



Reduced versus standard dose craniospinal irradiation with chemotherapy to treat medulloblastoma

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Abstract

Background: Current treatment for medulloblastoma involves craniospinal irradiation (CSI) with a radiation boost to the posterior fossa and adjuvant chemotherapy following surgical resection. Due to neurotoxic effects of CSI—particularly its impact on cognitive function and intelligence quotient (IQ)—recent efforts have focused on reducing CSI dosage. This systematic review compares standard-dose CSI (SDCSI) versus low-dose CSI (LDCSI) in terms of relapse rate, event-free survival (EFS), progression-free survival (PFS), and overall survival (OS).

Methods: A systematic search was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two reviewers independently screened studies for eligibility and extracted data on study design, patient demographics, CSI dosage, chemotherapy regimens, EFS, OS, relapse rates, and reported side effects.

Results: Out of 749 identified studies, 24 met the inclusion criteria for this review. Reported 5-year EFS ranged from 27.3% to 83%, and 5-year OS ranged from $41 \pm 8\%$ to $94.7 \pm 3.4\%$. Commonly reported adverse effects included hematologic toxicity, secondary malignancies, disease progression, nausea/vomiting, and cognitive impairment. IQ outcomes ranged from 71 to 98.6, with studies consistently showing that LDCSI was associated with a smaller decline in IQ compared to SDCSI. Factors such as age, molecular subgroup, and histological features were identified as important variables for risk stratification.

Discussion: LDCSI combined with chemotherapy may provide sufficient treatment efficacy for medulloblastoma while mitigating neurocognitive decline. Future research should focus on optimizing chemotherapy regimens and refining treatment stratification based on molecular and histological subtypes, particularly in standard- versus high-risk patients.

Keywords

medulloblastoma, craniospinal irradiation (CSI), chemotherapy, systematic review, overall survival, progression-free survival, event-free survival



Introduction

Medulloblastoma is the most common malignant brain tumor in children and adolescents, accounting for over 60% of embryonal tumors in patients aged 0–19 years, with peak incidence occurring at age 9 or younger [1]. Current standard-of-care treatment includes surgical resection followed by craniospinal irradiation (CSI)—typically 23.4 Gy for standard-risk patients and 36 Gy for high-risk patients—combined with a posterior fossa boost of 54–56 Gy [2].

Although CSI is a cornerstone of treatment, its neurotoxic effects—particularly the potential for decreased intelligence quotient (IQ) and cognitive impairment—have driven efforts to reduce CSI doses [3]. However, a landmark randomized controlled trial demonstrated that reducing CSI alone led to significantly increased relapse rates, resulting in the abandonment of that approach [4]. Subsequent strategies have sought to reduce CSI in conjunction with adjuvant chemotherapy [5, 6], decreased radiation boosts [7, 8], or hyperfractionation [9], though outcomes have varied.

This systematic review aims to determine whether reduced-dose CSI, with or without chemotherapy, yields comparable survival outcomes to standard-dose CSI (SDCSI). Specifically, we examine how different medulloblastoma treatment strategies impact event-free survival (EFS), progression-free survival (PFS), overall survival (OS), and adverse effect profiles, with particular attention to cognitive outcomes.

Materials and methods

Search strategy

A systematic literature search was conducted using PubMed and Embase on June 11, 2024, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. No filters or restrictions were applied. Studies were included if they evaluated radiation therapy (with or without chemotherapy) and reported EFS, PFS, or OS. The protocol was registered in PROSPERO (CRD42024557864) and made publicly available. Two independent reviewers (IH and MG) screened all titles, abstracts, and full texts for eligibility. Discrepancies were resolved by a senior author.

Quality assessment

Study quality was assessed using the methodological index for non-randomized studies (MINORS) checklist. The MINORS items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate), with a maximum possible score of 16 for non-comparative studies (from eight categories) and 24 for comparative studies (from 12 categories). The methodological quality of each study was determined based on the overall MINORS score. The methodological quality was considered low if the MINORS score was 0 to 8 (0 to 16 for comparative studies), moderate if scored 9 to 12 (17 to 20 for comparative studies), and high if scored 13 to 16 (21 to 24 for comparative studies).

Data extraction

For each included study, data were extracted on study design, author, trial type, country, study duration, number of participants, sex, age range, radiation and chemotherapy regimens, EFS, PFS, OS, treatment-related toxicities, relapse, mortality, and IQ/cognitive outcomes. Microsoft Excel (Office 2011, Microsoft Corporation) was used for data organization and synthesis.

Results

Study selection

The initial search identified 749 studies, with 167 duplicates removed. The remaining 582 articles were screened by title and abstract, resulting in 200 full-text articles for review. After applying inclusion/exclusion criteria, 24 studies were included in the final analysis. The PRISMA flowchart (Figure 1) illustrates the selection process.

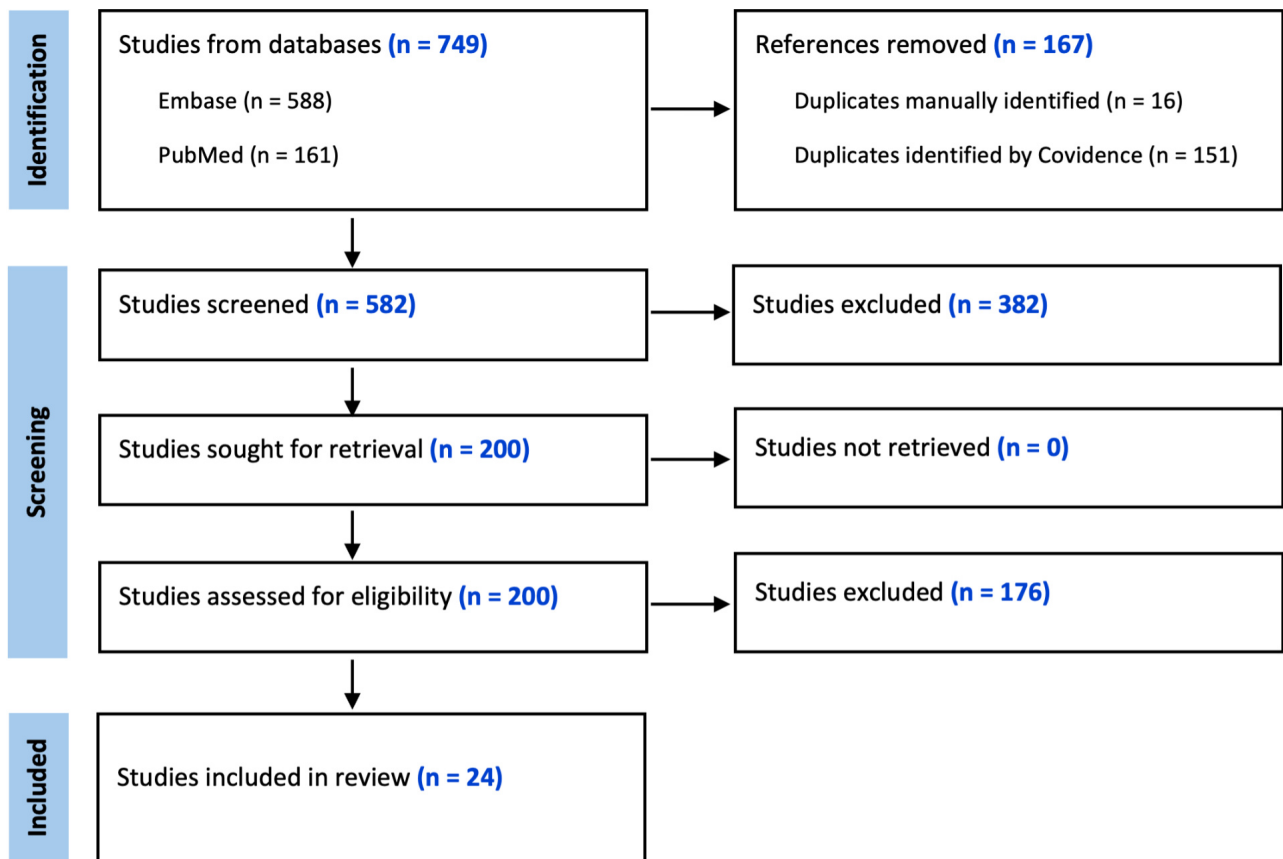


Figure 1. Flowchart of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Adapted from [10]. © 2021 Page MG, et al. Licensed under a CC BY 4.0.

Methodological and quality index

The mean ± standard deviation (range) of the MINORS scores for comparative studies discussing outcomes of survival on radiation-treated medulloblastoma was 18.5 ± 1.3. For noncomparative studies, the mean MINORS score was 13.7 ± 1.5. The methodological quality was high for 11 studies, moderate for 12 studies, and low for 1 study. Overall, the methodological quality was 16.3 ± 2.8 for all 24 studies. The total MINORS score is reported for each study in Figure 2.

Study characteristics and patient demographics

Levels of evidence (LOE) for each study, assessed using the Oxford Centre for Evidence-Based Medicine (OCEBM) framework [11], included 3 Level II, 19 Level III, and 2 Level IV studies. The included studies were published between 1994 and 2022 [5, 7, 8, 12–32]. Of the 24 studies, 22 were prospective [5, 7, 8, 12–25, 27–29, 31, 32] and 2 were retrospective [26, 30]. The cumulative sample included 2,463 patients (~61% male, ~39% female), with ages ranging from 0.2 to 60 years. A detailed summary is provided in Table 1.

Table 1. Study parameters, levels of evidence (LOE), and patient demographics.

Study	Method	LOE	Country	Study range	Number of patients (M/F)	Age range [#] (average)
Allen et al., 2009 [12]	Prospective trial	III	USA	NR	124 (80/44)	3–20 (7.8)
Ashley et al., 2012 [13]	Prospective trial	III	USA	Oct 2000–Jun 2006	74 (40/34)	0.6–3 (NR)
Carrie et al., 2009 [14]	Prospective trial	III	France	Dec 1998–Oct 2001	55 (NR)	5–18 (9.9)
Christopherson et al., 2014 [15]	Prospective single-institutional trial	III	USA	1963–2008	53 (38/15)	1.2–18.5 (7.1)
Dufour et al., 2021 [16]	Prospective multi-institutional trial	III	France	Jan 2009–Feb 2021	51 (34/17)	5–19 (8)

Table 1. Study parameters, levels of evidence (LOE), and patient demographics. (continued)

Study	Method	LOE	Country	Study range	Number of patients (M/F)	Age range [#] (average)
Gajjar et al., 2006 [5]	Prospective non-randomized trial	III	USA	Oct 1996–Aug 2003	134 (90/44) SR: 86 (53/33) HR: 48 (37/11)	3–21 (7.6) SR: 3.1–20.2 (8.7) HR: 3.1–17 (6.6)
Gupta et al., 2022 [17]	Prospective trial	III	India	Aug 2006–Feb 2010	20 (14/6)	5–14 (8)
Jakacki et al., 2012 [18]	Prospective non-randomized trial	III	USA	Mar 1998–Nov 2004	161 (92/69)	3.1–21.6 (8.7)
Lannering et al., 2012 [19]	Prospective randomized trial	II	Germany*	Jan 2001–Dec 2006	338 (211/127)	4–21 (NR)
Lee et al., 2020 [20]	Prospective trial	III	Korea	Oct 2005–Apr 2018	40 (23/17)	3.8–31.5 (8.5)
Massimino et al., 2012 [21]	Prospective trial	III	Italy	1986–1995	73 (38/35)	3–21 (9.5)
Merchant et al., 2008 [8]	Prospective multi-institutional trial	III	USA	Oct 1996–Aug 2003	86 (53/33)	3–21 (8.7)
Michalski et al., 2021 [7]	Prospective randomized trial	II	USA	Apr 2004–Jan 2014	464 (301/163) IFRT: 227 (150/77) PFRT: 237 (151/86) LDCSI: 116 (84/32) SDCSI: 110 (70/40)	IFRT vs. PFRT: 3–21.8 (8.1) SDCSI vs. LDCSI: 3–8 (5.7)
Okada et al., 2020 [22]	Prospective trial	III	Japan	2006–2014	48 (37/11) SR: 35 (26/9) HR: 13 (11/2)	3–18 (NR) SR: 7.6 (NR) HR: 6.6 (NR)
Packer et al., 1994 [23]	Prospective multi-institutional trial	III	USA	1983–1993	63 (41/22) SDCSI: 57 (NR) LDCSI: 6 (NR)	1.5–21 (9)
Packer et al., 2006 [24]	Prospective randomized multi-institutional trial	II	USA	Dec 1996–Dec 2000	379 (193/186)	3–21 (NR)
Pezzotta et al., 1996 [25]	Prospective non-randomized trial	III	Italy	Jul 1985–Dec 1989	38 (20/18) SR: 11 (NR) HR: 27 (NR)	0.6–14 (7.8)
Rieken et al., 2011 [26]	Retrospective single institutional chart review	IV	Germany	1985–2009	66 (36/30) RCT: 47 (NR) RT: 19 (NR)	2–60 (11)
Rutkowski et al., 2009 [27]	Prospective multi-institutional trial comparison	III	Germany	Aug 1987–Jul 1993	72 (44/28) HIT-SKK'87: 29 LR: 14 HR: 15 HIT-SKK'92: 43	0.2–2.9 (1.8)
Sirachainan et al., 2018 [28]	Prospective trial	III	Thailand	2008–2013	23 (17/6)	3.8–24.2 (9)
Sung et al., 2013 [29]	Prospective trial	III	Korea	Oct 2005–Sep 2010	20 (14/6)	1.9–21.4 (6.7)
Tian et al., 2020 [30]	Retrospective single institutional chart review	IV	USA	Aug 1990–Feb 2015	32 (25/7) PF: 22 (17/5) TB: 10 (8/2)	3–10 (5.5)

Table 1. Study parameters, levels of evidence (LOE), and patient demographics. (continued)

Study	Method	LOE	Country	Study range	Number of patients (M/F)	Age range [#] (average)
Wahba et al., 2013 [31]	Prospective trial	III	Egypt	Jan 2005–Dec 2008	33 (21/12)	0.5–20.4 (6.1)
Yasuda et al., 2008 [32]	Prospective non-randomized trial	III	Japan	NR	16 (8/8)	3–21 (NR)

HIT-SKK'87 and '92: (Brain Tumor Radiotherapy for Infants and Toddlers with Medulloblastoma) 1987 and 1992; HR: high risk; IFRT: involved field radiation therapy; LDCSI: low-dose craniospinal irradiation; LR: low risk; M/F: male/female; NR: not reported; RCT: radiochemotherapy; RT: radiation therapy; SDCSI: standard-dose craniospinal irradiation; SR: standard risk. *: Study included multiple countries within Europe, including Austria, Switzerland, France, Italy, Sweden, Denmark, Norway, Spain, the Netherlands, and the United Kingdom. #: Age listed in years.

Effect of craniospinal irradiation on survival

Table 2 outlines survival outcomes across included studies. Reported survival endpoints varied, though 3-, 5-, and 10-year rates were most common.

Table 2. Study survival percentages grouped by year.

Survival percentages	Author	EFS ± SD (95% CI)	PFS ± SD (95% CI)	OS ± SD (95% CI)
3-year survival percentages	Dufour et al., 2021 [16]	NR	78 (65–88)	84 (72–92)
	Okada et al., 2020 [22]	NR	SR: 90.5 ± 5.2 HR: 100	SR: 93.9 ± 4.2 HR: 100
	Packer et al., 1994 [23]	90 ± 4	90 ± 4	NR
	Rieken et al., 2011 [26]	NR	LPFS: 73 DPFS: 87	Overall: 84
	Tian et al., 2020 [30]	NR	NR	PF: 59.1 TB: 70
4-year survival percentages	Ashley et al., 2012 [13]	50 ± 6	NR	69 ± 5.5
5-year survival percentages	Allen et al., 2009 [12]	NR	43 ± 5	52 ± 5
	Gajjar et al., 2006 [5]	SR: 83 (73–93) (<i>p</i> = 0.046) HR: 70 (55–85)	NR	SR: 85 (75–94) (<i>p</i> = 0.04) HR: 70 (54–84)
	Jakacki et al., 2012 [18]	NR	Regimen A: 71 ± 11 Regimen B: 59 ± 10	Regimen A: 82 ± 9 Regimen B: 68 ± 10
	Lannering et al., 2012 [19]	Overall: 82 ± 2 STRT: 77 ± 4 HFRT: 78 ± 4	NR	STRT: 87 ± 3 HFRT: 85 ± 3
	Lee et al., 2020 [20]	71.1 ± 8	NR	73.2 ± 7.9
	Massimino et al., 2012 [21]	Overall: 48 ± 6 Patients ≤ 10 years: 38 ± 8 Patients > 10 years: 59 ± 8	NR	Overall: 56 ± 6 Patients ≤ 10 years: 41 ± 8 Patients > 10 years: 73 ± 8
	Merchant et al., 2008 [8]	83 ± 5.3	NR	94.7 ± 3.4
	Michalski et al., 2021 [7]	IFRT: 82.5 (77.2–87.8) PFRT: 80.5 (75.2–85.8) LDCSI: 71.4 (62.8–80) (<i>p</i> = 0.028) SDCSI: 82.9 (75.6–90.2)	NR	IFRT: 84.6 (79.7–89.5) PFRT: 85.2 (80.5–89.9) LDCSI: 77.5 (69.7–85.3) (<i>p</i> = 0.049) SDCSI: 85.6 ± 3.5 (78.7–92.5)
	Packer et al., 1994 [23]	Overall: 83 ± 6	Overall: 85 ± 6	Overall: 85 ± 6 SDCSI: 83 ± 6 LDCSI: 83 ± 20

Table 2. Study survival percentages grouped by year. (continued)

Survival percentages	Author	EFS ± SD (95% CI)	PFS ± SD (95% CI)	OS ± SD (95% CI)
	Packer et al., 2006 [24]	Overall: 81 ± 2.1 Regimen A: 82 ± 2.8 Regimen B: 80 ± 3.1	NR	Overall: 86 ± 1.9 Regimen A: 87 ± 2.6 Regimen B: 85 ± 2.8
	Pezzotta et al., 1996 [25]	Overall: 47.4 SR: 27.3 HR: 55.6	55.26	NR
	Rieken et al., 2011 [26]	NR	LPFS: 62 DPFS: 77	Overall: 73
	Sirachainan et al., 2018 [28]	NR	41.8 ± 12.2	60 ± 11.2
	Sung et al., 2013 [29]	70 ± 10.3	NR	73.9 ± 10.2
	Tian et al., 2020 [30]	NR	NR	PF: 50 TB: 58.3
	Wahba et al., 2013. [31]	79	NR	85
	Yasuda et al., 2008 [32]	82 (59–100)	Patients ≤ 5 years: 75 (45–100) Patients > 5 years: 88 (65–100)	Overall: 82 (59–100) Patients ≤ 5 years: 75 (45–100) Patients > 5 years: 88 (65–100)
6-year survival percentages	Carrie et al., 2009 [14]	95 (62–87)	75	78 (66–90)
9-year survival percentages	Packer et al., 1994 [23]	72 ± 13	NR	NR
10-year survival percentages	Christopherson et al., 2014 [15]	67	71	67
	Gupta et al., 2022 [17]	NR	63.2 (52.1–74.4)	74.1 (63.9–84.1)
	Massimino et al., 2012 [21]	42.6 ± 6	NR	46 ± 6
	Rieken et al., 2011 [26]	NR	LPFS: 43 DPFS: 71	Overall: 53
	Rutkowski et al., 2009 [27]	NR	HIT-SKK'87: 48.3 ± 9.3 HIT-SKK'92: 55.2 ± 9.2	HIT-SKK'87: 55.2 ± 9.3 HIT-SKK'92: 63.6 ± 7.6
	Sirachainan et al., 2018 [28]	NR	NR	48 ± 14

CI: confidence interval; DPFS: distal progression-free survival; EFS: event-free survival; HFRT: hyperfractionated radiation therapy; HIT-SKK'87 and '92: (Brain Tumor Radiotherapy for Infants and Toddlers with Medulloblastoma) 1987 and 1992; HR: high risk; IFRT: involved field radiation therapy; LDCSI: low-dose craniospinal irradiation; LPFS: local progression-free survival; NR: not reported; OS: overall survival; PF: posterior fossa; PFRT: posterior fossa radiation therapy; PFS: progression-free survival; SD: standard deviation; SDCSI: standard-dose craniospinal irradiation; SR: standard risk; STRT: standard radiation therapy; TB: tumor bed. 95% CI noted in parenthesis and SD documented if reported.

The lowest 5-year EFS was 27.3%, observed in standard-risk patients treated with SDCSI plus posterior fossa and tumor bed boosts [25]. In this study, high-risk patients who also received chemotherapy had a higher 5-year EFS (55.6%), though this difference was not statistically significant. Notably, patients receiving a posterior fossa boost ≥ 50 Gy had significantly better EFS (58.6%) than those receiving < 50 Gy (14.3%, $p = 0.0236$). Younger patients exhibited significantly worse EFS than older ones ($p = 0.0110$) [25].

The highest 5-year EFS (83%) was reported in three studies [5, 8, 23]. One study demonstrated significantly better outcomes in the standard-risk group versus high-risk (83% versus 70%, $p = 0.046$) [5]. The best reported 6-year EFS was 95% (95% CI: 62–87) in patients treated with hyperfractionated radiotherapy and reduced boost volumes without chemotherapy [14]. Another study found significantly better 5-year EFS in SDCSI patients (82.9%) than in low-dose CSI (LDCSI) patients (71.4%, $p = 0.028$) [7].

	Allen et al. 2009	Ashley et al. 2012	Carrie et al. 2009	Christopherson et al. 2014	Dufour et al. 2021	Gajjar et al. 2006	Gupta et al. 2022	Jakacki et al. 2012	Lanrerger et al. 2012	Lee et al. 2020	Massimino et al. 2012	Merchant et al. 2008	Michalski et al. 2021	Okada et al. 2020	Packer et al. 1994	Packer et al. 2006	Pezzotta et al. 1996	Rieken et al. 2011	Rutkowski et al. 2009	Sirachanian et al. 2018	Sung et al. 2013	Tian et al. 2020	Wahba et al. 2013	Yasuda et al. 2008	
1. A clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
3. Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
4. Endpoints appropriate to the aim of the study	1	2	2	1	2	2	2	1	2	1	2	2	2	2	2	2	2	2	1	2	2	2	1	2	
5. Unbiased assessment of the study endpoint	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	1	2	2	
7. Loss to follow-up less than 5%	0	1	1	2	0	0	2	0	0	0	0	0	0	0	1	2	0	2	0	0	0	0	0	2	
8. Prospective calculation of the study size	2	1	1	1	2	1	1	1	1	1	1	2	1	2	1	1	2	2	2	2	2	2	2	1	
Items 9-12 for comparative studies only																									
9. An adequate control group							0	0	0		0		0	0	0	0	0	0	0				0	0	
10. Contemporary groups							2	2	2		2		2	2	2	2	2	2	2				2	2	
11. Baseline equivalence of groups							1	0	2		1		2	1	0	0	2	0	1				2	2	
12. Adequate statistical analyses							2	2	2		2		2	2	1	2	2	2	2				2	2	
Total MINORS score	13	14	14	14	14	18	15	16	19	10	18	14	19	19	17	19	20	24	18	18	14	13	19	16	21
Maximum possible MINORS score	16	16	16	16	16	24	16	24	24	16	24	16	24	24	24	24	24	24	24	16	16	24	16	24	

Total MINORS score reflecting methodological quality high moderate low

Figure 2. Methodological index. MINORS: methodological index for non-randomized studies.

The lowest 5-year OS ($41 \pm 8\%$) was observed in patients under 10 years of age, compared to $73 \pm 8\%$ in older patients [21]. The highest 5-year OS ($94.7 \pm 3.4\%$) was reported in patients with average-risk disease treated with 23.4 Gy CSI and posterior fossa/tumor bed boosts followed by chemotherapy [8]. In the same study showing a superior 5-year EFS in standard-risk patients, a significantly higher 5-year OS was also observed (85% versus 70%, $p = 0.04$) [5].

Delayed initiation of radiotherapy (> 28 days post-surgery) significantly reduced OS ($p = 0.02$) [26]. Additionally, chemotherapy administered before radiotherapy was associated with significantly lower OS ($p = 0.04$) [26] and PFS ($p = 0.047$) [30], though one study reported no significant impact [12].

Craniospinal irradiation’s impact on cognitive function

Cognitive deficits, declines, impairment, or reduction in IQ were reported in 10 studies [7, 13–15, 17, 20, 26, 27, 31, 32]. The highest rate of cognitive dysfunction was 49% of patients with medulloblastoma [15] (Table S1). There were higher rates of cognitive impairment in patients treated with radiotherapy alone than with radiochemotherapy [26]. Using the Wechsler’s scale, the lowest average IQ reported out of all 24 studies was 71, which used reduced CSI [20]. The highest IQ reported was a 98.6, which was obtained using a reduced CSI dose followed by chemotherapy [7]. This randomized clinical trial compared SD versus LDCSI in average-risk medulloblastoma and found that children administered SDCSI exhibited significantly greater decline in IQ compared to children treated with LDCSI ($p = 0.02$) at the first time point, 4–15 months after diagnosis [7]. In the same study, patients who received a radiation boost to the posterior fossa radiation therapy (PFRT) had significantly lower IQ than those who received a radiation boost to the involved field radiation therapy (IFRT) ($p = 0.01$) at the first time point [7]. Neither of these observations remained statistically significant at the second time point, 27–48 months after diagnosis. When comparing average IQ results of SDCSI with chemotherapy to healthy controls within their corresponding age group, healthy controls had a significantly higher IQ score ($p < 0.001$) [27].

Two studies reported the rate of IQ point decline. In one study, there was an average 2-point IQ reduction in the span of 6 years [13]. Another study reported IQ decline at a rate of < 1 point per year over the span of 10 years, but with no statistical significance using regression analysis [17]. In studies using LDCSI, there was a reduction in IQ in 28.6% of patients that was insignificant ($p = 0.07$) [31], and 25% of the patients assessed for neurocognitive function had a 10-point IQ depreciation [32].

Molecular subgroup and histological morphology's impact on survival

Molecular subgroups and tumor histological morphology also impacted the survival of patients with medulloblastoma. The existence of molecularly distinct groups was predicted in 2002 based on gene expression [33]. Later, these were further categorized into four different subgroups: Wingless (WNT), Sonic hedgehog (SHH), Group 3, and Group 4 [33]. Named after its role in the canonical WNT signaling pathway, the WNT subgroup has the best prognosis out of all 4 subgroups, followed by Group 4, SHH, and lastly Group 3 with the poorest prognosis [33]. In addition to genetic profiling into subgroups, medulloblastoma is also classified based on histological morphology, which includes classic medulloblastoma (CMB), desmoplastic medulloblastoma (DMB), nodular medulloblastoma (NMB), and large cell/anaplastic medulloblastoma (LCA) according to the 2002 World Health Organization (WHO) classification [34]. Studies reporting histological morphology are depicted in Table S1. The WNT and Group 4 subgroups often have classic histology, SHH often has desmoplastic/nodular histology, and Group 3 has classic histology but with a higher prevalence of LCA morphology, and are often metastatic with a poor prognosis [35]. These trends remained consistent with what we systematically extracted from studies, with subgroup and histology being statistically significant predictors in prognosis.

LCA medulloblastoma had a markedly poorer prognosis, with histology being the most statistically prognostic factor ($p = 0.039$) [16] and a higher treatment failure hazard ratio (3.9) [5]. There was a significantly worse survival rate ($75 \pm 6.4\%$ LCA versus $89 \pm 1.9\%$ non-LCA, $p = 0.005$) [24] and 5-year EFS rate ($73 \pm 6.4\%$ LCA versus $83 \pm 2.3\%$ non-LCA, $p = 0.087$) [24] when compared to other non-anaplastic morphologies. Patients with CMB had significantly worse OS rates compared to patients with DMB/NMB ($40 \pm 11\%$ versus $88.9 \pm 10.5\%$, $p = 0.006$) [27]. In terms of molecular subgroups, patients in Group 4 who were administered LDCSI had lower EFS compared to those treated with SDCSI, which was borderline statistically significant ($p = 0.047$) as mentioned previously [7]. Additionally, SHH and Group 3 had an inferior prognosis when compared to WNT and Group 4 [16].

Discussion

This comprehensive systematic review evaluates OS and relapse rates between LD and SDCSI for the treatment of medulloblastoma. The most notable findings include: (1) LDCSI was associated with higher OS, (2) but lower EFS compared to SDCSI, and (3) cognitive impairment was less frequent in patients treated with combined radiochemotherapy versus radiation alone. The discrepancy between higher OS but lower EFS in the LDCSI cohort is likely attributable to the addition of chemotherapy, which may reduce progression despite higher relapse rates. Previous randomized controlled trials comparing LDCSI alone to SDCSI found a significant increase in relapses with LDCSI, underscoring the necessity of incorporating chemotherapy [4]. While chemotherapy can mitigate disease progression and serve as maintenance therapy, it may also contribute to toxicities that decrease EFS.

The timing of chemotherapy and radiation was also found to influence survival outcomes. Two studies demonstrated significantly reduced OS and PFS in patients receiving pre-irradiation chemotherapy compared to those treated post-radiation [26, 30]. Moreover, delaying radiotherapy initiation beyond 28 days post-surgical resection was associated with significantly reduced OS [26]. A retrospective cohort analysis supported this, reporting a 5-year OS of 82% in patients receiving immediate postoperative radiation, versus 63.4% in those with delayed treatment ($p < 0.001$) [36].

Hematologic toxicity was frequently reported, consistent with the known myelosuppressive effects of both radiation and chemotherapy. Studies have shown that using proton therapy (PT) to treat medulloblastoma reduces hematological toxicity [37], as does the addition of autologous hematopoietic stem cell transplant (ASCT) [38, 39]. A previous systematic review also found that PT had reduced hematological toxicities [40]. While high-dose therapy (HDT) with ASCT has demonstrated superior PFS in multiple myeloma, it has not shown OS benefits and is associated with increased treatment-related mortality [41]. Whether these findings extend to medulloblastoma remains unclear and warrants further investigation.

Cognitive impairment remains a critical long-term concern. Nearly half of the studies reviewed reported neurocognitive side effects. The highest average IQ (98.6) was observed in patients treated with 18 Gy LDCSI plus chemotherapy [7], while the lowest (71) was reported with 23.4 Gy LDCSI plus chemotherapy [20]. Total radiation dose may explain this discrepancy: Michalski et al. (2021) [7] administered 54 Gy total, while Lee et al. (2020) [20] used 75.6 Gy. Whether differences in CSI dosage (18 Gy versus 23.4 Gy) result in meaningful cognitive variation remains to be determined.

Advanced imaging studies using quantitative magnetic resonance imaging (qMRI) have shown reduced white matter volume and lower IQ in medulloblastoma patients treated with chemoradiation compared to surgical-only treatment of low-grade astrocytoma [42, 43]. IQ scores were significantly correlated with normal white matter volume, highlighting radiation's dose-dependent neurocognitive effects [44]. These findings suggest that qMRI could be a valuable tool in future research evaluating white matter loss and its relationship to radiation dose and cognitive decline.

Survival outcomes are also influenced by tumor biology. Further risk stratification is commonly categorized by age of diagnosis, tumor size, the presence or absence of metastasis, margins after resection, histology, and gene abnormalities [45]. As mentioned previously, the WHO subdivided medulloblastoma for further classification based on histology [34] and, more recently, molecular subgroups based on genetic analysis [35]. In our study, patients with anaplastic histology or Group 3 molecular subtypes experienced poorer prognoses [5, 16, 24]. Notably, Group 4 patients treated with LDCSI demonstrated significantly lower EFS [7]. Although over half of our reviewed studies classified medulloblastoma histologically, only five studies [5–7, 17, 20] classified medulloblastoma into their molecular subgroups. Studies continue to demonstrate molecular subgroups' impact on survival in patients with medulloblastoma [46]. Given the growing evidence of molecular subtypes' prognostic value, their integration into risk stratification frameworks may inform treatment de-escalation strategies and help optimize radiation and chemotherapy dosing.

Several limitations must be considered. First, many studies did not explicitly separate relapse data for SD versus LDCSI, limiting our ability to perform a meta-analysis. Second, inconsistent risk stratification across studies resulted in some high- and average-risk patients being treated similarly, likely contributing to the variability in outcomes. Third, due to incomplete reporting, we could not assess the impact of specific chemotherapy regimens, cycles, or drug types, nor the influence of radiation delivery techniques. Lastly, out of 749 studies that were screened, only 24 were included in our systematic review.

LDCSI combined with chemotherapy appears to be a viable treatment option for medulloblastoma, with potential benefits in reducing long-term neurotoxicity. However, further research is needed to evaluate whether LDCSI offers statistically significant advantages over SDCSI, particularly when stratifying by molecular and histological subtypes. Longitudinal studies assessing cognitive outcomes, treatment toxicity, and survival—while accounting for chemotherapy regimens and radiation techniques—are essential to refine risk-adapted treatment approaches for this complex pediatric malignancy.

Abbreviations

ASCT: autologous hematopoietic stem cell transplant

CMB: classic medulloblastoma

CSI: craniospinal irradiation

DMB: desmoplastic medulloblastoma

EFS: event-free survival

IQ: intelligence quotient

LCA: large cell/anaplastic medulloblastoma

LDCSI: low-dose craniospinal irradiation

MINORS: methodological index for non-randomized studies

NMB: nodular medulloblastoma

OS: overall survival

PFS: progression-free survival

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PT: proton therapy

qMRI: quantitative magnetic resonance imaging

SDCSI: standard-dose craniospinal irradiation

SHH: Sonic hedgehog

WHO: World Health Organization

WNT: Wingless

Supplementary materials

The supplementary table for this article is available at: https://www.explorationpub.com/uploads/Article/file/1001366_sup_1.pdf.

Declarations

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Author contributions

IH: Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Visualization, Writing—original draft, Writing—review & editing. MG: Data curation, Investigation, Methodology, Writing—original draft, Writing—review & editing. MB: Investigation, Methodology, Writing—original draft, Writing—review & editing. ET: Conceptualization, Investigation, Methodology, Project administration, Resources, Writing—review & editing. EF: Methodology, Project administration, Resources, Validation, Writing—review & editing. All authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

The primary data for this systematic review were sourced online from databases listed in the methods. Referenced articles are accessible on the database. Additional supporting data are available from the corresponding author upon request.

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