### ORIGINAL RESEARCH

**Investigative Otolaryngology** 

## Diagnostic pathway and stage migration of sinonasal malignancies in the era of the COVID-19 pandemic

Christian M. Meerwein MD<sup>1,2</sup> Thomas M. Stadler MD<sup>1,2</sup>

### Correspondence

Christian M. Meerwein, MD, Department of Otorhinolaryngology, Head & Neck Surgery, University Hospital Zurich, Frauenklinikstrasse 24, Zurich 8091, Switzerland.

Email: christian.meerwein@usz.ch

### **Abstract**

Objectives: The COVID-19 pandemic bears the risk of delayed cancer diagnoses.

Methods: Study on the diagnostic pathway of sinonasal malignancies during the COVID-19 pandemic.

Results: Median time from first symptom to treatment initiation was not increased during the pandemic: 137 days (interquartile range [IQR] 104-193) vs 139 days (IQR 103-219) (P = .60). Median time from first appointment at our institution to treatment initiation was even reduced in 2020: 18 days (IQR 11-25) vs 11 days (IQR 7-17) (P = .02). A trend toward advanced tumor stages during the pandemic was seen: 11/30 patients (36.7%) ≥ stage 4 in 2018 to 2019 vs 12/19 patients (63.2%)  $\geq$  stage 4 in 2020 (P = .064).

Conclusion: Both, time to diagnosis and time to treatment initiation were similar during the pandemic. However, a higher proportion of advanced tumors stages was observed. Despite the pandemic, we provided a swift diagnostic workflow, including a virtual tumor board decision and a prompt treatment initiation.

Level of Evidence: 4.

### KEYWORDS

delay, malignancy, nasal vestibule carcinoma, nasopharyngeal carcinoma, pandemic, sinonasal, tumor

#### INTRODUCTION 1

Among many other challenges in patient management, the recent COVID-2019 pandemic with months of national lockdowns in many countries worldwide bears a substantial risk of delayed cancer diagnosis.<sup>1</sup> Possible reasons for a delay in the oncological pathway are both, patient and health care system related. Screening, case identification, and

Christian M. Meerwein and Thomas M. Stadler contributed equally to this work as first authors.

Michael B. Soyka and David Holzmann contributed equally to this work as last authors.

referral in symptomatic cancer have all been affected by the pandemic.<sup>2</sup> Along with the call for social distancing, many patients have postponed their medical appointments, since they fear healthcare interactions or mistakenly believe, that health care systems are shut to all but COVID-19 patients.3 With regard to three common cancers (a. breast, b. colorectal, and c. lung) recent data indicated a significant decline in newly diagnosed patients during the pandemic.<sup>4,5</sup> For head and neck cancer, the sixth most common cancer worldwide, which typically reveals a short tumor volume doubling time, a delayed treatment initiation was shown to significantly impact overall survival (OS) for patients undergoing upfront surgery or radiotherapy (RT).<sup>6,7</sup> For sinonasal

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<sup>&</sup>lt;sup>1</sup>Department of Otorhinolaryngology, Head & Neck Surgery, University Hospital Zurich, Zurich, Switzerland

<sup>&</sup>lt;sup>2</sup>University of Zurich, Zurich, Switzerland

<sup>&</sup>lt;sup>3</sup>Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland

malignancies in particular, specific data on incidence and stage distribution during the pandemic is rare. Owing to their growth pattern, characterized by locally aggressive expansion and close relationship to pivotal neuro-vascular structures, patients often present at an advanced T category, with involvement of dura, orbit, or brain. Based on these facts, most institutions advocate for initiation of head and neck cancer treatment within 4 to 6 weeks of diagnosis. With this study on the diagnostic pathway and management of sinonasal malignancies during the COVID-19 pandemic in Switzerland, we aimed to compare the pandemic era (2020) to the prepandemic years (2018-2019). In particular, we wanted to investigate absolute numbers of newly diagnosed rhinologic tumors, time from first symptom to diagnosis and treatment initiation, time from first appointment at our institution to treatment initiation and a possible stage migration to more advanced tumors during the pandemic.

### 2 | METHODS

### 2.1 | Study design

This study received ethical approval from the ethics committee of the Canton of Zurich, Switzerland. Patients with documented denial to contribute personal health-related data to research were not included. We retrospectively reviewed a consecutive cohort of patients treated for sinonasal malignancies (primary sinonasal tumor, nasopharyngeal carcinoma, and nasal vestibule carcinoma) at the department of otorhinolaryngology at the University Hospital Zurich (Switzerland) between January 2018 and December 2020. The cohort was divided into two groups: control group (prepandemic era, January 2018-December 2019) vs index group (pandemic era, January 2020-December 2020). Patients with documented denial to contribute personal health-related data to research were not included. Tumors were staged according to the eighth edition of the American Joint Committee on Cancer staging system. 10

Patients underwent endonasal-endoscopic biopsy and exploration of the tumor under general anesthesia. In all patients, staging of the neck was performed with ultrasound-guided fine needle aspiration cytology (FNAC) of suspicious lymph nodes. Cross-sectional imaging with computed tomography (CT), magnetic resonance imaging (MRI), and hybrid positron-emission tomography (PET) imaging was performed. Treatment plans were discussed at our multidisciplinary tumor board.

# 2.2 | Patient characteristics, treatment protocols, outcome measures, and follow-up

The following patient data and tumor data were collected: age, gender, risk factors, history of SARS-COV19-infection (patient, close social environment), symptoms at initial presentation, onset of first symptoms, first contact with family doctor, first contact with private ENT, first contact at University Hospital Zurich (tertiary referral center), date of biopsy, initial clinical classification (cT, cN, cM), tumor stage, time from first diagnosis

to biopsy (days), time from first symptom to treatment initiation at our institution (days), time from first contact at our institution to treatment initiation (days), histopathological work-up, location of primary tumor, primary treatment protocols, duration of follow up (months), and state at last follow-up. Of note: Only patients with terminated initial treatment protocols were included for the follow up calculation (45/49 patients).

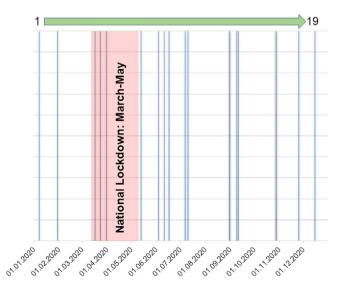
### 2.3 | Variables and statistical analysis

The normality of distribution was checked using the Kolmogorov-Smirnov test. Data are either presented as median and interquartile range (IQR) or as mean ± standard deviation (SD), depending on the normality of data distribution. Differences between intervals (first symptom to biopsy, first symptom to treatment initiation, first appointment at our institution to treatment initiation) in the control group (2019-2019) and the index group (2020) were calculated using the Mann-Whitney *U*-test. Differences among the control and index group regarding the distribution of initial tumor stage were calculated using contingency tables and Fisher's exact test. Accordingly, symptoms at initial presentation among different tumor stages were compared. A post-hoc analysis for the given sample and alpha level of .05 using "clincalc.com" was performed. The end of follow-up was December 2020. A *P*-value less than .05 indicated significance. Statistics used SPSS version 22 (IBM, Armonk, New York).

### 3 | RESULTS

### 3.1 | Patient and tumor characteristics

A total of 49 consecutive patients were included: prepandemic era (30 patients, 2018-2019) vs pandemic era (19 patients, 2020). The



**FIGURE 1** Distribution pattern of newly diagnosed sinonasal malignancies (blue pillars, each indicating one patient) over the year 2020 (n=19). The national lockdown in Switzerland is indicated separately in red color

## Laryngoscope Investigative Otolaryngology

absolute numbers of newly diagnosed tumors in 2020 was slightly higher, when compared to the two previous years (19 patients 2020 vs 30 patients 2018-2019). Figure 1 displays details on the distribution pattern of new tumor diagnoses during the year 2020 in relation to the national lockdown. None of the included patients or their close relatives in the pandemic group had a past medical history of documented COVID-19 infection or quarantine. Symptoms at initial presentation are presented in Table 1: although we observed a trend toward an increased prevalence of manifest symptoms along with advanced tumor stage, there was no statistically significant association.

Table 2 provides detailed information on both, patients and tumor characteristics at initial presentation. In total, 8/49 patients with nasal vestibule carcinomas, 11/49 patients with nasopharyngeal carcinomas and 30/49 patients with primary sinonasal malignancies were identified, Distribution of those three tumor entities was similar between the prepandemic and the pandemic group (P = .196). Among the nasopharyngeal carcinomas, 9/11 tumors were EBV-associated squamous cell carcinomas (SCC), while histopathological workup revealed undifferentiated nasopharyngeal SCC in 2/11 tumors. Among the 30 primary sinonasal malignancies, histopathology showed

Symptoms	Total	1	II	Ш	IV	Fisher's Exact Test (P value)
Nasal obstruction	29	2	10	4	13	.122
Epistaxis	28	4	8	5	11	.653
Hyposmia	5	0	1	0	4	.582
Pain	18	3	1	2	12	.064
Double vision	4	0	0	0	2	.281

**TABLE 1** Distribution of symptoms depending on initial tumor stage

Characteristics	Total	2020	2018-2019			
Number of patients (n)	49	19	30			
Gender (n)						
Female	19	6	13			
Male	30	13	17			
Age at diagnosis (median, 1-3. IQR)	66	52	70			
	(IQR 47-74)	(IQR 45-72)	(IQR 53-74)			
Risk factors (n)						
Smoking	19/49	7/19	12/30			
Wood dust exposure	6/49	4/19	2/30			
Leather dust exposure	1/49	0/19	1/30			
Entity (n)						
Nasopharyngeal carcinoma	11	7	4			
Nasal vestibule carcinoma	8	1	7			
Primary sinonasal tumor	30	11	19			
Initial clinical T classification according to clinical and radiological assessment (n)						
cT1						
cT2	9	2	7			
cT3	10	2	8			
cT4	9	5	4			
	21	10	11			
Initial N classification (n)						
cN0	40	13	27			
cN+	9	6	3			
Initial M classification (n)						
cM0	45	17	28			
cM1	4	2	2			

**TABLE 2** Patients and tumor characteristics

adenocarcinoma in 7/30 patients, SCC in 7/30 patients, sinonasal undifferentiated carcinoma (SNUC) in 6/30 patients, sinonasal mucosal melanoma in 6/30 patients, olfactory neuroblastoma in 3/30 patients and adenoidcystic carcinoma in 1/30 patient. As seen in Table 3, 30/49 patients presented with stage III or stage IV disease. When comparing the

**TABLE 3** Distribution of tumor stage across the prepandemic group (2018-2019) and the pandemic group (2020)

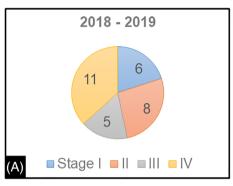
Year	Stage						
	ī	II	III	IV	< IV	≥ IV	
2018-2019	6	8	5	11	19	11	
2020	1	4	2	12	7	12	
Fisher's Exact Test	P = .318			P = .064			

prepandemic group and the pandemic group with regard to tumor stage, we observed a trend toward tumor stage migration to more advanced tumors in 2020: 11/30 patients (36.7%)  $\geq$  stage 4 in 2018 to 2019 vs 12/19 patients (63.2%)  $\geq$  stage 4 in 2020 (P = .064; Table 3, Figure 2).

# 3.2 | Time to diagnosis, time to treatment initiation, and time to treatment initiation at tertiary referral center

As indicated in Table 4 and Figure 3, both, median time from first symptom to biopsy proven diagnosis and median time from first symptom to treatment initiation were similar in the prepandemic and the pandemic group. However, time interval from the first

FIGURE 2 Distribution pattern of the initial tumor stage (stage I-IV) in the prepandemic (A, 2018-2019, a total of 30 newly diagnosed tumors) vs the pandemic era (B, 2020, a total of 19 newly diagnosed tumors)





**TABLE 4** Overall and stage dependent distribution of investigated intervals

Interval		Stage							
Days		ī	II	III	IV	Median			
Symptom-Biopsy									
2018-2019	Median, IQR	134 (113-162)	123 (100-140)	148 (82-187)	101 (71-124)	123 (82-156)			
2020	Median, IQR	190	115 (91-179)	177 (73-195)	116 (99-171)	129 (104-192)			
Mann-Whitney-	-U					P = .17			
Symptom-Initiation	of treatment								
2018-2019	Median, IQR	179 (148-205)	138 (110-195)	143 (113-237)	116 (88-151)	137 (104-193)			
2020	Median, IQR	219	172 (138-207)	188 (71-213)	127 (97-171)	139 (103-219)			
Mann-Whitney-	-U					P = .6			
First referral-Initiat	ion of treatment								
2018-2019	Median, IQR	17 (11-35)	13 (12-21)	28 (25-28)	18 (8-27)	18 (11-25)			
2020	Median, IQR	29	11 (11-15)	8 (5-12)	8 (5-15)	11 (7-17)			
Mann-Whitney-	-U					P = .02			



**FIGURE 3** In this study, we investigated (a) time from first symptom to biopsy proven diagnosis, (b) time from first symptom to treatment initiation, and (c) time from first referral to our institution to treatment initiation. USZ; University Hospital of Zurich, Switzerland

appointment at our institution to treatment initiation was significantly shorter during the pandemic, when compared to the prepandemic era.

### 3.3 | Primary treatment protocols

Initial treatment protocols consisted of surgery alone in 6/49 patients, neoadjuvant chemotherapy + definitive radiochemotherapy in 10/49 patients, surgery + adjuvant radio(chemo)therapy in 22/49 patients, primary radio(chemo)therapy in 10/49 patients, and best supportive care in one patient.

### 3.4 | Follow-up, outcome

The overall median follow up of the cohort was 15 months (IQR 7-23). For the control group (2018-2019), the median follow up was 22 months (IQR 15-25), while for the pandemic group, it was 4 months (IQR 4-7).

In the prepandemic group, most of the patients were free of disease at the last follow up (23/30, 79.3%). Seven patients (21.1%) had developed local persistence or recurrence, of whom two patients (6.8%) had synchronous distant metastases.

### 4 | DISCUSSION

### 4.1 | Main findings

In this tertiary referral center study on the management of sinonasal malignancies in the COVID-19 era in Switzerland we found that both, absolute time to biopsy proven diagnosis and time to treatment initiation were similar during the pandemic, when compared to prepandemic years. However, an increased proportion of advanced tumors stages (≥ stage 4) as possible indirect indicator of diagnostic delay prior to referral to the tertiary cancer center was observed. Despite the pandemic, we were able to provide a targeted and swift oncological treatment path at our institution, which included an interdisciplinary tumor board discussion in all cases and even resulted in a decreased time from first appointment to treatment initiation. Importantly, even during the two pandemic-"waves" during spring and late autumn 2020, no tumor boards were cancelled or delayed and all sessions were held virtually. The absolute number of newly diagnosed sinonasal tumors in 2020 was not lower, when compared to the two previous years.

The COVID-19 pandemic is a tremendous challenge for health care systems worldwide. Along with the burden of the disease, national wide lockdowns and limited health care system resources have secondarily complicated access to medical care and postponed urgently indicated medical treatments. For instance, in the United Kingdom, national cancer screening programs, which accounted for approximately 5% of all annual cancer diagnoses, have been suspended.<sup>2</sup> The Netherlands Cancer Registry reported declining cancer incidence rates up to 40% at the peak of the pandemic.<sup>5</sup>

Additionally, data showed that patients with recently diagnosed cancer had significantly increased risk of COVID-19.11 For head and neck cancer and sinonasal malignancies in particular, only limited data on the sequelae of the pandemic are available so far. 12 Data from the COVIDSurg collaborative estimated a 12-week cancellation rate of 38.9% for head and neck cancer surgery, while for benign head and neck procedures numbers were estimated even higher, with 81.5%. 13 Although it was shown that standard head and neck cancer therapy is safe and need not to be withheld during the pandemic, recent data on nasopharyngeal carcinomas indicated a pandemic-related delay in the diagnostic pathway and treatment initiation. 13,14 For the entity of sinonasal malignancies, there is a lack of data concerning tumor stage migration in the pandemic era. Sinonasal malignancies represent 3% to 5% of all head and neck cancers and their growth is associated with potential affection of pivotal neurovascular structures, such as brain, dura, carotid artery, and optic nerve. 15,16 Typically, patients present at an advanced stage, since the tumor expands unnoticed for a long time and often leads to alarming symptoms at an advanced stage.<sup>17</sup> Despite evolvement of new treatment strategies, namely advanced transnasal-endoscopic surgical techniques and high precision RT, 5-year OS and local control rates in the prepandemic era plateaued around 58% to 68%. 15,18-20 Our study cohort reflects the last 3 years of newly diagnosed sinonasal malignancies at a tertiary referral center in Switzerland. Review of initial T classification revealed locally advanced tumors in the vast majority of all subjects (29/39 patients ≥ cT3). As various series have shown, tumor stage strongly predicts prognosis in sinonasal tumors, since especially tumors staged as T4b, with involvement of dura and/or brain, go along with poor DFS and OS. 19-21 Accordingly, for nasopharyngeal carcinomas OS significantly depends on initial T category, with 5-year survival rates of 91% reported for T1 tumors vs 68% for T4 tumors.<sup>22,23</sup>

Pandemic associated reasons for a potential diagnostic delay in cancer care are manifold and include (a) patient's fear of contacts with health care providers, which lead to less patient visits during the pandemic (b) patients are concerned that potential healthcare-capacity issues may interfere with the optimal treatment of their disease, (c) lower participation or downregulation of screening programs, and (d) delayed referral from primary care to specialist and tertiary referral center. 1,2,5,24,25 Turri-Zanoni et al recently published on the management of patients with sinonasal tumors during the pandemic and set a list of five recommendations, among which avoidance of a delay in diagnosis was named as first point.<sup>17</sup> Thereby, they opted for prompt radiological assessment of the patient to define the extension of the cancer and recommended an endoscopic-assisted transnasal biopsy of the tumor. 17,26 In contrast to the previous mentioned data from the UK and the Netherlands, the absolute number of newly diagnosed sinonasal tumors at our department was not lower in 2020, when compared to the two previous years.<sup>5</sup> Also, we found no diagnostic delay from onset of first symptoms (as documented in the patient's medical history) to diagnosis and treatment initiation. However, an indirect delay due to an irrational patient's fear of contact with health care providers may have translated into an increased proportion of advanced tumor stages (36.7% ≥ stage 4 in 2018-2019 vs 63.2% ≥

stage 4 in 2020). Interestingly, despite the pandemic, we managed to initiate treatment even quicker, when compared to the era 2018 to 2019. This also included a virtual interdisciplinary tumor board decision. This finding might be explained by an increased awareness of potential prehospital diagnostic delay and a streamlining of pivotal cases at a tertiary referral center due to postponement of elective cases. With regard to possible learnt lessons from the current situation, the pandemic forces the health care system to use alternative ways of cancer patient care, such as telemedicine. These technologies must be empowered, to serve as adjunct to patient screening, therapy planning, and follow-up.<sup>27</sup>

### 4.2 | Limitations

Besides its retrospective design, we acknowledge that our study has some noteworthy limitations. First, we included all newly diagnosed sinonasal tumors in 2020, a post-hoc power analysis at an alpha level of .05 revealed, that our study was underpowered (21.4%). Second, we included three different rhinologic tumor entities in our cohort, which exhibit a different biological behavior. However, distribution of those three tumor entities was similar between the prepandemic and the pandemic group. Third, the follow up, in particular of the pandemic group, is too short to provide reliable statements in terms of outcome. Fourth, the pandemic itself had its course of lockdowns, exertion, and loosened periods, which could bias our results. Thus, further studies on larger cohorts are necessary to better understand the impact of the COVID-19 pandemic on sinonasal malignancies and head and neck cancer care in general.

### 4.3 | Conclusion

Absolute time to diagnosis and time to treatment initiation were similar during the pandemic, when compared to prepandemic era. A trend toward an increased proportion of advanced tumors as an indirect indicator of a diagnostic delay was observed, bearing the risk of a poorer outcome. Despite the pandemic, we were able to provide a targeted and swift diagnostic workflow, including a virtual tumor board decision. This effort even resulted in a decreased time from first appointment to treatment initiation at our institution.

### **CONFLICT OF INTEREST**

The authors declare no potential conflict of interest.

### ORCID

Christian M. Meerwein https://orcid.org/0000-0002-8674-1007
Thomas M. Stadler https://orcid.org/0000-0002-1262-0720
Panagiotis Balermpas https://orcid.org/0000-0001-5261-6446
Michael B. Soyka https://orcid.org/0000-0003-4179-4989
David Holzmann https://orcid.org/0000-0002-8176-8358

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