

A meta-analysis of the efficacy of intra-arterial chemotherapy for the management of retinoblastoma patients

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Abstract

Background. Intra-arterial chemotherapy (IAC) is considered a unique technique for retinoblastoma (Rb) management and has widespread applicability as a first-line or second-line treatment due to the high globe survival rates.

Objectives. This meta-analysis aimed to assess the efficacy of IAC approach among patients with Rb.

Materials and methods. This study outlined the most recent research on IAC effectiveness in Rb treatment. We carried out a systematic search for published papers examining IAC treatment among patients with Rb using electronic search engines, including Embase, Web of Science (WoS), PubMed, OVID, and Google Scholar, until October 2021.

Results. This meta-analysis included 39 observational studies with 2604 treated eyes and 3112 individuals who were eligible for inclusion. Enucleation rates varied from 0% to 43.7% in the chosen trials, with an odds ratio (OR) of 0.52 (95% confidence interval (95% CI): 0.41–0.66, $p < 0.0001$). A range of 30–100% was reported for globe salvage across 27 investigations involving 2310 eyes. The estimated OR of globe salvage was 2.41, with 95% CI of 1.6–3.63 and a p -value < 0.0001 . The combined total effect sizes and the death rate for the proportion of cases with metastatic Rb were as follows: OR = 0.03 (95% CI: 0.03–0.03) and OR = 0.05 (95% CI: 0.04–0.05, $p < 0.0001$), respectively.

Conclusions. Retrospective trials have shown that intra-arterial-based therapy for Rb is an effective choice. Intra-arterial chemotherapy also reduced enucleation and metastasis incidence rates. The paucity of evidence in the literature necessitates further high-level studies.

Key words: metastases, retinoblastoma, globe salvage

Cite as

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Background

Retinoblastoma (Rb) is an intra-ocular cancer that mainly affects young people throughout the world and carries life-threatening consequences. This type of cancer was identified in about 8000 patients globally.¹ A systemic delivery of intravenous chemotherapy (IVC) was the standard care approach that achieved encouraging results in Rb using laser adjunctive therapy and cryotherapy, while advanced Rb cases showed modest outcomes with IVC.

Since the development of intra-arterial chemotherapy (IAC), the direct intra-arterial delivery of chemotherapy has become the standard of care for salvage therapy at numerous tertiary ocular facilities globally.² This method assisted in the treatment of advanced Rb cases that would have otherwise been enucleated.^{1,3} Before the emergence of IAC, enucleation was performed in around 80% of advanced Rb cases classified as group D or E, according to the International Classification of Retinoblastoma (ICRB) group.⁴

Compared to intravenously delivered systemic chemotherapy, IAC has achieved higher levels of chemotherapy in tumor tissue and better outcomes. The systemic chemotherapeutic adverse effects of ototoxicity and neurotoxicity were reduced by IAC treatment.⁵ Furthermore, IAC can be delivered in 1 day, and the tumor can be controlled with 2 to 3 sessions.

Intra-arterial chemotherapy is beneficial as second-line therapy in refractory Rb that leads to improved globe salvage of eyes that would have otherwise been enucleated. However, patient selection and the procedure's complications have raised many concerns. Intra-arterial chemotherapy is an invasive therapeutic method necessitating an experienced team with multiple specialties, including a neurosurgeon, an interventional radiologist and a pediatric oncologist. In addition, IAC requires specialized centers and advanced techniques. However, through proper application in professional hands, the advantages of IAC outweigh its drawbacks.^{6,7}

Although IAC has demonstrated superior efficacy in terms of global salvage rates, the metastasis incidence rate among Rb patients treated with IAC remains unknown. In 2016, Yousef et al. conducted a systematic review of the evidence for IAC use in Rb treatment.⁸ Since then, several studies have been carried out. However, most patient cohort reports using comparative data were of insufficient quality, and differences in sample sizes led to challenging critical evaluation of problems and outcomes.⁹

Objectives

To assess the current research and update the existing evidence on the clinical effectiveness of IAC in patients with Rb, particularly those with advanced disease, we set out to review the studies conducted to date. The information provided by this meta-analysis is expected to help doctors in their clinical work.

Materials and methods

The current investigation was conducted according to the predetermined procedure based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocol.

Search strategy

Following the treatment of Rb with IAC, eligible trials assessed a minimum of one of the following outcomes: enucleation rate, metastatic incidence, globe salvage, or mortality. Studies describing the results of combined IAC and intravitreal treatment (IVT) were also included.

We considered research studies published in all languages and conducted in humans. The inclusion was not restricted by study size. Editorials, irrelevant research studies and review articles were all eliminated. The study search procedure is depicted in Table 1. The following criteria were met by the studies included in this meta-analysis: 1) well-designed prospective and retrospective studies; 2) studies that targeted Rb patients; 3) IAC therapy was the interventional procedure; 4) results of IAC therapy, either alone or in conjunction with IVT, were included in the investigation.

The exclusion criteria were as follows: 1) case reports, editorials, review articles, abstracts only, and research with a limited sample size (less than 10 subjects); 2) studies with missing or incomplete data and different outcomes other than the outcomes of interest; 3) studies performed with aims other than examining IAC outcomes in Rb; 4) study articles with therapeutic procedures other than IAC.

Identification

As shown in Table 1, we first conducted a search using a combination of MeSH terms and keywords related to IAC and Rb in electronic databases, including Embase, PubMed, Google Scholar, OVID, and the Cochrane Library, up until October 2021. After omitting duplicates, the retrieved papers were compiled into a single End-Note file. We examined the titles and abstracts to rule out the articles that did not discuss how IAC affected patients with Rb, enucleation rates, globe salvage, metastasis rate, or mortality. The collected studies were examined for pertinent information.

Screening

The first author's name, time frame, location, publication year, target patients, research procedure, number of subjects, demographics, and applicable clinical treatment features were all summarized in a predesigned form, as shown in Fig. 1. The assessment period was also related to the statistical analysis of odds ratios (ORs) with 95% confidence intervals (95% CIs) regarding relationships,

Table 1. Search strategy for each database

Database	Search strategy
PubMed	#1 "intra-arterial" [MeSH Terms] OR "chemosurgery procedures" [All Fields] OR "retinoblastoma" [All Fields] #2 "enucleation" [MeSH Terms] OR "globe salvage" [All Fields] OR "metastasis" [All Fields] OR "mortality" [All Fields] #3 #1 AND #2
Embase	#1 'intra-arterial chemotherapy'/exp OR 'chemosurgery procedures'/exp OR 'retinoblastoma'/exp #2 'enucleation'/exp OR 'ICBG'/exp OR 'globe salvage'/exp OR 'metastasis'/exp OR 'mortality'/exp #3 #1 AND #2
Cochrane Library	#1 (intra-arterial chemotherapy):ti,ab;kw OR (chemosurgery procedures):ti,ab;kw OR (retinoblastoma):ti,ab;kw (Word variations have been searched) #2 (enucleation):ti,ab;kw OR (globe salvage):ti,ab;kw OR (metastasis):ti,ab;kw OR (mortality):ti,ab;kw (Word variations have been searched) #3 #1 AND #2
OVID	#1 "intra-arterial chemotherapy" OR "chemosurgery procedures" [All Fields] OR "retinoblastoma" [All Fields] #2 "enucleation" OR "globe salvage" [All Fields] OR "metastasis" [All Fields] OR "mortality" [All Fields] #3 #1 AND #2
Google Scholar	#1 "intra-arterial chemotherapy" OR "chemosurgery procedures" OR "retinoblastoma" #2 "enucleation" OR "globe salvage" OR "metastasis" OR "mortality" #3 #1 AND #2

MeSH – medical subject headings; ti,ab;kw – terms in either title or abstract or keyword fields; exp – exploded indexing term.

Study title/ ID	
Author's name/ year	
Time frame	
Target population (number and characteristics)	
Country/settings	
Study design and intervention description	
Language	
Number of eyes treated	
Follow-up duration	
Outcome assessed	
Chemotherapy used	
Analysis method/instruments	
Results	
Quality assessment	
Comments	

Fig. 1. Predesigned form for data extraction

information resources, outcome assessment, and quantitative and qualitative review methodologies. Two authors independently evaluated the non-randomized controlled trials for study quality.

Information was gathered independently by 2 authors to determine if a study met the inclusion criteria. In case of a dispute, the corresponding author made the final decision. Data were individually extracted if there was variation in the data obtained from one of the trials. Two authors independently assessed procedural quality to determine the degree of bias in the retrieved studies.

The risk of bias

The Cochrane risk-of-bias tool was used to assess bias risk and procedural quality (RoB 2; Cochrane

Collaboration, London, UK).¹⁰ Following data extraction, the authors evaluated the quality of the eligible studies according to the Cochrane Collaboration criteria. The risk of bias was assessed as low, moderate or high. The bias risk was evaluated based on the randomization technique, blinding of the outcome assessment, missing data, and selective reporting. Any inconsistencies or disputes were addressed by re-examining the original publication.

Statistical analysis

The estimated ORs and 95% CIs were calculated. We also calculated the I^2 index, which was predicted to be between 0% and 100%. The I^2 index values of roughly 0% were evaluated as negligible heterogeneity, while those over 25% were perceived as minimal heterogeneity, with 50% and 75% indicating moderate and high heterogeneity, respectively.¹¹ In order to ascertain the correct model to be used, we analyzed the main discrepancies and similarities between the studies, including the effect size, discrepancies in the population characteristics, number of IAC sessions, follow-up duration, and methods. Based on the discrepancy assessment, all analyses used a random effects model. The stratification of studies per result category was performed for the subgroup analysis. A value of $p < 0.05$ indicated statistical significance for differences between the assessed outcomes in the analyzed studies. The Egger's regression test for quantitative bias assessment was performed (bias was present if $p \leq 0.05$) and funnel plots were used to qualitatively assess bias. The calculated p-values were two-sided. All measurements and graphs were created using Reviewer Manager (RevMan) software v. 5.3 (The Nordic Cochrane Centre Inc., Copenhagen, Denmark).

Results

Characteristics of the included studies

Initial search engine results identified 614 potential articles (Fig. 2). Thirty-nine articles^{3,12–49} published up until 2021 met the meta-analysis inclusion criteria after full-text evaluation and review. A total of 2604 eyes were treated in the included studies. Only 4 studies were prospective,

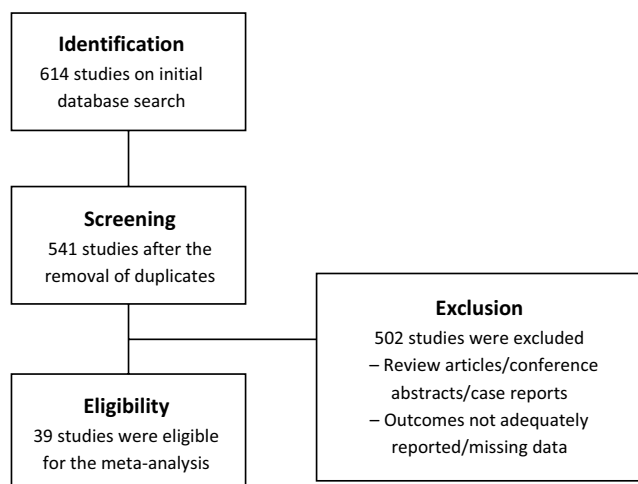


Fig. 2. Flowchart of the study search strategy

while most were retrospective ($n = 35$). The number of participants with Rb in the trials ranged from 10 to 500 at the beginning of the study. The chemotherapeutic drugs used included carboplatin, melphalan and topotecan. Indications for IAC were reported in all trials among Rb patients. Table 2 provides a summary of the major characteristics of the included research.

Enucleation rate

Nineteen studies explicitly assessed the enucleation rate with IAC. The rate of enucleation ranged from 0% to 43.7%, with the highest rate (>50%) reported by Hua et al. in 2018.³⁹ The estimated total pooled OR of enucleation rates was 0.53 (95% CI: 0.42–0.65, $p < 0.001$) with a considerably high level of heterogeneity ($I^2 = 98\%$), as shown in Fig. 3.

Globe salvage

The globe salvage rate was reported in 27 investigations of 2310 treated eyes and ranged from 30% to 100%. The overall percentage of Rb patients who underwent IAC treatment was 76.4%. With substantial heterogeneity ($I^2 = 90\%$), the calculated overall OR for globe salvage was 2.05 (95% CI: 1.62–2.60, $p < 0.001$), as shown in Fig. 4.

Table 2. The main characteristics of the included studies

Author's name, publication year	Region, study design	Treated eyes, n	Unilateral eye disease, %	Age [months], median (range)	Sessions, median (range)	Follow-up duration [months], median (range)	Chemotherapeutic agent
Abramson et al. (2010) ¹²	USA, prospective	28	82	11 (3–88)	3.2 (1–6)	15 (3–37)	topotecan, melphalan, carboplatin
Gobin (2011) ¹³	USA, retrospective	91	–	–	–	13	melphalan, topotecan, carboplatin, methotrexate
Munier et al. (2011) ¹⁴	Switzerland, retrospective	13	–	–	–	7	melphalan
Peterson et al. (2011) ¹⁵	USA, retrospective	17	38	18 (9–32)	1.4 (1–2)	8.6 (3–12)	melphalan (7.5 mg)
Suzuki et al. (2011) ¹⁶	Japan, retrospective	408	39	–	3.7 (1–18)	79 (58)	melphalan
Marr et al. (2012) ¹⁷	USA, retrospective	26	4	18 (0–62)	2.3 (1–4)	14 (1–43)	topotecan, carboplatin, melphalan
Muen et al. (2012) ¹⁸	UK, prospective	15	NA	17 (11–150)	1–3	9 (3–16)	melphalan
Thampi et al. (2013) ¹⁹	USA, retrospective	20	38	15 (7–63)	NA	15 (1–29)	melphalan
Venturi et al. (2013) ²⁰	Italy, retrospective	41	–	–	–	13	melphalan
Ghassemi et al. (2014) ²¹	Iran, retrospective	24	58	39 (14–120)	NA	17 (3–36)	topotecan + melphalan
Shields et al. (2014) ²²	USA, retrospective	70	63	20 (4–392)	3 (1–6)	–	melphalan + topotecan + carboplatin
Taich et al. (2014) ²³	Argentina, retrospective	27	–	–	–	11.7	melphalan and topotecan
Parareda et al. (2014) ²⁴	Spain, prospective	12	73	21 (7–51)	2.6 (1–5)	29.5 (6–57)	melphalan (3–5 mg)

Table 2. The main characteristics of the included studies – cont.

Author's name, publication year	Region, study design	Treated eyes, n	Unilateral eye disease, %	Age [months], median (range)	Sessions, median (range)	Follow-up duration [months], median (range)	Chemotherapeutic agent
Akyüz et al. (2015) ²⁵	Turkey, retrospective	56	–	–	–	11.9	melphalan
Ong et al. (2015) ²⁶	Taiwan, retrospective	17	42	18 (2–50)	3 (1–6)	22 (5–43)	–
Abramson et al. (2016) ²⁷	USA, retrospective	120	–	–	–	36	melphalan, topotecan, carboplatin, methotrexate
Chen et al. (2016) ²⁸	China, retrospective	13	–	–	2.6 (2–4)	28 (9–65)	melphalan, topotecan, carboplatin
Leal-Leal et al. (2016) ²⁹	Mexico, prospective	11	100	22.6 (12–36)	–	14.3 (1.8–28)	melphalan (4 mg), topotecan (1 mg)
Michaels et al. (2016) ³⁰	USA, retrospective	19	88	29 (5–192)	–	–	melphalan or topotecan
Tuncer et al. (2016) ³¹	Turkey, retrospective	24	77	NA	–	29 (6–55)	melphalan
Chen et al. (2017) ³²	China, retrospective	107	33	20 (4–95)	3.1 (2–5)	9.1 (1–26)	melphalan (0.5 mg/kg), topotecan (1 mg)
Fabian et al. (2017) ³³	UK, retrospective	64	33	11 (0.6–144)	55 (11–156)	38.7	melphalan
Munier et al. (2017) ³⁴	Switzerland, retrospective	25	100	33.5 ±25.9	–	–	melphalan (2.8–7.5 mg)
Reddy et al. (2017) ³⁵	UK, retrospective	9	–	–	–	–	melphalan, topotecan
Rishi et al. (2017) ³⁶	India, retrospective	10	20	26 (11–59)	3.8 (3–5)	21	melphalan, topotecan
Francis et al. (2018) ³⁷	USA, retrospective	436	38	13.4 (0.1–195)	–	26.5 (0–119.7)	melphalan, topotecan, carboplatin
Funes et al. (2018) ³⁸	Argentina, retrospective	97	–	–	4 (1–14)	48.7 (12–79)	carboplatin
Hua et al. (2018) ³⁹	China, retrospective	84	65	16 (4–96)	–	14.2 (3–28)	melphalan, topotecan
Kiratli et al. (2018) ⁴⁰	Turkey, retrospective	30	–	–	2.6	4.0 (1–16)	melphalan, topotecan
Rojanaporn et al. (2019) ⁴¹	Thailand, retrospective	27	–	–	–	32	melphalan, topotecan, carboplatin
Yassa et al. (2019) ³	Egypt, retrospective	30	–	–	–	14.2 (6–20)	melphalan
Liu et al. (2020) ⁴²	Malaysia, retrospective	14	–	–	–	17	melphalan, topotecan, carboplatin
Batu Oto et al. (2020) ⁴³	Turkey, retrospective	21	–	–	–	–	melphalan
Rishi et al. (2020) ⁴⁴	India, retrospective	24	–	–	–	28.6	melphalan, topotecan
González et al. (2021) ⁴⁵	Colombia, retrospective	100	39	8.70 (4.53–18.55)	–	29 (16–59)	melphalan + topotecan
Linde and Mustak (2021) ⁴⁶	South Africa, retrospective	25	–	–	–	47	melphalan + topotecan
Oporto et al. (2021) ⁴⁷	Chile, retrospective	35	–	–	–	36.5	melphalan, topotecan
Shields et al. (2021) ⁴⁸	USA, retrospective	341	–	–	–	–	melphalan, topotecan, carboplatin
Li et al. (2022) ⁴⁹	China, retrospective	73	–	–	–	7	melphalan, topotecan, carboplatin

NA – not applicable.

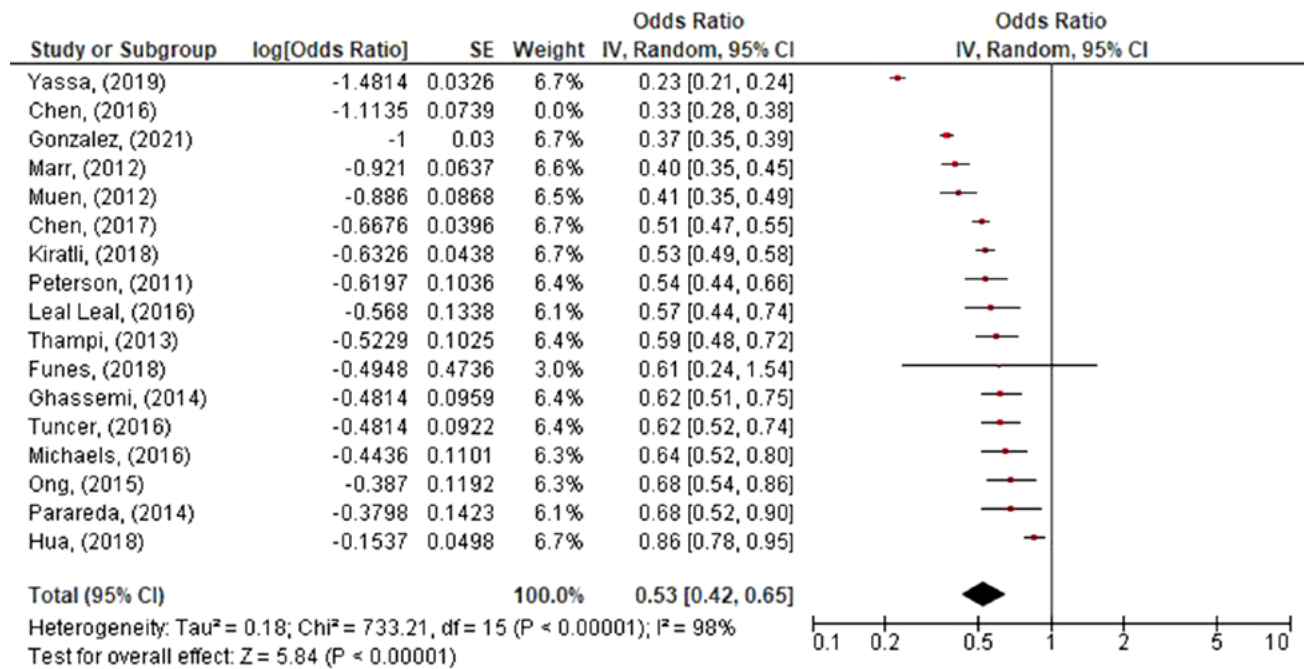


Fig. 3. Forest plot of the overall estimated effect sizes of enucleation rate

OR – odds ratio; 95% CI – 95% confidence interval; SE – standard error; df – degrees of freedom.

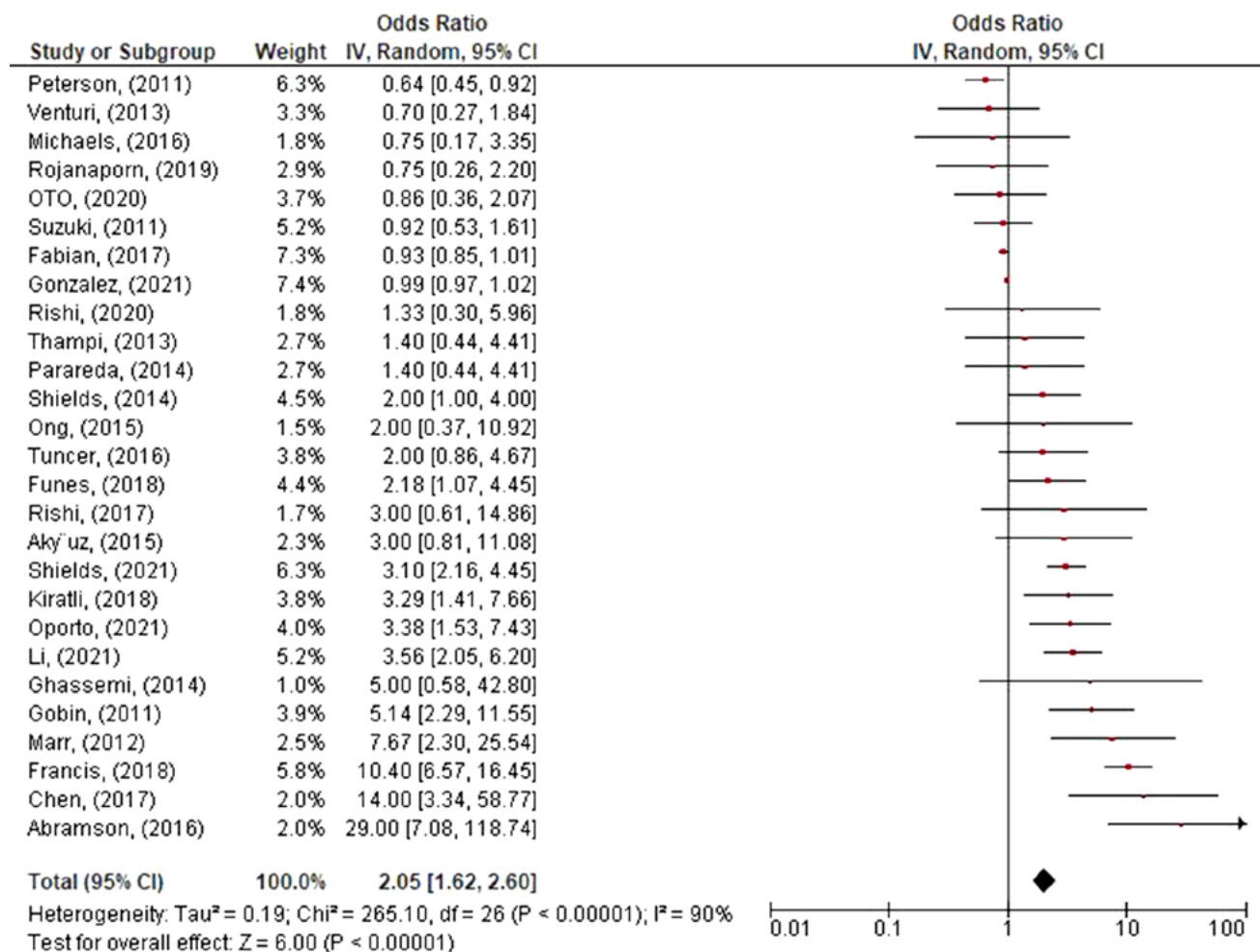


Fig. 4. Forest plot of the overall estimated effect sizes of globe salvage

OR – odds ratio; 95% CI – 95% confidence interval; SE – standard error; df – degrees of freedom.

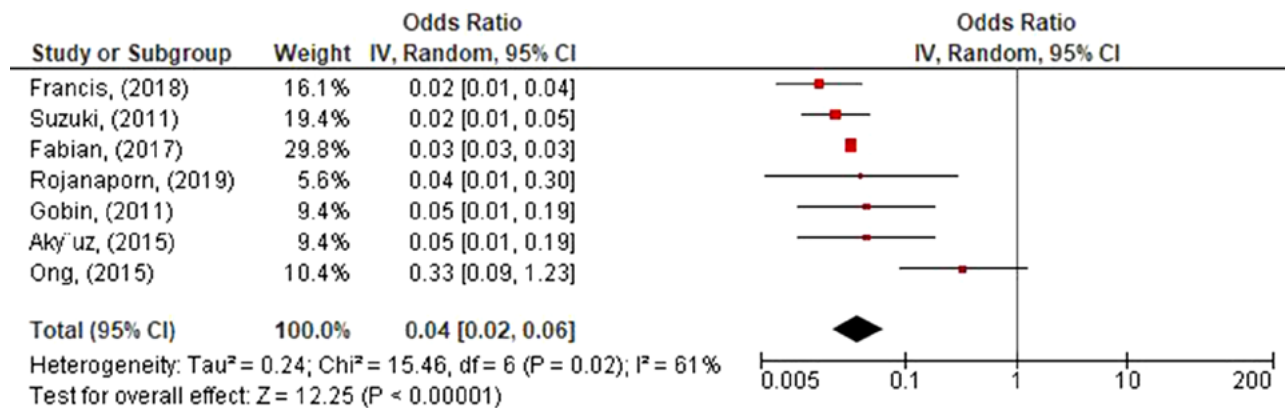


Fig. 5. Forest plot of the overall estimated effect sizes of metastasis

OR – odds ratio; 95% CI – 95% confidence interval; SE – standard error; df – degrees of freedom.

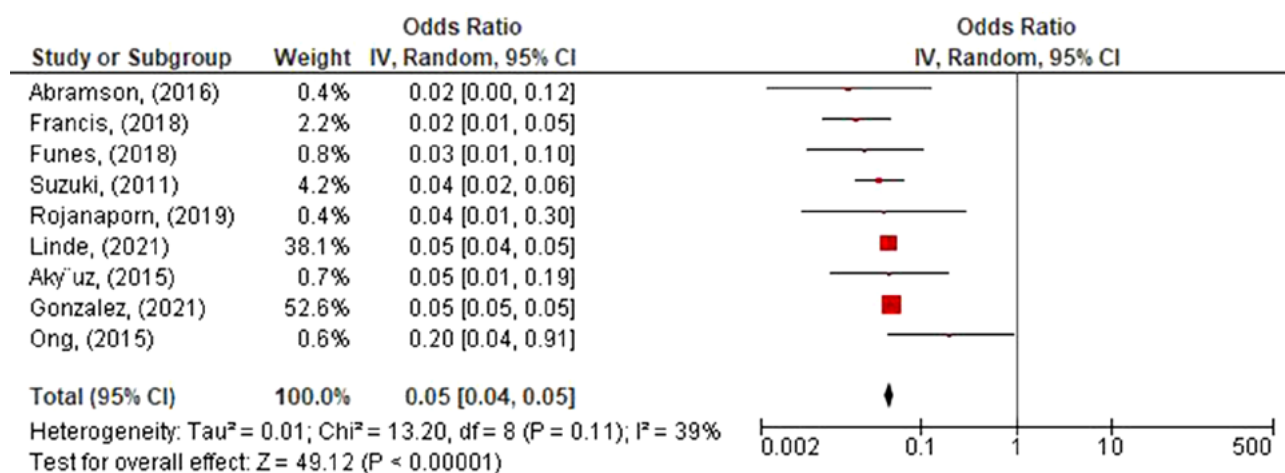


Fig. 6. Forest plot of the overall estimated effect sizes of mortality rate

OR – odds ratio; 95% CI – 95% confidence interval; SE – standard error; df – degrees of freedom.

Metastasis rate

According to 7 studies, the metastasis rate was 2.4%. The total impact size of the proportion of metastatic disease had an OR = 0.04 (95% CI: 0.02–0.06, $p < 0.001$). The estimated heterogeneity was 61% (Fig. 5).

Mortality rate

Nine studies with a total population of 1896 patients reported the mortality rate. The estimated overall mortality rate was 1.3%. The pooled mortality rate effect size had an OR = 0.05 (95% CI: 0.04–0.05, $p < 0.001$) with a low level of heterogeneity ($I^2 = 39\%$) (Fig. 6).

There were no adjustments for age, ethnicity or gender because none of the studies accounted for these factors.

Publication bias

There was no evidence of publication bias as shown by the symmetrical funnel plots (Fig. 7), where the vertical line

represented the summary of the estimated effect size. Moreover, Egger's test did not detect significant publication bias, and the estimated p -values for Fig. 7 were 0.317, 0.294, 0.527, and 0.461. Despite this, most studies included in this meta-analysis had low procedural quality because of the limited size of the study populations. None of the research studies had a selective bias in reporting or inadequate data on outcomes.

Discussion

Most cancer patients, including those with Rb, are treated with systemic chemotherapy, which has a high frequency of treatment-related adverse effects.⁵⁰ Yamane et al. published the first study on targeted intra-arterial ophthalmic chemotherapy for Rb patients in 2004.⁵¹ Despite the difficulties with small blood vessel catheterization, IAC has emerged as the first alternative to Rb treatment, with broad applicability around the globe. Before IAC, around 80% of Rb cases eventually required to be enucleated to minimize hematogenous tumor dissemination and central nervous system involvement.⁵²

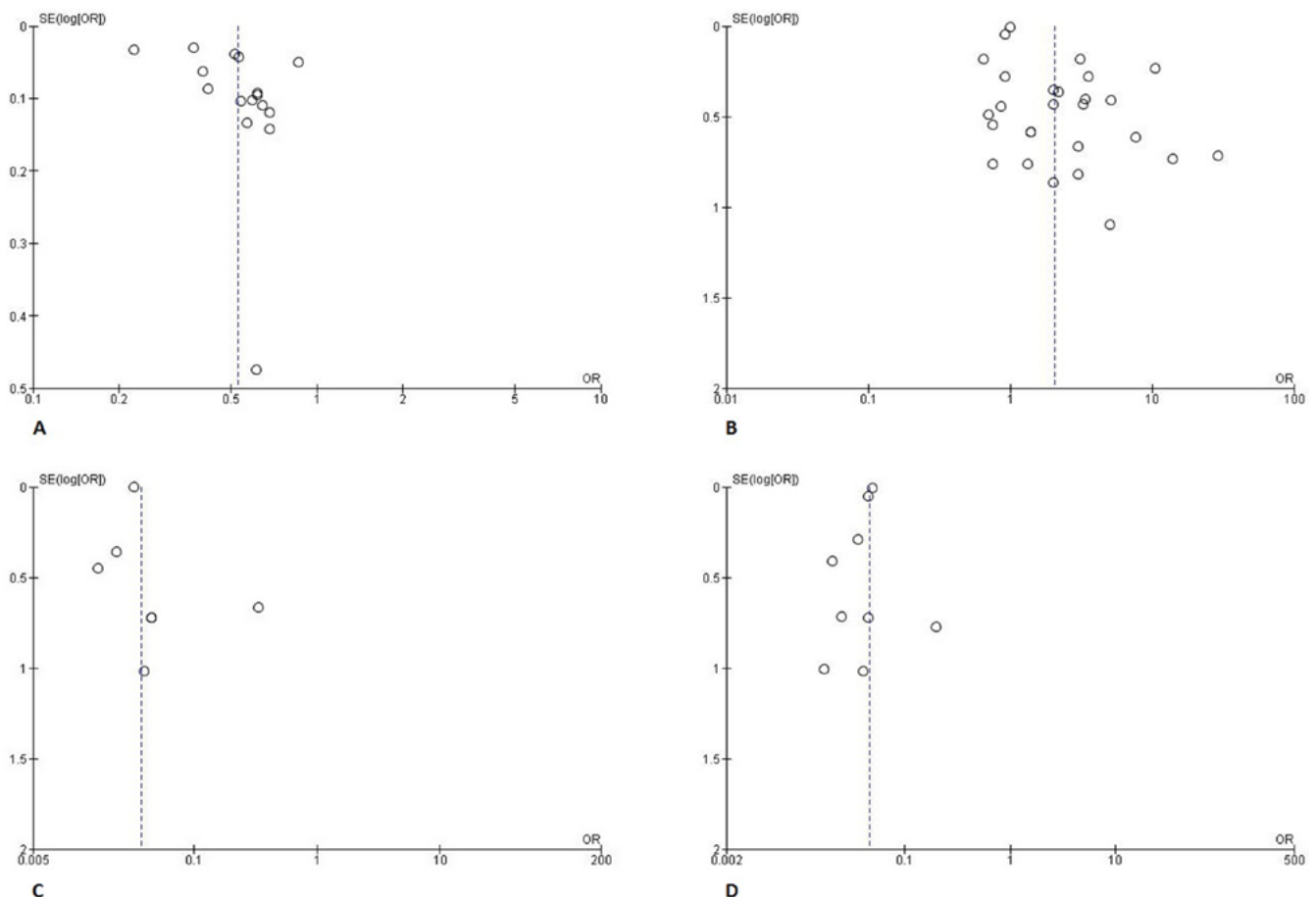


Fig. 7. Funnel plots for qualitative assessment of publication bias. A. Enucleation rate; B. Globe salvage; C. Metastasis rate; D. Mortality rate
OR – odds ratio; SE – standard error.

The current meta-analysis comprised 39 papers that assessed the key outcomes and complications of IAC for subjects with Rb. We conducted this study to provide updated evidence on the utility and effectiveness of the IAC technique by including recent trials that adopted diverse medications for Rb treatment. This study revealed a significantly improved enucleation rate after IAC in Rb patients. The clinical benefits of IAC in globe conservation were reported in several research articles. In the present meta-analysis, the estimated overall globe salvage with IAC was 76.4%, which is in accordance with the rates observed by Yousef et al. in their systematic review of 12 articles.⁸

According to our findings, the overall metastasis rate was estimated to be 2.4%, which is comparable to the estimations of 2.1% from the pooled analysis of Yousef et al.⁸ Moreover, Chen et al. showed that patients with advanced Rb had a 2.7% overall metastasis rate with IAC.⁵³ The likelihood of metastatic eye disease is greatly increased by the presence of histopathologic risk factors. In nations with well-developed hospital facilities, this risk significantly decreases to less than 10%.⁵⁴

Most adverse effects reported after IVC use would effectively disappear with symptomatic treatments. Rational use of IVC is crucial to minimize adverse events. Many

systemic and ocular problems have been observed as a result of the high doses of chemotherapy used to treat eyes, despite the potential therapeutic efficacy, and the high rates of globe salvage achieved with IAC. The most frequently reported ocular problems were eyelid edema, retinal ischemia, retinal detachment (in around 25% of patients), vitreous hemorrhages, and retina atrophy. Clinical consequences that are temporary and typically self-limiting include retinal detachment and hemorrhages, though they may have long-term consequences and endanger vision, unlike ischemic attacks. Thus, long-term follow-up is recommended to assess vision. Moreover, IAC-related vascular injuries can be reduced through angiographic analysis and precise micro-catheter placement. Neutropenia and fever were among the commonly observed systemic side effects, with bronchospasm present in about 10% of cases, which required bronchodilators for its management.^{9,54}

Kaliki et al. classified metastasis as a high risk in patients with a 4% mortality rate and a low risk in Rb patients with 0% mortality.^{55,56} Besides, metastasis incidence rate and secondary malignancies among patients with heritable Rb are higher than in non-heritable Rb patients. Sarcoma, leukemia, melanoma, and brain cancers are the most commonly reported secondary malignancies. Recurrent radiotherapy and melphalan use with IAC have

been associated with mutations and resulted in secondary malignancies. Regarding IVC, carboplatin and etoposide have been linked with an increased risk of secondary malignancies. However, the total drug dose received also plays an important role and needs to be considered when assessing secondary malignancy risk. Moreover, most of the reported cases of metastasis and secondary malignancies received radiotherapy either previously or concomitant to chemotherapy. Therefore, radiotherapy could be the reason for secondary malignancy rather than the chemotherapy used.

Limitations


There are some limitations to the current meta-analysis. First, it lacks any high-level randomized controlled trials and is based primarily on retrospective data. Second, few studies assessed disease progression and survival rates following IAC. Third, there was significant heterogeneity seen in the published results; and fourth, there was limited stratification of Rb patients according to disease severity factors such as tumor size, vitreous tumor or sub-retinal fluid seeds, and prior treatment.


Conclusions

In summary, retrospective trials have shown that intra-arterial-based therapy is an effective alternative for treating Rb. This method also reduced enucleation and metastasis rates; however, the paucity of evidence in the literature necessitates further high-level randomized controlled studies.

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