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Bilateral Wilms' Tumour: A Ten Year Experience in Two Academic Centers in Johannesburg

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Bilateral Wilms Tumour: A Ten-Year Experience in Two Academic Centres In Johannesburg

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Declaration

I, Zubrina Joan Solomon declare that this research report is my own work. It is being submitted in fulfillment of the requirements of the degree of Master of Medicine in the Department of General Surgery at the University of the Witwatersrand, Johannesburg.

This research report is being submitted by published paper. Please note that the manuscript in presented here as the final draft in the format requested by the journal (South African Journal of child health).

It has not been previously submitted for any degree or examination at this or any other University. This report does not utilize any previous or current work produced by another individual.

Zubrina J. Solomon

____7th_____dayof__November_____2019_____in___Johannesburg_____

Dedication

To my Mother, Poppy, who encouraged me to always reach my potential in light and love(1966-2015).

To my husband and unyielding compass, Nick, who encourages and supports me every day. No one sets higher goals and holds me more grounded.

Presentations arising from this study

1. SAAPS(South African association of Paediatric surgeons and Paediatrics) congress 10- 14 September 2014(Cape Town, South Africa). Bilateral Wilms tumour: A ten year experience in two academic centers.

2. University of Witwatersrand Paediatric Surgery Research meeting 01 October 2016.

3. SIOP(Société international d'Oncologie Pediatrique) International oncology congress 19-21 October 2016(Dublin, Ireland). Bilateral Wilms tumour: A ten year experience in two academic centers.

Publications arising from this study

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List of Abbreviations and Symbols

BWT	Bilateral Wilms Disease
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Academic Hospital
NWTSG	National Wilms' Tumour Study Group
SIOP	Société international d'Oncologie Pediatrique(SIOP)
COG	Children's oncology group
IVC	Inferior vena cava
WT	Wilms tumour
FNA	Fine needle aspirate
IGr	Interqaurtile range
GFR	Glomerular filtration rate
CI	Confidence interval

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Manuscript

Abstract

Background: Nephroblastoma is the commonest genitourinary malignancy affecting 1 in 10,000 children worldwide. Five to 10% present bilaterally.
Method:Retrospective record review of nephroblastomas at Chris Hani Baragwanath and Charlotte Maxeke Academic Hospitals from 1 January 2003 to 31 December 2013.
Results: Eighteen patients (7.70%) presented with bilateral disease, they presented at a younger age than those with unilateral disease. Three patients presented with metachronous disease (tumour to contralateral kidney) at median age of 23 months, initial tumour presentation was at median of 2 months, the remaining 14 with synchronous disease at a median age of 27 months. Treatment followed aspects of the SIOP 9 protocol. Two patients died prior to surgery. Thirteen kidneys were removed in entirety. Twelve patients had nephron sparing surgery with 6 microscopically positive resection margins. Two patients with residual microscopic disease relapsed. Three kidneys demonstrated unfavourable histology. Nephroblastomatosis was identified in one kidney. Eight patients are alive and disease free and three patients are alive with disease. This cohort of patients have an overall and disease-free survival of 66.67% and 55.56%. Neither age above 2 years nor metachronous disease was associated with a poorer prognosis.
Conclusion: Bilateral nephroblastoma is a complex disease. The majority of patients presented with advanced local disease. Relapse was more commonly influenced by the presence of microscopically positive margins than metastatic disease at presentation.

CHAPTER 1 *(n)*

Introduction

Wilms Tumour (WT), the commonest genitourinary malignancy, affects 1 in 10,000 children worldwide. [1, 2] Five to ten percent of patients present with bilateral disease. [1,3] Synchronous disease is presentation with simultaneous bilateral tumours or presentation of a contralateral tumour within two months of the first. Approximately 1% of patients, initially diagnosed with unilateral nephroblastoma, will subsequently develop a lesion in the contralateral kidney, defined as metachronous. [4, 5]

Early diagnosis of Bilateral Wilms Tumour (BWT), and follow-up of contra-lateral kidneys in those with unilateral disease are key to preserving renal function. [4] The challenge in management of patients with BWT is balancing cure and preservation of renal function through nephron sparing surgical techniques.

South Africa is classified as an upper middle-income country (UMIC) [6]. Medical management and health infrastructure varies enormously across provinces. Some regions are comparable with developed countries whereas others lack infrastructure and resources, preventing early referral and diagnosis. The absence of access to supportive care, often without the option of transplant, makes the management of BWT difficult, particularly as patients present late, limiting the treatment options available.[1, 5]

Two quaternary care hospitals in Johannesburg, Charlotte Maxeke Johannesburg Academic (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH), both in the Gauteng province, serve an estimated population of 17.3 million people, 3.5 million under 16 years of age.[7] These are the only government-funded hospitals that offer paediatric surgery, renal transplantation and associated support care facilities, in the region. Patients are managed by a multidisciplinary paediatric oncology team.

Management of patients presenting with synchronous tumours is in accordance with the SIOP 9 for neo-adjuvant chemotherapy, followed by surgery as opposed to the earlier COG management which involved initial surgery followed by adjuvant chemotherapy.

An ultrasound guided percutaneous, retroperitoneal Tru-cut biopsy or FNA is performed after radiological identification by either ultrasound or computerised tomography (CT) of a renal mass. In this cohort neo-adjuvant chemotherapy was initiated with vincristine and actinomycin D. Once the neo-adjuvant protocol had been completed (4 to 8 weeks on average in the majority of patients), tumours were re-imaged by CT to assess response, if there was poor or no chemotherapeutic response a further 5 cycles with the addition of Adriamycin was added and then nephron-sparing surgery was performed. Management of patients with BWT is based on the goal of providing effective curative treatment, whilst preserving sufficient functioning renal parenchyma. [4,5] Management of metachronous disease is the same as for patients with unilateral nephroblastoma.

This study describes our experience and outcomes of patients with BWT over the period 2003 to 2013 and compares this with other institutions. [4, 5]

CHAPTER 2

Materials and methods

All children between the ages of 0 and 16 years, who presented with BWT to the Paediatric Oncology Units at both hospitals from 1 January 2003 to 31 December 2013 were included. Institutional approval was obtained from the Human Ethics Research Committee of the University of the Witwatersrand (Ethics clearance certificate No. M140629). Patient demographics, diagnosis, tumour histological subtype, neo-adjuvant treatment, surgical intervention (including timing of surgery and surgical technique), post-operative management and outcome (survival, renal function and complications) were recorded from clinical files.

Statistical analyses were performed using Statistica Version 13 (Tibco Software Inc.). The ages for patients are expressed as a function of medians and IQr. Overall and disease-free survival analyses were performed using Stata Version 14.2. Where Glomerular filtration rate (GFR) was calculated using the modified Schwartz Formula.

CHAPTER 3

Results

WT occurred in 224 patients, at a mean age of 39.5 months (range 1 to 172). Eighteen patients (7.70%) were diagnosed with BWT at a median age of 30 (range 9 to 145).

Three of the 18 patients (16.60%) presented with metachronous disease (Table 1) at a median age of 44 months (range 25 to 145). The initial tumour presentation for these 3 patients was at median age of 2 months (range 2 to 31).

One patient has, Beckwith-Wiedemann Syndrome and hemi-hypertrophy, with hypermethylation of H19DMR on chromosome 11p15. This was familial, as his mother had a unilateral WT at 3 years of age. His management involved bilateral nephron sparing surgery, 90% of the left kidney and 40% of the right kidney were preserved. Histological assessment demonstrated positive resection margins in the left nephrectomy specimen, which had an epithelial predominant (intermediate) histology. This patient was well and disease free at last follow up at 92 months post diagnosis. Another patient with metachronous disease had rhabdomyomatous transformation in the initial kidney in which a total nephrectomy was previously performed. The patient and his family refused any surgical intervention on the contralateral kidney.

The patients with synchronous disease presented at a median age of 27 months (range 9 to 60). Patient presentation characteristics, management and outcomes are illustrated in table 2.The vast majority of patients presented with stage III disease. Diagnostic presenting stage was made on CT scan imaging.

Three patients (16%) presented with discordant histology, 2 with anaplastic histology. One of the patients with anaplastic histology has died from the initial disease process and the other is alive and

free of disease with no history of relapse. Both patients that presented with stage IV disease (lung metastases) were treated with high-risk chemotherapeutic protocol and lung radiation. One patient received a total nephrectomy on one side and partial nephrectomy on the other, that showed triphasic histology. This patient was still alive and free of disease at last follow up. The other had anaplastic histology and died before a staged partial nephrectomy could be performed. None of the histology specimens taken from the entire cohort demonstrated nephroblastomatosis in isolation. One patient with synchronous BWT had teratoid histology diagnosed on bilateral open biopsies.

Fifteen operative procedures were performed (Table 3): 9 had a nephrectomy of the index kidney with partial nephrectomy of the contralateral kidney. Three patients had bilateral partial nephrectomy and 3 cases had nephrectomy only of the index kidney. Four patients presented with caval thrombus, but only 1 patient required renal vein exploration and caval thrombectomy at operation post neo-adjuvant chemotherapy. There was 1 intraoperative tumour rupture (patient with teratoid histology bilaterally).

Of all patients operated on, one died before further surgery, one refused further surgery and one kidney had no radiological or clinical evidence of disease after neo-adjuvant chemotherapy, having initially had a positive diagnosis on histology. Both patients were alive at last follow up. Of the kidneys that had nephron sparing surgery, 6 had positive microscopic margins. Two of these patients (33.30%) relapsed outside the renal bed, however with a p value of 0.7778 this relapse was not statistically significant.

One patient developed a urinoma 1 month post right partial nephrectomy for which a double J stent was inserted and removed a month later.

The Kaplan Meier Curves (Fig. 1 and Fig. 2) demonstrate an overall and event free survival of 66.67% (12/18) and 10/18 (55.56%) respectively over a 10-year period.

The six mortalities were due to cardiac failure associated with Adriamycin, 27 months after initiation (one patient), sepsis (2 patients) and metastatic disease progression (3 patients). There was a low level of recurrence of disease for patients older than 24 months. Only 1 of the 3 patients with metastatic disease at relapse had died.

Two patients developed renal failure. The GFR results were 11.6 and 9.7ml/min per 1.73m^2 respectively. This presented in the immediate post-operative period, secondary to overwhelming sepsis with subsequent multi-organ failure. Neither survived long enough to receive renal replacement therapy. The majority of patients (57%) maintained a normal GFR and 29% had mild renal dysfunction when GFR was calculated with a range of 11.6 to 128.4ml/min/1.73m^2. Of the patients with mild renal dysfunction (all had nephrectomy and partial nephrectomy) at least 50% of the renal parenchyma of the kidney that underwent partial nephrectomy was left in situ. Only 1 of these patients was on chronic antihypertensive medication post operatively, having been normotensive preoperatively.

CHAPTER 4

Discussion

In common with other studies, we found the commonest presenting symptom of BWT to be an abdominal mass.[1, 4, 5, 9] Synchronous disease accounts for 4 to 7% of all WT presenting at a younger age than unilateral disease. This is supported by the data in our series [9, 10].

The literature suggests that 35% of BWT are metachronous, and the remaining 65% synchronous. [12] Our series found a smaller percentage (17.60%) of patients with metachronous disease. One patient with genetic predisposition, hypermethylation of H19DMR on chromosome 11p15, which is seen as a prognostic factor associated with relapse [12], has remained disease free.

The published incidence of metastases is approximately 10% [7], in our series, 5 of the 18 patients (28%) developed metastatic disease. Eleven percent (two patients) presented with metastatic disease. The majority of our patients presented with advanced local disease. In a paper assessing the challenges to treatment in Sub Saharan Africa it has been noted that patients often present with more advanced disease and associated malnutrition. [13]

The typical triphasic histological structure was the commonest histological finding in our series, concordant with current literature.[14] Risk stratification for WT according to the SIOP guidelines relies on histology to stratify patients into low, intermediate and high risk.[15] This is considered with regards to treatment together with post-operative loco-regional and systemic stage. According to this risk stratification for post-operative assessment, the majority (67%) of our patients were intermediate risk patients, 33% were high risk and none of the patients had low risk. All patients were treated accordingly. In keeping with the literature, 2(11%) of histological specimens were anaplastic and this may predict a poor chemotherapeutic response.[4,5,9] Anaplasia may be focal or diffuse, with focal anaplasia being associated with a better outcome [4,9,15]Discordant histology can be present in up to 20 percent of cases.[16]

Nephrogenic rests (nephroblastomatosis) are precursor lesions of WT. [17] They are seen in up to 90% of synchronous and 94% of metachronous lesions. [18] Only one patient displayed nephrogenic rests in the initial histological specimens and has not developed a recurrence. A potential explanation for this unusual histological presentation is that the reporting is not standardised and without dedicated expert review, nephroblastomatosis may have been missed.

Nephroblastomatosis presents a diagnostic challenge as it can appear radiologically and histologically similar. [14] Close monitoring for conversion to WT in patients who have this histological finding is warranted. [5]

COG completed a prospective multi institutional study in 2015. These individuals were treated with neo-adjuvant chemotherapy for 6 to 12 weeks before nephron-sparing surgery. This protocol showed improved early outcomes and is now the practice in the COG group for BWT. [18]

The preservation of renal function is more challenging in patients presenting with advanced disease resistant to chemotherapy or in patients with metachronous WT. [4,5] Surgical decision making is critical and careful consideration should be given to whether to operate on both kidneys simultaneously , or stage the surgery. The current recommendation is to operate on the kidney least affected by the disease process.[17]

Surgical techniques are varied and innovative. [22] In Cape Town [4], techniques have moved away from definitive control of the renal hilum and toward the use of topical cooling of the kidney together with the use of diathermy or ultrasonic scalpel to perform nephron-sparing surgery. Surgeons in Kwazulu-Natal consider isolation of the renal vasculature at the hilum to be an important part of the operation.[5] Davidoff et al have described manual compression of vessels post identification before the parenchyma are oversewn with absorbable suture and the exposed renal parenchyma may be coagulated with an argon beam to further ensure haemostasis.[23]

At operation we excise the tumour utilizing monopolar diathermy. This allows excellent haemostasis and visualization when required to close the calyceal system, whilst avoiding the need for vascular control or induced hypothermia.

Regardless of the technique used, it is important to avoid traction or torsion of the arteries in order to prevent spasm, intimal damage and vascular occlusion. [23]

Complications of surgical management of BWT are minor and infrequent.

We aim to resect all gross macroscopic tumour, with the knowledge that on occasion residual microscopically positive margins may remain. We have found that this disease is adequately treated with the adjuvant chemotherapy. In our cohort 2 of the 6 kidneys that had positive microscopic margins on histology post nephron sparing surgery relapsed. Several reports have suggested that overall survival for patients with positive margins is not negatively affected and the most important factors for relapse are histology type and the presence of metastases. Bilateral nephron sparing surgery is often possible despite the large size of some tumours, and should be attempted despite the possibility of microscopically positive margins [22, 23] that said, should resection leave insufficient nephron mass and cause renal failure, renal transplantation remains an option. Few patients in our cohort came to need renal replacement.

With advancing treatment regimens the outcome of renal function in these patients is improving. [4, 8, 11, 15, 20, 21] However, with varying follow up times, no conclusions regarding long-term risks of failure into adulthood can be made. Recently a 15-year follow-up found that the long-term risk of renal failure was 15%. [22] Renal dysfunction in our series was infrequent and was mild in those patients who

developed it therefore validating the decision to forego placement of renal replacement lines in these patients in the post- operative period. Since these functions are calculated in the intermediate period, they may well worsen secondary to the effect of and nephrotoxic drugs in the long term. Many centres avoid abdominal radiation to patients who have received nephron sparing surgery because of its renal toxicity and risk of secondary malignancy. [14] Three patients who survived to surgery with IVC thrombi received post-surgical radiation therapy to the entire abdomen. From the clinical files there is no mention of whether the residual kidney was shielded during radiation. Their renal function and development of secondary malignancies, will require long-term follow-up.

Disease free and overall survivals in BWT have improved. [3,8,15,22] South African studies have reported encouraging survival rates ranging from 70-85% for BWT[4,5] at varying times of follow-up. Our survival curves demonstrate that most individuals died early in the disease process, either from advanced disease or complications of treatment. After a latent period, the remaining deaths were attributed to relapse. Our findings show a lower overall and disease-free survival of 66.67% and 55.56% respectively at the time of last follow up (follow-up period extended to 9 years).

The cohort from Hadley et. al[5] had a higher survival rate. A similar SIOP protocol to our unit is followed and they only had 2 additional patients in their cohort (n=20), thus a comparison with their group is more apt. They operated on more tumours that weighed more than > 1000g and had a higher rate of discordant histology (56%). In their paper, only 4 patients had visceral metastases at presentation: 2 to both lung and liver, 2 to lung only and 3 with rupture[5]which translates into 30% compared with 61.10% of advanced stage III disease in our entire cohort. Our longer period of follow up could have attributed to the ability to detect deaths secondary to progression of the disease occurring later than 2 years (deaths associated with adverse treatment and tumour related events).

Limitations

This is a retrospective study and comprised of a small sample size given the rarity of the disease entity. This makes a comparative study of the various surgical techniques difficult and prevented definitive associative conclusions from being made about the recurrence, long term outcomes, survival and adjuvant medical management on survival. The two patients lost to follow up have implications for the conclusions drawn here as they cannot be categorized and it is difficult to assess their contribution in this relatively small series. In addition non-standardized methods of pathological reporting, pathologist inexperience and a non-dedicated histology teams could have negatively affected the results.

Recommendations

A further prospective study regarding the management of our patients according to the current SIOP protocols would effectively provide more information regarding our improvement of the management of these patients with an opportunity to intervene more readily at specific points of management. However, for assessment of the renal function outcomes, a follow up of the current group of patients would inform us better on the long term post-operative course as the mild deterioration may either remain static or progressively worsen which cannot be predicted from the current data available and time of follow up. We are involved in a comparative study between our cohort of patients, and similar cohorts in Oxford, United Kingdom and Auckland, New Zealand and Nigeria. This large collaborative study may provide us with improved insights into the management of this complex group of patients. However, to truly provide insight into our management of this entity based on the profile of South African patients, a combined study between the three major paediatric surgical units should be performed. Radionucleotide GFR determination post operatively appears to be the way forward for appropriate renal function monitoring.

Conclusion

The majority of synchronous patients (73%) presented late with higher local stage disease. Patients that were operated rarely required renal replacement therapy or transplant (11% who developed sepsis related renal failure). Patients should still have routine long-term follow-up to assess the need for any future potential renal replacement therapy or transplant and to assess for recurrence of disease. Nephroblastomatosis, found only in one patient, was a rare finding. The presence of microscopically positive margins on histology specimens (50% of partial nephrectomy specimens) was not a significant predictor of recurrent disease. Although a 3rd of these patients (2 patients) relapsed, this did not translate into a worse overall survival. Recurrence, when located outside the renal bed, predicted poor survival. A fair overall and event free survival (66.67 and 55.56 per cent respectively) was achieved with neo-adjuvant chemotherapy and nephron-sparing surgery despite late presentation. Other tertiary level hospitals in South Africa deal with late presenting patients and have shown better survival rates at shorter periods of follow up. However, the main factor affecting outcome in our group if management is considered equal when comparison is made to other South African centers (managing patients according to the SIOP protocol) is the much higher percentage of late stage presenters with advanced local disease.

Figures and Tables

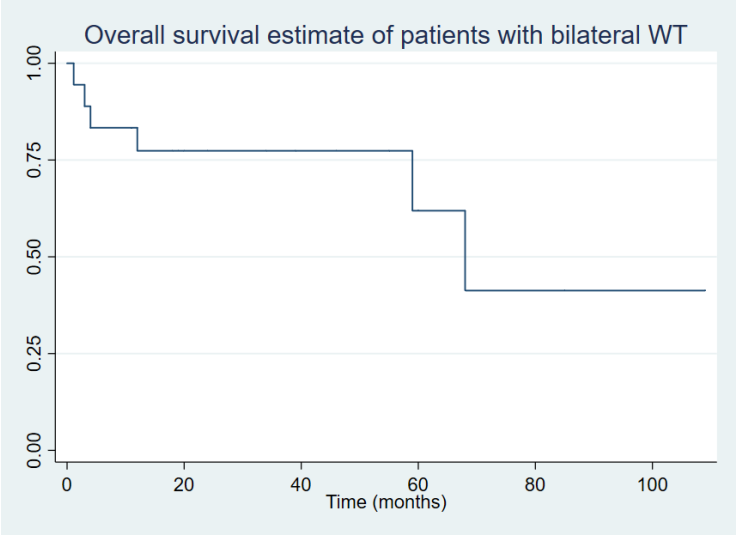


Figure 1. Overall survival of patients with Bilateral wilms tumours

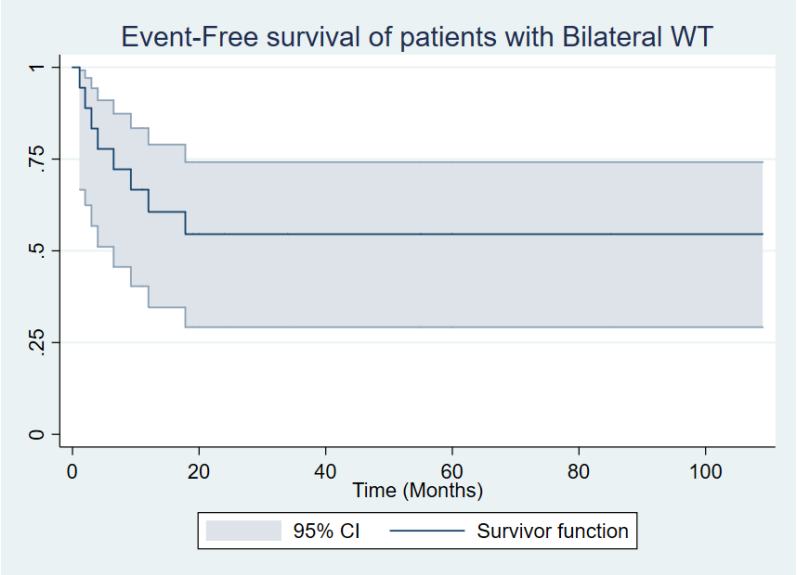


Table 2. Event free survival of patients with Bilateral Wilms tumour

Synchronous Bilateral Wilms Tumours													
Case no	**Age (m)**	**Sex**	**Presentation**	**Preop/ (Post op) local Stage: left**	**Preop/ (Post op) local Stage: Right**	**Mets/IVC extension Preop/ (intra-op)**	**Right Kidney Histology**	**Left Kidney Histology**	**Treatment**	**Positive margins**	**Relapse**	**Treatment**	**Outcome**
1	39	M	Mass	2(?)	3(3)	Lung/ (Y/N)	Triphasic	adipose tissue; adrenal	SIOP: (H.R); TN+WR; Rd	No	No	No	A
2	40	M	Mass	1(2)	1(2)	X	60% Necrosis	90% Necrosis	SIOP: VA; TN+PN	No	No	No	A
3	15	M	Mass	3(U)	3(U)	X	Unknown	Triphasic	SIOP 9: 4	No	No	No	DoD
4	33	F	Mass; HPT; CCF	3(1)	3(3)	(Y/N)	Triphasic	Biphasic	SIOP 9: 4; TN+PN	Yes	No	No	A
5	14	F	Mass	2(2)	3(3)	(Y/Y)	Triphasic	Biphasic	SIOP 9: 3; TN+WR+ Th; Rd	Yes	Lung	HR protocol	A
6	38	M	Mass; HPT; CCF	3(2)	3(3)	(Y/N)	Triphasic	Triphasic	SIOP 9: 4; TN+PN; Rd	Yes	No	No	AD
7	15	F	Mass; anaemia; low	3(U)	3(2)	X	NO Bx	Triphasic	SIOP 9: 4; TN+NIL	No	No	No	A
8	9	M	MASS; UTI	2(2)	3(2)	(Y/N)	Triphasic	Triphasic	SIOP: VA	No	Liver	Hp	DoD
9	22	M	Mass	1(2)	1(1)	X	Triphasic	Triphasic	SIOP: VA; BPN	No	Bilateral kidneys	VICE	DoD
10	27	M	Mass; Pedal oedema	2(U)	2(U)	X	Triphasic	Triphasic	SIOP:3; TN+WR	No	L kidney; Liver	Refused	AD
11	60	F	Mass	U(U)	3(3)	Lung (Y/N)	Anaplasia	Unknown	SIOP: HR; TN+NIL	No	No	No	DoD
12	34	F	Mass	3(3)	2(U)	X	Triphasic	TRI; NBL	SIOP: 4; TN+PN	No	No	No	A

13	36	F	Mass	1(2)	3(3)	X	Focal Anaplasia	Diffuse Anaplasia	SIOP: HR;TN+PN	No	No	No	A
14	16	M	Mass	3(3)	2(3)	X	No Bx	Tubular small and round cell	SIOP: VIN+ ACT D	No	No	No	DoD
15	36	M	Mass	U(2)	U(3)	Nil	Teratoid	Teratoid	SIOP:HR, Recurrent	Yes	No	No	A

Table 2. Synchronous bilateral Wilms tumour patient details

U= unknown, VICE = vincristine, ifosfamide, carboplatin, etoposide; HR: high risk protocol, TN= total nephrectomy, PN= Partial nephrectomy, BPN= bilateral partial nephrectomy, WR= wedge resection, DOD= died of disease, Rd= radiation; Th= Thrombectomy; Hp= Hepatectomy

Metachronous Bilateral Wilms Tumours													
Original Wilms tumour							**Metachronous Wilms tumour**						
Case no	**Age (m)**	**Sex**	**Clinical presentation**	**Stage**	**Histology**	**Rx**	**Interval(m)**	**Stage**	**Histology**	**Rx**	**Positive margins**	**Recurrence**	**Outcome**
1	23	M	Mass	2	Triphasic	x	2	3	Triphasic; NBL	SIOP VA; BPN	Yes	No	A
2	2	F	Mass	1	Triphasic	SIOP: 1;LN	34	3	Triphasic	SIOP4; RPN;HP	Yes	Yes	DoD
3	31	M	Mass; Haematuria	1	Triphasic	SIOP: 1;LN	113	4	Rhabdo	SIOP 4; VICE	No	No	AD

Table 1. Metachronous bilateral wilms tumour cases

VICE = vincristine, ifosfamide, carboplatin, etoposide; HR: high risk protocol, DoD= died of disease, Rhabdo=rhabdomyomatous change. NBL= nephroblastomatosis, RPN= Right partial nephrectomy, BPN= Bilateral partia nephrectomy

Surgical procedures performed		
No. Cases	**Index Kidney**	**Contralateral**
5(29.4%)	Nephrectomy	Wedge resection
3(17.6%)	Partial Nephrectomy	Partial Nephrectomy
4(23.5%)	Nephrectomy	Partial Nephrectomy
3(17.6%)	Nephrectomy	No surgery
1(5.8%)	Needle biopsy	Needle biopsy
1(5.8%)	Needle biopsy	No surgery

Table 3. Summary of Surgical procedures performed on patients with Bilateral Wilms tumour

CHAPTER 5

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Appendices

Appendix A: Approved protocol

Appendix B: Ethics clearance

Appendix C: Submission confirmation from SAJCH

Appendix D: Turn it in report

Appendix E: Protocol outcome page

Appendix A

Bilateral Wilms'tumour: a Ten Year Experience in Two Academic Centers

1. Abstract

Wilms'tumour (nephroblastoma) is the most common genitourinary malignancy affecting 1 in 10 000 children worldwide, of which 5 to 10% will have a bilateral presentation. Relatively little data exists detailing the experience of Bilateral Wilms' tumours and patient outcomes (survival and renal function) in Gauteng and we aim to describe this experience at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over the last ten years. This description may further impact on risk assessment, diagnosis, and management and improve the implementation of international protocols. This will involve a retrospective collection of patient data from clinical files and the laboratory data from all paediatric oncology patients presenting with Bilateral Wilms'Tumour over the ten year period 2003-2013.

2. Introduction

Wilms'tumour (nephroblastoma) is the most common genitourinary malignancy affecting 1 in 10 000 children worldwide.[1,2]

Amongst children presenting with Wilms'tumours, 5 to 10% will have a bilateral presentation.[3, 4] Some series have found slightly higher incidences.[1,3] However, only two South African Institutions have described their experience of Bilateral Wilms'Tumour, and made comparison to the international experience.[5,6] South Africa does not necessarily fit the description of a generally resource poor or developing country, as some areas can be compared with developed countries with regards to medical management and infrastructure. In fact at both Charlotte Maxeke Johannesburg Academic and Chris Hani Baragwanath Academic Hospitals, access to transplant and supportive care facilities are available. At the opposite end of the spectrum, where infrastructure and resource constraints prevent early referral and diagnosis, as well as access to supportive care and organ transplantation, the management of this disease is quite difficult as patients present late, limiting the treatment options available.[1, 5,7,8]

Bilateral Wilms'tumours tend to occur with either equal frequency amongst sexes or more commonly in females, with white being more affected than black individuals.[9,10,11] Across developing and developed countries the most common presenting feature of disease is an abdominal mass.[1,5,6,12,13] The effects of co-morbidities and congenital abnormalities have been investigated.[3, 12] However the effect of HIV on outcomes in South Africa is unknown.

Synchronous disease, referring to simultaneous bilateral tumours, accounts for 4 to 7 % of all Wilms'tumours and tends to present at a younger age than unilateral Wilms'tumours.[3,13,14] About 1% of Unilateral Wilms'Tumour patients will develop sequential disease which leads to an entity called metachronous disease[6,15] which tends to have a higher risk of development when nephrogenic rests are present, and in children younger than 12 months. Thus within the cohort of patients presenting with bilateral Wilms' Tumour, 35% of the tumours are metachronous, with the remaining 65% being synchronous.[16]

Histological most Bilateral Wilms'tumours (BWT) are of a favorable histological type.[12,17] Favorable histology is defined as the absence of anaplasia (poorly developed cells), which may be focal or diffuse.[10,14] Approximately 10% of synchronous BWT have unfavorable histology, which is linked to a poor chemotherapeutic response.[10,14] Up to 20% of these cases are associated with aniridia; hemi hypertrophy; genitourinary syndromes or one of the overgrowth syndromes. [9,18,19,20] These associations may not always be present.[8,12,13] The triphasic appearance, which contains a combination of Blastemal(one of the embryological structures giving rise to the kidney), epithelial and stromal (e.g. muscle, cartilage, bone) components each showing varying degrees of differentiation is the most common presentation for favorable histology.[20]

Nephrogenic rests are the precursor lesions of Wilms'Tumour.[21] They may be seen in up to 90% of synchronous lesions and 94% of metachronous disease.[15] The presence of these rests in the resected specimen should prompt regular, close follow up.[6] Many histological subtypes exist, predicting poor chemotherapeutic response, as is the case with Rhabdomyomatous change [5, 22] or more aggressive behaviour with early advanced disease in the case of Blastemal predominant tumours.[14, 23]

The staging system for Wilms'Tumour was developed by the National Wilms'Tumour Study Group (NWTSG) and consists of 5 stages. Bilateral renal involvement is automatically denoted as Stage V disease, however, each kidney is then staged individually into stage I to IV depending on extent of the disease.[4, 14] The incidence of metastases is approximately 10%.[12]

The management of BWT raises difficult management decisions where the treating physicians need to balance complete excision of the disease (which is dependent on the anatomy of the tumor), with the increased risk of late onset of renal failure.[5, 6] Preserving renal function may be even more difficult

when patients present with advanced disease which is resistant to chemotherapy or in patients presenting with metachronous Wilms'tumor. [5, 6]

The protocols for the management of unilateral Wilms'tumour have been well established, [23, 24] however a standard protocol for the management of Bilateral Wilms'disease has yet to be compiled.[4,9] Even though no clear protocol exists, much can be drawn from the protocols used for unilateral Wilms'tumors.[11, 19]

Two bodies of authority exist with regard to the management protocols of Wilms'Tumor, the National Wilms' Tumor Study Group (NWTSG) and the Société international d'Oncologie Pediatrique(SIOP), neither of whom have performed any randomized controlled trials on therapy for patients with Bilateral Wilms'Tumour.[4,23,25] In developing countries the SIOP management protocol, including a special protocol developed for developing countries, is most feasible as the majority of patients present with advanced disease, and neoadjuvant chemotherapy makes surgery safer and allows a similar outcome as compared with NWTSG.[24,26]

Management of patients with BWT is based on the obvious goal of providing effective curative treatment, whilst simultaneously preserving sufficient functioning renal parenchyma.[6,18] Early diagnosis of BWT, and dedicated follow up of contra lateral kidneys in those with unilateral disease are key.

At present, the recommended management of synchronous BWT is percutaneous biopsy, followed by neo-adjuvant chemotherapy, at the conclusion of which nephron-sparing resection is undertaken.[4,18,19] This includes various combinations of resective options, in Synchronous disease total nephrectomy of one kidney (if anatomically unable to preserve a functioning pole), with nephron sparing surgery (heminephrectomy) of the contralateral kidney.[19] If anatomically feasible, bilateral hemi-

nephrectomies can be performed, leaving functioning renal mass bilaterally. In patients presenting with metachronous disease, as only one kidney remains, an attempt at nephron sparing surgery is obviously indicated.[3] If this cannot be achieved the alternative is to render the patient anephric, thus necessitating dialysis and subsequent renal transplantation, which in itself has its own consequences relating to lifelong immunosuppression and drug toxicities.[6, 15, 16]

Wilms'Tumour is amongst one of the most chemo-sensitive paediatric cancers.[27] Neo-adjuvant chemotherapy has resulted in the reduction in size of many large tumours which without chemotherapy would not have received nephron sparing surgery and been salvaged.[19,28] Preoperative chemotherapy is well tolerated and without long term toxicity.[23] Trials on preoperative chemotherapy have found that continuing preoperative chemotherapy beyond 12 weeks is unlikely to facilitate resection and the recommendation of 12 weeks of intensive neo-adjuvant chemotherapy is supported.[23]

Bilateral nephron sparing surgery is often possible despite the large size of some tumours, and should be attempted despite the possibility of microscopically positive margins; this does not necessarily reduce survival.[17]

Renal salvage is primarily performed to reduce the incidence of post operative renal failure.[3,18] Nephron sparing surgery may either be in the form of partial nephrectomy in which the tumour is resected with a margin of normal renal parenchyma, or with enucleation where there is no attempt made by the surgeon to obtain microscopically clear margins.[18]

Innovations in chemotherapy and surgical techniques[6,16,27] have led to improvements in the implementation of nephron sparing surgery. Worldwide there has been a reduction in the use of radiation for the management of BWT with improved use of chemotherapy.[4,6, 23]

The outcome of renal function in these patients has been investigated [3, 13, 18, 19, 25] and found to be improving. The most common etiology for failure being bilateral nephrectomy(74%) for persistent or recurrent tumours.[4] With advancing treatment regimens the rates of end stage renal disease amongst Wilms'Tumour patients have declined from 16.4 percent in the first and second National Wilms'Tumour Studies to 9,9% in the third NWTS and finally 3.9% in the NWTS4.[3] However, when compared with the renal failure rate in unilateral Wilms'Tumours the incidence of end stage renal failure is significantly higher, 0,6% in unilateral tumors compared with 11.5%.[3,4] Within the group of Bilateral Wilms', the incidence of ESRD in metachronous BWT is twice as high as in the Synchronous group: 18% versus 9%.[3] However, with varying follow up times, no true conclusions regarding long term risks of renal failure into adulthood can be made. Recently in a 15 year follow up it was found that long-term risk of renal failure was 15%.[28] Again the incidence regarding the outcome of end stage renal failure in South Africa is not well known, although it is a recognized long-term outcome.[5]

Complications of management of Bilateral Wilms'Tumour are minor and infrequent; the most commonly found being adhesive bowel obstruction and hemorrhage.[1,4,3,5,6,17] Bilateral Wilms'Tumour patients also have a higher occurrence of secondary malignancies compared with Unilateral Wilms'.[3]

It has been established that survival, both disease free and overall survival has improved with advancements in the management of Bilateral Wilms'in the last few decades.[3,4,11, 13,20,25] However, unilateral Wilms'tumor patients still have a higher survival.[4,10] Studies conducted in South Africa found encouraging survival rates ranging from 70-85% overall[5,6] , although these were at varying times of follow-up.

Reasons for poor prognosis include age more than 2 years, unfavorable histology and advanced local stage[9, 11,13, 15] , although these features have not been found to be statistically significant in all series.[6,15, 28]

Clearly, the literature demonstrates that Bilateral Wilms'tumour is a curable disease and that even though no standardized management protocol exists the outcomes for patients are improving with innovations in bimodal treatment. We would like to describe what our experience has been with Bilateral Wilms'Tumours in the patient population at both Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

This study will contribute to furthering our knowledge on the features and outcomes of patients with Bilateral Wilms'Tumour at the 2 hospitals as well serve as a comparison to other series done in both South Africa and Africa. In addition our experience will be compared with international series and we may assess how well we are managing our patients with regards to international standards and protocols. This study will further have the potential to impact on risk assessment, diagnosis, management, healthcare resource allocation and policy planning. The results of this study could potentially impact on the management of patients with Bilateral Wilms'Tumour in other centers.

3. Problem statement

There is very little data, if any, available on the experience of Bilateral Wilms' tumours and patient outcomes (survival and renal function) in the greater Gauteng area. This study will further have the potential to impact on risk assessment, diagnosis, management, healthcare resource allocation and policy planning, as well as the improvement of implementation of international protocols (both in standardization and individualization of treatment).

4. Aims and Objectives

4.1.Aim

To review our experience of Bilateral Wilms'Tumours over the last ten years at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

4.2.Objective

4.2.1. To study the characteristics of patients presenting with Bilateral Wilms'Tumour.

4.2.2. To establish the percentage of Wilms' Tumour patients who present with Bilateral Wilms'Tumour.

4.2.3. To determine the survival (disease free and overall) of patients with Bilateral Wilms'Tumour.

4.2.4. To describe post management residual renal function.

4.2.5. To describe treatment protocols used in CMJAH and CHBAH's, University of the Witwatersrand.

4.2.6. To describe the surgical options utilized at the previously reference University Institutions.

5. Research Methodology

1.1. Design

The nature of the study will be retrospective.

1.2. Setting

The Paediatric Oncology and Paediatric Surgical Units at both CMJAH and CHBAH.

Study population

Records of patients diagnosed with Bilateral Wilms'Tumour at both Hospitals

Period

Records from January 2003 to December 2013

1.3. Sample size

Approximately 5-10% of 1/100 000 children worldwide diagnosed yearly. Estimated 15 to 30 cases over the 10 year period.

1.4. Inclusion and Exclusion criteria

All newly diagnosed patients (children aged 0 to 16 years) with Bilateral Wilms' Tumour at CHBAH and CMJAH over the last ten years (2003-2013). In addition patients initially diagnosed with unilateral Wilms'Tumour who later developed Wilms'Tumour in the contralateral kidney will also be included as they form part of the definition of bilateral Wilms'Tumour patients. Exclusion criteria will be children with unilateral Wilms'Tumour only (however the total numbers of unilateral tumors diagnosed will be collected to establish the percentage of patients with Bilateral Wilms'Tumour in comparison with Unilateral Wilms' tumour).

1.5.Data collection

Once ethical approval has been granted, the researcher will obtain the data from hospital files(oncology clinic files) as well as the National Health Laboratory Services (NHLS) Records of all the patients diagnosed with Bilateral Wilms'Tumour during the period 2003-2013 at CHBAH and CMJAH. Patient demographics, diagnosis, stage of cancer, histological subtype, neoadjuvant treatment, surgical intervention(including timing of surgery and surgical technique), post operative management and outcome will be reviewed(Appendix A).

6. Data analysis

The data will be recorded in an Excel spreadsheet and survival (disease free and overall) will be determined using the Kaplan Meier score. In addition comparisons between groups depending on staging, surgical intervention and co-morbidities will be compared for descriptive purposes.

7. Ethical considerations

- This protocol will be presented to the post graduate committee of the University of Witwatersrand (WITS) and Human Research Ethics committee (HREC) of WITS.
- Written permission will be requested from the research review board of Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital.
- Data will be collected from the Paediatric Oncology and Paediatric Surgery departmental records (and databases) with permission from the CEOs at both CMJAH and CHBAH.
- Data will also be collected by the researcher from the National Health Laboratory records with permission from the head of department of pathology (Professor Hale).
- No names or hospital numbers will be recorded during data collection and writing up of the reports. Anonymity and Confidentiality of the patients will be upheld. The access to, handling of data, as well as keeping of records will be solely handled by the researcher and supervisors. The data will be kept for the completion of the study only and researchers will be responsible for the safe keeping of this data.
- As this is a retrospective study involving the clinical records and laboratory data there is no need for informed consent to be obtained.
- This study is intended to be conducted at a MMed level with the possibility of publication and presentation for discussion at conferences.
- Patient research data will be accessed only by the named investigators and any hard copies of data will be kept in locked facilities.

8. Limitations

The study depends upon the availability and completeness of the clinical records (Pediatric Oncology and Paediatric Surgery departments and National Health Laboratory records for the allotted period of time (2003-2013). Since this study serves as a retrospective description of experience of Bilateral Wilms'Tumours and the number of sample patients to be included is rather small; given the incidence of the disease worldwide; predictions cannot be made regarding the effect of surgical techniques and medical management on survival.

9. Project outline

9.1.Funding

The costs involved in this study will be covered by the researcher. Projected costs involve printing and copying of the proposal (including ethics application forms) and research report. Data capturing and statistical analysis will be done electronically onto an excel sheet and thus will involve no additional costs.

9.2.Time frame

The data collection will commence in 2014 after postgraduate protocol and ethics approval have been obtained.

March-May 2014	Protocol compilation and protocol assessment(including literature review) Ethical assessment and approval Postgraduate assessment and approval
May 2014 - August 2014	Data collection and capturing
September 2014 –November 2014	Data analysis
December 2014-February 2015	Thesis write up
March 2015- May 2015	Research paper write up
June 2015	Submission of report for approval and publication

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Appendix A: Data collection sheet

Patient number: _____

Demographics

Age at diagnosis(months)	
Sex	
Race	
HIV status	**CD4 count:**
Weight	
Height	

Mode of presentation

Palpable Abdominal mass or distension	
Hypertension	
Anaemia	
Fever	
Cardiomyopathy	
Intestinal obstruction	
Other	

Co morbidities

Family History of Wilms/ Cancer	
Hemihypertrophy	
Days – Drash syndrome	
Genito- urinary abnormality(specify)	
WAGR	
Beckwith- Weidemann Syndrome	
Other	

Diagnostic modalities

	Yes/No	**Elaborate on findings**
Ultrasound		
Computed tomography		
Biopsy		
Lymph node sampling		
Echo		
Follow up Echo	**Dates**	

Other		

Computed Tomography follow up findings

Post Adjuvant chemo	**Dates**	**Findings**

Genetics

	Yes/No	**Elaborate on findings**
Genetic studies		

Stage and Histological Subtype

Stage	**I**	**II**	**III**	**IV**
Left kidney				
Right kidney				
Synchronous/ metachronous				
Age at second presentation(if metachronous)				
Nodal involvement	**Yes**	**No**	**Elaborate on findings**	

Metastatic disease	**Yes**	**No**	**Organ of metastasis**	
Histological subtype				
Left kidney				
Right kidney				
Histological grade as applicable	**Low**	**Moderate**	**High**	
Left kidney				
Right kidney				
Favourable	**Left**		**Right**	
Anaplasia (unfavourable)	**Left**		**Right**	
Diffuse/focal anaplasia	**Left**		**Right**	

Treatment

Neoadjuvant Chemo				
Chemotherapeutic regimen				
Length of neoadjuvant Rx				
Treatment interruption?	**Yes**		**No**	
Reason for interruption				

Cycle repeated	**Yes**		**No**	
How many times?				
Length of each repeat		**Drugs used**		
1				
2				
3				
Post operative Chemotherapy				
Chemotherapeutic regimen				
Length of Rx				
Treatment interruption?	**Yes**		**No**	
Stage at interruption				
Reason for interruption				
Cycle repeated	**Yes**		**No**	
How many times?				
Reason for repeat				
Length of each repeat		**Drugs used**		
1				
2				
3				
Post operative radiation	**Yes**	**No**	**Area irradiated**	

Reason for irradiation	**Positive margins**	**Positive lymphnodes**	**Metastatic disease**	**Caval thrombus**	**Other**

Surgery

Surgery			**Yes**		**No**	
Issues precluding surgery						
Timing Post Diagnosis						
Surgical procedure (elaborate)						
Bilateral nephrectomy			**Yes**		**No**	
Unilateral nephrectomy			**Left**		**Right**	
Enucleation			**Left**		**Right**	
Partial nephrectomy			**Left**		**Right**	
Explants/back table dissection/re-implantation			**Left**		**Right**	
Insitu cooling +/- preservation solution			**Left**		**Right**	
Staged resection						
Biopsy only:			**right**		**Left**	
Lymph node biopsy done?	**Yes**	**No**	**Elaborate**			
Intra-operative complications (elaborate)						
Post operative complications (elaborate)						

Surgical Margins status	**Positive**		**Negative**	
Tumour rupture				
Change of tumour stage intra-operative	**Yes**	**No**	**Pre op stage**	**Intraop/postop stage**
			Left	**Right**
Tumour size/weight	**Right**		**Left**	
Insertion of tenkoff/ permcath(elaborate)				
Follow Up Surgical intervention(elaborate)				

Other treatment considerations

Need for transfusion	**Yes**	**No**	
Timing of transfusion	**Pre op**	**Intra-op**	**Post op**
Reason for transfusion			
	Yes : elaborate		**No**
Antihypertensive medication			
TB prophylaxis			
Nutritional support			
Other			

Complications

Bowel obstruction	**Yes**		**No**	

Time to bowel obstruction development				
Excessive Bleeding	**Yes**		**No**	
Genitourinary complications	**Yes**		**No**	
Elaborate				
Other complications(elaborate)				
Action taken to treat complication				

Renal function

Pre operatively	**Creatinine**	**GFR**	**Mild Renal Dysfunction**	**moderate Renal Dysfunction**	**ESRD**
Post operatively					
@ 6/12					
@ 12/12					
@Last follow up(include date)					
Need for Antihypertensives	**Pre operatively**		**Postoperatively**		
	Time to DX		**Time to Dx**		
ESRD					
Time to ESRD from diagnosis					
Need for dialysis	**Yes**		**No**		
	Pre op		**Post op**		
Reason for dialysis					
Complications of dialysis					

Renal transplant	**Yes**		**No**	
Time to transplant from diagnosis				
Reason for transplant				
Transplant type	**RLD**		**Cadaveric**	
Complications related to transplant if any				

Outcomes

Relapse/recurrence	**Yes**		**No**	
Area of relapse				
Time from diagnosis to relapse				
Diagnostic tool used to Diagnose(elaborate)				
Time from surgery to relapse				
Management of relapse (elaborate)				
Secondary tumours (elaborate)				

Survival

Still living	**Yes**		**No**	
Disease free	**Yes**		**No**	
Date of death (age)				
Cause of death (elaborate)				
Duration of follow up				

Appendix B

R14/49 Dr Zubrina Joan Solomon

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140629

NAME: (Principal Investigator)	Dr Zubrina Joan Solomon
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Bilateral Wilms' Tumour: A Ten Year Experience in Two Academic Centres
DATE CONSIDERED:	27/06/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Jerome Loveland
APPROVED BY:	Professor P Cleaton-Jones, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/08/2014

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 Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C

Submission Confirmation for Bilateral Wilms Tumour: A Ten-Year Experience in Two Academic Centres In Johannesburg

From:SAJCH (em@editorialmanager.com)
To:zubrina.solomon@yahoo.com
Date:Tuesday, April 16, 2019, 11:17 AM GMT+2
CC: "Alta Withers" withers.alta@gmail.com, "Theshni Govender" theshni.govender@gmail.com, "Janet Poole" janet.poole@wits.ac.za, "Rosalind Wainwright" rosalind.wainwright@wits.ac.za, "Geoffrey Candy" geoffrey.candy@wits.ac.za, "Jerome Loveland" loveland@wol.co.za

Dear Dr Solomon,

Your submission entitled "Bilateral Wilms Tumour: A Ten-Year Experience in Two Academic Centres In Johannesburg" has been received by journal South African Journal of Child Health

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is https://www.editorialmanager.com/sajch/.

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to South African Journal of Child Health.

Kind regards,

South African Journal of Child Health

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Remove my information/details) Please contact the publication office if you have any questions.

SAJCH **12:28 PM (22/08/2019)**

to me

CC: "Alta Withers" withers.alta@gmail.com, "Theshni Govender" theshni.govender@gmail.com, "Janet Poole" janet.poole@wits.ac.za, "Rosalind Wainwright" rosalind.wainwright@wits.ac.za, "Geoffrey Candy" geoffrey.candy@wits.ac.za, "Jerome Loveland" loveland@wol.co.za

Ref.: SAJCH01678R1
Bilateral Wilms Tumour: A Ten-Year Experience in Two Academic Centres In Johannesburg

Dear Dr Solomon,

South African Journal of Child Health has received your revised submission.
You may check the status of your manuscript by logging onto Editorial Manager at (https://www.editorialmanager.com/sajch/).

Best wishes,
South African Journal of Child Health

Appendix D

08901071:Zubrina_Solomon.docx

by Marietha Nel

Submission date: 16-May-2019 12:12PM (UTC+0200)
Submission ID: 1131382575
File name: nments_8a27f480-1d10-4c46-846f-031b7999bd47_Zubrina_Solomon.docx (26.82K)
Word count: 3159
Character count: 16214

08901071:Zubrina_Solomon.docx

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Appendix E

University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
FACULTY OF HEALTH SCIENCES
ASSESSORS MEETING

CANDIDATE: Dr. Zubrina **Solomon**

Date of Assessor Group Meeting: 11th June 2014

School / Department / Division: **GENERAL SURGERY**

[X] Yes [ ] No Is the research question clearly identified and described?

Comments:

[X] Yes [ ] No [ ] Not entirely

Is the design of the study and methods used appropriate for the research question being asked?

Comments:

Is the study feasible within:

i. the applicant's resources? [X] Yes [ ] No

ii. the departments resources? [X] Yes [ ] No

iii. the time frame? [X] Yes [ ] No

Solomon

Do you recommend:

i. shortening / lengthening of the protocol? Please specify and explain.

ii. the appointment of a co-supervisor? [X] Yes [ ] No

Nominee/s : Prof G. Candy.

Overall recommendation regarding the protocol :

i. revision of the protocol to the Supervisor (if HOD approval is also required, please specify): [ ] Yes [ ] No
(**Candidates**: one copy, list of corrections, supervisor approval letter – submit to PG Office)

ii. revision of the protocol to the satisfaction of the Assessor Group: [ ] Yes [ ] No
(**Candidates**: six copies, list of corrections, supervisor approval letter – submit to PG Office)

iii. revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting: [ ] Yes [ ] No
(**Candidates**: six copies, list of corrections, supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator for PhD all six copies to be submitted to the PG Office)

iv. candidate goes ahead: [X] Yes [ ] No

Assessor Names and Signatures :

Prof M. Smith

Prof G. Candy

Dr. C. Penny

Dr. A. Sparaco

Assessor Group Chair

11th June 2014

Date