Original article

Renal tumor in developing countries: 142 cases from a single institution at Shanghai, China

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Background: **The clinical management of children with renal tumors including Wilms' tumor, clear cell sarcoma, rhabdoid tumor and other renal tumors in our center was designed according to the National Wilms' Tumor Study Group protocols.**

Methods: **A total of 142 consecutive patients who had been diagnosed as having renal tumors at Shanghai Children's Medical Center were reviewed retrospectively in the period of December 1998 and September 2012. Diagnosis and treatment were decided by a multi-disciplinary team including oncologists, surgeons, pathologists and sub-specialized radiologists.**

Results: **The median age of the patients at the time of diagnosis was 27 months. The tumor stages of the patients were as follows: stage I 24.6%, stage II 23.2%, stage III 32.3%, stage IV 14.1%, and stage V 5.6%. Favorable histology was diagnosed in 80.3%, anaplasia in 4.2%, clear cell sarcoma in 9.8%, rhabdoid tumor in 4.9%, and other renal tumors in 0.7% of the patients. The event-free and overall 5-year survival rates were 80% and 83%, respectively. Tumor relapse and progress was seen in 25 patients (17.6%). The median relapse time was 6 months (range: 2-37 months). Seven relapsing patients were re-treated and four of them got second complete remission (three in stage II, one in stage I).**

Conclusion: **A multi-disciplinary team work model is feasible in developing countries, and the renal tumors protocols basically from developed countries are safe in developing countries.**

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Key words: **China;**
developing country;
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Introduction

Renal tumors are among the most common malignant solid tumors in children, accounting for 5%-6% of all malignant childhood tumors, with Wilms' tumor (WT) being the most common renal malignancy.[1] The refinement of multimodal therapy, which can include surgery, chemotherapy, and radiation therapy, has remarkably improved the outcome of children with renal tumors, with an overall survival rates of 90% in developed countries.[2,3] The treatment of WT is one of the great success stories in oncology; however, certain subgroups of patients still do not fare well, including those with anaplastic histology, bilateral diseases, and recurrent diseases.[4,5]

Specific challenges are faced in treating children with renal tumors in developing countries. Children often present late with advanced diseases, and abandonment of treatment is a common cause of treatment failure. Surgery, chemotherapy, and radiotherapy are often given in different hospitals, with no communication between the different specialists. Treatment failures may also result from the lack of child-specialized radiotherapy experts. These challenges must be considered when adopting treatment guidelines to local conditions.

Collaborative groups and multi-disciplinary teams have contributed immensely to the increasing survival over recent decades in developed countries, but are not yet widely implemented in developing countries. Since 1998 we have followed this effective working model for the treatment of childhood cancer, including renal tumors in Shanghai Children's Medical Center.

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We organized a multi-disciplinary team consisting of oncologists, surgeons, pathologists, and sub-specialized radiologists, and established a tumor board for coordinating diagnosis, treatment evaluation, and patient transfer among oncologists, surgeons, and radiologists.

The present study aimed to evaluate renal tumors characteristics and to report the treatment results in patients admitted to Shanghai Children's Medical Center from between 1998 and 2013. In our center, children with renal tumors, including WT, clear cell sarcoma, rhabdoid tumor, and other renal tumors, were treated according to the National Wilms' Tumor Study Group (NWTSG) protocol.[6]

Methods

Children who had been pathologically diagnosed with renal tumors at our hospital from December 1998 through September 2012 were enrolled in the study. The study was approved by the Institutional Review Board of Shanghai Children's Medical Center. Diagnosis and treatment were decided by a multi-disciplinary team consisting of oncologists, surgeons, pathologists, and sub-specialized radiologists.

The medical records of patients with renal tumors were reviewed retrospectively in terms of age at diagnosis, sex, mode of presentation, involved kidney, preoperative treatment, type of surgery, stage, postoperative treatment modalities, follow-up period, and outcome (including complications, tumor recurrence, and survival). Anaplasia was considered an "unfavorable" histological feature, and tumors without anaplasia were considered histologically "favorable". Clear-cell sarcoma and malignant rhabdoid tumor of the kidney are considered distinct tumor types, and they are also discussed in our study. In all patients, clinical staging was determined according to the criteria of the third and fourth NWTSG, based exclusively on the anatomic extent of the tumor, without considering genetic, biological, or molecular markers. Histological classification was as defined by the NWTSG study.[6]

The modalities used to investigate the patients included abdominal ultrasonography, computed tomography (CT), and chest CT; CT scan was performed to define the tumor origin within the kidney, evaluate the possible presence of a second renal tumor in the opposite kidney, assess caval extension, and depict hepatic metastases. The combination of CT and ultrasonography was the most useful and accurate method for preoperative diagnosis and assessment of patients. Bone marrow smear, bone scanning, and head magnetic resonance imaging (MRI) were used to evaluate the patients with clear-cell sarcoma of the kidney and malignant rhabdoid tumor before chemotherapy. Serial measurements of lesions were performed with CT or MRI during follow-up.

Most of the patients with unilateral renal tumors were treated surgically, followed by postoperative chemotherapy with or without radiotherapy. The exact protocol depended on patient age and tumor stage, and was determined according to the NWTSG protocols. For patients with bilateral WT (BWT) or a tumor that could not be removed completely at the first presentation, preoperative chemotherapy was administered.

Systemic chemotherapy was given according to the NWTSG protocol.[6] Patients with stage I-II favorable histology or with stage I focal anaplastic histology received WT-1 (dactinomycin and vincristine) for 19 weeks. Patients with stage III-IV favorable histology, with stage II-III focal anaplastic histology, or with stage I diffuse anaplastic histology received WT-2 (doxorubicin, dactinomycin, and vincristine) for 25 weeks. Patients with stage II-III diffuse anaplastic histology, with stage I-III clear cell sarcoma, or with stage IV focal anaplastic histology received WT-3 (cyclophosphamide, doxorubicin, vincristine, and etoposide) for 25 weeks. Patients with stage I-IV rhabdoid tumor or with stage IV diffuse anaplastic histology and clear cell sarcoma received WT-4 (carboplatin, cyclophosphamide, doxorubicin, vincristine, and etoposide) for 27 weeks. Patients with stage IV or unresectable stage III tumor received WT-5 (ifosfamide, vincristine, and etoposide) for six weeks, followed by reassessment for feasibility of surgical management, and were then assigned a post-surgical regimen based on the original staging. Radiation therapy (XRT) was started within 10 days post-operation for patients whose primary tumors were initially resected. For those younger than 12 months of age, XRT was omitted or delayed until they were 12 months old. For patients with liver and/or lung metastatic diseases, whether to administer metastatic site XRT was based on discussion between the physician, radiologist, and parents.

Statistical analysis

Event-free survival was defined as the time from study entry to the first occurrence of progression, relapse, death from any cause, or loss to follow-up. Survival was defined as the time from study entry to death from any cause. Patients without events were censored at the time of their last follow-up. The collected data were analyzed using SPSS software version 13.0. The Kaplan-Meier method was used to assess the survival rates.

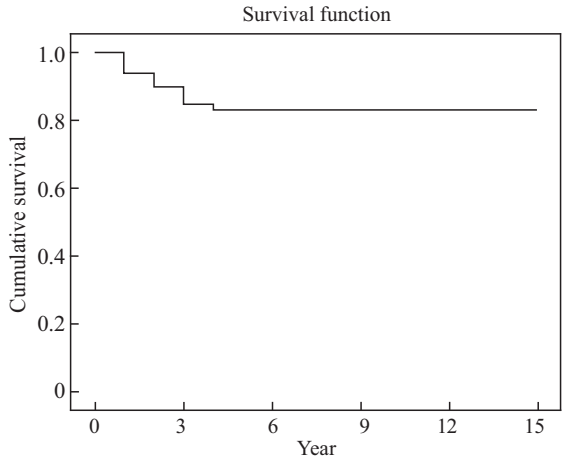

Fig. 1. The overall survival for renal tumor patients estimated by Kaplan-Meier method.

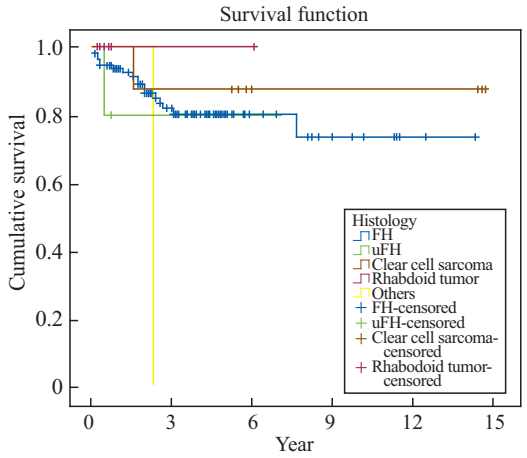

Fig. 2. The overall survival for renal tumor patients with FH (blue), uFH (green), clear cell sarcoma (brown), rhabdoid tumor (purple) and other renal tumors (yellow). FH: favorable histology; uFH: unfavorable histology.

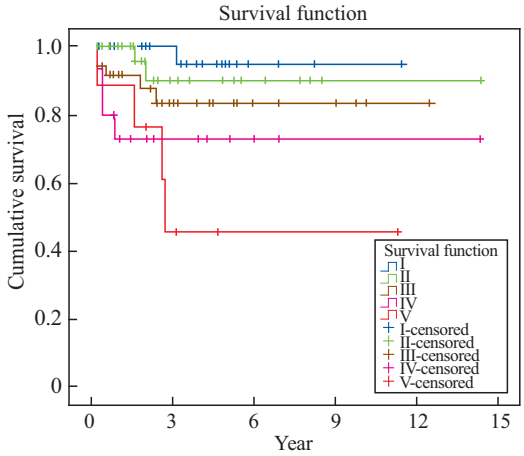

Fig. 3. The overall survival for renal tumor patients estimated by stage Kaplan-Meier estimations.

Results

A total of 142 patients diagnosed as having renal tumors were admitted to the Shanghai Children's Medical Center. The median follow-up of the patients was 32 months (range: 3-175 months). Of these patients, 82 were male and 60 were female, with a male to female ratio of 1.4:1. The median age of the patients at the time of diagnosis was 27 months (range: 3-173 months). Of the 142 patients, 102 (71.8%) were 0-4 years old: 21.8% were below 1 year old, 19% were 1-2 years old, 19% were 2-3 years old, and 12% were 3-4 years old. The event-free and overall 5-year survival rates of the patients were 80% and 83%, respectively (Fig. 1).

Favorable histology was observed in 114 (80.3%) patients, unfavorable histology in 6 (4.2%), clear cell sarcoma in 14 (9.8%), rhabdoid tumor in 7 (4.9%), and other renal tumor in 1 (0.7%). There was no statistically significant difference in patients with different histological findings (P=0.232; Fig. 2).

Tumor stage was defined at the time of initial examination: 35 patients (24.6%) in stage I, 33 (23.2%) in stage II, 46 (32.4%) in stage III, 20 (14%) in stage IV, and 8 (5.6%) in stage V. The overall 5-year survival rates were 95%, 90%, 81%, 71% and 45% for stage I, stage II, stage III, stage IV, and stage V, respectively (Fig. 3). In 8 patients who had tumor thrombus in the inferior vena cava at diagnosis, 6 survived with event-free. Hematogenous metastases were noted at diagnosis in 19 patients including 14 patients with pulmonary metastases, 4 patients with hepatic lesions, and 1 patient with both pulmonary and hepatic metastases. Two patients received lung irradiation, and one of them relapsed.

Tumor relapse and progression occurred in 25 patients (17.6%): 2 in stage I, 6 in stage II, 9 in stage III, 6 in stage IV, and 4 in stage V. The sites of relapse were the abdomen (7 patients), chest wall (1), lung (6), liver (4), and both lung and liver (1). The median time of relapse was 6 months (range: 2-37 months). Seven patients with relapse were retreated, and four of them achieved complete remission (3 in stage II, and 1 in stage I).

At the time of diagnosis, 116 patients were scheduled for complete nephrectomy, and 9 had rupture of the tumor during the operation. One patient at presentation underwent partial nephrectomy and 25 patients were subjected to needle biopsy. Twenty-five patients were given 6-8 week pre-surgical chemotherapy when the tumor could not be completely removed at the first presentation, and radiation therapy was given after surgery. Of the 25 patients, 20 (80%) are still alive, and 5 (20%) once experienced progressive disease or relapse.

None of the patients received XRT before initial surgery. Following the surgery, XRT was given to 65 patients. Three of these patients (4.6%) had hepatic veno-occlusive disease, characterized by hepatomegaly, ascites, and increased bilirubin at 33-63 days after XRT. The patients recovered within 15 days after supportive care without use of anticoagulants. In patients with liver and/or lung metastatic diseases, only two patients received metastatic site XRT (both in the lung) based on the decision made by the physician, radiologist, and parents. No cardiac toxicity, renal failure, lung toxicity, or toxic deaths occurred in our study.

Discussion

In the present study, we evaluated renal tumors characteristics and treatment results of the patients admitted to Shanghai Children's Medical Center, China between 1998 and 2013. The patient male to female ratio at our institution was 1.4:1, which is similar to that in Europe but different from in the NWTS where females are predominant. The median age of patients in our study (27 months) was younger than in the NWTS (32 months).[7] Furthermore, compared with the NWTS-5,[8] the present study had a lower percentage of stage I patients (35% *vs*. 24.6%) and a higher percentage of stage III patients (22.7% *vs*. 32.3%). The differences may be due to delayed presentation of our patients or to multiple transfers among different hospitals before admission to our center.

The rate of favorable histology in our study was 80.3%, compared with 92.2% in the NWTS-5.[8] Although there were few patients in the "other histology" group, the survival rate significantly differed between the two groups. In the NWTS-5, the 4-year relapse-free survival rates for stages I, II, III, and IV were 92%, 83%, 85.3%, and 74.6%, respectively, and for stage V were 74% for favorable histology and 40% for unfavorable histology.[9] In the United Kingdom Wilms' Tumor Study (UKWS-2/3), the 4-year event-free survival rates for stages I, II, III, IV, and V were 86.5%, 82%, 82%, 70%, and 70%, respectively.[10] The event-free survival rates in the present study were similar to those in the previous study.[8]

NWTS-5 results showed that surgery alone may be an adequate treatment for children below 2 years old at diagnosis with stage I favorable histology WT weighing less than 550 g.[11] Accordingly, we adjusted our protocol for stage I patients to avoid unnecessary chemotherapy. The NWTSG has recommended preoperative chemotherapy under certain circumstances including the occurrence of WT in a solitary kidney, BWT, tumor in a horseshoe kidney, tumor thrombus in the inferior vena cava above the level of the hepatic veins, and respiratory distress resulting from the presence of extensive metastatic tumor. The International Society of Paediatric Oncology (SIOP) strategy of giving preoperative chemotherapy is based on the premise that preoperative therapy reduces the risk of tumor rupture during surgery, thereby reducing the likelihood of local and distant recurrence. A second advantage is that response to treatment may provide a valuable prognostic indicator.[12] Our study showed that pre-surgical chemotherapy was effective against advanced renal tumors. Of the 25 patients who were given 6-8 week pre-surgical chemotherapy and post-surgical radiation therapy, 20 (80%) patients are still alive and 5 (20%) once experienced progressive disease or relapse.

Of the 14 patients in our study with pulmonary metastases, 2 received lung irradiation (one relapsed), and 12 did not (three relapsed). The first WT study by the United Kingdom Children's Cancer Study Group reported a survival rate of only 65% in patients with lung metastases who did not receive radiation therapy.[13] Our present findings raise questions about the role of lung irradiation.

The management of BWT has evolved from primary surgical extirpation to kidney-preserving resection after preoperative chemotherapy. However, current treatments remain suboptimal for some patients including those with anaplastic, bilateral, or recurrent disease with favorable histologic features. In stage V patients, preoperative chemotherapy has the advantage of reducing tumor volume, and the treatment response may provide a valuable prognostic indicator.[14] In our study, 5.6% of the patients were of stage V; these patients showed very poor prognosis with an overall 5-year survival rate of 45%. The overall survival rate of our patients was lower than that of SIOP (an overall 10-year survival rate of 69%).

Chemotherapy regimens using ifosfamide, etoposide, carboplatin, and topotecan in combination have been developed to improve outcomes in recurrent patients.[15,16] For the treatment of relapsed patients, we used WT-3 with cyclophosphamide, doxorubicin, vincristine, and etoposide. For other histology, re-treatments were individualized. Of the seven treated relapsed patients in our study, 4 achieved complete remission within 24-94 months. A review of 54 patients in consecutive trials at St. Jude Children's Hospital showed disease-free survival rates for children with recurrent WT ranging from 50% to 70%.[17] It remains to be proven whether stem cell transplantation is more efficacious than conventional chemotherapy. In our study, two patients received stem cell transplantation, of whom one died from disease progression and the other

was lost to follow-up after continued second complete remission for 7 months. There is not yet a way to better tailor systemic therapy intensity to the risk of secondary failure, underscoring the need for novel treatment approaches.

In conlcusion, a multi-disciplinary teamwork model is feasible in a developing country, and the basic renal tumors protocols from developed countries are safe for use in a developing area. The event-free and overall 5-year survival rates in Shanghai Children's Medical Center were similar to those in the NWTS-4 and UKWS-2/3 studies in stage I, II, III, IV WT patients. Our institution showed poorer outcome in stage V patients, which seemed to be at least partly due to the approach of preserving renal parenchyma.

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Contributors: Pan C proposed the study and wrote the first draft. Cai JY analyzed the data. All authors contributed to the design and interpretation of the study and further drafts. Tang JY is the guarantor.

References

1 Dome JS, Perlman EJ, Ritchey ML, Coppes MJ, Kalapurakal J, Grundy PE. Renal tumors. In: Poplack DG, Pizzo PA, eds. Principles and Practice of Pediatric Oncology, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2006: 905-932.
2 Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010;28:2625-2634.
3 Grigoriev Y, Lange J, Peterson SM, Takashima JR, Ritchey ML, Ko D, et al. Treatments and outcomes for end-stage renal disease following Wilms tumor. Pediatr Nephrol 2012;27:1325-1333.
4 Kalapurakal JA, Dome JS, Perlman EJ, Malogolowkin M, Haase GM, Grundy P, et al. Management of Wilms' tumour: current practice and future goals. Lancet Oncol 2004;5:37-46.
5 Green DM, Breslow NE, Beckwith JB, Finklestein JZ, Grundy P, Thomas PR, et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 1998;16:3744-3751.
6 D'Angio GJ, Breslow N, Beckwith JB, Evans A, Baum H, deLorimier A, et al. The treatment of wilms' tumor: results of the third National Wilms' Tumor Study Group. Cancer 1989;64:349-356.
7 Hamilton TE, Ritchey ML, Haase GM, Argani P, Peterson SM, Anderson JR, et al. The management of synchronous bilateral Wilms tumor: a report from the National Wilms Tumor Study Group. Ann Surg 2011;253:1004-1010.
8 Breslow NE, Collins AJ, Ritchey ML, Grigoriev YA, Peterson SM, Green DM. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 2005;174:1972-1975.
9 Dome JS, Cotton CA, Perlman EJ, Breslow NE, Kalapurakal JA, Ritchey ML, et al. Treatment of anaplastic histology Wilms' tumor: results from the fifth National Wilms' Tumor Study. J Clin Oncol 2006;24:2352-2358.
10 Popov SD, Sebire NJ, Pritchard-Jones K, Vujanić GM. Renal tumors in children aged 10-16 years: a report from the United Kingdom Children's Cancer and Leukaemia Group. Pediatr Dev Pathol 2011;14:189-193.
11 Shamberger RC, Anderson JR, Breslow NE, Perlman EJ, Beckwith JB, Ritchey ML, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms Tumor Study-5. Ann Surg 2010;251:555-558.
12 Metzger ML, Dome JS. Current therapy for Wilms' tumor. Oncologist 2005;10:815-826.
13 Pritchard J, Imeson J, Barnes J, Cotterill S, Gough D, Marsden HB, et al. Results of the United Kingdom Children's Cancer Study Group first Wilms' Tumor Study. J Clin Oncol 1995;13:124-133.
14 Venkatramani R, Malogolowkin M, Davidson TB, May W, Sposto R, Mascarenhas L. A phase I study of vincristine, irinotecan, temozolomide and bevacizumab (vitb) in pediatric patients with relapsed solid tumors. PLoS One 2013;7:e68416.
15 Malogolowkin M, Cotton CA, Green DM, Breslow NE, Perlman E, Miser J, et al. Treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms Tumor Study Group. Pediatr Blood Cancer 2008;50:236-241.
16 Abu-Ghosh AM, Krailo MD, Goldman SC, Slack RS, Davenport V, Morris E, et al. Ifosfamide, carboplatin and etoposide in children with poor-risk relapsed Wilms' tumor: a Children's Cancer Group report. Ann Oncol 2002;13:460-469.
17 Metzger ML, Stewart CF, Freeman BB 3rd, Billups CA, Hoffer FA, Wu J, et al. Topotecan is active against Wilms' tumor: results of a multi-institutional phase II study. J Clin Oncol 2007;25:3130-3136.

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