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ORIGINAL ARTICLE

Malignant Renal Tumors in Childhood: Report of 54 Cases Treated at a Single Institution

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Background: Wilms tumor is the most common primary renal malignancy occurring in childhood. Significant improvement has been made in the treatment of children with Wilms tumor. However, the treatment of patients with non-Wilms renal tumors remains challenging.
Methods: Between 1991 and 2010, 70 children with renal tumors were diagnosed at a single institution. Fifty-four patients were histologically confirmed and divided into three groups, including 42 Wilms tumors, seven clear cell sarcomas of kidney, and five malignant rhabdoid tumors. Most patients underwent unilateral nephrectomy and lymph node sampling followed by adjuvant chemotherapy. Twenty-one of these patients subsequently received radiotherapy.
Results: During follow-up, 12 patients died of progressive disease and one died of operative mortality. One patient with unilateral pleural metastases subsequently underwent hematopoietic stem cell transplantation. The median survival time of all patients was 88 months.

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Children under 2 years of age at diagnosis with Wilms tumor or clear cell sarcoma of kidney had an excellent survival rate of 100% compared to the 0% survival rate of MRT.
Conclusion: Younger age at diagnosis bore a better prognosis than did older age, whereas a diagnosis of malignant rhabdoid tumor portended a worse prognosis. Younger patients and appropriate treatment may have contributed to the improved prognosis of clear cell sarcoma of kidney.

1. Introduction

Pediatric renal tumors represent a relatively common group of childhood solid neoplasms, in which both diagnosis and treatment are highly dependent on the histopathological findings.[1–3] Wilms tumor (WT) is the most common renal tumor in children and represents approximately 95% of all pediatric renal malignancies.[4] WT was also the first solid malignancy in which the value of adjuvant chemotherapy was established. Treatment for WT is one of the perceived successes of pediatric oncology, with long-term survival in >90% of the cases for localized disease and >70% of the cases for metastatic disease.[5] In addition, a few patients have genetic abnormalities predisposing to WT development, which result in renal dysfunction in the long term and may be exacerbated by cancer treatment regimens. Awareness of late consequences of cancer treatment is important, as early recognition can improve outcome.[6]

Malignant renal tumor histology is the most important factor in determining prognosis.[7,8] Successful treatment of malignant renal tumors requires meticulous attention to correct staging of the tumor and good communication among the pediatric surgeon, pathologist, and oncologist.[9–11] The aim of this study is to illustrate our clinical experience in the long-term follow-up of children with three common malignant renal tumors treated according to the Taiwan Pediatric Oncology Group (TPOG) W91 and W97 protocols.

2. Materials and Methods

Throughout the period 1991—2010, 70 children with histological confirmation of renal tumors were treated at Chang Gung Children's Hospital, Taoyuan, Taiwan. We reviewed the charts of these patients throughout the whole disease course, including long-term follow-up, paying particular attention to the details of postoperative stage, pathological findings, and outcomes. Sixteen patients were excluded because of benign histology or non-Wilms renal tumors other than clear cell sarcoma of kidney (CCSK) or malignant rhabdoid tumor (MRT). There were renal cell carcinomas in six cases, renal sarcoma in five cases, paraganglioma in two cases, angiomyolipoma in one case, mesoblastic nephroma in one case, and renal tumor without histological diagnosis in one case.

2.1. Treatment

The analyzed patients were treated by a consistent policy of surgical removal with histological verification followed by chemotherapy with or without radiotherapy. There were 32 boys and 22 girls with a median age of 25 months (range 2—176 months). All patients underwent nephrectomy and lymph node sampling followed by adjuvant chemotherapy. Chemotherapy regimens included the TPOG W91 and W97 protocols varying according to treatment era. TPOG W91 was the first WT study of the TPOG. This study began in July 1991 and ended in December 1997. TPOG W97 was a revised version of TPOG W91. The important revisions are as follows: used single dose of dactinomycin; shortened duration of treatment for stage I disease; preoperative chemotherapy for patients with bilateral disease; patients with stage IV disease; massive unresectable tumor or significant caval extension; no preoperative chemotherapy for infants less than 6 months of age; introduction of etoposide and carboplatin into protocols for high-risk patients. According to the original staging criteria stipulated in the protocol, 21 patients received postoperative radiotherapy plus chemotherapy and the others received chemotherapy alone.

2.2. Statistical analyses

Data were abstracted on patient demographics, tumor histology, staging, number of lymph nodes sampled, and disease-specific and overall patient outcomes. Statistical analyses were performed with SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant. Overall survival is defined as the time from randomization until death from any cause, and it is measured in the intent-to-treat population. Disease-free survival is defined as the time from cancer diagnosis until recurrence of tumor or death from any cause.

The time to tumor recurrence was determined by follow-up images. Kaplan—Meier survival analysis was conducted to determine actuarial survival; 95% confidence intervals (95% CIs) were calculated for the survival estimation (Figure 1). Owing to the observational nature of the study, institutional review board approval was granted by expedited review. The data were further crosschecked with the TPOG database that collected all the pathology reports of cancer in the territory.

3. Results

Overall, 54 cases were identified. The main clinical characteristics of all the patients are summarized in Table 1. The histological diagnosis was WT in 42 patients (78%), CCSK in seven patients (13%), and MRT in five patients (9%). The

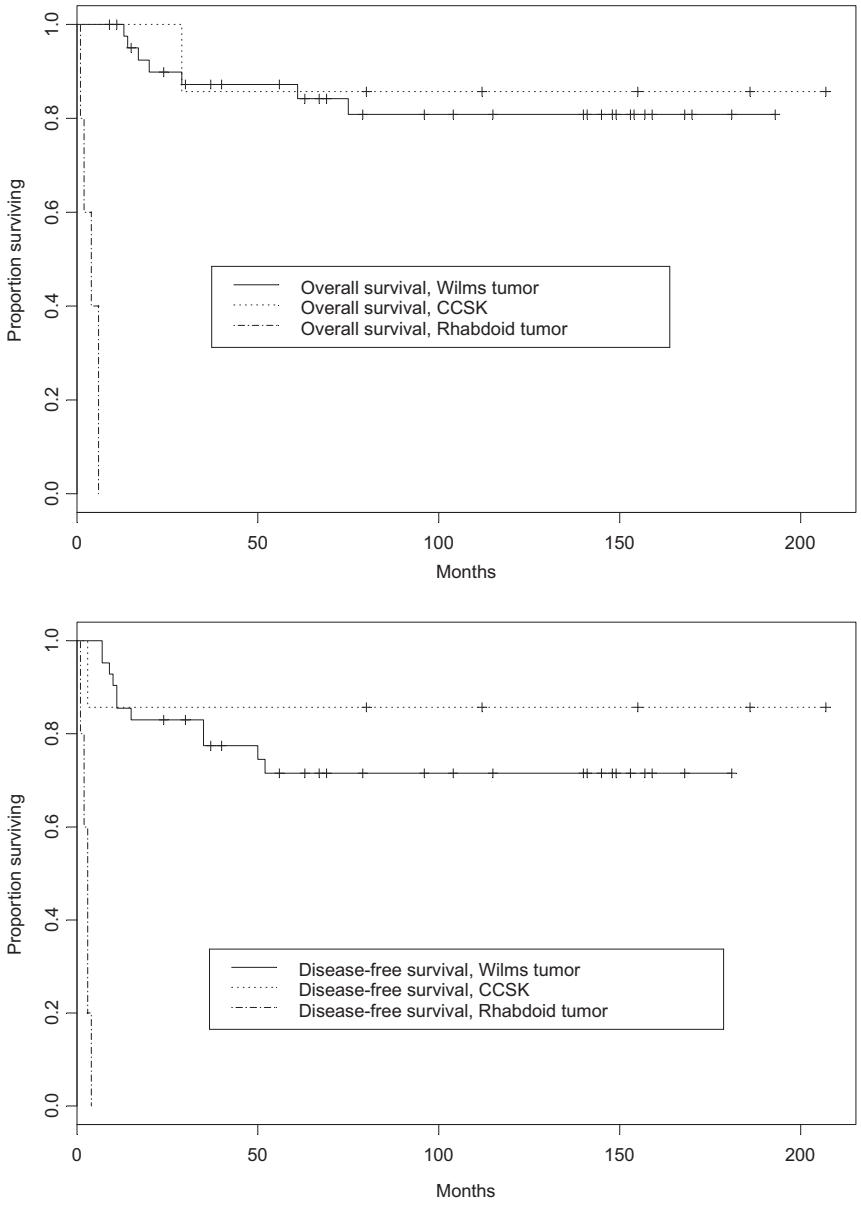

Figure 1 Overall and disease-free survival by Kaplan—Meier estimates. CCSK = clear cell sarcoma of kidney.

tumor weight also varied widely, from 70 g to 1500 g. The tumors were confined to one kidney in 50 cases (24 left, 26 right), and both kidneys in four cases.

Of the children diagnosed with WT, 16 (30%) had stage I disease, 10 (19%) had stage II, nine (17%) had stage III, two (4%) had stage IV, four (7%) had stage V disease, and one was unclassified due to insufficient information. For patients with CCSK, four (7%) had stage I, one (2%) had stage II, one (2%) had stage III, and one (2%) had stage IV. For patients with MRT, five (9%) were classified as stage IV with distant metastasis. Two patients had lung metastases at the initial presentation; one of them subsequently developed brain metastasis. For the other three patients, two had liver metastasis and one had brain metastasis at diagnosis. Seven associated anomalies were present in six patients (11.1%) as shown in Table 2. One patient had more than one anomaly. Moreover, a positive correlation between tumor size and outcome was not observed in our series. There was no statistically significant difference in outcome between the two protocols used.

During follow-up, 12 patients died of progressive disease and one died of operative mortality. Of those 54 patients, 10 patients had documented pulmonary metastasis. Lung metastasis was confirmed by chest computed tomography (CT) scan at diagnosis in five patients (9.3%), and the other five patients were finally diagnosed by radiological follow-up examinations. Nine of the 10 patients with lung metastasis at diagnosis or follow-up eventually died of metastatic disease. One patient with unilateral pleural metastases required high-dose chemotherapy and tandem autologous stem cell rescue, who subsequently underwent allogeneic hematopoietic stem cell transplantation.

The collective median survival time of all patients was 88 months. For patients with WT and CCSK, the 5-year

Table 1 Demographics and clinical characteristics.

	n	%
Sex		
Male	32	59
Female	22	41
Laterality		
Left	25	46
Right	25	46
Bilateral	4	8
NWTSG stage		
Stage I	20	37
Stage II	11	20
Stage III	10	19
Stage IV	8	15
Stage V	4	7
Unknown	1	2
Tumor weight		
500 g	28	52
≥500 g	14	26
Unknown	12	22
Tumor histology		
Wilms tumor	42	78
Clear cell sarcoma of kidney	7	13
Malignant rhabdoid tumor	5	9
Adjuvant therapy		
Chemotherapy	54	100
Radiotherapy	21	39
Tumor recurrence		
No	37	69
Yes	17	31

NWTSG = National Wilms Tumor Study Group.

Table 2 Associated anomalies in the six patients with Wilms tumor in this study.

Associated anomalies	*n*
Hypospadias	1
Hydronephrosis	1
Congenital cataracts	1
Congenital heart disease	1
Dysmorphism	2
Congenital hydrocephalus	1

overall survival rates were 83.3% and 85.7%, respectively. Moreover, children under 2 years of age at diagnosis with WT or CCSK had an excellent survival rate of 100% compared with that of MRT, which was usually fatal within 1 year of diagnosis (Table 3).

4. Discussion

WT is one of the successes of pediatric oncology, with an overall cure rate of over 85%, using relatively simple therapies.[12,13] Despite these successes, controversy continues regarding the optimal management of children with unilateral, favorable histology WT.[14,15] Two different approaches have been recommended by different investigators: immediate nephrectomy or pre-nephrectomy chemotherapy followed by delayed nephrectomy.[4,16] However, it is difficult to compare the two approaches head-to-head precisely. The overriding message is that most patients with WT survive long term, regardless of the sequence of therapeutic interventions. The data reported here suggest that younger patients with WT or CCSK generally have a good prognosis. The role of high-dose chemotherapy followed by stem cell rescue or transplantation is undefined in recurrent WT patients.[17–19] However, high-dose chemotherapy intensification and hematopoietic stem cell support could be an effective treatment for patients with WT who experience relapse.[20,21]

WT is the most common renal tumor of childhood. However, other epithelial, mesenchymal, and neuroectodermal neoplasms may also arise in the kidney during childhood, several of which show specific age distributions.[22,23] In the past, CCSK was initially considered an unfavorable histology WT variant. However, in 1970 it was recognized as a separate clinicopathological entity by Kidd.[24] Marsden et al[25] subsequently called the tumor the "bone metastasizing renal tumor of childhood", and Beckwith and Palmer[26] were the first to use the term "clear cell sarcoma".

In our study, the outcome of CCSK seems not inferior to the outcome of WT described in the literature.[27–29] There are two reasons which may explain why results differ. First, our patients who were treated with chemoradiation experienced an improved relapse-free survival from a longer course of therapy when using vincristine, doxorubicin, and dactinomycin. The other reason is that no CCSK patient had bilateral disease (stage V) or positive CT or magnetic

Table 3 Overall survival and disease-free survival of patient subgroups.

Variables	Overall survival (mo)	*p**	Disease-free survival (mo)	*p**
Histology				
WT	162.79 ± 10.35		136.13 ± 11.54	
CCSK	181.57 ± 23.54	<0.001	177.86 ± 26.98	0.001
MRT	3.80 ± 1.02		2.60 ± 0.51	
WT and CCSK				
Age ≤2 y	Unestimated (no event case)	<0.004	198.30 ± 8.51	0.003
Age >2 y	138.11 ± 15.95		110.28 ± 16.08	

**p*-value calculated by log-rank test.
CCSK = clear cell sarcoma of kidney; MRT = malignant rhabdoid tumor; WT = Wilms tumor.

resonance imaging of the brain at diagnosis. CCSK has a unique constellation of chromosomal and molecular features and should no longer be viewed as an unfavorable histological variant of WT.[8] However, it is essential to acknowledge the limitation of this study is that it is a single institutional study with a small cohort size.

MRT is an uncommon tumor that may occur outside of renal and central nervous system sites. Particularly troubling are the dismal survival rates for the very young.[30] However, in the five patients who had distant metastasis at diagnosis which contributed to their worse prognosis, subsequent mortality was reasonable. Two patients presenting with central nervous system metastases at diagnosis had an even worse prognosis.

In conclusion, reduction of tumor volume due to preoperative chemotherapy facilitates tumor removal by surgery and may prevent intraoperative tumor spill and the deleterious effects of radiation in young children.[5,31] Children under 2 years of age at diagnosis with WT or CCSK had an excellent survival rate of 100% compared to that of MRT. It is possible to interpret that as the younger patients having been diagnosed at earlier stages of the disease. Regardless of location, all MRT are highly aggressive, have a poor prognosis, and tend to occur in children less than 2 years of age. Younger age at diagnosis bore a better prognosis than did older age, whereas a diagnosis of MRT portended a worse prognosis. Treatment strategies need to be refined for patients with MRT, although the number of analyzed cases is too small to draw definitive conclusions.

Conflict of interest

The authors state that there are no conflicts of interest regarding the publication of this article.

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