ORIGINAL RESEARCH

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Increasing stage and depth of invasion (DOI) in patients with tongue cancer during the COVID-19 pandemic: A time series study

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Abstract

Background and Aims: The outbreak of the Coronavirus disease 2019 (COVID-19) pandemic had a significant effect on the diagnosis and treatment of head and neck cancers. Therefore, in this study, we decided to discuss the impact of COVID-19 on the stage and histological characteristics of patients with tongue cancer from March 2020 to March 2021 and compared to the previous 3 years.

Methods: In this time series study, patients diagnosed with squamous cell carcinoma of the operated tongue cancer were divided into two groups. Patients who operated from March 2020 to March 2021 ($n = 36$) and patients who operated 3 years ago ($n = 70$) were included in the study. The results were analyzed using SPSS 21 software.

Results: The study found that during the pandemic, the stage of tongue cancer in patients who underwent surgery was higher than before the pandemic ($p = 0.01$). Moreover, the depth of invasion was significantly higher during the COVID-19 outbreak in the pathology sample of the patients ($p = 0.006$), while the involvement of lymph nodes and other variables between the groups was not statistically significant.

Conclusion: COVID-19 has adverse effects on the diagnosis and treatment of tongue cancer. Also, it leads to advanced stages of the tumor and increases the depth of invasion of the cancer. Hence, it is important to plan correctly and appropriately for the diagnosis and treatment of these patients in conditions such as the COVID-19 pandemic.

KEYWORDS
COVID-19, mouth neoplasms, neoplasm staging, tongue cancer

1 | INTRODUCTION

The incidence of oral squamous cell carcinoma (SCC) is increasing worldwide.[1] Few studies have been conducted on clinical and pathological factors related to the prognosis of tongue SCC.[2] Most tongue cancers are diagnosed in early tumor stages (cT1 or cT2, cN0), for which complete surgical resection is the preferred treatment.[3] Now, the tumor-lymph node metastasis (TNM) staging system is commonly used to determine the prognosis of patients with tongue SCC. However, a significant difference in prognosis has been

observed in similarly treated patients with the same clinical stage.[4] The eighth edition of the American Joint Committee on Cancer (AJCC) staging guidelines included depth of invasion (DOI) in pathological stage T of oral cavity cancer.[5] DOI can be measured clinically (or using intraoral ultrasound)[5,6] and finally histologically. The AJCC supports the use of DOI instead of tumor thickness, and differences in tumor thickness and DOI may affect up to 7.5% of oral cancer patients in pathological T.[7] It is classified as low (less than or equal to 5 mm), moderate invasion (6–10 mm), and deep invasion (greater than or equal to 10 mm). Much information is available on the association of tumor thickness or DOI with cervical lymph node metastasis. It has been published that many studies have emphasized its role as a reliable predictor.[8] Based on previous studies, invasion pattern, tumor size (T) and tumor stage are important parameters in oral SCC in predicting lymphatic metastases.[9] Although it has been shown that the DOI is one of the important factors in predicting lymph node metastasis, different effects regarding its prognostic role have been reported in different anatomical locations of the oral cavity.

In late December 2019, a cluster of severe acute respiratory syndrome-like viral pneumonia cases appeared in Wuhan, China. In the following months, the disease quickly spread to the whole of China, as well as to more than 120 countries around the world, and the number of infected patients gradually increased.[10] Coronavirus disease 2019 (COVID-19) has caused significant changes in the diagnosis of oral cancer.[11] Due to the transmission of COVID-19 through droplets and airborne particles during the pandemic in many countries dental care procedures were performed only in emergency cases. This action eliminated the possibility of early detection of oral cancer and minimized the risks of diagnosis.[12] During the time of COVID-19, the whole world was in quarantine, and dental clinics were closed. Thus, the opportunity for oral cavity screening is significantly impaired and, as a result, the detection of malignant and/or potentially malignant lesions is delayed, leading to a delay in the diagnosis of oral cancer.[12] Considering the prevalence of tongue cancer and the possible effects of COVID-19 on patients, we decided to do an overview of tongue cancer patients during the period of COVID-19 and compare it with the 3 years before COVID-19 in terms of staging and DOI in Amir Alam Hospital in Tehran.

2 | METHODS

2.1 | Participants

In this time series study, all patients referred to Amir Alam Hospital related to Tehran University of Medical Sciences in the year from March 2020 to March 2021, who were diagnosed with SCC of the tongue based on the histological confirmation, were selected.

A checklist was designed by the researcher. This checklist includes demographic information, tumor size and cancer stage based on the TNM staging system, tumor thickness, and tumor depth that were recorded in the pathology sheet, as well as information about metastasis to neck lymph nodes, extracapsular spread, tumor margin status, perineural spread, and lymphovascular spread. This information was extracted according to the patient's files and entered into the Excel file. If there is a lack of information in the patient file, a phone call will be made and the information will be completed. This information is collected from the files of patients with tongue cancer in the period 3 years before the COVID-19 pandemic and is considered a measure of the period before the COVID-19. All information obtained from patients will be published without mentioning their names and characteristics.

2.2 | Study outcomes

2.2.1 | Primary outcome

Increasing staging and DOI in patients with tongue cancer during the COVID-19 pandemic.

2.2.2 | Secondary outcome

Evaluation of mean tumor volume, reconstruction of defect, perineural, and lymphovascular invasion in pathology.

2.3 | Statistical analysis

Statistical analysis of data was done using SPSS 21 software. Independent t test or Mann–Whitney test was used to check the difference of quantitative variables between two groups, and the χ^2 test or Fisher's exact test was used to compare qualitative variables. All tests were two-sided. p value < 0.05 was considered statistically significant.

3 | RESULT

In this study, 15 females and 21 males with a median age of 54 years in Group A and 35 females and 35 males with a median age of 54 years in Group B were included. Between the two groups, there were no significant differences in mean age ($p = 0.81$) and the sex distribution of patients ($p = 0.41$). In Group A, 10 patients, and in Group B, 24 patients had lymph node involvement. However, this difference between the two groups was not statistically significant ($p = 0.49$). In Group A, 19 patients were in Stages 3 and 4 and 17 patients were in Stages 1 and 2 at the time of surgery. In Group B, 20 patients showed Stages 3 and 4 and 50 showed Stages 1 and 2. Statistically, the ratio of patients with Stages 3 and 4 in patients referred at the time of the COVID-19 outbreak had significantly increased compared to the same period before the outbreak of COVID-19 ($p = 0.01$). The mean DOI in pathology was 11.2 mm in Group A and 8.1 mm in Group B. This difference was statistically

TABLE 1 Demographic characteristics, depth of invasion, and stage of tongue cancer in the two groups of study.

	Before COVID-19 pandemic	During COVID-19 pandemic	pValue
Age	53.33 ± 14.65	54.02 ± 14.82	0.81
Gender			
Male	35	21	0.71
Female	35	15	
Mean depth of invasion (mm)	8.1	11.2	0.006
Stages			
1 and 2	50	17	0.014
3 and 4	20	19	

significant during COVID-19 compared to the same period before ($p = 0.006$) (independent t test) (Table 1).

The median tumor volume in Group A was 5.54 cm³, whereas in Group B was 4.8 cm³, and tumor volume in patients referred during of COVID-19 period did not increase significantly ($p = 0.32$). Reconstruction was performed with various flaps in 10 patients in Group A, and in 30 patients in Group B, which was not statistically significant between the two groups ($p = 0.12$) (χ^2 test). In pathology, perineural invasion was described in 13 patients in Group A and 21 cases in Group B, and there was no statistically significant difference ($p = 0.52$). Six patients and 10 patients in the A and B groups, respectively, had lymphovascular invasion and in the two groups of patients was not statistically significant ($p = 0.74$).

4 | DISCUSSION

The COVID-19 disease has affected all aspects of the healthcare system around the world.[13] High-risk people, such as cancer patients, are more likely to have reduced access to services. A disease with advanced stages requires more complex and longer treatment, which affects the quality of life of patients and will increase the number of deaths.[14] Because the way of transmission of COVID-19 is through droplets and airborne particles, it has led to the reduction of dental activities only for emergency cases, and because dentists have played an important role in the early diagnosis of oral cancer, but with the emergence of COVID-19, the diagnosis of malignant lesions and/or premalignant is delayed.[12] In the study by Jensen et al., a 62% increase in tumor size and a 20% increase in nodal metastases were shown in a 1-month delay in the treatment of head and neck cancers.[15]

This study was conducted to investigate the effect of the COVID-19 outbreak on the staging and DOI of tongue cancer and to compare the results with those before COVID-19. Retrospectively, patients with oral cavity carcinoma who underwent surgery were evaluated. The overall results showed that the median age

was 54 years in the two groups. In Riju et al.'s study, the mean age of patients was 51.27 years during COVID-19 and 51.08 years in pre-COVID.[16] In our study, the number of male patients was more than women in Group A but in Group B the number of male and female patients was equal. In the Riju et al. study, the incidence of the disease in both periods was higher in men than in women.[16] In Group A, 10 patients, and the Group B, 24 patients had lymph node involvement. However, this difference between the two groups was not statistically significant ($p = 0.49$). The number of people who had extracapsular involvement of lymph nodes increased during the 1 year of the start of COVID-19 compared to the period before the epidemic, but it was not statistically significant. Riju et al. reported, that in 55.2% of patients in the COVID-19 period and in 27.7% of patients in pre-COVID-19 a modified radical neck dissection was performed ($p = 0.002$). There was no statistically significant difference in pathological factors (nodal staging, pattern of invasion, or node ratio) among the two groups. There was no difference in the quality of surgical resection; thus tumor resection margin and node resection between the COVID-19 period and pre-COVID-19 were comparable.[16] Kewlani et al. in 2020 in India compared the outcomes of patients with oral SCC between the COVID-19 period and pre-COVID-19. They reported that these groups differed in terms of bone invasion and extranodal extension were different from each other, and it was statistically significant and higher in the pandemic period compared to the previous period.[17] In our study statistically, the number of patients with advanced stages of cancer during the COVID-19 outbreak had significantly increased compared to the same period before the outbreak of COVID-19 ($p = 0.014$). Kewlani et al. described, the advanced stage at the time of presentation is quite common. There was no change in stage or disease distribution in patients with OSCC.[17] In Riju et al.'s study, 73% of tumors during COVID-19 were in the advanced T stage compared with 51% in pre-COVID ($p = 0.034$) which was statistically significant.[16] During COVID-19, 80% of patients showed an advanced tumor stage, and 38.7% of patients were inoperable during this period. Therefore, patients with a new diagnosis have worse survival than patients before COVID-19.[16] Metzger et al. reported a significantly higher pathological T staging during COVID-19, when compared to before COVID-19 ($p = 0.046$), but there was no difference in pathological N staging between the two groups ($p = 0.843$). There was a tendency for higher union for international cancer control stages during COVID-19 in comparison to pre-COVID-19, although the difference was not statistically significant ($p = 0.116$).[18] The difference between mean DOI in the two groups was statistically significant during the outbreak of COVID-19 compared to the same period before ($p = 0.006$). No study has investigated the difference in DOI in patients with tongue cancer in the period before and after the COVID-19 pandemic. Among the people who underwent surgery with the diagnosis of SCC of the tongue, the average tumor volume in patients referred during the period of COVID-19 increased compared to the period of the epidemic, which was not statistically

significant. Also, the average tumor volume in patients referred during the period of epidemic 19 increased. The mean tumor volume in Group A was 10.50 cm^3, whereas in Group B was 7.77 cm^3 ($p = 0.32$). Based on previous studies, the increase in tumor size associated with COVID-19 causes significant effects on prognosis and quality of life.[19,20] There was no statistically significant difference between the two groups in terms of the need for reconstruction ($p = 0.12$). Riju et al. used a local flap to reconstruct the surgical defect (50% during the COVID-19 period vs. 38% before the COVID-19 period).[16] Although the rate of perineural and lymphovascular involvement increased in patients referred during the period of COVID-19, this difference was not statistically significant.

In recent studies, long-term treatment delay has shown negative effects on the survival rate of oral cancer patients.[16] These patients are at greater risk for a severe disease that will lead to adverse outcomes.[20] In larger tumors, complications and mortality are higher, so a treatment regimen including surgical and adjuvant methods is needed. Although the outcome of patients with oral cancer has improved in recent years,[21] the increase in tumor size caused by COVID-19 has a great impact on prognosis and quality of life.[22,23] Studies conducted in Turkey during the COVID-19 pandemic showed that delay in referral was associated with a high incidence of T3/T4 head and neck cancers and an increase in the average time from the onset of symptoms to hospitalization.[24] In a study in Japan, patients with lung cancer reported delays in treatment during the COVID-19 pandemic,[25] and in China,[26] the initiation of radiation therapy in patients with nasopharyngeal carcinoma was delayed. Also, studies have reported a large impact of COVID-19 on patients with breast cancer, leading to higher mortality and fewer intensive care unit admissions.[27] In Iran, a study was shown that during the outbreak of COVID-19, patients had more advanced stages of laryngeal cancer and the tumor volume was larger compared to patients before the outbreak.[28] In addition to interrupting care and preventive health care visits, the COVID-19 pandemic has led to a significant increase in some risk factors for oral cancer, including increased smoking and alcohol consumption, poor diet, and increased incidence of obesity and poor oral hygiene.[29] Identifying the problem and increasing people's understanding of oral cancer and the need to access a specialist when seeing a problem in the oral cavity is essential.[30] Oral examination screening visits were significantly disrupted and resulted in missed or delayed diagnoses of oral cancer.[31] The data of our study help to pay special attention to patients with oral cancer in the spread of COVID-19 or the occurrence of similar diseases. The long-term effects of this epidemic are not yet clear, and the overall impact will take years to show on different populations. So, plans should be defined so that if epidemics occur again, the problems will not be repeated. Fast and convenient access to care should be provided. Development of remote medical services to accelerate the diagnosis of diseases.[21] It is also very important to increase people's awareness of the importance of cancer screening, diagnosis, and treatment.[14]

4.1 | Limitations

There are limitations in this research. The nature of our study was retrospective. Also, this study was done with a limited number of patients. Also, because of the relatively recent onset of COVID-19, survival rates in the two groups are not comparable. So, it is suggested to conduct a study with a larger sample size considering survival in two groups. It would have been better to compare "lifestyle habits, smoking, alcohol drinking, family history, hemoglobin level, P16 marker, body mass index, neutrophil–lymphocyte ratio, history of COVID-19 involvement, duration of symptom to diagnosis" in the two groups, it can be considered in future studies.

5 | CONCLUSION

COVID-19 has led to many side effects related to tongue cancers. It was due to a lack of proper access to treatment and delay in it. This event leads to advanced stages of the tumor and a more aggressive occurrence and increases the DOI of the disease. Early detection and treatment of tongue cancer is very important in its successful treatment, which during the epidemic can be helped with the help of virtual consultations in addition to face-to-face visits. Also, proper planning and faster initiation of oncology services in compliance with safety principles can reduce the current problem and prevent the development of tongue cancer and other cancers.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
The study protocol was approved by the local ethics review committee of our institution (Tehran University of Medical Sciences). The approval ID is IR.TUMS.AMIRALAM.REC.1401.009. Consent was obtained from all participants in the COVID-19 period.

TRANSPARENCY STATEMENT
The lead author Amin Beheshti affirms that this manuscript is an honest, accurate, and transparent account of the study being

reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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