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Treatments for children with newly diagnosed medulloblastoma - A systematic review of randomised controlled trials

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Introduction

Medulloblastoma (MB) is the most common malignant brain tumour in children and young people accounting for 15-20% of all brain tumours in children. The median age of diagnosis is 7 years but it can also occur during adulthood (1).

MB is a highly heterogenous disease. In the 2021 World Health Organization (WHO) classification of central nervous system tumours, MB is categorised using both molecular and histological criteria (1, 2).

The standard treatment approach for MB typically involves neurosurgery with maximal safe surgical resection followed by craniospinal irradiation (CSI) and chemotherapy. For treatment purposes, patients are initially divided by age -those younger than 3 years and those aged 3 years and older. Each age group is further subdivided into low-risk, standard-risk and high-risk categories. This standard treatment approach results in long-term survival rates of 60-80% (1).

Children who survive MB treatment are at risk of long-term complications including neurological and neurocognitive impairments. There is a growing interest in refining treatment strategies-particularly in reducing the neuropsychological burden associated with CSI-while continuing to maintain or improve survival outcomes.

Objective

The aim of this systematic literature review (SLR) is to provide a comprehensive overview of randomised controlled trials (RCTs) assessing therapies in newly diagnosed MB.

Method

We conducted a SLR following PRISMA guidelines, to identify RCTs assessing treatments in children (aged 0 to 21 years) with newly diagnosed MB. Eligibility criteria are shown in Table 1.

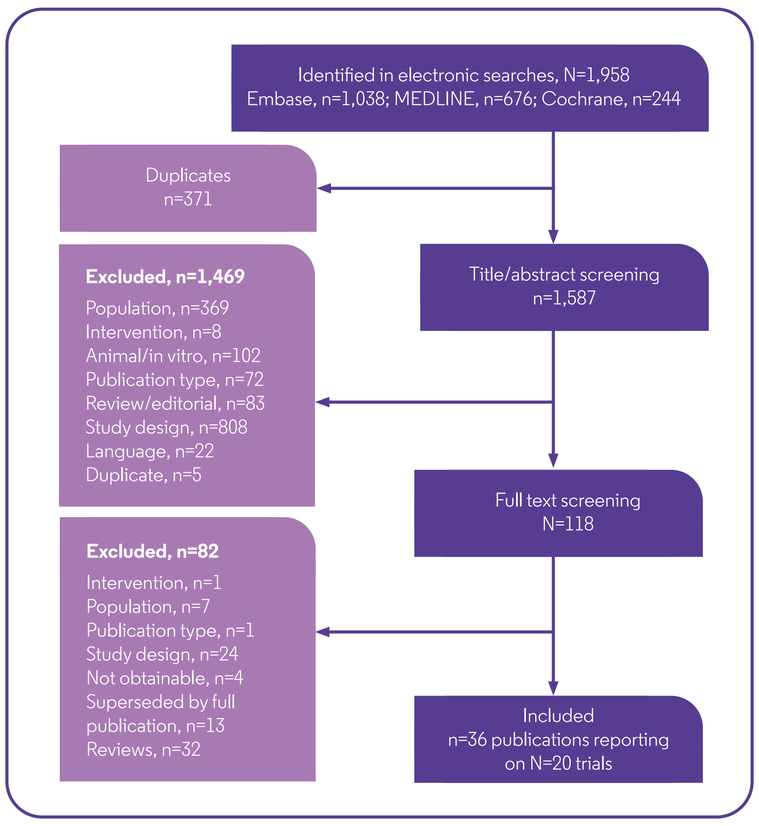
Table 1: Eligibility criteria for the SLR

Criteria	Include	Exclude
Population	Children (aged 0 to 21 years) diagnosed with MB receiving treatment at first-line (newly diagnosed) • Any risk groups (low-risk/ favourable-risk, standard-risk, high-risk) or molecular disease groups (WNT, SHH, Group 3, Group 4, non-WNT/ non-SHH)	• Patients with any other disease • Adults >21 years diagnosed with MB • Children (< 18 years) diagnosed with MB receiving treatment as second-line or above (recurrent MB). • Studies reporting outcomes on a mixed aged population (children and adults > 21 years) of patients diagnosed with MB where data for the children sub-group (aged 0 to 21 years) are not reported separately.
Intervention / Comparator	• Interventions evaluated alone or in combination with each other versus any other intervention including any type of: • Surgery • Radiotherapy • Chemotherapy • Gene therapy • Oncolytic virus	Interventions not directed to treat MB (interventions aimed to treat other aspects related to the disease i.e. side-effects of treatments)
Outcomes	• Clinical efficacy (event-free survival [EFS], progression-free survival [PFS] and overall survival [OS]) • Safety • Neuropsychological outcomes • QoL, patient reported outcomes	Any outcomes not of interest
Study design/ publication type	• RCTs any phase • Full publications • Conference abstracts	• Animal/*in vitro* studies • Editorials • Reviews • Letters • Non-randomised trials • Case studies • Case reports • Observational studies
Date of publication	No restriction	
Language of publication	English language only	Other non-English studies

Results

Searches were run on 9 June, 2025. A PRISMA diagram with details of the number of records identified, and selection of publications, is shown in Figure 1.

Figure 1- PRISMA diagram

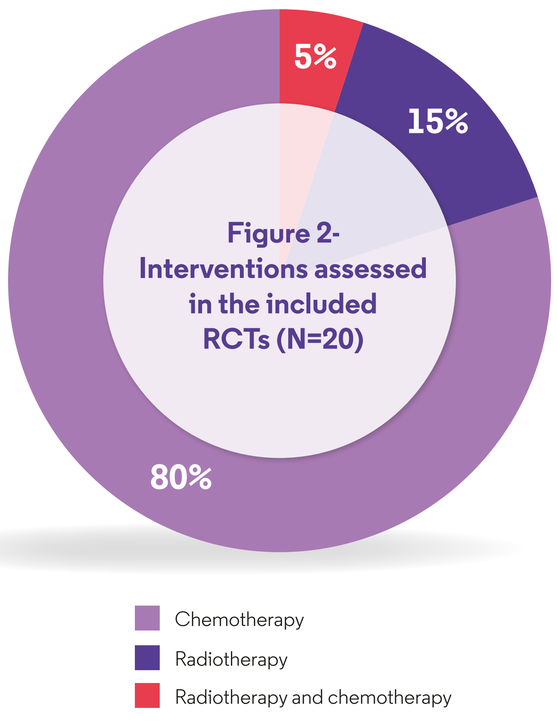


In total, 36 publications reporting on 20 trials were included in the SLR (3-38). Of these, 16 trials (80%) evaluated chemotherapy interventions (3, 8-11, 16, 17, 19, 22, 23, 26, 30-33, 38), 3 trials (15%) assessed radiotherapy (7, 18, 20) and 1 (5%) investigated a combination of both (4). There were no RCTs assessing surgery or gene therapies.

The sample size ranged from 16 (26) to 464 (20) (median 183.5). Length of follow-up was reported in 16 studies ranging from 2.5 (16) to 10 years (8).

Age eligibility criteria varied across the trials. Eleven trials included patients older than 3 years with upper age limits ranging from 15 to 21 years (3, 7, 9, 16, 18-20, 22, 23, 32, 33). Seven trials included patients younger than 3 years, with upper limits between 13 and 21 years (4, 8, 10, 17, 26, 31, 38). Two trials focused specifically on infants, defined as younger than 36 months (11, 30).

Of the 10 studies that defined population risk, 5 focused on high-risk/high-stage patients (3, 19, 22, 32, 38), 3 on average-risk/standard-risk patients (18, 20, 23), 1 on low-stage patients (7) and 1 included both high-risk and low-risk groups (4).



Of the 4 trials assessing radiotherapy interventions, 2 compared reduced-dose with standard-dose radiotherapy (4, 7), 1 compared hyperfractionated radiotherapy (HFRT) with standard radiotherapy (18) and 1 trial compared 2 radiotherapy interventions: involved field radiation therapy (IFRT; radiation to tumor bed) versus posterior fossa radiation therapy (PFRT; radiation to the entire posterior fossa) and low dose versus standard-dose CSI (20). Details of the radiotherapy interventions evaluated in the included studies are shown in Table 2.

Table 2- Radiotherapy interventions assessed in the included studies

Ref. ID	Trial name	Risk category (as defined by authors)	Intervention	Comparator
Michalski-2021(20)	ACNS0331	Average risk	Involved field radiation therapy (IFRT) (all patients aged 3-21) Low-dose CSI, 18 Gy (patients aged 3-7)	Posterior fossa radiation therapy (PFRT) (all patients aged 3-21) Standard-dose CSI, 23.4 Gy (patients aged 3-7)
Bailey-1995*(4)	SIOP II	High-risk and Low-risk	Low-dose radiotherapy, 25 Gy (Low-risk)	Standard-dose radiotherapy, 35 Gy (Low-risk)
Lannering 2012(18)	HIT-SIOP PNET 4	Standard-risk	Hyperfractionated radiotherapy (HFRT)	Standard radiotherapy
Deutsch-1996(7)	POG 8631/CCG 923	Low-stage	Reduced dose radiotherapy: 2,340 cGy	Standard dose radiotherapy: 3,600 cGy

*The SIOP II trial evaluated chemotherapy and radiotherapy interventions. The radiotherapy interventions described in the table above only applied to Low-risk patients. In addition to this randomisation, all patients (High-risk and Low-risk) were randomised to two arms: chemotherapy before radiotherapy and no chemotherapy before radiotherapy.

The chemotherapy interventions evaluated included: chemotherapy before radiotherapy versus no chemotherapy before radiotherapy (5 studies) (4, 16, 32, 33, 38), adjuvant chemotherapy compared to no adjuvant chemotherapy (5 studies) (3, 8, 17, 26, 31). The remaining 7 studies investigated different drugs, dosages and treatment regimens (9-11, 19, 22, 23, 30).

Five-year OS rates were reported in 11 studies (8, 11, 17-20, 23, 31-33, 38) ranging from 43% (11) to 86% (18, 23). Ten-year OS rates were reported in 3 studies (24, 28, 31) and these were: 45% (31), 78% (28) and 81.3% (24). Five-year EFS rates (as defined by authors) were reported in 12 studies (4, 8, 11, 17-20, 23, 31-33, 35) and ranged from 32% (11) to 82.4% (20). Two studies (19, 20) reported EFS and OS rates by molecular sub-groups: SHH (Sonic Hedgehog), WNT (Wingless), MB-Group 3 and MB-Group 4.

Details of grade ≥3 adverse events were reported in 9 studies (8, 11, 16, 17, 19, 20, 23, 33, 35). The most commonly reported grade ≥3 adverse events were hematological toxicity. Other adverse event commonly reported was ototoxicity.

Neurocognitive and quality of life outcomes were reported in 8 studies (5, 6, 13, 19-21, 27, 36). Key findings include a significant decline over time in both intellectual and academic performance, with greater deterioration observed in children diagnosed at a younger age.

Overall, the reporting of details to assess risk of bias was unclear. The method of randomisation and allocation concealment was only reported in two studies (4, 33). Due to the nature of interventions blinding of participants and care providers was not possible and all the studies were open label. Blinding of outcome assessors for EFS was only reported in one study (11). Intention-to-treat analysis was conducted in 6 studies (4, 11, 18, 23, 30, 31). Finally, reporting of lost to follow-up was only reported in three studies (10, 30, 32).

Discussion

We conducted a SLR following the PRISMA guidelines to identify RCTs assessing therapies in children with newly diagnosed MB. In total, 20 studies were identified evaluating chemotherapy and radiotherapy interventions. There was a high heterogeneity across studies in terms of interventions and population including variations in age and risk groups. Only two studies focused specifically on infants (<36 months old). Two studies reported outcome data by MB molecular sub-groups. Key findings from neurocognitive outcomes showed that children who survive MB are at risk of significant decline in both intellectual and academic performance.

Conclusion

This SLR provides an overview on how treatment for MB has evolved with therapies being stratified for different risk-groups with the aim to optimise survival outcomes while minimising the neuropsychological burden associated with the therapies. The evidence from RCTs in children with newly diagnosed MB is limited. More RCTs are needed to evaluate the efficacy of therapies in this field.

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