Challenges and outcome of Wilms' tumour management in a resource-constrained setting

J. C. H. Wilde, W. Laméris, E. H. van Hasselt[1], E. M. Molyneux[2], H. A. Heij, E. G. Borgstein[1]

ABSTRACT

Background: To review the results of Wilms' tumour patients in a tertiary referral hospital in a developing country and to find ways of improving long-term survival. **Patients and Methods:** Between January 1998 and May 2004, 40 patients with Wilms' tumour (WT) were admitted to Queen Elizabeth Central Hospital. Their files were reviewed and general physical condition on admission, pre-operative investigations, management and outcome were noted. **Results:** The mean age of presentation was 4.2 years with an equal distribution between the sexes. The mean BMI was 15 kg/m² and more than 80% of the patients were either mildly (PCV <33%) or severely anaemic (PCV <24%). All patients presented with abdominal distension. Half of them had additional complaints including abdominal pain, haematuria, dyspnoea, oedema and or weight loss. Thirty-nine out of the forty patients received pre-operative chemotherapy. Of the 36 patients that underwent surgery, 32 underwent total nephrectomy, one a partial nephrectomy, and in three the tumour was irresectable. There were no intra-operative tumour ruptures. Only 15% of the patients completed their post-operative course of chemotherapy. The 1-year survival lies between 25% and 53%. Fifteen of the 36 patients operated were known to have a recurrence. **Conclusion:** The patients presented in an advanced stage of the disease. Survival rates are disappointing and recurrence rates are high. Some improvement in outcome may be expected with the implementation of more aggressive treatment protocols but early diagnosis, completion of treatment regimens are needed. Pro-active follow-up is essential to measure outcome.

Key words: Nephroblastoma, Wilms' tumour, treatment outcome

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Department of Paediatric Surgery, Paediatric Surgical Center, Amsterdam, The Netherlands, Departments of [1]Surgery, [2]Paediatrics, Queen Elizabeth Central Hospital, Blantyre, Malawi

Address for correspondence:
Dr. Jim C.H. Wilde,
Paediatric Surgical Center,
1105 AZ Amsterdam, The Netherlands.
E-mail: j.c.wilde@amc.uva.nl

INTRODUCTION

Nephroblastoma (Wilms' tumour, WT) is one of the most common, malignant paediatric tumours in Africa[1,2] and the most common malignant, paediatric kidney tumour in the world.[3] It accounts for 6% of all paediatric malignancies treated at Queen Elizabeth Central Hospital in Blantyre, the only tertiary referral hospital in Southern Malawi.[4] Cancer management in most parts of Africa faces specific problems. The patients often present late with advanced tumours and are in poor general health. Diagnostic facilities are often lacking and chemo- and radiotherapy are either scarce or not available at all. Follow-up is made difficult because patients often live far away from the hospital and transportation to and from the hospital is expensive.

Several African studies have shown the overall survival of WT's to be lower than that in developed countries. The 2 year event-free survival recorded in Zimbabwe and Kenya was 65%[5] and 35%[6] respectively. This compares unfavourably with the 2-years event free survival of 89% and 5-years survival of 95% recorded by the International Society of Paediatric Oncology (SIOP) for localised disease.[7] It should be noted, however, that in resource-constrained countries 80% of WT patients have only limited access to appropriate specialist care, resulting in the much poorer outcome.[8]

In this retrospective, descriptive study we evaluated the clinical presentation, treatment and outcome of patients that presented with a WT in a resource-constrained setting. We investigated several factors that might possibly lead to poor outcome. As we plan to introduce new treatment protocols to increase long-term survival, the current analysis was important to identify areas at which the current treatment can be improved.

PATIENTS AND METHODS

In this retrospective observational study, all patients with a histologically confirmed WT that were treated from January 1998 to May 2004 at Queen Elizabeth Central Hospital were identified. This hospital is fully

funded by government and patients do not bear costs. The clinical files were reviewed and where possible basic demographics were collected. The presenting complaints and duration thereof were documented. On physical examination, the patients nutritional status (poor, fair, good), the presence of an abdominal mass, the location and its estimated size were noted. Packed cell volume (PCV) was recorded and the percentage of anaemic patients was calculated.

Pre-operative investigations included an abdominal ultrasound scan (USS), a chest x-ray and either a fine needle aspiration biopsy (FNABx) or surgical biopsy. Tumour size and location at USS were recorded whenever possible. Of the patients who received chemotherapy, the type and number of pre- and post-operative courses were noted. The effect of the chemotherapy on tumour size was evaluated both clinically and with USS. The duration of follow-up was determined and the 1-year survival was estimated.

RESULTS

A total of 47 children were treated for WT during the study period, seven patients treated for Wilms´ tumours but in whom the histology result could not be retrieved were excluded. Forty patients were included in the study with a mean age of 4.2 years (range 0.83–13.2) at admission. The sexes were almost equally affected (1: 0.9).

All patients presented with abdominal distension or a mass. The mean duration of the presenting complaint was 3.2 months (range 0.3–12 months). Nineteen patients (48%) presented with a single complaint, the other 21 patients presented with additional complaints. The types of additional complaints are presented in Table 1. Abdominal pain and haematuria were the most frequent additional complaints. In Figure 1, the patient flow through the study is presented.

One patient was HIV-positive and in seven patients the HIV-status was not known. The nutritional status was clinically judged good in 15% of patients, fair in 33% and poor in 50% (2% unknown). The mean BMI available in 21 patients was 15 kg/m^2. Measurement of PCV at admission showed that 23% presented with severe anaemia (PCV<24%), 60% with mild anaemia (PCV<33%) and 17% was not anaemic.

All 40 patients underwent an USS of the abdomen. Twenty patients had a tumour of the right kidney, 18 of the left and 2 patients had bilateral tumours. The tumour was measured by USS in 23 patients and the mean diameter was 12 cm. In 17 cases, however, the tumour was too large to measure accurately. In only 10 patients, a chest X-ray was performed. No lung metastases were found. Chest X-ray was not routinely done pre-operatively and was at sometimes not available for technical reasons. In 38 of 40 patients (95%), a pre-operative FNA or surgical biopsy was performed. In 20 patients (53%), the diagnosis of Wilms´ tumour was pre-operatively confirmed by FNA or surgical biopsy, in 7 patients (18%) histological examination was inconclusive, and of 11 patients (29%) the histology result could not be found.

One patient underwent a nephrectomy without receiving pre-operative chemotherapy. Thirty-nine patients received pre-operative chemotherapy. Of

Table 1: Additional complaints in Wilms´ tumour patients

	Frequency	Percentage
Additional complaints		
Abdominal pain	6	15
Weight loss	5	12
Haematuria	6	15
Dyspnoea	2	5
Bilateral oedema	2	5
Total	21	52
No additional complaints	19	48
Total	40	100

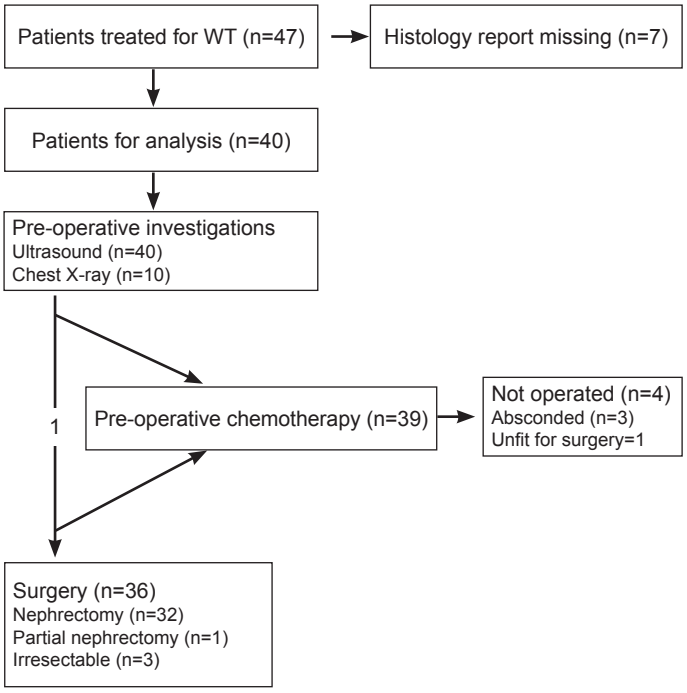


Figure 1: Patient flow through the study

these, 19 patients received vincristine; the other 20 were initially treated as a Burkitt's lymphoma (BL) with cyclo-phosphamide because a definite diagnosis could not be made on USS. They later switched to vincristine when either biopsy results were known or no regression was seen on the regimen of chemotherapy started. The number of courses and the type of post-operative chemotherapy given varied greatly. Eighty-five percent of the patients failed to complete post-operative chemotherapy.

Thirty-six out of the original 40 patients had operation. Three patients absconded during pre-operative treatment and one patient was found to be unfit for surgery. Thirty-two patients underwent a nephrectomy, one patient had a partial nephrectomy and in three patients involvement of adjacent structures was so extensive that the tumour was considered irresectable. In total, 42% of the primary tumours involved the surrounding structures. The structures that were most often involved were the colon and/or mesentery (n=7), liver and diaphragm (n=6) and the abdominal wall (n=2). There were no intra-operative tumour ruptures.

The mean length of follow-up was 11 months and ranged from 1 day to 59 months. Eight deaths were documented. One patient died 1 day post-operatively due to cardio-respiratory arrest; the other seven were due to tumour recurrence. Events that were used to measure survival were death, "home on palliative care" and lost to follow-up. This gives a 1-year post-operative survival of 25%. If, however, those lost to follow-up are assumed to be alive, the 1-year post-operative survival was 53%. A survival curve is presented in Figure 2. The real survival after 1 year will lie between 25–53%.

Fifteen patients (42%) had a confirmed recurrence. In 14 patients, recurrences were detected with chest radiographs and ultrasound. In one patient, a local recurrence was found at surgery. The mean time between operation and presentation of the recurrence was 17 months (4–59 months). In the patients with a documented recurrence, seven deaths were confirmed; the other eight patients were sent home on palliative care and excluded from follow-up. Eight patients had distant metastasis, occurring in lung (n=6) and liver (n=2).

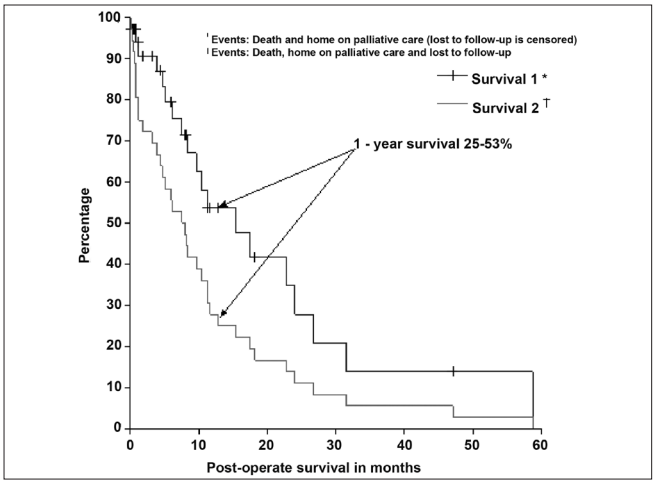


Figure 2: Wilms' tumour patients' survival

DISCUSSION

This retrospective study highlights the problems associated with the treatment of WT in a resource poor setting. Late presentation, the poor nutritional status, anaemia, the unavailability of the correct chemotherapeutic agents and low compliance to the chemotherapy regimen, lack of intra-operative staging and radiotherapy all play a role in poor survival.

The mean age at presentation of our group of patients was higher than that of children in the developed world (4.2 years vs. 3.5 years).[9] In all cases, the presenting complaints included that of an abdominal mass. More than half presented with additional complaints including abdominal pain, haematuria, weight loss or abdominal distension. These additional complaints which are rarely reported in the developed world are consistent with late presentation.

We consider a fine needle biopsy (FNABx) to be essential in our setting. Due to the lack of specific ultrasound experience and the high prevalence of Burkitt's lymphoma (BL) at Queen Elizabeth Central Hospital, it is necessary to differentiate between the two. Many patients started on chemotherapy for BL after the initial history taking, physical examination and abdominal ultrasound, but were switched to local WT chemotherapy of vincristine when the biopsy results became known.

Seventeen patients (43%) were lost to follow-up. This in combination with the short and incomplete follow-up (mean 11.2 months) makes it hard to draw conclusions about long-term survival. One can only estimate the 1-year survival rate which we found to be between 25% and 53%. This is well below the 5-year overall survival rate for WTs treated in the developed world which is 90%.[10]

A limitation of the study was that the data were collected retrospectively. Data that were not properly recorded during admission or follow-up may therefore

have not been included in the analysis. Unfortunately, seven patients that were treated for a WT during the study period had to be excluded. Although, surgical specimens were routinely sent for histological examination their histology results could be retrieved from the medical chart or from the histology database. Whether the results were not recorded or went missing is unclear. Another limitation of the study was that during the time of analysis, histological staging was not yet carried out. The histology reports would only mention whether or not it was WT. The retrospective design of this study does not allow reliable staging post-hoc. Despite the lack of accurate staging, it can be assumed that patients with advanced tumours were described in this study as in almost half of the patients surrounding structures were involved in the tumour at surgery.

There are opportunities to improve the survival rates. Delayed presentation and poor nutrition reflect poverty and will improve as the country's economy improves. However, improving chemotherapy regimens in patients with advanced tumours may significantly improve outcome. To improve the chemotherapy regimen, the tumour stage and grade must be known. The requirements for this are: good pre-operative ultrasound, good and rapid histological assessment of the tumour, availability of the essential chemotherapeutic agents and a more pro-active follow-up strategy. To achieve these goals we will implement a new treatment protocol prescribing standardized pre-operative ultrasound with recording of tumour characteristics and standardized histological staging of all specimens. The protocol also includes early consultation of our nutritional rehabilitation unit for support in malnourished patients. Optimizing the supportive aspects of WT treatment sets an achievable goal and our unit intends to report on this in a new prospective study.

REFERENCES

1. Mwanda OW. Cancers in children younger than age 16 years in Kenya. East Afr Med J 1999;76:3-9.
2. Mukiibi JM, Banda L, Liomba NG, Sungani FC, Parkin DM. Spectrum of childhood cancers in Malawi 1985-1993. East Afr Med J 1995;72:25-9.
3. Stiller CA, Parkin DM. International variations in the incidence of childhood renal tumours. Br J Cancer 1990;62:1026-30.
4. Sinfield RL, Molyneux EM, Banda K, Borgstein E, Broadhead R, Hesseling P, *et al*. The prevalence, presentation of paediatric malignancies in Blantyre Malawi in the HIV era, 1998 -2003. Pediatr Blood Cancer 2007;48:515-20.
5. Nkrumah FK, Danzo AK, Kumar R. Wilms' tumour (nephroblastoma) in Zimbabwe. Ann Trop Paediatr 1989;9:89-92.
6. Abdallah FK, Macharia WM. Clinical presentation and treatment outcome in children with nephroblastoma in Kenya. East Afr Med J 2001;78:S43-7.
7. de Kraker J, Graf N, van Tinteren H, Pein F, Sandstedt B, Godzinski J, *et al*. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): A randomised controlled trial. Lancet 2004;364:1229-35.
8. Pritchard-Jones K, Pritchard J. Success of clinical trails in childhood Wilms' tumour around the world. Lancet 2004;364:1468-70.
9. Cancer in Children. Clinical Management, fourth edition. Edited by P.A. Voûte, C. Kalifa and A. Barrett:2005. p. 259-63.
10. Weirich A, Ludwig R, Graf N, Abel U, Leuschner I, Vujanic GM, *et al*. Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. Ann Oncol 2004;15:808-20.

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