

Nutritional Profile, Fatigue and Appetite of Patients with Cancer at Hospital Santo Antônio, Blumenau - SC

<https://doi.org/10.32635/2176-9745.RBC.2021v67n4.1375>

Estado Nutricional, Fadiga e Appetite de Pacientes com Câncer atendidos no Hospital Santo Antônio, Blumenau - SC
Estado Nutricional, la Fatiga y el Appetito de los Pacientes con Cáncer en el Hospital Santo Antônio, Blumenau - SC

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ABSTRACT

Introduction: Cancer is a chronic, multifactorial disease, and a major public health problem. Nutrition plays a key role both in prevention and treatment of this disease. Simultaneously, the patient commonly complains of fatigue and lack of appetite, which can change its nutritional status. **Objective:** To evaluate the nutritional profile, fatigue, and appetite of patients with cancer in chemotherapy at Hospital Santo Antônio. **Method:** Cross-sectional and observational study with convenience non-probabilistic sample. The patients with cancer were interviewed during chemotherapy treatment, through semi-structured questionnaire addressing sociodemographic and health data, 24-hour dietary recall survey, European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire Core 13 and Cancer Appetite and Symptom Questionnaire. **Results:** The sample consisted of 100 patients, with higher incidence of breast cancer (n=36), followed by colorectal (n=16) and lung (n=11). Besides, overweight (n=22) and obesity (n=28) were found, and 82 participants reported more frequent symptoms of nausea and diarrhea in the gastrointestinal tract. There was insufficient intake of energetic food, carbohydrates and fibers and beyond the recommended for lipids, vitamins C and selenium. According to the appetite scale, the mean was 2.05 (±0.77) and in the fatigue scale, the mean was 28.76 (± 8.35). Appetite was related to fatigue. **Conclusion:** The study demonstrated that the majority of cancer patients undergoing chemotherapy were overweight and obese, with insufficient energetic intake and hyperlipidic diet. The reduction of the appetite interfered with food intake, and it is related to the aggravation of fatigue.

Key words: Nutritional Status; Neoplasms/drug therapy; Fatigue; Appetite.

RESUMO

Introdução: O câncer é uma doença multifatorial crônica e um grande problema de saúde pública. A nutrição possui papel fundamental tanto na prevenção quanto no tratamento dessa doença. Concomitantemente ao câncer, é comum pacientes apresentarem queixas de fadiga e falta de apetite, o que pode alterar o seu estado nutricional. **Objetivo:** Avaliar o estado nutricional, a fadiga e o apetite de pacientes com câncer em tratamento quimioterápico no Hospital Santo Antônio. **Método:** Pesquisa transversal e observacional com amostra não probabilística de conveniência. Os pacientes foram entrevistados durante o tratamento quimioterápico por meio de questionário semiestruturado contemplando: dados sociodemográficos, saúde, Recordatório Alimentar de 24 horas, escala *European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire Core 13* e escala *Cancer Appetite and Symptom Questionnaire*. **Resultados:** Participaram do estudo 100 indivíduos, com maior incidência de câncer de mama (n=36), seguido de cólon/reto (n=16) e pulmão (n=11). Além disso, observaram-se sobrepeso (n=22) e obesidade (n=28), e 82 participantes referiram sintomas do trato gastrointestinal, sendo náuseas e diarreia os mais citados. Houve consumo alimentar insuficiente de alimentos energéticos, carboidratos e fibras; e superior ao recomendado de lipídeos, vitamina C e selênio. A escala de apetite apresentou média de 2,05 (±0,77) e a escala de fadiga média de 28,76 (±8,35). O apetite esteve relacionado à fadiga. **Conclusão:** A maioria dos pacientes com câncer em tratamento quimioterápico tinha sobrepeso e obesidade, consumo energético insuficiente e hiperlipídico. A redução do apetite interferiu no consumo alimentar, além disso, esteve relacionada ao agravamento da fadiga.

Palavras-chave: Estado Nutricional; Neoplasias/tratamento farmacológico; Fadiga; Apetite.

RESUMEN

Introducción: Cáncer es una enfermedad multifactorial crónica y un problema de salud pública. La nutrición tiene un papel fundamental en la prevención cuánto en lo tratamiento de esa enfermedad. Junto el cáncer eres común que los pacientes tienen síntomas de fatiga y carencia de apetito, eso puede empeorar lo estado nutricional. **Objetivo:** El estudio busco evaluar el estado nutricional, la fatiga y el apetito de los pacientes con cáncer en el Hospital Santo Antônio. **Método:** Estudio transversal y observacional con muestra no obtenida por conveniencia. Los pacientes se han entrevistados en el momento de la quimioterapia, por un cuestionario, que abordaban datos sociodemográficos y de salud, Recuerdo 24 horas y la aplicación del *European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire Core 13* y del *Cancer Appetite and Symptom Questionnaire*. **Resultados:** Participaron del estudio 100 personas, con mayor incidencia de cáncer de mama (n=36), seguido de colon/recto (n=16) y pulmón (n=11). Además, se observaron sobrepeso (n=22) y obesidad (n=28). La población de estudio tenía sobrepeso (n=22), obesidad (n=28) y 82 participantes informaron síntomas del tracto gastrointestinal, siendo las náuseas y la diarrea las más citadas. Hubo una ingesta dietética insuficiente de alimentos energéticos, carbohidratos y fibras; y superior a los lípidos recomendados, vitamina C y selenio. La escala de apetito mostró un promedio de 2,05 (± 0,77) y la escala de fatiga promedio 28,76 (±8,35). El apetito estaba relacionado con la fatiga. **Conclusión:** El estudio demostró que la mayoría de los pacientes con cáncer sometidos a quimioterapia tenían sobrepeso y obesidad, con una ingesta energética insuficiente y hiperlipídica. La reducción del apetito interfirió con el consumo de alimentos, además, se relacionó con el agravamiento de la fatiga.

Palabras clave: Estado Nutricional; Neoplasias/tratamiento farmacológico; Fatiga; Apetito.

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INTRODUCTION

Cancer is a malignant disease because abnormal cells divide without control and can invade nearby tissues and organs and/or spread to other regions of the body^{1,2}. The National Cancer Institute José Alencar Gomes da Silva (INCA) estimates that for each year of the triennium 2020-2022, 625,000 new cases of cancer in Brazil will occur³.

The nutritional status of the patient with cancer changes in the course of the treatment⁴, malnutrition is the most frequent condition because of metabolic alterations as the increase of energetic demand resulting from tumor growth, in addition to the reduction of food intake^{5,6}. However, chemotherapy treatment, mainly glucocorticoids can promote weight gain by water retention and increase of body fat as happens in breast cancer^{4,7}.

Another common manifestation found in patients in chemotherapy treatment are the alterations of the taste sensory cells because they diminish the intensity of the flavors and impact the food intake⁸⁻¹⁰. Appetite suppression is also related to emotional suffering after cancer diagnosis and to inflammatory response provoked by the tumor that can create hypothalamic changes affecting the desire for food^{11,12}.

Fatigue is also a concomitant condition mainly in more advanced stages of the disease. It is characterized by physical, emotional, and cognitive tiredness that does not ameliorate with sleep or rest and contributes to reduce the physical and daily activities damaging the quality of life and worsening the prognosis^{13,14}. The physiopathology of fatigue associated with cancer is not fully understood in the literature, of difficult management, being necessary interventions and early detection by the multi-disciplinary team¹⁵.

In order to achieve the correct intervention and management of the secondary effects of the basal disease and the chemotherapy treatment, considering the importance of the nutritional diagnosis of the patient with cancer, this study had the objective of evaluating the nutritional status of patients with cancer in chemotherapy treatment at Hospital Santo Antônio of Blumenau, SC.

METHOD

Cross-sectional, observational, non-probabilistic study with sampling by convenience carried out in the months of March, August, and September 2020 at Hospital Santo Antônio, in Blumenau, SC. The Institutional Review Board approved the study, number CAAE: 25833219.9.0000.5359 and report 3.768.208.

Patients older than 18 years of age with neoplasm in chemotherapy treatment at Hospital Santo Antônio de Blumenau, SC were evaluated. Patients hospitalized with edema, mental confusion and unable to respond to the research questions were excluded. Data were collected in the chemotherapy room after signing the Informed Consent form (ICF). Socioeconomic, clinical, anthropometric data related to the evaluation of fatigue and appetite were collected.

The sociodemographic and clinical data included age, sex, marital status, education, month income, primary diagnosis, chemotherapy cycle, presence of systemic metastasis, gastrointestinal symptoms, time of diagnosis, surgical procedure, use of nutritional supplement, route of feeding, use of alternative treatment, practice, frequency and duration of physical activity, sleep hours and quality.

For the evaluation of the nutritional status, body weight, regular weight reported, and height were measured. Body weight and height were collected according to the “*Norma Técnica do Sistema de Vigilância Alimentar e Nutricional*”¹⁶ (Technical Standard System of Food and Nutrition Surveillance), with an electronic scale, BK-00 FAN Balmak[®]. The current and regular weight were utilized to calculate weight loss and the Body Mass Index (BMI), classifying the value of adults pursuant to the World Health Organization (WHO)¹⁷ and older adults, per the Pan-American Health Organization (PAHO)¹⁸. The Tricipital Skinfold (TSF) and the arm circumference (AC) were measured too for further calculation of muscular arm circumference (MAC) and its adequacy (%MAC). MAC was classified according to Frisancho¹⁹ and interpreted in line with Lee and Nieman²⁰. The abdominal circumference was measured in accordance with WHO²¹. Due to the paucity of cutoff values for different populations, abdomen circumference was not measured for older adults²¹.

Food intake was evaluated per Food Recall (R24h), analyzed with the software DietBox[®], and the data obtained were compared with recommendation of energy (25 Kcal/Kg/day) and macronutrients (1 g/Kg current weight for protein, 25% of energetic recommendation for lipids and remaining percentage for carbohydrate) for patients with cancer of the “*Projeto Diretriz*”²². The values of micronutrients vitamins C (75 mg for men and 60 mg for women), E (12 mg for men and women) and A (625 mcg for men and 600 mcg for women), selenium (45 mcg for men and women) and fibers (25 g for men and women) were compared to the Dietary Reference Intakes²³.

The instrument European Organisation for Research and Treatment of Cancer (EORTC QLQ FA13)²⁴ validated and translated to Brazil by Silva et al.²⁵ was utilized to measure fatigue. It has 13 closed questions

addressing three dimensions: physical, psychological, and cognitive. The responses were in Likert-scale: 1 – no, 2 – a little, 3 – moderately and 4 – very²⁵.

The scale Cancer Appetite and Symptom Questionnaire (CASQ), of Halliday et al.²⁶ was utilized to evaluate appetite specifically for patients with cancer, validated and translated for Brazil by Spexoto et al.²⁷. CASQ is a unifactorial instrument with 5-points Likert-response options.

The data collected were tabulated in Microsoft Excel®, version 7, with analysis of the quantitative variables described in mean and standard deviation and of the categorical variables in absolute and relative frequencies. After the Shapiro-Wilk normality test, most of the variables were parametric, utilizing Pearson correlation and test t of Student. For non-parametric variables, (income, time of diagnosis, time of surgery, frequency of physical activity, recommendation of intake of vitamins C and A, food intake of vitamin E, intake and recommendation of selenium, total, physical, and cognitive fatigue), Spearman correlation and Mann-Whitney U test were utilized. The values of $p < 0.05$ were considered statistically significant.

RESULTS

100 patients joined the study, mean age of 55.91 (± 10.69) years, mostly females, married/stable union, average income of R\$ 1,933 ($\pm 1,012.35$) and sedentary (Table 1). More than half reported nausea and poor or satisfactory sleep with mean of 7.59 (± 2.55) hours slept per day. There was prevalence of history of breast and colorectal cancer (Table 2), previous surgery and no metastasis (Table 2). The mean time from diagnosis, last surgery and beginning of chemotherapy cycle was 17.95 (± 25.48), 15.98 (± 26.41) and 3.16 (± 2.48) months, respectively. Most of them did not undergo alternative treatments.

The utilization of nutritional supplement was not prevalent (Table 3). The BMI of more than half of the patients was scored as overweight, either for the current or regular BMI. Mean regular BMI was 28.81 (± 5.67) Kg/m² and current, 26.78 (± 5.14) Kg/m². Mean weight loss was 6.14%. Muscle status of upper limbs was eutrophic without fat accumulation in abdomen.

Dietary intake of vitamins E and A was adequate, mean intake of energetic food, carbohydrate and fibers was poor and lipids, vitamin C and selenium (Table 4) was above recommended.

CASQ's scale mean was 2.05 (± 0.77), mean fatigue, 28.76 (± 8.35), physical was bigger than psychological and cognitive fatigue. Statistical analysis showed significant

Table 1. Sociodemographic and health data of oncologic patients. March to September 2020. Blumenau, SC

Variables	N	%
Sex		
Female	67	67
Male	33	33
Marital Status		
Married/stable union	75	75
Single, widower and divorced	25	25
Education		
Elementary	63	63
High school and University	37	37
Physical Activity		
Yes	25	25
No	75	75
Sleep quality		
Poor	32	32
Regular	30	30
Good	21	21
Very good	17	17
GIT Symptoms		
Nausea	56	-
Diarrhea	30	-
Flatulence	27	-
Vomit	24	-
Cramps	14	-
Constipation	13	-

Caption: GIT = Gastrointestinal Tract.

correlation between CASQ with intake ($r=0.299$) and adequacy ($r=0.291$) of calories and proteins (intake: $r=0.258$; adequacy: $r=0.269$), intake of carbohydrates ($r=0.222$) and lipids ($r=0.198$). The intake and adequacy of selenium had significant correlation both in CASQ scale ($r=0.278$ for both) and total fatigue ($r=-0.220$). Total fatigue correlated positively with protein adequacy ($r=0.287$) (Table 4).

The scale of total fatigue and/or its subscales (physical, psychological, and cognitive) had significant statistic correlation with the following variables: age, regular BMI, percentage of adequacy of MAC, time of surgery and CASQ scale (Table 5).

The Mann Whitney test revealed statistically significant association between sex and total fatigue ($p=0.010$) as well as in the subscales physical fatigue ($p=0.010$) and psychological fatigue ($p=0.035$), higher in women than

Table 2. Clinical characteristics of oncologic patients. March to September 2020. Blumenau, SC

Variables	N	%
Primary Diagnosis		
Breast	36	36
Colorectal	16	16
Lung	11	11
Stomach/esophagus	8	8
Male reproductive system (prostate, extragonadal germinative, testicle)	7	7
Non-Hodgkin Lymphoma	6	6
Female reproductive system (cervix, endometrium, ovary)	5	5
Head and neck	4	4
Others (liver, neuroendocrine, skin, sarcoma of soft parts and leukemia)	7	7
Metastasis		
Yes	38	38
No	62	62
Surgery		
Yes	55	55
No	45	45
Current Treatment		
Chemotherapy	77	77
Chemotherapy and radiotherapy	18	18
Chemotherapy and transplantation of progenitor cells	5	5
Alternative treatment methods		
Yes	40	40
No	60	60
Alternative methods utilized		
Graviola (Soursop)	29	29
Aranto (<i>Kalanchoe daegrementiana</i>)	15	15
Orapronobis (<i>Barbados gooseberry</i>)	6	6
Fruit and/or vegetables juice, saffron or curcumim	6	6
Others (aloe, "pau-pelado" (<i>Euphorbia tirucalli</i>), janaúba (<i>Himatanthus drasticus</i>), "garrafada" (beverage)	6	6

in men. The practice of physical activity associated with total ($p=0.031$) and psychological fatigue ($p=0.003$), showing possible effect in its reduction. CASQ scale did not present significant association with sex, metastasis, surgery, alternative treatment, practice of physical activity and intake of nutritional supplement.

Table 3. Characteristics of feeding and nutritional status of oncologic patients. March to September 2020. Blumenau, SC

Variables	N	%
Use of Nutritional Supplement		
Yes	42	42
No	58	58
Classification of regular BMI		
Low weight	7	7
Eutrophic	27	27
Overweight	29	29
Obesity	37	37
Classification of current BMI		
Low weight	11	11
Eutrophic	39	39
Overweight	22	22
Obesity	28	28
Classification AC*		
No risk	33	33
Elevated risk	11	11
Very high risk	15	15
Classification AMC		
Lean/low reservoir muscle tissue	10	10
Below average/deficit risk	8	8
Average	34	34
Above average	18	18
Good nutrition/excess fat	30	30
Classification %AMC		
Severe depletion	3	3
Moderate depletion	5	5
Mild depletion	11	11
Eutrophic	81	81

Captions: BMI = Body Mass Index; AC = Abdominal Circumference; AMC = Arm muscle circumference; %AMC = Percentage of arm muscle circumference. (*) Adult patients.

DISCUSSION

Most of the patients interviewed were overweight and sedentary and association of CASQ with fatigue scale was found. CASQ was more determinant for food intake than fatigue scale. In addition, selenium through food intake was related with CASQ and to fatigue scale.

Regarding gender and age, the result of this study was similar to Campos et al.²⁸ where 63% of the participants were females with mean age of 53.2 years.

Table 4. Food intake and recommended values, percent of adequacy of intake of oncologic patients and correlation with fatigue scale and CASQ. March to September 2020. Blumenau, SC

Nutrient	Mean \pm standard deviation	Scale CASQ (p)	Total fatigue (p)
Energy			
Intake (kcal)	1,487.35 \pm 512.91	0.003^a	0.735
Recommendation (kcal)	1,814 \pm 368.57	0.439 ^a	0.451
Adequacy (%)	82.51 \pm 23.65	0.003^a	0.222
Carbohydrate			
Intake (g)	197.26 \pm 75.46	0.027^a	0.811
Recommendation (g)	290.34 \pm 58.97	0.439 ^a	0.451
Adequacy (%)	68.96 \pm 24.76	0.101 ^a	0.958
Proteins			
Intake (g)	70.34 \pm 39.03	0.009^a	0.082
Recommendation (g)	72.58 \pm 14.74	0.439 ^a	0.451
Adequacy (%)	96.21 \pm 45.90	0.007^a	0.018
Lipids			
Intake (g)	55.07 \pm 25.63	0.048^a	0.792
Recommendation (g)	40.32 \pm 8.19	0.439 ^a	0.451
Adequacy (%)	136.27 \pm 57.36	0.068 ^a	0.939
Vitamin C			
Intake (g)	182.54 \pm 341.52	0.889 ^a	0.587
Recommendation (g)	64.95 \pm 7.09	0.148	0.107
Adequacy (%)	278.84 \pm 474.82	0.818 ^a	0.469
Vitamin E			
Intake (g)	9.65 \pm 9.56	0.447	0.977
Recommendation (g)	12	-	-
Adequacy (%)	98.22 \pm 101.09	0.310 ^a	0.977
Vitamin A			
Intake (g)	588.26 \pm 609.27	0.736 ^a	0.361
Recommendation (g)	608.25 \pm 11.81	0.148	0.107
Adequacy (%)	98.22 \pm 101.09	0.710 ^a	0.464
Selenium			
Intake (g)	76.06 \pm 57.13	0.005	0.028
Recommendation (g)	45	-	-
Adequacy (%)	169.02 \pm 126.95	0.005	0.028
Fibers			
Intake (g)	17.74 \pm 8.63	0.388 ^a	0.895
Recommendation (g)	25	-	-
Adequacy (%)	70.94 \pm 34.51	0.388 ^a	0.895

Caption: CASQ = Cancer Appetite and Symptom Questionnaire.

(a) Pearson correlation.

Values in bold are statistically significant ($p \leq 0.05$).

The predominant cancers were breast, colorectal and lung. A recent study²⁹ carried out in Caxias do Sul concluded that hematologic cancer was incident with eutrophic (42%) and overweight (39%) nutritional

profile, unlike the current study where overweight and obesity were more prevalent.

The patients reported more nausea, followed by diarrhea and flatulence, unlike a study of Rio Grande

Table 5. Correlation between fatigue and its subscales with sociodemographic and health variables and scale CASQ of oncologic patients. March to September 2020. Blumenau, SC

Variables	N	Physical Fatigue (p)	Psychological Fatigue (p)	Cognitive Fatigue (p)	Fatigue Total (p)
Age	100	0.001	0.001^a	0.056	<0.001
Income	100	0.787	0.787	0.837	0.903
Regular BMI	100	0.124	0.185 ^a	0.103	0.010
Current BMI	100	0.175	0.175 ^a	0.548	0.072
AC	59	0.819	0.790 ^a	0.369	0.934
%MAC	100	0.004	0.044^a	0.303	0.004
Frequency of physical activity	25	0.562	0.562	0.735	0.357
Duration of physical activity	100	0.196	0.082 ^a	0.243	0.817
Sleeping hours	100	0.063	0.284 ^a	0.767	0.199
Time of diagnosis	100	0.470	0.653	0.660	0.515
Time of surgery	100	0.928	0.495	0.030	0.811
Number of symptoms of GTI	82	0.676	0.237 ^a	0.735	0.709
Chemotherapy cycle	100	0.249	0.581 ^a	0.348	0.437
CASQ	100	<0.001	<0.001^a	0.486	<0.001

Captions: BMI = Body Mass Index; AC = Abdominal circumference; %MAC = Percent of muscle arm circumference; GIT = Gastrointestinal tract; CASQ = Cancer Appetite and Symptom Questionnaire.

(a) Pearson Correlation.

Values in bold are statistically significant ($p \leq 0.05$).

do Sul³⁰, where xerostomia, inappetence, dysgeusia and nausea were found. Likewise, the “*Inquérito Brasileiro de Nutrição Oncológica (IBNO)*”³¹ – Brazilian Enquiry of Oncology Nutrition encountered inappetence, nausea, xerostomia and dysgeusia as main symptoms reported by patients with cancer in chemotherapy treatment. These symptoms can be due to the chemotherapy treatment affecting neoplastic and normal cells with high capacity of replication, particularly of the gastrointestinal tract causing diarrhea, nausea, flatulence, vomits, xerostomia, constipation, mucositis, dysphagia, and anorexia³⁰⁻³².

Appetite reduction is a symptom found in patients in chemotherapy treatment affecting food intake as is the case of the present study, similar to what was found by Campos et al.²⁸, compromising the appetite, worsening the quality of life, and diminishing food intake which negatively impacts the prognosis.

Food intake of macronutrients and selenium was statistically associated with reduction of the appetite, dissimilar to the study of Dutra et al.³³ where the symptoms of nutritional impact were not determinant of food intake.

Furthermore, appetite reduction is related to the worsening of fatigue in physical, psychological, and total dimensions, similar to what was concluded after applying the EORTC QLQ-30 where association among weight loss, nausea and vomits in patients in Spain³⁴ was detected.

Fatigue is common in patients in chemotherapy treatment which did not present any significant relation with physical activity and sleeping in the patients evaluated, but in the literature^{14,35,36}, the opposite occurs. Conservation of energy, behavior intervention and sleeping, further to physical practice, particularly aerobic are strategies to manage fatigue³⁷.

Protein intake showed strong association with fatigue. Cancer and treatment-related muscle mass loss happens because of negative protein and energetic balance, which are related to diminishing of food intake and/or bioavailability of nutrients and excessive production of pro-inflammatory cytokines, neuro-endocrine deregulation and stimulation of metabolic factors and inhibition of anabolic factors^{38,39}.

A case-control study⁴⁰ concluded that reduced intake of vitamins A, E, B6, B9 and B12, selenium and zinc have great impact over muscle health and fatigue. It is possible that nutritional reduction provokes atrophy of the muscle fibers and diminishing of oxidative capacity. As determined in the current study, selenium alone impacted patients' fatigue.

The heterogeneity of the population investigated can be a bias as well as the sample size and period of treatment as great part of the participants were in the first cycle of treatment. Another limitation of the study is the utilization of R24h because information can be missed

or forgotten. Despite these limitations, it contributed for the evaluation and investigation of the relation between nutritional status, fatigue, and appetite of patients with cancer because so far, there are no studies addressing this subject. The multidisciplinary healthcare team should consider the results in the protocols of treatment to improve the quality of life of the patients.

More studies on that matter are recommended to help the treatment and management of patients with cancer and survival. Future studies should correlate chemotherapy medications and cancer staging with the variables investigated.

CONCLUSION

The characteristics of individuals diagnosed with cancer in chemotherapy treatment were presented with prevalence of the nutritional profile overweight. Food intake was related with appetite as anticipated. Selenium was related to appetite as well as with different types of fatigue, but more studies are necessary to elucidate the mechanisms. However, the importance of the nutritionist in the multiprofessional team is emphasized to minimize and avoid the adverse effects of the basal disease and of the chemotherapy treatment.

CONTRIBUTIONS

Eduarda Kormann and Vanessa Korz contributed substantially for the study design and conception, collection, analysis and/or interpretation of the data, wording, and critical review. Tatiane dos Santos Aligleri contributed substantially for the study design and conception and critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING SOURCES

None.

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Recebido em 17/12/2020
Aprovado em 9/4/2021