NUTRITIONAL STATUS OF CHILDREN WITH WILMS' TUMOUR ON ADMISSION TO INKOSI ALBERT LUTHULI CENTRAL HOSPITAL IN DURBAN, SOUTH AFRICA AND ITS INFLUENCE ON OUTCOME

by

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ABSTRACT

Introduction: In developing countries the prevalence of malnutrition on admission amongst children with cancer can be as high as 69%. High rates of malnutrition occur due to factors such as poverty, co-morbidities, late presentation and advanced disease process. Weight has been shown to be an inaccurate parameter for nutritional assessment of patients with solid tumours as it is influenced by tumour mass. The importance of nutritional resuscitation and support of children with cancer has been emphasised in the literature, however, nutritional assessment and management of children with cancer is not consistently implemented throughout the centres treating these patients. Malnutrition on admission has been shown to increase the risk of toxicity and infection amongst children with cancer. The influence of malnutrition at the time of admission on outcome has not, however, been conclusively established.

Aim: The aims of this study were to determine the prevalence of malnutrition amongst children with Wilms‟ Tumour on admission to hospital, as well as the influence thereof on outcome after two years. Furthermore, it aimed to determine the level of nutritional support that the children received on admission to hospital.

Objectives:

a) To determine the prevalence of malnutrition using a combination of anthropometric and biochemical markers, defined by the AHOPCA algorithm.
b) To determine the influence of nutritional status on admission on the outcome, in terms of overall survival and death, amongst children with Wilms' Tumour admitted to IALCH between 2004 and 2012.
c) To determine the level of nutritional support prescribed to children with Wilms‟ Tumour within the first two weeks of admission to IALCH between 2004 and 2012.

Methods: Seventy six children diagnosed with Wilms' Tumour and admitted to IALCH between 2004 and 2012 were studied prospectively. Nutritional assessment took place before starting treatment and included weight, height, mid upper arm circumference (MUAC), triceps skinfold thickness (TSFT) and serum albumin. Overall nutritional status was classified using a combination of MUAC, TSFT and albumin. Outcome was determined at two years after the date of admission. Time until commencement of nutritional intervention after admission, and nature thereof, were recorded.

Results: Stunting and wasting was evident in 12 and 15% of patients, respectively. By classifying nutritional status using a combination of MUAC, TSFT and albumin, the prevalence of malnutrition was shown to be 67%. Malnourished children did not have significantly larger tumours than those who were well-nourished on admission. Malnutrition was not a predictor of poor outcome at two years after admission. Eighty four percent of patients received nutritional resuscitation within two weeks of admission, in the form of oral supplements, nasogastric feeds, or a combination thereof.

Conclusion: When classifying nutritional status, utilisation of weight and height in isolation can lead to underestimation of the prevalence of malnutrition amongst children with Wilms' Tumour. Nutritional assessment and classification of children with solid tumours should include MUAC and TSFT. Malnutrition at the time of admission was not shown to be related to poorer outcome after two years. This may be due to the effects of early aggressive nutritional resuscitation as part of management by a multidisciplinary team.

PREFACE

This dissertation was written between January 2013 and December 2015, under the supervision of Dr Nicola Wiles and Dr Kirthee Pillay using data collected from children with Wilms‟ Tumour on admission to Inkosi Albert Luthuli Central Hospital (IALCH) between 2004 and 2012.

Signed: _____ Date: _____
Lauren Frances Lifson (candidate)

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

Signed: _____ Date: _____
Dr Nicola Wiles (Supervisor)

Signed: _____ Date: _____
Dr Kirthee Pillay (Supervisor)

DECLARATION OF ORIGINALITY

I, Lauren Frances Lifson, hereby declare that:

i. The research reported in this thesis, except where otherwise indicated, is my original research.

ii. This dissertation has not been submitted for any degree or examination at any other university.

iii. This dissertation does not contain other person‟s data, pictures, graphs or other information unless specifically acknowledged as being sourced from those persons.

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Signed:_____ Dated:_____

Lauren Frances Lifson (candidate)

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION TO THE PROBLEM AND ITS SETTING

1.1. Importance of the study

Different types of childhood cancers and the prevalence thereof, vary by age (Ward, DeSantis, Robbins, Kohler & Jemal 2014; Stack, Walsh, Comber, Ryan & O'Lorcain 2007). Wilms' Tumour is a renal tumour that is usually unilateral in nature, but can occur bilaterally on rare occasions (Kaste, Dome, Babyn, Graf, Grundy, Godzinski, Levitt & Jenkinson 2008). It is a type of cancer found predominantly amongst young children and accounts for approximately 5% of all childhood cancers in developed countries (Ward *et al* 2014; Stack *et al* 2007). In African countries it is the most commonly occurring solid tumour (Stefan 2015) and accounts for 12% of all childhood cancer cases recorded in South Africa (Stefan & Stones 2012). Furthermore, Wilms' Tumour is one of the most common types of childhood cancer occurring in rural areas of South Africa‟s Eastern Cape Province (Somdyala, Bradshaw, Gelderblom & Parkin 2010).

There is a paucity of information regarding the prevalence of cancer in children in developing countries as well as the prevalence of malnutrition in this population. This is due to the under-diagnosis of paediatric cancers in these countries, as well as a lack of simple measures for recording and capturing patient related data, such as cancer registries (Stefan, Baadjes & Kruger 2014). As is the case in most developing countries, children with Wilms' Tumour in South Africa face many challenges that can affect their prognosis. These challenges include delayed presentation, high rates of treatment abandonment, poverty, as well as ignorance and lack of education amongst some communities (Paintsil, David, Kambugu, Renner, Kouya, Eden, Hesseling, Molyneux & Israels 2015; Wilde, Lameris, van Hasselt, Molyneux, Heij & Borgstein 2010; Abuidris, Elimam, Nugud, Elgaili, Ahmed & Arora 2008). Disease stage and histology are considered to be the most important prognostic indicators amongst children with Wilms' Tumour. Staging of the tumour occurs post-operatively, and stage of disease is determined by factors such as tumour extension beyond the kidney, presence of lymph nodes or metastases, tumour rupture or the presence of bilateral tumours. The histological classification of a tumour is dependent on the types of cells that are predominant in the tumour. The cell distribution determines whether or not a tumour is classified as being

„favourable" or „unfavourable" (Kaste *et al* 2008), depending on the type of cells, and predominance thereof, within the tumour (Poole 2010).

Paediatric malnutrition is a widespread problem in both developing and developed countries. Worldwide, 15% of children are underweight and 25% are stunted [United Nations Children's Fund (UNICEF) 2015]. In sub-Saharan Africa, more than one fifth of all children are underweight, more than one third are chronically malnourished (stunted) and just under one tenth are acutely malnourished (wasted) (UNICEF 2015). Three large studies have been conducted in South Africa in order to determine the prevalence of malnutrition amongst South African children. The National Food Consumption Survey (NFCS), conducted in 1999, showed the national prevalence of stunting, wasting and underweight to be 21.6%, 3.7% and 10% respectively (Labadarios, Steyn, Maunder, MacIntyre, Swart, Gericke, Huskisson, Dannhauser, Voster & Nesamvuni 2000). The National Food Consumption Survey-Fortification Baseline (NFCS-FB) of 2005, showed a slight improvement in the prevalence of stunting and underweight (18% and 9.3%) and a slight deterioration in the prevalence of wasting (4.5%) (Labadarios, Swart, Maunder, Kruger, Gericke, Kuzwayo, Ntsie, Steyn, Schloss, Dhansay, Jooste, Dannhauser, Nel, Molefe & Kotze 2008). The third survey, the South African National Health and Nutrition Examination Survey (SANHANES-1), released in 2013, showed the lowest prevalence of stunting, wasting and underweight, at 15.4%, 2.9% and 5.8% 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).

Available studies have shown that 45-69% of children with cancer in developing countries are malnourished on admission to hospital (Sala, Rossi, Antillon, Molina, de Maselli, Bonilla, Hernandez, Ortiz, Pacheco, Nieves, Navarrete, Barrantes, Pencharz, Valsecchi & Barr 2012; Israels, Borgstein, Jamali, de Kraker, Caron & Molyneux 2009; Israels, Chirambo, Caron & Molyneux 2008). Malnutrition amongst this population can lead to increased mortality and treatment abandonment rates (Sala *et al* 2012), as well as increased risk of complications (Murry, Riva & Poplack 1998). Many risk factors for a poor outcome amongst children with cancer, such as age, are not modifiable. Malnutrition, on the other hand, is a risk factor that can be modified if the correct steps are taken (Orgel, Sposto, Malvar, Seibel, Ladas, Gaynon & Freyer 2014).

Assessment of nutritional status of children with cancer needs to be standardised amongst centres treating these patients (Rogers, Melnick, Ladas, Halton, Baillargeon & Sacks 2008). Weight has commonly been used in isolation in order to classify nutritional status; however a growing body of research has emphasised the importance of including arm anthropometry measurements as part of the classification criteria for these patients (Israels *et al* 2008; Tazi, Hidane, Zafad, Harif, Benchekroun & Ribeiro 2008; Garofolo, Lopez & Petrilli 2005). In order for nutritional intervention to be implemented, classification of nutritional status of children with cancer needs to be conducted as soon as possible after admission. This will allow for malnourished children, or those at risk of becoming malnourished, to be identified. By reducing the time period that children are classified as being malnourished during their treatment period (for example, by implementing nutritional interventions as soon as possible after admission), the negative effects of poor nutritional status on admission can be significantly reduced (Orgel *et al* 2014).

There is a paucity of data relating to children with cancer, and Wilms' Tumour in particular. Although some studies have found a significant correlation between malnutrition on admission and poorer outcome (Sala *et al* 2012; Mejia-Arangure, Fajardo-Gutierrez, Reyes-Ruiz, Bernaldez-Rios, Mejia-Dominguez, Navarrete-Navarro & Martinez-Garcia 1999; Viana, Murao, Ramos, Oliveira, de Carvalho, de Bastos, Colosimo & Silvestrini 1994), others have failed to show any significant link between these two variables (Pedrosa, Bonilla, Liu, Smith, Davis, Ribeiro & Wilimas 2000; Wessels, Hesseling, Van Ommeren & Boonstra 1999; Weir, Reilly, McColl & Gibson 1998). Of further concern is the fact that many children in previous studies may have been incorrectly classified as being well-nourished when in fact they were malnourished (Lemos, de Oliveira & Caran 2014; Israels *et al* 2008; Tazi *et al* 2008).

When weight and height are used in isolation in order to classify nutritional status, malnutrition in children with Wilms' Tumour can be masked (Lemos *et al* 2014; Israels *et al* 2008; Tazi *et al* 2008) due to factors such as tumour mass and fluid shifts (Rogers 2014). In addition to these, utilisation of serum albumin as an indicator of nutritional status can also lead to underestimation of the prevalence of malnutrition when used in isolation. This is because albumin levels can be affected by several disease-related factors, thereby limiting its efficacy as a marker of nutritional status (Tazi *et al* 2008). Given the fact that many studies

in the past used weight, height and Body Mass Index (BMI), or serum albumin levels, in isolation in order to classify nutritional status (Burke, Lyden, Meza, Ladas, Dasgupta, Wiegner & Arndt 2013), it can be posited that the rates of malnutrition amongst Wilms' Tumour patients could have been under-reported, leading to a significant underestimation of the actual prevalence of malnutrition amongst this population to date. Arm anthropometry, specifically MUAC and TSFT, should be incorporated in order to accurately classify their nutritional status (Sala *et al* 2012) as these measures are independent of tumour size (Tah, Nik Shanita & Poh 2012; Brennan, Gill, Pennells, Eden, Thomas & Clayton 1999). Utilisation of biochemistry (namely serum albumin) and anthropometry measurements in combination has been shown to improve the sensitivity of classification of nutritional status (Sala *et al* 2012).

Nutritional intervention amongst children with cancer has been shown to be effective in improving nutritional status (Holzinger, Shaik & Hadley 2007). However, implementation of nutritional assessments and interventions in centres treating children with cancer, both internationally and in South Africa, is erratic and lacks standardisation (Schoeman 2011; Ladas, Sacks, Brophy & Rogers 2006). Inkosi Albert Luthuli Central Hospital (IALCH) is a Durban-based hospital and is classified as a National Central Hospital which services all of South Africa as well as patients from neighbouring countries on occasion. On a tertiary level, IALCH serves as a referral hospital for patients residing throughout KwaZulu-Natal (KZN) and the seaboard areas of the Eastern Cape (Department of Health 2014). This study took place between 2004 and 2012. During this time, IALCH was the only state-run hospital treating children with Wilms‟ Tumour in the KZN province. Each subject admitted between 2004 and 2012 was followed up for a period of two years from the date of admission to IALCH. A local study, which assessed prevalence of malnutrition but not the effect thereof on outcome, showed that 45% of patients admitted to IALCH with Wilms' Tumour were malnourished on admission. Furthermore, these authors showed that nutritional intervention, in the form of oral and enteral supplementation, leads to significant improvement in nutritional status amongst these subjects (Holzinger *et al* 2007).

There is a dearth of data analysing the influence of nutritional status on outcome amongst children with Wilms' Tumour internationally and in South Africa. This study was important in order to accurately determine the nutritional status of children with Wilms' Tumour on

admission to hospital. Furthermore, it was important in order to determine the influence of nutritional status at the time of admission on disease outcome amongst a sample whose nutritional status had been accurately classified.

The following questions therefore arise:

- What is the prevalence of malnutrition amongst children with Wilms‟ Tumour on admission to a South African hospital?
- Does nutritional status on admission influence the outcome after two years amongst children with Wilms‟ Tumour?
- What level of nutritional support was prescribed to children with Wilms‟ Tumour within the first two weeks of admission to IALCH during the study period?

This study was necessary as it would serve to provide important baseline data in an area that has not been widely researched. It was anticipated that the results of this study would help to establish the prevalence of malnutrition amongst this population when admitted to hospital and the influence thereof on outcome. Due to the fact that IALCH serves patients spanning two provinces, it was thought that the results of this study could be applied to a wide variety of South Africans with potentially diverse socioeconomic backgrounds and environments. By understanding the influence of nutritional status on disease outcome, it was anticipated that this would help to better define the role of nutritional intervention and support amongst this population, as well as to improve the efficacy thereof. Furthermore, this study would help to emphasise the importance of standardisation, with regards to classification methods, when assessing nutritional status amongst this population.

1.2. Statement of the problem

The purpose of this study was to determine the prevalence of malnutrition amongst children with Wilms‟ Tumour on admission to IALCH. Furthermore, it aimed to determine the correlation between nutritional status on admission and outcome, as well as to determine the level of nutritional intervention that the subjects received within the first two weeks of admission.

1.3. Research objectives

The objectives of this study were:

1.3.1 To determine the prevalence of malnutrition using a combination of anthropometric and biochemical markers, defined by the Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) algorithm.

1.3.2 To determine the influence of nutritional status on admission on the outcome, in terms of overall survival and death, amongst children with Wilms' Tumour admitted to IALCH between 2004 and 2012.

1.3.3 To determine the level of nutritional support prescribed to children with Wilms' Tumour within the first two weeks of admission to IALCH between 2004 and 2012.

1.4. Hypotheses

1.4.1 The utilisation of weight, height and albumin in isolation would underestimate the prevalence of malnutrition.

1.4.2 The use of arm anthropometry in combination with albumin would give a more accurate result regarding the prevalence of malnutrition.

1.4.3 The overall outcome, in terms of survival, of subjects who were malnourished on admission would be lower compared to those who were well nourished on admission.

1.5. Inclusion and exclusion criteria

This study was limited to:

- Children up to the age of 13 years old who were admitted to the paediatric surgery ward at IALCH hospital and diagnosed with Wilms' Tumour between 2004 and 2012.
- Children whose anthropometric measurements were taken by registered dietitians.
- Children whose nutritional status was classified based on weight, height, MUAC, TSFT and biochemical measurements taken on admission to hospital, *before* the initiation of the treatment course (chemotherapy, radiotherapy and/or surgery).

This study excluded:

- Children whose anthropometric and biochemical measurements were taken after treatment was initiated.

- Children whose initial anthropometric and biochemical measurements were taken at a follow up admission (in other words, not on the admission when they were initially diagnosed with Wilms' Tumour).

1.6. Definition of terms

Basal Metabolic Rate: The minimal energy expended for the maintenance of respiration, circulation, peristalsis, muscle tonus, body temperature, glandular activity, and other vegetative functions of the body‟ (Block, John, Borer, Pucci, Bruce, Silver, Christopher, Drake, Vogl, Jangid & Whitman 2007, p1159).

Body Mass Index: The BMI gives a representation of a person's weight in relation to their height in order to classify their nutritional status. It is calculated using weight, in kilograms, divided by the square of a person‟s height, in metres (Stedman 2005, p193).

Children with Wilms' Tumour: For the purpose of this study, this was defined as patients up to the age of 13 years, who had been diagnosed with Wilms‟ Tumour after undergoing a biopsy.

Malnutrition: For the purpose of this study, children were classified as malnourished if at least one of these criteria were fulfilled:

- MUAC and TSFT between the fifth and tenth percentiles
- MUAC less than the fifth percentile and TSFT more than the tenth percentile
- MUAC more than the tenth percentile and TSFT less than the fifth percentile
- Albumin less than 35g/L

Those who met at least one of the following criteria were classified as severely malnourished:

- MUAC and/or TSFT below the 10^{th} centile
- Albumin below 32g/L

Mid Upper Arm Circumference: An anthropometric measurement used for classification of nutritional status and 'the best anthropometric predictor of mortality currently available' (Walters, Sibson & McGrath 2012).

Outcome: For the purposes of this study, outcomes were described in terms of overall survival and death at two years after the initial admission to hospital.

Triceps Skinfold Thickness: An anthropometric measurement which is taken at the mid-point of the child's upper arm. 'A skinfold is held between the investigator's thumb and index finger (subcutaneous fold without muscle). The caliper is placed about 1 mm below the left hand, perpendicular to the skinfold. The right hand holds the caliper and the measurement is read within 3 seconds (so that pressure does not compress the subcutaneous tissue)' (Hall, Allanson, Gripp & Slavotinek 2007, p67).

Tumour burden The amount of a subject‟s weight that is attributed to the mass of their tumour. The mass of the tumour can be determined by weighing the tumour after it has been surgically removed.

Wilms' Tumour: Also known as Nephroblastoma. 'A malignant tumour of the kidney; occurs almost exclusively in children. Thought to develop from embryonic structures' (Freshwater & Maslin-Prothero 2005, p384).

1.7. Abbreviations

AHOPCA:	Asociación de Hemato-Oncología Pediátrica de Centro América
BMI:	Body Mass Index
COG:	Children's Oncology Group
HFA:	Height for Age
IALCH:	Inkosi Albert Luthuli Central Hospital

KZN:	KwaZulu-Natal
MUAC:	Mid Upper Arm Circumference
TSFT:	Triceps Skinfold Thickness
WFA:	Weight for Age
WFH:	Weight for Height
WHO:	World Health Organization
UNICEF:	United Nations Children's Fund

1.8. Assumptions

The following assumptions were made:

- All dietitians who took the anthropometric measurements (weight, height, MUAC and TSFT) did so accurately and as per the standard practices at IALCH.
- Biochemical measurements were taken and analysed accurately.
- Patient records accurately reflected nutritional interventions undertaken for each patient.
- Progression of cancer stages amongst individuals with Wilms‟ Tumour was not generalizable, and may have been influenced by factors such as histology, genetics and environmental influences.

1.9. Summary

Studies have shown that childhood cancer is a serious and relevant problem affecting children both internationally and in South Africa. Studies have found that 45-69% of children with cancer in developing countries are malnourished, and the prevalence of malnutrition amongst children with Wilms' Tumour in KZN has been shown to be similarly high. However, many previous studies potentially underestimated the prevalence of malnourished children in their samples due to inaccurate classification of nutritional status. Some studies analysing children with cancer have found malnutrition on admission to hospital to be a poor prognostic indicator, while others have not been in agreement. In general, there is a serious dearth of studies conducted on children with Wilms' Tumour, with only a few having taken place in a South African setting.

It was anticipated that this study would provide an accurate indication of the prevalence of malnutrition amongst children with Wilms' Tumour presenting to IALCH between 2004 and 2012, as well as to describe the influence of nutritional status at the time of admission on outcome. Furthermore, it was anticipated that this study would shed light on the dietary interventions received amongst this sample in a South African setting, consequently helping to improve medical and nutritional management of this population group in the future. This study did not address the influence of type and duration of treatment on nutritional status or outcome of the subjects.

1.10. Dissertation overview

This dissertation consists of six chapters. The first chapter addresses the reasons why such an investigation is relevant and necessary, and presents the study objectives. The second chapter discusses the current literature regarding paediatric nutritional status, paediatric cancer and the role of dietary intervention amongst this population. The third chapter discusses the methodology utilised in the study, while the fourth chapter presents the results after the statistical analyses were conducted. Chapter five discusses the results of this study in relation to the literature discussed in chapter two. Finally, chapter six concludes the dissertation and provides recommendations for future research based on the results obtained.

1.11. Referencing style

This dissertation has been written using the referencing style of the Discipline of Dietetics and Human Nutrition, University of KwaZulu-Natal.

CHAPTER 2: REVIEW OF THE RELATED LITERATURE

In order to facilitate a better understanding of the problem at hand, this chapter will review the literature relating to children with cancer as well as paediatric malnutrition. The first section will delve into the background relating to paediatric cancer and paediatric malnutrition. It will discuss the prevalence, treatment, survival, prognostic indicators and challenges associated with paediatric cancer patients, focusing specifically on developing countries. The second section will focus on nutritional assessment utilising both anthropometric and biochemical measurements, methods of classifying nutritional status and problems associated therewith. The third section will focus on the pathogenesis of malnutrition amongst children with cancer, including cancer cachexia, as well as examine the relationship between nutritional status and outcome. In addition, it will assess the role of nutritional intervention in the treatment and management of this population.

2.1. Childhood cancer

The incidence of types of cancer amongst adolescents and children varies by age. Wilms' Tumour, also known as Nephroblastoma, is a type of cancer that contributes to approximately five percent of all childhood cancer cases in developed countries (Ward *et al* 2014; Stack *et al* 2007). It is not commonly seen in children older than ten years of age (Steliarova-Foucher, Stiller, Kaatsch, Berrino, Coebergh, Lacour & Parkin 2004). In Europe, Wilms' Tumour is the eighth most commonly occurring cancer amongst children from birth to 14 years of age, constituting 5.7% of all paediatric cancers between 1978 and 1997 (Magnani, Pastore, Coebergh, Viscomi, Spix, Steliarova-Foucher 2006). Figure 2.1 shows the prevalence of the ten most commonly occurring paediatric cancers in America.

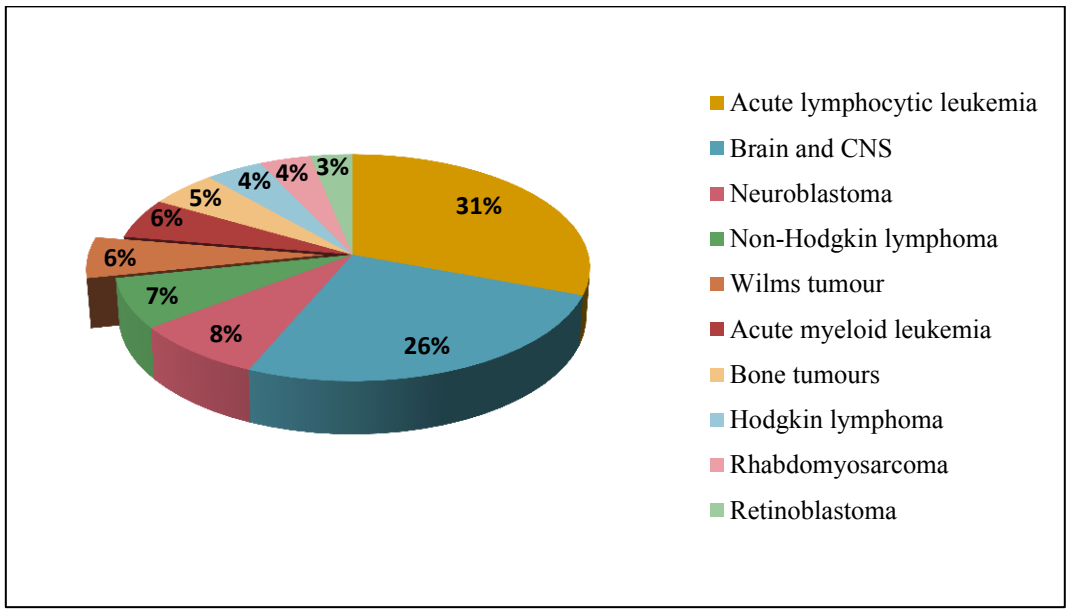

Figure 2.1: Estimated prevalence of childhood cancers among American children between 0 and 14 years of age (Ward *et al* 2014)

Data on the prevalence of paediatric cancers in developing countries is lacking. This is due to factors such as the under-diagnosis of paediatric cancers, as well as a lack of simple measures for recording and capturing patient related data, such as cancer registries (Stefan *et al* 2014). The only known tumour registry in Africa dedicated solely to the documentation of paediatric cancer was developed by the South African Children's Cancer Study Group and has been in place for more than 25 years (Stefan & Stones 2012). A recent survey has shown that Wilms' Tumour accounts for more than 10% of childhood cancers in many African countries. In certain African countries the prevalence was found to be more than four times higher than that of developed countries (Stefan 2015). In South Africa, Wilms' Tumour patients account for 12% of paediatric cancer cases, making it the fourth most common cancer amongst this population (Stefan & Stones 2012). In rural areas of the Eastern Cape, the prevalence of paediatric cancer has been shown to be 2.8% of all cancers, with Wilms' Tumour and brain tumour being the most common types (Somdyala *et al* 2010). Wilms' Tumour remains the most predominant solid tumour in African countries (Stefan 2015).

2.1.1. Diagnosis of Wilms' Tumour

If a child is suspected to have Wilms' Tumour, a series of tests and investigations are carried out on admission to hospital. Clinical signs and symptoms include an abdominal mass or

distended abdominal veins. Immediate investigations include blood and urine tests, as well as a chest X-ray. An ultrasound is considered to be compulsory as part of the investigations of these patients, and doctors may deem it necessary to perform a Computed Tomography (CT) scan of the abdomen. Finally, a biopsy is performed in order to confirm diagnosis of Wilms' Tumour (Poole 2010).

2.1.2. Factors affecting prognosis in developing countries

In general, stage and histology are considered to be the most important factors influencing the prognosis of children with Wilms' Tumour (Kaste *et al* 2008). However, when compared to developed countries, poorer outcomes have been observed amongst paediatric oncology patients in developing countries due to a variety of factors (Figure 2.2) (Paintsil *et al* 2015; Wilde *et al* 2010; Abuidris *et al* 2008).

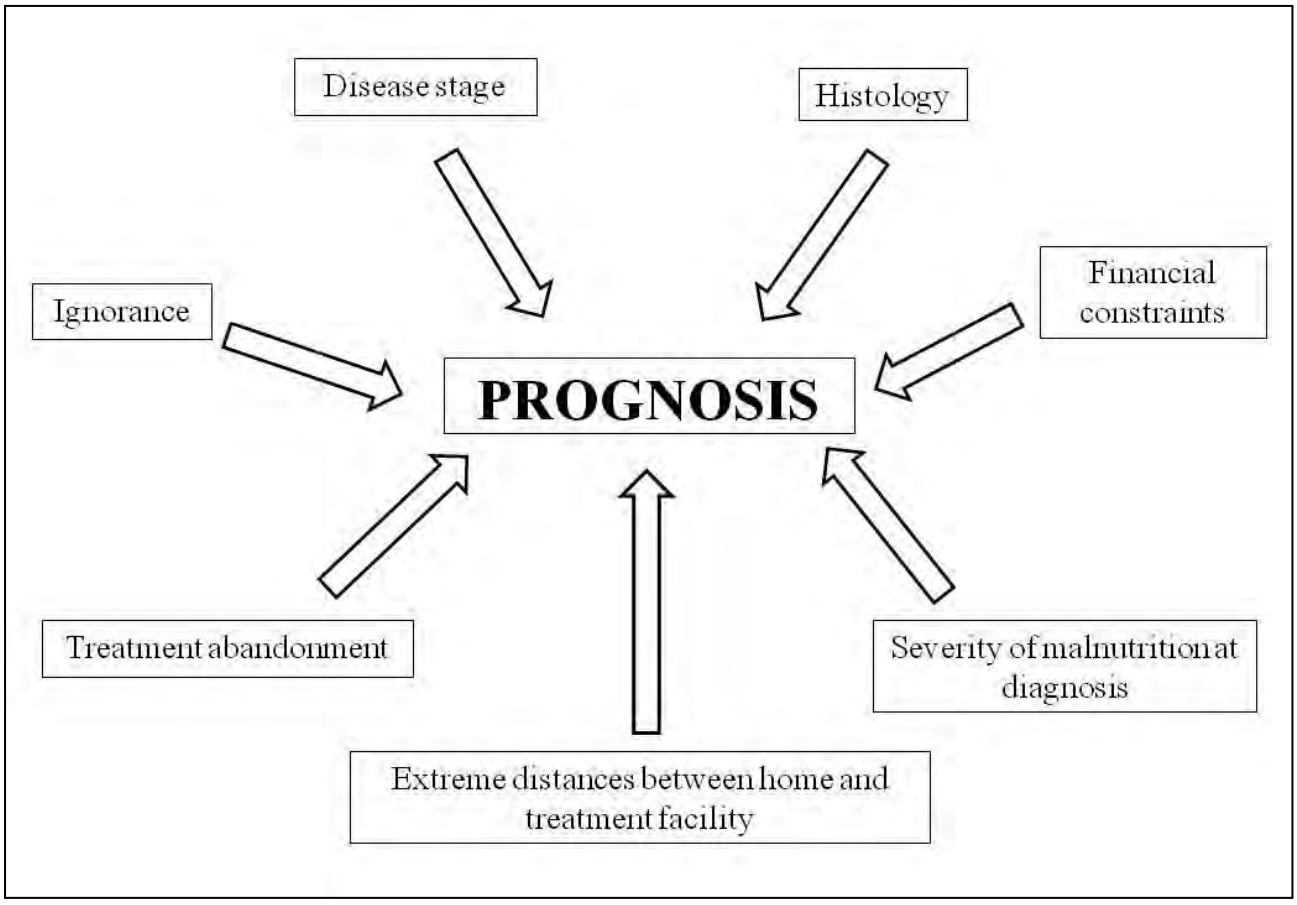

Figure 2.2: Factors affecting prognosis of children with cancer in developing countries

Late presentation, in particular, is a common problem in this setting (Paintsil *et al* 2015; Yao, Li, Xiao, Gao, Dong, Xiao & Lv 2012; Wilde *et al* 2010; Abuidris *et al* 2008; Ekenze, Agugua-Obianyo & Odetunde 2006), and can often be exacerbated by poverty and ignorance (in the form of lack of education) amongst some communities (Stones, de Bruin, Esterhuizen & Stefan 2014; Yao *et al* 2012). In a Nigerian hospital, Ekenze *et al* (2006) found that, on average, their patients presented after almost five months of displaying symptoms of Wilms' Tumour. Consequently, the majority of their sample presented in the later stages of disease (stage three and four), while no patients presented in the initial stage of disease (stage one). In a study conducted by Abuidris *et al* (2008) in Sudan, 78.4% of their Wilms' Tumour patients presented in stage three or four. A local study conducted in KZN showed that children from rural areas presented to hospital with Wilms' Tumour later than children from urban areas. Furthermore, the children from rural areas were more likely to present with larger tumour masses and a more advanced stage of disease (Hadley & Jacobs 1990). Israels *et al* (2009), who conducted a similar study in a hospital in Malawi, found that children with larger tumours were more likely to be malnourished.

Treatment-related problems provide further challenges which can contribute to poor outcome amongst this population (Paintsil *et al* 2015; Ekenze *et al* 2006). Treatment abandonment poses a particular problem (Madani *et al* 2006), with as many as 48% of patients in countries in the sub-Saharan Africa region failing to complete their treatment programmes (Paintsil *et al* 2015). Figures for abandonment have been shown to be as high as 62% amongst children with Wilms' Tumour (Abuidris *et al* 2008). In developing countries, many patients abandon treatment due to financial constraints, as some of the treatments and drugs are not subsidised (Abuidris *et al* 2008; Ekenze *et al* 2006). Severe poverty, which is present in many developing countries, means that caregivers are often unable to afford the costs of travelling to and from the hospital for treatment, as well as the cost of lodging and food during the hospital stay, further contributing to high rates of treatment abandonment. A study conducted by Abuidris *et al* (2008) showed that for various reasons, including financial constraints, only 11% of their sample of Wilms' Tumour patients completed the treatment programme, while 27% received no treatment whatsoever. The average cost of treating a Wilms' Tumour patient in Sudan, for example, can be as high as US$890[1] (R12 255) (Abuidris *et al* 2008). In South Africa, the cost of treating Wilms' Tumour patients in public hospitals according to the

[1] Exchange rate as of 03 November 2015 $:R = 1:13.77

Societe Internationale d'Oncologie Pediatrique (SIOP) treatment protocols can exceed US$5000 (R68 850) depending on the stage of disease (Stefan, Stones, van Zyl & Uys 2014). The majority, if not all, treatment at IALCH is subsidised by the government, depending on parental income (Department of Health, Western Cape Government 2015).

Factors shown to significantly increase the rate of treatment abandonment include living far from the treatment facility (Slone, Chunda-Liyoka, Perez, Mutalima, Newton, Chintu, Kankasa, Chipeta, Heimburger, Vermund & Friedman 2014), severity of malnutrition at diagnosis (Antillon, Rossi, Molina, Sala, Pencharz, Valsecchi & Barr 2013; Sala *et al* 2012) and poor maternal education (Slone *et al* 2014; Abuidris *et al* 2008; Ekenze *et al* 2006). After chemotherapy and surgery, many parents may assume that their child is cured in light of the fact that symptoms such as abdominal distension have resolved, and do not understand the need for returning to the hospital in order for treatment to be completed (Abuidris *et al* 2008). In addition to this, many drugs are simply unavailable in resource-limited countries (Wilde *et al* 2010; Ekenze *et al* 2006).

2.1.3. Treatment guidelines for patients in resource limited settings

A group of experts have developed guidelines specifically for the treatment of children with Wilms' Tumour in resource limited settings, based on guidelines developed by the SIOP in 2001. Wilms' Tumour can be diagnosed using ultrasonography, while minimum treatment for curative intent in these settings involves pre- and post-operative chemotherapy as well as surgical resection of the tumour. When available and when necessary, radiotherapy can be used as an adjunct to the above therapies. However, it is not considered to be absolutely vital for the curative treatment of these patients. Both social and financial support, including extensive counselling, should be provided to the families of patients in order to ensure treatment compliance and prevent treatment abandonment (Israels, Moreira, Scanlan, Molyneux, Kampondeni, Hesseling, Heij, Borgstein, Vujanic, Pritchard-Jones & Hadley 2013).

2.1.4. Survival in developed versus developing countries

Paediatric cancers have been prevalent for decades and, in both developed and developing countries, the overall incidence has continued to increase (Ward *et al* 2014; Steliarova-Foucher *et al* 2004; Chintu, Athale & Patil 1995). Survival, on the other hand, has shown significant improvement over the years, due to factors such as increasingly advanced treatment and improved management of patients (Ward *et al* 2014; Kaste *et al* 2008; Steliarova-Foucher *et al* 2004). Furthermore, the establishment of multi-disciplinary co-operative groups, such as the Children's Oncology Group (COG) and SIOP, involving collaboration amongst experts on a national and international level has also contributed to the improved survival rates (Kaste *et al* 2008).

Death rates amongst this population have declined by more than 50% in America. Furthermore, in the case of several types of cancer, including Wilms' Tumour, those who survive more than five years have been shown to have a favourable chance of long-term survival (Ward *et al* 2014). Wilms' Tumour patients in America have seen five year survival rates improve from 73% in the 1970s to 93% between 2005 and 2011 (SEER Cancer Statistics Review 1975-2011). Similarly, since 1978 steady improvements in the five year survival rates of European children with renal tumours have also been observed (Magnani *et al* 2006). However, survival rates in developing countries are significantly worse, especially in the region of sub-Saharan Africa. In South Africa, five year survival rates of children with Wilms' Tumour have been shown to be just over 60%, while the overall survival rate of children with cancer is 52% (Stones *et al* 2014). In other developing countries, however, survival rates can fall as low as 11% (Paintsil *et al* 2015; Abuidris *et al* 2008) while the average short-term survival rate in sub-Saharan Africa (SSA) is 39% (Paintsil *et al* 2015). Children of Black ethnic origin have been shown to have significantly poorer survival rates than those of other ethnic origins (Stones *et al* 2014).

2.1.5. Malnutrition at diagnosis in developing countries

The prevalence of malnutrition amongst paediatric cancer patients in developing countries has been shown to range from 45-77% (Sala *et al* 2012; Israels *et al* 2009; Israels *et al* 2008; Garofolo *et al* 2005). Given the high prevalence of paediatric malnutrition in South Africa, as shown by the SANHANES-1 (2013) and NFCS (1999 and 2005) studies mentioned

previously, a similar prevalence would be expected amongst South African children with Wilms' Tumour. In KZN in particular, more than twice as many children from rural areas were shown to present to hospital in a malnourished state in comparison to their urban counterparts (Hadley & Jacobs 1990). Furthermore, in this province malnutrition has been shown to occur in almost half of Wilms' Tumour patients on admission to hospital (Holzinger *et al* 2007).

Other issues that are cause for concern amongst children with Wilms' Tumour in developing countries include the fact that children with larger tumours on admission have been shown to be more severely malnourished than those with smaller tumours (Israels *et al* 2009). Furthermore, according to several studies children with solid tumours are more likely to be malnourished (Murphy, White & Davies 2009; Tazi *et al* 2008; Brennan *et al* 1999), and present with increased severity of malnutrition compared to those with haematological tumours (Garofolo *et al* 2005). Additionally, the intake of the majority of nutrients can be significantly lower in children with solid tumours compared to haematological malignancies (Tah *et al* 2012). Factors that could contribute to the development of malnutrition amongst these children include insufficient dietary intake as well as the effect of the prolonged presence of malignant disease due to delayed presentation to hospital (Israels *et al* 2009). Therefore it is important to emphasise the importance of nutritional assessment amongst this population in order to detect patients who are malnourished, or at risk of becoming malnourished, on admission. This will allow for the necessary nutritional rehabilitation to take place as soon as possible after admission to hospital. The assessment of nutritional status amongst children with cancer will be discussed in the following section.

2.2. Nutritional assessment of children with cancer

Poor nutritional status can contribute to increased mortality rates as well as an increased rate of treatment abandonment (Sala *et al* 2012). Furthermore, it can lead to an increased risk of complications and can impact the absorption, excretion and metabolism of anti-neoplastic drugs that the majority of children with cancer receive (Murry *et al* 1998). The classification of nutritional status should therefore be considered as an integral part of every child's initial assessment on admission to hospital for cancer treatment and management (Lemos *et al* 2014; Linga, Shreedhara, Rau & Rau 2012; Murphy *et al* 2009).

2.2.1. Methods used to assess nutritional status

There are several methods available to classify nutritional status amongst the paediatric population. Weight, height and BMI are commonly used to classify nutritional status (Murphy *et al* 2009; Ladas *et al* 2006) as they are affordable, easy and quick anthropometric measurements that can be performed by most staff at a health facility (Orgel *et al* 2014). However, studies have shown that when weight and height are used in isolation in order to classify nutritional status, malnutrition in children with Wilms' Tumour can be masked (Lemos *et al* 2014; Israels *et al* 2008; Tazi *et al* 2008) because of factors such as tumour mass and fluid shifts (Rogers 2014). This can lead to many malnourished patients being incorrectly classified as well-nourished (Lemos *et al* 2014; Israels *et al* 2008; Tazi *et al* 2008). Due to the fact that many studies in the past used only weight, height and BMI to classify nutritional status (Burke *et al* 2013), it is possible that the rates of malnutrition amongst Wilms' Tumour patients could have been under-reported, leading to a significant underestimation of the actual prevalence of malnutrition amongst this population to date.

The term corrected weight refers to the weight of a subject when tumour weight (obtained post-operatively) is subtracted from admission weight. This has been used previously (Israels *et al* 2009) and may provide a more accurate indication of nutritional status when weight and height measurements are used. However, corrected weight should not be considered to be an accurate reflection of nutritional status in isolation, as the tumour weight at the time of surgery is usually smaller than on admission due to the provision of pre-operative chemotherapy (Israels *et al* 2009). Murphy *et al* (2009) emphasised that height, weight and BMI should only be used in order to screen patients initially and should not be considered a comprehensive or accurate method of classifying nutritional status amongst this population. The authors emphasised that the incorrect classification of malnourished children as "well-nourished" can lead to a worsened prognosis (Murphy *et al* 2009).

2.2.2. Arm anthropometry

Arm anthropometry, specifically MUAC and TSFT, should be incorporated in the nutritional assessment of children with Wilms' Tumour in order to accurately classify their nutritional status (Sala *et al* 2012). These measures are independent of tumour size (Tah *et al* 2012; Brennan *et al* 1999), and are affordable and relatively easy for a trained professional to

conduct (Hoffmeister, Storer, Macris, Carpenter & Baker 2013). Both MUAC and TSFT have been shown to be feasible tools for classification of nutritional status in developing countries in particular (Sala *et al* 2012; Garofolo *et al* 2005). MUAC provides a measure of body fatness, while TSFT measures muscle mass (Ramsey, Farrell & Pencharz 1992). MUAC measurements have the added advantage of being less severely affected by fluid shifts compared to TSFT measurements (Tah *et al* 2012).

Tazi *et al* (2008) demonstrated the discrepancies that can transpire when using weight and height alone in order to assess nutritional status. In a sample of 100 children with cancer, 37% and 20% of children were classified as being malnourished when utilising weight- and height-for-age measurements respectively. However, when arm anthropometry was included as part of the anthropometric assessment, the prevalence of malnutrition was noted to be as high as 50%. The same trend was observed in a much larger study involving 1787 children with cancer conducted by Sala *et al* (2012). In this study, the prevalence of malnutrition increased from 28% when BMI was used, to 63% when arm anthropometry was included in the anthropometric assessment. Similar evidence for the superior accuracy of arm anthropometry compared to weight, height and BMI amongst this population has been demonstrated in several other studies discussed in Table 2.1 (Israels *et al* 2008; Tazi *et al* 2008; Garofolo *et al* 2005).

Table 2.21: Studies assessing the most accurate methods of classifying nutritional status amongst children with cancer

Study	Objectives	Subjects	Methods	Results	Limitations	Conclusion
Nutritional status at admission of children with cancer in Malawi. Israels *et al* (2008) Location: Malawi	To determine the prevalence of malnutrition on admission amongst children with cancer.	128 children 1-16 years HM = 74.2% ST = 20.3% Other/unknown = 5.5%	Prospective cohort study. Malnutrition determined using: • Weight • Height • MUAC • TSFT • AMA	Prevalence of malnutrition: HFA = 44.5% WFA = 39.8% WFH = 17.2% AMA = 55.1% TSFT + MUAC = 59.3% TSFT + MUAC > 10th percentile = 4.7%	Small sample size Selection bias	Malnutrition was common amongst this population on admission to hospital. AA was a more sensitive measure of nutritional status.
Nutritional status at diagnosis of children with malignancies in Casablanca. Tazi *et al* (2008) Location: Morocco	To determine the prevalence of malnutrition amongst children with cancer at diagnosis.	100 children under the age of 18 years HM = 58 ST = 38 CNS tumours = 4	Prospective cohort study Malnutrition determined using: • Weight • Height • MUAC • TSFT • AMC • Albumin	Prevalence of malnutrition: • WFA = 37% • HFA = 20% • BMI = 33% • TSFT = 50% • MUAC = 39% • AMC = 42% • Albumin = 28% Using AA, malnutrition more prevalent, severe amongst children with ST vs. HM	Small sample size Selection bias	High prevalence of malnutrition amongst children with cancer at diagnosis. AA was a more sensitive measure of nutritional status, especially for children with ST.

Table 2.1 Continued

Study	Objectives	Subjects	Methods	Results	Limitations	Conclusion
High prevalence of malnutrition among patients with solid non-haematological tumors as found by using skinfold and circumference measurements Garofolo *et al* (2005) Location: Brazil	To compare anthropometric classification methods, and compare severity of malnutrition amongst children with ST versus HM.	127 children HM = 59 ST = 68	Cross-sectional study Malnutrition determined using: • Weight • Height • MUAC • TSFT • AMC	Prevalence of malnutrition - HM vs. ST: WFH/BMI = 6.8 vs. 29.4% MUAC = 25.4 vs. 44.1% TSFT = 33.9 vs. 45.6% AMC = 10.2 vs. 33.8% Overall prevalence of malnutrition: TSFT = 40.2% MUAC = 35.4% WFH/BMI = 18.9%	Small sample size	Malnutrition was common amongst this population. Children with ST were more likely to be malnourished. Weight measurements were not sensitive measures of malnutrition amongst this population.

Abbreviations:

AA	Arm Anthropometry	HM	Haematological Tumours
ALL	Acute Lymphoblastic Leukaemia	MUAC	Mid Upper Arm Circumference
AMA	Arm Muscle Area	ST	Solid Tumours
AMC	Arm Muscle Circumference	TSFT	Triceps Skinfold Thickness
BMI	Body Mass Index	WFA	Weight for Age
EFS	Event Free Survival	WFH	Weight for Height
HFA	Height for Age	WT	Wilms' Tumour

2.2.3. Biochemistry

One of the criteria often used as part of the nutritional assessment of children with cancer is serum albumin levels (Sala *et al* 2012; Tah *et al* 2012; Israels *et al* 2009; Murphy *et al* 2009; Elhasid, Laor, Lischinsky, Postovsky & Weyl Ben Arush 1999). Albumin is a protein that is synthesised in the liver, and measurement thereof can give an indication of visceral protein status (Brennan 1998). When used in isolation, measurement of serum albumin is considered by many to be an unreliable indicator of nutritional status due to the wide spectrum of factors that can influence albumin status (Tazi *et al* 2008). Albumin levels can appear elevated due to factors such as dehydration or corticosteroid treatment, whereas levels can decrease in response to inflammation, malabsorption and liver disease (Fuhrman 2002). Furthermore, the fact that it is a negative acute phase protein means disease-related factors such as temperature can affect albumin levels (Brennan 1998). It also has a long half-life of approximately 20 days (Fuhrman 2002).

Nonetheless, albumin does have a place in the nutritional assessment of patients (Ladas *et al* 2006). Albumin has been shown to be a very useful measure in combination with anthropometric measurements, as it improves the sensitivity of nutritional classifications (Sala *et al* 2012). Albumin is considered to be low when levels fall below 35g/l (Heber, Greenway, Kaplan, Livingston, Salvador & Still 2010). In a study of 1513 children with cancer in developing countries, Sala *et al* (2012) showed that the inclusion of albumin as a criterion for the classification of nutritional status added considerable value. When comparing classifications using measurements of arm anthropometry alone (MUAC and TSFT) to measurements including both arm anthropometry and albumin, those classified as severely malnourished increased from 45% to 59%.

2.2.4. Current practices and the lack of a gold standard

A significant problem associated with determining the prevalence of malnutrition is that there is no gold standard to accurately assess nutritional status amongst children with cancer (Burke *et al* 2013; Rogers & Ladas 2011; Israels *et al* 2008; Elhasid *et al* 1999), which route of feeding to choose and when to initiate nutritional interventions (Ladas *et al* 2006).

The COG conducted an international survey amongst 125 institutions treating paediatric oncology patients in order to determine common practice in relation to nutritional management of this

population. Of concern was the fact that this survey showed there was no uniform protocol being exercised amongst the institutions surveyed. Just over half of the institutions had specific criteria for conducting nutrition interventions, while only 46% of children underwent a nutritional assessment on admission. The majority of institutions utilised weight and height as their primary tools for classification of nutritional assessment, while only five percent included MUAC and TSFT measurements (Ladas *et al* 2006).

An unpublished survey of eight South African paediatric oncology units conducted by Schoeman (2011) showed a similar lack of uniformity with regards to management of these children. Nutritional assessment on admission was not routinely conducted at all units and different assessment tools were used. Furthermore, only 62% of units utilised MUAC as part of their nutritional assessments, while only 37% included measurements of TSFT. According to the COG, current nutrition related practices amongst this population are based on opinions instead of evidence-based protocols (Rogers *et al* 2008).

In order to try to standardise assessment and classification of nutritional status amongst children with cancer, an algorithm for nutritional classification and support was developed at a meeting held by the AHOPCA consortium. The algorithm is based on data gathered from seven developing countries and incorporates arm anthropometry, albumin, weight loss and percentage of ideal body weight measurements as classification criteria (Sala *et al* 2005).

According to the algorithm, adequately nourished subjects are those whose weight is more than 90% of their ideal body weight (IBW), with albumin above 35g/L, MUAC and TSFT more than the 10^{th} centile and having experienced weight loss of less than 5% of their body weight. They need to meet all of these criteria in order to be classified as adequately nourished. According to this classification, those who are considered to be mildly malnourished based on MUAC and TSFT, are classified as adequately nourished if they meet all of the other criteria mentioned above. Subjects are classified as being depleted (malnourished) if at least one of the following criteria are met: they are 60-89% of their IBW, their TSFT and/or MUAC is between the 5^{th} and 10^{th} centile, they have experienced weight loss of 5-10%, or their albumin is between 32 and 35g/L. Severely malnourished subjects are those who are either less than 60% of their IBW, have a MUAC and/or TSFT below the 10^{th} centile, have experienced more than 10% weight loss or have an albumin level of below 32g/L (Sala *et al* 2005).

Initially, the algorithm stated that both MUAC and TSFT had to be below a certain value in order for a subject to be classified as malnourished. These criteria have since changed, stipulating that all subjects with either MUAC *or* TSFT below a certain level be classified as malnourished. This was done in order to increase the sensitivity of the algorithm and to encourage interventions amongst a larger proportion of subjects (Sala *et al* 2005).

2.3. Pathogenesis of malnutrition and the role of nutritional intervention

In order to formulate effective and appropriate nutritional protocols and interventions amongst children with cancer, it is imperative to understand the causes and mechanisms underlying the development of their malnutrition. Malnutrition is defined as a state of disequilibrium caused by an imbalance between the intake and loss of substrates (Mora 1999). When the body experiences a prolonged period of starvation, an adaptive response occurs. This leads to changes in hormone levels and, consequently, a reduction in the metabolic rate. Furthermore, fat is utilised for fuel in order to preserve lean body mass, thereby prolonging survival (Bines & Heine 2005, p180).

Unfortunately, the development of malnutrition amongst cancer patients is often more complicated than this. A culmination of several underlying mechanisms can sometimes lead to a phenomenon involving anorexia, severe weight loss and muscle wasting, known as cancer cachexia (Fearon, Strasser, Anker, Bosaeus, Bruera, Fainsinger, Jatoi, Loprinzi, MacDonald, Mantovani, Davis, Muscaritoli, Ottery, Radbruch, Rovasco, Walsh, Wilcock, Kaasa & Baracos 2011). This section will look at factors that can contribute to the development of malnutrition amongst children with cancer, with specific focus on cancer cachexia. The relationship between nutritional status on admission and outcome, as well as the role of nutritional intervention amongst this population will also be discussed.

2.3.1. Anorexia and reduced oral intake

Studies have shown that children undergoing chemotherapy often fail to meet their nutritional requirements for all macronutrients (Skolin, Axelsson, Ghannad, Hernell & Wahlin 1997) due to insufficient dietary intake, leading to the development of malnutrition (Skolin, Wahlin, Broman, Koivisto Hursti, Vikstrom Larsson & Hernell 2006; Skolin *et al* 1997). Skolin *et al* (2006)

conducted a study on 22 children undergoing chemotherapy to assess which factors negatively influenced dietary intake. Although the sample size was small, the authors found that altered taste and learned food aversions were the two most common side-effects that led to reduced oral intake. Children also experienced vomiting, nausea and mouth sores. Furthermore, these children showed signs of physiological taste alterations with significantly higher sensitivity to bitter tastes and an impaired ability to correctly identify tastes (Skolin *et al* 2006). Other factors that can contribute to reduced oral intake include mucositis, tension between children and their caregivers regarding eating, tumour burden and cancer cachexia (Burke *et al* 2013). The tumour burden is the amount of the subject‟s weight that is attributed to tumour mass, and can be determined after surgery once the tumour has been removed. Lastly, impaired gastrointestinal motility can cause early satiety, thereby limiting oral intake (Fearon *et al* 2011).

2.3.2. Increased Basal Metabolic Rate

It is thought that the disease process itself plays a role in the progressive development of malnutrition amongst children with cancer (Israels *et al* 2009) over and above factors contributing to reduced dietary intake as discussed earlier (Skolin *et al* 2006). This could be attributed to the fact that metabolic alterations occur in many patients with cancer (Den Broeder, Oeseburg, Lippens, van Staveren, Sengers, van‟t Hof & Tolboom 2001). Holroyde, Gabuzda, Putnam, Paul & Reichard (1975) showed that patients with metastatic disease exhibited increased energy expenditure due to altered glucose metabolism and subsequent increases in Cori cycle activity, which contributed to progressive weight loss. Furthermore, children with solid tumours were shown to have an increased Basal Metabolic Rate (BMR). For some patients, this increased BMR may resolve after the first or second chemotherapy treatment (Den Broeder *et al* 2001).

2.3.3. Cancer cachexia

When reduced oral intake and anorexia occur in combination with increased metabolic demands, the development of malnutrition in children with cancer can often be attributed to a debilitating syndrome called cancer cachexia. An international consensus defined cancer cachexia as "a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without a loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (Fearon *et al* 2011). Muscle wasting and loss of lean body

mass is devastating for the cancer population in particular, as it has been shown to be associated with a significant increase in treatment related toxicity and time to tumour progression (Prado, Baracos, McCargar, Reiman, Mourtzakis, Tonkin, Mackey, Koski, Pituskin & Sawyer 2009).

There are three phases of cachexia, namely precachexia, cachexia and refractory cachexia. Patients with precachexia may experience some symptoms of cachexia, such as anorexia, without demonstrating significant unintentional weight loss. Patients are considered to be cachectic when they demonstrate involuntary weight loss of more than 5% over a six month period, or experience persistent weight loss of more than 2% with a BMI of less than 20 kg/m^2. Patients classified as experiencing refractory cachexia are often in an extremely catabolic state. Their cancer often progresses at a rapid rate and is less responsive to therapy. In such situations, palliative management of patients is often more appropriate and, in many situations, the benefit of artificially feeding patients is often not justified when weighed against the potential risks and discomfort associated therewith. Instead of trying to reverse muscle and weight loss, interventions for these patients are rather aimed at alleviating acute symptoms and distress (Fearon *et al* 2011).

The severity of cachexia can be related to the degree of hypercatabolism that a patient experiences. Although inflammation is thought to be a cause of cachexia, it can sometimes occur in the absence of obvious systemic inflammation, therefore the measurement of indices such as C-reactive protein cannot be solely relied upon to classify severity. Tumour metabolism can further drive catabolism (Fearon *et al* 2011).

The assessment of muscle strength and mass is useful when assessing cachectic severity. There is no set standard for how best to measure such factors, and some tests such as magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DXA) imaging are simply not available or accessible to many patients. Arm muscle area and hand grip dynamometry, on the other hand, are often more practical tools for assessing muscle strength and mass in cancer patients. Analysis of physical functioning and a patient's psychosocial status can also be useful when assessing cachexia severity. Various tests and questions can be utilised to assess these, including analysing a patient's perceived quality of life, as well as determining how they feel regarding their reduced food intake and any guilt or distress associated therewith (Fearon *et al* 2011).

2.3.4. Relationship between nutritional status on admission and survival

It is evident that malnutrition, which develops due to a combination of factors mentioned above, can have a significant impact on children with cancer. Opinions regarding the strength of utilising nutritional status on admission as a prognostic indicator are conflicting (Rogers 2014). Furthermore, there is a paucity of data assessing this relationship, particularly when it comes to children with solid tumours (Rogers & Ladas 2011).

A large proportion of the research analysing this relationship has been conducted on children with haematological malignancies. A study conducted by Hoffmeister *et al* (2013) on children who underwent an hematopoietic cell transplant showed a significant relationship between arm muscle area and both short- and long-term event free survival (100 days and three years post-transplant, respectively). A large trial with 1787 children with cancer (solid tumours and haematological malignancies) was conducted by Sala *et al* (2012). The study demonstrated a significant link between malnutrition at diagnosis and increased mortality rates amongst children with solid tumours, including Wilms' Tumour. This relationship was not significant for children with haematological malignancies. When assessing children with solid tumours at two years post-diagnosis, 26% of children who were severely malnourished at diagnosis were alive with no adverse events, compared to 59% of those who were adequately malnourished at diagnosis. This was compared to 58% and 72%, respectively amongst children with haematological malignancies. Other studies, albeit on much smaller sample sizes, support the prognostic significance of malnutrition at diagnosis (Mejia-Arangure *et al* 1999; Viana *et al* 1994). Malnutrition has also been linked to increased risk of relapse (Viana *et al* 1994), infections and toxicity (Orgel *et al* 2014).

In contrast to this, studies have also shown a lack of evidence for a relationship between malnutrition and outcome. A large study of 1025 children concluded that nutritional status at diagnosis should not be considered to be a strong indicator of prognosis amongst children with haematological malignancies (Weir *et al* 1998). This evidence has been supported by further studies (Pedrosa *et al* 2000) including research conducted on South African children with Wilms' Tumour (Wessels *et al* 1999). The significance of this relationship will unfortunately remain inconclusive until more studies are conducted. After a comprehensive review of the literature, only four studies assessing the relationship between nutritional status on admission and outcome amongst children with cancer, with specific focus on solid tumours, were found. These studies are described in Table 2.2.

Table 2.2: Studies assessing the relationship between nutritional status at diagnosis and outcome amongst children with solid tumours

Study	Objectives	Subjects	Methods	Results	Limitations	Conclusion
Effect of malnutrition at the time of diagnosis on the survival of children treated for cancer in El Salvador and Northern Brazil Pedrosa *et al* (2000) Location: El Salvador and Brazil	To determine the relationship between malnutrition at diagnosis and survival.	443 children • HM = 283 • ST = 160	Prospective cohort study. Malnutrition determined using: • Weight • Height	Prevalence of malnutrition: • WFA = 23.5% • HFA = 22.8% • WFH = 15.7% No significant difference between survival rates of malnourished vs. well-nourished subjects.	AA not used to classify nutritional status. Relatively small sample size when looking at ST group separately.	No significant relationship between nutritional status at diagnosis and outcome.
Nutrition, morbidity, and survival in South African children with Wilms' Tumor. Wessels *et al* (1999) Location: South Africa	To determine the effect of nutritional status at diagnosis on the morbidity of treatment and outcome.	59 children with Wilms' Tumour.	Descriptive study (chart review). Malnutrition determined using: • Weight • Height	Prevalence of malnutrition = 35% Estimated survival rates for normal vs. malnourished children = 56% vs. 74%	AA not used to classify nutritional status Small sample size.	Malnutrition at diagnosis not related to poorer outcome or increased morbidity.

Study	Objectives	Subjects	Methods	Results	Limitations	Conclusion
Does body mass index at diagnosis or weight change during therapy predict toxicity or survival in intermediated risk Rhabdomyosarcoma? A report from the Children's Oncology Group Soft Tissue Sarcoma Committee. Burke *et al* (2013) Location: United States of America	To determine the effect of weight loss during therapy on toxicity and survival in Rhabdomyosarcoma patients.	468 children with Rhabdomyosarcoma between 2-21 years old.	Malnutrition determined using: • Weight • Height	9.8% of children were malnourished at baseline. Baseline nutritional status was not significantly related to survival. Weight loss associated with increased toxicity and length of hospital stay.	AA not used to classify nutritional status.	Nutritional status on admission was not significantly related to survival. Difficult to account for variability amongst different institutions regarding nutritional protocols/ intervention.

Study	Objectives	Subjects	Methods	Results	Limitations	Conclusion
Nutritional status at diagnosis is related to clinical outcomes in children and adolescents with cancer: A perspective from Central America Sala *et al* (2012) Location: Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua and Panama.	To assess nutritional status at diagnosis. To correlate nutritional status at diagnosis with outcomes (treatment abandonment, relapse and death).	1787 children 1-18 years old (of whom 1513 had all data for classification of nutritional status). HM = 1143 ST = 370	Prospective study. Malnutrition determined using: • Weight • Height • MUAC • TSFT • Albumin	Prevalence of malnutrition according to: • BMI = 28% • MUAC + TSFT = 21.4% moderate, 45.5% severe • MUAC + TSFT + albumin = 18% moderate, 59.2% severe • Type of cancer: ST = 56% Leukaemias (other than ALL) = 69% EFS two years post-diagnosis: • Well-nourished = 65% • Severely	Relatively small sample size of children with ST when divided into HM vs. ST groups.	There was a high prevalence of malnutrition amongst children with cancer in developing countries. AA was a sensitive measure of nutritional status amongst children with cancer. Malnutrition was significantly related to higher mortality rates amongst children with ST. Not significant for HM group. Malnutrition was significantly related to frequency of treatment abandonment amongst ST and ALL groups.

Study	Objectives	Subjects	Methods	Results	Limitations	Conclusion
				depleted = 48% EFS two years post diagnosis - ST vs. HM: • Severely depleted = 26 vs. 58% • Well-nourished = 59 vs. 72%		

Abbreviations:

AA	Arm Anthropometry	HM	Haematological Tumours
ALL	Acute Lymphoblastic Leukaemia	MUAC	Mid Upper Arm Circumference
AMA	Arm Muscle Area	ST	Solid Tumours
AMC	Arm Muscle Circumference	TSFT	Triceps Skinfold Thickness
BMI	Body Mass Index	WFA	Weight for Age
EFS	Event Free Survival	WFH	Weight for Height
HFA	Height for Age	WT	Wilms' Tumour

2.3.5. Weight loss during cancer treatment

Many recent studies have changed the focus of interest and, instead of only assessing nutritional status at the time of admission; have gone one step further by assessing weight changes during the course of cancer treatment. Several studies have demonstrated that progressive weight loss during therapy is common amongst children with cancer (Brinksma, Roodbol, Sulkers, Kamps, de Bont, Boot, Burgerhof, Tamminga & Tissing 2015; Orgel *et al* 2014; Antillon *et al* 2013; Burke *et al* 2013; Zimmermann, Ammann, Kuehni, De Geest & Cignacco 2013). Zimmermann *et al* (2013) conducted a study which monitored changes in BMI during treatment. The results showed a steady increase in the prevalence of malnutrition from 5.8% at baseline to 36% after 60 days and 47% by the end of the treatment period. These findings were supported by Burke *et al* (2013) who found that, after six months of treatment, 18.2% and 18.7% of patients lost more than 5% and 10% of their baseline weight, respectively. Antillon *et al* (2013) suggested that nutritional status at six months after the commencement of treatment is a more accurate indicator of survival compared to nutritional status on admission. Children who were well-nourished or moderately malnourished at this stage of treatment had a significantly more favourable chance of surviving than those who were classified as severely malnourished (Antillon *et al* 2013).

Orgel *et al* (2014) took this a step further by assessing the influence of weight extremes during treatment on event free survival as well as treatment-related toxicity. In their large sample of over 2000 children, they found that children who were underweight for more than 50% of the time during the induction and intensive (pre-maintenance) phases of treatment had significantly poorer survival compared to those who were underweight for shorter periods of time during treatment. Children who presented in an undernourished state on admission and remained underweight for more than 50% of the pre-maintenance treatment period were almost twice as likely to relapse or die compared to those who were adequately nourished during treatment. Of significance was the finding that children who presented as underweight but who gained weight and were subsequently classified as well-nourished during the treatment period had a much lower risk of relapse, toxicity or death. Their risk thereof was comparable to those who presented in a well-nourished state. This finding was also supported in a study conducted by Antillon *et al* (2013).

2.3.6. The role of nutritional intervention

Unlike many unmodifiable risk factors for cancer, such as age and gender, nutritional status can be changed or altered if nutritional interventions are implemented (Orgel *et al* 2014). Nutritional intervention amongst children with cancer should aim to meet the patient's needs, both nutritional and psychosocial, on an individualised basis. Furthermore, the type of intervention should be appropriate for the specific patient's situation and if the gut is working it should be utilised whenever possible (Van Eys 1998). However, according to a survey of 125 institutions treating children with cancer worldwide, nutrition related practices (such as time of assessment and criteria used, estimation of nutritional requirements and timing, type and route of nutritional intervention) were shown to be erratic and inconsistent. More than half of these institutions did not conduct nutritional assessments at diagnosis, while a variety of criteria were used in order to determine if and when nutritional interventions were implemented (Ladas *et al* 2006).

Several studies have shown the benefits and effectiveness of nutritional intervention (De Waele, Mattens, Honore, Spapen, De Greve & Pen 2015; Sacks, Hwang, Lange, Tan, Sandler, Rogers, Womer, Pietsch & Rheingold 2014; Antillon *et al* 2013; Barbosa, Pedrosa & Cabral 2012). The efficacy of nutritional intervention amongst children with Wilms' Tumour in particular has also been demonstrated by Holzinger *et al* (2007). The authors showed that provision of supplementation, in the form of oral nutritional supplements and/or enteral feeding, led to significant weight gain in the majority of patients.

As described in the definition mentioned earlier, cachexia cannot be reversed or "cured" by conventional types of nutritional interventions (Fearon *et al* 2011). Many cachectic patients are hypermetabolic, as demonstrated in the study conducted by Dev, Hui, Chisholm, Delgado-Guay, Dalal, Del Fabbro & Bruera (2015). However, when compared to cachectic patients with normal metabolic rates, the two groups were shown to have a similar prognosis. Furthermore, hypermetabolism was not shown to have a strong influence on velocity of weight loss or symptom burden. This emphasises the importance of treating and addressing all potential nutrition-related symptoms of cachexia, including nausea, constipation and early satiety along with hypermetabolism, in order to prevent weight loss and facilitate weight gain amongst this population (Dev *et al* 2015).

Although nutritional intervention and resuscitation amongst these patients is more challenging than for patients with simple malnutrition, it has been shown that it can be successful. De Waele *et al*

(2015) conducted a study over a period of one year to assess the efficacy of nutritional intervention amongst cachexia patients, in the form of intensive personalised dietary programs and continued support from a dietitian and doctor. Although this study had a small sample size, it showed that nutritional support was beneficial and important amongst the cachectic population. The subjects who received dietary intervention were shown to have significantly shorter hospital stays compared to the control group (3.4 days versus 37.6 days), as well as significantly improved survival. They also tended to show a better response to treatment and were shown to have a more stable body weight during the course of the study compared to the control group (De Waele *et al* 2015).

In addition to this, the psychological aspects of cachexia, for both the patient and their family, need to be addressed. Studies have shown that patients and their families show poor understanding of cachexia, including its causes and the symptoms associated therewith. They often attributed continued weight loss to perceived absence of dietary interventions, which left them feeling hopeless and isolated and could be detrimental to the quality of life of patients and their family members (Reid, McKenna, Fitzsimons & McCance 2010). The importance of multidisciplinary team (MDT) management of these patients, who are notoriously difficult to treat, should be emphasised (De Waele *et al* 2015).

2.4. Conclusion

Developing countries face many debilitating problems related to the treatment of children with cancer, which lead to increased treatment abandonment (Paintsil *et al* 2015; Madani *et al* 2006), rates of malnutrition (Sala *et al* 2012; Israels *et al* 2009; Israels *et al* 2008; Garofolo *et al* 2005) and poorer survival (Paintsil *et al* 2015; Abuidris *et al* 2008). Many developing countries have failed to effectively collaborate in order to optimise the management and treatment of children with cancer (Ekenze *et al* 2006). MDT management is important (Barbosa *et al* 2012; Ekenze *et al* 2006) and has proven to be effective amongst cancer patients in particular (De Waele *et al* 2015). It is important to establish sensitive methods whereby the nutritional status of children with cancer can be accurately classified and those at high risk of becoming malnourished can be identified early (Elhasid *et al* 1999). Furthermore, these methods need to be standardised amongst all institutions treating children with cancer in order to gain an understanding of the true prevalence of malnutrition amongst this population.

There is a paucity of research focusing on Wilms' Tumour in general, and particularly in a South African setting. In order to treat this disease effectively while taking into account the unique

challenges that are present in a resource limited setting, it is important to understand how modifiable factors, such as nutritional status, influence disease outcome, and how nutritional intervention can be used most effectively in order to improve outcome. This will guide health care providers and policy makers in the right direction in order to provide the most efficacious treatment for this population, including developing guidelines relating to the most effective nutritional management. This study, which had a sample incorporating two provinces in South Africa, aimed to provide an accurate prevalence of malnutrition on admission amongst Wilms' Tumour patients. Furthermore, it aimed to determine the influence of malnutrition at the time of admission on outcome after two years, as well as the level of nutritional support provided to children with Wilms' Tumour at IALCH. The methodology of this study will be discussed in the next chapter.

CHAPTER 3: METHODOLOGY

In this chapter the following sections relating to the methodology used in this study are discussed: the literature relating to the particular research methodology utilised, the population and sample selection, statistical analysis of the data as well as ethical considerations of the study.

3.1. Type of study

This prospective observational study utilised a cohort study design in order to assess the prevalence of malnutrition amongst children with Wilms' Tumour at IALCH between 2004 and 2012.

3.2. Background information on study site

IALCH is classified as a National Central Hospital and services a large catchment area spanning two of South Africa's seven provinces, including all districts in KZN and the seaboard area of the Eastern Cape. It is a referral hospital for all tertiary and district hospitals in the KZN province (Department of Health 2014) (Figures 3.1 and 3.2) and has a catchment area of over ten million people (Stats SA 2011). Furthermore, it also accepts referrals from the seaboard area of the Eastern Cape, and other parts of the country on occasion. According to the most recent census data, almost 45% of households in KZN are situated in rural areas. Black Africans make up the vast majority of the population in KZN (86.8%), followed by the Indian/Asian (7.4%) White (4.2%) and Coloured (1.4%) population groups (Stats SA 2011). In the Eastern Cape, Black Africans make up 86.3% of the population, followed by Coloureds (8.3%), Whites (4.7%) and Indians/Asians (0.4%). Therefore, although this is a single centre study, the study population is reflective of the demographics of the entire province (and South Africa as a whole) due to its unusually large catchment area. Table 3.1 provides demographic information regarding education and income of the different ethnic groups in South Africa. Furthermore, it provides information regarding the use of public health facilities by different ethnic groups.

Table 3.1: Demographic information for different ethnic groups in SA (Stats SA 2011)

	Black	**Coloured**	**White**	**Indian/Asian**
Education – No school (%)	10.5	4.2	0.6	2.9
Education – Gr 12 (%)	27.1	25.4	40.8	40.4
Income (R/annum)	60 613	112 172	365 134	251 541
Utilisation of public health care (%)	87.84	8.55	2.32	1.55

Data was collected by the dietitians who were working in the paediatric surgical ward at IALCH between 2004 and 2012. This data was initially collected to be utilised in a broader study, however, it was subsequently utilised in two separate studies. The first study focused on the influence of nutritional status on the outcome of subjects, while the second focused on the influence of nutritional status on toxicity. For the purpose of this dissertation, only the first study is discussed.

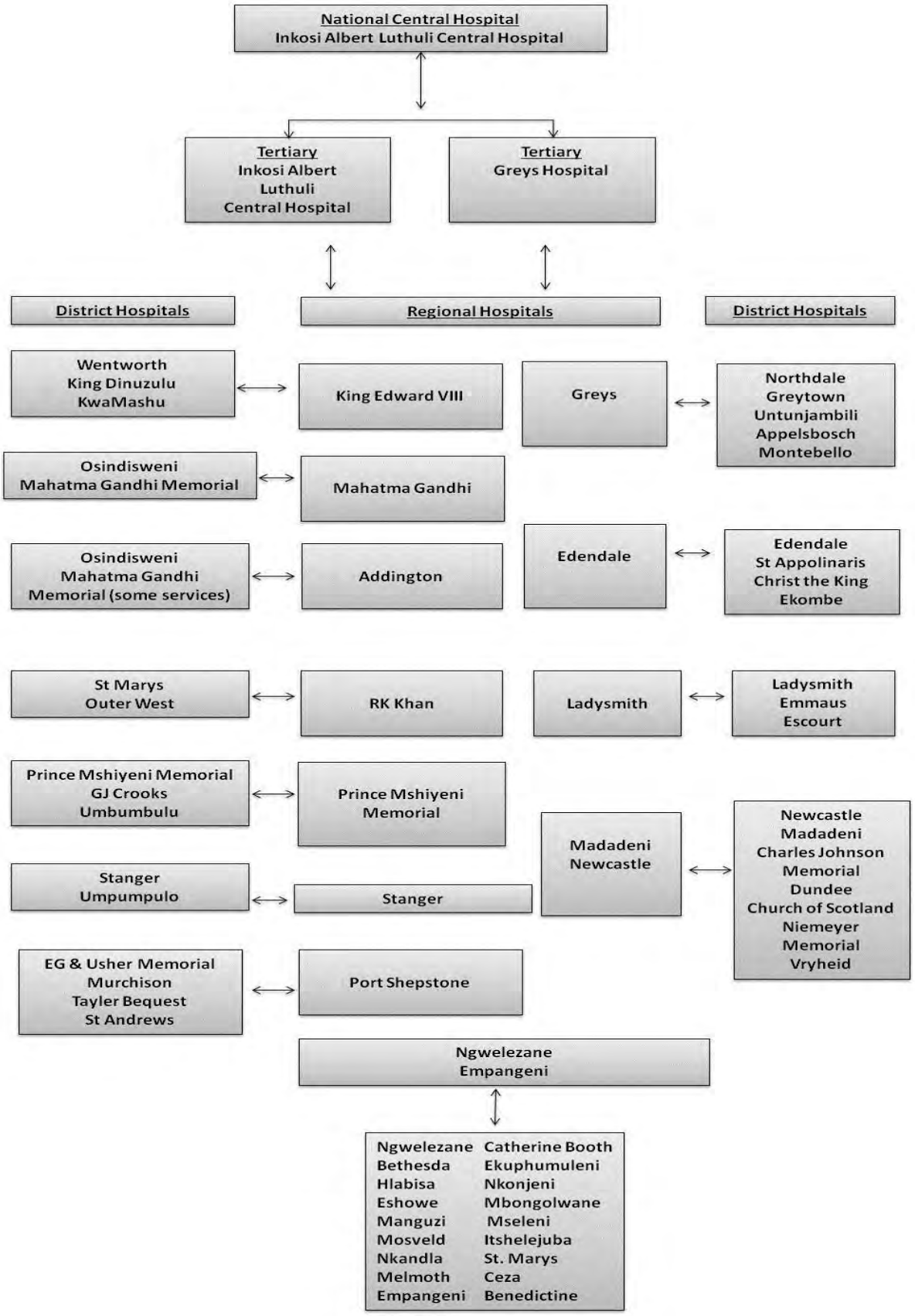

Figure 3.1: Framework for KZN hospitals referring to IALCH (Department of Health 2014)

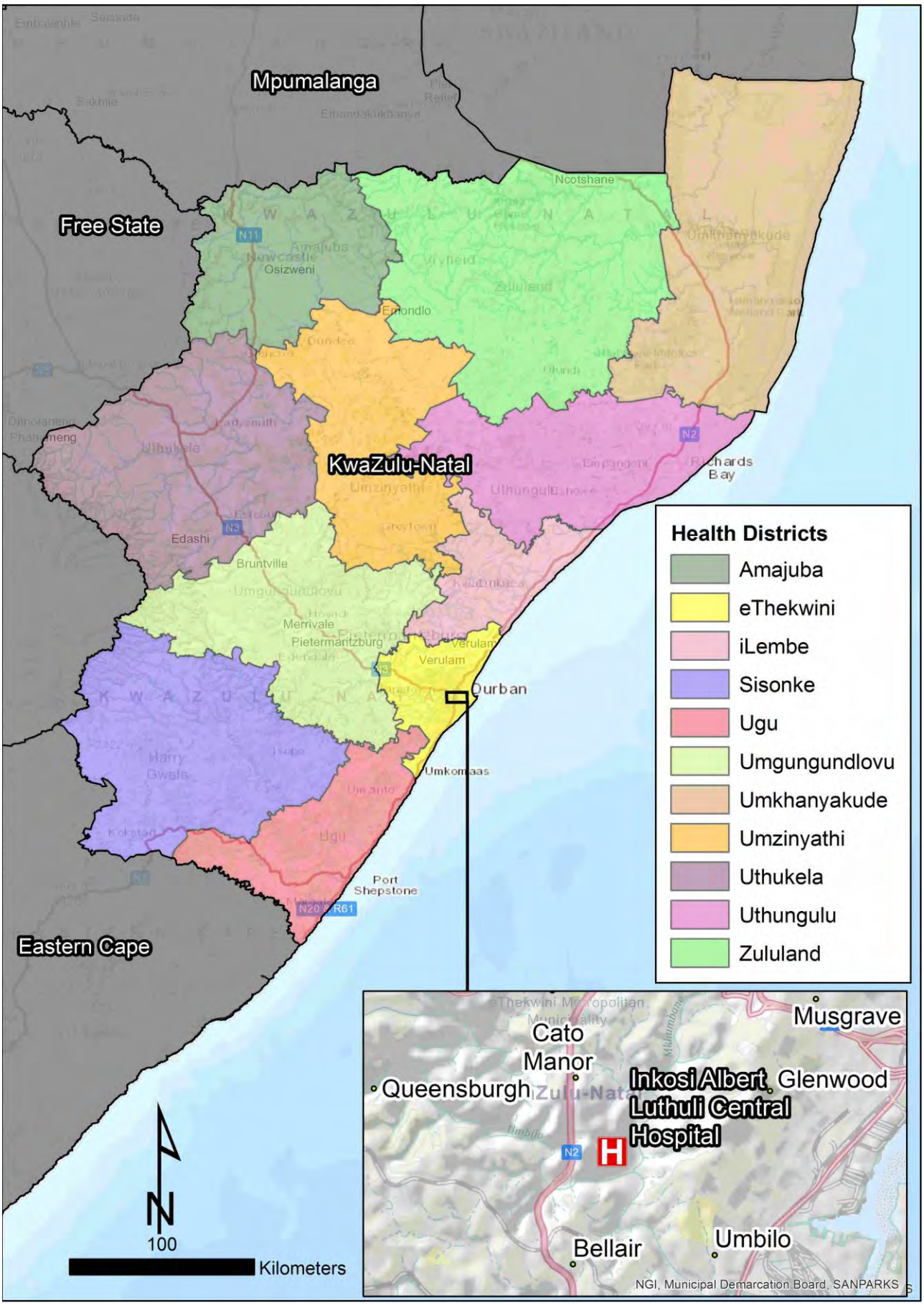

Figure 3.2: Map of health districts in the KZN Province (adapted from Department of Health 2014)

3.3. Study design

3.3.1. Prospective observational studies

Observational studies employ a study design by which the investigator merely observes the study population without implementing any type of intervention (Mann 2003). The prevailing opinion that results obtained from observational trials are inferior to those of randomised controlled trials has been challenged. In contrast to this belief, it has been shown that observational studies that have been rigorously designed and well conducted can provide results of a similarly high standard to those obtained from randomised controlled trials (Concato, Shah & Horwitz 2000).

A prospective observational study is defined as "an observational study, often longitudinal in nature, for which the consequential outcomes occur after study commencement" (Berger, Dreyer, Anderson, Towse, Sedrakyan & Normand 2012). In other words, this study design implies that the group of people selected for the study do not display the outcome of interest at the time of initial selection. This allows the researcher to identify one or more potential variables that may influence the outcome, and collect the relevant data related to these variables. At the end of the research period, the researcher is then able to analyse the data to determine which (if any) variables influenced whether or not the outcome did in fact occur (Mann 2003). In this study, the outcome of interest refers to whether or not the subject was alive at two years after their initial admission and diagnosis.

Conversely, retrospective studies involve looking back at information that has already been gathered (Berger *et al* 2012), sometimes for completely different purposes (Mann 2003). These data are analysed after the exposures and outcomes have already occurred (Berger *et al* 2012). From this information, the investigator attempts to ascertain if there is a link between variables (Mann 2003). Advantages and disadvantages of these two study designs are detailed in Table 3.2.

Table 3.2: The advantages and disadvantages of prospective versus retrospective studies (Berger *et al* 2012; Euser, Zoccali, Jager & Dekker 2009; Mann 2003).

	Advantages	Disadvantages
Prospective	• Possibility of collecting additional information relating to outcome/exposure • Improved accuracy of data collected (as variables are identified before the study commences)	• Time consuming • Expensive • Potential loss of efficiency due to prolonged study period • Subjects lost to follow up • Vulnerable to confounding variables
Retrospective	• Time-efficient • Allows for researchers to answer new questions without having to collect new data • Cheaper to conduct	• Incomplete data sets • Definition of exposure and outcome may be difficult • Data often collected for a different purpose

3.3.2. Cohort studies

Cohort studies are considered to be an effective study design to determine objectives such as incidence, cause (Mann 2003) and prognosis (Thadhani & Tonelli 2006; Mann 2003). The major aim of cohort studies is to compare groups, either exposed or unexposed to a certain variable, in order to determine their risk of experiencing a single or multiple outcomes. Prospective cohort studies are considered to be the most effective type of observational study when analysing this particular relationship (Thadhani & Tonelli 2006). At the end of the study, the number of subjects who experience the specific outcome are assessed in relation to whether they were exposed or unexposed at baseline (Euser *et al* 2009). The data are usually analysed in order to determine the relative risk ratio, which is defined as "the ratio of the probability of developing the condition if exposed to a certain variable compared with the probability if not exposed" (Mann 2003).

A significant advantage of prospective cohort studies is that they minimise the debate regarding what is the cause and what is the effect, as the outcome had not yet occurred at the time of initiating the trial (Mann 2003). Furthermore, more than one hypothesis can be tested, and several possible effects of a particular exposure can be assessed, when utilising this study design (Euser *et al* 2009; Thadhani & Tonelli 2006). Results from these studies can be further generalised to wider populations (Euser *et al* 2009). Unfortunately cohort studies may not allow the researcher to determine causation due to the presence of confounding variables (Euser *et al* 2009).

3.4. Study population and sample

Between 2004 and 2012, the period during which this study was conducted, IALCH was home to the only state-run specialised paediatric oncology unit treating children with Wilms' Tumour in the KwaZulu-Natal (KZN) province. Therefore, all children in KZN suspected of having Wilms' Tumour were referred to IALCH for diagnosis and treatment.

The study population included 88 children between the ages of 6 months and 13 years who were admitted to the paediatric surgery ward at IALCH between 2004 and 2012 and diagnosed with Wilms' Tumour. Two of these children were excluded as their anthropometric data was collected after the initiation of nutritional intervention and/or chemotherapy. A further ten children were excluded as their full medical files could not be located, which led to incomplete data. The final sample consisted of 76 children whose data were analysed.

3.5. Study methods and materials

This section outlines the different methods utilised to assess nutritional status, and focuses on the rationale behind the criteria that were chosen to classify overall nutritional status.

3.5.1. Anthropometry

Between 2004 and 2012, subjects were assessed by the ward dietitian after admission to the paediatric surgical ward. Their anthropometric measurements took place before the initiation of any interventions in the form of nutritional supplementation or chemo/radio-therapy. This data was recorded in a Microsoft Excel spreadsheet on the IALCH Dietetics department's server in order to be utilised for this study.

Anthropometric status was assessed using weight, height, MUAC and TSFT measurements. Body weight and height were measured using a Nagata electronic weight and height measurement scale (Model BW-1122H). Infants were weighed on a Nagata electronic baby scale (Model BW-20) and their length measured with a measuring tape (supine position). Weight was recorded to the nearest 100g and height and length to the nearest 1cm. Subjects wore light clothing and no shoes when measurements were taken. Height measurements were taken while subjects stood up straight on the electronic scale with their back against the height-meter, looking straight ahead. These scales are calibrated annually by the manufacturer in order to ensure and maintain accuracy. Excised tumour

weight was recorded by the paediatric surgeon post-operatively and the corrected weight was utilised for statistical analysis in order to give a more accurate reflection of nutritional status on admission.

In order to measure MUAC, the midpoint between the acromion process of the scapula and olecranon process of the ulna was determined while the left forearm was bent at a right angle. A non-stretchable measuring tape was then used to measure the circumference at the midpoint while the arm hung straight down, to the nearest 0.1cm. TSFT was measured on the same midpoint using a Harpenden skinfold caliper and recorded to the nearest 0.1cm. Both measures were performed in triplicate and the average recorded in order to ensure accuracy.

Weight and height measurements were utilised to determine weight for age (WFA), length for age (LFA)/height for age (HFA), weight for height (WFH)/weight for length (WFL) and BMI depending on the age of the subject. These were classified according to age and gender matched norms utilising the STAT GrowthCharts app (Austin Physician Productivity, LLC 2012), which classifies subjects according to Z-scores using the WHO growth charts. These WHO growth charts were developed based on data collected from children of different ethnic backgrounds, from six diverse geographical areas during the WHO Multicentre Growth Reference Study. MUAC and TSFT measurements were compared with age and gender matched norms and interpreted using the Frisancho percentile charts (Frisancho 1981). Although the Frisancho charts were based on a sample of only white people, they were the only charts that allowed classification of MUAC and TSFT based on the same sample. Furthermore, several related studies used the Frisancho charts in order to classify nutritional status of their samples (Murphy *et al* 2009; Israels *et al* 2008; Tazi *et al* 2008; Garofolo *et al* 2005). Therefore, use of the same charts in this study allowed for more direct comparison of the results of this study to these previous studies.

3.5.2. Biochemistry

Albumin levels were routinely assessed on admission to hospital, and albumin was considered to be low if levels were below 35g/L (Heber *et al* 2010). Albumin levels were tested in the laboratory at IALCH using Bromocresol Green (BCG). BCG is a compound that has been shown to bind to human serum albumin. Upon interaction with serum albumin the fluorescent characteristic of the BCG changes, turning it bright green. The intensity of the fluorescence gives an indication of the quantity of albumin present in the sample being tested (Trivedi, Saxena, Siddiqui & Qasim 1997).

3.5.3. Classification of nutritional status

In order to classify subjects as malnourished or well-nourished, a combination of arm anthropometry and albumin were used. These variables were selected based on an analysis of variables utilised by a variety of studies measuring nutritional status in the past (Table 3.3), as well as recommendations regarding classification of nutritional status amongst children with cancer from recent literature (Sala, Antillon, Pencharz, Barr & AHOPCA Consortium 2005).

Table 3.3: Variables used to classify nutritional status in previous studies

Author	Wt	Corr wt	Ht	WFA	HFA	WFH	BMI	MUAC	TSFT	Alb
Brennan *et al* 1999	X		X			X		X	X	
Elhasid *et al* 1999	X									X
Pedrosa *et al* 2000	X		X	X	X	X				
Pietsch & Ford 2000	X		X	X	X	X	X			X
Garofolo *et al* 2005	X		X			X	X	X	X	
Holzinger *et al* 2007	X		X							
Israels *et al* 2008	X		X	X	X	X		X	X	
Tazi *et al* 2008	X		X	X	X	X	X	X	X	X
Israels *et al* 2009	X	X	X		X	X		X	X	
Murphy *et al* 2009	X		X				X	X	X	X
Burke *et al* 2013	X		X				X			

Wt - Weight, Corr wt - Corrected weight, Ht - Height, Alb - Albumin

Table 3.3 shows that there was no standard protocol being utilised by researchers in order to classify nutritional status amongst children with cancer. Due to the improved sensitivity and accuracy of arm anthropometry when assessing nutritional status amongst this population (Lemos *et al* 2014; Israels *et al* 2008; Tazi *et al* 2008; Garofolo *et al* 2005), and children with solid tumours in particular (Sala *et al* 2012; Tah *et al* 2012; *et al* 1999), this study utilised MUAC and TSFT measurements as part of the criteria to classify nutritional status. Albumin was also included alongside arm anthropometry in order to improve sensitivity (Sala *et al* 2012). Measurements utilising weight and height were not included in this classification system due to the evidence that these parameters often grossly underestimate the prevalence of malnutrition amongst children with cancer (Lemos *et al* 2014; Israels *et al* 2008; Tazi *et al* 2008; Garofolo *et al* 2005). Over and above this, nutritional status was classified utilising variables in isolation (MUAC and TSF, albumin, BMI) to assess the differences between these methods of classification.

In order to classify overall nutritional status in this study, a combination of anthropometry and biochemistry was used. Subjects who met at least one of these criteria were classified as malnourished:

- MUAC and TSFT between the fifth and tenth percentiles
- MUAC less than the fifth percentile and TSFT more than the tenth percentile
- MUAC more than the tenth percentile and TSFT less than the fifth percentile
- Albumin less than 35g/L

Those with a MUAC and/or TSFT below the 10^{th} centile, or albumin levels below 32g/L, were classified as being severely malnourished.

This combination of criteria, which have been modified and utilised in previous studies (Antillon *et al* 2013; Tazi *et al* 2008), was adapted from the guidelines developed at the AHOPCA congress in 2005 (Sala *et al* 2005).

3.5.4. Level of nutritional support

Any nutritional support that subjects received was recorded in their electronic files by the dietitian at the time of intervention. Early intervention was considered to be any dietary intervention that took place within two weeks of admission, before the commencement of treatment. Data relating to the type of assessment and the type of nutritional intervention (oral, enteral or parenteral) were documented for analysis.

3.6. Data analysis

Anthropometric measurements were recorded on a Microsoft Excel spreadsheet which was only accessible to the Dietetics Department at IALCH in order to ensure confidentiality. Outcome data was obtained by the researcher using electronic patient records and would have been recorded by the doctor. Once the data had been collected it was entered onto a Microsoft Excel spreadsheet on two separate occasions. After this the two data sets were given to an independent party for comparison in order to detect any discrepancies. The data was then analysed using the Statistical Package for Social Sciences (SPSS) version 21. Descriptive tests as well as the Chi-Squared test of independence were carried out in order to analyse the data. For this study, a p value of less than 0.05 was considered to be significant. Table 3.4 provides details regarding each objective, the relevant variables related to each objective as well as how the data was analysed.

Table 3.4: Data analysis of objectives

Objectives	Variables	Method of analysis
To determine the prevalence of malnutrition using a combination of anthropometric and biochemical markers, defined by the AHOPCA algorithm.	Weight Height BMI MUAC TSFT Albumin	Descriptive statistics
To determine the influence of nutritional status on the outcome of children with Wilms' Tumour.	Nutritional status • Well-nourished or malnourished Outcome • Alive or dead	Chi-square test of independence Significance below 0.05
To determine the level of nutritional support prescribed to children with Wilms' Tumour on admission.	Nutritional intervention	Descriptive statistics

3.6.1. Reliability and validity

If the reliability and validity of a measurement is not known, one would not be able to determine if the results of a study utilising that measurement are accurate. Validity refers to "whether a study is able to accurately answer the questions it was intended to answer". In order for a study to be valid, the measurements of outcomes need to provide a true reflection of the situation that is being analysed or assessed. Validity of a study can be further broken down into internal validity (how accurately a measurement reflects what it was intended to reflect) and external validity (how well the study information can be generalised to other populations) (Berger *et al* 2012).

According to Sapp & Jensen (1997), "the goal of scientific measurement is to develop instruments with a minimum of systematic error that are sufficiently precise so as to minimize chance errors during the measurement process". Although repeated measurements of the same variable may never be identical, if measurements are conducted correctly then it can be expected that the results would be consistently similar. Reliability refers to the trustworthiness of the measurement tools used in a study and is defined as “the extent to which an experiment, test, or any measuring procedure yields the same results on repeated trials” (Carmines & Zeller 1979, p11). Over the course of this study, the same procedures and steps were followed when taking all anthropometric measurements. This was in line with the standard protocols used to take anthropometric measurements as determined by the IALCH Dietetics Department. Measurements for TSFT, in particular, were repeated three times and an average taken in order to minimise inaccuracies that

may have occurred when taking skinfold measurements. Furthermore, biochemistry tests were conducted as per the policies and procedures specified in the pathology laboratories.

3.7. Reduction of bias

Bias refers to a situation when "results of a study systematically deviate from the truth because of non-random factors". Selection bias, information bias and confounders are considered to be the main categories of bias (Thadhani & Tonelli 2006). Bias can occur before, during and after a trial, and should be given due consideration at all stages (Pannucci & Wilkins 2010). In this study, the main concerns regarding bias were inter-observer bias, transfer (loss to follow up) bias, confounding variables and selection bias. These are discussed next.

3.7.1. Inter-observer bias

With regards to anthropometric measurements, non-random errors are a potential source of bias and can occur if the equipment utilised in the study produces inaccurate measurements (Carmines & Zeller 1979, p14). The electronic scales utilised in this study were calibrated annually, therefore reducing the risk of this type of bias. More than one dietitian worked in the paediatric surgical ward over the time period during which data was gathered. This may have introduced the risk of inter-observer bias, as the dietitians may have used different techniques when taking anthropometric measurements, which could have affected the reliability of the results. However, according to Pannucci & Wilkins (2010), this type of bias can be minimised by having standardised protocols relating to the collection of data. In the Dietetics Department at IALCH, measurement of anthropometric indices as part of the process of classifying nutritional status is standardised throughout the department and all dietitians follow the same standardised steps when taking weight, height, MUAC and TSFT measurements for all patients. Therefore it was assumed that all measurements for this study were taken consistently and accurately. Furthermore, when data was collated during the study period, no changes in coding or parameters occurred throughout the duration of compilation of the database, thereby limiting the risk of inaccuracies.

3.7.2. Transfer bias

Transfer bias can occur due to high rates of loss to follow up. This type of bias can affect the outcome of the trial by negatively affecting the validity (Dettori 2011), and can occur if uneven

numbers of subjects from each group are lost to follow up (Pannucci & Wilkins 2010). In this current study loss to follow up rates were low, with only eight subjects not following up for the full two year period. Of these eight subjects, all but two completed their treatment regimens.

3.7.3. Confounding variables

Confounding variables are those that can have a direct and independent influence on both the exposure and outcome being analysed. All variables that could potentially have an influence should be analysed in order to ensure all eventual confounding variables are accounted for (Mann 2003). Stage and histology are considered to be the strongest prognostic indicators amongst children with cancer (Kaste *et al* 2008). In this study, stage and histology were considered to be confounding variables and the influence of this on outcome was addressed by means of a regression analysis.

3.7.4. Selection bias

Subject selection bias refers to selecting a cohort that does not represent the broader population of subjects who could potentially develop the outcome in question (Thadhani & Tonelli 2006). Although this was a single-centre study, this type of bias was minimised due to the large catchment area of IALCH, which services over ten million people.

3.8. Ethical considerations

Ethical clearance was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Reference: BE025/13) (Appendix A). In addition to this, approval was obtained from the Medical Manager at IALCH (Appendix B) as well as the KZN Department of Health Research Committee (Reference: HRKM 227/13) (Appendix C) to conduct this study. Individual consent was not required as data was obtained by the ward dietitian as part of the nutritional assessment of each patient on admission. In order to ensure the confidentiality and anonymity of each participant, data was coded when added to the database. Subjects were not identified in the study as no names or surnames were revealed.

3.9. Summary

This chapter discussed the methods utilised to classify nutritional status in order to determine the influence thereof on outcome. The chapter examined the reasons why specific measurements were

chosen as part of the criteria to determine nutritional status, including analysis of available literature relating to this topic. It focused on the steps taken in order to ensure that the results produced by this study would be valid and reliable. Furthermore, it detailed how bias was addressed at all stages of the study in order to ensure the results were as accurate as possible. The next chapter discusses the results of this study.

CHAPTER 4: RESULTS

This chapter presents the results of the study. The characteristics of the sample are presented in order to facilitate a better understanding of the population in question. Furthermore, the results of the data analyses are assessed in order to describe the true prevalence of malnutrition amongst this population, as well as the relationship between nutritional status and outcome.

4.1. Sample characteristics

The study sample consisted of 76 children with Wilms' Tumour. Half of the sample (50%; n = 38) was made up of males, and the other half females (50%; n = 38). The majority of the sample consisted of Black African children (97.3%; n = 74), while 2.6% (n = 2) comprised White and Coloured children. The mean age of the subjects was four years and eight months (SD ± 2.89), and the median age was three years and ten months (IQR = 37.32 months). The anthropometric and demographic characteristics of the sample are presented in Table 4.1. Median height for males and females was 0.98 (IQR = 0.23) metres, while females on average weighed slightly more than males (16.99kg versus 16.56kg). Consequently, the mean BMI for females [16.17kg/m^2 (SD ± 2.69)] was slightly higher than that of males [15.30kg/m^2 (SD ± 1.83)]. The mean albumin level amongst the sample was 38.61g/L (SD ± 5.87).

Table 4.1: Anthropometric and demographic characteristics of the study population

	Mean	Median	IQR	Min	Max	SD
Age (months)						
Combined (n = 76)	55.77	46.50	37.32	11.04	149.04	34.68
Males (n = 38)	56.58	46.98	31.74	11.04	149.04	35.16
Females (n = 38)	54.95	45.54	48.72	14.04	147.00	34.66
Weight (kg)						
Combined (n = 76)	16.77	15.25	5.73	7.50	43.18	6.99
Males (n = 38)	16.56	15.53	4.62	8.54	34.58	6.04
Females (n = 38)	16.99	14.56	7.88	7.50	43.18	7.91
Height (m)						
Combined (n = 75)	1.02	0.98	0.23	0.64	1.58	0.19
Males (n = 37*)	1.01	0.98	0.22	0.64	1.50	0.19
Females (n = 38)	1.03	0.98	0.29	0.72	1.58	0.20
BMI (kg/m^2)						
Combined (n = 75)	15.73	15.94	3.14	10.31	23.85	2.32
Males (n = 37*)	15.30	15.29	3.63	12.71	20.07	1.83
Females (n = 38)	16.17	16.68	2.49	10.31	23.85	2.69

* Height was not available for one of the subjects; SD=Standard deviation

Details relating to the distribution of disease stage by gender are shown in Table 4.2. Most of the patients presented in stages three to five (71%; n = 54), while just over one quarter of the study sample presented in stage one or two (29%; n = 22).

Table 4.12: Distribution of disease stage by gender

	Stage 1 (n = 6)	**Stage 2 (n = 16)**	**Stage 3 (n = 19)**	**Stage 4 (n = 29)**	**Stage 5 (n = 6)**
Male, n, (%)	3 (50)	8 (50)	11 (58)	12 (41)	4 (67)
Female, n, (%)	3 (50)	8 (50)	8 (42)	17 (59)	2 (33)

Table 4.3 shows the distribution of disease stage by the age of the subjects. The mean age was the lowest for those in stage one. The majority of the subjects presented in stage four, with the highest mean age of 5.68 years.

Table 4.3: Distribution of disease stage by age

Stage	**Count**	**Max Age**	**Min Age**	**Mean Age**	**SD**
1	6	3.5	0.92	1.93	0.85
2	16	11.58	1.17	4.65	3.17
3	19	12.42	1.83	4.35	2.60
4	29	12.25	1.5	5.68	3.05
5	6	4.25	2.5	3.32	0.62

4.1.1. Prevalence of malnutrition on admission

Table 4.4 shows the prevalence of malnutrition according to various anthropometric measurements that are commonly utilised to classify nutritional status. According to WFA, HFA and BMI results, most of the sample was classified as well-nourished. However, according to arm anthropometry measurements, the prevalence of malnutrition was much higher. Of particular concern is the fact that the prevalence of severe malnutrition remained below 6% when arm anthropometry was not utilised, and increased to over 43 and 32% when MUAC and TSFT were assessed respectively.

Table 4.4: Anthropometric classification of study population

	Female		Male		Combined		
	n	**%**	**n**	**%**	**n**	**%**	**Total %**
WFA (n = 71*)							
Normal	25	54.35	21	45.65	46	64.79	NW 64.79
Underweight, mild (<-1 SD)	9	56.25	7	43.75	16	22.53	
Underweight, moderate (<-2 SD)	3	37.50	5	62.50	8	11.27	UW 35.21
Underweight, severe (<-3 SD)	0	0.00	1	100.00	1	1.41	
HFA (n = 75**)							
Normal	28	60.87	18	39.13	46	61.33	NW 61.33
Underweight, mild (<-1 SD)	9	45.00	11	55.00	20	26.67	
Underweight, moderate (<-2 SD)	1	16.67	5	83.33	6	8.00	UW 38.67
Underweight, severe (<-3 SD)	0	0.00	3	100.00	3	4.00	
BMI (n = 75**)							
Normal	25	47.17	28	52.83	53	70.67	NW 70.67
Underweight, mild (<-1 SD)	10	76.92	3	23.08	13	17.33	
Underweight, moderate (<-2 SD)	2	40.00	3	60.00	5	6.67	UW 29.33
Underweight, severe (<-3 SD)	1	25.00	3	75.00	4	5.33	
MUAC (n = 74[#])							
Normal	10	66.67	5	33.33	15	21.13	NW 21.16
Underweight, mild (<-1 SD)	8	44.44	10	55.55	18	24.32	
Underweight, moderate (<-2 SD)	5	55.55	4	44.44	9	12.16	UW 79.72
Underweight, severe (<-3 SD)	15	46.87	17	53.12	32	43.24	
TSFT (n = 71[##])							
Normal	12	60.00	8	40.00	20	28.17	NW 28.17
Underweight, mild (<-1 SD)	4	28.57	10	71.43	14	19.72	
Underweight, moderate (<-2 SD)	8	57.14	6	42.86	14	19.72	UW 71.83
Underweight, severe (<-3 SD)	12	52.17	11	47.82	23	32.39	

* Five subjects could not be classified due to insufficient age specific growth charts – WHO WFH growth charts not available for children over the age of ten years.
** Height information not available for one subject
[#] MUAC not available for two subjects
[##] TSFT not available for five subjects
NW – Normal Weight; UW – Underweight

Figure 4.4 shows a comparison between different combinations of measurements when classifying nutritional status. When albumin was utilised to classify nutritional status in isolation, 70% (n = 53) of subjects were classified as being well-nourished. In this study, a combination of MUAC, TSFT and albumin was used to classify overall nutritional status. Interestingly, when looking at these three indicators combined, eight subjects were classified as being malnourished based on their albumin levels alone (in other words, their arm anthropometry measurements were normal but their albumin levels were low). The results showed that two thirds (n = 47; 66.67%) of the sample (n = 72) were malnourished on admission to hospital.

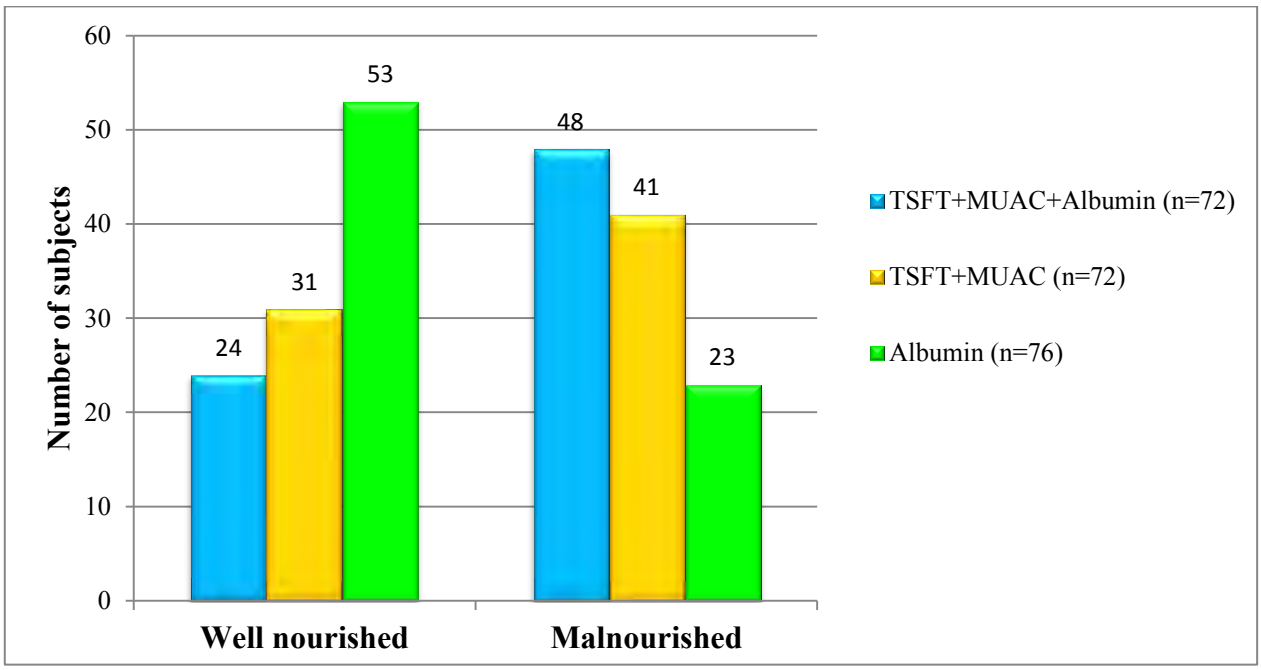

Figure 4.1: Prevalence of malnutrition using biochemical and anthropometric measurements

4.2. Influence of stage of disease and tumour burden on nutritional status

In this section, the influence of stage of disease and tumour burden on nutritional status is assessed.

4.2.1. Stage of disease and nutritional status

The influence of stage of disease on nutritional status was analysed using the Fisher"s exact test. Although it was difficult to make conclusions about the relationship between these two variables due to the small sample sizes in each group, this analysis showed a trend towards increased prevalence of malnutrition amongst those in stages two to four (Table 4.5). Those in stage five had a lower prevalence of malnutrition compared to stages two to four. Overall, the influence of stage of disease on nutritional status was not significant ($p = 0.152$).

Table 4.5: The association between stage of disease and nutritional status

Malnourished	Stage 1 (n = 5)	Stage 2 (n = 13)	Stage 3 (n = 19)	Stage 4 (n = 29)	Stage 5 (n = 6)	Total (n = 72)	p-value
Yes, n, (%)	1 (20)	9 (69.23)	13 (68.42)	22 (75.86)	3 (50)	48 (66.67)	p=0.152
No, n (%)	4 (80)	4 (30.77)	6 (31.58)	7 (24.14)	3 (50)	24 (33.33)	

* Four subjects did not have TSFT therefore their overall nutritional status could not be classified

4.2.2. Tumour burden and nutritional status

Figure 4.2 shows the tumour burden distribution amongst the sample. Tumour burden is a reflection of the percentage of the subject's total body weight that consists of tumour mass. Most of the subjects (86.5%; n = 64) had a tumour burden of less than 10%, while for almost 15% (n = 10) of subjects their tumour accounted for more than 10% of their total body weight. In addition to this, the relationship between nutritional status and tumour burden was assessed using the Mann Whitney test. Results showed that subjects who were malnourished did not have significantly larger tumour masses than those who were well-nourished (p = 0.339). It should be noted that two children did not undergo surgery; therefore the weight of their tumours could not be determined.

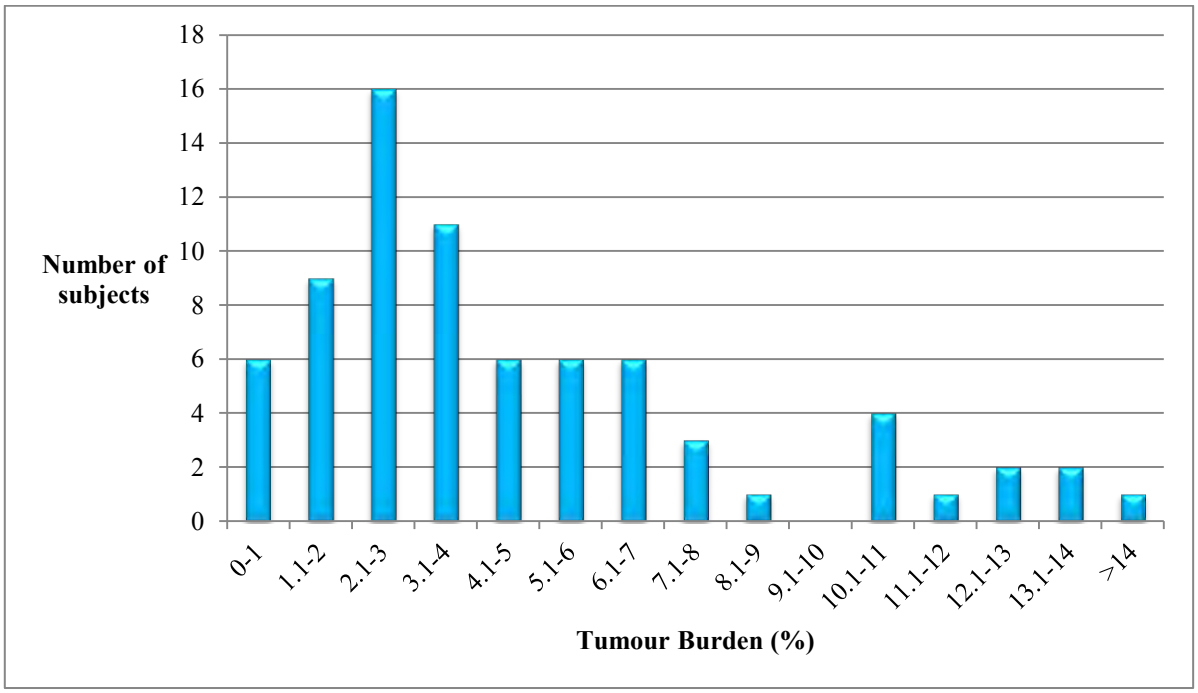

Figure 4.2: Distribution of tumour weight as a percentage of total body weight

4.3. Nutritional status and outcome

The influence of nutritional status upon admission and outcome after two years is presented in Tables 4.6 and 4.7. The overall nutritional status could not be classified for five subjects as their TSFT measurement was not recorded. Outcome was defined as a subject being either dead or alive. It should be noted that the outcome of 14 of the subjects could not be described due to the following reasons: (i) eight subjects were lost to follow up (of those who were lost to follow up, only two failed to complete treatment); (ii) six subjects completed their treatment course (chemotherapy and/or radiotherapy and surgery) but did not return for their scheduled follow ups over the course of two years post initial admission. The rate of treatment abandonment for this sample was 2.6%.

Table 4.36: The association between malnutrition on admission and outcome; 2 years

		Outcome				Total	
		Dead		Alive			
		n	%	n	%	n	%
Malnourished	**Yes**	13	31.71	28	68.30	41	100.00
	No	4	19.05	17	80.95	21	100.00
Total		17	27.42	45	72.58	62	100.00

Of the 62 subjects, two thirds (n = 41) were classified as being malnourished on admission according to their MUAC, TSFT and albumin results. Seventeen (27.42%) of the 62 subjects died during the two year follow up period. Of the 17 subjects who died within the two year follow up period, 13 (76.47%) were malnourished on admission. Of the 45 subjects who were alive within the two year follow up period, 28 (62.22%) were malnourished on admission. No significant relationship between nutritional status on admission and outcome after two years was demonstrated utilising the Chi-squared test of independence ($p = 0.443$).

It was also noted that no significant relationship was found between severity of malnutrition and outcome. Table 4.7 shows that those who were well-nourished and those who were severely malnourished on admission were equally prevalent in the group of subjects who survived ($p = 0.163$).

Table 4.37: The association between severity of malnutrition and outcome

		Degree of malnutrition						Total	
		Normal		Malnourished		Severely malnourished			
		n	%	n	%	n	%	n	%
Outcome	**Dead**	4	25.00	6	37.50	6	37.50	16	100.00
	Alive	17	36.96	12	26.09	17	36.96	46	100.00
Total		21	33.87	18	29.03	23	37.10	62	100.00

Binary logistic regression analysis was conducted in order to account for confounding variables that are known to have a significant influence of prognosis (stage and histology). No significant relationship between nutritional status and outcome was found, despite correcting for stage and histology ($p = 0.711$).

4.4. Level of nutritional support received

Most of the study sample (84.2%; n = 64) were provided with nutritional supplementation within two weeks of admission. Just over 10% (n = 8) received supplements more than two weeks after admission and were therefore not included. Only 5.3% (n = 4) of the sample did not receive any nutritional supplementation. Of those who received nutritional supplementation, 87.5% (n = 56) received oral supplementation. Oral supplementation refers to a nutritional supplement, a nutritious snack (for example yoghurt, full cream milk or a sandwich), or a combination of the two. Of the remaining subjects, 9.4% (n = 6) received nasogastric (NG) feeds, whereas 3.1% (n = 2) received a combination of oral and NG supplementation. There was no significant relationship between the severity of malnutrition and whether or not the subjects received supplements ($p=0.768$). Furthermore, there was no significant relationship between severity of malnutrition and type of nutritional support received ($p=0.620$).

4.5. Summary of results

The results of the statistical analyses assessing the prevalence of malnutrition and the influence of nutritional status on outcome were presented in this chapter. The following are the most noteworthy results:

Of the total sample of 76 children with Wilms' Tumour, exactly half were male and half were female. Black African children made up 97.3% of the sample, and the majority of the sample presented late (in stages three to five). The mean age amongst the sample was 4.65 years, while 67% of the sample was aged five years or younger.

The prevalence of malnutrition was assessed using a variety of measurements. When WFA, HFA and BMI were used to classify nutritional status, 35.3%, 38.7% and 29.4% of subjects were classified as being malnourished, respectively. Of those who were classified as being malnourished utilising WFA, HFA or BMI, less than 6% were classified as being severely malnourished. When arm anthropometry measurements were analysed, the prevalence of malnutrition increased substantially to 79.7% and 72% for MUAC and TSFT, respectively. Similarly, the prevalence of severe malnutrition increased to 43.2% and 32.4% respectively. Nutritional status was also classified using biochemistry by measuring albumin levels. According to albumin levels, 70% of patients were well-nourished. In order to classify the overall nutritional status, arm anthropometry measurements were utilised in combination with albumin. According to this classification system, the overall prevalence of malnutrition amongst this sample was 67%.

There was a trend towards an increased prevalence of malnutrition amongst subjects who presented in stages two to four, however, this was not found to be statistically significant. When tumour burden was analysed, it was found to account for more than 10% of total body weight in almost 15% of the subjects in this sample. Subjects who were malnourished were not found to have significantly larger tumours compared to those who were well-nourished.

During the two year follow up period, 27.4% of the sample had died. Just over 76% of those who died were malnourished on admission, whereas 62.2% of those who survived were malnourished on admission. No significant relationship between the influence of nutritional status on admission, or the degree thereof, on outcome was found, even after accounting for confounding variables (stage of disease and histology).

Just over 84% of subjects were provided with nutritional supplementation, in the form of oral supplements and/or NG feeds, within two weeks of admission. The next chapter discusses the results of this study.

CHAPTER 5: DISCUSSION

The purpose of this study was to investigate the influence of nutritional status at the time of admission on outcome. Three objectives were developed in order to address the research question. Firstly, to determine the prevalence of malnutrition using a combination of anthropometric and biochemical markers, defined by the AHOPCA algorithm. The second objective was to determine the association between nutritional status on admission on the outcome, in terms of overall survival and death, amongst children with Wilms' Tumour. The third objective was to determine the level of nutritional intervention prescribed to the subjects. This chapter discusses the results presented in the previous chapter.

5.1. Sample characteristics

The mean age of the sample was 46.5 months (IQR = 37.32 months). This is in keeping with previous research amongst South African children with Wilms' Tumour conducted by Holzinger *et al* (2007) and Visser *et al* (2014), which showed medians of 3.66 and 3.95 years respectively. Half the sample was made up of females and half males. Almost all the subjects were of Black African ethnicity (97.3%) while 2.6% of the sample was made up of White and Coloured subjects. This is in line with the population profile of the province according to the latest census information, which shows that almost 90% of the KZN population comprises Black African, while 7.4% are Indian and 4.2% are White. Similarly, the overall population of South Africa is made up of Black Africans (79.2%), followed by White (8.9%) and Coloured (8.9%) individuals (Stats SA 2011). Just over 70% of the sample presented in disease stages three to five. This is in accordance with previous studies (Abuidris *et al* 2008), including a study conducted at IALCH which showed over 67% of children with Wilms' Tumour presented in stages three to five (Holzinger *et al* 2007).

5.2. Assessment of nutritional status

5.2.1. Anthropometry

When classifying overall nutritional status amongst this sample, a combination of MUAC, TSFT and albumin was utilised. In this study, 66.67% of the subjects were found to be malnourished on admission to hospital.

Assessment of nutritional status of children with solid tumours is problematic due to the effect of tumour weight on body weight measurements (Rogers 2014). In this study, the tumour mass (obtained post-operatively) was subtracted from admission weight in order to attain a more accurate reflection of nutritional status. The drawback of this, however, is that by the time the patient goes for surgery the tumour size is often considerably smaller than at the time of admission due to the effects of prior neoadjuvant therapy (Israels *et al* 2009). This can consequently lead to overestimation of the prevalence of well-nourished subjects when used in isolation. In this study, after having corrected for tumour mass, measurements utilising weight continued to underestimate the prevalence of malnutrition. When comparing the prevalence of malnutrition according to WFA, HFA and BMI (12.68%, 12% and 12% respectively) to MUAC and TSFT measurements (55.40% and 52.11% respectively), the lack of correlation between these different types of anthropometric measurements was striking.

According to the data from the nutritional surveys conducted amongst South African children in 1999, 2005 and 2012, the prevalence of stunting (low HFA) slowly declined from 21.6% in 1999 to 15.4% in 2012 (Shisana *et al* 2013; Labadarios *et al* 2008; Labadarios *et al* 2000). However, stunting continues to be a significant problem in South Africa. In this study, 12% of the sample was stunted, which corresponds to the national prevalence. Stunting is a reflection of chronic under-nutrition (Dewey & Begum 2011). One may therefore not expect the prevalence to be significantly higher amongst children with Wilms' Tumour when presenting to hospital compared to that of the general population, as they usually present after an acute period of symptoms, which would not contribute to long-term nutritional impairment prior to admission. In this study, the prevalence of underweight, as classified by low WFA, was found to be higher than the latest report by the SANHANES-1 study in 2012 (12.68% versus 5.8%). Low WFA can be a reflection of short- and/or long-term malnutrition (De Onis & Blossner 1997). A higher prevalence of short-term malnutrition could be expected amongst this study's sample population as a consequence of disease related symptoms such as nausea, vomiting and loss of appetite prior to presentation to hospital.

This study found the prevalence of malnutrition to be just over 66%. Previous studies in developing countries have found the prevalence of malnutrition amongst children with cancer to range from 45 to 77% (Sala *et al* 2012; Israels *et al* 2009; Israels *et al* 2008; Garofolo *et al* 2005). Sala *et al* (2012) conducted a large study which included 1787 children with cancer from seven developing countries in Central America. The authors used similar categories to classify nutritional status as were used in this study, namely MUAC, TSFT and albumin. Malnutrition was found to be present

in 77.2% of the sample (18% moderate and 59.2% severe), while 59% of those with solid tumours were malnourished. It is evident that the prevalence of malnutrition found in the present study corresponds to similar studies previously conducted.

The results of this study are in agreement with several other studies which addressed the fact that measurements utilising body weight for classification of nutritional status amongst children with cancer, without including arm anthropometry measurements, often leads to an underestimation of the prevalence of malnutrition (Israels *et al* 2008; Tazi *et al* 2008; Garofolo *et al* 2005). This is particularly pertinent to children with solid tumours (Tazi *et al* 2008; Garofolo *et al* 2005) as malnutrition amongst children with solid tumours can be masked (Lemos *et al* 2014; Israels *et al* 2008; Tazi *et al* 2008) by factors such as tumour mass and fluid shifts (Rogers 2014). Arm anthropometry includes MUAC, which provides a measure of body fatness, and TSFT which measures muscle mass (Ramsey *et al* 1992). Of importance amongst children with solid tumours is the fact that arm anthropometry measurements are independent of tumour size (Tah *et al* 2012; Brennan *et al* 1999).

Because many studies in the past assessed the prevalence of malnutrition amongst children with solid tumours using weight and height measurements in isolation (Burke *et al* 2013; Pedrosa *et al* 2000; Wessels *et al* 1999), it is possible that the prevalence of malnutrition amongst this population has been grossly underestimated. After conducting a comprehensive search of the literature, only four published studies assessing the prevalence of malnutrition amongst South African children with Wilms' Tumour were found (Visser *et al* 2014; Holzinger *et al* 2007; Davidson, Hartley, Desai, Daubenton, Rode & Millar 2006; Wessels *et al* 1999). Wessels *et al* (1999) found that 35% of their sample was malnourished, while Davidson *et al* (2006) and Visser *et al* (2014) found the prevalence of malnutrition to be 20.7% and 10.3% respectively. Holzinger *et al* (2007), who conducted their study at IALCH, found a prevalence of 45%. This study was performed from 2002 to 2005 and did not include the same patient population as the present study. Unfortunately, all of these studies were limited by the fact that they used weight and height in isolation and did not include arm anthropometry in their classification. Furthermore, the studies by Wessels *et al* (1999) and Holzinger *et al* (2007) had relatively small sample sizes (59 and 37 respectively).

To date there is no published research assessing the prevalence of malnutrition amongst South African children with Wilms' Tumour utilising arm anthropometry measurements. The current study was therefore important and necessary in order to determine the true prevalence of

malnutrition amongst this specific population. The results of this study are in line with the aforementioned literature which emphasises the superior accuracy of arm anthropometry measurements when classifying nutritional status amongst this population. It is evident that arm anthropometry measurements should be considered as standard criteria with which to classify nutritional status of Wilms' Tumour patients in the future.

The AHOPCA algorithm, on which this study's criteria for classifying nutritional status was based, incorporates arm anthropometry, albumin, weight loss and percentage of ideal body weight measurements. Initially, the algorithm stated that both MUAC and TSFT had to be below a certain value in order for a subject to be classified as malnourished. These criteria have since changed, stipulating that all subjects with either MUAC *or* TSFT below a certain level be classified as malnourished. This was done in order to increase the sensitivity of the algorithm and to encourage interventions amongst a larger proportion of subjects (Sala *et al* 2005).

5.2.2. Biochemistry

The results from this study showed that, in isolation, albumin considerably underestimated the prevalence of malnutrition (30%). This is in agreement with previous research by Tazi *et al* (2008), which showed that the prevalence of malnutrition according to albumin was 28%. However, when the authors classified nutritional status according to arm anthropometry, the prevalence of malnutrition increased to 39% and 50% using MUAC and TSFT respectively. When including albumin in combination with MUAC and TSFT as part of the assessment of overall nutritional status in the current study, the prevalence of malnutrition increased by almost 10%. Due to its low specificity, albumin is considered to be a poor indicator of nutritional status when assessed in isolation (Fuhrman 2002). However, previous research by Sala *et al* (2012) has shown the inclusion of albumin as one of a combination of criteria when classifying nutritional status does add considerable value to the accuracy and sensitivity of the classification methodology. The results of this study were in agreement with this evidence.

Interestingly, when looking at all indicators combined (TSFT, MUAC and albumin), eight subjects were classified as being malnourished based on their albumin levels alone. A possible explanation for this could be that their MUAC and TSFT measurements were not accurate. Alternatively, these subjects could have been suffering from significant inflammation or infection, which could have led to worsened hypoalbuminemia compared to other subjects (Fuhrman 2002).

Hypothesis one, that the utilisation of weight, height and albumin in isolation would underestimate the prevalence of malnutrition, is therefore accepted. Hypothesis two, that the utilisation of arm anthropometry and albumin in combination would allow for more accurate classification of nutritional status, is also accepted.

5.3. Influence of disease stage and tumour burden on nutritional status

A common problem in many developing countries is that of late presentation of children with cancer to hospitals (Paintsil *et al* 2015; Yao *et al* 2012; Wilde *et al* 2010; Abuidris *et al* 2008; Ekenze *et al* 2006). Children in developing countries may display symptoms of cancer for months before presenting to hospital (Ekenze *et al* 2006). This is often due to lack of education amongst the general population (Yao *et al* 2012). As a consequence of this, many children present to hospital in the latter stages of disease (Ekenze *et al* 2006). A study conducted in KZN, a region where almost half of all households are situated in rural areas (Stats SA 2011), showed that children living in rural areas were more likely to present to hospital with Wilms' Tumour later than children from urban areas, and with more advanced disease (Hadley & Jacobs 1990). Late presentation and advanced disease stage on admission can have extensive consequences, as children with larger tumours on admission have been shown to be more severely malnourished than those with smaller tumours (Israels *et al* 2009). This in turn can negatively affect their outcome (Sala *et al* 2012) and can contribute to poorer prognosis (Kaste *et al* 2008).

A Sudanese study showed that over 78% of the sample of children with Wilms' Tumour presented in stages three or four (Abuidris *et al* 2008), and a previous study conducted at IALCH showed that over 67% of children with Wilms' Tumour presented in stages three to five (Holzinger *et al* 2007). It is evident that the results of this study are in agreement with previous literature. In this study, 71% of the sample presented in stages three to five and 15% had a tumour mass that accounted for over 10% of their total body weight. Those in stages two to four showed a trend towards an increased likelihood of being malnourished; however the influence of disease stage on nutritional status was not found to be significant.

5.4. Factors affecting the outcome of children with cancer

This study attempted to identify as many factors as possible which could have affected outcome, in order to determine the prognostic significance of nutritional status on admission. Stage and histology are considered to be the most important factors influencing the prognosis of children with

Wilms' Tumour (Kaste *et al* 2008). In this study, stage and histology were shown to have no influence on the outcome of this sample after two years. Furthermore, no significant relationship between severity of malnutrition on admission and outcome was found.

As discussed previously, there are a myriad of factors that affect outcome of children with cancer in developing countries. These include advanced stage of disease at presentation, treatment abandonment, histology, lack of education amongst some communities, severity of malnutrition on admission, extreme distances between home and treatment facility, financial constraints and delayed presentation (Paintsil *et al* 2015; Slone *et al* 2014; Antillon *et al* 2013; Sala *et al* 2012; Yao *et al* 2012; Wilde *et al* 2010; Abuidris *et al* 2008; Ekenze *et al* 2006; Madani *et al* 2006; Hadley & Jacobs 1990). Some factors, namely lack of education and delayed presentation, are variables beyond the scope of this study.

In developing countries, many patients abandon treatment due to financial constraints, as some of the treatments and drugs are not subsidised (Abuidris *et al* 2008; Ekenze *et al* 2006). Families who have to travel far distances to and from the treatment facility as well as pay for board and lodging while children are admitted to hospital also experience severe financial strain (Abuidris *et al* 2008). In the sub-Saharan Africa region, treatment abandonment occurs in as many as 48% of patients (Paintsil *et al* 2015), while children with Wilms' Tumour in Sudan have been shown to have a treatment abandonment rate of over 60% (Abuidris *et al* 2008).

Facilities, many of which address the abovementioned problems experienced at other hospitals in developing countries, are put in place at IALCH in order to try to prevent treatment abandonment. State-run hospitals in South Africa, such as IALCH, provide free or subsidised services to patients depending on their parental income (Department of Health, Western Cape Government 2015). In most cases all treatment, including surgery, chemo- and radio-therapy, imaging, drugs and nutritional supplements and feeds are provided to patients for a nominal fee or completely free of charge. Furthermore, the services of other health professionals such as physiotherapists, occupational therapists, social workers and psychologists are available when required.

Treatment of children with cancer at IALCH is supported by the Childhood Cancer Foundation South Africa (CHOC), which runs an accommodation facility on the hospital grounds. This facility provides accommodation for caregivers whose children are receiving treatment in the oncology wards at the hospital. This serves to substantially alleviate the burden placed on caregivers to find

accommodation close to the hospital for prolonged periods of time while their children undergo treatment. Lastly, hospital transport is provided for most patients who need to travel from outlying areas. These measures all serve to alleviate the financial burden caregivers may face when their children are treated for cancer at IALCH, and may have contributed to a very low rate of treatment abandonment amongst this sample.

The aforementioned array of factors have the potential to influence the outcome of children with cancer when receiving treatment in hospitals in developing countries. However, in this study it was evident that these factors did not have as much of a positive influence as they may have had at other hospitals or in other countries, due to the superior facilities and services available to the patients and their families at IALCH. Furthermore, the patients in this sample had the advantage of being managed by an MDT, including a dietitian. Most of these children received early individualised dietary intervention within two weeks of admission to hospital. This included a nutritional assessment on admission to determine which type of dietary intervention would be most appropriate for each patient. Individualised dietary interventions have been shown to be effective in achieving weight gain amongst children with cancer during the course of treatment (De Waele *et al* 2015). Attainment of normal nutritional status for more than 50% of the treatment period has been shown to reduce the risk of poorer outcome that has been associated with malnutrition on admission (Orgel *et al* 2014).

5.5. Influence of poor nutritional status on admission and outcome

The results of this study showed that just over two thirds of the sample was malnourished on admission to hospital. Nutritional status was not shown to be significantly related to outcome. The correlation between nutritional status on admission and outcome has not been conclusively established in previous studies, with some studies showing a significant relationship between these two variables while others did not.

Most of the previous research has focused on analysing this relationship amongst children with haematological malignancies, with few studies focusing on children with solid tumours. A large study by Hoffmeister *et al* (2013) analysed 733 American children with haematological malignancies who had undergone an haematopoietic stem cell transplant. They found that those with an arm muscle area below the 5th percentile had significantly worse event free survival at 100 days and three years post-transplant. Hoffmeister's study was strong as it had a large sample size and utilised arm anthropometry when classifying nutritional status. A limitation to previous studies

similar to this one includes small sample sizes as well as failure to include arm anthropometry (Mejia-Arangure *et al* 1999; Viana *et al* 1994). A study with a large sample of 1025 children with haematological malignancies, conducted in the United Kingdom, found no evidence that nutritional status on admission was a prognostic indicator of outcome. While this sample size was substantial, Weir *et al* (1998) did not use arm anthropometry when classifying nutritional status.

Results from previous studies amongst children with solid tumours are similarly inconclusive. One of the largest studies conducted to date, by Sala *et al* (2012), included children with solid and haematological malignancies from seven developing countries in Central America. The strength of this study lay in its large sample size, accurate classification of nutritional status as well as the multiple locations from which children were sampled. The authors found a significant relationship between malnutrition and higher mortality rates amongst children with solid tumours, but not haematological malignancies (Sala *et al* 2012). Similar studies found no significant relationship between these variables; however none of these studies took arm anthropometry into account in their study design (Burke *et al* 2013; Pedrosa *et al* 2000; Wessels *et al* 1999). South African researchers, Wessels *et al* (1999) focused specifically on children with Wilms' Tumour in their retrospective study. Limitations related to their classification methods for nutritional status, which focused solely on weight and height, were discussed. In order to compensate for the potential overestimation of adequate nutritional status that had been shown to occur when using weight and height measurements in isolation, they considered any subject with a weight for height less than 90% of the expected value to be poorly nourished. In conclusion, hypothesis three, which proposed that subjects who were malnourished on admission would have a worse outcome compared to those who were well-nourished on admission, is rejected.

5.6. Level of nutrition support provided

In this study, nutritional interventions within two weeks of admission to hospital were implemented for more than 80% of the study sample. Nutritional intervention included an initial assessment of nutritional status as well as implementation of oral and/or nasogastric supplements.

Children with cancer often struggle to meet their nutritional requirements, due to factors such as gastrointestinal complications (Barbosa *et al* 2012), which is why nutritional intervention amongst this population is extremely important. As discussed previously, nutritional intervention has been shown to lead to effective weight gain amongst children with cancer (De Waele *et al* 2015; Sacks *et al* 2014; Antillon *et al* 2013; Barbosa *et al* 2012; Holzinger *et al* 2007). Wessels *et al* (1999)

emphasised the importance of utilising clinical judgement in addition to anthropometric assessment in order to determine which patients are in need of nutritional intervention. When treating these patients, the challenge faced by the dietitian is to prevent further worsening of nutritional status, as well as to attempt to reverse any deterioration in nutritional status that may have already occurred. Children with solid tumours in particular are often in need of nutritional interventions. Compared to children with haematological tumours, those with solid tumours have been shown to practice food restrictions more often and experience significantly worse eating problems, including nausea, vomiting and loss of appetite (Tah *et al* 2012).

An international study that assessed the nutrition-related practices amongst 125 institutions around the world found inconsistent practices related to nutritional interventions (Ladas *et al* 2006). A similar study conducted amongst South African hospitals also showed a similar lack of uniformity (Schoeman 2011). It is unfortunate that there are no standardised guidelines related to nutritional intervention which can be implemented throughout centres that treat children with cancer, as the efficacy of nutritional intervention is well documented (De Waele *et al* 2015; Sacks *et al* 2014; Antillon *et al* 2013; Barbosa *et al* 2012). Nasogastric feeding in particular has been shown to be very effective in order to achieve weight gain amongst children with cancer (Brinksma *et al* 2015; Barbosa *et al* 2012; Holzinger *et al* 2007). Furthermore, it has been shown to be effective even amongst subjects with cancer cachexia (De Waele *et al* 2015) as well as the South African Wilms' Tumour population (Holzinger *et al* 2007). However, the fact that there was no significant relationship between severity of malnutrition and type of support received suggests that both oral nutritional supplements as well as NG feeds have a role in the nutritional management of severely malnourished subjects.

5.7. Multidisciplinary team management

Multidisciplinary team (MDT) management of children with cancer is especially important in developing countries, where a myriad of factors contribute to poorer outcomes amongst this population. Research has shown that a country's socio-economic status is a major determinant of the nutritional status of the population (Dowler 2005, p140). Irrespective of whether a country is developed or developing, the literature has demonstrated that weight loss during treatment occurs frequently amongst this population (Brinksma *et al* 2015; Orgel *et al* 2014; Antillon *et al* 2013; Burke *et al* 2013; Zimmermann *et al* 2013). The MDT approach has been shown to be lacking in developing countries. Effective MDT management helps to improve and promote collaboration amongst health professionals who are treating a patient, as well as encourage standardisation of

management (Ekenze *et al* 2006). Involvement of a variety of health professionals, including a dietitian, in the treatment and follow up of these patients may lead to improved quality of life, and has shown to be effective in improving nutritional status amongst patients with cancer cachexia (De Waele *et al* 2015).

The greatest weight changes amongst children with cancer have been shown to occur within three months of diagnosis (Brinksma *et al* 2015), thus emphasising the importance of early and aggressive nutritional intervention. Antillon *et al* (2013) showed that multidisciplinary management, in the form of a combination of nutritional management and intervention as well as chemotherapy treatment to control the malignant disease, contributed to improved nutritional status after six months of treatment. The authors showed that, of those who were classified according to arm anthropometry as being severely depleted on admission, almost two thirds improved and were classified as either moderately malnourished or adequately nourished. Furthermore, improved nutritional status was noted amongst 77% of the moderately malnourished subjects, who were classified as adequately nourished after six months. For the subjects who were severely malnourished but for whom an improvement in nutritional status was seen by six months, the overall survival probability at five years post admission was similar to those whose nutritional status was adequate on admission (Antillon *et al* 2013).

In a similar study, Orgel *et al* (2014) found that children with leukaemia who were underweight for more than 50% of their treatment period had significantly worse outcomes. However, those who were initially underweight but who gained weight and maintained their normal weight for more than 50% of the treatment period had similar risk for the occurrence of an event as those who maintained a normal weight throughout treatment. Therefore nutritional monitoring is imperative amongst this population, and nutritional intervention needs to be implemented as early as possible.

5.8. Summary

It is evident that childhood cancer is a serious problem in developing countries. Just over two thirds of this sample was malnourished on admission to hospital. Nutritional status should be assessed as early as possible in order to improve nutritional status or prevent malnutrition from developing. Utilisation of a combination of arm anthropometry and albumin provide accurate criteria for assessing nutritional status amongst this population. This helps to minimise the risk of underestimation of malnutrition, which commonly occurs when weight and height are used in isolation in order to classify nutritional status.

The majority of children with Wilms' Tumour were found to be malnourished on admission to IALCH during the period of this study. The relationship between poor nutritional status on admission to hospital and outcome has not been conclusively stipulated in the past. A myriad of factors can affect the outcome of this population, particularly in developing countries where factors such as poverty and poor education exacerbate the problems already faced by children with cancer and their families. This study found that malnutrition on admission did not contribute to significantly poorer outcomes. Aggressive early nutritional assessment, intervention and management of these children may help to reduce the negative impact that malnutrition on admission may have on outcome. Furthermore, the involvement of a multidisciplinary team in the management of children with Wilms' Tumour may help to improve their nutritional status and quality of life.

CHAPTER 6: CONCLUSION

Childhood cancer continues to be a serious problem worldwide and in developing countries in particular. The prevalence of malnutrition amongst children with cancer on admission to hospital is high amongst developing countries, where poverty is rife and resources are limited. Wilms' Tumour is a commonly occurring solid tumour in African countries. This study was conducted at IALCH and included 76 children diagnosed with Wilms' Tumour between 2004 and 2012.

The following objectives were investigated in this study:

- To determine the prevalence of malnutrition using a combination of anthropometric and biochemical markers, defined by the AHOPCA algorithm.
- To determine the influence of nutritional status on admission on the outcome, in terms of overall survival and death, amongst children with Wilms' Tumour admitted to IALCH between 2004 and 2012.
- To determine the level of nutritional support prescribed to children with Wilms‟ Tumour within the first two weeks of admission to IALCH between 2004 and 2012.

This chapter concludes the findings of the study related to the above objectives. Furthermore, it discusses the limitations of the study as well as recommendations for future research and for dietetic practice.

6.1. Conclusion of the study findings

6.1.1. Prevalence of malnutrition according to anthropometry

Utilisation of weight and height measurements in isolation can lead to an underestimation of the prevalence of malnutrition amongst children with Wilms‟ Tumour. This study showed that arm anthropometry should be included as part of a standardised method of classifying nutritional status amongst children with solid tumours.

6.1.2. Prevalence of malnutrition according to biochemistry

The findings of this study showed that albumin can add sensitivity to the classification of nutritional status amongst children with cancer when used in conjunction with other measurements. However,

it should not be considered as a marker of nutritional status in isolation as it leads to an overestimation of adequate nutritional status.

6.1.3. Nutritional status and outcome

This study revealed that no correlation existed between nutritional status on admission and outcome. Many of the previous studies that assessed this relationship were conducted in developing countries where resources and facilities are severely limited. The subjects in this study were treated by a multidisciplinary team of health care professionals throughout their treatment period. Furthermore, the subjects were treated at a high-level hospital while their caregivers were supported by CHOC. This may have helped to minimise treatment abandonment. This study showed that poor nutritional status on admission did not lead to worsened outcomes amongst this population. Holistic and MDT management may play a role in improving the outcome of children with Wilms' Tumour who are poorly nourished on admission.

6.1.4. Level of nutritional intervention

The majority of subjects received nutritional support on admission to hospital. Nutritional assessment on admission is vital in order to determine which patients are malnourished or at risk of becoming malnourished. This allows the dietitian to identify the most appropriate nutritional intervention for each subject promptly, before nutritional status worsens.

6.2. Study limitations

The sample size was relatively small compared to other international studies. Due to financial and time constraints, this study was limited to only those patients presenting with Wilms' Tumour at IALCH between 2004 and 2012. However, this research is still relevant and important given the paucity of research on children with Wilms' Tumour, both internationally and in South Africa. Furthermore, based on an extensive literature search, this is the first South African study to use arm anthropometry to classify nutritional status amongst this population.

This study may be subject to selection bias due to the fact that it was conducted at a government hospital. However, it is important to note that IALCH serves a catchment area spanning two provinces in South Africa and is therefore representative of a wide spectrum of the South African population.

Although the Frisancho charts were used in this study to classify nutritional status, this was not ideal as these charts are based on a population made up of only Caucasian subjects.

6.3. Recommendations

6.3.1. Recommendations for dietetic practice

It is important to have international standardisation with regards to nutritional assessment on admission at all centres treating children with cancer. This is important in order to identify those in need of aggressive nutritional assessment as early as possible, in an attempt to improve their nutritional status timeously. Tumour registries need to be established in all countries in order to fully understand the prevalence of paediatric cancer. Arm anthropometry should be used as an integral part of nutritional assessment amongst children with cancer, particularly those with solid tumours.

More emphasis needs to be placed on MDT management of these patients. Cancer has numerous and wide-ranging consequences, both physically and emotionally. It is difficult to improve nutritional status alone and holistic management is needed in order for nutritional management to be successful.

6.3.2. Recommendations for future research

In the past, studies such as this have focused on the nutritional status of the subjects on admission in relation to outcome (Burke *et al* 2013; Sala *et al* 2012; Pedrosa *et al* 2000; Wessels *et al* 1999). However, recent studies have placed more focus on maintaining adequate nutritional status throughout the treatment period as opposed to focusing only on nutritional status on admission (Orgel *et al* 2014; Antillon *et al* 2013). This is due to the fact that the literature has demonstrated that weight loss during treatment occurs frequently amongst this population (Brinksma *et al* 2015; Orgel *et al* 2014; Antillon *et al* 2013; Burke *et al* 2013; Zimmermann *et al* 2013). Zimmerman *et al* (2013) showed a steady increase in the prevalence of malnutrition from 5.8% on admission to 47% by the end of the treatment period. Similarly, Burke *et al* (2013) found that almost 20% of subjects lost more than 5% and 10% of their baseline weight after six months. It has been postulated that nutritional status at six months after treatment has commenced has been shown to be a more accurate prognostic indicator of survival than that at baseline (Antillon *et al* 2013).

Future research should focus on nutritional management of children with cancer during the treatment period. This research should focus on the association between the type and duration of intervention and their influence on weight and outcome. This will help to determine the most effective methods with regards to timing and type of nutritional intervention in order to prevent the progressive weight loss that is commonly seen amongst these subjects during cancer treatment.

In spite of considerable support offered to the subjects of this study, several were still lost due to a lack of follow up. An epidemiological-based study to identify factors which continue to contribute to loss due to lack of follow up in this setting could be beneficial.

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APPENDIX A: ETHICAL CLEARANCE 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 Lauren Lifson's study "Nutritional status of children with nephroblastoma (Wilms' tumour) 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 Lifson's request to BREC dated 10 June 2014 to use the data from the above BREC approved study towards a Masters in Dietetics (Reg No 214583578) has been noted by BREC. BREC has noted that no new data is being collected.

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: APPROVAL FROM IALCH MEDICAL MANAGER

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

15 May 2014

Ms L F Lifson
Department of Dietetics
IALCH

Dear Ms Lifson

Re: Ref No: BE 025/13: Nutritional status of children with nephroblastoma (Wilms' tumour) upon admission to Inkosi Albert Luthuli Central Hospital in Durban, South Africa and its influence on outcome.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg , 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

.....

Dr K E Letebele
Medical Manager

APPENDIX C: APPROVAL FROM DEPARTMENT OF HEALTH

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM 227/13
Enquiries : Mr X Xaba
Tel : 033 – 395 2805

Dear Prof GP Hadley

Subject: Approval of a Research Proposal

1. The research proposal titled **'Assessment of the prevalence of undernutrition amongst South African paediatric nephroblastoma patients on admission to hospital'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutgé
Chairperson, Health Research Committee
Date: 08/08/2013