The Safety and Effectiveness of Melphalan-Based Intra-Arterial Chemotherapy for Retinoblastoma: An Updated Single-Arm Systematic Review and Meta-Analysis

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Melphalan-based intra-arterial chemotherapy was considered an innovative treatment for retinoblastoma patients because high rates of globe salvage could be obtained. Now it has been widely applied for primary or secondary treatment of retinoblastoma. This meta-analysis summarizes the most up-to-date evidence regarding the safety and effectiveness of melphalan-based intra-arterial chemotherapy in the treatment of retinoblastoma. The authors searched PubMed, EMBASE, and the Web of Science electronic databases for studies investigating the safety and effectiveness of melphalan-based intra-arterial chemotherapy in the treatment of retinoblastoma. Studies reporting outcomes and complications of melphalan-based intra-arterial chemotherapy for the treatment of retinoblastoma patients would be included. A total of 33 observational studies that involved 1900 patients and 2336 eyes were included. The overall globe salvage rate was 79.6% (773/971 eyes, 0.74 [95% CI: 0.66, 0.80]) for patients treated with IAC as primary therapy in 28 studies. The overall globe salvage rate was 66.4% (923/1391 eyes, 0.68 [95% CI: 0.60, 0.76]) for patients treated with IAC as secondary therapy in 25 studies. The most common ocular complications were retinopathy (32%) and palpebral edema (29.7%). The most common systemic complications were nausea/vomiting (20.9%). The overall metastasis rate was 1.1% (21/1793 patients, 0.038 [95% CI: 0.020, 0.048]). Twenty-nine studies that involved 1783 patients reported the mortality and the overall mortality was 1.5% (26/1783 patients, 0.029 [95% CI: 0.020, 0.048]). Our meta-analysis showed that melphalan-based IAC treatment was an option for retinoblastoma patients with acceptable efficacy according to retrospective studies. Further high-quality randomized control trials are necessary to provide more accurate and reliable results.

1. Introduction

Retinoblastoma is the most common ocular malignancy in children, and the incidence is about 11 new cases per million individuals under 5 years old in Europe and the US [1, 2]. 75% of these patients will present with unilateral disease, with a median age peak of 2 to 3 years [1, 3]. Enucleation, systemic chemotherapy, radiotherapy, and local therapies are considered standard treatment methods. However, in the past decade, intra-arterial chemotherapy (IAC) was used for improving tumor control and increasing globe salvage rates as a primary or secondary treatment [4].

IAC, a local administration method, importantly avoided several adverse reactions caused by systemic chemotherapy such as ototoxicity and neurotoxicity [5]. Before the application of IAC, nearly 80% of advanced patients would eventually be forced to choose enucleation [6]. In recent years, melphalan-based intra-arterial chemotherapy has been extensively applied for the treatment of retinoblastoma patients [7]. Other major combination chemotherapy drugs include topotecan, carboplatin, and methotrexate. Though an increasing number of centers worldwide have adopted IAC, the optimal role for IAC is still undetermined.

Some previous systematic reviews have provided an extensive assessment of the evidence for IAC use in retinoblastoma [8, 9]. Since these studies, there have been several further studies published. In addition, the lack of
randomized controlled trials makes the pivotal assessment of effectiveness and adverse reaction rates difficult. The authors conducted this systematic review and meta-analysis and provided an updated review of the IAC technique for the treatment of retinoblastoma patients.

**2. Method**

2.1. Inclusion Criteria. Studies that investigated the safety and effectiveness of melphalan-based intra-arterial chemotherapy for retinoblastoma and reported any of the following: globe salvage, ocular complications, systemic complications, metastasis, and death would be included.

2.2. Retrieval Strategy. This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations. This study was not a human or animal experiment; thus, ethical approval was not necessary. PubMed, EMBASE, and the Web of Science electronic databases were searched with the terms “intra-arterial chemotherapy,” “intra-arterial therapy,” “melphalan,” and “retinoblastoma.” In addition, reference lists of the included studies were manually checked for potentially eligible studies, and Google Scholar search engines were used to find additional references. The last search was performed on October 8, 2021, without any restriction to the language of publication.

2.3. Literature Screening and Data Extraction. Two authors independently completed the literature screening and data extraction. The extracted general data included author, year, chemotherapy agents, follow-up, country of publication, and sample size. The main outcomes contained globe salvage, ocular complications, systemic complications, metastasis, and death. A third reviewer would be invited if there were any disputes.

2.4. Evaluation of Literature Quality. The methodological qualities of the non-RCTs were assessed independently by two authors using the Methodological Index for Non-Randomized Studies (MINORS) [10].

2.5. Statistical Analysis. Outcomes were estimated by calculating the pooled odds ratio (OR) (95% confidence intervals (CIs)) by RevMan software (version 5.1; Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was assessed by the $I^2$ test. $I^2 < 50\%$ suggests low heterogeneity. The analysis result of the single rate meta-analysis method was adopted (P2 and SE2 data), which requires effect size conversion [11]. Conversion of effect indicators: $Pt = OR/(1 + OR)$, 95% CI lower limit conversion: $LL = LLOR/(1 + LLOR)$, and 95% CI upper limit conversion: $UL = ULOR/(1 + ULOR)$.

**3. Results**

3.1. Search Results and Characteristics of Included Studies. A total of 581 potential articles were initially identified through database searches on 8 October 2021. A total of 537 studies were considered potentially eligible for further assessment after duplicates were removed. Finally, 33 observational studies [5, 11–42] that involved a total of 1900 patients and 2336 eyes published between 2011 and 2021 met the inclusion criteria and were included in this meta-analysis after a full-text review. All these studies reported indications for IAC as primary or secondary. Figure 1 shows the literature selection process. Table 1 summarizes the details of the included studies.

3.2. Literature Quality. All studies were assessed using the MINORS score (Table 2). All included studies scored 13–14. Due to the lack of a control group, the risk of bias was found in all the studies, and this was moderate throughout.

4. Outcomes

4.1. Globe Salvage. Thirty-three studies that involved 1900 patients and 2336 eyes reported globe salvage rates of 30% to 100%. The overall globe salvage rate was 79.6% (773/971 eyes) for patients treated with IAC as primary therapy in 28 studies. After pooling single-arm studies, the overall effect size of the proportion of globe salvage was 0.74 (95% CI: 0.66, 0.80) (Figure 2). The overall globe salvage rate was 66.4% (923/1391 eyes) for patients treated with IAC as secondary therapy in 25 studies. After pooling single-arm studies, the overall effect size of the proportion of globe salvage was 0.68 (95% CI: 0.60, 0.76) (Figure 3).

4.2. Ocular Complications. Ocular complications are described in Table 3. The most common ocular complications were retinopathy, with 8 events of 25 eyes and 25 patients (32%); palpebral edema, with 22 events of 74 eyes and 68 patients (29.7%); choroidal occlusion, with 5 events of 25 eyes and 21 patients (20%); and retinal detachment, with 28 events of 158 eyes and 148 patients (17.7%).

4.3. Systemic Complications. Systemic complications are described in Table 3. The most common systemic complications were nausea/vomiting, with 115 events of 549 patients (20.9%); cardiorespiratory disturbances, with 4 events of 25 patients (16%); and neutropenia, with 7 events of 64 patients (10.9%).

4.4. Metastasis. Thirty studies that involved 1793 patients reported the metastasis rate. Most patients in these studies did not have metastasis. The overall metastasis rate was 1.1% (21/1793 patients). After pooling single-arm studies, the overall effect size of the proportion of metastasis was 0.038 (95% CI: 0.020, 0.038) (Figure 4). Details are shown in Table 4.

4.5. Death. Twenty-nine studies that involved 1783 patients reported the mortality, and the overall mortality was 1.5% (26/1783 patients). After pooling single-arm studies, the overall effect size of the proportion of metastasis was 0.029
581 of records identified through database searching

537 of records after duplicates removed

491 articles excluded after the screening of the following items:
1. Reviews
2. Titles
3. Abstract

46 unique abstracts remain for further evaluation

13 studies excluded after full text review based on:
1. Intervention method
2. Outcomes

537 of records after duplicates removed

46 unique abstracts remain for further evaluation

13 studies excluded after full text review based on:
1. Intervention method
2. Outcomes

33 studies included for systematic review and meta-analysis

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**Figure 1:** Flow diagram shows the process of literature selection.

**Table 1:** Characteristics of included studies.

| Study                  | Chemotherapy agents                                      | Number of eyes | Primary number of eyes | Secondary number of eyes | Follow-up duration (months) | County/region | Design     |
|-----------------------|----------------------------------------------------------|----------------|------------------------|--------------------------|-----------------------------|---------------|------------|
| Abramson, et al. 2016 | Melphalan, topotecan, carboplatin, and methotrexate      | 120            | 60                     | 60                       | 36.0                        | USA           | Retrospective |
| Akyüz, et al. 2015    | Melphalan                                                | 56             | 12                     | 44                       | 11.9                        | Turkey        | Retrospective |
| Chen, et al. 2017     | Melphalan, topotecan, and carboplatin                     | 107            | 30                     | 77                       | 13.6                        | China         | Retrospective |
| Chen, et al. 2016     | Melphalan, topotecan, and carboplatin                     | 13             | NA                     | 28                       | 28                          | China         | Retrospective |
| Francis, et al. 2018  | Melphalan, topotecan, and carboplatin                     | 436            | 228                    | 208                      | 23.6                        | USA           | Retrospective |
| Funes, et al. 2018    | Melphalan, topotecan, and carboplatin                     | 97             | 35                     | 62                       | 48.7                        | Argentina     | Retrospective |
| Ghassemi, et al. 2014 | Melphalan, topotecan, and carboplatin                     | 24             | 6                      | 18                       | 17                          | Iran          | Retrospective |
| Gobin, et al. 2011    | Melphalan, topotecan, and methotrexate                    | 91             | 43                     | 48                       | 13.0                        | USA           | Retrospective |
| Hua, et al. 2018      | Melphalan and topotecan                                  | 84             | 0                      | 84                       | 14.2                        | China         | Retrospective |
| Kiratli, et al. 2018  | Melphalan and topotecan                                  | 30             | 30                     | NA                       | 4.0                         | Turkey        | Retrospective |
| Leal-Leal, et al. 2016| Melphalan and topotecan                                  | 11             | 0                      | 11                       | 14.3                        | Mexico        | Retrospective |
| Li, et al. 2021       | Melphalan, topotecan, and carboplatin                     | 73             | NA                     | NA                       | 7                           | China         | Retrospective |
| Liu, et al. 2020      | Melphalan, topotecan, and carboplatin                     | 14             | 1                      | 13                       | 17.0                        | Malaysia      | Retrospective |
| Marr, et al. 2012     | Melphalan, topotecan, and carboplatin                     | 26             | 26                     | NA                       | 14                          | USA           | Retrospective |
| Michaels, et al. 2016 | Melphalan, topotecan, and carboplatin                     | 19             | 7                      | 12                       | 13.0                        | USA           | Retrospective |
| Muen, et al. 2012     | Melphalan                                                | 15             | 0                      | 15                       | 9                            | UK            | Retrospective |
| Munier, et al. 2011   | Melphalan                                                | 13             | 9                      | 4                        | 7.0                          | Switzerland   | Retrospective |
### Table 1: Continued.

| Study                        | Chemotherapy agents           | Number of eyes | Primary number of eyes | Secondary number of eyes | Follow-up duration (months) | County/region | Design       |
|------------------------------|-------------------------------|----------------|------------------------|--------------------------|-----------------------------|---------------|--------------|
| Munier, et al. 2017          | Melphalan                     | 25             | 25                     | NA                       | 41.7<sup>a</sup>            | Switzerland   | Retrospective|
| Ong, et al. 2015 Oporto, et al. 2021 | Melphalan and topotecan       | 35             | NA                     | NA                       | 36.5                        | Taiwan        | Retrospective|
| Parareda, et al. 2014        | Melphalan                     | 12             | 12                     | NA                       | 29.5                        | Spain         | Prospective  |
| Peterson, et al. 2011        | Melphalan                     | 17             | 0                      | 17                       | 8.6<sup>b</sup>             | USA           | Retrospective|
| Reddy, et al. 2017           | Melphalan and topotecan       | 9              | 0                      | 9                        | 21.0                        | UK            | Retrospective|
| Rishi, et al. 2017           | Melphalan and topotecan       | 10             | 2                      | 8                        | 26.0                        | India         | Retrospective|
| Rishi, et al. 2020 Rojanaporn, et al. 2019 | Melphalan, topotecan, and carboplatin | 27             | 7                      | 20                       | 32<sup>a</sup>              | Thailand      | Retrospective|
| Shields, et al. 2014         | Melphalan, topotecan, and carboplatin | 70             | 36                     | 34                       | 19.0                        | USA           | Retrospective|
| Shields, et al. 2021         | Melphalan, topotecan, and carboplatin | 341            | 160                    | 207                      | NA                          | USA           | Retrospective|
| Suzuki, et al. 2011          | Melphalan                     | 408            | 50                     | 358                      | 74.0                        | Japan         | Retrospective|
| Taich, et al. 2014           | Melphalan and topotecan       | 27             | 5                      | 22                       | 11.7                        | Argentina     | Retrospective|
| Thampi, et al. 2013          | Melphalan                     | 20             | 12                     | 8                        | 15                          | USA           | Retrospective|
| Tuncer, et al. 2016          | Melphalan                     | 24             | 24                     | NA                       | 29                          | Turkey        | Retrospective|
| Venturi, et al. 2013         | Melphalan                     | 41             | 17                     | 24                       | 13.0                        | Italy         | Retrospective|

Number<sup>a</sup>: median; NA: not available.

### Table 2: MINORS appraisal scores for the included retrospective studies.

| Study                        | Methodologic items<sup>*</sup> | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Total |
|------------------------------|--------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|-------|
| Abramson, et al. 2016        |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Akyüz, et al. 2015           |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Chen, et al. 2017            |                                | 2 | 2 | 0 | 2 | 0 | 2 | 1 | 0 | 0  | 2  | 0  | 2   | 13    |
| Chen, et al. 2016            |                                | 2 | 2 | 0 | 2 | 0 | 2 | 1 | 0 | 0  | 2  | 0  | 2   | 13    |
| Francis, et al. 2018         |                                | 2 | 2 | 0 | 2 | 0 | 2 | 1 | 0 | 0  | 2  | 0  | 2   | 13    |
| Funes, et al. 2018           |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Ghassemi, et al. 2014         |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Gobin, et al. 2011            |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Hua, et al. 2018              |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Kirali, et al. 2018           |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Leal-Leal, et al. 2016        |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Li, et al. 2021               |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Liu, et al. 2020              |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Marr, et al. 2012             |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Michaels, et al. 2016         |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Muen, et al. 2012             |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Munier, et al. 2011           |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Munier, et al. 2017           |                                | 2 | 2 | 0 | 2 | 0 | 2 | 1 | 0 | 0  | 2  | 0  | 2   | 13    |
| Ong, et al. 2015              |                                | 2 | 2 | 0 | 2 | 0 | 2 | 1 | 0 | 0  | 2  | 0  | 2   | 13    |
| Oporto, et al. 2021           |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Parareda, et al. 2014         |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Peterson, et al. 2011         |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
| Reddy, et al. 2017            |                                | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 0  | 2  | 0  | 2   | 14    |
5. Discussion

Systemic chemotherapy remained the standard care for most advanced cancer patients, such as nonsmall cell lung cancer [43] and gastric cancer [44]. Systemic administration means that the drug will be acted on throughout the body, and it is more likely to have drug-related adverse effects.

A combination of intravenous chemotherapy with vincristine, etoposide, and carboplatin was the classical chemotherapy for retinoblastoma in the past [1]. Yamane et al. [45] first reported the selective ophthalmic arterial infusion of chemotherapy in 2004. Subsequently, despite the apparent technical challenge of effectively catheterizing a small vessel, this technique has become widely utilized. As a
Table 3: Complication.

| Complications                                | No. of events | Total eyes | Rate     | Total patients |
|----------------------------------------------|---------------|------------|----------|----------------|
| **Ocular complications**                     |               |            |          |                |
| Avascular retinopathy                        | 5             | 158        | 0.032    | 137            |
| Arteriolar sclerosis                         | 2             | 12         | 0.167    | 11             |
| Aseptic cellulitis                           | 2             | 35         | 0.057    | 29             |
| Cataract                                     | 12            | 201        | 0.060    | 165            |
| Chorioretinal atrophy                        | 31            | 626        | 0.050    | 535            |
| Choroidal occlusion                          | 5             | 25         | 0.200    | 21             |
| Choroidal ischemia                           | 7             | 341        | 0.021    | 313            |
| Conjunctiva chemonis                         | 1             | 14         | 0.071    | 14             |
| Extraocular muscle paresis                   | 0             | 24         | 0.000    | 22             |
| Internal carotid artery occlusion            | 0             | 24         | 0.000    | 22             |
| Loss of eyalshes                             | 21            | 165        | 0.127    | 143            |
| Multinucleated macrophages in choroid and retina | 2           | 12         | 0.167    | 11             |
| Neovascular glaucoma                         | 1             | 26         | 0.038    | 24             |
| Neovascularisation                           | 55            | 366        | 0.150    | 338            |
| Oculomotor nerve palsy                       | 2             | 35         | 0.057    | 29             |
| Ophthalmic artery occlusion                  | 0             | 24         | 0.000    | 22             |
| Oclusive vasculopathy                        | 22            | 276        | 0.080    | 232            |
| Optic nerve disorder                         | 2             | 24         | 0.083    | 15             |
| Ophthalmoplegia                              | 10            | 123        | 0.081    | 121            |
| Phthisis                                     | 7             | 132        | 0.053    | 112            |
| Ptosis                                       | 25            | 366        | 0.068    | 330            |
| Periocular edema                             | 107           | 1019       | 0.105    | 829            |
| Palpebral oedema                             | 22            | 74         | 0.297    | 68             |
| Palpebral erythema                           | 1             | 25         | 0.040    | 25             |
| Periorbital pigmentation                     | 1             | 35         | 0.029    | 29             |
| Retinopathy                                  | 8             | 25         | 0.320    | 25             |
Table 3: Continued.

| Complications                  | No. of events | Total eyes | Rate  | Total patients |
|--------------------------------|---------------|------------|-------|----------------|
| Retinal atrophy                | 2             | 12         | 0.167 | 11             |
| Retinal detachment             | 28            | 158        | 0.177 | 148            |
| Retinal ischemia               | 13            | 341        | 0.038 | 313            |
| Retinal artery precipitation   | 6             | 79         | 0.076 | 70             |
| Strabismus                     | 3             | 54         | 0.056 | 60             |
| Vitreous hemorrhage            | 55            | 448        | 0.123 | 366            |
| Vascular spasm                 | 2             | 25         | 0.080 | 21             |

**Systemic complications**

|                     |               |            |       |                |
|---------------------|---------------|------------|-------|----------------|
| Anaphylaxis         | 3             |            | 0.039 | 77             |
| Bronchospasm        | 34            |            | 0.062 | 549            |
| Cardiorespiratory disturbances | 4 | | 0.160 | 25 |
| Fever               | 47            |            | 0.081 | 579            |
| Groin hematoma      | 1             |            | 0.067 | 15             |
| Limb ischemia       | 7             |            | 0.109 | 64             |
| Neutropenia         | 7             |            | 0.000 | 349            |
| Nausea/vomiting     | 115           |            | 0.209 | 549            |
| Stroke              | 2             |            | 0.002 | 846            |
| Transfusion         | 1             |            | 0.001 | 680            |
| Thromboembolism     | 0             |            | 0.000 | 14             |
| Vascular dissection | 0             |            | 0.000 | 313            |
| Vasospasm           | 2             |            | 0.080 | 25             |

**Table 4:** The overall effect size of the proportion of metastasis.
local administration method, intra-arterial chemotherapy has been performed in 26 countries worldwide in the last seven years [46]. Intra-arterial chemotherapy for retinoblastoma has been adopted as a first-line treatment option by numerous tertiary centers, and Ravindran et al. [9] performed a meta-analysis with 20 studies with a 35.6% globe salvage rate. However, various drugs were adopted in different studies. Besides, there have been several novel studies published afterward. Thus, it is necessary to update the results.

We conducted this meta-analysis with 33 studies involving a total of 1900 patients and 2336 eyes to evaluate melphalan-based intra-arterial chemotherapy for the management of retinoblastoma patients. IAC was used in all studies, and the chemotherapy drugs should include melphalan. The overall globe salvage rate was 79.6% for patients treated with IAC as primary therapy and 66.4% for patients treated with IAC as secondary therapy. These results were similar to a newly published systemic review performed by Runnels et al. [8], which included 24 studies. The globe salvage rate was lower than that reported by Ravindran et al. [9], which included 20 studies. However, IAC used by primary or secondary was not considered in that study. Periocular edema (10.5%) was the most common ocular complication reported in the systemic review performed by Runnels. However, the most common ocular complication in our study is retinopathy (32%), followed by palpebral edema (29.7%). Besides, we reported a lower rate of metastasis (1.1%) and death (1.5%).

5.1. Limitations of This Study. First, due to the lack of randomized controlled trials, we cannot perform this meta-analysis based on high-level studies. Second, several other chemotherapeutic regimens were included besides melphalan, though we have tried to limit the study to at least melphalan. This may still lead to a certain degree of heterogeneity. Third, little information was known about progression-free survival and disease control rates after IAC treatment, as these are important indicators of treatment effectiveness.

### Table 4: Metastasis and death.

| Study                      | Number of patients | Number of metastasis | Number of deaths |
|----------------------------|--------------------|----------------------|------------------|
| Abramson, et al. 2016      | 60                 | 0                    | 1                |
| Akyüz, et al. 2015         | 46                 | 2                    | 2                |
| Chen, et al. 2017          | 73                 | 0                    | 0                |
| Chen, et al. 2016          | 10                 | 0                    | NA               |
| Francis, et al. 2018       | 300                | 5                    | 6                |
| Funes, et al. 2018         | 81                 | 0                    | 2                |
| Ghassemi, et al. 2014      | 24                 | 0                    | 0                |
| Gobin, et al. 2011         | 78                 | 2                    | 0                |
| Hua, et al. 2018           | 62                 | 0                    | 0                |
| Kiratli, et al. 2018       | 28                 | NA                   | 0                |
| Leal-Leal, et al. 2016     | 11                 | 0                    | 0                |
| Li, et al. 2021            | 71                 | NA                   | NA               |
| Liu, et al. 2020           | 14                 | 0                    | 0                |
| Marr, et al. 2012          | 25                 | 0                    | NA               |
| Michaels, et al. 2016      | 17                 | 0                    | 0                |
| Muen, et al. 2012          | 14                 | 0                    | 0                |
| Munier, et al. 2011        | 13                 | 0                    | 0                |
| Munier, et al. 2017        | 25                 | 0                    | 0                |
| Ong, et al. 2015           | 12                 | 3                    | 2                |
| Oporto, et al. 2021        | 29                 | 0                    | 0                |
| Parareda, et al. 2014      | 11                 | NA                   | NA               |
| Peterson, et al. 2011      | 15                 | 0                    | 0                |
| Reddy, et al. 2017         | 9                  | 0                    | 0                |
| Rishi, et al. 2017         | 10                 | 0                    | 0                |
| Rishi, et al. 2020         | 15                 | 0                    | 0                |
| Rojanaporn, et al. 2019    | 26                 | 1                    | 1                |
| Shields, et al. 2014       | 67                 | 0                    | 0                |
| Shields, et al. 2021       | 313                | 0                    | 0                |
| Suzuki, et al. 2011        | 343                | 8                    | 12               |
| Taich, et al. 2014         | 26                 | 0                    | 0                |
| Thampi, et al. 2013        | 16                 | 0                    | 0                |
| Tuncer, et al. 2016        | 22                 | 0                    | 0                |
| Venturi, et al. 2013       | 34                 | 0                    | 0                |
| Total (event)              |                    | 21                   | 26               |
| Total (patients)           |                    | 1793                 | 1783             |
| Rate                       |                    | 1.1%                 | 1.5%             |

NA: not available.
5.2. Conclusions. Our meta-analysis showed that melphalan-based IAC treatment was an option for retinoblastoma patients with acceptable efficacy according to retrospective studies. Further high-quality randomized control trials are necessary to provide more accurate and reliable results.

Data Availability
All data generated or analyzed during this study are included within the article.

Ethical Approval
It was not required as this research was a meta-analysis.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Yang Cao contributed to designing the study and writing this article. Mi Zhou and Min Tian were responsible for collecting the data and performing the statistical analysis. Hong-bin LV contributed to reviewing this article.

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