The challenge of nephroblastoma in a developing country

S. O. Ekenze*, N. E. N. Agugua-Obianyo & O. A. Odetunde
Sub-Department of Paediatric Surgery, University of Nigeria Teaching Hospital, Enugu, Nigeria

Received 24 April 2006; revised 8 May 2006; accepted 19 June 2006

Background: Advances in paediatric oncology has tremendously improved the outcome in children with nephroblastoma. In most developing countries, however, the survival rate is still very low.

Objective: To study the outcome and the impediments to the management of nephroblastoma in Southeast Nigeria.

Methods: Analysis of 42 children managed for nephroblastoma over a 10-year period (January 1995–December 2004) at the University of Nigeria Teaching Hospital, Enugu, Nigeria is made. Diagnosis was based on clinical, radiologic and histologic evaluation.

Results: The peak age incidence was 2–5 years with a male:female ratio of 1.1:1. Abdominal mass was the main presentation in all the children. Treatment consisted of nephroureterectomy followed by adjuvant chemotherapy with Vincristine, Actinomycin D and Cyclophosphamide. Adriamycin was added for metastatic disease. Twenty-two children (52.3%) had stage III disease, 13 (31.0%) had stage IV, while the remaining seven (16.7%) children had stage II. Stage I disease was not encountered. Seven children had inoperable tumor requiring pre-operative chemotherapy. While 25 children were available for evaluation, 17 were lost to follow up. Four children died of complications of treatment, while 11 relapsed with poor outcome. With a mean follow up of 21 months, the 5-year survival rate is 40%.

Conclusion: Morbidity and mortality with nephroblastoma is high in our environment. Late presentation, poverty, ignorance and poor compliance to treatment constitute a great challenge to the paediatric oncologist in a developing country. Solutions may lie in improving health funding and health information in the health care delivery system. Free health care for children with malignancy is advocated. Collaboration with institutions in the privileged parts of the world may help.

Key words: nephroblastoma, challenges, late presentation

*Correspondence to: Dr S. O. Ekenze, c/o Department of Surgery, University of Nigeria Teaching Hospital, Enugu, Nigeria. E-mail: soekenze@yahoo.com

Introduction

Nephroblastoma is the most common malignant neoplasm of the urinary tract of children [1]. It is an embryonal neoplasm of the kidney in which blastemal, stromal and epithelial cell types are present in variable proportions [2]. Since the classical description by Wilms in 1899, the management of the tumor has evolved from surgery alone to the multimodal treatment with surgery, chemotherapy and radiotherapy [3, 4]. Collaboration among surgeons, pediatricians, pathologists, and institutions practicing pediatric oncology led to the formation of cooperative study groups with the aim of coordinating research on this tumor, comparing outcome of the different treatment modalities and standardizing treatment [4, 5]. The net result of these efforts is a remarkable improvement of outcome.

In many developing countries, however, the outcome of treatment is still poor [6, 7]. Factors identified as contributing to this include late presentation, persisting poverty, the possibility of a more aggressive tumor in these countries and lack of collaboration among institutions [6–8]. This study looks at the outcome and the limitations to management of nephroblastoma in southeastern Nigeria.

Patients and methods

The University of Nigeria Teaching Hospital, Enugu is a major tertiary hospital that takes care of children with neoplastic diseases in southeastern Nigeria. Children are either referred from the peripheral hospitals or from the pediatric department of our hospital. Diagnosis of nephroblastoma is based on the clinical feature of abdominal mass, ultrasonography, and intravenous urography. Confirmation of diagnosis follows histological evaluation of the operative specimen. From January 1995 to December 2004, 42 children were managed for nephroblastoma by the pediatric surgical unit. These cases were analyzed. Data on age at presentation, sex, clinical features, investigation, and findings at operation as well as the other modalities of treatment applied were obtained from the case notes, and the hospital cancer registry. Also assessed were the complications of treatment, outcome, duration of follow up and documented difficulties encountered in the management. The data was analyzed using EPI info version 6.
results
There were 22 boys and 20 girls with a male:female ratio of 1.1:1. Their age ranged from 7 months to 11 years (mean 4.1 years). Of these children, 17 were less than 2 years old, 16 were aged 3 to 5 years, while the remaining 9 were aged 6 to 11 years.

clinical presentation
All the children presented with abdominal mass. The average duration of this symptom before presentation was 4.7 months (range 1–8 months). Weight loss, fever and hematuria were present in 24, 14 and 5 children respectively. Twenty-three (54.8%) of the children were managed at peripheral hospital before referral to the pediatric surgical unit while the rest were referred by the pediatric department of the hospital.

evaluation
Ultrasonography, intravenous urography and chest radiograph were carried out on all the children. The results showed right tumor in 23 children and left tumor in 19 children. Chest radiograph showed metastatic features in six children, while ultrasonography revealed liver involvement in four children. Definitive diagnosis was based on histopathological evaluation of the specimen obtained during operation. Anemia was present in 14 (33.3%) children requiring preoperative blood transfusion.

treatment
Nephro-ureterectomy was the initial treatment in 35 children. Seven children who required preoperative chemotherapy were found to have inoperable tumor during exploratory laparotomy. Biopsy of the mass was carried out and tissue diagnosis obtained. The findings at operation in the rest of the children include stage II disease in seven children, stage III disease in 20 children and stage IV disease in eight children. The inoperable tumors were found at re-operation to be stage III in two children and stage IV in five children. Secondary tumor deposits were found in the liver in six children.
Chemotherapy was initiated in all the children 6–20 days after operation. The seven children that received preoperative chemotherapy had four doses of weekly injections before operation and continued with the same agents after reoperation. The agents used were Actinomycin D (15 μg/kg body weight), Vincristine (1.5 mg/m²), Cyclophosphamide (400 mg/m²). Adriamycin at the dose of 50 mg/m² monthly was added to the regimen of those with stage IV disease as well as the children that developed recurrence. In all, 18 children received regular chemotherapy while the rest could either not afford the drugs or were lost to follow up.
For radiotherapy the 35 children with stages III and IV disease were sent to Ibadan and Lagos where radiotherapy facilities were available.

outcome
Eleven children relapsed. Of these, nine had earlier defaulted from treatment for financial reason. Surgery-related complications was encountered in six children and include massive and fatal primary hemorrhage in a child undergoing re-operation after preoperative chemotherapy, surgical site infection in four children and adhesive small bowel obstruction in one child. The surgical site infection and adhesive small bowel obstruction responded to conservative management.
Overall, 25 children were available for follow up while 17 were lost to follow up. The follow-up period ranged from 8 months to 86 months (average 21 months). There were 11 recorded deaths on the whole, four of which followed complications of treatment, while seven resulted from relapse. The four treatment related deaths were from massive primary hemorrhage in one child and severe unremitting septicemia in three children.
With only 10 children alive after 5 years of treatment among those available for evaluation, our 5-year survival was 40%. Of the survivors, six had stage II disease while four had stage III disease.

discussion
The total number of children in this study may not be a reflection of the true incidence of this neoplasm in Enugu and the adjoining areas of southeastern Nigeria. It is common for some children with major illness to be taken to the herbalist or prayer houses instead of hospital. This is partly due to the parent’s preferences and partly to ignorance [9].
The peak age incidence of 2–5 years and the sex ratio obtained in this study are in keeping with reports elsewhere [1–3, 6, 7]. The distribution of the stages, however, differs from what is obtainable in the developed countries. While most studies from developed countries indicate that stage I disease is the most common stage [4, 5] our study revealed that most of our cases presented with stages III and IV disease. This in addition to the absence of stage I disease and the average duration of symptoms of 4.7 months in our series suggests that most of our patients presented late for treatment. This is a major limitation in our management of nephroblastoma. Late presentation is a common problem in many developing countries and may be related mostly to ignorance and poverty [8, 10]. Most of these children are usually first managed in a primary care centre where facilities and qualified personnel needed for early diagnosis are lacking [11]. The other factor that may have contributed to the late stage at presentation is the possibility that this tumor behaves more aggressively in developing countries [8].
Collaborative efforts among surgeons, pathologists, pediatricians and radiation oncologists have been regarded as a major factor in the excellent outcome from current management of nephroblastoma [3–5, 12]. For some unknown reasons, this multidisciplinary approach is lacking in the management of nephroblastoma in the period under review. In addition there was no collaboration with other institutions managing this disease within and outside the country. Multidisciplinary team management and collaboration with other institutions allow for exchange of ideas, standardization of therapy, as well as encouraging research.

The definitive treatment of nephroblastoma involves surgery, chemotherapy and radiotherapy. In this series, surgery was done on all the children and the complications compares with what obtains in most parts of the world [13].

original article

Annals of Oncology

Volume 17 | No. 10 | October 2006
doi:10.1093/annonc/mdh167 | 1599
Chemotherapy on the other hand was not given regularly according to established schedule of NWSG or SIOP on all the patients. The major reason for this is resource deficieny. Most of the patients are poor and because a free health care facility is not available in most developing countries, these drugs are not affordable to many of the patients. An additional factor is the unavailability of the drugs especially the second line drugs.

The number of children that relapsed in this study is very high. This high relapse rate may be the result of late presentation as well as poor compliance with chemotherapy regimen. It is possible that the variant of nephroblastoma in our environment is more aggressive and chemoresistant. Also disturbing in this series is the large number of children that were lost to follow up. High relapse rates as well as loss to follow up have also been reported from other developing countries [7, 8]. Ignorance, poverty and poor communication between the doctor and patients may play a role in the abandonment of treatment.

Nephroblastoma is regarded as one of the successes of pediatric oncology with long term survival approaching 90% and 70% for localized and metastatic diseases respectively [3, 5]. Viewed against this backdrop, the overall outcome of treatment of nephroblastoma in this study is very poor. Though the survival for Stage II disease in this series (85.7%) compares with reports from more developed countries, the result of treatment for advanced disease is abysmal. This poor result in our sub-region is a reflection of problems peculiar to the least developed and developing countries, problems with fundamental issues such as poverty, ignorance, inadequate drug supply and lack of collaboration.

**conclusion**

Treatment of nephroblastoma in our environment is associated with a poor outcome. Factors such as late presentation, poverty, ignorance, poor compliance to treatment and lack of multidisciplinary collaboration remain major challenges in managing these patients in a developing country.

Poverty eradication, improvements in health funding, health information and health care delivery system are advocated. Free health care for all children and establishment of collaboration with institutions will improve the results.

**author contributions**

Study conception and design: S. O. Ekenze; Acquisition of data: S. O. Ekenze, O. A. Odeteunde; Analysis and Interpretation of data: S. O. Ekenze, O. A. Odeteunde, N. E. N. Agugua-Obianyo; Drafting of manuscript: S. O. Ekenze; Critical revision: N. E. N. Agugua-Obianyo, S. O. Ekenze.

**references**