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Clinical features, treatment, and outcomes of bilateral Wilms' tumor: A systematic review and meta-analysis

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ABSTRACT

Background: Wilms' tumor(WT) is the most common malignant renal tumor of childhood. Despite the good prognosis of WT, bilateral Wilms' tumor (BWT) still has a poor outcome. We systematically reviewed the literature on BWT, aiming to define its clinical features, treatment, and outcomes.
Methods: PubMed, OVID EMbase, Web of Science, and Cochrane Library were systematically searched for studies published from 1980 to 2017. Case series and comparative studies reported clinical data of BWT patients were included.
Results: A total of 32 studies comprising 1457 patients were retained for primary outcome. Hemihypertrophy, cryptorchidism, and Beckwith–Wiedemann syndrome(BWS) are the most common congenital anomalies and syndrome. 86% of patients had favorable histology (FH). Patients with local stage I or II accounted for 64%, and 12.6% had metastasis at diagnosis. Bilateral nephron-sparing surgery (NSS) was achieved in 33.8%. Recurrence and renal failure occurred in 20% and 8%. The overall survival (OS) was 73%. In comparative studies, OS of patients undergoing bilateral NSS was similar to that of other operation types.
Conclusion: Prognosis of BWT has been improved but is significantly poorer than WT. Bilateral NSS was recommended by most centers to preserve more renal volume. However, finding a balance between retaining renal function and avoiding recurrence remains a question.
Type of study: Systematic review.
Level of evidence: Level IV.

Wilms' tumor (WT), also called nephroblastoma, is the most common malignant renal tumor of childhood, affecting approximately one in 10,000 children. Over decades, modality of diagnosis and treatment has evolved, making WT one of the great successes of pediatric oncology. Through standardized treatment, outcomes of WT have been improved dramatically, with an overall cure rate of over 85%.

Unfortunately, the current status of bilateral Wilms' tumor (BWT) is totally a different scene. BWT accounts for 5%–8% [1] of all WTs, which can be synchronous or metachronous. Despite the good prognosis of WT, treatment for BWT is challenging, resulting from high risk of relapse and renal failure. It's widely accepted that relapse is partly associated with tumor residual, while the small kidney volume is related to renal failure, thus making surgery for BWT a controversial topic. To preserve renal function, nephron-sparing surgery (NSS) was advocated in recent years. The SIOP 2001 protocol considers NSS an acceptable option for noncentral unilateral tumors and reported that recurrence rate in NSS patients was one-third that of the total nephrectomy group [2]. However, it is uncertain whether bilateral NSS improves prognosis of BWT patients.

Therefore, we systematically reviewed articles about clinical features, treatment and outcomes of BWT, in order to give a clear picture of the diseases, sum up surgical experience and determine the optimal treatment.

1. Methods

This study was conducted and reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.

1.1. Search strategy

A systematic literature search of PubMed, OVID EMbase, Web of Science and Cochrane Library was performed to identify all studies, published after 1980, that provided clinical data of BWT patients. Medical subject headings (MeSH) or free text words were executed during the search. The combination of terms ["Wilms' tumor" or

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"nephroblastoma"] and ["bilateral" or "Stage V"] was used. References of articles retrieved were also considered. The publication language was limited to English. Database search was conducted in September 2017.

1.2. Inclusion and exclusion criteria

We included studies that have been published and reported either the primary outcome (characteristics, treatment and outcomes of BWT cases) or the secondary outcome (comparison of different surgical procedures). In addition, case number of the study that reported the primary outcome should be ≥5. Conference abstracts, case reports and studies contained no original data (letters, opinions, reviews) were excluded.

1.3. Study selection, and data extraction

After discarding duplicate references, we screened titles and abstract of all studies to determine eligibility for full-text review, followed by reviewing full-text versions of the potentially relevant studies. If multiple articles reported data of the same population, the study with the largest sample size was included. The following variables of interest were extracted from the articles: study characteristic (country, study period, sample size, study design), clinical features (sex, age, histology, congenital anomalies, local stage of the poorer side, metastasis status at diagnosis), treatment (preoperative chemotherapy or initial surgery, surgical approach), outcomes (rate of survival, relapse and renal failure).

1.4. Quality assessment

To evaluate the quality of the included studies, modified Newcastle–Ottawa Scale (NOS) (Supplement, Table S1) was applied to assess the quality of studies for primary outcome, and the studies were categorized as high quality (score 5 or 6), moderate (score 3 or 4), and low (score 1 or 2). NOS was applied to assess the quality of studies for secondary outcome.

1.5. Statistical analysis

Analyses were performed using Stata 13.0 and Microsoft Excel 2010. Random effects models were used because of heterogeneity in diagnosis and treatment. Heterogeneity was assessed by calculating the Q-statistic and the I^2. A P-value of <0.05 for the Q-statistic was considered to be statistically significant. An I^2 of $>40\%$ was also considered to be an indication of substantial heterogeneity. For continuous data, sample size-weighted grand means and standard deviations of sample means (or medians, whichever was reported) were calculated. Categorical data were described in percentages. Meta-analysis was performed to calculate proportions with corresponding 95% confidence intervals. As to comparative studies, the results were only reviewed owing to difference in study design.

2. Results

2.1. Search results and study characteristics

Through the database searches, 471 studies were identified for further assessment. After screening titles and abstracts, full-text of 52 relevant articles was reviewed for eligibility, and finally 33 studies were retained and selected for data extraction. Fig. 1 shows a flowchart for selection of studies. 26 were case series [3–28]; 5 were retrospective cohort studies [20,29–32]; 1 was a prospective clinical trial [33]. A total of 1457 cases were involved to obtain primary outcome (1368 were synchronous and 89 were metachronous). The detailed characteristics of selected studies are listed in the Supplement, Table S1. Quality assessment of studies was shown in the Supplement Tables S1 and S2. Heterogeneity of data reported in the pooled results was listed in the Supplement Table S3.

2.2. Primary outcome

2.2.1. Clinical features

Mean age at diagnosis of patients with BWT was 28 ± 5.92 months. Overall, 582 of 1433 patients (40%, 95% CI 38%–43%) were male. The common isolated congenital anomalies were hemihypertrophy and aniridia, incidence of which was 54 in 1024 (0.04, 95% CI 0.03–0.06) and 17 in 446 (0.03, 95% CI 0.01–0.05) respectively. Among male patients, 34 of 184 cases (0.17, 95% CI 0.11–0.23) had cryptorchidism; 16 of 177 (0.08, 95% CI 0.04–0.12) had hypospadias. With regard to genetic syndromes, 38 of 934 patients (0.03, 95% CI 0.02–0.05) had Beckwith–Wiedemann syndrome (BWS); 23 of 702 patients (0.02, 95% CI 0.01–0.03) had Denys–Drash syndrome (DDS); 22 of 822 patients

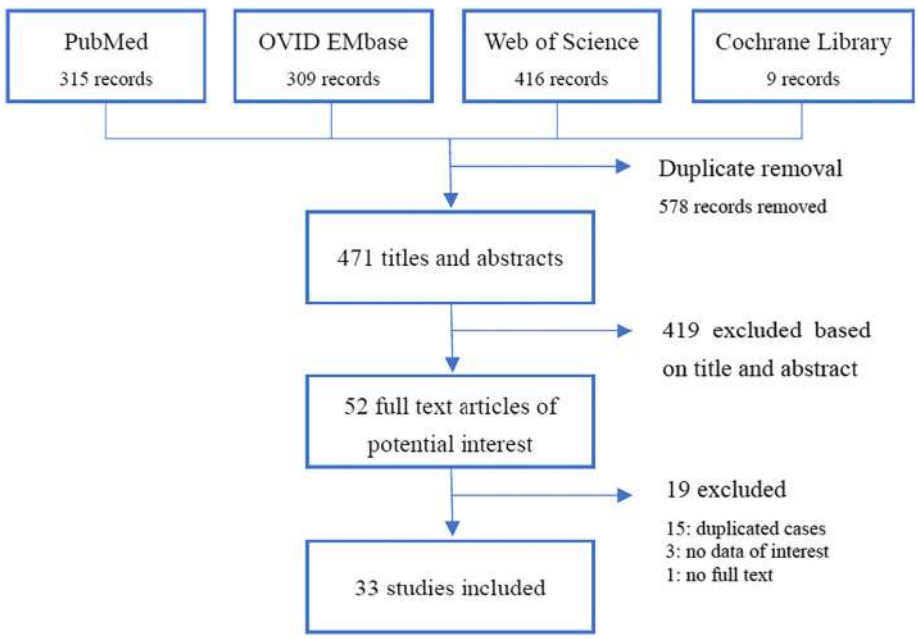

Fig. 1. Flow chart for study selection.

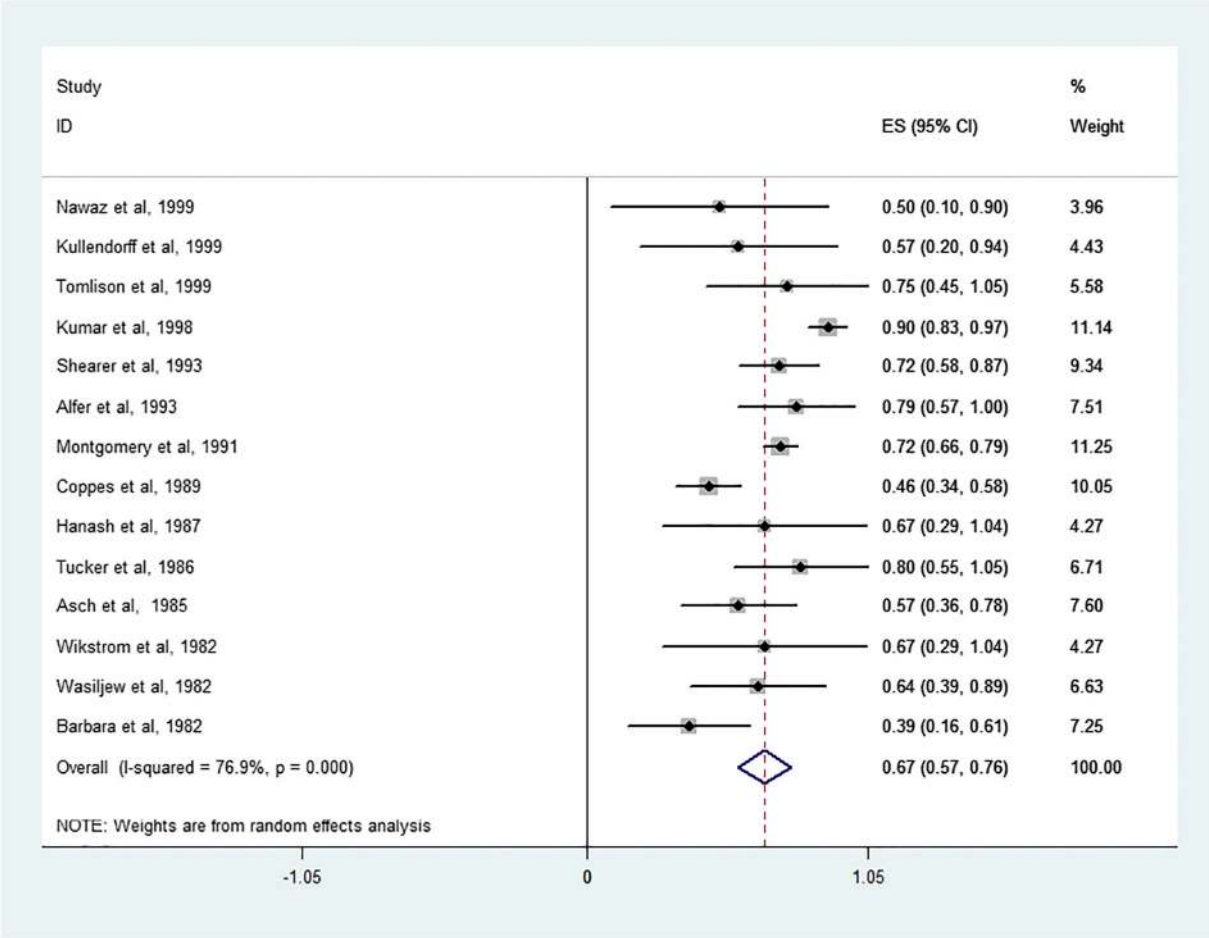

Fig. 2. Meta-analysis for overall survival of BWT patients before 2000 in 14 studies. ES, estimate.

(0.02, 95% CI 0.01–0.03) had Wilms Tumor–Aniridia–Genitourinary Malformation–Mental Retardation Syndrome (WAGR syndrome). 900 of 1057 cases (0.86, 95% CI 0.82–0.90) has favorable histology (FH). 463 of 751 patients (0.64, 95% CI 0.57–0.71) were diagnosed as local stage I or II. Presence of metastasis at diagnosis was reported in 162 of 1158 patients (0.13, 95% CI 0.11–0.14), most of which (93.2%) were pulmonary metastasis.

2.2.2. Treatment

862 of 1188 patients (72.5%) received neoadjuvant chemotherapy, while the other patients received initial resection. The proportion of patients experienced neoadjuvant chemotherapy changed greatly in the past few decades——170 of 353 patients (48.2%) before 2000 and 692 in 835 (82.9%) after 2000. Among 859 patients who underwent surgery, 290 (33.8%) had bilateral partial nephrectomy; 348 (40.5%) had total unilateral total nephrectomy with contralateral partial nephrectomy; 149 (17.3%) had unilateral total nephrectomy; 41 (4.8%) had unilateral partial nephrectomy; and 26 (3.0%) had bilateral total nephrectomy.

2.2.3. Outcomes

The overall survival (OS) was 685 in 923 (73%, 95% CI 67%–79%). The most common cause of death was progression or recurrence of the disease which represented 74% of deaths. The OS improved during the past few decades, which was 322 of 468 (67%, 95% CI 57%–76%) (Fig. 2) before 2000 and 363 of 455 (79%, 95% CI 73%–86%) (Fig. 3) after 2000. The disease recurred in 171 of 765 patients (0.20, 95% CI 0.14–0.27). The sites of recurrence were as follows: 22 of 129 (17%) to the lung, 5 of 126 (4%) to the liver, local alone in 106 of 167 patients (63%). As to renal function, 51 of 630 children (8%) were reported to develop renal failure. The median follow-up time was 9.55 years.

2.3. Secondary outcome

A total of 4 studies compared prognosis of different operation types——3 of which reported difference between bilateral NSS and other types; 1 of which discussed impact of margin status.

Hubertus et al. [4] compared the rate of hypertension after bilateral NSS (PN/PN) and unilateral partial plus contralateral total nephrectomy (PN/TN). It was shown that hypertension was less frequent in the PN/PN group (20% vs 66.7%, $p = 0.043$). The relapse rate of PN/TN and PN/PN group was 8.3% and 20% respectively, and OS was independent of type of surgery. Oue et al. [31] reported the survival rate of patients who underwent bilateral NSS and who did not. No matter the survival with a native kidney (without hemodialysis or a renal transplant) or survival with normal renal function was higher among the bilateral NSS group, but the differences were not statistically significant. Furtwangler et al. [30] compared progression free survival (PFS) and OS between patients who had NSS and who had complete nephrectomy on at least one kidney. There was no significant difference in 5 years OS between two groups ($p = 0.93$). However, PFS of the NSS group was lower (60% vs 85%, $p = 0.005$).

Kieran et al. [32] showed that the surgical margin status was not correlated with local recurrence rates, since recurrence rates were similar in patients with positive and negative margins (20% vs 37.5%, $p = 0.47$). The only two patients whose histology was focal anaplasia were in the negative margins group, and no recurrence occurred on them. It should be noted that all of the patients with positive margins and two

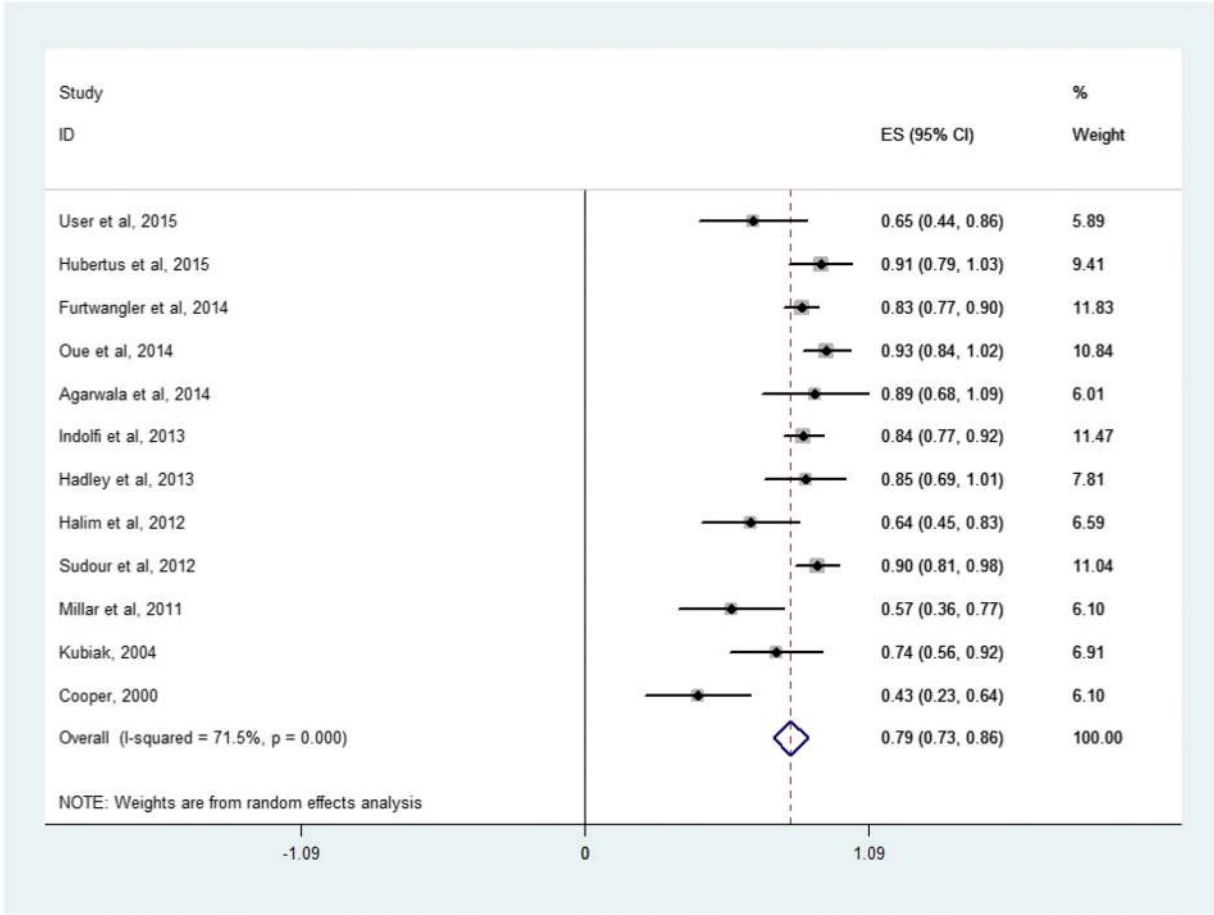

Fig. 3. Meta-analysis for overall survival of BWT patients after 2000 in 12 studies. ES, estimate.

with focal anaplasia in the negative margins group did undergo adjuvant flank radiotherapy.

3. Discussion

According to our results, data about BWT patients from different studies were various, especially in treatment and prognosis. It reflected that we still had great challenge in treating BWT and were unable to reach an agreement. Nevertheless, what can be confirmed is that prognosis of BWT has been improved, with OS from 67% to 79%, over the past few decades, which was resulted from the progress in diagnosis and treatment.

As we all know, the histology of tumor is a risk factor for prognosis, and unfavorable histology (UH) is thought to be associated with poor prognosis. Fortunately, 86% patients presented with a histology of FH in our results. Another clinical feature of BWT which was beneficial to treatment and prognosis was that local stage of more than half of patients were stage I or II. The lower stage enabled us to achieve complete resection of tumor. The most common site of metastasis was lung, so that it was necessary for us to pay attention to the lungs in diagnosis and follow up.

Though improved, the OS of BWT was still remarkably lower than WT, and the recurrence rate (20%) remained high. Progression or recurrence of the disease accounted for 74% of all deaths, which meant more effort was needed in prevention of recurrence. The renal function was also an important factor that influences the patient's quality of life, while 8% of BWT patients developed renal failure which was dramatically higher than patients with unilateral WT (0.7%) [34]. Based on that, surgeons should try to control recurrence and preserve renal function when treating BWT.

One of the changes in treatment for BWT was the application of neoadjuvant chemotherapy. Since several studies [18,20,35] reported that neoadjuvant chemotherapy was helpful to preserve renal function without survival to be compromised, it has already been accepted by most of surgeons. According to our results, the proportion of patients received neoadjuvant chemotherapy increased from 48.2% to 82.9%.

The introduction of concept of NSS was another important change. It is widely accepted the volume of the remaining kidney is correlated with future renal function. However, only 38.6% patients had remaining kidneys of both sides after surgery. A large part of patients had complete nephrectomy on one side. Even worse, once the disease recurred, the limited volume of kidney made treatment a dilemma. In order to preserve renal function, more and more medical centers supported the use of bilateral NSS. When comparing survival of bilateral NSS to other operation types, it was shown in 3 studies [29–31] that there was no significant difference between groups. And Hubertus et al. [29] showed rate of hypertension which to a certain extent may reflect the renal function was lower in bilateral NSS group. Those results supported the aggressive use of NSS, while what we were worried about also happened. One study showed PFS of the NSS group was significantly lower ($p = 0.005$) [30], which meant NSS may lead to tumor residuals. Because the design of each study was different, it was unavailable to pool the results and only qualitative results can be provided. Kieran et al. [32] conducted a study to determine whether margin status impacted local tumor recurrence. It was shown that local recurrence rates were not associated with margin status. One factor differing between two groups was adjuvant radiotherapy status. All of patients with positive margins received adjuvant radiotherapy which may prevent the recurrence. The results reminded us that treatment of BWT is an integrated process. When the use of NSS increases the risk of relapse,

measures to decrease the risk are demanding. Sometimes, adjuvant treatment overweighs degree of tumor resection, so clinical decision should take factors of all aspects into account. With rational use of chemotherapy, radiotherapy or other adjunctive therapy, the inclusion criteria for NSS may be expanded.

Our systematic review and meta-analysis have limitations. First, there were so few comparative studies, especially high-quality studies, that we were unable to get pooled results to compare different operation types. Second, owing to the low incidence of BWT, sample size of several studies was small, which may result in bias. In addition, guidelines for diagnosis and treatment were diverse, causing greater heterogeneity. As described previously, a series of factors have impacts on the prognosis of BWT, while our study only included a small part of them. The data on surgery timing, chemotherapy, radiotherapy effect on patients' outcomes were hard to collect because each study provides the data in different forms. In addition, the follow-up time varied among studies so that it was not possible to estimate OS of a certain time, such as 5-year OS, and pooling studies regardless of difference in follow-up time would definitely cause bias.

In conclusion, these system review and meta-analysis suggest that prognosis of BWT has been greatly improved. However, the high risk of recurrence results in a relatively poor prognosis comparing to WT. The development of renal failure also makes a difference to patients' quality of life. To preserve renal function, NSS is widely supported, while it may bring an increased risk of relapse which should be controlled by other treatment such as chemotherapy and radiotherapy. In a word, how to balance between preserve renal function and preventing recurrence is still challenging, stressing the need for further studies, especially prospective, comparative studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2018.08.022.

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