COVID-19 CORONAVIRUS

Head and Neck Cancer during COVID-19 pandemic: Diagnosis and treatment delays?

Original Article

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Abstract

Objectives: To evaluate the impact of Coronavirus disease 2019 (COVID-19) pandemic on the diagnostic and therapeutic approaches of patients with head and neck cancer (HNC).
Study design: Clinical data analysis of HNC patients who started treatment before COVID-19 pandemic period: from September 1st, 2018 to March 10th, 2020 (Group A) and after COVID-19 pandemic period: from March 11th, 2020 to September 30th, 2021 (Group B).
Results: We included 177 patients. After the onset of COVID-19 pandemic, there was larger tumoral extent and more advanced regional lymph node involvement. Moreover, there was a longer duration of symptoms until medical evaluation (p=0,009). However, the time interval between the histological diagnosis and the beginning of the treatment was shorter (p=0,008), even in the subgroup of patients who underwent surgery.
Conclusions: Despite the significant delay in seeking medical care, there was a quick response in approaching patients with HNC during the COVID-19 pandemic.
Keywords: COVID-19; Head and neck cancer; Delayed Diagnoses; Time-to-treatment

Introduction

Head and neck cancer (HNC) accounts for approximately 5.3% of all cancers worldwide[1]. Considering its aggressive behavior and rapid progression, a delay in the diagnosis and treatment of this cancer is associated, in most cases, with a poor long-term prognosis[2,3]. The time interval from the onset of symptoms to medical observation, diagnosis confirmation, and the start of treatment is influenced by numerous factors, including patient-dependent factors, characteristics of the tumor, and the health care service[4].

On March 11, 2020, the World Health Organization declared the coronavirus disease (COVID-19) a pandemic, which inevitably

led to the temporary suspension of routine hospital activity and changes in the clinical management of all patients, including those being considered for priority treatment such as cancer patients. In addition to the restrictions imposed by the COVID-19 pandemic in terms of access to health care services, the fear among the population, especially during the first pandemic phase, led to a decrease in the number of people seeking medical care[5,6]. Thus, there were concerns about possible delays in the diagnosis and start of treatment of patients with HNC. The objective of this study was to compare patients with HNC who were treated in the pre- and post-COVID-19 period with regard to the duration of symptoms, time to diagnosis and treatment, type of treatment, and prognosis. Accordingly, patients who started treatment 18 months before the beginning of the COVID-19 pandemic were compared with those who were treated in the 18 months following the start of the pandemic. The main objective was to assess the impact of the COVID-19 pandemic on the diagnosis and management of patients with HNC.

Materials and Methods

Study design and population:

This was a single-center retrospective cohort study which involved the review of the clinical records of all adult patients (>18 years) with an initial diagnosis of HNC in the department of otorhinolaryngology (ORL) of the Vila Nova de Gaia/Espinho Hospital Center between September 2018 and September 2021.

Study variables:

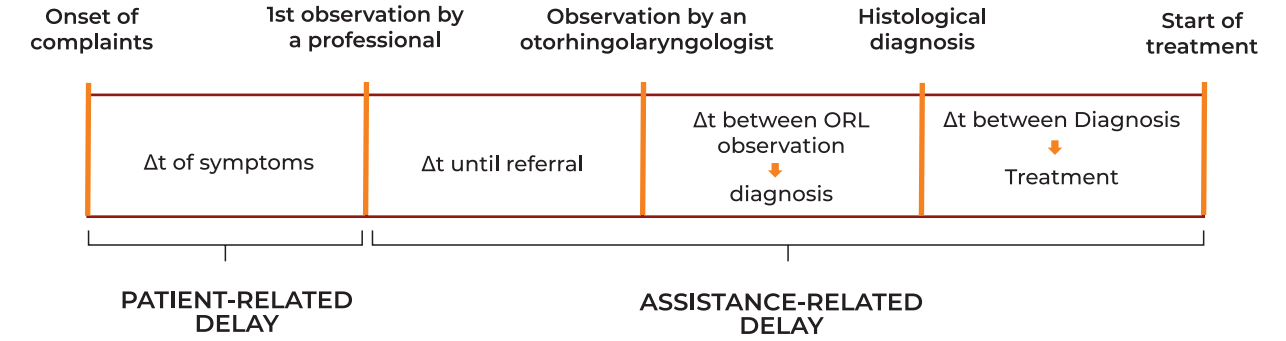
The patients were divided into two groups: Group A (pre-COVID-19) – patients who started treatment before the COVID-19 pandemic (between September 1, 2018, and March 10, 2020); Group B (post-COVID-19) – patients who started treatment after the start of the COVID-19 pandemic (between March 11, 2020, and September 30, 2021). The analyzed variables included sex, age, functional capacity (according to the Karnofsky and ECOG scales; Figure 1), presenting symptoms of the disease, location of the first medical evaluation, tumor site, histological type of the tumor, primary treatment, and mortality one year after the histological diagnosis. Tumor clinical staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging (2017). In addition, the following time intervals were analyzed (in weeks), as shown in Figure 2. Patient-related delay was defined as the interval of time since symptom

Figure 1
Karnofsky and ECOG functional scale

KARNOFSKY FUNCTIONAL SCALE		ECOG PERFORMANCE SCALE	
100%	Without signs or complaints; without evidence of disease	0	Normal activity, without limitations
90%	Able to carry on normal activities with some effort		
80%	Normal activity with effort	1	Limitation of activities requiring great physical effort
70%	Can care for self, but unable to work		
60%	Requires occasional assistance; unable to work	2	Out of bed > 50% of the time
50%	Requires considerable assistance and frequent medical care		
40%	Requires special medical care	3	In bed > 50% of the time; only able to care for self
30%	Severely disabled, hospitalization necessary but death not imminent		
20%	Very sick, requires active supportive treatment	4	Bedridden; unable to care for self
10%	Moribund, imminent death		

Abbreviation: ECOG - Eastern Cooperative Oncology Group

Figure 2
Time intervals analyzed in this study



Interval of time or duration of symptoms: between the onset of symptoms and the first medical evaluation.
Interval of time until referral: between the first medical evaluation and referral and evaluation by an otorhinolaryngologist.
Interval of time from evaluation by an otorhinolaryngologist to histological diagnosis.
Interval of time from histological diagnosis to the start of treatment.
Δt – time interval.

onset until the date of the first medical evaluation. Assistance-related delay was the interval of time between the first medical evaluation and beginning of treatment.

Statistical analysis:
Descriptive analysis was performed, with the results expressed as means (M) and standard deviations (SD) for continuous variables with a normal distribution, and as medians and interquartile ranges (IQR) for those with a non-normal distribution. The categorical variables were presented as the number of cases (n) and percentages. For the bivariate analysis, the categorical variables were compared using the chi-square test or Fisher's exact test, while the continuous variables were compared using the Mann-Whitney test or t-test for independent variables. SPSS® software, version 25.0, was used and the level of statistical significance was set at $p<0.05$.

Results

Characterization of the sample

The study included 177 patients, with 153 men (86.4%) and 24 women (13.6%). Their age at diagnosis varied between 28 and 98 years (M ± SD 62.7 ± 13.0 years). Seventy-seven patients started treatment before the COVID-19 pandemic - Group A (43.5%) and 100 patients started treatment after the beginning of the pandemic - Group B (56.5%). There was a higher degree of functional capacity (measured by the Karnofsky index) among patients in Group B than in those in Group A (A=8; B=9) (p=0.035). There were no statistically significant differences between the two groups in the remaining analyzed parameters (Table 1).

Clinical presentation and type of tumor

The most frequent presenting symptoms were odynophagia in Group A (24.7%) and dysphonia in Group B (33.0%). More than half of the patients in both groups (A=50.6%; B=54.0%) were initially evaluated at the emergency department. There was no difference in the location of the first medical evaluation between the pre- and post-pandemic periods (p=0.905). The most frequent tumor site was the larynx (A=28.5%; B=32.0%) and squamous cell carcinoma was the most prevalent histological type (A=84.4%; B=86.0%).

Tumor clinical staging

With regard to the tumor clinical staging, most patients had a locally advanced-stage tumor or a metastatic tumor (stage III or IV) (Group A=76%; Group B=85.2%). The post-COVID-19 group had a higher proportion of patients in stage III (A=8.0%; B=18.9%) (p=0.04) and stage IVB (A=8.0%; B=24.2%) (p=0.005). In the post-COVID-19 group, the proportion of patients with advanced tumor extension (T3 or T4) was

Table 1
Demographic and clinical characteristics of the patients in the two groups: A and B

Characteristic	Group A (Pre-COVID-19) n = 77 (43,5%)	Group B (Post-COVID-19) n = 100 (56,5%)	p-value
Sex, n (%)			
Female	8 (10,4)	16 (16,0)	0,280
Male	69 (89,6)	84 (84,0)	
Age (years), M (SD)	61,16 (13,6)	63,39 (13,1)	0,157
Functional capacity, median (IQR)			
ECOG	1 (0)	1 (0)	0,126
Karnofsky	8 (1)	9 (1)	**0,035**

Chi-square test, Fisher's test, Mann-Whitney test and t-test for independent samples were used.
Abbreviations: n, number of cases; M, mean; SD, standard deviation; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group

Table 2
Characteristics related to the clinical presentation and type of tumor

Characteristic	Group A (Pre-COVID-19) n = 77	Group B (Post-COVID-19) n = 100	p value*
Presenting sign/symptom, n (%)			
Dysphonia	16 (20,8)	33 (33,0)	0,254
Odynophagia	19 (24,7)	25 (25,0)	
Cervical mass	14 (18,2)	14 (14,0)	
Oral lesion	9 (11,7)	5 (5,0)	
Other	19 (24,7)	23 (23,0)	
Location of first evaluation, n (%)			
Emergency department	39 (50,6)	54 (54,0)	0,905
Primary health care	27 (35,1)	33 (33,0)	
Secondary health care	11 (14,3)	13 (13,0)	
Tumor site, n (%)			
Larynx	22 (28,5)	32 (32,0)	0,532
Oropharynx	20 (26,0)	30 (30,0)	
Oral cavity	11 (14,3)	6 (6,0)	
Hypopharynx	6 (7,8)	13 (13,0)	
Nasopharynx	5 (6,5)	6 (6,0)	
Nasal cavity and PNS	6 (7,8)	6 (6,0)	
Other	7 (9,1)	7 (7,0)	
Histological type, n (%)			
Squamous cell carcinoma	65 (84,4)	86 (86,0)	0,768
Other	12 (15,6)	14 (14,0)	

* Chi-square test
Abbreviation: PNS, paranasal sinus

significantly higher than in the pre-COVID-19 group (A=60.3%; B=75.8%) (p=0.031), as was the proportion of patients with advanced regional lymph node involvement (N3) (A=9.3%; B=24.5%) (p=0.009). On the other hand, there were no statistically significant differences between the two groups with regard to the proportion of patients with distant metastases (p=0.09).

Primary treatment

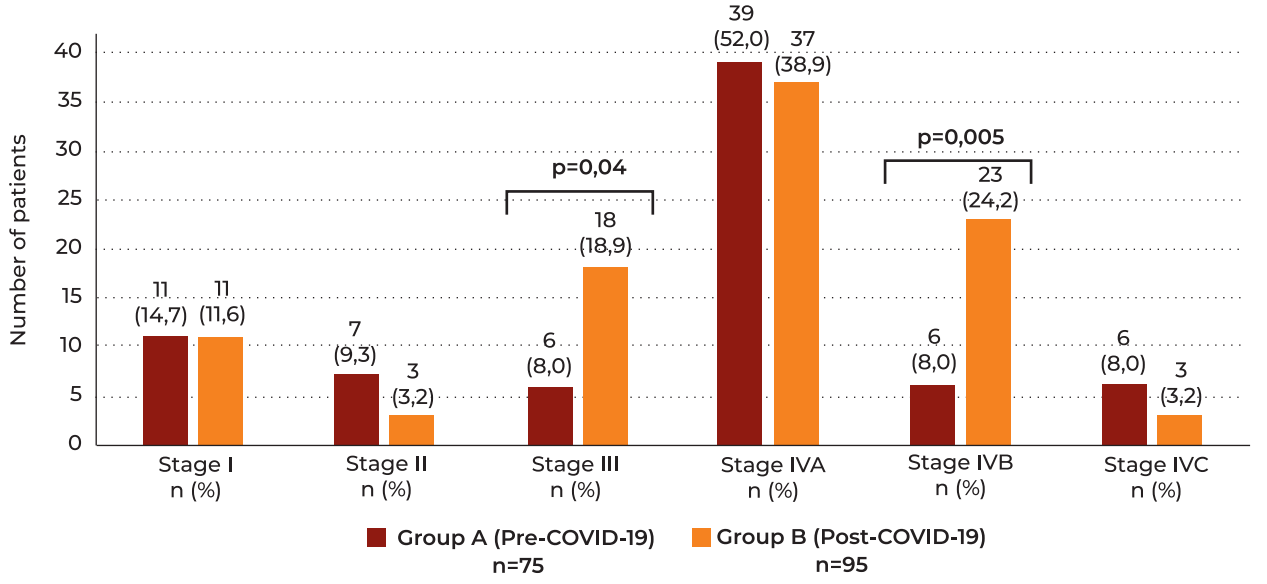
Most patients in both groups underwent treatment with curative intent (A=82%; B=83%). There was a statistically significant difference in the proportion of patients who underwent treatment with palliative intent between the two groups (A=14%; B=4%) (p=0.016). Additionally, a higher proportion of

patients in the post-COVID-19 group could not receive the treatment because of their poor condition; therefore, only supportive care was proposed (B=11%; A=3%) (p=0.036).

Treatment with curative intent

The analysis of the subgroup of patients who underwent treatment with curative intent showed that the proportion of patients who underwent surgery was significantly higher in the pre-COVID-19 group (A=52.4%; B=31.3%) (p=0.009), whereas in the post-COVID-19 group, there was a higher proportion of patients who underwent non-surgical treatment (B=67.5%; A=42.9%) (p=0.003).

Figure 3
Clinical staging in each group (8thed. AJCC)



* Two tumors excluded: Non-Hodgkin lymphoma in the nasopharynx; melanoma in the nasopharynx
ǂ Five tumors excluded: two melanomas of the nasal cavity and paranasal sinuses; melanoma of the nasopharynx; two non-Hodgkin lymphomas of the nasal cavity and paranasal sinuses.

Figure 4
Primary treatment

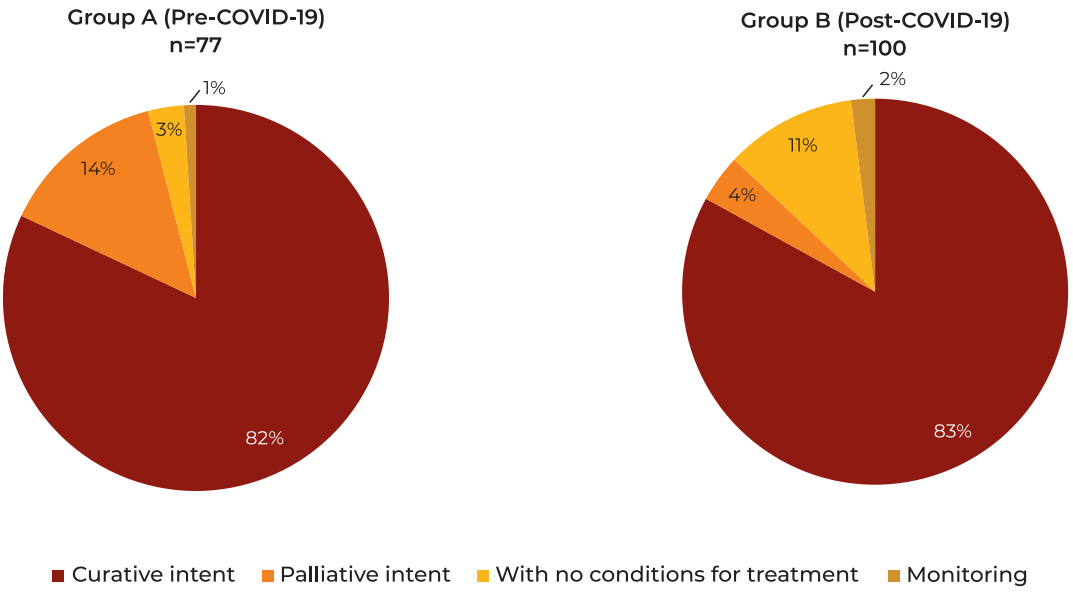
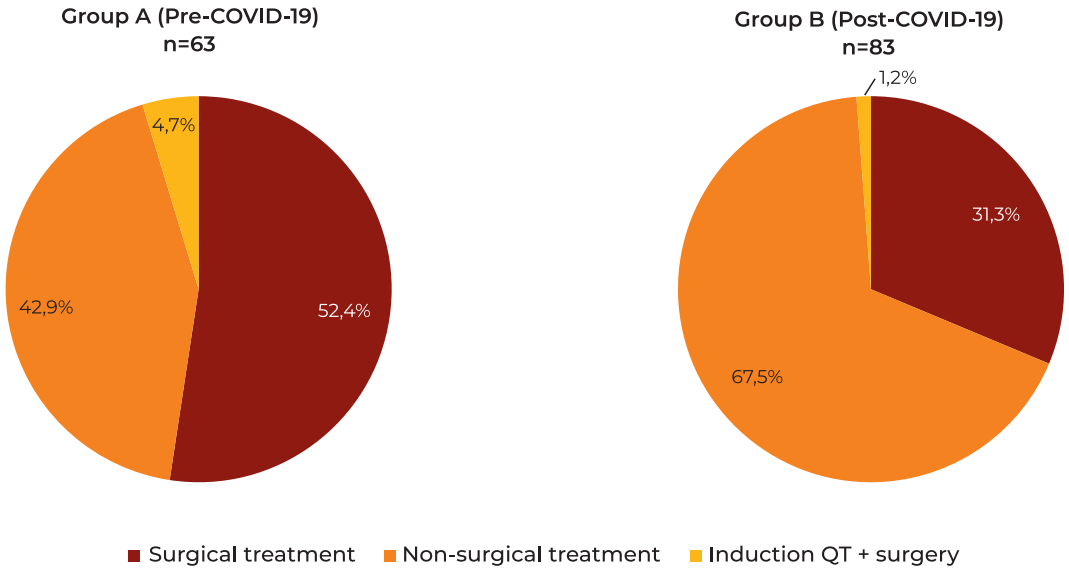


Figure 5
Type of curative treatment



Time intervals

With regard to the analyzed time intervals, as described in Figure 6, the median duration of symptoms in the post-COVID-19 group (B=12.9) was longer than that in the pre-COVID-19 group (A=8.6), and the difference was statistically significant (p=0.009). With regard to the timing of referral and time interval between the ORL consultation and histological diagnosis, there were no differences between the two groups. On the other hand, the time interval between the diagnosis and the start of treatment was significantly shorter in the post-COVID-19 group (B=6) than in the pre-COVID-19 group (A=8) (p=0.008). The analysis of assistance-related delay (time elapsed since the first medical evaluation until the start of treatment) showed no differences between the two groups (A=13.5; B=13) (p=0.523).

Overall, the median time from symptom onset to treatment initiation was 20.6 weeks in the pre-COVID-19 group and 24.1 weeks in the post-COVID-19 group; however, the difference was not statistically significant (p=0.141).

As shown in Table 3, in the subgroup of patients who underwent surgery, there was a statistically significant reduction in the number of weeks that elapsed between the histological diagnosis and intervention in the post-COVID-19 period (A=9; B=5) (p=0.009). However, in the subgroup of patients who underwent non-surgical treatment, the median time until the start of treatment was similar in both periods (A=7.5; B=7) (p=0.317).

Moreover, there was a statistically significant negative correlation between the tumor stage and time interval between the first medical evaluation and treatment initiation (r=-0.195; p = 0.019).

Prognosis

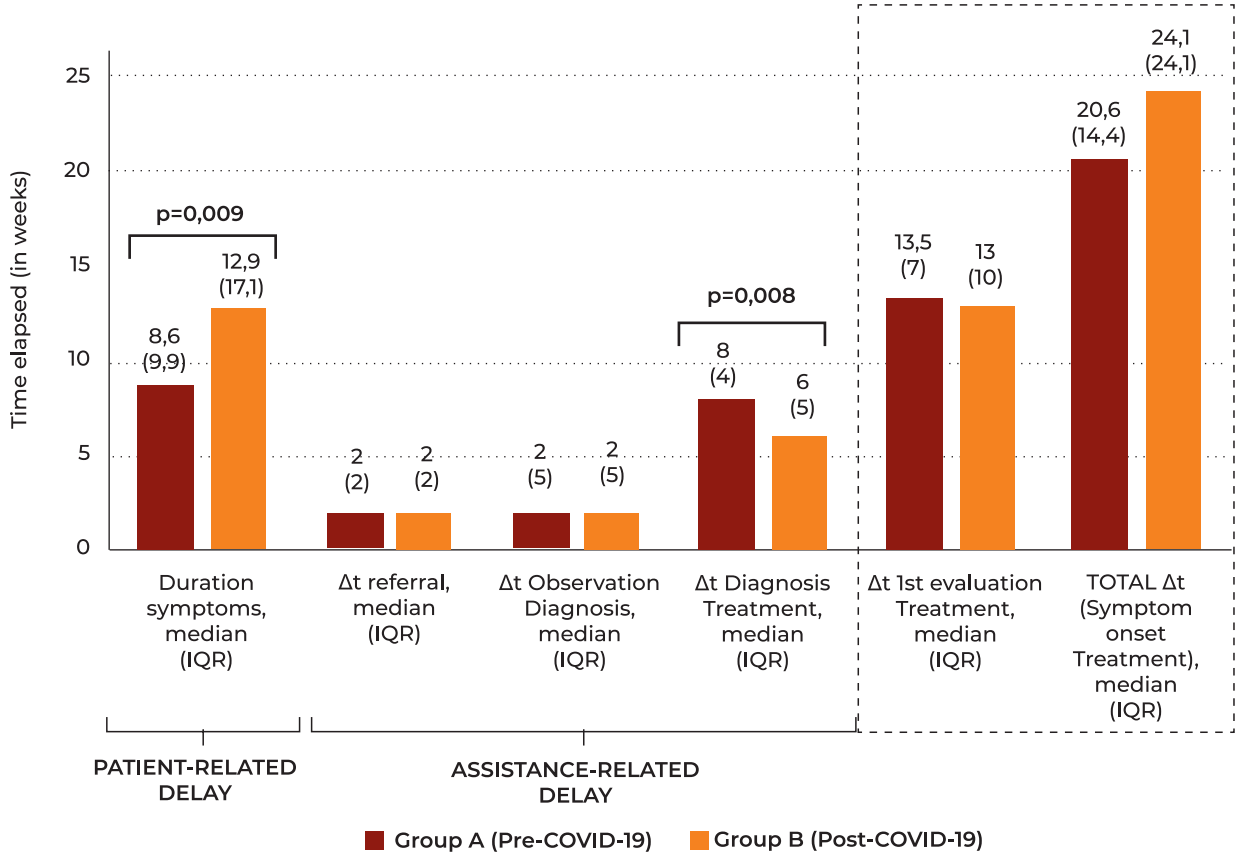
The time interval (in months) between the histological diagnosis and date of death for each patient was recorded. The proportion of patients with survival ≤ 12 months was similar in both groups (A=28.6%; B=29%) (p=0.95).

Discussion

The timely diagnosis and treatment of patients with HNC are associated with a better long-term prognosis[7]. The diagnosis requires a biopsy (often performed in the operating room) as well as complementary diagnostic tools to determine the tumor stage. The involvement of a multidisciplinary team in this complex process is essential for the optimal clinical management of patients with HNC.

However, the restrictions imposed by the

Figure 6
Time intervals in the two groups (in weeks)



Abbreviations: Δt, time interval; IQR, interquartile range

Table 3
Time interval between diagnosis and treatment (in weeks)

Type of treatment	Group A (Pre-COVID-19) Median (IQR)	Group B (Post-COVID-19) Median (IQR)	p-value*
Surgical treatment	9 (6)	5 (4)	0,009
Non-surgical treatment	7,5 (3)	7 (6)	0,317

* Chi-square test
Abbreviation: IQR, interquartile range

emergence of the COVID-19 pandemic inevitably led to a restructuring of health services, which translated into the relocation of professionals to areas dedicated to COVID-19 activities, suspension of consultations and scheduled surgeries, and compulsory screening for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before surgical procedures. All these limitations have raised concerns about possible delays in the diagnosis and start of treatment of patients with HNC, after the surge of the COVID-19 pandemic. In the present study, it was observed that more than half of the patients received their first clinical evaluation in the emergency department in both pre- and post-COVID-19 periods. Odynophagia and dysphonia were the most frequently reported presenting symptoms in the pre-COVID-19 and post-COVID-19 periods, respectively. This difference may be explained by the fact that after the pandemic, many patients with

odynophagia were referred to areas dedicated to respiratory patients and COVID-19 (ADR) and consequently, were not observed by an otorhinolaryngologist.

With regard to clinical tumor staging, tumors were larger (T3 or T4) and regional node involvement was more advanced (N3) in the post-COVID-19 period, which is in line with other reports in the literature (8-10) . In fact, according to the study conducted by Kiong et al ., 39.4% of tumors were classified as T3/4 in the pre-COVID-19 period, compared to 52% of tumors in the post-COVID-19 period (p = 0.025)[10]. In addition, according to Stevens et al., the risk of advanced node involvement at diagnosis (N3, N3a, and N3b) was twice as high in the post-COVID-19 period as in the pre-COVID-19 period (odds ratio [OR]=2.14; p=0.011)[8].

The delay in the diagnosis and management of patients with HNC has been classically attributed to:

1) patient-related factors: fear of diagnosis, illiteracy, and low socioeconomic status; 2) factors related to the nature of the disease, such as the duration of the asymptomatic period and tumor location; 3) factors related to the healthcare system[11]. The COVID-19 surge forced a reduction in routine care, creating another barrier to timely access to health care. Moreover, the mandatory lockdown and fear of contracting COVID-19, especially in the first phase of the pandemic, contributed to the exacerbation of this situation (6).

In fact, as other authors have described[9,12], in the post-COVID-19 period, there was a significant increase in the number of weeks elapsed between symptom onset and the first medical assessment (A=8.6; B=12.9) (p=0.009). However, in our sample, the time interval between the histological diagnosis and the start of treatment was significantly shorter in the post-COVID-19 period (A=8; B=6) (p=0.008). This difference was due to the reduced time interval until the intervention in the subgroup of patients selected for surgery (A=9; B=5) (p=0.009), which may be a consequence of the suspension of the majority of scheduled surgical procedures during the pandemic period, with mostly only priority interventions, such as cancer surgeries, being performed. Nevertheless, the proportion of patients undergoing surgery was lower during this period, which may in part be explained by the fact that the patients in the post-COVID-19 group had more advanced diseases.

Our findings are in line with those of a study published by Schoonbeek et al., in which 8,468 patients with an initial diagnosis of HNC were evaluated over the period encompassing 2018, 2019, and 2020. The authors observed that regardless of the type of treatment, the time interval from the first medical evaluation to the start of treatment was considerably shorter in the year of the COVID-19 pandemic (2020), including during the first pandemic wave (March–June, 2020) (p<0.001) [13].

The main limitations of the present study are its retrospective nature and small size of the sample. In addition, this was a single-center study; therefore, it may not accurately reflect the real situation in the entire country.

The present study demonstrated that during the COVID-19 pandemic, the clinical capacity to manage and treat patients with an initial diagnosis of HNC was maintained. However, further multicenter and prospective studies are necessary to assess the true impact of the COVID-19 pandemic on the long-term prognosis of patients with HNC.

Conclusion

During the COVID-19 pandemic, patients with HNC significantly delayed seeking medical care. However, there was a reduction in the time interval between the diagnosis of the disease and the start of treatment. Thus, despite the overloading and restructuring of the healthcare services due to the emergence of the COVID-19 pandemic, this single-center study showed that patients with HNC continued to receive effective care.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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