The prognosis of prechemotherapy blastemal predominant histology subtype in Wilms tumor: A retrospective study in China

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Abstract
Purpose: This study aimed to retrospectively analyze survival outcomes for Chinese patients with prechemotherapy blastemal predominant histology type Wilms tumors (WTs).

Methods: We collected and analyzed clinical data concerning patients aged <15 years with favorable histology (FH) WTs treated at the Sun Yat-Sen University Cancer Center from December 2005 to May 2016, based on the Children’s Oncology Group protocol. Pathological specimens were collected through biopsy or surgical resection before initiation of chemotherapy. We analyzed survival outcomes involving different prechemotherapy histology subtypes.

Results: We enrolled 97 patients with FH WTs (median follow-up, 71.5 months; range, 22.2-170.7). The total recurrence rate was 17.5%, and the subtype recurrence rates were as follows: blastemal predominant (45.5%), mixed (7.5%), epithelial (14.3%), and mesenchymal (9.5%) (P = .010). Five-year event-free survival (EFS) and overall survival (OS) rates were 84.9% and 81.4%, respectively. Respective 5-year EFS and OS rates for subtypes were as follows: blastemal predominant (54.5% and 68.2%), mixed (90.0% and 88.9%), epithelial (85.7% and 85.1%), and mesenchymal (90.5% and 94.7%). Multivariate survival analyses showed that the blastemal predominant subtype was an independent prognostic factor of EFS (P = .001) and OS (P = .017).

Conclusions: Our findings showed that prechemotherapy blastemal predominant WTs had higher recurrence and lower EFS and OS rates. Our findings suggested that, albeit with some deficiencies, blastemal predominant histology WT–diagnosed prechemotherapy may have prognostic relevance. Further research into other

Abbreviations: COG: Children’s Oncology Group; CR: complete response; EFS: event-free survival; FH: favorable histology; JWiTS: Japanese Wilms Tumor Study; NWTS: National Wilms Tumor Study; SIOP: International Society of Pediatric Oncology; SYSUCC: State Key Laboratory of Oncology in South China; WT: Wilms tumor; UH: unfavorable histology

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DOI: 10.1002/pbc.28567

Pediatric Blood Cancer. 2020;67.e28567. wileyonlinelibrary.com/journal/pbc 1 of 8

https://doi.org/10.1002/pbc.28567
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Potential confounding variables are required to determine whether such patients warrant altered risk-stratified therapy.

**KEYWORDS**

children, China, pathological subtypes, survival rate, Wilms tumor

### 1 | INTRODUCTION

Wilms tumor (WT) is a common pediatric extracranial solid tumor, accounting for approximately 5% of all pediatric malignancies. With the development of a multidisciplinary treatment approach comprising surgery, chemotherapy, and radiotherapy, there has been an increase in the overall survival (OS) rate of WT of >90%. Moreover, for advanced stage patients, the OS rate has become promising, at >80%.

There are two typical strategies for therapy. The National Wilms Tumor Study (NWTS) group, now part of the Children’s Oncology Group (COG), has been studying the treatment and prognosis of children with WT in the United States and Canada. The NWTS-5 protocol proposes primary nephrectomy, followed by adjuvant chemotherapy and radiotherapy. The COG pretherapy studies have defined pathology using two histological classifications, namely, those with favorable histology (FH) and those with unfavorable histology (UH), indicating the presence of anaplasia. According to the COG protocol, the prechemotherapy blastemal predominant type is not considered to be a high-risk factor, and intensive treatment is not required for the FH type. However, in Europe, global cooperative studies have predominantly been performed by the International Society of Pediatric Oncology (SIOP) and preoperative chemotherapy is recommended. The SIOP classification of pathology is based on the proportion of total necrosis and the predominant form of cell in the remaining feasible cells, and is split into three distinct risk groups. The postchemotherapy blastemal predominant type is categorized into a high-risk group and intensive therapy is provided. However, the prognosis concerning the prechemotherapy blastemal predominant subtype remains controversial. There are few reports concerning the relationship between prechemotherapy FH WT subtypes and prognosis.

In our center, treatment for our patients is based on the NWTS-5 (COG) protocol. According to the COG protocol, FH WTs are divided into the following subtypes, namely, mesenchymal, epithelial, blastemal predominant, and mixed. All pathological specimens in our center were collected either as surgical resections or through biopsy before chemotherapy.

In this study we retrospectively analyzed the clinical features, therapeutic effects, and prognostic factors of different subtypes of FH WTs in our cancer center, to reevaluate the prognosis of the blastemal predominant subtype before initiation of chemotherapy and to provide clinical insights for further optimizing the treatment protocol.

### 2 | MATERIALS AND METHODS

#### 2.1 | Patients

Data from the clinical database of Sun Yat-Sen University Cancer Center (SYSUCC) was retrieved to identify children and adolescents aged ≤15 years with primary WT who had been referred to SYSUCC from 2005 to 2016. All pathological specimens were collected either through biopsy or surgical resection before initiation of chemotherapy. UH specimens that contained focal anaplasia or diffuse anaplasia were excluded. Although the initial pathology had been classified during patient therapy according to the COG protocol, our pathologist reclassified all the pathological specimens retrospectively, according to SIOP WT 2001 histological criteria. The FH WTs were reclassified into four subtypes: mesenchymal, epithelial, blastemal predominant, and mixed. Each subtype was defined as having >66% of each histological feature (% of a tumor). We also undertook a central review of the surgical notes and an imaging review. Clinical staging was based on the COG Staging System.

Detailed data such as sex, age, symptoms, medical history, place of primary tumor, surgery or radiotherapy, regimen of chemotherapy, response, and follow-up results were collated. The study was undertaken with Research Ethics Board oversight. This was a retrospective study with an exemption to consent. This trial was approved by the Sun Yat-Sen University Cancer Center Ethics Committee and registered with the Chinese Clinical Trial Registry (registration no. ChiCTR1900023240). All original data were deposited on http://www.researchdata.org.cn (RDD number RDDA2019001046).

#### 2.2 | Treatment

When possible, primary tumor surgical resection was performed. A biopsy specimen was acquired for histological examination when a tumor was not optimally resectable at diagnosis. After two to three preoperative chemotherapy courses, reevaluation for resection was considered. Chemotherapy was administered after resection according to the NWTS-5 protocol. Most stage III and IV patients received radiotherapy. Radiotherapy was administered at 10.8 Gy in six fractions (1.8 Gy per fraction). Ten stage III patients (including one blastemal predominant subtype) received a modified NWTS-5 protocol
FIGURE 1 Patients enrolling in the study

128 children and adolescents were diagnosed with Wilms Tumors

17 patients were diagnosed with an unfavorable histology

111 patients were diagnosed with favorable histology Wilms Tumors

Excluded
1 patient did not complete treatment
3 patients were lost to follow-up after treatment
10 patients were over-treated due to wrong staging

97 study patients were enrolled

and did not receive radiotherapy because of another ongoing clinical trial (ChiCTR-PRRC-12002525). The other 87 were not enrolled in any other separate clinical trial.

2.3 Evaluation of efficacy and toxicity

For chemotherapy, the response was evaluated using sensitive and specific imaging technologies such as computed tomography or magnetic resonance imaging every two courses, according to the revised Response Evaluation Criteria in Solid Tumors 1.1. Complete response (CR) was defined as no detection of tumor. All toxicity results related to chemotherapy or radiotherapy were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

2.4 Statistical analysis

Statistical analysis was performed using the SPSS software version 23.0 (IBM, Chicago, IL). Comparisons between two groups were performed using Student’s t-test for continuous data and a chi-square test for categorical data. Event-free survival (EFS) rate was calculated from the date of the pathological diagnosis of WT to disease progression, relapse, or death from any cause or last follow-up. OS was calculated from the date of diagnosis until death or the date of the last visit. Survival curves were estimated using the Kaplan-Meier method. The prognostic value in predicting the OS and EFS rates was assessed using multivariate Cox proportional hazards regression analysis. All covariates that affected survival (level of significance, \( P < .10 \)) in univariate analysis were included in a multivariate Cox proportional hazards model. Results are presented as mean ± standard deviation. All statistical tests were two-sided, and a significant difference was considered when the \( P \)-value was <.05.

3 RESULTS

3.1 Patient characteristics

At SYSUCC, 128 children and adolescents were diagnosed with WTs between 2005 and 2016. Of these, 17 patients were diagnosed with UH and were excluded from further analysis. One patient did not complete therapy, 3 patients were lost to follow-up after treatment, and 10 patients were excluded because of incorrect staging. In total, 97 patients with an FH type were enrolled. The median age at diagnosis was 2 years (range, 2 months to 10 years), and there were 51 male patients and 46 female patients (Figure 1). Of the 97 patients’ prechemotherapy pathological specimens, 40 mixed, 14 epithelial, 21 mesenchymal, and 22 blastemal predominant WT subtypes were identified during the reclassification. Stage I-IV disease accounted for 14 (14.4%), 14 (14.4%), 49 (50.5%), and 20 (20.7%) patients, respectively. Patient clinical characteristics are presented in Table 1.

3.2 Treatments and response

All stage I and II patients received surgical resection at diagnosis. For stage III and IV patients, 40 patients received surgical resection at initial diagnosis and 38 patients were administered two to three courses of neoadjuvant chemotherapy before surgery. In line with the COG...
protocol, first-line adjuvant chemotherapy was administered after resection to all patients as the mainstay modality throughout their treatment. One patient (0.9%) died of an infection after one course of neoadjuvant chemotherapy, 62 patients were administered radiotherapy during chemotherapy, and 10 stage III patients (comprising 1 blastemal predominant type and 9 nonblastemal predominant types) underwent a modified COG protocol and did not receive radiotherapy. Due to tumor progression after chemotherapy, two stage IV patients did not receive radiotherapy as they died before radiotherapy could be administered. Relapsed or refractory stage I and II patients were treated with stage III and IV regimens, and patients with recurrent III and IV recurrence were enrolled in a high-risk regimen involving the administration of pirarubicin, cyclophosphamide, vincristine, carboplatin, and etoposide.

### 3.3 Outcome

After a median follow-up of 71.5 months (range, 22.3-170.7 months), we observed one patient with the mesenchymal subtype who developed a second cancer, namely, acute myeloid leukemia and who had achieved CR after chemotherapy. One patient died of an infection after one course of neoadjuvant chemotherapy, and 16 patients had recurrences (blastemal predominant \([n = 9]\), mixed \([n = 4]\), epithelial \([n = 2]\), and mesenchymal \([n = 1]\) subtypes). Among the recurrences, one stage II patient developed liver metastasis and two stage II patients developed lung metastases, and these patients were classified with blastemal predominant subtypes. Four stage III patients developed lung metastasis, liver metastasis, pelvic metastasis, and progressive disease in the kidney, respectively. There were seven stage IV patients who had lung recurrences. One stage IV patient developed brain metastasis. Only one stage IV patient had a recurrence in situ, which was identified in the left kidney. Concerning the different subtypes, the recurrence rates were as follows: blastemal predominant (45.5%), mixed (7.5%), epithelial (14.3%), and mesenchymal (9.5%) \((P = .010)\). The 5-year EFS and OS rates were 84.9% and 81.4%, respectively. The respective 5-year EFS and OS rates for the four subtypes were as follows: blastemal predominant (54.5% and 68.2%), mixed (90.0% and 88.9%), epithelial (85.7% and 85.1%), and mesenchymal (90.5% and 94.7%) (Figure 2).

Univariate analysis of the investigated prognostic factors on survival is shown in Table 2. A multivariate Cox proportional hazards model included the covariates that affected survival at a level of significance of \(P < .10\) in univariate analysis. Multivariate analysis (Table 3)
FIGURE 2  (a) Overall survival and (b) event-free survival of favorable histology Wilms tumors with different histopathology subtypes; (c) overall survival and (d) event-free survival of patients with stage I and II FH Wilms tumors classified as nonblastemal or blastemal subtypes; (e) overall survival and (f) event-free survival of patients with stage III and IV nonblastemal or blastemal subtypes
The treatment strategies used in this study, from 2005 to 2016, followed the COG protocol. We found that the prechemotherapy blastemal predominant subtype had a poorer prognosis compared to other FH types. Multivariate survival analyses showed that the blastemal predominant subtype was an independent prognostic factor for EFS ($P = .001$) and OS ($P = .017$). In the subgroup analysis, the blastemal predominant subtype demonstrated a poor OS and EFS in stage I and II patients ($P = .012$ and $P = .001$, respectively) and in stage III and IV patients ($P = .041$ and .003, respectively).

Both COG and SIOP protocols are widely accepted and used in the treatment of WT internationally. In China, the COG protocol has been used with regard to WT treatment for many years. Using the NWTS classification, the pathological evaluation system was divided into two histological categories: FH and UH, based on prechemotherapy histology of tumor samples. However, classification in the SIOP protocol relies on the necrosis-related pathological results or the amount of feasible cells left after preoperative chemotherapy. Our results suggested a poor prognostic outcome for patients with the blastemal predominant subtype before preoperative chemotherapy. Although the NWTS still considers the blastemal predominant subtype to be an FH type, the tumor specimens were obtained before chemotherapy and could not be compared with the SIOP protocol.

One of the SIOP-9/GPOH studies showed that the 4-year recurrence-free survival regarding blastemal predominant subtype was 61% compared to the epithelial (100%), mesenchymal (100%), and mixed (89%) subtypes.9 Another of the SIOP-9/GPOH studies reported that the blastemal WT’s 5-year survival rate was 58.4%.10 The authors suggested that patients with a postchemotherapy blastemal predominant WT subtype should be classified as having a high-risk tumor.11 The SIOP 93-01/GPOH and SIOP 2001/GPOH studies showed that tumor biology affects the prognosis of primary lung metastases in patients with nephroblastoma.12

In Japan, based on the Japanese Wilms Tumor Study (JWiTS) protocol, which was a modified version of the NWTS-5(COG) protocol, Kinoshita et al reported that the 5-year OS and relapse-free survival (RFS) rates for patients with blastemal predominant tumors were 65.4% and 54.2%, respectively, which was poorer than other FH WTs.13 Their pathology results were obtained without preoperative chemotherapy, as in China. Aoba et al stated that blastemal predominant tumors had a higher relapse rate, and that the relapse tumors were resistant to any form of treatment. Their results were similar to our findings, demonstrating that prechemotherapy blastemal predominant WT had a significantly worse prognosis compared to those of the other subtypes14; however, the cohort comprised only 33 patients treated over 24 years, which is the limitation of that study. Koshinaga et al found no significant difference between prechemotherapy blastemal predominant type WT and nonblastemal type WT in terms of RFS (78.8% vs 84.5%; $P = .201$) and OS (89.3% vs 93.5; $P = .45$), respectively.15 The prognosis of the prechemotherapy blastemal predominant type WT according to the JWiTS protocol remains controversial.

The COG protocol classifies blastemal predominant WT as part of the FH group. Breslow et al enrolled a large FH WT cohort and found a worse prognosis for the blastemal subtype. The adverse outcome in this blastemal subtype was predominately explained due to the advanced tumor stage.16 However, in our study, even blastemal subtypes at the same stage had worse outcomes than other FH WTs. In a
recent report from the Children’s Oncology Group Study AREN0532, the results of that study indicated that in seven patients with stage III blastemal-type WT, five patients experienced a relapse. This result was consistent with SIOP findings, in which histologic response to preoperative chemotherapy was found to play an important role in predicting outcome.27

The NWTS-5 study prospectively evaluated the prognostic significance of 1p and 16q loss of heterozygosity (LOH) in WT and found that approximately 5% of patients had both 1p and 16q LOH with a significantly increased risk of recurrence. The RFS and OS of 1p and 16q LOH were 65.9% and 77.5%, respectively (P = .01 and .04).18 However, these examinations were not routinely performed at our center.

The molecular biology data for our patients were not examined; therefore, we could not explain the significant difference in outcomes. However, findings reported in the following studies may help to explain our results. Marta et al reported that YY1 expression was higher in the blastemal component of tumors, and high nuclear expression positively correlated with metastasis. YY1 may be considered as a metastasis risk factor in WT.19 Hontecillas-Prieto et al suggested that HMGA2 plays a prominent role in the pathogenesis of the blastemal WT subtype, and is heavily connected with relapse and chemotherapy resistance.20 Walz et al reported that an undifferentiated blastemal histology is associated with considerably reduced expression of the mature Let-7a and miR-200 families (responsible for mesenchymal-to-epithelial transition) in miRNA-PG mutant tumors. The combination of SIX and miRNA-PG mutations in the same tumor was found to correlate with RAS activation and a greater rate of recurrence and death.21

Van Leeuwen et al examined different WT components and found that the blastema is the most likely component to metastasize but is also the most sensitive to therapy.22 This may explain why blastemal predominant WT had more lung recurrences but stage III and IV patients could still achieve CR after salvage therapy. Khine et al used flow-cytometric analysis of the proliferation index to find differences between components of WT and they found that the proliferation index of epithelium was higher than blastema and stroma.23 The potential use of a proliferation index in predicting prognosis may result in a different prognosis for FH WT. Pode-Shakked et al studied cancer stem cells within WT and observed NCAM1 and Ki-67 expression in P-WT Xn, mostly within the expanded blastema component, and P-WT Xn overexpressed genes are known to be associated with a poor WT prognosis.24 Raved et al also reported that cancer stem cells of blastemal NCAM + ALDH1 + WT correlated with disease progression and poor clinical outcome.25 Trink et al used a meta-analysis of published microarray datasets and found that higher stage tumors tended to localize closer to the blastemal archetype in gene expression space.26

Although retrospective, the data we presented were based on a long follow-up period (median, 71.5 months) using a large representative sample of patients who had undergone an FH WT NWTS-5 protocol, as well as a systemic staging workup using sensitive and specific imaging technologies and histological confirmation to evaluate the prognostic value of the predominant blastemal subtype. However, this study had some limitations. First, patients with stage IV lung metastases in the NWTS protocol should have had total lung radiotherapy of 10.8 Gy/6F. In China, radiotherapy technology is still developing and requires further improvement, and the association between long-term toxicity, prognosis, and radiotherapy remains unknown. Radiotherapy doctors have been reluctant to perform whole-lung radiotherapy for children due to concerns regarding long-term side effects.27 Only five patients with residual lung metastases underwent 10.8 Gy/6F radiotherapy, which may have resulted in a higher recurrence rate of lung metastasis. Of note, there were 10 stage III patients who did not receive local radiotherapy because of another trial ChiCTR-PRRC-12002525, and this may have been a further limitation to our study. Second, our center had not carried out genetic tests such as 1q gain and 1p and 16q LOH tests, and intensive treatment for these patients may also affect their survival. Finally, the retrospective nature of the analysis is also a limitation.

Our study findings showed that patients with prechemotherapy blastemal predominant type WT had a higher recurrence rate and a lower EFS and OS. Our findings suggest that blastemal predominant histology-diagnosed prechemotherapy may have prognostic relevance, similar to that found in postchemotherapy samples. Further research into other potential confounding variables, such as biological risk, in a larger cohort, is necessary to determine whether such patients warrant altered risk-stratified therapy.

ACKNOWLEDGMENTS
The authors would like to thank the children and their families for agreeing to participate in the study, and Chunmei Chen for developing the study database.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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How to cite this article: Huang J, Zhang Y, Zhen Z, et al. The prognosis of prechemotherapy blastemal predominant histology subtype in Wilms tumor: A retrospective study in China. Pediatr Blood Cancer. 2020;67:e28567. https://doi.org/10.1002/pbc.28567