HK J Paediatr (new series) 2009;**14**:108-114

Prognostic Factors and Outcome of Wilms' Tumour in a Tertiary Children's Hospital, China

LL ***Yang,*** MJ ***Li,*** ML ***Zheng,*** S ***Xu,*** DX ***Tang,*** YF ***Han***

Abstract Wilms' tumour is the most frequent malignant neoplasm of the kidney in children. Multimodal treatment was used in treating this tumour, and it has achieved the best results for any tumour group. We studied all the patients who underwent surgery for unilateral Wilms' tumour at Children's Hospital, Zhejiang University School of Medicine during the 15-year period from January 1992 through December 2006. A total of 92 patients were treated for the unilateral Wilms' tumour during the study period, among whom 11 patients were excluded out of this analysis due to the loss of first follow-up after discharge from the hospital. The overall survival of the 81 patients was 76.6%. Cox analysis revealed that anaplastic histology, stage III and without preoperative treatment are risk factors for Wilms' tumour. Pre-operative treatment plays an important role in the treatment of Wilms' tumour and it will lead to better outcome for the patients. Treatment for Wilms' tumour with anaplastic histology and tumour recurrence remains a big challenge in China. The overall survival is still lower than that in developed countries and multi-modality treatment should be optimised for Wilms' tumour patients in China.

Key words Chemotherapy; Nephrectomy; Outcome; Treatment; Wilms' tumour

Laboratory Center, Department of Research and Education, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China

LL **Yang** (楊莉麗) *MB, MSc*

Division of Pediatric Surgical Oncology, Department of Pediatric Surgery, Children's Hospital, Zhejiang University School of Medicine; Hangzhou, China

MJ **Li** (李民駒) *MD*
S **Xu** (徐珊) *MD*
DX **Tang** (唐達星) *MD*

Department of Research and Education, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China

ML **Zheng** (鄭美玲) *MPH*

Department of Epidemiology and Statistics, Qiqihar Medical University, Qiqihar, China

YF **Han** (韓雲峰) *MPH*

Correspondence to: Professor MJ **Li**

Received January 22, 2009

Introduction

Wilms' tumour is the most frequent malignant neoplasm of the kidney in children. Multimodal treatment was used in treating this tumour, and it has achieved satisfactory results. With the most favourable prognosis among solid tumours, the survival rate of Wilms' tumour has reached 85%.[1]

With the expansion of the modern cancer services and access of resources, the outcome of cancer in children has also been improved in recent years in China. This study was to investigate risk factors and outcome of patients with Wilms' tumour, and to report our experience in treating Wilms' tumour at a tertiary Children's Hospital in East China.

Methods

The study included all the patients who underwent surgery for unilateral Wilms' tumour at Children's Hospital,

Zhejiang University School of Medicine during the 15-year period from January 1992 through December 2006. Patients who were lost in the first follow-up were excluded. All data were collected from the clinical and pathological records of the patients up to December 2007. This retrospective study was approved by the Institutional Review Board of Zhejiang University School of Medicine. Informed consents were obtained from the parents or guardians before all kinds of treatment modalities were initiated.

The following demographics were reviewed and recorded, including age of the patients at the time of diagnosis, gender, the time for any kind of initial treatment, possibility of surgical resection when the tumour was diagnosed, staging and tumour histology, location of the tumour, rupture of the tumour (prior to surgery or during the surgical procedure), presence of para-aortic lymph nodes compromised by the neoplasm, treatment modalities, follow-up period and outcome (including tumour recurrence and survival).

Age at the time of diagnosis was divided into three categories: zero to 23 months, 24 to 47 months, 48 months or more. The staging and histological sub-typing corresponded to those systems established by the NWTS (Table 1).[2] Tumour histology was classified into two subtypes: favourable histology and anaplastic histology. The compromising of para-aortic lymph nodes by neoplastic cells was classified into two levels: negative and positive. Treatment modalities were classified into two: I nephrectomy without pre-operative treatment; II nephrectomy with pre-operative treatment. Preoperative treatment included systemic chemotherapy and/or transcatheter arterial chemoembolization (TACE). Parents decided which kind of pre-operative treatment regime given for their children and informed consents were obtained. The follow-up data were updated to December 2007.

The regime of preoperative systemic chemotherapy was worked out according to the SIOP6 protocol.[3] Patients with stage I, II and favourable histology received vindesine (VDS, Minsheng Pharmaceuticals Inc, Hangzhou, China) and actinomycin D (ACTD, Haizheng Pharmaceuticals Inc, Taizhou, China) for 4 weeks. Patients in stage III, IV with favourable histology and stage II, III, IV with anaplastic histology received VDS, ACTD plus pirarubicin (THP, Main Luck Pharmaceuticals Inc, Shenzhen, China) for 4 weeks. Various drug doses were as follows: VDS 4 times as 3 mg/m^2 injections once weekly, ACTD 15 μg/kg on five consecutive days, THP 2 times of single dose 20 mg/m^2 on two consecutive days. Dosage of drugs was reduced to two-thirds in the patients of young age (infancy or body weight <12 kg).[4] In order to minimise the side effects of anthracycline, we used pirarubicin (4'-O-tetrahydropyranyldoxorubicin, THP) instead of adriamycin (ADR) in this study. THP is a new anthracycline antibiotic with an antitumour efficacy similar to that of ADR but much less cardiotoxity than ADR due to different pharmacodynamic properties.[5]

The criteria of pre-operative TACE was as following: the maximal tumour diameter greater than 10 cm, suspicion of capsular penetration, involvement of periaortic lymph nodes, inferior vena cava invasion or distal metastasis, and tumour with anaplastic histology. TACE procedure was performed via an arterial approach under DSA (Digital Subtraction Angiography) control. Embolization emulsion consisting of THP 40 mg/m^2, VDS 3 mg/m^2 and iodized oil (lipiodol, Guerbet, Aulna-Sons-B, France) 5-10 ml was infused into the renal artery. In some patients, two weeks short-term systemic chemotherapy with vindesine 3 mg/m^2

Table 1 Staging systems adopted by NWTS[2]

Stage	
I	Kidney-confined; Specimen-confined (no positive margins); No renal sinus vessel involvement >2 mm; No tumour rupture
II	Tumour not kidney-confined; Specimen-confined (no positive margins); Tumour thrombus in extra-renal vessels (thrombus removed complete)
III Residual tumour in abdomen	Not specimen-confined (positive surgical margins) and/or invasion into vital structures (not fully resectable); Tumour rupture pre- or peri-operatively and/or tumour wedge-biopsied pre-treatment; Peritoneal contamination by tumour or implants on peritoneal surface; Positive lymph nodes (renal hilar, periaortic or beyond)
IV	Distant lymph node metastases; Haematological metastases (lung, liver, bone, brain)
V	Bilateral renal tumours (at time of initial diagnosis)

for one time and actinomycin D 15 μg/kg daily in a 5-day course were given after TACE. So the total dose of THP, VDS and ACTD was the same as conventional preoperative systemic chemotherapy. Surgical resection was carried out two weeks after TACE.

Postoperative treatment was based on tumour histology and the stage after surgery. The treatment regimen was given according to the protocol established by Beijing Children's Hospital, China.[6] But only 11 patients received postoperative renal bed radiotherapy due to the refusal of the parents and limitation of the radiotherapy facility in the hospital.

The assessment of survival took into account deaths that occurred as a result of the Wilms' tumour or as a direct consequence of the chosen treatment (date of death). For censored cases, the survival was counted up to the last date before lost to follow up, or up to the end date of the study (December 31, 2007).

Statistical analysis was conducted by SPSS 16.0 software. Survival function was analyzed using Kaplan-Meier method and compared with log-rank test. Univariate and Multivariate Cox proportional risks model was established to evaluate the risk factors for prognosis of Wilms' tumour.

Results

A total of 92 patients were treated for the unilateral Wilms' tumour during the study period. Excluding 11 patients who were lost to the first follow-up after discharge from the hospital, 81 patients were enrolled in this study. Among the 11 patients, 6 were in stage I, 4 in stage II and 1 in stage IV.

The basic features of the patients are summarised in Table 2. The median age of the patients was 28 months with the range from 5 months to 132 months. The female to male ratio was 1.38. Of the 81 patients, 37 had left-sided

Table 2 Basic features of the study patients

Variables	N	%	Death (n)	%
Gender				
Female	47	58.0	8	17.0
Male	34	42.0	9	26.5
Age (months)				
0-23	26	32.1	5	19.2
24-47	28	34.6	6	22.1
>=48	27	33.3	6	22.2
Staging				
I	21	25.9	1	4.76
II	26	32.1	4	15.4
III	29	35.8	11	37.9
IV	5	6.2	1	20.0
Histopathology				
Favourable histology	72	88.9	13	18.7
Anaplastic histology	9	11.1	4	55.6
Resectability at the time of diagnosis				
Yes	49	60.5	8	16.3
No	32	39.5	9	28.1
Rupture of tumour during the surgical procedure				
Yes	10	12.3	6	60.0
No	71	87.7	11	15.5
Abdominal para-aortic lymph nodes				
Positive	18	22.2	5	27.8
Negative	63	77.8	12	19.1
Treatment modality				
I (nephrectomy without preoperative treatment)	25	30.9	11	44.0
II (nephrectomy with preoperative treatment)	56	69.1	6	10.7

Wilms' tumours and 44 had right-sided tumours. No difference was found in the outcome of different locations. Most of the patients were diagnosed at stage II and III. Only five patients were at Stage IV. Four of them presented lung metastatic disease and one had liver metastasis at diagnosis.

Twenty-five patients underwent nephrectomy without pre-operative treatment, and 56 received preoperative treatment before nephrectomy. Among the 56 patients with preoperative treatment, 16 received conventional preoperative systemic chemotherapy, and 40 received TACE.

A total of 16 patients had tumour recurrence in this series, among them, 13 patients were local recurrence (13/81,16%) and 3 distant recurrence. Seventeen patients in this series resulted in death to the last follow-up in December 2007. Eleven patients (11/25, 44.0%) died in the group without pre-operative treatment and 6 died in the group with preoperative treatment (6/56, 10.7%).

The median length of the follow-up was 3 years and 5 months with the range from 0 to 168 months. The five-year overall survival rate for this cohort of patients was 76.6%, which was achieved after two years and ten months, and was maintained up to the end of the follow-up (Figure 1). The five-year survival rate was 70.9% for the patients diagnosed with Wilms' tumour during 1992-1999, and 83.3% for the patients during 2000-2006. No significant difference in survival rate was observed during the two periods (P=0.105); However, the survival rate showed a trend of increase since the year 2000.

The five-year survival rates for the patients at stage I, II, III and IV, regardless of histology, were 94.4%, 87.6%, 62.1% and 75.0%, respectively. The log-rank test showed significant difference in survival in different stages (P=0.016) (Figure 2). The five-year survival rates stratified according to histology, regardless of staging, were 80.9% for favourable histology and 55.6% for anaplastic histology. Significant difference was found between the curves (P=0.030) (Figure 3). The patients with favourable histology had higher survival rate than those with anaplastic histology. Different treatment modalities also showed a marked difference in the cumulative survival rate and the patients with pre-operative treatment had a higher survival than those without (88.4% vs. 54.9%, P<0.001) (Figure 4).

As demonstrated in the univariate Cox analysis, patients having anaplastic histology showed a significant greater risk of death compared with those having favourable histology (HR=3.200, 95% CI=1.037-9.869). Patients at stage III had a higher risk of death than those in other stages (HR=9.007, 95% CI=1.162-69.828). Significant greater risk of death was also observed in those patients having rupture of tumour during the surgical procedure (HR=6.211, 95% CI=2.255-17.108) and in those with positive para-aortic lymph nodes (HR=6.620, 95% CI=2.590-16.920). For the patients treated with modality II, significant lower risk of death was found as compared with those with modality I (HR=0.187, 95% CI= 0.069-0.510) (Table 3).

In the multivariate Cox analysis, histopathology and treatment modality showed statistical significance. The risk of death in the patients with anaplastic histology

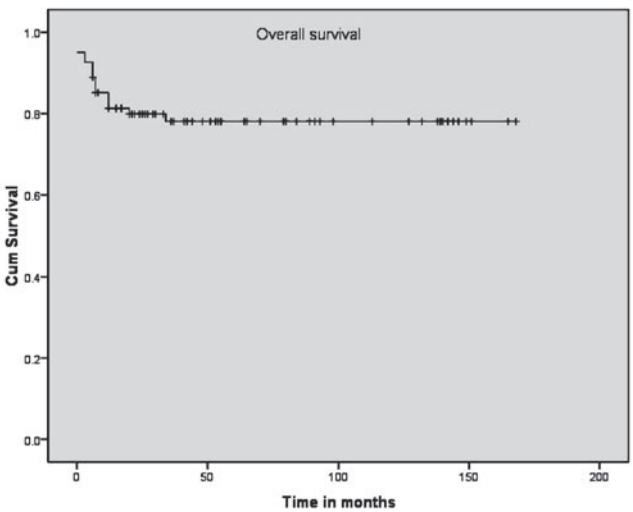

Figure 1 Overall survival rate of children with Wilms' tumour in this cohort of patients.

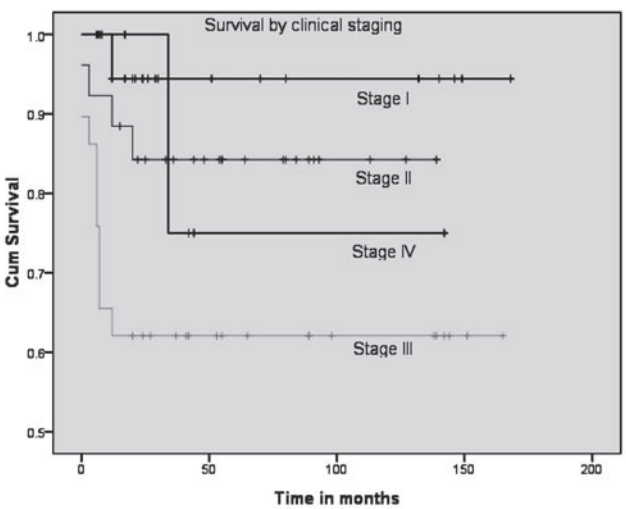

Figure 2 Five-year survival rates for the patients at different stages.

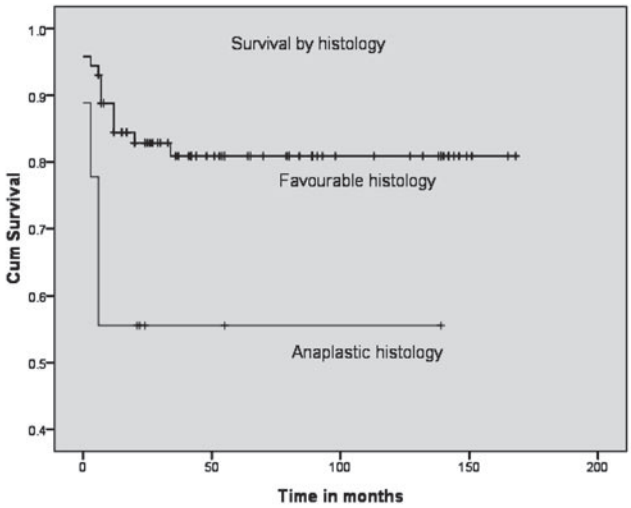

Figure 3 Five-year survival rates for the patients with different histology.

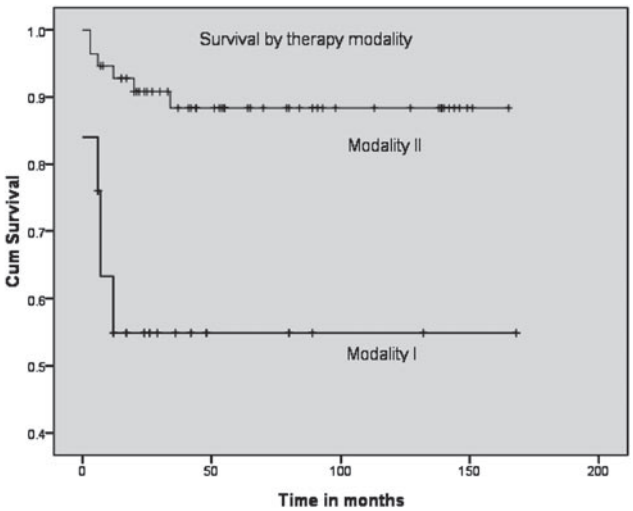

Figure 4 Five-year survival rates for the patients with different therapy modality.

Table 3 Results from the univariate and multivariate Cox analysis

Variables	HR†	95% CI	HR‡	95% CI
Gender				
Male	1.000		1.000	
Female	0.619	0.239-1.605	0.366	0.082-1.381
Age				
0-23	1.000		1.000	
24-47	1.055	0.322-3.457	2.163	0.496-9.422
>=48	1.114	0.340-3.653	1.021	0.214-4.860
Staging				
I	1.000		1.000	
II	3.153	0.352-28.235	12.370	0.907-139.472
III	9.007*	1.162-69.828	18.388*	1.542-219.215
IV	3.854	0.242-61.684	13.353	0.848-143.244
Histopathology				
Favourable histology	1.000		1.000	
Anaplastic histology	3.200*	1.037-9.869*	6.781*	1.336-34.429*
Resectability at the time of diagnosis				
No	1.000		1.000	
Yes	0.529	0.204-1.372	0.261	0.061-1.127
Rupture of tumour during the surgical procedure				
No	1.000		1.000	
Yes	6.211*	2.255-17.108*	1.291	0.320-5.210
Abdominal para-aortic lymph nodes				
Negative	1.000		1.000	
Positive	6.620*	2.590-16.920	1.653	0.425-5.780
Treatment modality				
I (nephrectomy without preoperative treatment)	1.000		1.000	
II (nephrectomy with preoperative treatment)	0.187*	0.069-0.510	0.050*	0.012-0.213

*: variables with significance; †: raw hazard ratio; ‡: hazard ratio adjusted for all variables in the table.

was approximately seven times higher than those with favourable histology (HR=6.781, 95% CI=1.336-34.429); however, no statistical significance was found for rupture of tumour and positive para-aortic lymph nodes (HR=1.291, 95% CI=0.32-5.210; HR=1.653, 95% CI=0.425-5.780). Stage III was still a high risk of death for the patients (HR=18.388, 95% CI=1.542-219.215). The risk of death for patients with preoperative treatment remained significantly low (HR=0.050, 95% CI=0.012-0.213) (Table 3).

Discussion

Wilms' tumour is the commonest primary renal tumour in childhood. It commonly presents as an asymptomatic abdominal mass in children between 2 and 4 years old.[6] Our results revealed an overall survival rate of 76.6%, which is similar to the EUROCARE I Study, which presented a 5-year survival rate of 75% for the children diagnosed with kidney tumours during 1978-1984,[7] but far lower than that in the recent clinical trials, which presented an overall survival rate of 85%.[6] If only considering those patients from 2000-2006 in the present study, the survival rate reached 83.3%, which is similar to the results reported previously.[7,8] The survival rate demonstrated a tendency towards increase when compared with that of Wilms' tumour patients during 1992-1999 (70.9% to 83.3%), though with no statistical significance. The low survival in 1990s is partly due to relatively low social-economical status of most families, the scarcity of chemotherapy drugs and the high rates of declining treatment by the parents for their children with tumour recurrence.

Factors associated with the prognosis for the patients with Wilms' tumour were reported in the previous clinical trials. Staging, rupture of the tumour and histology were the most significant factors.[2,9,10] For the patients in the present study, the five-year survival rate according to the staging were 94.4% for Stage I, 87.6% for Stage II, 62.1% for Stage III, and 75.0% for Stage IV. Patients at stage I and II had a good prognosis for survival which is similar to those reported. But for those at stage III and IV, the risk of death was high. Patients at stage III have a particularly high risk of death and the survival was very low. Different from the reports,[1,7,8,11] our patients at stage IV showed a higher survival than those at stage III. The survival rate for patients at stage IV is far higher than reported.[1,7,8,11] It may be due to the small sample (only 5 patients) at stage IV in this study. All those five patients received standard preoperative systematic chemotherapy and TACE, and only one of them died due to overall metastasis.

For stage III, most of the deaths occurred in patients with tumour recurrences or without complete oncology therapy. Due to the heavy economic burden and concern of poor outcome, some parents refuse treatment for their children with tumour recurrence. Thirteen of the sixteen children with tumour recurrence died. All the thirteen children died after the parents declined the treatment for them. In relation to histology, the survival rate was 80.9% for favourable histology and 55.6% for anaplastic histology. Four out of the nine patients with anaplastic histology died. And treatment for tumour with anaplastic histology remains a challenge for the pediatric oncologists.

In the univariate analysis, the risk of death was associated with anaplastic histology, rupture of the tumour, stage III and without preoperative chemotherapy. Our results showed that rupture of the tumour exposed the patients to a six-fold greater risk of death; however, this variable lost its significance when adjusted for other variables in multivariate analysis. Approximately 70% of the patients with tumour rupture in surgery resulted in tumour recurrence and death. Pre-operative evaluation is particularly essential for those patients with "inoperable" or "unresectable" tumours.[12-16] Preoperative chemotherapy including TACE can lead to tumour necrosis and tumour size reduction, and increase the rate of complete resection in surgery.[4] The results in this study indicate that preoperative treatment can decrease the risk of death for the patients with Wilms' tumour and achieve excellent results for patients. The patients with pre-operative treatment show a significantly higher survival rate of 88. 4% compared with those without (54.9%). The survival in the patients with pre-operative treatment is similar with that reported by studies from Europe.[17] A randomised study performed by UKCCSG revealed that all children with non-metastatic Wilms' tumour should receive chemotherapy prior to tumour resection.[18] Our results also suggest pre-operative treatment plays an important role in the treatment of Wilms' tumour and it will lead to better outcome for the patients. However, the role of pre-operative TACE in comparing with systemic chemotherapy alone remained undetermined, further study is needed to verify the indication of TACE prior to definitive surgery. Compromising of para-aortic lymph nodes in multivariate Cox analysis was not significantly related to the risk of death, but showed a tendency to higher risk, which is similar to Grabois and coworkers' reports.[11]

Conclusions

The present data show that anaplastic histology, stage III and preoperative chemotherapy are prognosis indicators for Wilms' tumour. In this series, survival rate for Wilms' tumour is still lower than the developed countries. We conclude that the major reasons are as follows: treatment for recurrent Wilms' tumour is still a big challenge in our country; the majority of the children have no medical insurance and their parents should pay for the heavy cost themselves; for the patients in advanced stage and for those with tumour recurrence, some parents may refuse or discontinue the treatment for them.

References

1. Varan A. Wilms' tumor in children: an overview. Nephron Clin Pract 2008;108:c83-90.
2. D'Angio GJ, Breslow N, Beckwith JB, et al. Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. Cancer 1989;64:349-60.
3. Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000;27:443-54.
4. Li MJ, Huang Y, Tang DX, Zhou YB, Tang HF, Liang JF. Treatment of advanced Wilms' tumor. Zhonghua Zhong Liu Za Zhi 2006;28:791-5. [in Chinese]
5. Munck JN, Riggi M, Rougier P, et al. PPharmacokinetic and pharmacodynamic advantages of pirarubicin over adriamycin after intraarterial hepatic administration in the rabbit VX2 tumor model. Cancer Res 1993;53:1550-4.
6. Bai JW. Wilms' tumor. In: Zhang JZ, editors. Modern pediatric oncologic surgery. Beijing: Beijing Science Publishing House, 2003:245-54.
7. Ahmed HU, Arya M, Tsiouris A, et al. An update on the management of Wilms' tumor. Eur J Surg Oncol 2007;33:824-31.
8. Plesko I, Kramárová E, Stiller CA, Coebergh JW, Santaquilani M; EUROCARE Working Group. Survival of children with Wilms' tumour in Europe. Eur J Cancer 2001;37:736-43.
9. Breslow N, Sharples K, Beckwith JB, et al. Prognostic factors in nonmetastatic, favorable histology Wilms' tumor. Results of the Third National Wilms' Tumor Study. Cancer 1991;68:2345-53.
10. Shamberger RC, Guthrie KA, Ritchey ML, et al. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. Ann Surg 1999;229:292-7.
11. Grabois MF, Mendonça GA. Prognosis for patients with unilateral Wilms' tumor in Rio de Janeiro, Brazil, 1990-2000. Rev Sauda Publica 2005;39:731-7.
12. Ritchey ML, Pringle KC, Breslow NE, et al. Management and outcome of inoperable Wilms' tumor. A report of National Wilms Tumor Study-3. Ann Surg 1994;220:683-90.
13. Oue T, Kubota A, Okuyama H, et al. Megatherapy with hematopoietic stem cell rescue as a preoperative treatment in unresectable pediatric malignancies. J Pediatr Surg 2003;38: 130-3.
14. Grundy RG, Hutton C, Middleton H, et al. Outcome of patients with stage III or inoperable WT treated on the second United Kingdom WT protocol (UKWT2); a United Kingdom Children's Cancer Study Group (UKCCSG) study. Pediatr Blood Cancer 2004;42:311-9.
15. Mahmood A, Ghafoor T, Badsha S. Wilms' tumour: presentation and treatment. J Coll Physicians Surg Pak 2004;14:142-5.
16. Ritchey ML. The role of preoperative chemotherapy for Wilms' tumor: the NWTSG perspective. National Wilms' Tumor Study Group. Semin Urol Oncol 1999;17:21-7.
17. Spreafico F, Bellani FF. Wilms' tumor: past, present and (possibly) future. Expert Rev Anticancer Ther 2006;6:249-58.
18. Mitchell C, Pritchard-Jones K, Shannon R, et al. Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3) by the UK Children's Cancer Study Group. Eur J Cancer 2006;42:2554-62.

Reviewer's Commentary

Prognostic Factors and Outcome of Wilms' Tumour in a Tertiary Children's Hospital, China

This is a single centre retrospective review of the risk factors and outcome of children with Wilms' tumour. A new approach TACE (transcatheter arterial chemoembolization) has been applied to a significant number of patients with the intention of shrinking the tumour for better respectability in the 2nd look surgery. Even it was shown to be safe but we cannot ignore the fact that it is an invasive procedure with potential additional risk to the patients. Furthermore, Wilms' tumour has a very favourable prognosis with current systemic chemotherapeutic approach. Simply applying a low intensity pre-operative chemotherapy regimen, most Wilms' tumours responded and shrank. Therefore, most oncologists consider routine pre-operative TACE for Wilms' tumours as **ethically unacceptable**. The role of TACE should be restricted to a highly selected group of patients whose Wilms' tumours remain unresectable after pre-operative chemotherapy.

Dr. Chi-Fung **Chan**
Deptartment of Paediatrics
Queen Mary Hospital, Hong Kong