MANAGEMENT AND OUTCOMES OF PATIENTS TREATED FOR WILMS' TUMOR AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other university.

Signature:  **Date:** 14th November, 2023

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SUPERVISORS'APPROVAL

This thesis has been submitted for examination with our approval as university supervisors.

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DEDICATION

To my ever supportive dad, Daniel Rugwe, mum, Elizabeth Rugwe, Sisters: Ruth Rugwe and Njeri Rugwe, and brother, David Rugwe

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ABSTRACT

Background

Wilms' Tumour also known as Nephroblastoma, is a highly curable renal malignancy of childhood and is considered one of the success stories in modern medicine with excellent 5-year survival rates of greater than 90%. Management of Wilms Tumour is a paradigm of successful interdisciplinary approach and uses multimodal treatments. Various treatment protocols have been put in place to guide in the management of patients with Wilms' Tumour. The two most common protocols in use worldwide are NWTSG/COG and SIOP; NWTSG/COG recommends upfront surgery whereas SIOP recommends pre-operative chemotherapy. Nevertheless, it continues to produce dismal survival rates in the developing countries. Some of the factors contributing to these outcomes include: late presentations, abandonment of treatment, lack of medical personnel, lack of funds and lack of medical infrastructure. Over time, our health care has greatly improved. We now have better healthcare systems in terms of better imaging and diagnostics, better surgical skills, better access to healthcare and better awareness among health care workers. This study therefore aims to assess the current outcomes of patients managed for Wilms' Tumor post the improvement in the healthcare systems.

Broad Objective

This study intends to evaluate the management and outcomes of patients treated for Wilms' Tumour at the Kenyatta National Hospital.

Study design and site

This was a retrospective cross-sectional study of patients with Wilms' Tumour diagnosed and treated between 1st January 2015 to 31st December 2019 at Kenyatta National Hospital.

Materials and Methods

Files of patients managed for Wilms' tumour between 1st January 2015 to 31st December 2019 were obtained from the records department. A data abstraction tool was used to extract information. Data collected included: socio-demographic characteristics, disease stage, histology type, imaging modality used in staging of disease, treatment modality/modalities utilized in the management, treatment protocol used for treatment (NWTSG/COG versus SIOP) and the outcome at 2 years post treatment.

Data management

Data analysis was performed using STATA 11.0. Socio-demographics was analysed using medians and frequency distributions (percentages). Clinical characteristics such as stage and presenting symptoms were described using frequency distributions and were presented in form of pie- charts. Patients with an absolute indication of radiotherapy to the flank were described as a proportion of the number that actually received the radiotherapy to the total number of those who

required radiotherapy. The 2- year overall survival was estimated using Kaplan-Meier which is a non- parametric test.

Expected main outcome

The expected outcome of this study was that the outcomes of patients managed for Wilms' Tumour will have improved post the improvement of the healthcare systems in the developing nations.

LIST OF TABLES

ACRONYMS AND ABBREVIATIONS

WT	Wilms' Tumour
COG	Children Oncology Group
SIOP	International Society of Paediatric Oncology
NWSTG	National Wilms' Tumour Study Group
MTRH	Moi Teaching and Referral Hospital
KNH	Kenyatta National Hospital
ERC	Ethical Review Committee
IR	Ionizing Radiation
CT	Computed Tomography
IVC	Inferior Vena Cava
MRI	Magnetic Resonance Imaging
US	Ultrasound
CXR	Chest X-Ray
AP	Antero-Posterior
PA	Postero-Anterior
FH	Favourable Histology
UH	Unfavourable Histology
Gy-	Gray
NHIF	National Hospital Insurance Fund

DEFINITION OF TERMS

Gray (Gy) – unit used to measure the amount of absorbed ionizing radiation absorbed.

CHAPTER 1

INTRODUCTION

1.1 Background Information

Wilms' Tumor, commonly referred to as nephroblastoma, is the most prevalent primary malignancy of the kidney in children It is believed to arise from foci of persistent embryonal cells that give rise to the renal tissue known as nephrogenic rests (2). It contributes to 5% of childhood cancers globally (1). In Africa, it takes the third place in terms of prevalence of pediatric malignancies and it ranks among the top six malignancies of childhood in Kenya (2). It is a highly curable neoplasm and remains one of the most extensively studied tumors globally. The 5-year survival rate of children with WT has improved considerably from 20% in the 1960s to the current rate of approximately 90% (3). The improvement in survival rates has been achieved through concerted efforts and the use of multimodal treatment approaches. The modalities used in treatment include: surgery (nephrectomy; partial or total), chemotherapy and radiotherapy (2,4,5). It is a highly chemo and radiosensitive tumor. The utilization of one, two or all of the treatment modalities is largely dependent on the stage of the disease. Management of WT remains a paradigm of successful interdisciplinary management in an effort to maximize cure rates and minimize treatment related complications. It has been considered one of the success stories in modern medicine. The team involved in the management comprises of: pediatric surgeons, pathologists, pediatric oncologists, and radiation oncologists

Multi-disciplinary collaborative groups are engaged in the management of WT. With regards to the staging of the disease, both pathological and imaging studies are used. Pathology primarily assesses the local extent of disease whereas imaging studies are used to evaluate regional and distant extent of disease. Stage I is defined as tumor that is limited to the kidneys and is entirely excised with no distant spread of the tumor (metastases). Stage II is tumor that has spread beyond the kidney but is entirely taken out during surgery. Distant metastases are absent. Stage III is a tumor that is described by the following: tumor that is not completely excised either as gross or microscopic residual disease post-surgery, there was tumor rupture either pre-operatively or intraoperatively, there are involved lymph nodes and lastly presence of peritoneal implants with no distant metastases. Stage IV indicates presence of distant metastases (lung, bone, liver and brain). Stage V is bilateral Wilms' Tumor (6,7,8).

Various treatment protocols have been put in place to guide in the treatment of WT. However, the two most common protocols in use worldwide are: National Wilms' Tumor Study group (NWTSG/COG) and the International Society of Pediatric Oncology (SIOP). The major difference between NWTSG/COG and SIOP protocol is in the scheduling of surgery. SIOP recommends upfront pre-operative chemotherapy except in the very young infants (<6 months) whereas NWTSG/COG recommends upfront surgery before any treatment is given (5). Both are followed by postoperative chemotherapy or radiotherapy if indicated. COG/NWTSG protocol is mostly utilized in North America while SIOP

protocol is common in the European countries (5). Surgery and chemotherapy remain the standard of care for the different stages. Radiotherapy is prescribed in stage III disease; where it remains an absolute indication, presence of anaplastic cells and in special situations in patients with stage IV WT (8).

Nevertheless, the excellent improved survival rates of >90% at 5 years are notably only experienced in affluent countries (2) In medium income countries, 80% of the patients will be alive after 5 years (2,3) Unfortunately only 20-50% of the patients with WT will be alive at 5 years in the resource-limited countries (3) This dismal survival has been attributed to: late presentations, lack of finances, limited access to healthcare in terms of lack of proper health infrastructure, shortage of trained medical personnel and long distances to treatment centers and abandonment of treatment which subsequently affects outcomes (1,2,3).Late presentations is associated with a higher disease burden which will not be fully eradicated by the treatment(s) given. This will result with a limited survival and therefore poor outcomes. Lack of finances will deter patients with Wilms' Tumor from receiving treatment resulting in poor outcomes. With regards to poor health infrastructure, most developing countries have very few or no tertiary referral centers where specialized treatment is given and therefore patients with Wilms' Tumor may have to travel to neighboring countries or abroad to get treatment. Most patients lack the funds to travel and opt to succumb to their disease. This is devastating because some of these cases are potentially curable when treatment is given. Also, some developing countries lack radiotherapy machines which is one of the modalities used in the treatment of Wilms'

Tumor. This will result in poor outcomes in the end. With regards to shortage of trained medical personnel, developing countries lack sufficient pediatric surgeons and oncologists who are involved in the management of Wilms' Tumor and therefore have to wait for long periods of time to be reviewed as the cues are long resulting in disease progression and poor outcomes. Abandonment of treatment is very common mostly due to finances and this results to poor outcomes as well.

Over time, the developing counties have had better healthcare systems in terms of better imaging and diagnostics, better surgical skills, better access to healthcare and infrastructure more trained health care workers. This study intends to assess the current outcomes of patients managed for Wilms' in the developing nations (Kenya) after the advancement in healthcare.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction and Epidemiology

Most cases of WT occur before 10 years of age with a peak age of between 3 to 4 years (9). It affects boys and girls equally. The etiology is unknown. It may arise as a hereditary or sporadic tumor. WT may also arise in the setting of specific genetic disorders (9,10,11). The syndromes associated with WT are as listed.

Table 1: Genetic syndromes associated with Wilms' Tumor

Disease
Beckwith-Wiedemann Syndrome
Bloom Syndrome
Denys-Drash Syndrome
Li-Fraumeni Syndrome
Perlman Syndrome
Sotos Syndrome
Simpson-Golabi-Behemel syndrome
WAGR Syndrome

Adopted from Principles and Practice of Radiation Oncology, seventh edition

Most tumors are solitary lesions. However, it can also occur as multifocal lesions within a single kidney in 5-10% or can be bilateral in 5% (12).

2.2 Genetics, pathology and histological features

WT is genetically heterogeneous and may be multi-genetic in origin (13,14). Among the genetic changes implicated in the development of WT the most common include: chromosome 11p13(WT-1), chromosome 11q15(WT-2) and loss of heterozygosity(LOH) at 16q and 1p (14,15). Other genetic changes with variable prevalence include CTNNB1 (3p22), IGF2 (11p15), TP53 (17p13) and MYCN (2p24) (16). Wilms' Tumors develop from nephrogenic rests (NR) (18). NR are unusual resolute clusters of embryonal cells that resemble microscopic malformations of the immature kidney. They are found in 30-40% of the kidneys with WT (19). Nephrogenic cells are classified into two main types: intra lobar and peri-lobar (18).

Histologically, the classical characteristics of Wilms' Tumor is that of a triphasic pattern made up of blastemal, stromal and epithelial constituents. The percentage and level of differentiation of these constituents differ significantly and this results in countless tumor appearances. Monophasic and biphasic variants are also common (19). The triphasic appearance seldom causes a diagnostic strain to the pathologist. However, the presence of only one constituent may cause a diagnostic difficulty and other differential diagnoses should be considered including: clear cell carcinoma, renal cell carcinoma metanephric adenoma, mesoblastic nephroma and synovial sarcoma (19).

Blastermal component represents the least differentiated of the three constituents and presumed to have the highest malignant potential. It is composed of small cells that are round and stain blue (small round blue cells). They have nuclei that overlap and have brisk

mitotic activity. Various histological patterns of blasterma have been described which include: diffuse, serpentine, basaloid and nodular. However, these patterns are of no significance in terms of prognosis. Their identification is however useful in differentiating it with other small round blue cell tumors when the tumor is made up of the blastermal constituent as the only component (19). The stromal component is made up of mesenchymal cells that are densely packed and undifferentiated. The epithelial component may demonstrate an entire spectrum of diverse forms from well differentiated cells that form tubule-like structures to immature epithelial cells that form rosette-like structures (18) It is important to note that primitive, highly proliferative blastermal component responds to chemotherapy more readily whereas the more differentiated forms; stromal and epithelial constituents are usually less responsive to chemotherapy and therefore these tumors may show minimal response to chemotherapy that is given pre-operatively (18, 19).

Another histological variant includes anaplastic WT. Anaplastic WT accounts for 5-8% of all WTs (19). The criteria used in the diagnosis of anaplasia include the following: an enlarged cell, mitotic figures that are atypical and multipolar and a nucleus that has hyperchromasia. All the three features must be present (20) Anaplasia may be focal or diffuse. The previous is defined as a focus of anaplastic cells that is clearly demarcated within a primary intra-renal tumor. Diffuse anaplasia is defined as anaplasia that is not localized and extends beyond the tumor capsule (20). Anaplastic cells are resistant to chemotherapy and are indicative of poor prognosis. Presence of anaplasia (focal or

diffuse) makes the histology of the tumor an **unfavorable** one while the absence of anaplasia makes the tumor's histology **favorable.**

It is important to emphasize that the **histological classification** criteria used by the Children Oncology Group (NWTS/COG) and SIOP differ. Histological assessment of tumor responsiveness to chemotherapy (chemotherapy induced regressive changes) and cell differentiation is essential for risk-group classification by SIOP, whereas in NWTS/COG the histological classification only takes into account the presence or absence of anaplastic cells and stratifies into either **unfavorable histology** (presence of anaplasia) **favorable histology** (absence of anaplasia) (21).

Table 2: Histologic risk classifications for Wilms tumor

	International Society of Paediatric Oncology (SIOP)	**Children's Oncology Group (COG)**
Low risk	*Cystic partially differentiated nephroblastoma** Completely necrotic Wilms tumor	*Cystic partially differentiated nephroblastoma**
Intermediate risk	Epithelial, stromal, mixed, regressive types Focal anaplasia	Favorable histology Wilms tumor No evidence of anaplasia
High risk	Diffuse anaplasia Blastemal type	Diffuse anaplasia Focal anaplasia

Adopted from Principles and Practice of Radiation Oncology, seventh edition.

2.3 Clinical presentation and imaging techniques

Presenting signs and symptoms are due to the local presence of the tumor or as a result of metastases. An abdominal mass is the most frequent presentation. It is present in 80% of the cases. Other symptoms and signs that are usually present in 20-30% of the cases include: hematuria, pain in the abdomen, elevated blood pressure, anemia, fever, loss of appetite, shortness of breath, constipation and nausea (17) Production of hormonal

substances by the tumor may lead to paraneoplastic syndromes such as hypercalcemia, acquired von Willebrand disease and erythrocytosis (22)

Core needle biopsy is not routinely done to confirm diagnosis of WT. This is to prevent seeding of tumor cells along the needle tract. However, a tissue diagnosis is considered in the following scenarios: children who are above 10 years, voluminous lymphadenopathies, in children <6 months of age, when the renal parenchyma is not visible and when there are numerous calcifications in the kidney (23). Therefore, radiological studies have a significant role in the evaluation of WT (22,23). Imaging is particularly important in surgical planning, assessment of the contralateral kidney and assessment for presence of any distant metastases. The imaging modalities utilized include can be categorized into those that assess the local-regional disease and those that assess for distant metastases. For assessment of local disease, a renal ultrasound, abdominal CT or MRI may be used. In the assessment of metastatic disease, it is important to note that the most common anatomic sites of distant metastases are the lung followed by the liver and to a lesser extent to bones and brain. Therefore, a chest x-ray or a CT chest will evaluate for pulmonary metastases. Liver metastases may be evaluated using an abdominal ultrasound, CT abdomen or MRI abdomen. Imaging of the brain and bones is only done when clinically indicated.

Ultrasonography is the initial imaging technique in children with an abdominal mass that is suspicious. It does not use ionizing radiation (IR) and is non-invasive (24). US is used to evaluate whether the abdominal mass is intra or extra-renal and its relationship with the

adjacent organs. In addition, it is useful for the assessment of caval patency and for detection of presence of tumor thrombus in the IVC and evaluation of the contra-lateral kidney (23). It may also be staging information in detecting the presence of lymph node metastases, intraperitoneal implants and hepatic lesions (24) However, it is largely operator dependent and has limited field of view and therefore this may preclude complete assessment invasion of nearby structures by the tumor and therefore further imaging studies are needed for further characterization and staging.

An abdominal MRI is the complementary imaging of choice; it does not utilize IR and has the best soft tissue resolution (24). It precisely assesses for any extension of tumor into the renal vein, IVC, hepatic veins and to the right atrium and it is considered the most precise radiological modality in assessing for the presence of a renal tumor thrombus (23) However, it is laborious to conduct an MRI in children since they are unable to stay still and therefore may require sedation. A contrast enhanced abdominal CT may be carried out when an MRI is unavailable. Unfortunately, it carries the risk of exposure to IR (23,24).

Assessment of pulmonary metastases can be done using either a CT chest or CXR. CT chest is more sensitive and able to detect tiny pulmonary nodules as compared to the conventional chest radiography (24). The recommended transverse diameter of the pulmonary nodules should be at least 3mm to be regarded as metastases (24) CXR are performed in the AP or PA views.

2.4 Staging, prognostic factors and treatment

Staging of WT is dependent on imaging and surgical studies. The two most commonly used criteria for staging is based on SIOP and CO

Table 3: Staging of Wilms' Tumor

III	Viable tumor present at resection margin(s)	Residual tumor or nonhematogenous metastases confined to abdomen
	Abdominal lymph nodes contain viable or nonviable tumor	Involved abdominal lymph nodes
	Viable or nonviable thrombus present at resection margins of ureter, renal vein or inferior vena cava	Peritoneal tumor implants
	Viable or nonviable tumor thrombus in the inferior vena cava removed piecemeal by a surgeon	Tumor spillage before or during surgery
	Preoperative or intraoperative tumor rupture, if confirmed by microscopic examination (viable tumor at the surface of the specimen at the area of rupture)	Gross residual tumor in abdomen
	Wedge or open biopsy before preoperative chemotherapy or surgery	Biopsy of tumor (including fine needle biopsy) prior to removal of kidney
	Tumor implants (viable or nonviable) in the abdomen	Resection margins involved by tumor or transection of tumor during resection (i.e. piecemeal excision of tumor)
	Tumor (viable or nonviable) penetrated through the peritoneal surface	
IV	Hematogenous metastases (lung, liver, bone, brain) or lymph node metastases outside the abdominopelvic region	Hematogenous metastases or spreads beyond abdomen
V	Bilateral tumors at diagnosis; each side should be substaged according to the above criteria	Bilateral tumors at diagnosis; each side should be substaged according to the above criteria

With regards to the prognosis, the factors that are predictive of outcome include:

- Stage
- The gene expression profile
- Tumor size
- Age
- Histologic type

Survival and stage of disease is directly related, the higher the stage, the lower the survival rate. In terms of age, the overall survival of children who develop WT at a younger age (<2 years) is higher than in the older children (23) Presence of anaplasia and large size portends poor prognosis.

Treatment

Treatment of WT is multi-modal and includes: surgery, chemotherapy and radiotherapy. The use of one, two or all modalities is largely dependent on the stage of the disease. The two major protocols used globally that guide in the management are COG/NWSTG and SIOP. The major difference is in the timing of surgery, COG/NWTSG advocate for primary surgery whereas SIOP advocate for pre-operative chemotherapy (5) However, there is no major disparity in the outcomes between the two protocols (20)

Surgery

It is the standard treatment for Wilms' Tumor. The surgery performed is known as a nephrectomy. There are different types of nephrectomies which include:

1. Simple nephrectomy- the entire kidney is removed
2. Partial nephrectomy- involves removing a portion of the kidney
3. Radical nephrectomy- surgical procedure that involves removing the kidney, and the surrounding tissues such as the adrenal glands, ureter and the neighboring lymph nodes (26,27)

Complications associated with surgery (nephrectomy) include: wound infection, intra-operative hemorrhage, other visceral organ injuries and intestinal obstruction. It is important to note that, surgery is also indicated even in metastatic disease (27).

Chemotherapy

The COG guidelines recommends surgery as initial therapy. Therefore, the post-operative chemotherapy in COG/NWSTG protocol entails:

Stage I (FH/UH) and II FH- 18 weeks of Dactinomycin and Vincristine

Stage III and IV FH- 24 weeks of Dactinomycin, Vincristine and Doxorubicin

Stage II to IV UH- 24 weeks of Vincristine,Cyclophosphomide, Etoposide and Doxorubicin (24,25,26)

Pre-operative chemotherapy in this protocol is indicated in the following situations

1. Tumor extension to the inferior vena cava
2. Inoperable Wilms' Tumor; tumor extending to adjacent organs and thereby removing the kidney will require removal of the organs involved (21,22)

3. Situation of bilateral synchronous Wilms' Tumor

The SIOP protocols recommends pre-operative chemotherapy, however the regimen and number of cycles given pre-operatively are largely dependent on whether the tumor is localized or metastatic. For localized disease, four weeks of dactinomycin and vincristine are given. In metastatic disease, six weeks of dactinomycin, vincristine and etoposide are given. This is then followed by surgery in both cases. With regards to the post-operative chemotherapy in this protocol then an additional of:

Stage I FH/UH- 17 weeks of Dactinomycin and Vincristine are given

Stage II FH- 26 -28 weeks of Dactinomycin, Vincristine and Epirubicin are given

Stage III and IV FH- 26-28 weeks of Dactinomycin, Vincristine and Epirubicin are given

Stage II-IV UH-24 weeks of Vincristine, Cyclophosphomide, Etoposide and Doxorubicin (22,23,24)

Radiotherapy

Radiotherapy in Wilms' Tumor is indicated in the following situations

1. Stage III disease
2. Stage I-IV disease with unfavorable histology (focal and diffuse histology)
3. Patients with stage IV disease with pulmonary or liver metastases whose response is slow after 6 weeks of chemotherapy
4. Local recurrence

5. Presence of brain metastases

Radiotherapy to the flank is given in the following scenarios:

1. All Stage III disease with favorable histology however with no diffuse tumor spillage intra-operatively.
2. All stage I-IV disease with unfavorable histology

Radiotherapy to the entire abdomen is given in stage III disease when there is diffuse tumor spillage intra-operatively.

Radiotherapy to the entire lung or liver is given in given to patients who are slow responders to chemotherapy at 6 weeks post treatment. Radiotherapy to the brain is given in patients with brain metastases.

Table 3: Radiotherapy doses to various anatomic sites

Stage	Radiation Treatment
Stage I-II, FH	• NONE
Stage III, FH Stage I-III, focal anaplasia Stage I-III, DA, CC	• 10.8 to the flank • 19.8 if patient is ≥ 16 yr.
Stage III, DA Stage I-III, Rb	• 19.8 Gy to the flank • 10.8 Gy to the flank if patient is < 12 mo.
Stage III by virtue of tumor rupture or peritoneal mets.	• 10.5 Gy to whole abdomen if preop tumor rupture • 21 Gy to whole abdomen if diffuse peritoneal mets noted at the time of surgery.
Recurrent abdominal disease	• 12.6-18 Gy if < 12 mo. 21.6 Gy if prior dose was ≤ 10.8 Gy • *Boost of up to 9 Gy to gross residual disease after surgery
Lung metastases	• 12 Gy to whole lung 10.5 Gy if < 12 mo. • *NOTE: only treat infant if persistent mets at week 6 of induction chemotherapy
Brain metastases	• 21.6 Gy to whole brain + 10.8 Gy IMRT/stereo boost 30.6 Gy to whole brain if patient is ≥ 16 yr.
Liver metastases	• 19.8 Gy to whole liver
Bone metastases	• 25.2 Gy to the lesion + 3 cm margin • 30.6 Gy if patient is ≥ 16 yr.
Unresected lymph node metastases	• 19.8 Gy

Adopted from Principles and Practice of Radiation oncology 7th edition

The timing of radiotherapy should be not later than 9 days from the surgery date 9 (27).

Bilateral Wilms' Tumor

Also termed as stage V Wilms' Tumor. The goals of management are to preserve renal function and achieve cure rates of the tumor. Pre-operative chemotherapy is ideally indicated before surgery to facilitate renal salvage (25).

Recurrent disease

The most common frequent anatomic site for recurrent disease is usually in the lungs. The overall survival for these patients is usually 24-30% (27). Patients with relapsed disease are usually managed using high doses of chemotherapy with transplantation of stem cells of the bone marrow. Best results are reported when using a chemotherapy regimen of ifosfomide, carboplatin and etoposide (ICE) (27,28)

2.5 Theoretical review

Various studies have been undertaken in Kenya and Africa at large to estimate the overall survival of patients treated for Wilms' Tumors in these regions.

A collaborative Wilms 'Tumor Africa Project that evaluated the outcomes of these patients in eight institutes in sub-Saharan Africa (Vivian Paintsil et al 2015) estimated the two-year overall survival at 25%.

In Kenya, a retrospective study done in 2012 at MTRH by C.N. Tenge et al 2012 described a two-year overall survival rate of 47% of patients treated for WT. In terms of distribution by stage, a majority (>50%) present with late-stage disease (stage IV-V). .Another retrospective study done by P.M Mwamba et al estimated the distribution by stage of patients with WT in Kenya to be; stage I-1.5%, stage II-13.2%, stage III-36.8%, stage IV-41.2% and stage V-7.4%. A study in Malawi reported two-year survival rate of 46%, which is strikingly like what was reported in the Kenya study (10).

2.6 Statement of the problem

Previous studies done that estimate the outcomes of children with Wilms' Tumor in the developing world have shown dismal results. These outcomes have been attributed to lack of finances, late presentations, inadequate medical personnel and lack of infrastructure.

Over time, we have had better healthcare systems in terms of better imaging and diagnostics, better surgical skills, better access to healthcare and better awareness among health care workers.

This study aims to assess the outcomes post the improvement in health care systems.

2.7 Research questions

1. What is the management and outcomes of patients with Wilms' Tumor at Kenyatta National Hospital?

2.8 Objectives

Primary objective

To describe the management and outcomes of patients with Wilms' Tumor at Kenyatta National Hospital

Specific objectives

1. To determine the socio-demographics and clinical characteristics of the patients managed for Wilms' Tumor at Kenyatta National Hospital.

2. To evaluate the proportion of patients with stage III and stage I-IV with unfavorable histology who receive radiotherapy to the flank

3. Estimate the 2-year overall survival of the patients managed for Wilms' Tumor at Kenyatta National Hospital.

2.9 Justification

Wilms' Tumor presents a major source of mortality and morbidity for children in Kenya. The outcomes of these patients has been dismal. Factors attributed to these outcomes are majorly related to poor healthcare and late presentations. In support of this, local studies that have been done have demonstrated that majority of the patients present in stage III and IV. As noted, absolute indications for radiotherapy are: Stage III and IV and unfavorable histology regardless of stage. Over time, our health care has greatly improved. Therefore, this study aimed to assess the proportion of patients with stage III WT that receive radiotherapy and also evaluated whether the outcomes of patients with WT have changed with the improved healthcare and possibly come up with recommendations that may further ameliorate the same.

CHAPTER 3

METHODOLOGY

3.1 Research Design

The design adopted was an analytical retrospective cross-sectional study of medical records of Children with Wilms' tumor treated at Kenyatta National Hospital (KNH) between January 1, 2017, and December 31, 2019.

KNH was established in 1901 with a bed capacity of 1800. KNH became a State Corporation in 1987 with a Board of Management and is at the apex of the referral system in the Health Sector in Kenya. It covers an area of 45.7 hectares and within the KNH complex are College of Health Sciences (University of Nairobi), the Kenya Medical Training College; Kenya Medical Research Institute and National Laboratory Service (Ministry of Health).

KNH has 50 wards, 22 out-patient clinics, 24 theatres (16 specialized) and Accident & Emergency Department. Out of the total bed capacity of 1800, 209 beds are for the Private Wing.Because of its strategic geographical location and the health capacity of the facility it is accessible to the majority of the population in the country.

3.2 Study Population

The study participants were children with a diagnosis of Wilms' tumor aged between 0 and 16 years treated at the Kenyatta National Hospital from 1st January 2015 to 31st December 2019.

Inclusion Criteria

- All patients between ages 0-16 with Wilms; Tumor treated between January 1st 2015 to December 31st 2019

Exclusion criteria

None

3.3 Sampling frame

Total number of children managed for Wilms' Tumor in the Oncology unit from 1st January 2015 to 31st December 2019 was 51. A complete enumeration was utilized and therefore a census population was used

N= 51 children

3.4 Sampling Technique

None as the entire population of the patients treated for Wilms' Tumor between 1st January 2015 to 31st December 2019 was included.

3.5 Instruments

Data abstraction tool was used

3.6 Data collection

Files of patients diagnosed and treated for Wilms tumor were obtained from the records department. A data abstraction tool was utilized to extract information and has been attached in appendix 2. Data collected included: socio-demographic characteristics, disease stage, histology type, imaging modality used in staging of disease, treatment modality/modalities utilized, treatment protocol utilized in the management (NWTSG/COG versus SIOP) and outcome at 2 years post treatment from the medical records. Survival was defined from the last day of follow up or by obtaining information by means of a phone call to the patients' parents after obtaining an informed consent. A research assistant was engaged in the data collection process.

3.7 Ethical Considerations

The study proposal was reviewed and approved by Kenyatta National Hospital (KNH) Ethical Review Committee (ERC). The objectives of the study were explained, and permission sought to carry out the study at Kenyatta National Hospital. During data collection, I as the principal investigator emphasized on issues of confidentiality and privacy as well as restricted access to the information collected.

3.8 Data Processing and Analysis

Data collected was entered into a secure computerized database designed solely for the purpose of data collection and entry. Unique patient identifiers was used. Data cleaning and data analysis was performed using STATA 11.0. A statistician was engaged in the data processing and analysis.

For descriptive statistics, socio-demographic was analyzed using medians and frequency distributions (percentages). Clinical characteristics such as stage and presenting symptoms were described using frequency distributions and were presented in form of pie-charts. For the Patients with an absolute indication of radiotherapy to the flank (stage III and those with stage I-IV with an unfavourable histology) was analyzed as a proportion of the number of patients who actually get radiotherapy to the number that is required to get the radiotherapy.The 2-year overall survival was estimated using Kaplan- Meier method which is a non-prametric test.

3.9 Study limitation

Being a retrospective study, there was some missing information from the files. In addition, this study had a limited population size.

3.10 Research timelines

The stud was approved by the ethics committee and it was conducted over a period of six months.

3.11 Budget

The following table gives the estimated budget of the study

Item	cost in Ksh
1. Stationary	5000
2. Printing and binding	20000
3. Research assistant	35000
4. Statistician	40000
5 Publication	20000
6. Computer/laptop	50000
7. Miscellaneous	10000
8. Ethics fee	5000
TOTAL	**185000**

BUDGET JUSTIFICATION

This was a retrospective study which involved reviewing records of patients treated for Wilms' Tumor at Kenyatta National Hospital from 1st January 2015 to December 31st 2019. The patient's records were not computerized and therefore, I was required to obtain the general records books for the names and file numbers of the patients, then retrieved all the physical files from the filing section and perused through them in order extract the necessary data. I therefore required assistance from a research assistant in tracing the patients' files and in the data collection. During my study, I required a computer which assisted me in data entry. I also consulted a statistician who assisted in data processing and analysis.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 RESULTS

A total of 51 patients with Wilms' Tumor was analyzed. 51% were female and 49% were male. They ranged in age from 0.5 years to 16 years with a mean age of 4 years. The age distribution was as follows: 0.5-4; 34 patients, 5-9 years; 12 patients and above 10 years; 5 patients

Table 1: Gender distribution.

Gender	**Frequency**	Percentage %
Male	25	49
Female	26	51
Total	51	100

Figure 1: Gender distribuion

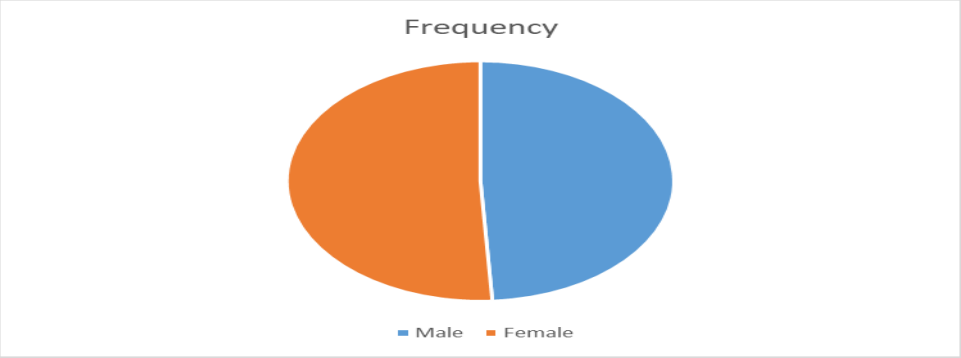
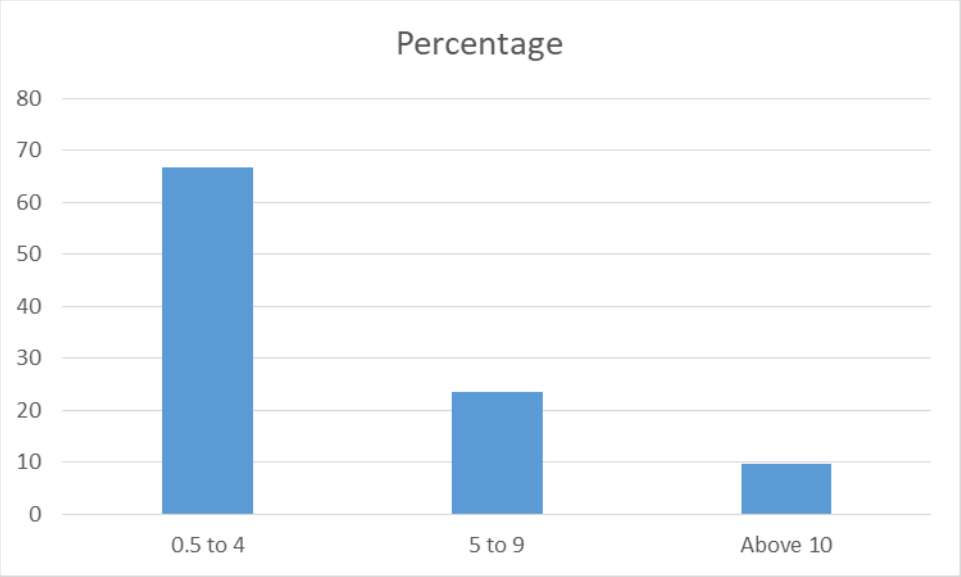


Table 2:Age distribution

Age	Frequency	Percentage %
0.5-4	34	66.67
4-9	12	23.53
Above 10	5	9.80
Total	51	100

Figure 2: Age distribution

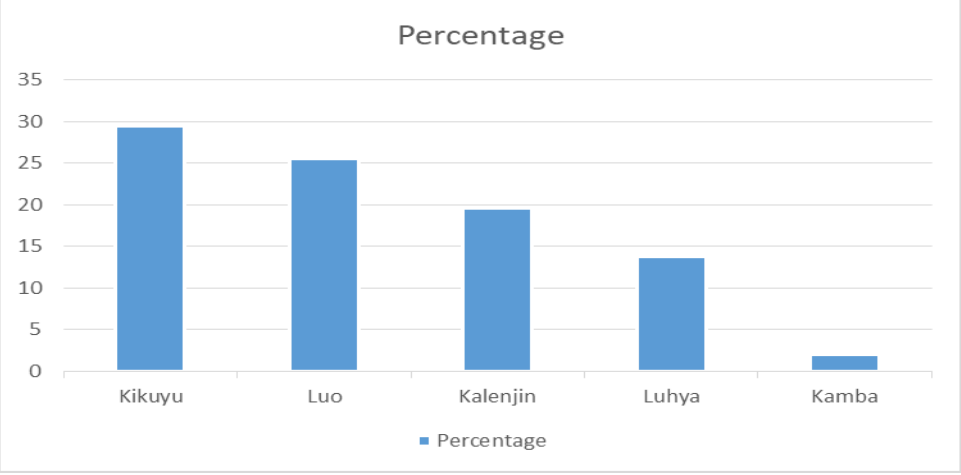


In terms of tribe distribution, Kikuyu represented 29.4 %(15), Luo 25.5% (13), Kalenjin 19.6% (10). Luhya 13.7% (7) and Kamba 2% (1).

Table 3: Ethnicity distribution

Ethnicity	**Frequency**	**Percentage%**
Kikuyu	15	29.4
Luo	13	25.5
Kalenjin	10	19.6
Luhya	7	13.7
Kamba	1	2
Total	51	100

Figure 3: Ethnicity distribution

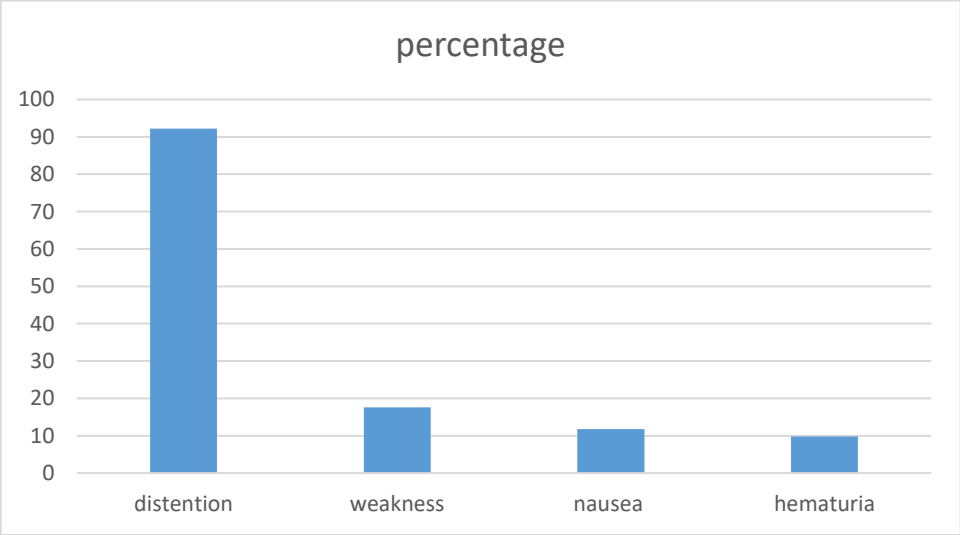


The most common presenting symptom was abdominal distention at 92.2% followed by generalized body weakness at 9%, nausea and vomiting at 6% and the least common symptom was hematuria at 5%

Table 4: Presenting symptoms

Presenting symptom	**Frequency**	**Percentage %**
Abdominal distention	47	92.16
General weakness	9	17.64
Nausea and vomiting	6	11.76
Hematuria	5	9.80

Figure 4: Presenting symptom distribution

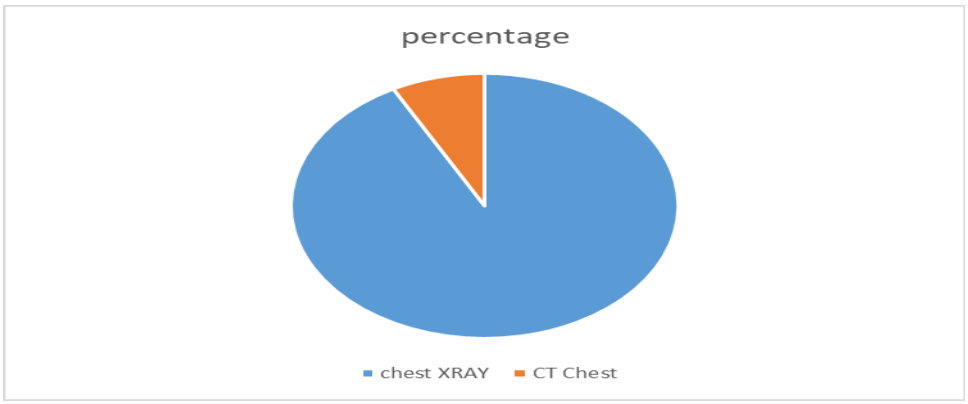


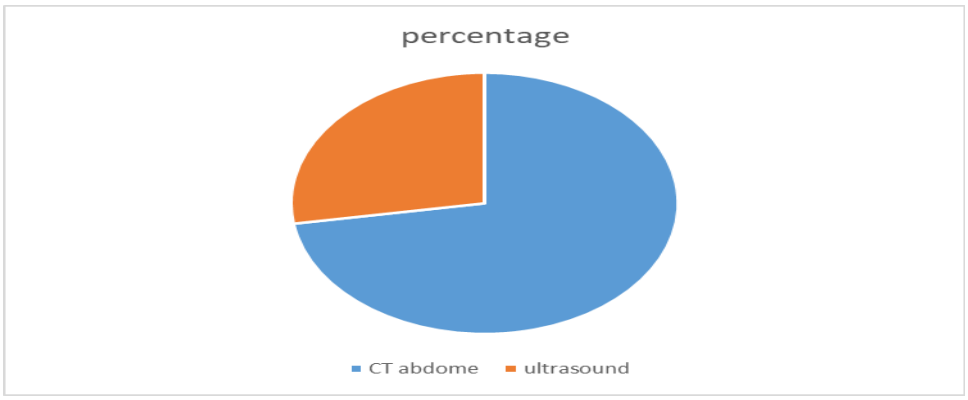
Imaging modality used in staging of disease; for the abdomen, an abdominal CT scan represented 72.5% whereas abdominal ultrasound 27.5%. For chest imaging a chest X-ray represented 92.2% whereas a CT chest was at 7.8%

Figure 5: Imaging modality

Imaging (abdomen)	**Frequency**	**Percentage%**
CT abdomen	37	72.5
Abdominal ultrasound	14	27.5
Total	51	100

Imaging (chest)	**Frequency**	**Percentage%**
Chest X-ray	47	92.2%
CT chest	4	7.8
Total	51	100


percentage
chest XRAY
CT Chest

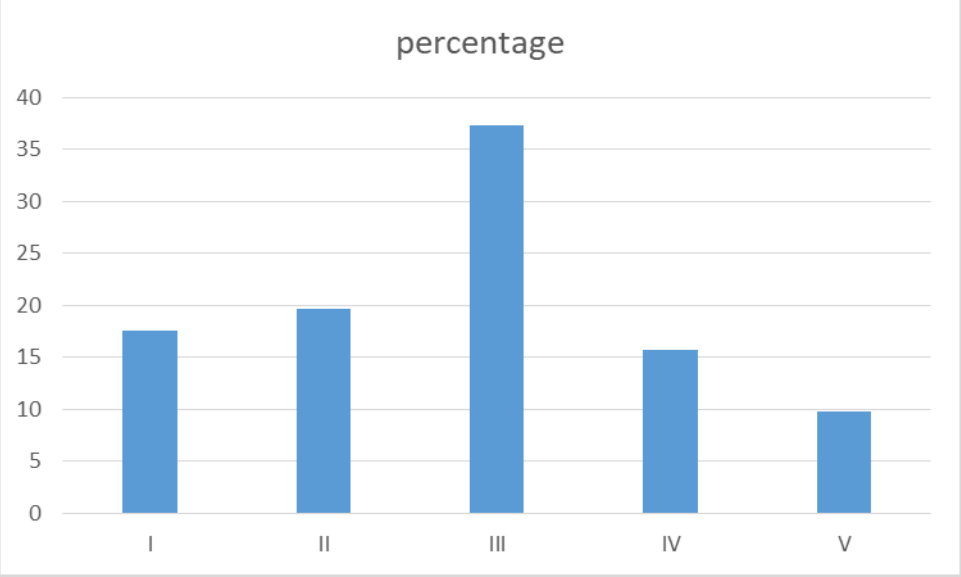

percentage
CT abdome
ultrasound

Most patients presented with stage III disease at 37.3% followed by stage II at 19.6%, stage I at 17.6%, stage IV at 15.7% and lastly stage V at 9.8%.

Table 6: Stage distribution

Stage	**Frequency**	**Percentage%**
Stage I	9	17.6
Stage II	10	19.6
Stage III	19	37.3
Stage IV	8	15.7
Stage V	5	9.8
Total	51	100

Figure 6: Stage distribution

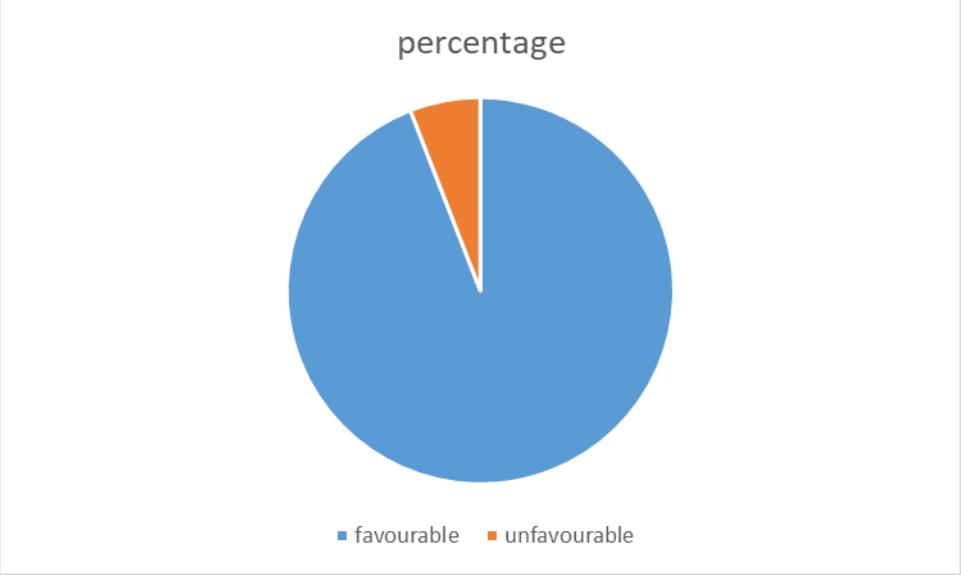


In terms of histological features, most patients had a favorable histology at 94.1% and those with unfavorable histology represented 5.9%.

Table 7: Histological features

Histology	Frequency	Percentage
Favourable	**48**	**94.1**
Unfavourable	**3**	**5.9**
Total	**51**	**100**

Figure 7: Histological features

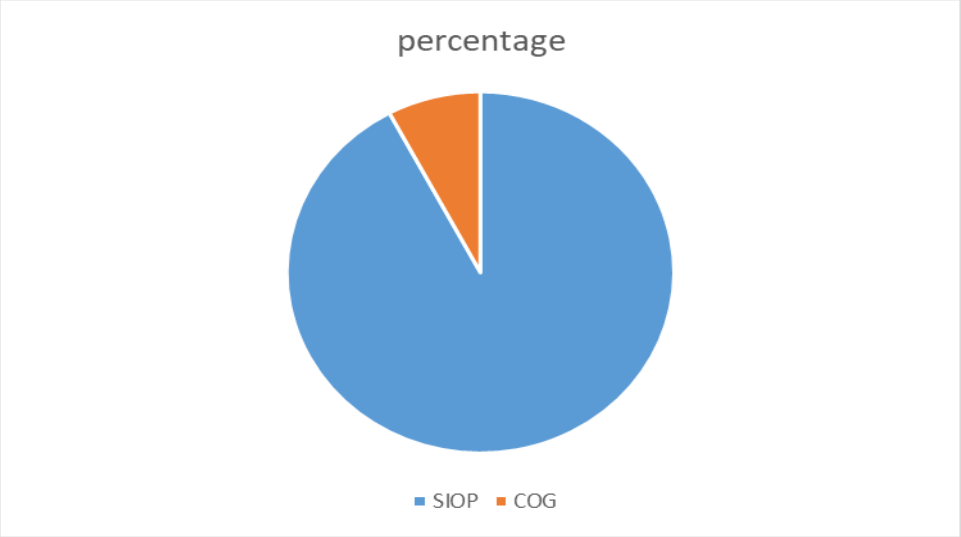


The treatment protocol that was utilized most at Kenyatta National Hospital was SIOP at 92.2% and COG at 7.8%

Table 8: Treatment protocol

Treatment protocol	Frequency	Percentage
SIOP	47	92.2
COG	4	7.8
Total	51	100

Figure 8: Treatment protocol

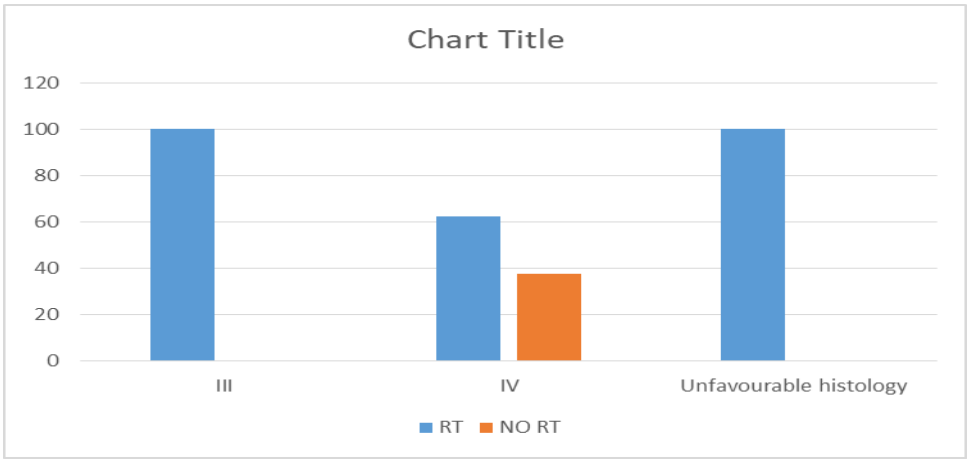


Proportion of patients with an absolute indication for radiotherapy (stage III and IV and unfavorable histology regardless of stage) that got radiotherapy stood at 90% and those that did not receive radiotherapy at 10%.

Table 9: Proportion of patients eligible for radiotherapy that got radiotherapy

Indication	**total**	**Radiotherapy**	**No radiotherapy**
Stage III	19	19	0
Stage IV	8	5	3
Unfavourable histology	3	3	0
Total	30	27	3

Figure 9: Proportion of patients eligible for radiotherapy that got radiotherapy



All patients except one were alive after a follow up of 2 years representing 99.6% survival.

4.2 DISCUSSION

Wilms' Tumor is one of the most curable childhood malignancies with excellent survival rates of greater than 90% at 5 years. Unfortunately, the survival rates for the patients with Wilms' Tumor in the developing countries is dismal and has been attributed to a myriad of factors including: late presentation, lack of finances and treatment abandonment. Major initiatives in the recent years have concentrated on educating the health care workers in the developing countries on early detection of the disease that will eventually contribute to better survival.

The results of this study show that the mean age at diagnosis is 4 years. The peak age at diagnosis is between 2 and 3 years which is comparable to other series done in Kenya and Africa. There was a slight predominance of female children in the study which also correlates to other reported series. However, other series report male predominance or equal distribution in regard to gender. The Kikuyu ethnicity were over-represented in this study as compared to other ethnicities.

The most common presenting symptom was abdominal distention which is associated with advanced disease. The imaging modality utilized in staging of disease in the abdomen was a CT abdomen over an abdominal ultrasound. A CT scan is more sensitive in detecting nodal and local disease extent as compared to an ultrasound whose evaluation is usually user dependent. With regards to imaging modality used in evaluating the chest, chest X-ray is popular as compared to a CT chest. A CT chest is superior in evaluating metastases

in the lungs as compared to a chest X-ray which will dictate whether escalation of treatment is needed if lung metastases are detected and in the end lead to better outcomes.

Majority of the patients in the study presented with stage III disease which is a late-stage disease. This is comparable to other local and regional studies that have been conducted that shows that majority of the patients present in the late stage. This could possibly be explained by circumstances that lead to both patient and health care system delays. Patient delays usually result from outdated health beliefs, poor reputation of public hospitals, preference for alternative medicine and financial difficulties. Disease stage has been documented as one of the most important prognostic factors. However, there are still huge differences when we compare outcomes in versus low income countries. Patients in the high income countries present with early stage disease which results in better outcomes.

From the study, it is evident that the management protocol which has been adopted by Kenyatta National Hospital for the management of patients with Wilms' Tumor is the SIOP protocol. Of note, both SIOP and COG have similar outcomes and none is superior to the other.

Majority of the patients who are eligible for the radiotherapy received the treatment. This is an improvement from previous studies which showed that majority did not. Some factors attributing to this are: beliefs that radiotherapy should not be given to children by some healthcare workers and also paucity of radiotherapy centers that led to long waiting queues with the abandonment of the treatment altogether.

50 of the 51 patients which predicted a probability of 99.6% chance of being alive at 2 years post treatment. This is a great improvement from a local study that was conducted between 2013 and 2016 that showed an estimated two year survival at 67%. The single death was attributed to disease related complications.

CHAPTER 5

5.1 SUMMARY, CONCLUSIONS AND RECCOMMENDATIONS

In summary, the outcome of children with Wilms' Tumor has improved over the years in the developing countries despite advanced stage at presentation. Some of the factors contributing to the improved outcomes are better imaging and diagnostics, better surgical skills, better access to healthcare and better awareness among health care workers. Enrollment to the national healthcare insurance scheme NHIF has partly closed the gap on financial constrains therefore enabling patients receive treatment.

Our survival probabilities of patients with Wilms' Tumor are approaching those of patients in high income countries.

However, late presentation is still a challenge. This study recommends that more effort be pit in educating and creating awareness among the healthcare workers about Wilms' Tumor especially with regards to the presenting symptoms of the disease. This will enable the health practitioners have a high degree of suspicion which will eventually lead to early detection of the cancer and better survival outcomes.

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APPENDICES

APPENDIX I: CONSENT FORM

Consent by parents / guardian for participation in the study.

Study title- Management and outcomes of patients treated for Wilms' Tumor at Kenyatta National Hospital

PART A.

Introduction

My name is Anne Waceke, a Master's student at the University of Nairobi, department of a diagnostic and radiation medicine. I am conducting a study on the management and outcomes of patients treated for Wilms' Tumor at Kenyatta National Hospital.

Wilms' Tumor also known as nephroblastoma is the most common primary malignancy of the kidney in children. It is believed to arise from nephrogenic rests which persistent embryonal cells that give rise to the kidney. It is a highly curable neoplasm and has been considered one of the success stories in modern medicine with a 5-year overall survival rate of >90%. Management of Wilms' Tumor is multimodal and consists of surgery, chemotherapy and radiotherapy. The use of one, two or all modalities of treatment is largely dependent on stage of the disease. Unfortunately, the outcomes of patients with Wilms' Tumor in developing countries is dismal.

Purpose of the study

The study aims assess the management and outcomes of patients managed for Wilms' Tumor at Kenyatta National Hospital and identify any modifiable factors that may be contributing to the poor outcomes and possibly come up with recommendations to improve them. The information obtained is also important for the attainment of a Masters Degree in Radiation Oncology for the principal investigator.

Study procedure

The information required from you is in the data collection chart. The study will not in any way affect your treatment or follow-up schedule.

Risks and benefits to the participant.

No risks are directly related to the study. The benefit will be participation in a study that will identify treatment gaps in any and pave way for improvement in the treatment delivery if modifiable gaps are identified.

Study costs

If you take part in this study, there will be no payment from you or to you. No added investigations will be required from you**.**

Confidentiality

The data collection chart is strictly confidential. Your name will not appear in it and your hospital number is for follow-up purposes only. If you so wish, you shall be given a copy of this consent form.

Participant information.

Your participation in this study is voluntary and failure to participate or withdrawal from the study will not affect your management in any way or stage.

Contacts and questions

The researcher conducting this study is Dr. Anne Waceke. You may ask any questions you may have now of if you do have questions later, you are encouraged to contact her through the mobile number +254712159913 or email annerugwe@gmail.com.

If you have questions or concerns regarding the study and would like to talk to someone other than the researcher(s). You are encouraged to contact the following:

The Director, KNH/University of Nairobi- ethical review committee

Telephone 726300-9 or (254-020) 2726300 Ext 44102

PART B

Participant consent form

I have understood the above information which has been fully explained to me by the investigator and I voluntarily consent to participate.

Signature

……..

FOMU YA OMBI LA RIDHAA

Kichwa cha Utafiti:Matokeo na matibabu ya wagonjwa wa Tumor ya Wilms' katika Hospitali Kuu ya Kenyatta

Utangulizi

Jina langu ni Anne Waceke Rugwe, mwanafunzi wa Chuo Kikuu cha Nairobi ambaye anafuatilia mafunzo ya ugonjwa wa saratani. Tumor ya Wilms' ni saratani ya figo ambayo inaathiri watoto sana.Ni saratani ambayo ina tiba na ambayo viwango vya kuishi miaka mitano baada ya matibabu ni zaidi ya asilimia tisini.Njia za matibabu ya ugonjwa huu inajumuisha:upasuaji,tiba ya mionzi, na chemotherapy.Hata hivyo, kiwango cha kuishi cha watoto wenye ugonjwa huu katiki nchi zinazoendelea iko chini sana.

Nia ya utafiti

Utafiti huu inalenga kutafuta matokea na matibabu ya watoto ambao wana saratani ya Tumor ya Wilms' katika Hospitali Kuu ya Kenyatta.

Hatari na faida kwa mshiriki

Hakuna hatari zinazohusiana moja kwa moja na utafiti huu.

Gharama za kusoma

Ukishiriki katika utafiti huu, hakutakuwa na malipo kutoka kwako au kwako.

Habari ya mshiriki

Ushiriki wako katika utafiti huu ni kwa hiari na kutoshiriki, kushiriki au kujiondoa kwa utafiti hautaathiri matibabu yako hata kidogo

Maswali na mawasiliano

Mtafiti anayefanya utafiti huu ni Dr Anne Waceke. Unaweza kuuliza maswali yoyote ambayo unaweza kuwa nayo kupitia nambari ya simu +254712159913 au barua ya pepe annerugwe@gmail.com.

Ikiwa una maswali au wasiwasi kuhusu utafiti huu na ungependa kuzungumza na mtu mwengine isipokuwa mtafiti, unahimizwa kuwasiliana na nambari ifuatayo

Mkurugenzi, kamati ya ukaguzi na maadili ya KNH/Chuo Kikuu cha Nairobi

Simu 726300-9 au (254-020)2726300 Ext 44102

Sahihi

……..

Tarehe……

APPENDIX 2: DATA ABSTRACTION TOOL

MANAGEMENT AND OUTCOMES OF PATIENTS TREATED FOR WILMS' TUMOR AT KENYATTA NATIONAL HOSPITAL

QUESTIONNARE NO:

Tick where appropriate

SECTION 1: GENERAL INFORMATION

1.AGE

2.GENDER

MALE FEMALE

3. RESIDENCE

4.ETHNICITY

YEAR OF DIAGNOSIS

SECTION 2: MEDICAL HISTORY

PRESENTING SYMPTOM

a) Abdominal swelling
b) Abdominal mass
c) Hematuria
d) Nausea and vomiting
e) General body weakness

Imaging modality utilized in the assessment of distant metastases

Chest

Chest X-ray CT chest

Abdomen

Abdominal ultrasound CT abdomen

HISTOLOGICAL CLASSIFICATION

Favorable Unfavorable

Pre-surgery chemotherapy (SIOP) **Primary surgery (COG/NWTSG)**

Treatment modality (tick where appropriate)

Surgery **chemotherapy** **radiotherapy**

STAGE OF THE DISEASE

a) **Stage I**
b) **Stage II**
c) **Stage III**
d) **Stage IV**
e) **Stage V**

Outcome at 2 years post treatment

Alive **Dead (year)**

Code:-

10 Day 1500/=
For Access to patients
Records
Code 4030
Bill

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Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/475

15th December 2021

Dr. Anne Waceke Rugwe
Reg. No. H58/35767/2019
Dept. of Diagnostic Imaging and Radiation Medicine
Faculty of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 15 DEC 2021 KNH/UoN-ERC P.O. Box 20723 - 00202 NAIROBI

Dear Dr. Rugwe,

RESEARCH PROPOSAL: MANAGEMENT AND OUTCOMES OF PATIENTS TREATED FOR WILMS' TUMOR AT KENYATTA NATIONAL HOSPITAL (P738/09/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P738/09/2021.** The approval period is 15th December 2021 – 14th December 2022.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely

PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Dean-Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Diagnostic Imaging and Radiation Medicine, UoN
Supervisor: Dr. P.N. Njiraini, Dept. of Diagnostic Imaging and Radiation Medicine, UoN