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Diagnostic Patterns and Delays of Head-and-Neck Cancer during Coronavirus Disease 2019 Pandemic: A Single-Center Cross-Sectional Study from South Italy

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Abstract: Since a national lockdown was introduced across Italy in early 2020 in response to coronavirus disease 2019 (COVID-19) pandemic, access to health-care services has been limited or suspended. In this cross-sectional study, we examined the delay in the diagnosis and treatment of newly diagnosed head-and-neck cancer (HNC) patients. A total of 59 sequential patients (30 females and 29 males, age 67±14) with HNC were examined between January and September 2020. The average diagnostic delay detected was 152.53 days±62.02 standard deviation (SD) (median 155, range 36–335). Specifically, the average delay between onset of symptoms and first consultation/start of diagnostic pathway (patient delay, D1) was 97.59 days±54.75 SD (median 98, range 13–212), whereas the time needed to reach a final diagnosis (professional delay, D2) was 54.93 days±46.64 SD (median 33, range 4–186). Forty-six patients underwent treatment (surgery, chemotherapy, and/or radiotherapy) within 18.65 days±13.6 SD (median 16, range 1–53) of receiving a diagnosis (treatment delay, D3). Although diagnostic (D1+D2) and treatment (D3) delays were similar for all disease stages and were in line with pre-pandemic data, majority of patients were diagnosed with advanced HNC. Awareness of patterns and delays of HNC diagnosis during COVID-19 pandemic may inform future decisions involving a restricted access to health care.

Keywords: Coronavirus disease 2019, Severe acute respiratory syndrome coronavirus 2, Lockdown, Head-and-neck cancer, Maxillofacial surgery, Delay

1. Introduction

Head-and-neck cancer (HNC) is one of the most common malignancies worldwide with a 5-year survival rate of 57% in Italy, a figure that largely reflects the tumor stage at presentation and the development of locoregional recurrences, distant metastases, and second primary tumors[1,2]. Both medical and surgical treatment protocols are dictated by the assessment of disease staging, which reflects an estimate of the biological and clinical behavior of the

tumor. The American Joint Committee on Cancer/Union for International Cancer Control (UICC/AJCC staging) is a widely adopted staging system and is used to evaluate prognostic outcomes and inform treatments guidelines, which differ greatly according to the stage of the tumor[3].

The unfavorable effects of delay on oncologic, functional, and psychosocial outcomes in HNC are undisputed[4,5]. Timing is indeed one of the most important prognostic factors, particularly in high proliferative tumors such as HNCs. Longer delay between onset of symptoms and diagnosis correlates with advanced cancer staging, which, in turn, leads to more aggressive surgical and/or chemoradiation therapies, higher morbidity and loss of function, lower quality of life (QoL), and lower overall survival rate[4]. Moreover, the onset of tumors in such a peculiar anatomical district may be psychologically debilitating as it has a remarkable impact on esthetics and social relation both pre- and postoperatively[5]. Early diagnosis of HNC is, therefore, crucial for a more favorable prognosis in terms of disease stage, survival, and QoL. To achieve this aim, it is important to minimize the delays in the diagnosis and treatment of HNC[6,7].

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020, following a rapid global spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In Italy, local restrictions and modified referral pathways were instituted early in 2020, and the fast nationwide spread of this virus led to the institution of social distancing measures and of the so-called lockdown. Italy applied one of the most restrictive measures outside of China, with confinement measures for the population and the closing of all public activities and stores besides shops for basic needs. With regard to health care, all services and treatments for non-life-threatening conditions were temporarily suspended, including screening programs and outpatient referrals. In particular, maxillofacial surgeons, ear-nose-throat (ENT) physicians, and dentists are considered high-risk workers, and therefore, surgical procedures were limited to emergencies, such as airway impairment, hemorrhages, severe infections, facial fractures, and malignant tumors[8-11].

Although cancer treatments were not suspended, the lockdown may have led to unintended effects on the ability to detect neoplasia in their first stages. Therefore, the aim of this study was to assess the diagnostic and treatment delay of HNC patients during COVID-19 pandemic.

2. Materials and methods

2.1. Study design and settings

This cross-sectional study included patients attending the maxillofacial unit at the first policlinic university hospital, University of Campania "Luigi Vanvitelli," Naples, between January and July 2020. The study was conducted in adherence with the Declaration of Helsinki principles guidelines and conformed to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for observational studies. Patients attended our unit through two main pathways, namely: 1. Referral from general practitioner or dentist and 2. Direct emergency appointment through university hospital.

2.2. Ethics approval

All patients provided written informed consent for the management of personal data before participating in the study. The study was approved by the ethics committee of the University of Campania "Luigi Vanvitelli" (prot. 0013333, 29 April 2021).

2.3. Inclusion and exclusion criteria

All patients recruited for this study met the following inclusion criteria: (1) Patients of both genders, all ages and races, with the presence of clinical findings consistent with HNC; (2) histopathological and, if relevant, immunohistochemical confirmation of the diagnosis was available; and (3) patients were able to give consent if older than 18 years. Patients with previous non-HNC diagnosis were excluded from this study.

2.4. Patient interview and data collection

One researcher interviewed the selected patients under the guidance. The interview was carried out to explain the nature of the study and asking the participants about the onset of symptoms and date of first medical consultation. Data were collected using a custom datasheet. The time elapsed between the reported onset of symptoms and the first maxillofacial consultation was labeled as "D1," the duration between the first maxillofacial consultation and communication of the diagnosis was labeled as "D2." The duration between the final diagnosis and the beginning of the proposed treatment was labeled as "D3." The total diagnostic delay was considered as D1 + D2. To control potential bias resulting from patients being unable to recall precisely the information requested, patient's medical records were consulted and when discrepancy was detected, the patients were contacted by phone, email, or instant messaging services to provide any missing information or correction.

2.5. Patient examination and severity scoring

All participants and relevant investigations were examined independently by two researchers (G.C. and G.L.G.) and the severity of the presentation was assessed using tumor, node, and metastasis scoring and staging according to the AJCC/UICC staging system for HNC.[3] The outcomes were discussed with senior author (N.C.), who tabulated the data using an Excel spreadsheet.

2.6. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM

Corp.). Descriptive statistics of demographic characteristics were expressed as mean, median, percentage, and standard deviation (SD). Analysis of variance (ANOVA) with Tukey's *post hoc* test was used for the assessment of continuous variables that were normally distributed in our cohort. $P<0.05$ was considered as statistically significant. In our model, variables with $P<0.020$ detected in the univariate analysis, if any, were included in a multiple logistic regression model by the stepwise forward method. Pearson's correlation coefficient was employed to assess the relationship between delay and age (analyzed as continuous variables) whereas the Chi-square test was used to show whether there was a relationship between stage at diagnosis (I-IV) and delay (four quartiles), both analyzed as categorical variables.

3. Results

3.1. Patients' demographics and characteristics

A total of 59 sequential patients (30 females and 29 males) were diagnosed with HNC between January and July 2020 and followed up until September 2020. Age at the time of diagnosis ranged from 36 to 91 years old with a mean of 67±14 years.

About half of our patients (n=29, 49.2%) were diagnosed with oral squamous cell carcinoma, 9 patients (15.3%) with salivary glands carcinomas, 7 patients (11.9%) with cutaneous squamous cell carcinoma, 4 patients (6.8%) with non-Hodgkin lymphoma, 2 patients (3.4%) with melanoma, 1 patient (1.7%) with oropharyngeal carcinoma, 1 patient (1.7%) with carcinoma of the rhinopharynx, 1 patient (1.7%) with concurrent oral squamous cell and sinonasal carcinomas, and 1 patient (1.7%) with myofibroblastic sarcoma. Finally, 4 patients (6.8%) received a diagnosis neck metastasis from other primary tumor (**Table 1**).

Most patients (61%) were diagnosed with advanced HNC, with 11 patients staged as Stage III (8 III, 1 IIIA, and 2 IIIC) and 25 patients as Stage IV (4 IV, 6 IVA, 14 IVB, and 1 IVC). Fourteen patients were staged as Stage I (11 I, 2 IA, and 1 IB) and nine patients as Stage II (7 II and 2 IIA). Among these 59 patients, 28 (47.5%) underwent surgery, 7 patients (11.9%) received radiotherapy, 5 patients (8.5%) received chemotherapy, 6 patients (10.2%) were referred for a combined chemo/radiotherapy treatment, and 13 patients (22%) were lost after diagnosis or refused to the proposed therapeutic plan. Patient demographics are summarized in **Table 1**.

3.2. Delay analysis

The average diagnostic delay detected was 152.53 days ±62.02 (median 155, range 36–335). Specifically, the average delay between onset of symptoms and first specialist consultation/start of diagnostic pathway (D1) was 97.59 days±54.75 SD (median 98, range 13–212), whereas the time needed to reach a final diagnosis (D2) was 54.93 days±46.64 SD (median 33, range 4–186). Forty-six patients underwent treatment (surgery, chemotherapy and/or radiotherapy) within 18.65 days±13.6 SD (median 16, range 1–53) from receiving a diagnosis (treatment delay, D3) (**Figure 1)**. Detailed subgroup analysis is reported in **Figure 2**.

The difference between mean diagnostic delay in male (mean=147.21, SD=71.52) and female (mean=157.67, SD=51.94) patients was not statistically significant (t-test, $P=0.522$). Similarly, the diagnostic delay of patients at first diagnosis (mean=150.73, SD=63.6) and those with recurrence of disease (mean=160.39, SD=56.69) was not significantly different ($P=0.646$). In other words, HNC patients who were already in follow-up experienced the same delay as those who were diagnosed with HNC for the 1st time. There was a weak positive correlation between delay and age (Pearson's $r=0.2$). Although there were peaks of 310 and 350 days in the total delay for Stage IV patients, analysis of subgroups revealed that there was no statistically significant difference of delay in the four cancer stage groups (ANOVA, $P=0.773$). Further, we found no relationship between cancer stage and diagnostic or treatment delay ($P=0.76$ and 0.357, respectively). With regard to first-line treatment modality (chemotherapy, radiotherapy, chemo-radiotherapy, or surgery), mean total delay was over 200 days for all subgroups except surgery, which had a considerably lower total delay (main=147.32, SD=73.11), albeit not significant. In summary, these data show that there were similar patterns of diagnostic and treatment delay regardless of cancer stage and treatment.

4. Discussion

SARS-CoV-2 pandemic has important repercussions for health care beyond COVID-19, particularly with regard to the effects of lockdown restrictions on health and well-being. In this cross-sectional study of 59 patients diagnosed with HNC, we show that the average time between onset of symptoms and diagnosis was 152.53 days, whereas the average treatment delay was 18.65 days.

Diagnostic delay can be seen as the sum of patient delay (reported as D1 in our study), which is the time between the onset of symptoms and first medical consultation, and the professional or provider delay (reported as D2), that is, the time between the first medical examination and the final diagnosis[6]. Although high variability is reported, which reflects different contexts and health-care systems, patient delay usually extends between 1.6 and 5.4 months, while professional delay ranges between 5 and 21 weeks. Importantly, prognosis is worse when the delay reaches 3 months or more[6,7]. In out cohort, the average delay between onset of symptoms and first consultation (patient delay, D1) was 97.59 days, that is, roughly 3 months. Although this delay falls within previously reported "acceptable" ranges, it may contribute to the poor prognosis of advanced HNCs.

Table 1. Patients' demographics

Gender		Staging	
	n (%)		**n (%)**
Male	29 (49.2%)	I	11 (18.6%)
Female	30 (50.8%)	IA	2 (3.4%)
Age		IB	1 (1.7%)
	Mean (±SD)	II	7 (11.9%)
Age	67 (±14)	IIA	2 (3.4%)
Therapy		III	8 (13.6%)
	n (%)	IIIA	1 (1.7%)
Chemo/radio	6 (10.2%)	IIIC	2 (3.4%)
Chemotherapy	5 (8.5%)	IV	4 (6.8%)
Radiotherapy	7 (11.9%)	IVA	6 (10.2%)
Refused/lost	13 (22.0%)	IVB	14 (23.7%)
Surgery	28 (47.5%)	IVC	1 (1.7%)
Diagnosis			
	n (%)		**n (%)**
Parotid adenocarcinoma	1 (1.7%)	Oral squamous cell carcinoma	29 (49.2%)
Parotid polymorphous low-grade adenocarcinoma	1 (1.7%)	Oral squamous cell carcinoma + sinonasal carcinoma	1 (1.7%)
Parotid gland squamous cell carcinoma	1 (1.7%)	Non-Hodgkin lymphoma	4 (6.8%)
Submandibular gland metastasis from lip squamous cell carcinoma	1 (1.7%)	Myofibroblastic sarcoma	1 (1.7%)
Submandibular gland adenoid cystic carcinoma	1 (1.7%)	Cutaneous squamous cell carcinoma	7 (11.9%)
Minor salivary gland adenoid cystic carcinoma	2 (3.4%)	Melanoma	2 (3.4%)
Minor salivary gland adenocarcinoma	1 (1.7%)	Neck lymph node metastasis from melanoma	1 (1.7%)
Minor salivary gland carcinoma ex pleomorphic adenoma	1 (1.7%)	Neck lymph node metastasis from occult primary	2 (3.4%)
Oropharynx carcinoma	1 (1.7%)	Neck lymph node metastasis from breast cancer	1 (1.7%)
Rhinopharynx carcinoma	1 (1.7%)		

Maxillofacial surgeons, ENT, and dentists are high-risk practitioners since the anatomical district to be examined requires patients to remove their facemasks. Moreover, during surgery, droplets and aerosol particles production is possible – for example in tracheostomy procedures, use of rotating or piezoelectric instruments, or diathermocoagulation; therefore, standard and transmission-based precautions, which include but are not limited to personal protective equipment, should be used at all times to reduce the chance of contagion[8-11]. In Italy and specifically in our university hospital, surgical procedures were limited to emergencies: Airway impairment, hemorrhages, severe infections, facial fractures, and malign tumors.

Emotional response such as fear and denial is strongly related to diagnostic delay in cancer patients, affecting mostly D1 timeframe[12-14]. The restrictions established during the lockdown may have lead patients to refrain from any action or to self-medicate. Although oncological treatments were not suspended during 2020 pandemic, delays in cancer diagnosis have been reported in the literature[14-19]. In one example, Papautsky and Hamlish reported pervasive delay during breast cancer care[16]. The delay was consistent across multiple factors suggesting that

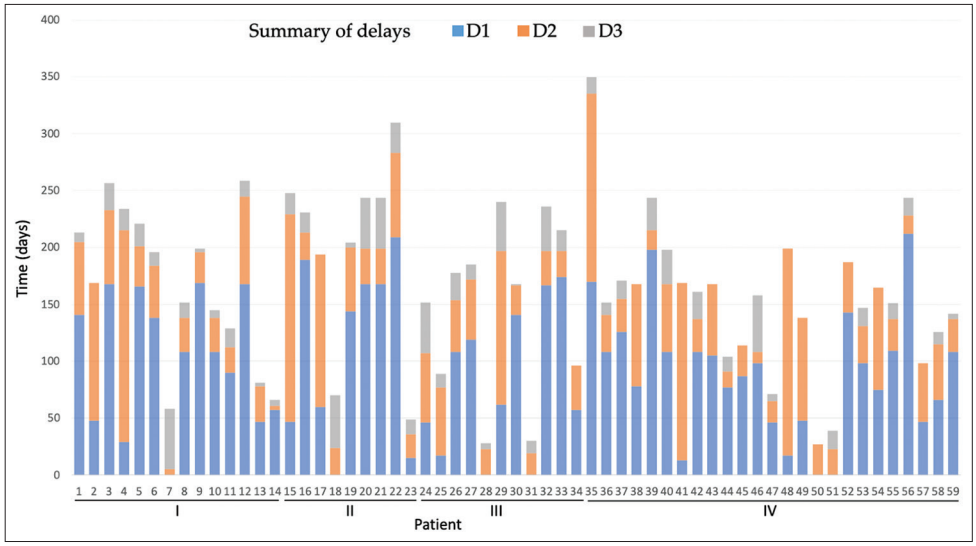

Figure 1. Delay in the referral, diagnosis, and treatment of 59 patients with cancer of the head-and-neck cancer. Delays are reported as color-coded histograms, specifically: D1 (blue), the time elapsed between the reported onset of symptoms and the first medical or dental consult; D2 (orange), time between first consultation and diagnosis; D3 (gray), time from final diagnosis to beginning of treatment. Numbers on histograms indicate time (days).

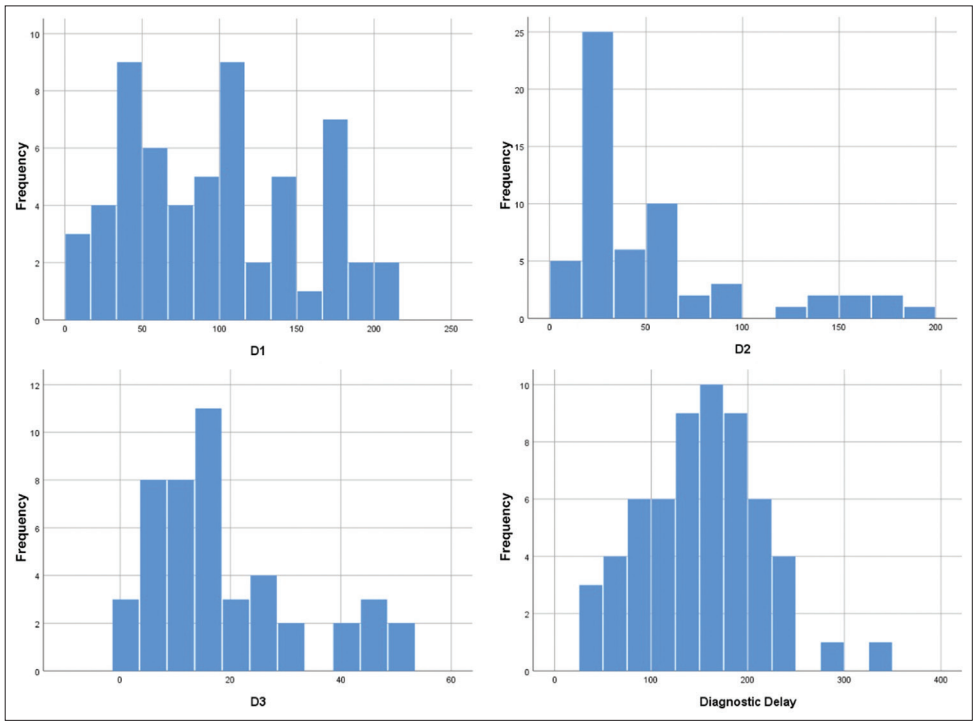

Figure 2. Frequency distribution of delay, namely: D1, patient delay; D2, professional delay; D3, treatment delay; D1+D2, diagnostic delay. X-axis, time range (days); Y-axis: Frequency (number of patients).

it is not based on risk stratification of patients rather it is due to widespread barriers come in place after the beginning of the pandemic, affecting mostly cancer survivors in clinical outcomes, mental health, pain, and QoL. Wang *et al.* (2020) developed a team-based approach to reduce the obstacles encountered while treating bladder cancer patients, strictly prioritizing treatments to optimize the clinical outcome[15]. The authors also suggested delaying post-treatment surveillance when possible, choosing specific chemotherapy treatments for localized bladder cancer, and increasing the treatment period between cycles of palliative systemic therapy in metastatic patients.

Although our cohort study does not support a correlation between overall delay and HNC staging, it is likely that early diagnosis of cancers has been hampered during COVID-19 pandemic. Del Vecchio Blanco *et al.* (2020)

assessed the impact of COVID-19 on early diagnosis and prevention of colorectal cancer[16]. The authors foresee more advanced stages at diagnosis, 20% reduction of effectiveness of screening on mortality, and higher costs due to advanced stage patients case in the future. They, therefore, proposed to include general practitioners in risk stratification assessment to prioritize high-risk patients, to strengthen the adherence to post-surgical guidelines to reduce over-prescription, and to better schedule endoscopies anticipating or postponing the procedure following precise indications.

Treatment delay (D3) was in line with the current literature in our cohort. Strikingly, it has been reported that treatment plans were delayed and/or changed in almost all patients diagnosed with COVID-19, influencing severely the clinical outcomes. Bogani *et al.* (2020) reported a case series of patients affected by both gynecological cancer and COVID-19[7]. The authors highlighted a high mortality rate (13.5%) and described a delay on both chemotherapy and surgical treatment. Ozturk *et al.* (2020) reviewed the clinical guidelines for plastic surgery detailing several clinical scenarios[17]. The authors indicated that definitive reconstruction could be delayed for select cases and less invasive, more conservative procedures should be preferred when possible. Delays in oncological surgical treatments may be acceptable as patients are eligible for neoadjuvant treatments. Ginsburg *et al.* (2020) analyzed the potential differences of outcome in delayed radical prostatectomy during the pandemic[18]. The results showed that it did not lead to worse oncological outcomes.

COVID-19 pandemic was faced by head-and-neck and maxillofacial surgeons all over the world, with clinical and surgical practice adjusted accordingly. Reducing non-essential personnel, postponing elective procedures, managing PPE availability in wards, while trying to balance patients' health care and doctor safety are some of the key challenges[19-24]. Multicenter collaboration and telemedicine are strongly suggested, although an increased likelihood of biased clinical examination or impossibility of communicating to elderly patients may have contributed to the diagnostic delay[25]. In terms of treatment, changes in both ablation and reconstruction were advocated, together with shifting from high- to low-risk procedures and analyzing the potential outcomes of non-surgical management to inform future decisions[26-28]. Complex free flap reconstruction was not recommended, and suggestions were made to favor the use of primary closure skin grafts and local or regional flaps to minimize surgery time and hospitalization, thus likely affecting patients' morbidity and mortality rate[17]. An American and European Society for Radiation Oncology Consensus provided practice recommendation of radiotherapy management of head-and-neck tumors and giving insights into the appropriate therapeutic schemes to perform in face of the new risk-benefit balance during the pandemic[29].

Our study does not come without limitations. We described the demographics and delay in the diagnosis and treatment of HNC patients in South Italy. However, we could not make comparisons with previous years. Nevertheless, we believe that it is important to share our experience to offer real life data that can be used to inform future lockdown policies. Interestingly, our data are in line with previous pre-pandemic studies undertaken in Italy[30]. In one example, Marella *et al.* (2018) reported that the average delay of patients (who were later diagnosed with oral carcinoma) from onset of signs and/or symptoms and seeking medical care was 112 days, whereas an average delay of 40 days was observed between the first biopsy and treatment[30]. This is in agreement with recent reports demonstrating that there was not a significant change in the diagnostic delay for HNC during lockdown[31]. In another study from Northeast Italy, a large cohort of patients diagnosed with HNSCC was examined[32]. The median time to treatment initiation, equivalent to treatment delay (D3), was 28 days in the pre-pandemic era[32], whereas, in this study, we reported a median treatment delay of 16 days (mean 18.65±13.6 days). While these data suggested that lockdown restrictions did not affect the diagnostic and treatment delay of HNC patients, further well-designed retrospective studies are needed to better assess this correlation.

Reporting some of the highest numbers of COVID-19 cases globally, Italy was the first country in Europe to implement an extensive containment plan to control the spread of the disease. Overall, researchers believe that containment measures and general lockdown implementation are effective in flattening the contagion curve, especially during early stages and on large areas[33-37]. While lockdown has had an effect on quality of care and QoL well beyond COVID-19, the wider consequences of lockdown on health care are hard to compare, particularly because not every country applied the same measures and each one introduced restriction at different times and had a different level of cases and saturation of hospital capacity. In a recent study from Italy, HNC survivors, who are particularly vulnerable to the deleterious consequences of lockdown and social distancing, were found to be at high risk for a worsening in QoL related to COVID-19[38]. An international cross-sectional study conducted during the COVID-19 pandemic also showed that QoL of head-and-neck health care workers was also significantly impacted, particularly in low- and middle-income countries[39]. All these variables make it difficult to gauge the significance and impact on QoL of the diagnostic delay detected in our study. Other limitations of our study are directly related to the cross-sectional study design and include recall bias. Importantly, we included patients attending our unit from January 2020, that is, before the pandemic was officially declared, because Italy was the first country affected by COVID-19 in Europe and local restrictions or fear of contagion were already present in early 2020. Furthermore,

the timeframe of our investigation did not allow us to compare to previous years and to define the severity and differences of HNC between the past and the current COVID era. Studies are ongoing to assess the difference, if any, in the diagnostic delay of HNC patients in 2020 compared to previous years. Nevertheless, we believe that it is important to share our data with the scientific community to better inform future decisions concerning health care.

5. Conclusions

Our study shows the time elapsed between onset of symptoms and treatment approached in an average of 6 months in newly diagnosed HNC during the first half of 2020. Specifically, the mean diagnostic delay for HNC was 152.53 days, whereas the mean treatment delay was 18.65 days. While we do not currently know whether COVID-19 restrictions affected HNC outcomes, our results seem to be in line with pre-pandemic data. Furthermore, awareness of the patterns and delays in the diagnosis and management of these cancer patients may help stakeholders to plan evidence-based strategies for the provision of health-care services in South Italy and worldwide.

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Conflict of interest

No conflicts of interest were reported by all authors.

Author contributions

G.C., conceptualization. R.R. and M.F., methodology. N.C., visualization. G.C., writing – original draft preparation. G.L.G. and N.C., Writing – review and editing. N.C., project administration. G.T., supervision. All authors have read and agree to the published version of the manuscript.

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