Nephroblastoma - A 25-year review of a South African unit

Nephroblastoma at a South African hospital

Yolandi Thelma Visser MB ChB, DCH, Ronelle Uys MB ChB, Anel van Zyl MB ChB, M Med(Paed), FC Paed(SA), CMO(SA), Daniela Cristina Stefan MD, M Med(Paed), FC Paed(SA), CMO(SA), MSc(UK), PhD

Department of Paediatrics and Child Health, Stellenbosch University, Faculty of Health Sciences, Tygerberg Hospital

Corresponding author: Prof. DC Stefan, PO Box 19063, Department of Paediatrics and Child Health, Tygerberg Hospital and Stellenbosch University, Tygerberg, Cape Town 7550 South Africa.

Physical Address: Francie van Zijl Avenue, Clinical Building, 2nd Floor, Room 2091A, Tygerberg Campus, Western Cape, South Africa
**Abstract**

Rationale: To determine the outcome of patients with nephroblastoma in a South African hospital

Objective: To determine if there is a difference in the outcome of patients with nephroblastoma comparing two treatment protocols SIOP (Société International D’Oncologie Pédiatrique Protocol) versus NWTS (National Wilms’ Tumour Study Protocol)

Methods and results: A retrospective audit of children diagnosed with nephroblastoma at Tygerberg Hospital over 25 years (1983-2007). One hundred and seven patients were included in the study and 98 analysed. The average age at diagnosis was 3.8 years. Most patients (37%) presented with stage 1 disease, followed by patients with stage 3 (27%). Most patients were treated according to the SIOP protocol (61%). Gender and race did not influence the outcome. Patients with stage 1 and 2 disease had the best outcome (76% versus 43% for stages 3 and 4). The SIOP group had a better outcome than the NWTS group (p value 0.001). The two groups had an equal distribution of stage of presentation. The tumour volumes were bigger in the NWTS group (1004cm$^3$ compared to 613cm$^3$). Nutritional status did not influence the outcome although more patients were underweight for age in the SIOP group. Statistical methods used were: Kaplan Meier, Gehan’s Wilcoxon Test, Chi – square test and the Fisher exact test

**Discussion**

Contrary to other studies, patients treated according to the SIOP protocol had a statistically significant better outcome. Larger collaborative studies are needed to investigate this result in Africa.

Key words: nephroblastoma; Wilms tumor; Africa; treatment protocols; outcome

Abbreviations: SIOP (Société International D’Oncologie Pédiatrique Protocol); NWTS (National Wilms’ Tumour Study Protocol)

**Introduction**

Childhood cancers are rare, comprising about 1% of all cancers. Nephroblastoma or Wilms tumour (WT) accounts for 6-7% of all childhood cancers$^1$ and is the most common renal tumour in childhood. In 2010, data from the tumour registry of the South African Children’s Cancer Study Group (SACCSG) showed that WT was the fourth most common childhood cancer in South Africa$^2$. Major improvements in the diagnosis and treatment of childhood cancers over the last 50 years have resulted in a high cure rate of approximately 90% in developed countries.$^1$ Sadly, the success rate is far lower in South Africa and other developing countries, mostly due to a delay in seeking medical attention or to a lack of access to health care$^1$ or due to optimal therapy not being available$^3$. 
Race disparities have been studied in the past; in 2011 a study by Jason et al found that African people had a higher incidence of WT than Caucasians. African patients were 79% more likely to develop WT than Caucasian patients and they tended to present with more advanced disease, but the overall survival rate was the same.

Treatment modalities have been studied extensively over the past 25 years. The National Wilms Tumour Study Protocol (NWTS) and the Société International D’Oncologie Pédiatrique Protocol (SIOP) are currently the 2 most common protocols being used globally. The NWTS protocol stipulates surgery upfront, followed by neo-adjuvant chemotherapy, while the SIOP protocol begins with chemotherapy after which surgery is performed. Management of Wilm’s tumor was researched previously in a developing country (India) comparing the two protocols showing equivalent clinical outcomes.

At Tygerberg Hospital in Cape Town, South Africa, the NWTS protocol was initially used (from 1983), but in 1989 it was decided to change the protocol to SIOP. The rationale for using a different protocol was based on the clinical presentations of the children: large tumours at diagnosis, advanced disease and plans for a common national protocol. The pre-operative chemotherapy is utilised to decrease the tumour volume in order to make surgery easier and to reduce the complication rate thereof.

The aim of the study is to compare the outcome of the patients treated with the two different treatment protocols (SIOP vs NWTS).

**Methods**

The study population included all paediatric patients (<15 years) diagnosed and treated for nephroblastoma at Tygerberg Hospital’s Pediatric Oncology unit from 1 January 1983 to 31 December 2007.

Data were collected from the Tygerberg Hospital tumour registry and from the folders of the patients.

The following information was captured for each patient: date of birth, date of diagnosis, gender, ethnic group, staging, treatment protocol, surgery, pathology and radiotherapy reports, nutrition and outcome.

All cases diagnosed were histologically confirmed by a pathologist and reviewed by a tumor board.

The extracted data were recorded in Excel format. Descriptive statistics including frequency tables, histograms, means and standard deviations was performed. The survival/outcomes were demonstrated with Kaplan Meier curves and with the use of Gehan’s Wilcoxon Test the p-values were calculated. A p-value of <0.01 were chosen as significant before the data was analyzed. Chi square or test calculations were used to determine if there is a difference between expected and measured data in more than one category.
**Ethical Approval**

Ethical approval for this study was obtained from the Health Research Ethics Committee of the University of Stellenbosch. The superintendent of Tygerberg Hospital approved the retrieval of data from the Tygerberg Hospital folders. Confidentiality of the patients was maintained at all times. Individual consent was not required as it was a descriptive retrospective study.

**Results**

**Location**

Tygerberg Hospital is a tertiary hospital located in Parow, Cape Town, serving the Eastern Metropolitan region of Cape Town and the North-Eastern districts of the Western Cape Province. The hospital was officially opened in 1976 and provides healthcare to over 3.6 million people (2.4 million children) being the largest hospital in the Western Cape and the second largest hospital in South Africa.

The patients in this study came from the Tygerberg Hospital’s drainage area (Western Cape 61%), followed by Namibia, Northern Cape and Eastern Cape provinces.

**Ethnicity**

South Africa consists of a diverse population in terms of ethnicity but this can broadly be classified into Black, White or Caucasian and coloured or Mixed ethnicity. The Coloured population genetically consists of an ancestral mix between European and various Southern African Black tribes. This ethnic group is widespread across South Africa but there is a higher concentration of this population group specifically in the Western Cape region. The percentage distribution of ethnic groups shows 32.9% blacks, 48.8% coloured, 15.7% whites, and 1% Asian/Indian.

**Demographic results**

One hundred and seven patients were diagnosed with nephroblastoma at Tygerberg Hospital between 1 January 1983 and 31 December 2007. Ninety-eight patients were included in the study; 9 patients were excluded due to lack of complete information (including stage V disease). There were 54 (55%) girls and 44 (45%) boys. The average age at diagnosis was 3.8 years, ranging from 3 months - 14 years, with most patients being coloured (52%), followed by black (34%) and white patients (14%). The colored females (35%) were the most numerous.
Staging and diagnosis

All patients were staged according to the international guidelines\(^5\).

The staging of nephroblastoma was based on abdominal ultrasound, chest radiography, abdominal and chest (if indicated) computerized tomography (CT scan). The staging was completed after surgery with a pathology report.

Associations between survival, stage of disease and ethnic group were assessed.

Stage 1 disease was most common at presentation (37%), followed by stage 3 (24%) and stage 4 (21%) disease for the whole group.

Pathology data from only 38 patients was analysed. Most of the pathology reports were old printed copies and could not be read and some copies were missing from records. The average tumour volume in the SIOP was considerably smaller 613cm\(^3\) than in the NWTS group 1004cm\(^3\) due to the preoperative chemotherapy effect.

Protocols and outcome

Patients were treated according to NWTS protocol from 1983-1989 and according to the SIOP protocol from 1989 onwards. There were 39 cases (39%) in the first group and 59 cases (61%) in the second group.

There were 50 patients who received curative radiotherapy. The average ionized radiation used were 27 GY (gray), ranging from 9-51GY over a 3-4 week period (as per protocol).

The overall survival for the whole group was 76.5% irrespective of the treatment protocol used. There was no statistically significant difference between male and female (75% of males and 78% of females).

Overall survival between different ethnic groups was similar: 76.5% for the coloured population, 78.6% for the whites and 75.8% for the black patients (fig 1).

The outcome of patients with stage 1 and 2 approaches the values reported in developed countries: 81.6% and 93.3% respectively. Less rewarding results were obtained after the treatment of stage 3 and 4 75% and 57% respectively. (fig 2). Patients (2) with stage V were not analysed due to missing information.

The overall survival for early stages (1 and 2) varied between 80% for whites, 82% for the colored population and 88% for the black children. The outcome for stages 3 and 4 for the blacks was 69%, for the colored group 64% and 75% for the whites, No statistical significance could be demonstrated.

Comparing the groups treated with the 2 protocols, the distribution of stages was similar: both groups had 54% of the patients with stage 1 and 2 disease and 46% of patients with stage 3 and 4 disease.

Comparing the outcome between the 2 groups, the survival for all stages in NWTS was 61.5%
and 86.4% for SIOP with marked difference between the stages (fig 3, fig 4) with a p-value of 0.002.

The analysis of nutritional status showed that 7.5% of patients in the SIOP group were underweight for age compared to 2.8% in the NWTS group (underweight for age = weight between -2 and -3 Z score). The weights of 12 patients in the SIOP group and 2 patients in the NWTS group were unavailable.

Discussion

Nephroblastoma is a common childhood tumour in Africa and has in developed countries a good prognosis if treated early. The overall survival approaches 90% in developed countries. In developing countries, for a variety of reasons the survival rates seldom approach these figures. Moreira et al found an overall 5 year survival in Sub Saharan Africa of 71%. Most patients in developing countries, especially Sub-Saharan Africa, present late due to limited access and poor health care facilities, poor education and the paucity of adequate trained medical staff and this has a direct effect on outcome. Associated co-morbidities that has a high prevalence eg. tuberculosis, HIV, malaria and malnutrition also has an effect on the presentation and outcome of disease in these countries. As mentioned above early presentation is vital for a good outcome.

There are no published studies to compare the 2 common protocols used for the treatment of the African child with Wilms tumor.

In our study there were slightly more females than male patients. Reports have shown that there is a varying male to female ratio that ranges from 2:3 to 1:1.

The median age of children with nephroblastoma is reported to be 42 months of age which is the same as our median age of 44 months. A similar South African study showed a median age of 39 months. There is a study from the GFAOP (Groupe Franco-Africain d'Oncologie Pédiatrique) group who report a median age of only 36 months in their cohort of patients.

The racial distribution of our patients reflects the population of South Africa and is representative of Western Cape. It is stated in the literature that nephroblastoma is more common in Africa than in developed countries.

Stage, with histology, is one of the two most important predictors of prognosis and survival in children with nephroblastoma. Stage 1 and 2 disease are classified as local disease and when using the NWTS protocol can be resected completely. These tumours have a good prognosis of >90% 5 year survival in developed countries and in Sub Saharan Africa >76% as per Moreira et al. Unfavourable histology (anaplasia) has a poor overall survival of 37-82% compared to favourable histology overall survival of 86-98%.

This study did not gather data on the histology of the operative specimens but data on the staging was obtained. Stage 1 disease was most common at presentation (37%), followed by stage 3 (24%) and stage 4 (21%) disease for the whole group. This differs from other figures from other African countries which quote that over 70% of their patients had advanced stage at presentation.
The study of the GFAOP\textsuperscript{3} showed an incidence of stage 1 disease of 34\% while advanced stage disease only accounted for 40\% of their patients.

The two different treatment strategies which are widely accepted and used internationally SIOP and NWTS showed previously similar outcome results.\textsuperscript{5}

In this study the group treated according to the SIOP protocol had a significantly better outcome than the NWTS patient group, especially for the patients with stages 1 and 2 disease (91\% versus 76\%). Patients with stage 3 and 4 disease in the SIOP group had a survival rate of 82\% versus 43\% for the NWTS group. The SIOP group had a better outcome than the NWTS group (p value 0.001).

Most of our patients were treated according to the SIOP protocol (61\%). Gender and race did not influence the outcome which is for the first time described in the literature for an African population. A study from Poole\textsuperscript{13} showed that their stage 4 survival rate using SIOP was of approximately about 45\%, while another South African study\textsuperscript{11} using NWTS had a survival rate of 54\%.

Our two groups analysed had an equal distribution of stage of presentation.

The average tumour volume in the NWTS group was significantly larger than in the SIOP group (1004cm\textsuperscript{3} compared to 613cm\textsuperscript{3}) since the SIOP group received pre-operative chemotherapy. Surgical complications with tumor spillage did not contribute to the upstaging of the tumor and there was no significant change in surgical methods during the study time period.

Nutritional status did not influence the outcome although more patients were underweight for age in the SIOP group. There were no major demographic differences between the two patient groups. On analysis of the patients’ nutritional status, it was found that they were mostly malnourished with more patients being underweight in the SIOP group, but that did not have any effect on the outcome.

Not enough information was available to correlate the pathology risk protocol with the outcome. Pathology reporting has changed and become more sophisticated over the years and thus could have had an effect on the results. Anaplasia which often leads to chemotherapy resistance was identified in only 2 patients, one in each group.

Protocols were followed correctly in all cases analyzed and there was no evidence to suggest deviation from the protocols used. All patients had chemo- and radiotherapy as per protocol. Supportive care could have played a role in the improved outcome in more recent years when the SIOP protocol was used, but this is difficult to quantify. There were no major changes in the supportive care provided to the two patient groups.

This study confirms that gender and race did not influence the patient outcome. The data shows that the main variable affecting outcome is the stage of presentation and the protocol used. The only factor that remained a significant predictor of death was the treatment protocol used, which was previously not described.
Possible reasons for the difference in results in comparison to the literature include differences in demographic and genetic characteristics, nutritional status, tumour volume, pathology risk reporting protocols in the different eras, improvement in surgical skills, as well as protocol deviation and supportive care.

No genetic testing was available at Tygerberg hospital during the study period, thus this could not be investigated further.

**Limitations of the study**

There are a number of limitations to the study. The data only represents children seen at Tygerberg Hospital pediatric oncology unit. This was a small retrospective study representing a specific population. Some patients were not included in this study since essential information was not available. With regards to the pathology reports, since reporting methods also changed during the study period, it complicated the interpretation of the tumour volumes. In addition, only half of the patients’ tumour volumes could be found.

**Conclusions**

The result that our patient population has a better outcome when treated with the SIOP protocol is highly significant and needs further research. This study also demonstrates that differences in ethnic group were not significant in the outcome, black, colored and white children having similar survival graphs when presented with the same stages.

Larger studies are needed in identifying the optimal treatment protocol for the treatment of the African children with nephroblastoma and a better characterization of the disease.

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**Disclosure**

None
References

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7. Stefan DC “Distribution of childhood cancer in Africa” Presentation IARC Cork 2011
Fig 1: Corelation of survival with the ethnic group

Fig 2: Corelation of stages and outcome (p-value=0.01)

Fig 3: Comparing the outcomes of the stages treated with the NWTS protocol
Fig 4: Comparing the outcomes of the stages treated with the SIOP protocol

![Bar chart comparing outcomes of stages 1 & 2 vs stages 3 & 4 treated with the SIOP protocol.](#)

- **Stage 2 groups: stages 1 & 2**
  - **Survived**: 91%
  - **Died**: 9%

- **Stage 2 groups: stages 3 & 4**
  - **Survived**: 82%
  - **Died**: 18%