Title page

Title: Assessment of Nutritional Status in Children with Cancer – a Narrative Review

Authors: Karina Viani, RD[1]; Amita Trehan, MD[2]; Bianca Manzoli, RD[1]; Judy Schoeman, MSc[3]

1. Instituto de Tratamento do Câncer Infantil (ITACI), Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, São Paulo, Brazil.
2. Pediatric Hematology Oncology Unit, Advanced Pediatric Center, Postgraduate Institute of Medical Education & Research, Chandigarh, India
3. Pediatric Oncology Unit, Department of Pediatrics, Steve Biko Academic Hospital & University of Pretoria, Pretoria, South Africa

Address for correspondence:

Karina Viani, RD

148 Rua Galeno de Almeida, Pinheiros

05410-030 São Paulo, SP, Brazil

Phone: +55 11 26618924

viani.karina@gmail.com

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Abbreviations key table

Abbreviation	Full term
ALL	acute lymphoblastic leukemia
AMDR	acceptable macronutrient dietary ranges
BIA	bio-electrical impedance analysis
BMI	body mass index
BMI/A	body mass index for age
CRP	serum c-reactive protein
CT	computerized tomography
DXA	dual energy X-ray absorptiometry
EFS	event free survival
H/A	height-for-age
HC	hip circumference
HICs	high income countries
HSCT	hematopoietic stem cell transplant
LMICs	low- and middle-income countries
MUAC	mid-upper arm circumference
MUAC/A	mid-upper arm circumference for age
PODC	Pediatric Oncology in Developing Countries
SAM	severe acute malnutrition

SIOP	International Society of Pediatric Oncology
TSFT	triceps skinfold thickness
TSFT/A	triceps skinfold thickness for age
UNICEF	United Nations Children's Fund
W/A	weight-for-age
W/H	weight for height
W/H	Weight-for-height
WC	Waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio

Abstract

A child's appropriate development stems in large part from proper nutrition. Malnutrition is an adverse prognostic factor in children with cancer, and its prevalence is highly variable. Currently, there is no standardized definition and assessment method of nutritional status in pediatric oncology. A complete nutritional assessment includes anthropometry, biochemical, clinical and dietary assessments. In this article, we explore these methods and suggest practical approaches for pediatric cancer units depending on the levels of care that these can provide. We also advise on monitoring and follow-up of children with cancer during and after treatment, and discuss potential areas for future research.

Keywords: anthropometry; levels of care; malnutrition; nutritional assessment; pediatric oncology

1. Introduction

"If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have the safest way to health." (Hippocrates) The outcome of pediatric cancer is one of the success stories of the last century. However, the excellent outcome is restricted to high income countries (HICs).[1] A large majority of children with cancer live in low- and middle-income countries (LMICs) and frequently have associated comorbidities, one of them being under-nutrition, a modifiable risk factor for the outcome in pediatric malignancies.[2,3] In HICs overweight and obesity is a public health issue and impacts on cancer survival. Thus, it is also a modifiable prognostic factor.[4,5] The "double burden" of malnutrition is an increasing problem in LMICs.[6] In order to address these modifiable nutritional prognostic factors it becomes necessary to implement longitudinal nutritional assessment in children with cancer, on the basis of which well informed, appropriate nutritional interventions can be implemented. This article is written in the context of a comprehensive supplement of PBC on nutritional perspectives in pediatric oncology.

Nutrition is essential for appropriate growth and development and a critical component in optimization of clinical outcomes. Malnutrition, which includes under and over-nutrition, has an adverse effect on health and health-related quality of life.[7] The importance of an optimal nourished state cannot be over-emphasized. Under-nutrition, which is rampant in LMICs, can increase treatment-related morbidities, mortality and abandonment of therapy, as well as negatively affect quality of life.[7-10] Over-nutrition is also associated with adverse clinical outcomes.[3,11]

Traditionally, nutritional assessment is performed by (1) anthropometric measurements, (2) biochemistry, (3) clinical assessment and (4) dietary history. Assessment is a dynamic process and is required at diagnosis, during therapy and

survivorship to evaluate the child's nutritional status and the adequacy of intake to allow for appropriate timely intervention.[12] However, to date there are no standard clinical practice guidelines for prospective uniform monitoring of the nutritional status in children with cancer.[13-15] In this manuscript we revise methods for nutritional assessment to determine the nutritional status of children with cancer, which can be adapted to the resources and levels of care of each Institution.

2. Nutritional assessment methods

The Nutrition Working Group (NWG) of the International Society of Pediatric Oncology (SIOP), Committee on Pediatric Oncology in Developing Countries (PODC) recommends a standardized method of nutritional assessment of children with cancer.[16] The assessment needs to be simple and cost effective, and done with ease even in resource limited settings. In most LMICs the goal is to determine a child's nutritional status with minimal assessments.

The extent of the nutritional assessment is dependent on the infrastructure and personnel of the pediatric cancer unit. The NWG recommends the minimum nutritional assessment to include weight, height and mid-upper arm circumference (MUAC), plotted on growth charts, calculation of body mass index (BMI), along with a directed clinical examination for signs of inadequate intake and micronutrient deficiencies. As capacity increases, nutritional laboratory tests can be undertaken, as well as an in-depth dietary intake analysis together with advanced body composition studies.[16]

TABLE 1 High risk factors for malnutrition (under and overnutrition) in children with cancer[12,16,56,62,63]

Diagnosis
Solid tumors in advanced stages *(neuroblastoma, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma)*
Central nervous system tumors *(craniopharyngioma, medulloblastoma, astrocytoma, ependymoma)*
High Risk acute lymphoblastic leukemia, lymphoma
Nasopharyngeal carcinoma
Multiple relapsed and high-risk leukemias
Treatment
Irradiation to the gastrointestinal tract
High-dose cranial/craniospinal radiotherapy
Prolonged corticosteroid therapy with large doses
Major abdominal surgery
Undergoing HSCT or presenting graft vs. host disease
Symptoms
Nausea, vomiting
Diarrhea
Severe mucositis
Patient demographics
Infancy
Anthropometry
W/H or BMI/A z score <-2 or >+2
MUAC < percentile 10 or > percentile 90
Weight loss or poor weight gain during the last few weeks
Dietary intake
Inability to meet energy and protein needs for the last few days

Abbreviations: MUAC (mid-upper arm circumference) W/H (weight-for-height); BMI/A (body mass index-for-age)

2.1. Nutrition screening tools

In institutions with limited resources, a screening tool can be used and patients at higher risk for nutritional depletion can be prioritized. Nutritional screening in pediatrics aims to recognize patients at risk to enable proactive care to those at the highest need of nutrition intervention. In children with cancer, however, most patients present a baseline degree of nutritional risk, depending on the type and stage of the malignancy. For example, patients with advanced disease, receiving intensive therapy and having borderline nutritional status at diagnosis have high nutritional risk. as presented in in Table 1.

There are various screening tools in pediatrics to assess a child's nutritional risk; some are depicted in Table 2. There is insufficient evidence to choose one over another based on their predictive accuracy, however it's important to use validated instruments. The subjective global nutritional assessment (SGNA) for children is a validated tool able to predict nutrition related complications in pediatrics.[17] SCAN is the only nutritional screening tool developed specifically for childhood cancer, identifying patients at risk for nutritional compromise based on a simple scoring system determined by the patients' dietary intake, weight loss, type and stage of disease, treatment and clinical signs of undernutrition.[18]

TABLE 2 Nutritional screening tools for risk assessment of malnutrition in children and adolescents

Screening tool	Information collected to determine the risk of malnutrition
Simple Pediatric Nutritional Risk Score to identify children at risk of malnutrition (PNRS)[54]	Anthropometric data Food intake Gastrointestinal problems (diarrhea and vomiting) Symptoms that may interfere with appetite (pain, dyspnea, depression) Disease classified according to severity
Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP)[55]	Weight and height Questions regarding food intake and disease risk
Screening Tool for Risk of Nutritional Status and Growth (Strong $_{Kids}$)[56]	Subjective clinical evaluation of undernutrition High risk of undernutrition Food intake Weight loss or other losses (diarrhea, nausea, vomiting)
Paediatric Yorkill Malnutrition Score (PYMS)[64]	Body mass index Recent weight Loss Changes in food intake
Nutrition Screening tool for childhood cancer (SCAN)[18] *pediatric oncology specific instrument	Type of cancer determines whether or not there is a risk of malnutrition Intensity of treatment (chemotherapy, radiotherapy, HSCT) Gastrointestinal complications and symptoms Food intake Weight loss Subjective clinical evaluation of malnutrition

HSCT: hematopoietic stem cell transplant

2.2. Anthropometric measures

The World Health Organization (WHO) uses weight, height and BMI for classifying a patient's nutritional status. These measurements are then plotted on WHO growth charts or data tables according to age and gender to determine the appropriate percentile or Z-score for height-for-age (H/A), weight-for-age (W/A), weight for height, (W/H), BMI for age (BMI/A), MUAC for age (MUAC/A) and triceps skinfold thickness (TSFT) for age (TSFT/A). The Z-score determines if the child is stunted, underweight or wasted.[19,20] The parameters used in the different levels of care as described by SIOP PODC are given in Table 3. The classification of nutritional status based on weight and height has drawbacks for children with cancer as measures of weight can be distorted by large tumor masses, hydration status and organomegaly.[21] MUAC is a cheap, rapid and easy measurement of a child's nutritional status, and one that is sensitive for measuring musculature, available protein stores and lean body mass. Arm anthropometry is considered more sensitive in the nutritional assessment of children with cancer as it has the advantage of being independent of abdominal tumor mass, temporary gains in total body water and ethnicity.[4,8,21-23] SIOP PODC recommends that MUAC be used as an anthropometric measurement in children with malignancies.[4,16]

It is essential to ensure the correct methods of measurements of all parameters in monitoring nutritional status as described by the United Nations Children's Fund (UNICEF) and WHO.[24] MUAC measurements in children under 5 years of age can be done with the UNICEF color band as seen in Fig. 1,[24] and for older children a non-stretching measuring tape can be used.[4,25] A MUAC less than <110mm is indicative of severe acute malnutrition (SAM), while for older children measurements less than the 5th percentile or -2 Z-score for age and sex indicates under-nutrition.[4,26] The SIOP

PODC recommendations for assessing children with cancer to determine nutritional status by MUAC are given in Table 4 and are feasible for centers levels 0 and 1.[4,16]

TABLE 3 Anthropometry parameters in order of importance according to the level of care[16,32]

LEVEL OF CARE	**Level 0 and 1** *(none & basic)*	**Level 2** *(limited care)*	**Level 3 & 4** *(optimal & maximal care)*
Parameters	Height	Height	Height
	Weight	Weight	Weight
	MUAC	MUAC	MUAC
	H/A	H/A	H/A
	W/A	W/A	W/A
	W/H	W/H	W/H
	MUAC/A	MUAC/A	MUAC/A
		BMI/A	BMI/A
		TSFT	TSFT
		TSFT/A	TSFT/A
		Waist circumference	Waist circumference
			BIA
			DXA
Frequency	0) None	Follow-up at risk-patients on scheduled visits	Routine follow-up visits
	1) Follow-up at risk-patients if possible, on scheduled visits		

Abbreviations: MUAC (mid-upper arm circumference); H/A (height-for-age); W/A (weight-for-age); W/H (weight-for-height); MUAC/A (mid-upper arm circumference-for-age); BMI/A (body mass index-for-age); TSFT (triceps skinfold thickness); TSFT/A (triceps skinfold thickness -for-age); BIA (bio-electrical impedance analysis); DEXA (dual energy X-ray absorptiometry)

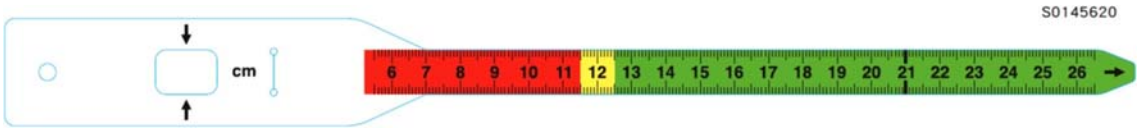

FIGURE 1. UNICEF mid-upper arm circumference (MUAC) color band. Green indicates good nourishment, yellow moderate acute malnutrition, and red indicates severe acute malnutrition (SAM)

TABLE 4 SIOP PODC recommendations for nutritional status cutoffs[4,19]

Age group	Acute malnutrition	SAM
6 months to 5 years	MUAC <12.5 cm	MUAC <11.0 cm
> 5 years without tumor mass	W/H <-2 Z-score	W/H <-3 Z-score
> 5 years with a tumor mass	MUAC <13.5 cm	MUAC <11.5 cm

Abbreviations: MUAC (mid-upper arm circumference); W/H (weight-for-height); SAM (severe acute malnutrition)

As an example, we assess a 6-year-old female admitted with a big abdominal mass. On anthropometric evaluation, she weighs 18.5kg (W/A Z-score -0.60), has a height of 119cm (H/A Z-score 0.75) and BMI/A Z-score -1.67 (by WHO growth charts). Her MUAC is 105mm (Z-score<-3). While the BMI diagnoses a normal child with a risk for undernourishment, MUAC indicates SAM. The evident discrepancy supports MUAC to be a better indicator of nutritional status in children with cancer at diagnosis, attributed to a falsely elevated weight owing to the abdominal mass.

2.3. Body composition

Cancer treatment can alter the energy reserves in muscle and fat. An evaluation to identify the type of nutritional impairment, adipose and/or muscle, is required. Fat and fat-free mass can be reflected by MUAC, TSFT, dual energy X-ray absorptiometry

(DXA), bio-electrical impedance analysis (BIA) and quantitative computerized tomography (CT) scan, among other techniques.[27,28] BMI is unable to distinguish between fat mass and lean mass rendering it a poor measure for body composition.[27] Body composition can be appraised by sophisticated methods such as total body potassium and air plethysmography, with the current clinical gold standard being DXA.[28] BIA measures total body water, fat mass and fat free mass by calculating resistance of the body to a small alternating current. Regression equations used to estimate body composition are based on a specific population and thus are useful for subjects who match the control population in size and shape. The available BIA prediction equations are, however, not suitable for obese children, as hydration of fat free mass decreases in obesity, leading to under-estimation of fat free mass in these individuals.[29]

DXA has been described as the most commonly used densitometric technique for children throughout the world as it gives accurate measures of whole-body fat mass, lean body mass and bone mineral content. Its advantages include accuracy and reproducibility, however it does not discern visceral from subcutaneous fat, which can be done with three dimensional imaging techniques.[27] DXA scans and CT imaging are recommended for body composition analysis when available.

It is to be noted that body composition can also be easily assessed by simple anthropometric measures. MUAC is a validated measure for assessing fat free mass and TSFT measures the fat mass.[22] These measures can be done in any setting obviating the need of expensive equipment. Sophisticated methods of body composition are not easily available in routine clinical practice and are only recommended for centers with compatible capacity.

TABLE 5 Biochemical parameters to determine nutritional status[22,31]

LEVEL OF CARE	Level 0 and 1 *(none & basic)*	Level 2 *(limited care)*	Level 3 & 4 *(optimal & maximal care)*
Parameters protein status	Albumin *(half-life 14-21 days)*	Albumin *(half-life 14-21 days)*	Albumin *(half-life 14-21 days)*
		Transferrin *(half-life 8-9 days)*	Transferrin *(half-life 8-9 days)*
			Prealbumin *(half-life 2-3 days)*
			Retinol Binding Protein *(half-life 12 hours)*
Parameters electrolytes	Magnesium	Magnesium	Magnesium
		Calcium	Calcium
			Zinc
			Selenium
Parameters vitamins	Thiamine *(vit B1)*	Thiamine *(vit B1)*	Thiamine *(vit B1)*
		Cobalamin (v*it B12)*	Cobalamin (v*it B12)*
			Riboflavin *(vit B2)*
			Vitamin A
			Vitamin D
			Vitamin E
Frequency	0) None	Follow-up at risk-patients on scheduled visits	Routine follow-up visits
	1) Follow-up at risk-patients if possible, on scheduled visits		

2.4. *Biochemical evaluation*

Biochemical measures can give additional information about a patient's protein status *(serum albumin, pre-albumin, transferrin, creatinine*)[22], organ function (*serum*

urea, creatinine, liver enzymes)[12], bone health (*serum calcium, magnesium, and vitamin D*), anemia (*iron studies and vitamin levels*), evidence of inflammation (*serum c-reactive protein* [CRP]) and nutritional deficiency (*specific mineral- and vitamin levels*)[30] as depicted in Table 5. Albumin is commonly used as an index of nutritional assessment, with a value of <32 g/L being taken as low.[8] However, it is affected by hydration status, inflammation and liver function. A study in 40 children with cancer found hypoalbuminemia to be a poor indicator of under-nourished status as it was not associated with weight loss during treatment.[31] However, as reported by Sala et al. in a study of more than 1500 children with cancer at diagnosis in Central America, addition of low albumin levels to MUAC and TSFT at diagnosis increased the proportion of those who were classified as severely nutritionally depleted from 45% to 59%.[3]

In LMICs, expensive laboratory tests are not routinely available. Depending on the institutional infrastructure, nutritional laboratory tests can be done to screen for endemic and preventable micronutrient deficiencies in at-risk patients[16]. Table 5 details the tests that can be done according to different levels of care.[16]

2.5. Clinical assessment

A child needs to undergo regular clinical assessment for signs of malnutrition and vitamin and/or mineral deficiencies (Table 6). Evaluation of loss of subcutaneous fat, muscle wasting, skin and hair changes, recent change in weight, edema, and evidence of vitamin and mineral deficiencies are vital in children with under-nutrition.[25,32-34]

TABLE 6 Clinical signs[32,37]

Parameters clinical status	Presence of muscle wasting
	Loss of subcutaneous fat
	Recent weight change (*loss must not be related to fluid retention or loss of fluid*)
	Presence of edema at ankles, sacrum or face
	Hair changes *hair changes, sparse, depigmentation)*
	Eye changes *(dry conjunctiva, keratomalacia)*
	General signs of vitamin & mineral deficiency
Conditions that may affect the nutritional status	Inability to chew and swallow
	Loss of appetite
	Presence of vomiting, diarrhea, constipation, flatulence, belching or indigestion

Nutritional status is also often affected by the patient's primary disease, associated comorbidities such as tuberculosis, HIV and parasitic infections. The treatment of the malignancy per se can compromise the nutritional status by the issues of inability to chew and swallow, the presence of vomiting, loss of appetite, diarrhea, constipation, flatulence, belching or indigestion, mucositis, nausea, dysphagia, taste aversions and xerostomia.[4,22,32] Furthermore, hospitalization, especially when prolonged, can be very stressful for the children and their families and significantly impact the patient's social life and mental health, resulting in a compromised nutritional status.[35]

2.6. Dietary intake

Children with cancer require a diet adequate in protein and energy during treatment. A poor oral intake can lead to deterioration of nutritional status affecting immune status

and organ dysfunction thus requiring intervention.[4,32] Therefore, a complete dietary history is required for a nutritional assessment. Baseline evaluation should include dietary history to ascertain the intake of macro- and micro-nutrients and identify known food aversions, allergies, or intolerances.[12] A retrospective food recall of food and drinks, as well as the quantity the child consumed in the past 24 hours, is a simple and feasible method that allows the assessment of dietary quality and composition. The habitual daily intake of food items consumed during the past week at home can be included, as this is invaluable for determining current eating patterns, family behavior as well as food security at home.[36,37] The recommended macronutrient intake for children can be based upon the acceptable macronutrient dietary ranges (AMDR), which present ranges as a percentage of total calories. For fat, 30 to 40% is recommended between the ages of 1 and 3 years, and 25 to 35% between the ages of 4 and 18 years, with 45 to 65% of energy from carbohydrate, and 10 to 35% from protein.[38]

3. Monitoring and follow-up

Children with cancer often undergo treatment for prolonged periods of time depending on disease state and response to therapy. Regular nutritional monitoring, during and after treatment, is essential to ensure adequate growth and development, provide appropriate interventions when required and prevent worsening of a child's nutritional state. The nutritional risk changes with time according to duration and intensity of treatment. The patient's follow up with a dietitian should conform to the intensity of treatment and consist of a nutritional support strategy adapted to individual nutritional needs, nutritional status, gastrointestinal function, and current or expected side effects of treatment. Patients receiving periods of intensive treatment require

follow-up at a maximum interval of 3 weeks. Children on less intensive treatment need to be optimally evaluated 3 monthly, and 6 to 12 monthly intervals while on the maintenance phase of treatment. The intensity of treatment can be evaluated according to the intensity of treatment rating scale.[39]

Ideally, we suggest that all patients be provided with routine follow-up assessments as constant nutritional monitoring consults are important opportunities to provide the home caregiver with continuing nutrition education. However, this may not be feasible for many pediatric cancer units, since repeated visits require resources and trained personnel. It is recommended that, depending on institutional nutritional infrastructure, nutritionally at-risk patients should be followed-up as a priority, when possible, on a consistent schedule.[16]

4. Nutritional assessment in survivors

The nutritional status is dynamic and nutritional changes in survivors are often overlooked because of lack of follow-up. Nutritional assessment and guidance should start soon after the oncological diagnosis and extend through survivorship. This aids in preventing or reversing nutritional deficiencies, preserves lean body mass, minimizes nutrition-related side effects and improves the quality of life of future survivors.[40] Priority must be given to patients who underwent hematopoietic stem cell transplantation or prolonged intensive chemotherapy, especially at a younger age, as they are more prone to nutrition-related late effects of cancer therapy.[41,42] Survivors of childhood cancer have an increased risk of developing metabolic syndrome and reduced bone mass as treatment-related side effects. Bone mass reduction may be exacerbated by vitamin D deficiency during and after completion of therapy.[43-46] Additionally, patients with other nutritional risk factors such as inadequate eating

habits, smoking, sedentary lifestyle, alcoholism, require follow up. On completion of the treatment for the primary disease, a nutrition follow-up timeline and recommended evaluations should be established. Nutritional education should be part of this follow up.[47] A suggested plan is outlined in Table 7.

TABLE 7 Proposed nutritional assessment for childhood cancer survivors

Nutritional risk	**Proposal**
No nutritional risks	1st year: every 6 months After 1st year: annually
Presence of nutritional risk (inadequate eating habits, hypertriglyceridemia, high cholesterol levels, etc.), or well-nourished	1st year: every 3 months 2nd to 5th year: every 6 months From 5th year onward: annually
Undernourished	Monthly assessment until normal nutrition status
Obese	Every 3 months

Waist circumference (WC) and hip circumference (HC) are used to determine the waist-to-hip ratio (WHR). The cut-off points for WC, indicating increased visceral fat, classification are 80cm for women and 94 cm for men.[48] To determine the risk of cardiovascular disease, the cut-off point for WHR is 0.85 for women and 0.90 for men.[48] Furthermore, waist-to-height ratio, a proxy for central (visceral) adipose tissue, has been shown to be better than BMI for obesity classification in childhood cancer survivors.[49] BMI, from 18 years of age is categorized as underweight (BMI <18.5kg/m^2), normal weight (BMI 18.5-24.9kg/m^2), overweight (BMI 25-29.9kg/m^2) or obese (BMI ≥ 30kg/m^2).[50] To assess the dietary intake of survivors, we suggest

habitual daily intake or 24-hour recalls to be utilized. Some laboratory tests (lipids, cholesterol, creatinine, fasting blood sugar, calcium and vitamin D) may improve the detection of nutritional abnormalities. TSFT, biceps, subscapular and suprailiac skinfolds can be used to estimate body fat percentage.[51] However, for centers with limited resources, we suggest BMI along with WC and MUAC, an evaluation of diet quality and nutritional clinical examination are sufficient for the assessment of survivors. In resource rich centers, whole body composition, best analyzed using DXA, is recommended to evaluate sarcopenic obesity which cannot be assessed by BMI.

5. Nutritional assessment as a research tool

No 'gold standard' for nutritional assessment in children with cancer has achieved consensus opinion in studies of nutrition and outcome. Complete accurate and continuous nutritional assessment is required to enable research with regards to nutrition and its complex relationship with the response to therapy, prognosis and survival. This will also help establish research priorities and clinical interventions, adapted to different levels of care.

Areas for research include (i) Extremes of weight alter the outcome in pediatric cancers. Under-nutrition at diagnosis is a significant poor prognostic factor in children, demonstrating a lower event free survival (EFS) and greater treatment related mortality.[3,8,13] The pathophysiology is considered to be linked to poor tolerance to chemotherapy, increase in risk of infections and a poor bone marrow reserve.[3] In recent years, obesity and overweight have been observed to have an undesirable impact on EFS. These adverse effects are considered to be related to adipocytes decreasing the efficacy of chemotherapy and pharmacodynamic changes related to obesity.[11,13,52] (ii) Nutritional status is dynamic, changes whilst a patient with a

malignancy is on therapy and is infrequently included as one of the variables for clinical outcomes in clinical trials.[14,15] Body composition changes during and after therapy.[27] The relationship of the nutritional status before, during and after treatment on survival is required for the advancement of nutritional science. Childhood cancer survivors are known to have a predisposition towards obesity and the metabolic syndrome. Sarcopenic obesity has been identified in approximately 40% of survivors of acute lymphoblastic leukaemia.[53] Longitudinal multicentric studies which include body composition are desirable to identify the cause and effect and allow for early intervention. (iii) Research has focused more on outcomes in hematological malignancies and their relationship to the nutritional status. Literature on the impact of nutritional status on the outcome in solid tumors is limited. The pathophysiology and interplay of mechanisms of the cause and effect of the tumor with the status of nourishment needs elucidation.[8,21,50,54] (iv) Interventional studies involving dietary modifications are faced with methodological challenges as these studies require to be randomized and double blinded for an accurate assessment.[55] Food is complex and diverse with dietary behaviors differing from person to person. Measures to evaluate compliance and adherence are lacking. In addition, the type of cancer and type of treatment further confound an interventional study. Phase III clinical trials of focused nutritional interventions, with nutritional supplements (proteins/energy rich products), in the setting of pediatric cancers is required to analyze the efficacy of the intervention during and after completion of therapy. (v) Pharmacokinetics and pharmacodynamics of drugs are known to alter with a change in the nutritional status. The dosing required in severely under-nourished and obese patients is not clear. Studies have been performed in animal models with minimal research in humans. Increased bone marrow toxicity, prolongation of the half-life of drugs with greater undesirable effects have been

observed with extremes of body weight. A better understanding of pharmacokinetic variance depending on the body composition is required to facilitate appropriate therapeutic dosing.[56] (vi) Trace elements and vitamins may have an impact on the outcome of a malignancy. Micronutrient deficiencies are rampant especially in LMICs. Vitamin deficiencies can damage DNA which may be a factor in the causation of malignancies. Considerable metabolic damage can occur when there is a suboptimal intake of vitamins and minerals. Deficiency of folate has been implicated in treatment-related mortality in studies from India. Selenium, a trace element, has been seen to affect outcomes in hematological and solid malignancies. The cause and effect of these deficiencies are an area needing research.[52,53] (vii) Nutrition and genetics (nutrigenomics and proteomics). Nutrients can regulate transcription factors and modify gene expression. The interplay between diet and the genome can determine an individual's health and susceptibility to disease with cancer and cardiovascular disease being the foremost diseases being linked to genomics.[57,58] In addition, nutrients can alter and modify the epigenome. Epigenetically active nutrients can damage DNA which may be a factor for the causation of malignancies. Certain nutrients (e.g. amino acids, B complex group of vitamins) have a profound effect on the metabolic pathway with resultant defects and diseases. 'Nutritional epigenetics' could be the future for personalized medicine and targeted interventions.[59,60] (viii) The gut microbiome plays a role in the development of the body's immune system and an altered microbiome can change the inflammatory response, result in DNA damage and bacterial metabolites which can be carcinogenic or tumor suppressor in nature. Dysbiosis of the gut microbiome has been observed at diagnosis of a malignancy and following chemotherapy. This change of the microbiome is considered to play a role in decreasing the outcome of cancer by influencing treatment. The role of microbiota

in the cause and effect and the therapeutics of childhood malignancies is a less explored area for future research.[61]

6. Conclusions

Nutritional assessment is easy, can be tailored to the institution's available resources and is critical to allow for appropriate and timely nutritional intervention in children with malignancies. Both under and overnutrition have adverse consequences in the outcome of childhood cancers, thus longitudinal nutritional assessment is important as childhood cancer survivors have been seen to have major issues related to nutrition. The role of nutritional status in pediatric cancer is a potential area for future research. This article is written to educate and advise on nutritional assessment of children with cancer and is complementary to the other articles in this PBC supplement.

Conflict of interest

The authors have no conflict of interest to report.

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