Acta Clin Croat (Suppl. 4) 2022; 61:19-25
doi: 10.20471/acc.2022.61.s4.2

Original Scientific Paper

THE IMPACT OF COVID-19 ON HEAD AND NECK CANCER TREATMENT DELAY

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SUMMARY – The aim of this study was to demonstrate the impact of COVID-19 pandemic on the number and characteristics of head and neck cancer patients in two consecutive periods, pre-pandemic and pandemic. For this purpose, we performed a retrospective analysis of patients with primary carcinomas of head and neck mucosal sites, salivary gland tumors, as well as neck metastases. Two pre-COVID-19 years (2018-2019) and two pandemic years (2020-2021) were compared. Demographic data, overall number of patients, TNM classification of the two most affected sites (oral cavity and larynx), time from symptom onset to first outpatient admission to our department, and time from first admission to treatment initiation were noted. Study results revealed a higher number of patients during the pandemic period and difference in the distribution of tumor sites ($\chi 2=33.68$, df=9, $p<0.001$). Oral cavity cancer prevailed over laryngeal cancer during the pandemic period. A statistically significant difference was observed in delay of initial presentation to head and neck surgeon for oral cavity cancer during the pandemic period ($p=0.019$). Furthermore, significant delay was found for both sites concerning time from initial presentation to the beginning of treatment (larynx: $p=0.001$ and oral cavity: $p=0.006$). Despite these facts, there were no differences in TNM stages comparing two observed periods. Study results indicated that there was a statistically significant delay of surgical treatment for both cancer sites observed (oral cavity and larynx) during the COVID-19 pandemic. A survival study is necessary in the future to definitely reveal the true consequences of COVID-19 pandemic on treatment outcomes.

Key words: *COVID-19; Head and neck cancer; Pandemic; Delay in care*

Introduction

COVID-19 pandemic has brought upon major changes in healthcare utilization around the world. Every country in the world has had to reorganize its healthcare service according to its possibilities and peculiarities. In Croatia, total lock down was in force from March 16, 2020 until May 4, 2022, and during that period the availability of primary healthcare service was restricted to mostly telemedical and e-mail communication, and hospital system was set to treat only emergency cases and patients suffering from malignant disease[1]. Almost 90% of medical facilities involved in the treatment of patients suffering from malignant disease reported difficulties in providing their full spectrum of care and 55.34% of them reported that they had to reduce their capacity due to COVID-19 patient overload, shortage of medical

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staff, shortage of operating theaters and intensive care unit (ICU) beds[2]. It is very important to note that the recommendations considering treatment of malignant tumors in the early days of the pandemic were consistent with choosing nonsurgical methods (chemo-radiotherapy) whenever possible, or when surgery was the only possible treatment, it should have been postponed, if possible[3]. In patients suffering from head and neck tumors, the extent of surgery was reduced whenever possible, meaning that only simple reconstructive options were chosen instead of complex microsurgical reconstructive procedures[4]. Most of the above-mentioned circumstances were present during 2020 and 2021, and are still encountered today, although anecdotally. In this study, the authors wanted to examine the following: 1) the proportion of head and neck cancer patients during the COVID-19 pandemic at the Department for Otorhinolaryngology and Head and Neck Surgery, Zagreb University Hospital Center compared to the pre-COVID period; 2) the existence of any TNM stage difference in oral cavity cancer and laryngeal cancer between the two periods observed; 3) and whether there was a delay in initial presentation and beginning of treatment in the period of the pandemic compared to the pre-pandemic period.

Patients and Methods

Patients with primary head and neck carcinomas of mucosal origin, salivary gland carcinomas, neck metastases from unknown primaries, skin tumors or distant tumors, skull base tumors, etc., who were referred to the Department of ENT and Head and Neck Surgery, Zagreb University Hospital Center in the period between January 1, 2018 and December 31, 2021 were evaluated. Recurrent tumors, primary skin tumors and thyroid gland tumors were excluded from the study. In order to find the possible impact of COVID-19 pandemic on the overall number of cases, distribution of tumor subsites and stages, the four-year observational period was divided in two groups, as follows: pre-COVID-19 group including 2018 and 2019, and COVID-19 group including 2020 and 2021. TNM staging was performed only for the two most frequent sites of origin, oral cavity and larynx, i.e., two sites that according to the treatment policy of our department are almost exclusively treated by primary surgery. All decisions related to treatment were confirmed by the institutional Multidisciplinary Team (MDT) for head and neck tumors. Noteworthy, during the pandemic, MDT conferences were incomplete and a bit irregular, which resulted in the lack of some data in our digital database. *In situ* lesions in both oral cavity and larynx were excluded from TNM staging. Tumors were classified according to the 2018 American Joint Committee on Cancer (AJCC) staging rules. One of the main aims of this study was to evaluate the possible impact of COVID-19 pandemic on the delay of patient initial presentation and beginning of treatment. With this purpose, history data were evaluated. The time elapsed from symptoms onset to the initial presentation to the Department outpatient clinic (in days, time 1) and time elapsed from first visit to treatment initiation (time 2) was captured. All statistical analyses were performed using SAS (version 23). The normality of distribution was tested using Shapiro-Wilks test, while homogeneity of variance was tested using Levene test. Differences between the groups of independent continuous variables were analyzed using t-test and Mann-Whitney test. Differences in the prevalence of individual conditions were compared using the χ^2-test. Statistical significance was defined as $p<0.05$.

Results

A retrospective study was performed. During the 4-year observed period, 691 patients with head and neck malignancies were treated at our department. Two consecutive periods were compared. The 2018-2019 period before COVID pandemic was compared to the 2020-2021 period during COVID-19 pandemic. In the first and second period, 320 and 271 patients were treated, respectively. Distribution of different malignancy sites was compared, as shown in Figures 1 and 2. Difference in the distribution was statistically significant ($\chi^2=33.68$, df=9, $p<0.001$). Further analyses were performed for the sites most frequently involved, i.e., larynx and oral cavity. During the pandemic period, more patients were diagnosed with oral cavity cancer compared to laryngeal cancer. In the first period, there were 101 (75.9%) patients with laryngeal cancer and 32 (24.1%) patients with oral cavity cancer. During the pandemic period, there were 85 (49.1%) patients with laryngeal cancer and 88 (50.9%) patients with oral cavity cancer (Table 1). Demographic characteristics are shown in Table 2. The majority of patients diagnosed with laryngeal and oral cavity cancers were males in the seventh life decade. TNM staging was performed using 2018 AJCC classification, and results are shown in Table 3. Pearson χ^2-test

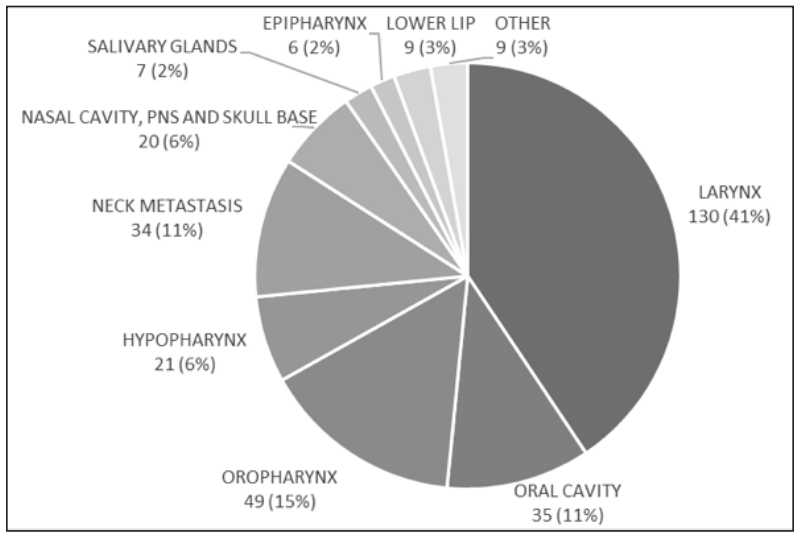

Fig. 1. Site distribution of tumors 2018-2019.

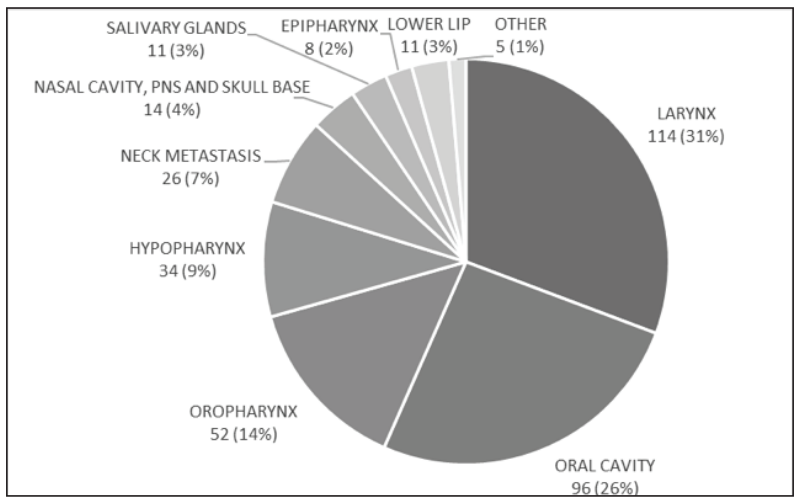

Fig. 2. Site distribution of tumors 2020-2021.

was used to test differences in T, N, M status, as well as disease stage between the two periods for both sites observed. There were no statistically significant differences between two periods in T (χ^2=4.635, df=3, p=0.201), N (χ^2=2.745, df=2, p=0.254) or disease stage (χ^2=4.862, df=3, p=0.182) either in laryngeal cancer or oral cavity cancer group: T (χ^2=1.312, df=3, p=0.726), N (χ^2=1.540, df=3, p=0.673), disease stage (χ^2=1.613, df=3, p=0.656). Furthermore, two time frames of interest were analyzed, i.e., first timeframe from the onset of symptoms to first visit to head and neck surgeon, and second from first visit to head and neck surgeon to treatment initiation (Table 4). Statistically significant difference was observed in delay of first visit to head and neck surgeon in patients with oral cavity cancer. A significant delay of treatment was also recorded after first visit to head and neck surgeon for both localizations (Table 4).

Table 1. Incidence of laryngeal and oral cavity cancers in two consecutive periods

	2018-2019		2020-2021	
	n	%	n	%
Larynx	101	75.9	85	49.1
Oral cavity	32	24.1	88	50.9

Table 2. Age and sex distribution

		Larynx			Oral cavity		
		2018-2019	2020-2021	p	2018-2019	2020-2021	p
Sex	Male	92 (91.1%)	73 (85.9%)		19 (59.4%)	60 (68.2%)	
	Female	9 (8.9%)	12 (14.1%)		13 (40.6%)	28 (31.8%)	
Age (years)		63.89±9.29	65.86±9.97	0.166	61.16±11.72	63.50±11.86	0.339

Table 3. Clinical TNM stage

TNM stage		Larynx			Oral cavity		
		2018-2019	2020-2021	p	2018-2019	2020-2021	p
T	1	48 (47.5%)	43 (50.6%)	0.201	6 (18.8%)	23 (26.1%)	0.726
	2	19 (18.8%)	23 (27.1%)		13 (40.6%)	27 (30.7%)	
	3	23 (22.8%)	10 (11.8%)		4 (12.5%)	13 (14.8%)	
	4	11 (10,9%)	9 (10.6%)		9 (28.1%)	25 (28.4%)	
N	0	85 (84.2%)	78 (91.8%)	0.254	18 (56.3%)	59 (67.0%)	0.673
	1	4 (4.0%)	1 (1.2%)		5 (15.6%)	8 (9.1%)	
	2	12 (11.9%)	6 (7.1%)		8 25.0%)	19 (21.6%)	
	3	0 (0%)	0 (0.0%)		1 (3.1%)	2 (2.3%)	
M	0	100 (99.0%)	85 (100%)		32 (100%)	86 (97.7%)	
	1	1 (1%)	0 (0%)		0 (0%)	2 (2.3%)	
Stage	1	48 (48.0%)	43 (50.6%)	0.182	6 (18.8%)	19 (21.6%)	0.656
	2	15 (15.0%)	21 (24.7%)		9 (28.1%)	23 (26.1%)	
	3	19 (19.0%)	9 (10.6%)		2 (6.3%)	12 (13.6%)	
	4	18 (18.0%)	12 (14.1%)		15 (46.9%)	34 (38.6%)	

Table 4. Time 1 is time elapsed from onset of symptoms to first visit to head and neck surgeon and time 2 is time elapsed from first visit to treatment initiation

	Larynx			Oral cavity		
	2018-2019	2020-2021	p	2018-2019	2020-2021	p
2018-2019 (days)	60 (14, 1000)	90 (7, 730)	0.122	37.5 (6, 180)	60 (7, 720)	0.019
2020-2021 (days)	21.5 (0, 163)	31.5 (1, 400)	0.001	26 (8, 58)	37 (8, 155)	0.006

Discussion

The results of this study revealed a larger overall number of cancer patients in the COVID-19 two-year period compared to the pre-COVID-19 period, i.e., 371 *vs*. 320. Moreover, in the COVID-19 period, we found a statistically significant increase in the number of oral cancer cases, with drop in the number of laryngeal cancer cases. On the contrary, analyzing a 6-week period at the beginning of the pandemic, Kiong *et al*. report on a 25% reduction of newly diagnosed head and neck cancer tumors compared to the same period of 2019[5] . Similarly, Solis *et al*. found 22% fewer patients in the six-month COVID-19 period compared to the six-month period before March 11, 2020, when the pandemic was announced[6] . The increase in the overall number of patients in this study could be explained by longer periods evaluated and the fact that some medical facilities involved in the care of head and neck cancer patients were partially or completely closed for non-COVID-19 patients during the pandemic. Noteworthy, the vast majority of oral cancer patients in the Zagreb area were historically treated at the Department of Oral and Maxillofacial Surgery, Dubrava University Hospital. However, from the beginning of March 2020 till the end of July 2021, Dubrava University Hospital was designated as a special COVID-19 hospital, treating only COVID-19 patients. As a direct consequence, the number of oral cancer patients in the years 2020 and 2021 increased significantly compared to the years 2018 and 2019, so much so that the overall number of oral cancer patients in that period had topped the number of laryngeal cancer patients at our department. Given the fact that the maxillofacial unit at Dubrava University Hospital had almost exclusively treated all of the facial trauma and dental emergency patients in the Zagreb area in the pre-COVID-19 period, during the pandemic a large number of these patients were referred to our department, which as a consequence was very challenging for the operating schedule of the department. Unlike the rise in the number of oral cancer patients during the COVID-19 period, the cause of the drop of laryngeal cancer patients is not so clear. A possible reason could be the very natural history of laryngeal and hypopharyngeal cancer, in which patients tend to ignore the initial symptoms of the disease combined with fear of contracting COVID-19 in the healthcare system. Furthermore, the availability of primary care physicians such as family medicine doctors and dentists had been significantly constrained during the pandemic, which resulted in delays of patient referrals to tertiary care centers for diagnostic and treatment procedures. Moreover, the vast majority of ENT departments in local and county hospitals, which usually are involved in the initial diagnostic process of head and neck cancer patients and their referral to tertiary care centers, were closed or designated for emergency service only. We believe that all the above mentioned and combined resulted in the drop of laryngeal and hypopharyngeal cancer cases treated at our department during the observed period of the pandemic. As Table 4 shows, the median number of days elapsed from the onset of symptoms of laryngeal cancer to the first visit to our outpatient clinic increased from 60 to 90 days. The same timeframe also rose statistically significantly for oral cancer patients. Despite delay in patient referral that we recorded in our cohort of patients, we did not find a statistically significant change in TNM and stage distribution in the two periods compared. We found no statistically significant rise in the share of stage III and stage IV cancer patients in the COVID-19 period compared to the pre COVID-19 period either. Tevetoglu *et al*. also found a statistically significant rise in delay in time elapsed from the onset of symptoms to the first visit to a specialized head and neck cancer center in oral cancer patients, while delay in laryngeal cancer patients was marginally higher in the COVID-19 period. They also observed a significant rise in the number of T3 and T4 laryngeal cancer and rise in the number of patients with regional metastases (N+ necks) in oral cancer patients[7]. The rise in time elapsed from the onset of symptoms to initial referral was also observed by others[5-7]. The possible reason that we did not find a statistically significant proportion of advanced cases in the COVID-19 period lies in the fact that the time from symptom onset to the initial visit to our department was shorter in both periods observed (pre-COVID-19 and COVID-19) in comparison to other authors[5-7]. That by itself is a sign of high tertiary care availability at our department and in Croatia in general, even during the time of the COVID-19 pandemic despite all the challenges that we have been exposed to. A statistically significant delay in time elapsed from the first visit to the beginning of treatment in the COVID-19 period compared to the pre-COVID-19 period that we observed in our study for both sites, oral cavity and larynx, is what sets our study apart compared to other similar studies[5-8]. As

we have mentioned before, during the COVID-19 period, our department was faced with a sudden increase of oral cancer, facial trauma and dental emergency patients, especially patients with deep neck infections. At the same time, because of the changes made at the level of whole Zagreb University Hospital Center and adjustments made in order to combat the pandemic, the Department was faced with drop of operating theaters, drop in available anesthesiology staff, and drop of available ICU beds. All of these combined resulted in delay of treatment initiation. Moreover, that especially concerns oral cancer patients whose surgical treatment is more complex in comparison to laryngeal cancer patients, in ways that it very often includes microvascular reconstruction, which prolongs operating time and patients need to be hospitalized in ICU beds for a few days after surgery. The above mentioned difficulties related to the COVID-19 period were noted all over the world, so some of the official guidelines or recommendations in the early months of the pandemic suggested to delay early stage head and neck cancer treatment and to prioritize late stage patients in starting treatment[3,9]. Despite the fact that these recommendations were made with the best possible intentions, primarily to prevent the spread of COVID-19 amongst patients and healthcare staff, and to prevent curable late stage cancer patients to become incurable, we believe that such approach will have high drop in the overall disease specific survival rate. In a study on 51,655 patients, Murphy *et al*. clearly showed that time spent from the onset of symptoms to the beginning of treatment was a strong and independent prognostic factor and that early stage disease was highly prone to 'upstaging' in comparison to late stage disease with progression of time. They showed that delay in treatment for 31 to 60 days decreased survival of stage I and II patients, but did not so in patients with stage III and IV disease[10,11]. Furthermore, every additional delay for 30 days decreases survival by 4.6%[12]. Not only does delay in surgical treatment reduce overall survival but also delay in starting primary and adjunct radiotherapy is a strong prognostic factor[13]. Considering short time passed from the end of our observational period (especially for COVID-19 period), we were not able to do overall survival study or any treatment outcome study. That remains our task for the future. We are very aware of some of the shortfalls of these retrospective study, especially the approximation of the duration of symptoms before the first visit. Also, the time between the first visit and the MDT meeting is not uniform because MDT meetings were not regularly held during the pandemic.

Conclusion

The results of this study show that due to the sudden increase in the number of patients with oral cancer referred to our department, drop of available anesthesiology staff, drop of available ICU beds, drop of available operating theaters, postponement of surgery for PCR positive patients, there was a statistically significant delay of the beginning of surgical treatment for both sites of cancer observed (oral cavity and larynx). In the observed period, there was no increase in the number of patients with advanced stage disease. The future overall survival study will definitely reveal the impact of the COVID-19 pandemic and its consequences on the treatment of head and neck cancer patients at the Department for ENT and Head and Neck Surgery, Zagreb University Hospital Center.

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Sažetak

UTJECAJ PANDEMIJE COVID-19 NA ODGODU LIJEČENJA BOLESNIKA S KARCINOMIMA GLAVE I VRATA

K. Gršić, I. Blivajs, M. Pastorčić Grgić, D. Prgomet, J. Lukinović, O. Vugrinec, L. Matoc, B. Miličić i *D. Leović*

Cilj ove studije bio je utvrditi utjecaj pandemije COVID-19 na broj bolesnika s karcinomima glave i vrata te njihove karakteristike u vremenu prije i za vrijeme pandemije. U tu svrhu provedena je retrospektivna studija kod bolesnika s primarnim sluzničnim karcinomima glave i vrata, žlijezda slinovnica i onih s metastazama na vratu. Provedena je usporedba dviju godina prije pandemije COVID-19 (2018. i 2019.) i dviju pandemijskih godina (2020. i 2021.). Izračunati su i prikazani demografski podaci, ukupan broj bolesnika, TNM klasifikacija dvaju najučestalijih sijela (usna šupljina i grkljan), vrijeme potrebno da se bolesnik od pojave prvih simptoma javi specijalistu našeg Odjela (1. razdoblje) i vrijeme od prvog specijalističkog pregleda do početka terapije (2. razdoblje). Rezultati su pokazali veći broj bolesnika u razdoblju pandemije i razliku u distribuciji tumorskih sijela u odnosu na dvije godine prije pandemije (χ^2=33,68, df=9, p<0,001). Za vrijeme pandemije karcinom usne šupljine bio je učestalilji od karcinoma grkljana. U pandemijskom razdoblju utvrđeno je statistički značajno produljenje vremena do prvog specijalističkog pregleda kod bolesnika s karcinomom usne šupljine (p=0,019), kao i vremena od prvog pregleda specijalista do početka terapije za oba sijela (grkljan: p=0,001, usna šupljina: p=0,006). Usprkos tomu nije bilo razlika u TNM stupnjevima bolesti između dvaju promatranih razdoblja. Ovi rezultati pokazuju značajno produljeno vrijeme do početka liječenja tumora tijekom pandemije, i to za oba sijela, usnu šupljinu i grkljan. U budućnosti je potrebno provesti studiju preživljenja koja bi otkrila posljedice pandemije COVID-19 na ishode liječenja ovih bolesnika.

Ključne riječi: *COVID-19; Karcinom glave i vrata; Pandemija; Odgođeno liječenje*