FACTORS INFLUENCING CLINICAL RESPONSE TO NEOADJUVANT THERAPY AMONG PATIENTS WITH WILMS TUMOR AT MUHIMBILI NATIONAL HOSPITAL.

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FACTORS INFLUENCING CLINICAL RESPONSE TO NEOADJUVANT THERAPY AMONG PATIENTS WITH WILMS TUMOR AT MUHIMBILI NATIONAL HOSPITAL.

By

Leonard Selestine

A Dissertation Submitted in Partial Fulfillment of the Requirement for the Degree of Master of Medicine in General Surgery of the

Muhimbili University of Health and Allied Sciences

October, 2024

CERTIFICATION

I, the undersigned, certify that I have thoroughly reviewed and hereby endorse the acceptance of the dissertation titled **"Factors influencing clinical response to neoadjuvant therapy among patients with Wilms tumor at Muhimbili National Hospital",** in fulfillment of the requirements for the degree of Master of Medicine in General Surgery at Muhimbili University of Health and Allied Sciences.

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Date: _____

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DR. GODFREY MCHELE

(Co - Supervisor)

Date_____

DECLARATION AND COPYRIGHT

I, **Leonard Selestine**, declare that the dissertation I have submitted is entirely my own original work, and I have not previously presented it to any other university or institution for any degree or qualification. I acknowledge that any concepts or materials sourced from external references have been appropriately cited in the dissertation. Moreover, I pledge not to submit this dissertation to any other university or institution for a similar or any other degree award.

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DEDICATION

This dissertation work is dedicated to my beloved family, particularly to my parents, for their enduring tolerance and patience during my absence from home throughout my postgraduate studies. Their constant support and understanding have been invaluable throughout this journey.

ABSTRACT

Background: The combination of neo-adjuvant therapy, surgery, and adjuvant therapy has resulted in a cure rate exceeding 90% for non-metastatic Wilms' tumors in developed nations, yet the cure rate in low-income countries is inferior. Neo-adjuvant therapy is essential for reducing tumor size, down-staging the disease, and enhancing surgical outcomes. Nonetheless, despite the completion of neo-adjuvant therapy, available evidence in our setting reveals a proportion of patients presenting with gross tumors intraoperatively. This increases the likelihood of tumor rupture and spillage, impacting the overall treatment outcomes of Wilms tumor patients.

Aim: The primary objective of this study was to determine the factors influencing clinical responses to neo-adjuvant therapy among patients with Wilms tumors at Muhimbili National Hospital (MNH) in Dar es Salaam.

Methods: A retrospective hospital-based cross-sectional analytical study was conducted at Muhimbili National Hospital in Dar es Salaam, enrolling data from children diagnosed with Wilms tumors between January 1, 2018 and December 31, 2023. Data on patients' demographics, nutritional status, site of the disease, stage of the disease, histological subtype, treatment regime, and intraoperative complications (such as tumor rupture or spillage) were collected. We analyzed the data using SPSS version 26. The prevalence ratio was used as a measure of association between dependent and independent variables, with a p-value of less than 0.05 considered statistically significant.

Results: A total of 113 Wilms tumor patients who met the inclusion criteria were recruited in the study; 69.1% (n = 70) were aged four years or younger, and the rest (38.9%) were older than 4 years (n = 43). The median age at presentation was 48 months, with an interquartile range (IQR) of 24 to 60 months and an approximate male-to-female ratio of 1:1. The right and left kidneys were affected equally and synchronous bilateral disease found in only one patient. Abdominal mass or swelling was a predominant symptom (98.2%), with 46% presenting with stages III and IV (advanced

disease) at the time of diagnosis. The majority of the patients had an intermediate-risk histology (63.7%), a low-risk 7.1%, and a high-risk 29.2%.

The overall response to neoadjuvant chemotherapy in tumor volume reduction among patients with Wilms tumors in our setting is significant *(P<0.001);* however, its effect is hindered by delayed presentation with advanced disease, an older age group, and malnutrition presenting with relatively large tumor volume at the time of diagnosis *(P<0.05)*. About 42.5% experienced a major decrease in tumor volume (> 50%), and the majority of the patients exhibited a stable disease (63.7%), (29.2%) a partial response, and 6.2% experienced a progressive disease. Tumor spillage was the predominant intraoperative complication (23%), and it was significantly associated with the older age group.

Conclusion: Late presentation with older age group, advanced disease and malnutrition at diagnosis are modifiable essential factors to enhance the neoadjuvant therapy clinical response among Wilms tumor patients at MNH. This will reduce intraoperative tumor rupture and spillage and improve the overall treatment outcomes.

Keywords; Neoadjuvant therapy, Wilms tumor,

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LIST OF ABBREVIATIONS

COG - Children's Oncology Group

CT - Computed Tomography

EFS - Event-Free Survival

FS - Free Survival

KCMC - Kilimanjaro Christian Medical Centre

LD - Longest diameter

MNH - Muhimbili National Hospital

MUHAS - Muhimbili University of Health and Allied Sciences

NWTSG - National Wilms Tumor Study Group

OS - Overall Survival

SIOP - International Society of Pediatric Oncology

UK - United Kingdom

WAGR - Wilms tumor, Aniridia, Genitourinary anomalies, Intellectual disabilities (formerly mental Retardation).

DEFINITIONS OF TERMS

Complete response: disappearance of all target lesions

Partial response: at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Progressive disease: at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable disease: Neither sufficient shrinkage to qualify for partial response (PR) nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum LD since the treatment started.

A major decrease in tumor volume: decrease of tumor volume >50% from the baseline

Some decrease in tumor volume: Decrease of tumor volume between 30% and 50% from the baseline

Increase in tumor volume: increase in tumor volume >30% from the baseline

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Wilms tumor, also known as Nephroblastoma, is an embryonal type of kidney cancer and the most common pediatric solid tumor in Africa (1). Worldwide, an estimated one case per 10,000 pediatric populations below the age of 15 is diagnosed with Wilms tumor annually, with a higher incidence in blacks compared to whites (1,2).

Among children in sub-Saharan Africa, Nephroblastoma holds the distinction of being the most prevalent intra-abdominal tumor within this age group (3). After leukemia and lymphoma, Wilms tumor ranks as the third most prevalent pediatric childhood cancer at MNH, where it is the second most frequently diagnosed childhood cancer in Tanzania (4). Most studies report that the age at diagnosis ranges from 2 to 5 years (1,2). An approximate 1:1 male-to-female ratio has been reported, with other studies showing male or female predominance (2).

The majority of patients present with abdominal mass or swelling, which may be discovered incidentally because they are typically painless but might be associated with abdominal pain, hematuria, weight loss, and hypertension (2). Due to late presentation, 53.6% of patients in low-resource settings present with advanced disease at diagnosis (2). About 10 to 15% have associated congenital anomalies such as WAGR, Beckwieth-Wiedeman syndrome, and Danish Trash syndrome (1,2,5).

A 2-year survival rate of over 95% has been achieved in developed countries for non-metastatic disease, which is significantly higher compared to low-resource settings (6). The SIOP has been widely adopted in sub-Saharan Africa due to the delayed presentation of the patients with gross tumors, and it has shown that neo-adjuvant chemotherapy has advantages in shrinking the tumor, downstaging the disease, and reducing the risk of tumor rupture, bleeding, and distant metastasis (1,2,5).

Muhimbili National Hospital is also adhering to the SIOP protocol in the management of children with Wilms tumors, where all patients diagnosed with Wilms tumors clinically are initiated on neo-adjuvant chemotherapy with vincristine and Actinomycin D for 4 weeks for localized disease followed by nephrectomy, or for those with distant metastases, vincristine, Actinomycin D, and doxorubicin for 6 to 9 weeks followed by nephrectomy. The duration of neo-adjuvant therapy is increased from the standard 4 to 6 weeks if the tumor volume reduction is considered insufficient for resectability. Thereafter, patients are stratified based on the SIOP surgical staging and histological findings as either low risk, intermediate risk, or high risk, which will determine the need for postoperative chemotherapy with or without adjuvant radiotherapy (7).

Available evidence in our setting demonstrated a certain proportion of patients with Wilms tumors still exhibit evident gross tumors during surgery, despite having completed conventional or additional cycles of neoadjuvant chemotherapy (6). This situation significantly raises the risk of complications, with tumor spillage more than 30%, and incomplete resection, which are more likely to occur under these circumstances(6). This study focused on the assessment of the factors influencing clinical response to neoadjuvant therapy among patients with Wilms tumor treated at MNH between January 2018 and December 2023.

1.2 Problem Statement.

Nephroblastoma, the most common renal tumor in children, exhibits an overall survival rate approaching 90% in developed countries. This high cure rate is attributed to the current multimodal treatment approach, which includes neoadjuvant chemotherapy, surgery, and adjuvant therapy. However, in low-resource settings, the cure rate is significantly lower, with late presentation and relatively advanced disease being among the predisposing factors (6).

Neo-adjuvant therapy is essential for reducing tumor size, down-staging the disease, and reducing intraoperative surgical complications such as tumor rupture or spillage. Previous study in our setting revealed 100% of patient presented with abdominal mass/swelling at diagnosis and a proportional of them demonstrating overtly gross tumor intraoperatively with intraoperative tumor spillage observed in 33% despite of completion of conventional or extended cycles of neoadjuvant chemotherapy (6).

Yet no study has been done to evaluate the factors influencing the clinical response to neoadjuvant therapy among Wilms tumor patients at Muhimbili National Hospital. Therefore, this research project, aimed at assessing the factors influencing clinical response to neoadjuvant therapy among Wilms tumor patients at MNH.

1.3 Conceptual Framework

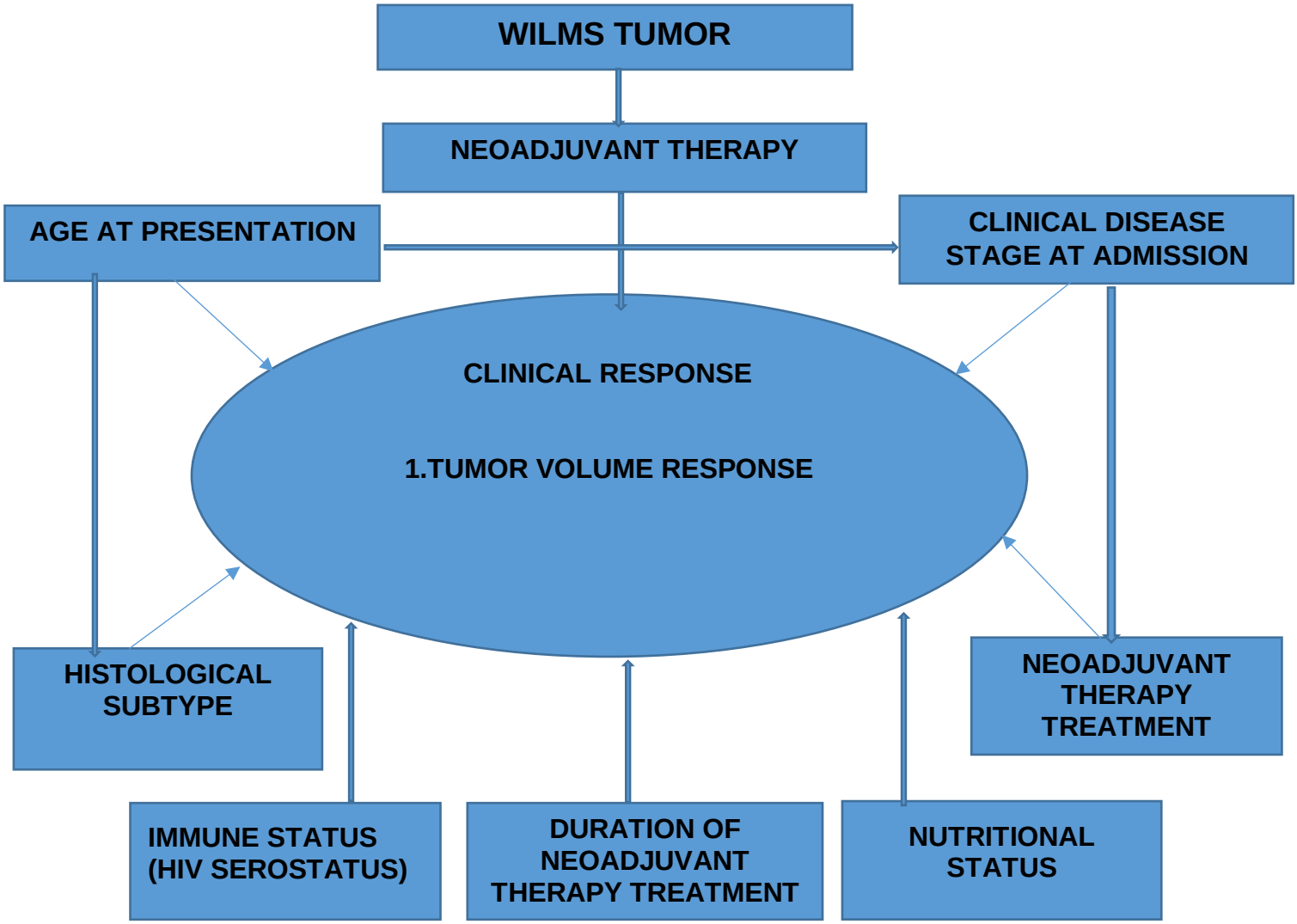


Figure 1: Conceptual Framework

All patients with Wilms tumors treated following the SIOP protocol received neoadjuvant therapy. The clinical response assessed at the end of neoadjuvant therapy is expected to be: 1. change in tumor volume (reduction in tumor volume, increase in tumor volume, no change in tumor volume);This clinical response was affected by patient demographics, i.e., age, clinicopathological characteristics (clinical disease stage at presentation, nutrition status, immune status (e.g., HIV), and histological subtype of Wilms tumor), type of neoadjuvant treatment regime, and duration of neoadjuvant therapy treatment.

1.4 Rationale of the Study.

identifying the factors influencing clinical responses to neoadjuvant therapy among patients with Wilms tumors in our setting aimed at enhancing our understanding of neoadjuvant therapy clinical response and the factors influencing it, as some factors may be modifiable, and hence improving cancer care and outcomes among Wilms tumor patients at MNH.

Furthermore, understanding these factors will help to predict the response to neoadjuvant therapy and help to avoid prolongation of the duration of neoadjuvant treatment from the standard duration 4 to 6 weeks, as tumor growth or failure of tumor volume reduction in the standard 6 week cycles may imply poor response in a certain group of patients with particular characteristics, hence no need for extending additional cycles of neoadjuvant therapy and delaying surgical management, which may predispose to tumor extension to other organs.

1.5 Research Questions

1.5.1 Primary research question

What are the factors influencing clinical response to neoadjuvant therapy among patients with Wilms tumor at Muhimbili National Hospital?

1.5.2 Secondary research questions

1. What are the clinical characteristics influencing neoadjuvant therapy clinical response among patients with Wilms tumor at MNH?
2. What are the pathological characteristics influencing neoadjuvant therapy clinical response among patients with Wilms tumor at MNH?
3. What are the neoadjuvant therapy treatment regimens influencing the clinical response of patients with Wilms tumor at MNH?

1.6 Objectives

1.6.1 Broad Objective

To assess the factors influencing clinical responses to neoadjuvant therapy among patients with Wilms tumor at Muhimbili National Hospital from January 2018 to December 2023.

1.6.2 Specific Objectives

1. To describe the clinical characteristics of patients with Wilms tumor at MNH from 1st January 2018 to 31st December 2023.
2. To describe the pathological characteristics of Wilms tumor at MNH from 1st January 2018 to 31st December 2023.
3. To describe the neoadjuvant therapy treatment regimens provided to patients with Wilms tumor at MNH from 1st January 2018 to 31st December 2023.
4. To determine the factors influencing neoadjuvant therapy clinical response among patients with Wilms tumor at MNH from 1st January 2018 to 31st December 2023.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Demographic characteristics

Wilms tumor is primarily a childhood renal malignancy affecting children below 15 years of age. It is extremely rare above this age group (8). It affects both sexes equally, with other studies revealing a male or female predominance (2,3,9,10). There is a significant variation in mean age at presentation between Western and Sub-Saharan African countries, which affects the treatment outcomes on these two sides of the world (2,9).

Age at diagnosis (less than 2 years and above 4 years) has recently been documented in two UK studies as an independent prognostic factor for treatment outcomes. Whether older age groups need more intensive treatment to improve treatment outcomes has not yet been explored. Singh P et al. 2022 in India reported the median age at diagnosis was 31 months with a range of 4–96 months, with the male gender accounting for 60.7% (2). On the contrary, a female predominance of 52.4% was found by a study done in Pakistan, with males accounting for 44.75 and the mean age at diagnosis being 38.7 plus or minus 28.66 months (11). A study done in KCMC's northern part of Tanzania revealed the mean age at presentation was 44.7 months, with 25.6% presented above 5 years of age and a male to female ratio of 1.4:1 (12).

Another study done in 2016 in the northern part of Tanzania revealed the average age at diagnosis to be higher compared to the reported literature (53 months versus 41–45 months). A slight predominant male gender was observed with a male-to-female ratio of 1.3:1, consistent with other findings in Africa, but it differs from the larger studies conducted by the NWTSG, which reported an almost equal gender distribution (13).

2.2 Clinical characteristics.

A palpable or visible abdominal mass is universally found in almost all Wilms tumor patients across all ethnic groups at presentation. In the majority of patients, the disease

is unilateral; however, approximately 10% of patients have synchronous bilateral disease (3,7,14). Bilateral Wilms tumors are typically diagnosed at a younger age compared to unilateral cases and are often associated with cancer predisposition syndromes such as WAGR syndrome, Denys-Dash syndrome, and the Beckwith-Wiedemann spectrum. The treatment of bilateral Wilms tumors is typically more complex and requires a longer duration of therapy due to these underlying conditions (15). Pritchard-Jones K et al. (2016) in the UK and Germany reported palpable abdominal mass, abdominal pain, and hematuria to be the most common clinical presentations. (9)

While Ghafoor et al. 2020 in Pakistan demonstrated 75% of patients presented with an abdominal lump (12), a study conducted at All India Medical Sciences revealed 50% of patients presented with an abdominal lump, hematuria (7.1%), vomiting (7.1%), left-sided disease (57.1%), and one patient had bilateral disease (11). Okello et al. 2019 at Mbarara regional referral hospital reported all patients presented with an abdominal mass. Weight loss and abdominal pain accounted for 40% each, fever and hematuria constituted 36% and 20% respectively (3).

A study done in KCMC revealed all patients presented with a visible or palpable abdominal mass. Other reported symptoms were vomiting, abdominal pain, and fever. One patient had associated Hypospadias and undescended testicles with none having a bilateral disease. The majority of patients had stage 4 disease 38.5% mostly with liver and pulmonary metastasis, stages 1,2, and 3 accounted for 25.6%,17.9%, and 15.4% respectively (12).

The stage at Diagnosis is an important parameter that influences the treatment response of patients diagnosed with Wilms tumor as late presentation is often associated with advanced disease stage and poor prognosis (7). Unlike pathological staging which depends on the surgery and histopathological findings, clinical staging is achieved through proper history, physical examination, and supportive radiological imaging.

The SIOP staging system is based on post-neoadjuvant chemotherapy and histological examination of the sampled tissue. Stage I tumor is limited to the kidney and is completely resected with clear margins, renal sinus vessels are not involved but the intra-renal vessels may be involved. Stage II tumors extend beyond the kidney or the renal capsules (completely resected with clear margins), Stage III tumors involve incomplete excision of the tumor beyond the resection margins, any abdominal lymph node involved, tumor rupture, or prior wedge resection biopsy of the tumor, tumor thrombi present at resection margins of vessels or ureter, Stage IV hematogenous spread to the lungs, Brain, liver, lymph node outside the abdominal cavity and Stage V is a bilateral renal tumor at diagnosis (8). Singh et al in India revealed the majority of the patient presented with stage II and III disease 78.6%, while 7.1% and 3.6% were stage I and IV respectively with metastasis to the liver and lungs each accounting for 10.7%. All patients received neoadjuvant chemotherapy, and post-operative staging was 17.9%,46.4%,21.4%,10.7%, and 3.6% for stages I, II, III, IV, and V respectively (2). Similar findings were seen in Nigeria in a study done by S.Wabada where the majority of patients presented with stage III disease(36.4%), 29.5% had stage IV disease, and stage I, II, and V accounted for 11.4%,20.5%, and 2.3% respectively (5).

2.3 Pathological characteristics of Wilms tumor

The SIOP classifies the Histological subtype of Wilms tumor as Low risk (completely necrotic Nephroblastoma or cystic partially differentiated Nephroblastoma), Intermediate risk (Nephroblastoma-epithelial type, stromal type, mixed type, regressive and focal anaplasia),and High risk (Nephroblastoma – Blastemal type, Diffuse anaplasia) (11,16). The classical histological findings in Wilms tumor is the triphasic pattern which includes epithelial, stromal, and blastemal components however neoadjuvant therapy affects this pattern by reducing or enhancing certain elements(17). About 90% of Wilms tumors demonstrate favorable histology which confers a good prognosis. A study done in Moshi Tanzania revealed 89.7% of patients had favorable

histology (blastemal, epithelial, and stromal tissues) and the rest had unfavorable histology (12). Various research has reported similar results (2,18,19).

Ghafoor et al. 2020 in Pakistan demonstrated that the predominant histological subtype was mixed type 41.2% followed by anaplastic 20% and regressive type 12.9%(11). Histopathological evaluation of 51 patients in Malawi revealed 20% had high-risk tumor subtypes and the majority of the patients had intermediate-risk subtypes 71%, (10 regressive,11 stromal,7 epithelial,4 mixed and 4 unspecified) (7).

2.4 Neoadjuvant treatment regime

The development of the structured standardized protocol in the treatment of WT by the SIOP and NWTSG/COG has remarkably improved the prognosis and survival of WT patients with a cure rate of more than 90% for non-metastatic disease in developed countries unlike in low-income countries (3,4).

The COG advocated for upfront nephrectomy followed by postoperative chemotherapy and radiotherapy for certain cases, whereas the SIOP, which is widely used in most African countries, recommends neoadjuvant therapy followed by nephrectomy and postoperative chemotherapy with or without radiation therapy depending on the surgical staging and SIOP risk stratification (20).

Neoadjuvant Chemotherapy in our setting consisted of 4weeks of treatment with two drugs Vincristine (weeks 1,2,3,4) and Actinomycin D (weeks 1,3) for localized disease and 6 weeks of three drug regimens for metastatic disease with Vincristine weekly and Actinomycin D (week 1,3,5) and Doxorubicin (week 1,5). If after 6 weeks still there is a gross tumor, the duration is prolonged to 9 to 10 weeks before Nephrectomy (21). Israel et al in Malawi observed that a significant decrease in tumor size was noted for those who had three-drug regimens where a major decrease in tumor size was observed in 69% of patients and none of the patients had no change in tumor size or growth of tumor at the end of neoadjuvant chemotherapy (7).It is not clear whether prolonging the length of neoadjuvant chemotherapy has an impact on tumor volume reduction in

all patients with Wilms tumor. This research will assess the impact of the neoadjuvant therapy regime and the length of therapy on tumor volume reduction at MNH.

2.5 Factors influencing neoadjuvant therapy clinical responses.

A change in tumor volume measured by radiological imaging has traditionally been considered a response to neoadjuvant therapy. Response to Chemotherapy is also a prognostic factor in Wilms tumor treatment (22). Multiple studies have demonstrated that a range of factors, encompassing clinical, pathological, and genetic factors, can impact the observed outcomes in this regard. The clinical responses to neoadjuvant therapy have been evaluated in different studies specifically in terms of tumor volume reduction, downstaging of the disease, and reduction in intraoperative tumor rupture and spillage (2,9,11,13,23).

Based on our specific circumstances, available data reported a proportion of patient still present with significant tumors during surgery. This situation poses a higher risk of complications such as tumor rupture, spillage, and incomplete resection. Furthermore, it is noteworthy that there is a lack of publicly available information regarding the clinical responses of patients with Wilms tumor to neoadjuvant therapy and the factors that may influence these responses in our particular setting. Israel et al 2012 in Malawi demonstrated that 53% of patients who received neoadjuvant chemotherapy had a major decrease in tumor size (more than 50% decrease) and 39% had some decrease (less than 50%),5% had no change in tumor size and 3% had tumor growth at the end of preoperative chemotherapy. Of those who had the two drug regimens 47% had a major decrease in tumor size and 42%, 7%, and 4% had some decrease, no change in tumor size and growth of tumor respectively. A significant decrease in tumor size was noted for those who had three-drug regimens where a major decrease in tumor size was observed in 69% of patients and none of the patients had no change in tumor size or growth of tumor at the end of neoadjuvant chemotherapy (6).

The results of a study done at the All India Institute of Medical Sciences, upon evaluation, using a CT scan (RECIST 1.1) post-neoadjuvant therapy, majority of patients had stable disease 64.3%, 35.7% showed partial response and the none of the patients had a complete response. There was statistically significant downstaging and reduction in tumor volume in 71.4% (tumor volume decrease >50%) after neoadjuvant chemotherapy, and 28.6% had less than 50% tumor volume reduction (2).

Tasken et al 2019 demonstrated variability in tumor volume reduction after neoadjuvant therapy among patients with Wilms tumors in Pakistan. The median tumor volume at diagnosis was 583ml (IQR 368-903) and the reduction was 68%. However, three patients had increased tumor volume greater than 10% during the neoadjuvant therapy treatment of which two had anaplastic histology (tumor volume 26 and 26.5%) and one had an increase in stromal predominance (tumor volume 34%). Tumor volume reduction was significantly correlated with increased blastemal components with higher stromal and epithelial components associated with less reduction in tumor volume(13).

Various studies demonstrated patients with Nephroblastoma with blastemal component shrunk significantly(13). Middleton et al 2020 in their study on radiological and histological findings in Nephroblastoma found no significant correlation between change in tumor volume and histopathological risk stratification (24). The increased blastemal component has also been linked to poor chemotherapy response compared to epithelial and stromal components (25).

Research findings indicate that a significant proportion of children with cancer in developing nations, ranging from 45% to 77%, present with malnutrition upon admission to the hospital (26). The presence of poor nutritional status has an impact on the progression of malignant diseases. Researchers have reported a reduced tolerance to chemotherapy among malnourished patients, attributed to altered metabolism of antineoplastic drugs, heightened susceptibility to infections, and unfavorable clinical outcomes. However, the connection between malnutrition and the

associated morbidity and mortality rates remains a topic of debate and controversy (27).

In a study conducted by Lifson et al, 2017 on the prevalence of malnutrition among South African children with Wilms tumor (WT) assessed using arm anthropometry measurements, results indicated a tendency towards increased malnutrition rates among those in stages II-IV of the disease. Approximately 67% of the subjects were classified as malnourished based on their Mid Upper Arm Circumference (MUAC), Triceps Skin Fold Thickness (TSFT), and albumin levels. Interestingly, the influence of the disease stage on the nutritional status was not found to be statistically significant, even after accounting for confounding variables known to affect prognosis, such as stage and histology. Furthermore, the study did not identify a significant relationship between nutritional status and the outcome of the disease (26).

Likewise, previous studies have been unsuccessful in establishing a correlation between the nutritional status of patients upon admission and their outcomes in cases of Wilms tumors. The majority of research in this area has primarily concentrated on examining this relationship among children with hematological malignancies, while studies specifically focusing on children with solid tumors, such as Wilms tumor, are relatively limited in number (28).

This study will also investigate how the nutritional status of patients upon admission affects the clinical response to neoadjuvant therapy in individuals diagnosed with Wilms tumor. By addressing this specific aspect, the study aims to contribute valuable insights to the ongoing scientific discourse regarding the influence of nutritional status on the treatment outcomes of Wilms tumor. Furthermore, it seeks to bridge the existing data gap within our setting pertaining to this particular area of research.

Children in Africa with malignant solid tumors often had advanced local and systemic disease and inadequate nutrition that hindered their treatment even before the HIV pandemic (29). Having a weakened immune system likely increases, the risk of

developing cancer. In the United States, tumors make up approximately 2% of the AIDS-defining events in children, but this incidence may differ in developing countries (30). Among HIV-infected children, the most common tumors are non-Hodgkin's lymphoma, smooth muscle tumors (leiomyosarcomas), and Kaposi's sarcoma (found only in Africa) (30). In a study conducted in Zimbabwe on HIV infected pediatric patients with malignancy, Wilms tumor accounted for 19.7% of cases, similar to acute lymphoblastic leukemia, while Kaposi's sarcoma and non-Hodgkin's lymphoma accounted for 15.8% and 22.4% respectively (31).

In Tanzania, the prevalence of HIV among patients with pediatric malignancy was found to be very low 2.8%, of which majority has Kaposi's sarcoma and none of the patient had Wilms tumor (32). This study will also asses the influence of HIV serostatus on clinical response to neoadjuvant therapy among patients with Wilms tumor at MNH.

CHAPTER THREE

3.0 MATERIAL AND RESEARCH METHODOLOGY

3.1 Study Design

A 5years retrospective hospital-based cross-sectional analytical study was employed at Muhimbili National hospital involving patients with pathologically confirmed Wilms tumor admitted at Pediatric Oncology ward from 1st January 2018 to 31st December 2023.

3.2 Study Area

Muhimbili National Hospital is a National Referral Hospital with 1500-bed capacity that also serves as a research center and university teaching hospital. It also has 32 specialized clinics that attend 2,000 outpatients each week and accommodate 1,000 to 1,200 inpatients. The Pediatric Oncology Unit at MNH is a section in the Pediatric complex building consisting of the Upendo and Tumaini oncology ward with a 60-bed capacity, isolation facilities, procedure room, and chemotherapy preparation rooms. An estimate of 7 to 15 new patients with Wilms tumor are diagnosed monthly with up to 100 patients annually.

3.3 Study Population

Patients admitted at pediatric surgery and pediatric oncology ward at MNH with pathologically confirmed Wilms tumor between 1st January 2018 to 31st December 2023 who met the inclusion criteria.

3.4 Study Sample

The study sample included patients who have been treated for Wilms tumor at MNH following the SIOP protocol between January 1, 2018, and December 31, 2023.

3.5 Recruitment Criteria

3.5.1 Inclusion criteria

i. Children below 15 years with a diagnosis of Wilms tumor treated following the SIOP protocol
ii. Children with Pre and Post neoadjuvant therapy CT scan results

3.5.2 Exclusion criteria

i. Children below 15 years of age with a diagnosis of Wilms tumor underwent surgery without receiving neoadjuvant therapy.
ii. Children who received neoadjuvant therapy elsewhere and then referred to MNH with no information about tumor volume prior or treatment regime given.

3.6 Sample Size Estimation and Selection

The study enrolled a total of 113 participants to determine the factors influencing neoadjuvant therapy clinical responses among patients with Wilms tumors at MNH. Type 1 error of less than 5% at a 95% confidence interval was considered statistically significant.

The sample size was determined using the following formula:

$N = Z^2 \times P \times (1-P)/X^2$

Where,

N=Sample size

Z = level of confidence (1.96 for 95% confidence level)

p = expected proportion (0.08 from the previous study done in Kilimanjaro Tanzania by Abezune)

X= margin of error (5%)

N= 1.96X1.96X 0.08(1-0.08)/0.05X0.05

N=113

The total sample size calculated was 113

3.7 Sampling Technique

A simple random sampling technique was applied

3.8 Variables

3.8.1 Independent variable

Age, Sex, nutrition status, Immune status (HIV serostatus), Duration of symptoms prior presentation to hospital, Hemoglobin level (Hb) Abdominal mass/swelling, Hematuria, Hypertension, Associated congenital anomalies, clinical stage, neoadjuvant treatment regime, Duration of neoadjuvant therapy, histological subtype, Tumor size/volume, Lung metastasis, Liver Metastasis, Brain Metastasis.

3.8.2 Dependent variable

- Neoadjuvant therapy clinical response status

  Change in tumor volume/size

Complete response, Partial response, Stable disease, Progressive disease.

- A major decrease in tumor volume (>50% of the initial tumor volume)
- Some decrease in tumor volume
- No change in tumor volume
- Increase in tumor volume

3.9 Data Collection Methods and Measurements

Demographic and clinical data was collected using a structured checklist from patient's case files, and radiological and histopathological records were retrieved from the hospital's HMIS (**Jeeva system**).

The structured checklist was used to document data of all Wilms tumor patients treated at MNH who met the inclusion criteria. The following variables was recorded; patient

demographics (age and sex), nutrition status, HIV serostatus, clinical presentation, clinical staging, type of neo-adjuvant therapy regime, Duration of neo-adjuvant therapy, Tumor volume from CT scan before and after completion of neoadjuvant therapy, clinical stage post neoadjuvant therapy, histological subtypes and intraoperative complication such as tumor spillage or rupture.

Clinical data of change in tumor volume at admission and post-neo-adjuvant therapy was evaluated using CT scan images available in the database and the patient's radiologist report for the exact tumor volumes with ellipsoid formula (4/3pie x a x b x c) where a, b and c are radii in three dimension.

Tumor volume reduction of >50% was considered as a major decrease in tumor volume and those with a > 30% increase in tumor volume was considered as increased tumor volume.

Complete response referred to disappearance of all target lesion, Partial response: at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Progressive disease: at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable disease: Neither sufficient shrinkage to qualify for partial response (PR) nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum LD since the treatment started.

Change in clinical disease stage post neo-adjuvant therapy was obtained from the radiological investigations by comparing CT scan findings before and after completion of neo-adjuvant therapy

3.10 Investigation Tool Validity and Reliability

The validity of the content, construct, and criteria of a checklist was assessed, and the reliability of a checklist was tested by its internal consistency and interpersonal reliability.

3. 11 Data Analysis.

The data was managed and analyzed using the Statistical Package for Social Sciences (SPSS) version 23 program. Numerical variables were presented as median, and Interquartile range. Descriptive data were presented in frequency and proportion in frequency distribution tables and diagrams (boxplot and whisker chart, and histograms).

Comparison of the patient's tumor volume before and after neoadjuvant therapy was evaluated using Wilcoxon sign rank test due to skewing of the distribution of tumor volume. To determine the correlation between the independent variables and tumor volume reduction a gamma regression model was used employing a generalized estimating equation. A P-value of <0.05 was considered statistically significant.

3.13 Ethical consideration

This study was reviewed by the ethical committee of Muhimbili University of Health and Allied Sciences, and ethical clearance was granted by the MUHAS Research Ethics Committee **(Reference No.: DA.282/298/01.C/1803)**, ethical clearance number **MUHAS-REC-07-2023-1803**. Permission for data collection was granted by the research and consultancy unit of MNH **(Reference No.: MNH/TRCU/Perm/2023/463)**. Throughout the study period, all ethical principles were strictly adhered. Confidentiality, anonymity, protection of privacy, and personal information were meticulously observed.

CHAPTER FOUR

4.0 RESULTS

4.1 Demographic and clinical characteristics of the study participants

This study enrolled data from 113 Wilms tumor cases that met the inclusion criteria. The proportion of males and females was 49.6% (n = 56) and 50.4% (n = 57), respectively, with an approximate male-to-female ratio of 1:1. Among these cases, 61.9% (n = 70) were aged four years or younger, while the remaining were older than 4 years (38.1). The median age at presentation was 48 months, with an interquartile range (IQR) of 24 to 60 months.

The vast majority of patients, accounting for 93.8% (n = 106), exhibited a generally normal nutritional status upon presentation, while only a small proportion, 6.2% (n = 7), were identified as malnourished based on the MUAC for those under five years and Body Mass Index (BMI) for those aged 5years and above. In terms of HIV serostatus, approximately 71.7% (n = 81) of participants tested negative, 26.6% (n = 30) had an unknown serostatus, and merely 1.8% (n = 2) were found to be HIV-positive. Abdominal mass or swelling was the predominant symptom affecting 98.2% (n = 111) of patients, followed by abdominal pain in 29.2% (n = 33), hematuria in 15.9% (n = 18), and hypertension in 12.4% (n = 14). Other symptoms, such as weight loss and fever, were present in 21.2% of cases. The right- and left-sided diseases was affected equally while synchronous bilateral disease was only seen in one patient. Additionally, associated congenital anomalies, including situs inversus and umbilical hernias, were identified in only two patients.

The radiological staging obtained at the time of diagnosis was 5.3%, 48.7%, 11.5%, and 34.5% for stages I, II, III, and IV, respectively. About 42.5% (n = 48) achieved more than 50% tumor volume reduction (major decrease). In terms of the radiological response to neoadjuvant chemotherapy evaluated using the RECIST 1.1 criteria, the majority of patients, accounting for 63.7% (n = 72), demonstrated a stable disease post-neoadjuvant chemotherapy. Additionally, 29.2% (n = 33) exhibited a partial response,

6.2% (n = 7) experienced progressive disease, and only one patient achieved a complete radiological response to neoadjuvant chemotherapy (**See table 1 below)**.

Table 1: Demographic and clinical characteristics of the study participants

Variable	Frequency (n)	Percent (%)
Age group (months)		
≤ 48	70	61.9
>48	43	38.1
Median age in months (IQR)	48 (24, 60)	
Sex		
Male	56	49.6
Female	57	50.4
Nutritional status		
Normal	106	93.8
Mild acute malnutrition	1	0.9
Moderate malnutrition	5	4.4
Severe acute malnutrition	1	0.9
HIV serostatus		
Positive	2	1.8
Negative	81	71.7
Unknown	30	26.5
Abdominal swelling/Mass	111	98.2
Abdominal pain	33	29.2
Hematuria	18	15.9
Hypertension	14	12.4
Other symptoms	24	21.2
Median duration of illness (IQR)	2.0 (1.0, 5.0)	
Site of the disease		
Right	56	49.6
Left	56	49.6
Bilateral	1	0.9
Associated congenital anomalies[$]	2	1.8
Clinical stages at presentation		
I	6	5.3
II	55	48.7
III	13	11.5
IV	39	34.5
Tumor volume reduction		
Major decrease (>50%)	48	42.5
No change in tumor volume	31	27.4
Others	34	30.1
Radiological response		
Complete	1	0.9
Partial	33	29.2
Progressive disease	7	6.2
Stable	72	63.7

[$]Type of congenital anomalies- Situs inversus and umbilical hernia

4.2 Pathological characteristics of the study participants

All participants in the study underwent nephrectomy (n = 113), and the specimens were submitted for histopathological diagnosis and staging. Risk stratification was conducted according to the SIOP WT 2001 staging criteria, resulting in 7.1% (n = 8) being categorized as low risk, 63.7% (n = 72) as intermediate risk, and 29.2% (n = 33) as high risk.

Blastemal-predominant tumors dominated the high-risk group at 30%, while diffuse anaplasia constituted 2.7%. In the low-risk group, completely necrotic tumors were the most prevalent at 5.3%, followed by partially cystic differentiated tumors at 1.8%. Within the intermediate-risk group, epithelial predominant tumors were the most common at 24.8%, followed by mixed type at 17.7%, stromal type at 16.8%, and regressive and focal anaplasia at 4.4%.

The post-operative SIOP pathological staging of the participants revealed that 33.6% (n = 38) were classified as stage II, 31% (n = 35) as stage III, 25.7% (n = 29) as stage IV, and stage I accounted for 9.7% (n = 11).

Table 2: Pathological characteristics of the study participants

Variable	Frequency (n)	Percent (%)
Histological subtype		
Low risk	8	7.1
Intermediate risk	72	**63.7**
High risk	33	29.2
Specific histopathological subtype		
Completely necrotic	6	5.3
Partially cystic differentiated	2	1.8
Epithelial type	28	24.8
Stromal type	19	16.8
Mixed type	20	17.7
Regressive and focal anaplasia	5	4.4
Blastemal type	30	26.5
Diffuse anaplasia	3	**2.7**
Post – operative SIOP pathological staging		
I	11	**9.7**
II	38	33.6
III	35	31.0
IV	29	**25.7**

Key: SIOP- International society of pediatric Oncology

4.3 Neoadjuvant therapy treatment regimen

The neoadjuvant chemotherapy treatment regime was predominantly determined by the clinical disease stage at the time of diagnosis. A two-drug regime consisting of Actinomycin D and Vincristine (AV) was prescribed in 55.8% (n = 63) of patients for stages I, II, and III, and a three-drug regime consisting of Actinomycin D, Vincristine, and Doxorubicin (AVD) was prescribed in 44.2% (n = 50) of the participants with stage IV disease and some patients with stage III disease.

About 52.9% received a four-week' duration of neoadjuvant chemotherapy for localized disease, and 35.4% received a six-week' duration of neoadjuvant chemotherapy for those with metastatic disease at the time of diagnosis. A response to neoadjuvant chemotherapy was assessed by thoraco-abdominal CT at the end of 4 and 6 weeks for localized and distant metastatic disease, respectively.

An approximate 79.6% (n = 90) of the participants had additional cycles of neoadjuvant chemotherapy of varying duration prior to nephrectomy, predominantly due to insufficient tumor volume reduction in post-neoadjuvant CT for both localized and metastatic disease.

Table 3: Neoadjuvant therapy treatment regime

Variable	Frequency (n)	Percent (%)
Type of neoadjuvant chemotherapy regimen		
AV	63	55.8
AVD	50	44.2
Duration of neoadjuvant therapy treatment		
Four weeks (4)	62	**54.9**
Five weeks (5)	4	3.5
Six weeks (6)	40	**35.4**
Seven weeks (7)	1	0.9
Eight weeks (8)	5	4.4
Nine weeks (9)	1	0.9
Additional duration (n = 90)		
One week (1)	5	5.6
Two weeks (2)	43	47.8
Three weeks(3)	9	10.0
Four weeks (4)	29	32.2
Five weeks (5)	2	2.2
Six weeks (6)	2	2.2

Key: AV- Actinomycin D, Vincristine; AVD- Actinomycin D, Vincristine, Doxorubicin

4.4 Factors influencing clinical response to neoadjuvant therapy among patients with Wilms tumor at MNH.

The clinical response to neoadjuvant therapy was assessed through a reduction in tumor volume, determined by comparing contrasted abdominal CT scans prior to and after neoadjuvant therapy.

The study evidently demonstrated that neoadjuvant chemotherapy significantly decreases tumor volume in Wilms tumor patients. Prior to neoadjuvant chemotherapy, the median tumor volume was found to be 7125 cm3, with an interquartile range (IQR) of 3312 to 11884. Following neoadjuvant therapy, the median tumor volume was reduced to 3621 cm3, with an interquartile range (IQR) spanning from 1708 to 7798. **(Figure 1).**

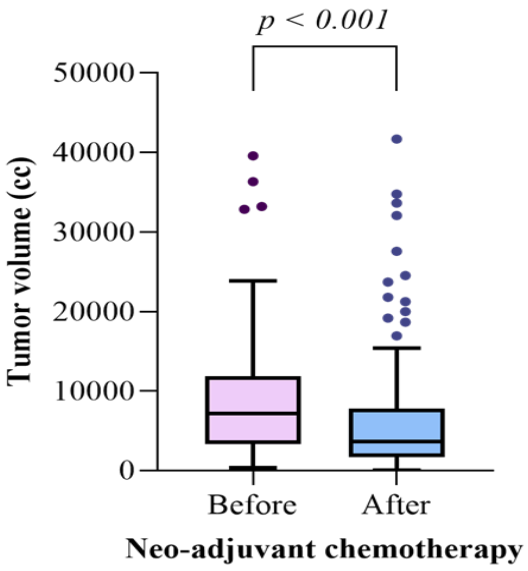


Figure 2: Boxplot and Whiskers chart summarizes the Median, Interquartile range, Maximum and Minimum tumor volumes before and after neoadjuvant chemotherapy.

4.5 Factors associated with tumor volume reduction after neoadjuvant treatment

The older age group (>48 months) demonstrated a greater tumor volume post-neoadjuvant chemotherapy (with an excess of 0.416 cm3) compared to those aged 48 months or younger (P = 0.02) (**refer to Table 4**, **Figure a**). Furthermore, malnourished children displayed a higher tumor volume compared to those with normal nutritional status (P = 0.023) (**see Table 4**, **Figure b**).

Patients diagnosed with clinical stage 2 disease exhibited a more significant reduction in tumor volume compared to those in stage 3 disease, with respective p-values of 0.023 and 0.261 (**refer to Table 4**). Additionally, neoadjuvant therapy treatment for more than six weeks was significantly correlated with tumor volume reduction (P<0.011).

More importantly, the study findings indicate that for every monthly increase in duration of illness, prior to neoadjuvant therapy there was a statistically significant increase in tumor volume by 0.063 cm3 (p = 0.023). Conversely, the histological subtype of Wilms tumor did not show a statistically significant association with tumor volume reduction.

Table 4: Factors associated with tumor volume reduction after treatment with neoadjuvant therapy.

Table 4: Factors associated with tumor volume reduction after treatment with neoadjuvant

Variable	Category	Coefficient (β)	95% Confidence Interval		p – value
			Lower	Upper	
Age group (years)	>48	0.416	0.07	0.77	**0.020**
	≤ 48	Ref			
Histological subtype	Low risk	-0.574	-1.28	0.13	0.111
	Intermediate	0.017	-0.36	0.40	0.931
	High risk	Ref			
Duration of neoadjuvant	4	-0.637	-1.53	0.26	0.163
	5	-0.001	-1.15	1.15	0.999
	6	-0.946	-1.68	-0.22	**0.011**
	≥ 7	Ref			
Nutritional status	Malnourished	0.812	0.11	1.51	**0.023**
	Normal	Ref			
Duration of illness		0.063	0.02	0.10	**0.003**
Type of Neoadjuvant	Two Drugs	-0.131	-0.81	0.55	0.704
	Three Drugs	Ref			
Distant metastasis	Yes	-0.373	-1.06	0.32	0.288
	No	Ref			
Hypertension	Yes	0.248	-0.25	0.75	0.330
	No	Ref			
Other symptoms	Yes	0.106	-0.30	0.51	0.606
	No	Ref			
Clinical stage	Stage 1	-0.324	-1.01	0.36	0.349
	Stage 2	-0.487	-0.91	-0.07	**0.023**
	Stage 3	-0.236	-0.65	0.18	0.261
	Stage 4	Ref			

Key: Ref: Reference Category

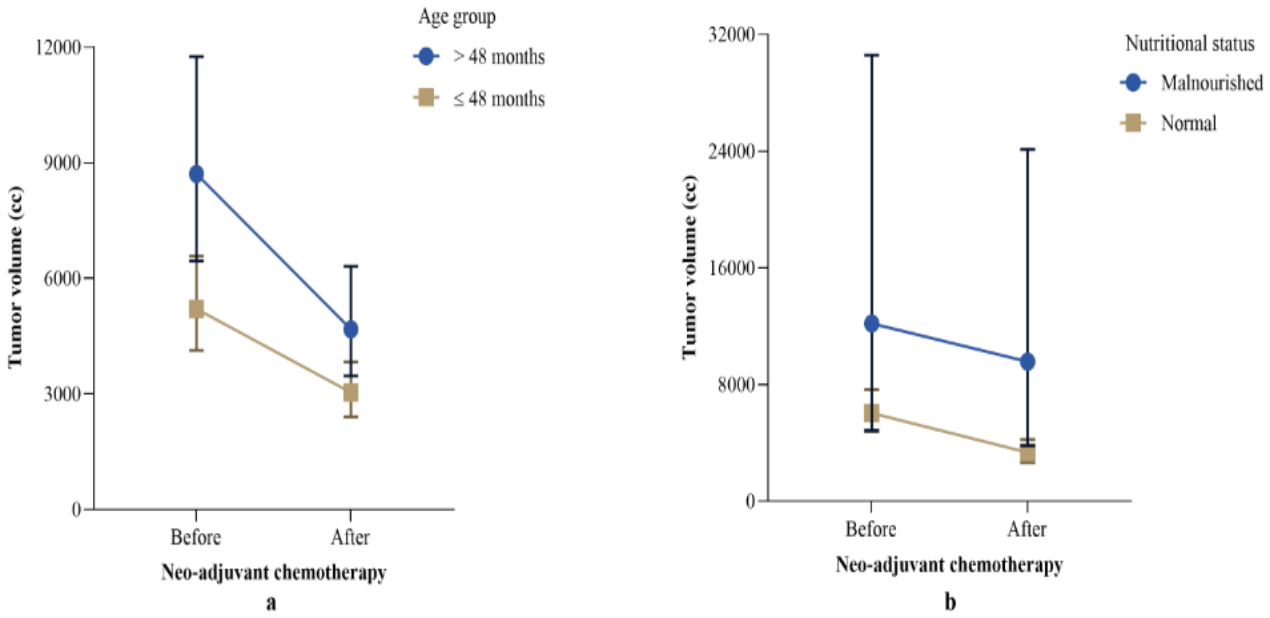


Figure 3:. Graphical presentation of the marginal mean of change in tumor volume prior to and after neoadjuvant therapy based on Age (figure a) and Nutrition status (figure b).

CHAPTER FIVE

5.0 DISCUSSION

The assessment of Wilms tumors' responsiveness to neoadjuvant chemotherapy is a key factor in risk and treatment stratification in the SIOP studies. Neoadjuvant chemotherapy aimed at decreasing the tumor size, downstaging the disease, and enabling safe surgery. Findings in this study demonstrated that neoadjuvant chemotherapy significantly reduces tumor volume prior to nephrectomy ($P < 0.001$), aligning with a study done by Singh et al. in India (2). However, its response was influenced by various clinical and pathological characteristics of Wilms tumor patients. The clinical responses obtained post-neoadjuvant therapy were as follows: The majority (63.7%) of the patients exhibited a stable disease, 29.2% exhibited a partial response, and 6.2% had a progressive disease. About 42.5% experienced a major decrease in tumor volume (>50%), and one patient had a complete response following neoadjuvant therapy.

Comparable findings were demonstrated in a study done by Singh et al. in India, where they found 64.3% exhibited a stable disease, 35.7% had a partial response, and none of the patients had a complete response or progressive disease (2). A slight increase in the prevalence of progressive disease in our study can be attributed to a relatively older age at presentation (median age 48 months compared to 31 months in the earlier study) with gross tumors and malnutrition. About 38% of the participants in our study were older than 4 years, and 6.8% were malnourished. Older age and malnutrition were associated with relatively higher tumor volumes at diagnosis, as demonstrated by figures a and b above, and negatively affected the response to neoadjuvant therapy (P value <0.05).

Previous research findings suggest that a significant percentage of children with cancer in developing countries, ranging from 45% to 77%, are admitted to the hospital with malnutrition, often attributed to poverty and advanced disease(26).The presence of poor nutritional status has an impact on the progression of malignant diseases.

Researchers have reported a reduced tolerance to chemotherapy among malnourished patients, attributed to altered metabolism of antineoplastic drugs, heightened susceptibility to infections, and unfavorable clinical outcomes(27) **.** Lifson et al. in South Africa reported a malnutrition prevalence of over 66% among patients with Wilms tumors upon admission(26). Conversely, in our study, the proportion of patients with malnutrition was less than 10% at diagnosis. However, this figure could be underestimated because nutritional status was determined using the mid-upper arm circumference (MUAC) for those under 5 years old and the body mass index (BMI) for those 5 years and older unlike in the earlier study where MUAC, Triceps Skin Fold Thickness (TSFT), and albumin levels, were used which are unaffected by tumor mass. BMI may not be reliable indicator of nutrition status in children with solid tumors like Wilms tumors as it can be influenced by the tumor mass.

Additionally, older age group is associated with more adverse biological features of Wilms tumor with increased chemotherapeutic resistance unlikely to be found in children younger than 2 years. Alternatively, Children under 2 years old may have a better response due to high systemic vincristine exposure, owing to decreased drug clearance; however, there is limited pharmacokinetic data in this age group(33).

A six-week duration of neoadjuvant chemotherapy was associated with a higher tumor volume reduction for both localized and metastatic disease ($P = 0.011$). Notably, there was no statistically significant difference in tumor volume reduction between patients who received two drug regimens (VA) and three (VAD) drug regimens ($P > 0.05$). This is in contrast to the study done by Israel et al. in Malawi, which revealed a three-drug regime (VAD) being associated with higher tumor volume reduction compared to a two-drug regime (7). These subsequent findings were biased by inter-observer measurement because they were based on clinical examination findings, which are difficult to obtain accurate measurement due to tumor irregularity, as opposed to our study, which used an objective assessment based on a contrasted abdominal CT scan.

The International Society of Pediatric Oncology (SIOP) divides Wilms tumor patients into three risk categories based on the histological classification: low, intermediate, and high. This attempted to spare patients with less aggressive tumors from the side effects of radiation and chemotherapy while stepping up treatment for those with more aggressive tumors. The radiological response of neoadjuvant chemotherapy measured by change in tumor volume has been correlated with histopathological findings of Wilms tumors and used to preoperatively predict the histological classification of Wilms tumors by some researchers (24).

In our study we found that Low risk histological subtype (completely necrotic, partially cystic differentiated) demonstrated a considerable decrease in tumor volume compared to intermediate risk and high risk (Diffuse anaplasia and blastemal predominant) P value 0.111 and 0.931 respectively. Similar findings were demonstrated by Tasken et al. in Finland where intermediate risk tumors (epithelial predominant and stromal subtype) where associated with lesser change in tumor volume and increased tumor volume being attributed to unfavorable histology (diffuse anaplasia)(13). Still there is lack of statistical significance in predicting the tumor risk classification based on preoperative radiological changes and this is supported by a study done by Middleton et al in South Africa revealing similar findings.

CHAPTER SIX

6.0 STUDY LIMITATIONS, MITIGATION, CONCLUSION AND RECOMENDATION

6.1 Study Limitations and Mitigation

Given the retrospective nature of this study, it is prone to some limitations. Additionally, an assumption was made that the tumors were ellipsoid in shape, and the radii of the tumor in three planes were used to facilitate the calculation of the tumor volume using the ellipsoid formula. In reality, tumors are irregular in shape and unlikely to be symmetrical. This may have contributed to the overestimation of the tumor volume. However, the CT findings were reviewed and approved by a qualified radiologist regarding the tumor size prior to and after neoadjuvant therapy. Furthermore, neither the radiologist nor the clinician were aware of the histological subtype of Nephroblastoma during the entire duration of neoadjuvant therapy. Additionally, all nephrectomies were performed by different experienced pediatric surgeons, and histological samples were evaluated by experienced pathologists.

6.2 Conclusion

Overall clinical response to neoadjuvant chemotherapy in tumor volume reduction among patients with Wilms tumor in our setting is significant, however its effect is influenced by delayed presentation with advanced disease, older age group, and malnutrition presenting with relatively large tumor volume at the time of diagnosis. Notably There is insufficient evidence to recommend radiological changes in tumor volume post neoadjuvant chemotherapy to predict the SIOP risk stratification of Wilms tumor subtype.

6.3 Recommendations

Strategies to enhance public awareness concerning Wilms tumor, and prompt referral from primary health care facilities to pediatric cancer treatment centers are crucial to reduce proportions of older age with advanced disease stages at diagnosis which negatively impacted responses to neoadjuvant therapy among Wilms tumor patients at MNH.

Triceps skin fold (TSF) should be adopted to assess nutrition status for older children with Wilms tumors aged 5 years and above, as BMI is unadvisable since it can underestimate the magnitude of malnutrition in patients with solid tumors due to its susceptibility of being influenced by the tumor mass.

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APPENDICES

Appendix 1: Structured Checklist for Data Collection

REG N0……..

1. Demographic characteristics
    i. Age…….
    ii. Sex……...
2. Nutritional status
    i. Normal
    ii. Mild Acute Malnutrition
    iii. Moderate Malnutrition
    iv. Severe acute Malnutrition
3. HIV serostatus
    i) positive
    ii) Negative
    iii) Unknown
4. Clinical presentation
    i.) Abdominal swelling/mass
    ii.) Abdominal pain
    iii.) Hematuria
    iv.) Anemia HB……
    v.) Hypertension
    vi.) Others……
5. Site of the disease
    i) Right
    ii) Left
    iii) Bilateral

6. Associated congenital anomalies…….
7. Clinical stage at presentation (Radiological) from CT scan findings
    ii) I
    iii) II
    iv) III
    v) IV
    vi) V
8. Is there distant metastasis?
    i) Yes
    ii) No
9. If Yes which organs are involved?
    i) Lungs,
    ii) Liver
    iii) Pleura ….
    iv) Others……

10. Type of neoadjuvant chemotherapy regime

    i) Two drugs……
    ii) Three drugs…….

11. Duration of neoadjuvant therapy treatment…….

12. Tumor size/volume from CT scan before neoadjuvant ……after neoadjuvant……

    i) Major decrease……
    ii) some decrease…….
    iii) No change in tumor size…….
    iv) Increase in tumor growth…….

13. Radiological response i) complete ii) partial iii) incomplete iv) stable

14. Post Neoadjuvant therapy clinical staging(Radiological) from CT scan

    i) I
    ii) II
    iii) III
    iv) IV
    v) V

15. Operation done

    i.) yes
    ii.) No

16. if yes

    i) Complete resection
    ii) Incomplete resection

17. Intra op complications

    i) Yes
    ii) No

18. If yes

    i) Tumor rupture/spillage
    ii) Bleeding
    iii) Injury to adjacent structures……
    iv) Others…….

19. Histological subtype

i. Low risk (Completely necrotic, partially cystic differentiated)
ii. Intermediate risk (epithelial type, stromal type, mixed type, regressive and focal anaplasia)
iii. High risk (Blastemal type, Diffuse anaplasia)

20. Post-operative SIOP pathological staging

i) I
ii) II
iii) III
iv) IV
v) V

Appendix 2: Ethical Clearances

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/1803

Date: 13/07/2023

MUHAS-REC-07-2023-1803
LEONARD SELESTINE
SCHOOL OF MEDICINE
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: FACTORS INFLUENCING CLINICAL RESPONSE TO NEOADJUVANT THERAPY AMONG PATIENTS WITH WILMS TUMOR AT MUHIMBILI NATIONAL HOSPITAL.

Reference is made to the above heading,

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 13/07/2023
EXPIRATION DATE OF APPROVAL: 13/07/2024

STUDY DESCRIPTION:
Purpose:
The purpose of this retrospective observational cross-sectional study is to determine the factors influencing clinical responses to neoadjuvant therapy among patients with Wilms tumor at Muhimbili national hospital.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014831.pdf and in the MUHAS archives.

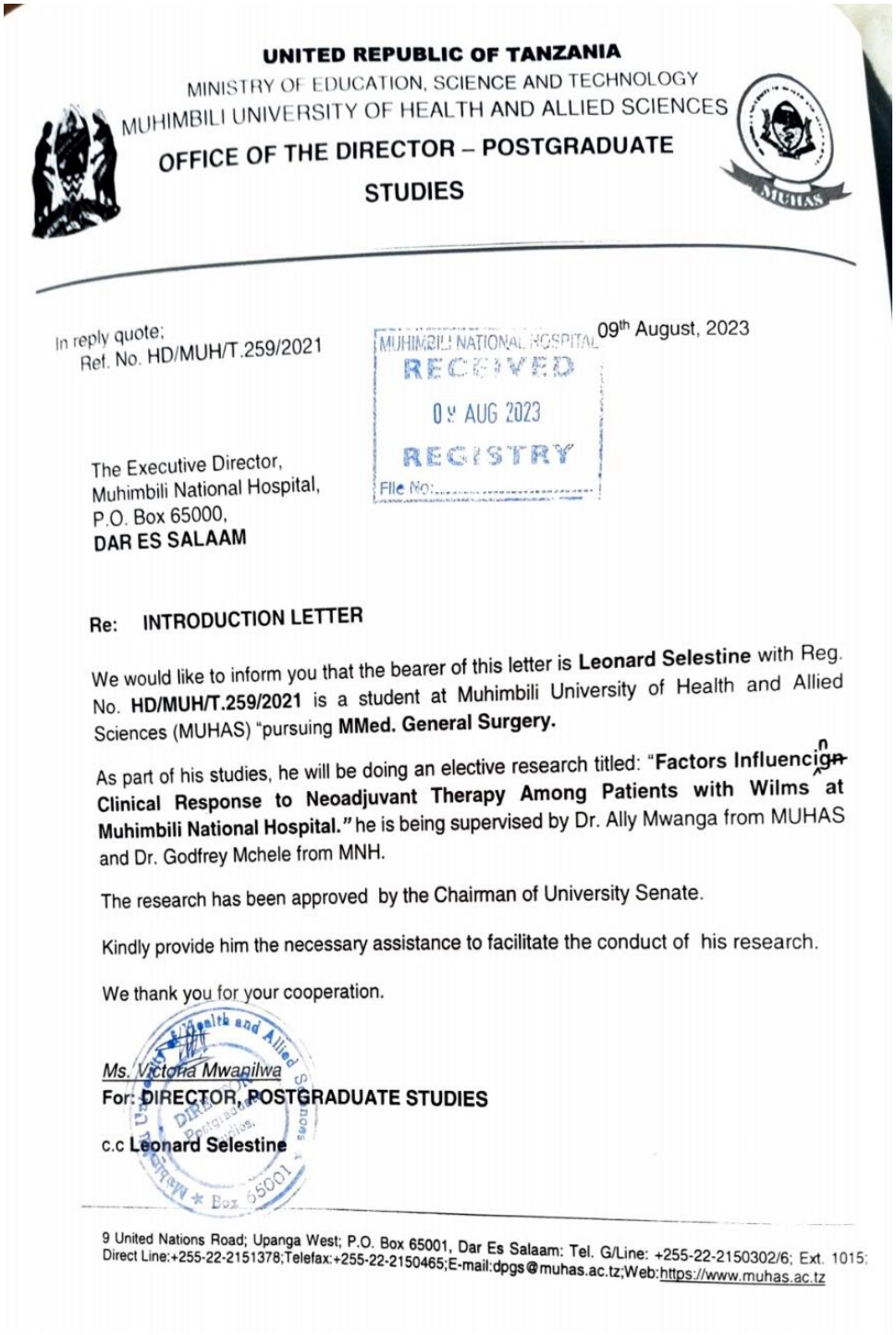
The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain material transfer agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country,
8. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
9. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
10. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.

Dr. Nahya Salim Masoud,
Chairperson, MUHAS Research and Ethics Committee



Appendix 3: introduction letter



UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;
Ref. No. HD/MUH/T.259/2021

09th August, 2023

MUHIMBILI NATIONAL HOSPITAL
RECEIVED
09 AUG 2023
REGISTRY
File No:

The Executive Director,
Muhimbili National Hospital,
P.O. Box 65000,
DAR ES SALAAM

Re: INTRODUCTION LETTER

We would like to inform you that the bearer of this letter is **Leonard Selestine** with Reg. No. **HD/MUH/T.259/2021** is a student at Muhimbili University of Health and Allied Sciences (MUHAS) "pursuing **MMed. General Surgery.**

As part of his studies, he will be doing an elective research titled: "**Factors Influencing Clinical Response to Neoadjuvant Therapy Among Patients with Wilms at Muhimbili National Hospital."** he is being supervised by Dr. Ally Mwanga from MUHAS and Dr. Godfrey Mchele from MNH.

The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

c.c **Leonard Selestine**

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

Appendix 4: Permission Letter

3THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

MUHIMBILI NATIONAL HOSPITAL

In reply please quote;

Ref. No.: MNH/CRTCU/Perm/2023/463 **Date: 14th August, 2023**

Head of Department,
- Paediatrics and Child Health
- Medical Records

Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH.

Name of Student	**Leonard Selestine**
Title	**"Factors influencing Clinical Response to Neoadjuvant Therapy Among Patients with Wilms Tumor at Muhimbili National Hospital".**
Institution	Muhimbili University of Health and Allied Sciences
Supervisors	Dr. Ally Mwang (MUHAS)
Co - Supervisor	Dr. Godfrey Mchele (MNH)
Period	14th August, 2023 to 14th January, 2024

Approval has been granted to the above mentioned student to collect data at MNH. **A final study report should be lodged with Clinical Research, Training and Consultancy Unit.** Dissemination of study findings to MNH stakeholders shall be overseen by Dr.Godfrey Mchele (MNH) Co – supervisor.

Kindly ensure that the student abide to the ethical principles and other conditions of the research approval.

Sincerely,

HEAD TEACHING, RESEARCH & CONSULTANCY UNIT
P.O. Box 65000
DAR-ES-SALAAM
MUHIMBILI NATIONAL HOSPITAL

Dr. Jessie Mbwambo
Head of Clinical Research, Training and Consultancy Unit

c.c DMS, DICT
c.c Dr. Godfrey Mchele
c.c **Leonard Selestine**

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