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# COVID-19 and head and neck cancer management. Experience of an oncological hub comprehensive cancer centre and literature review

## *COVID-19 e gestione dei tumori testa e collo. Esperienza di un hub oncologico, Centro di riferimento terziario, e review della letteratura*

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SUMMARY

COVID-19 severely impacted the healthcare system in most industrialised countries and contributed to the postponement of many elective healthcare services. As most national and international surgical associations promptly drew up guidelines to preserve time-dependent surgery, the Lombardy Region, the epicentre of the outbreak of COVID-19 in Italy, also created differentiated pathways for COVID-19 and non-COVID-19-related health services based on a hub/spoke design. At the Department of Otorhinolaryngology and Head and Neck Surgery of the European Institute of Oncology (IEO), we needed to rearrange our assistance pathways, as a designated oncological hub, to guarantee gold-standard treatments to cancer patients. Specific protocols were developed for the management of regional patients and extra-regional patients confined to self-isolation due to the lockdown and stay-at-home policy. Specific assistance trajectories were created for cancer patients coming from other hospitals needing life-saving procedures. Herein, we report the outcomes of patients undergoing head and neck treatments at the IEO Department of Otorhinolaryngology and Head and Neck Surgery, with the aim to evaluate the efficacy of all the measures adopted as an oncological hub during the COVID-19 pandemic and compare our data with that in the international peer-reviewed published medical literature regarding the consequences of COVID-19 on the management of head and neck cancer patients.

KEY WORDS: head and neck cancer, COVID-19, delay, oncological hub, treatment

RIASSUNTO

*Il COVID-19 ha avuto un grave impatto sul sistema sanitario di molti paesi industrializzati e ha contribuito al ritardo di esecuzione di numerosi trattamenti e procedure chirurgiche in elezione. La maggior parte delle associazioni chirurgiche nazionali e internazionali ha prontamente redatto delle linee guida per cercare di preservare i tempi di attesa relativi a chirurgie inderogabili. La Regione Lombardia, epicentro dell'epidemia di COVID-19 in Italia, ha creato percorsi differenziati per pazienti COVID-19 e non COVID-19 basati su un sistema di centri hub/spoke. Presso il Dipartimento di Otorinolaringoiatria e Chirurgia Cervico-Facciale dello IEO, divenuto hub oncologico, abbiamo dovuto riorganizzare i nostri percorsi di assistenza, per garantire le cure standard ai malati di cancro. Sono stati sviluppati protocolli specifici per la gestione dei pazienti regionali ed extraregionali, costretti all'autoisolamento a causa della politica di lockdown e "stay-at-home". Sono state create specifiche traiettorie di assistenza per i malati di cancro provenienti da altri ospedali e necessitanti di chirurgie salvavita. In questo lavoro, riportiamo i risultati relativi al trattamento dei pazienti oncologici, testa collo, presso la Divisione di Otorinolaringoiatria e Chirurgia Cervico-Facciale dell'Istituto Europeo di Oncologia, di Milano, con l'obiettivo di valutare l'efficacia di tutte le misure adottate come hub oncologico durante il COVID-19 e confrontare i nostri dati con quelli della letteratura internazionale.*

PAROLE CHIAVE: *tumori testa e collo, COVID-19, ritardo, hub oncologico, trattamento*

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## Introduction

Since February 2020, the COVID-19 pandemic declaration led most national authorities and governments to impose restrictive measures, primarily aimed at containing the spread of the virus, and thus preventing the national healthcare systems from reaching a "breaking point".

The "lockdown", a term referring explicitly to actions related to mass quarantines or "stay-at-home" orders, severely impacted the healthcare system in most industrialised countries and contributed to many elective healthcare services being postponed.

During the first COVID-19 wave, it was estimated that at least 21 million elective operations were cancelled globally, partly due to concerns over post-operative SARS-CoV-2 infection and partly due to capacity issues within hospitals [1,2]. Most national and international surgical associations promptly drew up guidelines to protect time-dependent surgery from the same consequence [3].

The Lombardy Region was the epicentre of the first outbreak of COVID-19 in Italy. The Lombardy Regional Authorities created differentiated pathways for COVID-19 and non-COVID-19-related health services to face the emergency, based on a hub/spoke design [4]. More specifically, new healthcare pathways were defined by temporarily abrogating private for-profit activities, thus extending the service availability to cancer patients needing nondeferrable life-saving treatments [4].

The European Institute of Oncology (IEO) has become a regional reference "hub" for the treatment of cancer patients, together with the National Cancer Institute of Milan. At the IEO Department of Otorhinolaryngology and Head and Neck Surgery, we needed to rearrange the assistance pathways to guarantee gold-standard treatments to patients debilitated by cancer-related dysphagia or by the disease itself. At the same time, it was mandatory to perform life-saving surgeries to avoid possible complications such as airway obstruction of the upper respiratory tract or haemorrhage, thus minimising the hospitalisation time.

In this paper, we report the outcomes of patients undergoing head and neck treatments at the IEO Department of Otorhinolaryngology and Head and Neck Surgery of Milan with the aim to evaluate the efficacy of all the measures adopted as an oncological hub during the COVID-19 lockdowns. We also provide a contemporary review of the most recent international peer-reviewed biomedical publications.

## Materials and methods

*Oncological hub reorganisation*

From the beginning of pandemic outbreak, access to the hospital was granted to patients only. Surgical masks were mandatory upon entry, and body temperature was measured via infrared thermometers.

Before hospitalisation, head and neck cancer patients underwent a telephone triage, investigating their general health status and possible contacts with COVID-19 patients. At the hospital, all patients underwent blood analysis and chest X-ray as per protocol. From April 1st 2020, a nasopharyngeal swab was also collected during preoperative assessment. The date of the surgery was scheduled within five days from the swab, during which time all patients were instructed to self-isolate.

The treatment of low-risk tumours, such as thyroid tumours, was temporarily ceased, and patients were offered active surveillance.

We worked to optimise the oncological network and the continuity of care for patients coming from other COVID-19 hospitals. Specific management pathways were developed to evaluate head and neck cancer patients coming from other centres, including rapid accesses to the IEO for new visits and surgical procedures scheduled on the basis of the patient's condition and urgency of treatment.

We made every effort to reduce surgical times and avoid postoperative stay in the Intensive Care Unit, by opting for minimally-invasive techniques rather than open approaches. Where possible, we chose to reconstruct surgical defects with local flaps rather than with free vascularised flaps.

The anaesthetic protocol was set to minimise aerosol generation and potential exposure to undetected COVID-19 infection in patients with false-negative swab tests [5]. All the staff involved was obliged to wear complete personal protection equipment (PPE), and only the anaesthetist and the nurse had access to the operating room during the anaesthetic procedure. As the operators were in contact with areas with a high possibility of viral infection, they had to wear full PPE throughout the surgical procedure. During the post-operative period, all patients were in single rooms with surgical masks, and healthcare professionals who visited them were equipped with full PPE. Meticulous attention was paid to patients with a tracheotomy. Healthcare professionals were asked to wear FFP2 masks associated with a surgical mask, water-repellent disposable gown or apron, gloves and protective goggles or visor. The surgeons provided the patient's family members with a daily update on the outcome of the intervention and clinical progress by telephone [5].

For the outpatient and follow-up visits, all patients were evaluated with a telephone or telemedicine visit during the Italian lockdown in March and April 2020. Asymptomatic patients were rescheduled with follow-up visits after at least 6 months. Patients from other Italian regions reporting suspicious symptoms were asked to refer to local hospitals

and healthcare providers, while patients in the Lombardy region were scheduled with emergency IEO outpatient visits.

The study was approved by the Institutional Ethical Committee and comply with the principles stated in the Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

*Data extraction*

We retrospectively reviewed the department databases and clinical records of all head and neck cancer patients examined or treated at the IEO Department of Otorhinolaryngology and Head and Neck Surgery, during our COVID-19 hub activity.

For outpatient visits, we retrospectively reviewed data from the 2020 oral cavity, pharyngeal and laryngeal databases. Two dedicated surgeons, F.C and R.D.B., reviewed all clinical records to retrospectively assess any reported delay in the first visit/follow-up due to COVID-19 infection or fear of accessing hospitals.

For all the head and neck cancer patients surgically treated in our institute, we performed data extraction from the multidisciplinary board (MDB) discussion database between April and June 2020 (Group A). This period represents the most critical time in terms of rearrangement of the healthcare system and management of cancer patients, under special institutional guidelines during the COVID-19 pandemic [6].

We collected data regarding age, tumour site, clinical staging defined as early (I-II), intermediate (III) and advanced (IV) and type of surgery. Surgical treatments included mini-invasive procedures such as transoral laser microsurgery (TLM), open partial horizontal laryngectomy (OPHL), transoral glossectomy or oral cavity resections, robotic surgery (TORS), or major surgical (sub/total excision of the organ with the possible need for reconstruction).

We retrospectively assessed the "care pathway interval" (CPI), defined as the time between the onset of symptoms and the first visit, and the "time-to-treatment interval" (TTI), defined as the interval between MDB and treatment. For statistical analysis, the 2020 retrospective cohort of patients (Group A) was compared with a homogenous control group (Group B) from the 2019 MDB database (April to June 2019).

*Contemporary literature review*

We conducted a literature review of the latest studies using the Pubmed (National Library of Medicine, USA) and Embase (Elsevier) bibliographic databases. For the search, we used the key-words ("COVID" AND "delay" AND "head and neck" AND "cancer"). We considered only articles written in English and with fully available abstracts. One author, F.B., reviewed all the abstracts and selected only the articles focusing on the impact of COVID-19 on the healthcare system. Only articles reporting the incidence of cancer, the time to visit (CPI), diagnosis, staging and treatment (TTI), compared to non-COVID controls, were selected for data extraction.

*Statistical analysis*

Patient characteristics were summarised either by count and percent or mean and standard deviation (SD) for all categorical variables and age at the first visit, respectively. Categorical variables were compared by Fisher's exact test; the Shapiro-Wilk test was used to check the normality assumption for the distribution of age; calendar years were then compared by the two-sample Wilcoxon test. TTI and CPI were estimated by the Kaplan-Meier method; calendar years were compared for the delay in surgery by the log-rank test. At the time of the analysis, there were no censored times. After checking the proportional hazard assumption, univariate Cox regression analysis was run using surgery as the event of interest, and the results were tabulated as hazard ratios (HR) alongside 95% confidence interval (CI). The 2019 calendar year entered the Cox model as a reference level. All tests were two-tailed and considered significant at the 5% level. All analyses were done using SAS 9.4 (Cary, N.C., USA).

## Results

Between March and April 2020, due to COVID-19, 60% of all IEO scheduled outpatient visits (both first and follow-up visits) were postponed. From the outpatient visit database, we noted a COVID-19 related reduction of about 11% in March, and 20% in April. All follow-up visits were rescheduled as telephone contacts or remote visits. Nonetheless, in 2020, about 31% of patients treated in our Department for head and neck cancer had experienced a COVID-19-related delay in accessing the hospital for the first visit due to the lockdown and fear of COVID-19 contagion.

For the head and neck cancer patients treated in our institution, Group A (April-June 2020) comprised 81 patients. Among these, radiotherapy or chemoradiotherapy was indicated in 42 cases (52%), and best supportive care was indicated for only one (1%) case. Two (2%) patients experienced the impact of COVID-19 infection: one suffered from pneumonia during preoperative assessment, without any influence or delay on the patient's treatment; the other patient did not complete radiation therapy, and underwent surgery.

Therefore, surgery was indicated in 38 cases (47%). Four

patients could be operated in their primary hospitals, and the other two patients refused surgery. Thus, they were excluded from the statistical analysis. As shown in Figure 1A, 10 cases (31%) were clinically staged as early (I-II), 4 (13%) intermediate (III) and 18 (56%) advanced stage (IV). All early-stage patients (100%) were treated with mini-invasive surgery. By contrast, among the 4 intermediate-stage patients, 2 were referred for mini-invasive surgery (TORS/TLM), and the other 2 for major surgery. Among the 18 advanced-stage patients, mini-invasive surgery was performed in 6 cases (33%), including 2 TORS, 1 TLM, 1 OPHL and two neck dissections for an unknown primary tumour. Twelve (67%) advanced-stage patients received major surgery.

Group B (April to June 2019) comprised 87 patients. Radiotherapy or chemoradiotherapy and best supportive care were indicated in 37 cases (43%) and 7 cases (8%), respectively. Surgery was indicated in 43 cases (49%). Among these, we excluded 5 patients who were not treated in our institute (n = 4) or refused surgery (n = 1). Thus, we considered 38 surgical patients for the statistical analysis. As shown in Figure 1B, 9 cases (24%) were early stage (I-II), all treated with mini-invasive surgery (100%). Among 13 intermediate cases (stage III; 34%), 10 patients (77%) underwent mini-invasive surgery, while 3 (23%) benefited from major surgery (all cases were oral cavity cancers). Among 16 advanced cases (IV) (42%), 14 (88%) underwent major surgery, while 2 (12%) mini-invasive treatments (1 TORS, 1 neck dissection for nodal recurrence of nasopharynx cancer).

At statistical analysis (Tab. I), no significant differences were observed in patient characteristics between groups A and B in terms of tumour site, type of surgery, clinical staging, age and CPI. However, univariate analysis showed that median TTI in Group A (2020) was significantly lower than for to group B (2019), 13.0 days and 22.5 days, respectively (p = 0.01), (Tab. II and Fig. 2) which corresponds to a significantly higher hazard ratio (HR = 1.8, 95% CI: 1.2,3.0, p = 0.02) (Tab. III).

*Literature review*

A total of 82 records were retrieved based on the search strategy. After manual screening for relevant titles and abstracts, a total of 6 studies were included in the literature review (Fig. 3).

The incidence of head and neck cancer was evaluated in three studies showing that, during the first wave, there were significantly fewer (25%) new cases compared to the number of new cases in 2019 (p = 0.01) [7-9]. Regarding the trend of the time to visit defined as CPI, we found that there was a relevant increase in the study conducted by Tevetoğlu et al. (p = 0.02) [10] in contrast with the study by Kiong et al. (p = 0.391) [8].

However, an extension of the time to diagnosis was not significant in two studies [8,9], while Yao et al. reported a longer time to diagnosis (p = 0.02) but not to staging [11]. Four studies showed a significant increase in tumour size (p = 0.042) [8] and in T stage [9,10,12] at presentation in the COVID group. A worsening of N stage was not found [8,12].

Finally, concerning TTI, no alterations in initial therapies modalities were registered [7,9-11], while only one study reported a significant extension of TTI (45 *vs* 35 days, p = 0.004) between the same period in 2019 and 2020 [12]. Table IV summarises this data.

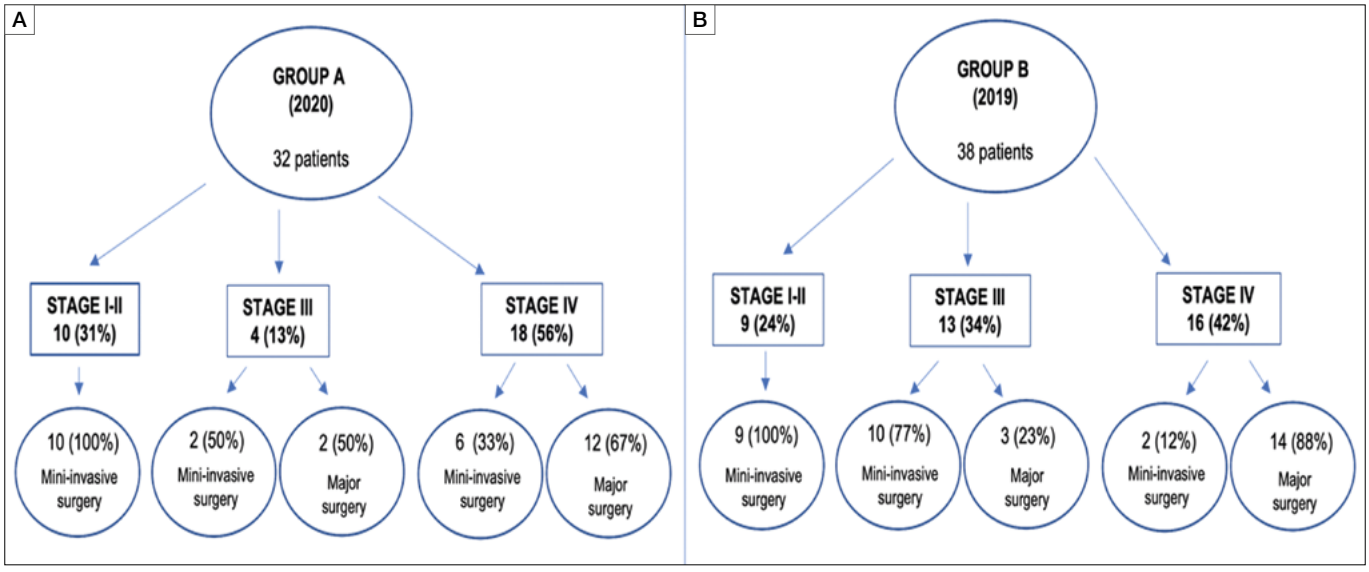


**Figure 1A-B.** Type of surgery distribution in relation of clinical staging between group A (2020) and B (2019).

**Table I.** Characteristics of Groups A and B.

| Characteristic | | Overall N = 70 (%) | Calendar year | | p-value |
|---|---|---|---|---|---|
| | | | Group A (2020) N = 32 (%) | Group B (2019) N = 38 (%) | |
| **Tumour site** | Oral cavity | 27 (38.6) | 11 (34.3) | 16 (42.1) | |
| | Larynx | 16 (22.9) | 9 (28.1) | 7 (18.4) | |
| | Oropharynx | 13 (18.5) | 6 (18.8) | 7 (18.4) | |
| | Other (i.e., skin, thyroid, paranasal sinus) | 14 (20) | 6 (18.8) | 8 (21.1) | 0.74 |
| **Surgery type** | Min-invasive surgery | 38 (54.3) | 17 (53.1) | 21 (55.3) | |
| | Major surgery | 32 (45.7) | 15 (46.9) | 17 (44.7) | 0.81 |
| **Clinical stage** | Initial (I-II) | 19 (27.1) | 10 (31.3) | 9 (23.7) | |
| | Intermediate (III) | 17 (24.3) | 4 (12.4) | 13 (34.2) | 0.12 |
| | Advanced (IV) | 34 (48.6) | 18 (56.3) | 16 (42.1) | |
| **Age, years** [b] | | 64.1 (13.1) | 64.9 (13.4) | 63.4 (13.1) | 0.55 |
| **Days from symptoms to first visit (CPI)** | | 72 (34,93) | 79 (34,121) | 67 (30,93) | 0.96 |

*[a] Fisher's exact test for all categorical variables, log-rank test for days from symptoms to first visit, two-sample Wilcoxon test for age. [b] Min: 17; Max: 82; SD: standard deviation.*

**Table II.** Time-to-treatment interval (TTI) between group A and B.

| Risk factor | | Events/at risk | Median (95% CI) | p-value |
|---|---|---|---|---|
| **Calendar year** | 2019 | 38/38 | 22.5 (16,30) | |
| | 2020 | 32/32 | 13.0 (12,16) | 0.01 |
| **Overall** | | 70/70 | 19 (15,22) | |

*95% CI: 95% confidence interval.*

## Discussion

The COVID-19 pandemic brought about a sudden and intense change in routine healthcare activities, constraining most countries to implement emergency reorganisation and legislative measures in order to cope with and limit the spread of the virus [13].

During the pandemic outbreak, the IEO was nominated as one of the comprehensive cancer centres eligible for the building of the regional hub-and-spoke network. The specialised hubs for oncology have been connected with spokes to design a parallel health network for the specific referral of patients with cancer, to direct the delivery of nondeferrable healthcare [4].

The urgency of treatment for an oncologic patient in the COVID-19 era is even more pressing when considering head and neck cancer patients suffering from dysphagia, hoarseness, or risk of fatal haemorrhage.

In our experience, even if one-third of the 2020 head and neck cancer patients had a COVID-19-related delay in accessing hospitals, due to the stay-at-home policy, "lockdown" restrictions and fear of COVID-19 contagion, we did not record any change, between 2020 and 2019, in the surgery type, tumour clinical staging, or CPI.

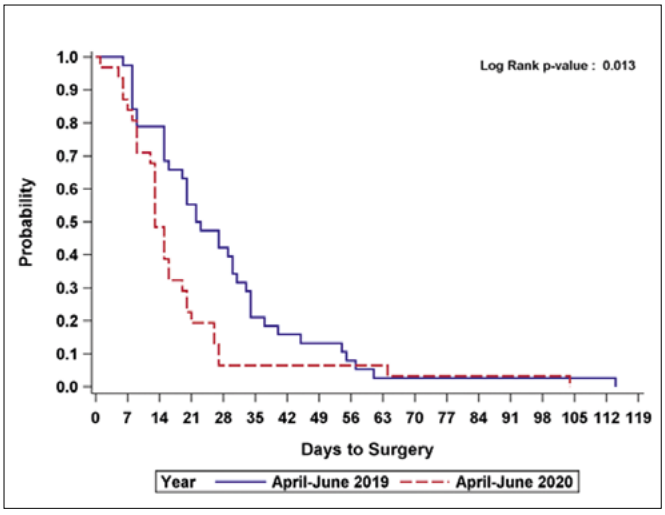


**Figure 2.** Time to treatment interval (TTI) between group A and B.

**Table III.** The risk of delayed day of treatment (surgery).

| Calendar year | HR (95% CI) | p-value |
|---|---|---|
| 2019 | Ref | |
| 2020 | 1.8 (1.1,3.0) | 0.02 |

*HR: hazard ratio; 95% CI: 95% confidence interval; Ref: reference.*

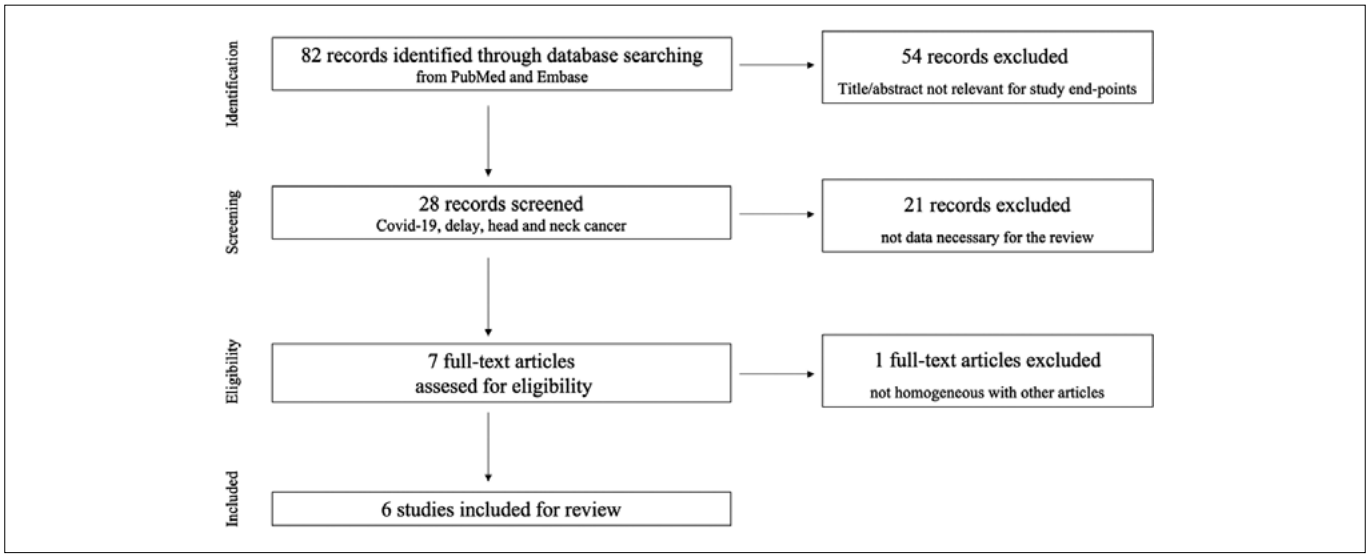


**Figure 3.** Literature review flow chart.

**Table IV.** Summary results of the literature review.

| Year | Author | Country | COVID group - pre-COVID group n (time) | Outcomes | Results - differences in COVID group |
|---|---|---|---|---|---|
| Feb 21 | Kiong KL et al. [8] | USA | 183 (May-Jun 20) – 252 (May-Jun 19) | Incidence<br>Time to visit (CPI)<br>Time to diagnosis<br>Time to staging | Reduction in new H&NC (25%). No longer time to visit (p = 0.391), no longer time from histologic diagnosis to visit (p = 0.133). Significant increase in tumor size (p = 0.042) and T stage (p = 0.025) but no increase in N stage or AJCC 8th stage |
| Oct 21 | Gazzini L et al. [9] | Italy | 45 (Mar 20-Jan 21) – 79 (May 19-Mar 20) | Incidence<br>Time to diagnosis<br>Time to staging<br>Time to treatment (TTI) | Fewer cases per month (p = 0.01) and fewer new diagnoses (p = 0.01). Non-significant increase in time to diagnosis (73.5 *vs* 64 days, p = 0.18) or time to treatment (30.4 *vs* 28.9, p = 0.77). Less early cT stage (p = 0.03) and more advanced cT stage |
| Feb 21 | Tevetoglu F et al. [10] | Turkey | 61 (Mar-Sep 20) – 64 (Mar-Sep 19) | Time to visit (CPI)<br>Time to staging<br>Time to treatment (TTI) | Significant increase of T3-4 tumors (p = 0.049), increased N stage in oral cavity cancer (p = 0.024), increased time to visit (p = 0,02). No significant increase in time to surgery (p = 0.06) |
| Oct 21 | Yao P et al. [11] | USA | 26 (Mar-Jul 20) – 68 (Sep 19-Jan 20) | Time to diagnosis<br>Time to staging<br>Time to treatment (TTI) | Longer time to diagnosis (P = 0.02; hazard ratio [HR], 0.54; 95% CI, 0.32-0.92). No statistically significant differences in time to staging or time to treatment |
| Aug 21 | Metzger K et al. [12] | Germany | 59 (Jan-Dec 20) – 566 (10-19) | Time to staging<br>Time to treatment (TTI) | Longer time to treatment (45 *vs* 35 days, p = 0.004), higher pathological T (p = 0.046), no difference in pN (p = 0.843), higher UICC stages (p = 0.116) |

This aspect is clearly in contrast with other investigators who report a longer time to diagnosis and tumour staging at the time of diagnosis. In 2021, Teveteglu et al. reported a significantly higher (p = 0.02) mean time from the beginning of the first symptom to hospital admission in patients treated in 2020 compared to those treated in 2019 [10]. Similarly, Yao et al. found that patients in the COVID-19 group had a significantly longer time to diagnosis than the pre-COVID-19 group after adjustment for age and cancer diagnosis (p = 0.02; HR, 0.54; 95% CI, 0.32-0.92) [11].

Such discrepancies might be explained by the fact that, despite difficulties in accessing our institute, the intensive

telephone triage and remote follow-up visits helped to identify and distinguish patients who needed critical attention and a short-term hospital visit from those who could be postponed.

Furthermore, in contrast to findings reported by other investigators [8,9,12] regarding a higher incidence of advanced-stage diseases during COVID-19, we did not observe any significant difference between Group A (2020) and Group B (2019). In addition to the protective effect of the telephone triage and telemedicine visits for patients from outside the region, the oncological network with the other regional hospitals enabled us to facilitate patient management by establishing dedicated outpatient visits and operating room sessions. Patients coming from other hospitals were scheduled for surgery after a quick preoperative assessment where the primary non-IEO referring surgeon was asked to complete a detailed form with the patient's characteristics and tumour staging. This synergised effort led to Group A (2020) having a lower risk of experiencing a treatment delay than Group B (2019) ($p = 0.02$). Indeed, we did not observe any difference in clinical staging between 2020 and 2019, due to tumour progression before treatment.

Long-term follow-up data of patients operated in 2020 are not yet available. Future studies will permit evaluation of the real impact of the COVID-19 pandemic on survival and recurrence rates. Furthermore, focusing on the intermediate-stage tumours, the attempt to reduce surgical duration by choosing a minimally-invasive rather than an open approach, and to reconstruct surgical defects with local flaps rather than with free vascularised flaps, raises the question about the future medium- and long-term functional implications of these alternative surgeries on swallowing, breathing and voice restoration.

## Conclusions

Despite the dramatic impact of COVID-19 on the national healthcare system, our preliminary data, coming from an oncological hub, strongly support the importance of creating a synergised and functional continuum of healthcare through a hub-and-spoke network.

The cooperation between designated cancer centres with regional hospitals and distant healthcare providers through telematic triage and telemedicine visits seems to provide an effective rescue parachute for fragile cancer patients needing nondeferrable and life-saving medical care.

More studies in the coming years will evaluate the effect of COVID-19 and the efficacy of the oncological hub rearrangement on long-term oncological and functional outcomes.

### *Conflict of interest statement*

The authors declare no conflict of interest.

### *Funding*

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### *Authors' contributions*

MA: conceptualization; DS, FB and GP: data curation; DR: formal analysis; FC and JZ: writing – original draft. MT, RDB and FC: writing – review and editing.

### *Ethical consideration*

This study was approved by the Institutional Ethics Committee (Istituto Europeo di Oncologia, IRCCS) (code IEO 2432).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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