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EXPERIENCE AND OUTCOMES OF NEPHROBLASTOMA IN JOHANNESBURG, 2004-2016

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Master of Medicine (MMed) in Paediatric Surgery degree. Written in the submissable format according to JPS guidelines.

Johannesburg, 2022

DECLARATION

I, Seo-Hwa Chung, declare that this Research Report is my original work. It is being submitted for the Master of Medicine (MMed) in Paediatric Surgery degree at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at any other university previously.



Signed on the 20th day of June 2022 in Johannesburg

DEDICATION

This research report is dedicated to Shang-Ju Chiang for allowing me to complete this work by offering endless love and support.

ABSTRACT

Background: Patients with nephroblastoma in low- and middle-income countries historically presented with advanced disease and poor outcomes, as is shown in previous South African studies. This study is to report our institution's contemporary results as compared to the past with advances in disease management.

Methods: Retrospective review of the clinical records of patients 16 years and younger diagnosed with nephroblastoma and undergoing multidisciplinary management between 01 January 2004 and 31 December 2016 at the two teaching hospitals affiliated to University of the Witwatersrand.

Results: Two hundred and sixty-five patients were identified of which 47 were excluded leaving a total study cohort of 218 patients. The stage distribution was: stage I – 69 (31.7%), stage II – 33 (15.1%), stage III – 36 (16.5%), stage IV – 65 (29.8%), stage 5 – 15 (6.9%). The five-year overall survival was 85.4% and for each of the stages was as follows: stage I – 96.4%, stage II – 92.3%, stage III – 79.3%, stage IV – 72.2%, stage V – 92.9%.

Conclusion: The survival outcomes of this cohort improved compared to our previously reported series, and are now comparable to outcomes from institutions in high-income countries. In our previous series (1998-2003), the 4-year overall survival was 76%, stage I and II combined 89%, and stage III, IV, V combined were 66.75%. Early recognition and diagnosis contributes to a more favourable outcome and over the years these improvements have in turn lead to an improvement in the outcomes of our patients.

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LIST OF ABBREVIATIONS

CHBAH – Chris Hani Johannesburg Academic Hospital

CMJAH – Charlotte Maxeke Johannesburg Academic Hospital

CNB – Core needle biopsy

COG – Children's Oncology Group

CT – Computed tomography scan

FNA – Fine needle biopsy

IVC – Inferior vena cava

LMIC – Low- and middle-income countries

LN – Lymph node

RA – Right atrium

RV – Renal vein

SIOP – International Society of Paediatric Oncology

WAGR – Wilms tumour, aniridia, genitourinary and mental retardation syndrome

1. INTRODUCTION

Nephroblastoma affects 1 in 10000 children under the age of 15 years worldwide and the reported incidence varies depending on various ethnic groups[1]. Nephroblastoma is the most common childhood renal malignancy, comprising 99% of primary renal tumours and 13% of all childhood cancers in South Africa[2]. In many low- and middle-income countries (LMIC), childhood cancers are often underserved, as nutritional and infective diseases are prioritized, particularly tuberculosis, community acquired pneumonia, gastroenteritis and Human immunodeficiency virus related morbidities[3]. The majority are diagnosed between the ages of 1 and 5 years with a peak incidence between 3 and 4 years of age[1,4].

The incidence of bilateral disease is reported to be between 5% and 11%[5–8]. Most children present with an asymptomatic abdominal mass that is noted by the caregiver during routine activities (76%)[9]. Thirty-seven percent present with abdominal pain, 23% with fever, 25% with hypertension and either microscopic (25%) or gross (19%) haematuria[9]. Anorexia and weight-loss are common presenting signs. Less common presentations include acute peritonism secondary to tumour rupture[10] or with cardiac arrhythmias secondary to intra-cardiac tumour extension[11].

Two protocols lead the management of nephroblastoma. The Children's Oncology Group (COG) Renal Tumours Committee, previously National Wilms Tumour Study Group and The International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group, the UMBRELLA SIOP-RTSG 2016[12,13]. The COG protocol advocates upfront nephrectomy and staging, followed by chemotherapy in order to avoid administration of unnecessary or inappropriate chemotherapy. The SIOP protocol recommends neoadjuvant chemotherapy to decrease the tumour bulk and reduce potential intraoperative complications such as tumour rupture or spillage. The exception to neoadjuvant chemotherapy in the SIOP protocol is in patients aged 6 months and under (182 days), completely cystic tumours or suspicions alternate diagnosis, where upfront surgery is performed to avoid the toxic effects of chemotherapy in younger children[14]. The exception to upfront resection in COG is tumour thrombus in the inferior vena cava (IVC) above the hepatic veins, tumours involving contiguous structures, bilateral tumours, tumour in a solitary kidney, and pulmonary compromise due to pulmonary metastases[12,15]. Lymph node (LN) sampling is always recommended at time of

nephrectomy, the number of nodes are at least seven by both groups[16–18]. The histological classifications and staging systems for the two protocols vary slightly, with the COG basing their classification on favourable and unfavourable histology (anaplasia), tumour weight, LOH at 1p and 16q[19,20], whilst SIOP bases their reporting on the tumour volume and chemotherapy response into low risk tumour (completely necrotic), high-risk tumour (blastemal or diffuse anaplasia), and intermediate-risk tumours (other histology)[14,19,21]. The COG staging system is pre-chemotherapy and SIOP post-chemotherapy where there is an element of chemotherapy induced necrosis, hence in SIOP the presence of necrotic tumour in the renal sinus or at the margin >5mm away from viable tumour it is downstaged, however if present at the resection margin with viable tumour <5mm from the margin, present in lymph nodes, peritoneal implants or transected thrombus, it is upstaged, otherwise the staging criteria are similar. The staging is as follows, stage I is where the tumour is limited to the kidney and completely resected, stage II where the tumour extends beyond the kidney but is completely resected en-bloc, stage III is where gross or microscopic tumour remains whether at the margins, lymph nodes, peritoneum, transected thrombus, or there has been tumour rupture or an open biopsy (not upstaged by needle biopsy), stage IV where there is haematogenous metastases or to lymph nodes outside the abdomen, and stage V is where there is bilateral involvement with each side sub-staged[22].

In both groups, stage IV (metastatic disease) is diagnosed with computed tomography scans (CT), and histological confirmation if uncertain. If pulmonary metastases have disappeared after six weeks of three-drug chemotherapy (vincristine, actinomycin D and doxorubicin) and the tumour is of favourable histology, radiation is no longer given. If the metastases remain, then another course of chemotherapy is given following which they may elect to perform whole lung radiation, metastastectomy or both with the aim of reducing the amount of radiation to the lungs[16,23–25]. In cases of isolated liver metastases, local resection after neoadjuvant chemotherapy is appropriate. If the metastatic lesion requires more extensive resections, then further chemotherapy is suggested prior to resection. Any metastases other than lung or liver should be resected if feasible[16]. In cases of intravascular thrombus, both groups advocate neoadjuvant chemotherapy to allow for reduction in size to facilitate safe removal, although some in COG advocate for upfront resection if infra-hepatic. In cases of thrombus supra-hepatic and higher, cardiopulmonary bypass may be required to aid in the thrombectomy[16,26–28].

For stage V disease (bilateral Wilm's tumour) both protocols suggest six weeks of neoadjuvant chemotherapy followed by reimaging for nephron-sparing surgery of at least one kidney, and if only a partial response then repeated chemo and definitive surgery at 12 weeks. If salvage of adequate functional renal tissue is not feasible, renal transplant may occasionally be required[15,29,30]. Relapse of disease is most often reported to be in the lung and pleura (50-60%), abdominal recurrence (30%) and distant sites (10-15%). Overall survival after relapse is poor (48%). A general principle for the treatment of relapsed nephroblastoma is to use agents not used for primary therapy[15].

The two teaching hospitals affiliated to the Department of Paediatric Surgery, University of the Witwatersrand are Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) which serve the population of Johannesburg, extending to the rest of the Gauteng Province as well as the neighbouring countries. Gauteng has a population of approximately 15 million, of which 3.7 million are under 15 years of age[31]. Proceeding the adoption of the SIOP Umbrella protocol, we followed the modified SIOP-9 protocol consisting of a course of neoadjuvant chemotherapy, followed by surgery and adjuvant chemotherapy with or without radiotherapy. The modified SIOP-9 nephroblastoma treatment protocol showed no significant change in survival between four and eight weeks of preoperative treatment in non-metastatic disease. Therefore four weeks of two-drug chemotherapy (vincristine and actinomycin D) for stage I, II and III, and six weeks of three-drug chemotherapy (vincristine, actinomycin D and doxorubicin) for stage IV was given. Pathological staging was determined using the SIOP WT 2001 staging criteria, and histological risk classification, which combined determined post-operative therapy[32].

Worldwide there are reported significant global disparities in outcomes between the LMIC and high-income countries. Particularly in Africa, there is an increased incidence but under reporting, limited resources, delayed diagnosis and poor patient follow-up which have been attributed to worse outcomes[33]. Within South Africa, multiple major paediatric surgical centres including our own reported on their experiences of nephroblastoma showing their outcomes[34–37]. The aim of the current study was to examine the more recent cohort, analyse and compare the outcomes to the various centres in South Africa.

Improvement in data reporting and studies are required to identify barriers to optimal care and identify country specific solutions to improve outcomes for this highly curable malignancy. These studies could use nephroblastoma as the flagship tumour to improve on the disparities,

be it diagnosis, treatment, or resources, which would translate into improved outcomes, and hence the aim of the study was to critically analyse the management and outcomes of nephroblastoma in Johannesburg, and compare to the historical cohorts in South Africa.

2. MATERIAL AND METHODS

A retrospective descriptive study was conducted at the Department of Paediatric Oncology and Paediatric Surgery at CMJAH and CHBAH. Patients eligible for inclusion were those diagnosed with nephroblastoma between 01 January 2004 and 31 December 2016 under the age of 16 years. Initial identification was made from the oncology registry and patients were cross referenced against hospital files, radiology and histology reports. Patients excluded from the study were those referred after surgery, patients who did not undergo surgery and those with significant missing data. Data was collected and recorded on a Microsoft Excel spreadsheet with each patient allocated a unique identification number for confidentiality. The data was analysed using descriptive statistics. Continuous data was summarised using the mean and standard deviation when normally distributed and median with interquartile range if skewed. The categorical data was expressed as frequencies and proportions where necessary. Data was analysed using Stata 14 and tables and graphs were used to display relevant data.

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) - clearance certificate number M171049.

3. RESULTS

3.1 A total of 265 patients were identified. Forty-seven patients were excluded, leaving a study cohort of 218 patients (Figure 1).

3.2 Age distribution and presentation

The age range at diagnosis was two to 183 months, with a median of 40 months. There was a slight female predominance (1.1:1) and marginally more right-sided tumours in those with unilateral disease (n=105, 51.7%). The most frequent presenting symptoms were abdominal mass (n=132, 60.6%), abdominal distension (n=64, 29.4%), loss of weight (n=55, 25.3%) and anorexia (n=49, 22.5%). Hypertension requiring treatment was noted in half of our patients where the blood pressure was known (n=101, 51.3%). There were six patients with known predisposing conditions of which four had hemi-hypertrophy. Of these six patients, one had Denys-Drash syndrome and another had WAGR (Wilms tumour, aniridia, genitourinary and mental retardation) syndrome and one had Beckwith-Wiedemann syndrome with hemi-hypertrophy (Table 1).

3.3 Staging and risk stratification

The operative stage distribution were 69 (31.7%) for stage I, 33 (15.1%) for stage II, 36 (16.5%) for stage III, 65 (29.9%) for stage IV and 15 (6.9%) for stage V (Table 2).

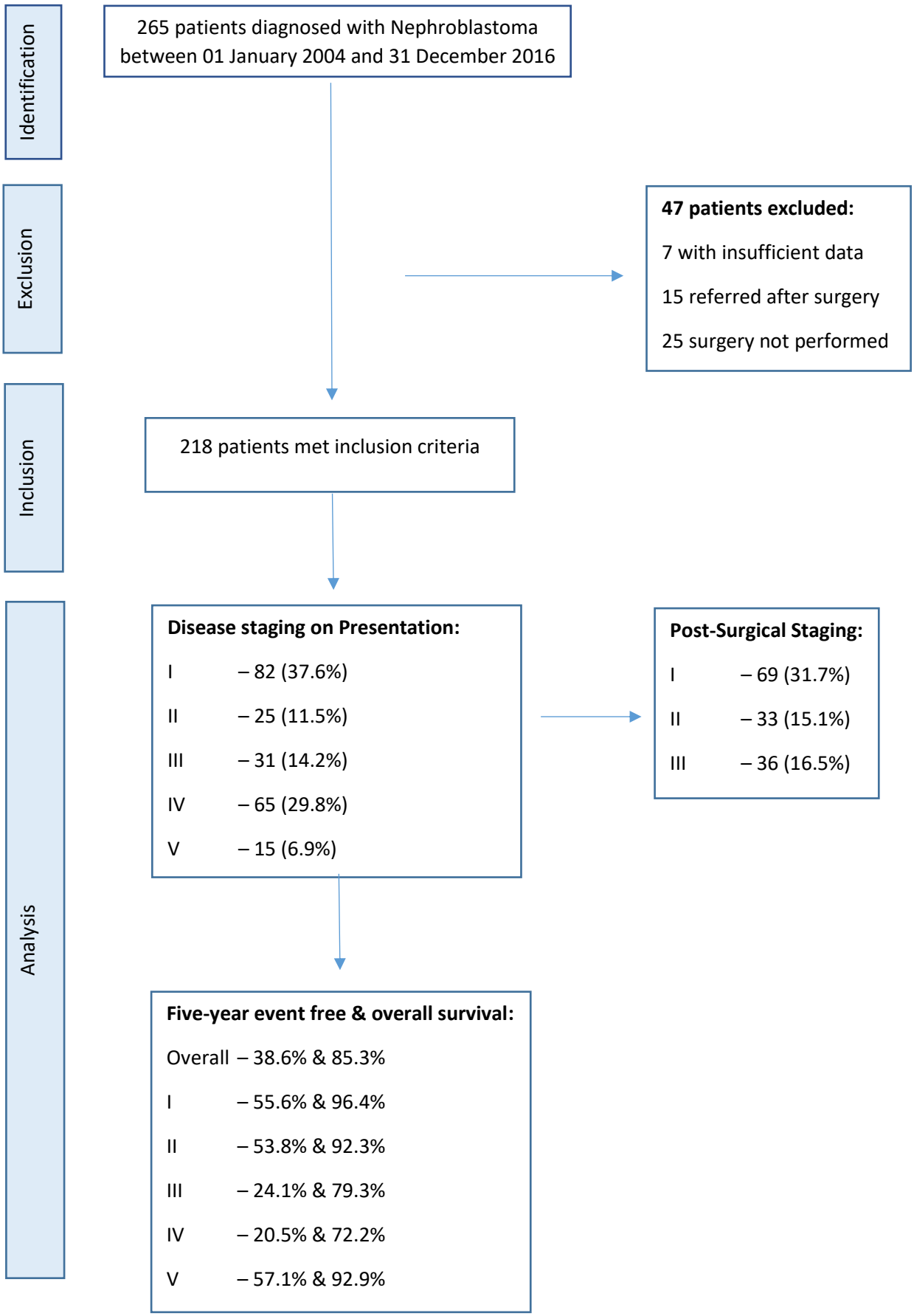


Figure 1: Flow diagram depicting patient inclusion

Table 1: Presentation of each stages

Disease staging	Total	Stage I	Stage II	Stage III	Stage IV	Stage V
Patient numbers (%)	218 (100%)	69 (31.7%)	33 (15.1%)	36 (16.5%)	65 (29.8%)	15 (6.9%)
Median age (months)	40	31	38	46	52	33
Male:Female	1:1.1	1:0.8	1:1.2	1:1.3	1:1.4	1:0.9
Ethnicity						
Black	198 (90.8%)	57 (82.6%)	33 (100%)	34 (94.4%)	63 (96.9%)	11 (73.3%)
White	11 (5%)	6 (8.7%)	0	2 (5.6%)	0	3 (20%)
Indian	6 (2.8%)	3 (4.3%)	0	0	2 (3.1%)	1 (6.7%)
Coloured	3 (1.4%)	3 (4.3%)	0	0	0	0
Referral area						
Inter province	163 (74.8%)	56 (81.2%)	23 (69.7%)	23 (63.9%)	50 (76.9%)	11 (73.3%)
Outer province	40 (18.3%)	8 (11.6%)	9 (27.3%)	10 (27.8%)	11 (16.9%)	2 (13.3%)
Foreign	15 (6.9%)	5 (7.2%)	1 (3%)	3 (8.3%)	4 (6.2%)	2 (13.3%)
Laterality						
Right	105 (51.7%)	33 (47.8%)	17 (51.5%)	23 (63.9%)	32 (49.2%)	15 (100%)
Left	98 (48.3%)	36 (52.2%)	16 (48.5%)	13 (36.1%)	33 (50.8%)	15 (100%)
Tumour mass (mean)	565g	380g	732g	745g	631g	273g
<550g	136 (62.4%)	51 (73.9%)	18 (54.6%)	18 (50%)	38 (58.5%)	11 (73.3%)
>550g	72 (33%)	16 (23.2%)	15 (45.4%)	17 (47.2%)	23 (35.4%)	1 (6.7%)
Not weighed	10 (4.6%)	2 (2.9%)	0	1 (2.8%)	4 (6.1%)	3 (20%)
Adrenalectomy	54 (24.8%)	9 (16.7%)	8 (14.8%)	10 (18.5%)	24 (44.4%)	3 (5.6%)
Involved	8 (14.8%)	0	1 (12.5%)	2 (20%)	5 (20.8%)	0
Upper pole	5 (62.5%)	0	1 (100%)	1 (50%)	2 (40%)	0
No anaplasia	181 (88.7%)	66 (95.7%)	29 (93.5%)	31 (88.6%)	45 (78.9%)	10 (83.3%)
Anaplasia	23 (11.3%)	3 (4.3%)	2 (6.5%)	4 (11.4%)	12 (21.1%)	2 (16.7%)
Focal	10 (43.5%)	2 (66.7%)	1 (50%)	1 (25%)	6 (50%)	0
Diffuse	13 (56.5%)	1 (33.3%)	1 (50%)	3 (75%)	6 (50%)	2 (100%)
Complete necrosis	11 (5%)	3 (27.3%)	3 (27.3%)	2 (18.1%)	3 (27.3%)	0
Blastemal predominance	31 (14.2%)	5 (16.1%)	5 (16.1%)	9 (29%)	9 (29%)	3 (9.7%)
Risk stratification						
Low	12 (5.5%)	3 (4.3%)	2 (6%)	2 (5.6%)	4 (6.2%)	0
Intermediate	166 (76.1%)	60 (87%)	25 (75.8%)	23 (64.9%)	48 (73.8%)	11 (73.3%)
High	40 (18.3%)	6 (8.7%)	6 (18.2%)	11 (30.5%)	13 (20%)	4 (26.7%)
Positive margins & LN	11 (5%)	-	-	6 (16.7%)	5 (7.7%)	0
Positive margins only	55 (25.2%)	-	-	25 (69.4%)	20 (30.8%)	10 (66.7%)
Positive LN only	31 (14.2%)	-	-	17 (47.2%)	12 (18.5%)	2 (13.3%)
Syndromic	6 (2.8%)	2 (2.9%)	2 (6%)	0	0	2 (13.3%)
Hemihypertrophy	3 (50%)	2 (100%)	0	0	0	1 (50%)
Hemihypertrophy + BWS	1 (16.7%)	0	0	0	0	1 (50%)
DDS	1 (16.7%)	0	1 (50%)	0	0	0
WAGR	1 (16.7%)	0	1 (50%)	0	0	0
Relapse	30 (13.8%)	6 (8.7%)	2 (6.1%)	5 (13.9%)	10 (15.4%)	7 (46.7%)
Local	13 (43.3%)	2 (33.3%)	1 (50%)	1 (20%)	5 (50%)	4 (57.1%)
Lung	13 (43.3%)	3 (50%)	1 (50%)	2 (40%)	4 (40%)	3 (42.9%)
Liver	2 (6.7%)	1 (16.7%)	0	1 (20%)	0	0
Lymph node	2 (6.7%)	0	0	1 (20%)	1 (10%)	0
Overall survival (5-year)	85.4%	96.4%	92.3%	79.3%	72.2%	92.9%
Event-free survival (5-year)	38.6%	55.6%	53.8%	24.1%	17%	57.1%

LN = Lymph node; BWS = Beckwith-Wiedemann syndrome; DDS = Denys-Drash syndrome; WAGR = Wilms tumor, aniridia, genitourinary and mental retardation syndrome

Table 2: Comparison of staging pre-operative and post-operative after neoadjuvant chemotherapy

Disease stage (N=218)	Staging on presentation	Operative staging
Stage I	82 (37.6%)	69 (31.7%)
Stage II	25 (11.5%)	33 (15.1%)
Stage III	31 (14.2%)	36 (16.5%)
Stage IV	65 (29.8%)	65 (29.8%)
Local stage I	15 (23.1%)	21 (32.3%)
Local stage II	14 (21.5%)	16 (24.6%)
Local stage III	36 (55.4%)	28 (43.1%)
Stage V	15 (6.9%)	15 (6.9%)
Local stage I	1 (6.7%)	5 (33.3%)
Local stage II	0	0
Local stage III	4 (26.7%)	10 (66.7%)
Unknown	10 (66.7%)	-

After radiological imaging, 204 patients (93.6%) underwent tumour biopsy either by percutaneous retroperitoneal fine needle biopsy (FNA), core needle biopsy (CNB) or open biopsy followed by neoadjuvant chemotherapy. Of these, the majority of patients had a FNA (n=129, 63.2%) or CNB only (n=22, 10.8%), both FNA and CNB (n=36, 17.6%) or open biopsy (n=3, 1.5%). Four patients (2%) had biopsies of which type was not specified and ten patients (4.9%) did not have documentations of whether biopsies were done or not. The remaining fourteen patients (6.4%) did not receive biopsies prior to their surgical resections. Of these, five (35.7%) were patients under the age of six months, five (35.7%) had cystic lesions, two (14.3%) were deemed primarily resectable by the assessing surgeon, one (7.1%) was ruptured on presentation and one (7.1%) had no documented reason for not receiving a biopsy prior to resection of tumour.

Tumour mass ranged between 40g and 3750g of which 136 (62.4%) were less than 550g (Table 1). Ipsilateral adrenalectomy was performed with the nephrectomy and documented in 54 patients (24.8%) and of these eight (14.8%) had tumour infiltration. In those with tumour involvement in the adrenals, five involved the upper pole of the kidney, three were either middle or lower poles.

Histological subtyping and risk grouping was determined using the SIOP WT 2001 classification. Anaplasia was noted in 23 (11.3%) of all reported specimens, of which ten (4.9%) were focal (intermediate risk) and thirteen (6.4%) diffuse (high risk). In terms of histological risk stratification, 12 (5.5%) were low risk, 166 (76.1%) intermediate risk and 40 (18.3%) were of high risk. All of the low risk histology were due to total necrosis post neoadjuvant chemotherapy. Intermediate risk were due to mixed (<2/3 necrosis) type (n=65, 39.2%), regressive (>2/3 necrosis) type (n=64, 38.6%), stromal type (n=15, 9%), epithelial type (n=13,

7.8%) and focal anaplasia (n=9, 5.4%). High risk groups were due to blastemal type (n=27, 67.5%), diffuse anaplasia (n=10, 25%) or both blastemal predominance and diffuse anaplasia within the same specimen (n=3, 7.5%) (Table 1). Those without anaplasia showed a survival of 89%, focal anaplasia was 75% and diffuse anaplasia showed the worse outcome at 60% (Figure 2). There were no difference in outcomes between the patients with low and intermediate risk as they had a five-year overall survival of 90% and 90.3% respectively but those of high risk had a lower survival rate at 64.7%.

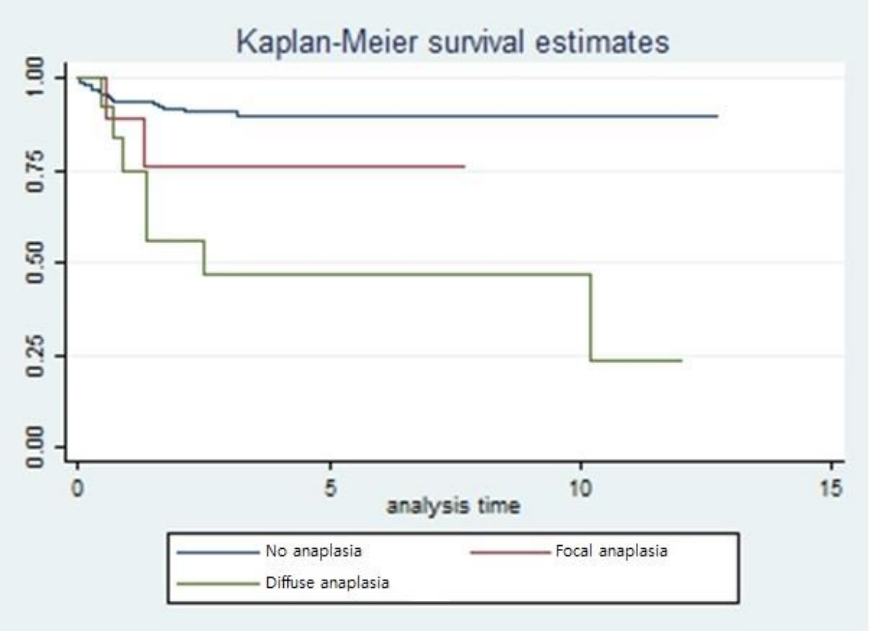


Figure 2: Survival by presence of anaplasia

There were nine cases of tumour ruptures, of which six (2.8%) were pre-operative and three (1.4%) intra-operative ruptures. Tumour resection margins were positive in 46 cases (21.1%) with microscopic residual disease at the edge of the resection margin of the tumour surface or vasculature.

Lymph nodes were sampled in 154 cases (70.6%), predominantly renal hilar and aorto-caval nodes and occasionally mesenteric nodes when appropriate. Of the nodes that were sampled, 31 (20.1%) were positive for tumour infiltration, upstaging the disease. The remaining 64 (29.4%) did not have sampling either because the surgeon could not find any nodes according to the operation notes (n=11, 5%) or sampling was not considered by the surgeon (n=53,

24.3%). As per the SIOP protocol for stage III disease, flank adjuvant radiation therapy was given to those patients who had positive resection margins or positive LN.

3.4 Vascular extensions

Forty-four patients (20.1%) had vascular extensions of tumour at presentation and the level of thrombus was recorded as renal vein (RV), inferior vena cava (IVC) or right atrium (RA). Thirteen extended into RV (5.9%), 27 to IVC (12.4%) and four into RA (1.8%). All patients with documented vascular extensions received neoadjuvant chemotherapy and tumour thrombus regression was noted post NACT in 28 of these patients (63.6%) of which 14 (31.8%) had complete thrombus clearance preoperatively (Table 3).

Table 3: Local tumour staging of patients with tumour thrombus on presentation

				Stage I	**Stage II**	**Stage III**			
Thrombus level pre-neoadjuvant chemotherapy	**Thrombus level post-neoadjuvant chemotherapy**			**Negative resection margin**		**Positive resection margin**			**Positive LN**
	No thrombus	RV	IVC			Tumour edge	RV	IVC	
RV (N=13)	6	7	0	1	2	4	7	-	5
IVC (N=27)	8	10	9	6	4	5	9	5	3
RA (N=4)	0	3	1	0	1	0	2	1	0
Total (N=44)	**14**	**20**	**10**	**7**	**7**	**9**	**18**	**6**	**8**

3.5 Metastatic disease

Sixty-seven patients (30.7%) presented with metastatic disease, 65 in unilateral disease and two in metachronous bilateral disease. Preoperative local staging were divided into stage I (n=15, 22.4%), stage II (n=14, 20.9%) and stage III (n=38, 56.7%). The median age was 52 months which was higher than the overall cohort age. In terms of the known tumour masses, 39 (62.9%) were less than 550g and 23 (37.1%) above 550g. The most common site of metastasis was to the lung alone (n=45, 67.2%), followed by lung and liver (n=12, 17.9%), and to liver alone (n=6, 8.9%). Remaining cases were to the lung plus other distant sites such as brain or bone (n=4, 6%). Metastatic disease was either managed with chemotherapy alone, with the addition of radiation therapy and/or surgical resection by various methods indicated by location of metastases.

3.6 Bilateral disease

The incidence of bilateral disease was 6.9% (n=15). Synchronous disease accounted for 80% (n=12) and the remaining 20% (n=3) were metachronous. The median age at presentation was 33 months (range 8-58 months), which was younger than the cohort with unilateral disease whose median age of presentation was 40 months (range 2-183 months). The synchronous group had a median age of 33 months whereas the metachronous group was of 31 months. No patients required renal transplantation during the study period. Four patients had tumour extension to the IVC, of which three had clearance post neoadjuvant chemotherapy and the fourth had persistent thrombus necessitating a cavotomy for thrombectomy during the nephrectomy. Two of the three patients in the metachronous group presented with metastatic disease as opposed to the synchronous group where no patients presented with metastatic disease giving an overall incidence of metastasis of 13.3% in the bilateral disease. Surgical resection margins were positive for microscopic disease in ten patients (66.7%) following planned nephron-sparing surgery on at least one kidney. Relapse was noted in seven patients (46.7%), three local relapse, two in the lung and the remaining two had local and lung or liver relapse (Table 4).

Table 4: Bilateral disease: Synchronous & Metachronous

Case No.	Age - months	Presenting local stage		Operative local stage		Type of surgery		Margins		Histology		Risk stratification	Metastasis	Relapse	Outcome
Synch		**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**				
1	14	U	I	I	I	Partial	Radical	Neg	Neg	Epith	U	Intermediate	No	No	Alive
2	8	U	U	III	III	Enucleation	Enucleation	Edge	Edge	Mix	Mix	Intermediate	No	Local	Alive
3	77	II	II	I	I	Partial	Partial	Neg	Neg	Mix	Mix	Intermediate	No	Local	Dead
4	10	U	U	III	I	Partial	Radical	Edge	Neg	Strom	Epith	Intermediate	No	No	Lost to follow-up
5	45	III	II	III	III	Partial	Enucleation	Edge	Edge	Regre	Regre	High – Diffuse anaplasia	No	Local	Alive
6	17	U	U	I	I	Partial	Radical	Neg	Neg	Blast	Epith	High – Diffuse anaplasia	No	No	Alive
7	33	U	U	III	III	Radical	Partial	Edge	Edge	Epith	Regr	Intermediate	No	No	Alive
8	58	U	U	III	I	Enucleation	Radical	Edge	Neg	Epith	Regr	Intermediate	No	No	Alive
9	38	III	III	III	III	Radical	Partial	RV	Edge	Mix	Bi	Intermediate	No	Lung	Alive
10	37	I	III	I	III	Partial	Radical	Neg	RV	Mix	Regr	Intermediate	No	No	Alive
11	39	U	U	I	III	Radical	Partial	Neg	Edge	Regr	Mix	Intermediate	No	No	Alive
12	24	I	I	I	III	Radical	Enucleation	Neg	Edge	Mix	Mix	Intermediate	No	Local + liver	Alive
Meta															
1	31	U	III	-	I	RHT	Radical	-	Neg	Blast	U	High	Lung	Local + lung	Alive
2	23	II	III	II	III	Partial	Partial	Neg	Edge	Epith	Mix	Intermediate	No	No	Alive
3	39	U	III	I	I	Radical	Partial	Neg	Neg	Blast	U	High	Lung	Lung	Alive

Synch = Synchronous; Meta = Metachronous; R = Right; L = Left; U = Unknown; Neg = Negative; Mix = Mixed; Reg = Regressive; Strom = Stromal; Epith = Epithelial; Blast = Blastemal; RHT = Refusal of hospital treatment

3.7 Morbidity

Surgery-related morbidities were noted in fourteen patients (6.4%), and were divided into immediate, early and late. In the immediate group, there were three patients with intraoperative tumour ruptures and one patient who necessitated a planned relook after packing with swabs for bleeding. Tumour mass was noted to be above 750g in all three of the intraoperative ruptures and the bleeding tumour weighed 2700g. Early complications included bleeding, pus collection and urinary leaks that necessitated relook laparotomies in four patients, Pus and urine collections were all from bilateral WT who received enucleation or partial nephrectomy as part of their management. Late complications occurred in six patients which included bowel obstruction secondary to external compression from recurrent disease, adhesions, intussusception or volvulus. Timing of bowel obstruction varied between two weeks and seventeen months post initial laparotomy. Bowel resection and anastomosis were needed in three of these patients.

3.8 Outcomes

Relapse was defined by return of disease to any location after completion of treatment. The relapse rate was 11.9% (n=26) and of these, 46.2% were local and 53.8% distant. Distant relapse was divided into lung (38.5%), liver (7.7%) and lymph nodes (7.7%). Of these patients, one had local and lung relapse and the other local and liver relapse. Almost a third of the patients (n=9, 34.6%) who presented with relapse had died by the end of the study period. Twenty patients (76.9%) had relapse within a year of completing their initial treatment of which ten (38.5%) were within a year of diagnosis. High risk histology was noted in nine patients (34.6%) and seven patients (26.9%) had positive involvement of LN.

The five-year overall survival was 85.4% and for each of the stages was as follows: 96.4% for stage I, 92.3% for stage II, 79.3% for stage III, 72.2% for stage IV and 92.9% for stage V (Figure 3). Age at diagnosis were divided into below and above five years of age (Figure 4). The logrank test for equality of survivor functions was used to assess the statistical significance of the observed differences in survival in the two age groups and there was a statistically significant difference in the survival functions between the two age groups ($p<0.0001$). The tumour mass was categorised as below and above 550g and a statistically significant difference was noted in the survival of individuals ($p<0.001$) (Figure 4).

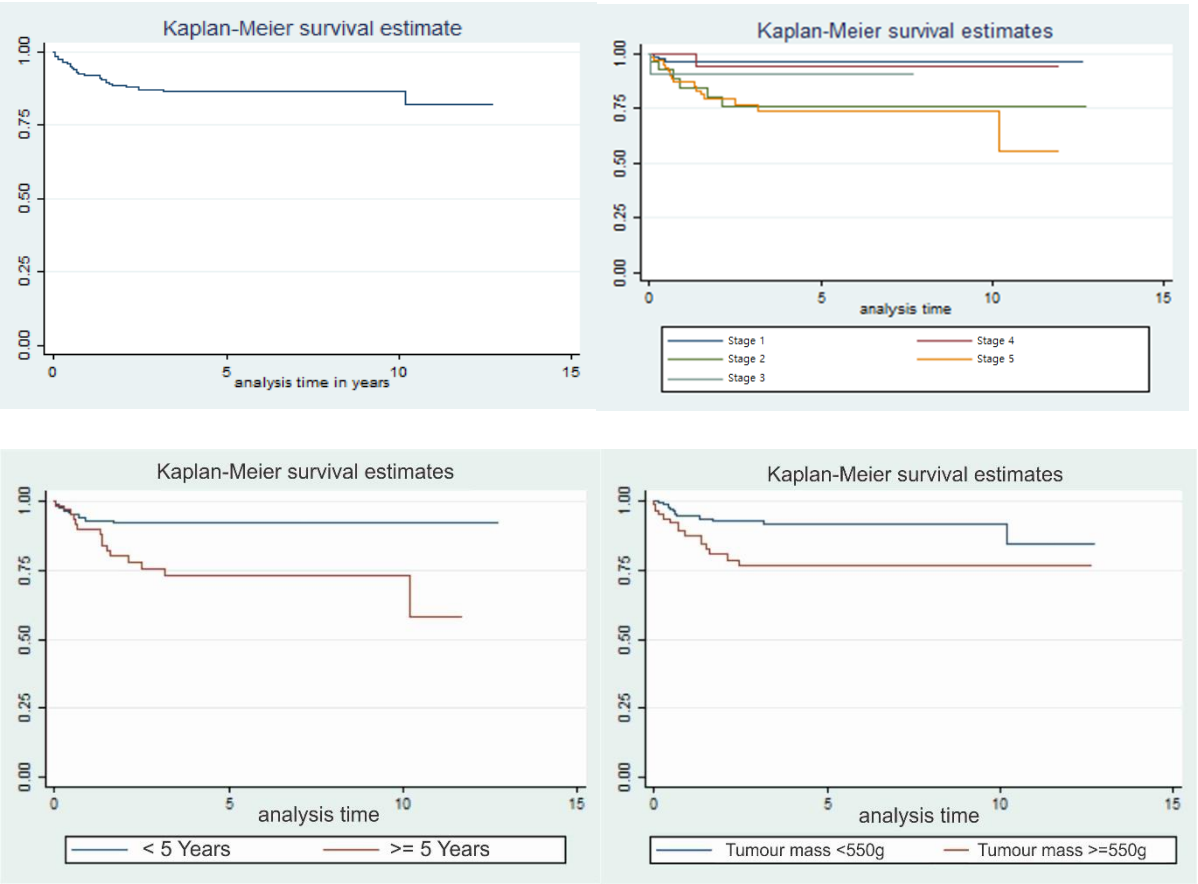


Figure 3: Survival by stage, age & tumour mass

4. DISCUSSION

Nephroblastoma is the most commonly encountered paediatric solid organ tumour in Sub-Saharan Africa, accounting for one third of the cases in our paediatric population[3]. In a previous study performed at CHBAH, the incidence of paediatric solid tumours was reported to be similar[38], necessitating investment into improving the management of this disease. Following the SIOP-9 protocol, patients in this study were given multimodality treatment that was modified based on their risk profile to offer the most effective therapy whilst simultaneously minimising adverse effects. The majority of patients received neoadjuvant chemotherapy and subsequent resection following a reduction in tumour size. Radiation therapy was given in cases of tumour positive LN, positive resection margins, metastases not responding to adjuvant chemotherapy or patients with relapse of disease. When a child presented with a renal mass suspicious of malignancy, a chest radiograph and staging CT were performed and the majority of the patients received a percutaneous retroperitoneal FNA and/or a CNB of the mass. In select cases, as open biopsy of the mass was performed. Once the diagnosis was confirmed, neoadjuvant chemotherapy was initiated, where after imaging was repeated and surgery subsequently performed. Thereafter adjuvant chemotherapy and/or radiotherapy were administered as indicated depending on the staging of tumour.

Our overall five-year survival rates has shown improvement from 76% to 85.4% compared to the previous study performed at our centre[34]. Earlier stage of disease (stage I and II) constituted approximately half the patients (n=102, 46.8%), which was more than the 34% documented in our previous study, indicating an earlier presentation and diagnosis of disease than previously seen. Median age at presentation of 40 months was in keeping with other South African centres (39.2 to 45.6 months)[34–36]. The frequency of our patients' presenting symptoms differed slightly to the reported numbers but the most commonly encountered symptom was an abdominal mass in 60.6% of cases which was in keeping with the literature[9]. The incidence of hypertension requiring treatment on presentation was unusually high in our cohort at 51.7% and very few series have reported an incidence of hypertension as high as ours[9,39,40]. We have no explanation for this high incidence of hypertension in our patients. No specific investigations were performed for the hypertension which prevented us from further analysis but no specific morbidities were noted in those with hypertension. Said

hypertension was presumably due to the activation of the renin-angiotensin-aldosterone system. Post neoadjuvant chemotherapy and nephrectomy, all patients with hypertension were taken off anti-hypertensive medications as their blood pressures had normalised.

Neoadjuvant chemotherapy was based on the initial pre-operative biopsy taken. Once the nephrectomy specimen was received by the pathologists, the characteristics of the tumour cells were documented. The specimen was then viewed for presence and degree of necrosis and histological pattern, this including blastemal, epithelial or stromal composition and predominance as well as the presence and type of anaplasia. Anaplasia is an indicator of unfavourable prognosis and is reported as either focal or diffuse. Approximately 4.5-6% of nephroblastoma specimens demonstrate anaplasia[9,41,42]. In this series the incidence of anaplasia was documented to be slightly higher, noted in 23 (11.3%) of specimens, with a similar distribution between the focal and diffuse groups. Based on the predominant cell pattern and presence or absence of anaplasia, the patients were risk stratified and managed with the appropriate post-operative chemotherapy protocol.

With regards to the surgical management of unilateral disease, the aim was to perform a radical nephrectomy with or without resection of surrounding structures depending on degree of tumour infiltration. All nephrectomies were performed via a transperitoneal laparotomy. The current consensus regarding adrenalectomy in unilateral nephrectomy is that adrenalectomy is not mandatory to improve outcome however removal does not adversely affect adrenal function[43]. Adrenal-sparing surgery was performed where feasible however en bloc resection of the adrenal gland was completed in 54 (25.2%) of cases. Of these, eight (14.8%) demonstrated histological confirmation of tumour invasion. Half of the patients with documented adrenal disease presented with metastatic disease, however none developed local relapse. Tumour mass was documented by most of the pathologists examining the specimens however volume was not noted despite SIOP protocol suggesting volume measurements[16].

The SIOP-9 protocol recommends simultaneous LN sampling during the nephrectomy. Based on a mathematical calculation performed by Saltzman et al, a yield of 6-10 resected LN is recommended in order to reduce the risk of false-negative LN status[44]. As we did not follow a stringent protocol specifying the number of LN to be sampled, LN sampling was dictated by the operative findings and dependant on the surgeon. Where the LN were quantified in the histology report, the number of LN ranged from one to twenty-eight per nephrectomy specimen and the number of tumour-involved LN were reported. In the cases of failure of LN submissions,

the operative report stated that no LN were found intraoperatively or that they were sampled during the procedure but not identified amongst the specimen by the pathologists. We acknowledge that this is a potential shortcoming of this paper, potentially under-reporting stage III disease as demonstrated by the difference in disease staging at presentation and the post-operative staging (14.2% vs 16.5%).

One fifth of cases presented with intravascular extensions, however after neoadjuvant chemotherapy, 31.8% (n=14) of these patients completely cleared their intravascular thrombus radiologically, and 28 (63.6%) showed a degree of tumour thrombus regression that allowed adequate surgical management either by direct renal vein (RV) exploration or caval thrombectomy during the initial nephrectomy. Twenty-seven cases (12.4%) presented with intracaval extensions which was slightly higher than reported (4-10%)[26]. No patients presented with clinical signs and symptoms suggestive of caval obstruction, and all were diagnosed by CT scan or Doppler ultrasound. Extension into the IVC was more common with right-sided tumours (66% right and 25% left) which is explained by the shorter right RV. The remainder of caval disease occurred in bilateral tumours (9%), consistent with the reported incidence[45–48]. Cavotomies were performed in attempt of thrombectomy and adjuvant chemotherapy was given if there was tumour left behind or positive margins noted on histology. Intracardiac extensions were noted in 2% (reported incidence 1-3%)[11,46,49–51] but fortunately there were no cases where there were residual thrombus extensive enough requiring interventions such as cardiopulmonary bypass.

The incidence of metastatic disease was 30.7%, which was higher than the reported incidence of metastatic disease in South Africa at 20-25%[34–36]. These were diagnosed on the staging CT at time of presentation and patients were treated with the appropriate neoadjuvant chemotherapy regimen followed by nephrectomy and continued adjuvant chemotherapy. Those that did not resolve after the adjuvant chemotherapy were assessed for either radiation therapy or surgical resection. A total of six patients underwent a surgical procedure for either diagnostic or therapeutic purposes for their metastases. Three patients underwent thoracotomies and one thoracoscopic resection for metastatic lung lesions. One patient required a laparotomy for resection of hepatic metastatic lesions. One underwent a thoracoscopic biopsy to confirm histology before neoadjuvant chemotherapy. Two of these patients subsequently demised, of which one had a large tumour (1220g) with high risk histology due to blastemal predominance and the other had relapse of disease in the lungs.

Relapse of disease was documented in 26 patients (11.9%). Surgeries that were performed as part of management included laparotomies for resection of recurrent local disease, liver biopsy to confirm histology or formal liver resections in nineteen patients. Thoracotomy or thoracoscopic lung biopsy or resections were performed in six patients. One patient was taken to theatre for a retroperitoneal LN biopsy to confirm relapse.

Patients presenting with bilateral disease received two-drug neoadjuvant chemotherapy (vincristine and actinomycin D) followed by re-imaging to assess response. If there was no response or poor response, further cycles of chemotherapy was given with the addition of adriamycin. These patients were then proceeded to surgery which included radical nephrectomy, partial nephrectomy or enucleation of the tumour. Urinary leak and infection are known as the most commonly encountered post-operative complications following nephron-sparing surgery for Wilms[52]. Three patients in the synchronous group had surgery-related morbidities which included urinary leaks and pus collections following partial nephrectomy of one kidney which all necessitated relook laparotomies.

The five-year survival was higher than the previously reported ten-year survival at our institute, demonstrating that the survival of these patients can be expected to be higher in the early years post diagnosis and management. However due to recurrences and renal failure, mortality rates increase in later years[5].

One of the well-known benefits of neoadjuvant chemotherapy in nephroblastoma is that it decreases the risk of surgery-related complications as compared to when a primary nephrectomy is performed[53,54]. Our overall surgery-related complications were 6.4% which is comparable to a study performed by another SIOP-9 group where the majority of the cases received neoadjuvant chemotherapy [55,56]. The most common immediate complication was tumour rupture followed by bleeding then urine leak. Late complications requiring intervention included bowel obstruction. Of the fourteen patients that had documented surgery-related morbidity, only one had died by the end of the study period.

On following the SIOP principles, the multidisciplinary management approach to this disease has demonstrated improvement in our survival outcomes over the years and the surgical complication rates are similar to those in high-income countries, bringing our results in line with those reported as the international standards.

5. CONCLUSION

With respect to overall outcome of disease, there are several factors that are recognised to prognosticate. These include age at time of diagnosis, stage at presentation, tumour mass, histology and response of metastatic lung lesions to chemotherapy[9]. Favourable outcomes are noted in patients that are diagnosed younger, those of lower disease stages and those with a smaller tumour mass.

We still encounter many patients presenting with advanced disease due to poor referral systems. Community centre outreach programs may improve the timing of referral of these patients and hopefully contribute to earlier presentation of disease and improved outcome.

We have shown improvement in our survival outcomes when compared to our previous study and our outcomes are equivalent to those of a high-income countries using the same SIOP-9 protocol. Early recognition and diagnosis is key in the management of nephroblastoma and we hope to further improve our management and consequently patient outcomes with time.

One of the biggest limitations of this study was incomplete data due to missing records, which was due to suboptimal record keeping. This resulted in exclusion of patients which may have affected the results. We have realised the importance of good record keeping and are working on improving it with the use of our online database. The variable level of pathologist and reporting methods in histopathology may have adversely affected how the data was interpreted.

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APPENDIX 1

	COG	SIOP
Stage I	Tumour is limited to the kidney and has been completely resected. The tumour was not ruptured or biopsied before removal. No penetration of the renal capsule or involvement of renal sinus vessels.	The tumour is limited to the kidney or surrounded with a fibrous pseudocapsule if outside the normal contours of the kidney and is completely resected. The tumour may be protruding (bulging) into the pelvic system and dipping into the ureter, but it is not infiltrating their walls. The vessels of the renal sinus are not involved. Intrarenal vessels may be involved. Presence of necrotic tumour in the renal sinus or perirenal fat does not upstage to stage II. Percutaneous cutting needle biopsy is allowed.
Stage II	Tumour extends beyond the capsule of the kidney but was completely resected with no evidence of tumour at or beyond the margins of resection. There is penetration of the renal capsule or invasion of the renal sinus vessels.	The tumour extends beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into the perirenal fat but is completely resected. Thetumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma, but it is completely resected en bloc. The tumour infiltrates adjacent organs or the vena cava but is completely resected. Percutaneous cutting needle biopsy is allowed.
Stage III	Gross or microscopic residual tumour remains post-operatively including inoperable tumour, positive surgical margins, tumour spillage surfaces, regional lymph node metastases, positive peritoneal cytology, or transected tumour thrombus. The tumour as ruptured or biopsied before removal.	Incomplete excision of the tumour, which extends beyond resection margins (gross or microscopic tumour remains post-operatively). Any abdominal lymph nodes are involved. Tumour rupture before or during surgery (irresepective of other criteria for staging). The tumour has penetrated the peritoneal surface. Tumour implants are found on the peritoneal surface. The tumour throbu present at resection, margins of vessels, or ureter are transected or removed piecemeal by the surgeon. The tumour has been surgically biopsied (wedge or open biopsy) prior to pre-operative chemotherapy or surgery.
Stage IV	Haematogenous metastases or lymph node metastases outside the abdomen (e.g lung, liver, bone, and brain).	Haematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region.
Stage V	Bilateral renal involvement is present at diagnosis.	Bilateral renal tumours at diagnosis. Each side has to be substaged according to the above classifications.

APPENDIX 2

The revised SIOP working classification of renal tumours of childhood (2001)
I – Low risk tumours ➢ Mesoblastic nephroma ➢ Cystic partially differentiated nephroblastoma ➢ Nephroblastoma – completely necrotic (following preoperative chemotherapy)
II – Intermediate risk tumours ➢ Nephroblastoma – epithelial type ➢ Nephroblastoma – stromal type ➢ Nephroblastoma – mixed type ➢ Nephroblastoma – regressive type ➢ Nephroblastoma – focal anaplasia type
III – High risk tumours ➢ Nephroblastoma – blastemal type ➢ Nephroblastoma – diffuse anaplasia type ➢ Clear cell sarcoma of the kidney ➢ Rhabdoid tumour of the kidney

APPENDIX 3

EXPERIENCE AND OUTCOMES OF NEPHROBLASTOMA IN JOHANNESBURG, 2004-2016

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Chris Hani Baragwanath Academic Hospital

INTRODUCTION:

Childhood cancer comprises of less than 1% of all malignant diseases [1]. It is the second most common cause of childhood death in the developed world but more than 80% of those affected can be cured. However in the developing world, cancer as cause of death is dropped down the list by many other causes such as nutritional and infective diseases particularly Tuberculosis and Human Immunodeficiency Virus [2]. Nephroblastoma is the most common malignant neoplasm of the urinary system in children. It comprises 5.5-7% of all childhood tumours and 97.7% of all renal primary tumours [1,3]. Seventy-eight percent of nephroblastomas are diagnosed between the ages of 1-5 years with a peak incidence between 3-4 years of age and is reported to have a female predominance [3].

Affecting 1 in 10000 children under the age of 15 years worldwide, the incidence varies depending on various ethnic groups, ranging from 6-9 per 1 million in Caucasians to 10 per 1 million in Black populations [4]. Of these patients with Nephroblastoma, 5-7% present with bilateral disease [4,5]. Most children usually present with an asymptomatic abdominal mass. Up to 25% have hypertension, and haematuria has been reported, 18.2% being gross and 24.5% microscopic. Coagulopathy, anorexia, weight-loss and fever have been reported in 10% of these children [6]. Rarely, cardiac arrhythmias may result from intra-cardiac extension of tumour thrombus, haemorrhage or rupture of tumour. Imaging used to determine location, size and extent of tumour includes abdominal ultrasound and computed tomography (CT) scan. As the most common sites of metastasis are the lungs and liver, a chest CT should be included in the workup process.

The teaching hospitals affiliated to the Department of Paediatric Surgery at University of Witwatersrand are Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). These two hospitals combined serve the population of Johannesburg but does extend beyond Pretoria and even to neighbouring countries at times. Johannesburg and surrounding areas have a population of approximately 17 million, of which 3.5 million are under 16 years of age. The Paediatric Oncology Unit manages the patients primarily and involves the surgeons as appropriate. Paediatric surgical oncology refers to a specialized area of oncology that involves the surgeons in the management and cure of cancer where possible. Two other Paediatric Surgery units in South Africa described their experiences of Nephroblastoma over 25 years and presented their outcomes [7,8]. There has previously been a description of the Johannesburg experience over a period of 6 years [9] so

we wanted to expand and analyse a longer period in order to compare our outcomes with our previous years, with the other South African units, as well as international outcomes.

STUDY OBJECTIVES:

1. To determine the total numbers of patients diagnosed with Nephroblastoma at CMJAH and CHBAH from 1st January 2004 to 31st December 2016.
2. To characterize the presentation of these patients.
3. To compare staging at presentation to the operative staging.
4. To assess how patients with metastatic disease were managed.
5. To assess how patients with IVC/intra-cardiac extensions were managed.
6. To assess how patients with bilateral disease were managed.
7. To assess operation-associated morbidity and mortality.
8. To ascertain the role of chemotherapy and radiotherapy in different stages and risk groups.
9. To ascertain the event-free and overall survival.
10. To compare the patient outcomes based on their risk stratification.

METHODS:

a) Design: Retrospective descriptive study

b) Site of study: Paediatric Oncology Unit at CMJAH and CHBAH

c) Study population: Patients from the ages of 0 to 16 years diagnosed with Nephroblastoma from 1st January 2004 to 31st December 2016.

d) Sampling:

i. Size: Based on the previous study of 63 patients in 6 years, we are looking to have approximately 130 patients.

ii. Selection: A convenience sampling method will be used.

iii. Inclusion criteria: All patients admitted to Paediatric Oncology Unit with the diagnosis of Nephroblastoma from 1st January 2004 to 31st December 2016.

iv. Exclusion criteria: Patients with incomplete data and patients referred to CMJAH / CHBAH after surgery.

e) Measuring tool: Hospital files, films/reports from Radiology and histology reports from National Health Laboratory Services.

f) **Data collection:** Each of the patients will be allocated a unique study identification number in order to maintain confidentiality. The variables on the data sheet will include date of birth, age at diagnosis, sex, ethnicity, date of first contact, date of last contact, HIV status, tumour site (right/left/bilateral/poles), caval/cardiac extension, metastasis, stage at presentation, histopathology, neoadjuvant therapy, adjuvant therapy, type of surgery done, operative diagnosis, risk stratification, disease-free survival, status (alive/dead/lost to follow up) and cause of death.

g) **Pilot study:** Not required.

h) **Sources of bias:**

   i. Patients lost to follow up may affect final outcomes – I will try contact the patients in order to obtain further information.

   ii. Incomplete data or missing records – these patients will be excluded from the study.

DATA ANALYSIS:

- All data collected on spreadsheet will be analysed using descriptive statistics.
- Categorical data will be represented in proportions and frequencies.
- Association between the variables will be assessed using chi-squared test.
- 95% confidence level will be used for the analysis of data

ETHICS:

Ethics clearance from the University of Witwatersrand Human Ethics Committee has been applied for and is pending. Permission will be obtained from the CEO of CHBAH and CMJAH for the collection of data from the respective hospitals once ethics clearance has been received. Application for NHLS data request will be made once Ethics clearance has been received. Parental consent will not be required as this will be a retrospective study.

TIMING:

I plan to start collecting and analyzing the data from November 2017, pending Ethics committee approval, and hope to complete the data collection by the December 2017 in order to start the data analysis and write up in January 2018.

	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
Literature review	✓	✓								
Preparing protocol	✓	✓	✓							
Ethics application			✓							
Protocol assessment				✓						
Collecting data				✓	✓					
Data analysis						✓	✓			
Paper write-up								✓	✓	✓

FUNDING:

None will be necessary as there will not be any costs incurred in performing the research.

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APPENDIX 4

R14/49 Dr S-H Chung

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M171049

NAME: (Principal Investigator)	Dr S-H Chung
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Paediatric Surgery Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Experience and outcomes of nephroblastoma in Johannesburg 2004-2017
DATE CONSIDERED:	27/10/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr D Harrison
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	18/12/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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Principal Investigator Signature _____ Date _____

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[1] Reisen B, Kovach SJ, Levin LS, et al. Thoracic duct-to-vein anastomosis for the management of thoracic duct outflow obstruction in newborns and infants: a case series. J Pediatr Surg. 2020;55:234-9. doi: 10.1016/j.jpedsurg.2019.10.029. Reference to a journal publication with an article number:

[2] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. Heliyon. 2018;19:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205 Reference to a book:

[3] Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000. Reference to a chapter in an edited book:

[4] Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 2009, p. 281–304. Reference to a website:

[5] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13 March 2003].

Reference to a dataset: [dataset] [6] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/ xwj98nb39r.1.

For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927–34) (see also Samples of Formatted References). Journal abbreviations source Journal names should be abbreviated according to the List of Title Word Abbreviations

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