatin	• 5-year EFS 82% versus 80%, 5-year overall survival 87% versus 85% EFS not affected by adjuvant chemotherapy regimen • 10-year EFS 76% and overall survival 81% for the whole cohort
Merchant *et al.* [25]	86 (3–21 years)	Prospective study: CSI 23.4 Gy, conformal posterior fossa radiotherapy 36 Gy and primary site radiotherapy 55.8 Gy and dose-intensive chemotherapy	• 5-year EFS 83% • Cumulative incidence of posterior fossa failure 4.9% First study to show that less than posterior fossa radiotherapy is as effective as entire posterior fossa radiotherapy
SIOP PNET4 [30,31]	340 (4–21 years)	Conformal fractionated CSI (23.4 Gy) and boost to the whole posterior fossa (54 Gy) versus hyperfractionated CSI (36 Gy), posterior fossa treatment (60 Gy) and boost to the tumour bed (68 Gy) with concomitant chemotherapy with vincristine and adjuvant chemotherapy with eight cycles of cisplatin, lomustine and vincristine	No difference in survival and incidence of severe hearing loss • 5-year EFS (77% in standard treatment versus 78% in HFRT) • 5-year overall survival (87% versus 85%) • 10-year EFS 76% versus 78%; $P = 0.81$ • Severe hearing loss was not significantly different between the two arms
ACNS 0331 [28]	464 (3–21 years)	3–21 years: randomised between posterior fossa radiotherapy (n = 237) and involved-field radiotherapy (n = 227) 3–7 years: CSI dose randomised between low-dose (18 Gy; n = 116) and standard dose (23.4 Gy; n = 110)	• Low-dose CSI associated with lower survival (5-year EFS 72% versus 83%) • No difference in 5-year PFS (82% versus 80%) and overall survival (84% versus 85%) between different boost volumes (involved field versus posterior fossa)
High risk			
SIOP PNET3 [32]	68 (2.8–16.4 years)	Two courses of etoposide, carboplatin, cyclophosphamide and vincristine followed by CSI of 35 Gy and a posterior fossa boost of 20 Gy in 12 fractions	• 5-year EFS: 35% • 5-year overall survival: 44%
St Jude Medulloblastoma-96 study [34]	48 (3–21 years)	Risk-adapted radiotherapy (M0–M1: CSI 36 Gy and M2–3: 39.6 Gy; tumour bed boost to a total of 55.8 Gy) followed by four cycles of dose-intensive chemotherapy	• 5-year EFS 70% for all high-risk • 5-year EFS 66% for metastatic disease ($n = 42$)
CCG 9931 [37]	124 (3–22 years)	Five alternating monthly cycles of chemotherapy (cisplatin, cyclophosphamide, etoposide and vincristine alternating with carboplatin and etoposide) followed by HFRT (40 Gy CSI with tumour boost to 72 Gy delivering 1 Gy twice daily)	• 5-year EFS 43% and 5-year overall survival 52%

Table 1 (*continued*)

Study	No. patients and age group	Treatment approach	Results and comments
Gandola *et al.* [38]	33 (3.2–34 years)	Postoperative chemotherapy with methotrexate, etoposide, cyclophosphamide and carboplatin in a 2-month schedule followed by HART (CSI dose of 39 Gy delivered as 1.3 Gy per fraction twice daily followed by a posterior fossa boost of up to 60 Gy delivered in 1.5 Gy fractions, given twice daily	• 5-year PFS 72% • 5-year overall survival 70%
COG 99701 [36]	161 (3.1–21.6 years)	CSI 36 Gy with a boost of 19.8 Gy to posterior fossa and to metastatic sites. Pre-radiation carboplatin (15–30 doses) with weekly vincristine. Maintenance chemotherapy: cyclophosphamide and vincristine (regimen A) or cyclophosphamide, vincristine and cisplatin (regimen B)	• No difference in 5-year PFS (71% versus 59%, $P = 0.36$) and overall survival (82% versus 68%, $P = 0.68$) between the two maintenance regimens
POG 9031 [33]	224 (3–12 years)	Randomised study: three cycles of preoperative chemotherapy using cisplatin and etoposide followed by radiotherapy (n = 112) or radiotherapy followed by chemotherapy (n = 112). M0–1 disease: CSI to a dose of 35.2 Gy in 22 fractions and posterior fossa boost was 18 Gy in 10 fractions. M2–3 disease: CSI 40 Gy in 25 fractions and boost dose of 14.4 Gy in eight fractions	• 5-year EFS (66% versus 70%, $P = 0.54$) and overall survival (73% versus 76%, $P = 0.47$) were similar with chemotherapy before or after radiotherapy • 3-year EFS for M2–3 disease was >60%
Taylor *et al.* [40]	34 (3–15 years)	Metastatic medulloblastoma: CSI 39.68 Gy in 1.24 Gy per fraction twice daily followed by whole posterior fossa boost of 22.32 Gy and spinal metastatic boost of 9.92 Gy with or without weekly concurrent vincristine followed by eight cycles of maintenance chemotherapy using vincristine, [AQ1] CCNU and cisplatin	• 3-year EFS 59% • 3-year overall survival 71%

CSI, craniospinal irradiation; HART, hyperfractionated accelerated radiotherapy; EFS, event-free survival; PFS, progression-free survival; HFRT, hyperfractionated radiotherapy.

fraction twice daily followed by a posterior fossa boost of up to 60 Gy delivered in 1.5 Gy fractions, given twice daily). After a median follow-up of 82 months, the 5-year PFS and overall survival were 72% and 70%, respectively. However, similar impressive survival rates could not be replicated in a series of 34 patients treated with a similar regimen in the UK [39]. In this retrospective series, at a median follow-up of 45 months, the estimated overall survival was 56%. Another study evaluated the role of HART (CSI 39.68 Gy in 1.24 Gy per fraction twice daily followed by whole posterior fossa boost of 22.32 Gy and spinal metastatic boost of 9.92 Gy) with or without weekly concurrent vincristine followed by maintenance chemotherapy using vincristine, CCNU and cisplatin in 34 patients with metastatic medulloblastoma [40]. At a median follow-up of 4.5 years, the 3-year EFS and overall survival were 59% and 71%, respectively.

Summary of Treatment

Based on the above studies (Table 1), the current radiotherapy treatment for high-risk medulloblastoma is CSI of 36–39.6 Gy with a posterior cranial fossa boost to a dose of 54–55.9 Gy in 1.8 Gy fractions. Patients with gross spinal disease receive boost radiotherapy to a total dose of 50.4 Gy in 1.8 Gy fractions. After radiotherapy, patients will receive maintenance chemotherapy. Current clinical trials in high-risk medulloblastoma are exploring risk-adapted approaches based on molecular genetics (see below) to improve clinical outcome. A European randomised high-risk multi-stratified trial evaluating the role of high-dose chemotherapy and the role of a hyperfractionated accelerated regimen is being planned.

Timing of Radiotherapy

In the SIOP PNET4 study, the 5-year EFS of a group of patients ($n = 30$) whose radiotherapy was delayed beyond 49 days was significantly reduced compared with the group who started radiotherapy earlier (0.67% versus 0.81%; $P = 0.04$) [30]. The current recommendation is that post-operative radiotherapy should not be delayed beyond 40 days after surgery and ideally should be started within 28 days of surgery.

Infant Medulloblastoma

About 50% of medulloblastoma are diagnosed in children younger than 5 years [41]. About 30% of infant medulloblastoma presents with cranial or spinal metastases at diagnosis. A chemotherapy only approach is generally adopted in children aged younger than 3–5 years to delay or avoid the need for radiotherapy [7]. However, a chemotherapy only approach generally yields a 5-year EFS of 30–50% [10,42–44]. The role of radiotherapy for infant medulloblastoma remains unclear.

The Baby-POG study of postoperative chemotherapy and delayed radiotherapy in 62 children aged younger than 3 years with medulloblastoma reported a 5-year PFS of 31.8% and a 5-year overall survival of 39.9% [45]. The CCG 9921 study in 92 children younger than 3 years, including 61 non-metastatic patients, showed that disease control could be obtained with intensive postoperative chemotherapy alone, avoiding radiotherapy, especially for low-stage patients with a 5-year EFS of 41% and a 5-year overall survival of 54% [42]. In this study, radiotherapy was given only to children with residual tumour after induction chemotherapy, with metastatic disease or in case of relapse. In the BBSFOP French study, children younger than 5 years were treated with chemotherapy alone and focal radiotherapy with high-dose chemotherapy was given only as a salvage treatment [46]. This study reported a 5-year EFS of 29%, but with a better 5-year overall survival of 70% for children with low-stage medulloblastoma, illustrating the role of focal radiotherapy with high-dose chemotherapy as an effective salvage treatment. The COG P9934 study reported an improvement in 4-year EFS (50%) and overall survival (69%) with the addition of focal radiotherapy in completely resected medulloblastoma in children younger than 5 years compared with the previous POG 9233 trial [44]. In the HITSKK ′92 study ($n = 43$), children younger than 3 years with medulloblastoma were treated with postoperative chemotherapy together with intraventricular methotrexate [43]. Radiotherapy was given only if there was residual disease and children were older than 18 months at the end of chemotherapy. The 5-year PFS was 82% and the 5-year overall survival was 93% for children who had a complete resection. Magnetic resonance imaging showed asymptomatic leukoencephalopathy in 19 of 23 children and the mean intelligence quotient was also lower than that of healthy controls, suggesting that intraventricular methotrexate could cause neurological side-effects.

In a meta-analysis of 260 children younger than 5 years, Rutkowski *et al.* [47] reported an excellent 8-year EFS of 86% and overall survival of 95% in desmoplastic/nodular medulloblastoma and medulloblastoma with extensive nodularity. These data were confirmed in the German trial HIT 2000 with a 5-year EFS of 90% for patients with non-metastatic desmoplastic/nodular medulloblastoma/medulloblastoma with extensive nodularity [48]. The recently reported SJYC07 study treated 76 children aged <3–5 years based on three risk groups [49]. Children with low-risk disease (non-metastatic desmoplastic medulloblastoma) received systemic therapy only, the intermediate-risk group (non-metastatic classic/anaplastic medulloblastoma) received systemic treatment and focal radiotherapy and the high-risk group (metastatic medulloblastoma) received intensified chemotherapy with or without CSI. Although the 5-year EFS was 31.3% for the whole cohort, children with SHH medulloblastoma had an improved 4-year EFS of 51.1% compared with 8.3% for group 3 and 13.3% for group 4 ($P < 0.0001$). Further analysis revealed two distinct methylation subgroups within the SHH group: iSHH-I (32%) and iSHH-II. The 5-year EFS was significantly better for the iSHH-II subgroup compared with the iSHH-I subgroup (75% versus 28%; $P = 0.0028$). Future studies of infant medulloblastoma would incorporate risk stratification based on molecular profiling [8].

Recent Advances in Radiotherapy Techniques

Target Volume Delineation for Craniospinal Irradiation

Delineation of the whole subarachnoid space as clinical target volume for CSI is important in ensuring the optimal clinical outcome. There is clear evidence that inadequate coverage of the cribriform plates, the temporal lobes, and the inferior aspect of the thecal scan can lead to an increased risk of recurrence [29,50–52]. A recent study highlighted that the cerebrospinal fluid flows beyond the inner table of the skull along the ‘dural sheaths’ of cranial nerves [53]. Although traditional CSI using field-based techniques adequately covers these areas, highly conformal radiotherapy techniques may inadvertently miss parts of the clinical target volume, if these structures are not carefully delineated [54]. The SIOPE Brain Tumour Radiotherapy Group has, therefore, published a consensus guideline on craniospinal target volume delineation for high-precision radiotherapy [55].

Optimal Radiotherapy Technique and Radiotherapy Quality Assurance

High-precision radiotherapy techniques, such as IMRT, either with static fields or volumetric modulated arc therapy, such as TomoTherapy® CSI, and proton therapy, improve dose conformity and decrease integral dose and dose to selected organs at risk. A recent comparison of different techniques of craniospinal radiotherapy across 15 European centres showed that highly conformal radiotherapy techniques have dosimetric advantages compared with three-dimensional-conformal radiotherapy and proton therapy often leads to the lowest mean dose to organs at risk [56]. For most organs, ranges in mean doses were wide and overlapping between techniques, making it difficult to recommend one radiotherapy technique over another. Figure 1 shows the dose distribution with photon and proton beam techniques.

In the context of the implementation of new radiotherapy techniques, dose de-escalation for low-risk medulloblastoma and a new schedule of high-dose

Fig 1. Dose distribution of craniospinal irradiation with (A) photon and (B) proton beam techniques.

chemotherapy in combination with radiotherapy, it is crucial to carry out quality controls of target volume delineation and treatment plans. Indeed, the French experience of quality control has shown a reduction in the rate of relapses by detecting and improving major deviations of field position before the start of treatment [26]. Radiotherapy quality assurance is therefore essential to ensure that the technique of radiotherapy is uniform and does not adversely affect survival or late effects.

Proton Beam Therapy

Proton beam therapy has the physical advantage of delivering the lowest possible dose to normal tissues adjacent to tumour and therefore has the potential to reduce treatment-related toxicities. A phase II single-arm study of 59 patients with medulloblastoma treated with proton therapy showed a 5-year PFS of 80% and overall survival of 83% [57]. The 5-year cumulative rate of grade 3–4 hearing loss was 16%. Full-scale intelligence quotient decreased by 1.5 points (95% confidence interval 0.9–2.1) per year after a median follow-up of 5.2 years. A retrospective multi-institute study reported no difference in 6-year relapse-free survival (78.8% versus 76.5%), overall survival (82% versus 87.6%) and patterns of failure between proton ($n = 45$) and photon ($n = 43$) therapies [58]. In another retrospective study of children with medulloblastoma ($n = 84$), cochlear doses were lower in the group treated with protons ($n = 38$), but grade 3–4 toxicities were similar with both protons and photons ($n = 46$) [59]. The PNET4 study evaluated ototoxicity based on a central review of the latest audiograms using two methods: the German Hirntumour study (HIT) grading system and the Brock method. Using the HIT grading system, grade 3–4 ototoxicity was seen in 15% with standard dose radiotherapy and 17% with HFRT, which are comparable with the phase II proton study. Using the Brock method, the incidence of grade 3–4 ototoxicity was 4% in both arms of the PNET4 study. Although a clear benefit for proton therapy has yet to be shown, a randomised clinical trial is unrealistic and a robust prospective outcome evaluation is encouraged.

Outcome, Patterns of Recurrence and Late Effects

With modern treatment, the outcome in medulloblastoma is excellent, with a 5-year PFS of 70–80%. Recent studies reported outcome based on molecular subgroups (Table 1). For example, the WNT group and non-metastatic group 4 with whole chromosome 11 loss or whole chromosome 17 gain have the best outcome of >90% survival, whereas group 3 with metastases or SHH with TP53 mutation have the least survival of <50% [60]. About 30% of children will have a relapse, which is the most common cause of death in patients with medulloblastoma [52,61–63].

Recurrences may occur in either a single compartment or in multiple sites [64,65]. A phase III trial by Packer *et al.* [22] reported 73 treatment failure events. In 23 patients a brain or spinal metastasis alone was reported. In 20 patients there was posterior fossa progression alone and in 16 patients there were posterior fossa and brain/spinal metastasis. The median time of progression or relapse differs with M staging; in M0, M1 and M2/3 subgroups they were 2.0 years, 1.6 years and 1.1 years, respectively ($P = 0.028$) [66]. Although the majority of recurrences are within 5 years of primary surgery, 12% of recurrences occur after 5 years (late relapse). The patterns of disease may vary according to the time of recurrence. For example, the CCG 9931 trial reported the pattern of progression as local in 57% and distant in 43% with a late relapse ($n = 7$) [23]. By contrast, in 61 patients who relapsed earlier than 5 years from diagnosis, 84% presented with distant relapse (with or without local recurrence) and 16 % with only local recurrence ($P = 0.029$). Spinal involvement, alone or in combination with a local relapse, was only seen in patients with early relapse.

The patterns of relapse after proton therapy are not different from photon therapy. In a study of 109 patients treated with proton therapy for medulloblastoma, 16 had a relapse at a median follow-up of 39 months [62]. Isolated single compartment failures occurred in 11 patients (four in the spine, four in the supratentorial brain and one in the posterior fossa) and the relapses were in multiple sites in the remaining five patients.

The common late-effects after CSI include cataracts, patchy alopecia, endocrine dysfunction, impaired growth and bone development, neurocognitive dysfunction, and ototoxicity. Less common effects include second neoplasms, cerebrovascular events, and cardiac and pulmonary toxicities [67]. Growth hormone deficiency is the most common (40–80%) endocrine dysfunction and can develop after a dose as low as 18 Gy. About 70% of long-term survivors can

develop some element of neurocognitive dysfunction [2]. Growth hormone deficiency and early puberty can contribute to impaired growth, whereas radiotherapy can directly impair vertebral growth leading to reduced sitting height.

Although recurrence is the most common (60%) cause of death in long-term survivors, second neoplasms cause 12% of deaths [68]. A recent meta-analysis of six studies (total 1114 patients) reported a 10-year cumulative incidence of 6.1% for secondary neoplasms [69]. Fifty-eight per cent of secondary neoplasms were malignant, with high-grade glioma being the most common (45%). The most common secondary benign neoplasm was meningioma (67%). A significant proportion of secondary neoplasms occur in the areas of radiotherapy exit dose. It is not clear whether widespread adoption of proton therapy for children with medulloblastoma might lead to a decline in second neoplasms.

Management of Recurrence

There is usually no curative treatment for recurrences after a standard treatment involving CSI. Further surgical resection followed by standard chemotherapy or high-dose chemotherapy with autologous stem cell transplantation and re-irradiation using conventional radiotherapy, brachytherapy, and radiosurgery were evaluated. The prognosis in recurrent disease was poor, with a reported 2-year overall survival of 15–25% [23,63].

Recently there have been reports of clinical efficacy with re-irradiation [70–73]. In an early study where patients were treated with either fractionated stereotactic radiotherapy ($n = 21$) to a dose of 24 Gy (median dose per fraction 4 Gy, range 1.8–7.5 Gy) or radiosurgery ($n = 8$) to a single dose of 15 Gy (range 10–18 Gy) after a previous total tumour dose of 54 Gy, the overall tumour control rate was 89.7%, at a mean follow-up of 88.5 months [74]. Another study of 13 patients who received re-irradiation to a mean cumulative dose of 84 Gy reported 5-year PFS of 48% and overall survival of 65% [70]. In a more recent retrospective review, 14 of 38 children with recurrent medulloblastoma received radiotherapy as part of salvage treatment [71]. The median overall survival for 11 standard-risk patients was 5.39 years (range 0.3–11.9 + years) and for three high-risk patients was 4.94 years (0.1–6.6 + years). The 10-year overall survival from initial diagnosis was 45% for standard-risk medulloblastoma patients treated with re-irradiation compared with 0% for patients who did not receive re-irradiation. However, given the limitations of these studies, including the small number of patients treated, the routine applicability of re-irradiation treatment must be considered with caution and further multicentric prospective studies are needed to evaluate the role of re-irradiation for recurrent medulloblastoma [75].

Current Clinical Trials

During the past few years, genome-wide transcriptional profiling has led to the identification of distinct molecular subgroups (Table 2). The revised World Health Organization classification published in 2016 recognised the following groups: Wnt, SHH-TP53 wild-type, SHH_TP53 mutant and non-Wnt/non-SHH group [1]. The molecular characterisation is still ongoing to better identify the considerable heterogeneity [76–78]. A consensus on risk stratification has been recently published [60]. Future trials may incorporate the different clinico-pathological features such as differential sensitivity to systemic therapy and prognosis of these subtypes to individualise treatment approaches (Figure 2).

Table 2
A summary of characteristics of different subtypes of paediatric medulloblastoma

WNT group (11%)	SHH group (p53 mutant) (30%)	Group 3 (non-WNT, non-SHH) (15%)	Group 4 (non-WNT/non-SHH, glutamatergic) (35%)
• 0–12 years	• Bimodal age (<3 years and >16 years)	• Exclusively in children, male infants	• All ages, but rare in infants • Male > female (3:1)
• Typically midline tumour	• Hemispherical in location	• 0% with metastasis at diagnosis	
• Vascular tumours that lacks blood–brain barrier and, therefore, highly sensitive to chemotherapy, even if does not cross blood–brain barrier	• Rarely presents with disseminated disease	• Sensitive to PI3 kinase and MTOR inhibitors • Sensitive to pemetrexed and gemcitabine	
• 5-year survival >90% • PNET4 study showed most favourable outcome but higher risk of relapse in children aged > 16 years	• 5-year survival 75%	• 5-year survival 50%	• 5-year survival 75–90%
• Current trials: aim to minimise radiotherapy with standard chemotherapy, e.g. SIOP PNET5 and SJMB12	• Current trial: SJMB12 study evaluating lower radiotherapy dose and removing alkylators	• Clinical trial: SJMB12 study: evaluating role of pemetrexed, gemcitabine, VCR, cisplatin and cyclophosphamide	• Clinical trial: SIOP PNET5

PI3: Phosphoinositide 3-kinase, MTOR:Mammalian target of rapamycin , VCR: vincristine.

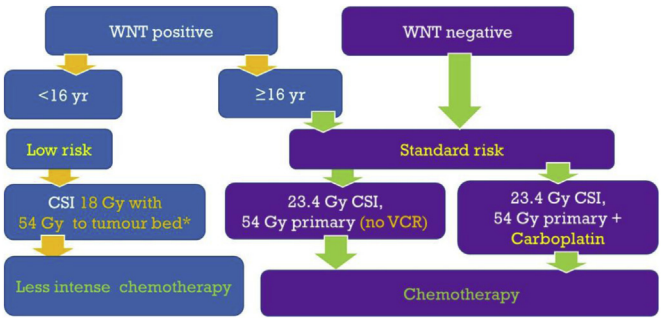

Fig 2. Simplified study schema for the SIOP PNET5 trial.

Conclusion

CSI continues to be the cornerstone of the treatment of medulloblastoma. During the last decade different fractionated radiotherapy regimens and innovative technologies, such as IMRT and proton therapy, have been studied to try to reduce treatment toxicities. Currently, the 5-year EFS is more than 80% for standard-risk medulloblastoma and up to 70% for high-risk medulloblastoma. New clinical trials are mandatory, based on genetic stratification, to find the correct balance between tolerance and overall survival. Re-irradiation may be considered as a therapeutic option in locally recurrent disease, but more studies are needed to establish its appropriate role.

Conflict of interest

None declared.

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