

Prevalence of Cachexia After Curative Cisplatin-Based Concurrent Chemoradiation in Head and Neck Cancers

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Research Article

Keywords: head neck cancer, sarcopenia, atrophy, muscle wasting

Posted Date: April 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-447761/v1>

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Abstract

Purpose

We determine the frequency of cachexia among head and neck squamous cell carcinoma patients treated with cisplatin-based chemoradiation with curative intent and presenting no evidence of disease.

Methods

Consecutive patients were included from January 2014 to February 2017. Participants were over 18 y.o. and diagnosed with head and neck squamous cell carcinomas previously treated with definitive or adjuvant chemoradiation. Eligible patients were in regular follow-up for at least 2 years, with no evidence of disease. Body weight, height, mid-arm muscle circumference, muscle strength, and nutritional status were measured, and blood tests were obtained. The main outcome was the presence of cachexia, and self-reported dysphagia.

Results

120 patients were included, 73% were male, and age was 59 y.o. (range, 21–78). The most common primary site was oropharynx (42%). Median follow-up was 42 mo. (range, 24–125 mo.). Most patients presented locally advanced disease at diagnosis: 73% T3-T4 and 72% N+. Dysphagia was a major complaint (73%). Cachexia was diagnosed in 23 (20.7%) and 10 (8.6%) patients according to Fearon and Evans criteria, respectively. Cachectic patients presented lower mid-arm muscle circumference ($p < 0.05$). In addition, lower muscle strength levels ($p < 0.05$) were found among cachectic patients according to Evans criteria, and there was an association between the presence of dysphagia and the diagnosis of cachexia.

Conclusions

Head and neck squamous cell carcinoma patients with no evidence of disease frequently present cachexia after chemoradiation in a long-term follow-up. More effective preventive and therapeutic strategies for cachexia are required in this scenario.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for more than 90% of the cancers of the head and neck. Approximately 2% of all cancer-related deaths occur in HNSCC patients. Exposure to tobacco, alcohol and human papillomavirus infection are the most related causes. More than 60% of all HNSCC patients are diagnosed with locally advanced disease[1, 2], and they are treated with surgery followed by adjuvant radiation therapy, delivered as a single modality or concurrently with cisplatin, or with definitive cisplatin-based concurrent chemoradiotherapy, in the curative setting[1, 2].

The 5-year overall survival rate is increasing over the recent decades, reaching approximately 60%[3–6] as a consequence of advances in diagnosis and treatments, better patient selection and multidisciplinary approach. However, HNSCC patients with no evidence of disease after treatment completion usually present a high frequency of late treatment-related toxicities (e.g., dysphagia, xerostomia, hypothyroidism, ototoxicity, osteoradionecrosis, and dental problems, among others)[7–9] with a negative impact in terms of survival and quality of life[10–12].

Cancer cachexia (CC) is a syndrome characterized by muscle loss, with or without loss of adiposity, which cannot be reverted by food support[13], and sometimes linked to dysphagia, one of the most common post-treatment symptoms in these HNSCC patients (25-67%)[10–12]. Cachexia pathophysiology is not completely understood. Cachectic patients show increased systemic inflammation and general metabolic dysfunction, which culminates in muscular atrophy, loss of muscular function, and fatigue.[14, 15].

The diagnosis of cachexia is generally based on body weight loss and there are several diagnostic criteria for cancer cachexia[16, 17]. Fearon et al (2011) defined cachexia based on the presence of a weight loss >5% over the past six months; or body mass index (BMI) <20 kg/m² and any degree of weight loss >2% over the past six months; or sarcopenia. Following these criteria, Jager-Wittenaar (2017) detected a 42% prevalence of cachexia in newly diagnosed HNSCC patients, which negatively impacted on quality of life (QoL), cancer morbidity, treatment completion, and it was also related to lower overall survival rates¹⁸, [18]. Evans diagnostic criteria (2008) defined cachexia based on the presence of a 5% weight loss in 12 months or less, or BMI <20 kg/m², plus three out of the following five criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, or abnormal biochemistry (increased C-reactive protein > 5.0 mg/L; low hemoglobin < 12 g/dL, and low serum albumin <3.2 g/dL)¹⁷. In a retrospective study, 361 consecutive HNSCC patients were evaluated according to the Evans criteria, pre, immediately after, 6, and 12 months post-treatment. The frequency of cachexia was 6.1%, 41%, 18.4%, and 18.7% respectively, and the presence of cachexia in this population was related to higher chances of both cancer recurrence and death[19].

Although it remains speculative, treatment-related toxicities are considered among the main causative reasons for cachexia after cancer treatment in disease-free patients[20]. No standard treatment is effective in reversing or preventing cachexia, but a multimodal approach including physical exercise, nutritional support, and medications can be considered on an individual basis. Here, in a cross-sectional observational study, we aimed to determine the cachexia frequency in HNSCC patients using the Fearon and Evans abovementioned diagnostic criteria after chemoradiotherapy in the curative setting.

Methods

Patient Selection

This is a cross-sectional observational study. We consecutively recruited 120 HNSCC survivors treated in our hospital from 2014 to 2017. Eligible patients were older than 18 y.o. and had a histological diagnosis of squamous cell HNSCC, primarily located in nasopharynx, oropharynx, hypopharynx, larynx, or oral cavity. In addition, patients must have received definitive or adjuvant cisplatin-based chemoradiotherapy and must have been followed up for at least two years after the end of the treatment. At the study entry, all patients were considered disease-free based on clinical, radiological, and endoscopic regular studies. Patients with synchronous second tumors or other primary neoplasm were excluded. The Institutional review board of the Instituto do Câncer do Estado de São Paulo /Faculdade de Medicina da USP approved this study (1.339.832). All patients signed informed consent before any study-related activity. Importantly, all patients received regular clinical assessment and monitoring of nutritional support before and during cancer treatment, and also during their follow-up, following local institutional protocols.

Data assessment

All assessments were made at the same visit. Body weight (kg) was measured using electronic scales and standing height (cm) was measured using a stadiometer. Mid-arm muscle circumference was obtained by the circumference of the left upper arm, measured at the midpoint between the tip of the shoulder and the tip of the elbow. Albumin, hemoglobin, C-reactive protein (CRP), and clinical data were obtained through medical records. Grip strength was measured using a hand dynamometer (Model 5030L1, Indiana, USA). The examiner first demonstrated the procedure and then gave the dynamometer to the subject. After that, the participant was positioned appropriately. The test was performed in the sitting position with the elbow in a 90° flexion. Participants were instructed to exert maximal force. Three attempts with each arm were made with a 90 seconds interval and the results were then recorded. The maximum force considered was the greatest value obtained from each individual (kgf). Each patient filled the Patient-Generated Subjective Global Assessment (PG-SGA) Short Form. This questionnaire provides information about weight, food intake, symptoms, functional status, disease state, metabolic stress, and nutritional physical examination. All variables were summed, and the data presented in a grouped manner. Moreover, the patients were categorized into three groups A (well-nourished), B (moderately malnourished), and C (severely malnourished).

Cachexia diagnoses

Patients were classified as cachectic using the following two diagnostic criteria:

- Fearon et al. (2011): weight loss >5% over past 6 months (in absence of simple starvation); or BMI <20 kg/m² and any degree of weight loss >2%; or appendicular skeletal muscle index consistent with sarcopenia (mid-arm muscle area) and any degree of weight loss >2%[16].
- Evans et al. (2008): weight loss of at least 5% in 12 months or less , or BMI <20 kg/m², plus three of the following five criteria: decreased muscle strength (defined as low level of strength according to the age [21]); fatigue (as referred by patients); anorexia (as referred by patients); low fat-free mass

index according mid-arm muscle circumference; or abnormal biochemistry (increased C-reactive protein > 5.0 mg/L, low hemoglobin < 12 g/dL, and low serum albumin <3.2 g/dL)¹⁷.

Statistical Analysis

Analyses were performed in GraphPad Prism, Version 7.0 (GraphPad Software, La Jolla, USA) and IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, USA). All patients were included in descriptive statistics. Patients' characteristics were depicted and presented as mean \pm standard deviation (SD) or range, or their frequency and percentage. In order to compare cachectic and non-cachectic patients, the values of each variable were firstly tested to normal Gaussian distribution using the Shapiro-Wilk normality test and, when appropriate, compared by unpaired two-tailed T-test or Mann-Whitney test. Frequencies were compared by Fisher's Exact Test. Patients with missing data for cachexia were not included in group comparisons. Results were considered statistically significant at $p < 0.05$.

Results

The characteristics of the included patients are shown in table 1. The mean age was 59 y.o. (± 9.8) and there was a predominance of males (73.6%). The most common primary site was oropharynx (41.6%), followed by larynx (24.2%) and oral cavity (19.2%). The most common presentation was locally advanced disease (T3-T4, 72.5%; N+, 71.6%). The mean body weight was 63kg (± 11.8). The overall frequency of cachexia was 20.7% and 8.6% according to Fearon or Evans criteria, respectively. Although most of our patients complained of some degree of dysphagia (73.3%), only 3.3% of them were dependent on a feeding tube. The median follow-up (from the end of the cancer treatment until the study entry) was 42.5 months (range, 24-125 months).

Comparisons between cachectic and non-cachectic patients according to Fearon criteria are summarized in table 2. No statistical differences were detected between cachectic and non-cachectic patients regarding age, muscle strength, and blood tests, but cachectic patients presented lower mid-arm muscle circumference mean (24.0 versus 27.1 cm, respectively, $p < 0.001$). A higher percentage of moderately malnourished patients was found among cachectic patients (60.9%) compared with the non-cachectic ones (10.3%). No severely malnourished patients were seen, but the most part of cachectic patients were moderately malnourished (64%). Thus, cachectic patients according to Fearon criteria presented a lower mid-arm muscle circumference without decreased muscle strength and with no biochemical differences.

Cachectic patients according to Evans criteria showed lower muscle strength and mid-arm muscle circumference as compared with non-cachectic patients (20 kgf vs 28.2 kgf, and 24.5 cm vs 26.6 cm, respectively). There were no differences regarding albumin, hemoglobin, and CRP levels. According to these criteria, 80% of the cachectic patients presented a moderate malnourished status in comparison to 13% of non-cachectic patients (table 3). In other words, cachectic patients evaluated with Evans criteria presented a decrease in both muscle mass and muscle function, not associated with biochemical differences.

Table 4 shows the frequency of dysphagia in our population according to each cachexia diagnostic criteria. All patients diagnosed with cachexia, according to Evans criteria, manifested dysphagia. There is a trend which suggests an association between the diagnosis of cachexia and the presence of dysphagia in these patients ($p < 0.06$). This association was not observed when the diagnosis of cachexia was established according to Fearon's criteria (in which 73% of cachectic presented with dysphagia).

Discussion

Cancer cachexia is the most common cancer-related syndrome. Cachectic patients show poor performance, lower treatment responses, and dismal prognosis [13, 22]. Indeed, cancer cachexia is present in different types of cancer and different stages and it is estimated that cachexia is responsible for around 20% of all cancer deaths [16, 23–27].

In this study, after a long-term clinical follow up, we detected a high prevalence of cachexia according to two standardized diagnostic criteria in disease-free patients post cisplatin-based chemoradiotherapy with curative intent. In addition, we demonstrated that cachectic patients presented lower muscle mass and strength. Cachexia present a trend to be associated with dysphagia when diagnosed according to Evans diagnostic criteria ($p < 0.06$) and 73% of cachectic patients manifested dysphagia according to Fearon criteria.

In newly diagnosed HNSCC patients, cachexia frequency is at least 42% when diagnosed using Fearon criteria [27] and 6.1% when diagnosed using Evans criteria [19]. In our population, the percentage of cachexia was 20.7% and 8.6% according to Fearon and Evans, respectively, in disease-free HNSCC patients, after multimodal treatment. This distinction is important because there is a concept that cancer cachexia syndrome is associated with metabolic disturbances related to the tumor presence [15, 20]. Kwon and coworkers [19] showed that cachexia in HNSCC patients increases by 41% immediately after the end of the treatment as compared with pre-treatment values (6.1%). Nevertheless, according to the authors, the cachexia frequency decreases to 18% after 6 to 12 months post-treatment, approximately two times the frequency here observed two years after treatment completion.

In this context, we found a high percentage of dysphagia in our cohort. Dysphagia is correlated to body and muscle mass loss in cancer and non-cancer patients [28, 29], and this fact could explain at least part of our results. This data supports the idea that the cachexia in disease-free patients could be a side effect of cancer treatment and, as such, classified as a late toxicity. Indeed, around 50% of all head and neck cancer patients present dysphagia after treatment [30].

Cachexia in disease-free patients could be also attributed to a cisplatin side effect. This hypothesis is supported by recent data showing that cisplatin causes a muscle mass reduction. Damrauer et. al. showed in an animal model and cell cultures that cisplatin could regulate the proteolysis pathway leading to muscle wasting [31]. However, there are no clinical data to support this hypothesis.

Recently, Grossberg et al. showed that there is no correlation between body mass loss and survival in radiotherapy-treated HNSCC patients[32]. However, the authors described that pre- and post-radiotherapy muscle mass depletion was associated to shorter overall survival. Our data suggest that cachexia in disease-free patients has a muscle component, but we did not perform any survival or cancer recurrence analysis, so further studies are needed to better elucidate this question.

Our study demonstrated that severe weight loss was important in the diagnosis of cachexia, but muscle mass and strength alterations, hemoglobin and CRP are also important issues to evaluate metabolic dysfunction, which could be a trigger to weight loss. It is worth mentioning that cachectic patients in our cohort did not show a difference in metabolic markers when compared with non-cachectic patients. In fact, muscle mass and metabolic markers are mortality predictors in different types of cancer[33–35].

This study had some limitations. First, it was not possible to perform a more accurate analysis of muscle area using CT-scans images. Second, other late toxicities (e.g., xerostomia, hypothyroidism, esophageal toxicity, and others) could contribute to cachexia development in our patients, and these alterations could also have some impact on muscle mass, strength, biomarkers, and quality of life. Third, we did not evaluate the impact of the cachexia on disease recurrence and survival, and this long-term study is underway.

In conclusion, HNSCC patients treated with chemoradiotherapy after a minimum of 2-years of treatment completion presented cachexia, and cachectic patients presented impairment in muscle mass. Cachexia could be also associated with dysphagia and related to a worse muscle function. Cachexia and metabolic dysfunction should thus be better studied to elucidate its pathophysiology and prognostic impact on cancer HNSCC survivors in order to improve their outcomes.

Declarations

Acknowledgments

We thank all the patients and their families.

Funding

São Paulo Research Foundation (FAPESP) supported this work (Grant 2014/00172-9 and 2016/20187-6).

Conflict of interest

None declared.

All authors have full control of all primary data and agree to allow the journal to review their data if requested.

Authors' contributions

G.C.J., W.N., T.G.R and E.F.S designed the study. T.G.R., E.F.S., G.C.J. and M.A.V.K. carried out the data collection. W.N performed the statistical analysis. All authors interpreted the results and wrote the manuscript. All authors and approved the final manuscript.

Ethics approval

The Institutional review board of the Instituto do Câncer do Estado de São Paulo /Faculdade de Medicina da USP approved this study (1.339.832)

Consent for publication

N/A

Availability of data and material

Yes

Code availability

N/A

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Tables

Table 1. Clinical characteristics		
Characteristic	N	%
Total	120	100
Age, mean (SD) (years)	58.4 (10.0)	
Time post treatment completion, mean (range) (months)	42.5 (24-125)	
Body weight, mean (SD), (kg)	63.3 (13.1)	
Sex		
Male	89	73,6
Female	32	26,4
Primary cancer site		
Oropharynx	50	41.6
Larynx	29	24.2
Oral cavity	23	19.2
Hypopharynx	9	7.5
Nasopharyngea	9	7.5
T staging		
T1	9	7.5
T2	20	16.7
T3	28	23.3
T4	59	49.2
Unknown	4	3.3
N staging		
N0	33	27.5
N1	25	20.8
N2	49	40.8
N3	12	10
Unknown	1	0.8
Feeding tube dependence	4	3.3
Dysphagia	88	73.3

Presence of cachexia		
According to Fearon (2011) *	23	20.7
According to Evans (2008) **	10	8.6
*111 patients evaluated for cachexia; **115 patients evaluated for cachexia.		

	Cachectic (n=23)	Non-cachectic (n=88)	p value
Age, mean (SD) (years)	61.5 (9.0)	57.5 (10.1)	0.08
Muscle strength (kgf)	26.4 (8.2)	28.0 (8.8)	0.47
Mid-arm muscle circumference (cm)	24.0 (2.6)	27.1 (2.9)	<0.01
Blood analysis			
Albumin, mean (SD) (g/dL)	4.4 (0.4)	4.6 (0.6)	0.35
Hemoglobin, mean (SD) (g/dL)	13.3 (1.4)	13.6 (1.6)	0.39
C-reactive protein, mean (SD) (mg/L)	8.5 (10)	7.2 (12.8)	0.65
Nutritional status			
Well nourished	9	79	
Moderately malnourished	14	9	<0.01*
Severely malnourished	0	0	
*Fisher exact test.			

	Cachectic (n=10)	Non-cachectic (n=105)	p value
Age, mean (SD)	58.7 (6.6)	58.6 (10.0)	0.98
Muscle strength (kgf)	20.0 (4.0)	28.2 (8.6)	0.01
Mid-arm muscle circumference (cm)	24.5 (2.5)	26.6 (3.0)	0.03
Blood analysis			
Albumin, mean (SD) (g/dL)	4.3 (0.3)	4.5 (0.5)	0.22
Hemoglobin, mean (SD) (g/dL)	13.0 (1.3)	13.6 (1.5)	0.29
C-reactive protein, mean (SD) (mg/L)	6.3 (4.3)	7.3 (12.5)	0.78
Nutritional status			
Well nourished	2	96	
Moderately malnourished	8	14	< 0.01*
Severely malnourished	0	0	
* Fisher exact test			

		Cachexia			
Fearon Criteria		Yes	No	Total	p value
	No	6	23	29	0.96*
Dysphagia	Yes	17	65	82	
Evans Criteria					
	No	75	30	105	0.06*
Dysphagia	Yes	10	0	10	
*Fisher exact test					