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A ten-year retrospective study of the clinical, sociodemographic, and survival characteristics of patients with oral and pharyngeal squamous cell carcinomas

Estudo retrospectivo de dez anos das características clínicas, sociodemográficas e de sobrevida de pacientes com carcinomas epidermóides orais e faríngeos

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ABSTRACT

Objective: This study evaluated the epidemiological profile of patients diagnosed with squamous cell carcinoma, as well compared oral and pharyngeal lesions regarding the survival of these patients. Material and Methods: Convenience sampling was employed to select the participants, who had their medical records of the period 200-2009 investigated. Sociodemographic and clinical-pathological data were collected and correlated with site of the lesion, TMN classification, of the tumor, and survival of the patients. Fisher's and Chi-square tests, Kaplan-Meir curve associated with the Long Rank Mantel-Cox test, and Cox's regression for survival analysis were performed to evaluate the results. Results: Sixty-year-old illiterate females presented higher prevalence of oral cancer with a more severe lymphonodular infiltration, worse tumor staging, and chemo and radiotherapy treatment. Meanwhile, sixty-year-old illiterate males presented higher prevalence of pharyngeal cancer, lower rates of lymphonodular infiltration, and chirurgical treatment. The survival of the patients with oral cancer was correlated with the lymphonodular infiltration level, while for patients with pharyngeal cancer the survival was correlated with chirurgical treatment. Thus, head and neck cancer are still diagnosed belatedly, mainly when it affects the pharynx.Conclusion: Therefore, preventive and educative strategies, as well as amplification of access to health care should be considered targets for achieving reduction in the mortality rates of populations with oropharyngeal cancer.

Key word: Mouth Neoplasms, Pharyngeal Neoplasms, Epidemiology, Survival Rate

RESUMO

Objetivo: Este estudo avaliou o perfil epidemiológico dos pacientes com diagnóstico de carcinoma espinocelular e comparou lesões orais e faríngeas quanto à sobrevida desses pacientes. Material e Métodos: Amostragem por conveniência foi utilizada para selecionar os participantes que tiveram seus prontuários médicos do período 200-2009 investigados. Os dados sociodemográficos e clínico-patológicos foram coletados e correlacionados com o local da lesão, a classificação da TMN, do tumor e a sobrevida

dos pacientes. Os testes de Fisher e qui-quadrado, curva de Kaplan-Meir associada ao teste de Long Rank Mantel-Cox e regressão de Cox para análise de sobrevivência foram realizados para avaliar os resultados. Resultados: Mulheres analfabetas de sessenta anos de idade apresentaram maior prevalência de câncer de boca com infiltração linfonodular mais grave, pior estadiamento do tumor e tratamento quimioterápico e radioterápico. Enquanto isso, os analfabetos do sexo masculino, com 60 anos de idade, apresentaram maior prevalência de câncer de faringe, menores taxas de infiltração linfonodular e tratamento quirúrgico. A sobrevida dos pacientes com câncer de boca foi correlacionada com o nível de infiltração linfonodular, enquanto nos pacientes com câncer de faringe a sobrevivência foi correlacionada com o tratamento quirúrgico. Assim, o câncer de cabeça e pescoço ainda é diagnosticado tardiamente, principalmente quando afeta a faringe.Conclusão: Portanto, estratégias preventivas e educativas, bem como a ampliação do acesso à assistência à saúde, devem ser considerados alvos para a redução das taxas de mortalidade de populações com câncer de orofaringe.

Palavras-Chave: Neoplasias Bucais, Neoplasias Faríngeas, Epidemiologia, Taxa de Sobrevivência

1 INTRODUCTION

The head and neck are among the 10 areas of the body that are most frequently affected by cancer. A high prevalence of this type of cancer has been observed in Brazilian men, and it is the 4th most common malignant neoplasm in this gender[1]. Squamous cell carcinomas are the most common tumours of the head and neck and mainly affect the oropharyngeal area[2]. There are clinical differences between these two regions regarding the incidence of lesions, risk factors to which each are is exposed, and diagnosis, which is more difficult if the lesion is in the pharynx. Regarding lesions of the oral cavity, the most commonly affected areas are tongue and the buccal floor. In the pharynx, the base of the tongue is the site that is most commonly affected by malignant neoplasias[3].

Characterizing the frequencies and distributions of oral cancer lesions aids health organizations in the planning of strategies to reduce the incidence and mortality of this disease[4]. Therefore, the aims of this study were to evaluate the epidemiological profiles of patients diagnosed with squamous cell carcinomas and to compare oral and pharyngeal lesions regarding the survival of these patients.

2 MATERIAL AND METHODS

2.1 DATA ANALYSIS AND CLASSIFICATION

Patients with squamous cell carcinomas of the oral cavity and pharynx composed the sample of this study, and these patients were selected by convenience. All of the

participants were patients of the Cancer Institute of Ceara (Brazil) – Hospital Haroldo Juacaba between the years of 2000 and 2009.

Sociodemographic data, such as age, gender, education level, and type of hospital admission (public or private) were collected. Clinical-pathological information was also collected including the type of tumour, localization, tumor-node-metastasis (TNM) staging of the lesion, type of treatment (surgical or chemo/radiotherapy), and the survival rate of the patients.

The recommendations of the World Health Organization (WHO) were followed for classifying the lesions according to their localization (oral lesions and pharyngeal lesions). The lesions were also classified according to the TNM index (7th edition INCA) from I to IV following the recommendations of the WHO and the International Classification of Diseases (CID)[5].

The survival of the patients was calculated subtracting the date of death (day, month, year) from the date on which treatment was initiated (day, month, year) and is expressed in weeks.

3 STATISTICAL ANALYSIS

The data were analysed using the Statistical Package for Social Sciences 15.0 (SPSS). Fisher and chi-square tests were performed to analyse the categorical variables with a significance level of 95% ($p<0.05$). Survival was considered a dichotomic variable and was analysed with Fisher's, chi-square, and log-rank Mantel-Cox tests. Additionally, Cox regression for survival analysis was performed to identify the factors that significantly influenced the survivals of the patients.

4 ETHICAL ASPECTS

This study was approved by the Ethics Committee of Research, protocol number 011/2011, of the hospital at which the patient data were collected.

5 RESULTS

5.1 LOCALIZATION OF THE LESIONS

Oral cavity lesions (170, 33.3%) were more frequent than lesions in the pharynx (136, 20.8%) in the female patients. In the male patients, the opposite pattern was found, i.e., the squamous cell carcinoma lesions were more frequently diagnosed in the pharynx

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(519, 79.2%) than in the oral cavity (341, 66.7%; p<0.001). Lesions in the pharynx were more frequently diagnosed in patients aged approximated 60 years (318, 48.5%), and those in the oral cavity were more frequently diagnosed in patients over 60 years of age (305, 59.7%; p<0.001).

The variables of the ethnicity of the patient and the type of hospital admission (private or public) did not significantly influence the distribution of the squamous cell carcinomas (p = 0.809, and p = 0.813, respectively). Regarding educational level, the illiterate patients presented with a greater relative number of oral cavity lesions (431, 91.3%) than pharyngeal lesions (550, 85.5%; p= 0.045). Among those patients who had completed elementary school, pharyngeal lesions were more frequent (63, 9.8%) than oral cavity lesions (30, 6.4%; p= 0.045).

No differences were observed regarding the sizes and possible metastases of the squamous cell carcinomas when oral cavity and pharyngeal lesions were compared (p = 0.964). However, an examination of lymphonodular infiltration revealed that the 0 and 1 categories were more strongly associated with oral cavity lesions, and the 2 and 3 categories were more frequently associated with pharyngeal lesions (p< 0.001).

Regarding the staging of the tumours, stages I, II, and III were more frequently observed in the oral cavity lesions (15, 5.7%; 44, 16.7%, and 70, 26.5%, respectively) than in the pharyngeal lesions (15, 3.8%; 44, 11.2% and 80, 20.4%, respectively). Stage IV lesions were more frequently observed among the pharyngeal (254, 64.6%) lesions than the oral cavity lesions (135, 51.1%; p=0.007).

Moreover, oral cavity lesions were more strongly associated with surgical treatment (208, 40.7%), and the pharyngeal lesions were more strongly associated with radio- (411, 62.7%) and chemotherapy (234, 35.7%; p<0.001).

The risk factors of familiar medical history (p=0.998), smoking habits (p=0.299), and the association between smoking and drinking (0=0.349) did not present significant associations with the distribution of the lesions regarding their localizations. However, alcohol consumption presented a stronger association with pharyngeal lesions (182, 79.1%) than with oral cavity lesions (79, 65.8%; p=0.007).

5.2 TEN-YEAR SURVIVAL RATES

The analysis of the survival rates over 10 years, here calculated in months and analysed with Kaplan-Meier curves, demonstrated that the mean global survival rate for squamous cell carcinoma was 65.9±3.1 months, which was significantly greater than that

found for the same type of lesion when located in the pharynx (49.4±2.7 months; p<0.001).

None of the analysed sociodemographic variables in relation to the squamous cell carcinoma locations significantly modified the mean survival rates of the patients as follows: gender (oral cavity, p=0.159; pharynx, p=0.218), age (oral cavity, p=0.689; pharynx, p=0.607), ethnicity (oral cavity, p=0.872; pharynx – p=0.682), education level (oral cavity, p=0.697; pharynx – p=0.759), place of residence (oral cavity, p=0.153; pharynx, p=0.498), and type of hospital admission (oral cavity, p=0.153; pharynx, p=0.433).

Regarding the clinical variables, the findings were diverse between the two anatomical locations. The size of the tumour seemed to affect the survival rate when the lesion was located in the oral cavity (p=0.030), i.e., smaller tumours were associated with higher are survival rates (T1=98.5±9.0, T2=63.6±7.7, T3=60.0 ±7.4, and T4=60.3±6.5). However, the same did not appear to be true for tumours in the pharynx (p=0.090).

Lymph node involvement exhibited an inverse correlation with survival rate for the squamous cell carcinomas in the oral cavity (p=0.005), i.e., lower levels of involvement were correlated with higher survival rates (N0=74.1±5.0, N1=54.0±9.0, N2=45.1±9.3, and N3=27.0±9.1).

The presence or absence of metastasis was correlated with the survival rate for the lesions in the oral cavity (p=0.003), but this was not true for lesions located in the pharynx (p=0.636). Squamous cell carcinomas in the oral cavity in the absence of metastasis were correlated with higher survival rates (65.0±4.0) than those with metastasis (6.5±6.5).

The stages of the lesions in the oral cavity (p=0.027) and pharynx (p=0.038) were also correlated with survival rates. Lower staging was associated with a higher survival rate. Stage I lesions differed in relation to all other stages (oral cavity, I: 98.5±9.0, II: 63.6±8.8, III: 61.4±7.2, and IV: 60.2±6.0; pharynx, I: 57.5±6.9, II: 62.2±9.3, III: 42.5±6.5, and IV: 41.4±4.0).

Regarding the therapeutic approaches employed and the survival rates, surgical treatment was correlated with the survival rate for the squamous cell carcinomas that were located in the oral cavity (p< 0.001). The patients who underwent surgical procedures presented with higher survival rates (in months: 74.4±4.9) than did those who did not undergo surgery (51.5±3.9). No correlation between surgical procedures and survival rates was observed among the patients with squamous cell carcinomas affecting the pharynx (p=0.150).

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Radiotherapy was correlated with the survival rates of the patients with pharyngeal cancer (p=0.024), but no such correlation was present for the squamous cell carcinomas that were located in the oral cavity (p=0.867). The patients with squamous cell carcinomas in the pharynx who were treated with radiotherapy exhibited a higher survival rate (50.7± 2.8) than the non-treated patients (35.1±5.8).

Chemotherapy was associated with a lower survival rate (31.9±4.4) among the patients with oral lesions (p<0.001). However, this therapeutic approach exhibited no relationship with the survival rate when the squamous cell carcinoma was located in the pharynx (p=0.902).

Regarding risk factors, family history was not associated with survival rate at either anatomical site. However, alcohol consumption was correlated with a lower survival rate among the patients with oral cavity (p=0.011) and pharyngeal (p=0.002) lesions, and smoking habits and the alcohol/smoking association were only correlated with lower survival rates among the oral cancer cases (p=0.011 and p=0.023, respectively).

5.3 FACTORS INFLUENCING SURVIVAL RATES: COX REGRESSION

Using Cox's logistic regression model for the survival rates, the factors that significantly influenced the survival rates of the patients with squamous cell carcinomas were lymph node involvement for the tumours located in the oral cavity and surgery as the therapeutic approach for the tumours located in the pharynx (Table 1).

5.4 EVALUATION OF THE VARIABLES ASSOCIATED WITH LYMPH NODE INVOLVEMENT IN PATIENTS WITH ORAL CANCER

No statistically significant differences were observed in terms of the different stages of lymph node involvement in association with the sociodemographic variables, which included gender, age, ethnicity, and education level. However, the patients from rural areas exhibited a stronger association with cancer stage 0,2 e 3 while the patients from urban areas exhibited a stronger association with stage 2 cancer (Table 2).

Regarding the type of hospital admission (public or private), the patients from the Universal Health System exhibited a strong correlation with stage 3 and 4 cancers with lymph node involvement, and the patients from the private sector were much more strongly associated with stage 1 and 2 cancers (Table 2).

Examination of the relationship of lesion size with lymph node involvement demonstrated that size 2 and 3 tumours were associated with cancer stages 0 and 1, respectively. Moreover, the size 4 tumours were correlated with cancer stages 3 and 4 with lymph node involvement, and the presence of metastasis was highly associated with level 3 lymph node involvement.

Stages I, II and III were associated with level 0 lymph node involvement. Additionally, stage III lesions were associated with level 1 lymph node involvement. Stage IV, was associated with levels 2 and 3 lymph node involvement.

Regarding the therapeutic approaches employed, surgical treatment was often performed when the tumours were associated with level 0 lymph node involvement. The non-surgical treatment approaches were more strongly associated with levels 1, 2 and 3.

Regarding radiotherapy, no differences were observed between the levels of lymph node involvement. However, as with chemotherapy, radiotherapy was less frequently employed for squamous cell carcinomas at stages 0 and 1 and more frequently employed to treat level 2 and 3 lesions.

5.5 PHARYNGEAL CANCER

Regarding gender, most of the individuals who did not undergo surgical treatment were women (118, 22.4%), and those who did were men (111, 86.0%; p=0.003).

No associations of surgical or non-surgical treatments with sociodemographic variables were observed: age (p=0.942), ethnicity (p=0.206), education level (p=0.141), place of residence (p=0.536), and type of hospital admission (p=0.154).

Regarding the relationship between tumour size and treatment, those who presented with tumour with sizes that were classified as 2 and 3 were more likely to undergo surgical treatment (26, 35.6% and 24, 32.9%, respectively), and size 4 tumours (149, 46.6%) were more strongly associated with a non-surgical approach (p= 0.001).

Tumours with level 2 lymph node involvement were much likely to be treated with a surgical approach (23, 31.5%), and tumours associated with level 3 lymph node involvement were more likely to not undergo surgical treatment (65, 20.3%) (p=0.020). No difference in the choice to undergo surgical tumour removal was observed in relation to the presence or absence of metastasis (p=0.560).

Regarding tumour stage, the surgical approach was the most commonly employed therapy for squamous cell carcinomas that were classified as stages II (15, 20.5%) and III

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(19, 26.0%). However, the cases that were classified as stage IV were associated with a non-surgical treatment choice (218, 68.1%; p=0.009).

No association existed between surgical treatment and radiotherapy (p=0.102). However, an inverse relationship was observed between the surgical and chemotherapeutic approaches. Chemotherapy was less frequently employed by individuals who underwent surgical treatment (98, 76.0%) than among to those who did not (203, 38.6%; p=0.002).

Family history (p=0.896), alcohol consumption (p=0.507), smoking habits (p=0.224), and the association of alcohol and smoking (p=0.051) were not associated with the choice of surgical or non-surgical treatment.

6 DISCUSSION

Squamous cell carcinomas in the oral cavity and pharynx were more prevalent in male individuals over 60 years old (Table 1), which aligns with other studies[6,7]. However, the women presented with more cases of squamous cell carcinomas in the oral cavity than in the pharynx (Table 1), which accords with the findings of Chaturved et al.[7](2013)

Head and neck cancers are still diagnosed in the advanced stages as depicted in Table 1 and confirmed by other studies[8]. However, comparison of the two anatomical locations revealed that pharynx tumours were more likely to present at stage IV[8] (Table 1). Lack of awareness of tumours and the low growth rates of these tumours are possible causes for the late diagnoses of squamous cell carcinomas in the head and neck, which cause painful symptoms only during the late stages[9].

Sociodemographic and educational factors are closely related to the two types of neoplasias because most of the neoplasias in both anatomic sites were found in non-schooled patients, especially those in the oral cavity 431 non-schooled patients had oral cancer (91.3%), and 550 had pharyngeal cancer (85.5%). The patients who did not complete elementary school had a higher prevalence of pharyngeal tumours (63, 9.8%) as opposed to the cases of oral cancer (30, 6.4%; Table 1). Among the oral cavity tumours, stages 3 and 4 lymph node involvement among the patients from the Universal Health System were present in 40 (87%) and 14 (77.8%) patients, respectively (Table 2). This finding could be related to the risk factors for squamous cell carcinomas in the oral cavity, i.e., the alcohol and smoking combination, which was more prevalent among the low-income sample, potentiated the risk of squamous cell carcinomas in this region by 4-fold[10]. In the pharynx, these contributory factors seem to be less influential[11,12].

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The direct influences on the survival rates of the patients were evaluated with a regression model. Lymph node involvement and the surgical treatment modality influenced the survival rates of the cases with oral and pharyngeal cancers (Table 1). These data do not accord with those from other studies that have highlighted factors, such as ethnicity, access to health services, and the presence of metastasis, as determinants of survival rates[13,15].

The relationship between lymph node involvement and the survival rates of individuals with head and neck cancers has previously been described by the American Joint Committee on Cancer (AJCC), which uses the TNM classification system[14,15,16]. However, studies suggest that other classification systems for lymph node infiltration should be used; for example, the system that evaluates the number of positive lymph nodes (pN) and the rate of lymphatic lymph nodes (lymph node ratio – LNR)[14,16] is viable. LJØKJEL et al.[17] (2014) affirmed that the TNM system is not a satisfactory determiner of the prognoses of patients with pharyngeal cancer who are also positive for HPV infection. In such cases, age and smoking habits should be investigated.

Roberts et al.[16] (2016) evaluated the relationships of these three systems in terms of the association of the classification of lymph node involvement with the survival rates of patients with head and neck cancer. Using Cox regression analysis, these authors observed that the worst prognoses occurred for the N2c stage (metastasis in the bilateral or contralateral lymph nodes), and the AJCC classification system suggested a pN>5 and an LNR value over 12.5%. A stronger correlation between survival rate and head/neck and pharyngeal cancers was obtained using the pN system. These authors therefore suggest that the combination of the pN system and analysis of contralateral lymph node involvement with the TNM system would be the best prognostic system for carcinomas in the pharynx.

Lymph node infiltration was directly associated with patients from rural areas and those who used the Universal Health System. Advanced-stage lymph node involvement was correlated with tumour size and stage and metastasis (Table 2). The therapeutic choice was also correlated with the stage of lymph node infiltration. Thus, surgical procedures were performed when there was no lymph node involvement, and chemotherapy with radiotherapy was applied in cases with lymph node infiltration.

The relationship between the treatment modality and the survival rate of patients with tumours in the pharyngeal region has previously been discussed by Horne et al.[18] (2016) These authors evaluated the influence of different types of treatment on the

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survival rate and consider a possible relationship with HPV, which was found to be correlated with a higher survival rate and the different tumour stages when present. Surgical treatment was the only treatment modality that was correlated with a worse survival prognosis in stage I cases, which was similar to our findings that associated surgical treatment with a reduced survival rate (Table 1); in contrast, chemotherapy or surgical resection followed by radiotherapy/chemotherapy were correlated with higher survival rates[18].

The evaluation of the variables related to the surgical treatment of patients with pharyngeal tumours revealed a high prevalence of surgical treatment among men whose tumours presented at size 2 and 3, lymph node infiltration at stages 2 and 3, as well as a lower association with chemotherapy. Early diagnosis provides the possibility for an initial detection in the early stages and the application of surgery as the therapeutic approach, which, in turn, are factors that were closely related to higher survival rates (Table 1).

Higher survival rates seemed to occur when the lesions were in the oral cavity compared to those in the pharynx. Some studies have suggested that head and neck tumour stages are related to worse prognoses and reduced survival rates[19], and this notion could partially justify the obtained results.

Neoplasias in the head and neck are still associated with diagnoses, especially for those in the pharynx, and late diagnoses are correlated with worse prognoses. A sociodemographic relationship was observed, i.e., lymph node infiltration was observed more frequently in patients from rural areas and users of the Universal Health System. These findings suggest correlations of cancer stage with educational level and access to health services. The survival rates were correlated with lymph node involvement among the tumours located in the oral cavity and with therapeutic choice among the cases of pharynx cancer. Early diagnosis is crucial for reducing cancer-related mortality and should be associated with campaigns to provide information to the general population, especially those who have less access to education and health services.

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