INCIDENCE OF MALNUTRITION AS MEASURED USING SPECIFIC ANTHROPOMETRIC AND BIOCHEMICAL PARAMETERS AND ITS RELATIONSHIP WITH CHEMOTOXICITY IN CHILDREN WITH NEPHROBLASTOMA ADMITTED TO INKOSI ALBERT LUTHULI CENTRAL HOSPITAL BETWEEN 2004-2012

BY

KELLY SUE DRAPER
B.Sc Diet, PGDip Diet (UKZN)

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Dietetics and Human Nutrition
School of Agricultural, Earth and Environmental Sciences
College of Agriculture, Engineering and Science
University of KwaZulu-Natal
Pietermaritzburg
SOUTH AFRICA

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ABSTRACT

Introduction: The prevalence of malnutrition in children with cancer in developing countries is reported to be as high as 69%. Malnutrition is worse in developing countries as the diagnosis of cancer may be delayed due to poor access to health care. The assessment of the nutritional status of paediatric oncology patients on admission to hospital is crucial as nutritional status is known to influence treatment and clinical outcomes. Several studies suggest that concurrent malnutrition and cancer in children leads to reduced chemotherapy delivery due to impaired tolerance and increased toxicity. The influence of malnutrition on the prevalence, frequency and duration of chemotoxicity in South African children with nephroblastoma has not been well researched.

Aim: This study aimed to determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters and its relationship with chemotoxicity in children with nephroblastoma admitted to IALCH between 2004-2012.

Objectives:

a) To determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters in children with nephroblastoma admitted to IALCH between 2004-2012.
b) To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the prevalence of chemotoxicity.
c) To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the frequency and duration of chemotoxicity

Methods: Seventy-seven children between the ages of 1-12 years diagnosed with nephroblastoma and admitted to IALCH between 2004 and 2012 were studied prospectively. Nutritional assessment took place before treatment was started and included weight, height, mid upper arm circumference (MUAC), triceps skinfold thickness (TSFT) and serum albumin. The administration of Neupogen® was used as a surrogate for haemotoxicity and the frequency and duration of its use was recorded.

Results: When patients were classified by weight for age (WFA), height for age (HFA), weight for height (WFH) and body mass index (BMI) for age, malnutrition was seen in 37.5%, 39.5%, 28.4% and 30.3% of patients respectively. When the parameters MUAC and TSFT were used the prevalence of malnutrition was 56% and 52.7% respectively. There was a significant relationship between the prevalence of toxicity and MUAC. The mean frequency and duration of chemotoxicity was significantly higher in those defined as malnourished using MUAC. Frequency and duration of chemotoxicity were positively correlated. Serum albumin, when used alone, showed that 86% of the cohort had a normal nutritional status.

Conclusions: Nutritional assessment in children with solid tumours should include MUAC, TSFT as well as weight and height. This is because the use of weight and height alone could underestimate the prevalence of malnutrition. Children with nephroblastoma who have malnutrition according to their MUAC are more likely to experience more frequent and longer periods of chemotoxicity. Serum albumin should not be used in isolation to identify malnutrition.

PREFACE

This dissertation was written between January 2014 and September 2016 under the supervision of Dr Kirthee Pillay and Dr Nicola Wiles using data collected from children with nephroblastoma admitted to Inkosi Albert Luthuli Central Hospital, Durban between 2004-2012.

Signed: _____ Date: _____

Kelly Draper (candidate)

As supervisors of the candidate, we agree to the submission of this dissertation.

Signed: _____ Date: _____

Dr Kirthee Pillay (Supervisor)

Signed: _____ Date: _____

Dr Nicola Wiles (Co-supervisor)

DECLARATION OF ORIGINALITY

I, Kelly Sue Draper, declare that:

1. The entirety of the work contained in this dissertation is my original work, except where otherwise stated.

2. This dissertation, or any part of it, has not been submitted for any degree or examination at any other university.

3. Where other sources have been used they have not been copied and have been properly acknowledged.

4. This dissertation does not contain text, graphics or tables copied and pasted from the internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the relevant reference section.

Signed: _____ Date: _____

Kelly Draper (candidate)

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LIST OF ABBREVIATIONS

AMC	Arm Muscle Circumference
ALL	Acute Lymphoblastic Leukaemia
BCG	Bromocresol Green
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CDC	Centers for Disease Control and Prevention
COG	Children's Oncology Group
CT	Computerised Tomography
CTC	Common Toxicity Criteria
EC	Eastern Cape
FNA	Fine Needle Aspirate
GFR	Glomerular Filtration Rate
HFA	Height for Age
IALCH	Inkosi Albert Luthuli Central Hospital
IBW	Ideal Body Weight
INC	Intensive Nutritional Counselling
KZN	KwaZulu-Natal
MUAC	Mid-Upper Arm Circumference
NWTS	National Wilms' Tumour Study
PEM	Protein Energy Malnutrition
RDA	Recommended Dietary Allowance
SA	South Africa
SACCSG	South African Children's Cancer Study Group
SD	Standard Deviation
SIOP	The International Society of Paediatric Oncology
SPSS	Statistical Package for Social Science
TPN	Total Parenteral Nutrition
TSFT	Triceps Skinfold Thickness
UK	United Kingdom
UKCCSG	United Kingdom Children's Cancer Study Group
UNICEF	The United Nations Children's Fund
USA	United States of America

VMA	Vanillylmandelic Acid
WFA	Weight for Age
WFH	Weight for Height
WHO	World Health Organization
X-rays	X-radiations

CHAPTER 1: INTRODUCTION, THE PROBLEM AND ITS SETTING

1.1 Importance of the study

Nephroblastoma also known as Wilms' tumour[1] is a malignant renal tumour that is now recognised as the most common renal malignancy in children. Nephroblastoma accounts for ~7% of all paediatric cancers with a higher incidence reported among female black children (Poole 2010). It usually occurs sporadically, but it can be familial in about 1% of cases. Twentieth century developments in surgical techniques have improved the prognosis for this previously lethal malignancy. However, it was the discovery of the tumor's radio sensitivity and the introduction of active chemotherapy agents that greatly improved survival rates. With the overall survival rate of 90%, new treatment protocols are moving away from the main objective of maximising cure to maximising cure with minimal treatment-related toxicities (Poole 2010; Metzger & Dome 2005). However, 80% of children with nephroblastoma live in countries where resources are limited and survival rates are low as they often present with an advanced stage of disease, malnutrition and associated comorbidities (Stones, de Bruin, Esterhuizen & Stefan 2014; UNICEF 2006).

Malnutrition presents a challenge in children with cancer, including those with nephroblastoma. The prevalence of malnutrition worldwide varies from 6% to 50%, depending on the type of malignancy, the size, location and stage of the disease as well as the population being evaluated (Rickard, Foland, Detamore, Coates, Grosfeld, White, Weetman, Provisor, Loghmani, Oei, Yu & Baehner 1983; Rickard, Baehner, Coates, Weetman, Provisor & Grosfeld 1982; Donaldson, Wesley, De Wys, Suskind, Jaffe & van Eys 1981; Van Eys 1979). Malnutrition is associated with impaired immunocompetence, including depressed cell mediated immunity, reduced mucosal secretory antibody response and lower antibody affinity (Litchford 2012, p198). Thus, malnutrition has a synergistic relationship with infections and impacts on child mortality (Pelletier, Frongillo, Schroeder & Habicht 1995).

A study which evaluated the nutritional status of children with nephroblastoma in Malawi at diagnosis using anthropometry showed that about half of these patients were acutely malnourished at diagnosis. The true incidence, however, may have been underestimated by the large tumours which masked the true body weight (Israëls, Borgstein, Jamali, de Kraker,

[1] The term nephroblastoma is used throughout this dissertation.

Caron & Molyneux 2009). Malnutrition is worse in developing countries as poor access to health care can delay diagnosis of cancer and worsen malnutrition (Sala, Rossi & Antillon 2008). Adequate and appropriate nutrition in paediatric oncology patients is vital for maintaining ideal growth and development. It may also improve survival outcome, decrease toxicity, and improve quality of life (Rogers 2014). Thus, assessment of the nutritional status of paediatric oncology patients on admission is vital, as treatment and clinical outcomes are influenced by nutritional status (Tazi, Hidane, Zafad, Harif, Benchekroun & Ribeiro 2008).

Pietsch & Ford (2000) assessed the nutritional status of children with various malignancies over a two-year period in the USA on diagnosis using body mass index (BMI) for age, weight for height (WFH) and weight for age (WFA). The prevalence of malnutrition ranged from 1% to 46% (Pietsch & Ford 2000). Sala, Rossi, Antillon, Molina, de Maselli, Bonilla, Hernandez, Ortiz, Pacheco, Nieves, Navarrete, Barrantes, Pencharz, Valsecchi & Barr (2012) investigated the nutritional status at diagnosis in relation to clinical outcomes in children and adolescents with various malignancies from Central America. The authors found that when considering arm anthropometry alone, 18% of the patients had moderate depletion and 45% were severely depleted. When serum albumin was included, it increased the severely depleted group to 59% (Sala *et al* 2012).

Chemotherapy is used in the treatment or prevention of cancer. The type of chemotherapy most often used is cytotoxic drugs, which are destructive to living cells. This is a systemic therapy, which affects the whole body. The target of chemotherapeutic agents is not only limited to malignant tissue but affects normal cells as well. Rapidly dividing cells are typically the most affected (Grant 2008, p973). Certain tumours including nephroblastoma are very sensitive to chemotherapy. Chemotherapy can cause side effects such as nausea, vomiting, loss of appetite, mucositis, dysphagia and changes in bowel function. All of these could result in poor dietary intake resulting in malnutrition (Macpherson 2004, p107, p154). Children with cancer and concurrent malnutrition have been shown to be negatively affected in various ways, including reduced chemotherapy delivery because of impaired tolerance. This has resulted in a lower overall survival, increased toxicity and reduced quality of life (Israëls, van de Wetering, Hesseling, van Geloven, Caron & Molyneux 2009; Andrassy & Chwals 1998).

A Malawian study conducted on newly diagnosed nephroblastoma patients who often present with large tumours and a high degree of malnutrition, investigated if malnutrition had an effect on vincristine pharmacokinetics, specifically the clearance of the chemotherapeutic drug from the body. Anthropometric data, nutritional status and tumour size were documented for 11 Malawian and eight patients from the United Kingdom (UK). Vincristine was administered as part of the standard chemotherapy regime. It was found that the mean Z-score of (corrected) weight for height was substantially decreased in the Malawian patients compared to the UK patients. Mean tumour weight at diagnosis was larger and mean vincristine clearance was lower in Malawian patients than the better nourished UK patients. It was concluded that a decrease in chemotherapy drugs might need to be considered in malnourished patients in order to prevent increased prevalence and severity of toxicity (Israëls, Damen, Cole, van Geloven, Boddy, Caron, Beijnen, Molyneux & Veal 2010).

Another study, conducted two years later, in Malawian children with nephroblastoma investigated the efficacy and toxicity of The International Society of Paediatric Oncology (SIOP) preoperative chemotherapy protocol. Two types of chemotherapy regimens were administered depending on whether the patient had metastatic disease or not, and haematological toxicity during therapy was documented. It was concluded that preoperative chemotherapy for nephroblastoma patients resulted in substantial haematological toxicity in malnourished Malawian children (Israëls, Chagaluka, Pidini, Caron, de Kraker, Kamiza, Borgstein & Molyneux 2012).

Clinicians who manage children with cancer in such an environment encounter patients with advanced local and systemic disease. This is in part due to difficulties in accessing health services. Children with poor nutritional status, either due to dietary inadequacy or due to the catabolic effects of their malignancy, or both, are also encountered. Little is known of the effects of sub-optimal nutrition on disease progression or on the distribution and excretion of chemotherapeutic drugs. Studies from sub-Saharan Africa, in particular South Africa and Malawi suggest that there is an increased mortality amongst patients who are severely nutritionally depleted, allied to an increased toxicity of therapeutic drugs (Israëls *et al* 2009; Holtzinger, Shaik & Hadley 2007).

The treatment of nephroblastoma is dependent on the stage of the disease. There are five stages based on clinical pathology; 1) the tumour is limited to the kidney and is completely

excised; 2) the tumour is extending outside of the kidney and is completely excised; 3) residual tumour in the abdomen after surgery; 4) distant haematogenous metastases in the lung and liver; and 5) bilateral tumour at diagnosis. Currently, two approaches for treating nephroblastoma are considered: (i) According to the National Wilms' Tumour Study (NWTS), now the Children's Oncology Group (COG) (USA), surgery is performed first, with treatment according to the post-surgical stage. (ii) The Society of Paediatric Oncology (SIOP) (Europe) principle of treatment is to first give the child neo-adjuvant chemotherapy for 4-8 weeks to shrink the tumour. Surgery is then performed, with postoperative treatment according to the post-surgical stage. In South Africa and including Inkosi Albert Luthuli Central Hospital (IALCH) the European SIOP approach is used because patients often present with stage three and four nephroblastoma and more than half of the tumours are very large in size. Therefore, reducing the size and down staging the tumour would be beneficial (Poole 2010). During postoperative treatment (chemotherapy) the patient may experience chemotoxicity resulting in the need for Neupogen®, an immunostimulant, which is administered to all those experiencing grade four toxicity at IALCH (Hadley 2014; South African Medicines Formulary 2014, p390).

There is a lack of data published in South Africa that addresses malnutrition in nephroblastoma patients and its influence on chemotoxicity. This study was important as it would assess the nutritional status of children with nephroblastoma on admission to IALCH and determine if there was an association between nutritional status and prevalence, frequency and duration of chemotoxicity. By identifying this association, it could assist in improving existing protocols, available to the physician faced with a malnourished nephroblastoma patient. Chemotherapy doses could be reduced for such patients to decrease the possibility of chemotoxicity. This study would also reiterate the importance of nutritional support in the management of nephroblastoma patients.

1.2 Statement of the problem

The purpose of this study was to determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters and its relationship with chemotoxicity in children with nephroblastoma admitted to IALCH between 2004-2012.

1.3 Research objectives

The objectives of this study were:

1.3.1 To determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters in children with nephroblastoma admitted to IALCH between 2004-2012.

1.3.2 To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the prevalence of chemotoxicity.

1.3.3 To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the frequency and duration of chemotoxicity.

1.4 Hypotheses

The following hypotheses were tested in the study:

1.4.1 There was evidence of malnutrition in children with nephroblastoma admitted to IALCH between 2004-2012.

1.4.2 Malnutrition increases the prevalence of chemotoxicity.

1.4.3 Malnutrition increases the frequency and duration of chemotoxicity.

1.5 Study parameters

This study was limited to patients with nephroblastoma between 1-12 years of age admitted to the Paediatric Surgical Oncology ward at IALCH between 2004 and 2012. In this study only anthropometric measurements (weight, height, mid-upper arm circumference and triceps skinfold thickness) and serum albumin was used to assess nutritional status and determine the incidence of malnutrition. Clinical and dietary data were not recorded at the time of admission.

1.6 Assumptions

The following assumptions were made:

1.6.1 It was assumed that all the anthropometric measurements (weight, height, mid-upper arm circumference and triceps skinfold thickness) were taken accurately using the correct techniques by the Registered Dietician assigned to the Paediatric Surgical Oncology ward over the time period used in this study.

1.6.2 Blood samples were handled correctly and analysed accurately.

1.6.3 All patients started on Neupogen® had stage 4 chemotoxicity (life-threatening consequences; urgent intervention indicated) (U.S. Department of Health and Human Service 2009).

1.6.4 All patients started on prophylactic Neupogen® did not experience chemotoxicity at the time Neupogen® treatment was initiated but had been chemotoxic previously during treatment.

1.7 Definition of terms

Body Mass Index – Is calculated using weight and height measurements (W/H^2) to indicate overnutrition or undernutrition. It accounts for the differences in body composition by defining the level of adiposity and relating it to height, thus eliminating dependence on frame size (Hammond & Litchford 2012, p199).

Chemotoxicity – An adverse event that is possibly, probably, or definitely related to the agent or treatment, in this case chemotherapy (Common Toxicity Criteria Manual 1999).

Corrected weight – Body weight minus estimated tumour weight (Israëls *et al* 2010).

Duration – For the purpose of this study duration is the number of days chemotoxicity was experienced per episode of chemotoxicity.

Frequency – The number of occurrences in a defined population over a defined time-period (Carneiro & Howard 2010, p17).

Incidence – Is a measure of the rate at which new cases of disease occur in a population (Timmreck 2002, p 134).

Inkosi Albert Luthuli Central Hospital – A flagship tertiary and quaternary hospital providing patient care to persons in KwaZulu-Natal and parts of the Eastern Cape (Department of Health 2015).

Malnutrition – The condition arising from an inadequate or unbalanced diet. The causes may be a lack of one or more essential nutrients or inadequate absorption from the intestinal tract (Macpherson 2004, p 378).

Mid-upper arm circumference – The circumference of the arm measured at the halfway point between the acromion and olecranon process on the non-dominant side of the body and used to define nutritional status (Murphy, White & Davies 2009).

Nephroblastoma (also known as Wilm's tumour) – A malignant renal tumour of young children, composed of small spindle cells and various other types of tissue, including tubules and, in some cases, structures resembling fetal glomeruli, and striated muscle and cartilage. It is often inherited as an autosomal dominant trait (Stedman 2005, p1582).

Neupogen® (filgrastim) – It is an immunostimulant. Recombinant human granulocyte colony-stimulating factor is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Indications include severe neutropenia where it is used to accelerate neutrophil count recovery and thus reduce infections (South African Medicines Formulary 2014, p390).

Nutritional status – Is the current body status of a population group or person related to their state of nourishment (Kirch 2008, p1004).

Prevalence – Is the number of existing cases in a defined population at a defined point in time divided by the total number of people in that population at the same point in time (Carneiro *et al* 2010, p18).

Reliability – Reliability refers to the reproducibility and consistency of the instrument. It refers to the homogeneity of the instrument and the degree to which it is free from error (Bowling 2014, p170).

Serum albumin – Accounts for approximately 60% of total serum proteins. It transports major blood constituents and its major purpose is to maintain colloidal osmotic pressure (Litchford 2012, p198).

Triceps skinfold thickness – The skinfold measured at the halfway point between the acromion and olecranon process on the non-dominant side of the body and is used to define nutritional status (Murphy *et al* 2009).

Validity – Validity is an assessment of whether an instrument measures what it aims to measure (Bowling 2014, p170).

1.8 Summary

Malnutrition in paediatric patients with nephroblastoma continues to be a challenge, especially in developing countries. Assessment of the nutritional status of these patients on admission to hospital is extremely important as nutritional status is known to influence treatment and outcome. Various studies have shown that concurrent malnutrition and cancer in children leads to reduced chemotherapy delivery due to impaired tolerance and increased toxicity. The effect of sub-optimal nutrition on disease progression and the distribution and excretion of chemotherapeutic drugs is not well documented. Some studies have suggested that severely malnourished children with cancer have increased mortality which is as a result of increased toxicity of therapeutic drugs. This study aimed to determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters and its relationship with chemotoxicity in children with nephroblastoma admitted to IALCH between 2004-2012.

1.9 Dissertation outline

This dissertation is laid out as follows:

Chapter 1: Introduction, the problem and its setting

Chapter 2: Literature review

Chapter 3: Methodology

Chapter 4: Results

Chapter 5: Discussion

Chapter 6: Conclusion and recommendations

1.10 Referencing style

The referencing style used in this dissertation is in accordance with the referencing guidelines used at Dietetics and Human Nutrition, University of KwaZulu-Natal, Pietermaritzburg.

CHAPTER 2: REVIEW OF THE RELATED LITERATURE

The first part of this chapter will cover the literature related to nephroblastoma in children, including incidence, diagnosis, management and nutritional requirements. The second part of this chapter will cover the assessment of nutritional status as well as prevalence, consequences and management of malnutrition in children with nephroblastoma. The third part will cover the prevalence of chemotoxicity in children with nephroblastoma as well as the factors that influence nutritional status and chemotoxicity.

2.1 Nephroblastoma in children

Nephroblastoma is a cancer of the kidney that normally occurs in children. Dr Max Wilms, a German surgeon was the first to diagnose this type of tumour in 1899 so it is also known as Wilms' tumour. Nephroblastoma, the other name for this type of tumour is derived from "nephro" which means kidney and "blastoma" which is a tumour that consists of embryonic tissue that has not fully developed (Poole 2010).

2.1.1 Global and local incidence of nephroblastoma

Paediatric cancers are uncommon, comprising of about 1% of all cancers worldwide. Nephroblastoma accounts for 6-7% of all paediatric cancers in the developed world and is the most prevalent form of renal cancer in children younger than 15 years of age, representing approximately 95% of diagnoses. The most common form of renal cancer in adults is renal carcinomas, which is represented by only 2.6% of renal cancers in children younger than 15 years of age (Poole 2010; Stefan 2010; Berstein, Linet, Smith & Olshan 1999).

Nephroblastoma is most common among children younger than five years of age, with a very low incidence of nephroblastoma in the 10-14 and 15-19-year-old age groups. The incidence of nephroblastoma is highest in the first two years of life, followed by gradually decreasing rates as age increases. During the 21-year period from 1975 to 1995 the incidence of nephroblastoma worldwide did not vary substantially (Berstein *et* al 1999). Each year approximately 550 children and adolescents younger than 20 years of age are diagnosed with renal tumours in the USA. Of these, approximately 500 are nephroblastoma cases (Poole 2010; Berstein *et al* 1999).

Information about paediatric cancer in Africa is lacking, as there are few formal cancer registries across the continent (Stones *et al* 2014). Only about 2% of the total population of Africa is covered by population-based cancer registries (Forman, Bray, Brewster, Gombe Mbalawa, Kohle, Piñeros, Steliarova-Foucher, Swaminathan & Ferley 2014). In 2010 data from the tumour registry of the South African Children's Cancer Study Group (SACCSG) showed that nephroblastoma was the fourth most common paediatric cancer in South Africa (SA) and accounted for 12% of the total paediatric cancers in SA (Stefan & Stones 2012; Stefan 2010).

In the USA there was a slightly higher incidence in females than males for nephroblastoma between 1975-1995. However, incidence rates were similar by gender between 1990-1995. A study on nephroblastoma patients conducted in Cape Town, SA between 1979-2003 found 40.9% of the cohort to be male and 59.1% to be female (Davidson, Hartley, Desai, Daubenton, Rode & Millar 2006). In SA there was a slightly higher incidence for nephroblastoma among black African children compared to white children for the period 1975-1995. However, incidence rates by race were similar between 1986-1989 and 1990-1995.

2.1.2 Diagnosis of nephroblastoma

Patients with nephroblastoma frequently present with a palpable abdominal mass. Some may present with haematuria, fever or abdominal pain. Seldom is the diagnosis led by patients who present with renal vein or caval extension, development of varicocele, hepatomegaly, ascites or congestive heart failure (Gommersall, Arya, Mushtaq & Duffy 2005). Once a patient is suspected of having nephroblastoma various investigations are conducted to confirm the diagnosis.

The first step is to collect a 24-hour urine sample whilst the patient is on a normal diet or do a spot urine test for Vanillylmandelic acid (VMA): creatinine ratio. This is done to exclude neuroblastoma and to establish renal function. An ultrasound is done to obtain three dimensional measurements of the tumour; to establish if it is an intra-renal process; to investigate if it is cystic, solid or both; to search for other abnormalities in the abdomen and to exclude hepatic metastases. Two plain x-radiations (x-rays) of the chest in two directions are needed to exclude pulmonary metastases (Poole 2010).

The second step involves a computerised tomography (CT) scan of the abdomen to confirm intra-renal lesion with certain characteristics and relations to other structures such as lymph nodes, invasions of vessels, and other organs. This is also useful for measuring the tumour. If there is any doubt from the chest x-ray a CT-scan of the thorax is needed to further exclude or confirm metastases. A fine needle aspirate (FNA)/Trucut biopsy is required to confirm diagnosis, especially in large abdominal masses (Poole 2010). If there is still no confirmed diagnosis an open biopsy is conducted. These are the minimum diagnostic tests required and it is up to the physician to decide on more sophisticated investigations, if required (Poole 2010).

2.1.3 Medical and clinical management of nephroblastoma

Until the founding of the NWTS in 1969, clinical research was restricted due to the rarity of nephroblastoma (Davidoff 2009). The inception of the NWTS, and the four trials that followed, represented a supportive effort from numerous groups to treat patients in a structured manner so that statistically relevant comparisons of management variations could be made (Davidoff 2009). The aim of each consecutive NWTS was to maintain a high cure rate for patients with nephroblastoma, whilst decreasing the intensity and duration of therapy (Davidoff 2009). Management of nephroblastoma is based on surgical stage and histologic evaluation of the tumour (Poole 2010). Table 2.1 shows the clinical pathology staging of nephroblastoma.

Table 2.1: Clinical pathology staging of nephroblastoma (Poole 2010)

Stage	Clinical pathology staging
I	Tumour limited to the kidney; completely exercised
II	Tumour extending outside of the kidney; completely excised
III	Residual tumour in the abdomen after surgery Invasion beyond capsule Macroscopic or microscopic residual tumour Involved lymph nodes (or biopsy) Rupture or spillage of tumour Tumour seedlings on peritoneal surfaces Pre-treatment biopsy
IV	Distant haematogeneous metastases - lung, liver
V	Bilateral tumour at diagnosis

Surgery has long been known to be of importance in the treatment of nephroblastoma but based on the NWTS trials, chemotherapy and radiation therapies have also had a significant impact on improving the survival rates (Davidoff 2009). Other large randomised controlled trials, besides the NWTS, have also been designed, managed and published by various collaborative groups including the SIOP and the United Kingdom Children's Cancer Study Group (UKCCSG). Jointly these studies have allowed nephroblastoma treatment to be altered to minimise morbidity for those with low-risk disease and to maximise the prognosis for high-stage, high-risk patients (Gommersall *et al* 2005).

Treatment strategies vary between the USA and Europe, with the former favouring immediate nephrectomy and the latter favouring pre-operative chemotherapy. There is also a variation between the UK and European strategies. The UK strategies favour pre-nephrectomy chemotherapy only after the tumour has been biopsied (Gommersall *et al* 2005). These treatment strategies differ slightly in their approach depending on the use of neoadjuvant chemotherapy. However, stage II/III disease in either setting involves further adjuvant treatment with two-agent or three-agent chemotherapy, including radiotherapy in some cases. Patients with stage IV need three-agent chemotherapy and added lung irradiation, either immediately or when radiographic proof of the disease is shown. In

bilateral tumours preoperative chemotherapy is universally administered followed by nephron-sparing surgery (Gommersall *et al* 2005).

The management of nephroblastoma has been considerably modified over the last few decades of the 20th century resulting in a great reduction in associated morbidity. However, there are areas that need further refinement. Patients that relapse are currently given high-dose chemotherapy treatment regimes, which need to be optimised (Gommersall *et al* 2005).

The treatment of nephroblastoma is one of the great success stories in oncology. The survival rate is currently 90% in the developed world and this success has led to a change in treatment protocols from simply maximising cure to maximising cure with minimal treatment associated toxicities (Metzger & Dome 2005). However, this percentage is much lower in South Africa (Hadley & Jacobs 1990). A retrospective study over ten years (2000-2010) conducted at four major government hospitals in SA estimated that the overall survival rate at five years was 66% (Stones, Hadley, Wainwright & Stefan 2015).

Due to the various treatment protocols which increase the physiological stress on the body the nutritional requirements in patients with nephroblastoma are extremely important and must be met. Nutritional requirements in patients with nephroblastoma is discussed in the next section.

2.1.4 Changes in nutritional requirements of children with nephroblastoma

There are currently no specific and scientifically based nutritional requirements for children with nephroblastoma or cancer in general (Bauer, Jürgens & Frühwald 2011). A malignant tumour in children can cause a range of changes in metabolism, including the metabolism of energy. These alterations result from an increased Cori-cycle, an inability to down-regulate energy expenditure in conjunction with a reduction in energy intake, which can lead to poor use of nutrients (Andrassy & Chwals 1998; Holroyde, Gabuzda, Putnam, Paul & Reichard 1975).

A study, conducted in 2001 in the Netherlands studied the level of and changes in basal metabolic rate (BMR) in 13 children with a solid tumour at diagnosis and during treatment. The aim was to provide a more accurate estimation of energy requirements to allow for better provision of nutritional support. Before each BMR measurement, the patient needed to meet

specific criteria in order to exclude all factors that could influence BMR besides the tumour itself. This included: (1) no fever present; (2) last chemotherapy course at least 2 weeks prior; (3) no corticosteroids in the previous week; (4) haemoglobin concentration of > 0.6 g/dl; (5) surgery or radiotherapy at least 4 to 6 weeks prior to the measurement (Den Broeder, Oeseburg, Lippens, van Staveren, Sengers, van't Hof & Tolboom 2001). The authors showed that BMR at diagnosis, using indirect calorimetry, was greater in all patients when compared to the reference value (Schofield equation based on age, weight and gender for that patient). As treatment progressed, the difference between the measured BMR and the reference BMR decreased in all patients. This indicated that BMR in children with a solid tumour returned to the values found in the reference children. The increase in BMR that was identified in all children at diagnosis showed that the tumour was more than just an inactive mass which needed to be removed. This mass consists of tissue which is metabolically active and increases the BMR initially. This should be accounted for when energy requirements are calculated at diagnosis (Den Broeder *et al* 2001.)

In order to help maintain weight and prevent weight loss associated with cancer, it is important to individualise the energy needs of the patient (Grant & Hamilton 2012, p842). In paediatric oncology there are no universally accepted, evidenced-based guidelines for children with cancer. Adequate nutrition is required to allow for continued growth and development of the child whilst receiving cancer treatment and not just for metabolic homeostasis, as in adults (van Eys 1977). Nutrient requirements may be altered by many different factors. These include the effect of the disease on host metabolism, catabolic effects of cancer therapy and physiological stress caused by surgery, fever, malabsorption and infection (Grant & Hamilton 2012, p855).

The supplementation of vitamin and minerals above the reference nutrient intake is not recommended because there is a potential for toxicity and interactions with the efficacy of conventional treatment. Patients receiving enteral feeds or nutritionally complete oral sip feeds should not require additional vitamins and minerals. Patients on treatment that is less intense and eat only a few foods with a limited intake of fruit and vegetables may require a general multivitamin supplement (Ward 2007, p470).

Children with advanced cancer are at a greater risk of severe malnutrition than adults as there is more frequent and more aggressive multimodal treatment. The long-term nutritional effects

of cancer and its treatment on children are not well documented (Grant & Hamilton 2012, p855). The anticipated need for nutritional support of children with cancer is based on the nutritional status at diagnosis. Aggressive nutritional support may be important in the management of these children because adverse outcomes have been reported to be associated with malnutrition (Pietsch & Ford 2000). The nutritional status of children with nephroblastoma is addressed next.

2.2 Nutritional status of children with nephroblastoma

In this section the methods used to assess nutritional status, prevalence of malnutrition in children with cancer, consequences and management of malnutrition are discussed.

2.2.1 Assessment of nutritional status

Assessing the nutritional status of a patient is an important part of nutritional management since nutritional status affects response to illness. In paediatric patients' attention to nutritional status is imperative as they are also growing and developing. Thus, assessment of nutritional status is an important part of clinical evaluation in paediatric patients (Maqbool, Olsen & Stallings 2008, p5). Nutritional assessment should be done within 24 hours to 48 hours of admission for every patient and repeated regularly depending on the age of the patient, diagnosis, treatment, and other risk factors. There are four methods that can be used to assess nutritional status. These include anthropometry, biochemistry, clinical and dietary assessment (Mosby, Barr & Pencharz 2009). However, in this study only anthropometric measurements (weight, height, mid-upper arm circumference and triceps skinfold thickness) and serum albumin was used to assess nutritional status. Clinical and dietary data were not recorded at the time of admission. In the next section, the use of anthropometric measures and biochemical markers (serum albumin) in assessing nutritional status are discussed.

2.2.1.1 Anthropometric measures used to assess nutritional status

Anthropometry, which is widely used throughout the world, provides an inexpensive and non-invasive measure of the general nutritional status of a single person or a group of people (Cogill 2001, p10). Depending on the anthropometric indicator chosen, anthropometry can be used for various purposes (Cogill 2001, p10). Four of the main measures used for anthropometric assessment include: age, gender, length or height and weight. When these measures are used in conjunction with each other they can provide important information about a person's nutritional status. Three indices commonly used in the nutritional

assessment of children are weight for age (WFA), height/length for age (HFA) and weight for height/length (WFH). There are advantages and disadvantages with use of all three indices and these should be taken into account when using them to assess the nutritional status of paediatric oncology patients with tumours (Cogill 2001, p11).

Growth is an important indicator of health and nutritional status in paediatrics. This longitudinal data assists in identifying patients that are at risk of malnutrition and allows for the monitoring of a patient's clinical response to nutritional therapy (Maqbool *et al* 2008, p5). A variety of growth charts are available for the assessment of growth (Maqbool *et al* 2008, p5). Following a comprehensive review of anthropometric references, the World Health Organization (WHO) undertook the task of generating revised growth reference standards. Data was collected from healthy breastfed infants from six diverse countries. These growth standards are prescriptive as opposed to descriptive. They indicate how children should grow rather than how they grew at a particular time and place. The 2006 WHO growth charts reference standards include length/height for age, weight for age, weight for length/height, and BMI by age for children from birth to 60 months (De Onis 2006, pxvii).

Malnutrition is often diagnosed when one or more of the anthropometric indices show a deficit. It should not be assumed that such deficits are purely as a result of nutrient or energy deficiency. A significant shortfall in a physical measurement, demonstrating past or current malnutrition, could be a result of an absence of adequate food, increased rate of nutrient utilisation (as in many diseases), and/or decreased absorption or use of nutrients (WHO 1995). Table 2.2 describes the common terms for height and weight-based anthropometric indicators.

Table 2.2: Common terms for height-and weight-based anthropometric indicators (WHO 1995)

Anthropometric indicator	Terms describing outcomes	Terms describing process	Explanation
Low height for age	Shortness Stunted	- Stunting (gaining insufficient height relative to age)	Descriptive Implies long term malnutrition and poor health
Low weight for height	Thinness Wasted	- Wasting (gaining insufficient weight relative to height, or losing weight)	Descriptive Implies recent or continuing current severe weight loss
Low weight for age	Lightness Underweight	- Gaining insufficient weight relative to age, or losing weight	Descriptive Implies stunting and/or wasting

Height for age shows achieved linear growth and its deficits indicate long-term, cumulative inadequacies of health or nutrition. Stunting which is a result of past under nutrition or chronic malnutrition can be identified. It cannot measure short-term changes in malnutrition (Cogill 2001, p11; WHO 1995).

Weight for height reflects body weight relative to height. A low weight for height indicates current or acute malnutrition or wasting (Cogill 2001, p11). An advantage of this index is that it does not require knowledge of age. The term “wasting” is used to describe a recent and severe process that has led to a substantial loss of weight, usually as a result of acute starvation and/or severe disease (WHO 1995). Wasting in individual children can change rapidly and is a sensitive marker to changes in food availability or disease prevalence (Cogill 2001, p11).

Weight for age reflects body mass relative to chronological age. This index reflects both past (chronic) and/or present (acute) under nutrition but is unable to distinguish between the two (Cogill 2001, p11). Underweight which is based on weight for age is a combined measure of

stunting and wasting. It is suggested to be used as an indicator to assess changes in the degree of malnutrition over time (Cogill 2001, p11).

Body mass index is used to assess weight status in children and adolescents as well as adults. For BMI to be meaningful in growing children it must be compared to a reference standard that accounts for the child's age and gender. Body mass index is a measure of weight adjusted to height. It is calculated as weight in kilograms divided by the square of height in meters (Must & Anderson 2006). Body mass index for age provides a good indicator of levels of body fat, and a BMI out of the normal range is associated with an increased risk of poor health during childhood as well as later in life (Dinsdale, Ridler & Ells 2011).

Studies assessing nutritional status in paediatric oncology patients have relied almost exclusively on weight-related indices. In children with malignancy these indices can be misleading as tumour masses can contribute up to 10% of total body weight, and lead to an increase in weight for height. A study conducted by Hadley & Jacobs (1990) at King Edward VIII Hospital in Durban, SA showed that rural children with nephroblastoma had tumours greater than 10% of their body weight compared to their urban counterparts which were less than 5%. It is therefore possible for some children with tumours who would otherwise have an abnormally low weight for age to be classified as normal weight (Wessels, Hesseling, Van Ommeren & Boonstra 1999; Smith, Stevens & Booth 1991; Hadley & Jacobs 1990).

The use of arm anthropometry has been widely accepted worldwide, especially in developing countries (Mogendi, De Steur, Gellynck, Saeed & Makokha 2015). The mass of a tumour does not affect arm anthropometry, making it an ideal tool for assessment of nutritional status in children with cancer (Smith *et al* 1991). Mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSFT) are used to determine body fat and protein stores (Maqbool *et al* 2008, p10).

Smith *et al* (1991) assessed malnutrition at diagnosis in children with cancer. This case-control study, conducted in the UK, recruited 100 patients and 55 healthy controls. The anthropometric measurements were taken by one observer using standard techniques. The overall prevalence of malnutrition at diagnosis using the traditional assessment (height for age and weight for height) was 5%. The results from the arm anthropometry were markedly different. Mid-upper arm circumference showed that 20% of the patients were malnourished

compared to the controls and TSFT showed that 23% were malnourished compared to 2% of the controls. The patients were then divided into three sub-groups: leukaemia, solid tumours (abdominal) and solid tumours (extra-abdominal). The sub-groups did not differ in height for age or weight for height. However, the intra-abdominal solid tumour group had significantly lower MUAC and TSFT compared to the other two groups. Malnutrition was identified by MUAC in 35% of the patients with intra-abdominal solid tumours, 6.7% in extra-abdominal solid tumours and 15% in those with leukaemia. The same trend was identified with the TSFT, which was similarly distributed. Results showed that patients with intra-abdominal tumours were most likely to be malnourished (by arm anthropometry). These patients often have the largest tumour masses, although difficult to quantify. These patients also tend to be younger (and therefore smaller) than those with extra-abdominal tumours or leukaemia. Thus, the relative contribution of the tumour mass to weight for height is greater. Weight for height is likely to be most misleading in patients that are most likely to be malnourished (Smith *et al* 1991).

Oguz, Karadeniz, Pelit & Hasanoglu (1999) performed a similar control study, in Turkey, in 62 patients using arm anthropometry for a more accurate evaluation of nutritional status in children diagnosed with a solid tumour. The control group consisted of 31 healthy children. Height, weight, MUAC, and TSFT were measured using standard techniques in both the patients and the control groups. The WFH values of the patients and the control groups were not statistically different and malnutrition was not identified in either of the groups. The arm anthropometry values were found to be significantly lower among the cancer patients. Thirty percent had TSFT and 29% had MUAC values below the 5^{th} percentile while none of the control group fell into this category. Triceps skinfold thickness and MUAC together showed that 27% of the patients were malnourished at diagnosis. This study also compared the patients with intra-abdominal tumours to the those without. Mid-upper arm circumference and TSFT were found to be significantly lower in the intra-abdominal group. Thirty-five percent of the intra-abdominal group were malnourished while 16% of the children without were malnourished. The prevalence of malnutrition was significantly higher in the intra-abdominal tumour group when using arm anthropometry, whereas no difference was found using weight for height. This could be a result of excessive growth of intra-abdominal masses before diagnosis increasing the body weight, as well as localised effects of the masses leading to nutritional problems and adding to systemic effects (Oguz *et al* 1999).

A cross-sectional study by Garófolo, Lopez & Petrelli (2005), conducted in Brazil, evaluated 127 children aged over one year and adolescents diagnosed with cancer. The subjects were divided according to their disease type. A comparative analysis of deficits was conducted on WFH and BMI Z-score and TSFT, MUAC and arm muscle circumference (AMC). Measurements were taken at the same time during the first month of treatment, whilst receiving the first chemotherapy cycle. The analysis showed significantly higher deficits using TSFT (40.2%) and MUAC (35.4%) as opposed to weight for height Z-scores or BMI (18.9%). The study also indicated that solid tumour patients were statistically more malnourished than those with haematological malignancy diseases when using WFH Z-score or BMI and the AMC and MUAC indexes. There was a higher prevalence of malnutrition among patients with solid tumours compared to those with haematological tumours. The nature of the disease as well as the type of therapy could have been the cause of the increase in malnutrition (Garófolo *et al* 2005).

A large study conducted in seven countries in Central America found the same to be true. When using the standard method of BMI for age the percentage of malnourished children with cancer was 45%. However, when arm anthropometry (MUAC and TSFT) was used 63% of the children were malnourished (Sala *et al* 2012). These studies have identified the importance of using MUAC and TSFT to assess nutritional status in the paediatric oncology patient, especially in patients with intra-abdominal solid tumours.

2.2.1.2 Biochemical markers used to assess nutritional status

Biochemical values can be used to help estimate nutritional status in children with cancer (Mosby *et al* 2009). Serum albumin and pre-albumin mirror the adequacy of protein and calorie intake. The half-life of serum albumin is 14 to 20 days so it reflects long-term protein stores. The half-life of pre-albumin is 2 to 3 days and is therefore a better indicator of short-term calorie and protein stores (Maqbool *et al* 2008, p11). Two studies, one by Donaldson *et al* (1981) and one by Elhasid, Laor, Lischinsky, Postovsky & Arush (1999), both assessed the relationship between nutritional status and serum albumin on admission in children with cancer and children with solid tumours, respectively. Both studies found no significant correlation between the two. Elhasid *et al* (1999), however, found pre-albumin on admission and throughout chemotherapy was a good marker to evaluate the nutritional status of children with solid tumours. These biochemical markers alone are not reliable when assessing nutritional status as they are affected by various factors such as hydration status, sepsis,

stress, and acute illness. Nevertheless, poor nutritional intake and loss of appetite is associated with these situations, thus, hypoalbuminaemia still suggests a need for nutritional intervention (Maqbool *et al* 2008, p11). The prevalence of malnutrition in children with cancer is discussed next.

2.2.2 Prevalence of malnutrition in children with cancer

Malnutrition has been described and defined in many different ways, yet no consensus exists regarding a specific definition to identify children at risk (Wilcox, Nieburg & Miller 1989). Several factors influence the prevalence of malnutrition in children with cancer. These include: (1) different techniques used to assess nutritional status; (2) histological type and staging of malignancy during assessment; (3) the child's individual susceptibility to malnutrition in the ward and anticancer treatments whilst being classified; and lastly (4) the nonspecific definition of malnutrition (Bauer *et al* 2011). As a result, the prevalence of malnutrition in children with cancer has been reported as ranging from common to non-existent at diagnosis. A range from zero to about 50% has been reported depending on the type of cancer (Smith *et al* 1991; van Eys 1979).

Malnutrition is often a side effect of therapy in developed countries. Chemotherapeutic regimes often bring about nausea, vomiting and anorexia. Disorders of the gastrointestinal tract such as mucositis or diarrhoea are also common. All of these lead to a deterioration in the nutritional status of the child. Conversely, in less developed countries malnutrition is often already present at diagnosis (De Onis, Monteiro, Akre & Clungston 1993). A study, by Israëls *et al* (2010), evaluated the pharmacokinetics of Vincristine in Malawian patients with nephroblastoma compared to patients diagnosed and treated in the UK. When assessing nutritional status at diagnosis (Z-score of corrected weight for height was used) the Z-score for weight for height was significantly lower in the Malawian patients than in the UK patients. The corrected weight for height Z-score was less than -2 in seven of the 11 Malawian patients (64%) while all eight of the UK patients fell in the normal range. This showed that malnutrition was more prevalent in the patients from a developing country, Malawi (Israëls *et al* 2010).

The prevalence of malnutrition at diagnosis in newly diagnosed children with cancer presenting at a paediatric oncology ward in Morocco was comprehensively assessed. One hundred children were anthropometrically assessed (WFH, WFA, HFA, BMI, TSFT, MUAC

and AMC) and biochemical markers (serum albumin) were evaluated before therapy was initiated. The study showed a high prevalence of malnutrition when anthropometry was used: 37% by WFA; 20% by HFA; 33% by WFH Z-scores and BMI. Following the same trend as other studies a higher deficit was shown using TSFT (50%) and MUAC (39%). Malnutrition by conventional methods was found to be lower when compared with arm anthropometry. Patients with solid and central nervous system tumours showed larger deficits when compared to those with other malignant disease. Twenty-eight cases of malnutrition were identified according to serum albumin (3 severe, 8 moderate and 17 with mild malnutrition). The use of biochemical parameters alone when compared to anthropometric parameters detected a much lower prevalence of malnutrition (Tazi *et al* 2008).

A similar study conducted in Malawi assessed the nutritional status of 118 newly diagnosed paediatric oncology patients on admission to hospital. Anthropometry classified malnutrition as: 44.5% by HFA; 39.8% by WFA; and 17.2% by WFH. Arm muscle area showed that 55.1% of the patients were malnourished while MUAC and TSFT showed that 59.3% were malnourished. Once again arm anthropometry showed a higher degree of malnutrition even though the overall prevalence of malnutrition was high (Israëls, Chirambo, Caron & Molyneux 2008).

Accurate prevalence rates of malnutrition for the different cancer types remain difficult to derive after three decades of research. The limited number of studies with small sample sizes that made use of different methods and criteria to assess nutritional status, makes it almost impossible to present results on the prevalence of malnutrition in paediatric cancer patients. Also, since most studies were conducted on children with leukaemia, little is known about children with solid tumours (Brinksma, Huizinga, Sulkers, Kamps, Roodbol & Tissing 2012).

Now that the assessment of malnutrition and the prevalence of malnutrition in children with cancer have been described, the consequences and management of malnutrition is discussed next.

2.2.3 Consequences of malnutrition in children with cancer

Without adequate nutrition, skeletal muscles, including the heart muscles, waste and weaken. Brain development is stunted and impaired. Body temperature is suboptimal due to slow metabolism, growth slows down or stops and there is delayed wound healing (Sizer &

Whitney 2006, p199). Malnutrition causes hormonal changes and leads to compromised cytokine response resulting in decreased immune system (Schaible & Kaufmann 2007; Cunningham-Rundles, McNeeley, Moon 2005).

A study, conducted by Loeffen, Brinksma, Miedema, de Bock & Tissing (2015), assessed 269 paediatric patients with cancer. At diagnosis, 5.2% were malnourished (BMI Z-score < -2), 56.9% were well nourished and 7.1% were over nourished (BMI Z-score >2). Malnutrition at diagnosis and at 3 months after diagnosis was shown to have a significant effect on survival. Rapid weight loss (>5% in the first 3 months after diagnosis) also appeared to make paediatric cancer patients more vulnerable to bacterial infections (Loeffen *et al* 2015). The nutritional management of malnutrition in children with cancer is discussed next.

2.2.4 Nutritional management of malnutrition in children with cancer

Malnutrition is a common concern in the management of paediatric tumours. The metabolic alterations caused by cancer and the maintenance of nutritional homeostasis are crucial aspects of management. Adequate nutritional support may enhance therapy, decrease complications, improve immunological status, and hopefully, improve survival (Andrassy & Chwals 1998).

The main aims of nutritional support in the paediatric oncology patient are to reverse the malnutrition seen at diagnosis, to prevent the malnutrition associated with treatment and to promote weight gain. Early nutritional support improves immune competence, tolerance to treatment and quality of life. Nutritional support should therefore play a major part in therapy in order to reverse or prevent the effects of PEM (Ward 2007, p466).

In paediatric oncology there are currently no specific, universally agreed upon energy requirements, criteria for, timing of, and duration of nutritional interventions that exist (Bauer *et al* 2011). Numerous recommendations for nutritional requirements have been based on ideal body weight (IBW), BMI, and estimating energy needs. These nutritional requirements have not taken into account changes in body composition to show muscle wasting and body mass depletion. Weight loss is a poor indicator of malnutrition as it reflects past nutritional status rather than current. In paediatric oncology the main purposes of nutritional interventions are: the maintenance of body stores as close to ideal as possible, minimising

wasting, promotion of appropriate growth and development, and providing a good quality of life (Bauer *et al* 2011).

All children with cancer need nutrition intervention as part of treatment, starting from diagnosis to prevent or restore abnormalities in growth and development before nutritional status is severely compromised. It has been recommended that monthly assessments be done to evaluate the efficacy of the nutrition intervention (Bauer *et al* 2011). Figure 2.1 shows a screening schedule for nutritional status after diagnosis. The importance of nutritional support can be difficult to define clearly in paediatric oncology patients because tumour types, stage, and outcome variables are often heterogeneous (Andrassy & Chwals 1998).

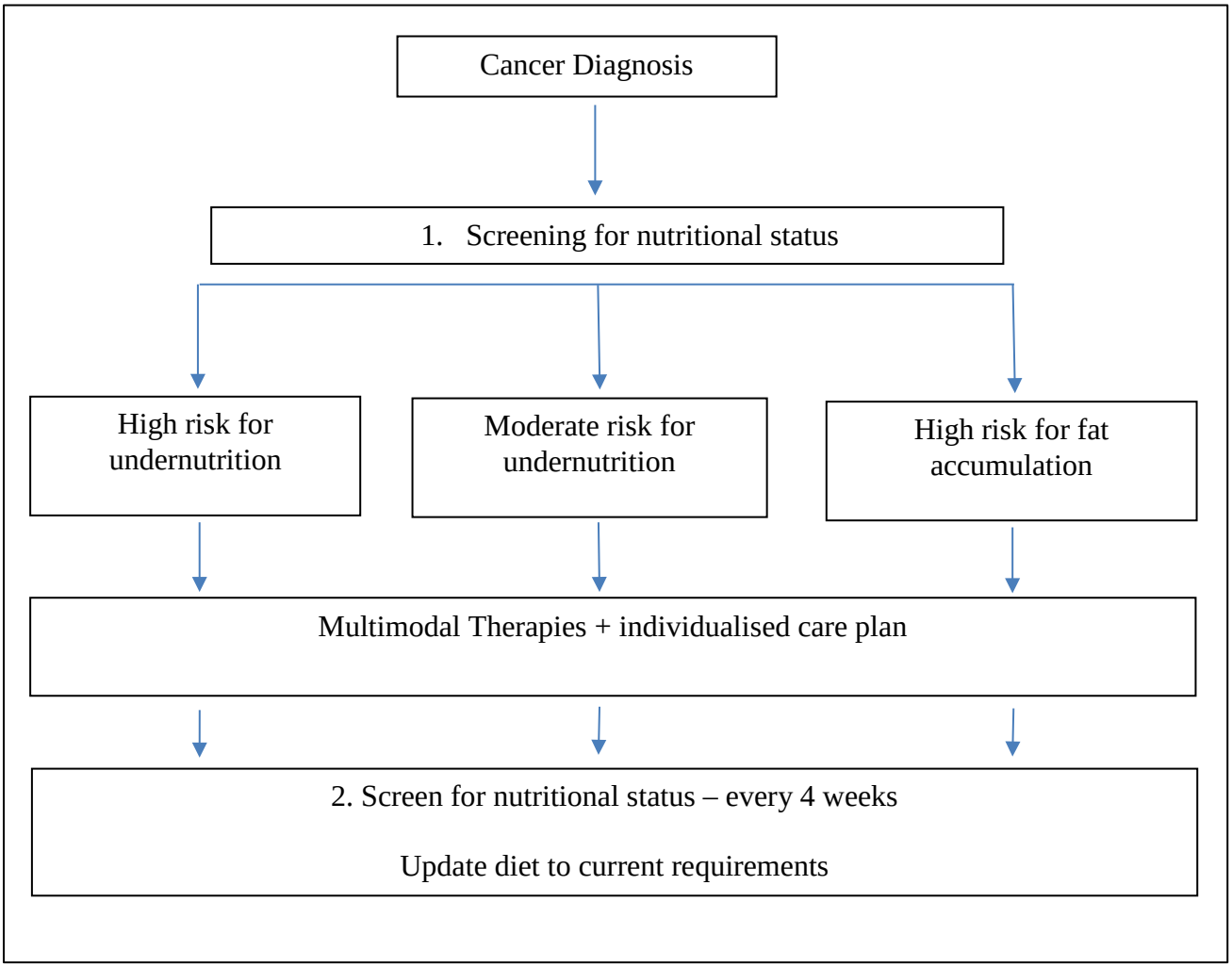

Figure 2.1: A screening schedule for nutritional status after diagnosis (after Bauer *et al* 2011).

A study, conducted by Rickard, Grosfeld, Kirksey, Ballantine & Baehner (1979), evaluated 28 children from the USA with advanced malignant disease (21 solid tumours, 7 leukaemia-lymphoma) and the effectiveness of enteral and parenteral feeding in supporting an adequate nutritional status and/or reversing protein-energy malnutrition (PEM). At the beginning of treatment, 21 patients received intensive nutritional counselling (INC) and oral supplementation. This included: age-appropriate individual counselling, provision of paediatric menus which featured children's favourite foods and an atmosphere conducive to eating in age- related play dining rooms. Two liquid supplements were presented to each child: Ensure-Plus,@ (Ross Laboratories, Columbus, Ohio), lactose free, and Instant Breakfast® (Carnation Company, Los Angeles, California) with milk. Seven patients received total parenteral nutrition (TPN). There was a decreased intake in 76% of the patients who received INC. The children with advanced solid tumours or relapsed leukaemia and lymphoma underwent intensive combined therapy and lost an average of 16% of body weight during the first month of treatment. This was while receiving an oral diet that provided an average of 48% of the Recommended Dietary Allowance (RDA) for energy. Twenty-two percent of body weight was lost on average in the nephroblastoma sub-group. This study showed that parenteral nutrition that delivered 90% of the RDA for energy and 2.5-3.0 g/kg/day protein could reverse pre-existing malnutrition in children with late stage malignancies and recurrent leukaemia or lymphoma who required aggressive, toxic anti-tumour therapy. Improved nutritional status was achieved when the WFH percentile, TSFT, serum albumin and transferrin serum concentrations normalised. All of these indicators occurred after 28 days of parenteral nutrition as opposed to an *ad libitum* oral diet which delivered less than 50% of the RDA for energy. If parenteral nutrition was stopped early (9-14 days) before the completion of toxic oncologic therapy, malnutrition was not reversed (Rickard *et al* 1979).

A similar study conducted a year later also in the USA, by Rickard, Kirksey, Baehner, Grosfeld, Provisor, Weetman, Boxer & Ballantine (1980) studied the effectiveness of enteral and parenteral nutrition in the management of children with Wilm's tumours. There were only nine patients (1-7 years) involved in this study, eight of which received enteral nutrition at the beginning of treatment, whilst one received TPN. Due to weight loss of more than 20%, WFH less than the 5th percentile, a decrease in serum albumin and energy intake less than 80% of the RDA, four of those who initially received enteral nutrition were started on TPN. The enteral nutrition comprised of oral supplements and a complete feeding program.

During the intensive cancer treatment period, dramatic weight loss was observed in the group receiving enteral nutrition. However, every patient receiving parenteral nutrition gained weight. The average energy intake in the enteral group was 64% ± 27% of the RDA whereas the TPN group received 105% ± 9% of the RDA. This study also showed that TPN for 28 days or longer restored weight for height. The children with nephroblastoma experienced severe malnutrition in conjunction with the initial aggressive cancer therapy. During the first 40 to 60 days of intensive treatment, there was a dramatic decrease in enteral intake, severe loss of weight and a decrease in skinfold thickness, serum albumin and transferrin concentrations (Rickard *et al* 1980).

Although TPN may help to reverse malnutrition it also has disadvantages which must be considered. Disadvantages of TPN include; potential risk from central venous access insertion such as arterial puncture or catheter misplacement; potential risk from ongoing use of central venous access for example infection or thrombus; increased risk of metabolic abnormalities including, hepatic dysfunction, acid-base disturbances, hyperglycaemia and hypoglycaemia; increased risk of overfeeding and increased financial cost and mortality compared with enteral feeding (Singer, Berger, Van den Berghe, Biolo, Calder, Forbes, Griffiths, Kreyman, Leverve & Pichard 2009).

For patients with a low nutritional risk, unless complicated by factors such as relapse, sepsis or major abdominal procedures, oral feeding is the best method if they are able to ensure adequate intake of nutrients (Ward 2007, p468). However, the majority will need high energy supplements and specific advice on eating problems which are related to the side effects of their treatment (Ward 2007, p468). Whenever nutritional intervention is indicated, the enteral route is preferred (Ward 2007, p468). Enteral nutrition has many practical and psychological advantages over parenteral nutrition. These include; a low risk of infection and other catheter- related complications, more normal play activities, and involvement of both parent and child. Enteral feeding maintains gut integrity, reduces the risk of bacterial translocation and is more economical (Ward 2007, p468). Nasogastric feeding during intensive treatment allows for improved nutritional status with minimal complications. It has also been shown to improve energy intake and well-being and to result in significant improvement in nutritional status when assessed by MUAC (Smith, Handy, Holden, Stevens & Booth 1992). Parenteral nutrition should be reserved for those who cannot meet their nutritional requirements through enteral feeding, such as patients with abnormal

gastrointestinal function related either to the tumour or following chemotherapy or radiotherapy treatments (Ward 2007, p468).

The success of an enteral nutrition programme for children with nephroblastoma is affected by several factors, including nutritional status at diagnosis, treatment protocol, phase of treatment, and tumour response (Rickard *et al* 1980). Malnutrition in children with cancer is an under researched topic within paediatric oncology and should not be accepted at any point of the disease or accepted as an unavoidable process. Nutritional strategies should be integrated as an essential part of paediatric oncology in order to prevent adverse effects caused by malnutrition (Bauer *et al* 2011). There are no specific nutritional management guidelines available for children with cancer despite the well documented need for adequate nutrition in the long-term outcome. This is a shortcoming that needs be addressed. The following section discusses chemotoxicity in children with nephroblastoma.

2.3 Chemotoxicity in children with cancer

Chemotoxicity is the toxicity that arises from the administration of chemotherapy (Mosby's Medical, Nursing, & Allied Health Dictionary 1998, p313, p1632). "Chemotherapy is the use of chemicals to destroy cancer cells on a selective basis. Cytotoxic agents do not kill the cancer cells directly but instead impair their ability to replicate. Toxicity is a condition that results from exposure to a toxin or to toxic amounts of a substance that does not cause adverse effects in smaller amounts" (Mosby's Medical, Nursing, & Allied Health Dictionary 1998, p313, p1632).

At IALCH the SIOP protocol is followed for children with nephroblastoma. This protocol involves the use of the chemotherapy agents: dactinomycin, vincristine and epirubicin prior to surgery. Post-surgery the same chemotherapy agents are used, with the addition of ifosfamide, etoposide and carbo-carboplatin (Bhatnagar 2009). Chemotherapy (antineoplastic agents) exert their effect on rapidly dividing cells and therefore has common toxicities, despite different modes of action. Side effects that impact on nutritional status include: mild to moderate nausea and vomiting; mucositis; paralytic ileus; gastrointestinal disturbances; decreased or loss of appetite (South African Medicines Formulary 2014, p350, 351, 354, 355; Santarpia, Contaldo & Pasanisi 2011).

The degree of chemotoxicity the patient experiences is graded according to the common toxicity criteria (CTC) shown in Table 2.3.

Table 2.3 Common Toxicity Criteria (European Organisation for Research and Treatment of Cancer 2016).

	Grade 0	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 (life-threatening)**
Allergy	None	Transient rash, fever < 38°C, 100.4°F	Urticaria, fever=38°C, 100.4°F, mild bronchospasm	Serum sickness, bronchospasm, requires parenteral medication	Anaphylaxis
BLOOD / BONE MARROW					
White Blood Cells(10^9/l)	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
Platelets (10^9/l)	WNL*	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
Haemoglobin (g/dl)	WNL*	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
Granulocytes (10^9/l) (ie.neuts.+baso.+eosin.)	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Lymphocytes (10^9/l)	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	<0.5
Hemorrhage (clinical) (includes nosebleeds, menorrhagia etc.)	None	Mild, no transfusion (includes bruise/ hematoma petechiae)	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, > 4 units transfusion per episode

* within normal limits

The dose of cytotoxic chemotherapy is individualised for each patient. There are two reasons for this. Firstly, individuals metabolise and eliminate drugs differently, and thus the same dose of a drug may have a different pharmacokinetic profile and presumably a different outcome among the individuals. Secondly there is a narrow therapeutic index for such drugs, with a small difference between the dose required to give a tumour response and that which causes unacceptable toxicity (Gurney 1996).

The next section reviews the prevalence of chemotoxicity in children with nephroblastoma and the factors that influence nutritional status and chemotoxicity.

2.3.1 Prevalence of chemotoxicity in children with cancer

Nutritional support has been highlighted as being an extremely important part of oncology care. However, very few studies have evaluated the role, if any; that nutrition plays in toxicity in the paediatric oncology population. A Malawian study, conducted on patients with nephroblastoma aimed to evaluate the pharmacokinetics of vincristine in these patients who generally present with malnutrition and large tumours and compare them to patients diagnosed and treated in the UK. The two patient populations showed a clear difference in nutritional status. The malnourished Malawian patients had lower vincristine clearance rates than a comparable patient population with better nutritional status (Israëls *et al* 2010).

The toxicity of preoperative chemotherapy was studied in children with nephroblastoma in Malawi. Patients that were diagnosed with unilateral tumours received preoperative chemotherapy. Patients with localised disease were placed on a two drug 4-week schedule and those with metastatic disease were placed on a three drug 6-week schedule. Of the 60 patients who received preoperative chemotherapy, 58% (n=35) experienced CTC grade three neutropenia and 27% (n=16) experienced CTC grade four neutropenia. Neutropenia was significantly more common in those that received the three drug schedule. This study depicts toxicity in a very low-income setting in sub-Saharan Africa. Forty percent of patients were stunted; a sign of chronic malnutrition. Considerable haematological toxicity was experienced in these malnourished Malawian children (Israëls *et al* 2012).

A recent study assessed if BMI at diagnosis or weight change during therapy predicted toxicity in intermediate risk rhabdomyosarcoma. Four hundred and sixty-eight patients aged 2-21 years were evaluated for grade 3 and 4 chemotoxicities, hospital days, and the number of

infections in patients with weight loss (>5% to 10% and >10% weight loss) compared to patients with no more than 5% weight loss. At week 12 there was no association between grade 3 and 4 toxicity and percentage weight change. At week 42, there was a trend toward more grade 3 and 4 toxicities in patients who lost more than 10% of weight from baseline to week 24. This study and the other two mentioned all suggested that dose reductions need to be considered in malnourished patients in order to prevent an increased incidence and severity of toxicity (Burke, Lyden, Meza, Ladas, Dasgupta, Wiegner & Arndt 2013).

2.3.2 Factors that influence nutritional status and chemotoxicity

Malnutrition has been allied to changes in drug disposition. This includes variations in absorption, protein binding, hepatic metabolism and renal elimination. Anti-neoplastic agents, unlike other agents, have a narrow therapeutic index. Thus, slight changes in drug concentrations or exposure may have a great impact on response and toxicity (Murry, Riva & Poplack 1998). There are few published studies that specifically address the impact of malnutrition on the pharmacokinetics of anti-neoplastic agents. Generalisations are made based on the limited pharmacokinetic data in malnourished children receiving non-anti-neoplastic agents (Murry *et al* 1998).

2.3.2.1 Absorption

Drug absorption can be affected by the presence or absence of food in the gastrointestinal tract (Synold, Relling, Boyett, Rivera, Sundlund, Mahmoud, Crist, Pui & Evans 1994). It can influence pH, surface area accessible for absorption and gastrointestinal transit time. In malnourished children these differences in absorption may alter treatment outcome or toxicity. (Synold *et al* 1994).

2.3.2.2 Drug-protein binding

Albumin is the most abundant plasma protein in humans. It accounts for 55-60% of the measured serum protein (Gosling 1995). Plasma proteins are important for binding drugs (Stuart, Arbuck, Fleming & Evans 1991). In malnutrition, total blood protein concentration is reduced. Proteins important for binding drugs (e.g., albumin) are also decreased. As a result of this decreased protein binding, there may be a substantial increase in the plasma-free drug fraction of highly protein-bound compounds and patients may experience variations in rate of response or have increased chemotoxicity (Murry *et al* 1998).

2.3.2.3 Hepatic metabolism

Liver oxidative metabolism is influenced by nutritional factors (Jorquera, Culebras & Gonzalez-Gallego 1996). The pharmacokinetics of antipyrine, an analgesic and antipyretic, was studied in malnourished children in India. An intravenous dose of 16 mg/kg body weight of antipyrine was administered to 10 children suffering from PEM and five controls were matched in age and gender (6 months to 5 years). The plasma half-life and the metabolic clearance rates were monitored. The plasma half-life was increased (10.4 hours) in the malnourished group, compared to 6.3 hours in the control. The metabolic clearance rate was decreased in the malnourished group (47.1 ml/hr per kg), compared to 70.1 ml/hr per kg in the control group. This showed a slower rate of biotransformation of antipyrine, and hence, slower action of mixed oxidative function. After 17 to 25 days of nutritional rehabilitation, five of the children were restudied, using themselves as controls. Their weight improved by 13-16%. The antipyrine plasma half-life decreased to 6.6 hours and the metabolic clearance rate increased to 66.5 ml/hr per kg. The control had very similar values, thus showing biological recovery (Narang, Mehta & Mathur 1977).

A very similar study was done on eight Sudanese children between the ages of 9 and 12.5 years. This study looked exclusively at the effect of improved nutritional status and liver metabolism of antipyrine. The patients were studied on admission to hospital and again after 3 or 4 weeks of being on a high protein, high energy diet. After treatment for malnutrition there was a significant 33% decrease in plasma half-life and a significant 64% increase in plasma clearance. This again shows that drug metabolism is impaired in malnourished children and with an improvement in nutritional status comes improvement in the hepatic metabolism of drugs (Homeida, Karrar & Roberts 1979).

2.3.2.4 Renal function

The effect of malnutrition on renal function is another important determinant of the pharmacokinetic behaviour of many drugs (Murry *et al* 1998). Alleyne (1967) investigated the effect of severe malnutrition on the renal function of severely malnourished Jamaican children. The study showed a positive correlation between glomerular filtration rate (GFR) and nutritional status (Alleyne 1967).

Careful alterations of dose regime in malnourished children are necessary to achieve effective therapeutic levels and concurrently avoid toxic effects (Mehta 1990). The relationship

between malnutrition, pharmacokinetics and pharmacodynamics of antineoplastic agents needs to be investigated further. This could lead to improved changes in dosing strategies and protocol design for the malnourished paediatric oncology patient (Murry *et al* 1998).

2.4. Conclusion

Nephroblastoma is a cancer of the kidney which typically occurs in children. It is the fourth most common paediatric cancer in SA. Once identified it is managed with chemotherapy, radiation and surgery, or a combination of the three depending on the stage. Identifying those at risk of malnutrition is extremely important in paediatric oncology patients, and especially those with solid tumours such as nephroblastoma. The use of arm anthropometry has been shown to accurately identify those at risk of malnutrition as it is not affected by tumour weight. Energy requirements have been shown to be elevated before treatment is commenced and thus provision of adequate nutrition before treatment is started and throughout treatment is imperative. Early nutritional support improves immune competence, tolerance to treatment and quality of life. However, there is no universally agreed upon energy requirement equations for such patients. In developing countries patients often present, severely malnourished with large tumours. This can have an effect on the treatment received, leading to decreased chemotherapy doses and increased risk of infection and chemotoxicity. Accurate nutritional assessment is important for accurate calculation of chemotherapy dosing and thus, minimising the chances of chemotoxicity. There is a lack of published South African data on malnutrition in nephroblastoma patients and its influence on chemotoxicity. This study aimed to determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters and its relationship with chemotoxicity in children with nephroblastoma admitted to IALCH between 2004-2012. The next chapter discusses the methods used in order to best assess these objectives.

CHAPTER 3: METHODOLOGY

This chapter discusses the type of study, background information on the study site, study design, study population and sample, methods and materials, statistical analysis, reduction of bias and ethical considerations.

3.1 Type of study

This was a prospective, observational study. It aimed to determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters and its relationship with chemotoxicity in children with nephroblastoma admitted to IALCH between 2004-2012.

3.2 Background information on study site

This study was conducted at IALCH (Figure 3.1) which is a flagship tertiary and quaternary level hospital situated in Durban, KwaZulu-Natal (KZN). Patients who come to IALCH are referred from a base hospital. It provides care to the whole of KwaZulu-Natal and part of the Eastern Cape (EC) (Figure 3.2). According to the 2011 South African Census, black Africans make up the largest proportion of the KZN population (86.9%) followed by Indians (7.5%), Whites (4%) and Coloureds (1.3%) (Stats SA 2011). The EC is similar in that the population is made up of black Africans (86.5%), Coloureds (8.3%), Whites (4.8%) and Indians (0.4%) (Stats SA 2011). The age category of 1-14 years, which was used in this study, makes up 31.9% and 33% of the total population in KZN and the EC respectively. Of this 31.9% in KZN, 50.5% are males and 49.5% are females and of the 33% in the EC, the distribution of males and females is 50.8% and 49.2%, respectively (Lehohla 2012a, p16, 18, 24, 42; Lehohla 2012b, p13, 14, 17, 28). The South African National Health and Nutrition Examination Survey (SANHANES-1), conducted in 2012, reported that 62.7% and 68.6% of households are at risk of hunger or food insecure in KZN and the EC, respectively (Shisana, Labadarios, Rehle, Simbayi, Zuma, Dhansay, Reddy, Parker, Hoosain, Naidoo, Hongoro, Mchiza, Steyn, Dwane, Makoae, Maluleke, Ramlagan, Zungu, Evans, Jacobs, Faber & SANHANES-1-Team 2013). Food insecurity is defined as the inability to access adequate quantities of nutritious foods required for optimal growth and development, thus, directly linked to malnutrition (Napoli, De Muro & Mazziotta, 2011).

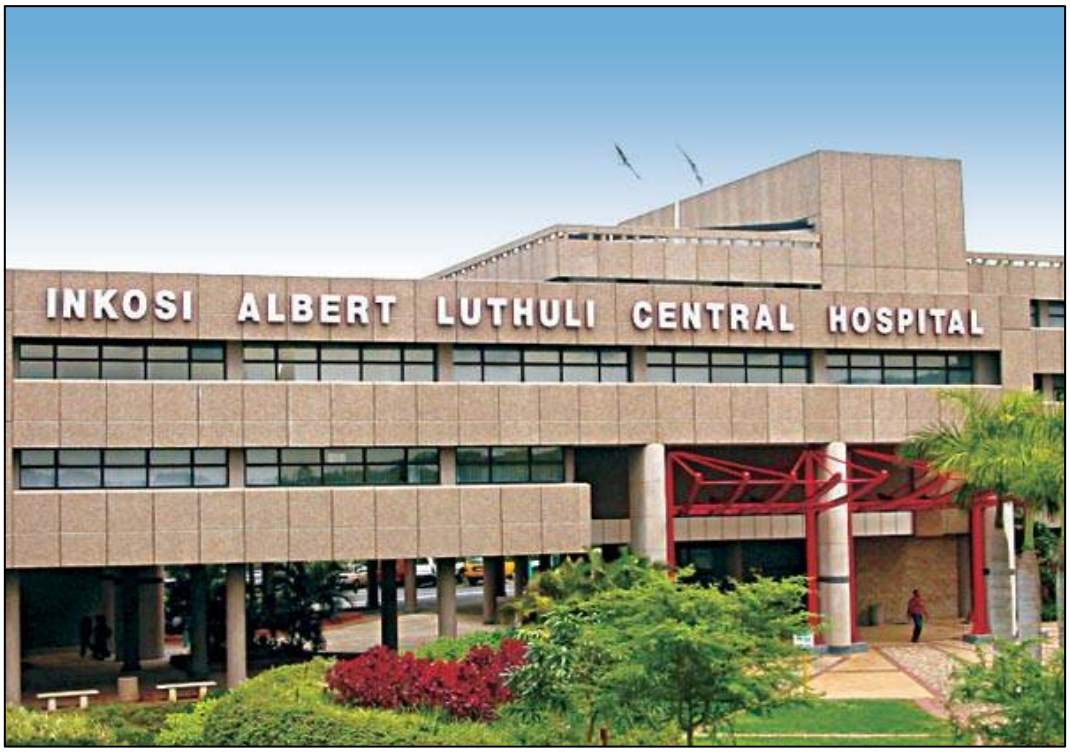

Figure 3.1: Entrance to IALCH

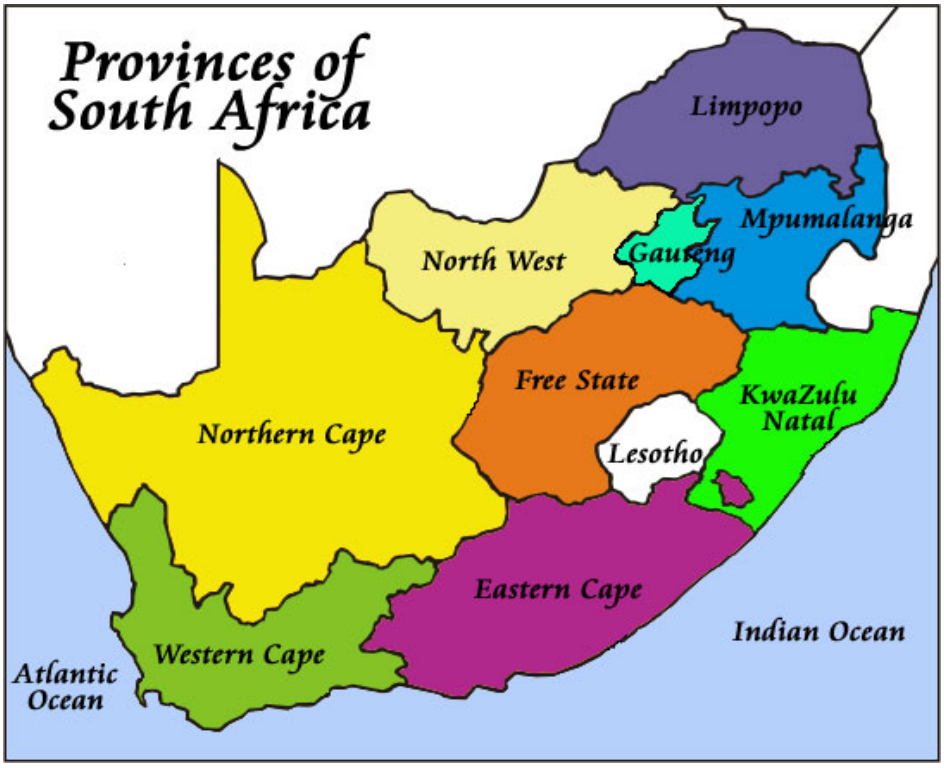

Figure 3.2: Map of the provinces of South Africa

3.3 Study design

The study design was a prospective cohort study. Cohort studies are proposed to be the most effective for determining the incidence and natural history of a condition. Research on risk factors relies heavily on cohort studies as a randomised control trial may be unethical. An advantage of a cohort study is that one can examine various outcome variables and they also allow for the calculation of the effect of each variable on the probability of developing the outcome of interest (Mann 2003).

For epidemiological studies a prospective study is a valuable tool with important applications. This type of study involves the comparison of a cohort of individuals displaying a particular exposure characteristic, with a group of individuals without the characteristic, in the format of a longitudinal study. This study, however, did not have a control group. A prospective study gives researchers the advantage of measuring outcomes in a pragmatic setting without the ethical and logistical restrictions as in other types of studies. The disadvantage of this type of study is the lack of internal validity due to the presence of selection bias and confounding variables (Bookwalla, Hussain & Bhandari 2011)

3.4 Study population and sample

The study population consisted of newly diagnosed nephroblastoma paediatric patients admitted to the Paediatric Surgical Oncology ward (B3W) at IALCH, between 2004 and 2012. These patients were between 1-12 years of age. Inkosi Albert Luthuli Central Hospital was the only state hospital treating newly diagnosed nephroblastoma patients in KZN at this time. Patients were excluded if anthropometric measurements were not correctly recorded on the data sheet or not measured before treatment was started. Patients were also excluded if they were diagnosed as not having nephroblastoma after further investigations. The final number in the sample was 77 out of 161 newly diagnosed nephroblastoma patients admitted to IALCH between 2004 and 2012.

3.5 Study methods and materials

3.5.1 Anthropometry

Anthropometric data was collected before treatment was started by the registered dietician assigned to the Paediatric Surgical Oncology ward. The anthropometric measurements taken included: weight, height, mid-upper arm circumference (MUAC) and triceps skinfold

thickness (TST). These measurements were recorded on a Microsoft Excel spreadsheet on the IALCH server.

Weight was measured using the ward scale (Nagata BW-1122H). Height was measured using the stadiometer attached to the scale, and infants (below 2 years) were measured on an infantometer. A non-stretch, flexible measuring tape was used to take MUAC measurements and a Harpenden skinfold caliper was used to measure TSFT. Mid-upper arm circumference and TSFT were taken halfway between the tip of the acromion process and the olecranon process (Oguz *et al* 1999). All measurements were taken three times and the mean value was used. Weight was measured to the nearest 0.1kg, height and MUAC to the nearest 0.1cm and TST to the nearest 0.1mm. The tumour weight was obtained from the patient files and rounded off to the nearest 0.01kg. A corrected weight for each patient was calculated by subtracting the tumour weight from the weight on admission. Use of the corrected weight would allow for a more accurate description of the nutritional status of this cohort.

Underweight (low weight for age), stunting (low height for age), wasting (low weight for height) and BMI for age were calculated and classified according to the WHO Z-score growth charts using an iPhone application called STAT Growth Charts (Maqbool *et al* 2008). The 2006 WHO growth charts were used as they are based on a multi-center study of children of diverse ethnic backgrounds from six diverse geographical regions (De Onis, Onyango, Borghi, Garza & Yang 2006). These are more relevant to the diverse nationalities of SA and are used internationally (Dinsdale *et al* 2011). The Centers for Disease Control and Prevention (CDC) charts based on North American children cannot be applied to children in developing countries, where such normative data seldom are available (Sala *et al* 2004). The Z-score or standard deviation (SD) score refers to the difference between the value for an individual and the median value of the reference population, divided by the standard deviation for the reference population (WHO 1995). The Z-scores where then classified into normal (>-1.0), mild (Z<-1.0), moderate (Z<-2.0) and severe (Z<-3.0) for each category. Mid-upper arm circumference and TSFT measurements were classified into normal and underweight using standards developed by Frischanco (1981).

3.5.2 Serum albumin

Blood samples were taken from each patient on admission to hospital and sent to the National Health Laboratory Service at IALCH for analysis of serum albumin. The method used is

based on the method of Doumas, Watson & Biggs (1971) and uses bromocresol green solution (BCG) as a binding dye. Serum or plasma albumin quantitatively binds to BCG to form an albumin-BCG complex that is measured as an endpoint reaction at 596/694 nm (Ngxamngxa 2016). A patient was considered malnourished if their serum albumin was less than 32 g/L and normal if it was ≥ 32 g/L (Sala *et al* 2011). These values were obtained from the patient files.

3.5.3 Chemotoxicity

Grade 4 toxicity was assumed if the patient was started on Neupogen®. This information was obtained by sending a list of the patients' hospital numbers to AME Africa, a private company that manages the computer software at IALCH. All patient files at IALCH are on the computer program Sorian. In order for a patient to receive Neupogen® it needs to have been ordered by the doctor using the Sorian programme. AME were able to determine if the patient had been prescribed Neupogen®, and on what dates it was prescribed by accessing the patient records. The dates where then analysed to determine the number of times that Neupogen® was ordered and for how many consecutive days the patient received it at a time. These results are reported in Chapter 4.

3.6 Statistical analysis

Statistical Package for Social Sciences (SPSS) version 17 was used for analysis of the data and a p-value of < 0.05 was considered as significant. The statistical tests used to analyse the data according to each objective is shown below:

Objective 1: To determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters in children with nephroblastoma admitted to IALCH between 2004-2012.

Each anthropometric index was analysed to determine the nutritional status of the children diagnosed with nephroblastoma. A chi-square goodness of fit test was applied to the indices WFA, HFA and WFH. A binominal test was applied to MUAC, TSFT and serum albumin. There is currently no standard protocol being utilised by researchers in order to classify nutritional status amongst children with cancer.

Objective 2: To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the prevalence of chemotoxicity.

A chi-square test of independence was applied to the categorical indices (MUAC, TSFT, WFA, HFA and WFH). An independent samples t-test was applied to serum albumin.

Objective 3: To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the frequency and duration of chemotoxicity
A non-parametric Kruskal Wallis test was applied to the categorical indices (MUAC, TSFT, WFA, HFA and WFH). A Pearson's correlation test was applied to serum albumin. The average number of days for which toxicity was present was used for the duration of toxicity.

Binomial and chi-square tests which are both non-parametric were used as these do not require data to be normally distributed. They were selected on the basis of their suitability to what analysis was required and the fact that the data was categorical.

3.7 Reduction of bias

For the purpose of this study, the reduction of bias is explained with regards to the anthropometric and biochemical measurements.

3.7.1 Anthropometry

Body weight was measured to the nearest 0.1 kg using a digital scale in the ward and height was measured to the nearest centimetre using a stadiometer, which was attached to the scale or an infantometer. The scale was calibrated annually as per department policy to minimise measurement errors. All measurements were taken three times and the mean used in calculations. All measurements were taken by a registered dietician trained in taking anthropometric measurements. This assisted with reduction of inter-observer error, however, bias between measurers is unavoidable. Anthropometric measurements were taken for each patient before treatment was started as treatment can affect nutritional status.

3.7.2 Biochemical

Biochemical parameters (serum albumin) were measured on admission for each patient. The National Health Laboratory Services protocol was adhered to when data was collected to ensure validity. Only correctly completed request forms with patient details completed fully and accurately were accepted. The details on the sample labels correlated with the details on the request forms. The type and volume of the primary sample on collection were correct. Samples were rejected if they were received in a leaking, cracked or broken container; the sample was not appropriate for a particular test; in the wrong anticoagulant tube; insufficient sample size; haemolysed or clotted or if there was obvious contamination. Sample collection was done by aseptic technique and was transported to the laboratory within specified time

frames. The laboratory conducted internal quality control tests three times per day and external quality assurance, where values obtained from the IALCH laboratory were compared to results from other laboratories (Ngxamngxa 2016).

3.8 Reliability and validity

Reliability is concerned with the consistency, stability and repeatability of the informants' accounts as well as the ability of the researcher to collect and record information accurately. This requires that a researcher using the same or similar methods should obtain the same or similar results every time the methods are used on the same or similar subjects (Brink, van de Walt & van Rensberg 2006, p118). Validity is concerned with the accuracy and truthfulness of scientific findings. Establishing validity requires, 1) determining the extent to which conclusions effectively represent empirical reality, and, 2) assessing whether concepts devised represent or measure the categories of human experience that occur (Brink *et al* 2006, p118).

Throughout this study the same methods were employed when taking anthropometric measurements, thus, ensuring reliability and validity. In addition, only patients whose anthropometric measurements were obtained before treatment was started and whose measurements were recorded accurately were included in the study. Measurements were taken according to IALCH dietetics department protocol and an average of the three measurements were recorded. To ensure validity of the serum albumin results the National Health Laboratory Services protocol was adhered to.

3.9 Data quality control

All data was entered into two different Excel spreadsheets and cross-checked to detect any inconsistencies. Data was anonymised before analysis.

3.10 Ethical considerations

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the Nelson R Mandela School of Medicine, University of KwaZulu-Natal (Reference BE 025/13) (Appendix A). Permission was obtained from the Department of Paediatric Surgery at IALCH to use the data (Appendix B). Ethical approval was also obtained from the Hospital Manager at IALCH (Appendix C). Patient confidentiality was adhered to by assigning each patient a number and removing their name and hospital number from the data set.

CHAPTER 4: RESULTS

This chapter presents the results of study according to the objectives outlined in Chapter 1.

4.1 Sample characteristics (n=77)

The study sample consisted of 77 children with nephroblastoma. Table 4.1 shows the characteristics of the sample.

Table 4.1: Sample population characteristics according to age, gender and ethnic background

Characteristics	n	%*
Age (in years)		
0-2	24	31.2
3-5	35	45.5
6-12	18	23.4
Gender		
Male	38	49.4
Female	39	50.6
Race		
Black	75	97.4
White	1	1.3
Coloured	1	1.3
Indian	0	0

* Percentage of total sample (n=77)

Most of the subjects fell into the 3-5-year age category (n=35; 45.5%) and the mean age of the sample was 4 years and 7 months (SD ±2 years and 11 months). There was an even distribution with gender as 49.4% were males (n=38) and 50.6% were females (n=39). Figure 4.2 shows sample population characteristics according to race.

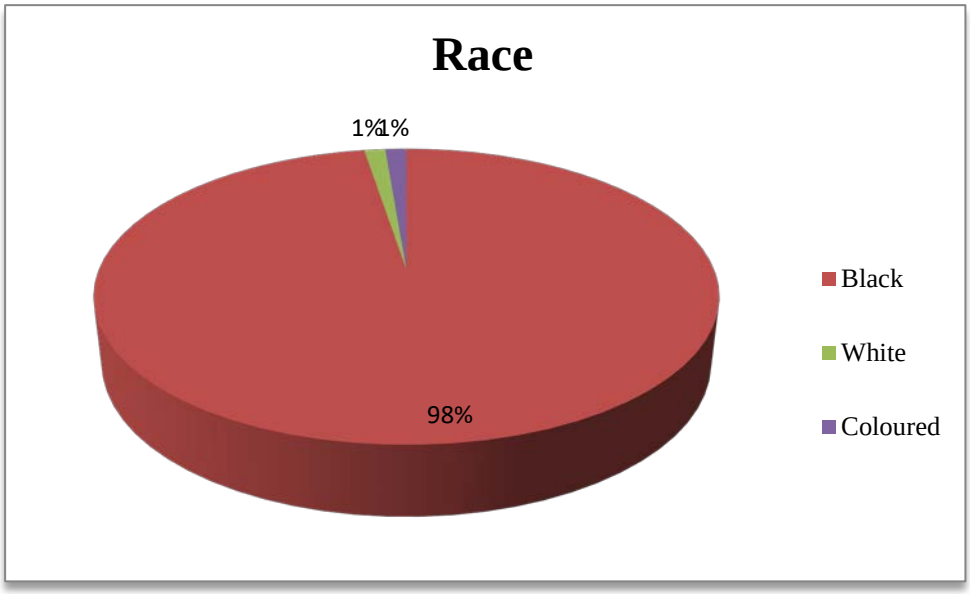

Figure 4.1 Sample population characteristics according to race

Nearly all of the subjects were black African (n=75; 97.4%) apart from one White and one Coloured subject. There were no Indians in the sample.

Table 4.2 shows the mean weight, height and serum albumin values for the sample.

Table 4.2 Mean weight, height and serum albumin for the sample

	Mean ± SD
Weight (kg)	16.70 ± 7.10
Height (m)	1.01 ± 0.20
Serum albumin (g/dl)	38.58 ± 5.79

SD=standard deviation

The mean weight of the sample was 16.70 ±7.10 kg. The mean height was 1.01 ± 0.20 m. The mean serum albumin was 38.58 ± 5.79 g/dl.

4.2 The incidence of malnutrition in children with nephroblastoma on admission as measured using specific anthropometric parameters

Each anthropometric index (WFA, HFA, WFH, MUAC, TSFT and BMI for age) was analysed individually to assess nutritional status on admission. Corrected weights (weight on admission minus tumour weight) were used to classify nutritional status. Table 4.3 shows the

number of males and females who were normal or had mild, moderate or severe malnutrition using parameters WFA, HFA, WFH and BMI for age.

Table 4.3: Subjects with normal nutritional status, mild, moderate or severe malnutrition according to gender

	Male		Female		Total	
	n	**%**	**n**	**%**	**n**	**%**
Weight for age					*	
Normal	21	29.2	24	33.3	45	62.5
Mild malnutrition (<-1SD)	7	9.7	11	15.3	18	25.0
Moderate malnutrition (<-2 SD)	5	6.9	3	4.2	8	11.1
Severe malnutrition (<-3SD)	1	1.4	0	0	1	1.4
Height for age					#	
Normal	19	25.0	27	35.5	46	60.5
Mild malnutrition (<-1SD)	11	14.5	9	11.8	20	26.3
Moderate malnutrition (<-2 SD)	5	6.6	1	1.3	6	7.9
Severe malnutrition (<-3SD)	3	3.9	1	1.3	4	5.3
Weight for Height					α	
Normal	26	38.8	22	32.8	48	71.6
Mild malnutrition (<-1SD)	3	4.5	6	8.9	9	13.4
Moderate malnutrition (<-2 SD)	3	4.5	3	4.5	6	9
Severe malnutrition (<-3SD)	3	4.5	1	1.5	4	6
BMI for age					×	
Normal	28	36.8	25	32.9	53	69.7
Mild malnutrition (<-1SD)	3	3.9	9	11.8	12	15.8
Moderate malnutrition (<-2 SD)	3	3.9	3	3.9	6	7.9
Severe malnutrition (<-3SD)	3	3.9	2	2.6	5	6.6

*n=72 because measurements were not taken before treatment started, no graph available for >10yrs

n=76 because measurements were not taken before treatment started

α n=67 because measurements were not taken before treatment started, no graph available for >10yrs

× n=76 because measurements were not recorded

Results showed that more than half of the subjects (both male and female combined), had a normal nutritional status using WFA (n=45, 62.5%), HFA (n=46, 60.5%), WFH (n=48, 71.6%) and BMI for age (n=53, 69.7%) respectively. The prevalence of malnutrition when classified by WFA, HFA, WFH and BMI for age in this cohort was 37.5%, 39.5%, 28.4% and 30.3% respectively, when considering all values below normal to be "malnourished". Table 4.4 shows the number of males and females who were normal and malnourished using the parameters MUAC and TSFT.

Table 4.4: Upper arm anthropometrics for males and females

	Male		Female		Total	
	n	**%**	**n**	**%**	**n**	**%**
MUAC					*	
Normal	15	20.0	18	24.0	33	44.0
Malnutrition	22	29.3	20	26.6	42	56.0
TSFT					#	
Normal	18	25.0	16	22.2	34	47.2
Malnutrition	18	25.0	20	27.7	38	52.7

*n=75 because measurements were not taken before treatment started
#n=72 because measurements were not taken before treatment started

Using MUAC alone 29.3% of males (n=22) and 26.6% of females (n=20) presented with malnutrition. When TSFT was used alone, 25.0% of males (n=18) and 27.7% of females (n=20) were classified as malnourished. The number classified as malnourished was 56% (n=42) using MUAC alone and 52.7% (n=38) using TSFT alone.

Although there was a significant number with normal nutritional status in this cohort, especially for the parameters WFA, HFA, WFH and BMI for age; more than a third of the patients were measurably malnourished using each parameter with the exception of WFH, where only 28% were deemed malnourished. Table 4.5 shows the classification of nutritional status of the sample using serum albumin.

Table 4.5: Classification of nutritional status using serum albumin values (n=77)

	Male		Female		Total	
Serum albumin (g/dl)	**n**	**%**	**n**	**%**	**n**	**%**
Normal (>32 g/dl)	31	40.3	35	45.5	66	85.7
Malnourished (≤ 32 g/dl)	7	9.1	4	5.2	11	14.3

Using serum albumin alone, 40.3% of the males (n=31) and 45.5% of the females (n=34) were classified as having a normal nutritional status. A binominal test showed that a statistically significant portion of the sample (male and females) (n=66; 86%) were found to have a normal nutritional status when serum albumin alone was used to classify malnutrition ($p<0.05$).

4.3 The influence of malnutrition on the prevalence of chemotoxicity

To investigate this objective an analysis was done on each 'nutritional status' parameter to detect any difference between patients with and without chemotoxicity. There was a statistically significant relationship between the prevalence of chemotoxicity and MUAC. A significant number of those with 'normal' MUAC measurements did not experience chemotoxicity [χ^2 (1, n=75) = 4.968, p=0.026].

A clinically significant relationship was found between each of the parameters and the chemotoxicity experienced in those patients classified as malnourished. Those malnourished according to MUAC were 76%, TSFT 68.4%, WFA 70.4%, HFA 66.6%, WFH 73.7% and BMI for age was 69.5%. More than two thirds of the patients who were classified as malnourished (using either of the parameters) experienced chemotoxicity. Figure 4.2 shows the prevalence of chemotoxicity experienced amongst those classified as malnourished.

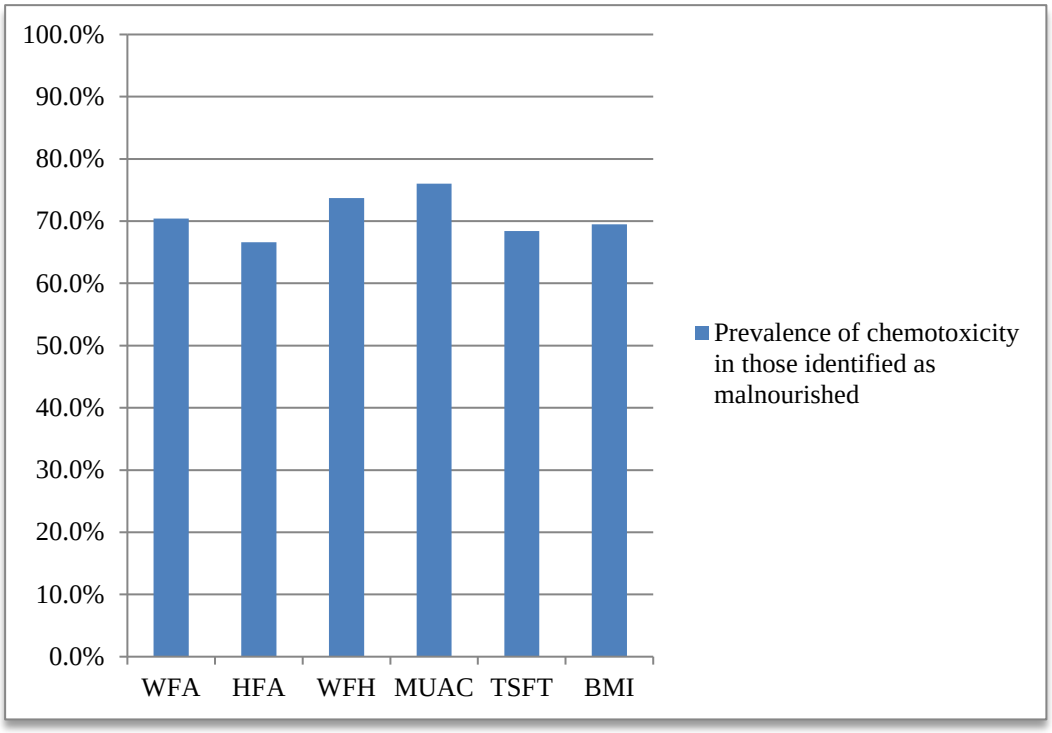

Figure 4.2: Prevalence of chemotoxicity in those identified as malnourished

There was no significant difference in the serum albumin measurements between those with and without chemotoxicity ($p>0.05$). Table 4.6 shows the group statistics for serum albumin and chemotoxicity.

Table 4.6: Group statistics for serum albumin and chemotoxicity

Chemotoxicity	n	Serum albumin (g/dl) (Mean ± SD)
Present	50	37.76 ± 5.99
Absent	27	40.11 ± 5.28

More than two thirds of the cohort experienced chemotoxicity (64.9%) during treatment. However, the mean serum albumin value for those that experienced chemotoxicity and those that did not, was 37.76 g/dl and 40.11 g/dl respectively.

4.4 The influence of malnutrition on the frequency and duration of chemotoxicity

The frequency of chemotoxicity was measured as the number of times the subject experienced chemotoxicity during treatment at IALCH and the duration of chemotoxicity was measured as the average number of days for which chemotoxicity was present during treatment. Table 4.7

shows the minimum, maximum, mean and standard deviation for chemotoxicity frequency and duration.

Table 4.7: Frequency and duration of chemotoxicity experienced (n=75×)

	Minimum	Maximum	Mean	Std. deviation
Chemotoxicity frequency#	0	14	2.04	2.65
Chemotoxicity duration*	0	25	3.62	4.02

× Unable to obtain data for all 77 subjects
Number of times experienced during treatment
*Measured in days

The non-parametric Kruskal-Wallis test showed that for MUAC, the frequency of chemotoxicity and duration of chemotoxicity was statistically significantly higher in those classified as malnourished [χ^2 (1, n=75) = 4.601, p=0.032; χ^2 (1, N=75) = 6.110, p=0.013 respectively]. There was a clinically significant relationship between those identified as malnourished using BMI for age and the duration of chemotoxicity experienced. The group with normal nutritional status experienced chemotoxicity for an average of three days while those classified as malnourished experienced chemotoxicity for an average of six days. The other nutritional status measures (WFA, HFA, WFH, TSFT and albumin) showed no significant correlation with frequency and duration of chemotoxicity.

Frequency and duration of chemotoxicity were positively correlated (r=0.225, p=0.025). Thus, the greater the frequency of chemotoxicity the greater the duration of chemotoxicity. There was a negative correlation between serum albumin and chemotoxicity in these patients. However, these results were not statistically significant.

4.5 Summary of results

In summary approximately a third of the cohort were classified as malnourished using the indices WFA, HFA, WFH and BMI for age. When MUAC and TSF were used to assess nutritional status the prevalence of malnutrition in the cohort increased to above 50%. When serum albumin alone was used to classify nutritional status, 86% of the sample was found to have a normal nutritional status. The frequency and duration of chemotoxicity was significantly higher in those classified as malnourished using the MUAC parameter. There was a clinically significant relationship between those identified as malnourished using BMI

for age and the duration of chemotoxicity experienced. Those identified as malnourished by BMI for age experienced a greater duration of chemotoxicity. A positive correlation was found between frequency and duration of chemotoxicity. The next chapter discusses the results of the study.

CHAPTER 5: DISCUSSION

This study aimed to determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters and its relationship with chemotoxicity in children with nephroblastoma admitted to IALCH between 2004-2012. This chapter discusses the results presented in chapter 4.

5.1 Sample characteristics

There was an even distribution of males and females in the sample, 49.4% and 50.6%, respectively. A study on nephroblastoma patients conducted in Cape Town, SA found 40.9% of the cohort to be male and 59.1% to be female (Davidson *et al* 2006). Although other studies have found a female predominance (Poole 2010), the gender distribution of the subjects in this sample was even.

Nearly all the subjects in this current study were of black African decent which is in keeping with the higher incidence of nephroblastoma found in the black African population. This suggests that nephroblastoma may be more prevalent in the black African population or an indication that mostly black African patients attend IALCH. It is possible that nephroblastoma is being diagnosed in other race groups, however, they are more likely being treated privately.

The mean age of the sample was 4 years 7 months and the median 3 years 9 months. This is in keeping with the fact that nephroblastoma is most common among children younger than five years of age (Berstein *et al* 1999). This is also similar to the age of the subjects reported in a local study by Holzinger *et al* (2007) where the median age of the subjects was 3 years 11 months.

5.2 Assessment of nutritional status

5.2.1 Anthropometry

In this study WFA, HFA, WFH, MUAC, TSFT, BMI for age and serum albumin were used to assess nutritional status. This study found that the nutritional status of the majority of the subjects on admission was normal when using the parameters WFA, HFA and WFH. Yet, more than a third of the cohort was still malnourished when using the WFA, HFA and BMI for age parameters. The WFH parameter showed that slightly less than a third of the sample were malnourished. The prevalence of malnutrition according to WFA, HFA, BMI for age and WFH was 37.5%, 39.5%, 30.3% and 28.4% respectively. South Africa is faced with the

problem of malnutrition even when other contributing factors are ignored. When the burden of nephroblastoma is added the prevalence of malnutrition is worsened due to alterations in metabolism (Andrassy & Chwals 1998).

When arm anthropometry was used to classify nutritional status the prevalence of malnutrition increased to more than half of the cohort. The prevalence of malnutrition was 56% using MUAC and 52.7% using TSFT. The same trend was found in two studies conducted in developing countries, Morocco and Malawi, on children with cancer (Tazi *et al* 2008; Israëls *et al* 2008). The Moroccan study found malnutrition prevalence to be 37% by WFA; 20% by HFA; 33% by WFH Z-scores and BMI. Arm anthropometry showed a higher prevalence of malnutrition: 50% using TSFT and 39% using MUAC. In the Malawian study malnutrition prevalence according to anthropometry was: 44.5% by HFA; 39.8% by WFA; and 17.2% by WFH. MUAC and TSFT showed that 59.3% of the cohort was malnourished. A large study with a cohort of 1787 patients, conducted in seven countries in Central America found the same to be true. While using the method of BMI for age the percentage of malnutrition in children with cancer was 45%. However, arm anthropometry (MUAC and TSFT) showed the prevalence of malnutrition to be greater at 63% (Sala *et al* 2012). This finding is also in keeping with other studies which showed a high prevalence of malnutrition (Israëls *et al* 2010; De Onis *et al* 1993).

Numerous studies have also found that the use of arm anthropometry is a more reliable measure of malnutrition, and thus an important method of assessing nutritional status in children with cancer, especially those with tumours and intra-abdominal tumours such as nephroblastoma (Sala *et al* 2012; Israëls *et al* 2008; Tazi *et al* 2008; Garófolo *et al* 2005; Oguz *et al* 1999; Smith *et al* 1991). This can be explained by the fact that the tumour mass can mask the effect of nutritional depletion on body weight and that the body utilises its nutritional reserves stored in the form of skeletal muscle protein and fat which results in the early decline in MUAC and TSFT (indicative of subcutaneous fat). The prevalence of malnutrition would be lower when using parameters that use weight (Wessels *et al* 1999), as these measures may inadvertently include the mass of the tumour. This current study tried to account for this by “correcting” the patient’s weight by subtracting the tumour weight from the patient’s weight on admission. However, one must bear in mind that the tumour was already reduced in size by pre-operative chemotherapy, therefore not correcting the weight

fully. Thus, the hypothesis that there was evidence of malnutrition in children with nephroblastoma on admission to IALCH between 2004-2012 is accepted.

5.2.2 Serum albumin

Using serum albumin alone as a marker for nutritional status showed that only 14% of this sample was malnourished. Donaldson *et al* (1981) and Elhasid *et al* (1999) both assessed the relationship between nutritional status and serum albumin on admission in children with cancer and children with solid tumours, respectively. Both studies found no significant correlation between the two. Pietsch & Ford (2000) measured nutritional status at diagnosis in children with cancer in Tennessee, USA. The authors found that only 12% of the cohort was malnourished when albumin was used as a marker. This reiterates that albumin is not a good marker for malnutrition especially when used on its own (Maqbool *et al* 2008, p11).

5.3 The influence of malnutrition as determined by anthropometry and serum albumin on the prevalence of chemotoxicity

This study, showed that there was a statistically significant relationship between chemotoxicity and malnutrition, when malnutrition was identified using MUAC. A clinically significant relationship was also found between each of the parameters and the prevalence of chemotoxicity in those identified as malnourished. Thus, the hypothesis that malnutrition increases the prevalence of chemotoxicity is accepted. Israëls *et al* (2012) found that chemotoxicity was also experienced in malnourished Malawian children. Forty percent of the patients were stunted, which showed chronic malnutrition. A very similar percentage (39%) of stunting was found in this current study. Israëls *et al* (2010) showed that the malnutrition experienced by these patients was associated with significantly decreased clearance and higher serum levels of chemotherapy (Israëls *et al* 2010). This explains, in part, why malnourished patients experience chemotherapy-related toxicity (Israëls *et al* 2012). This reiterates that dose reductions need to be considered for patients that present with malnutrition on admission in order to prevent an increased incidence and severity of toxicity (Israëls *et al* 2012; Israëls *et al* 2010; Israëls *et al* 2009).

There are various ways to decrease the prevalence of chemotoxicity. These include accurate and early detection of malnutrition, ensuring that MUAC is measured, in order to identify those at risk and to provide nutritional support as soon as possible. Measurements need to be continued throughout treatment to ensure that malnutrition is avoided or identified. Early

diagnosis is vital as well as improving all aspects of supportive care. This includes careful attention to the management of chemotoxicity and nutritional needs. If early chemotherapy is reduced this would allow for a period of time in which to improve the nutritional status of malnourished patients (Burke *et al* 2013; Israëls *et al* 2012; Mehta 1990).

5.4 The influence of malnutrition as determined by anthropometry and serum albumin on the frequency and duration of chemotoxicity

This study showed that the frequency and duration of chemotoxicity was significantly higher in patients classified as malnourished by MUAC on admission. With an increase in frequency of chemotoxicity there was also an increase in the duration of chemotoxicity. The duration of chemotoxicity was doubled in those who were malnourished according to BMI for age. This study also showed that patients with a serum albumin greater than 32g/dl on admission had a lower frequency and duration of chemotoxicity.

A study conducted in South Africa found the opposite to be true. Fifty-nine children with nephroblastoma were divided into a normal or malnourished group. The projected survival rate was 56% for the normal group and 74% for the malnourished group. The researchers concluded that poor nutritional status at diagnosis, as determined by anthropometry, had no effect on morbidity of treatment or survival in children with nephroblastoma (Wessels *et al* 1998). However, this study only used weight as a measure of malnutrition which has been shown to be a less sensitive marker in patients with tumours. Thus, these results could have been different had other measures been employed.

There are currently no specific and scientifically based nutritional recommendations for children with cancer. A balanced diet with sufficient protein and high energy intake is required to prevent the extreme overload of carbohydrates and fat consumption often seen in children with cancer (Bauer *et al* 2011). Early nutritional intervention has been shown to improve immune competence and tolerance to treatment (Ward 2007, p466).

By implementing nutritional support on admission and throughout treatment and assessing nutritional status to ensure that adequate nutrition is being provided the frequency and duration of chemotoxicity may be reduced. Thus, the hypothesis that malnutrition increases the frequency and duration of chemotoxicity is accepted.

5.5 Summary

Nutritional status is an extremely important part of assessment in patients diagnosed with nephroblastoma as these patients often present with malnutrition. In this study the prevalence of malnutrition was 37.5%, 39.5%, 30.3% and 28.4% when using the parameters WFA, HFA, BMI for age and WFH respectively. The prevalence of malnutrition increased to more than half when MUAC (56%) and TSFT (53%) were used. Thus, MUAC and TSFT are vital measures to include when assessing nutritional status in children with nephroblastoma. Weight by itself is not a very sensitive or reliable indicator of nutritional status and may underestimate the true prevalence of malnutrition. Early assessment of nutritional status on admission is imperative so that nutritional interventions can be implemented quickly in order to prevent further malnutrition caused by the disease itself and chemotoxicity from the treatment received.

Poor nutritional status, identified by MUAC, on admission can lead to an increased risk of experiencing chemotoxicity as well as increased frequency and duration of chemotoxicity. This could be decreased by identifying those at risk and by providing nutritional support as soon as possible. Nutritional assessment should be ongoing whilst the patient undergoes treatment so that nutritional interventions can be evaluated and adjusted if needed.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 Introduction

The aim of this study was to determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters and its relationship with chemotoxicity in children with nephroblastoma admitted to IALCH between 2004-2012. The specific objectives were:

(i) To determine the incidence of malnutrition as measured using specific anthropometric and biochemical parameters in children with nephroblastoma admitted to IALCH between 2004-2012.

(ii) To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the prevalence of chemotoxicity.

(iii) To determine the influence of malnutrition as measured using specific anthropometric and biochemical parameters on the frequency and duration of chemotoxicity.

This chapter concludes and critiques the study and gives recommendations followed by implications for further research.

6.2 Conclusion of the study

After assessing nutritional status, it was found that malnutrition was prevalent in children admitted to IALCH with nephroblastoma. The prevalence of malnutrition according to WFA, HFA, BMI for age and WFH was 37.5%, 39.5%, 30.3% and 28.4% respectively but when arm anthropometry was used the prevalence of malnutrition increased to 56% and 52.7% for MUAC and TSFT respectively. The use of MUAC is imperative in order to identify those with poor nutritional status, especially because the weight of the tumour positively influences the results of WFA, WFH, BMI for age and HFA. In this study albumin alone was found to be an unreliable indicator of malnutrition as it underestimated the prevalence of malnutrition.

The prevalence of chemotoxicity was increased in those with poor nutritional status identified by MUAC. Poor nutritional status as identified by MUAC was linked to an increased frequency and duration of chemotoxicity. This study highlights the importance of including arm anthropometry in the nutritional assessment of children with nephroblastoma. It can identify those with malnutrition more accurately, allowing for early, aggressive nutritional support thus leading to better outcome.

6.3 Study limitations

The following are the limitations of the study:

6.3.1 This study was conducted at a government hospital, which may lead to selection bias. However, IALCH treats patients from two provinces in South Africa and is therefore representative of a wider spectrum of the South African population.

6.3.2 The sample size was small as most subjects had to be eliminated because their anthropometric measurements had not been correctly recorded on the data sheet or not measured before treatment was started. Patients were also excluded if they were diagnosed as not having nephroblastoma after further investigations. Eighty-four out of 161 patients were excluded. Even though the sample size was small, this study is still important as it provides important data on an area of paediatric cancer that has not been widely researched in SA, especially KZN and the EC.

6.4 Recommendations for dietetic practice

The following recommendations are made:

6.4.1 MUAC should be included in the nutritional assessment of all nephroblastoma patients at diagnosis and should be measured throughout treatment to ensure accurate classification of nutritional status.

6.4.2 Albumin alone should not be used to identify malnutrition but could be used in combination with other anthropometric indicators.

6.4.3 Optimal nutrition should be provided to nephroblastoma patients on admission and throughout treatment in order to decrease the prevalence, frequency and duration of chemotoxicity.

6.4.4 An internationally accepted, standardised method for assessing nutritional status in paediatric patients with cancer on admission to hospital should be developed. This would help to ensure that all malnourished patients are identified and provided with adequate nutrition. This would assist in preventing loss of lean body mass, improving clinical outcomes, improved tolerance of treatment and improved quality of life.

6.4.5 Effective, complete and accurate cancer registries should be initiated in all countries to better understand the prevalence of the condition.

6.4.6 There should be early detection of children with pre-existing malnutrition and a high risk of substrate depletion before cancer therapies start. This could be done by assessing MUAC and TSFT on admission.

6.5 Implications for further research

6.5.1 Similar studies should be conducted in other provinces of SA to assess if results are comparable.

6.5.2 Future studies should assess if weight changes during chemotherapy affect chemotoxicity and if the type of chemotherapy received influences chemotoxicity.

6.5.3 This study only assessed grade 4 chemotoxicity because Neupogen® is only administered once the patient is classified as grade 4. Future studies could assess if nutritional status influences the different grades of chemotoxicity.

6.5.4 The body composition of nephroblastoma patients could be analysed to determine if pharmacokinetics is influenced by variations in body composition.

6.5.5 Further clinical and basic research programs should establish guidelines to evaluate the efficacy and impact of nutritional interventions in children with cancer.

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APPENDIX A: ETHICS APPROVAL LETTER FROM UKZN

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

26 June 2014

Prof. GP Hadley
Department of Paediatric Surgery
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Prof Hadley

PROTOCOL: Assessment of the prevalence of under-nutrition amongst South African paediatric nephroblastoma patients on admission to hospital. REF: BE025/13.

We wish to advise you that Ms K Draper's study "Nutritional status and treatment elated chemotoxicity in children with nephroblastoma on admission to IALCH, Durban" has been approved by the sub-committee of the Biomedical Research Ethics Committee as a substudy of the above study. Ms Kelly Draper's request to BREC dated 10 June 2014 to use the data from the above BREC approved study towards a Masters in Dietetics has been noted by BREC.

This approval will be **ratified** by a full Committee at its next meeting taking place on 08 July 2014.

Yours sincerely

Mrs A Marimuthu
Senior Administrator Biomedical Research Ethics Committee

APPENDIX B: PERMISSION LETTER TO USE DATA

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli
Central Hospital
Department: Paediatric Surgery
Postal Address :Private Bag x03 Mayville, 4058
Physical Address: 800 Bellair Road Mayville, 4091
Tel.: 031 240 1579
Fax.: 031 240 1667

To Whom It May Concern:

I, Professor G.P. Hadley (MP1067517), have already obtained ethical clearance from BREC (Ref:025/13) and give Kelly Draper (Student number: 205506325) permission to use the data acquired by the Department of Paediatric Surgery at Inkosi Albert Luthuli Cantral Hospital on nephroblastoma patients for her Master's degree in Dietetics.

Kind Regards

11.04.2014

Professor GP Hadley
Hadley@ukzn.ac.za

APPENDIX C: APPROVAL LETTER FROM IALCH

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: BE 025/13
Enquiries: Medical Management

3 June 2014

Ms K Draper
Department of Dietetics
IALCH

Dear Ms Draper

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Nutritional status and treatment related chemotoxicity in children with nephroblastoma on admission to Inkosi Albert Luthuli Central Hospital, Durban.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

.....
Dr K E Letebele
Medical Manager