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Research Article

Nutritional Assessment in Children and Adolescents with Cancer in Three Independent Prospective Cohort Studies: At Diagnosis, During, and After Treatment

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Abstract

Background: In children with Cancer, the nutritional status may be compromised by chemotherapy, radiotherapy, antiemetics, mucositis, decreased smell, taste, lethargy, increased sleep time, and anorexia. So, nutritional status evaluation is essential at diagnosis, during, and after therapy.

Aims: Evaluate the nutritional status in three independent prospective cohort studies: at the time of diagnosis, during, and after treatment.

Methods: This prospective cohort research comprises all children and adolescents consecutively diagnosed at the Oncological Treatment Center from August 2018 to March 2019. Inclusion criteria: aged (1 and 18 years) regular outpatient follow-up. Exclusion criteria: associated diseases that interfere with nutritional status. Patients were divided into three independent Study Groups: Study 1 (newly diagnosed Cancer); Study 2 (undergoing cancer therapy ≥ 3 months; Study 3 (complete cancer therapy and < five years follow-up). All evaluations were performed 0, 30, and 180 days after inclusion.

Results: Sixty-seven cancer patients were grouped into leukemias/lymphomas, central nervous system (CNS) tumors and other solid tumors. The nutritional status was: Study 1 (malnourished was significantly higher after 30 days; abdominal circumference was lower at 30 days). Study 2 and study 3 (no difference was observed between the three moments). Study 3 (Abdominal Circumference was higher at 180 days than inclusion).

Conclusion: Cancer treatment initially impacts body composition by reducing Weight and BMI through a decrease in fat but with no change in muscle reserves. The recovery in nutritional status occurs with increases in fat reserves six months after diagnosis. An adequate dietary intake can improve nutritional status, prevent energy imbalances, and improve fat and muscle reserves.

Keywords: *Cancer; Children; Adolescents; Nutritional Status*

Abbreviations

CNS: Central Nervous System; BMI: Body Mass Index; IARC: International Agency for Research on Cancer; BSF: Biceps Skinfolds; TSF: Triceps Skinfolds; SSSF: Subscapularis Skinfolds; SISF: Supra Iliac Skinfolds; HFA: Height-for-Age Z-Score; WFA: Weight-for-Age Z-Score; BMIFA: BMI-for-Age Z-Score; SDS: Standard Deviation Scores; TUA: Total Upper Arm Area; MUAC: Mid-Upper Arm Circumference (cm); AMA: Arm Muscle Area (mm^2); AFA: Arm Fat Area; AFI: Arm Fat Index

Background

The International Agency for Research on Cancer (IARC) estimated globally that every year, 215,000 cancer cases are diagnosed in children under 15 years and around 85,000 in adolescents between 15 and 19 years [1]. In Brazil and developed countries, it represents the first cause of death from the disease among children and adolescents under 19 years of age, corresponding to 8% of the total [2]. In 2023, The Brazil National Cancaer Institute estimated 7930 new childhood cancer cases and 2704 deaths [3]. Cancer and treatments negatively affect the nutritional status during and after therapy [4]. In children diagnosed with Cancer, some degree of malnutrition was observed in 8% to 50% [5-10]. On the other hand, childhood obesity is now a significant issue and an expected adverse outcome in childhood cancer survivors [11-13].

Indeed, the nutritional status may be compromised by chemotherapy, radiotherapy, antiemetics, mucositis, decreased smell, taste, lethargy, increased sleep time, and anorexia [13-16]. So, poor feeding and malabsorption combined with increased energy expenditure can contribute to weight loss in a short period [17]. In addition, these patients have a decline in physiological functions and immunosuppression with a risk of infections, further increasing the impairment of nutritional status and a worse prognosis [18,19].

Thus, in children with cancer, caloric needs are as high as 130 - 150% of estimated basal energy expenditure, associated with increased protein intake to restore damaged tissue from the effects of chemotherapy and meet the hypercatabolic demands during the initial treatment [20]. So, nutritional health is the cornerstone of managing children with cancer, and a balanced intake of nutrients is essential for adequate growth and development [21]. Consequently, nutritional status evaluation is essential at diagnosis, during, and after therapy [22] and must be assessed in serial anthropometric measurements using quantitative parameters [23].

Aims of the Study

In children and adolescents with cancer: evaluate the nutritional status in three independent prospective cohort studies: at the time of diagnosis, during, and after treatment.

Methods

Study design and patients

Demographic, clinical characteristics and severity of nutritional status using anthropometric indicators were evaluated in this prospective cohort research. The convenience sample consisted of all children and adolescents consecutively diagnosed at the oncological treatment center of the Botucatu Medical School from August 2018 to March 2019. The inclusion criteria were children aged between 1 and 18 years under regular outpatient follow-up. The exclusion criteria were cancer associated with genetic diseases that may interfere with nutritional status.

Patients were divided into three independent study groups: Study 1: newly diagnosed cancer patients; Study 2: patients undergoing cancer therapy for at least three months; Study 3: patients with complete cancer therapy and in less than five years follow-up.

Anthropometric assessment

Biceps (BSF), triceps (TSF), subscapularis (SSSF), and supra iliac (SISF) skinfolds were obtained using an adipometer with a pressure of 10 g/mm^2. Measurements were taken on the right side of the body, with two non-consecutive repetitions for each measurement. The final measure constituted the average of the two values. All measurements were carried out by a qualified assessor who underwent prior assessment training and calibration. The results were interpreted separately and expressed in millimeters (mm). Height-for-age z-score (HFA), Weight-for-age z-score (WFA), and BMI-for-age z-score (BMIFA) were expressed as standard deviation scores (SDS) according to the World Health Organization [24-26]. Weight or Height z-scores greater or less than two SDS were considered abnormal growth. For BMIFA, the classification was: malnutrition (z score less than -2), eutrophic (between -2 and 1), overweight (between 1 and 2), and obesity (≥ 2) [27].

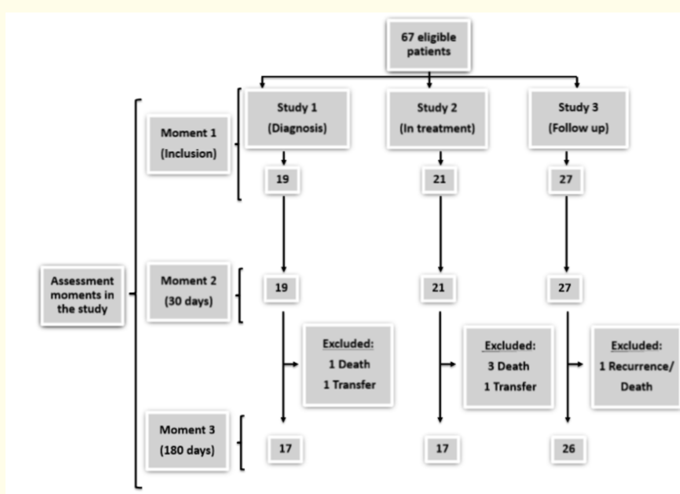
Subsequently, total upper arm area (TUA), mid-upper arm circumference (cm) (MUAC), arm muscle area (mm^2) (AMA), arm fat area (AFA), and arm fat index (AFI) were obtained according to Frisancho (1981) [28]. Fat reserve by AFA and AFI were considered: percentile < 5 (low-fat reserve); percentile between 5-85 (normal fat reserve); and percentile > 85 (high-fat reserve) [28-31]. For muscle reserve, AMA was considered: percentile < 5 (low muscle reserve), percentile between 5 - 95 (normal muscle reserve), and percentile > 95 (high muscle reserve).

Statistical analysis

Data were collected, entered into an Excel spreadsheet, and analyzed using GraphPad Prism version 7.00 for Windows (GraphPad., *et al*.). The Kolmogorov-Smirnov Test was used to evaluate the distribution of variables and define parametric and non-parametric tests. Categorical variables were presented as numbers and percentages, and continuous variables were presented as median and interquartile ranges. The ANOVA Test was used for statistical comparisons, followed by the Dunn or Bonferroni Multiple Comparisons test. Statistical tests were two-tailed, with a significance level of $p < 0.05$.

Results

The flowchart shows the distribution of 67 cancer patients recruited, evaluated and excluded in the three studies. Patients were grouped according to cancer subtypes, and the proportions corresponded to studies 1, 2, and 3: Leukemias/lymphomas 42%, 62%, and 37%; Central nervous system (CNS) Tumors 32%, 19%, and 11%; Other solid tumors 26%, 19%, and 52%.



Flowchart: *Distribution of the sample in study 1, study 2 and study 3, in the three evaluation moments.*

Table 1 shows the patients' baseline characteristics and demonstrates the homogeneity between the groups, with a statistically significant difference only for the number of people at home.

	Study Group 1	Study Group 2	Study Group 3	p<
	Median (IQR)			
Age at the first visit, months	44 (21 - 155)	93 (54 - 128)	114 (63 - 148)	ns
Sex: Male, n (%)	9 (47)	7 (33)	16 (59)	ns
Age of fathers, years	32 (25 - 38)	37 (32 - 41)	37 (30 - 46)	ns
Age of mothers, years	32 (23 - 38)	32,5 (29 - 38)	36 (30 - 41)	ns
Number of rooms	5 (4 - 6)	6 (5 - 8)	6 (5 - 7)	ns
Number of people at home	4 (3 - 4)	5 (4 - 5,5)	4 (3 - 5)	0,04*
Number of children at home	2 (1 - 2)	2 (1 - 3)	2 (1 - 3)	ns
Crowding index (person/room)	0,6 (0,6 - 0,8)	0,7 (0,4 - 1,0)	0,7 (0,5 - 1,0)	ns

Table 1: Baseline characteristics of the patients in the three study groups.

Table 2 presents the proportion of eutrophic, malnourished, and overweight/obese patients at three different moments of analysis. In study 1, the number of malnourished patients was significantly higher after 30 days of inclusion. In study 2 and study 3, no statistically significant difference was observed between the moments.

		0 (Inclusion)	After 30 days	After 180 days	Highlights
	Nutritional status	%			
Study group 1	Eutrophic	58	53	82	0 -30 days > proportion of malnourished (p = 0.03)
	Malnourished	21	42	06	
	Overweight/obese	21	05	12	
Study group 2	Eutrophic	62	62	59	Not significant
	Malnourished	19	09	06	
	Overweight/obese	19	29	36	
Study group 3	Eutrophic	63	63	65	Not significant
	Malnourished	04	00	04	
	Overweight/obese	33	37	31	

Table 2: *The proportion of nutritional status at Inclusion, 30 and 180 days for the three study groups.*

Table 3 analyses the z scores of weight, stature, and BMI in three study groups. In study 1, the weight and BMI at 30 days were lower than those at inclusion. In study 2, the stature at 180 days was higher than at inclusion and 30 days.

		0 (inclusion)	After 30 days	After 180 days	
		z score			
Study group 1	Weight	-0,07	-0,69	0,15	30 days < than inclusion
	Stature	0,06	0,03	0,42	Not significant
	BMI	-0,42	-1,21	-0,91	30 days < than inclusion
Study group 2	Weight	-0,67	-0,28	-0,11	Not significant
	Stature	-0,87	-0,85	-0,42	180 days > than inclusion, and 30 days
	BMI	-0,06	-0,03	-0,01	Not significant
Study group 3	Weight	0,92	0,88	0,73	Not significant
	Stature	0,16	0,23	0,4	180 days > than inclusion, and 30 days
	BMI	0,16	0,79	0,745	Not significant

Table 3: *Weight, stature, and body mass index groups ' z score of the three study groups.*

Table 4 analyses the abdominal circumference and body composition. In study 1, abdominal circumference, MUAC, TUA, and AFA were lower at 30 days than at inclusion. Also, the AFA and AFI were lower at 180 days. No statistically significant difference was observed for AMA. The analysis of study 2 presents that MUAC, TUA, and AMA were higher at 180 days than inclusion. In study 3, abdominal circumference, MUAC, and AMA were higher at 180 days than inclusion.

		0 (inclusion)	After 30 days	After 180 days	p<
		Median (IQR)			
Study group 1	Abdominal Circumference	63 (53-67)	56 (53 - 62)	59 (52 - 66)	0,003*
	Mid-upper arm circumference	19 (16,5 -21,5)	17 (15 - 19)	18 (16 - 21)	0,01*
	Total upper arm area	29 (21,6 -36,7)	23 (17,9 -28,7)	25,7 (20,3 - 35)	0,01*
	Arm fat area	9,5 (5,5 - 12,1)	7 (4,3 - 9)	8 (5 - 11,4)	0,002*
	Arm fat index	31 (28,9 - 33)	30,5 (27 -31,4)	29,7 (27 - 32,7)	0,03*
	Arm muscle area	19,2 (14,8 -24)	16 (14 - 21,6)	17,5 (14 - 24)	ns
Study group 2	Abdominal Circumference	59,5 (54,2 -66)	60 (55 - 67,7)	61,5 (56,6 -67,2)	ns
	Mid-upper arm circumference	19,5 (16-20)	19 (17-20)	21 (17-21)	0,004*
	Total upper arm area	31 (23,6 -34,2)	31 (23,6 -34,2)	35 (24,43 - 35)	0,004*
	Arm fat area	11,3 (4,7-14,6)	12,4 (4,8-14,5)	11,8 (5,5- 14,9)	ns
	Arm fat index	35,4 (23 - 42,9)	36,6 (22- 42,9)	36,8 (24,2 - 41,4)	ns
	Arm muscle area	18 (16,4- 20,9)	19,4 (16,4-21)	20,9 (17,4- 3,3)	0,001*
Study group 3	Abdominal Circumference	65 (55 - 76)	65,5 (55- 78,1)	66 (54,2 - 80,7)	0,03*
	Mid-upper arm circumference	20 (17,7- 24,7)	20 (18 - 24,6)	20,5 (18,7- 26,3)	0,04*
	Total upper arm area	31,8 (25 - 48,8)	31,8 (25,7-48)	33,4 (28 - 55,4)	ns
	Arm fat area	9,8 (8,2 - 19,6)	9,83 (8 - 19,6)	10,6 (7,8- 20,7)	ns
	Arm fat index	31,1 (29- 42,5)	31,86 (29- 38)	30,6 (28,6- 41,1)	ns
	Arm muscle area	22,6 (17- 29,6)	22,4 (17,5 - 32)	22,6 (19,3- 30,8)	0,02*
Friedman's Test and Dunn's Multiple Comparisons Test; # Pearson's chi-square test; *: Statistically significant; ns=no significant					

Table 4: *Abdominal circumference, mid-upper arm circumference, total upper arm area, arm fat area, arm fat index, and arm muscle area. Data is presented as median and interquartile range (25 - 75%).*

Discussion

The current research describes the trajectory of nutritional status in 67 children and adolescents with Cancer. The sample was divided into three independent studies: Study 1 (recent diagnosis), study 2 (undergoing therapy for at least three months), and study 3 (completed cancer therapy). The main results were homogeneity regarding sociodemographic characteristics. The interpretation of the nutritional status referring to specific cancers was very difficult, as the literature on the prospective assessment of subjects is scarce. Thus, the discussion was mainly related to hematological Cancer, which has more studies available.

Analysis of study 1

In study 1, the impact of chemotherapy was probably the main contributing factor to the decrease in BMI and fat reserves. Recovery occurred incompletely at 30 and 180 days of evaluation but was still lower than at diagnosis. A literature study also observed a continuous decrease in BMI in patients with malignant solid tumors [32]. However, other studies reported increased BMI since the beginning of treatment, particularly in patients with ALL and craniopharyngioma [33-35]. Childhood cancer begins to gain fat mass in the first six months after diagnosis, that is, during the most intensive treatment period. However, data from these studies were collected retrospectively and mostly at intervals greater than six months. Studies with shorter time intervals of assessments could determine with greater precision the period in which recovery begins to occur. However, there is a paucity of data on body composition changes in children with cancer [36]. On the other hand, despite initial weight loss, patients with hematological and solid malignancies are at risk of overweight/obesity, and the highest prevalence was found in childhood cancer survivors [35,37]. Regarding height, the patients' growth remained stagnant during the evaluated period.

On the other hand, the patient's muscle mass was normal for age. It remained stable during treatment, confirming that variations in Weight and BMI are initially more related to loss of fat reserves. However, there is controversy regarding low muscle mass reserve at diagnosis and during treatment in ALL and solid cancer patients [38,39]. This relationship would be justified by accentuated weight loss or inflammation secondary to tumor activity [40]. Low muscle mass reserve is alarming, as it may result in lower tolerance to chemotherapy, greater risk of infections, and worse outcomes [38,41]. Therefore, more studies on the factors related to changes in muscle mass reserve are necessary.

The increase in fat reserves during treatment is worrying, as levels increase even years after therapy [41,42]. Therefore, BMI monitoring during and after treatment is necessary for preventive measures. Changes in body composition may also be related to decreased intake and decreased physical activity due to motor disability, fatigue, and growth hormone deficiency [40]. These variables were not evaluated in Study 1.

Analysis of study 2

In study 2, most children and adolescents were eutrophic in the three assessment times. So, they grew and maintained their BMI practically unchanged. These patients had already been undergoing cancer treatment for at least three months. Therefore, it would be plausible that the children and adolescents were already in recovery since their first assessment, both for weight and BMI, as described in the literature [33-35]. This hypothesis was confirmed, as no statistically significant difference was observed in the nutritional classification of the WFA and BMIFA z-score. Several studies describe an increase in BMI and fat reserves, especially in patients with ALL [34-36]. The recovery can be influenced by tube feeding and recovery in malnourished individuals, but there is a fine line between catch-up growth and overfeeding [34,35].

Association between increased BMI and age, sex or parental BMI was demonstrated [34,35,43]. Other studies found no association with energy intake, treatment intensity, symptoms, or physical activity [44]. One factor associated with increased BMI is corticosteroids, as they increase the food intake of energy [45,46]. However, the impact of corticosteroids on BMI is contradictory [34,47]. Study 2 has yet to evaluate this association.

In study 2, both at 30 and 180 days, 29% and 36% of patients were found to be overweight and obese, respectively. The rate was above the prevalence expected for the same geographical area [48]. Studies describe obesity as one of the most adverse outcomes in patients with childhood cancer [13,49,50]. This increase in fat reserves may occur when energy consumption exceeds their needs [43].

There was an increase in muscle mass during the study 2. However, this increase was insufficient to change the muscle reserve. Therefore, nutritional recovery occurred in this group of children through fat gain and a slight increase in muscle reserve. This result is controversial in the literature describing the presence of low muscle reserve in cancer patients, both at diagnosis, during therapy, and after treatment [38,39].

Analysis of study 3

In study 3, no weight gain was found between the assessments at the inclusion, 30 days and 180 days. Like in study 2, the rate of overweight and obese children was above that expected [48]. At the time of inclusion, at 30 days and 180 days, 33%, 37%, and 31% of patients were respectively overweight and obese. These results, according to studies, describe obesity as one of the most common adverse outcomes in childhood cancer survivors [13,35,37,49,50], particularly in ALL survivors who could have a high probability of obesity in childhood, adolescence, and adulthood [50-57].

Final discussion

So, it is challenging to determine the prevalence of overweight/obesity during and after childhood cancer treatment, considering that different types of cancer are treated with different therapies with a limited number of studies and generally with small samples [49]. The increase in fat reserves, represented by the increase in AFA that correlates with BMI values, favors the theory that patients with cancer are at risk of being overweight and obese [35,37,49]. Thus, the increase in fat reserves during treatment is a concern, as there are reports of an increase even years after the end of therapy in childhood cancer [41,42]. High fat reserve accumulated during treatment may continue and increase the risk of morbidities associated with overweight/obesity, such as type II diabetes mellitus, systemic arterial hypertension, and cardiovascular diseases [58]. Therefore, weight control in these patients must be carried out carefully through assessments of BMI at regular intervals. In this research, the increase in muscle mass reserve was insufficient to change the nutritional status, as the patients began and ended within the normal range of muscle reserve.

The research has some limitations. Firstly, the results were mainly interpreted concerning hematological tumors. Secondly, the results should not be generalized. The strengths that can be considerable: Firstly, the research was executed in a single center with good adherence and low dropout patients. Secondly, the methods of nutritional evaluation are easy to use. Thirdly, the same investigator approached all patients.

This research emphasizes the importance of assessing nutritional status, and regularly measuring body composition is recommended to establish specific nutritional interventions and avoid malnutrition or overweight/obesity [38,59]. If considering only Weight and Height, the nutritional status may be undervalued. The assessments of fat reserve by AFA and the muscle reserve by AMA are imperative. In addition, measuring MUAC is crucial for nutritional assessment, as it expresses the sum of bone, muscle, and adipose tissue [60,61].

Conclusion

In conclusion, cancer treatment initially impacts body composition by reducing weight and BMI through a decrease in fat but with no change in muscle reserves. The recovery in nutritional status occurs with increases in fat reserves six months after diagnosis. An adequate dietary intake can improve nutritional status, prevent energy imbalances, and improve fat and muscle reserves. Such measures may contribute to a better prognosis for children with cancer.

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