

Weight loss as a prognostic factor for recurrence and survival in oropharyngeal squamous cell carcinoma patients

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Abstract. Although the mortality rate of oropharyngeal squamous cell carcinoma (OPSCC) has been decreasing over the last 30 years, there has been a significant increase in the frequency of diagnosis of this type of cancer in several countries. Beyond the classic prognostic factors, such as TNM stage, there is a lack of predictive factors for recurrence and treatment response. A retrospective analysis of patients with OPSCC treated at the Oncology Department of the Santa Terezinha University Hospital between 2007 and 2012 was performed, with the aim of identifying new prognostic factors. In addition to the significance of clinical stage as a prognostic factor for recurrence, OPSCC patients with advanced TNM stage and those treated with radiotherapy, chemoradiation or palliative measures, had a worse prognosis. Patients with moderate or severe weight loss (>5%) at diagnosis had a higher tumor recurrence rate compared with those with mild or no weight loss (P=0.007). Furthermore, 76.9% of patients with moderate or severe weight loss, as opposed to 13.3% of patients with mild or no weight loss, eventually succumbed to the disease (P=0.0001). These data suggest that moderate and severe weight loss at diagnosis is a prognostic factor for OPSCC and it is associated with disease recurrence.

Introduction

Head and neck tumors are a major public health concern, particularly in developing countries, as they are associated with high morbidity and mortality rates (1,2). This type of cancer has an incidence of 2-3%, making it the sixth most common type of cancer worldwide (3). Based on data collected between 2007 and 2011, the newly diagnosed cases of oropharyngeal cancer were 10.9 per 100,000 inhabitants per year, with 2.5 deaths per 100,000 individuals. The 5-year overall survival for this type of cancer was reported to be 62.7% (4).

The extent of the disease in terms of local invasion, lymph node involvement and distant organ metastases at the time of diagnosis is an important prognostic factor, with a 5-year survival rate of 75% for localized (stage I) oropharyngeal carcinomas and <25% for metastatic (stage IV) disease (5).

Over 90% of upper airway/digestive tract cancers are of the squamous cell carcinoma (SCC) type. This disease is multifactorial, as its development results from the interaction of environmental and genetic factors (6). The great majority of lesions in the pharynx occurs in the oropharynx (40-50%); the tonsillar region is affected in 40% and the base of the tongue in 30% of the cases (7). Oropharyngeal cancers include malignant neoplasms occurring in the tonsillar region, base of the tongue, soft palate and posterior pharyngeal wall (8).

The most important etiological factor for the development of head and neck cancer is tobacco use, with the relative risk increasing 10-fold in smokers (9). Smoking together with alcohol consumption produce a synergistic tumorigenic effect (10) that increases the risk of head and neck SCC 40-fold (2). This association is responsible for >80% of the cases of oropharyngeal cancer diagnosed worldwide (11), whereas smoking and alcohol cessation acts protectively against the development of head and neck SCC (12). Furthermore, over the last decades, a strong causal association between human papillomavirus (HPV) infection and the development of SCC has been established (7,13), characterizing HPV infection as

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another important risk factor for oropharyngeal SCC (OPSCC) development (14,15).

In addition to these major factors, diet also affects the risk of cancer development. Certain vitamins or pigments, such as carotenoid, may be protective when included in a balanced diet. However, vitaminosis, particularly from vitamin A, beta-carotene and selenium, and folate deficiency, may represent nutritional risks for cancer development (16,17). Another nutritional factor associated with the development of OPSCC is the consumption of mate and chimarrão (*Ilex paraguariensis*) (18-20), which is quite popular in Latin American countries.

Early diagnosis of OPSCC is a major factor affecting survival. The survival rate may reach 94% when the lesions are small and localized; however, it decreases to 25% in metastatic disease (21). Weight loss has been reported as a sign of cancer, as 25% of patients with an involuntary weight loss of >5% body weight in 6 months are diagnosed with cancer (22). In head and neck cancer, critical weight loss (>5% in 1 month or >10% in 6 months) has been reported in 20-57% of the patients at diagnosis, usually caused by dysphagia and/or loss of taste or appetite (23).

Given the incidence, mortality and consequent impact on health caused by head and neck tumors, it is crucial to identify factors that may be of predictive and prognostic value. The objective of the present study was to identify factors associated with prognosis and recurrence in patients diagnosed with OPSCC.

Materials and methods

Study cohort. The medical records of patients diagnosed with OPSCC and treated at the Oncology Department of the Santa Terezinha University Hospital (Joaçaba, Brazil) between 2007 and 2012 were retrospectively analyzed after obtaining approval from the hospital's Research Ethics Committee.

The inclusion criteria were histologically confirmed OPSCC and completion of the treatment schedule. Patients for whom medical records or weight measurements were unavailable were excluded from the study. The study cohort was composed of 45 patients. However, for the mortality analysis, 4 patients were excluded due to withdrawal of treatment or death by another cause. Furthermore, for the recurrence analysis, 16 patients were excluded due to disease progression, finally leaving a total of 29 patients.

All 45 patients were treated and staged by the same professional (G.M.). Medical records were reviewed to extract data on patient and tumor characteristics. The patients were classified by sex, age, tumor subsite localization (soft palate, tongue base or tonsils), tumor stage (based on the TNM staging classification) (24), time with symptoms (>5 or <5 months), type of treatment, risk factors (smoking, smoking and consumption of alcoholic beverages and no smoking) and weight loss at diagnosis (moderate and severe, when the patients exhibited a decrease of 5 kg or >5% of their initial body weight over a period of 6 months, and mild when the weight loss was <5 kg or <5% body weight) (25).

Statistical analysis. Statistical analyses were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk,

NY, USA). To compare the groups, Fisher's exact test and Pearson's Chi-squared univariate analysis were used. A P-value of <0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics. To identify factors potentially associated with recurrence in OPSCC, 45 patients diagnosed between 2007 and 2012 were retrospectively investigated. The mean age of this cohort at diagnosis was 57.6 years, and 86.7% of the patients were male. In this patient cohort, 93.3% (41) of the patients were smokers, and 71.1% (32) also reported heavy alcohol consumption. Only 6.7% (3) of the patients were non-smokers or ethanol abusers. The most common tumor subsite localization was the base of the tongue, affecting 51.1% (23) of the patients, followed by the tonsils in 31.1% (14) and the soft palate in 17.8% (8) of the cases (Table I).

From the initial cohort, 4 patients abandoned treatment and the 5-year overall survival rate among the remaining 41 patients was 46.3%. A total of 12 patients did not respond to treatment and were therefore not evaluated for recurrence.

Follow-up. After treatment, 29 patients were followed up and 7 (24%) developed recurrence. When comparing the patients without recurrence to those with recurrence, there were no differences regarding tumor subsite localization, tumor size (T), lymph node involvement or type of treatment. In the group of patients who were symptomatic for <5 months 15.8% had recurrence, whereas 40% of patients who were symptomatic for >5 months had recurrence. Among patients who did not have metastases at diagnosis, 20% developed recurrence, compared with 50% amongst those with metastases at diagnosis. However, these results were not statistically significantly different. Tumor stage differed significantly ($P=0.022$) between the groups with and without recurrence. Among patients with stage I and III disease, 16.7 and 11.1%, respectively, developed recurrence, while 35.7% of stage IV patients developed recurrence.

Role of weight loss in recurrence. Another factor associated with recurrence was weight loss. In this cohort, 100% of patients without weight loss or with only mild weight loss at diagnosis did not have recurrence. However, 43.8% of patients with moderate or severe weight loss developed recurrence ($P=0.007$; Table II).

Survival analysis. At 5 years, 19 of the 41 patients (46.3%) remained alive, while 22 (53.7%) had succumbed to the disease. When comparing the surviving and deceased patient groups, tumor subsite localization did not differ significantly between the two ($P=0.47$). Although 83.3% of patients with tumors in the soft palate survived, only 45.5 and 30.8% of patients with tumors in the base of the tongue and tonsils, respectively, survived.

In the present study, the statistical analysis demonstrated that TNM stage was an important prognostic factor for survival, both when analyzed separately as well as in the clinical stages. In patients with T1, T2 and T3 tumors, the survival rate was 66.7, 75 and 64.3%, respectively. However, only 23.1% of patients with T4a and none of the patients with T4b survived ($P=0.003$). In the group of patients without lymph node invasion (N0), 70.6%

Table I. Baseline characteristics of patients with nasopharyngeal squamous cell carcinoma.

Characteristics	n (%)
Mean age, years	57.6
Sex	
Male	39 (86.7)
Female	6 (13.3)
Tumor subsite localization	
Tongue base	23 (51.1)
Tonsils	14 (31.1)
Soft palate	8 (17.8)
Risk factors	
Smoking	10 (22.2)
Smoking + alcohol consumption	32 (71.1)
No smoking	3 (6.7)

survived, whereas among patients with lymph node invasion (N1), only 29.2% survived (P=0.01). Patients without distant metastasis at diagnosis (M0) had a survival rate of 54.5%, while those with metastasis (M1) had a 12.5% survival rate at 5 years (P=0.037). The survival rate for patients with stage I, II and III disease was 80, 100 and 80%, respectively, while only 24% of patients diagnosed at stage IV survived (P=0.0006).

The type of treatment was also associated with differences in survival. Patients treated with surgery alone had a survival rate of 75%, whereas patients treated with radiotherapy or radiochemotherapy had survival rates of 33.3 and 37.5%, respectively. None of the patients who received palliative therapy survived (P=0.018).

Finally, weight loss proved to be a powerful prognostic factor for survival in OPSCC. In the group with no weight loss or only mild weight loss, 86.7% of patients survived. However, among patients with moderate or severe weight loss at diagnosis, the survival rate was only 23.1% (P=0.0001) (Table III).

Discussion

In the present study, the mean age of patients with OPSCC was 57.6 years, and the majority were men and smokers. Previous studies reported a similar profile for OPSCC patients, with a mean age of 59 years (26) and an 80.3% male predominance (27). In a study published by Perry *et al* (2015), 79.3% of the patients with OPSCC were men, and 85.6% were smokers in the entire cohort (28). Although tobacco and alcohol consumption are well-documented risk factors for head and neck cancer, their role in oropharyngeal cancer is less clear (9). In this cohort of patients, the most common subsite was the base of the tongue (51.1%), which was different from a study on 37,452 OPSCC patients reporting that the most commonly affected subsite was the tonsils (1). In the present study, the 5-year overall survival rate was 46.3%, which was similar to the SEER 2016 data (4), reporting a survival rate of 43% specifically for this type of tumor. The poor prognosis of oropharyngeal cancer when compared with oral cavity cancer may be associated with the fact that oropharyngeal cancer

is not frequently diagnosed at an early stage. Only 14% of patients were diagnosed with early-stage disease, whereas the majority (55%) were diagnosed with regional metastasis (4). The recurrence rate in the present study was 24%, which was higher compared with that reported previously by Garden *et al* (2013) and Roskies *et al* (2016), who demonstrated a recurrence rate of 18 and 11%, respectively (29,30). The increased recurrence rate reported herein may be due to late diagnosis, as 79.3% of patients were diagnosed with stage III and IV disease.

Of the patients evaluated, 45.5% were diagnosed with advanced local disease (T4) and 58.5% with lymph node involvement, showing a predominance of more advanced stage at diagnosis, consistently with previous findings (1,3). Tumor size (T), lymph node involvement (N) and distant metastasis (M) were not associated with recurrence, but they were important prognostic factors for survival in OPSCC. Over the last four decades, it has been demonstrated that extranodal spread is the single most important prognostic factor for SCC of the head and neck (31). In addition, another study reported that tumor size, lymph node involvement and distant metastasis are not only important prognostic factors for survival, but also for recurrence in OPSCC patients (32). The late diagnosis in these patients is also reflected by clinical stage, as 61% were diagnosed at stage IV, which is common for this type of cancer (14). Clinical stage was an important factor associated with recurrence and prognosis in these patients. The mortality rate for stage IV disease reached 76%, while it was 20, 0 and 20% for stages I, II and III, respectively. Further research demonstrated that TNM stage has a good prognostic power, mainly in non-HPV oropharyngeal cancer cases (33).

Although the majority of the patients were diagnosed with advanced-stage disease, 65.5% had been symptomatic for <5 months prior to diagnosis, which further supports the hypothesis that early-stage OPSCC does not commonly present with alarming symptoms (3,34). In a Brazilian study, the mean evolution time (the time between the initiation of symptoms to diagnosis) for patients with OPSCC was 6.4 months (35). Furthermore, it has been reported that the time from symptom onset to treatment initiation is correlated not only with more advanced disease stage at diagnosis, but also with OPSCC patient survival (3). However, in the present study, the time from symptom onset to treatment initiation was not correlated with recurrence.

Chemoradiation therapy is used for patients who are not surgical candidates due to extensive tumor burden (26). The majority of the patients in this study (58.5%) were treated with chemoradiation due to the late stage at diagnosis. It was observed that the type of treatment, which depends on tumor stage, was correlated with survival. Patients treated with surgery had a survival rate of 75%, while patients treated with radiotherapy and chemoradiation had a survival rate of 33.3 and 37.5%, respectively. None of the patients who received palliative treatment survived.

In the present study, moderate or severe weight loss proved to be an important prognostic factor in OPSCC. A total of 76.9% of patients with moderate or severe weight loss succumbed to the disease, while 86.7% of patients with mild or no weight loss survived (P=0.0001). Furthermore, we observed an important

Table II. Clinical characteristics of patients with nasopharyngeal squamous cell carcinoma, with and without tumor recurrence.

Characteristics	Without tumor recurrence n=22 (%)	With tumor recurrence n=7 (%)	P-value
Tumor subsite			0.5
Tongue base	10 (71.4)	4 (28.6)	
Tonsil	6 (75.0)	2 (25.0)	
Soft palate	6 (85.7)	1 (14.3)	
Time of symptoms			0.16
>5 months	6 (60.0)	4 (40.0)	
<5 months	16 (84.2)	3 (15.8)	
Weight loss			0.007
None/mild	13 (100.0)	0 (0.0)	
Moderate/severe	9 (56.2)	7 (43.8)	
T			0.74
1	5 (71.4)	2 (28.6)	
2	2 (66.7)	1 (33.3)	
3	9 (81.2)	2 (18.2)	
4a	5 (71.4)	2 (28.6)	
4b	1 (100.0)	0 (0.0)	
N			0.45
N0	12 (80.0)	3 (20.0)	
N1	10 (71.4)	4 (28.6)	
M			0.23
M0	20 (80.0)	5 (20.0)	
M1	2 (50.0)	2 (50.0)	
Stage			0.022
I	5 (83.3)	1 (16.7)	
II	-	-	
III	8 (88.9)	1 (11.1)	
IV	9 (64.3)	5 (35.7)	
Treatment			0.75
Surgery	11 (84.6)	2 (15.4)	
Radiotherapy	2 (40.0)	3 (60.0)	
Radiochemotherapy	10 (76.9)	3 (23.1)	

Statistical analysis was performed using the Fisher's exact test and Pearson's χ^2 univariate analysis. Bold print indicates statistical significance.

correlation between weight loss and disease recurrence (P=0.007). It is known that patients with head and neck SCC are at high risk for weight loss due to the disease course and treatment, and that this weight loss ranges from 6 to 12% of the body weight (36-39). A prospective, randomized, multicenter trial demonstrated that a high body mass index (BMI >25 kg/m²) at the start of radiotherapy is positively associated with survival in patients with OPSCC (40). Furthermore, it has been demonstrated that severe weight loss is associated with worse quality of life (QoL), poorer treatment tolerance, delayed recovery, postoperative complications, prolonged hospitalization and an unfavorable prognosis (41-43). Additionally, weight loss was found to be strongly correlated with increased mortality rate (44). Loss of $\geq 5\%$ of the body weight in 6 months is an unfavorable risk factor associated with decreased overall survival in HPV-related head and neck SCC patients (45). In a recent study, 2,399 patients with nasopharyngeal carcinoma were categorized as critical weight loss (CWL $\geq 4.6\%$) or

non-critical weight loss (non-CWL), and the results suggested that CWL is an independent prognostic factor for overall survival, treatment failure-free survival, and locoregional treatment failure-free survival, irrespective of chemotherapeutic modality, radiotherapy technique, or BMI (46).

The results presented in this study highlight that preventing therapy-associated weight loss should be a priority in these patients. Clinical guidelines recommend that enteral nutrition should be initiated if undernutrition is present or if food intake is markedly reduced for >7-10 days (47). However, further studies are required to determine the best enteral feeding methods (48) and the composition of the optimal supplemental formula (49). Furthermore, the effect of weight loss may be due to a complex interaction amongst multiple factors. Therefore, future studies should be focused on elucidating the association of these multiple factors with weight loss (50).

The main limitations of the present study are the retrospective nature of the analysis and the small sample size.

Table III. Prognostic factors of mortality in patients with nasopharyngeal squamous cell carcinoma.

Prognostic factors	Survivor group n=19 (%)	Deceased group n=22 (%)	P-value
Tumor subsite			0.47
Tongue base	10 (45.5)	12 (54.5)	
Tonsils	4 (30.8)	9 (69.2)	
Soft palate	5 (83.3)	1 (16.7)	
T			0.003
1	4 (66.7)	2 (33.3)	
2	3 (75.0)	1 (25.0)	
3	9 (64.3)	5 (35.7)	
4a	3 (23.1)	10 (76.9)	
4b	0 (0.0)	4 (100.0)	
N			0.01
N0	12 (70.6)	5 (29.4)	
N1	7 (29.2)	17 (70.8)	
M			0.037
M0	18 (54.5)	15 (45.5)	
M1	1 (12.5)	7 (87.5)	
Stage			0.0006
I	4 (80.0)	1 (20.0)	
II	1 (100.0)	0 (0.0)	
III	8 (80.0)	2 (20.0)	
IV	6 (24.0)	19 (76.0)	
Treatment			0.018
Surgery	9 (75.0)	3 (25.0)	
Radiotherapy	1 (33.3)	2 (66.7)	
Radiochemotherapy	9 (37.5)	15 (62.5)	
Palliative	0 (0.0)	2 (100.0)	
Weight loss			0.0001
None/mild	13 (86.7)	2 (13.3)	
Moderate/severe	6 (23.1)	20 (76.9)	

The statistical analyses was performed using the Fisher's exact test and Pearson's χ^2 univariate analysis. Bold print indicates statistical significance.

In conclusion, we herein demonstrated that moderate or severe weight loss at diagnosis is strongly associated with tumor recurrence. Regarding prognosis, OPSCC patients diagnosed at a more advanced TNM stage, patients treated with radiotherapy, chemoradiation or palliative treatment, and those patients with moderate or severe weight loss had a worse prognosis. It may be concluded that observation of the patient's weight may be important as an early indicator of tumor recurrence and an important prognostic factor of OPSCC.

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Availability of data and materials

The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ARB: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript. KDH: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript. CB: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; JSB: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; RC: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; SFB: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript.

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Ethics approval and consent to participate

The present study was approved by the Institutional Ethics Committee (Comitê de Ética em Pesquisa Unoesc/HUST; approval no., 292.382).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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