RESEARCH COMMUNICATION

Outcomes of Pediatric Nephroblastoma in Southern Thailand

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Abstract

Background and aims: The outcomes of nephroblastoma (Wilms' tumor, WT) in our institute and other developing countries are notably below results in most developed countries. The objective of this study was to review treatment outcomes of pediatric nephroblastoma in southern Thailand during the past decade and attempt to isolate factors associated with a poor prognosis. Patients and methods: The records of 34 WT patients, aged less than 16 years, who were operated on in Songklanagarind Hospital, Thailand, during the period from January 1996 to December 2007 were reviewed. The management protocol followed the scheme of the US National Wilms Tumor Study Group (NSWTG). Results: Thirteen cases (38.2%) were diagnosed as stage I, 4 (11.8%) as stage II, 13 (38.2%) as stage III and 2 (5.9%) as stage IV. Two cases with bilateral disease (stage V) had stage I tumors in both kidneys. Four-year overall survival (OS) and event free survival (EFS) rates were 65.2% and 52.7%, respectively. Univariate analysis by Log-rank test revealed statistically significant associations between OS and nodal status (p- value < 0.01), manifestation of gross hematuria (p-value 0.02), and tumor size of 10 centimeters or more (p-value 0.02). Multivariate analysis found only the nodal status to be independently associated with OS at a Hazard Ratio of 16.6 (p-value < 0.01). Eight of 13 stage I cases and 6/13 stage III cases had relapsed, with two-year post-relapse survival of 42.8%. Significantly poorer outcome was found in cases with early relapse within 200 days after enrollment (p-value 0.02). Conclusion: The poor outcome of pediatric nephroblastoma in southern Thailand seems to be related at least in part to failures in primary treatment in stage I patients. Large tumor size and gross hematuria were associated with risk of a poorer outcome.

Key Words: Nephroblastoma - Wilms' tumor - hematuria - survival - prognosis

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Introduction

Like most pediatric malignancies, a survival rate of Nephroblastoma (Wilms' tumor or WT) patient has noticeably improved with modern multidisciplinary cancer management. WT survival rates as reported in large trials conducted in high-income countries generally approach 90% (Tournade et al., 2001, Breslow et al., 2004, Metzger and Dome, 2005, Ahmed et al., 2007) and current research focuses mainly on more specific issues, such as reduction of toxicity and surveillance for late effects. However, WT in developing countries where resources are limited and techniques and treatment modalities still some years behind western countries, still remains a condition with relatively high mortality, although efforts are being made to adopt modern protocols.

In this study, we retrospectively reviewed the treatment outcomes of WT in a tertiary-setting institute in lower southern Thailand with an emphasis on identification of factors associated with treatment failure. Hopefully, the data can suggest modification of current treatment protocols to make them more suitable for the clinical context of developing countries and improve outcomes.

Patients and Methods

The medical records of pediatric patients aged less than 16 years who were treated for WT in Songklanagarind Hospital from January 1996 to December 2007 were reviewed. During the period, management of WT in the institute was conducted in a multidisciplinary fashion and followed the scheme of the US' National Wilms' Tumor Study Group (NWTSG). Staging work-ups included abdominal ultrasonography, abdominal computerized tomography (CT), chest x-rays and bone marrow aspiration biopsy. Chest CT was not performed on a routine basis.

Primary nephrectomy was attempted in all cases, except for those with known bilateral disease, advanced unresectable tumor, or when the physical status of the patient was not fit for a major operation. Post-operative adjuvant chemotherapy and/or radiation therapy was given according to the NWTS-3/4 algorithms.

After tumor removal, the patients were followed-up every 3 months. Chest x-rays and abdominal ultrasonograms were scheduled every 6 months in the first 4 years and annually thereafter.

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Relapse of disease was diagnosed when a patient with localized disease subsequently developed either local recurrence or distant metastasis. Rescue treatment began with second-line chemoradiation therapy, followed by surgical removal in cases in which a residual disease was localized.

Survival rates are based on both hospital-based data and community-based data gathered by the Cancer Unit of our institution, (Songklanagarind Hospital, a university hospital and the major tertiary institution and referral center in southern Thailand). Univariate survival analysis used the Log-Rank test and multivariate analysis followed Cox's hazard analysis. Associations are considered statistically significant with a p-value less than 0.05. Calculations and graph drawing were done with the Stata statistical package, version 6.0. Access to clinical records was approved by the Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (project number 50/368-022).

Results

Demographic data

During the 12-year period, 35 pediatric patients were diagnosed and managed as nephroblastoma (although the diagnosis in one case was reconsidered as a clear cell sarcoma of the kidney after histopathological review). The remaining 34 nephroblastomas comprised 82.9% (34 of 41 cases) of all pediatric renal neoplasms treated by the institute during the same period. The median age at the time of diagnosis was 2.13 years (95% confidence interval 1.52 – 3.49 years). The male to female ratio was 1.27. Primary tumors occurred to the right kidney in 15 cases (44.1%) and left kidney in 17 cases (50.0%), with 2 cases (5.9%) of bilateral disease. Associated anomalies were noted in 3 cases, including a case of albinism, a case of aniridia and a case that had penoscrotal type hypospadias and unilateral undescended testis.

Presentation and staging

The main clinical presentations were a palpable abdominal mass in 16 cases (47.1%), abdominal distension in 12 cases (35.3%), and 2 cases each (5.9%) of abdominal pain, isolated gross hematuria and incidental finding in abdominal trauma. Hematuria was recorded in 11 patients (32.4%), with 6 patients (17.6%) showing microscopic blood in their urine.

Thirteen cases (38.2%) were diagnosed as stage I, 4 cases (11.8%) as stage II, 13 cases (38.2%) as stage III and 2 cases (5.9%) as stage IV. Two cases with bilateral disease (stage V) had stage I tumor in both kidneys. Unfavorable histology was detected in 3 cases (8.8%), including one in stage I case and 2 in stage III cases. Eighteen patients (52.9 %) had tumor size of 10 centimeters or more.

Primary nephrectomy was performed in 29 cases. The remaining 5 patients initially treated by neoadjuvant chemotherapy included 2 cases with bilateral disease, 1 case with liver metastasis, 1 case with large size tumor and a case that had respiratory tract infection prohibiting general anesthesia. Together with the nephrectomy, concomitant hepatic metastasectomy was done in one patient and distal pancreatectomy in a case of direct tumor invasion. In the cases with bilateral disease, partial nephrectomies were performed after 4 sessions of chemotherapy.

Table 1. Univariate Survival Analysis of Clinical Parameters

Parameter		Number	OS (%)	p-value
Overall		34	65.2	
Gender	Male	19	76.5	0.10
	Female	15	50.0	
Age	< 2 years	15	30.1	0.14
	> 2 years	19	77.8	
Tumor size	< 10 cm	14	84.6	0.02
	> 10 cm	18	43.7	
Nodal status	N0	32	69.7	< 0.01
	N1	2	0.0	
Histology	Favorable	31	62.8	0.92
	Unfavorable	#3	100	
Incomplete adjuvant treatment*				
	yes	6	50.0	0.41
	no	24	74.2	
Hematologic toxicity	yes	5	60.0	0.59
	no	29	66.5	
Gross hematusia	absent	29	71.6	0.02
	present	5	0.0	
Neoadjuvant**	no	29	68.6	0.94
	yes	5	80.0	

OS, 4-year overall survival, #presence of anaplasia, *only stages I-III analyzed, **2-year OS

Clinical outcomes

As of August 2008, the median post-operative duration was 65.8 months (95% confidence interval 48.5 – 95.5 months). Hematologic toxicity was reported in 5 cases (14.7%). Six cases (20.0 % of stage I-III cases) did not receive complete adjuvant therapy due to socioeconomic limitations or toxicity. No patient died of complications from the primary treatment. The two-year overall survival (OS) and event free survival (EFS) rates were 70.6% and 62.3%, respectively. Four-year overall survival (OS) and event free survival (EFS) rates were 65.2% and 52.7%, respectively (Figure 1A). The two patients with bilateral disease were alive without disease for 386 and 1091 days following the diagnosis. OS and EFS by stage are shown in Figure 1B. For stage I cases, when 4-year OS was 73.3%, 4-year EFS was only 35.4% (Figure 2).

Univariate analysis by Log-rank test revealed a statistically significant association between OS and nodal status (p- value < 0.001), manifestation of gross hematuria (p-value 0.02), and tumor size of 10 centimeters or more (p-value 0.02) (Table 1). Nodal status and large tumor size were also associated with event free survival with p-values at 0.004 and 0.02, respectively. When multivariate analysis was performed, only the nodal status was independently associated with OS at a Hazard Ratio of 16.6 (95% confidence interval 2.6-107.4).

Relapse analysis

Eight of 13 stage I cases had relapse and six events occurred to 13 stage III cases. Of the relapse cases, 11

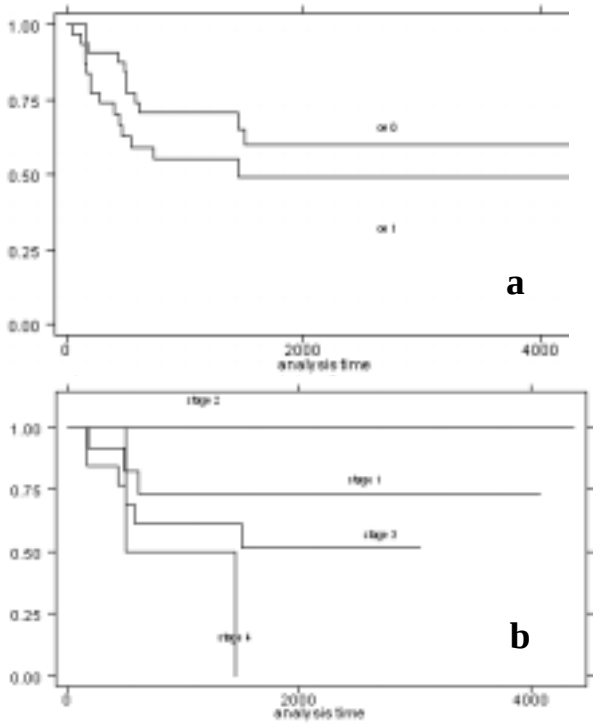

Figure 1. A) Kaplan-Meier Curves showing Overall Survival (OS) and Event Free Survival (EFS), B) OS by tumor stage (4-year OS rates in stages I, II, III and IV were 73.3%, 100.0%, 61.5% and 0%, respectively)

events were diagnosed within 730 days (Table 2). With rescue treatments, one- and two-year survival rates after relapses were 58.6% and 42.8%, respectively. There was one operative death after a hepatic resection. Significantly poorer outcome was found in cases with an early event within 200 days after diagnosis (p-value 0.02) (Figure 3).

Discussion

The incidence of pediatric nephroblastoma in Thailand in 2002 was estimated at 2.2 per million population aged

Table 2. Cases with Relapse of Disease by Stage

	Relapse at day	Relapse type	Treatment	Follow-up (days)	Status
I	121	Local recurrence	C + R	52	Died*
	197	Liver metastasis	C + S + R	413	Died
	273	Liver metastasis	C + S + R	482	Alive
	400	Liver/lung metastasis	C + R	85	Died
	543	Lung, maxillar and right ulnar metastasis	C + S + R	2,785	Alive
	1,451	Local recurrence	C + S + R	172	Alive
	4,428	Lung metastasis	C + R	4,037	Alive
	734	Lung/bone metastasis	C + S + R	688	Alive
III	148	Liver/lung metastasis	C+ IVR	16	Died
	150	Lung metastasis	C + S + R	284	Died
	161	Local recurrence and lung metastasis	C	0	Died
	197	Pelvic metastasis	C + R	298	Died
	438	Local recurrence	C + S + R	1,060	Died
	463	Local recurrence	C + S + R	111	Died

C, Chemotherapy; S, Surgery; R, Radiotherapy; IVR, Intervention radiology (chemoembolization of liver metastasis); *Died of disease

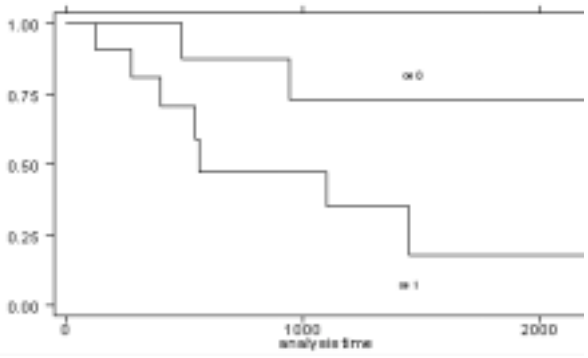

Figure 2. Kaplan-Meier Curves showing OS and EFS in Stage I Patients

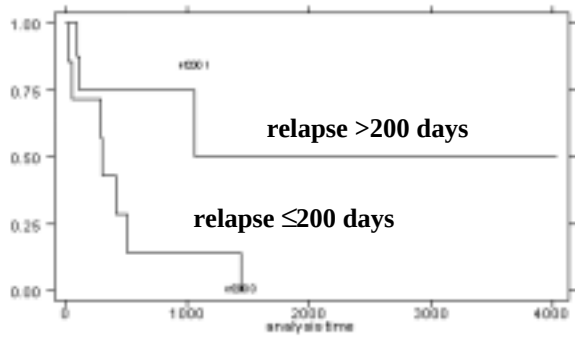

Figure 3. Survival Curves showing Survival Probability with Relapse after 200 days as Compared to Earlier

< 15 years (Thai Pediatric Oncology Group, 2007) which was comparable with the incidence rate in other Asian countries (Stiller and Parkin, 1990; Hung et al., 2004). Treatment of WT in this country is usually carried out in a tertiary-level medical center and usually follows the scheme of the National Wilms Tumor Study (NWTS) Group, which is part of the larger US Children's Oncology Group. In general, WT outcomes in Thailand and other developing countries have been behind those reported in large trials from western countries (Wiangnon et al., 2004). Our institute, a tertiary care center in a developing country, has been in the situation of knowledge user, that is to say, following protocols already established rather than developing new ones. With WT, the treatment protocols from large multi-institutional trials have been adopted for our practice with to the hope of achieving the same success rates, despite the fact that there are certain discrepancies in fundamental resources and supporting teams, and cultural differences to consider.

In the study period, for WT, we had followed the management scheme of the NWTSG noted earlier (Breslow et al., 2004, Uba and Chirdan, 2007). However, while survival rates of patients enrolled in the NWTS trials have reached more than 90% in the last two decades (D'Angio et al., 1989; Metzger and Dome, 2005, Ahmed et al., 2007), the 4-year OS in our series was only 65%. Questions are thus in order regarding the factors that led to this large outcome gap, and the objective of this study was to attempt to identify factors associated with the poorer prognosis in our cases that might then suggest protocol adjustments which might improve our outcomes.

Studies on WT aside from larger trials have reported

varying outcomes, from no survivors beyond 2 years to almost 90% OS at 5 years (Yildiz et al., 2000; Hung et al., 2004; Abd El-Aal et al., 2005; Kutluk et al., 2006; Seyed-Ahadi et al., 2007; Uba and Chirdan, 2007). Delayed diagnosis, lack of resources such as chemotherapy and radiation, and poor therapeutic compliance are suspected to be crucial factors that lead to poor outcomes (Yaris et al., 2004; Kutluk et al., 2006; Uba and Chirdan, 2007). In our institutes and other major referral centers in Thailand, resources are not the main problems as adjuvant chemo-radiation therapy is widely available and can be reimbursed under the National Health Insurance system. However, we did find the problems of late diagnosis and therapeutic compliance. The OS in cases with incomplete adjuvant treatment was lower, and although the statistical analysis did not show significant impact of poor compliance on the outcomes, a problem with compliance should be regarded as a manageable factor. Supporting travel expenses or providing a part of the chemotherapeutic at local hospital may help in this regard. Also, the social values of certain ethnic groups in this region have been associated with poor therapeutic compliance (Nijinikaree et al., 2008) and a counseling program with respect to people with beliefs that act against compliance might improve curative opportunities.

When we look at our subgroup of stage-I patients alone, the results are still relatively poor, and in addition, the gap between 4-year OS and 4-year EFS is quite wide. The results indicate that treatment failure at stage I is an issue that needs to be examined more closely. In this study, nodal status was the sole independent factor associated with OS. Nevertheless, other factors that showed significant impact on survival, tumor size and the manifestation of gross hematuria are also worth discussion.

Tumors greater than 10 cm were found to be significantly associated with higher chance of surgical complication in one NWTS4 study.(Ritchey et al., 2001) However, unlike renal cell carcinoma which is another common renal malignancy, tumor size is not taken into consideration in the current WT staging scheme. One issue that was often of concern in our pediatric tumor conferences was whether a very huge tumor should be literally assigned to stage I, according to the NSWT classification. It should be noted that over a half of the WT cases of this study were larger than 10 centimeters and survival analysis showed that large initial tumor size was associated with poorer survival probability. From the surgical point of view, association between the tumor size and compromised outcomes might be explained by 2 technical factors. First, a large tumor has more risk of intraoperative spillage and, although major spillage indicates a higher stage of disease by NWTS staging, not all spillage events were adequately reported in our institution and a minor spillage occurring during an operation was sometimes disregarded by some surgeons. Secondly, large tumor might prohibit a successful 'vascular control first' technique, and the chance of a hematogenous spreading during a surgical mobilization might be higher even when the tumor capsule is intact. This hypothesis is supported by the fact that that 75% of our relapse events involved distant metastasis. Reducing tumor spread either by pre-operative chemotherapy or a technical refinement to control the outflow vessels first should improve our outcomes in the future. Although tumor size was not considered directly, tumor weight was taken into account in the NWTS5 study with a prior observation that a tumor of less than 550 grams had better prognosis (Green et al., 1994).

When the extent of the tumor beyond the renal capsule is defined as a locally advanced WT by the NWTS staging scheme, extension through the renal sinus is not regarded as advanced disease until the tumor goes beyond the renal pelvis. On a histopathological review of stage I cases enrolled as NWTS 3, the presence of renal sinus invasion was among the 'microsubstaging factors' associated with relapse (Weeks et al., 1987). With the retrospective nature of our study, we had no opportunity to review the parameters of sinus invasion; however the correlation between gross hematuria and poorer OS in our cases suggests a significant impact of tumor invasion through the inner doorway.

Although our overall results were poorer, our survival after relapse was comparable with other series in the era prior to autologous stem cell transplantation (Dome et al., 2002; Park et al., 2006; Reinhard et al., 2008) . Consistent with a recent report (Reinhard et al., 2008), our data suggest that early relapse cases have a worse outcome. An intensive follow-up program should be in place during the early post-operative period, especially during the first 200 days, following a nephrectomy.

In summary, we analyzed the outcomes of pediatric WT cases treated at the major referral center in southern Thailand. We confirmed inferior survival rates compared to those reported by standard multi-institutional trials from developed countries. The data suggested considerable room for improvement in therapeutic compliance, and indicate improved care should be provided for patients with larger tumors or who present with gross hematuria.

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