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Review

COVID-19 screening protocols for preoperative assessment of head and neck cancer patients candidate for elective surgery in the midst of the pandemic: A narrative review with comparison between two Italian institutions

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ABSTRACT

Background: Preoperative screening had a key role in planning elective surgical activity for head and neck cancer (HNC) during the COVID-19 pandemic.

Methods: All patients undergoing surgery for HNC at two Italian referral hospitals (University of Padua and National Cancer Institute [NCI]) during the peak of the COVID-19 epidemic in Italy were included. Accuracy of screening protocols was assessed.

Results: In the Padua protocol, 41 patients were screened by pharyngeal swab. The entire sample (100%) was admitted to surgery, diagnostic accuracy was 100%. In the NCI protocol, 23 patients underwent a telephone interview, blood test, and chest CT. Twenty patients (87%) were negative and were directly admitted to surgery. In the remaining 3 (13%), pharyngeal swab was performed. The screening was repeated until a negative chest CT was found. Diagnostic accuracy was 85%.

Conclusions: Dedicated screening protocols for COVID-19 allow to safely perform elective HNC surgery.

Introduction

The COVID-19 pandemic has led to a progressive and significant strain on healthcare systems worldwide. The ideal management of COVID-19 patients has been improved and standardized by various reports dealing with risk-stratification, therapy, and follow-up [1–3]. However, optimized protocols for administration of routine activity in specific COVID-free surgical departments are still lacking [4]. Nonetheless, this is an essential point to take into consideration in preparation for the restart of conventional activity in the post-epidemic (or endemic) phase. In this context, early identification of SARS-CoV-2 infected patients is the basis for adequate definition of subsequent planning in both in- and outpatient settings. However, etiological diagnosis is not always straightforward, especially when introduced in the framework of a screening protocol. In particular, nasal/nasopharyngeal and oropharyngeal swabs might be burdened by a high false

negative rate. On the other hand, radiologic examinations (chest radiogram or computed tomography [CT]), while being able to provide data on pulmonary status, may lead to a significant rate of false positive and false negative results. These drawbacks are even more pronounced in mildly symptomatic or non-symptomatic patients. For this reason, institutional screening protocols should consider the integration of different diagnostic methods to reach levels of diagnostic accuracy that are suited for routine clinical applications. The importance of identifying SARS-CoV-2 infection prior to surgery is even more relevant in patients affected by cancer requiring major procedures, as possible onset of COVID-19 in such a fragile condition as during the post-operative course of oncologic patients could potentially lead to catastrophic outcomes. Moreover, spread of the infection within a surgical department would put other patients and personnel at risk.

The aim of our retrospective study was to describe the screening and surgical activities of two Northern Italian (one in Lombardy and the

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other in Veneto regions) referral Institutions for management of head and neck cancer (HNC) during the peak phase (mid-March – mid-April 2020) of the COVID-19 epidemic, detailing their respective institutional COVID-19 screening protocols, related outcomes, and diagnostic accuracy.

Materials and methods

The study included all patients undergoing surgery under general anesthesia for HNC at two Italian tertiary referral academic hospitals during the peak of the pandemic diffusion of COVID-19 in Italy: the Unit of Otorhinolaryngology – Head and Neck Surgery, Azienda Ospedaliera di Padova, University of Padua (Veneto, Italy), and the Department of Otorhinolaryngology, Maxillofacial, and Thyroid Surgery, National Cancer Institute (NCI) of Milan, University of Milan (Lombardy, Italy). Both diagnostic and therapeutic interventions were reviewed.

Screening protocols

The two Institutions of the present study applied different pre-operative COVID-19 screening protocols (Fig. 1).

1. *Padua protocol.* Patients received nasal/nasopharyngeal and oropharyngeal swabs within 1 week prior to surgery. The sample was analyzed for viral genome equivalents with qualitative real-time reverse-transcription polymerase chain reaction (RT-PCR). During the time from swab to surgery, patients were asked to maintain isolation and avoid external contacts that could potentially harbor

SARS-CoV-2 infection. Depending upon the patient’s conditions, provenance, and specific logistical circumstances, the swab was performed at either a local institution in the patients’ region of residence or at the University of Padua. The result of the screening test was available in a time frame ranging from 4 hours (urgent cases) to 5 days, and in the meantime patients were recommended to maintain home isolation and minimize contacts with cohabitants. Patients displaying symptoms compatible with COVID-19 (fever, dry cough, tiredness, shortness of breath, aches and pain, sore throat, diarrhea, nausea, runny nose, loss of olfaction and/or taste) and not attributable to cancer were instructed to maintain home isolation and refer to their general practitioner for further instructions, as per national guidelines. Patients showing the aforesaid symptoms or other findings compatible with COVID-19 (*i.e.* desaturation, interstitial pneumonia, fever of unknown origin) during postoperative hospital admission underwent qualitative RT-PCR on respiratory secretions (either pharyngeal or tracheobronchial in presence of a tracheostomy) and were placed under prophylactic isolation until receiving the test results.

2. *Milan NCI protocol.* Patients planned for surgery underwent a telephone interview to rule out the presence of active symptoms potentially related to COVID-19. If this was not the case, on the day of the hospitalization they underwent blood test (focusing on lymphocyte count, lactate dehydrogenase [LDH], fibrinogen, D-dimer, and C-reactive protein [CRP]) and chest CT scan through a dedicated path. In case of absence of radiological suspicion of SARS-CoV-2 infection, patients were admitted and prepared for the procedure scheduled the following day. In case of chest CT signs of potential COVID-19 infection, nasopharyngeal swabs were taken and patients

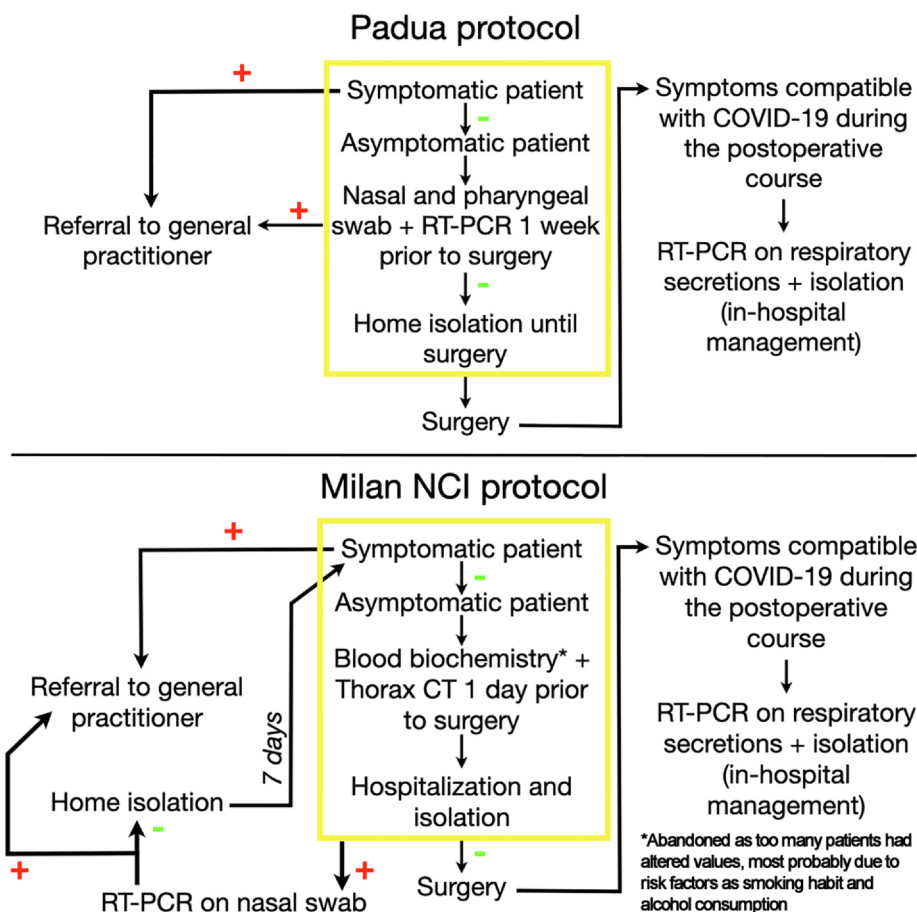


Fig. 1. Panel summarizing the two protocols analyzed in the present study. Yellow boxes highlight screening steps. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Characteristics and surgical features of 64 HNC patients screened for SARS-CoV-2.

Variable	Padua series (n = 41)		Milan NCI series (n = 23)	
	No. of patients	Prevalence % (95% CI) ^a	No. of patients	Prevalence % (95% CI) ^a
Age, median (IQR), years	68 (52–76.5)	–	72 (62.5–78.5)	–
<i>Gender</i>				
Male	32	78.0 (63.3–88.0)	13	56.5* (36.8–74.4)
Female	9	22.0 (12.0–36.7)	10	43.5* (25.6–63.1)
<i>Comorbidity</i>				
None	9	22.0 (12.0–36.7)	0	0.0*
Any	32	78.0 (63.3–88.0)	23	100.0* (85.7–100)
CCI, median (IQR)	5 (2–8)	–	5* (2–5.5)	–
<i>Tumor status</i>				
Primary	27	65.9 (50.5–78.4)	16	69.6* (49.1–84.4)
Recurrent	14	34.1 (21.6–49.5)	7	30.4* (16.6–50.7)
<i>Tumor site</i>				
Oropharynx	8	19.5 (10.2–34.0)	2	8.7* (2.4–26.8)
Larynx	7	17.1 (8.5–31.3)	3	13.0* (4.5–32.1)
Sinonasal tract	5	12.2 (5.3–25.5)	0	0.0*
Hypopharynx	4	9.8 (3.9–22.5)	1	4.3* (0.8–20.9)
Oral cavity	4	9.8 (3.9–22.5)	11	47.8* (29.2–67)
Salivary glands	3	7.3 (2.5–19.4)	0	0.0*
Other	4	9.8 (3.9–22.5)	4	17.4* (6.9–37.1)
Neck	6	14.6 (6.9–28.4)	2	8.7* (2.4–26.8)
<i>Type of surgery</i>				
Open	24	58.5 (43.4–72.2)	15	75.0** (53.1–88.8)
Transnasal endoscopic	6	14.6 (6.9–28.4)	0	0.0**
TLM/TORS	10	24.4 (13.8–39.3)	5	25.0** (11.2–46.9)
Combined	1	2.4 (0.4–12.6)	0	0.0**
<i>Histology</i>				
SCC	23	56.1 (41–70.1)	13	65.0** (43.3–81.9)
Other epithelial	6	14.6 (6.9–28.4)	4	20.0** (8.1–41.6)
Other non-epithelial	12	29.3 (17.6–44.5)	3	15.0** (5.2–36)
<i>Neoadjuvant treatment</i>				
No	40	97.6 (87.4–99.6)	20	100.0** (83.9–100)
Yes	1	2.4 (0.4–12.6)	0	0.0**
<i>Adjuvant treatment</i>				
No	19	46.3 (32.1–61.3)	11	55.0** (34.2–74.2)
Yes	17	41.5 (27.8–56.6)	6	30.0** (14.5–51.9)
n.a.	3	7.3 (2.5–19.4)	3	15.0** (5.2–36)
<i>Postoperative complications</i>				
No	33	80.5 (66.0–89.8)	18	90.0** (69.9–97.2)
Yes	8	19.5 (10.2–34.0)	2	10.0** (2.8–30.1)
Hospital stay, median (IQR), days	5 (1–10)	–	7.5** (2.3–7.8)	–

Legend: ^a95% CIs were calculated using the Wilson method; CCI = Charlson Comorbidity Index; IQR = Interquartile Range; TLM = Transoral Laser Microsurgery; TORS = Transoral Robotic Surgery; n.a. = not applicable.

* Calculated on the entire Milan NCI series (n = 23).

** Calculated on the subset of patients of the Milan NCI series undergoing surgery (n = 20).

were discharged at home waiting for swab results with instructions to maintain strict isolation. If pharyngeal swabs were negative, the same presurgical triage (telephone call, biochemical tests, and chest CT scan) was repeated 7 days later, whereas in case of COVID-19 positivity the patient's general practitioner was informed in order to begin clinical surveillance as per government indications. If symptoms suspicious for COVID-19 infection arose in the postoperative period, patients were transferred to an internal "grey zone" of COVID-19 surveillance, submitted to further blood tests, chest CT, and nasal/nasopharyngeal swab while maintaining strict isolation.

Variables analyzed

The following data were extracted from institutional databases: patient-related variables (age at surgery, gender, comorbidities), tumor-related variables (site, subsite, primary vs. recurrent tumor, histology, grade/subtype, cTNM, pTNM), treatment-related variables

(neoadjuvant treatment, surgical and reconstructive details, surgical time, need for tracheostomy, intensive care unit [ICU] stay, postoperative complications, length of hospitalization, indication to adjuvant treatments), and variables related to the preoperative COVID-19 screening protocols adopted (type of investigations employed, number of positive cases, patients submitted to further investigations in the postoperative period, and development of symptomatic COVID-19 during in-hospital stay and/or 2-week postoperative course).

Diagnostic performance of screening

The aim of the study was to provide a descriptive analysis of 2 series of HNC patients treated by similar diagnostic and therapeutic algorithms during the pandemic outbreak, evaluating the diagnostic performance of two different screening protocols adopted in similar academic institutions located in two geographically close Italian Northern regions (Lombardy and Veneto). Efficacy of the screening strategy was

intended as the ability to prevent severe, SARS-CoV-2-related respiratory/cardiovascular postoperative complications in patients receiving elective surgery for HNC, alongside with spread of infection towards other patients and hospital staff. Calculation of the diagnostic performance of the different methodologies in determining the status of SARS-CoV-2 infection (regardless of severity and presence of symptoms) was beyond the aim of the study.

Classification of cases was performed as follows: the screening result was considered as *diagnostic test* (i.e. “negative” patients were those eligible for surgery as the screening showed no findings attributable to a subclinical phase of COVID-19; in contrast, when the screening test showed findings compatible with COVID-19, patients were defined as “positive” and surgery was delayed until normalization of the screening test); the entire perioperative course (i.e. including the 2-week post-discharge period) was considered as the *gold standard evaluation* (i.e. patients developing symptoms attributed to COVID-19 through nucleic acid-based test on respiratory secretions in this time frame were considered as “false negative” of the screening; patients resulting positive at first screening who turned out to be negative at subsequent evaluations and did not develop COVID-19 throughout the perioperative period were considered as “false positive”). The choice of considering a 2-week time span to define results as either “false negative” or “true negative” was justified by: 1) the fact that during the inclusion period patients were instructed to maintain home isolation following discharge, as per governmental warning, and 2) the need to prioritize the negative (NPV) over the positive predictive value (PPV), being the selection of “true negatives” (i.e., non-infected patients) the main objective of the protocols. Sensitivity, specificity, PPV, NPV, and accuracy were calculated accordingly.

Results

Padua series

Between March 16th and April 17th, 2020, 41 patients, 32 males and 9 females (age range, 52–76 years; median, 68; mean, 64.5) met inclusion criteria. Relevant comorbidities were revealed in past medical history in 32 patients (78.0%). Demographic and clinical features are listed in Table 1. Primary HNC was diagnosed in 27 (65.9%) cases, while 14 (34.1%) underwent surgery for recurrent/persistent lesions. Oropharynx, larynx, and sinonasal tract were the primary site of tumor origin in 8 (19.5%), 7 (17.1%), and 5 (12.2%) patients, respectively.

All nasal/nasopharyngeal and oropharyngeal swabs were negative. Chest CT before surgery (not systematically included in this screening strategy) was available in 9 (22.0%) patients, and none showed lesions suspicious for interstitial pneumonia or other radiological signs of COVID-19. Each patient declared that they respected home isolation with minimum contact to cohabitants during the time between the test and surgery. Moreover, none of the patients developed symptoms suspicious for COVID-19, nor did any declare contact with a subject diagnosed with SARS-CoV-2 infection. The entire sample (100%) was therefore admitted for surgery without any other preventive or diagnostic measures.

Open surgical approaches were the most frequently performed in this series (58.5%), followed by transoral laser or robotic procedures (24.4%). Concurrent neck dissection was indicated in 41.5% of patients, and tracheostomy in 26.8%. Reconstruction of the primary site was required in 24.4% of cases, mostly involving harvesting of a free flap (7/10 reconstructions, 70.0%).

After surgery, ICU surveillance for 24–48 hours was indicated in 31.7% of patients. At pathological examination, squamous cell carcinoma (56.1%) prevailed over other histologies. During hospitalization, 14.6% of patients had symptoms unrelated to their primary underlying condition (including fever, cough, sudden desaturation, signs of interstitial pneumonia, and bronchial hemorrhage), thus requiring a second nasal and pharyngeal swab (N = 3) or tracheobronchial secretions

sampling through tracheostomy (N = 3) to rule out COVID-19. RT-PCR on these samples were negative in all cases. Eight (19.5%) postoperative surgical complications were registered and median hospitalization time was 5.5 days (range, 1–35).

Diagnostic performance of the COVID-19 screening method was excellent, with specificity, NPV, and accuracy all 100%, whereas sensitivity and PPV were not assessable for lack of events.

Milan NCI series

In the period between March 24th and April 20th, 2020, 23 HNC patients, 13 males and 10 females (age range, 23–84 years; median, 72; mean, 65), were evaluated by the above-mentioned preoperative COVID-19 screening protocol. Demographic and clinical features are listed in Table 1.

Soon after the screening program started, it became evident that blood test exams could not reliably screen patients with HNC. In fact, 10 of 23 (43.5%) subjects screened had from 1 to 3 parameters beyond the normal range, possibly due to the high rate of smoking and alcohol consumption in these patients. This observation led to abandon biochemistry as a screening method and use it as ancillary information to stratify risk of infection in uncertain cases.

Chest CT was negative in 20 patients (87.0%), who were therefore submitted to surgery the subsequent day. Among remaining 3 (13.0%) patients who had a first chest CT suspicious for COVID-19, 2 were re-submitted to a second CT 15 days later, which was negative (and carried to surgery in one case only since the other was discovered to harbor lung metastases), while one patient repeated the triage twice (15 and 30 days after the first CT) since she was deemed positive even at the second one. After each CT, all these patients received a nasopharyngeal swab that was negative.

The sites involved by the tumor were: oral cavity (47.8%), oropharynx (17.4%), thyroid (17.4%), larynx (13.0%), and hypopharynx (4.3%). Sixteen (69.5%) patients had been evaluated for primary lesions, while 7 (30.5%) were referred to us for persistent/recurrent disease after surgery or (chemo)radiation. Three patients were not operated for oncologic non-COVID-19-related issues: one for progression of a tongue cancer beyond surgical resectability, one for progression to distant lung metastases, and one for impossible laryngeal exposure of a T1b glottic cancer (therefore treated by radiation therapy). As a consequence, we performed 20 surgical procedures, of which 15 (75.0%) were major surgeries (7 with free flaps reconstruction), and 5 (25.0%) minor transoral tongue or laser-assisted laryngeal procedures.

None of these patients developed signs or symptoms of COVID-19 during hospitalization (range, 1–21 days; mean, 6). One patient presented mild fever and respiratory problems at 7 days after surgery that included segmental mandibulectomy, neck dissection, and free flap reconstruction. He therefore received chest CT (showing mild interstitial thickening) and nasopharyngeal swab (negative for SARS-CoV-2). All patients underwent a postoperative follow-up visit at least 2 weeks after discharge or received a telephone call and did not refer COVID-19-related signs or symptoms.

Therefore, chest CT scan showed a sensitivity and PPV that were not assessable due to the lack of events. On the other hand, specificity, NPV, and accuracy were 85%, 100%, and 85%, respectively.

Discussion

We herein describe two different screening protocols adopted for preoperative identification of SARS-CoV-2 infection in HNC patients to be electively managed by surgery in the midst of a devastating viral epidemic. The Padua protocol focused on the use of preoperative pharyngeal swab, while the Milan NCI protocol was based on assessment of symptoms, blood test, and chest CT, possibly followed by pharyngeal swab. Each protocol reflects the specificity of the crisis that heterogeneously hit Italian regions: in Veneto (where Padua is located),

19,030 of 536,798 (3.5%) patients who underwent pharyngeal swab were positive to the time of writing, whereas the analogous proportion in Lombardy (where Milan is located) accounted for 85,775 cases of a total of 607,863 patients tested (14.1%). Thus, in the most severely hit area, more aggressive screening including both CT and, in case of suspicion, RT-PCR on swab was adopted, whereas a purely RT-PCR-based protocol was adopted where the pandemic was more contained [5]. With special reference to the Padua protocol, although a shorter time span between swab and surgery would have been preferable, it must be considered that both knowledge on timing of the infection and diagnostic resources (e.g. rapid test kits for urgent cases) were limited during the inclusion period. Moreover, it has been demonstrated that the rate of positive swab within 1 week from an initially negative test is low (3.5%) and mostly regards symptomatic subjects with worsening conditions [6]. While the relatively small number of patients does not allow making any definitive conclusions, both algorithms effectively selected non-infected patients in the preoperative phase, even during the pandemic peak of COVID-19 in one of the earliest and most involved areas of the European Union.

However, preoperative screening tools to be adopted for future triage of patients who are electively managed for HNC should be progressively refined in light of novel evidence and advances in the field of diagnostic testing, especially during the post-epidemic (endemic) phase, whose length and future impact on worldwide health care systems are far to be fully appreciated. Interestingly, it has been recently suggested that testing the asymptomatic population with a relatively inexpensive test (i.e. \$50 or cheaper) might be cost-effective during the epidemic phases of the pandemic (i.e. with R_e 1.6 or higher), otherwise providing a reduction in infections, deaths, and hospitalizations despite the non-cost-effectiveness. Moreover, a test as cheap as \$5 would be cost-effective even in the non-epidemic (endemic) phase. If the cost could be reduced to \$3 or less, then a test performed on a 14-day basis would be cost-effective regardless of R_e value [7]. Since operating on patients affected by SARS-CoV-2 implies potentially dramatic consequences [8], screening asymptomatic subjects prior to surgery is likely to provide a favorable cost-benefit, if not cost-effective, ratio.

Blood chemistry

To date, there is no clear-cut indication that blood chemistry can serve as a screening tool to identify SARS-CoV-2-positive patients. However, preoperative blood chemistry is routinely performed in most Institutes and could provide useful information without additional costs. A series of reports described the most common alterations in COVID-19 infection [9,10], with the primary aim of identifying high-risk patients. The most frequently reported changes were decreased lymphocyte count and increased LDH, alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer, and CRP. However, their diagnostic performance, especially in asymptomatic and mildly symptomatic patients, remained exceedingly low [11,12]. Moreover, their frequent alterations in HNC patients due to the high incidence of alcohol- and tobacco-related organ damage may hamper the ability of these tests to screen for COVID-19 in this subset. Notwithstanding, these alterations should be routinely assessed to stratify the risk of infection and prioritize the indication for adjunctive screening tests. Although blood chemistry was part of the Milan NCI screening protocol, biochemical alterations were rarely relied upon, as they are frequently attributable to underlying conditions unrelated to COVID-19.

Computed tomography

The role of CT in first-line diagnosis and screening of COVID-19 patients is a much-debated topic. The proposed rationale is to speed-up diagnosis and prevent issues related to shortages of RT-PCR tests. However, data regarding this specific aspect are variable and should be carefully interpreted to identify the advantages and drawbacks [13].

Ai *et al.* evaluated the diagnostic performance of chest CT in 1014 cases during the Wuhan epidemic, highlighting its extremely high sensitivity (97%) and its potential in the routine screening of COVID-19 patients [14]. However, these results should be analyzed in light of two critical factors: 1) no clear gold-standard diagnostic test for SARS-CoV-2 infection was available at the time of the study to use as a reference, with sensitivity analysis obtained only by including the portion of RT-PCR-positive patients; 2) the investigation was performed on symptomatic/hospitalized patients, thus excluding asymptomatic and mildly symptomatic subjects, which clearly represents the vast majority of patients to be electively treated for HNC. Furthermore, lung alterations routinely examined by CT (i.e. ground-glass opacity, consolidation, reticulation/thickened interlobular septa, and nodular lesions) are not specific for COVID-19 and may be encountered in many inflammatory lung alterations (quite frequent in the HNC population), as in any viral pneumonia. In this view, the PPV would decrease proportionally with a decrease of disease prevalence, rendering this approach less effective in non-epidemic areas.

When assessing the diagnostic performance of CT in a less symptomatic population, such as the “Diamond Princess” cohort, Inui *et al.* demonstrated a substantial decrease in the diagnostic performance of CT. In particular, only 54% of asymptomatic infected subjects had lung opacities at imaging (defined as pure ground-glass opacity, ground-glass opacity with interlobular septal thickening, and ground-glass opacity with consolidation) [15]. These results warn against the exclusive use of CT as a screening method for SARS-CoV-2 infection, but do not exclude its utility in association with other exams. In this regard, Ren *et al.* reported high sensitivity (92%) by combining CT and RT-PCR, thus identifying an optimal solution for preoperative screening [16].

Nucleic acid detection

RT-PCR aims to identify the presence of SARS-CoV-2 RNA sequences in biological samples and is currently recommended as the standard test for diagnosis of SARS-CoV-2 infection. However, its diagnostic accuracy remains unclear and is difficult to assess, especially in asymptomatic patients, given the lack of robust data [17]. Most evidence is based on a series of hospitalized COVID-19 patients and/or symptomatic patients, where reference standards for comparison of results are unclear [18].

The “threat” of false negative result is directly related to critical issues including site of sampling, sampling method, timing, and sampling safety for healthcare providers. A recent review on collection of respiratory specimens in symptomatic patients during the SARS, MERS, and H1N1 epidemics revealed that nasopharyngeal aspirate had the highest positive rate when performed within 2 weeks of onset of symptoms [19]. Combined sampling of nasal and oropharyngeal swabs was the safest method for medical staff. Results driven from experience in previous epidemics are yet to be validated in the current SARS-CoV-2 pandemic.

Rates of positivity with quantitative RT-PCR depends on the sampling site. Considering the upper respiratory tract, the highest positive rates in COVID-19 patients were found in nasal swabs (63–73%), followed by oropharyngeal swabs (32–61%) [20]. These data reflect the results of Zou *et al.* on viral load of the upper respiratory tract, where higher viral loads were registered in the nasal cavity than in the oropharynx [21]. Among sampling of the lower respiratory tract, sputum collection was positive in 49–89% of cases, while bronchoalveolar lavage (BAL) had the highest diagnostic yield with 93–100% positivity [22–24]. Notably, selection bias might have affected the actual rates of positivity for BAL, considering that the collection procedure is generally performed in intubated patients, and thus in severe clinical scenarios for patients with COVID-19. Despite the higher diagnostic performance of lower respiratory tract specimens, the risk of exposure during sample collection and the technical demand of BAL advise against its routine use for screening. A reasonable balance between the above-mentioned issues is probably represented by nasal swab, which, as suggested by

some authors, may be combined with oropharyngeal swabs or sputum collection to increase sensitivity [18,25].

Time represents another significant variable that may affect RT-PCR results. On 866 respiratory specimens, Yang *et al.* demonstrated that sputum collection and nasal swab had the highest positive rates for both severe and mild COVID-19 cases within 14 days of disease onset. However, the authors did not recommend pharyngeal swabs for diagnosis, given the remarkable decrease in positive rate during the first 7 days of disease onset in both severely and mildly affected patients [23].

Not least, various primers and probe sets for SARS-CoV-2 detection by RT-PCR have been recommended by the World Health Organization. Molecular diagnostic accuracy may depend on the molecular tool used. The first study performing a comparative analysis of several primer-probe sets, including that for the N gene and Orf1 gene, revealed higher sensitivity rates with the combination of Orf1ab (China), 2019-nCoV_N2, N3 (USA), and NIID_2019-nCoV_N (Japan) [26].

Serology

At the time of writing, serology for SARS-CoV-2 is gaining increasing interest [27–29], as its theoretical utility ranges from a pre-treatment/pre-trial recruitment screening tool to a potential method to assess immunity on a large population-based scale. However, a number of limitations make serology a suboptimal tool to screen patients requiring oncologic surgery. One of the major drawbacks of serological assays is the time span required for detection of antibodies following infection, which is paramount for screening purposes: Pan *et al.* demonstrated that sensitivity of serological immunochromatographic test takes almost one week to increase from 11% within the first week following symptom onset to 93% thereafter [30]. If one considers that the incubation time of COVID-19 is estimated to be 6.4 days [31], the large majority of infected patients would not be detected in the first 2 weeks of the disease. When focusing specifically on IgM, seroconversion is observed in 12–85% of patients within the first week after the onset of symptoms, varying substantially according to the laboratory methodology [32–34]. Thus, there is increasing consensus that IgM serology should be considered not earlier than 5 days from symptom onset and when clinical suspicion is high despite a negative nucleic acid-based diagnostic result [28]. However, both Zhao *et al.* and Guo *et al.* showed that incorporation of serology in a multi-test diagnostic might be beneficial compared to testing only for nucleic acids, with sensitivity increasing from 52–67% to 98–99% [32,34].

Some lines of evidence suggest that the degree of seroconversion is directly associated with severity of disease in terms of both clinical and biochemical manifestations [35,36]. This further undermines the potential utility of serology in the screening of asymptomatic patients. Moreover, non-uniformity among commercially available kits and potential cross-reactivity with respect to antibodies against non-SARS-CoV-2 coronaviruses further discourage the application of serology as preoperative screening method [28].

Considering that recent reports documented that IgG seroconversion occurs in almost all patients infected with SARS-CoV-2 [37], future elucidation about the role of antibodies in predicting immunity for COVID-19 will also be essential in the preoperative screening setting, as patients displaying IgG could be exempted from other expensive and time-consuming screening tests prior to surgery.

Conclusions

Although based on two small cohorts of patients, the present study suggests that different screening protocols for SARS-CoV-2 infection were effective for preoperative screening of HNC patients who were candidates for surgery. Even during the peak of the epidemic phase, pharyngeal swab alone or a combination of symptom evaluation, generic blood tests, and chest CT were able to adequately select patients for

surgery, apparently including only those without COVID-19. However, each diagnostic test presents specific drawbacks in terms of accuracy and cost-related issues that must be placed into perspective when considering preoperative screening for elective surgery. In this view, further studies will need to assess a combination of various diagnostic methods aimed at optimizing diagnosis while maintaining a favorable cost-benefit ratio, especially in the post-epidemic (endemic) phase of COVID-19. Optimal integration and modulation of different screening strategies will be paramount to cope with the “silent threat” of asymptomatic endemic infections [38].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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