MJS PUBLISHING

REVIEW ARTICLE

The impact of the COVID-19 pandemic on time to treatment in head and neck cancer management: a systematic review

Malte Grumstrup Simonsen[a] [ID], Amanda-Louise Fenger Carlander[a] [ID], Kathrine Kronberg Jakobsen[a] [ID], Christian Grønhøj[a,b] [ID] and Christian von Buchwald[a,b] [ID]

[a]Department of Otolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [b]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Background and purpose: Coronavirus disease 2019 (COVID-19) caused a need for reorganization in the healthcare systems. First, we aimed to determine the impact of the COVID-19 pandemic on time to treatment in head and neck cancer (HNC) patients. Second, we aimed to determine the impact of COVID-19 on tumor stage and changes in treatment regimens used.

Material and methods: A systematic search in PubMed and Embase was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Inclusion criteria were: (1) Studies including patients with head and neck squamous cell carcinomas; (2) Studies containing a comparison of time to treatment; (3) Studies containing a well-defined time interval with restrictions on health care due to COVID-19 and a well-defined time interval without restrictions.

Results: A total of 19 studies were included comprising 24,898 patients treated for HNC cancer. Six studies (10.1% of the patients) reported an increase in waiting time within at least one interval, while seven studies reported a decrease (83.2% of the patients), and six studies found no significant effect. No changes in treatment modalities were observed. Seven of 15 studies (12.7% of the patients) observed an increase in either overall stage, size, or tumor node and metastasis classification during the COVID-19 pandemic. Among these, two studies reported increased waiting times as well.

Interpretation: The impact of the COIVD-19 pandemic on time to treatment was heterogenous and subject to considerable intercountry and interregional variations. A tendency toward a higher T-classification was observed. In conclusion, otorhinolaryngology departments demonstrated resilience, as the pandemic led to only slight alterations in time to treatment.

Introduction

Coronavirus disease 2019 (COVID-19) caused a profound need for reorganization in the healthcare systems worldwide. The prompt global spread led to the World Health Organization (WHO) declaring the virus a pandemic on the 11th of March 2020 [1]. Globally, resources were reallocated toward the prevention and care of COVID-19 patients, potentially impacting the availability of diagnostics and treatment of other diseases [2–5].

The management of head and neck cancer (HNC) patients underwent comprehensive evaluation, given the transmission of COVID-19 primarily through the nasal and respiratory pathways [6]. Guidelines regarding medical care of HNC patients were made, including recommendations for the management of potential treatment delays [7, 8]. Along with the reduction in elective procedures on medical care centers [9, 10], many dental clinics closed during the early stages of the pandemic, removing an important healthcare provider [11]. Diversion of resources and the increased risk of exposure to COVID-19 for patients seeking medical care raised concerns of increases in time to treatment in HNC [8, 12].

Studies indicate that increases in time to the treatment of HNC patients are associated with a higher tumor stage and worse survival, although the results have been inconsistent, possibly due to large heterogeneities in study designs and definitions of treatment delay [13, 14].

The aim of this systematic review was to determine the impact of the COVID-19 pandemic on time to treatment in HNC patients as well as to elucidate the impact of COVID-19 on tumor stage and treatment regimens used.

Methods and materials

This systematic review followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

Search strategy

A systematic search was conducted in PubMed and Embase with the final search being on 13th of October 2023. Two authors (MG and ALFC) independently screened the studies eligible for inclusion.

The following keywords were identified: 'Time to treatment' and 'head and neck squamous cell carcinomas', and they were subsequently assigned to their corresponding MeSH-term (PubMed) or emtree-term (Embase). For completeness, synonyms of the keywords were also included in the final search. With the exposure of the study being the COVID-19 pandemic, publication year was set to be not earlier than January 2020. The full search can be found in the supplementary material.

Eligibility criteria

Full-text studies were included according to the following criteria: (1) Studies including patients with head and neck squamous cell carcinomas (HNSCC), (2) Studies containing a comparison of time to treatment, and (3) Studies containing a well-defined time interval with restrictions on health care due to COVID-19 and a well-defined time interval without.

Studies were excluded if there was no measurement of time to treatment, no comparison between a COVID-19 and a non-COVID-19 group, less than 10 participants, no data specifically on HNC, and no full-text was available. Studies not published in Danish, Norwegian, Swedish, or English were also excluded.

Data items

The subsequent data were retrieved: Author, publication year, geographical location of study population, study period, age, number of patients, definition of time to treatment, tumor sites, treatment modality used, oncological outcome (Tumor Node and Metastasis [TNM] classification, changes in Union for International Cancer Control (UICC) stage grouping or changes in mean tumor size), and time to treatment including a definition of the time interval measured.

In this review, the term 'time to treatment' was used to describe any interval from the debut of symptoms until the beginning of therapy. 'Symptom' was defined as the first day of symptoms, as reported by the patient. 'Specialist' was defined as the first visit to the respective healthcare center, which determines diagnosis and initiates treatment.

Assessment of outcomes

Reporting quality and risk of bias was assessed using the 20 component AXIS-tool for cross sectional studies [16]. Appraisal was done by one researcher (MGS) (Supplementary material for details).

Results

Study selection

The literature search yielded 578 results after removal of duplicates. A total of 36 full texts were assessed for eligibility, with 14
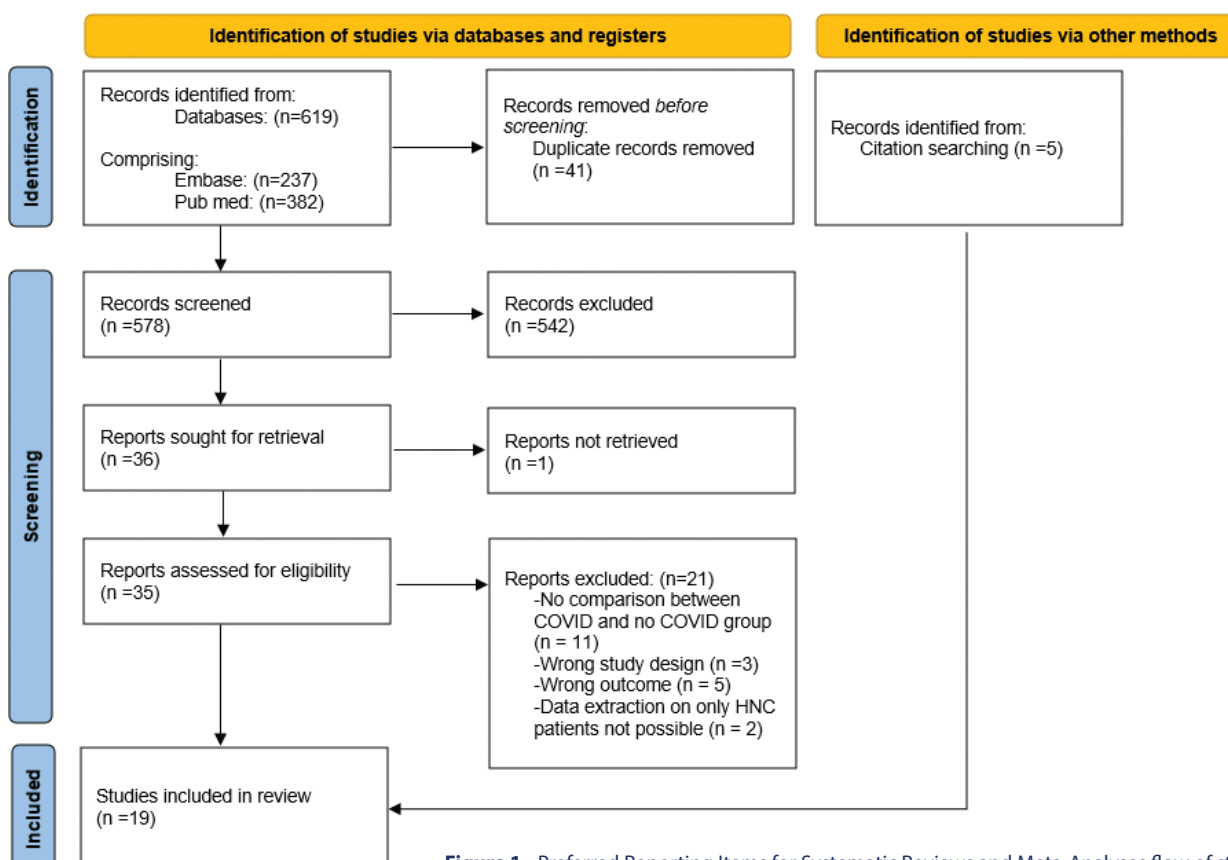

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow of study selection.

studies meeting the inclusion criteria [17–30]. Additionally, five studies were identified through screening of references [31–35]. A total of 19 studies were enrolled [17–35] (see Figure 1).

Study characteristics

A total of 24,898 patients were included. Median number of patients in the study was 265 (range: 49–10,880). The types of HNCs assessed were: Ten studies reported on all the HNCs [18, 19, 20, 23, 25, 27–30, 33], three studies looked at specifically HNSCC [24, 32, 35], while six studies only assessed either sinonasal, nasopharyngeal, oral, or laryngeal cancer [17, 21, 22, 26, 31, 34]. Twelve studies analyzed data from a single tertiary center [17–19, 21, 22, 24, 26, 30, 31, 32, 33, 35], while seven studies obtained data from a register [20, 23, 25, 27–29, 34]. Geographic locations included: Croatia [17], Germany [25, 26, 34, 35], England [18], Italy [19], the Netherlands [20], Scotland [29], Switzerland [21], Turkey [22], Wales [27], Canada [23], the United States [24, 28, 30, 32, 33], and China [31]. Median age of the patients was 64.5 years (range: 50.5–72.5 years). Median male to female ratio was 2.4 (range: 1.2–10.2). Periods defined as 'non-COVID-19' and 'COVID-19' varied between studies, with some [19, 20, 22–24, 27–35] choosing an interval within a lockdown period from the respective country as a marker of the COVID-19 period, and others [17, 18, 21, 25, 26, 28] defining January 2020 as the beginning of the COVID-19 period. Treatment was either surgery, radiotherapy, chemotherapy, chemoradiotherapy, or a combination. A full overview of study characteristics is shown in Table 1.

Time to treatment intervals

A total of 13 different time intervals were reported, encompassing the period from onset of symptoms to initiation of treatment, see Figure 2. Five studies [24, 30, 31, 33, 34] used intervals that did not fit in the intervals mentioned in the figure. Heimes et al. analyzed 'time to intervention' [34], Yao et al. reported on intervals starting from initial documented suspicion of cancer [30], Yang et al. analyzed time to treatment in each step in a pathway from diagnosis to treatment [31], and Kiong [33] and Solis [24] included the interval between the patient's initial diagnosis at another medical center and their first appointment at Kiong and Solis' respective centers.

Time to treatment

Six studies found no significant difference in time to treatment across all intervals investigated ($n = 1,616$) [19, 24, 29, 33–35].

Six studies found a significant increase in time to treatment in the COVID-19 group within at least one interval ($n = 2,503$) [17, 18, 22, 26, 30, 31]. Increases in days from specialist to initiation of treatment were observed in two studies [17, 26]. Gršić et al. observed an average increase of 11 days (26 days vs 37 days, $p = 0.006$) and 10 days (21.5 days vs 31.5 days, $p = 0.001$) for patients with oral and laryngeal cancer, respectively ($n = 691$)

[17]. Similarly, Metzger et al. identified an average increase of 10 days (35 days vs 45 days, $p = 0.04$) across all HNCs ($n = 624$) [26]. Additionally, both Gršić et al. and Tevetoğlu et al. ($n = 116$) found an increase in the symptom to specialist interval for oral cancer of 22.5 days (37.5 days vs 60 days, $p = 0.019$) [17] and 2.4 days (16.6 days vs 19.0 days, $p = 0.02$), respectively [22].

Zubair et al. investigated the interval from referral to initiation of treatment and found an increase of 23.3 days in the COVID-19 group compared to the non-COVID-19 group (49.2 days vs 72.5 days, $p = 0.027$) ($n = 104$) [18]. Yao et al. reported, among other intervals, on the time from first documentation of cancer suspicion to diagnosis and observed that patients in the COVID-19 group had a significantly longer time to diagnosis than the non-COVID-19 group (hazard ratio: 0.54, $p = 0.02$) ($n = 94$) [30]. Yang et al. identified significant increases in days in the COVID-19 group regarding waiting time for: pathological biopsy (5 days vs 15 days, $p = 0.012$), radiotherapy immobilization and simulation (3.5 days vs 16.5 days, $p < 0.001$), validation of position and plan (20 days vs 61 days, $p < 0.001$), and initiation of radiotherapy (28 days vs 36 days, $p = 0.005$) ($n = 874$) [31]. The median duration of increased time to treatment across studies was 11 days, with intervals ranging from 7 to 41 days. In total, increased time to treatment was observed in Croatia [17], Germany [26], England [18], Turkey [22], the United States [30], and China [31].

Seven studies found a significant decrease in time to treatment in the COVID-19 group within at least one interval ($n = 20,779$) [20, 21, 23, 25, 27, 28, 32]. A decrease of 5 days from specialist to treatment was observed by Schoonbeek et al. (31 days vs 26 days, $p < 0.001$) ($n = 8468$) [20]. In addition, a decrease in time from the date of biopsy to treatment was also found (37 days vs 30 days, $p < 0.01$) [20]. Psychiaris et al. found a decrease of 27.9 days from specialist to treatment (76.6 days vs 48.7 days, $p > 0.01$) ($n = 265$) [23]. They also found a decrease of 12.9 days in the interval from specialist to presentation at multidisciplinary team (MDT) conference in the COVID-19 group compared to the non-COVID-19 group (38 days vs 25.1 days, $p = 0.0001$) [23].

Two studies found a decrease in the interval from diagnosis to initiation of treatment [25, 28]. Heckel et al. found a decrease of 3.5 days in the COVID-19 group (23 days vs 19.5 days, $p = 0.013$) [25], while Tasoulas et al. found a decrease of 3 days decrease (46 days [95% CI: 46–47] days vs 43 [95% CI: 42–43]) ($n = 10,880$) [28].

Two studies found a decrease in the period from referral to specialist. Abelardo et al. found a decrease of one and a half days in the COVID-19 group (9.5 days vs 8 days, $p > 0.01$) ($n = 143$) [27]. Stevens et al. found a decrease of 3 days (11 days vs 8 days, $p = 0.008$) [32], and Meerwein et al. found a 7-day decrease from referral to initiation of treatment (18 days vs 11 days, $p = 0.02$, $n = 49$) [21]. The median duration of decreased time to treatment across studies was 5 days, with intervals ranging from 1.5 to 28 days. In total, decreased time to treatment was found in the Netherlands [20], Germany [25], Switzerland [21], Wales [27], Canada [23], and the United States [28, 32]. A full overview is presented in Table 2.

[AQ3]

Table 1. Overview of study characteristics.

Authors, country of the study, publication year	Centre/database	Study period (non-COVID-19)	Study period (COVID-19)	Time to treatment intervals	No. of patients	Age*	M/F ratio(s)**	Site	Outcomes
Europe									
Gršić, Croatia, 2022	Zagreb University Hospital	2018 + 2019	2020 + 2021	Symptoms to specialist	691	61.1; 66.4	1.5; 10.2	Oral, Larynx	Time to treatment, Clinical TNM classification, UICC overall stage
Zubair, England, 2022	Royal London Hospital	January to October, 2019	January to October, 2020	Referral to specialist, Referral to treatment, Diagnosis to treatment	104	N.A.	N.A.	HNC	Time to treatment, UICC overall stage
Heckel, Germany, 2023	UCC-R (Eastern part of Bavaria)	2019	2020	Diagnosis to treatment	706	63.0	2.3; 2.8	HNC	Time to treatment, Clinical TNM classification, Pathological TNM classification, UICC overall stage
Metzger, Germany, 2021	Heidelberg University Hospital	2010–2019	2020	Specialist to treatment	624	65	1.4	Oral cancer	Time to treatment, Pathological TNM classification, UICC overall stage
Kourtidis, Germany, 2022	Charité Hospital, Berlin ENT surgery dept.	March 2019 to March 2020	March 2020 to March 2021***	Symptom to diagnosis, Diagnosis to treatment	94	67.4; 69	2.4; 3.3	HNSCC	Time to treatment, Clinical TNM classification
Heimes, Germany, 2021	Maxillofacial departments of Kiel, Mainz, and Berlin	June to November, 2018, June to November, 2019	June to November, 2020***	Time to intervention	653	N.A.	N.A.	Oral cancer	Time to treatment, T and N classification, UICC overall stage
Lucidi, Italy, 2022	University Hospital of Modena, Italy	March to October, 2019	March to October, 2020***	Specialist to treatment	265	66.4; 68.5	N.A.	HNC	Time to treatment, UICC overall stage
Schoonbeek, Netherlands, 2021	Netherlands Cancer Registry	March to June, 2018, March to June, 2019	March to June, 2020***	Specialist to treatment, Biopsy to treatment	8468	66.1 ; 66.4	1.7 ; 1.9	HNC	Time to treatment, UICC overall stage
Drake, Scotland, 2022	MDT data from West of Scotland	March to May, 2019	March to May, 2020***	Referral to diagnosis, Referral to treatment	236	61.5 ; 63.7	2.1 ; 3.4	HNC	Time to treatment
Meerwein, Switzerland, 2021	University Hospital, Zürich	2018 + 2019	2020	Symptom to biopsy, Symptom to treatment, Referral to treatment	49	66	1.6	Sinonasal Nasopharynx	Time to treatment, Clinical TNM classification, UICC overall stage
Tevetoglu, Turkey, 2021	Cerraphasa Medical Faculty, Istanbul	March to September, 2019	March to September, 2020***	Symptom to specialist, Specialist to treatment	116	60.3 ; 64.3	4.5 ; 6	Oral, Larynx	Time to treatment, T and N classification
Abelardo, Wales, 2022	Hywe Dda University Health Board	April to November, 2020	April to November, 2020***	Referral to specialist, Referral to MDT, Referral to treatment	143	72 ; 72.5	2	HNC	Time to treatment

Table 1. (Continued).

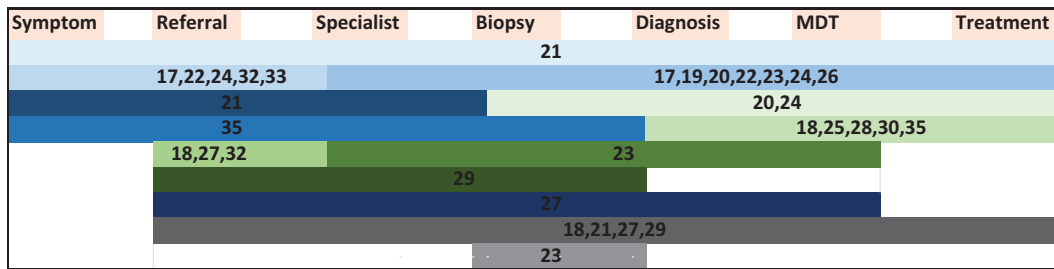| Authors, country of the study, publication year	Centre/database	Study period (non-COVID-19)	Study period (COVID-19)	Time to treatment intervals	No. of patients	Age*	M/F ratio(s)**	Site	Outcomes
Northern America									
Psycharis, Canada, 2023	Cancer and diagnosis committee's database of the McGill University Health Centre Cancer Registry	July 2019 to February 2020	March to October, 2020***	Specialist to MDT, Specialist to treatment, Biopsy to diagnosis	265	57 ; 61	2.2 ; 2.8	HNC	Time to treatment, TNM classification
Solis, USA, 2021	University of California, Davis, ENT Surgery Department	September 2019 to March 2020	March to September, 2020***	Symptom to specialist, Biopsy to surgery, Specialist to surgery, Scan to treatment, Diagnosis to first visit	137	65.5	2.5	HNSCC	Time to treatment, TNM classification, Median tumor size
Yao, USA, 2021	Tertiary Academic Medical Hospital in New York City	September 2019 to January 2020	March to July, 2020***	Suspicion to diagnosis, Suspicion to stageing, Diagnosis to treatment	94	64	1.2	HNC	Time to treatment
Kiong, USA, 2022	University of Texas M.D. Anderson Cancer Center	May to June, 2019	May to June, 2019	Symptom to specialist, Diagnosis to first visit, First visit to MDT	231	65	3.2	HNC	Time to treatment, TNM classification, Median tumor size, UICC overall stage
Tasoulas, USA, 2023	National cancer database (NCDB)	2019	2020	Diagnosis to treatment	10880 (in 2020)	64 (in 2020)	1.9 (in 2020)	HNC	Time to treatment
Stevens, USA, 2022	Vanderbilt University Medical Center	March to July, 2019	March to July, 2020***	Referral to specialist, Symptom to specialist	268	62.9 ; 64.5	3.1 ; 2.7	HNSCC	Time to treatment, Clinical TNM classification, Pathological TNM classification, Upstaging (c < p)
Asia									
Yang, China, 2020	Fudan University Shanghai Cancer Center	December 2019 to January 2020	January to February, 2020***	Pathological consultation report, Report from biopsies, Imaging examination, Radiotherapy immobilization and simulation, Validation of position and plan, Initiation of treatment	874	50.5	2.7 ; 3	Nasopharynx	Time to treatment, UICC overall stage

This table shows the baseline characteristics of the studies included.

N.A.: data not available; HNC: all head and neck cancers; HNSCC: head and neck squamous cell carcinomas; No: number; M/F: male/female; MDT: multidisciplinary team conference; TNM: Tumor, Node and Metastasis; UICC: Union for International Cancer Control; COVID-19: coronavirus disease 2019.

*Data on age are separated with a ';' when more than one average age is presented. The first value indicated corresponds to the non-COVID-19 group, and the second value to the COVID-19 group.

**M/F ratios are separated with a ';' when more than one M/F ratio is presented. The first value indicated corresponds to the non-COVID-19 group, and the second value to the COVID-19 group.

***COVID-19 period is within a lockdown period from the respective country.

Symptom	Referral	Specialist	Biopsy	Diagnosis	MDT	Treatment
				21		
	17,22,24,32,33			17,19,20,22,23,24,26		
21				20,24		
35					18,25,28,30,35	
	18,27,32			23		
		29				
			27			
				18,21,27,29		
			23			

Figure 2. Intervals investigated in included studies from the onset of symptoms to initiation of treatment. Each study is referenced with their corresponding reference number. The length of each bar represents a specific interval, and each bar corresponds to only one interval.

Changes in treatment regimens

Six studies reported on treatment regimens, and none found chances in treatment regimens used in the COVID-19 groups [19, 20, 23, 25, 26, 32].

Stage, TNM classification, and tumor size

Fifteen studies [17–26, 31–35] reported on oncologic outcomes ($n = 13,625$), and none found a decrease in oncologic burden during the COVID-19 period. Eight studies found no significant difference in oncologic outcomes ($n = 11,890$) [17, 18, 20, 21, 23, 25, 31, 34], and seven studies observed an increase in at least one of the oncologic parameters ($n = 1735$) [19, 22, 24, 26, 32–35].

Ten studies reported on UICC stage [17–26, 31, 33, 34], and nine found no significant differences [17, 18, 20, 21, 25, 26, 31–34]. Lucidi et al. found that average UICC stage was higher in the COVID-19 group compared to the non-COVID-19 group ($n = 265$). They did not further assess T-, N-, and M-stage [19].

T-classification was assessed in 11 studies [17–26, 32–35], and seven found no significant relation [17, 21, 23, 25, 32, 34, 35]. Four studies found an increased prevalence of T3/T4 tumors in the COVID-19 group [22, 24, 26, 33]. Tevetoğlu et al. observed an increase from 28 to 53% in the COVID-19 period ($p = 0.02$, $n = 116$) [22]. Similar increases were found by Metzger et al. (36–52%, $p = 0.046$, $n = 624$) [26], Solis et al. (40.3–61.7%, $p = 0.02$, $n = 137$) [24], and Kiong et al. (39.4–52%, $p = 0.03$, $n = 231$) [33]. Two of the studies further investigated primary tumor size; Solis et al. found an increased median tumor size from 3.0 cm in the non-COVID-19 group compared to 4.5 cm in the COVID-19 group [24]. Similarly, Kiong et al. found an increased mean tumor size from 2.5 cm in the non-COVID-19 group to 2.9 cm in the COVID-19 group [33]. N-classification was assessed in the same 11 studies as T-classification [17, 21–26, 32–35], and 10 found no significant relation [17, 21–26, 33–35]. Stevens et al. identified an increased risk for patients presenting with nodal metastases in the COVID-19 group (adjusted odds ratio 1.8, $p = 0.03$) ($n = 268$) [32]. The presence of patients with metastatic disease at time of diagnosis was assessed in eight studies [17, 21, 23–25, 32, 33, 35], and seven found no relation [17, 21, 23–25, 32, 33]. Kourtidis et al. observed an increased frequency of metastatic disease (0% vs 10%, $p = 0.022$) in the COVID-19 group compared to the non-COVID-19 group ($n = 94$) [35]. Among the six studies that found increases in T, N, or M classification [22, 24, 26, 32, 33, 35], two further investigated the impact on UICC stage, and both found no significant effect [26, 33]. In total, increases in at least one oncologic parameter were observed in Germany [26, 35], Italy [19], Turkey [22], and the United States [24, 32, 33]. A full overview is presented in Table 3.

Discussion

This systematic review investigating the impact of the COVID-19 pandemic on time to treatment intervals, treatment regimens, and tumor stage or size for HNC patients found modest variations in time to treatment, no effect on treatment regimens used, and a tendency toward presentation at a higher T-classification [22, 24, 26, 33]. To our knowledge, this is the first systematic review assessing the impact of COVID-19 on time to treatment.

The effect of COVID-19 on the time to treatment in HNC was divergent. Six studies reported an increase in waiting time within at least one interval [17, 18, 22, 26, 30, 31], while seven studies reported a decrease [20, 21, 23, 25, 27, 28, 32]. Across the examined intervals, on specific trends were noted. No relationship was observed between increased time to treatment and an increase in tumor stage, TNM classification, or size.

Most of the included patients found a decrease in time to treatment, which accounts for 20,779 out of 24,898 (83.5%), primarily due to the inclusion of the two largest studies [20, 28]. Overall, the pandemic resulted in marginal changes in time to treatment; among the studies that found increased time to treatment, the median increase was only 11 days across all intervals, suggesting that otorhinolaryngology and head & neck departments prioritized HNC care during the pandemic.

The heterogeneity of the results may be due in part to the differing impacts of the COVID-19 pandemic on various countries as well as disparities in healthcare organization and accessibility across nations [36, 37]. Furthermore, studies from Germany [25, 26] and the United States [28, 30, 32] showed opposing results, suggesting not only intercountry but also interregional differences.

Different factors could be associated with the increases in time to treatment observed [38]. First, the risk of viral exposure associated with visiting a medical facility may affect the time from onset of symptoms to seeking medical attention [39], and fear of overloading an already overwhelmed medical sector might contribute [38]. In this study, we found a tendency to

Table 2. Time to treatment and changes in treatment modalities in the COVID-19 group compared the non-COVID-19 group.

Study	Site	Interval	Relation	Quantity (non-COVID-19 vs COVID-19)	P-value	Change in treatment modality
Eastern European studies						
Gršić et al.	Oral	Symptom to specialist	PR	37.5 days vs 60 days (difference: +22.5 days)	0.019*	Not reported
	Oral	Specialist to treatment	PR	26 days vs 37 days (difference: +11 days)	0.006*	
	Larynx	Specialist to treatment	PR	21.5 vs 31.5 days (difference: +10 days)	0.001*	
	Larynx	Symptom to specialist	NR	60 days vs 90 days (difference: +30 days)	0.122	
Tevetoğlu et al.	Oral + Larynx	Symptom to specialist	PR	16.6 days vs 19.01 days (difference: +2.41 days)	0.049*	Not reported
		Specialist to treatment	NR	2.5 days vs 2.9 days (difference: +0.4 days)	0.06	
Western European studies						
Zubair et al.	HNC	Referral to specialist	NR	7.1 days vs 11.9 days (difference: +4.8 days)	0.068	Not reported
		Referral to treatment	PR	49.23 vs 72.5 days (difference: +23.27 days)	0.027*	
		Diagnosis to treatment	NR	24.7 days vs 29.2 days (difference: +4.5 days)	0.58	
Heckel et al.	HNC	Diagnosis to treatment	IR	23 days vs 19.5 (difference: −3.5 days)	0.013*	No change in treatment modality
Metzger et al.	Oral	Specialist to treatment	PR	35 days vs 45 days (difference: +10 days)	0.04*	No change in treatment modality
Kourtidis et al.	HNSCC	Symptom to diagnosis	NR	9.5 days vs 15 days (difference: +5.5 days)	0.054	Not reported
		Diagnosis to treatment	NR	3 days vs 3.2 days (difference: +0.2 days)	0.264	
Heimes et al.	Oral	Time to intervention	NR	22.99 days vs 26.66 days (difference: +3.67 days)	p > 0.05	Not reported
Schoonbeek et al.	HNC	Specialist to treatment	IR	31 days vs 26 days (difference: −5 days)	p < 0.001*	No change in treatment modality
		Biopsy to treatment	IR	37 days vs 30 days (difference: −7 days)	p < 0.001*	
Drake et al.	HNC	Referral to diagnosis	NR	No overall data		
		Referral to treatment	NR	No overall data		
Meerwein et al.	Sinonasal + nasopharynx	Symptom to biopsy	NR	123 vs 129 days (difference: +6 days)	0.17	Not reported
		Symptom to treatment	NR	137 days vs 139 days (difference: +2 days)	0.60	
		Referral to treatment	IR	18 days vs 11 days (difference: −7 days)	0.02*	
Abelardo et al.	HNC	Referral to specialist	IR	9.5 days vs 8 days (difference: −1.5 days)	<0.01*	Not reported
		Referral to MDT	NR	41.5 days vs 35.5 days (difference: −6 days)	0.40	
		Referral to treatment	NR	78 days vs 68 days (difference: −10 days)	0.16	
Southern European studies						
Lucidi et al.	HNC	Specialist to treatment	NR	47.6 days vs 44 days (difference: −3.6 days)	p > 0.05	No change in treatment modality
Northern American studies						
Psycharis et al.	HNC	Specialist to MDT	IR	38 days vs 25.1 days (difference: −12.9 days)	0.0001*	No change in treatment modality
		Specialist to treatment	IR	76.6 days vs 48.7 days (difference: −27.9 days)	0.001*	
		Biopsy to diagnosis	NR	14.1 days vs 9.9 days (difference: −4.2 days)	0.142	
Solis et al.	HNSCC	Symptom to specialist	NR	133 days vs 112 days (difference: −21 days)	0.483	Not reported
		Biopsy to treatment	NR	53 days vs 52 days (difference: −1 day)	0.737	
		Specialist to treatment	NR	29 days vs 27 days (difference: −2 days)	0.310	
		Scan to treatment	NR	42 days vs 40 days (difference: −2 days)	0.126	
		Diagnosis (elsewhere) to first visit	NR	25 days vs 27 days (difference: 2 days)	0.938	
Yao et al.	HNC	Suspicion to diagnosis	PR	COVID-19 group less likely to be diagnosed (HR = 0.54)	0.02*	
		Suspicion to staging	NR	COVID-19 group more likely to be diagnosed (HR = 1.01)	>0.9	
		Diagnosis to treatment	NR	COVID-19 group more likely to be diagnosed (HR = 1.55)	0.12	

Table 2. (Continued).

Study	Site	Interval	Relation	Quantity (non-COVID-19 vs COVID-19)	P-value	Change in treatment modality
Kiong et al.	HNC	Symptom to specialist	NR	12 weeks vs 12 weeks (difference: 0 weeks)	0.391	Not reported
		Diagnosis (elsewhere) to first visit	NR	20 days vs 25 days (difference: +5 days)	0.133	
		First visit to MDT	NR	2 days vs 2 days (difference: 0 days)	0.507	
Tasoulas et al.	HNC	Diagnosis to treatment	IR	46 days vs 43 days (difference: −3 days)	(95% CI: 46–47) vs (95% CI: 42–43)*	
Stevens et al.	HNSCC	Referral to specialist	IR	11 days vs 8 days (difference: −3 days)	0.003*	No change in treatment modality
		Symptom to specialist	NR	6.82 weeks vs 6.54 weeks (difference: −0.28 weeks)	0.872	
Asian studies						
Yang et al.	Nasopharynx	Pathological consultation report	NR	3 days vs 2 days (difference: −1 day)	0.111	Not reported
		Report from biopsies	PR	5 days vs 15 days (difference: +10 days)	0.012*	
		Imaging examination	PR	1 day vs 8 days (difference: +7 days)	>0.001*	
		Radiotherapy immobilization. and simulation	PR	3.5 days vs 16.5 days (difference: +13 days)	>0.001*	
		Validation of position and plan	PR	20 days vs 61 days (difference: +41 days)	>0.001*	
		Initiation of treatment	PR	28 days vs 36 days (difference: +8 days)	0.005*	

This table shows the difference in time to treatment when comparing the non-COVID-19 group with the COVID-19 group across each examined interval.

HNC: all head and neck cancers; HNSCC: head and neck squamous cell carcinomas; NR: no relation (neither significant increase nor decrease in time to treatment during the COVID-19 period); HR: hazard ratio; PR: positive relation (significant increase in time to treatment during COVID-19 period); IR: inverse relation (significant decrease in time to treatment during the COVID-19 period); MDT: multidisciplinary team conference; COVID-19: coronavirus disease 2019.

*Significant value.

increased T-classification [22, 24, 26, 33], which could indicate a delay in the pre-hospital phase, with patients presenting with symptoms later than optimal. Second, reallocation of resources might limit access to specialist consultations and diagnostic biopsies, thus increasing the time to diagnosis [38]. Third, anticipation of or actual shortage of critical care might lead to a reduction in surgical capacity, increasing the time to initiation of surgery [38]. While there have been indications of radiotherapy compensating for decreased surgical activity within other cancers [40], we did not observe any changes in the treatment modalities used during the COVID-19 pandemic [19, 20, 23, 25, 26, 32].

On the other hand, the COVID-19 pandemic could also be associated with the decreases in time to treatment observed [8–10, 41, 42]. Some hospitals experienced reductions in routine and elective procedures [8–10], and care could be diverted to treatments, which could not be postponed such as cancer treatment. Additionally, patients' initial reluctance to seek medical attention might result in subsequent presentation at a more advanced T-stage, as indicated in the studies [22, 24, 26, 33], thus requiring more urgent and rapid treatment. Since only five studies assessed pre-hospital time to treatment intervals [17, 22, 24, 32, 33], we were not able to draw further conclusions on the potential impact of pre-hospital delay. The two largest studies [20, 28] encompassing a total of 19,348 patients collectively (77.4% of all patients included) were both registry-based and showed a small reduction in time to treatment. However, neither of these included time intervals starting from the onset of symptoms.

Moreover, during the initial phases of the pandemic, incidence rates of numerous cancers, including HNC, declined in several countries – possibly due to the above-mentioned factors influencing patients' healthcare-seeking behavior, reducing cancer patient volume [41–43].

While results on time to treatment were inconsistent, a tendency was observed with respect to oncologic outcomes. Seven of 15 studies observed an increase in at least one oncologic parameter during the COVID-19 pandemic [19, 22, 24, 26, 32, 33, 35]. However, only one study [19] observed an increase in overall stage, while nine studies did not find an effect on overall stage [17, 18, 20, 21, 25, 26, 31, 33, 34]. Four of 11 studies observed increased T-classification [22, 24, 26, 33]. Two studies assessed primary tumor size, and both found an increase during the COVID-19 pandemic [24, 33]. Only two studies observed an increase in an oncologic parameter and a simultaneous increase in time to treatment [22, 26], indicating that other factors may have played a role, e.g. delay in the pre-hospital phase.

Considering the close relationship between T-classification and disease prognosis [44], these results suggest worsened prognosis among patients diagnosed with HNC during the pandemic in some regions. However, we were not able to include survival outcomes in this study due to the recency of the pandemic. Nonetheless, a higher T-classification has other implications such as more extensive surgery, wider radiation fields, and increasing patient morbidity [45, 46].

Table 3. Oncologic outcomes in the COVID-19 group compared to the non-COVID-19 group.

Study	Site	Oncologic outcome	Relation	Quantity (non-COVID-19 vs COVID-19)	*P*-value
Eastern European studies					
Gršić et al.	Oral + Larynx	Clinical TNM classification	NR		
		UICC numerical stage	NR		
Tevetoğlu et al.	Oral + Larynx	T classification	PR	Proportion of T3/T4 tumors: 28% vs 53%	0.049*
		N classification	NR		
Western European studies					
Zubair et al.	HNC	UICC numerical stage	NR		
Heckel et al.	HNC	Clinical TNM classification	NR		
		Pathologic TNM classification	NR		
		UICC numerical stage	NR		
Metzger et al.	Oral	Pathologic T-classification	PR	Proportion of T3/T4 tumors: 36% vs 52%	0.046*
		Pathologic N-classification	NR		
		UICC numerical stage	NR		
Kourtidis et al.	HNSCC	T classification	NR		
		N classification	NR		
		M classification	PR	0 (0%) vs 5 (10%)	0.022*
Heimes et al.	Oral	T and N classification	NR		
		UICC numerical stage	NR		
Schoonbeek et al.	HNC	UICC numerical stage	NR		
Drake et al.	HNC	No data with statistical testing			
Meerwein et al.	Sinonasal + nasopharynx	Clinical TNM classification	NR		
		UICC numerical stage	NR		
Abelardo et al.	HNC	No data			
Southern European studies					
Lucidi et al.	HNC	UICC numerical stage	PR	Average UICC stage higher in COVID-19 period	0.023*
Northern American studies					
Psycharis et al.	HNC	TNM classification	NR		
Solis et al.	HNSCC	T classification	PR	Proportion of T3/T4 tumors: 40.3% vs 61.7%	0.0244*
		N classification	NR		
		M classification	NR		
		Median tumor size	PR	3.0 cm vs 4.5 cm	0.0002*
Yao et al.	HNC	No data			
Kiong et al.	HNC	TNM classification	NR		
	HNC	UICC numerical stage	NR		
	HNC	Mean size of tumor	PR	2.5 cm vs 2.9 cm	0.042*
	HNSCC only	T classification	PR	Proportion of T3/T4 tumors: vs 39.4% vs 52.0%	0.025*
	HNSCC only	N classification	NR		
	HNSCC only	UICC numerical stage	NR		
	HNSCC only	Mean tumor size	NR		
Tasoulas et al.	HNC	No data with statistical testing			
Stevens et al.	HNSCC	Clinical T classification	NR		
		Clinical N classification	PR		0.028*
		Clinical M classification	NR	Patients in COVID-period more likely to present with nodal metastases compared to non-COVID-19 (adjusted OR: 1.846)	
		Pathologic TNM classification	NR		
		Upstaging (C < P)	NR		
Asian studies					
Yang et al.	Nasopharynx	UICC numerical stage	NR		

This table shows the differences in oncologic outcomes (tumor stage, TNM classification, size, etc.), when comparing the non-COVID-19 group with the COVID-19 group. Quantity and *p*-values are indicated when there is a significant difference.

HNC: all head and neck cancers; HNSCC: head and neck squamous cell carcinomas; NR: no relation (neither significant increase nor decrease in oncologic outcome during the COVID-19 period); PR: positive relation (significant increase in oncologic outcome during the COVID-19 period); MDT: multidisciplinary team conference; TNM: Tumor Node and Metastasis; UICC: Union for International Cancer Control; COVID-19: coronavirus disease 2019.

*Significant value.

This study is limited by the studies selected for analysis containing considerable variation in definitions of time to treatment intervals. This highlights the importance of more standardized definitions of time to treatment to increase comparability and generalizability. Also, the definition of COVID-19 periods as well as the subtypes of HNCs analyzed varied. Due to the recency of the pandemic, studies lack important clinical endpoints like 5-year survival rates, and comparison of COVID-19 and non-COVID-19 periods that are not analogous might be subject to seasonal variance of patient flow. Individual studies suffering from limitations including the inherent retrospective design with studies assessing time intervals beginning from the onset of symptoms might be subjected to recall bias. Also, the study by Tasoulas et al. [28] used the National Cancer Database, which might have incorporated patients from the four other American studies [24, 30, 32, 33]. Finally, variations in healthcare structures, the prevalence and severity of COVID-19 as well as discrepancies in restrictions imposed by distinct government authorities may influence medical systems differently. This complexity hinders broad conclusions applicable across diverse geographical areas.

In conclusion, this systematic review found that the impact of the COIVD-19 pandemic on time to treatment was heterogenous and subject to considerable intercountry and interregional variations. No change in treatment modalities used was observed. Consensus on definitions on time to treatment is required to enhance the overall generalizability. No significant impact on overall stage was observed, but a tendency toward a higher T-classification was observed in both Europe and the United States. In conclusion, otorhinolaryngology and head & neck departments seemed to have prioritized HNC care during the pandemic.

Disclosure statement

The authors report there are no competing interests to declare.

Ethics declaration

All articles included in this review have been ethically approved from the appropriate ethics committee.

Data availability statement

Data are available on the PubMed and Embase databases.

References

[1] World Health Organisation. Emergency overview, Coronavirus disease (COVID-19) pandemic. Available from: https://www.who.int/europe/emergencies/situations/covid-19

[2] Brindle ME, Gawande A. Managing COVID-19 in surgical systems. Ann Surg. 2020;272(1):e1–2. https://doi.org/10.1097/SLA.0000000000003923

[3] Emanuel EJ, Persad G, Upshur R, Thome B, M.P.H., Michael P, et al. Fair allocation of scarce medical resources in the time of covid-19. N Engl J Med. 2020;382(21): 2049–55. https://doi.org/10.1056/NEJMsb2005114

[4] World Health Organisation. Pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report, 27 August 2020. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS_continuity-survey-2020.1

[5] Matenge S, Sturgiss E, Desborough J, Hall Dykgraaf S, Dut G, Kidd M. Ensuring the continuation of routine primary care during the COVID-19 pandemic: a review of the international literature. Fam Pract. 2022;39(4):747–61. https://doi.org/10.1093/fampra/cmab115

[6] Heymann DL, Shindo N. COVID-19: what is next for public health? Lancet. 2020;395(10224):542–5. https://doi.org/10.1016/S0140-6736(20)30374-3

[7] Brindle ME, Doherty G, Lillemoe K, Gawande A. Approaching surgical triage during the COVID-19 pandemic. Ann Surg. 2020;272(2):e40–2. https://doi.org/10.1097/SLA.0000000000003992

[8] Mehanna H, Hardman JC, Shenson JA, Abou-Foul AK, Topf MC, AlFalasi M, et al. Recommendations for head and neck surgical oncology practice in a setting of acute severe resource constraint during the COVID-19 pandemic: an international consensus. Lancet Oncol. 2020;21(7):e350–9. https://doi.org/10.1016/S1470-2045(20)30334-X

[9] American College of Surgeons. COVID 19: Elective Case Triage Guidelines for Surgical Care, 12/8 2020. Available from: https://www.facs.org/media/33km00ma/guidance_for_triage_of_nonemergent_surgical_procedures_general_surgery.pdf

[10] OECD/European Union (2020). Health at a Glance: Europe 2020: State of Health in the EU Cycle, OECD Publishing, Paris. https://doi.org/10.1787/82129230-en.

[11] Abdelrahman H, Atteya S, Ihab M, Nyan M, Maharani AD, Rahardjo A, et al. Dental practice closure during the first wave of COVID-19 and associated professional, practice and structural determinants: a multi-country survey. BMC Oral Health. 2021;21(1):243. https://doi.org/10.1186/s12903-021-01601-4

[12] Thomson DJ, Palma D, Guckenberger M, Balermpas P, Beitler JJ, Blanchard P, et al. Practice recommendations for risk-adapted head and neck cancer radiation therapy during the COVID-19 pandemic: an ASTRO-ESTRO consensus statement. Int J Radiat Oncol Biol Phys. 2020;107(4):618–27. https://doi.org/10.1016/j.ijrobp.2020.04.016

[13] Graboyes EM, Kompelli AR, Neskey DM, Brennan E, Nguyen S, Sterba KR, et al. Association of treatment delays with survival for patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg. 2019;145(2):166. https://doi.org/10.1001/jamaoto.2018.2716

[14] Schutte HW, Heutink F, Wellenstein DJ, van den Broek GB, van den Hoogen FJA, Marres HAM, et al. Impact of time to diagnosis and treatment in head and neck cancer: a systematic review. Otolaryngol Head Neck Surg. 2020;162(4):446–57. https://doi.org/10.1177/0194599820906387

[15] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71

[16] Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open. 2016;6(12):e011458. https://doi.org/10.1136/bmjopen-2016-011458

[17] Gršić K. The impact of COVID-19 on head and neck cancer treatment delay. Acta Clin Croat. 2022;61(Suppl. 4):19–25. https://doi.org/10.20471/acc.2022.61.s4.2

[18] ZZubair A, Jamshaid S, Scholfield DW, Hariri AA, Ahmed J, Ghufoor K, et al. Impact of COVID-19 pandemic on head-neck cancer referral and treatment pathway in North East London. Ann R Coll Surg Engl. 2023;105(S2):S28–34. https://doi.org/10.1308/rcsann.2021.0360

[19] Lucidi D, Valerini S, Federici G, Miglio M, Cantaffa C, Alicandri-Ciufelli M. Head and neck cancer during covid-19 pandemic: was there a diagnostic delay? Indian J Otolaryngol Head Neck Surg. 2022;74(S2):3245–51. https://doi.org/10.1007/s12070-021-03050-5

[20] Schoonbeek RC, de Jel DVC, van Dijk BAC, Willems SM, Bloemena E, Hoebers FJP, et al. Fewer head and neck cancer diagnoses and faster treatment initiation during COVID-19 in 2020: a nationwide population-based analysis. Radiother Oncol. 2022;167:42–8. https://doi.org/10.1016/j.radonc.2021.12.005

[21] Meerwein CM, Stadler TM, Balermpas P, Soyka MB, Holzmann D. Diagnostic pathway and stage migration of sinonasal malignancies in the era of the COVID-19 pandemic. Laryngoscope Investig Otolaryngol. 2021;6(5):904–10. https://doi.org/10.1002/lio2.640

[22] Tevetoğlu F, Kara S, Aliyeva C, Yıldırım R, Yener HM. Delayed presentation of head and neck cancer patients during COVID-19 pandemic. Eur Arch Oto Rhino Laryngol. 2021;278(12):5081–5. https://doi.org/10.1007/s00405-021-06728-2

[23] Psycharis SS, Salameh S, Turkdogan S, et al. Prioritization of head and neck cancer patient care during the COVID-19 pandemic: a retrospective cohort study. J Otolaryngol Head Neck Surg. 2023;52(1):15. https://doi.org/10.1186/s40463-023-00625-w

[24] Solis RN, Mehrzad M, Faiq S, Frusciante RP, Sekhon HK, Abouyared M, et al. The impact of COVID-19 on head and neck cancer treatment: before and during the pandemic. OTO Open. 2021;5(4):2473974X211068075. https://doi.org/10.1177/2473974X211068075

[25] Heckel S, Bohr C, Meier J, Maurer J, Kuenzel J, Mueller K, et al. Head and neck oncology management in the time of COVID-19: results of a head and neck cancer center. J Cancer Res Clin Oncol. 2023;149(13):12081–7. https://doi.org/10.1007/s00432-023-05122-1

[26] Metzger K, Mrosek J, Zittel S, Pilz M, Held T, Adeberg S, et al. Treatment delay and tumor size in patients with oral cancer during the first year of the COVID-19 pandemic. Head Neck. 2021;43(11):3493–7. https://doi.org/10.1002/hed.26858

[27] AAbelardo E, Gravelle R, Scannell M, Shastri P, Vandekar M, Davies G, et al. Impact of coronavirus disease 2019 on head and neck urgent suspected cancer referral pathways in rural Wales. J Laryngol Otol. 2022;136(6):540–6. https://doi.org/10.1017/S002221512200069X

[28] Tasoulas J, Schrank TP, Smith BD, Agala CB, Kim S, Sheth S, et al. Time to treatment patterns of head and neck cancer patients before and during the Covid-19 pandemic. Oral Oncol. 2023;146:106535. https://doi.org/10.1016/j.oraloncology.2023.106535

[29] Drake I, Rogers A, Stewart M, Montgomery J. The impact of coronavirus disease 2019 on the head and neck cancer pathway in the West of Scotland. J Laryngol Otol. 2022;136(6):535–9. https://doi.org/10.1017/S0022215122000603

[30] Yao P, Cooley V, Kuhel W, Tassler A, Banuchi V, Long S, et al. Times to diagnosis, staging, and treatment of head and neck cancer before and during COVID-19. OTO Open. 2021;5(4):2473974X211059429 https://doi.org/10.1177/2473974X211059429

[31] Yang Y, Shen C, Hu C. Effect of COVID-19 epidemic on delay of diagnosis and treatment path for patients with nasopharyngeal carcinoma. Cancer Manag Res. 2020;12:3859–64. https://doi.org/10.2147/CMAR.S254093

[32] Stevens MN, Patro A, Rahman B, Gao Y, Liu D, Cmelak A, et al. Impact of COVID-19 on presentation, staging, and treatment of head and neck mucosal squamous cell carcinoma. Am J Otolaryngol. 2022;43(1):103263. https://doi.org/10.1016/j.amjoto.2021.103263

[33] Kiong KL, Diaz EM, Gross ND, Diaz EM, Hanna EY. The impact of COVID-19 on head and neck cancer diagnosis and disease extent. Head Neck. 2021;43(6):1890–7. https://doi.org/10.1002/hed.26665

[34] Heimes D, Müller LK, Schellin A, Naujokat H, Graetz C, Schwendicke F, et al. Consequences of the COVID-19 pandemic and governmental containment policies on the detection and therapy of oral malignant lesions – a retrospective, multicenter cohort study from Germany. Cancers (Basel). 2021;13(12):2892. https://doi.org/10.3390/cancers13122892

[35] Kourtidis S, Münst J, Hofmann VM. Effects of the COVID-19 pandemic on head and neck cancer stage and treatment duration. Cureus. 2022;14(7):e26744. https://doi.org/10.7759/cureus.26744

[36] World Health Organisation. Number of physicians (per 10 000 population) including generalists, specialist medical practitioners and medical doctors not further defined. Available from: https://data.who.int/indicators/i/CCCEBB2/217795A

[37] World Health Organisation. Number of COVID-19 cases reported to WHO. Available from: https://covid19.who.int/

[38] Ali JK, Riches JC. The impact of the COVID-19 pandemic on oncology care and clinical trials. Cancers (Basel). 2021;13(23):5924. https://doi.org/10.3390/cancers13235924

[39] Mo Y, Eyre DW, Lumley SF, Walker TM, Shaw RH, O'Donnell D, et al. Transmission of community- and hospital-acquired SARS-CoV-2 in hospital settings in the UK: a cohort study. PLoS Med. 2021;18(10):e1003816. https://doi.org/10.1371/journal.pmed.1003816

[40] SSpencer K, Jones CM, Girdler R, Roe C, Sharpe M, Lawton S, et al. The impact of the COVID-19 pandemic on radiotherapy services in England, UK: a population-based study. Lancet Oncol. 2021;22(3):309–20. https://doi.org/10.1016/S1470-2045(20)30743-9

[41] Dinmohamed AG, Visser O, Verhoeven RHA, Louwmana MWJ, van Nederveenj FH, Willems SM, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. Lancet Oncol. 2020;21(6):750–1. https://doi.org/10.1016/S1470-2045(20)30265-5

[42] Howlader N, Bhattacharya M, Scoppa S, Miller D, Noone A-M, Negoita S, et al. Cancer and COVID19: US cancer incidence rates during the first year of the pandemic. J Natl Cancer Inst. 2024;116(2):208–15. https://doi.org/10.1093/jnci/djad205

[43] Decker KM, Feely A, Bucher O, Czaykowski P, Hebbard P, Kim JO, et al. New cancer diagnoses before and during the COVID-19 pandemic. JAMA Netw Open. 2023;6(9):e2332363. https://doi.org/10.1001/jamanetworkopen.2023.32363

[44] Du E, Mazul AL, Farquhar D, Anantharaman D, Abedi-Ardekani B, Weissler MC, et al. Long-term survival in head and neck cancer: impact of site, stage, smoking, and human papillomavirus status. Laryngoscope. 2019;129(11):2506–13. https://doi.org/10.1002/lary.27807

[45] Pierik AS, Leemans CR, Brakenhoff RH. Resection margins in head and neck cancer surgery: an update of residual disease and field cancerization. Cancers (Basel). 2021;13(11):2635. https://doi.org/10.3390/cancers13112635

[46] Burnet NG. Defining the tumour and target volumes for radiotherapy. Cancer Imaging. 2004;4(2):153–161. https://doi.org/10.1102/1470-7330.2004.0054