

Oral cancer management in the SARS-CoV-2 Pandemic—Indian scenario

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ABSTRACT

The global burden of oral cancer rests on India's shoulders. Distant metastasis and extensive loco-regional spread result in a dismal 5-year prognosis. Tobacco chewing is the leading etiological factor. A lack of education among the masses combined with an inundated cancer care system account for high morbidity and mortality rates. The SARS-CoV-2 shows tropism for the oral mucosa. This viral tropism is thought to get augmented in oral cancer because of the upregulation of oral mucosal receptors and enzymes which enhance viral attachment and entry. The COVID-19 disease has caused a heavy blow to the cancer care sector in India because of paucity of COVID-19 centred health care regulations. This review highlights the need for the prompt creation of a national health policy which would prioritize and allow for the resumption of oral onco-surgical in light of COVID-19 pandemic.

Keywords: ACE2, COVID-19, furine, oral cancer

Introduction

Oral cancer constitutes the sixth and third most predominant cancer in Asia and India, respectively.^[1] It is the most prevalent cancer in men and ranks third among women.^[2] The International Agency for Research on Cancer has predicted that India would record 1.7 million cases of oral cancer in 2035.^[3]

Oral Squamous Cell Carcinoma (OSCC) has an extensive loco-regional spread with distant metastasis.^[4-6]

In a developing country like India, a lack of public awareness and poor cancer care facilities results in detection of malignancies at an advanced stage.^[3,7,8]

Background

The etio-pathogenesis of oral cancer can be broadly divided into tobacco habit and non-habit. The tobacco habit associated oral cancer cases represent the disproportionately larger subset.^[9] It is estimated that if existing population growth and smoking trends are maintained, smoker numbers would reach two billion by 2030.^[10] Currently in India, one in 17 males and one in 50 females have a predisposition to succumb to tobacco associated cancers. A recorded 20–40% of the Indian population chew tobacco in combination with condiments such as areca nut, slacked lime, and betel leaves (vernacular term: paan). Eleven percent of the Indian population are known to binge drink alcohol.^[11] The 5-year survival rate of oral cancer in tobacco–alcohol habitués is reduced to 29%.^[12] The non-habit related sub-set of oro-pharyngeal cancers in the country are predominantly attributed to viral infections such as Human Papilloma Virus and Human Immunodeficiency Virus and less commonly to Human Herpes Virus 8, Epstein–Barr Virus, Hepatitis B & C, and Chronic inflammation caused by poor oral hygiene, systemic disease like diabetes mellitus and hypertension also contribute to non-habit associated OSCC.^[11]

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV) caused the coronavirus disease 2019 (COVID-19). The first case of COVID-19 in India was detected in Trissur, Kerala in January 2020.^[13] India has since reported 508,953 cases and 15,685 deaths and ranks among the world's worst affected countries.^[14] The Indian government issued a nationwide lockdown which involved containment strategies to curtail the spread of the virus.^[13] This has resulted in a massive disruption of healthcare system in India. Most elective procedures and outpatient services have been deferred leading to slow down in cancer surgeries. The cancer care sector has had to scale back their services because of rationing of healthcare equipment. Preliminary reports from China stated that COVID-19 positive cancer patients showed poor clinical outcomes.^[15] The SARS-CoV-2 virus is known to have increased cellular tropism for the oral mucosa because of expression of Angiotensin Converting Enzyme 2 (ACE 2) receptors in epithelial cells and the ubiquitous presence of Furine enzyme.^[16]

This review is aimed at highlighting the need for designing and implementing healthcare policies in India that would prioritize oral onco-surgical therapeutics in the wake of the SARS-CoV-2 pandemic.

Pathogenesis and Replication of SARS-CoV-2

In humans, the SARS-CoV-2 virus binds to host ACE 2 receptor via a surface glycoprotein called the Spike (S) protein. The S protein consists of two subunits, S1 (ACE2 binding domain) and S2 (facilitates fusion into host cell via heptads repeats HR1 & HR2). Host cell membrane expressed serine proteases such as Transmembrane protease serine 2 (TMPRSS2) and Cathepsin L prime, the S protein. Co-expressed host enzyme proprotein convertase—Furine—cleaves at the spike protein at the S1/S2 cleavage site. This cleavage allows for the virus to penetrate the host. Two-third of the viral RNA is located in an open reading frame 1a/b (ORF 1a/b). The viral genome is then transcribed and translated within the host cell cytoplasm into two poly proteins (pp1a & pp1ab) which encode a replication transcription complex (RTC). The RTC gets transcribed into 16 non-structural and four main structural proteins—Spike glycoprotein (S), small envelope protein (E), matrix protein (M), and nucleocapsid protein (N). The envelope glycoprotein, nucleocapsid proteins, and the newly formed genomic RNA are assembled in the Endoplasmic Reticulum and Golgi complex to form as viral particles buds. The vesicles containing the virions fuse with host cell membrane and are released into the exterior.^[17-22]

COVID-19 and Oral Cancer: Upregulation of ACE2 Receptors and Furine in Oral Cavity Enhances SARS-CoV-2 Tropism

SARS-CoV-2 was isolated in 91.7% of self-collected saliva samples in infected patients, including those that were asymptomatic, up to 11 days after hospitalization.^[16] The oral cavity expresses ACE 2 receptors in the epithelium of buccal mucosa, tongue, minor salivary gland ducts, gingiva, stromal cells such as

fibroblasts and immune-modulatory cells. The ACE 2 receptor consists of a N terminal and a C terminal domain with a single transmembrane helix and intracellular segment. It is encoded by the ACE 2 gene located on the Xp22 chromosome.^[23,24] ACE 2 is a negative regulator of the Renin-Angiotensin System and converts Angiotensin II to Angiotensin (1-7), an apoptotic and vasodilative heptapeptide.^[25] ACE2 is also involved in innate and adaptive immune response and enhances inflammatory reactions via cytokines IL-1, IL-6, IL-8, and IL-10.^[23]

In tobacco habit associated oral cancer patients, the nicotine compounds upregulate ACE2 receptors in the oral mucosa via the $\alpha 7$ acetylcholine receptors ($\alpha 7$ -nAChR). Increase in ACE2 receptors has been shown to enhance viral gene replication, viral assembly, and entry into host cells via the Ribosomal protein S3 (RPS3) and SRC genes.^[16,23-28]

Furine is also expressed in oral epithelial cells, stromal fibroblasts, and T lymphocytes. Furine gets upregulated in oral cancer and is thought to facilitate tumor formation and progression. The oral epithelial cells acquire a tumorigenic phenotype via Furine mediated activation of growth factor (e.g, vascular endothelial growth factor C), matrix metalloproteinases, and cell adhesion molecules.^[16,29,30] The increased expression of Furine in malignant oral mucosa would increase viral fusion in oral cancer patients infected with SARS-CoV-2. Upregulated ACE 2 and Furine levels in tobacco related oral cancer patients indicate a higher vulnerability to the SARS-CoV-2 virus [Figure 1].^[17-22,31,32]

COVID-19 and Oral Cancer: Immunopathogenesis and Poor Prognosis

A robust and optimal host immune response is vital to prevent immunopathology in SARS-CoV-2 positive patients. Recent studies on COVID-19 disease progression have shown that an exaggerated pro-inflammatory cytokine response is seen in patients with co-morbidities such as hypertension, chronic obstructive pulmonary disease (COPD), diabetes, and coronary heart disease.^[24,33] One study hypothesized that the cytokine driven tissue injury seen in these patients could be because of pyroptosis—an inflammatory form of apoptosis.^[23] The increase in expression of ACE 2 receptors in oral cancer patients could justifiably upregulate T-cell-mediated responses (T-helper-2), cytotoxic reactions, and neutrophil inflammation. The nicotine induced aberrant T-cell cytokine gene expression (i.e, primary and secondary T-cell response) tobacco habitues could worsen inflammation induced damage in malignant oral mucosa infected by the SARS-CoV-2 virus [Figure 2].^[19,31-40]

Recommendations for Easing the Oral Cancer Burden in India during SARS-CoV-2 Pandemic

The SARS-CoV-2 positive cases in India are rising at an alarming rate. Delivery of emergency services and management of case load, especially for those with co-morbidities has taken a

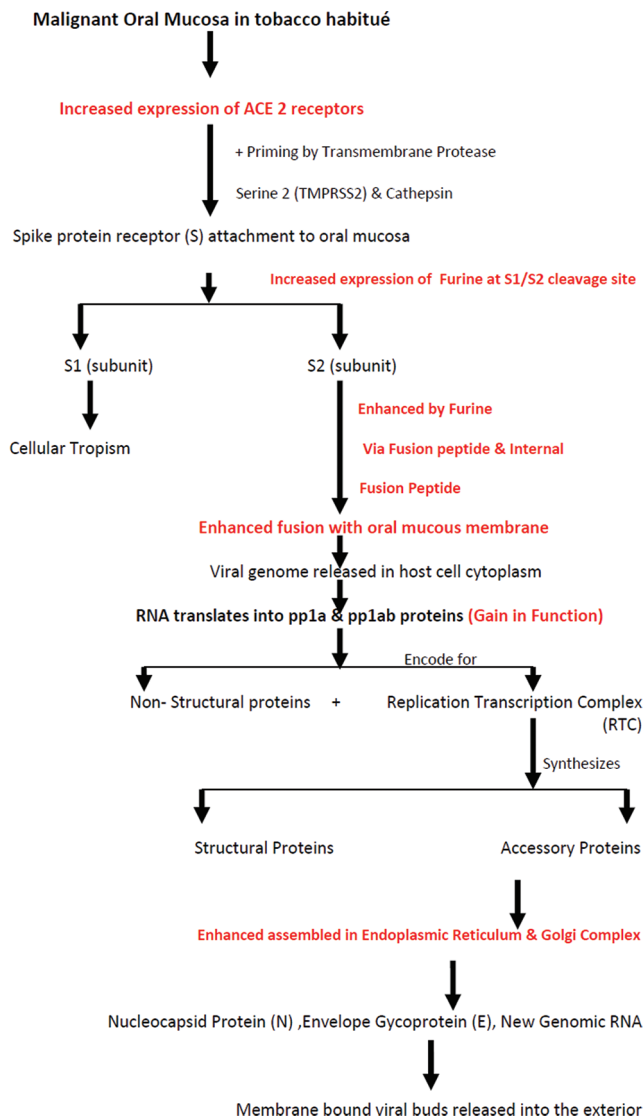


Figure 1: SARS-CoV-2 -Enhanced tropism to malignant oral mucosa in tobacco habitués.^[31]

major toll on the healthcare sector in the country. Healthcare resources (i.e., wards, operating rooms, ventilators) and manpower are being prioritized for SARS-CoV-2 positive patients. Elective surgeries including those for oral cancer have been suspended or delayed indefinitely. India already has a large number of late stage oral cancer cases and a long waiting list for oral cancer surgeries. An indefinite delay in surgical therapeutics would result in a further increase in the oral cancer case load. It could also render these cancer patients inoperable in a short time.^[35,41,42]

The National Health Service (NHS) in the United Kingdom has created “Cancer Hubs” to manage cancer cases amidst the COVID-19 pandemic. These centres solely cater to patients needing surgical intervention via a Tumour Board (a multidisciplinary team).^[41]

This article would like to highlight the utilization of the Indian Public health care system which is organized into a three tier

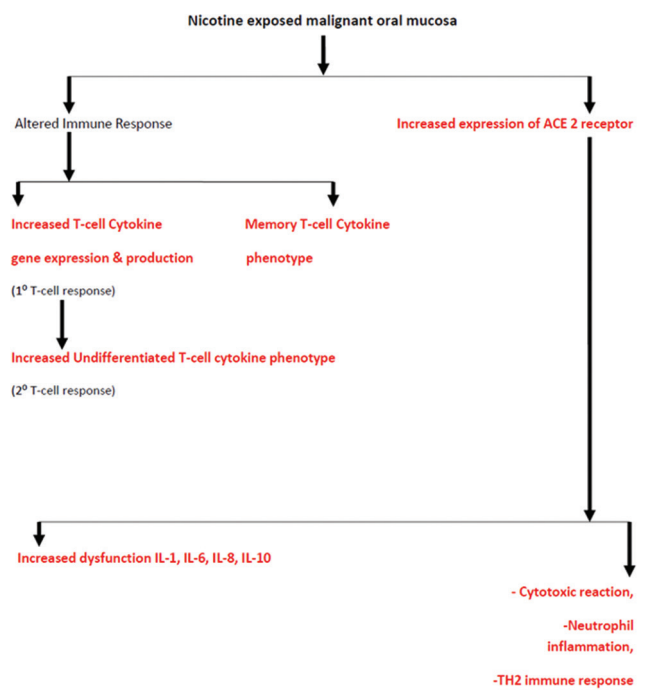


Figure 2: Increased vulnerability to SARS-CoV-2 induced cytokine damage in oral cancer patients due to an altered immune response.^[31]

system—primary, secondary, and tertiary care centres.^[42-45] This system could be mobilized to prioritize oral cancer therapeutics. The Primary Health Care Centres which function at the rural level could be used to identify and prioritize SARS-CoV-2 testing in patients with oral cancer. This would expedite pre-onco-surgical workup. Secondary Health Care Centres, which function at the district level, could prioritize biopsy sample collection to confirm stage and grade of oral cancer [Figure 3].

Primary care physicians are ideally positioned to deliver oral cancer care irrespective of patient’s age or gender because of their accessibility in the community, connections with the family, and personal relationships with patients. They could guide the patients regarding available health services, specialists, resources and also manage comorbid conditions, evaluate/treat depression and manage pain.^[46]

With the current pandemic escalating in India, there is an urgent need to draw-up national guidelines for onco-surgeons. The recommendations given by the Foundation of Head and Neck Oncology (FHNO), a non-government organization, could serve as a template to furnish such guidelines for oral cancer diagnosis, treatment, and follow-up.^[41]

The FHNO guidelines mandate the use of Personal Protective Equipment (PPE) for the surgical team, as onco-surgeries can result in potential aerosolization of viral particles. With India emerging as the second largest global producer of PPEs, supply is adequate. The guidelines take into consideration, the prognosis, age, and co-morbidities of cancer patients awaiting surgery. However, since intensive care facilities and availability

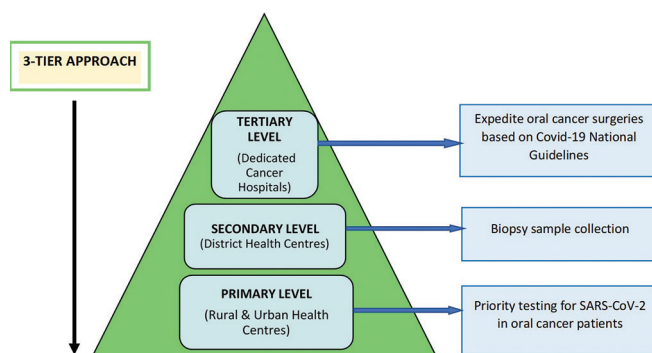


Figure 3: The Public Health care system in India can be mobilized by issuing national guidelines that expedite oral cancer therapeutics

of ventilators in the country are scarce, it becomes imperative for the onco-surgeon to weigh the risk-benefit ratio of surgical and/or adjuvant care for cancer patients. The FHNO also suggest minimizing post-surgical follow-up appointments and encourage the use of tele-consultation for triaging follow-up appointments.^[47]

Conclusion

The tobacco induced subset of oral cancer patients have an increased risk to contract and succumb to COVID-19 because of the upregulation of the ACE-2 receptor and the furine enzyme. These patients also stand the increased risk of an aberrant immune response via nicotine induced T-cell dysfunction. The pandemic driven disruption of treatment facilities for oral cancer and other malignancies is likely to continue for a long time. This necessitates prioritization of oral cancer care by Indian Public Health sector along with active involvement of Primary Care Physicians. Implementation of unified guidelines based on co-ordinated three-pronged approach which includes prevention/education, service delivery and research should be undertaken at primary, secondary and tertiary health care level across the country

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Conflicts of interest

There are no conflicts of interest.

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