

ORIGINAL ARTICLE

Meta-analysis of the effect of preoperative chemotherapy on Wilms' tumor

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Summary

Purpose: To evaluate the effect of preoperative chemotherapy on the event-free survival (EFS) and overall survival (OS) of Wilms' tumor in children, and to provide a basis for further improvement of clinical therapeutic effect and research level.

Methods: Relevant studies before July 2017 were retrieved from PubMed, EMBASE, Web of Science and other databases, and two evaluators were responsible independently for the studies' selection, data extraction and cross-checking according to the inclusion and exclusion criteria. EFS and OS of patients were assessed using hazard ratio (HR) and 95% confidence interval (CI). All analyses, including publication bias assessment, were performed using Stata 12 software.

Results: 12 studies meeting the criteria, with a total of 1639 patients, were finally enrolled. Meta-analysis showed that the preoperative chemotherapy combined with surgery, compared with surgery alone, could improve the EFS and OS of patients with Wilms' tumor (HR=1.26, 95% CI 1.07, 1.48 and 1.12 (1.03, 1.22, respectively). Both sensitivity analysis and publication bias assessment revealed that the results were reliable with no significant publication bias.

Conclusions: Compared with surgery alone, preoperative chemotherapy combined with surgery can increase the EFS and OS and improve the prognosis of patients.

Key words: event-free survival, meta-analysis, overall survival, preoperative chemotherapy, Wilms' tumor

Introduction

Wilms' tumor is one of the common malignant solid tumors in children, whose incidence rate is about 7.8/100 million, accounting for 97% in renal tumors in children [1]. Wilms' tumor frequently occurs in children aged below 6 years, but seldom in adults. Surgical resection and postoperative chemotherapy have always been the main therapeutic methods of Wilms' tumor for a long time [2]. After surgical resection of the tumor, residual lesions and slightly disseminated tumor cells are destroyed via postoperative chemotherapy, which can reduce the hazard of tumor recurrence, and effectively improve the patient quality of life. However, a considerable number of patients still have

no chance for operation because of large tumor size or invasion and metastasis [3].

The concept of preoperative chemotherapy was first proposed by the International Society of Pediatric Oncology (SIOP), and it was applied in the Wilms' tumor in children, achieving ideal results. Preoperative chemotherapy can downsize the primary tumor and create good operation conditions for patients who lost the chance for operation originally; at the same time, it is also possible to control the locoregional spread and distant metastasis and postpone the operation for some patients after removal of metastasis, thus increasing the chance for operation [4,5].

In the past 30 years, with the development of surgery-based comprehensive treatment, especially the preoperative and postoperative chemotherapy, the long-term survival rate after operation of Wilms' tumor has been significantly improved. According to National Wilms' Tumor Study Group (NWTSG), the 2-year event-free survival (EFS) of patients with Wilms' tumor is more than 85% [5,6]. Although many international organizations, such as SIOP and NWTSG, are currently committed to the study of chemotherapy of Wilms' tumor, major differences in indications for preoperative chemotherapy still exist between them. SIOP argues that the direct surgical resection is only applicable for unilateral Wilms' tumor for patients less than 6 months old, while other patients should receive chemotherapy first before surgical resection. NWTSG holds the opinion that preoperative chemotherapy should be performed only in those patients with tumor invading vena cava, bilateral Wilms' tumor and solitary kidney, and other patients should receive postoperative chemotherapy according to the pathological stage [7,8].

In order to clarify the therapeutic effect of preoperative chemotherapy on Wilms' tumor, all relevant studies on the operative treatment after preoperative chemotherapy of Wilms' tumor published before July 15, 2017 were collected and analyzed using the Meta-analysis method to evaluate the effect of preoperative chemotherapy on the EFS and overall survival (OS), so as to provide a basis for further improvement of clinical therapeutic effect and research level.

Methods

Search strategy

Relevant studies before July 15, 2017 were retrieved from PubMed, EMBASE, Web of Science and other databases with "preoperative chemotherapy", "neoadjuvant therapy" and "Wilms' tumor" as keywords. Inclusion criteria: (1) studies in English; (2) studies with pathological diagnosis of Wilms' tumor; (3) studies comparing the effect of preoperative chemotherapy on EFS and OS of Wilms' tumor. EFS was defined as no recurrence or metastasis of tumor in the follow-up for more than 5 years. Exclusion criteria: (1) Case reports and clinical self examinations; (2) To avoid duplication of data, repetitive studies in the same research series were excluded; (3) Surgery alone groups that received preoperative radiotherapy.

Data extraction

Two evaluators were independently responsible for the study selection, data extraction and cross-checking according to the inclusion and exclusion criteria. In

case of disagreement, a third evaluator was recruited to reach a consensus. Specific steps of literature screening: (1) The evaluators had read the title and abstract to exclude unqualified studies; (2) they have read the full text of the studies that might meet the inclusion criteria to exclude unqualified and include qualified studies; (3) Studies that were not confirmed as qualified or not in the above processes had to be confirmed through supplementary information or contacting the author. The information extracted included the year, author, country, type of research, number of patients, survival, HR, 95% CI and follow-up time and a standard form was made for these data.

Quality assessment

According to the Newcastle-Ottawa Scale (NOS) system, the quality of each paper was assessed, and those with more than 5 points could be deemed as higher quality of research. Only high-quality studies could be included for subsequent analysis.

Statistics

Statistical analysis was performed using Stata 12 software (StataCorp LP, College Station, TX). HR and 95% CI were used to assess the effect of preoperative chemotherapy on EFS and OS. Cochran Q test was used for the heterogeneity between studies. If there was no statistical heterogeneity between studies ($p > 0.01$, $I^2 < 50\%$), meta-analysis was performed using the fixed effect model. If there was statistical heterogeneity between studies, the random effect model was used for analysis. The stability and reliability of results were evaluated *via* the sensitivity analysis. Begg's funnel plots and Egger's linear regression were used to analyze the potential publication bias.

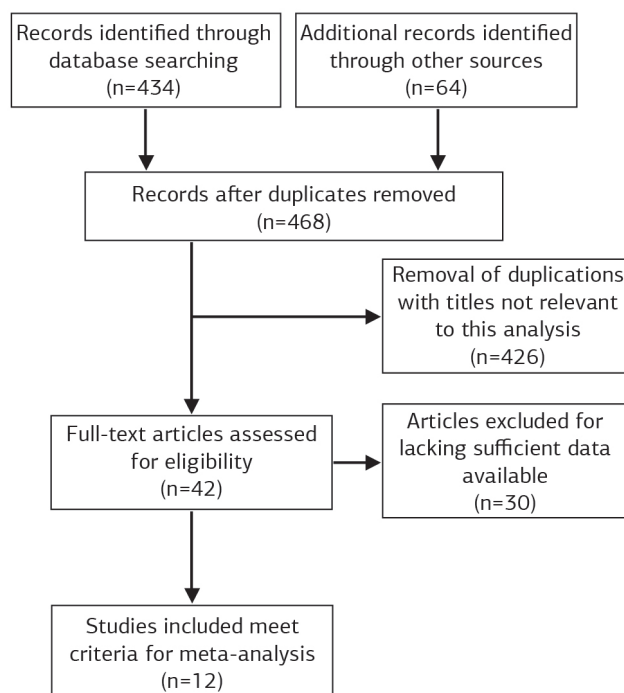


Figure 1. The flowchart of literature search and selection procedure.

Results

Study characteristics

A total of 468 relevant studies were retrieved. After the title and abstract were read, 42 studies were included, and finally 12 of them with a total of 1639 patients were included according to the inclusion and exclusion criteria [9-20]. Study screening process is shown in Figure 1, and study characteristics and survival in Tables 1 and 2. These studies were conducted in different countries, meeting high quality standards according to the NOS system. Follow-up ranged from 60 to 300 months.

Effect of preoperative chemotherapy on EFS

The effect of preoperative chemotherapy on EFS was studied after operation of Wilms' tumor in a total of 10 papers, including 765 patients receiving preoperative chemotherapy and 782 patients undergoing direct surgical treatment. The results of heterogeneity test showed no statistical heterogeneity between studies ($p=0.898$, $I^2=0\%$), so the meta-analysis was performed using the fixed effect model. The results revealed that the pooled HR was 1.26 (95% CI=1.07-1.48), suggesting that preoperative chemotherapy can improve the patient's EFS (Figure 2A).

Table 1. Main characteristics of studies included in the meta-analysis

Study authors	Country	Study design	Patients, n	Survival analysis	Maximum months of follow-up	NOS
Spreafico et al	Italy	RD	443	EFS/OS	103	7
Verma et al	India	RD	108	EFS/OS	120	5
Oue et al	Japan	RD	31	EFS/OS	157	5
Sarhan et al	Egypt	RD	22	OS	132	5
Naguib et al	Egypt	RD	53	EFS/OS	60	6
Safdar et al	Pakistan	RD	40	EFS	70	5
Mitchell et al	UK	RD	186	EFS/OS	144	7
Weirich et al	Germany	RD	329	EFS	60	6
Yildiz et al	Turkey	RD	106	EFS/OS	300	6
Kumar et al	UK	RD	70	OS	180	5
Shaul et al	America	RD	15	EFS/OS	120	5
Coppes et al (a)	Mix	RD	131	EFS/OS	108	6
Coppes et al (b)	Mix	RD	105	EFS/OS	84	6

RD: retrospective design, EFS: event-free survival, OS: overall survival, NOS: Newcastle-Ottawa Scale

Table 2. HRs and 95% CIs for patient survival in association with preoperative chemotherapy in the enrolled studies

Year	Study authors	Patients		EFS		OS	
		PC+SU	SU	HR(95%CI)	p value	HR(95%CI)	p value
2017	Spreafico et al	185	258	1.530 (0.950,2.450)	0.076	2.410 (1.190,4.840)	0.012
2016	Verma et al	59	49	1.382 (0.651,2.642)	0.207	1.384 (1.036,1.850)	0.020
2014	Oue et al	24	7	1.531 (0.792,2.960)	0.110	1.343 (0.834,2.159)	0.055
2010	Sarhan et al	16	6	NM	NM	1.375 (0.579,3.268)	0.416
2008	Naguib et al	27	26	1.263 (0.755,2.228)	0.525	1.089 (0.930,1.274)	0.280
2006	Safdar et al	21	19	1.225 (0.884,2.322)	0.619	NM	NM
2006	Mitchell et al	92	94	1.250 (0.680,2.300)	0.520	0.840 (0.380,1.880)	0.180
2001	Weirich et al	258	71	2.101 (1.036,4.264)	0.034	NM	NM
2000	Yildiz et al	8	98	1.007 (0.664,1.527)	0.670	1.128 (0.850,1.497)	0.512
1998	Kumar et al	57	13	NM	NM	1.567 (1.011,2.230)	0.035
1992	Shaul et al	7	8	1.143 (0.445,2.938)	0.595	1.929 (1.019,3.297)	0.027
1992	Coppes et al (a)	24	107	1.226 (0.882,1.959)	0.387	0.991 (0.814,1.206)	0.567
1992	Coppes et al (b)	60	45	1.022 (0.608,1.671)	0.489	0.987 (0.833,1.168)	0.549

PC: preoperative chemotherapy, SU: initial surgery, EFS: event-free survival, OS: overall survival, NM: not mentioned

Effect of preoperative chemotherapy on OS

The effect of preoperative chemotherapy on OS after operation of Wilms' tumor was studied in a total of 10 papers, including 559 patients receiving the preoperative chemotherapy and 711 patients undergoing direct surgical treatment. The results of heterogeneity showed no statistically significant heterogeneity between studies ($p=0.060$, $I^2=43.6\%$), so the meta-analysis was performed using the fixed effect model. The results revealed that the pooled HR was 1.12 (95% CI=1.03-1.22), suggesting that preoperative chemotherapy can improve the patient OS (Figure 2B).

Sensitivity analyses

Sensitivity analysis was performed to detect the effect of individual studies on the combined HR. The results of meta-analysis were reliable and statistically significant (Figure 3), and no individual study affected significantly the final results.

Publication bias

The publication bias was analyzed using Begg's funnel plots and Egger's test. As shown in Figure 4, the graph basically showed a symmetrical inverted funnel shape; the p value of EFS and OS in Egger's test was 0.213 and 0.087 respectively, revealing no significant publication bias.

Discussion

Wilms' tumor is one of the most common solid tumors in childhood, causing great harm to the physical and mental health of children and great economic losses to their families. Therefore, improving the treatment efficacy and research level of Wilms' tumor is of great significance for the healthy growth and quality of life of children [21,22]. In recent years, preoperative chemotherapy has played a pivotal role in improving the treatment effect of Wilms' tumor [23,24]. In this

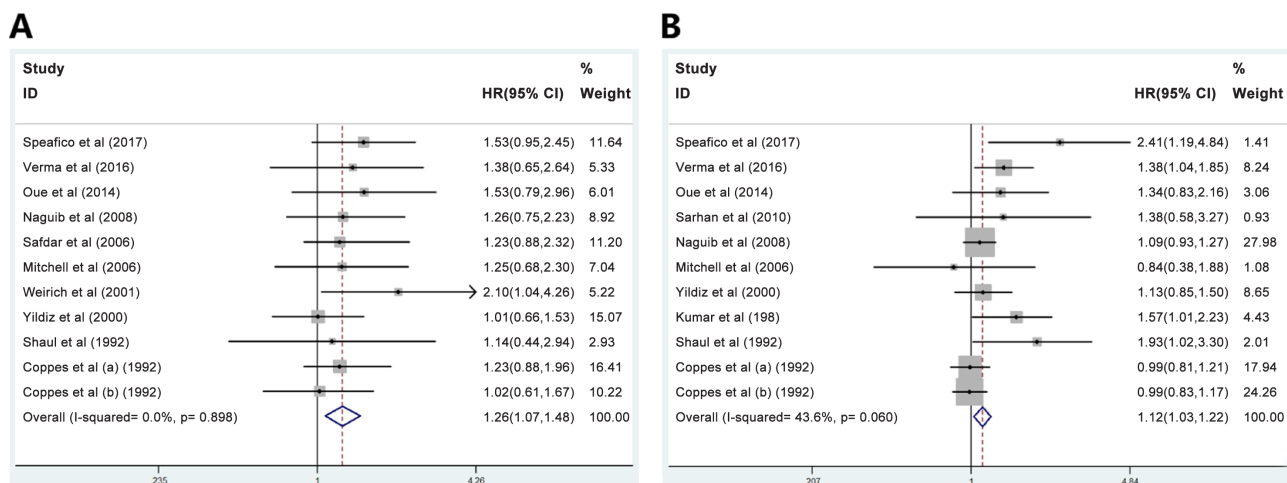


Figure 2. Forest plots of merged analyses of EFS (A) and OS (B).

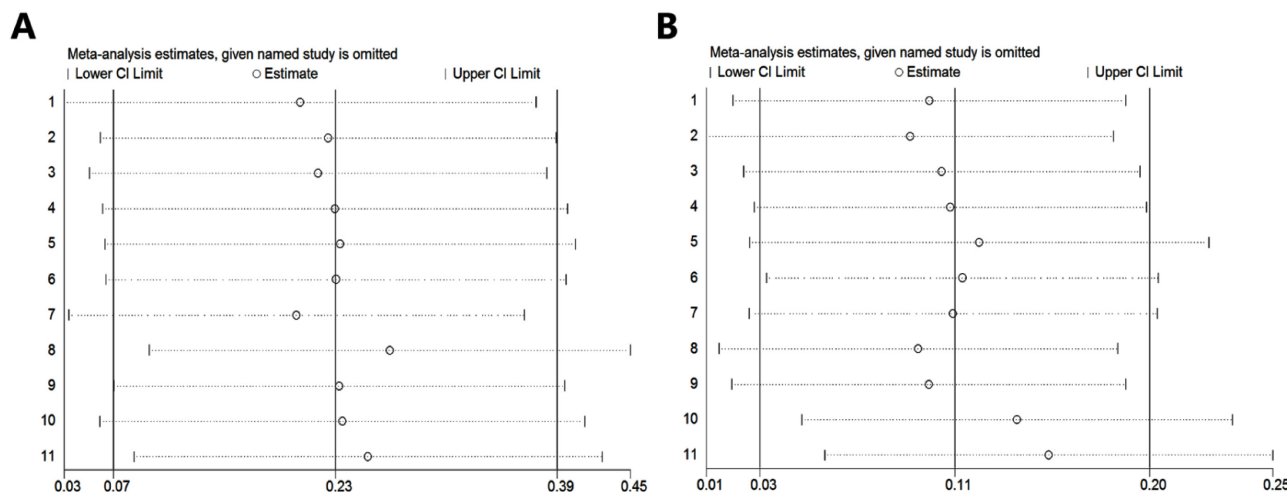


Figure 3. (A) Effect of individual studies on the pooled HR for EFS; (B) Effect of individual studies on the pooled HR for OS. The results showed no individual study affected significantly the final results.

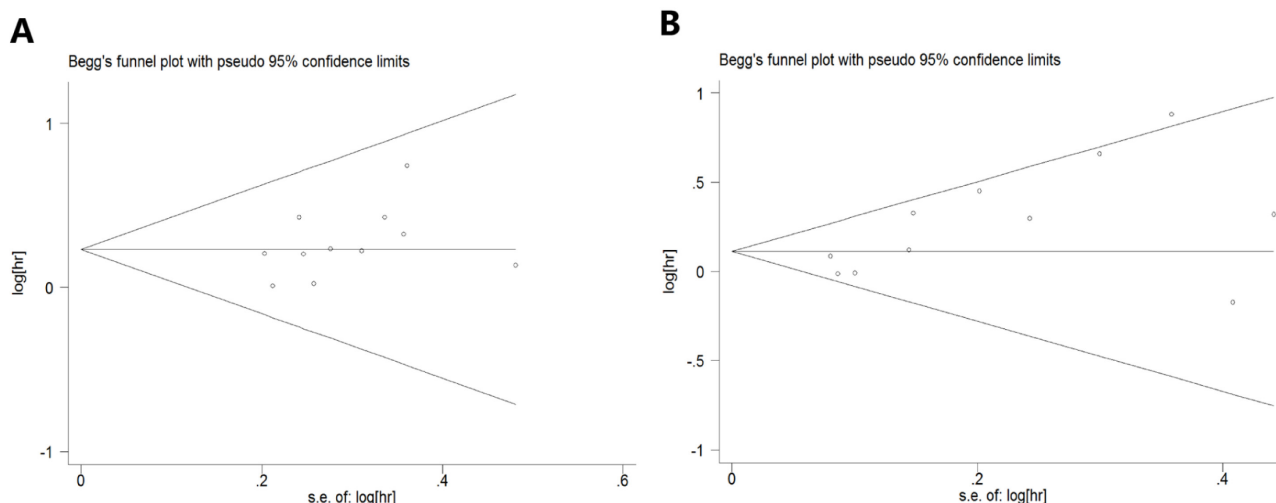


Figure 4. Begg's funnel plot of publication bias test for EFS (A) and OS (B). Basically the Figures show a symmetrical inverted funnel shape, revealing no significant publication bias.

paper, 12 high-quality studies with a total of 1639 cases published before July 15, 2017 were summarized and comprehensively analyzed the effect of preoperative chemotherapy on EFS and OS of Wilms' tumor.

In 10 studies with a total of 1547 patients, the effects of preoperative chemotherapy+surgery and surgery alone on EFS of Wilms' tumor were compared (765 vs 782). Meta-analysis showed a statistically significant difference between the two groups, and the combined HR was 1.26 (95% CI=1.07-1.48), suggesting that preoperative chemotherapy can improve the patient's EFS. Besides, in 10 studies with a total of 1270 patients, the effects of preoperative chemotherapy+surgery and surgery alone on OS of Wilms' tumor were compared (559 vs 711) and showed a statistically significant difference between the two groups, and the combined HR was 1.12 (95% CI=1.03-1.22), suggesting that preoperative chemotherapy can improve the patient OS.

SIOP used to release several multi-center large-sample reports on the preoperative chemotherapy. In SIOP2 study 138 patients with Wilms' tumor were enrolled, including 86 patients receiving 20 Gy preoperative radiotherapy and 5-day preoperative chemotherapy using actinomycin D, and 52 patients undergoing surgery alone. The results showed that the tumor rupture rate in the preoperative radiotherapy+chemotherapy group was significantly decreased compared with that in the surgery-alone group (5 vs 20%) [25]. SIOP5 results revealed that there were no significant differences in tumor rupture rate and postoperative EFS between the preoperative chemotherapy+surgery group and the surgery-alone group [26]. More patients were enrolled in SIOP9, but the results were similar to those in previous studies [27].

In conclusion, a controversy still exists about the application of preoperative chemotherapy for children without local invasion and distant metastasis, while no consensus has been reached on the effect of preoperative chemotherapy on the disease prognosis [7]. However, its effects in tumor shrinkage and reduction of the intraoperative tumor rupture rate have been widely affirmed and create good surgical conditions for children who cannot be subjected to surgery temporarily or have a higher risk of forced surgery, especially for those with giant tumor, intravenous tumor embolus and tumor infiltration [28,29]. In particular, preoperative chemotherapy has become an important means in research and the late-stage tumor therapy. Performing surgery after the tumor is reduced *via* preoperative chemotherapy can increase the chance of complete excision and significantly reduce the surgical risk [30]. In addition, the tumor size is reduced after preoperative chemotherapy, so that more renal tissues can avoid being excised and more renal parenchyma can be retained, which is more valuable for bilateral and single kidney [31]. Moreover, the sensitivity of tumor to preoperative chemotherapy can be used to guide the postoperative chemotherapy drugs and predict the sensitivity of patients to postoperative chemotherapy [32].

Sensitivity analysis refers to the comparison of meta-analysis results to investigate the stability of results through changing the inclusion criteria and eliminating the low-quality studies using different statistical methods and model analysis of the same data. In this paper, the sensitivity of research indexes was analyzed, and the results, consistent with the meta-analysis, revealed that they were reliable and stable. The symmetry of funnel plot and the concentration of midline can be used

to roughly determine whether there is a publication bias and its size. In this paper, the funnel plot analysis of included studies revealed that there was no clear publication bias, further improving the reliability of conclusions.

We acknowledge that the present study presents some shortcomings: (1) The number of patients enrolled was small, and all studies were in English, possibly creating a hidden publication bias, so more large-sample studies without language restrictions are needed to improve the accuracy of results; (2) More subgroup analysis was not performed, such as the effects of tumor staging, pathological pattern and preoperative chemotherapy regimens on the preoperative chemotherapeutic effect; (3) The prognosis of patients was affected not only by preoperative chemotherapy and surgery, but also by postoperative chemother-

apy to a large extent; however, the specific postoperative chemotherapy regimen was not explained in most original studies, and different postoperative chemotherapy regimens may affect the reliability of postoperative EFS and OS.

Conclusions

Compared with surgery alone, preoperative chemotherapy combined with surgery can increase the EFS and OS and improve the prognosis of patients. In the future, more large-sample high-quality studies are needed to further confirm this conclusion.

Conflict of interests

The authors declare no conflict of interests.

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