Influence of chemoradiotherapy on nutritional status, functional capacity, quality of life and toxicity of treatment for patients with cervical cancer

Influência da quimiorradioterapia no estado nutricional, capacidade funcional, qualidade de vida e toxicidade do tratamento para pacientes com câncer cervical

Mariah Azevedo Aredes[1]
Marcelly Ricci Garcez[2]
Gabriela Villaça Chaves[3]

Keywords:
Cervical Cancer, Uterine. Drug-Related Side Effects and Adverse Reactions. Chemoradiotherapy. Nutritional Status. Quality of Life.

Unitermos:
Câncer de Colo Uterino. Efeito Colateral. Quimiorradioterapia. Estado Nutricional. Qualidade de Vida.

Endereço para correspondência:
Gabriela Villaça Chaves
Hospital do Câncer II – Instituto Nacional de Câncer (INCA)
Rua Equador, 831 – Santo Cristo – Rio de Janeiro, RJ, Brasil – CEP: 20220-410
E-mail: gabrielavc@gmail.com

Submissão:
18 de agosto de 2017

Aceito para publicação:
7 de outubro de 2017

ABSTRACT

Introduction: The adverse effects provoked by antineoplastic therapy may aggravate preexisting alterations of the nutritional status and can result in a larger chance of toxicity, bringing about other adverse consequences, such as a diminished response and tolerance of the treatment and reduction of quality of life (QoL). **Objective:** The objective of this study was to assess the influence of chemoradiotherapy on the nutritional status, functional capacity, and quality of life (QoL), associating these indicators with toxicity and interruption of oncologic treatment in women with cervical cancer. **Methods:** Prospective cohort study performed on 49 women, who underwent treatment between August 2015 and January 2016. For data collection, two appointments took place with the researcher in charge: the first one occurring the day before the first chemotherapy session (T0) and the other one after 35 days (T1). Nutritional status was measured by anthropometry and computed tomography (skeletal muscle index – SMI), functional capacity by handgrip strength (HGS) and Karnofsky Perfomace Status (KPS), and application of QoL questionnaire (EORTC QLQ-C30). **Results:** There was significant reduction in weight, BMI, HGS, KPS and QoL between T0 and T1. The interruption of chemotherapy was significantly associated with the variables of nutritional status assessed, in addition to a significant QoL reduction according to worsening nutritional status. Women that interrupted their treatment due to acute toxicity also had an SMI median significantly smaller in relation to those who concluded the treatment and 83% of these patients presented cachexia. **Conclusion:** Chemoradiotherapy treatment in patients with cervical cancer had changed negatively nutritional parameters, function capacity and QoL.

RESUMO

Introdução: Os efeitos adversos provocados pela terapia antineoplásica podem agravar alterações preexistentes do estado nutricional, que resultam em maior chance de toxicidade, além de outras consequências adversas, como diminuição da resposta e tolerância ao tratamento e redução da qualidade de vida (QV). **Objetivo:** O objetivo do estudo foi avaliar a influência da quimiorradioterapia sobre o estado nutricional, capacidade funcional e QV, associando esses indicadores à toxicidade e interrupção do tratamento oncológico em mulheres com câncer de colo uterino. **Método:** Foi realizado um estudo de coorte prospectivo com 49 mulheres submetidas ao tratamento quimiorradioterápico entre agosto de 2015 e janeiro de 2016. Para coleta de dados, foram realizadas duas consultas com o pesquisador responsável: a primeira ocorreu no dia anterior à primeira sessão de quimioterapia (T0) e a outra após 35 dias (T1). Em ambas as consultas, o estado nutricional foi avaliado por antropometria, a capacidade funcional pela força de preensão palmar (FPP) e pelo Karnofsky Performance Status (KPS) e foi aplicado um questionário específico para QV (EORTC QLQ-C30). Adicionalmente, foi utilizada a tomografia computadorizada para avaliação da massa magra (índice de músculo esquelético - IME) disponível no T0. **Resultados:** Houve redução significativa no peso, IMC, FPP, KPS e QV entre T0 e T1. A interrupção da quimioterapia foi significativamente associada às variáveis de estado nutricional, além de uma redução significativa da QV de acordo com a piora do estado nutricional. As mulheres que interromperam seu tratamento devido à toxicidade aguda também apresentavam mediana de IME significativamente menor em relação àquelas que concluíram o tratamento e 83% dessas pacientes apresentaram caquexia. **Conclusão:** O tratamento quimiorradioterápico em pacientes com câncer de colo uterino impactou negativamente nos parâmetros nutricionais, na capacidade funcional e na QV.

1. Mestranda do Programa de Pós-Graduação em Oncologia do Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), Rio de Janeiro, RJ, Brasil.
2. Graduanda em Nutrição, Iniciação Científica do Instituto Nacional de Câncer (INCA), Rio de Janeiro, RJ, Brasil.
3. Nutricionista, PhD, Departamento de Nutrição Hospital do Câncer II/INCA, Rio de Janeiro, RJ, Brasil.

INTRODUCTION

Cervical cancer represents the fourth most common neoplasia in the female population and one of the main causes of death among women worldwide[1]. In Brazil it is the third most common, excluding non-melanoma skin tumors, and according to the estimates of the National Institute of Cancer, 16,340 new cases were expected for 2016[2]. The majority of instances of cervical cancer occur in developing countries[1], with close to 50% diagnosed in advanced stage[3]. In this treatment weekly chemotherapy with cisplatin were given concomitantly with external-beam radiotherapy[4,5].

Cisplatin is the most effective cytotoxic agent against cervical cancer[6]. The administration with combination of radiotherapy to the whole pelvic region and the dose being divided into daily applications (25 fractions), is suggested as the first line of treatment for patients with locally advanced cervical cancer (stage II through IVA according to the staging system of the International Federation of Gynecology and Obstetrics)[4].

The incidence of toxicity described in chemoradiotherapy is elevated, with hematologic[7] and gastrointestinal toxicity being the most commonly found in these cases[8]. The presence of symptoms with a nutritional impact, such as nausea, vomiting, and anorexia can reduced nutritional intake and accelerates muscle loss[9] which results in impaired muscle function[10]. This depletion may reflect on different functional tests, such as hand grip strength (HGS), a good indicator of nutrition status and clinical outcome[10,11].

The adverse effects provoked by antineoplastic therapy may aggravate preexisting alterations of the nutritional status, creating a vicious cycle. This way, the depletion of the nutritional status can result in a larger chance of toxicity due to the combined oncologic treatment and bring about other adverse consequences, such as a diminished response and tolerance of the treatment and reduction of quality of life (QoL)[12]. Study in gynecological cancer patients indicated that nutritional status is a strong predictor of QoL in cancer patients[13]. On the other hand, QoL has also been used for assessing the tolerance to oncologic treatment, being essential to the measurement of the side effects of chemotherapy[14].

Despite the limited literature, an increased frequency of malnutrition has been shown in patients with cervical cancer, especially in women diagnosed in an advanced stage. However, the magnitude of the nutritional status alteration, the QoL and functional capacity that occur during the combined cancer treatment, and the relation between these factors and the treatment toxicity remain unknown. Therefore, the objective of this study was to assess the influence of chemoradiotherapy on the nutritional status, functional capacity, and quality of life; associating the patient's baseline indicators with toxicity and interruption of oncologic treatment in women with cervical cancer.

METHODS

Study Design and Data Collection

The present study is a prospective cohort, observational study, performed on women diagnosed with cervical cancer, registered in the National Institute of Cancer José Alencar Gomes da Silva, who have been proposed to undergo chemoradiotherapy. Inclusion criteria were all patients over 20 years old, who had never undergone prior treatment, had their diagnosis confirmed through histopathology report and underwent treatment between August 2015 and January 2016. Patients with HIV virus, kidney disease under dialysis treatment, with edema and/or ascites, having pacemaker or stent have been excluded.

The eligible patients were instructed about the project and all subjects gave written informed consent. The study was approved by the Research Ethical Committee of the institution under number 1150108/2015. Chemorradiotherapy treatment in Brazilian National Institute of Cancer consisted of weekly dose of cisplatin as the only type of chemotherapy, with a combination of daily doses of external-beam radiotherapy (25 fractions).

During the study period, 49 women diagnosed with cervical cancer with a chemoradiotherapy treatment proposal were enrolled. Of this group, 10 patients did not conclude treatment due to elevated toxicity from chemotherapy, one patient interrupted her treatment due to being diagnosed with pulmonary metastasis and four other patients abandoned treatment by their own choice. Therefore, the number of patients that concluded the proposed treatment and underwent evaluation at T1 was 34.

For data collection, two appointments took place with the researcher in charge: the first one occurring the day before the first chemotherapy session (T0) and the other one after 35 days (T1). The research interview included personal data (age, ethnicity, marital status); clinical history (histological type, stage, comorbidities) and data related to the oncologic treatment (type of chemotherapy, number of sessions, duration of treatment, and clinical intercurrences) - obtained from medical records; nutritional status (anthropometric measures and body composition assessment); QoL and functional capacity assessments. All notes and assessments were performed by the same trained researcher.

Nutritional Status

In T0 and T1, the anthropometry was performed by means of measurement of weight, height, mid-upper arm circumference (MUAC) and triceps skin fold thickness (TSF).

The patients were asked whether they had unintentional weight loss during the past 6 months. The calculation of the mid-arm muscle circumference (MUAMC) and corrected mid-upper arm muscle area (cMUAMA) was obtained using the values of MUAC and TSF, by means of specific formulas, and classified according to Frisancho[15]. The body mass index (BMI) was calculated using weight and height, and classified following the criteria of the World Health Organization and of the Pan American Organization of Health for the elderly. Likewise, percentage weight loss (%WL) was obtained using the following formula: Usual body weight – current body weight x 100/usual body weight.

Cancer cachexia was diagnosed following the International Consensus of Cachexia[16] that classifies cachexia into three stages: pre-cachexia, cachexia, and refractory cachexia. Pre-cachexia is defined as unintentional weight loss of up to 5% in six months with the presence of anorexia. Cachexia is defined as a loss of weight over 5% in six months, or the combination of weight loss >2% with a body mass index less than 20 kg/m^2. In refractory cachexia, patients do not present any response to antineoplastic therapy, with a limited functional capacity and a life expectation of less than three months. It was used the usual 6-month weight to calculate the percentage weight loss for cachexia diagnosis.

All patients enrolled who presented nutrition risk or malnutrition at T0 received nutritional counseling according to the hospital protocols.

Skeletal Muscle Mass Assessment

Skeletal muscle mass was assessed exclusively at T0, for patients who underwent computerized tomography (CT) up to 20 days before the first chemotherapy session. The CT assessment at T1 was not possible as this exam is not performed routinely after chemorradiotherapy. The skeletal muscle content for the diagnosis of sarcopenia was determined through analysis of the image of the cross section of the third lumbar vertebrae (L3). The images were analyzed using the software SliceOmatic 5.0 (Tomovision, Canada), allowing for specific demarcation of the skeletal musculature, expressed in Hounsfield Units (HU) in the range of -29 to +150[17]. The skeletal muscle index (SMI), that corresponds to the area of muscle tissue obtained from the image of the L3, normalized for height and expressed in cm^2/m^2, was used for sarcopenia classification, according to the cutoff established for women ($\leq$ 38.9 cm^2/m^2)[18].

Functional Capacity

The functional capacity was assessed by handgrip strength (HGS) using a dynamometer device (Jamar®), following the recommendations of the Brazilian Society of Hand Therapists[19]. The patient was asked to squeeze the dynamometer with as much strength as possible and the result was registered in kilograms (kg). Before beginning, a pre-test was performed so as to familiarize the patient with the device. The test consisted of two measurements, with a one-minute pause between each one, to later calculate the average.

Furthermore, Karnofsky performance scale (KPS) was performed by the same trained researcher and used for classifying the patients according to the degree of their functional disabilities, representing a general measurement of the independence of the individual in exercising self-care and their daily activities. The scale ranges between 0 and 100, the higher the value obtained, the better the performance of daily functions were assessed[20].

QoL Assessment and Oncologic Treatment Toxicity

QoL assessment was made by the questionnaire EORTC QLQ-C30, from the European Organization of Research and Treatment of Cancer (EORTC), validated for the Brazilian population[21]. EORTC QLQ-C30 comprises 30 items, divided into three parts. The first part addresses questions related to cognitive, functional, emotional, social and physical performance. The second part reports the individual's perception concerning her overall health. In both parts, a higher score relates to a good development of daily capacities. The last part presents the scale of symptoms and a higher score obtained in this questionnaire represents worsened symptoms.

For the evaluation of toxicity from radiotherapy and chemotherapy treatment, a specific questionnaire of National Cancer Institute Common Toxicity Criteria for adverse events, version 4.0, was used. The questionnaire determines the intensity of the symptoms presented, with a score ranging between 0 and 5.

Statistical Analysis

The data collected was stored in a database created in the statistical program SPSS version 22. Measures of central tendency and dispersion were calculated for continuous variables, and the proportions for categorical variables. Adherence to a normal curve was tested seeking to evaluate the symmetry of the distribution curve of the variables. A non-normal distribution of the variables was identified, except for age.

The difference between proportions was tested using the chi-squared test or Fisher's exact test. The difference between the medians was assessed by the non-parametric Mann-Whitney tests (independent variables) or Wilcoxon (related variables) for two groups, and the ANOVA Kruskal-Wallis test for more than two groups. For all of the analysis, p-value of $<.05$ was considered statistically significant.

RESULTS

The average age of the study population was 45±13.8 years old and the majority of patients being single or widow (61.2%). Concerning cancer stage, 81.6% of the women were diagnosed in stage II or III, the most prevalent histological type was squamous cell carcinoma (SCC) and 59.2% of the women did not present associated comorbidities (Table 1).

Concerning oncologic treatment, the median time of total duration of the treatment out of patients who completed the treatment (n=34) was 32 (26-47) days, and the amount of chemotherapy and radiotherapy sessions was 5 (5-6) and 22 (19-27) sessions, respectively. Regarding the patients who interrupted the chemotherapy, the median time of total duration of the treatment was 14 (8-32) days, and the amount of chemotherapy sessions was 3 (0-5). All the patients received the cisplatin as the only type of chemotherapy

Table 1 – Sociodemographic and clinical characteristics in baseline.

Variable	Results (n=49)
Age (years)[a]	45.0±13.8
Marital status[b]	
Single	25 (51.0)
Married	16 (32.7)
Divorced	3 (6.1)
Widow	5 (10.2)
Race/ethnicity[b]	
White	21 (42.9)
Pardo (mixed races)	22 (44.9)
Black	6 (12.2)
Comorbidities[b]	
No	29 (59.2)
Arterial hypertension	14 (28.6)
Arterial hypertension + Diabetes mellitus	3 (6.1)
Cardiac insufficiency	1 (2.0)
Others	2 (4.1)
Histological type[b]	
SCC	42 (85.7)
Adenocarcinoma	7 (14.3)
Cancer Stage †,[b]	
Stage I	9 (18.4)
Stage II	27 (55.1)
Stage III	13 (26.5)

SCC = squamous cell carcinoma; a = mean ± standard deviation; b = absolute number (percentage);
† Cancer stage classified as International Federation of Obstetrics and Gynecology (FIGO).

Toxicity and Interruption of Oncologic Treatment

Twenty point four percent (n=10) out of the 49 patients enrolled in the study discontinued chemotherapy due to severe toxicity, with the main causes being gastrointestinal (37.5%), hematologic (25%) and renal (25%). The interruption of radiotherapy occurred in only 8.2% of the patients in the study. Even when chemotherapy was interrupted due to severe toxicity, radiotherapy was maintained as the exclusive treatment.

The interruption of chemotherapy was significantly associated with the variables of nutritional status assessed in T0. Age over 65 years old, presence of comorbidities and the stage of the disease did not obtain a statistical difference (Table 2), as well as the summary score of QoL (Mann-Whitney Test; p=0.114). It is important to note that close to 83% of the patients that suspended their chemotherapy presented cachexia and %WL greater than 5%.

According to the Common Criteria of Toxicity (CCT), there was an incidence of symptoms related to chemoradiotherapy toxicity in 94% of the patients of the study, and approximately 79% reported at least one symptom with severity greater than grade II. The most frequent symptoms were: nausea (75.8%), fatigue (66.7%), diarrhea (60.6%), xerostomia (60.6%), dysgeusia (48.5%), pain (42.4%), constipation (27.3%), and vomiting (24.2%). The tested variables in Table 3 (age over 65 years old, comorbidities, stage, %WL, sarcopenia and cachexia) did not associate with the number or severity of symptoms outlined in the CCT (p>.05).

Influence of Chemoradiotherapy on Quality of Life, Nutritional and Funcional Parameters

Table 4 shows the parameters used for nutritional assessment, functional capacity and summary score for QoL before and after treatment with chemoradiotherapy, among patients who concluded the oncologic treatment (n=34). There was a significant reduction in weight, BMI, handgrip strength, KPS and QoL between T0 and T1. 41.2% of the population was diagnosed with pre-cachexia and cachexia in T0, and the stage of pre-cachexia doubled after treatment was completed. In relation to BMI classification before treatment, most of the patients showed an excess of weight (overweight and obese). However an increase in the frequency of malnutrition was observed after the completion of chemoradiotherapy (0% vs. 8.8%), as well as a reduction of the frequency of excess body weight (61.8% vs. 52.9%)

Figure 1 shows the difference between the nutritional status in patient´s baseline (T0) according to BMI or cachexia diagnosis in T0: 66.7% of the cachectic patients were classified as eutrophic according to BMI and 75% of the pre-cachectics were obese according to BMI. Moreover, more than half of the women with a BMI of ≥30 kg/m^2 were classified with pre-cachexia or cachexia.

Table 2 – Association of clinical variables and nutritional status with chemotherapy interruption.

Variables		Chemotherapy interruption		
		No n (%)	Yes n (%)	*p* value*
Age[a]	<65 years	32 (86.5)	9 (75.0)	0.350
	>65 years	5 (13.5)	3 (25.0)	
Comorbidities[a]	No	16 (59.3)	13 (59.1)	0.450
	Yes	11 (40.7)	9 (40.9)	
Cancer Stage[a]	Stage I	7 (18.9)	2 (16.7)	0.828
	Stage II	21 (56.8)	6 (50.0)	
	Stage III	9 (24.3)	4 (33.3)	
Percentage weight loss[b]	<5% in 6 months	25 (69.4)	2 (16.7)	0.001
	>5% in 6 months	11 (30.6)	10 (83.3)	
Diagnosis of Sarcopenia[c],[†]	No sarcopenia	28 (96.6)	6 (66.7)	0.011
	Sarcopenia	1 (3.4)	3 (33.3)	
Cachexia[a]	No cachexia	23 (62.2)	1 (8.3)	0.003
	Pre-cachexia	3 (8.1)	1 (8.3)	
	Cachexia	11 (29.7)	10 (83.3)	

a = study population equal 49 patients; b = total number equal to 48 patients because one patient was unable to report the usual weight; c = total number equal to 38 patients who had CT available at T0; † = muscle area analysis in the image of the cross section of the third lumbar (L3), and sarcopenia with skeletal muscle index (SMI) ≤ 38,9 cm^2/m^2; * Chi-square test.

Table 3 – Results of quality of life questionnaire (EORTC QLQ-C30) separated into its specific scales of patients with cervical cancer who completed the chemoradiotherapy treatment.

Variables	Results (n=34)				
	T0		T1		
	Mean	SD	Mean	SD	*p* value*
Summary score of QoL	75.03	16.34	69.77	15.56	0.006
Global health status	81.62	17.26	82.11	20.43	0.727
Physical function	78.24	19.72	69.41	24.73	0.037
Role function	72.55	34.30	53.92	37.17	0.047
Emotional function	57.11	30.09	62.25	33.41	0.334
Cognitive function	83.82	25.45	79.41	29.60	0.384
Social function	78.92	32.39	54.90	38.82	0.001
Total functional scale	71.10	18.97	64.84	19.42	0.041
Fatigue	27.78	26.84	37.91	30.72	0.132
Nausea and vomiting	13.40	22.06	27.94	26.50	0.001
Pain	34.31	31.50	23.53	32.08	0.141
Dyspnea	10.78	25.59	10.78	21.27	0.963
Insomnia	31.37	38.44	26.47	38.30	0.430
Appetite loss	12.74	24.64	27.45	37.13	0.048
Constipation	27.45	40.59	18.63	35.95	0.196
Diarrhea	1.96	7.96	40.20	39.17	0.0001
Financial difficulties	46.08	41.86	44.15	44.15	0.170
Total symptom scale	23.68	17.32	28.81	17.21	0.103

Summary score of QoL = (Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ 100-Fatigue+ 100-Pain+ 100-Nausea_Vomiting+ 100-Dyspnoea+ 100-Sleeping Disturbances+ 100-Appetite Loss+ 100-Constipation+ 100-Diarrhea)/13; * Wilcoxon test.

Table 4 – Nutritional assessment, functional capacity and quality of life before and after treatment of women with cervical cancer who completed chemo-radiotherapy.

Variables	Results (n= 34)		
	T0	T1	*p* value*
Weight (kg)[a]	67.0 (42 – 103)	66.15 (37.2 – 98)	0.003
BMI (kg/m^2)[a]	26.35 (17.48 – 43.56)	26.26 (16.10 – 41.78)	0.002
BMI classification[b]			
Underweight	0 (0)	3 (8.8)	
Healthy	13 (38.2)	13 (38.2)	
Overweight	21 (61.8)	18 (52.9)	
TSF (mm)a	25.0 (8 – 50)	25.5 (6 – 48)	0.936
***TSF classification[b]**			
Depletion	3 (8.8)	4 (11.8)	
No depletion	31 (91.2)	30 (88.2)	
MUAC (cm)[a]	29.8 (22 – 44)	30.0 (19.5 – 41.5)	0.687
MUAMC (cm)[a]	22.58 (17.88 – 31.71)	21.98 (17.51 – 27.52)	0.374
***MUAMC classification[b]**			
Depletion	3 (8.8)	5 (14.7)	
No depletion	31 (91.2)	29 (85.3)	
cMUAMA (cm^2)[a]	34.09 (18.96 – 73.55)	31.99 (17.91 – 53.81)	0.437
***MUAMA classification[b]**			
Depletion	2 (5.9)	5 (14.7)	
No depletion	32 (94.1)	29 (85.3)	
Percentage weight loss[b, †]			
<5%	22 (66.7)	22 (66.7)	
>5%	11 (33.3)	11 (33.3)	
Cachexia stage[b]			
No cachexia	20 (58.8)	17 (50.0)	
Pre-cachexia	3 (8.8)	6 (17.6)	
Cachexia	11 (32.4)	11 (32.4)	
HGS[a]	24.25 (10 – 32.5)	22 (12.5 – 33)	0.050
KPS (%)[a]	90 (60 – 100)	80 (60 – 100)	0.001
Summary score of QoL[a]	80.60 (27.56 – 100)	72.07 (30.13 – 97.78)	0.006

BMI = body mass index; TSF = triceps skinfold thickness; MUAC = mid-upper arm circumference; MUAMC = mid-arm muscle circumference; cMUAMA = corrected mid-upper arm muscle area; HGS = handgrip strength; KPS = Karnofsky performance scale; Summary score of QoL = (Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ 100-Fatigue+ 100-Pain+ 100-Nausea_Vomiting+ 100-Dyspnoea+ 100-Sleeping Disturbances+ 100-Appetite Loss+ 100-Constipation+ 100-Diarrhea)/13; a = median (minimum – maximum), Mann-whitney test; b = absolute number (percentage), Chi-square test; † = patient total equal to 33, because an individual did not know how to report the usual weight; * classified according to Frisancho (1990), percentile depletion ≤5 and percentile no depletion >5.

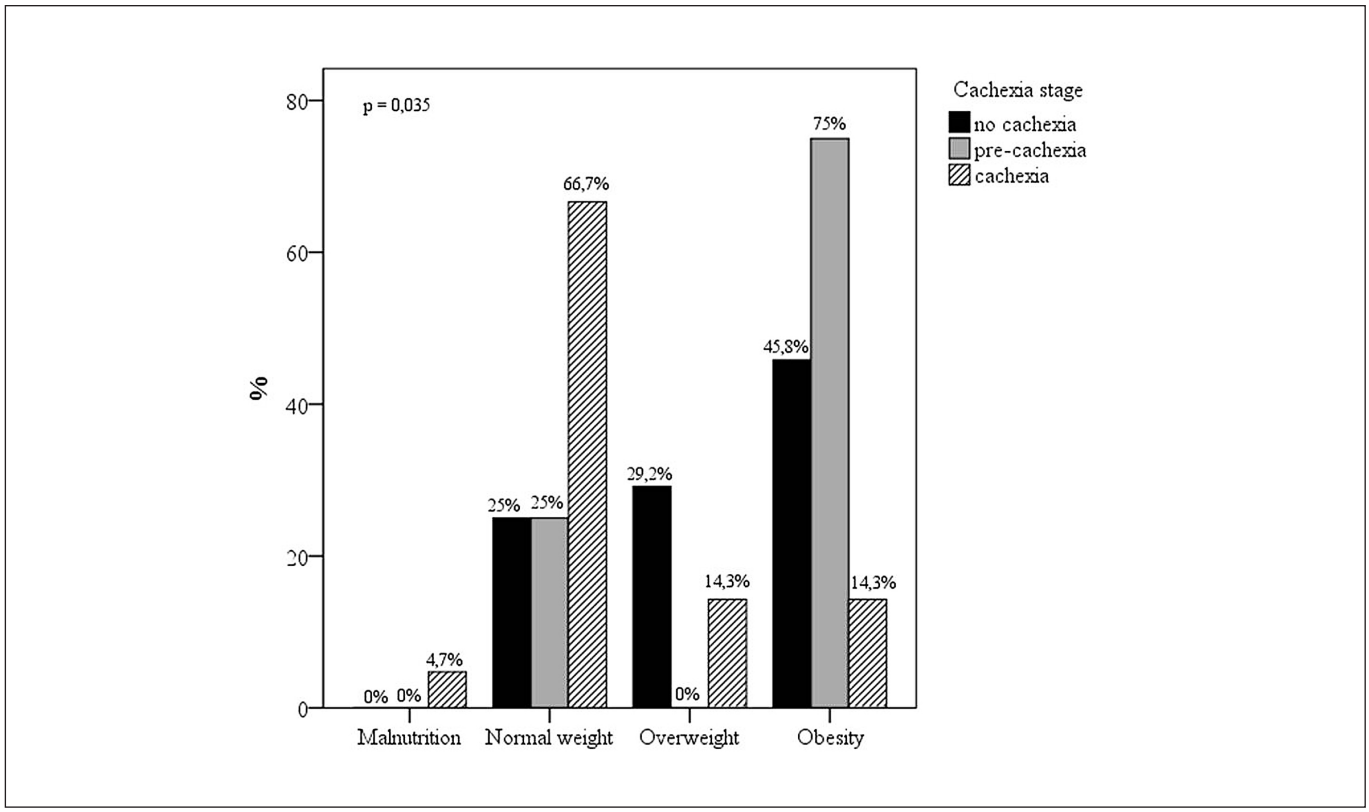

Figure 1 - *Body mass index according to cachexia diagnosis in baseline patient's.*

On the other hand, among the patients who had skeletal muscle index (SMI) assessed by CT bellow 38.9 cm^2/m^2, therefore sarcopenic, all of them presented a classification of cachexia according to Fearon et al.[16]. Meanwhile, patients with cachexia or pre-cachexia had SMI medians significantly less than those without a diagnosis of cachexia (no cachexia 51.02 [38.99-62.31]; pre-cachexia 48.82 [42.82 – 54.12]; with cachexia 40.85 [25.99 – 53.36] p=0.017) (Figure 2a). Women that interrupted their treatment due to acute toxicity from chemotherapy also had an SMI median significantly smaller in relation to those who concluded the treatment (39.57 [25.99 – 55.97] vs. 45.75 [36.42 – 62.31]; p=0.024) (Figure 2b).

The results obtained in the QoL assessment, separated into its specific scales, are presented in Table 3. When compared to the parameters assessed by the questionnaire between T0 and T1, there was a significant reduction in: physical capacity, role performance, social function and in the total functional scale. In the scale of symptoms, a significant increase was observed for the symptoms of nausea and vomiting, weight loss and diarrhea. The summary score of QoL also demonstrated a positive correlation between the nutritional status (NS) in both periods of evaluation (T0 and T1), as there was a significant reduction of the score according to worsening of NS (Table 5).

Table 5 – Summary score of quality of life obtained by the EORTC QLQ-C30 before and after chemoradiotherapy treatment according to nutritional status.

Nutritional Status Variables		Summary score of QoL (EORTC QLQ-C30)			
		T0 Median (min - max)	***p* value***	**T1** Median (min - max)	***p* value***
Percentage weight loss	< 5%	81.32 (50.81 – 100)	0.012	74.19 (38.72 – 97.78)	0,048
	≥ 5%	66.92 (27.56 – 93.08)		66.03 (30.13 – 90.51)	
Cachexia diagnosis	No cachexia	81.85 (50.81 – 100)	0.018	76.92 (38.72 – 97.78)	0,035
	Pre-cachexia	74.50 (57.52 – 87.39)		72.93 (56.50 – 90.51)	
	Cachexia	66.92 (27.56 – 93.08)		63.50 (30.13 – 76.50)	

* Mann-whitney test

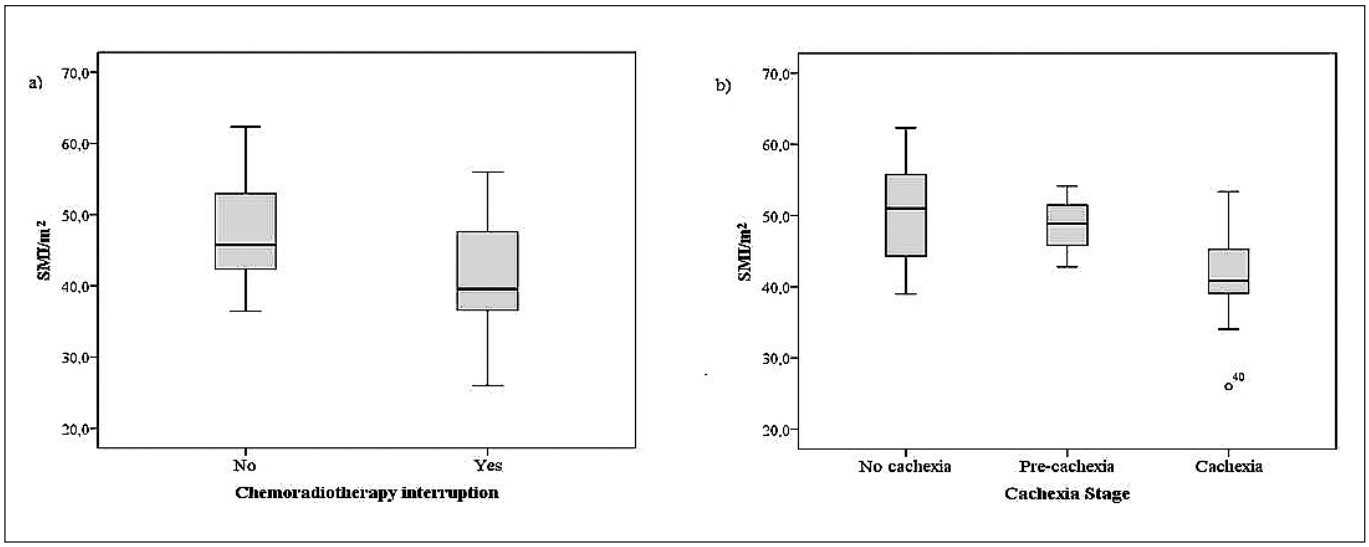

Figure 2 - *Comparison of pretreatment median values (in T0) of the skeletal muscle Index (SMI) according to (a) chemoradiotherapy interruption and (b) classification of cachexia..*

DISCUSSION

Considering that more than 50% of the patients with cervical cancer in developing countries are diagnosed in an advanced stage[3], chemoradiotherapy is the most frequent treatment used for this type of cancer, being chosen by patients that had a tumor size over 4 cm, when they are not indicated for surgery[4]. Chemotherapy enhances the effects of pelvic radiotherapy and provides greater efficiency against tumor cells[4]; however, the combined use of these oncologic therapies attacks both neoplastic cells and normal cells, increasing the risk of toxicity.

The present study registered treatment toxicity with a severity greater than grade II in about 80% of the sample. The gastrointestinal toxicities such as nausea and diarrhea are among the most common, corroborating other studies that find elevated incidence of toxicity in gynecologic tumors[8], in addition to the correlation between severity and the decline of the nutritional status[9]. The gastrointestinal symptoms can negatively impact the nutritional status by reduction of nutrient intake and the acceleration of muscular degradation, with worsened physical capacity and consequently QoL[22].

There are few studies that describe the nutritional status of patients with gynecological cancer. In this study, the nutritional profile of the patients with cervical cancer was obtained through different methods of nutritional assessment. According to BMI, 61.8% of the patients presented overweight. This result is even less than that described in a study performed by Kathiresan et al.[23], that found 75.8% of the patients with cervical cancer to be overweight upon diagnosis. A study of patients with different tumor sites, in chemotherapy, also observed an elevated prevalence of excess weight according to BMI, highlighting those patients that presented gynecologic tumors[24]. However, this study found a significant reduction in body weight and BMI, in addition to an increase in frequency of malnutrition after chemoradiotherapy treatment.

However, in spite of the low frequency of malnutrition diagnosed by BMI, close to 33% of the patients had cachexia and/or weight loss greater than 5% before the chemoradiotherapy. Other authors also reported weight loss from 26% to 40% among patients with gynecological cancer before treatment[25,26]. Weight loss and anorexia, present in cancer cachexia, can provoke a limitation in the doses of chemoradiotherapy, in addition to higher chances of treatment toxicity[27]. It has been suggested that %WL seems to be a better parameter than BMI in cancer patients that undergo chemotherapy[28] and a good prognosticator of Qol irrespective of the type of cancer[22].

Despite the wide use of anthropometric parameters for the determination of the nutritional status, BMI has a limited value since it is not capable of distinguishing the different body compartments[29]. The relevance of the quantification of muscle mass in cancer patients submitted to chemotherapy has increased in recent years due to the correlation between skeletal muscle content and the occurrence of toxicity that can determine a dose reduction or chemotherapy interruption[30].

Analyzing the variables that are correlated to the interruption of treatment, one can observe that only those related to the nutritional status presented a statistically significant association (diagnosis of cachexia and %WL). In addition, women that interrupted treatment had an SMI median significantly lower than those that did not interrupt treatment. Knowing the factors that can contribute to the reduction of toxicity risks is of utmost importance, and these factors suggest that the nutritional status before treatment

should be taken into consideration, recording not only body weight, but also %WL by the patient[31] and, whenever possible, the evaluation of the body composition. The lack of studies assessing the influence of chemoradiotherapy on nutritional status and QoL of cervical cancer patients makes this present study an important contribution to the identification of variables related to unfavorable outcomes to cancer treatment for this group.

According to the QoL parameters assessed in the questionnaire, a significant reduction in physical capacity, social function, total scale function and the summary score QoI after treatment was observed. Osann et al.[32] also showed that the application of radiotherapy associated with chemotherapy in patients with cervical cancer leads to a worsening of QoL. However, the perception of the patients concerning their overall health before and after the chemoradiotherapy treatment is considered to be satisfactory compared with the reference values of the EORTC for women with different cancer types and stages (59.3±24.9)[33].

QoL summary score in the study population showed a positive association between nutritional status at both points of evaluation, with a significant reduction of the score according to the worsening of nutritional status. Data of the present study corroborate findings in literature, that also observed values of QoL significantly less among cancer patients that presented larger weight loss or malnutrition, since malnutrition is considered an independent factor in the deterioration of QoL[13,22]. A recent systematic review concluded that the worsening of nutritional status is significantly related to the QoL reduction of cancer patients, independently of the site of tumor[22].

Some limitations of the study should be pointed out. The small sample size limited a detailed statistical analysis, especially the analysis between the different groups according their nutritional status. In addition, the inclusion of all cervical cancer patients who underwent chemoradiation therapy resulted in a sample with different stages of the disease, which may interfere with the different outcomes of oncologic therapy. Moreover, because it was an obsevational study, with a descriptive character on the influence of chemoradiotherapy treatment in a given population, it was not possible to perform the CT scan after treatment to confirm the changes in nutritional status related to body composition.

CONCLUSION

In accordance with the results of the present study, the combination of chemotherapy and radiotherapy for the treatment of cervical cancer caused significant reduction in weight and an increase in the frequency of malnutrition. In addition, significant impairment in function capacity and QoL were observed after the oncological treatment. The summary score of QoL also demonstrated a significant reduction according to worsening of nutritional status. The vast majority of patients who had chemotherapy suspended presented pre-cachexia or cachexia and significant pre-treatment weight loss.

The present study demonstrates the need to perform further studies for the target population, with nutritional intervention and joint action with oncologists, seeking to prevent or reduce treatment complications and consequently the optimization of chemoradiotherapy. Moreover, determining and recording the risk factors for interrupting antineoplastic therapy should be taken into account prior to treatment.

REFERENCES

1. Globocan. International Agency for Research on Cancer. Lyon; 2012 [cited 2017 Nov 30]. Available from: http://globocan.iarc.fr/Default.aspx
2. Brazil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva - INCA. Estimativa 2016: Incidência de câncer no Brasil. Brasília: Ministério da Saúde; 2016.
3. Thuler LCS, Bergmann A, Casado L. Profile of the patients with cervical cancer in Brazil, 2000-2009: secondary base study. Rev Bra Cancerol. 2012;58(3):351-7.
4. US Department of Health and Human Services. NCI Clinical Announcement. Bethesda: Public Health Service, National Institutes of Health; 1999.
5. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet. 2001;358(9284):781-6.
6. Omura GA. Chemotherapy for cervix cancer. Semin Oncol. 1994;21(1):54-62.
7. Kirwan JM, Symonds P, Green JA, Tierney J, Collingwood M, Williams CJ. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol. 2003;68(3):217-26.
8. Maduro JH, Pras E, Willemse PH, Vries EG. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. Cancer Treat Rev. 2003;29(6):471-88.
9. Hill A, Kiss N, Hodgson B, Crowe TC, Walsh AD. Associations between nutritional status, weight loss, radiotherapy treatment toxicity and treatment outcomes in gastrointestinal cancer patients. Clin Nutr. 2011;30(1):92-8.
10. Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr. 2011;30(2):135-42.
11. Hamada Y. Objective Data Assessment (ODA) methods as nutritional assessment tools. J Med Invest. 2015;62(3-4):119-22.
12. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, et al.; ESMO (European School of Medical Oncology). Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Ann Oncol. 2014;25(8):1492-9.
13. Gil KM, Gibbons HE, Jenison EL, Hopkins MP, von Gruenigen VE. Baseline characteristics influencing quality of life in women undergoing gynecologic oncology surgery. Health Qual Life Outcomes. 2007;5:25.
14. Fernandes WC, Kimura M. Health related quality of life of women with cervical cancer. Rev Latino Am Enferm. 2010;18(3):360-7.
15. Frisancho A. Anthropometric standards for the assessment of growth and nutritional status. Ann Arbor: University of Michigan Press; 1991.

16. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.
17. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85(1):115-22.
18. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.
19. Abdalla IM, Brandão MC. Forças de preensão palmar e da pinça digital. In: Sociedade Brasileira de Terapeutas da Mão. Recomendações para avaliação do membro superior. 2ª ed. São Paulo: SBTM; 2005.
20. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. Cancer. 1948;1(4):634-56.
21. Franceschini J, Jardim JR, Fernandes AL, Jamnik S, Santoro IL. Reproducibility of the Brazilian Portuguese version of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire used in conjunction with its lung cancer-specific module. J Bras Pneumol. 2010;36(5):595-602.
22. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer: a systematic review of the epidemiological literature. Nutr J. 2012;11:27.
23. Kathiresan AS, Brookfield KF, Schuman SI, Lucci JA 3rd. Malnutrition as a predictor of poor postoperative outcomes in gynecologic cancer patients. Arch Gynecol Obstet. 2011;284(2):445-51.
24. Tartari RF, Busnello FM, Nunes CHA. Perfil nutricional de pacientes em tratamento quimioterápico em um ambulatório especializado em quimioterapia. Rev Bras Cancerol. 2010;56(1):43-50.
25. Laky B, Janda M, Bauer J, Vavra C, Cleghorn G, Obermair A. Malnutrition among gynaecological cancer patients. Eur J Clin Nutr. 2007;61(5):642-6.
26. Das U, Patel S, Dave K, Bhansali R. Assessment of nutritional status of gynecological cancer cases in India and comparison of subjective and objective nutrition assessment parameters. South Asian J Cancer. 2014;3(1):38-42.
27. Arrieta O, Michel Ortega RM, Villanueva-Rodríguez G, Serna-Thomé MG, Flores-Estrada D, Diaz-Romero C, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. BMC Cancer. 2010;10:50.
28. Sánchez-Lara K, Ugalde-Morales E, Motola-Kuba D, Green D. Gastrointestinal symptoms and weight loss in cancer patients receiving chemotherapy. Br J Nutr. 2013;109(5):894-7.
29. Purcell SA, Elliott SA, Kroenke CH, Sawyer MB, Prado CM. Impact of body weight and body composition on ovarian cancer prognosis. Curr Oncol Rep. 2016;18(2):8.
30. Antoun S, Borget I, Lanoy E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. Curr Opin Support Palliat Care. 2013;7(4):383-9.
31. Bozzetti F; SCRINIO Working Group. Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. Support Care Cancer. 2009;17(3):279-84.
32. Osann K, Hsieh S, Nelson EL, Monk BJ, Chase D, Cella D, et al. Factors associated with poor quality of life among cervical cancer survivors: implications for clinical care and clinical trials. Gynecol Oncol. 2014;135(2):266-72.
33. Scott NW, Fayers PM, Aaronson NK, Bottomley A, Graeff A, Groenvold M, et al. EORTC QLQ-C30 Reference Values. This manual presents reference data for the QLQ-C30 based upon data provided by EORTC Quality of Life Group Members and other users of the QLQ-C30. July 2008. [cited 2017 Dec 4]. Available from: http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual2008.pdf

Local de realização do estudo: Instituto Nacional de Câncer (INCA), Rio de Janeiro, RJ, Brasil.

Trabalho apresentado no XVIII Fórum Paulista de Pesquisa em Nutrição Clínica e Experimental no GANEPÃO 2016, 70 Internacional Conference of Oncology/ Congresso Brasileiro de Nutrição e Câncer (ICNO/CBNC), Congresso Internacional de Nutrição, Exercício e Saúde (NEXSA) realizado de 15 a 18 de junho de 2016, no Centro de Convenções Rebouças – SP na modalidade de Temas Livres com o trabalho intitulado Impacto do tratamento quimiorradioterápico no estado nutricional, capacidade funcional e qualidade de vida em pacientes com câncer de colo de útero.

Conflito de interesse: Os autores declaram não haver.