Oral Cancer Diagnosis

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Oral cancer is a malignant condition on the lips or in the oral cavity including the tongue, gingiva, mouth floor, parotid, salivary glands, and throat. More than 90% of oral cancer is oral squamous cell carcinoma (OSCC). Fourier transform infrared spectroscopy (FTIR) is a modern diagnostic tool with great potential to provide rapid, objective and accurate early diagnosis of oral cancer, as well as accurate OSCC grading for better cancer management.

Keywords: oral cancer diagnosis ; oral squamous cell carcinoma ; OSCC ; oral epithelial dysplasia ; oral potentially malignant disorder ; OPMD ; early cancer diagnosis ; grading of dysplasia ; fourier transform infrared spectroscopy ; FTIR

1. Introduction

Oral cancer is the eighth most common cancer worldwide with an estimated 657,000 new cases and 330,000 deaths annually in 2020, and these numbers are expected to double by 2035 according to the World Health Organization (WHO) [1]. Despite easy access to the oral cavity for examination and significant advances in treatment, oral cancer patients often face very high morbidity and mortality rates due to late-stage diagnosis, which accounts for approximately 70% of all new cases [2]. The 5-year survival rate for oral cancer patients ranges from 20 to 90% depending on the stage of diagnosis [3]. Early-stage oral cancer often manifests as subtle mucosal lesions classified as oral potentially malignant disorders (OPMD) [4][5]. Early detection and effective management of these lesions are critical for improving survival rates and preventing oral cancer progression.

The gold standard for oral cancer diagnosis is a biopsy and subsequent histopathological evaluation under a microscope. This process is invasive, time-consuming, and subject to inter-observer variability [6]. Furthermore, histopathological assessment based on tissue morphological alterations does not provide an accurate risk assessment for OPMDs and tends to detect oral cancer at late stages [7]. Various adjunctive techniques have been proposed to facilitate the screening and diagnosis of oral cancer such as exfoliative cytology (cytobrush) [8], vital tissue staining [9], and the use of chemoluminescence or autofluorescence [10][11][12]. However, despite the continuous effort of improvement, most techniques still exhibit limited ability to provide accurate information and help clinicians detect oral cancer in its early stage [13]. Recently, molecular markers and salivary tests have been investigated for their potential in early oral cancer detection [14][15][16]. However, so far, no single biomarker can reliably validate the presence or predict the prognosis of oral cancer [17][18].

The search for a fast, simple, accurate, and cost-effective diagnostic method for early oral cancer detection is still underway. One promising technique is Fourier transform infrared (FTIR) spectroscopy, which provides molecular fingerprints of biological samples based on vibrational transitions of chemical bonds in the samples upon interaction with infrared light. FTIR is a non-invasive and label-free method that can detect early bimolecular changes associated with a neoplasm condition even before the emergence of morphological abnormalities, which strongly supports its role in early cancer detection [19][20]. To date, considerable research work has demonstrated competitive to superior performance of FTIR in comparison to conventional cancer screening and diagnostic techniques, making it a potentially powerful clinical tool in modern medicine [21][22][23][24].

2. Oral Malignant and Potentially Malignant Disorders

Oral cancer is a malignant condition on the lips or in the oral cavity including the tongue, gingiva, mouth floor, parotid, salivary glands, and throat. More than 90% of oral cancer is oral squamous cell carcinoma (OSCC) [25][26]. Oral carcinogenesis is a highly complex multifactorial process that arises when epithelial cells are affected by different genetic changes. There are several well-known risk factors for oral cancer such as smoking and alcohol consumption. Oral cancer is 2–3 times more prevalent in men than women [27].

The vast majority of oral cancer patients have pre-existing oral lesions called oral potentially malignant disorders (OPMDs) that precede the development of OSCC. OPMDs consist of a group of mucosal lesions associated with a higher risk of malignant transformation. The worldwide prevalence rate of OPMDs is estimated to be 4.47% [28]. The most common OPMDs encountered in clinical practice include leukoplakia (white patch), erythroplakia (red patch), lichen planus, and oral submucous fibrosis. While the clinical manifestations of OPMDs are common, it is very hard to predict the outcome for individual cases following the detection of an OPMD [29][30]. The malignant transformation rate for OPMDs was recently reported to be 0.13–34%, with the majority of cases remaining unchanged, becoming enlarged or reduced in size, or even resolving completely [31]. Factors associated with an increased malignant transformation risk include gender, lesion site, lesion type, habits (such as alcohol consumption and smoking), and the histologic diagnosis of epithelial dysplasia [5]. The human papillomavirus as a risk factor has also been discussed, but its role remains controversial [32][33][34].

3. Current Diagnostic/Grading/Staging/Methods and Limitations

The clinical presentation of OPMDs is subject to further histological evaluation, which results in the diagnosis of hyperplasia, hyperkeratosis, oral epithelial dysplasia (OED), or OSCC [35]. OED is a range of cytological and architectural changes in oral epithelium caused by an accumulation of genetic alterations that are associated with an increased risk of progression to OSCC [36]. An OED can be graded as mild, moderate, or severe, based on the WHO's three-tier classification system. Grading of OED is used to assess the probability of malignant transformation, with a higher grade indicating a larger chance of malignant transformation [37][38]. There are no clear guidelines about treatment or follow-up for OED. Generally speaking, mild dysplasia is often conservatively managed through watchful waiting, while severe dysplasia may require excision of the lesion and active surveillance for recurrence [39].

Correct diagnosis and timely treatment of OPMDs play an essential role in early oral cancer detection and prevention. However, the WHO's gold standard grading system for OED has many limitations. First of all, the efficacy and usefulness of histopathological grading of precursor lesions for predicting malignant transformation have long been debated in the literature as malignant transformation can also occur in the absence of OED and histopathological grading alone is unable to provide a risk assessment for OED [7][40][41][42][43][44]. Secondly, this method is highly subjective, with wide intra- and inter-observer variability in the grading outcomes and poor reproducibility [45][46]. Thirdly, the histopathological evaluation process is time-consuming since every tissue biopsy needs to be manually examined, resulting in delays in patient treatment and care [47].

If OSCC is diagnosed, effective cancer management requires accurate cancer grading to establish suitable treatment plans, estimate the risk of recurrence, and predict patient prognosis. The current grading of OSCC utilizes both the TNM (Tumour, Node, Metastasis) system and histopathologic grading. The internationally accepted TNM system of cancer staging assesses the extent of tumor growth in the whole body based on the size of the primary tumor (T), the involvement of regional lymph nodes (N) as well as distant metastases (M). Meanwhile, the histopathologic grade (G1-G4) of OSCC is established according to tumor histology and cytomorphology of tumor lesions [48]. This multifactorial diagnostic system considers characteristics of the tumor (e.g., differentiation), the tumor-host interface (invasion), and host reactions (inflammation). Unfortunately, the histopathological grading of oral cancer is a subjective process and provides little or no value for predicting prognosis [49].

Therefore, there is an urgent need for a modern diagnostic tool that provides rapid, objective, and accurate diagnosis of OPMDs for early oral cancer detection and prevention, as well as accurate OSCC grading for better oral cancer management.

4. Fourier Transform Infrared Spectroscopy/Microspectroscopy

FTIR spectroscopy is an established analytical technique with diverse applications. It was traditionally used by chemists to characterize the molecular structures of a material. Molecules have discrete energy levels for electronic transitions, molecular vibrations, and molecular rotations. When a molecule is irradiated by infrared light, it absorbs a certain amount of the incident radiation at a specific energy/frequency and undergoes vibrational excitation from the ground state to a higher vibrational energy state. The unique pattern of infrared absorption by a particular molecule or functional group produces characteristic bands in their FTIR spectra. The band position is affected by the mass of vibration, the type of molecular bond (e.g. single or double bond), the intra- and inter-molecular environment, and the coupling with other vibrations; the band height is proportional to the concentration of corresponding chemical moieties, and the bandwidth provides an estimate of intermolecular interactions. FTIR spectroscopy provides a biochemical profile of proteins, nucleic

acids, lipids, and carbohydrates in a biological sample, called “biomolecular fingerprinting”. It is sensitive enough to probe subtle changes in molecular structure and microenvironment, such as the secondary structure of proteins, the mutation of nucleic acids, and the peroxidation of phospholipids.

FTIR spectroscopy has been investigated in the analysis of a variety of oral-cancer-related biological samples, including oral tissues, oral cells, and biofluids. It has also been used to study the oral tumor microenvironment as well as the effects of anti-cancer drugs. The biochemically based FTIR diagnostic approach offers several advantages over the morphologically based gold standard histopathology, among which the most notable benefit is its ability to detect pre-cancerous changes at early stages. The wealth of biochemical and structural information contained in FTIR spectra and images can be fully extracted using various multivariate analysis and machine learning techniques. FTIR in conjunction with chemometric data analysis has demonstrated high sensitivity, specificity, and accuracy in differentiating pathological oral cases from normal ones. Recent technological breakthroughs and advancements in infrared sources, waveguides, detectors, chip integrations, and software development further expedite the clinical translation of FTIR as a fast, economic, accurate, and automated diagnostic system. Integrated with other modern biomedical technologies, FTIR is expected to play a significant role in the early detection of oral cancers in the near future.

References

1. WHO Cancer Prevention. Available online: https://www.who.int/cancer/prevention/diagnosis-screening/oral-cancer/en/ (accessed on 20 December 2020).
2. Miller, K.D.; Siegel, R.L.; Khan, R.; Jemal, A. Cancer Statistics. Cancer Rehabil. 2018, 70, 7–30, doi:10.1891/9780826121646.0002.
3. Farah, C.S.; Woo, S.-B.; Zain, R.B.; Sklavounou, A.; McCullough, M.J.; Lingen, M. Oral Cancer and Oral Potentially Malig-nant Disorders. Int. J. Dent. 2014, 2014, 1–6, doi:10.1155/2014/853479.
4. Epstein, J.B.; Güneri, P.; Boyacioglu, H.; Abt, E. The limitations of the clinical oral examination in detecting dysplastic oral lesions and oral squamous cell carcinoma. J. Am. Dent. Assoc. 2012, 143, 1332–1342, doi:10.14219/jada.archive.2012.0096.
5. Speight, P.M.; Khurram, S.A.; Kujan, O. Oral potentially malignant disorders: Risk of progression to malignancy. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2018, 125, 612–627, doi:10.1016/j.oooo.2017.12.011.
6. Singh, S.; Ibrahim, O.; Byrne, H.J.; Mikkonen, J.W.; Koistinen, A.; Kullaa, A.M.; Lyng, F.M. Recent advances in optical diag-nosis of oral cancers: Review and future perspectives. Head Neck 2015, 38, E2403–E2411, doi:10.1002/hed.24293.
7. Warnakulasuriya, S. Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. Oral Oncol. 2020, 102, 104550, doi:10.1016/j.oraloncology.2019.104550.
8. Lousada-Fernandez, F.; Óscar, R.-G.; López-Cedrún, J.L.; López-López, R.; Muinelo-Romay, L.; Mercedes, S.-C.M. Liquid Biopsy in Oral Cancer. Int. J. Mol. Sci. 2018, 19, 1704, doi:10.3390/ijms19061704.
9. Kasthuri, M.; Babu, N.A.; Masthan, K.M.K.; Sankari, S.L. Toludine Blue Staining in The Diagnosis of Oral Precancer and Cancer: Stains, Technique and its Uses—A Review. Biomed. Pharmacol. J. 2015, 8, 519–522, doi:10.13005/bpj/737.
10. Shashidara, R.; Sreeshyla, H.S.; Sudheendra, U.S. Chemiluminescence: A diagnostic adjunct in oral precancer and cancer: A review. J. Cancer Res. Ther. 2014, 10, 487–491.
11. Cicciù, M.; Cervino, G.; Fiorillo, L.; D’Amico, C.; Oteri, G.; Troiano, G.; Zhurakivska, K.; Muzio, L.L.; Herford, A.S.; Crimi, S.; et al. Early Diagnosis on Oral and Potentially Oral Malignant Lesions: A Systematic Review on the VELscope® Fluorescence Method. Dent. J. 2019, 7, 93, doi:10.3390/dj7030093.
12. Nagi, R.; Reddy-Kantharaj, Y.-B.; Rakesh, N.; Janardhan-Reddy, S.; Sahu, S. Efficacy of light based detection systems for ear-ly detection of oral cancer and oral potentially malignant disorders: Systematic review. Med. Oral Patol. Oral Cir. Bucal 2016, 21, e447–e455, doi:10.4317/medoral.21104.
13. Lingen, M.W.; Tampi, M.P.; Urquhart, O.; Abt, E.; Agrawal, N.; Chaturvedi, A.K.; Cohen, E.; D’Souza, G.; Gurenlian, J.; Kalmar, J.R.; et al. Adjuncts for the evaluation of potentially malignant disorders in the oral cavity: Diagnostic test accuracy systematic review and meta-analysis-a report of the American Dental Association. J. Am. Dent. Assoc. 2017, 148, 797–813.
14. Bhatia, A.K.; Burtness, B. Novel Molecular Targets for Chemoprevention in Malignancies of the Head and Neck. Cancers 2017, 9, 113, doi:10.3390/cancers9090113.
15. Liyanage, C.; Wathupola, A.; Muraleetharan, S.; Perera, K.; Punyadeera, C.; Udagama, P. Promoter Hypermethylation of Tumor-Suppressor Genes p16(INK4a), RASSF1A, TIMP3, and PCQAP/MED15 in Salivary DNA as a Quadruple Bio

marker Panel for Early Detection of Oral and Oropharyngeal Cancers. Biomolecules 2019, 9, 148.

16. Yete, S.; Saranath, D. MicroRNAs in oral cancer: Biomarkers with clinical potential. Oral Oncol. 2020, 110, 105002, doi: 10.1016/j.oraloncology.2020.105002.
17. Celentano, A.; Glurich, I.; Borgnakke, W.S.; Farah, C.S. World Workshop on Oral Medicine VII: Prognostic biomarkers i n oral leukoplakia and proliferative verrucous leukoplakia—A systematic review of retrospective studies. Oral Dis. 2020, doi:10.1111/odi.13363.
18. Radhika, T.; Jeddy, N.; Nithya, S.; Muthumeenakshi, R. Salivary biomarkers in oral squamous cell carcinoma—An insig ht. J. Oral Biol. Craniofac. Res. 2016, 6, S51–S54, doi:10.1016/j.jobcr.2016.07.003.
19. Bogomolny, E.; Huleihel, M.; Suproun, Y.; Sahu, R.K.; Mordechai, S. Early spectral changes of cellular malignant transf or-mation using Fourier transform infrared microspectroscopy. J. Biomed. Opt. 2007, 12, 024003, doi:10.1117/1.27171 86.
20. Papamarkakis, K.; Bird, B.; Schubert, J.M.; Miljković, M.; Wein, R.; Bedrossian, K.; Laver, N.M.V.; Diem, M. Cytopathol ogy by optical methods: Spectral cytopathology of the oral mucosa. Lab. Investig. 2010, 90, 589–598, doi:10.1038/labin vest.2010.1.
21. Kumar, S.; Srinivasan, A.; Nikolajeff, F. Role of Infrared Spectroscopy and Imaging in Cancer Diagnosis. Curr. Med. Ch em. 2017, 25, 1055–1072, doi:10.2174/0929867324666170523121314.
22. Bellisola, G.; Sorio, C. Infrared spectroscopy and microscopy in cancer research and diagnosis. Am. J. Cancer Res. 20 11, 2, 1–21.
23. Bel'Skaya, L.V. Use of IR Spectroscopy in Cancer Diagnosis. A Review. J. Appl. Spectrosc. 2019, 86, 187–205, doi:10. 1007/s10812-019-00800-w.
24. Su, K.-Y.; Lee, W.-L. Fourier Transform Infrared Spectroscopy as a Cancer Screening and Diagnostic Tool: A Review a nd Prospects. Cancers 2020, 12, 115, doi:10.3390/cancers12010115.
25. Lambert, R.; Sauvaget, C.; Cancela, M.D.C.; Sankaranarayanan, R. Epidemiology of cancer from the oral cavity and or o-pharynx. Eur. J. Gastroenterol. Hepatol. 2011, 23, 633–641, doi:10.1097/meg.0b013e3283484795.
26. Messadi, D.V. Diagnostic aids for detection of oral precancerous conditions. Int. J. Oral Sci. 2013, 5, 59–65, doi:10.103 8/ijos.2013.24.
27. Rivera, C. Essentials of oral cancer. Int. J. Clin. Exp. Pathol. 2015, 8, 11884–11894.
28. Mello, F.W.; Miguel, A.F.P.; Dutra, K.L.; Porporatti, A.L.; Warnakulasuriya, S.; Guerra, E.N.S.; Rivero, E.R.C. Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. J. Oral Pathol. Med. 2018, 47, 633–640, doi:10.1111/jop.12726.
29. Villa, A.; Sonis, S. Oral leukoplakia remains a challenging condition. Oral Dis. 2018, 24, 179–183, doi:10.1111/odi.1278 1.
30. Scully, C. Challenges in predicting which oral mucosal potentially malignant disease will progress to neoplasia. Oral Di s. 2013, 20, 1–5, doi:10.1111/odi.12208.
31. Warnakulasuriya, S.; Ariyawardana, A. Malignant transformation of oral leukoplakia: A systematic review of observation al studies. J. Oral Pathol. Med. 2016, 45, 155–166, doi:10.1111/jop.12339.
32. Gupta, S.; Gupta, S. Role of human papillomavirus in oral squamous cell carcinoma and oral potentially malignant disor ders: A review of the literature. Indian J. Dent. 2015, 6, 91–98.
33. Gómez, S.; Chimenos-Küstner, E.; Marí, A.; Tous, S.; Penin, R.; Clavero, O.; Quirós, B.; Pavon, M.A.; Taberna, M.; Ale many, L.; et al. Human papillomavirus in premalignant oral lesions: No evidence of association in a Spanish cohort. PL oS ONE 2019, 14, e0210070, doi:10.1371/journal.pone.0210070.
34. Chen, X.; Zhao, Y. Human papillomavirus infection in oral potentially malignant disorders and cancer. Arch. Oral Biol. 2 017, 83, 334–339, doi:10.1016/j.archoralbio.2017.08.011.
35. Ranganathan, K.; Kavitha, L. Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral poten-tially malignant disorders. J. Oral Maxillofac. Pathol. 2019, 23, 19–27, doi:10.4103/jomfp.JOMFP_13_19.
36. El-Naggar, A.K.; Grandis, J.R.; Takata, T.; Slootweg, P.J. WHO Classification of Head and Neck Tumours; World Health Organ-ization: Geneva, Switzerland, 2017; Volume 9.
37. Mehanna, H.; Rattay, T.; Smith, J.; McConkey, C.C. Treatment and follow-up of oral dysplasia—A systematic review an d meta-analysis. Head Neck 2009, 31, 1600–1609, doi:10.1002/hed.21131.
38. Warnakulasuriya, S.; Reibel, J.; Bouquot, J.; Dabelsteen, E. Oral epithelial dysplasia classification systems: Predictive value, utility, weaknesses and scope for improvement. J. Oral Pathol. Med. 2008, 37, 127–133, doi:10.1111/j.1600-071

4.2007.00584.x.

39. Awadallah, M.; Idle, M.; Patel, K.; Kademani, D. Management update of potentially premalignant oral epithelial lesions. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2018, 125, 628–636, doi:10.1016/j.oooo.2018.03.010.
40. Tilakaratne, W.M.; Sherriff, M.; Morgan, P.R.; Odell, E.W. Grading oral epithelial dysplasia: Analysis of individual feature s. J. Oral Pathol. Med. 2011, 40, 533–540, doi:10.1111/j.1600-0714.2011.01033.x.
41. Speight, P.M. Update on Oral Epithelial Dysplasia and Progression to Cancer. Head Neck Pathol. 2007, 1, 61–66, doi:1 0.1007/s12105-007-0014-5.
42. Dost, F.; Cao, K.L.; Ford, P.; Ades, C.; Farah, C.S. Malignant transformation of oral epithelial dysplasia: A real-world ev alua-tion of histopathologic grading. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2014, 117, 343–352, doi:10.1016/j.o ooo.2013.09.017.
43. Silverman, S., Jr.; Gorsky, M.; Lozada, F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patie nts. Cancer 1984, 53, 563–568.
44. Warnakulasuriya, S.; Johnson, N.W.; van der Waal, I. Nomenclature and classification of potentially malignant disorder s of the oral mucosa. J. Oral Pathol. Med. 2007, 36, 575–580, doi:10.1111/j.1600-0714.2007.00582.x.
45. Fischer, D.J.; Epstein, J.B.; Morton Jr, T.H.; Schwartz, S.M. Interobserver reliability in the histopathologic diagnosis of o ral pre-malignant and malignant lesions. J. Oral Pathol. Med. 2004, 33, 65–70.
46. Karabulut, A.; Reibel, J.; Therkildsen, M.H.; Praetorius, F.; Nielsen, H.W.; Dabelsteen, E. Observer variability in the hist ologic assessment of oral premalignant lesions. J. Oral Pathol. Med. 1995, 24, 198–200, doi:10.1111/j.1600-0714.199 5.tb01166.x.
47. Weaver, D.L.; Rosenberg, R.D.; Barlow, W.E.; Ichikawa, L.; Carney, P.A.; Kerlikowske, K.; Buist, D.S.; Geller, B.M.; Ke y, C.R.; Maygarden, S.J.; et al. Pathologic findings from the Breast Cancer Surveillance Consortium: Population-based outcomes in women undergoing biopsy after screening mammography. Cancer 2006, 106, 732–742.
48. Almangush, A..; Mäkitie, A.A.; Triantafyllou, A.; Strojan, P.; Strojan, P.; Rinaldo, A.; Hernandez-Prera, J.C.; Suárez, C.; Kowalski, L.P.; Ferlito, A.; et al. Staging and grading of oral squamous cell carcinoma: An update. Oral Oncol. 2020, 10 7, 104799, doi:10.1016/j.oraloncology.2020.104799.
49. Roland, N.J.; Daslin, A.W.; Nash J.; Stell P.M. Value of grading squamous cell carcinoma of the head and neck. Head N eck, 1992. 14(3): p. 224-9.
