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Meta of classical chemotherapy compared with high-dose chemotherapy and autologous stem cell rescue in newly diagnosed medulloblastoma after radiotherapy

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Abstract

Background: High-dose chemotherapy combined with autologous stem cell rescue (HDCT + ASCR) has been used to treat newly diagnosed medulloblastoma, but there was no high-level evidence to support its efficacy.

Methods: Databases were retrieved, and patients were divided into 2 groups: group A was radiotherapy combined with HCDT + ASCR, and group B was classical radiotherapy and chemotherapy. The clinical benefit rate, progression-free survival (PFS), overall survival (OS) and toxicities data were extracted.

Results: 22 clinical trials met the inclusion criteria, 416 in group A and 2331 in group B. There was no difference in CBR between 2 groups (80.0% vs 71.5%, *P*.262). The 3-year PFS (3-y PFS) of group A was significantly better than group B (79.0% vs 69.5%, *P* = .004). The analysis found that there was no difference between the 2 groups of the standard risk group or the high-risk group. In the standard risk group, the 5-y PFS of group A was significantly better than group B (83.6% vs75.6%, *P* = .004). Comparison of 3-y OS and 5-y OS between 2 groups of all MB patients showed no difference (*P* = .086; *P* = .507), stratified analysis was the same result. The gastrointestinal toxicity in group A was significantly higher than that in group B (*P* = .016), and the level 3/4 ototoxicity in high-risk group A was higher than that in group B (*P* = .001).

Conclusions: HDCT + ASCR can prolong 3-year PFS significantly, and prolong 5-y PFS significantly in the standard risk group, but increase gastrointestinal toxicity significantly for newly diagnosed medulloblastoma.

Abbreviations: ASCR = autologous stem cell rescue, CBR = clinical benefit rate, CR = complete response, CSRT = craniospinal radiotherapy, EFS = event-free survival rate, HDCT = high-dose chemotherapy, MB = Medulloblastoma, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, PRISMA = Preferred Reporting Items of the System Review and the Meta-Analysis, R = mild response, SD = stable disease, 3y OS = 3-year overall survival, 3-y PFS = 3-year progression-free survival, 5y OS = 5-year overall survival, 5-y PFS = 5-year progression-free survival.

Keywords: autologous stem cell rescue, high-dose chemotherapy, medulloblastoma, OS, PFS

1. Introduction

MB is the most common malignant brain tumor in children, accounting for about 20% of children's brain tumors.[1] Thirty years ago, the standard treatment for MB included surgery and craniospinal radiotherapy, with a 10-year survival rate of 45%.[2] Preradio therapy or postradiotherapy chemotherapy significantly improved survival, which resulted in a significantly improved 5-y survival rate of children in the standard risk group (i.e., no evidence of metastatic and residual lesions was <1.5 cm^2), up to 85%.[3] Effective chemotherapy also helped reduce the craniospinal radiotherapy (CSRT) dose required to treat standard risk MB. However, the 5-y survival rate of high-risk MB children aged 3 years or older (i.e. residual > 1.5 cm^2 or metastatic diseases) was <55%..[4–6]

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For nearly 30 years, multiple research groups had attempted to use HDCT + ASCR in order to further improve the efficacy of chemotherapy regimens and increase the survival rate of patients, or reduce the dose of CSRT for patients in the standard risk group to reduce the side effects. Scholars had attempted to apply HDCT combined with ASCR to first-line treatment of newly diagnosed MBs,[7–9]especially tended to apply HDCT + ASCR treatment regimen in high-risk group MB, and obtained certain efficacy, and the results showed that HDCT + ASCR may extend the survival period of patients.[10,11] A report by Sung showed the 3-y EFS in 6 patients with newly diagnosed high-risk MB/sPNET (>3 years old) and 8 newly diagnosed high-risk MB/sPNET patients (<3 years old) were 83.3 ± 15.2% and 62.5 ± 20.5%, respectively. The survival rate is better than the traditional treatment and might further increase the prognosis of patients with high-risk cerebral tumors.[12]The number of studies on the first-line HDCT combined with ASCR for the standard risk group MB patients was small, with the purpose of reducing the dose of radiotherapy and reducing radiation-related toxic and side effects while improving the curative effect. Gajjar et al conducted a single-arm prospective study on patients in both the standard risk group and the high-risk group. The standard risk group was given 23.4Gy CSRT and 4-cycle HDCT-ASCR, and the 5-y OS was 85% (75%–94%) and 5-y EFS was 83% (73%–93%).High-risk MB received 36.0–39.6Gy CSRT and 4-cycle HDCT-ASCR, with 5-y OS reaching 70% (95% CI 54%–84%) and 5-year event-free survival rate (EFS) 70%(55%–85%).[8]According to Nazemi's study, postoperative chemoradiotherapy, chemotherapy and ASCR were given to patients with MB in the high-risk group with initial onset. 5-y EFS and OS were 46 ± 11% and 50 ± 11%, respectively.[13] Therefore, the efficacy of this therapy in the initial treatment of MB patients was uncertain. Although some studies have shown that the application of HDCT-ASCR in the initial treatment stage of MB could improve the efficacy, there was still a lack of high-level evidence like randomized controlled studies and large sample clinical trials. As we all know, the toxic and side effects of this therapy were greater than that of conventional chemotherapy, and patients were at increased risk of treatment and need to bear high treatment costs. Therefore, it was necessary to evaluate the efficacy of this method in first-line treatment of MBs more credibly. So far, most of the relevant studies had been retrospective studies. Although there were some prospective studies, most of them were single-arm small sample clinical trials. No prospective randomized controlled studies with large samples had been found, and no other high-level evidences such as retrospective clinic study of enough large samples or meta-analysis had been found. In order to confirm the efficacy of HDCT + ASCR in first-line treatment for MBs, this paper compared the efficacy of conventional chemotherapy (group B) and HDCT + ASCR (group A) after postoperative radiotherapy using meta method, so as to provide higher level of evidence for guiding the clinical treatment decision of MBs.

2. Material and Methods

This study is meta-analysis, a retrospective collection of other published research, so the ethics committee or institutional review board is not applicable.

2.1. Data source

We conducted this meta-analysis according to the Preferred Reporting Items of the System Review and the Meta-Analysis (PRISMA) statements.[14] Literature retrieval was conducted according to the PICOS principle. To determine the researches included in the meta-analysis, we conducted an extensive search in 4 databases, involving Medline, EMBASE database, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from January 1988 to May 2018. A detailed and complete search strategy was provided in Supplementary 1 data, http://links.lww.com/MD/G880. That was limited to human clinical trials that published in English. All the retrieved literatures are imported into the management software for management, and the main content of management is to automatically combine with manual removal of duplicate literatures. By reading the title and abstract of the literature, and excluding duplicate literature, irrelevant literature and summary of the review, preliminary screening was conducted. Through careful reading of the full text of the remaining literature, secondary screening was conducted to obtain the literature that finally met our standards. In addition, the bibliographic list of all included references was manually retrieved and checked 1 by 1 to ensure that no studies were omitted. Selection criteria and procedures

The selected articles meet each of the following standards: (i) Treatment with chemotherapy and radiotherapy, with or without ASCR; (ii) The eligible patients enrolled should be normal hematologic, renal, hepatic and bone marrow function[15]; (iii) Can be used for tumor response, PFS or OS data; (iv) Trials in which primitive neuroectodermal tumors or other cerebral tumors were incorporated into MB or could not be isolated from MB patients were excluded.

The following detailed information was extracted from the included researches: the first author, country, year of publication, trial design, therapeutic schedule, patients enrolled, median age, tumor response and survival. All possible relevant theses were assessed independently by 2 researchers (ZMT and ZHD), and controversies were worked out through discussion and consultation. Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) was used to digitize Numbers to extract numerical values when progress or survival data was provided graphically only.

Patients with newly diagnosed medulloblastomas were divided into 2 groups according to different treatment methods: group A was treated with postoperative radiotherapy combined with HCDT + ASCR, B for postoperative classical radiotherapy and chemotherapy.

In order to evaluate quality, because we included noncomparative researches in our meta-analysis, we applied the Newcastle-Ottawa quality assessment scale.[16] The projects we chose concentrated on representativeness of research patients, certification that the result of interest was not show at the beginning of the research, full assessment results, sufficient follow-up time to produce results, and adequate follow-up. The results of each bias risk assessment were "yes", "uncertain" or "no".

2.2. Clinical endpoints

The clinical end-points involved tumor response rates, 5-year overall survival (5-y OS), 3-year overall survival (3-y OS), 5-year progression-free survival (5-y PFS) and 3-year progression-free survival (3-y PFS). The scheduled start time for this study was the OS for all identifiable MB patients who received ASCR as part of the initial treatment. The 5-y OS was the mainly endpoint, as it was widely mostly recognized and documented. Overall survival was calculated from the time of ASCR to the date of death or until the patient's last follow-up. PFS was defined from ASCR until disease progression, death, or the last follow-up. Tumor size was calculated by the product of the maximum diameter and the maximum vertical diameter in the MRI image. The disease response was classified as listed below: progressive disease (PD, >25% increase in tumor size or emergence of a new field of tumor), stable disease (SD, < 25% change in tumor size), mild response to tumor size reduction by -50% (MR, 25%), partial response to tumor size reduction by 50% (PR, > 50%), or complete response (CR, all measurable before tumor complete disappearance).

During treatment, studies monitored patient disease status and toxicities with appropriate laboratory evaluations and medical imaging results, and the toxicities were classed on the basis

of the National Cancer Institute's common toxicity criteria.[17] Our article provided only level 3 and 4 toxicities.

Moreover, all other usable clinical patient data were collected for ex post analysis (depending upon the usability of the data) to control for underlying biases in the patient population, identify the representativeness of the dataset, and construct new research hypotheses.

2.3. Statistical analysis

Stata version 12.0 and IBM SPSS Statistics 22.0 was used for all statistical analyses. We used the DerSimonian and Laird (D-L) random-effect models to aggregate log-transformed event rates, and used an χ^2-based Q statistical test to assess heterogeneity.[18] $P = .05$ was deemed to consider statistically significant. In order to confirm the entire heterogeneity of the inclusive cohort, we computed the I^2 statistics, and an I^2 >50% indicated high heterogeneity.

3. Results

3.1. Studies screening process

The screening process for all our related studies was shown in Figure 1. A total of 156 articles were initially retrieved from 4 literature retrieval databases. After reviewing the titles and abstracts, 108 articles were excluded because of their no relevant to the topic, and we then reviewed the full text of the remaining 48 articles. 26 of the studies were considered unqualified for the following reasons: (i) 13 of the studies did not include MB patients or were unable to extract MB

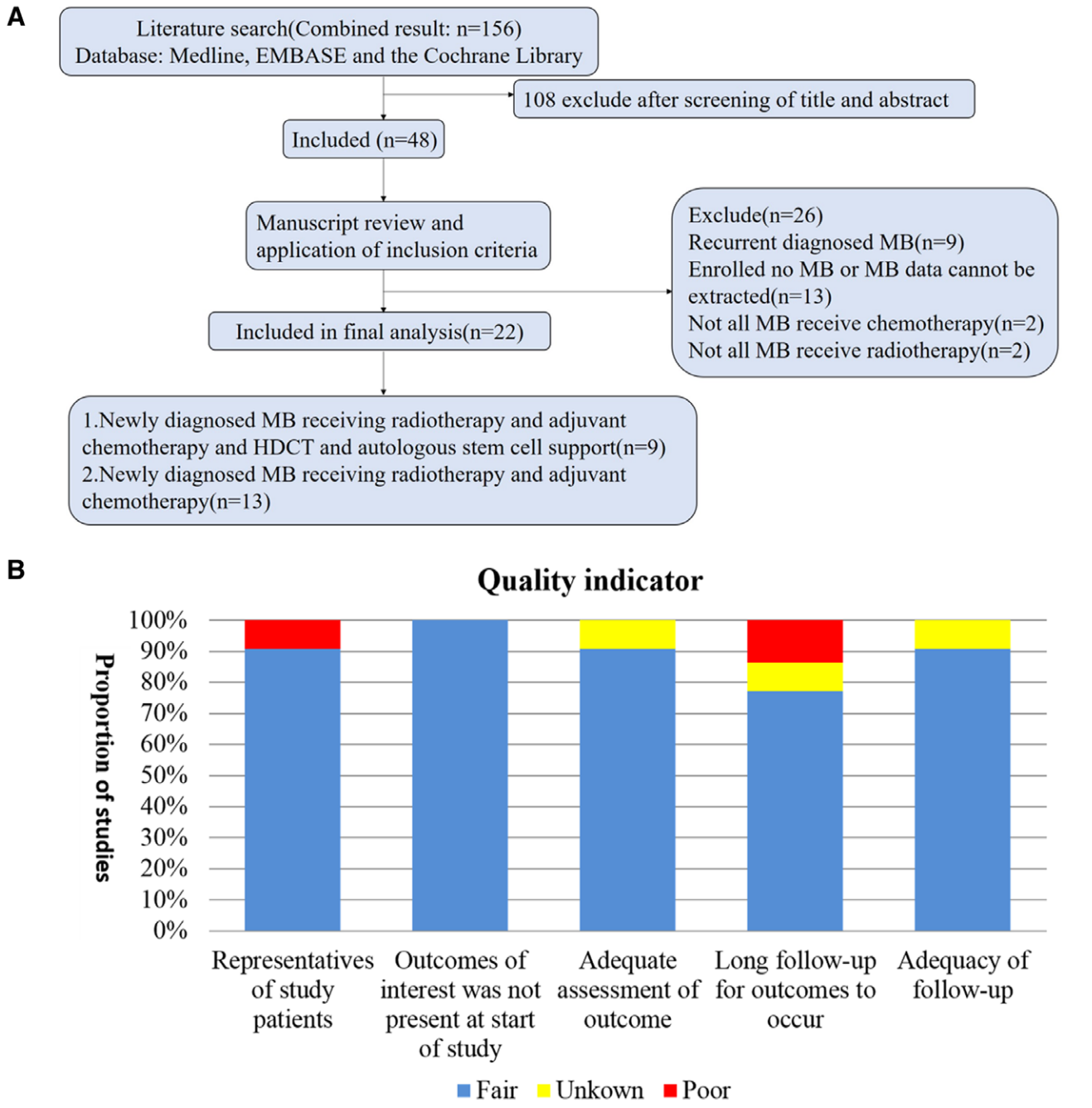

Figure 1. Clinical studies identified and screened for eligibility; selected methodological quality indicator.

related data from the articles; (ii) 9 studies enrolled recurrent MB patients; (iii) 2 studies did not receive chemotherapy; (iv) 2 studies did not receive radiotherapy. Finally, 22 articles included in our systematic review met all inclusion criteria[8,10,12,13,19–36](Fig. 1).

3.2. Characteristics included in the studies

We included 22 clinical trials for analysis, all of which were single-arm clinical studies. In all included studies, we found no randomized controlled studies that directly compared survival differences between the groups A/B.9 of these were about newly diagnosed medulloblastoma with HDCT + ASCR. Table 1 showed the characteristics of the inclusive researches, a total of 416 patients were included. In 4 articles, 361 MB patients received chemotherapy regimen of cyclophosphamide + cisplatin + vincristine, accounting for 86.2% of the total population.

Of these clinical trials were about MB with chemotherapy and radiotherapy. Table 2 was the characteristics of the 13 inclusive researches, including overall 2331 patients. Most MB patients were treated with triple chemotherapy, such as cisplatin + lomostine + vincristine, cyclophosphamide + cisplatin + vincristine, vincristine + cisplatin + etoposide, vincristine + cyclophosphamide + etoposide, vincristine + cyclophosphamide + etoposide, vincristine + carboplatin + etoposide, a total of 1361 patients, accounting for 65% of the total patients. Some patients were treated with vincristine + lomostine, accounting for about 373 patients, accounting for 27.4% of the total number. There were also partial applications of cyclophosphamide + vincristine, with about 271 people, or 19.9% of the total number.

The selected methodological quality of the inclusive researches was fair; most researches provided sufficient outcomes to confirm, included representative samples of patients, and had receivable length of follow-up (Fig. 1).

3.3. Overall survival

5-y OS was the major clinical endpoint of our research. A total of 18 trials were performed, including 236 patients in group A and 1925 patients in group B. The range of 5-y OS rate was between 25.0% and 87.0%. Article with the lowest 5-y OS rates was found using radiotherapy, HDCT + ASCR,[12] and the highest in the trial using radiotherapy and chemotherapy.[27] For 5-y OS of all MB patients with group A, data of 236 patients included in 6 trials were usable for analysis. The odds value of this group using D-L method was 2.223 (95%CI: 1.128–4.383), calculated by random-effects model (heterogeneity analysis: χ^2 = 16.62, I^2 = 63.9%, P = .011). Then we calculated the prevalence was 69.0% (95% CI: 53.0–81.4%), meaning the overall 5-y OS rate was 69.0% (95% CI: 53.0–81.4%). And in the group B, 1925 patients from 11 trials were available for further analysis. Using the same way, the overall 5-y OS rate was 74.3% (95% CI:66.2–81.0%) (Fig. 2), while the significant heterogeneity existed (I^2 = 91.8%, P = .001). Further analysis of heterogeneity detected no difference in 5-y OS between the 2 groups (69.0% vs 74.3%, P = .086) (Table 3).

By the same method, in the group A, the 5-y OS of the high-risk group was 64.0% (95%CI:46.7–78.2%) with small heterogeneity (I^2 = 48.1%, P = .086). In the Group B, the 5-y OS of the high-risk group was 69.0%(95%CI:60.2–76.6%) with significant heterogeneity (I^2 = 71.8%, P = .002) and the standard risk group was 76.9%(65.2–85.6%) with significant heterogeneity (I^2 = 91.6%, P<0.001) (Fig. 2). Further exploration of heterogeneity found no difference in 5-yOS between the 2 groups, either in the high-risk MB group or the standard risk group (64.0% vs 69.0%, P = .318;85.0% vs 76.9%, P = .089) (Table 3). Although

Table 1

Characteristics and efficacy results of newly diagnosed medulloblastoma with high-dose chemotherapy and autologous stem cell reinfusion included in the meta-analysis.

Reference	Country	year	Schedule	Classify[b]	Patients	Median age (yr)	CR	PR	SD	5-y OS (%)	3-y OS (%)	5-y PFS (%)	3-y PFS (%)
Ramaswamy	Canada	2016	S + R + HDCT + ASCR	NR	44	8.3	NR	NR	NR	NR	NR	77.0	NR
Merchant	USA	2009	S + R + HDCT + ASCR	Average-Risk	86	8.7	NR	NR	NR	NR	NR	83.0	NR
Fouladi	USA	2008	S + R + HDCT + ASCR	Average-Risk (control group)	35	7.81	NR	NR	NR	NR	NR	86.0	89.0
				Average-Risk (experimental group)	62	NR	NR	NR	NR	NR	NR	86.0	92.0
Sung	Korea	2007	S + R + HDCT + ASCR	High-Risk	4	123.5 mo	4	0	0	25.0*	50.0*	25.0*	50.0*
Gajjar	USA	2006	S + R + HDCT + ASCR	Average-Risk	86	8.7	NR	NR	NR	85.0	85.0	83	87.0
				High-Risk	48	6.6	NR	NR	NR	70.0	70.0	70.0	75.0
Dufour	France	2014	S + R + HDCT + ASCR	High -Risk	18	NR	NR	NR	NR	83.0	83.0	72.0	78.0
Perez	Spain	2005	S + R + HDCT + ASCR	High -Risk	3	9.3	3	0	0	33.3*	33.3*	33.3*	33.3*
8. Nazemi	USA	2016	S + R + HDCT + ASCR	High -Risk	10	6.7	NR	NR	NR	40.0	40.0	40.0	40.0
9. Sung	Korea	2013	S + R + HDCT + ASCR	High -Risk	20	9	16			73.9	NR	70.0	NR

NR, not reported, R: Radiotherapy, S: Surgery, 3-y OS, 3-year overall survival, 3-y PFS, 3-year progression-free survival, 5-y OS, 5-year overall survival, 5-y PFS, 5-year progression-free survival.
*By calculating the proportion of the number of survivals at this time.

Table 2

Characteristics and efficacy results of newly diagnosed medulloblastoma with chemotherapy and additional radiation included in the meta-analysis

Reference	Country	Year	Schedule	Classify*	Patients	Median age (yr)	CR	PR	SD	5-yOS (%)	3-yOS (%)	5-yPFS (%)	3-yPFS (%)
10. Esbenshade	USA	2017	S + R + C	High-risk	47	8.1	29	7	6	76.6	NR	70.2	NR
11. Yock	USA	2016	S + proton R + C	Standard-risk	14	6.6	NR	NR	NR	83	NR	80	83
				High-risk	45		NR	NR	NR		NR		
12. Bueren	USA	2016	S + C + HART + C	High-risk	123	8.2	31	24	39	74	NR	62	NR
13. Tarbell	USA	2013	S + R + C or S + C + R	High-risk	224	7.8	44	45	17	74.6	NR	68.1	NR
14. Ris	USA	2013	S + R + C (Regimen A: CCNU + CDDP + VCR)	Standard-risk	187	NR	NR	NR	NR	NR	NR	82	NR
			S + R + C (Regimen B: cyclo + CDDP + VCR)	Standard-risk	192		NR	NR	NR	NR	NR	80	NR
15. Rao	USA	2013	S + R + C	Standard-risk	363	NR	NR	NR	NR	83.90	NR	78.20	NR
16. Packer	USA	2013	S + R + C (Regimen A: CCNU + cisplatin + vincristine)	Standard-risk	379	NR	NR	NR	NR	87	NR	81	NR
			S + R + C (Regimen B: cisplatin + cyclo + vincristine)	Standard-risk			NR	NR	NR		NR		NR
17. Abd el-aal	Egypt	2005	S + R + C	High-risk	27	6.92	16	1	1	NR	48.4	NR	48.9
18. Taylor	UK	2004	S + C + R	Standard-risk	90	7.74	NR	NR	NR	76.7	83	74.2	78.5
19. Bailey	UK	1995	S + R + C	Not to clarify	364	6.58	NR	NR	NR	58.9	NR	58.9	NR
20. Krischer	USA	1991	S + R + C	Not to clarify	36	NR	NR	NR	NR	73.6	NR	68.0	NR
21. Tait	UK	1990	S + R + C	Not to clarify	125	NR	NR	NR	NR	54†	61†	54†	61†
22. Evans	USA	1990	S + R + C	Not to clarify	115	NR	NR	NR	NR	65	NR	59	NR

C = chemotherapy, Cyclo = cyclophosphamide, HART = hyperfractionated Accelerated Radiotherapy, R = radiotherapy, NR, not reported, S = surgery, 3-y OS = 3-year overall survival, 3-y PFS = 3-year progression-free survival, 5-y OS = 5-year overall survival, 5-y PFS = 5-year progression-free survival.

*Classify medulloblastoma into average-risk (≤1.5 cm^2 residual tumor and no metastatic disease) or high-risk medulloblastoma (>1.5 cm^2 residual disease or metastatic disease localized to neuraxis).

†Extracted by data extraction software.

the data comparison of the general-risk group we calculated had a trend of difference, this group of data in the group A was from an article, which might have a large data bias.

The results indicated that 3-y OS rate had no difference between 2 MB groups in all patients (69.1% vs 66.3%, P = .507) (Fig. 2) (Table 3). There was also no statistical difference in the 3-y OS of the high-risk groups or the standard risk groups between the 2 groups (62.9% vs 48.4%, P = .183; 85.0% vs 83.0%, P = .779) (Table 3).

3.4. Progression-free survival

Data extracted for analysis from 416 patients in group A and 2304 patients in group B, included in 21 trials. The 5-y PFS rate ranged from 25.0 to 86.0%, and the lowest and the highest data both noted in the group A.[12,25] For 5-y PFS in group A, our study included the analysis of 416 patients from 9 trials. The odds value of this group using D-L method was 3.096 (95%CI: 2.114–4.534), calculated by random-effects model (heterogeneity analysis:χ^2 = 21.20, I^2 = 52.8%, P = .020). The prevalence was 75.6% (95% CI: 67.9–81.9%), meaning the 5-year PFS rate was 75.6% (95% CI: 67.9 –81.9%). In group B, our research included the analysis of 2304 patients from 12 trials. Using the same way, the 5-y PFS rate was 71.1% (95% CI:65.0–76.6%), while the significant heterogeneity existed (I^2 = 88.4%, P = .001) (Fig. 3). The data of the 2 groups showed a trend of difference (75.6%vs 71.1%, P = .067) (Table 3).

By the same way, in the group A of MB, the 5-y PFS of the high-risk group was 62.5%(95%CI:48.7–74.6%) with small heterogeneity (I^2 = 30.7%, P = .205), and the standard risk group was 83.6% (78.7–87.6%) with small heterogeneity (I^2 = 0%, P = .938). And in the group B, the 5-y PFS of the high-risk group was 63.3%(95%CI:57.6–68.7%), also with small heterogeneity (I^2 = 37.8 %, P = .140) and the standard risk group was 75.6% (69.4–80.8%) with significant heterogeneity (I^2 = 81.3%, P < 0.001). (Fig. 2) Further exploration of heterogeneity found significant difference in 5-y PFS between the standard risk 2 groups (83.6% vs 75.6%, P = .004). Meaning in the standard risk group, there was a difference in 5-y PFS of 2 treatments. We found no difference in 5-y PFS between the 2 high-risk groups (62.5% vs 63.3%, P = .824) (Table 3), and this might be related to the small amount of data we included.

The results showed that the 3-y PFS rate was significantly different between the 2 groups in all patients (79.0% vs 69.5%, P = .004). There was no statistical difference in the 3-y PFS of the high-risk group between the 2 groups (63.5% vs 60.3%, P = .694) (Fig. 3) (Table 3). The data of the standard risk group showed a trend of difference (86.6% vs 78.5%, P = .078), but data in 1 group came from 1 article, so there might be bias.

3.5. Tumor response

Clinical benefit rate (CBR) (including CR, PR and SD) was also been analyzed. Since very few patients were able to achieve CR, the CR data were not analyzed separately. For CBR, we analyzed data from 448 patients in 7 trials. The CBR ranged from 47.3 to 100%, with the lowest value in the radiotherapy and chemotherapy group,[30] and the highest value in the radiotherapy and HDCT + ASCR groups.[10,12] The odds value of CBR of group B was 2.508 (95%CI: 0.977–6.436) as calculated by the random-effects model (heterogeneity analysis:χ^2 =41.54, I^2 = 92.8%, P.001). The prevalence was 71.5% (95%CI: 49.4–86.6%), meaning the CBR of group B was 71.5% (95%CI: 49.4–86.6%). By the same method, the CBR of group A was 80.0 % (95%CI: 57.3–92.3). There was no difference in clinical benefit between 2 groups (71.5% vs 80.0%, P = .262).

3.6. Toxicity

Within the selected studies, complications after radiotherapy, HDCT + ASCR and radiotherapy, chemotherapy were reported. Table 4 showed the toxic and side effects at higher levels (≥grade 3) in 2 groups. The mutual high-grade toxicities associated with HDCT + ASCR were hematologic toxicity with a combined incidence of 25.0% (95%CI: 10.8–47.8%), ototoxicity events 17.7% (95%CI: 7.8–35.1%), gastrointestinal toxicity 15.8% (95%CI: 7.2–31.0%), stomatitis 7.2% (95%CI: 4.0–12.6%)

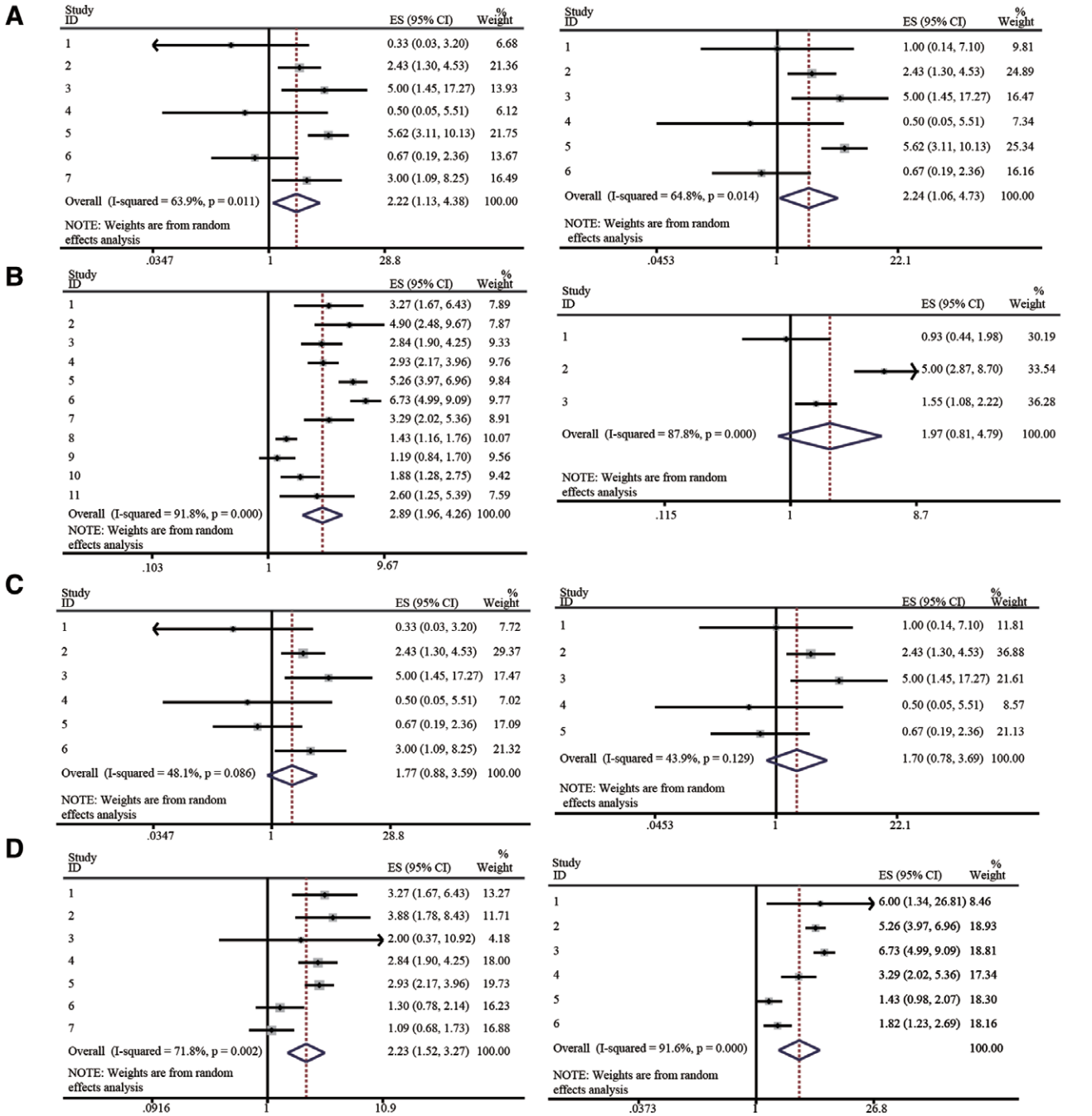

Figure 2. The 5-y/3-y overall survival for MBs. 5-y/3-y OS for all MB patients in group A (A). 5-y/3-y OS of all MB patients in group B (B). 5-y/3-y OS of patients in high-risk group A (C). 5-y OS of patients in high-risk group B (D). 5-y OS of patients in standard risk group B (E).

and hepatotoxicity 6.6% (95%CI: 3.6–11.8%), while nephrotoxicity 3.0% (95%CI: 0.2–30.5%) associated with HDCT + ASCR were relatively low in MB patients.

By comparing the grade 3/4 toxic and side effects of group A and group B, we found that the gastrointestinal toxicity of the radiotherapy and HDCT + ASCR group was higher than chemoradiotherapy group (*P*.016), and there was no statistical difference in other toxic and side effects (Table 4). Stratified analysis was carried out according to the standard risk group and the high-risk group, and the results showed that there was no statistical difference in grade 3/4 ototoxicity between the A/B group in the standard risk group (18.0% vs 20.8%, *P* = .516). In the high-risk group, the level 3/4 ototoxicity of group A was higher than that of group B (15.4% vs 2.0%, *P* = .001), and other toxic and side effects could not be compared.

3.7. Publication bias

There was no significant asymmetry in the funnel diagram of OS in MB patients undergoing postoperative radiotherapy and chemotherapy. (Document 1, Supplementary Digital Content, http://links.lww.com/MD/G880).

4. Discussion

According to the literature, the treatment of recurrent MB by HDCT + ACSR has been confirmed..[37,38] Therefore, since 2011, the NCCN cancer guidelines for the central nervous system have recommended this therapy as one of the options for adjuvant therapy in patients with local MB intracranial recurrence. In order to further improve the curative effect of newly diagnosed

Table 3

Comparison of various clinical endpoints of all/ high risk/ standard risk MBs between high-dose chemotherapy with autologous stem cell rescue and chemotherapy with radiotherapy.

		5-y OS		3-y OS		5-y PFS		3-y PFS	
		n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Rate (%)
All MBs	Group A	236	69.0 (53.0–81.4)	169	69.1 (51.5–82.6)	416	75.6 (67.9–81.9)	396	79.0 (70.2–85.7)
	Group B	1925	74.3 (66.2–81.0)	242	66.3 (44.7–82.7)	2304	71.1 (65.0–76.6)	301	69.5 (53.7–81.7)
	P value	0.086		0.507		0.067		**0.004**	
		5-y OS		5-y PFS		3-y OS		3-y PFS	
		n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Rate (%)
High risk MBs	Group A	103	64.0 (46.7–78.2)	103	62.5 (48.7–74.6)	83	62.9 (43.9–78.7)	83	63.5 (45.0–78.7)
	Group B	572	69.0 (60.2–76.6)	572	63.3 (57.6–68.7)	27	48.4	74	60.3 (37.9–79.1)
	P-value	0.318		0.824		0.183		0.694	
		5-y OS		5-y PFS		3-y OS		3-y PFS	
Standard risk MBs		n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Rate (%)
	Group A	86	85.0 (75–94)	269	83.6 (78.7–87.6)	86	85.0 (75–94)	269	86.6 (81.8–90.2)
	Group B	1070	76.9 (65.2–85.6)	1449	75.6 (69.4–80.8)	90	83 (75.2–90.9)	90	78.5 (69.9–87.1)
	P-value	0.089		**0.004**		0.779		0.078	

n = includes CR, PR, and SD, R = radiotherapy, S = surgery.

Bold values indicate a statistically significant difference between 2 groups ($P = .05$).

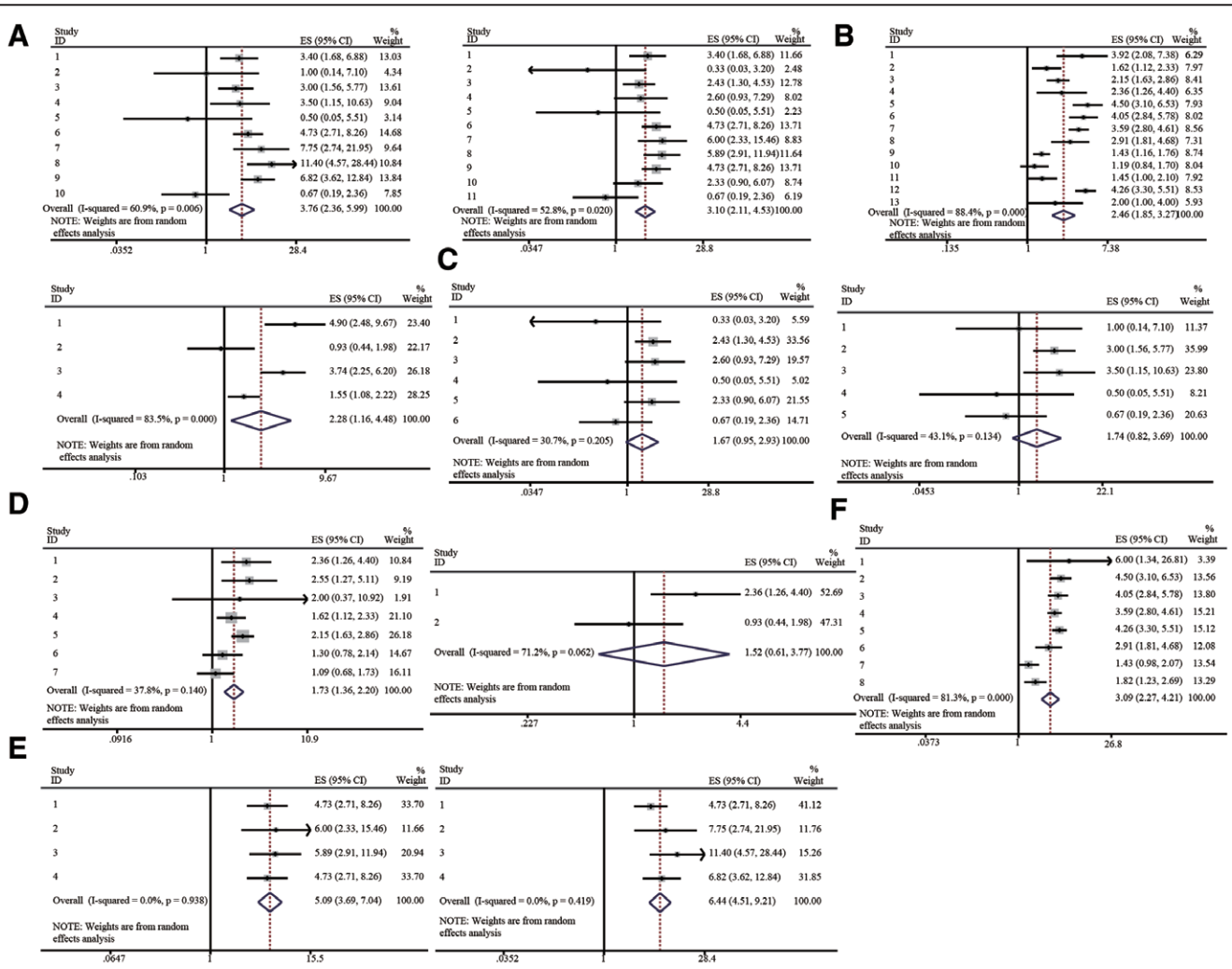

Figure 3. The 5-y/3-y progression-free survival for MBs. 5-y/3-y PFS for all MB patients in group A (A). 5-y/3-y PFS of all MB patients in group B (B). 5-y/3-y PFS of patients in high-risk group A (C). 5-y/3-y PFS of patients in high-risk group B (D). 5-y/3-y PFS of patients in standard risk group A (E). 5-y PFS of patients in standard risk group B (F).

Table 4

Comparison various grade 3/4 toxic event rates of MB between high-dose chemotherapy with autologous stem cell rescue and chemotherapy with radiotherapy.

	Ototoxicity		Hematologic toxicity		Stomatitis		Hepatotoxicity		Gastrointestinal toxicity		Nephrotoxicity	
	n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Rate (%)
Group A	138	17.7 (7.8–35.1)	23	25.0 (10.8–47.8)	154	7.2 (4.0–12.6)	154	6.6 (3.6–11.8)	43	15.8 (7.2–31.0)	154	3.0 (0.2–30.5)
Group B	1316	14.5 (8.6–23.4)	1471	44.6 (24.3–66.8)	152	5.1 (1.7–14.6)	794	5.0 (2.2–10.7)	270	6.0 (2.3–14.7)	758	4.4 (1.7–10.7)
P-value	0.365		0.076		0.496		0.46		0.016*		0.531	

R = radiotherapy, S = surgery.

*Bold values indicate a statistically significant difference between 2 groups (*P* = .05).

patients or reduce the radiation dose of the whole brain and spinal cord, some scholars have gradually tried to use HDCT + ACSR in the first-line treatment of MB patients. Some studies have shown that the method may further improve the prognosis of patients with brain tumors in high risk group, improve the event-free survival rate of patients, and increase the curative effect.[7–12] However, some studies had shown that HDCT + ACSR has no significant effectiveness in the newly diagnosed MB treatment. According to Nazemi's study, postoperative chemoradiotherapy, high dose chemotherapy and autologous stem cell rescue were given to patients with primary medulloblastoma in the high-risk group, the 5-y EFS and OS were 46 ± 11% and 50 ± 11%, respectively.[13] Like Nazemi's study, most of the existing studies are retrospective and small sample case observation studies, and there is no high-level evidence such as retrospective analysis of large cases, phase III clinical study of randomized control or meta-analysis. Therefore, the efficacy of HDCT + ACSR in the initial treatment of MB patients is uncertain. Since the HDCT + ASCR regimen is highly toxic and costly, it is particularly important to determine whether patients receiving this regimen can obtain an exact therapeutic effect. To answer this key question, we intend to conduct a meta-analysis based on existing research results. By searching Medline, EMBASE and Cochrane databases, we collected all the articles about postoperative radiotherapy sequential HCDT + ASCR or radiotherapy combined with common chemotherapy for newly diagnosed MB patients in the past 30 years, and conducted screening and data analysis. To compare the efficacy of initial MB receiving these 2 types of treatment, including CBR, OS and PFS, in order to determine whether the HCDT + ASCR treatment of newly diagnosed initial MB has a survival advantage over the traditional method. At the same time, the toxic and side effects of the 2 kinds of treatment methods were compared to clarify the exact effect and clinical value of the therapy, and guide clinical practice.

According to the conditions, literatures were searched for the clinical trials of classic therapy or radiotherapy combined with HCDT + ASCR for newly diagnosed medulloblastoma. According to the research purposes, a total of 22 articles meeting the requirements were included. A total of 2747 MB patients in 22 trials were included in the analysis: 416 patients in group A received radiotherapy combined with HCDT + ASCR, and 2331 patients in group B received postoperative classical radiotherapy and chemotherapy. Firstly, CBR, OS and PFS of the 2 groups were analyzed and compared. The results showed that HDCT + ASCR did not improve CBR in newly diagnosed MB patients (80.0% vs 71.5%, *P* = .262).There was a statistically significant difference in 3-y PFS between the 2 groups, that is, the 3-year progression-free survival in the radiotherapy and HDCT + ASCR groups was higher than that in the radiotherapy and chemotherapy groups (79.0% vs 69.5%, *P* = .004). The 5-y PFS in the radiotherapy and HDCT + ASCR groups were slightly higher than those in the radiotherapy and chemotherapy groups, but the difference was not statistically significant (75.6% vs 71.1%, *P* = .067).There was no difference in 3-y OS and 5-y OS between groups A and B of MB patients (*P* = .086; *P* = .507). In summary, HDCT + ASCR did not improve the clinical benefit, especially the overall survival of MB primary patients compared with conventional chemoradiotherapy. The more definite result was that the 3-year progress-free survival rate was improved. The results show that the efficacy and clinical value of the treatment have not been clearly affirmed. We further divided the 2 groups of patients into the high-risk group and the standard risk group for further stratified analysis. The results showed that the 5-y PFS of the standard risk group treated with radiotherapy combined with HDCT + ASCR was improved (83.6% vs 75.6%, *P* = .004). The 3-y PFS of the group also improved, but did not reach statistical difference (86.6% vs 78.5%, *P* = .078). Further comparison of OS, results between 2 groups of patients in different risk groups showed that this method did not achieve better results, including 3-y OS and 5-y OS, both in the high-risk group and the standard risk group (Table 3).To sum up, except is the possible improvement of the PFS of MB patients, especially those in the standard risk group, there is no clear therapeutic benefit in CBR and OS. This result suggests that for newly diagnosed MB patients, according to the existing clinical research results, HDCT + ASCR cannot be explicitly recommended as a conventional treatment.

In the papers included in this study, the chemotherapy regimen of HCDT + ASCR mainly include high-dose cyclophosphamide combined with cisplatin, vincristine, thiotepa or CM (cyclophosphamide, melphalan) + CTE (carboplatin, thiotepa, etoposide).The chemotherapy regimens in the classical chemoradiotherapy group mainly include triple chemotherapy regimens, vincristine + lomustine and cyclophosphamide + vincristine. The chemotherapy regimens in the group A were better than those in the group B in terms of both types and doses of chemotherapy drugs. In our study, grade 3/4 toxic and side effects of the 2 groups were also compared, and it was found that the gastrointestinal toxicity of the radiotherapy combined with HDCT + ASCR group was higher than that of the classical radiotherapy and chemotherapy group (15.8% vs 6.0%, *P* = .016). There was no statistical difference in hematological toxicity, ototoxicity, hepatotoxicity, renal toxicity and other aspects. To determine the reasons for the high gastrointestinal toxicity in group A patients, we carefully analyzed the specific chemotherapy regimen of each study and found that a dose-intensive chemotherapy was adopted in 1 article in group B.Itused 3 cycles of cisplatin (90 mg/m^2/day, day1, intravenous infusion) + etoposide (50 mg ≤ m^2, day 1 ≤ 21, oral) chemotherapy regimen after radiotherapy, and 8 cycles of cyclophosphamide (1.5 gm/m^2/day × 2 days, intravenous infusion) and vincristine (1.5 mg/m^2, days 1,8,15, intravenous infusion) chemotherapy regimens sequent, rather than general chemotherapy regimens. In order to avoid the possible deviation caused by this study, we removed it and compared the 2 groups again. The result was still that the gastrointestinal toxicity of patients in the HDCT + ASCR group was higher than that in the classical chemoradiotherapy group (15.8% vs 6.0%, *P* = .016), while there was no statistical difference in hematological toxicity, ototoxicity, hepatotoxicity, renal toxicity and other aspects. Patients were

stratified according to the standard risk group and high-risk group, and the results showed that in the high-risk group, the level 3/4 ototoxicity of the combined HDCT + ASCR group was higher than that of the general chemoradiotherapy group (15.4% vs2.0%, P = .001), while the level 3/4 ototoxicity of the A/B group was not statistically different in the general risk group (18.0% vs 20.8%, P = .516). To explore the causes of ototoxicity differences, we compared the chemotherapy regimens and specific doses in the 2 groups. We finded that the dose of cisplatin was the same in the classical chemoradiotherapy group and the combined HDCT + ASCR group, both at 75mg/m^2. The dose of cyclophosphamide was the difference, 1000 mg/m^2 in the classical chemoradiotherapy group, while 2000 mg/m^2 or 4000 mg/m^2 in the combined HDCT + ASCR group. The neurotoxic effect of cyclophosphamide may be the reason for the difference in ototoxicity when used in large group. Doses in conjunction with cisplatin, which needs further study and analysis. Other toxicities were not comparable due to the small amount of data included in the articles.

In summary, compared with the classical radiotherapy and chemotherapy regimen, radiotherapy combined with HDCT + ASCR improved the PFS, of some newly diagnosed MB patients, that is, 3-y PFS of the total patients and 5-y PFS of the standard risk group. However, the OS, of all newly diagnosed MB patients, both the high-risk group and the standard risk group, did not benefit from HDCT + ASCR. Perhaps an increase in the sample size would yield meaningful results. Because there were few OS data in the articles on the standard risk group, it could not be divided into different subgroups for further analysis. So, it is not clear that if different chemotherapy regimens affect the OS. Moreover, radiotherapy combined with HDCT + ASCR regimen has higher side effects and higher medical costs. Taken together, this study suggests that there is not enough evidence to recommend this method for postoperative adjuvant therapy in newly diagnosed medulloblastoma patients.

Of course, the study has some limitations. First of all, because of the high difficulty, high risk, high side effects of the treatment, and patients had to bear high medical costs, so generally only a small number of patients received treatment. Therefore, most of the existing studies were retrospective or small sample observational studies, lack of randomized controlled studies required by META analysis, so it would have a certain impact on the accuracy and credibility of the results. Second, due to the heterogeneity of the clinical studies included, the D-L model was selected to collect the overall results in order to reduce the impact of the study. However, due to the number of <20 studies and the limitations of the model itself, its impact on the results of the study could not be completely eliminated. Third, in the aspect of bias assessment, the study adopted funnel plot for analysis. Compared with Begg test and Egger test, it may reduce the credibility of the risk of bias and make the findings potentially publication bias. But no matter what, because the high risk, more and stronger side effects, complex clinical process and higher economic burden, it is difficult to accumulate large sample or higher-level research materials. Therefore, under the existing conditions, the results of this study still have a certain clinical value, worthy of attention and further study.

Author contributions

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