Oral cavity cancer screening and early detection in rural India

SB Sutcliffe, Two Worlds Cancer Collaboration Foundation, Kelowna, BC, Canada; **SS Broughton,** Two Worlds Cancer Collaboration Foundation, Kelowna, BC, Canada and Faculty of Health and Social Development University of British Columbia, Okanagan, Canada; **M Datta,** Faculty of Dentistry, University of British Columbia, Vancouver, Canada; **CSK Chaitanya Nallan,** Panineeya Institute of Dental Sciences, Hyderabad, India; **NDVN Shyam,** Government Dental College, Osmania University, Hyderabad, India; **P Kumari,** Department of Zoology, Nizam's College, Hyderabad, India; **JJ Mathews,** MNJ Institute of Oncology & Regional Cancer Centre, Hyderabad, India and Division of Palliative Medicine, Departments of Medicine and Oncology, Queen's University, Kingston, Ontario, Canada; **SM Wai,** Two Worlds Cancer Collaboration Foundation, Kelowna, BC, Canada; **JN Jagannath,** MNJ Institute of Oncology & Regional Cancer Centre, Hyderabad, India; **V Rapelli,** MNJ Institute of Oncology & Regional Cancer Centre, Hyderabad, India; **S Kumari,** MNJ Institute of Oncology & Regional Cancer Centre, Hyderabad, India; **G Palat,** MNJ Institute of Oncology & Regional Cancer Centre, Hyderabad, India; and **DM Laronde,** Faculty of Dentistry, University of British Columbia, Vancouver, Canada and Cancer Control Research, BC Cancer, Vancouver, Canada

An opportunity to apply novel technologies and expertise led to a regulatory board approved study of oral cancer in rural India where, compared to high-resource countries, oral cancer is more common, usually clinically advanced and symptomatic, challenging to palliate effectively, and associated with stigma, isolation, pain, distress and financial compromise in lesser-resourced settings, but is potentially curable if detected early.

Implementation of a screening and early detection programme requires understanding, mutual respect and trust between collaborators and institutional/organizational partners. The protection of participants in research, compliance with local and international human ethics board standards, and attention to rigorous conduct of research according to approved protocol requires interpretation, adaptation and contextualization consistent with clinical research in rural, community-based settings in low- and middle-income countries.

Oral cancer is the second most common cancer in India, impacting both sexes, with over 135,000 new cases and 75,000 deaths reported annually *(1)*, accounting for almost 30% of India's cancer burden *(2)*. Squamous cell carcinomas are most common, arising through stages of potentially malignant conditions ranging from hyperplasia to severe dysplasia *(3)*.

Mortality rates are high primarily due to delayed diagnosis and advanced stage at diagnosis *(4)*. The 5-year survival rate for early oral cancers is 60%, compared with 3% for advanced and/or metastatic disease *(5)*. The burden of oral cancer reflects reduced access to health-care resources and services due to cost, distance and time/opportunity; adverse social determinants of health; and higher exposure to risk factors such as smoked and smokeless tobacco use with betel quid, areca nut, alcohol and limited oral hygiene *(6-8)*.

Human papillomavirus (HPV) associated head and neck squamous cell cancers (HNSCC) whilst increasingly common in high-resource countries, are less so in India. The HPV-associated cancers have a different biology and a better prognosis; however, the impact upon management in India is less clearly defined. Recommendations have been proposed to guide practising oncologists in India when dealing with HPV-associated HNSCC *(9, 10)*.

Early detection of oral cancer offers the best chance for reducing mortality rates and improving treatment outcomes *(11)*. In high-resource countries, where access to dental care is widespread, oral cancer screening is often provided opportunistically in dental offices. Access to dental care in lesser-resourced settings is available to a minority of people *(12)*. Screening for oral cancer is a quick, painless and non-invasive examination to detect suspicious lesions at a time when treatment can reduce mortality. To be useful at a population level, interventions need to be deployed safely in the community, using simple technology, applied by available and appropriately-trained personnel.

Methods

The study represented a collaboration between a government-funded hospital, the MNJ Institute of Oncology & Regional Cancer Centre, the Pain Relief and Palliative Care Society (an NGO in Hyderabad), a government funded Dental College (GDC-Osmania University [GDC]), a private dental research institute (Panineeya Institute for Dental Sciences & Research Centre [PIDS]), the Faculty of Dentistry (UBC), the BC Cancer Research Centre and Two Worlds Cancer Collaboration (TWCC), a Canadian NGO.

The study was conducted in two phases – feasibility (n=114

subjects) and pilot (n=1116 subjects) – in rural, community locations using readily available technologies and minimal reliance on highly-qualified health-care professionals. A one day screening and detection camp established the feasibility and justification for proceeding to a pilot study. In addition to visual and fluorescence examination, conventional cytology and DNA image cytometry (DNA-ICM) of oral lesion brushings were used to identify high-risk lesions in the pilot study *(13,14)*.

Ethics approval was granted by UBC and MNJIO.

Subject enrolment

Male and female participants >19 years were commonly agricultural or unskilled labourers, poor and of low socioeconomic status, commonly illiterate requiring translation of documents, requiring interpreter assistance with comprehension, using surrogates for written signature and dependent upon daily employment for their livelihood i.e., losing income through time off to participate in clinical research whilst asymptomatic and unaware of illness. Awareness, promotion and participation required marching drummers, local community communication, village leader engagement to endorse participation, choice of day(s) for screening, minimizing absence from work, ease of travel and encouragement of compliance (facility, shade, privacy, toilets, hospitality) and navigation through the entire screening process.

Inclusion and exclusion criteria

Subjects were eligible for screening if 18 years or older (no upper limit) and able to understand and willing to sign a written informed consent form. Subjects were excluded if under 18 years of age, unwilling to provide consent, had a prior history of oral cavity cancer, or concomitant physical or mental disability precluding ability to comply with study protocol requirements.

Of the 1116 enrolees in the pilot study, the mean age was 47.98 ± 16.3 years (range 18–90), 46% were male, 24% were farmers, 25% were labourers, and the median annual income was 60,000 rupees (~US$ 725).

Site selection and facilities

For the feasibility study, a rural community school 50 kms from Hyderabad, was identified. Infrastructure upgrades – installation of secure, safe electricity supply, furniture, ambience (Figure 1), painting (Figure 2) and toilet facilities – were funded by TWCC.

For the pilot study, screening sites with existing basic infrastructure resulted in selection of local community health clinics in six villages around Hyderabad.

Training of investigators and volunteers

Forty-two personnel – clinicians, non-clinicians and volunteers – conducted the project. Three separate on-site workshops provided orientation to clinicians from PIDS and GDC and volunteers from Nizam College to the study protocol and data collection tools, emphasizing a sequential process recording demographics, medical history, risk factors, results of extraoral, intraoral white light and blue light (FV) examinations, and mucosal brushings for DNA analysis. Teaching sessions were followed by "hands-on" clinical sessions practising oral screening on each other using white-light, FV and mucosal brushing.

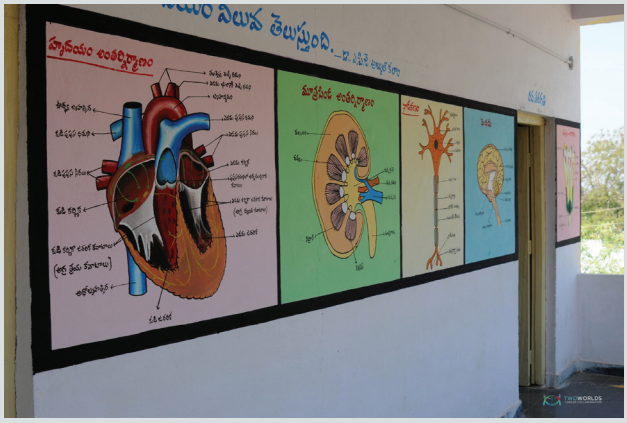
The coordination and management of personnel, with the assignment of activities to the appropriate levels of skill, maximized the efficient use of resources, both human and financial – social workers raised awareness of the upcoming screening camp in the villages, undergraduate students conducted registration and demographic data collection, dental students conducted the physical and oral examinations, dental specialists supervised examinations, clarified interpretations and conducted biopsies, and clinical supervisors oversaw the completion of all processes.

Study protocol

Prior to this study there was a limited familiarity with protocol-based, ethics-approved, clinical investigative research. The

Figure 1: Facility ambience following painting and facility upgrades

Figure 2: Decoration to enhance educational facility ambience



study protocol was developed iteratively over an 18-month period, incorporating current knowledge and practice as adapted to the context of a rural setting in India. Challenges included the rigorous adherence to the protocol to ensure standardized, quality interventions, language difficulties despite common use of English language, differences in dental techniques and infection control practices. Despite preferred local familiarity with phone cameras, the need for security of images necessitated training with study point-and-shoot cameras. The need for valid, credible and publishable results was emphasized with respect to policy formulation regarding population-based screening and early detection.

Risk assessment and examination forms to collect demographic and clinical data were adapted from previous Canadian screening studies and modified to incorporate local practices.

Screening camp process

Equipment and supplies (Figure 3) for screening were transported and set up at the venue on the day of the screening camp. Informed consent, demographic and risk habit information (risk assessment) were obtained at the registration desk (Figure 4) before participant being escorted into screening station rooms by volunteers. Individuals with a prior history of oral cancer or concomitant physical or mental disability precluding compliance with the study protocol were screened but excluded from the study. Team leaders ensured all screeners followed a systematic approach and filled out the risk assessment form completely.

Equipment and procedures

VELscopes were donated by LED Dental, Inc., and BC Cancer Research Centre (Cancer Imaging), shipped by air and, despite preparatory communications held with Indian Customs in Hyderabad, were released only after communications between senior Indian government officials and OCC project members, along with the payment of excise taxes.

DNA-ICM analysis was performed on specimens obtained with a cytology brush. The brush specimen was placed in a cell preservative vial, with vials from each screening day packaged and transported to the laboratory in Pune, India, for cytology and DNA-ICM assessment. Ideally, a training set of samples would have been available to the BCCRC research lab for comparative analysis and teaching, but support for samples leaving India was denied by the Indian Ethics Review Board.

Subject examination

Extraoral examination included inspection and palpation of the head and neck region for asymmetries, swellings, tenderness or skin lesions. Lymph nodes were assessed for size, mobility, texture and tenderness (Figure 5). Intraoral examination for the presence of lesions was by white light from handheld torches or headlamps (Figure 6). The margins, colour, appearance, texture, size and site of all detected lesions were documented, including colour digital photography (Figure 7).

Lesions were designated as high-risk and low-risk categories based on clinical diagnosis. Low-risk lesions included easily identifiable lesions such as candidiasis, geographic tongue and lesions known to be due to trauma. High-risk lesions included non-healing ulcers, red and white lesions with no known cause and lichen planus. Participants with lesions highly suspicious

Figure 3: Equipment and supplies provisions for screening facility

Figure 4: Registration of subjects by professional staff and volunteers

Figure 5: Extra-oral exam

Figure 6: **Intra-oral white light exam by flash-light**

Figure 7: **Digital photography of oral lesion(s)**

Figure 8: **Intra-oral FV examination using a VELScope**

Figure 9: **Photography of FV lesions with camera over the VELScope**

Figure 10: **Completion of Risk Assessment Form**

for cancer were reviewed by the oral medicine specialist (NC) and referred for biopsy.

Biopsies were performed under local anesthesia by scalpel or 4 to 5mm punch, with bleeding controlled using silver nitrate sticks. Specimens were placed in 10% formalin and transferred after every camp to GDC for pathology evaluation.

All participants irrespective of lesion presence received an FV exam in a darkened room (Figure 8). Areas retaining the normal apple green fluorescence were called FV negative (FV) while tissue that showed a loss of autofluorescence were categorized as FV positive (FV+). FV images were obtained using a digital camera with a filter, fitted over the VELscope (Figure 9). FV results, particularly FV+, were confirmed by study PIs to facilitate learning. Examination results were documented on the participants risk assessment form (Figure 10)

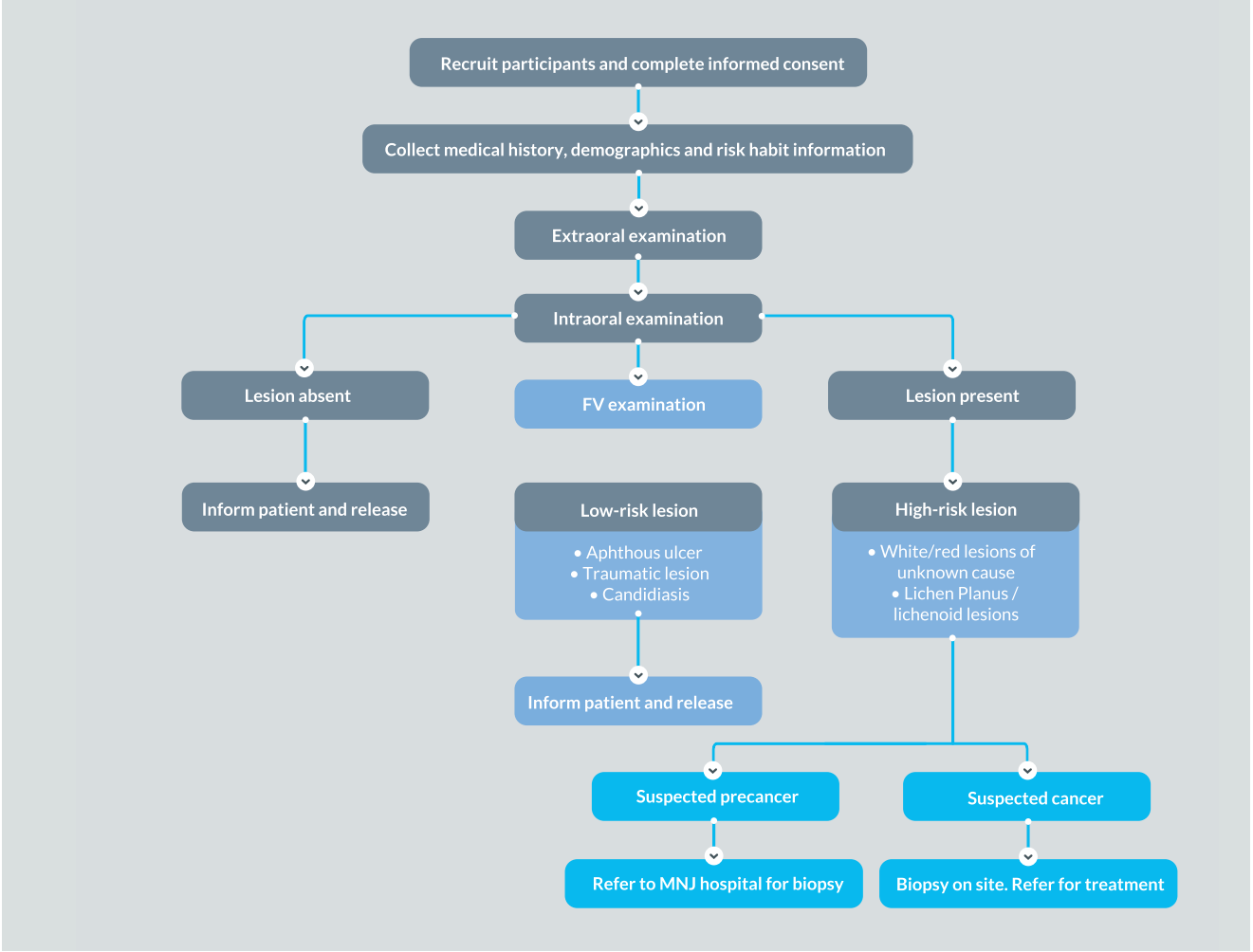
For each participant, oral brushings were collected from both lesion and non-lesion sites. DNA-ICM measured the presence of cells with abnormal DNA content (aneuploidy) or increased proliferating cells, which has shown to be associated with high-risk oral premalignant lesions (OPMLs) and oral cancers *(13,14)*. Incorrect/duplicate barcodes emphasized the need to double check the labelling on brushing vials and data entry. Cleaning of the DNA-ICM scans to distinguish debris or overlapping cells mimicking aneuploid cells was necessary for cytometry interpretation, requiring all abnormal cytometry results to be reassessed by a proficient, fully trained cytotechnician.

The screening protocol flowchart is shown in Figure 11.

Data acquisition, management and statistical considerations

Risk assessment form data was entered by study team members, initially in Excel (Figure 10), but subsequently using REDCap electronic data capture tools hosted at UBC to

Figure 11: Oral cavity cancer screening and early detection protocol flow chart



reduce data entry inaccuracies. Biopsy reports were uploaded on a secure cloud-based server hosted at the BC Cancer. Data analyses were done using the SPSS Version Software 27 (SPSS, Inc.) To determine the effectiveness of FV and DNA-ICM as adjunct screening tools, sensitivity and specificity analysis was done with histopathological diagnosis as the gold standard. For practical and ethical reasons, true sensitivity and specificity could not be determined as histopathology was not available for all participants.

Figure 12: Ceremony, recognition and team-building with local chiefs and community leaders

Results of the screening and early detection study

Results presented here are based upon 18 months of internet-based education and protocol development, a one day on-site study to establish feasibility (n= 114), a two month community pilot study (n=1116) and the shared analysis and interpretation of the findings.

Visual examination with white light revealed intra-oral lesions in 13.5% of subjects in the pilot study, and 13% in the feasibility study, Low-grade dysplasia was present in 2.2% of all subjects compared to 0.2% rate of dysplasia in a large randomized controlled trial in Kerala (*11*). Relevant OPMLs included dysplasias and a single case of carcinoma *in situ*. A history of chewing pan or tobacco was significantly associated with the presence of dysplasia ($p < 0.001$).

Using histology as the reference, the sensitivity of FV to detect dysplasia was 96% and specificity was 17%. The sensitivity of combined cytology and DNA-ICM for detecting dysplasia was 64% and specificity was 86% *(15,16)*.

Discussion

Reports of clinical research commonly focus on the scientific and medical content of studies conducted in high-resource settings. Although the same content relevance applies to low- and middle-income countries (LMICs), the conditions under which clinical research is conducted in these settings are not the same, and requires adaptation to local circumstances and available resources. This study required a collaboration between a local community with limited health awareness, literacy, education or transportation and a facility (an elementary school) requiring a secure electrical supply and upgrades to host public services: a local, predominantly volunteer health professional workforce comprising university students, medical and dental residents, fellows and specialists from academic tertiary urban institutions; an international dental clinical and research volunteer faculty with expertise in clinical practice, protocol-based clinical research, and technology development; and an international NGO comprising volunteers with clinical and academic experience, health administration, and funding. Approximately 20 months of scheduled virtual meetings across a 12-hour time-zone difference, were required for the development of the protocol, procedures, consents, data forms and ethics review documentation in India and Canada, and the establishment of a culture of mutual respect, trust and common purpose; i.e., a need for time, development of trust and true collaboration as partners conducting a study between a higher and a lesser-resourced country in which bi-directional knowledge flow characterized the relationship.

Large screening studies of oral cancer have been reported in India, all using visual examination as the primary screening tool (*11,17-19*). Adverse risk habits – smoking, alcohol, tobacco and pan chewing – are highly prevalent, reinforcing the need to introduce risk habit cessation counselling along with screening to achieve long-term success in reducing oral cancer rates.

Determining which lesions need further investigation based on clinical examination alone is difficult. Differentiating dysplastic from benign lesions requires a tissue biopsy. In this study, a small number of the lesions were biopsied on-site for final diagnosis. Compliance among participants referred to the hospital for biopsy was poor, for reasons including limited health awareness, ease of travel to the referral centre and loss of daily wages. As a result, the sensitivity and specificity of the adjunct screening tools used in this study cannot be accurately determined.

Follow-up and/or treatment for low-grade dysplasia lesions is controversial – longitudinal follow-up over time to monitor for malignant transformation, whilst ideal, is challenging in LMICs. Surgical excision reduces malignant transformation rates but overtreatment can cause undue morbidity as only a proportion will progress *(20-23)*.

It is possible to undertake screening for oral cavity cancer, in rural, community settings using available technology and personnel. Using scheduled health camps rather than community non-medical facilities required fewer facility upgrades and a more ready ability to conduct interventions, e.g., biopsies. It also would allow combining counselling, screening and general health check-ups. Locating screening sites in primary health-care centres could facilitate industrial and office worker participation, and might improve participant acceptance and follow-up.

Screening programmes are resource intensive and need to be addressed within an organized health system encompassing all aspects of disease control – prevention, risk factor control, registration, diagnosis, treatment and palliation of disease. Given the population size and the proportion with risk factor exposure in South Asia, optimizing screening tools for accurate lesion detection, triage and follow-up of positive, indeterminate, incomplete or equivocal findings is essential. A high sensitivity and specificity of screening interventions becomes a practical and economic necessity. In this regard, FV determination had a low specificity for screening, although its use for lesion delineation for surgical excision and follow-up is important. DNA-ICM combined with cytology may serve as a non-invasive intermediate tool to enhance specificity and determination of which lesions need follow-up or biopsy.

Conclusion

Adherence to overarching principles for the ethical conduct for human research guided the conduct of this research, identifying challenges associated with population-based oral cancer screening in a rural, community setting in Telangana, India, necessitating prioritization of processes to meet REB requirements and accepted standards of practice in India and Canada. Infrastructure, training of all staff and volunteers, triage and development of treatment pathways for screen-detected lesions were some of the major considerations.

Existing infrastructure, such as primary health centres in rural India, support from local NGOs, training primary health-care workers to conduct oral examinations with a triage system for those with detected lesions, engaging local village chiefs and community leaders (Figure 12) to promote awareness about the adverse effects of tobacco and alcohol consumption, can facilitate implementation of nation-wide screening programmes.

Screening is not a "stand-alone" activity. It must be linked with accessible diagnosis and treatment for positive screened individuals, and with prevention and risk factor control to reduce the incidence of oral cancers. Continuing clinical research is needed to identify optimal screening intervention(s)

– simple, applicable in community settings, use by available health-care personnel with limited requirement for medical/dental specialists, acceptable to subjects (high compliance), and with established sensitivity and specificity to permit triage of subjects to achieve cost effective, high-throughput oral cancer screening and early detection in countries like India with large, high-risk populations and limited resources. ■

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: *CA Cancer J Clin.* 2020 Jul;70(4):313. PMID: 30207593.
2. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, Rosenberg PS, Bray F, Gillison ML. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol.* 2013 Dec 20;31(36):4550-9. doi: 10.1200/JCO.2013.50.3870. Epub 2013 Nov 18. PMID: 24248688; PMCID: PMC3865341.
3. Ranganathan K, Kavitha L. Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. *J Oral Maxillofac Pathol.* 2019 Jan-Apr;23(1):19-27. doi: 10.4103/jomfp.JOMFP_13_19. PMID: 31110412; PMCID: PMC6503768.
4. Ranganathan K, Kavitha L. Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. *J Oral Maxillofac Pathol.* 2019 Jan-Apr;23(1):19-27. doi: 10.4103/jomfp.JOMFP_13_19. PMID: 31110412; PMCID: PMC6503768.
5. Ranganathan K, Kavitha L. Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. *J Oral Maxillofac Pathol.* 2019 Jan-Apr;23(1):19-27. doi: 10.4103/jomfp.JOMFP_13_19. PMID: 31110412; PMCID: PMC6503768.
6. Kumar S, Heller RF, Pandey U, Tewari V, Bala N, Oanh KT. Delay in presentation of oral cancer: a multifactor analytical study. *Natl Med J India.* 2001 Jan-Feb;14(1):13-7. PMID: 11242691.
7. Coelho KR. Challenges of the oral cancer burden in India. *J Cancer Epidemiol.* 2012; 2012: 701932. doi: 10.1155/2012/701932. Epub 2012 Oct 4. PMID: 23093961; PMCID: PMC3471448.
8. Mathew A, George PS, Ramadas K, Mathew BS, Kumar A, Roshni S, Jayakumar KNL, Booth CM. Sociodemographic Factors and Stage of Cancer at Diagnosis: A Population-Based Study in South India. *J Glob Oncol.* 2019 Jul; 5:1-10. doi: 10.1200/JGO.18.00160. PMID: 31322993; PMCID: PMC6690651.
9. Nandi S, Mandal A, Chhebbi M. The prevalence and clinicopathological correlation of human papillomavirus in head and neck squamous cell carcinoma in India: A systematic review article. *Cancer Treat Res Commun.* 2021; 26:100301. doi: 10.1016/j.ctarc.2020.100301. Epub 2020 Dec 30. PMID: 33401132.
10. Murthy V, Calcuttawala A, Chadha K, d'Cruz A, Krishnamurthy A, Mallick I, Nair S, Teni T, Pawar S, Talapatra K, Patil A, Bhatt A, Chatterjee S, Swain M, Narayanan P, Ghadyalpatil N, Singhal M, Kuriakose M, Prabhash K, Agarwal J, Parikh P. Human papillomavirus in head and neck cancer in India: Current status and consensus recommendations. *South Asian J Cancer.* 2017 Jul-Sep;6(3):93-98. doi: 10.4103/sajc.sajc_96_17. PMID: 28975111; PMCID: PMC5615888.
11. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, Rajan B; Trivandrum Oral Cancer Screening Study Group. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet.* 2005 Jun 4-10;365(9475):1927-33. doi: 10.1016/S0140-6736(05)66658-5. PMID: 15936419.
12. Pradeep Y, Chakravarty KK, Simhadri K, Ghenam A, Naidu GM, Vundavalli S. Gaps in need, demand, and effective demand for dental care utilization among residents of Krishna district, Andhra Pradesh, India. *J Int Soc Prev Community Dent.* 2016 Aug;6(Suppl 2):S116-21. doi: 10.4103/2231-0762.189737. PMID: 27652242; PMCID: PMC5022387.
13. Giaretti W, Monteghirfo S, Pentenero M, Gandolfo S, Malacarne D, Castagnola P. Chromosomal instability, DNA index, dysplasia, and subsite in oral premalignancy as intermediate endpoints of risk of cancer. *Cancer Epidemiol Biomarkers Prev.* 2013 Jun;22(6):1133-41. doi: 10.1158/1055-9965.EPI-13-01 47. Epub 2013 Apr 29. PMID: 23629518.
14. Li C, Wu L, Deng Y, Shen X, Liu W, Shi L. DNA aneuploidy with image cytometry for detecting dysplasia and carcinoma in oral potentially malignant disorders: A prospective diagnostic study. *Cancer Med.* 2020 Sep;9(17):6411-6420. doi: 10.1002/cam4.3293. Epub 2020 Jul 7. PMID: 32638539; PMCID: PMC7476813.
15. Datta M, Chaitanya N, Ndvn S, Palat G, Kumari P, Jacob J M, Jagannath J, Rapelli V, Kumari S, Broughton S, Sutcliffe S, Laronde DM. 2020. Challenges with conducting community oral cancer screening in rural India using white-light examination and fluorescence visualization. (In submission)
16. Datta M, Guillaud M, Chaitanya N, NDVN Shyam, Palat G, Kumari P, Rapelli V, Jagannath J, Kumari S, Broughton S, Sutcliffe S, Laronde DM.2022. Use of image cytometry in conducting oral cancer screening in rural India. *Cytopathology* (accepted June 2022). doi:10.1111/cyt.13159
17 Philip PM, Nayak P, Philip S, Parambil NA, Duraisamy K, Balasubramanian S. Population-based cancer screening through community participation: Outcome of a district wide oral cancer screening program from rural Kannur, Kerala, India. South *Asian J Cancer.* 2018 Oct-Dec;7(4):244-248. doi: 10.4103/sajc.sajc_104_17. PMID: 30430093; PMCID: PMC6190395.
18. Gupta PC, Mehta FS, Daftary DK, Pindborg JJ, Bhonsle RB, Jalnawalla PN, Sinor PN, Pitkar VK, Murti PR, Irani RR, Shah HT, Kadam PM, Iyer KS, Iyer HM, Hegde AK, Chandrashekar GK, Shiroff BC, Sahiar BE, Mehta MN. Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. *Community Dent Oral Epidemiol.* 1980;8(6):283-333. doi: 10.1111/j.1600-0528.1980. tb 01302.x. PMID: 6937277.
19. Arvind, Baghirath PV, Kumar JV. 2014. Prevalence of precancerous lesions and conditions in Telangana region, Andhra Pradesh, India. *J Indian Assoc Public Health Dent.* 12(1):23.
20. Pandey M, Thomas G, Somanathan T, Sankaranarayanan R, Abraham EK, Jacob BJ, Mathew B; Trivandrum Oral Cancer Screening Study Group. Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India. *Oral Oncol.* 2001 Jan;37(1):103-9. doi: 10.1016/s1368-8375(00)00070-1. PMID: 11120491.
21. Zhang L, Poh CF, Lam WL, Epstein JB, Cheng X, Zhang X, Priddy R, Lovas J, Le ND, Rosin MP. Impact of localized treatment in reducing risk of progression of low-grade oral dysplasia: molecular evidence of incomplete resection. *Oral Oncol.* 2001 Sep;37(6):505-12. doi: 10.1016/s1368-8375(00)00140-8. PMID: 11435177.
20. Holmstrup P, Dabelsteen E. Oral leukoplakia-to treat or not to treat. *Oral Dis.* 2016 Sep;22(6):494-7. doi: 10.1111/odi.12443. Epub 2016 Feb 11. PMID: 26785709.
22. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. *Head Neck.* 2009 Dec;31(12):1600-9. doi: 10.1002/hed.21131. PMID: 19455705.
23. Rock LD, Laronde DM, Lin I, Rosin MP, Chan B, Shariati B, Zhang L. Dysplasia Should Not Be Ignored in Lichenoid Mucositis. *J Dent Res.* 2018 Jul;97(7):767-772. doi: 10.1177/0022034517748639. Epub 2018 Jan 12. PMID: 29328891; PMCID: PMC6728589.