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Original Article

Efficacy evaluation of treatment for children with refractory renal tumor

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Abstract: Background and Objectives: The treatment for refractory renal tumor is still not satisfactory. The authors analyzed retrospectively their experience in the treatment of refractory renal tumor diagnosed from 2009 to 2014. Methods: A retrospective study of 28 patients with refractory renal tumor confirmed by pathology was analyzed in our center. The clinical characteristics of patients were illustrated and the efficacy of two different chemotherapy regimens was compared. Results: Among the 28 patients suffered with refractory renal tumor, 17 patients survived out of 28 patients. Eleven patients died, and nine of them died of disease relapse or progression. Pathology, extent of surgery and chemotherapy regimen were closely associated with 3-year overall survival (OS) and 3-year progression-free survival (PFS). In addition, pathology type and chemotherapy regimen had further impact on prognosis. The 3-year overall survival (OS) rate was 84.4% for patients with UH-1 regimen and 48.6% for patients with WT-2009 regimen, respectively (P=0.026). The 3-year progression-free survival (PFS) was 67% and 45%, respectively (P=0.048). The3-year survival rate appeared to be better in the UH-1 group than that in the WT-2009 group. Conclusion: Refractory renal tumor treatment outcome is reasonable but still needs further improvement. Selection of UH-1 regimen effectively improves the survival rate, though longer follow-up observation for safety is still needed.

Keywords: Refractory renal tumor, treatment, UH-1 regimen, WT-2009 regimen

Introduction

Children kidney cancer accounts for 7% of all childhood tumors, and most children renal tumors are Wilms Tumor [1] (WT, nephroblastoma). WT is one of the most common abdominal malignant solid tumors in children and the incidence rate is only second to neuroblastoma. With the multidisciplinary treatment approaches consisted of surgical resection of the primary tumor, standard use of radiotherapy and chemotherapy, 5-year survival rate of children with WT under 15 years old increased from 74% to 88% in the past decades [1]. Though the overall prognosis of WT has successfully improved, survival rate of 30% of children with renal tumors is less than 70%, mainly caused by unfavorable histology WT (UHWT) such as focal anaplastic WT (FAWT) as well as diffuse anaplastic WT (DAWT), and three special types-clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor of the kidney (MRT), renal cell carcinoma (RCC) [2]. The outcome of these types of WT is poor with the conventional treatment. For instance, UHWT accounts for 10% of the disease while is responsible for nearly 50% of WT deaths [3]. And we defined UHWT and special types of WT as refractory renal tumor. Owing to the low incidence of this class of patients and tolerance to intensive therapies, little randomized or prospective studies in the literature were published, especially in developing countries. The Chinese Wilms Tumor Study group was founded in 1998, and a nationwide multicenter cooperative study was started to improve the survival rate of children with renal tumors. A multicenter review conducted between 1998 and 2012 have shown that the 5-year overall survival rate was 52% in patients with UHWT [4]. These results were not satisfactory, so the protocol was sometimes modified by local institutions for better outcome. In our center, the management of refractory renal tumor consisted of initial biopsy, neoadjuvant

chemotherapy, tumor resection, followed by radiotherapy and adjuvant chemotherapy, according to the clinical stage and histological features. We continued to treat refractory renal tumor through further improved surgery and radiotherapy since 2009. At the same time, two different chemotherapy regimens were adopted. One regimen was WT-2009 formulated by Pediatric Oncology Wilms Tumor chemotherapy Collaborative Group of Chinese Anti-Cancer Association Professional Committee while the other was UH-1 revised by Children's Oncology Group (COG). In the present study, clinical characteristics of refractory renal tumor in our department were analyzed under the multidisciplinary treatment modality. Efficacy and safety of the two different chemotherapy regimens were also evaluated. These results will be informative and helpful to revise and perfect the current protocol.

Materials and methods

This study was approved by the Academic Committee of Tianjin Medical University Cancer Institute and Hospital and consented by the families of study participants. A retrospective study of patients with refractory renal tumor confirmed by pathology was analyzed in our center. One hundred and forty-three patients were diagnosed with WT from April 2009 to September 2014. Among them, 34 had refractory renal tumors. Six were excluded from this study for withdrawing treatment. A final 28 patients were analyzed here. A team consisted of pediatric oncologists, radiation oncologists, pathologists, radiologists worked together to complete diagnosis and treatment. Data collected included sex, age, primary tumor site, symptoms and tumor size at presentation, metastatic sites, lactate dehydrogenase level (Hitachi 7180 automatic biochemical analyzer and beckman biochemical analyzer), presence of tumor thrombus, standard clinical stage referring to the National Wilms Tumor Study Group (NWTSG), histological type, WT1 mutations in tumor tissue, surgical time, the extent of surgery, surgery complications, chemotherapy, chemotherapy-related serious adverse effect, short term side-effects of radiation therapy, the time to complete the treatment and follow-up data.

Surgery

Patients would receive initial tumor resection if appropriate. But those patients with huge tumor (tumor size >10 centimeter), presence of vena cava tumor thrombus, severe peripheral vascular invasion or difficulty in complete resection were prescribed to complete 2-4 courses of neoadjuvant chemotherapy before surgical resection of the primary tumor [5]. Gross total resection (GTR) is defined as removal >95% of visible and palpable tumor from the primary site and regional lymphatics. Subtotal resection (STR) is defined as removal <95% but >80% of tumor. Surgery extent was determined by review of the surgeon's operative report in conjunction with postoperative computed tomography (CT) or magnetic resonance imaging (MRI).

Chemotherapy

Twelve patients randomly received WT-2009 chemotherapy regimen. The initial preoperative chemotherapy regimen on WT-2009 was IEV (Ifosfamide 1.5 g/m^2/d, day 1-5, Mesna 0.3/m^2, q3h*4 times/d; Etoposide 3.3 mg/m^2/d, day 1-3; VCR 0.05 mg/kg, day 0, 8). Considering the maximum reaction of chemotherapy usually occurring in the sixth week, the chance of operation is determined by the imaging reassessment after two cycles of IEV, and initial clinical stage influences postoperative chemotherapy regimen [6]. Patients with stage II-IV FAWT received WT-2009 (2) (DD4A) for 25 weeks. Patients with stage II-IV DAWT and stage I-IV CCSK received WT-2009 (3) (Doxorubicin, VCR, Etoposide, cyclophosphamide) for 25 weeks. Patients with stage I-IV MRT receive WT-2009 (4) (carboplatin, Etoposide, cyclophosphamide) [4]. Sixteen patients who randomly received UH-1 regimen were given CPM1 + Doxorubicin + VCR and CPM5 + CBP + Etoposide alternately, and completed surgical resection of the primary tumor after 12 weeks of preoperative chemotherapy [7]. The internal between two cycles was 21-28 days in the two chemotherapy regimens.

Radiotherapy

Patients received external beam RT to their primary tumor within 10 days postoperation as part of their consolidation therapy. The dose administered ranged from 1080 to 2160 cGy (median, 1600 cGy) in 180 cGy fractions, 5 times a week. Patients with lung metastasis received lung irradiation 1200 cGy IMRT. High-dose radiation therapy has a significant impact

on survival, though it may increase the long term side-effects [3]. Radiation dose, scope and timing on other metastases were determined by the medical team. The radiation fields encompassed the prechemotherapy and presurgery primary tumor volume and regional lymph nodes with a 1-cm margin while protecting the contralateral kidney. Generally, the method was tolerated in all patients received RT (Radiotherapy). The main short term side-effects of radiotherapy in WT include skin and soft tissue injury, hyperpigmentation, intestinal discomfort, the affected skeletal muscle, cardiac toxicity, reproductive problems, kidney dysfunction, pulmonary fibrosis and occurrence of second malignancies [8].

Definition of treatment reaction

The treatment reaction was assessed as follows: Complete remission (CR): All primary and measurable metastases disappeared; Partial remission (PR): All the primary tumor and metastases measurable had reduction in volume of more than 50% but less than 90%; Stable disease (SD): All original tumor metastases and measurable volume is less than 50% but no progress; Progressive disease (PD): The emergence of new lesions, measurable lesion volume increased more than 25% already existed.

Follow-up and statistical analysis

After treatment, ultrasound, chest and abdomen computed tomography (CT), bone scan were implemented every 3 months (within 2 years) or 6 months (2-6 years) for regular follow-up and evaluation. Overall survival (OS) was defined as the time from the initial diagnosis to death from any cause or the most recent follow-up. Progression-free survival (PFS) was defined as the time from initial diagnosis to tumor progression or death. The statistical software SPSS 22.0 was used to analyze the collected data. Survival rates were assessed using the Kaplan-Meier method. The Log-Rank test and the Cox proportional hazards model were used to assess the independent prognostic factors. All *P* values were two-tailed. $P<0.05$ was considered to be significant statistically.

Results

Clinical manifestations

Of the 28 patients, 18 were females and 10 were males (F/M=1.8). Their ages at diagnosis ranged from 24 to 132 months with a median of 61.6 months. The time interval from onset of the first symptom to first presentation of a health professional varied from 2 days to 6 months. Seventeen patients (17/28, 60.7%) were in the left kidney, eleven (11/28, 39.3%) in the right. None had a family history of Wilms tumor or bilateral disease.

First diagnosed symptoms

Abdominal mass was the first presenting symptom in 20 patients (20/28, 71.6%), fever in 4 patients (4/28, 14.2%), gross hematuria in 4 patients (4/28, 14.2%). The presence of tumor thrombus by radiology check was found in 8 patients (8/28, 28.5%), no tumor thrombus in 20 patients (20/28, 71.5%). Lung metastasis at diagnosis was found in 15 patients (15/28, 53.5%), distant lymph node metastasis in 5 patients (5/28, 17.8%) and multi-system involvement (such as lung and bone, lung and lymph node metastasis) in 5 patients (5/28, 17.8%), bone metastasis in 1 patient (1/28, 3.5%).

Preoperative diagnosis

Five out of the 28 patients received resection in other hospitals and were transferred to our department after diagnosis with refractory renal tumor. Among the other 23 patients, 3 patients were diagnosed through lymphadenectomy and 20 were confirmed by ultrasound-guided biopsy. Tumor stage was determined at initial exploration. According to NWTSG staging, 26 (26/28, 92.9%) patients had stage IV and 2 (2/28, 7.1%) patients had stage III disease.

Clinical features and treatment of cases

Tumor sizes (CT maximum diameter value) ranged from 4 cm to 15 cm (mean 7.8 cm, median 8.2 cm). After preoperative chemotherapy, tumor sizes determined by gross pathology examination ranged from 3.5 cm to 9.0 cm (mean 4.6 cm, median 5.1 cm). Except the five patients who finished surgery outside our center, histopathologic examination revealed varying degrees of necrosis, hemorrhage fibrosis and so on. A total of 15 patients underwent gross total resection (15/28, 53.5%), 13 cases subtotal resection (13/28, 46.5%). Pathological analysis should consist of the ureteral stump, incisalmargin, fatty renal capsule, renal hilar

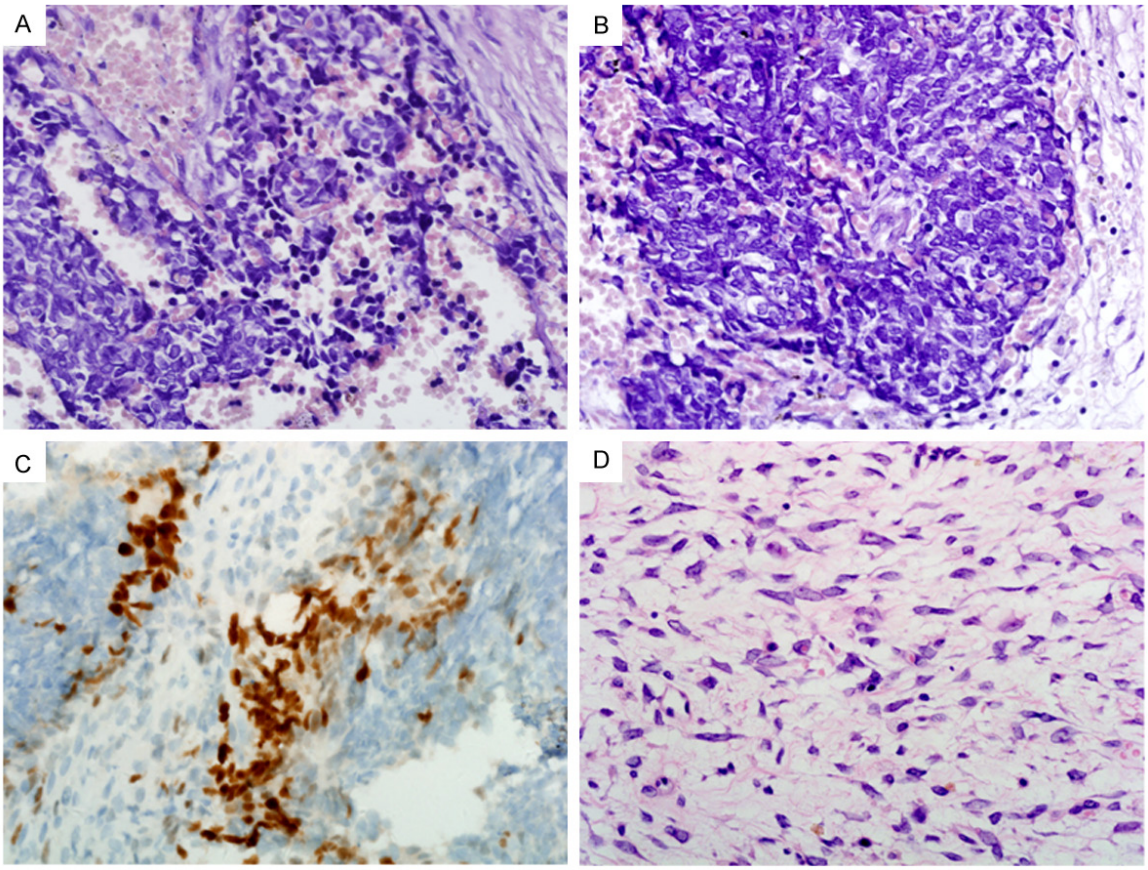

Figure 1. Partial typical pathology: A, B: (HE dye ×400) as UHWT (unfavorable histology WT); C: (IHC ×400 tumor tissues WT1 positive); D: (HE dye ×400) as CCSK (clear cell sarcoma of the kidney).

vessels and lymph node sampling check. At least two professional pathologists made the definite diagnosis or consultation decision, and the WT1 gene was analyzed in the tumor tissue in all cases. FAWT was diagnosed in 18 cases (18/28, 64.4%), DAWT in 6 cases (6/28, 21.4%), CCSK in 2 cases (2/28, 7.1%), and MRT in 2 cases (2/28, 7.1%) (**Figure 1**). The resection was complete remission (CR) in 10 patients (10/28, 35.7%), partial remission (PR) in 10 patients (10/28, 35.7%), stable disease (SD) in 8 patients (8/28, 28.6%). Clinicopathological features and treatment modalities in the two groups of patients with WT are listed in **Table 1** (Chi square test).

Outcomes

Up to the cut-off date for this study, none had been lost follow-up. Seventeen patients were still alive, including 2 cases of survival after recurrence without further treatment. Eleven patients died, and 9 of them died from disease progression or recurrence. The median time interval from CR/SD to recurrence/progression was 14.5 months (range 8-25 months). Three patients experienced disease progression. Six patients had relapses. Of these, two relapses occurred in local position, two in the contralateral kidney, one in pelvic cavity, one in ovary. Chemotherapy-related serious adverse events were defined as: 1) Grade III-IV myelosuppression after chemotherapy according to the WHO classification; 2) The use of anthracyclines such as doxorubicin affecting cardiac function such as B-type natriuretic peptide (BNP) more than 5000 pg/ml (vitas detection), subject to drugs such as digoxin, left ventricular ejection fraction (EF) less than 60% revealed by cardiac ultrasound examination, abnormal ECG monitor and influence the ongoing follow-up treatment, etc; 3) Agranulocytosis and fever after chemotherapy in need of drug treatment; 4) Liver and (or) kidney function changes subject to drug intervention postchemotherapy. In the 28 cases, seventeen cases experienced chemotherapy-related severe side-effects but

Table 1. Clinicopathological features and treatment modalities in the two groups of patients with WT

	WT-2009 (n)	UH-1 (n)	χ^2	P
Sex				
Male	4 (33.3%)	6 (37.5%)	1.000	0.570
Female	8 (66.7%)	10 (62.5%)		
Age				
<72 months	9 (75.0%)	9 (56.3%)	0.434	0.268
≥72 months	3 (25.0%)	7 (43.3%)		
Pathology				
FAWT and CCSK	8 (66.7%)	12 (75.0%)	0.691	0.472
DAWT and MRT	4 (33.3%)	4 (25.0%)		
WT1 in tumor tissue				
Negative	8 (66.7%)	12 (75.0%)	0.233	0.691
Positive	4 (33.3%)	4 (25.0%)		
Primary tumor site				
Left kidney	7 (58.3%)	10 (62.5%)	1.000	0.565
Right kidney	5 (41.7%)	6 (37.5%)		
Tumorthrombus				
Positive	4 (33.3%)	4 (25.0%)	0.691	0.472
Negative	8 (66.7%)	12 (75.0%)		
LDH				
<1500 U/L	7 (58.3%)	11 (68.8%)	0.698	0.430
≥1500 U/L	5 (41.7%)	5 (31.2%)		
The extent of surgery				
GTR	6 (50.0%)	9 (56.2%)	1.080	0.743
STR	6 (50.0%)	7 (43.8%)		
Surgery complications				
Negative	8 (66.7%)	12 (75.0%)	0.233	0.691
Positive	4 (33.3%)	4 (25.0%)		
Chemotherapy-related serious adverse effects				
Negative	5 (41.7%)	6 (37.5%)	0.050	1
Positive	7 (58.3%)	10 (62.5%)		
Short term side-effects of RT				
Negative	9 (75.0%)	11 (71.4%)	0.131	1
Positive	3 (25.0%)	5 (28.6%)		

NOTE: Both groups were doing chi square test for 2×2 tables and using the Fisher exact ratio when numbers <5; No statistical difference was found between the two regimens. Abbreviations: PFS: Progression-free survival, OS: Overall survival, FAWT: Focal anaplastic Wilms tumor, CCSK: Clear cell sarcoma of the kidney, DAWT: Diffuse anaplastic Wilms tumor, MRT: Malignant rhabdoid tumor of the kidney, LDH: Lactate dehydrogenase, GTR: Gross total resection, STR: Subtotal resection, RT: Radiotherapy.

eventually tolerated all cycles of chemotherapy. Eight patients had postoperative complications. Three patients who received WT-2009 regimen suffered surgical infections, one gastrointestinal discomfort. In the UH-1 group, one patient experienced surgical infections, two hemorrhage, one gastrointestinal discomfort. Timely radiotherapy was conducted as soon as complications were relieved.

According to univariate analysis (**Table 2**), pathological type (P=0.029, ANOVA), Surgery extent (P=0.022, ANOVA), chemotherapy (P=0.026, ANOVA) were closely related to 3-year OS. Gender (P=0.142, ANOVA), age (P=0.621, ANOVA), tumor tissue WT1 mutation (P=0.527, ANOVA), primary tumor site (P=0.171, ANOVA), tumor thrombus (P=0.533, ANOVA), lactate dehydrogenase (P=0.093, ANOVA), complica-

Table 2. Univariate analysis of clinicopathological features and treatment modalities in the 28 cases

Clinicopathological features and treatment modalities	Patients (n)	3-year OS (%)	MST (m)	P	3-year PFS (%)	Median PFS (m)	P
Sex							
Male	10	78.8	71	0.142	58.3	57	0.996
Female	18	70.7	59		61.1	56	
Age							
<72 months	18	71.3	61	0.621	66.7	60	0.338
≥72 months	10	64.0	64		48.0	50	
Pathology							
FAWT and CCSK	20	83.3	70	0.029*	74.3	67	0.001*
DAWT and MRT	8	37.5	49		25	30	
WT1 in tumor tissue							
Negative	20	73.8	65	0.527	65.0	60	0.594
Positive	8	56.3	53		46.9	46	
Primary tumor site							
Left kidney	17	80.9	68	0.171	66.7	64	0.338
Right kidney	11	50.9	45		48.0	42	
Tumor thrombus							
Positive	8	62.5	50	0.533	62.5	46	0.897
Negative	20	79.3	65		70	57	
LDH							
<1500 U/L	18	77.4	70	0.093	72.2	64	0.159
≥1500 U/L	10	68.6	55		40.0	42	
The extent of surgery							
GTR	15	85.6	73	0.022*	79.4	70	0.012*
STR	13	48.5	51		38.5	38	
Surgery complications							
Negative	20	69.3	61	0.600	54.5	54	0.442
Positive	8	67.5	70		45.0	62	
Chemotherapy regimen							
WT-2009	12	48.6	52	0.026*	41.7	45	0.048*
UH-1	16	84.4	71		73.9	67	
Chemotherapy-related serious adverse effects							
Negative	11	70.1	77	0.992	61.8	67	0.097
Positive	17	68.4	62		46.3	50	
Side-effects of RT							
Negative	20	80.0	67	0.140	65.0	60	0.553
Positive	8	56.3	49		46.9	45	

*P<0.05, Abbreviations: MST: median survival time, PFS: Progression-free survival, OS: Overall survival, FAWT: Focal anaplastic Wilms tumor, CCSK: Clear cell sarcoma of the kidney, DAWT: Diffuse anaplastic Wilms tumor, MRT: Malignant rhabdoid tumor of the kidney, LDH: Lactate dehydrogenase, RT: Radiotherapy.

tions after surgery (P=0.6, ANOVA), chemotherapy-related serious adverse events (P=0.992, ANOVA) and short term side-effects of radiotherapy (P=0.14, ANOVA) had little effect on OS. Additionally, pathological type (P=0.001, ANOVA), the extent of surgery (P=0.012, ANOVA), and types of chemotherapy (P=0.048, ANOVA) had greater impact on 3-year PFS.

The 3-year overall survival (OS) were 84.4% and 48.6% for patients who accepted UH-1 regimen and WT-2009 regimen, respectively (P=0.026, ANOVA) (**Figure 2**). The 3-year progression-free survival (PFS) were 67% and 45%, respectively (P=0.048, ANOVA) (**Figure 3**). The 3-year survival rate appeared to be better in the UH-1 group than that in the WT-2009 group.

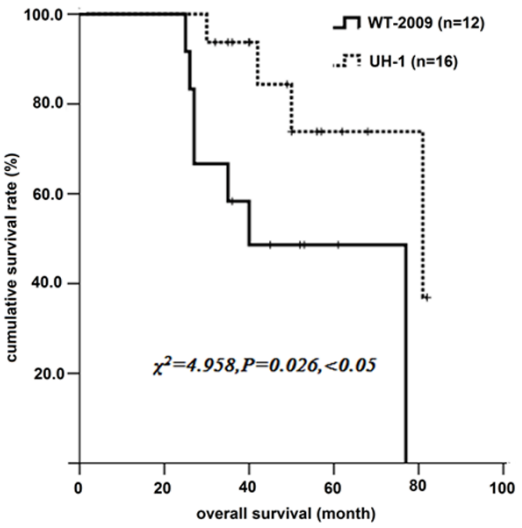

Figure 2. Kaplan-Meier survival curves showing overall survival according to chemotherapy regimen. The 3-year overall survival rate is significantly higher in the UH-1 group (P=0.026).

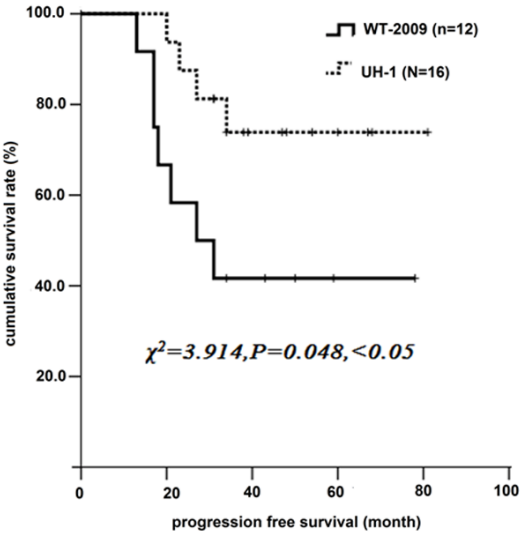

Figure 3. Kaplan-Meier curves showing progression free survival. The 3-year progression free survival is significantly higher in the UH-1 group (P=0.048).

Prognostic analysis

Chemotherapy regimen, pathological type and surgery extent were the three independent variables that influenced survival. Cox proportional hazard model prognostic analysis of these variables showed that OS in refractory renal tumor benefited from UH-1 chemotherapy regimen (P=0.011, COX). However, only chemotherapy regimen and pathological type significantly affected PFS (P=0.01, P=0.039, respectively, COX) (**Table 3**).

Discussion

It is imperative that a multidisciplinary approach to diagnosis and therapy should be undertaken for patients with Wilms tumor (WT). Although cure rate of the disease is 90% in developed countries [9], the diagnosis and treatment of WT still face with difficulty in developing countries due to late treatment, regional poverty, families of children with poor compliance and neglect of health issues [10, 11]. New treatment protocols for most WT patients are shifting their primary objective from maximizing cure to ensuring maximum cure while reducing treatment-related side effects. However, for children with refractory renal tumor, it is necessary to improve the prognosis by strengthening treatment intensity [12, 13].

Independent prognosis factors affecting the overall prognosis of WT included disease stage, pathological type, genetic abnormalities and age [14-16]. Wilms tumor usually occurs in children less than 2 years old [3]. The 5-year survival rate is only 63% in children over 10 years old, which is significantly lower than that of those younger ones [17]. It is difficult for older children with hematogenous metastasis who commonly seem to be refractory to obtain satisfactory results with conventional treatment [14]. The median age of children in our study was 61.6 months, younger than 72 months reported in the literature [18], so patients could not only bear high-intensive chemotherapy but also respond to chemotherapy. It is reported that malformation occurs in approximately 10% of WT patients [3], but nobody had malformation in present study. Consistent with other reports [19], most patients presented with palpable masses in our study. Our survival analysis revealed no statistically significant relationship between survival rate and tumor thrombus. This results is consistent with previous study reported by Shamberger [20]. The most common organ of hematogenous metastasis is the lung and distant metastases are the most important factors that affect the treatment effect [21]. In the current study, 15 patients (15/28, 53.5%) suffered lung metastasis at diagnosis, but no statistical difference was found in survival rate between patients with lung metastasis and those without.

Table 3. Using Multivariate COX model to analyze OS and PFS

	OS			PFS		
	P	Exp (B)	95.0% CI	P	Exp (B)	95.0% CI
Extent of surgery (GTR vs STR)	0.131	4.399	0.643-30.086	0.086	4.657	0.803-27.007
Chemotherapy regimen (UH-1 vs WT-2009)	0.011*	0.116	0.022-0.612	0.010*	0.130	0.027-0.620
Pathology (FAWT, CCSK vs DAWT, MRT)	0.421	1.991	0.372-10.653	0.039*	5.139	1.089-24.261

*P<0.05. Abbreviations: PFS: Progression-free survival, OS: Overall survival, GTR: Gross total resection, STR: Subtotal resection, FAWT: Focal anaplastic Wilms tumor, CCSK: Clear cell sarcoma of the kidney, DAWT: Diffuse anaplastic Wilms tumor, MRT: Malignant rhabdoid tumor of the kidney.

Evolving novel multimodal treatment is the first choice for the majority of children with WT. On the other hand, surgery is still the most important sector. In our center, consistent with the International Society of Peadiatric Oncology (SIOP), neoadjuvant chemotherapy is recommended to patients for reducing rupture during surgery rather than an initial surgery [22]. Because of the preoperative chemotherapy, no intraoperative complications such as tumor rupture occurred in the present study [23, 24]. Considering nephron-sparing surgery (NSS) increasing more chances of tumor rupture and positive surgical margins than nephrectomy [9, 25, 26], none received NSS in our center and all 28 children underwent unilateral nephrectomy without renal failure. Fifteen patients underwent gross total resection (GTR) and 13 underwent subtotal resection (STR). Univariate analysis showed GTR had significantly improved survival rate but Cox proportional hazards model analysis existed a negative result. However, on account of the retrospective nature of our study, small number of patients and advanced stage at diagnosis might have imposed bias.

Most published studies have reported that refractory renal tumor is associated with a poor prognosis. Undoubtedly, updated chemotherapy is the greatest contribution to improved survival rate of WT in recent decades. In our study, the 3-year PFS estimate appeared to be better in the UH-1 group (67%) than in the WT-2009 group (45%), which were both lower than the rate cited in previous reports [27]. Our lower rate may be caused by advanced clinical stage at diagnosis because of inadequate or deficient education by government agency as well as insufficient awareness and attention of parents in developing countries. It is reported that high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCR) might be promising options for recurrent Wilms tumor [28-30]. Survival rate for recurrent WT can reach up to 50% with current treatment [31]. Therapies with HDC and ASCR might provide references in the improvement of survival rates for patients with refractory renal tumor.

Twenty-four patients were diagnosed with FAWT and calculated an incidence of 16% of Wilms tumor patients, which was higher than that of 10% reported by COG [7]. But this was consistent with study by Dome JS [14], it seems that unfavorable pathology is more common in patients with neoadjuvant chemotherapy compared with patients without neoadjuvant chemotherapy. Patients with FAWT and CCSK were likely to have better prognosis than those with MRT and UAWT, which may result from chemotherapy resistance in the latter.

Previous studies have reported at least 60% of childhood cancer survivors presented with long-term sequelaes [27], which would bring trouble to further treatment [6]. Secondary neoplasm and congestive heart failure were observed in 6.7% and 4.4% of childhood cancer survivors, respectively [32, 33]. The percentage of patients with chemotherapy-related serious adverse effects and short term side-effects of radiation therapy in our study is 60.7% and 28.5%, respectively. However, our current analysis revealed no statistically significant relationship between the incidence of late effects and different chemotherapy regimens. But our study was too limited to draw definitive conclusions and more clinical data are needed.

The improved understanding of WT biology and its impact on prognosis has resulted in successful preclinical researches. For instance, dysregulated expression of WT1 and CTNNB1 were reported to be related with the risk of

tumor recurrence [34, 35]. In our study, expression of WT1 was detected by immunohistochemistry (IHC) and WT1 mutations were detected in 8 patients (28.5%), which is higher than 10-20% reported in the literature [36-38]. In light of further achievement of molecular characterization of WT, individualized treatment programs containing biological therapy represent a promising novel approach for refractory renal tumor treatment.

Refractory renal tumor is an extremely aggressive disease associated with rapid progression, frequent metastases and poor prognosis. Treatment outcome with UH-1 regimen of refractory renal tumor in a single center is reasonable but still need further improvement. We will continue to refine our ability and develop novel therapies by using the mounting knowledge for refractory renal tumor.

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Disclosure of conflict of interest

None.

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