Efficacy analysis of multidisciplinary treatment for Wilms tumor in a single center

Fengming Ji1 · Chengchuang Wu1 · Ye Li2 · Chenghao Zhanghuang1 · Jinrong Li1 · Li Li3 · Zhen Yang2 · Bing Yan1

Accepted: 1 February 2023
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2023

Abstract
Objective To analyze the efficacy of multidisciplinary treatment for Wilms tumor (WT) in Kunming Children’s Hospital, and investigate the risk factors affecting the prognosis of WT.
Methods 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 subjects 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 87.4%. 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 risk factors affecting the prognosis of children with WT. The results of the Cox proportional hazards model showed that only the histological type ($P = 0.018$) was the independent risk factor for the prognosis of WT.
Conclusion The efficacy of multidisciplinary treatment 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.

Keywords Wilms tumor · Multidisciplinary treatment · Histological type · Prognosis · Follow-up

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 staging systems and treatment strategies on WT. 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].

Fengming Ji, Chengchuang Wu and Ye Li have contributed equally to this work.

Bing Yan
yanbing29@163.com

1 Urology Surgery Department of Kunming Children’s Hospital, Xishan District, No. 288, Qianxing Road, Kunming, Yunnan 650100, People’s Republic of China
2 Oncology Department of Kunming Children’s Hospital, Kunming, Yunnan 650100, People’s Republic of China
3 Yunnan Province Clinical Research Center for Children’s Health and Disease, Yunnan Key Laboratory of Children’s Major Disease Research, Kunming, Yunnan 650100, People’s Republic of China
China is a multi-ethnic country with 56 ethnic groups, 55 of which are ethnic minorities. Yunnan is the province with the largest concentration of ethnic minorities in China and has 25 ethnic minorities with a population of more than 4000. It provides a natural advantage for studying public health issues among various ethnic groups. The socio-economic 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 [14–16].

Multidisciplinary treatment is currently recognized as a good tumor treatment model [17]. In this study, clinico-pathological and prognostic data of single-center and relevant literature were analyzed respectively, aiming to summarize and share WT multidisciplinary treatment experience for clinicians' reference.

Research data and methods

Research data

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, and (3) Lost to follow-up.

Treatment and follow-up

All patients’ protocols were decided by a multidisciplinary team. The team consisted of experienced urologist, onco-logist, radiologist, anesthetist, pathologist, nephrologist and ICU doctors. Patients who received upfront surgery were staged according to the COG staging system, and patients who received preoperative chemotherapy were staged according to the SIOP staging system. The children were followed up by telephone and outpatient, and the follow-up deadline was September 1st, 2022.

Research methods

Tumor volume of onset (TVO) was calculated based on the ruler measurement results after intraoperative tumor resection: TVO = length × width × height × 0.52 (ml). The optimal cut-off values of TVO and 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, ethnicity, tumor location, WT-1 mutation, TVO, 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 were <0.05, using two-tailed tests. Statistical analyses were performed using SPSS ver. 20.0.

Results

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 16.36 to 1912.08 ml. Postoperative chemotherapy was performed in 1–9 courses according to tumor stage and histological type. Postoperative recurrence occurred in nine children, with a recurrence rate of 13.24%. By September 1, 2021, a total of six children died, and the 5-year overall survival (OS) rate was 87.4% (Fig. 1).

ROC results

The results showed the area under the TVO ROC curve was 0.372, so the TVO has no predictive value for the prognosis in this study (Fig. 2A). The area under the TVR ROC curve was 0.890, P=0.002, with a 95% CI of 0.760–1000 (Fig. 2B). The maximal Youden Index (sensitivity + specificity − 1) showed the optimal cut-off value of TVR was 492.15 ml, and the sensitivity and specificity were 83.30% and 87.10%, respectively.

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 87.4%.
Kaplan–Meier survival analysis revealed that ethnicity \( (P=0.020) \) (Fig. 3A), TVR \( (P<0.001) \) (Fig. 3B), histological type \( (P<0.001) \) (Fig. 3C), and postoperative recurrence \( (P<0.001) \) (Fig. 3D) were risk factors for children with WT (Table 1). After multivariate analysis, the results indicated that only the histological type \( (P=0.018) \) was independent predictor for OS (Table 2).

**Discussion**

WT is one of the most common solid tumors in children. The incidence of North America and Europe are higher than East Asia [18]. A multi-center study during 1996–2015 from Kanata et al. [19] showed that in the centers of the investigation, there were 1395 patients from the UK and 537 from Japan, and Japanese patients have a significantly younger median age at diagnosis than those in the UK (28 months vs 39 months).

In recent years, with the development of tumor multidisciplinary treatment models, such as surgery, chemotherapy, radiotherapy, and immunotherapy, the 5-year OS rate of WT has increased dramatically from 25 to 90% [20, 21]. The difference between the SIOP and COG strategy for WT is whether preoperative chemotherapy is needed. At present, there is a certain consensus that is preoperative chemotherapy has no significant effect on the WT prognosis [22]. 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 [23, 24]. Moreover, preoperative chemotherapy can thicken tumor capsule 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% [25]. However, the 4–6-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 involvement of tumor and lymph node [26]. Therefore, whether to perform preoperative chemotherapy and the protocol should be determined by the multidisciplinary treatment team after a comprehensive evaluation. According to COG 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,
Table 1 Result of univariate analysis

| Variable            | No. | 5-Year OS (%) | P   | Variable            | No. | 5-Year OS (%) | P   |
|---------------------|-----|---------------|-----|---------------------|-----|---------------|-----|
| Sex                 |     |               |     | Tumor volume of resection |     |               |     |
| Male                | 33  | 93.93         | 0.438 | <492.15 ml         | 55  | 96.20         | <0.001 |
| Female              | 35  | 91.43         |      | ≥492.15 ml         | 13  | 58.40         |      |
| Age                 |     |               |     | Preoperative chemotherapy |     |               |     |
| <2 years            | 22  | 90.90         | 0.467 | Yes                 | 32  | 96.88         | 0.457 |
| ≥2 years            | 46  | 93.48         |      | No                  | 36  | 88.89         |      |
| Blood type          |     |               |     | Postoperative radiotherapy |     |               |     |
| A                   | 29  | 93.10         | 0.134 | Yes                 | 22  | 95.45         | 0.659 |
| B                   | 11  | 100.00        |      | No                  | 46  | 91.30         |      |
| AB                  | 6   | 100.00        |      | Histological type   |     |               |     |
| O                   | 22  | 86.36         |      | FH                  | 63  | 100.00        | <0.001 |
| Ethnicity           |     |               |     | UFH                 | 5   | 0.00          |      |
| Han                 | 43  | 97.67         | 0.020 | Yes                 | 7   | 100.00        | 0.462 |
| Minority            | 25  | 84.00         |      | No                  | 68  | 92.65         |      |
| Tumor location      |     |               |     | Lymph node metastasis |     |               |     |
| Left                | 37  | 97.30         | 0.056 | Yes                 | 17  | 100.00        | 0.527 |
| Right               | 31  | 87.10         |      | No                  | 51  | 90.20         |      |
| WT-1 mutation       |     |               |     | Recurrence          |     |               |     |
| Yes                 | 56  | 91.07         | 0.161 | Yes                 | 9   | 55.56         | <0.001 |
| No                  | 12  | 100.00        |      | No                  | 59  | 98.31         |      |
| Stage               |     |               |     |                     |     |               |     |
| II                  | 12  | 83.33         | 0.278 |                     |     |               |     |
| III                 | 50  | 96.00         |      |                     |     |               |     |
| IV                  | 6   | 83.33         |      |                     |     |               |     |

FH favorable histology, UFH unfavorable histology

Rutigliano et al. [27] 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 risk of intraoperative tumor rupture and the area of local radiotherapy after the operation.

In this study, the difference in prognosis between Han and ethnic minorities was 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
Table 2 Result of multivariate analysis

| Risk factors                  | P     | HR (95% CI)       |
|------------------------------|-------|-------------------|
| Race (Han vs. minority)      | 0.224 | 0.258 (0.029–2.296) |
| Tumor volume of resection (< 946.45 ml vs. ≥ 946.45 ml) | 0.212 | 0.226 (0.017–2.479) |
| Histological classification (FH vs. UFH) | 0.018 | 0.203 (0.006–4.050) |
| Recurrence (yes vs. no)      | 0.565 | 0.404 (0.018–8.864) |

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 [28]. 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 [29]. UFH is a vital risk factor for WT [30, 31]. In our study, histological type was the only independent risk factor of OS and the histological types of all five patients were UFH.

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 [32]. Anaplasia in WT is extremely rare before 2 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 [33]. There is no correlation between preoperative chemotherapy and anaplasia [34]. Research by Maschietto et al. [23] 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% [35].

In our center, the choice of preoperative chemotherapy depends only on tumor volume, distant metastasis, tumor activity, and the presence of inferior vena cava cancer thrombus, and the long-term survival rate of patients with WT is significantly improved with a multidisciplinary treatment 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.

Author contributions 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.

References

1. Stokes CL, Stokes WA, Kalapurakal JA et al (2018) Timing of radiation therapy in pediatric Wilms tumor: a report from the national cancer database. Int J Radiat Oncol Biol Phys 101(2):453–461
2. Coorens T, Treger TD, Al-Saadi R et al (2019) Embryonal precursors of Wilms tumor. Science 366(6470):1247–1251
3. Petiti J, Rosso V, Lo Iacono M et al (2018) Prognostic significance of The Wilms’ Tumor-1 (WT1) rs16754 polymorphism in acute myeloid leukemia. Leuk Res 67:6–11
4. Rakheja D, Khokhar S, Mitui M, Cost NG (2012) Immunohistochemical expression of GLUT1 and its correlation with unfavorable histology and TP53 codon 72 polymorphism in Wilms tumors. Pediatr Dev Pathol 15(4):286–292
5. Camp ND, James RG, Dawson DW et al (2012) Wilms tumor gene on X chromosome (WTX) inhibits degradation of NRF2 protein through competitive binding to KEAP1 protein. J Biol Chem 287(9):6539–6550
6. Hontecillas-Prieto L, García-Domínguez DJ, García-Mejías R, Ramírez-Villar GL, Sáez C, de Alava E (2017) HMGA2 overexpression predicts relapse susceptibility of blastemal Wilms tumor patients. Oncotarget 8(70):115290–115303
7. Raffensperger J (2015) Max Wilms and his tumor. J Pediatr Surg 50(2):356–359
8. Nakata K, Colombet M, Stiller CA, Pritchard-Jones K, Steliarova-Behline et al (2015) Incidence of childhood renal tumours: An international population-based study. Int J Cancer 137(2):331–333
9. Breslow N, Olshan A, Beckwith JB, Green DM (1993) Epidemiology of Wilms tumor. Med Pediatr Oncol 21(3):172–181
10. Bahoush G, Saeedi E (2020) Outcome of children with Wilms’ tumor in developing countries. J Med Life 13(4):484–489
11. Nakamura L, Ritchey M (2010) Current management of Wilms’ tumor. Curr Urol Rep 11(1):58–65
12. Vujanić GM, D’Hooghe E, Graf N et al (2021) Prognostic significance of histopathological response to preoperative chemotherapy in unilateral Wilms’ tumor: an analysis of 899 patients treated on the SIOP WT 2001 protocol in the UK-CCLG and GPOH studies. Int J Cancer 149(6):1332–1340
13. Chiang KM, Tsay YC, Vincent Ng TC et al (2019) Is hyperuricemia, an early-onset metabolic disorder, causally associated with cardiovascular disease events in Han Chinese. J Clin Med 8(8)
14. Indorewalla KK, O’Connor MK, Hudson AE, Guess DiTerlizzi C, Jackson J (2021) Modifiable barriers for recruitment and retention of older adults participants from underrepresented minorities in Alzheimer’s disease research. J Alzheimers Dis 80(3):927–940
16. Bell CN, Thorpe RJ Jr, Bowie JV, LaVeist TA (2018) Race disparities in cardiovascular disease risk factors within socioeconomic status strata. Ann Epidemiol 28(3):147–152
17. Pillay B, Wootten AC, Crowe H et al (2016) The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: a systematic review of the literature. Cancer Treat Rev 42:56–72
18. Li W, Hua RX, Wang M et al (2021) H19 gene polymorphisms and Wilms tumor risk in Chinese children: a four-center case-control study. Mol Genet Genomic Med 9(2):e1584
19. Nakata K, Williams R, Kinoshita Y et al (2021) Comparative analysis of the clinical characteristics and outcomes of patients with Wilms tumor in the United Kingdom and Japan. Pediatr Blood Cancer 68(10):e29143
20. Cox S, Büyükküçü A, Millar A (2020) Surgery for the complex Wilms tumour. Pediatr Surg Int 36(2):113–127
21. Zhang Y, Song HC, Yang YF, Sun N, Zhang WP, Huang CR (2021) Preoperative Wilms tumor rupture in children. Int Urol Nephrol 53(4):619–625
22. Junjun J, Xuelian Z, Dhruba K, Haiyang X, Lin Z, Shusen Z (2015) Efficacy of preoperative chemotherapy in treatment of children with Wilms’ tumor: a meta-analysis. Iran J Pediatr 25(2):e366
23. Groenendijk A, Speafico F, de Krijger RR et al (2021) Prognostic factors for Wilms Tumor recurrence: a review of the literature. Cancers (Basel) 13(13)
24. Powis M, Messahel B, Hobson R, Gornall P, Walker J, Pritchard-Jones K (2013) Surgical complications after immediate nephrectomy versus preoperative chemotherapy in non-metastatic Wilms’ tumour: findings from the 1991–2001 United Kingdom Children’s Cancer Study Group UKW3 Trial. J Pediatr Surg 48(11):2181–2186
25. Graf N, Tournade MF, de Kraker J (2000) The role of preoperative chemotherapy in the management of Wilms’ tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 27(3):443–54
26. Godzinski J, van Tinteren H, de Kraker J et al (2011) Nephroblastoma: does the decrease in tumor volume under preoperative chemotherapy predict the lymph nodes status at surgery. Pediatr Blood Cancer 57(7):1266–1269
27. Rutigliano DN, Kayton ML, Steinherz P, Wolden S, La Quaglia MP (2007) The use of preoperative chemotherapy in Wilms’ tumor with contained retroperitoneal rupture. J Pediatr Surg 42(9):1595–1599
28. Jain J, Sutton KS, Hong AL (2021) Progress update in pediatric renal tumors. Curr Oncol Rep 23(3):33
29. Green DM, Beckwith JB, Breslow NE et al (1994) Treatment of children with stages II to IV anaplastic Wilms’ tumor: a report from the National Wilms’ Tumor Study Group. J Clin Oncol 12(10):2126–2131
30. Dome JS, Perlman EJ, Graf N (2014) Risk stratification for wilms tumor: current approach and future directions. Am Soc Clin Oncol Educ Book 215–23
31. Vujanić GM, Gessler M, Ooms A et al (2018) The UMBRELLA SIOP-RTSG 2016 Wilms tumour pathology and molecular biology protocol. Nat Rev Urol 15(11):693–701
32. Dome JS, Cotton CA, Perlman EJ et al (2006) Treatment of anaplastic histology Wilms’ tumor: results from the fifth National Wilms’ Tumor Study. J Clin Oncol 24(15):2352–2358
33. Vujanić GM, Harms D, Sandstedt B, Weirich A, de Kraker J, Delemarre JF (1999) New definitions of focal and diffuse anaplasia in Wilms tumor: the International Society of Paediatric Oncology (SIOP) experience. Med Pediatr Oncol 32(5):317–323
34. Speafico F, Fernandez CV, Brok J et al (2021) Wilms tumour. Nat Rev Dis Primers 7(1):75
35. Maschietto M, Williams RD, Chagtai T et al (2014) TP53 mutational status is a potential marker for risk stratification in Wilms tumour with diffuse anaplasia. PLoS ONE 9(10):e109924

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.