Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Oral Oncology 107 (2020) 104813

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Letter to the editor

Diagnostic Tests for SARS-CoV-2: Implications in Head and Neck Oncology

Dear Editor,

Owing to the perplexing nature of SARS-CoV-2 and its asymptomatic spread [1], diagnostic dilemmas exist amongst healthcare practitioners. In the present scenario, to carry out surgical procedures, patients' diagnostic test reports for SARS-CoV-2 might be sought, particularly in Head and Neck Cancer (HNC) patients, who are more prone to develop COVID-19, as inferred from a cohort study in China [2]. In cancer patients, suspension of oncology treatment can have serious repercussions and should be prioritized.

To perform surgical procedures, many institutions have advocated SARS-CoV-2 screening as the utmost priority and have mandated it [3]. However, it is arduous to screen for and select COVID-19 negative patients for surgery as COVID-19 positive patients may even circumvent two weeks with negative testing. Hence, inappropriate pre-surgical screening for COVID-19 can be an impediment to safe HNC surgery [4]. Therefore, it is imperative that dentists, oral surgeons and oncologists have cognizance about the diagnosis and various modalities available for the same, their use, reliability and interpretation, in order to safeguard their patients, staff and themselves.

Synthesis from the present literature divulges that there is an array of diagnostic tests available or in the pipeline, for this pernicious disease (Table 1) [5–8], which either test for the virus itself or are serological tests detecting antibodies in blood. While the viral tests making use of RT-PCR or qRT-PCR and ELISA tests detecting antibodies usually require laboratories or specific conditions [9], rapid antibody tests can be done albeit any particular conditions. Although qRT-PCR remains the gold standard, it is not without fallibility [5]. Its sensitivity varies depending on the kits and PCR instrument deployed [9] and mostly takes long to be processed. Rapid RT-PCR tests that have been launched are processed faster but require special armamentarium and only a few can be done at a time depending upon machine capabilities and supply of reagents. RT-PCR test in principle has 100% sensitivity. Nevertheless, due to biology of the disease, for instance, inappropriate timing of sample collection in relation to disease onset or the virus not being present in the particular location being tested at the particular time results in some false negatives [3,9]. Other RT-PCR false negatives may be attributable to laboratories being under the cosh, substandard sample collection and preparation [9]. Healthcare practitioners must be aware of these problems as a single test report cannot be taken at face value.

Also, while nasopharyngeal swabs are predominant means of obtaining the sample, a single nasopharyngeal swab is only 63% sensitive, compared to bronchoalveolar lavage specimens being 93%, which however are difficult to obtain [5]. Hence, other samples are being researched. Saliva and GCF which can provide a quick and non-invasive sample have become increasingly popular for SARS-CoV-2 diagnosis, requiring further exploration [10].

Rapid serology tests, which do not require centralized facilities, detect antibodies wherein IgM antibodies are discerned in early disease whereas IgG are formed later & persist longer. Although rapid tests infer expedited diagnosis of COVID-19, false negatives and cross-reactivity are a bigger problem which cannot be overlooked [6–8].

Diagnostic tests should be correlated with clinical findings. While taking the history and during the oral examination, attention should be paid to features, such as dysgeusia/ageusia, dry mouth and exanthematous lesions like ulcers or blisters which might be initial symptoms of COVID-19, presenting even before fever, dry cough, and

https://doi.org/10.1016/j.oraloncology.2020.104813
Received 16 May 2020; Accepted 19 May 2020
Available online 21 May 2020

Table 1
Diagnostic tests for SARS-CoV-2.[**,****]

TEST	MECHANISM OF ACTION	ADVANTAGES	DISADVANTAGES/LIMITATIONS	TIME	LEVEL OF DETECTION/ SENSITIVITY
NASOPHARYNGEAL SWAB/SPUTUM/SALIVA/BRONCHOALVEOLAR LAVAGE					
RT-PCR/qRT-PCR	Samples undergo RNA extraction followed by qualitative RT-PCR for target detection	– Highly sensitive – Fairly reliable. – Detects current infection. – POC* tests available as well.	– Does not rule out early infection/past infection – Impaired assessment attributable to: ● Lack of a reference standard, ● Use of different sample collection/ transportation/preparation methods ● Varied viral dynamics across the time course of infection	3 h (usually 6–8 hrs.)	– High overall sensitivity but varies on the kits and PCR instrument. – Specificity of most of the RT-PCR tests is 100% – Occasional false-positive results may occur due to technical errors and reagent contamination.
IMPLICATIONS OF RT-PCR[***] +ve implies a confirmed positive case. −ve RT-PCR report might warrant to be corroborated with Antibody tests for elective treatments or a repeat RT-PCR in case of symptomatic cases.					
Loop-mediated isothermal amplification (LAMP) tests	Saliva samples involve DNA polymerase and 4 to 6 primers to bind to the target genome. After the addition of the sample, the amplified DNA is identified by turbidity, color, or fluorescence.	– Decreased test time - Inexpensive equipment – Simple method – Can detect current infections – Point of Care (POC)	– Performed at a specific temperature – Difficulty in optimizing primers & reaction conditions (more difficult than RT-PCR) – Background research still lacking. – Only positive if virus is still present at the time the test is done. – Unable to diagnose recovered patients.	< 1 h	The level of detection can be 75 copies per microlitre (highly sensitive)
Microfluidic RT-PCR devices (Lab-on-a-chip)	All the steps, like cell lysis, DNA extraction, and PCR amplification, can be integrated on a single microchip	– Small specimen volume – Fast detection – Incorporation of the gold standard test (PCR) in a portable miniature form – Affordable	– Not currently available for SARS-CoV-2 – These technologies can be adapted to detect SARS-CoV-2 RNA or protein – (More research required for the same)	< 10 min	100% clinical sensitivity and 87% specificity in HIV patients
BLOOD-TESTING					
Enzyme Linked Immunosorbent Assay (ELISA)	Uses enzymes linked to antibodies that can attach to the molecules that are being tested for and causes a colour change that can be measured by a specialized machine. An ELISA detects antibodies produced in patient blood due to infection with SARS-CoV-2	– Simple and inexpensive laboratory technique. – Well established and documented. – Perform testing for multiple samples at once	Require specialized laboratories	1–3 h	ELISA-based IgM and IgG antibody tests have greater than 95% specificity for diagnosis of COVID-19. – Specificity and sensitivity percentages vary among different brands available (FDA) – Sensitivity higher than or equal to rapid tests

(*continued on next page*)

Table 1 (*continued*)

TEST	MECHANISM OF ACTION	ADVANTAGES	DISADVANTAGES/LIMITATIONS	TIME	LEVEL OF DETECTION/ SENSITIVITY
Rapid tests: Antibody testing (IgG, IgM)	IgG and IgM detection using lateral flow immunoassay	– Fast detection – Easy to perform – POC* – No expensive equipment required	– Indicated for screening and not for early diagnosis. – Since antibodies appearance depends upon time, diagnosis by this method is limited to patients with a longer duration of illness. – Possible cross-reactivity with antibodies produced against other coronaviruses.	10–15 min (depending on the kit)	Diagnostic accuracy and optimal use of rapid Ab tests remain undefined. – Specificity and sensitivity percentages vary among different brands available (FDA) – Sensitivity usually lower than RT-PCR
IMPLICATIONS*** (when PCR is -ve and antibody test performed): IgG − IgM − No infection = Surgical Treatment may be performed IgG + IgM − May have had past infection and has recovered = Surgical Treatement may be performed IgG - IgM + Early stage/PCR false −ve = Advice Repeat PCR IgG + IgM + Recovery stage/PCR false −ve = Advise Repeat PCR					
Antigen detection	Monoclonal antibodies against the nucleocapsid protein of SARS–CoV-2 have been generated and can be used for antigen detection	Short time for result – POC* (Lateral flow antigen detection) also	– Not currently available for SARS-CoV-2 – Under development	Within minutes	Sub-optimal sensitivity for other respiratory syncytial viruses

* POC – Point-of-care tests are used to diagnose patients without sending samples to centralized facilities.

** Sensitivity and specificity might vary with tests from different manufacturers. Oral healthcare professionals should be updated with recent most guidelines and published data, in order to decide which test to be used.

*** Treatment to be carried out only if current CDC guidelines are fulfilled.

**** This table drafted by referring to [5–8].

other quintessential clinical symptoms. Self-acknowledged loss of taste and smell might be owed to the cellular entry receptors of SARS-CoV-2 (ACE2) and is a much stronger predictor of a positive COVID-19 diagnosis than self-disclosed fever [10].

Testing via saliva or GCF samples may be valuable and dentists and oral surgeons might play a pivotal role in early diagnosis. Hence, the practitioner must be apprised with the expression of the disease and test modalities available. The results should be interpreted prudently, and the clinicians must use their acumen while corroborating the results with the patient's history and clinical findings for their HNC patients.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

References

[1] Suri S, Vandersluis YR, Kochhar AS, Bhasin R, Abdallah M. Clinical orthodontic management during the COVID-19 pandemic. Angle Orthodont 2020. https://doi.org/10.2319/033120-236.1 [epub ahead of print, Date Accessed May 16, 2020].
[2] Wang H, Zhang L. Risk of COVID-19 for patients with cancer. Lancet Oncol 2020;21(4):e181. https://doi.org/10.1016/S1470-2045(20)30149-2.
[3] Panesar K, Dodson T, Lynch J, Bryson-Cahn C, Chew L, Dillon J. Evolution of COVID-19 guidelines for university of washington oral and maxillofacial surgery patient care. J Oral Maxillofac Surg 2020. https://doi.org/10.1016/j.joms.2020.04.034 [epub ahead of print, Date Accessed May 16, 2020].
[4] Day AT, Sher DJ, Lee RC, et al. Head and neck oncology during the COVID-19 pandemic: Reconsidering traditional treatment paradigms in light of new surgical and other multi-level risks. Oral Oncol 2020;105:104684. https://doi.org/10.1016/j.oraloncology.2020.104684.
[5] Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA 2020 [epub ahead of print, Accessed on 16 May 2020].
[6] Santiago I. Trends and innovations in biosensors for COVID-19 mass testing. ChemBioChem 2020. https://doi.org/10.1002/cbic.202000250 [epub ahead of print, Accessed on 16 May, 2020].
[7] Cheng MP, Papenburg J, Desjardins M, et al. Diagnostic testing for severe acute respiratory syndrome–related coronavirus-2. Ann Intern Med 2020. https://doi.org/10.7326/M20-1301 [epub ahead of print, Accessed on 16 May, 2020].
[8] Udugama B, Kadhiresan P, Kozlowski HN, et al. Diagnosing COVID-19: the disease and tools for detection. ACS Nano 2020;14(4):3822–35. https://doi.org/10.1021/acsnano.0c02624.
[9] De Virgilio A, Costantino A, Mercante G, Spriano G. How to increase the SARS-CoV-2 detection rate through the nasopharyngeal swab? Oral Oncol 2020;104802. https://doi.org/10.1016/j.oraloncology.2020.104802.
[10] Ren Y, Rasubala L, Malmstrom H, Eliav E. Dental care and oral health under the clouds of COVID-19. J Dent Res 2020. https://doi.org/10.1177/2F2380084420924385 p. 238008442092438 [Date Accessed May 16, 2020].

Anuraj Singh Kochhar[a], Ritasha Bhasin[b], Gulsheen Kaur Kochhar[c], Himanshu Dadlani[d,*]

[a] *Former Consultant Orthodontist, Max Hospital, Gurgaon, India*
[b] *International Dentist Advanced Placement Program, Faculty of Dentistry, University of Toronto, Canada*
[c] *Professor Pediatric & Preventive Dentistry, National Dental College & Hospital, Punjab, India*
[d] *Professor Periodontology, Kalka Dental College & Hospital, Meerut, India*
E-mail addresses: anuraj_kochhar@yahoo.co.in (A.S. Kochhar), ritasha.bhasin@mail.utoronto.ca (R. Bhasin), gulsheenuppal@gmail.com (G.K. Kochhar), himdent@hotmail.com (H. Dadlani).

* Corresponding author.