HEALTH SCIENCES

Impact of the COVID-19 pandemic on the severity of newly diagnosed cases of head and neck cancer in southern Brazil

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Abstract: This observational study aimed retrospectively assess the impact of the COVID-19 pandemic on the head and neck squamous cell carcinoma (HNSCC) diagnosis and severity of the disease in southern Brazil. All new cases diagnosed with HNSCC from March 11, 2019 to March 10, 2020 (pre-COVID-19) and from March 11, 2020 to March 10, 2021 (COVID-19) were included. The data collected were: date of the histopathological diagnosis, sociodemographic data, place of residence, data related to the tumor (location of the primary tumor, lymph node involvement, distant metastasis and TNM clinical staging), time elapsed between the diagnosis and treatment initiation. There was no significant difference in the number of new diagnoses in the COVID-19 group (n=45) compared to the pre-COVID-19 group (n=47). There was also no statistical difference regarding patients' sociodemographic profile, time between diagnosis and treatment, and overall TNM staging. However, the clinical N classification was more severe in the COVID-19 group (p=0.021). Patients diagnosed during the COVID-19 pandemic were 4.05 times more likely to have the N-stage more advanced (95% CI:1.62 – 10.12). Although there was no reduction in the number of new diagnosis of HNSCC during COVID-19 pandemic, the diagnosed cases showed lymph node metastasis in more advanced stages.

Key words: Health, Squamous Cell Carcinoma of Head and Neck, Diagnosis, Lymph Nodes, COVID-19 pandemic.

INTRODUCTION

By November 2022, there were 637,404,847 confirmed cases of COVID-19 and 6,608,893 deaths from the disease throughout the world. The first cases in Brazil were confirmed in February 2020 and, by the end of November 2022, there were 35,104,673 confirmed cases of COVID-19 and 689,341 deaths in the country reported to the World Health Organization (WHO 2023). In the year 2020, the mortality rate due to SARS-CoV-2 infection in Brazil was estimated to be 0.032% among individuals under 30 years of age, 0.22% among those 30 to 49 years of age, 1.2% among those 50 to 69 years of age, and 3.0% among those 70 years of age or older (Marra & Quartin 2021). Studies addressing predictive factors associated with a greater risk of the development of severe forms of the disease and a worse prognosis concluded that older male smokers, mainly over 65 years of age, and/or individuals with comorbidities were at greater risk of developing a critical or fatal form of COVID-19 infection (Izcovich et al. 2020, Ou et al. 2020, Zheng et al. 2020).

The pandemic led to delays in the diagnosis and treatment of other diseases, including cancers (Van Wyk et al. 2021). Authors reported a significant decrease in the weekly number of newly diagnosed cases of breast, lung, stomach,

pancreatic, esophageal, and colorectal cancer, with reductions ranging from 24.7% (p = 0.01) for pancreatic cancer to 51.8% (p < 0.001) for breast cancer (Kaufman et al. 2020). Others authors suggested that the delay in diagnosis due to the COVID-19 pandemic could result in more advanced disease stages, worse prognoses, and statistically significant increases in the number of deaths from breast, lung, esophageal, and colorectal cancer (Maringe et al. 2020).

The restrictions imposed by the pandemic also led to a reduction in the number of new diagnoses of head and neck cancer (Yao et al. 2021, Crossley et al. 2022). With the social distancing measures adopted to control the spread of COVID-19, it is believed that many patients postponed seeking care for the assessment of head and neck lesions, resulting in a delayed diagnosis and, consequently, a worse prognosis (Güneri & Epstein 2014). Few studies have investigated the impact of COVID-19 on the diagnosis and extent of head and neck cancer in low-income countries while considering confounding variables. The hypothesis tested here is that a reduction occurred in the number of patients diagnosed with head and neck squamous cell carcinoma (HNSCC) during the period of greater restrictions and social distancing imposed by COVID-19 and that such cases had indicators of more advanced stages of the disease. Thus, the aim of the present study was to investigate the impact of the COVID-19 pandemic on the number of new diagnoses of HNSCC and the severity of the cases diagnosed at a reference center for the treatment of head and neck cancer.

METHODS

This was a retrospective observational study conducted at the largest public hospital in the central region of the state of Rio Grande do Sul, Brazil, which is a reference center for the treatment of head and neck cancer. The STROBE guideline for observational studies was followed in this study. Data were collected by a single researcher from November 2021 to June 2022 and were obtained through histopathological reports and electronic medical records. The study was approved by the Research Ethics Committee of the Federal University of Santa Maria (CAAE: 52381921.2.0000.5346 / Approval Opinion number: 5.046.605).

All new patients diagnosed with squamous cell carcinoma of the mouth, oropharynx, hypopharynx, or larynx from March 11, 2019 to March 10, 2021 were included. Cases of recurrent disease were excluded from the sample. The groups were divided into a pre-COVID-19 group (cases diagnosed between March 11, 2019 and March 10, 2020) and COVID-19 group (cases diagnosed between March 11, 2020 and March 10, 2021). The date that marks the beginning of data collection in the COVID-19 group was the day on which the World Health Organization officially declared COVID-19 to be a pandemic (Cucinotta & Vanelli 2020). After this declaration, several measures were implemented in Brazil to mitigate the spread of SARS-CoV-2 (Albani et al. 2022).

The following data were collected: date of the histopathological diagnosis, sociodemographic characteristics of the patients (sex, ethnicity, age, and education level), place of residence (inside or outside the municipality where the hospital was located), lifestyle habits (smoking and alcohol intake), tumor characteristics (location of primary tumor, size of primary tumor, lymph node involvement, distant metastasis, and TNM clinical staging), and time elapsed between the histopathological diagnosis and the onset of treatment. Regarding alcohol intake, the patients were classified according to the frequency of consumption as non-alcoholic (no alcohol

intake or sporadic intake [< 5 days a week]) or alcoholic (one or more alcoholic drinks 5–7 days a week) (Koo et al. 2021). TNM clinical staging of the tumors was determined according to the 8th edition of the American Joint Committee on Cancer (Amin et al. 2017).

Data analysis

Data were analyzed descriptively, with the calculation of mean, standard deviation, and median values. The primary outcome was the number of cases diagnosed in the two periods (pre-COVID-19 and COVID-19). The secondary outcome was the severity of the disease. The Kolmogorov-Smirnov (for a sample size > 50) and Shapiro-Wilk (for a sample size < 50) tests were used to determine the normality of the sample. For statistical purposes, some variables were dichotomized. Age was dichotomized by the median (≤ 61 years of age / > 61 years of age); education level was dichotomized as < eight years of study or ≥ eight years of study; ethnicity was dichotomized as white/non-white; location of the primary tumor was dichotomized as mouth and oropharynx or hypopharynx and larynx. The components of the TNM staging system were determined individually (clinical T classification, clinical N classification, and distant metastasis) and final staging was investigated (I, II, III, and IV). Pearson's chi-square test and Fisher's exact test were used to test associations with categorical variables. The Student's t-test and Mann-Whitney test were used to compare the means of continuous variables in the pre-COVID-19 and COVID-19 groups. Logistic regression models were run to determine the odds ratio of greater severity of regional lymph node metastasis according to clinical and demographic variables. For such, the N classification was dichotomized as N0/N1 (absence or lesser severity of lymph node involvement) and N2/N3 (more advanced lymph node involvement). The following categorical variables were incorporated into the unadjusted model: sex, age, education, ethnicity, place of residence, smoking, alcohol intake, location of primary tumor, period of diagnosis (pre-COVID-19 or COVID-19). Variables with a p-value < 0.20 in the unadjusted model were incorporated into the adjusted model and those with a p-value < 0.05 after adjustments were considered significantly associated with the outcome. All statistical tests were performed using Statistical Package for the Social Sciences (SPSS version 21, PASW Statistics, Chicago, IL, USA).

RESULTS

Ninety-two new cases of HNSCC were diagnosed between March 11, 2019 and March 10, 2021: 47 in the pre-COVID-19 group and 45 in the COVID-19 group. No significant difference between groups was found with regards to the mean time elapsed between the definitive (histopathological) diagnosis and the onset of treatment: 94.46 ± 55.99 days in the pre-COVID-19 period and 80.81 ± 47.09 days in the COVID-19 period (p = 0.264). Mean age was 62.28 ± 10.64 years in the pre-COVID-19 group and 60.27 ± 7.50 in the COVID-19 group (p = 0.300). No significant differences between groups were found for other sociodemographic variables or in relation to lifestyle habits (Table I).

Data referring to the disease are displayed in Table II. No statistically significant differences were found with regards to the variables analyzed, except for the clinical N classification, for which a smaller number of cases diagnosed with N0 and N1 and a larger number of cases diagnosed with N2 and N3 occurred during the period of the COVID-19 pandemic compared to the pre-pandemic period (p = 0.021).

Table III displays the results of the binary logistic regression model (unadjusted and

Table I. Sociodemographic data and habits according to the period of diagnosis (pre-COVID-19 / COVID-19).

Variables	Pre-COVID-19 n (%)	COVID-19 n (%)	p-value*
Sex			
Woman	4 (8.5)	5 (11.1)	0.737**
Man	43 (91.5)	40 (88.9)	
Age			
≤ 61 years old	21 (44.7)	27 (60.0)	0.141
> 61 years old	26 (55.3)	18 (40.0)	
Place of residence			
Within the municipality	22 (46.8)	19 (42.2)	0.658
Outside the municipality	25 (53.2)	26 (57,8)	
Schooling			
< 8 years of study	34 (72.3)	31 (68.9)	0.716
≥ 8 years of study	13 (27.7)	14 (31.1)	
Ethnicity			
White	41 (87.2)	39 (86.7)	0.936
Not white	6 (12.8)	6 (13.3)	
Smoking			
No	4 (8.5)	2 (4.4)	0.677**
Yes	43 (91.5)	43 (95.6)	
Alcoholism			
No	19 (40.4)	12 (26.7)	0.163
Yes	28 (59.6)	33 (73.3)	
Total	47 (100)	45 (100)	

*Chi-Square Test; **Fisher's Exact Test.

adjusted) run to determine the odds ratio of diagnosing cases with a greater extent of lymph node involvement during the COVID-19 pandemic. After adjustments, patients diagnosed during the pandemic were 4.05 times more likely to have more advanced lymph node involvement (N2 and N3) compared to patients diagnosed in the pre-COVID-19 period (95% CI: 1.62 – 10.12).

DISCUSSION

With a population of approximately 210 million, Brazil accumulated a total of 11,202,305 cases of COVID-19 and 270,656 deaths from the disease between March 11, 2020 and March 10, 2021, at which time immunization of the population through vaccination was in a very incipient phase (Coronavirus Brasil 2023). In this period,

social distancing measures to combat the spread of COVID-19 were adopted by different states in the country (Aquino et al. 2020), which had a considerable impact on the reduction in the number of new diagnoses of cancer in all regions of the country (Marques et al. 2021). In the present study, however, no reduction was found in the number of new cases of HNSCC diagnosed during the pandemic. Moreover, no significant differences between the two study groups were found with regards to the overall TNM staging or the time elapsed between diagnosis and the onset of treatment. However, the extent of disease determined by lymph node metastasis was more severe in the COVID-19 group, as patients in this group were four times more likely to have a more advanced N stage (N2 and N3).

Table II. Data referring to the disease according to the period of diagnosis (Pre-COVID-19 / COVID-19).

Variables	Pre-COVID-19 n (%)	COVID-19 n (%)	p-value*
Tumor location			
Mouth	20 (42.6)	14 (31.1)	
Oropharynx	7 (14.9)	7 (15.6)	0.710
Hypopharynx	5 (10.6)	6 (13.3)	
Larynx	15 (31.9)	18 (40.0)	
Clinical T Classification***			
T1	7 (14.9)	6 (13.3)	
T2	10 (21.3)	5 (11.1)	0.644**
T3	11 (23.4)	11 (24.4)	
T4	19 (40.4)	21 (46,7)	
Clinical N Classification***			
N0	19 (40.4)	10 (22.2)	
N1	9 (19.2)	3 (6.7)	0.021
N2	14 (29.8)	25 (55.5)	
N3	4 (8.5)	7 (15.6)	
Distant metastasis***			
No	41 (87.2)	43 (95.6)	0.434**
Yes	5 (10.6)	2 (4.4)	
TNM clinical staging***			
I	7 (14.9)	5 (11.1)	
II	5 (10.6)	1 (2.2)	0.248
III	9 (19.2)	6 (13.3)	
IV	26 (55.3)	32 (71.1)	
Total	47	45	

*Chi-Square Test; **Fisher's Exact Test; *** Missing data.

To the best of our knowledge, only one previous study considered covariates that could be confounding factors when assessing the extent of the disease considering the pre-COVID-19 and COVID-19 periods. The study found an increased risk of more advanced clinical nodal staging during the pandemic (Stevens et al. 2022). In contrast, other studies addressing the impact of the COVID-19 pandemic on the diagnosis of new cases of HNSCC demonstrated a 22% to more than 50% reduction in new diagnoses during the pandemic, whereas disease stage and time of diagnosis were similar in groups analyzed before and during the pandemic (Solis et al. 2021, Crossley et al. 2022). This suggests that, although a similar number of patients received the diagnosis in both groups in the present study, patients in the COVID-19 group must have taken longer to seek care after the onset of the first signs and/or symptoms, which may have led to a delay in the diagnosis. Consequently, cases were diagnosed when greater lymph node involvement had already occurred. We did not investigate potential causes of delays in the diagnosis of head and neck cancer during the COVID-19 pandemic. Authors who have addressed this issue attributed delays in the diagnosis to factors associated with restrictions imposed by public health policies aimed at prioritizing care for patients with COVID-19 and minimizing the transmission of the disease. Moreover, patient-related factors, such as fear of contamination or patients already having contracted COVID-19, have been identified as contributors to delayed diagnoses (Ballal et al. 2023).

Studies have shown a significant reduction in the time between the definitive diagnosis and the onset of treatment during the COVID-19 pandemic compared to patients treated in the pre-pandemic period (Schoonbeek et al. 2022,

Table III. Assessment of the disease's extent, determined by the degree of lymph node involvement (absent or less severe versus more severe) and associated variables.

Clinical variables	Crude OR (95% CI)	p*	Adjusted OR (95% CI)	p**
Tumor location				
Mouth / oropharynx	1.0	0.191	1.0	0.083
Hypopharynx / larynx	0.57 (0.25 – 1.32)		0.45 (0.18 – 1.11)	
Alcoholism				
No	1.0	0.135	-	-
Yes	1.95 (0.81 – 4.70)			
Period of diagnosis				
Pre-COVID-19	1.0	0.005	1.0	0.003
COVID-19	3.50 (1.46 – 8.36)		4.05 (1.62 – 10.12)	

Crude binary logistic regression* and adjusted binary logistic regression**; OR: odds ratio; (-): variables not maintained in final model; CI: confidence interval.

Psycharis et al. 2023). In the present study, a slight reduction was found in the time elapsed until the onset of treatment in the COVID-19 group. Although not statistically significant, this reduction may be explained by a slightly smaller number of patients awaiting treatment, as reported by other authors (Schoonbeek et al. 2022), or because the cases were more severe and therefore prioritized. Despite this, the average time elapsed prior to the onset of treatment was high in both groups in the present study, particularly considering findings described by other authors (Yao et al. 2021). Previous studies found that the time elapsed between diagnosis and the onset of treatment was independently associated with the overall survival rate of patients with HNSCC, increasing the risk of five-year mortality (Murphy et al. 2016, Liao et al. 2017, Lauritzen et al. 2021). Efforts of health care providers and the health care system focus on diagnosing and treating cancer early, as the disease stage exerts an influence on the prognosis. A concern that arose for many professionals in this field was that the COVID-19 pandemic would negatively impact the time of diagnosis, disease progression, time to the onset of treatment, and the prognosis of cases of HNSCC (Aquino et al. 2020). Indeed,

studies addressing the impact of the COVID-19 pandemic on the diagnosis and treatment of HNSCC in Brazil within the context of the public health care system found that the pandemic led to a significant reduction in the total number of appointments, hospitalizations, patients attended, diagnostic exams, and surgical procedures (Alvarenga et al. 2023, Cunha et al. 2023).

No significant difference between groups was found in the staging of the cases diagnosed. However, it should be pointed out that more than two-thirds of the cases in both groups had advanced forms of the disease (stages III and IV), which is in agreement with data reported in previous studies (Bonzanini et al. 2020, Yao et al. 2021), and the COVID-19 pandemic may have further aggravated this scenario. South America experienced situations very similar to those experienced by countries in the northern hemisphere with regards to the COVID-19 pandemic, but with events occurring at later dates. Occurrence in countries of the northern hemisphere anticipated and continue to anticipate events that end up occurring in South America. Recent studies have shown an increase in tumor size as well as more advanced lymph node involvement in tumors diagnosed

in the COVID-19 period compared to the pre-COVID-19 period (Kiong et al. 2021, Marques et al. 2021, Solis et al. 2021). The present results confirm these findings. A scenario that was already worrisome proved to be more serious with the COVID-19 pandemic and our results serve as a warning about the importance of identifying and understanding these situations better, which can assist in the establishment of public health measures and the management of these patients.

Although the present investigation covered a one-year period, which may better reflect demographic and seasonal differences normally seen in different months of the year, this study has the limitation of being a retrospective study. Moreover, the absence of statistically significant differences between groups for some of the variables analyzed, such as the number of diagnoses in the two periods and the time elapsed between the definitive diagnosis and the onset of treatment, may have occurred due to the relatively small sample size. It was also not possible to investigate the time elapsed between the manifestation of the first signs and/or symptoms in the patients and the first visit to a health care provider. As this study was carried out at a tertiary care center, many patients may have first sought primary care units close to their homes and were referred to the tertiary service only for treatment. Thus, data on the early signs and/or symptoms could not be obtained. It was also not possible to obtain data regarding pathological staging (neither the T pathological classification nor the N pathological classification).

CONCLUSION

The present results demonstrate that cases of head and neck squamous cell carcinoma diagnosed during the COVID-19 pandemic had greater severity of clinical lymph node involvement, despite the number of cases diagnosed being similar to that of the pre-pandemic period. Longitudinal studies are needed to assess the impact of COVID-19 on the diagnosis and treatment of HNSCC, as well as morbidity and mortality rates.

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