

ORIGINAL ARTICLE

The influence of chemotherapy on nutritional status and oncological fatigue in cancer patients: Cross-sectional study

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Abstract

Introduction: chemotherapy can contribute to the impairment of nutritional status and increased fatigue.

Objective: the aim of this study is evaluate the influence of chemotherapy on nutritional status and oncological fatigue.

Methods: this is a study with patients undergoing chemotherapy. Data collection was performed in the first chemotherapy session, in the middle and in the last session.

Results: the final sample comprised 20 patients. There was an increase in the level of fatigue ($p < 0.05$), and a difference between the percentage of weight loss ($p < 0.05$). A direct relationship was found between fatigue and nutritional status ($R = 0.484$; $p = 0.031$).

Conclusion: fatigue increase during chemotherapy and nutritional status worsens throughout the sessions, with a direct relationship between fatigue and nutritional status.

Keywords: neoplasms, nutritional status, fatigue, chemotherapy, antineoplásicos, adverse event.

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Authors summary

Why was this study done?

- Cancer and chemotherapy can bring several limitations to patients;
- Patients may develop fatigue and a worsening of nutritional status, which tends to worsen during the chemotherapy period;
- It is important to understand how these symptoms develop during the chemotherapy period;
- We must also understand whether fatigue and nutritional status are related during this period.

What did the researchers do and find?

- Assessment of fatigue and nutritional status during the chemotherapy period;
- Application of questionnaires at three different moments of chemotherapy treatment;
- 20 patients with different types of neoplasms and on different chemotherapy protocols participated;
- There was an increase in fatigue and weight loss during the study;
- A direct relationship was found between fatigue and worsening nutritional status.

What do these findings mean?

- Patients experience worsening fatigue and nutritional status during chemotherapy, with a direct relationship between the two variables;
- Multimodal approaches must be designed to minimize these effects.

Highlights

- Cancer causes functional decline in many patients.
- Worse nutritional status and a worse overall perception of health and fatigue.
- Evaluate the influence of chemotherapy on the nutritional status and fatigue.
- Fatigue is present in most cancer patients during chemotherapy.
- Nutritional status tends to worsen throughout chemotherapy sessions.

INTRODUCTION

Cancer causes functional decline in many patients, caused by several conditions that can affect it, fatigue and anorexia are an example of this¹. It is necessary to implement multimodal approaches that encompass physical activity and nutritional counseling to intervene in the symptomatology, low physical performance and low quality of life of these patients, in addition to an evaluation of the effectiveness of these approaches applied in this specific population².

The current literature still lacks research using multimodal rehabilitation, combining physical exercise with nutritional interventions, as a form of intervention. However, studies have shown improvements in various aspects of quality of life for these patients, including physical endurance and depression³. In addition to the use of exercises, dietary counseling, oral supplements, enteral and parenteral nutritional support are also applied, showing promising results in the research carried out⁴.

It is known that there are currently several antineoplastic treatments, which may have curative, palliative, adjuvant or neoadjuvant intent, and can be used alone or in association. Among the main treatments used is chemotherapy, a form of systemic cancer treatment that uses antineoplastic drugs, in which its dose and frequency of administration will depend on the therapeutic regimen⁵.

The adverse effects of chemotherapy are very variable and can contribute to the nutritional impairment of the cancer patient, since symptoms that imply daily nutritional intake such as anorexia, nausea, vomiting, diarrhea, constipation, mucositis, xerostomia and dysgeusia, increase the tendency to the appearance of cachexia and malnutrition, which, in turn, intensify the adverse effects of treatment, generating a vicious cycle⁶⁻⁸.

In addition, some studies show that inadequate nutritional status of cancer patients is also related to a higher fatigue score. Cancer patients who experience a combination of anorexia and early satiety, exhibit worse nutritional status and consequently, a worse overall

perception of health and fatigue⁹.

The aim of this study was to evaluate the influence of chemotherapy on the nutritional status and oncological fatigue of cancer patients, as well as to verify the relationship between fatigue and nutritional status.

METHODS

Study design

This is an analytical study, carried out in three stages, namely in the first chemotherapy session, in the middle of the cycle and in the last session, in order to evaluate oncological fatigue and nutritional status, and the relationship between both, throughout the cycle performed by the patient. The study was approved by the research ethics committee of the Centro Universitário FMABC (#4.591.026). The study was designed following the STROBE guideline¹⁰.

Context

Participants were recruited during the month of January to June 2021, at the Luiz Rodrigues Neves Oncology Center, located in the municipality of São Caetano do Sul, in São Paulo, Brazil. The approach was made when the patients were undergoing chemotherapy, and from then on, the follow-up was initiated for those who accepted and signed the Informed Consent Form (ICF).

The application of the questionnaires and evaluation of the participants were carried out in the place where they received chemotherapy, so that the evaluators were the same for all patients, during the three approaches carried out, after which the follow-up was terminated.

Participants

Patients of all age groups, both sexes, with all types of neoplasms, regardless of the chemotherapy treatment applied, were included, and patients who failed to participate in any stage of the research, making an

adequate statistical analysis impossible, or who could not understand the questions in the questionnaires, were excluded. The participant was followed up until the time of the last chemotherapy session, completing the last assessment.

Variables

Cancer fatigue was assessed using the Fatigue Pictogram, an instrument composed of two sets of figures that assess the intensity and impact of fatigue on activities of daily living. The instrument is divided into two questions: “How tired have you felt over the last week?” referring to the individual’s perception of fatigue and “How much does feeling tired prevent you from doing what you want to do?” referring to how much fatigue is interfering with daily activities¹¹.

The first question has five answer possibilities: “not at all tired”, “a little bit tired”, “somewhat tired”, “moderately tired” or “extremely tired”. The second question has the following answer possibilities: “I can do everything I normally do”, “I can do almost everything I normally do”, “I can do some things I normally do”, “I do what I have to do” or “I can do very little”¹¹.

The instrument was presented to the participant and they were asked to indicate on the picture which answer represented them at that moment.

The two questions that make up the Fatigue Pictogram were divided into Pictogram A for the first question and Pictogram B for the second question, being grouped and classified as follows: “not at all tired” for “no fatigue”; “a little bit tired” for “mild fatigue”; “somewhat tired” and “moderately tired” for “moderate fatigue”; “extremely tired” for “extreme fatigue”. The second item was grouped as follows: “I can do everything I normally do” for “no fatigue”; “I can do almost everything I normally do” for “mild fatigue”; “I can do some the things I normally do” for “moderate fatigue”; and finally “I do what I have to do” and “I can do very little” for “severe fatigue”¹².

The assessment of nutritional status was performed through anthropometry, containing the anthropometric measurements: weight, height, arm circumference (AC), calf circumference (CC) and triceps skinfold (TSF), measured during chemotherapy, thus body mass index (BMI) was calculated, and the percentage of weight loss (%PWL), which was calculated using the usual weight as reported by the patient 3 months before the first weight measurement performed in this study, structuring the following formula: (usual weight “3 months ago” – current weight “of the first moment”/ current weight) x 100.

Finally, the Patient-Generated Subjective Global Assessment (PG-SGA), a method for assessing nutritional status through a combination of factors. The assessment is done in 7 steps in the following order: patient’s weight, food intake, symptoms in the last two weeks, activities and function, disease and its relation to nutritional requirements, metabolic demand and physical exam, the last three steps being done by the nutritionist. The item “disease and its relation to nutritional requirements” concerns all patient diagnoses, cancer disease staging and age; the item “metabolic demand” concerns the presence

of fever and use of corticosteroids; the item “physical exam” concerns the assessment of fat reserves, hydration status and muscle status¹³.

At the end, the participant is classified as well-nourished (stage A), with moderate/suspected malnutrition (stage B) or severely malnourished (stage C). This classification is made through the evaluation of the answers obtained in each item evaluated, in stage A patients have no deficits, in stage B they have some change in intake and loss of mass/fat, in stage C they have weight loss, severe functional deficit, severe intake deficit and symptoms that cause nutritional impact. The questionnaire also generates a final score, made through the sum of the answers given by the participants, the values obtained are divided as follows: 0-1 (No intervention required at this time); 2-3 (Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey and lab values as appropriate); 4-8 (Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms); ≥ 9 (Indicates a critical need for improved symptom management and/or nutrient intervention options)¹³.

Data source

To characterize the sample, a questionnaire formulated by the researchers was used to obtain the following data: name; gender; date of birth; age; diagnosis; medication used (chemotherapy).

Fatigue was assessed by the Fatigue Pictogram and nutritional status by anthropometric assessment and the PG-SGA questionnaire.

Bias

The fact that there is a very heterogeneous group, with varying ages, different neoplasms, with different medications used for chemotherapy can influence fatigue and nutritional status, for this reason this information was included in the data collection in order to better identify any variation related to the information mentioned above.

Study size

The sample used in the research was convenience sampling, by recruiting an available population, in a specific location, during a period of time necessary to carry out the evaluation of the variables in question¹⁴.

Quantitative variables

In order to optimize the analysis of the variables obtained through the aforementioned instruments, it was necessary to categorize the data. The answers obtained in the Fatigue Pictogram, both in the first and second questions, after classification into “no fatigue”, “mild fatigue”, “moderate fatigue” and “severe fatigue”, were categorized as follows: 1- no fatigue/mild fatigue; 2- moderate fatigue; 3- severe fatigue.

After the classification of the answers obtained in the PG-SGA into well-nourished (stage A), with moderate/suspected malnutrition (stage B) or severely malnourished (stage C), the following categorization was performed: 1-stage A; 2- stage B; 3- stage C.

Statistical methods

The data were previously organized with the aid of the Microsoft® Excel program and the database was prepared, subsequently the SPSS (Statistical Package for Social Research) program version 21.0 was used for statistical analysis. Quantitative data are presented as measures of central tendency and frequency. The normality of the data was initially determined by the Kolmogorov-Smirnov test according to the sample size. Student's t-test was used to compare the participants' responses to the Fatigue Pictogram. The repeated measures analysis of variance (ANOVA) test was used, followed by the Bonferroni post-hoc test to compare the anthropometric variables of patients undergoing chemotherapy. Pearson's

test was used to correlate fatigue with nutritional status (pictogram vs PG-SGA). Differences in these tests were considered statistically significant when the p-value was less than 0.05.

RESULTS

The study included 25 cancer patients undergoing chemotherapy at the Oncology Center of São Caetano do Sul, so that 20 participants who answered the questionnaires completely in the three moments of application were included in the study, and 5 participants were excluded due to lack of answers in any of the three moments of data collection (Figure 1).

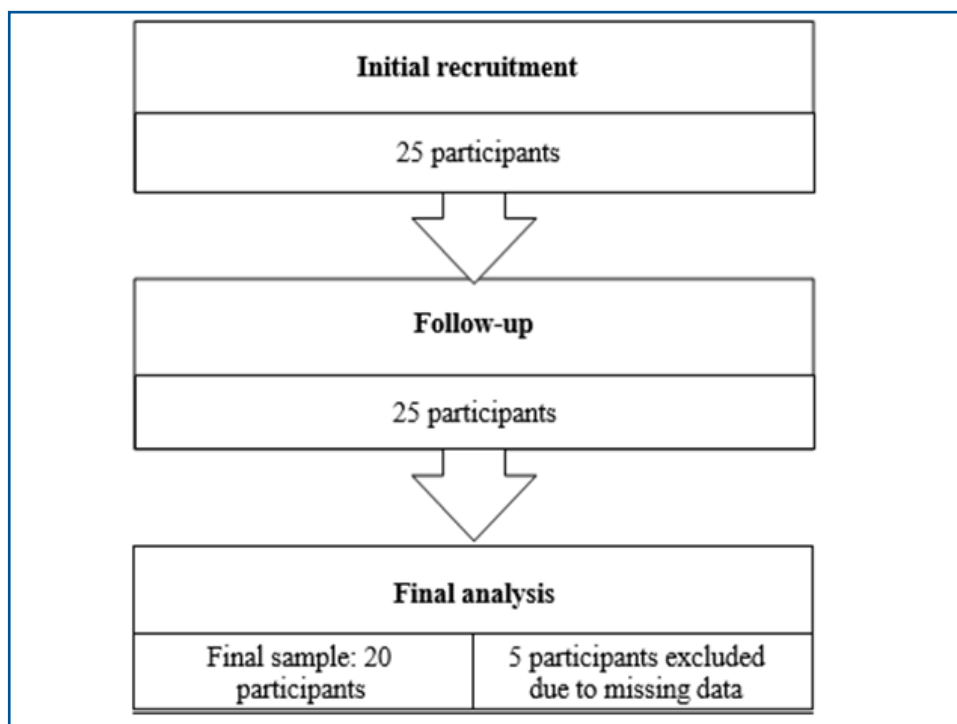


Figure 1: Flowchart with recruited participants, sample loss and sample

The majority of participants included in the study were female (80%), with a mean age of 59.1 years, with 45% diagnosed with colon cancer as the primary site, 40% with breast cancer and 5% with rectal, gastric or oesophageal cancer. All were undergoing chemotherapy, 25% were using the Doxorubicin/cyclophosphamide and paclitaxel (AC-T) protocol, 20% Leucovorin + 5-FU + oxaliplatin (FLOX), 15% 5-fluorouracil + leucovorin

(5-FU+LV), 10% 5-fluorouracil and leucovorin + bevacizumab (IFL+AVASTIN), while the others use the protocol 5-fluorouracil and leucovorin (IFL), S-1/oxaliplatin (SOX), Trastuzumab (TH), Carboplatin + paclitaxel (CARBO+TAXOL), Oxaliplatin and capecitabine (XELOX) or Oxaliplatin + fluoropyrimidines (OXALIPLATIN), as described in Table 1.

Table 1: Sociodemographic data

Sociodemographic data		
Sex - n (%)	Female	16 (80)
	Male	4 (20)
Age	Mean (SD)	59.1 (±8.42)
	Median	62.5

Continuation - Table 1: Sociodemographic data

Diagnosis and treatment - n (%)		
Primary location	Breast	8 (40)
	Colon	9 (45)
	Rectum	1 (5)
	Gastric	1 (5)
	Esophagus	1 (5)
Chemotherapy	AC-T	5 (25)
	5-FU+LV	3 (15)
	IFL+AVASTIN	2 (10)
	FLOX	4 (20)
	IFL	1 (5)
	SOX	1 (5)
	TH	1 (5)
	CARBO+TAXOL	1 (5)
	XELOX	1 (5)
	OXALIPLATIN	1 (5)
		N= 20

(n) total number of research participants; (SD) standard deviation; (AC-T) Doxorubicin/cyclophosphamide and paclitaxel; (5-FU + LV) 5-fluorouracil + leucovorin. (IFL + AVASTIN) 5-fluorouracil and leucovorin + bevacizumab; (FLOX) Leucovorin + 5-FU + oxaliplatin; (IFL) 5-fluorouracil and leucovorin; (SOX) S-1/oxaliplatin; (TH) Trastuzumab; (CARBO + TAXOL) Carboplatin + paclitaxel; (XELOX) Oxaliplatin and capecitabine; (OXALIPLATIN) Oxaliplatin + fluoropyrimidines.

Taking into account that the instruments were applied at three different times, we classify M1 as the first application, M2 as the second and M3 as the third and last application in all the analyses made. The following table presents the data regarding the participants' responses to the Fatigue Pictogram (Table 2).

The responses of the participants in the first, second and last application were also compared, with table 3 referring to the first question of the instrument and table 4 bringing the results obtained in the second question of the scale.

Table 2: Responses regarding the Fatigue Pictogram at the three moments of its use

	Pictogram A			Pictogram B		
	None/Mild	Moderate	Severe	None/Mild	Moderate	Severe
M1	60%	35%	5%	65%	20%	15%
M2	50%	50%	0%	65%	20%	15%
M3	55%	45%	0%	60%	20%	20%

(Pictogram A) "How tired have you felt over the last week?; (Pictogram B) How much does feeling tired prevent you from doing what you want to do?; (M1) Moment 1; (M2) Moment 2; (M3) Moment 3.

Table 3. Results referring to the responses of the first item of the tool in the first and third application

A1	A1 final	p-value
2.30±1.17	2.35±1.04	0.001*

*Student's t-test: significant difference between the first and last evaluation.

(A1 e A1 final) values relating to the question "How tired have you felt over the last week?"

Table 4: Results regarding the answers of the second item of the tool in the first and third application

B1	B1 final	p-value
2.10±1.25	2.35±1.46	0.001*

*Student's t-test: significant difference between the first and last evaluation.

(B1 e B1 final) values relating to the question "How much does feeling tired prevent you from doing what you want to do?"

Table 5 details the variables obtained through anthropometric evaluations, in which there was a significant difference in the PWL variable in the three moments of application, that is, from the first application to the third and from the second application again to the third and last.

As described in Table 6, there was a direct relationship between fatigue, through the Fatigue Pictogram, at the third moment of application with nutritional status, also at the third moment of application, according to the results obtained with the final SGA score (R = 0.484; p = 0.031).

Table 5: Description of the anthropometric variables of patients undergoing chemotherapy, collected at the three time points

Variables	M1	M2	M3	(df)F*
	Mean±SD	Mean±SD	Mean±SD	η ² (p)
				(2.38) 0.514 0.26
BMI	27.06±4.93	26.92±4.87	27.01±4.94	0.524 (2.38) 0.458 0.24
Weight	71.8±13.79	71.48±13.82	71.71±13.98	0.547 (2.38) 12.53 0.397
PWL	5.96±6.32	0.63±1.31Δ	0.96±1.62Ω	0.002* (2.38) 1.867 0.89
AC	26.81±3.43	26.61±3.49	26.55±3.33	0.175 (2.38) 0.984 0.49
CC	32.3±4.59	32.37±4.72	32.15±4.76	0.364 (1.19) 0.487 0.25
TSF	19.05±8.88	19.35±8.74	19.45±8.91	0.494

* ANOVA of repeated measures ΩBonferroni poshoc with significant difference between first and third application; Δ Bonferroni poshoc with significant difference between first and second application.

(M1) Moment 1; (M2) Moment 2; (M3) Moment 3; (BMI) Body mass index; (PWL) Percentage of weight loss; (AC) Arm circumference; (CC) Calf circumference; (TSF) Triceps skinfold.

Table 6: Correlation between fatigue and nutritional status (Fatigue Pictogram vs SGA)

		SGA 1	SGA 2	SGA 3
Pictogram 1	R	0.247	0.424	0.409
	p	0.293	0.062	0.062
Pictogram 2	R	0.224	0.400	0.382
	p	0.342	0.081	0.096
Pictogram	R	0.293	0.303	0.484*
	p	0.210	0.024	0.031

*Pearson's correlation; (Pictogram 1) Pictogram 1st application; (Pictogram 2) Pictogram 2st application; (Pictogram 3) Pictogram 3st application; (SGA 1) Patient-Generated Subjective Global Assessment 1st application; (SGA 2) Patient-Generated Subjective Global Assessment 2st application; (SGA 3) Patient-Generated Subjective Global Assessment 3st application; (R) Pearson Correlation Test; (p) p-value.

DISCUSSION

Fatigue and worsening of nutritional status are common symptoms in cancer patients, but they receive little attention in everyday clinical practice, but their identification, their mechanisms of occurrence, and adequate quantification are essential for the application of appropriate therapies¹⁵.

Most participants were diagnosed with colon cancer, followed by breast cancer, a similar result obtained in the validation of the Fatigue Pictogram for Portuguese, applying the tool in 584 patients, undergoing chemotherapy or radiotherapy in two different times, with a significant correlation between the responses of the first and second evaluation, corroborating the finding in this research¹⁶.

Breast cancer patients undergoing chemotherapy may have a higher level of fatigue during the middle of the cycle, already in the last application, they can recover from the symptom, in addition, when asked about the activities of daily living, the answers follow the same pattern as the first question, with the most limited patients in the second application and in the last application already recovered and with less complaint of fatigue¹⁷.

The results are similar to those found in the present research, since the amount of participants who reported moderate fatigue in the second application increased when compared to the beginning of the cycle, but this amount decreases again in the last response, in addition, no participant reported severe fatigue in the second and third application. The results of the second question of the pictogram are divergent from those obtained by Vaz *et al.*¹⁷, since the numbers show that there is no difference regarding the interference of fatigue in daily activities.

It is important to emphasize that the study by Vaz *et al.*¹⁷ was carried out with patients with a specific neoplasm and performing a specific chemotherapy protocol, which may justify the difference in results when compared to the present findings, since patients with different types of neoplasms were included, performing different chemotherapy protocols, which can bring different adverse effects, being important to identify these factors that can influence fatigue and its impact on activities of daily living.

An important clinical issue within oncology is the risk of deteriorating nutritional status. Although most of the sample in this study had adequate or high BMI, respectively 35% and 55% of the individuals at the first and last time points had some degree of malnutrition according to the categorical classification of the PG-SGA.

Similar findings were found in a Brazilian study that evaluated the nutritional status of cancer patients undergoing chemotherapy treatment, where, when comparing BMI with PG-SGA, it was observed that patients who were eutrophic, overweight or obese by BMI were classified as moderately malnourished according to the subjective global assessment¹⁸.

In addition, when evaluating 99 individuals, 60.6% of them were eutrophic according to BMI and only 31.3% were well nourished according to the PG-SGA¹⁹, values compatible with those obtained in the present study, where 60% of the patients were eutrophic, among them only 30%

were classified as well nourished in M1 and 25% in M3.

These results suggest that PG-SGA can more accurately identify cancer patients who are malnourished or at risk of malnutrition than BMI, since BMI measurement alone is insufficient for nutritional diagnosis¹⁸. It is important to note that in the present study, 40% of the sample was diagnosed with breast cancer, a neoplasm with a lower rate of malnutrition and a higher prevalence of overweight.

Changes in nutritional status were also identified when evaluating 153 individuals with gastric cancer at two moments of chemotherapy, in which their sample showed an increase in the rates of malnourished patients and at risk of malnutrition when comparing the first and second evaluation based on the MNA (mini nutritional assessment)²⁰.

Involuntary weight loss (IWL) is a frequent manifestation in cancer patients, its etiology is multifactorial and is related to physiological and pathological changes caused by cancer. The present study observed a prevalence of 65% of involuntary weight loss before starting chemotherapy treatment, a result similar to that found in the study by Silva and Bernardes²¹, which identified that more than half of their study population (67.5%), presented moderate or severe IWL.

On the other hand, the mean percentage of weight loss between the first and last collection was 0.965%, in which 40% (n=9) of the patients presented weight loss in this period, however, only 3 individuals presented significant loss (1-2% in 1 week or $\geq 5\%$ in one month). Contrary to the study presented by Carvalho *et al.*²², in which they observed a 40% frequency of severe weight loss in patients during chemotherapy treatment.

When evaluating the correlation between nutritional status and fatigue, it was seen that there was a direct but weak correlation, at the last moment of the evaluation, between the two variables, however, research that compares the relationship between them is scarce in the literature, some studies have identified direct associations between nutritional status and fatigue, which was the case with patients in the postoperative period of colorectal cancer, in which the intensity of fatigue was strongly associated with a worse nutritional status²³.

A similar result was seen by Sharour²⁴, so that the population studied was also patients with colorectal cancer, finding that in addition to an association between the presence of fatigue as one of the indications of a worse nutritional status, there was also a relationship with laboratory markers, such as sodium, potassium and hemoglobin levels.

It is important to understand the main adverse effects that can affect patients during chemotherapy so that interventions can be developed to improve or minimize these main findings, such as physical activity, for example, which can reduce fatigue levels and improve the nutritional status in this patients²⁵⁻²⁶.

CONCLUSION

Fatigue is present in most cancer patients during chemotherapy, impacting on their daily activities, increasing significantly during treatment, in addition,

nutritional status tends to worsen throughout chemotherapy sessions, with a direct but weak relationship between fatigue and nutritional status.

Author Contributions

All authors contributed to the manuscript. Bruna Cunha de Souza: Responsible for the development, data collection and writing of the study. Gabriela Crysthyna Ferreira Silva: Responsible for the development, data collection and writing of the study. Juliana Zangirolami-Raimundo: Responsible for the statistical analysis of the study. Olider Gardin Jr: Responsible for writing the study. Cintia Freire Carniel: Responsible for writing the study. Rodrigo Daminello Raimundo: Study coordinator. Responsible for developing and writing up the study.

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Conflicts of Interest

The authors report no conflict of interest.

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Resumo

Introdução: a quimioterapia pode contribuir para o comprometimento do estado nutricional e aumento da fadiga.

Objetivo: o objetivo deste estudo é avaliar a influência da quimioterapia no estado nutricional e na fadiga oncológica.

Métodos: trata-se de um estudo com pacientes em tratamento quimioterápico. A coleta de dados foi realizada na primeira sessão de quimioterapia, no meio e na última sessão.

Resultados: a amostra final foi composta por 20 pacientes. Houve aumento no nível de fadiga ($p < 0,05$) e diferença no percentual de perda de peso ($p < 0,05$). Foi encontrada relação direta entre fadiga e estado nutricional ($R = 0,484$; $p = 0,031$).

Conclusão: houve aumento da fadiga durante a quimioterapia e piora do estado nutricional ao longo das sessões, havendo relação direta entre fadiga e estado nutricional.

Palavras-chave: Neoplasias; estado nutricional; fadiga; quimioterapia; agentes antineoplásticos; evento adverso.

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