Efficacy Analysis of Multidisciplinary Treatment for Wilm’s Tumor in a Single Center

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Research Article

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Abstract

Objective

To analyze the efficacy of multidisciplinary treatment (MDT) for Wilm's tumor (WT) in Kunming Children's Hospital, and investigate the risk factors affecting the prognosis of WT.

Method

The clinic-pathological data were collected and analyzed in patients with unilateral WT treated in Kunming Children's Hospital from January 2017 to July 2021. Research objects were selected according to inclusion criteria and exclusion criteria. The risk factors and independent risk factors that affect the prognosis of patients with WT were determined by Kaplan-Meier survival analysis and Cox proportional hazards model, respectively.

Outcome:

A total of 68 children were included in this study, and the 5-year overall survival (OS) rate was 92.65%. Kaplan-Meier survival analysis results showed that ethnicity (P = 0.020), the tumor volume of resection (P = 0.001), histological type (P < 0.001), and postoperative recurrence (P < 0.001) were the factors affecting the prognosis of children with WT. The results of the Cox proportional hazards model showed that only the histological type (P = 0.028) was the independent risk factor for the prognosis of WT.

Conclusion

The efficacy of MDT for WT was satisfying. The histological type has important predictive value for the prognosis of WT, and the patient with unfavorable histology has a poor prognosis.

Background

Wilms' tumor (WT) is the most common kidney tumor in childhood, accounting for 90% of childhood kidney tumors[1]. WT is a malignant tumor of embryonic origin whose histology and gene transcription are closely related to the early kidney[2]. Mutations in WT1[3], TP53[4], WTX[5], and MYCN[6] genes are associated with the pathogenesis of WT. WT was named after Carl Max Wilhelm Wilms, who first reported pathological character on the disease in 1899[7]. WT mainly occurs within 5 years after birth. The incidence of sex female vs. male and position left vs. right are similar and the incidence of bilateral WT is about 5%-9%[8, 9]. Most children attend to hospital with an asymptomatic abdominal mass, and some children may present abdominal pain, hematuria, or high blood pressure[10].
Two major international collaborative organizations for renal tumors, Children’s Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP) have different strategies on WT treatment. The main controversy is whether preoperative chemotherapy is needed before nephrectomy: COG recommends surgery as a priority to accurately assess tumor stage, biology, and histology, followed by adjuvant therapy. Conversely, SIOP insists that preoperative chemotherapy can reduce tumor volume, surgical difficulty, and the risk of tumor rupture.[11-13].

Multidisciplinary treatment (MDT) is currently recognized as a good tumor treatment model[14]. In this study, clinico-pathological and prognostic data of single-center and relevant literature were analyzed respectively, aiming to summarize and share WT MDT experience for clinicians’ reference.

Research Data And Methods

1. Research data

1.1 Patients

All clinico-pathological data of WT children who were diagnosed with postoperative pathology in Kunming Children's Hospital from January 2017 to July 2021 were collected. Study cases were screened according to inclusion and exclusion criteria, and the included cases were followed up. Inclusion criteria: (1) Preoperative chemotherapy, operation and, postoperative chemotherapy were all completed in Kunming Children's Hospital. (2) All patients underwent radical resection and were confirmed as WT by postoperative pathology. Exclusion criteria: (1) Bilateral WT in patients. (2) Relative data were incomplete. (3) Lost to follow-up.

1.2 Treatment and follow-up

All patient protocols were decided by a multidisciplinary team. The team was consisted of experienced urologist oncologist radiologist anesthetist pathologist nephrologue and ICU doctors. The children were followed up by telephone and outpatient, and the follow-up deadline was September 1, 2021.

1.2 Research methods

The optimal cut-off values of tumor volume of onset (TVO) and tumor volume of resection (TVR) were determined by receiver operating characteristic (ROC) curves. To determine the factors influencing the prognosis of WT, the variables, including gender, age, blood type, whether national, tumor location, WT-1 mutation, the tumor volume of onset (TVO), the tumor volume of resection (TVR), preoperative chemotherapy, postoperative radiotherapy, histological type, lymph node metastasis and vascular metastasis, and recurrence, were analyzed. The Kaplan-Meier survival analysis and Cox proportional hazards model were carried for univariate and multivariate analysis to determine the risk factor and independent risk factor. There were significant differences when p-values are < 0.05, using two-tailed tests. Statistical analyses were performed using SPSS ver. 20.0.
Results

1.3 The general information

A total of 68 children were included in this study, including 33 males and 35 females. The median age of the patients was 36 months (6-264 months), and 22 of them were younger than 24 months. A total of 32 patients received preoperative chemotherapy, and all of them received radical nephrectomy with tumor volume ranging from 622.62 ml to 526.90 ml. Postoperative chemotherapy was performed in 1–9 courses according to tumor stage and histological type. Postoperative recurrence occurred in 9 children, with a recurrence rate of 13.24%. By September 1, 2021, a total of 6 children died, and the 5-year overall survival (OS) rate was 92.65% (Fig. 1).

1.4 ROC results

TVO was calculated according to abdominal enhanced CT measurement results before any treatment: TVO = length x width x height (ml). TVR was calculated based on the ruler measurement results after intraoperative tumor resection: TVR = length x width x height (mL). The results showed the area under the TVO-ROC curve was 0.039, so TVO has no predictive value for the prognosis in this study (Fig. 2). The area under the TVR-ROC curve was 0.890, P = 0.002, with a 95% CI of 0.760 ~ 1000 (Fig. 3). The maximal Youden Index (sensitivity + specificity–1) showed the optimal cut-off value of TVR was 946.45ml, and the sensitivity and specificity were 83.30% and 87.10%, respectively.

1.5 Prognostic factors for WT

In this study, 68 WT patients had a median survival time of 36.5 months and a 5-year OS rate of 92.65%. Kaplan-Meier survival analysis revealed that ethnicity (P = 0.020) (Fig. 4), TVR (P = 0.001) (Fig. 5), histological type (P<0.001) (Fig. 6), and postoperative recurrence (P<0.001) (Fig. 7) were risk factors for children with WT (Table 1). After multivariate analysis, the results indicated that only the histological type (P = 0.028) was independent predictor for OS (Table 2).
<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>5-Year OS (%)</th>
<th>P</th>
<th>Variable</th>
<th>No.</th>
<th>5-Year OS (%)</th>
<th>P</th>
</tr>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>33</td>
<td>93.93</td>
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<td>&lt;946.45 ml</td>
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<td>96.43</td>
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<tr>
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<td>Preoperative chemotherapy</td>
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<tr>
<td>&lt;2 years</td>
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<td>≥ 2 years</td>
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<td>No</td>
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<tr>
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<td>FH</td>
<td>63</td>
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<tr>
<td>O</td>
<td>22</td>
<td>86.36</td>
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<td>UFH</td>
<td>5</td>
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<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>Vascular invasion</td>
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<tr>
<td>Han</td>
<td>43</td>
<td>97.67</td>
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<td>7</td>
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<td>Minority</td>
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<td>Lymph node metastasis</td>
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<td>Left</td>
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<td>Recurrence</td>
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<td>Yes</td>
<td>56</td>
<td>91.07</td>
<td>0.161</td>
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<td>9</td>
<td>55.56</td>
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<td>83.33</td>
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</table>

Abbreviate: FH, Favorable histology; UFH, Unfavorable histology
Table 2
Result of multivariate analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Race (Han vs. Minority)</td>
<td>0.224</td>
<td>0.258 (0.029~2.296)</td>
</tr>
<tr>
<td>Tumor volume of resection (&lt;946.45 ml vs. ≥ 946.45 ml)</td>
<td>0.212</td>
<td>0.203 (0.017~2.479)</td>
</tr>
<tr>
<td>Histological classification (FH vs. UFH)</td>
<td>0.028</td>
<td>0.035 (0.002~0.698)</td>
</tr>
<tr>
<td>Recurrence (Yes vs. No)</td>
<td>0.565</td>
<td>0.404 (0.018~8.864)</td>
</tr>
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</table>

Discussion

WT is one of the most common solid tumors in children. In recent years, with the development of tumor MDT models, such as surgery, chemotherapy, radiotherapy, and immunotherapy, the 5-year OS rate of WT has increased dramatically from 25–90%\textsuperscript{15,16}. The difference between the SIOP and COG strategy for WT is whether preoperative chemotherapy is performed. At present, there is a basic consensus that preoperative chemotherapy has no significant effect on the WT prognosis\textsuperscript{17}, In the results of this study, whether preoperative chemotherapy was not a risk factor affecting the OS as well (P = 0.457). However, preoperative chemotherapy can reduce tumor volume, staging, complications, and postoperative treatment intensity\textsuperscript{18,19}. Moreover, preoperative chemotherapy can thicken tumor capsules and reduce the tumor’s blood supply, effectively reducing the risk of tumor rupture during operation. The results of previous studies of SIOP have shown that the incidence of tumor rupture in patients without preoperative chemotherapy are about 25%, and patients who have received preoperative chemotherapy are about 5%\textsuperscript{20}. However, the 4 to 6-week preoperative chemotherapy time increases the risk of tumor invasion and metastasis, chemotherapy drugs also cause necrosis, suppuration, hemorrhage, or fibrosis of tumor tissues and lymph nodes. It affects the surgeon's judgment of intraoperative lymph node tissue, and tumor staging in the postoperative pathological examination, which does not reflect the true tumor and lymph node involvement\textsuperscript{21}. Therefore, whether to perform preoperative chemotherapy and the protocol should be determined by the MDT team after a comprehensive evaluation. According to COP recommendations, preoperative chemotherapy should be performed for WT of the isolated kidney, bilateral WT, tumor invading adjacent organs, inferior vena cava tumor thrombus above the level of the hepatic vein, or unresectable WT. Secondly, Rutigliano et al.\textsuperscript{22} also pointed out that for children with ruptured WT, preoperative chemotherapy is conducive to the limitation of the ruptured tissue and avoids further local metastasis. It is also helpful to reduce the chance of intraoperative tumor rupture and the area of local radiotherapy after the operation.

Yunnan is the province with the largest concentration of ethnic minorities in China and has 25 ethnic minorities with a population of more than 4,000. It provides a natural advantage for studying public health issues among various ethnic groups. The socioeconomic status, demographic and physiological characteristics, lifestyle, environmental factors, and genetic susceptibility of diseases of different races and ethnic groups are diverse in the incidence of many chronic diseases\textsuperscript{23–25}. In this study, the difference in
prognosis between Han and ethnic minorities is a risk factor affecting the OS of WT. This finding provides a new perspective for the research of WT.

The histological type of WT is divided into favorable histology (FH) and unfavorable histology (UFH). FH includes blastemal, stromal, epithelial and mixed, and the classification based on the ratio of the three tissue types, blastemal, stromal and epithelial, on the broadest section of the tumor\[^{26}\]. About 7%-10% of the histological type are UFH type, also called anaplasia, whose typical characteristics are large and deep stained nuclei, and have atypical mitotic features\[^{27}\]. UFN is a vital risk factor for WT\[^{28, 29}\]. In our study, histological type was the only independent risk factor of OS and the histological types of all 5 patients were UFN.

UFH can be divided into focal anaplasia (FA) and diffuse anaplasia (DA). FA and DA also have significant differences in the prognosis of WT, and the 4-year EFS was 74.9% (95% CI: 59.9–85.0%) and 54.9% (95% CI: 46.2–62.7%), respectively\[^{30}\]. Anaplasia in WT is extremely rare before two years old, and the incidence gradually increases after the age of 4, and the anaplasia rate of tumor tissues above stage III are also significantly higher than the stages I and II\[^{31}\]. There is no correlation between preoperative chemotherapy and anaplasia\[^{32}\]. Research by Maschietto et al.\[^{18}\] found that tissue anamorphosis is related to mutations in the TP53 gene, and the 5-year event-free survival (EFS) rate of wild-type TP53 patients is 80%, while the 4-year EFS rate of mutant TP53 patients is only 44%\[^{33}\].

In summary, the long-term survival rate of patients with WT is significantly improved with an MDT model. Therefore, all departments should work closely together to develop individualized treatment protocols, screen and closely follow-up high-risk patients to improve overall survival. Meanwhile reducing long-term complications also needs to be further improved.

**Declarations**

**Competing interest:** The authors declare that they have no conflict of interest.

**Ethics approval and consent to participate:** The study was confirmed by the Kunming Children’ Hospital Ethics Committee

**Registry and the Registration No. of the study/trial:** N/A

**Animal Studies:** N/A

**Funding:** No applicable.

**Author’s contribution:** FMJ collected, analyzed data, and drafted the original manuscript; CCW and YL collected data and participated in to amend the manuscript; HCHZ collected and analyzed data; JRL and LL analyzed data; BY and ZY designed present study and amended the manuscript.

**Acknowledgements:** No applicable.
References


Figure 1

Kaplan-Meier survival curves of overall survival.
Figure 2

TVO-ROC curve
Figure 3

TVR-ROC curve
Figure 4

Kaplan-Meier survival analysis curve of ethnicity.
Figure 5

Kaplan-Meier survival analysis curve of TVR.
Figure 6

Kaplan-Meier survival analysis curve of histological type.
Figure 7

Kaplan-Meier survival analysis curve of postoperative recurrence.