Thesis

The impact of COVID-19 on oral squamous cell carcinoma's diagnostic stage - a retrospective study

submitted by

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Graz, 16th March 2023

Declaration of Academic Integrity

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Graz, 16th March 2023 *Dr. Bernhard Remschmidt p.m.*

Vorwort

Eine onkologische Diagnose hat einen unvergleichlichen Einfluss auf das weitere Leben von Patient*innen. Im Fachbereich der Mund-, Kiefer- und Gesichtschirurgie sind es vor allem orale Plattenepithelkarzinome, welche Ärzt*innen und Patient*innen vor große Herausforderungen stellen. Sowohl Operationen als auch Behandlungen sind aufwändig, lange und kompliziert.

Im Jahr 2017 wurden laut Statistik Austria in Österreich 1.323 bösartige Kopf-Hals-Tumore erstdiagnostiziert. Damit sind diese Tumore für ca. 3% der jährlichen Krebsneuerkrankungen in Österreich verantwortlich. Die Statistik beschreibt, dass ca. 50% dieser Tumore erst nach Durchbruch der Organgrenzen diagnostiziert werden, was einerseits das primäre Outcome verschlechtert (Notwendigkeit größerer Resektionen und plastischer Deckungen) und andererseits auch die 5-Jahres Überlebensrate negativ beeinflusst.

Seit die Weltgesundheitsorganisation (WHO) am 11. März 2020 die neuartige Coronavirus-Krankheit 2019 (COVID-19) zu einer globalen Pandemie erklärt hat, sind Gesundheitssysteme auf der ganzen Welt in unterschiedlichem Ausmaß betroffen. Die Pandemie zwang Gesundheitssysteme der Behandlung von Patienten mit COVID-19 Vorrang einzuräumen und stellt sie vor neue Herausforderung im Feld der Hygiene und dem Personalmanagement. All das beeinträchtigte die Möglichkeiten der Behandlung anderer erkrankter Patient*innen. Patient*innen hingegen wurden angehalten nur in dringenden Fällen Krankenhäuser und private Gesundheitseinrichtungen zu konsultieren um so Entlastung zu schaffen.

Nicht nur aufgrund eines eingeschränkten „notfallmäßigen“ Betriebes in den Krankenanstalten, sondern auch aufgrund der Zurückhaltung der Bevölkerung ärztliche Einrichtungen aufzusuchen, nahm das Studienteam an, dass es zu einem Zuwachs der Größe und der Invasivität bei Patient*innen mit oralen Plattenepithelkarzinomen kommen könnte. Nach Durchsicht der aktuellen Literatur konnten Arbeiten gefunden werden, die sich mit der Auswirkung der Corona-Pandemie auf die Größe und Invasivität von Karzinomen befassten. Es wurden auch Arbeiten gefunden, die sich speziell mit Karzinomen des Kopf-Hals Bereichs

beschäftigen. Eine Arbeit die sich jedoch ausschließlich auf orale Karzinome beschränkte konnte nicht gefunden werden.

Nach dem Studium der Humanmedizin an der Medizinischen Universität Graz begann ich mit der fachärztlichen Ausbildung im Feld der Mund-, Kiefer- und Gesichtschirurgie. Hier war es vor allem die Behandlung von onkologischen Patient*innen, welche mein Interesse weckte. Als ich zwei Jahre später mit der zahnärztlichen Ausbildung begann, welche für den Abschluss zum Facharzt notwendig ist, beschränkte sich das zu beachtende Behandlungsfeld im Wesentlichen „nur“ mehr auf die orale Cavität mit all ihren Facetten. Das Feld der Zahn-, Mund- und Kieferheilkunde bringt die Begegnung und Kontrolle vieler Patient*innen mit sich. Meist handelt es sich dabei um regelmäßige Konsultationen. Da sich das Arbeitsfeld in der zahnärztlichen Ausbildung fast ausschließlich auf die Mundhöhle beschränkt, erschien mir eine genaue und detaillierte Befundaufnahme in dem Fachbereich umso wichtiger. Auch die folgende Arbeit beschriebt die Wichtigkeit routinemäßige Kontrollen. Oft sind es diese, in welchen orale Karzinome frühzeitig enddeckt werden können und so eine rechtzeitige Behandlung für Patient*innen eingeleitet werden kann.

Schon zu Beginn der gemeinsamen Arbeit war das Ziel die Arbeit und die Ergebnisse der Untersuchung in einem peer-reviewten Pubmed gelisteten Journal zu publizieren. Nach der Datenauswertung und der signifikanten Statistik, wurde die Arbeit am 7. Mai 2021 im Journal „Oral Diseases” veröffentlicht und ist unter dem folgenden Link abrufbar: https://onlinelibrary.wiley.com/doi/10.1111/odi.14441

Danksagung

Vorweg und zu allererst gilt mein Dank meinem Betreuer, Prof. DDr. Luka Brcic, der mich bei der Durchführung der Studie und beim Erstellen dieser Arbeit betreute und mir stets für Fragen oder Unklarheiten zur Verfügung stand. Neben der fachlich so guten Betreuung möchte ich Luka für seine menschlich-kollegiale Art danken. Ich bin froh, dass wir uns kennen lernten und weiß, dass wir auch nach Abschluss des Projektes in- und außerhalb der Klinik in engem Kontakt bleiben werden. Auch bedanke ich mich bei meiner Zweitbetreuerin, Priv. Doz. DDr. Iva Brcic, die mir bei Erstellung dieser Diplomarbeit stets zur Seite stand.

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Die Zahnklinik betreffend möchte ich mich auch bei meiner Kleingruppe, den „Zwergen" für die gemeinsame Zeit bedanken. Allen voraus danke ich hier meiner Kommilitonin Laura Mente, ohne deren, immer zur Verfügung gestellten Lernunterlagen, ich das Studium bestimmt nicht so erfolgreich meistern hätte können.

Ich danke den Kieferchirurgischen Abteilungen in Dresden und Graz unter der Leitung von Univ.-Prof. DDr. Günter Lauer und Univ.-Prof. DDr. Wolfgang Zemann. Durch die Möglichkeit an diesen hervorragend geführten Abteilungen mitzuarbeiten konnte ich mich für das Fach der Mund-, Kiefer- und Gesichtschirurgie begeistern. Ein Dank gilt auch der Zahnklinik Graz unter der Leitung von Univ. Prof. DDr. Norbert Jakse, wo ich eine fundierte und vor allem praxisorientierte Ausbildung genießen durfte.

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Zu guter Letzt möchte ich mich bei meiner Freundin, meiner lieben Sophie bedanken. Jede neue Idee für eine wissenschaftliche Arbeit, jeder Vortrag und jede Präsentation ging durch ihre Ohren und über ihren Schreibtisch. Ich danke ihr für die stetige Unterstützung während der Zeit des Zahnmedizinstudiums und für jedes einzelne „viel Erfolg“ vor all meinen Prüfungen. Trotz Arbeiten an der Zahnklinik, Kieferchirurgischen Diensten, Betreuung von laufenden Forschungsprojekten und Aushilfe in diversen Privatpraxen, konnte ich mit ihr wunderschöne Orte bereisen und eine fantastische Zeit in Graz, Wien und Rund um die Welt genießen.

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Abkürzungen

OSCC	oral squamous cell carcinoma
WHO	World Health Organization
MRI	magnetic resonance imaging
BMI	body mass index
ECOG	Eastern Cooperative Oncology Group
HNSCC	head and neck squamous cell carcinoma

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Zusammenfassung

Die COVID-19-Pandemie hatte eine starke Auswirkung auf unser Leben und erschwerte nicht zuletzt Patient*innen den Zugang zu Gesundheitssystemen aller Art. Eine frühzeitige Diagnose von oralen Plattenepithelkarzinomen ist von entscheidender Bedeutung um ausgedehnte Therapien zu vermeiden und die 5-Jahres-Überlebensrate von Patient*innen zu erhöhen. Die aktuelle Studie zielt darauf ab, die Auswirkungen der Pandemie auf das Tumorvolumen oraler Karzinome zum Zeitpunkt der Erstdiagnose zu quantifizieren. In einer retrospektiven Studie wurden alle Patient*innen mit neu diagnostizierten oralen Plattenepithelkarzinomen zwischen März 2018 und März 2022 erfasst. Ausgewertet wurden das TNM-Stadium und das Tumorvolumen. Die Tumorvolumina wurden anhand von Pathologie oder Radiologie Berichten berechnet. Insgesamt wurden 162 neu diagnostizierte Tumorfälle in diese Studie aufgenommen. Davon wurden 76 (46,9 %) Fälle der "Prä-COVID-19"-Gruppe und 86 (53,1 %) der "COVID-19"-Gruppe zugeordnet. Patient*innen, die während des "COVID-19"-Zeitraums diagnostiziert wurden, wiesen im Vergleich zur Kontrollgruppe ein signifikant fortgeschrittenes T-Stadium ($p < 0{,}001$) und ein größeres mittleres Tumorvolumen ($53{,}16 \pm 73{,}55$ cm^3 vs. $39{,}89 \pm 102{,}42$ cm^3; $p = 0{,}002$) auf. Tumorvolumen und T-Stadium waren in der "COVID-19"-Gruppe im Vergleich zu den Daten vor der Pandemie deutlich fortgeschritten. Das Aufschieben der zahnärztlichen Routineuntersuchungen könnte dieses Ergebnis erklären. Zahnärzte und Grundversorger sollten daher bei Routineuntersuchungen besonderen Wert auf das Screening für orale Karzinome legen.

Abstract

The COVID-19 pandemic has had an impact on patients' access to primary care services. A timely diagnosis of oral squamosa cell carcinoma is paramount. This study aims to quantify the pandemic's effect on tumor volume at the time of initial diagnosis. In a retrospective study, all primarily diagnosed cancer patients between March 2018 and March 2022 were compiled. The TNM stage and the tumor volume were evaluated. Tumor volumes were calculated using pathology or radiology reports. In total, 162 newly diagnosed tumor cases were included in this study. Of these, 76 (46.9%) cases were allocated in the “pre-COVID-19” group and 86 (53.1%) in the “COVID-19” group. Patients diagnosed during the “COVID-19” period showed a significantly advanced T stage ($p < 0.001$) and larger mean tumor volumes (53.16 ± 73.55 cm^3 vs. 39.89 ± 102.42 cm^3; $p = 0.002$) when compared to the control group. Tumor volume and T stage were significantly advanced in the “COVID-19” group when compared to prepandemic data. We hypothesize that the postponement of routine dental check-ups may explain this finding. Hence, dentists and primary care providers are encouraged to place particular emphasis on screening during routine check-ups.

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ORIGINAL ARTICLE

The impact of COVID-19 on oral squamous cell carcinoma's diagnostic stage—A retrospective study

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Abstract

Objective: The COVID-19 pandemic has had an impact on patients' access to primary care services. A timely diagnosis of oral squamosa cell carcinoma is paramount. This study aims to quantify the pandemic's effect on tumor volume at the time of initial diagnosis.

Materials and Methods: In a retrospective study, all primarily diagnosed cancer patients between March 2018 and March 2022 were compiled; the TNM stage and the tumor volume were evaluated. Tumor volumes were calculated using pathology or radiology reports.

Results: In total, 162 newly diagnosed tumor cases were included in this study. Of these, 76 (46.9%) cases were allocated in the "pre-COVID-19" group and 86 (53.1%) in the "COVID-19" group. Patients diagnosed during the "COVID-19" period showed a significantly advanced T stage ($p<0.001$) and larger mean tumor volumes ($53.16 \pm 73.55\,cm^3$ vs. $39.89 \pm 102.42\,cm^3$; $p = 0.002$) when compared to the control group.

Conclusion: Tumor volume and T stage were significantly advanced in the "COVID-19" group when compared to prepandemic data. We hypothesize that the postponement of routine dental check-ups may explain this finding. Hence, dentists and primary care providers are encouraged to place particular emphasis on screening during routine check-ups.

KEYWORDS
COVID-19, dentistry, mouth neoplasms, squamous cell neoplasms, tumor burden

1 | INTRODUCTION

The oral cavity includes the lips, the hard and soft palate, the retromolar trigone, the two anterior thirds of the tongue, the gingiva and buccal mucosa, as well as the sublingual area (National Cancer Institute, 2022). In this anatomical region, oral squamous cell carcinoma (OSCC) is the most common cancer (Chamoli et al., 2021; Johnson et al., 2020; Panarese et al., 2019; Rivera, 2015). According to the Global Cancer Observatory, OSCC is one of the 20 most common tumors, with 377,713 cases worldwide (Sung et al., 2021). Following the literature, OSCC is more common among men and is primarily associated with excessive alcohol and tobacco consumption.

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It is likewise affiliated with the human papillomavirus (Chamoli et al., 2021; Johnson et al., 2020; Rivera, 2015). Furthermore, genetic predisposition should be mentioned as an additional risk factor (Chamoli et al., 2021; Johnson et al., 2020). Regardless of its location in the mouth, OSCC is, in the majority of cases, diagnosed at an advanced stage (Rivera, 2015). This delay in tumor diagnosis is predominately affiliated to the difficulty the patient has in perceiving signs and symptoms and interpreting them as harmful (Panzarella et al., 2014). Advanced tumor stage, however, leads to an extended surgical resection requiring microvascular reconstruction, which is often followed by radio- and/or chemotherapy (Wallner et al., 2022). In these cases, an impaired 5-year survival rate (e.g., positive N status) and therapy-associated toxicities (e.g., xerostomia, impaired quality of life, and osteoradionecrosis) have to be considered when planning treatment (De Felice et al., 2014). Therefore, a multidisciplinary approach is necessary to achieve the highest possible cure rate combined with the best functional and psychological outcome (Machiels et al., 2020).

The novel virus SARS-CoV-2, causing respiratory illness COVID-19, emerged at the end of 2019 and was quickly classified as a global pandemic by the World Health Organization (Cucinotta & Vanelli, 2020). The still ongoing pandemic tremendously affects healthcare systems as it forces them to prioritize the treatment of patients suffering from COVID-19. This, in turn, has had an impact on the treatment of other diseases through changes in the organizational processes, in routine clinical operations and through delays in the commencement of therapy treatment. A global collaborative study, in which 356 cancer centers from 54 countries participated, 88% described facing challenges in delivering care during the pandemic (Chilamakuri & Agarwal, 2021; Jazieh et al., 2020). Social distancing as a recommended measure to prevent the uncontrolled spread of COVID-19 may have also had an impact on the diagnosis and treatment of tumor patients. During the pandemic and the repeatedly issued lockdown policies, patients were asked to seek medical advice only in urgent cases and to postpone routine check-ups. Although patients undergoing active oncological therapy were hardly affected, several studies warned about the consequences of these canceled appointments (Alves et al., 2021). The comparison between the pre-COVID-19 period and the COVID-19 period demonstrate a decrease in biopsies for further histological examinations, illustrating the manner in which this postponement ultimately led to decreased cancer diagnoses (Arduino et al., 2021; Caldeira et al., 2022; Gomes et al., 2022). This development raises the cause for serious concern, given that nonsymptom-driven malignancy detections are associated with a lower stage at diagnosis rather than lesions detected during a symptom-directed examination (Holmes et al., 2003). Data from before the pandemic show that around 50% of patients subsequently diagnosed with OSCC were referred to a specialist by either their general practitioner or their dentist (Grafton-Clarke et al., 2019). Delayed diagnosis, in turn, has a negative impact on tumor progression, tumor spread, and overall survival rate (Graboyes et al., 2019; Ho et al., 2018; Rygalski et al., 2021).

The current study aimed to investigate the influence of the COVID-19 pandemic on tumor size consequent to a patient's initial diagnosis. From the information available to us, this research is the first to compare and examine the actual tumor volume of OSCC before and after the emergence of the COVID-19 pandemic (Balk et al., 2022; Kiong et al., 2021; Longo et al., 2021; Stevens et al., 2022; Tevetoğlu et al., 2021).

2 | MATERIALS AND METHODS

The present retrospective study was conducted at the department of Oral and Maxillofacial Surgery at the Medical University of Graz and was approved by the university's ethics committee (IRB00002556, EK-Nr:1235–2022).

The study cohort included all patients who were primarily diagnosed with OSCC in the period between March 2018 and March 2022. All patients between the ages of 18 and 99 without prior treatment were included. Patients with tumor recurrence in the head and neck area (after previous surgery, radiation, or chemotherapy) were excluded, as tumor diagnosis in the past leads to a strict follow-up with regular clinical examinations. Further criterion for patients´ exclusion was an inadequate clinical documentation. Data were obtained from the hospital information system.

The World Health Organization (WHO) declared COVID-19 a global pandemic on March 11, 2020 (World Health Organisation, 2022). The study's cohort was divided into two subgroups based on the date patients were presented to the university's interdisciplinary head and neck tumor board (committee of surgeons, pathologists, radiologists, and oncologists that make evidence-based recommendations for a patient's further treatment after malignancy diagnosis). The “COVID-19 group” was composed of patients whose initial diagnosis fell into the period between March 11, 2020 and March 11, 2022. The control group (i.e., “pre-COVID-19 group”) consisted of all patients from March 11, 2018 to March 10th, 2020.

To objectively quantify the volume of the OSCCs, pathology reports of the surgically resected specimens with tumor size documented in three dimensions (e.g., length, size, and depth) were used. In cases of tumors treated by means of primary radiation and/or chemotherapy, or best supportive care, rather than resection (e.g., advanced clinical stage or poor general condition); the tumor volume was obtained from radiologic assessments. Magnetic resonance imaging (MRI) was used without exception. To determine the actual size of the tumor, ellipsoid growth of the tumor was assumed. Therefore, the ellipsoid volume formula ($\text{length} \times \text{width} \times \text{depth} \times \pi \times 4/6$) was applied to calculate the tumor volume.

Furthermore, general demographic data, tumor location, TNM stage, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, as well as carcinoma-associated risk factors (e.g., tobacco consumption, alcohol consumption), and patients' comorbidities (e.g., diabetes mellitus) were recorded. When calculating the BMI, recent weight loss (within 6 months) was also taken into account.

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Retrospective data collection was carried out using a Microsoft Excel spreadsheet (Microsoft Corp.), and statistical analysis was performed using SPSS statistics (IBM Corp.). A *t*-test (age, BMI), the Fisher's exact test (sex, diabetes and administered therapy), the chi-squared test (ECOG), as well as the Mann–Whitney-U test (tumor volume) were used in order to compare the two study groups.

3 | RESULTS

A total of 162 newly diagnosed OSCC cases were presented to the university's tumor board within the investigated 4 years. 76 (46.9%) cases were placed in the "pre-COVID-19" group and 86 (53.1%) in the "COVID-19" group. There was a 13% increase in the total number of cases presented in the "COVID-19" period.

3.1 | Patient demographics

Patient characteristics did not differ between the "pre-COVID-19" group and the "COVID-19" period, with a similar mean age of 64.5 and 64.9 years ($p = 0.875$), BMI ($p = 0.168$) and sex ($p = 0.380$) (Table 1). There was no significant difference in terms of ECOG performance ($p = 0.406$), smoking ($p = 0.167$), or drinking ($p = 0.550$) status between the two groups. Fifty-two (68.4%) patients underwent surgery in the "pre-COVID-19" period and 51 (59.3%) in the "COVID-19" group ($p = 0.129$). Primary radiotherapy was used on 47 individuals ("pre-COVID-19" group: 20, "COVID-19" group: 27; $p = 0.313$) and 57 individuals received adjuvant radiotherapy ("pre-COVID-19" group: 21, "COVID-19" group: 36; $p = 0.047$). Chemotherapy was administered in 18 ("pre-COVID-19" group) and 20 ("COVID-19" group) patients ($p = 0.513$).

3.2 | Tumor characteristics

Regarding the anatomical distribution of the tumors, the sublingual space ($n = 59$) represented the most common subsite, followed by the mandible ($n = 42$), tongue ($n = 17$), maxilla ($n = 16$), lower lip ($n = 14$), buccal mucosa ($n = 11$), and upper lip ($n = 4$). Table 2 summarizes the OSCC tumor characteristics at the time of the patients' initial presentation at the department of maxillofacial surgery. Patients diagnosed during the pandemic showed significantly advanced T stages ($p < 0.001$) when compared to the control group. In terms of N ($p = 0.559$) and M ($p = 0.229$) staging, no differences between the two groups were observed. The mean tumor volume in the "COVID-19" group (mean 53.16 ± 73.55 cm^3) was significantly larger ($p = 0.002$) than in the "pre-COVID-19" group (mean 39.89 ± 102.42 cm^3). Figure 1 describes the OSCC actual tumor volume without prior treatment in the "pre-COVID-19" and "COVID-19" periods. Figure 2 illustrates the respective tumor volumes of the different anatomical subsites (buccal, lower lip, maxilla, sublingual, tongue, and upper lip) within the oral cavity.

TABLE 1 Detailed description of patients' demographics

	Pre-Covid-19 group	Covid-19 group	*p*-Value
Age			
Min	42.8	37.8	0.875
Max	88.9	90.6	
Mean	64.5	64.9	
SD	14.7	11.9	
SEX			
Male	48 (63.2%)	58 (66.7%)	0.380
Female	28 (36.8%)	29 (33.3%)	
Total	76	87	
BMI			
Min	16.7	14.6	0.168
Max	42.7	36.3	
Mean	26.2	25.2	
SD	4.8	4.7	
Diabetes mellitus			
Yes	12 (15.8%)	9 (10.3%)	0.212
No	64 (82.2%)	78 (89.7%)	
Tobacco (pack years)			
Smoker	41	55	0.167
Range	0–100	0–100	
Mean	18.0	22.9	
SD	22.1	22.7	
Alcohol			
Drinking	34 (44.7%)	50 (57.5%)	0.550
Non-drinking	42 (55.3%)	37 (42.5%)	
ECOG			
0	35 (46.1%)	43 (49.4%)	0.406
1	27 (35.5%)	28 (32.2%)	
2	10 (13.2%)	15 (17.2%)	
3	4 (5.3%)	1 (1.2%)	

4 | DISCUSSION

Oral squamous cell carcinoma compromises one of the 20 most prevalent and lethal tumors worldwide (Sung et al., 2021). Within the oral cavity, it is by far the most common tumor (Chamoli et al., 2021; Johnson et al., 2020; Panarese et al., 2019; Rivera, 2015). Adequate management of OSCC requires a timely diagnosis, as advanced growth within the limited confinements of the oral cavity may result in an invasion of adjacent tissues, which would further complicate treatment and negatively impact the patient's expected outcome. Shortly following the occurrence of novel SARS-CoV-2, the COVID-19 outbreak was declared a pandemic by the WHO in March 2020 (Cucinotta & Vanelli, 2020). A significant reduction in the use of in-person healthcare services was observed within the first several months of the pandemic (Ekman et al., 2021). The purpose of

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this study was to evaluate the impact of the COVID-19 pandemic on the initial tumor size of patients presenting with OSCC.

During the pandemic's initial phase, Xu et al. (2021) observed decreases in inpatient, emergency department, and outpatient visits by 30.2%, 37.0%, and 80.9%, respectively, in the United States. The conscious decision of patients not to seek in-person health care out of fear of exposure to SARS-CoV-2 has been cited as an important contributing factor (Xu et al., 2021). A survey study from New Zealand has shown that avoidance of health care, downplaying of symptoms, and fear of going out, on behalf of patients was commonly observed by their respective general practitioners (Wilson et al., 2021). An additional considerable factor for the significantly reduced use of in-person healthcare services can be traced back to the policy of delaying elective care as a means of limiting the spread of SARS-CoV-2 in healthcare facilities, as well as reducing the strain on resources of the healthcare system (Xu et al., 2021). The aforementioned aspects of the pandemic's sequelae on health care systems are likely to be even greater in low- and middle-income countries. Limited resources, poor infrastructure, scarcity of medical supplies along with personal protective equipment, shortage of health care providers and organized care teams, as well as poor access to technology can be considered adverse contributing factors in these areas (Bong et al., 2020; McMahon et al., 2020; Osseni, 2020).

TABLE 2 Detailed description of tumor characteristics

	Pre-Covid-19 group	Covid-19 group	*p*-Value
TNM			
T			
1	17 (22.4%)	7 (8%)	0.001
2	19 (25%)	14 (16.1%)	
3	10 (13.2%)	11 (12.6%)	
4	30 (39.5%)	55 (63.2%)	
N			
0	41 (53.9%)	46 (52.9%)	0.559
1	9 (11.8%)	7 (8%)	
2	25 (32.9%)	28 (32.2%)	
3	1 (1.3%)	6 (6.9%)	
M			
0	75 (98.7%)	83 (95.4%)	0.229
1	1 (1.3%)	4 (4.6%)	
Tumor volume (cm^3)			
Min	0.3	1.4	0.002
Max	691.2	414.2	
Median	12.8	25.6	
IQR	29.7	58.6	

The impact of the COVID-19 pandemic on the TNM staging of head and neck squamous cell carcinoma (HNSCC) at the time of diagnosis has already been investigated and described by several authors (Balk et al., 2022; Kiong et al., 2021; Solis et al., 2021; Stevens et al., 2022; Tevetoğlu et al., 2021). Tevetoglu et al. (2021) and Solis et al. (2021) demonstrated a significantly higher TNM stage when comparing tumors in the head and neck region during and before the COVID-19 pandemic in the field of otolaryngology. These results stand in contrast to the findings of Balk et al. (2022), where no difference regarding the TNM stage before and during the COVID-19 pandemic could be found in scrutinizing 612 cases. However, significantly more distant metastases were detected.

The TNM results of this study investigating oral squamous cell carcinoma (OSCC) are in accordance with the results of Tevetoglu et al. and Solis et al. (HNSCC) showing that there is a significant distinction between "pre-COVID-19 "and "COVID-19" groups regarding the T stage (Solis et al., 2021; Tevetoğlu et al., 2021).

Evaluation of the differences in tumor size dependent on the COVID-19 pandemic was conducted by Kiong et al. analyzing the largest cross-sectional diameter of the tumor. Although the overall TNM classification showed no significant difference between the "pre-COVID-19" and "COVID-19" groups, the tumor diameter was larger in the "COVID-19" group (Kiong et al., 2021). However, since tumors are known to grow infiltratively, this measuring method is partially suitable. The results of this study demonstrate an increase in the overall tumor volume in OSCC with the emergence of the

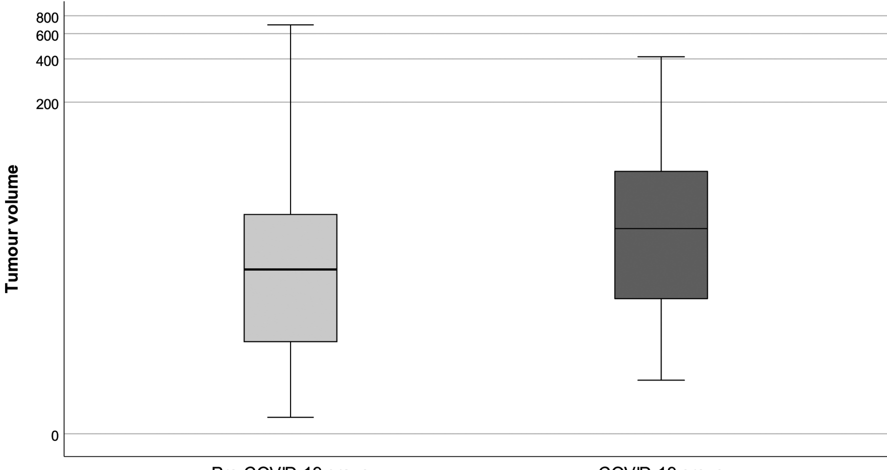

FIGURE 1 Differences in overall tumor volume between patients of the "pre-COVID-19" and "COVID-19" group. Tumor volume is given in cm^3.

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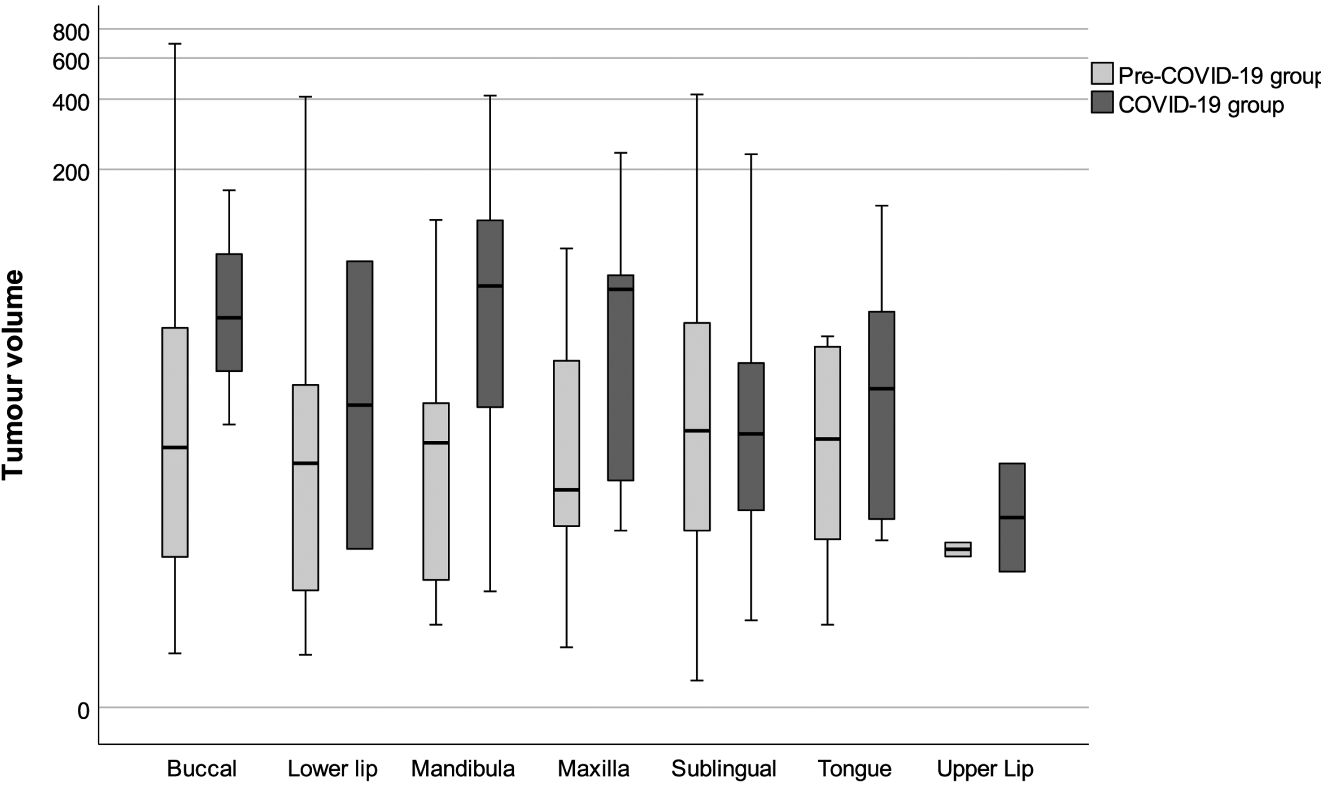

FIGURE 2 Differences in anatomical subsite-specific tumor volume between patients of the "pre-COVID-19" and "COVID-19" group. Tumor volume is given in cm^3.

COVID-19 pandemic. This development may be caused by the postponement of primary care services, such as routine dental check-ups as a consequence of lockdown policies and government based social restrictions, as well as the prioritized treatment of COVID-19 patients in clinical centers.

The following should be addressed when discussing the limitations of this study. Due to the retrospective nature and the single-center design of this study, the level of evidence has the potential to be minor compared with that of a COVID-19 multicenter trial. However, a multicenter study would have strong limitations such as, an inhomogeneous patient collective and/or study data resulting from different COVID-19 guidelines among the different participating countries. To the authors' best knowledge, this is the first study comparing three-dimensional tumor volumes between a "pre-COVID-19" and a "COVID-19" group. In future research projects, similar studies should be conducted in other countries to further evaluate the impact of the COVID-19 pandemic on oral health.

The results of this study report the profound impact of the COVID-19 pandemic on TNM stage and tumor volume of OSCC over a 4-year timeframe. A more advanced T stage leads to more advanced surgical treatment (e.g., extended tumor resection, free flap reconstruction) (Wallner et al., 2022). When comparing the incidence of chemoradiotherapy in OSCC patients between the "pre-COVID-19" and the "COVID-19" group, a substantial increase in adjuvant radiotherapy following the onset of the pandemic was observed. Similar findings have been made by Martelli et al. (2021). Thus, it can be reasoned that delayed diagnosis resulting in advanced initial tumor stage and volume had an impact on the chosen treatment. When considering the unfavorable sequelae of chemotherapy and radiation, an impairment to the quality of life of OSCC patients as a consequence seems likely (De Melo et al., 2018; Pierre et al., 2014). Furthermore, an increase in new OSCC cases can be expected in the near future due to reduced cancer screenings (e.g., biopsies) secondary to the prioritization of the management of COVID-19 patients during the pandemic (Arduino et al., 2021). The study invites dentists and general practitioners to place particular emphasis on oral cancer screening during upcoming routine examinations in order to detect carcinomas in a timely manner and consequentially initiate further treatment. Additionally, routine medical and timely dental check-ups should be considered essential medical care during pandemic lockdowns or announced social restrictions.

AUTHOR CONTRIBUTIONS

Conceptualization, B.R., J.G. and M.R.; methodology, B.R., J.G. and M.R.; software, B.R., J.G. and M.R.; validation, B.R., J.G., L.B., J.W., D.M. and M.R.; formal analysis, B.R. and M.R.; investigation, B.R., J.G. and M.R.; resources, B.R., J.G., L.B., J.W., D.M. and M.R.; data curation, B.R., J.G., D.M. and M.R.; writing—original draft preparation, B.R., J.G. and M.R.; writing—review and editing, B.R., J.G., L.B., J.W. and M.R.; visualization, B.R., J.G. and M.R.; supervision,

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REFERENCES

Alves, F. A., Saunders, D., Sandhu, S., Xu, Y., De Mendonça, N. F., & Treister, N. S. (2021). Implication of COVID-19 in oral oncology practices in Brazil, Canada, and the United States. *Oral Diseases*, *27*(S3), 793–795.

Arduino, P. G., Conrotto, D., & Broccoletti, R. (2021). The outbreak of novel coronavirus disease (COVID-19) caused a worrying delay in the diagnosis of oral cancer in north-West Italy: The Turin metropolitan area experience. *Oral Diseases*, *27*(S3), 742–743.

Balk, M., Rupp, R., Craveiro, A. V., Allner, M., Grundtner, P., Eckstein, M., Hecht, M., Iro, H., & Gostian, A. O. (2022). The COVID-19 pandemic and its consequences for the diagnosis and therapy of head and neck malignancies. *European Review for Medical and Pharmacological Sciences*, *26*(1), 284–290.

Bong, C. L., Brasher, C., Chikumba, E., McDougall, R., Mellin-Olsen, J., & Enright, A. (2020). The COVID-19 pandemic: Effects on low- and middle-income countries. *Anesthesia and Analgesia*, *131*(1), 86–92.

Caldeira, P. C., Schuch, L. F., Tavares, T. S., Santos-Silva, A. R., Vargas, P. A., Pérez-de-Oliveira, M. E., De Almeida, O. P., De Souza, L. B., Gonzaga, A. K. G., Mendonça, E. F., Sousa-Neto, S. S., Rivero, E. R. C., Modolo, F., dos Santos, J. N., Manieri, P. R., Nonaka, C. F. W., Alves, P. M., Libório-Kimura, T. N., Mendes, T. C. C., … Vasconcelos, A. C. U. (2022). Impact of the COVID-19 pandemic on public university laboratories of oral and maxillofacial pathology: A Brazilian multicenter study. *Oral Diseases*, *28*, 2423–2431.

Chamoli, A., Gosavi, A. S., Shirwadkar, U. P., Wangdale, K. V., Behera, S. K., Kurrey, N. K., Kalia, K., & Mandoli, A. (2021). Overview of oral cavity squamous cell carcinoma: Risk factors, mechanisms, and diagnostics. *Oral Oncology*, *121*, 105451.

Chilamakuri, R., & Agarwal, S. (2021). COVID-19: Characteristics and therapeutics. *Cell*, *10*(2), 206.

Cucinotta, D., & Vanelli, M. (2020). WHO declares COVID-19 a pandemic. *Acta Bio-Medica*, *91*(1), 157–160.

De Felice, F., Musio, D., Terenzi, V., Valentini, V., Cassoni, A., Tombolini, M., De Vincentiis, M., & Tombolini, V. (2014). Treatment improvement and better patient care: Which is the most important one in oral cavity cancer? *Radiation Oncology*, *9*, 263.

De Melo, N. B., Bernardino, Í. M., De Melo, D. P., Gomes, D. Q. C., & Bento, P. M. (2018). Head and neck cancer, quality of life, and determinant factors: A novel approach using decision tree analysis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, *126*(6), 486–493.

Ekman, B., Arvidsson, E., Thulesius, H., Wilkens, J., & Cronberg, O. (2021). Impact of the Covid-19 pandemic on primary care utilization: Evidence from Sweden using national register data. *BMC Research Notes*, *14*(1), 424.

Gomes, A. P. N., Schuch, L. F., Tarquinio, S. B. C., Etges, A., & Vasconcelos, A. C. U. (2022). Reduced demand for oral diagnosis during COVID-19: A Brazilian center experience. *Oral Diseases*, *28 Suppl 1(Suppl 1)*, 958–959.

Graboyes, E. M., Kompelli, A. R., Neskey, D. M., Brennan, E., Nguyen, S., Sterba, K. R., Warren, G. W., Hughes-Halbert, C., Nussenbaum, B., & Day, T. A. (2019). Association of Treatment Delays with Survival for patients with head and neck cancer: A systematic review. *JAMA Otolaryngology. Head & Neck Surgery*, *145*(2), 166–177.

Grafton-Clarke, C., Chen, K. W., & Wilcock, J. (2019). Diagnosis and referral delays in primary care for oral squamous cell cancer: A systematic review. *The British Journal of General Practice*, *69*(679), e112–e126.

Ho, A. S., Kim, S., Tighiouart, M., Mita, A., Scher, K. S., Epstein, J. B., Laury, A., Prasad, R., Ali, N., Patio, C., Clair, J. M. S., & Zumsteg, Z. S. (2018). Quantitative survival impact of composite treatment delays in head and neck cancer. *Cancer*, *124*(15), 3154–3162.

Holmes, J. D., Dierks, E. J., Homer, L. D., & Potter, B. E. (2003). Is detection of oral and oropharyngeal squamous cancer by a dental health care provider associated with a lower stage at diagnosis? *Journal of Oral and Maxillofacial Surgery*, *61*(3), 285–291.

Jazieh, A. R., Akbulut, H., Curigliano, G., Rogado, A., Alsharm, A. A., Razis, E. D., Mula-Hussain, L., Errihani, H., Khattak, A., De Guzman, R. B., Mathias, C., Alkaiyat, M. O. F., Jradi, H., Rolfo, C., & International Research Network on COVID-19 Impact on Cancer Care. (2020). Impact of the COVID-19 pandemic on cancer care: A global collaborative study. *JCO Global Oncology*, *6*, 1428–1438.

Johnson, D. E., Burtness, B., Leemans, C. R., Lui, V. W. Y., Bauman, J. E., & Grandis, J. R. (2020). Head and neck squamous cell carcinoma. *Nature Reviews. Disease Primers*, *6*(1), 92.

Kiong, K. L., Diaz, E. M., Gross, N. D., Diaz, E. M., Jr., & Hanna, E. Y. (2021). The impact of COVID-19 on head and neck cancer diagnosis and disease extent. *Head & Neck*, *43*(6), 1890–1897.

Longo, F., Trecca, E. M. C., D'Ecclesia, A., Copelli, C., Tewfik, K., Manfuso, A., Pederneschi, N., Mastromatteo, A., Russo, M. A., Pansini, A., Lacerenza, L. M., Marano, P. G., & Cassano, L. (2021). Managing head and neck cancer patients during the COVID-19 pandemic: The experience of a tertiary referral center in southern Italy. *Infectious Agents and Cancer*, *16*(1), 9.

Machiels, J. P., René Leemans, C., Golusinski, W., Grau, C., Licitra, L., & Gregoire, V. (2020). Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *31*(11), 1462–1475.

Martelli, A. J., Machado, R. A., Pereira, W. M., Silveira, D. M. M., Da Cruz Perez, D. E., & Martelli, J. H. (2021). Impact of the COVID-19 pandemic in the head and neck cancer treatment in the Brazil. *Oral Oncology*, *116*, 105148.

McMahon, D. E., Peters, G. A., Ivers, L. C., & Freeman, E. E. (2020). Global resource shortages during COVID-19: Bad news for low-income countries. *PLoS Neglected Tropical Diseases*, *14*(7), e0008412.

National Cancer Institute. (2022). *Dictionary of Cancer Terms: National Institutes of Health*. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/oral-cavity

Osseni, I. A. (2020). COVID-19 pandemic in sub-Saharan Africa: Preparedness, response, and hidden potentials. *Tropical Medicine and Health*, *48*, 48.

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Panarese, I., Aquino, G., Ronchi, A., Longo, F., Montella, M., Cozzolino, I., Roccuzzo, G., Colella, G., Caraglia, M., & Franco, R. (2019). Oral and oropharyngeal squamous cell carcinoma: Prognostic and predictive parameters in the etiopathogenetic route. *Expert Review of Anticancer Therapy*, *19*(2), 105–119.
Panzarella, V., Pizzo, G., Calvino, F., Compilato, D., Colella, G., & Campisi, G. (2014). Diagnostic delay in oral squamous cell carcinoma: The role of cognitive and psychological variables. *International Journal of Oral Science*, *6*(1), 39–45.
Pierre, C. S., Dassonville, O., Chamorey, E., Poissonnet, G., Riss, J. C., Ettaiche, M., Peyrade, F., Benezery, K., Chand, M. E., Leyssalle, A., Sudaka, A., Haudebourg, J., Santini, J., & Bozec, A. (2014). Long-term functional outcomes and quality of life after oncologic surgery and microvascular reconstruction in patients with oral or oropharyngeal cancer. *Acta Oto-Laryngologica*, *134*(10), 1086–1093.
Rivera, C. (2015). Essentials of oral cancer. *International Journal of Clinical and Experimental Pathology*, *8*(9), 11884–11894.
Rygalski, C. J., Zhao, S., Eskander, A., Zhan, K. Y., Mroz, E. A., Brock, G., Silverman, D. A., Blakaj, D., Bonomi, M. R., Carrau, R. L., Old, M. O., Rocco, J. W., Seim, N. B., Puram, S. V., & Kang, S. Y. (2021). Time to surgery and survival in head and neck cancer. *Annals of Surgical Oncology*, *28*(2), 877–885.
Solis, R. N., Mehrzad, M., Faiq, S., Frusciante, R. P., Sekhon, H. K., Abouyared, M., Bewley, A. F., Farwell, D. G., & Birkeland, A. C. (2021). The impact of COVID-19 on head and neck cancer treatment: Before and during the pandemic. *OTO Open*, *5*(4), 2473974X211068075.
Stevens, M. N., Patro, A., Rahman, B., Gao, Y., Liu, D., Cmelak, A., Wiggleton, J., Kim, Y. J., Langerman, A., Mannion, K., Sinard, R. J., Netterville, J. L., Rohde, S. L., & Topf, M. C. (2022). Impact of COVID-19 on presentation, staging, and treatment of head and neck mucosal squamous cell carcinoma. *American Journal of Otolaryngology*, *43*(1), 103263.
Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians*, *71*(3), 209–249.
Tevetoğlu, F., Kara, S., Aliyeva, C., Yıldırım, R., & Yener, H. M. (2021). Delayed presentation of head and neck cancer patients during COVID-19 pandemic. *European Archives of Oto-Rhino-Laryngology*, *278*(12), 5081–5085.
Wallner, J., Rieder, M., Schwaiger, M., Remschmidt, B., Zemann, W., & Pau, M. (2022). Donor site morbidity and quality of life after microvascular head and neck reconstruction with a chimeric, thoracodorsal, perforator-scapular flap based on the angular artery (TDAP-Scap-aa flap). *Journal of Clinical Medicine*, *11*(16), 4876.
Wilson, G., Windner, Z., Dowell, A., Toop, L., Savage, R., & Hudson, B. (2021). Navigating the health system during COVID-19: Primary care perspectives on delayed patient care. *The New Zealand Medical Journal*, *134*(1546), 17–27.
World Health Organisation. (2022). *About the COVID-19 pandemic*. World Health Organisation. https://www.health.gov.au/health-alerts/covid-19/about
Xu, S., Glenn, S., Sy, L., Qian, L., Hong, V., Ryan, D. S., & Jacobsen, S. (2021). Impact of the COVID-19 pandemic on health care utilization in a large integrated health care system: Retrospective cohort study. *Journal of Medical Internet Research*, *23*(4), e26558.

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