

The COVID-19 pandemic and its consequences for the diagnosis and therapy of head and neck malignancies

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Abstract. – **OBJECTIVE:** The COVID-19 pandemic and the measures accompanying it have been accused of having a negative influence on the frequency and methods of treatment of various diseases including head and neck cancer (HNSCC). To go further into this assumption, the diagnoses made, and treatments performed at one of Germany's largest head and neck cancer centres were evaluated.

PATIENTS AND METHODS: This study consisted of one single centre and involved a retrospective review of all patients with newly diagnosed or recurrent HNSCC. The diagnosis and treatment methods used in the pre-COVID-19 time period between March 1st, 2019, and March 1st, 2020, were analysed and compared with the COVID-19 time period from April 1st, 2020, until April 1st, 2021. The primary objective was defined as the number of malignant diagnoses and the secondary objectives as the disease stage and the time to therapy.

RESULTS: A total of 612 patients (160♀; mean 63 yrs.) were included. 319 patients (52%) were treated in the pre-COVID-19 time. The two groups did not differ in terms of age ($p=0.304$), gender ($p=0.941$), presence of recurrent disease ($p=0.866$), tumour subsite ($p=0.194$) or the duration from presentation to the multidisciplinary tumour board until start of therapy ($p=0.202$). There were no significant differences in the T stage ($p=0.777$), N stage ($p=0.067$) or UICC stage ($p=0.922$). During the pre-COVID-19 period more patients presented with distant metastases ($n=23$ vs. $n=8$; $p=0.011$).

CONCLUSIONS: This study shows that there was no significant change in either the number and severity of HNSCC diagnoses or the time until start of therapy at this large head and neck

cancer centre as a result of the COVID-19 pandemic.

Key Words:

COVID-19, SARS-COV2, Head and neck cancer, Head and neck surgery, Academic centre.

Introduction

The COVID-19 pandemic originated in Wuhan, China, in December 2019. Since then, more than 270 million infections and more than 5 million deaths have been recorded worldwide.

Germany, as one of the most populous countries in Europe, has recorded more than 6 million infections with more than 100 thousand deaths to date¹. In order to reduce the number of infections and the resulting mortality rates, a variety of measures have been adopted and implemented: nationwide lockdowns, social distancing and the postponement of surgery in order to retain enough capacity for dealing with possible waves of infection and the associated intensive medical care of the patients, to name but a few.

While these measures may be helpful in fighting the pandemic, the question arises as to whether they have a negative impact on the diagnosis and treatment of malignant diseases². In their national population-based modelling study for the United Kingdom population, Maringe et al³ estimated more than 3,000 additional deaths in the next 5 years due to a delay in the diagnoses of

breast, colorectal, oesophageal and lung cancer.

The worldwide incidence of head and neck cancer is approximately 900 thousand cases with 300 thousand deaths⁴, and preliminary data suggest that the number of affected patients diagnosed will decrease during the pandemic. Kiong et al⁵ compared a 6-week period before and during the COVID-19 pandemic and recorded a 25% reduction in newly diagnosed head and neck malignancies. In contrast, an analysis of various cancer entities in Bavaria, Germany showed no significant decrease in new diagnoses during the period of the COVID-19 pandemic⁶.

To address this topic, as its primary objective this study assessed the number of newly diagnosed cases of head and neck cancer at one of the largest head and neck cancer centres in Germany one year before and after the start of nationwide measures in Germany in March 2020. Secondary objectives included the tumour stage, the distance of the patient's residence from the hospital and the time from presentation to the multidisciplinary head and neck tumour board (TB) until the start of therapy.

Patients and Methods

This retrospective review included all HNSCC patients who presented at one single tertiary referral and academic cancer centre. It was approved by the Local Ethics Committee (approval number 21-370-Br) and carried out according to the Declaration of Helsinki.

The medical history of all patients presenting with the initial diagnosis of new or recurrent head and neck cancer between March 1st, 2019, and March 1st, 2020, defined as the "pre-COVID-19 time period", were compared with patients presenting between April 1st, 2020, and April 1st, 2021, referred to as the "COVID-19 time period". The time frame was chosen because the first nationwide lockdown in Germany was declared in March 2020. Additional inclusion criteria were as follows: a complete medical chart, HNSCC according to TNM 8th Edition and discussion at the institute's own weekly multidisciplinary head and neck tumour board. At this meeting the following recommendations were made: ablative surgery with or without microvascular reconstruction and laser surgery, primary chemo(immune)radiation, adjuvant chemo(immune)radiation, induction therapy, best supportive care and wait and scan.

The following exclusion criteria applied: carcinomas of the skin, thyroid, oesophagus and tra-

chea, incomplete medical charts, occurrence of other cancer entities in the head and neck.

The primary objective was the total number of new diagnoses of head and neck cancer at a tertiary referral hospital. The secondary objectives included the tumour characteristics, in particular the TNM and UICC stage, recurrent disease and tumour subsite, the distance of the patient's residence from the hospital and the treatment recommendations of the multidisciplinary head and neck tumour board, as well as the duration between presentation to the TB and start of therapy. The tumour stage was determined according to the 8th version of the UICC⁷.

Statistical Analysis

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test and each variable's histogram. Normally distributed variables were presented as mean \pm 1 SD, min – max, and were compared between groups via independent *t*-tests. Non-normally distributed variables are presented as median (25th; 75th percentile), min – max and compared between the groups via Mann-Whitney U tests.

Nominal variables are presented as N (%) and compared via cross tables and the χ^2 test.

Effect sizes are provided for each test: *r* is reported for independent *t*-tests and Mann-Whitney U tests, with *r* = 0.1 displaying a small effect, 0.3 = a medium effect and 0.5 = a strong effect. Phi/Cramer's V is reported for χ^2 tests, with 0.1 displaying a small effect, 0.3 = a medium effect and 0.5 = a strong effect.

The annual incidence ratio was calculated for the descriptive comparison of the annual incidence of treated patients and the number of malignancies during the pre-COVID-19 and COVID-19 time periods.

Results

Between March 1st, 2019, and April 1st, 2021, a total of 612 patients accounting for 651 malignancies were diagnosed with HNSCC at our department. Out of these, 319 patients (52%) with 330 tumours (50.7%) were diagnosed and treated during the pre-COVID-19 time period. The numbers were reasonably stable, with 293 patients (48%) and 321 tumours (49.3%) being treated during the COVID-19 time period.

Of the aforementioned patients, 527 (86.1%) were newly diagnosed with malignant disease

and 85 patients (13.9%) had recurrent disease. Out of these, 283 patients (88.7%) were newly diagnosed, and 36 patients (11.3%) had recurrent disease in the pre-COVID-19 time period interval. In the COVID-19 time period interval, 244 patients (83.3%) were newly diagnosed and 49 (16.7%, $p=0.866$) patients had recurrent disease.

Patient Characteristics

The two groups did not differ significantly with respect to sex ($p=0.941$) or age ($p=0.412$). Furthermore, the groups did not differ in terms of the presence of recurrent disease ($p=0.866$) or tumour subsite ($p=0.194$). Nor were there any differences between the two groups with regard to the recommendations made by the multidisciplinary head and neck tumour board ($p=0.485$) or with regard to the time between presentation to the TB and start of the recommended therapy ($p=0.202$). Furthermore, there was no difference in the catchment area before and during the pandemic, measured by the mean distance from the patient's address to our facility ($p=0.428$). The patient characteristics are presented in Table I.

Tumour Characteristics

With regard to tumour characteristics (Table II), there were no differences in the T stage ($p=0.777$) or the UICC stage ($p=0.922$)⁷.

Likewise, there was no significant difference with respect to the N stage ($p=0.067$). However, a detailed analysis of the N stages did reveal a difference within the N3 stage. In the pre-COVID-19 period group 45 patients (15.5%) presented with N3 metastasis in comparison to 23 patients (8.5%) of the COVID-19 period group ($X^2_{(1)} = 6.50$, $p = 0.011$, $\phi = 0.107$). In keeping with this, there was a significant difference in the diagnosis of distant metastases ($p=0.011$): in the pre-COVID-19 time period 23 patients (7.9%) presented with an M1 stage compared to only 8 patients in the COVID-19 time period (3%).

Discussion

Especially in the field of otorhinolaryngology, an attending doctor has an increased risk of infection by the coronavirus while examining and treating the nose and throat, which bears the danger of aerosol formation⁸⁻¹⁰. The restriction of routine examinations on the part of otorhinolaryngologists and the measures implemented because of the pandemic, i.e., curfews and contact

restrictions, led to patients visiting a doctor less frequently despite having symptoms¹¹⁻¹⁵. Overall, cancer patients seem to have visited other hospitals in Germany and in other countries less frequently during the COVID-19 pandemic^{13,16-22}.

In view of these facts, the results presented did not show a significant decrease in the diagnosis of malignant disease or even in the number of diagnoses of early and advanced stages. This is particularly evident in the treatment recommendations made, which did not differ significantly either before or during the pandemic. As a surrogate parameter for potential patient non-attendance, analysis of the median distance from the patient's address to the institution indicated that the pandemic restrictions had not had an adverse effect.

Nevertheless, our facility also had to reduce the extent of daily operations in order to retain enough capacity for possible COVID-19 cases. This led to concentrating on oncologically necessary operations in order to cope with the uninterrupted number of patients without causing disadvantages for the patients. This is particularly evident in the unchanged time between presentation to the multidisciplinary head and neck tumour board and the initiation of the recommended therapies. It is to be noted that this refers not only to primary surgical treatments but also to primary non-surgical therapies.

In summary, it can be concluded that the oncological treatment of head and neck cancer patients at our centre was not adversely affected by the measures taken due to the pandemic.

The available literature is inconclusive in determining the effect of the COVID-19 pandemic on head and neck oncology care. Tevetoglu et al²³ reported that during the COVID-19 pandemic (March 15th-September 15th, 2020) the number of T3 and T4-staged head and neck cancers, and consequently the need for reconstruction with regionally free flaps, increased significantly in comparison to the same six-month period from the previous year and was due to the delay in admission and the allocation of most of the resources attributed to the pandemic. A study²⁴ from China reported a significantly prolonged waiting time for the initiation of radiotherapy (28 days before the facility began to take action against the COVID-19 pandemic and 36 days afterwards) in patients diagnosed with nasopharyngeal carcinoma as the expression of limited capacity for radiation therapy during the pandemic.

Focusing on oral cavity carcinoma, Metzger et al²⁵ analysed a total of 624 patients, of whom 566

Table I. Patient characteristics.

	Total number n (%)	COVID-19 period group n (%)	Pre-COVID-19 period group n (%)	Statistical comparison
Total number of patients	612 (100)	293 (48)	319 (52)	Annual incidence ratio = 0.918
Total number of malignancies	651 (100)	321 (49.3)	330 (50.7)	Annual incidence ratio = 0.973
Sex (n, %)				
• Male	452 (73.9)	216 (73.7)	236 (74)	$X^2_{(1)} = 0.01,$ $p = 0.941,$ $\Phi = 0.003$
• Female	160 (26.1)	77 (26.3)	83 (26)	
Age (mean \pm 1 SD, min -max)	62.86 \pm 11.92 15.0-95.0	62.48 \pm 11.87 17-95	63.27 \pm 11.89 15-90	$t_{(610)} = 0.82,$ $p = 0.412,$ $r = 0.033$
Median distance from patient's address to institution, km (median [25 th ; 75 th percentile], min - max)	58 (23 ; 97) 0-3700	58 (20 ; 97) 0-3700	59 (26; 97) 0-1063	$Z = 0.79,$ $p = 0.428,$ $r = 0.031$
Recurrent disease				
• Yes	85 (13.9)	49 (16.7)	36 (11.3)	$X^2_{(1)} = 0.03,$ $p = 0.866,$ $\Phi = 0.007$
• No	527 (86.1)	244 (83.3)	283 (88.7)	
Tumour subsite				
• Oral cavity	74 (11.4)	32 (10)	42 (12.7)	$X_{2(6)} = 8.65,$ $p = 0.194,$ Cramer's V = 0.119
• Oropharynx	206 (31.6)	101 (31.4)	105 (31.8)	
• Hypopharynx	72 (11.1)	31 (9.7)	41 (12.4)	
• Larynx	150 (23)	79 (24.6)	41 (12.4)	
• Nasopharynx	24 (3.7)	10 (3.1)	14 (4.3)	
• Major salivary gland	64 (9.8)	39 (12.2)	25 (7.6)	
• Sinonasal	61 (9.4)	29 (9)	32 (9.7)	
Multidisciplinary tumour conference recommendation				
• Primary Surgery	362 (55.6)	174 (54.2)	188 (57)	$X_{2(7)} = 6.48,$ $p = 0.485,$ Cramer's V = 0.485
- Ablative surgery with microvascular reconstruction	104 (28.7)	49 (28.2)	55 (29.3)	
- Ablative surgery without microvascular reconstruction	228 (63)	113 (64.9)	115 (61.1)	
- Laser surgery	30 (8.3)	12 (6.9)	18 (9.6)	
• Primary chemo(immune)radiation	129 (19.8)	60 (18.7)	69 (20.9)	
• Adjuvant (chemo)radiation therapy	17 (2.6)	6 (1.9)	11 (3.3)	
• Induction therapy	51 (7.8)	29 (9)	22 (6.6)	
• Best supportive care	38 (5.8)	23 (7.2)	15 (4.6)	
• Wait and scan	54 (8.4)	29 (9)	25 (7.6)	
Median duration from presentation to the multidisciplinary tumour conference until start of therapy, days (range)	21 (13; 34) 0-397	21 (12; 33) 0-397	22 (14; 34) 0-373	$Z = 1.27,$ $p = 0.202,$ $r = 0.056$

were treated from 2010-2019 and only 58 in 2020. They stated that patients presenting in 2020 were diagnosed at a significantly higher tumour stage and experienced a prolonged average time of 42 days from the initial presentation until surgical therapy compared to 32 days in 2010-2019. Consequently, this results in a rather small number of

patients studied during the COVID-19 pandemic and thus yields heterogeneous groups due to the different time periods selected. In contrast, the results presented are based on comparable time periods, resulting in comparable patient numbers in addition to the inclusion of HNSCC rather than only carcinoma of the oral cavity.

Table II. Tumour characteristics.

	Total n (%)	COVID-19 period group (%)	Pre-COVID-19 period group (%)	Statistical comparison
Tumour stage (n, %)				
• Carcinoma in situ	23 (4.1)	13 (4.8)	10 (3.4)	
• T1	136 (23.3)	61 (22.4)	75 (25.7)	$X^{2(4)} = 1.84,$ $p = 0.777,$ Cramer's V = 0.056
• T2	156 (27.7)	73 (26.8)	83 (28.4)	
• T3	109 (19.3)	55 (20.2)	54 (18.5)	
• T4	140 (24.8)	70 (25.7)	70 (24)	
• N0	303 (53.8)	148 (54.4)	155 (53.3)	$X^{2(3)} = 7.17,$ $p = 0.067,$ Cramer's V = 0.108
• N1	87 (15.5)	46 (16.9)	41 (14.1)	
• N2	105 (18.7)	55 (20.2)	50 (17.2)	
• N3	68 (12.1)	23 (8.5)	45 (15.5)	
Distant metastases (n, %)				
• M0	527 (94.4)	260 (97)	267 (92.1)	$X^{2(1)} = 6.49,$ $p = 0.011,$ Phi = 0.108
• M1	31 (5.6)	8 (3.0)	23 (7.9)	
UICC stage (n, %)				
• 0 (Cis)	23 (4.1)	13 (4.8)	10 (3.4)	$X^{2(4)} = 0.92,$ $p = 0.922,$ Phi = 0.040
• I	136 (24.1)	65 (23.9)	71 (24.3)	
• II	97 (17.2)	47 (17.4)	50 (17.5)	
• III	84 (14.9)	42 (15.4)	42 (14.4)	
• IV	224 (39.7)	105 (38.6)	119 (40.8)	

Our results are in line with the multicentre study of Heimes et al²⁶ that reported no trend towards increased numbers of diagnoses or higher tumour stages for oral malignant lesions during the COVID-19 pandemic. This comprehensive study compared a period during the lockdown (from March 13th-June 16th 2020) and after the lockdown (from June 17th-November 1st 2020) in Germany with the same periods in 2018 and 2019, including a total of 653 cases from three different centres. However, the evaluation is restricted to oral cavity carcinomas.

Limitations

The limitations of the study include the inevitable bias of the retrospective character of the analysis. Furthermore, the results presented derive from one single centre, albeit one of the largest head and neck tumour centres in Germany. Accordingly, the results may not be transferrable to other institutions, e.g., smaller hospitals or centres not treating head and neck cancer. Nevertheless, our study was based on an appropriately high number of patients combined with an appropriately long-time interval in order to present a meaningful comparison and to make a sound statement in this setting.

As a consequence, multicentre studies are necessary to fully and comprehensively assess the effect of the COVID-19 pandemic on the oncological treatment of head and neck cancer patients.

Critical analysis of such data is necessary to ensure the care of our patients in the future in case of possible further pandemics.

Conclusions

This single-centre study at a large head and neck cancer centre does not show a distinctly negative impact of the COVID-19 pandemic on the number and the stages of diagnosed HNSCC. The distance of the patient's residence from the hospital, the treatment recommendations of the multidisciplinary tumour board and the time to initiation of the recommended therapies were not influenced by the pandemic measures.

Thus, there were no evident restrictions regarding the care of HNSCC patients at our centre during the COVID-19 pandemic.

Ethics Approval and Consent to Participate

The Ethics Committee of the University of Erlangen-Nuremberg has approved the paper presented (approval number 21-370-Br). The need for informed consent was waived by the Ethics Committee of the Friedrich-Alexander University of Erlangen-Nuremberg because this was a retrospective study. This study was carried out according to the Declaration of Helsinki (in accordance with the relevant guidelines and regulations).

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Matthias Balk: concept and design, acquisition of data, analysis and interpretation of data, writing of the main manuscript, final approval of the version to be published. Robin Rupp: acquisition of data, critical revision of the article. Antonio Vasconcelos Craveiro: acquisition of data. Moritz Allner: critical revision of the article. Philipp Grundtner: acquisition of data, analysis and interpretation of data. Markus Eckstein: critical revision of the article. Heinrich Iro: critical revision of the article, final approval of the version to be published. Markus Hecht: critical revision of the article. Antoniu-Oreste Gostian: concept and design, acquisition of data, analysis and interpretation of data, drafting and critical revision of the article, final approval of the version to be published.

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