


Status and Determinants of Early Detection of Oral Premalignant and Malignant Lesions in India

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Abstract

It has been over four decades since the launch of the National Cancer Control Programme in India, yet the cancer screening rates for oral cancer remain unremarkable. Moreover, India is bracing a large burden of oral cancer with poor survival rates. An effective public health programme implementation relies on a multitude of factors related to cost-effective evidence-based interventions, the healthcare delivery system, public health human resource management, community behaviour, partnership with stakeholders, identifying opportunities and political commitment. In this context, we discuss the various challenges in the early detection of oral premalignant and malignant lesions and potential solutions.

Keywords

cancer screening, oral cancer, mobile health, smokeless tobacco, health resources, community health workers, point-of-care

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Introduction

Oral cancer is the commonest cancer and cause of cancer-related death in Indian men.^{1–3} This high burden is predominantly due to the unabated use of smokeless tobacco (SLT) and areca nut in most parts of India.⁴ The Kerala Oral Cancer Screening Trial (KOCST) revealed a significant reduction in mortality (81%) and incidence (38%), respectively, of oral cancer following four rounds of screening through oral visual examination (OVE) by community health workers (CHWs) in the high-risk population and demonstrated cost-effectiveness.⁵ The operational framework launched by the Government of India (GOI) in 2016 under the National Program for Prevention and control of Cardiovascular, Diabetes, Cancer and Stroke (NPCDCS) envisioned 5-yearly OVE for adults aged 30–65 years.⁶

Even though the guidelines were formulated two decades ago, only 1.2% of men and 0.9% of women had ever undergone oral cancer screening (National Family Health Survey, NFHS-5).⁷ Still, about two-thirds of head and neck cancer

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patients are diagnosed at advanced stages, with poor 5-year survival rates.^{2,8} India spent \$3,01 851 on oral cancer in 2020; and will cost \$3 billion over 10 years.⁹ An annual savings of \$30 million might be realized if early detection and prevention reduced advanced disease by 20%.⁹

Through this review, we explored various challenges in the early detection of oral premalignant and malignant lesions in the Indian context and their potential solutions.

Oral Cancer Strategy in India: Current Scenario

The GOI has established Health and Wellness Centre (HWC) under the Ayushman Bharat Programme (2018) to screen for oral, breast, and cervical cancers, provide basic oral health care, referral, and follow-up for a community of up to 30 000 people.¹⁰ The accredited social health activist will educate community about cancer prevention, tobacco cessation, oral health, and screen adults aged 30 and older for tobacco use and symptoms using the community-based assessment checklist (CBAC).¹¹ The screened-positive individuals are referred to the HWC, where trained community health officer will screen by OVE and refer the patients with potentially malignant oral lesions to the primary or secondary level health centres (primary health centre/community health centre/district hospital) and follow-up as per the operational guidelines.^{6,12} By June 2021, 76 877 HWCs were established and 57.86 million people were screened for oral cancer at these HWCs.¹⁰ Oral screening will be combined with systemic physical examination during routine health check-ups at all HWCs and individuals aged 18-29 years old will be screened opportunistically. A dental surgeon/general surgeon/ENT specialist/Medical officer stationed at a primary or secondary health centres will also screen for potentially malignant oral lesions and refer patients for oral cancer treatment. Additionally, the dental surgeon will provide preventive, surgical and maxillofacial rehabilitative services in the form of education for oral hygiene and periodontal diseases, screening for non-conical diseases like gingivitis, periodontitis, malocclusion etc. with referral and management. The clinically diagnosed oral cancers will be referred to tertiary cancer centres or medical colleges for treatment, while suspicious lesions can be biopsied at the primary and secondary centres for histopathology. Dysplastic lesions that require surgery will be referred to tertiary hospitals and other lesions will be followed and counselled for tobacco cessation. All health centres will work in convergence with resources from the National Oral Health Program, National Tobacco Control Program and NPCDCS.^{6,12} Through the National Programme for Palliative Care, the GOI envisages a similar algorithm for provision of palliative care.¹³

Challenges in the Community

Socio-Demographic Factors

A recent secondary analysis of the nationally representative population survey for Indian women found several

socio-demographic and geographical characteristics related with cancer screening coverage. Oral cancer screening was positively associated with women's age, education, employment, health insurance, media use (radio and television), wealth quintiles, urban residence, and household headship.¹⁴ Epidemiological studies from the United States have revealed racial and ethnic disparities in cancer screening service utilization, with certain races having lower screening rates and a significantly higher burden of oral cancer cases and associated mortality.¹⁵ Geographic demarcation in the form of regions (North, South, Central, East, and Northeast) can serve as a proxy for ethnographic determinants for cancer screening in India, which has over fifty ethnic groups¹⁶ with a diverse distribution. A recent geospatial study found dense clustering for cancer screening among women in selected districts from southern (Kerala), central (Maharashtra, Madhya Pradesh), northern (Jammu and Kashmir, Punjab, and Uttar Pradesh), eastern (West Bengal), and north-eastern regions (Assam).¹⁷

Rural cancer screening is impeded by several factors. Poor cancer awareness, self-neglect and late presentation, poor health literacy, a lack of appropriate health infrastructure for early detection of oral lesions, the prevalence of alternative systems and unlicensed practitioners, tobacco and alcohol use, poor socioeconomic status combined with a lack of health insurance, social stigma, distance and transportation issues, and poor referral pathways all hamper early detection.¹⁸ With OVE as a screening measure for oral cancer, the operational framework is designed for low-resource settings with an aim to decentralise healthcare services and reach all ethnic groups and marginalized populations.⁶

Poorly Understood Natural History of Oral Lesions and Their Risk Factors

CHWs struggle to motivate the population for screening due to poorly understood natural history of oral premalignant disorders (OPMD) and cancer.¹⁹ OPMD are chronic by nature and the reported malignant transformation rate is 7.9%, over 12 months to 20 years.²⁰ Without symptoms, the community avoids screening and is in the notion that these oral lesions are benign.¹⁹

According to the International Agency for Cancer Research (IARC), tobacco smoking, SLT use, and areca nut products chewing are leading drivers for oral cancer, especially in south and south-east Asia.²¹ A meta-analysis of 17 case-control studies on smoking cessation found a 35% risk reduction in the risk of oral cancer within the first four years of cessation and a risk reduction to that of non-smokers after 20 years.²² A recent meta-analysis of 14 studies (case-control and cohort) showed a 28.9% risk reduction for oral cancer among former areca nut (without tobacco) users and significant risk reversal for oral cancer with long-term areca nut and tobacco cessation.²³ A recent evaluation of the body of evidence by the IARC working group found that there was sufficient evidence for oral cancer

prevention through cessation of tobacco smoking and areca nut chewing (with or without SLT).²¹

Extensive health education on the hazards of tobacco has been conducted across India, however, there is a lack of awareness of other risk factors like alcohol,^{24,25} poor oral hygiene,²⁶ micronutrient deficiencies,²⁵ chronic inflammation due to trauma from teeth and prosthetic devices,²⁷ high-risk oncogenic HPV infection,²⁸ alteration of the microbiome²⁹ and certain syndromes³⁰ that can accelerate transformation. Studies are exploring the effect of oral microbiome in oral mucosal immunity and in protection or facilitation of viral and bacterial infections which may subsequently prevent or enhance the periodontal diseases. It is important that oral cancer screening should be in conjunction with other oral screening parameters.³¹ Most Indian rural women apply tobacco paste to their teeth and gums to ease the pain.³² Highly addictive areca nut is widely used in the rural community due to its cultural acceptance.³³ Poor health literacy impedes understanding of the information provided by healthcare providers.³⁴ Research to identify gaps in awareness followed by context-specific health education interventions will improve cancer literacy.

Resistance to Quitting Risk Factors

Despite the reported decrease in tobacco consumption in Global Adult Tobacco Survey, 38.0% of men and 8.9% of women consume tobacco (NFHS-5, 2019-2021) and about 23.9% of Indians (223.79 million) consume areca nut.^{7,35} The resistance to quitting tobacco stems from several psychosocial and cultural factors. Daily wagers cite tobacco dependence for work efficiency. Urbanization and unregulated media add to peer pressure.³⁵⁻³⁷ Tobacco users undermine the risks associated with tobacco and it is only when the oral lesions lead to symptoms or debilitation that the patients feel the need to quit and seek advice. These factors discourage tobacco users from screening. The IARC working group has concluded that there is sufficient evidence for oral cancer prevention through behavioural interventions for tobacco cessation.²¹

Government Policies for Risk Factor Prevention

The World Health Organization (WHO) has acknowledged India as having the world's largest publicly funded tobacco control programme. Adopted strategies include integration of brief advice on quitting tobacco in primary care, a national toll-free quitline, a joint framework for TB-tobacco activities, the establishment of Southeast Asia's first-of-its-kind tobacco testing laboratory, and the mTobacco cessation programme which has 2.1 million self-registered users. Six months after enrolment, the average quit rate for both smokers and SLT users was 7%. The Global Adult and Youth Tobacco Surveys provide comprehensive tobacco surveillance. Between 2009 and 2016, these strategies cut adult cigarette consumption by 17%.^{38,39}

24 states and 3 union territories banned gutkha (SLT) by May 2013.⁴⁰ However, it is inconsistently enforced. A Mumbai study found that marketers circumvent legislation through twin packaging, flavouring tobacco, and areca nut. Loopholes in legislation related to manufacturing and sales need attention. Citizens and organizations that report such violations should be rewarded.⁴¹

Alcohol and poor oral hygiene act synergistically with tobacco in the malignant transformation of OPMD.⁴² National Oral Health Policy (2021 framework) envisions preventive oral health services at each HWC by 2025 and curative services by 2030. The policy proposes working synergistically with non-communicable disease control programmes and utilize low-cost oral hygiene aids.⁴³ India's alcohol control regulations and programmes are inconsistent and poorly executed. As of 2020, alcohol is fully prohibited in six states/UTs.⁴⁴ The remaining states/UTs have different legal drinking ages, district-wide prohibitions, or have temporarily banned alcohol. Pricing and taxation are revenue-driven. Alcohol advertising strategies must be regulated and monitoring of alcohol consumption must be strengthened.^{44,45}

Fear of Cancer Diagnosis

Cancer has deep-seated fears.⁴⁶ Following the screening, there is poor compliance for biopsies due to the apprehension of invasive procedures such as the unpleasant connotation of "biopsy" and its association with life-threatening disorders, notably cancer.⁴⁷ Cancer fatalism decreases optimism towards early diagnosis and symptom-seeking. Patients feel powerless over the events due to lengthy treatments and debilitation.⁴⁶ Patients from Punjab believed they would die due to their condition.⁴⁸ These negative perceptions discourage screening. Including oral cancer survivors and self-help groups in cancer awareness can help to alleviate cancer-related fears.

Financial Outcomes

In India, out-of-pocket expenses go hand in hand with direct treatment costs. Patients with health insurance are thought to be immune to the cost of care, yet they confront challenges. 64% of Karnataka households were unaware of health insurance schemes, and only 25% used them.⁴⁹ Complex processes, limited coverage, and lack of empanelled hospitals are other hurdles. Most insurance policies do not cover total treatment costs, locking a substantial number of patients in an endless cycle of debt. Disability-related job loss causes financial dependence.⁵⁰ The COVID-19 pandemic has exacerbated financial obstacles.⁵¹

The Free Diagnostics Service Initiative of the National Health Mission will lower the cost of diagnostics, which will benefit disadvantaged communities.⁵² Ayushman Bharat (Pradhan Mantri Jan Arogya Yojna) was launched as a step toward universal health coverage and financial protection by going cashless at the point of care for secondary and tertiary

care levels and providing affordable cancer medication through AMRIT (Affordable Medicines and Reliable Implants for Treatment) pharmacies.^{10,53} Appropriate utilisation of the allocated government budget along with corporate social responsibility funds will support screening programmes, research, and treatment.

Challenges in the Health System

Manpower Deficit

India faces a dearth of trained health workers and overburdened resources. The COVID-19 pandemic diverted health resources, including CHW, further denting screening services. The current doctor-to-patient ratio for cancer care in India is 1:2000 compared to 1:1000 which is the minimal threshold advised by WHO.^{54,55} There are limited standardized laboratories and cancer treatment centres, especially in remote areas. Tertiary Care Cancer Centres (TCCC) scheme aims to establish 20 State Cancer Institutes (SCI) and 50 TCCCs with grants of \$ 1,522,39,928 for each SCI and \$ 57,14,973 for each TCCC.⁵⁶ Recently, GOI established seven TCCCs and authorized seven more for north-eastern states that report highest cancer incidence (150-200 cases per 100 000 persons).^{2,57}

Dentists, who are the first point of contact for patients with oral complaints, are hesitant to undertake biopsies for reasons such as notion that biopsy is a specialist procedure, methodological ambiguity, lack of training, and medico-legal consequences.⁵⁸ Inconclusive biopsies cause a dilemma and loss of follow-up. These barriers cause disruption in cancer care continuum. Recent indigenous low-cost innovations such as point-of-care diagnosis layered with artificial intelligence and machine learning are emerging adjunct techniques to improve OPMD detection and biopsy.⁵⁹ The Indian Council of Medical Research provides early detection training for dentist; more platforms are needed for standardized training.

The KOCST is the only trial that employed mortality reduction as the primary outcome measure, a necessity for assessing impact of screening programme. In the latest reanalysis, researchers provided proof of principle that risk-based oral cancer screening will strengthen screening programmes through judicious use of scarce resources.⁶⁰ CBAC forms filled out by CHWs will help in identifying high-risk populations and baseline information to assess screening interventions.

Challenges Faced by Community Health Workers

CHWs cite poor incentives, supervisor issues, multiple tasks, and community rumours as challenges. Community members refuse screening due to difficult hospital appointments, transportation costs, and income loss.¹⁹ CHWs require

periodic training and a threshold for their competency and knowledge retention should be determined through their learning curves along with regular monitoring.

Studies in low-resource settings have demonstrated mHealth's value in real-time task-sifting for oral cancer screening, especially in remote communities. A multicentric prospective study reported high accuracy for teliagnosis employing an automated mHealth-enabled, dual-image device as a point-of-care triaging tool in comparison with onsite specialists (sensitivity:95%; specificity:84%), which will empower CHWs for defining OPMD.⁵⁹ A previous study has reported enhanced compliance with workplace screening by mobile health.⁶¹ Multi-centric study from Tamil Nadu reported that mobile technology was user-friendly, inspires CHW confidence, and decreases paper-based system time, resources, and maintenance.⁶² The most effective mHealth interventions are in settings where diagnostic and treatment pathways are already established.

However, mHealth study from Tamil Nadu reported that only 30.8% of screened-positive patients attended follow-up and didn't improve screening coverage.⁶² Poor network coverage, remote specialist availability, turn-around time for reporting, large data storage for image capturing to map the entire oral cavity, and on-site infrastructure maintenance are practical concerns. Data protection and security is essential and India follows gold-standard norms. Data storage can be reduced by taking images of the suspicious site and an apparently normal-looking site. Advancements enabling onsite cytology, biopsy, and telephonic reporting can be potential solutions.

Screening Accuracy

In the Kerala and Karnataka studies, screening by trained CHWs reported moderate sensitivity for detecting OPMD and oral cancer (67.4% and 60%, respectively).^{5,59} Misclassification in OVE is common due to heterogeneity of oral mucosal lesions. Presence of oral epithelial dysplasia is the most important risk factor for malignant transformation and can be classified as "high-risk" (moderate-18%; severe-39%), and "low-risk" (mild-6%).^{63,64} However, incisional biopsy is not feasible in large-scale, high-risk populations. Hence, optical-based adjuncts, vital staining, molecular markers, and cytopathologic platforms as point-of-care tests can enhance screening efficiency by aiding decisions about biopsy requirements and reducing hospital referrals.^{29,59,65-75} (Table 1)

Poor Referral

The GOI has clearly defined referral pathways for screened patients, yet they are poorly executed, resulting in 60-80% of patients seeking first care in private settings.⁷⁶ Poor access to government hospitals also hampers diagnosis and treatment. Current OPMD therapies also lack agreement. Patient navigation programmes help improve referrals. Health and

Table 1. Point of Care Diagnostics for Oral Cancer.

Name of the Diagnostics	Mechanism of Action	Strengths	Weakness
Optical imaging			
Auto-Fluorescence Imaging (AFI)	Detects the endogenous fluorophores (NADH, FAD, Collagen Matrix, and elastin), metabolic and morphologic changes related to carcinogenesis	Non-invasive, practical, cost-effective, high sensitivity (96%)	Low specificity (58%), false positivity in rich microvascularity (inflammation), false negativity in hyperkeratosis
Narrow Band imaging (NBI)	An endoscopic imaging visualizing neo- angiogenesis pattern in tissue using illumination light within the absorption spectrum of hemoglobin	Non-invasive, high accuracy in detecting oral cancer (sensitivity; 90-97%, specificity; 82-88%)	Lower sensitivity for dysplastic lesions (31%), false positivity, subjective pattern interpretation, commercialization pending
Diffuse Reflectance Spectroscopy (DRS)	Capacity of diffuse reflectance spectral data to discriminate normal tissue from pre-malignant and cancerous tissue	Non-invasive, high accuracy in detecting oral cancer (sensitivity; 98.6%, specificity; 83.2%) and dysplasia (sensitivity; 79%, specificity; 86%)	Longer acquisition times owing to limitation in scanning speed, commercialization pending
High Resolution Microendoscopy (HRME)	Visualization of light emitted by superficially applied fluorophores utilising a fiber-optic probe in direct contact with suspected tissue	Non-invasive, High accuracy in detecting oral cancer (sensitivity; 84%, specificity; 71%)	Low sensitivity in case of mild dysplasia (65%), commercialization pending, limited field review
Raman Spectroscopy (RS)	Visualization of the 'molecular fingerprint' (ie, variations of chemical components) of a tissue using vibrational spectroscopic technique	Non-invasive, high sensitivity (89%) and specificity (84%)	Dependence on visualization of morphological or structural lesions, commercialization pending, too large for routine clinics, time consuming
Vital staining			
Toluidine blue staining	Conventional tissue staining technique that stains dysplastic or cancerous cells with an increased or abnormal DNA content	High sensitivity (92.6%)	Low specificity (67.9%)
Lugol's iodine staining	Conventional tissue staining technique that results in no or pale staining for dysplastic or cancerous lesion, while the surrounding normal tissue appears brown in colour	Useful when selecting target sites for biopsy prior to treatment when there is a wide field of lesions	The stain is not picked up by orthokeratinized epithelium of hard palate
Oral cytology			
Exfoliative cytology	Collecting cells from oral mucosa by scrapping, brushing, or rinsing using a tongue blade or brush	Less invasive, highest accuracy among adjuncts (sensitivity, 92% and specificity 94%)	High false positive rates, delayed reporting, time consuming, costly
The oral brush biopsy	Minimally invasive brush biopsy coupled with an artificial intelligence aided tissue analysis	Less invasive, higher sensitivity (55-100%)	Lower specificity (23.5-100%) Delayed reporting, time consuming, costly
Biomarkers			
DNA methylation biomarkers	Measuring the methylation status of PAX1 and ZNF582 enables the detection of oral precancerous lesions and oral malignancies	Sensitivity and specificity of PAX1; 72% and 86% for mild dysplasia and ZNF582 methylation; 85%, 87% for moderate dysplasia respectively	Clinical translation is lengthy and expensive, not cost-effective, lacking lab facilities
miRNA biomarkers	miR-21, miR-155, miR-191 and miR-221 overexpression enables detection of oral carcinogenesis	High screening accuracy (about 92%)	Presently not cost-effective and lacking lab facilities. Ongoing research to expand as low cost PoC
mRNA biomarkers	mRNA biomarkers such as OAZ1, SAT and DUSP1 have increased expression levels in cancerous tissues	High sensitivity (92%) and specificity (86%)	Limited research for reliability and validity, not cost-effective, lacking lab facilities
Protein biomarkers	CD44 is a tumor-initiating biomarker and its overexpression is found in many malignancies, including oral cancer	High sensitivity (ranging from 71% to 84%)	Low specificity (ranging from 30% to 50%), not cost-effective, lacking lab facilities

wellness centres at the district and block levels will improve screening reach. National Cancer Grid can be instrumental in standardising guidelines for OPMD management.⁷⁷

Opportunities for Early Detection

Opportunistic Screening

Non-tobacco oral malignancies, especially tongue cancers in women, are emerging. The most prevalent HPV subtypes reported in head and neck malignancy studies from India are 16 and 18.⁷⁸ Wide variations in HPV prevalence in head and neck cancer tissues have been observed with higher prevalence in southern region (Trivandrum; 74%,⁷⁹ Dharwad;⁸⁰ 70.6%, Chennai;⁸¹ 51.9%), followed by eastern region (Kolkata;⁸² 69%, Cuttack;⁸³ 33.6%), northern region (Prayagraj;⁸⁴ 32%, New Delhi;^{28,85} 23-28%), north-eastern region (Guwahati;⁸⁶ 31.1%), central region (Sevagram;⁸⁷ 27.7%), western region (Mumbai;⁸⁸ 27.2%). Oropharyngeal cancers caused by HPV 16 and 18 are aggressive.⁸⁹ HIV and HPV have similar modes of sexual transmission. Therefore, integrated testing and anti-retroviral treatment centres (ICTC/ART) are important oral cancer screening opportunities.^{90,91} The health care providers trained for both the periodontal assessment for non-canonical pathologies and oral cancer screening along with appropriate referral and management will improve the screening coverage and outcomes.

Oral Potentially Malignant Disorders Registry

In India, the prevalence of OPMD ranged from 2.79 to 51.21%, and leukoplakia attributed to 17-35% of oral malignancies.⁹² The National Cancer Registry Program (NCRP; 1981) under the auspices of the Indian Council of Medical Research (ICMR), has 236 hospital-based cancer registries (HBCR) and 36 population-based cancer registries (PBCR). However, the PBCR coverage is only 10% (just .1% in the rural population).⁹³ NCRP Report (2020) recommends linking cancer registries to Ayushman Bharat, other insurance schemes, mortality databases, and health management information systems at the national and local levels to improve cancer statistics and surveillance.^{2,94} However, they need to be standardized following the national digital health blueprint to make them integrated and interoperable.⁹⁵ These registries can be a critical part of the surveillance strategy for identifying OPMD malignant transformation and early detection of oral cancer.

Learning From Other Countries

Taiwan is the only country with a nationwide high-risk cancer screening programme⁹⁵ while Spain is educating its workforce on oral cancer screening.⁵⁴ Japan has integrated cancer screening into general health screening.⁹⁶ Thailand is the first Asian country to introduce plain packaging, ban single-cigarette sales, and impose heavy taxation.⁹⁷ Adopting these strategies in India

can improve the early detection of oral cancer and risk factor prevention.

Conclusion

India's lagging oral cancer detection requires a multipronged solution. Improving health literacy will increase community cancer screening self-efficacy. Developing a high-risk tobacco user prediction model for preferential screening, using mobile technology and point-of-care techniques, high-grade OPMD surveillance, deploying mobile screening units to villages, integrating oral cancer screening into general health care, conducting opportunistic screening at strategic high-risk sites like workplaces and de-addiction centres, and strengthening education for oral cancer detection for all caregivers through a standardised e-learning platform will boost early detection. Empowering communities through active involvement, health autonomy, supportive supervision, and remuneration is critical to a sustainable screening programme.

Appendix

Abbreviations

OVE	Oral Visual Examination
SLT	Smoke-Less Tobacco
KOCST	Kerala Oral Cancer Screening Trial
CHWs	Community Health Workers
SCI	State Cancer Institutes
UTs	Union Territories
TCCC	Tertiary Care Cancer Centres
CBAC	Community-Based Assessment Checklist
GOI	Government Of India
WHO	World Health Organization
NFHS-5	National Family Health Survey-5
OPMD	Oral Pre-Malignant Disorders
HPV	Human Papillomavirus
HIV	Human Immunodeficiency Virus
ICTC/ART	Integrated Counselling and Testing Centre/ Anti-Retroviral Treatment

Author's Note

All authors declare that they have read the manuscript and believe that the manuscript represents honest work.

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