Original Research Paper

Dentistry

THE USE OF CDX BRUSH BIOPSY IN ORAL CANCER DETECTION

Sanam Akhavan	BDS SDM College of Dental Sciences & Hospital Sattur, Dharwad, Karnataka, India
Vatika Agarwal*	BDS, MDS Prosthodontics and Implantology Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India*Corresponding Author

ABSTRACT Oral squamous cell carcinoma is the most common group of cancers that affect the head and neck region. Detection in its early stages is a key factor to improve the survival rate and oral health professionals must play a leading role in this endeavor. Various diagnostic aids have been developed as an adjunct to the routine oral cancer screening, one of which is the oral brush biopsy (known as the OralCDx® Brush Test). The technique is non-invasive and relatively simple, allowing a painless and easy way to evaluate a suspicious lesion. The purpose of this article is to review the OralCDx test including its indications, advantages, disadvantages and applications in dentistry.

INTRODUCTION

Oral cancer is the sixth most common cancer globally, with an estimated incidence of over 400,000 cases annually (Parkin et al., 2001). However, unlike many other cancers, its incidence appears to be increasing (Warnakulasuriya, 2009). Early detection of malignant and premalignant oral lesions is recognized as one of the most efficient ways to reduce the high mortality rates of oral cancer and the morbidity associated with its treatment, which can leave patients with life-altering disturbances in speech, mastication, and dental health. If diagnosed early, oral cancer is one of the most treatable cancers, with survival rates exceeding 80% (Jemal et al., 2010). Unfortunately, most are detected in advanced stages, which is one of the reasons the 5-year survival rate has remained relatively stable at 45% for the last few decades (Platz et al., 1985; Mignogna et al., 2004). This is especially concerning considering the oral cavity is one of the most accessible and visible anatomical regions in the human body and one that is routinely examined by oral health professionals.

Tissue biopsy and histopathological examination remains the gold standard in diagnostic testing for oral mucosal lesions that are suspected of being cancerous or precancerous. However, tissue biopsy has several drawbacks because it is invasive, technique-sensitive and has psychological implications for patients (Naya et al., 2012). Furthermore, more than half of all patients with oral cancer have evidence of metastases at the time of diagnosis which is due, in part, to the fact early oral cancers may look identical to the harmless-appearing oral lesions that oral health professionals encounter in their daily practice. For these reasons, a variety of oral cancer diagnostic aids have been developed as adjuncts to the standard visual and tactile oral examination with the aim of improving early detection. Among them is the oral brush biopsy, also known as the OralCDx® Brush Test (CDx Laboratories, Inc., Suffren, NY, USA). The test is relatively inexpensive, non-invasive and well accepted by patients.

The purpose of this paper is to review OralCDx® Brush test technique, its role in oral cancer detection, and the implications for its use by oral health professionals.

REVIEW

The OralCDx® Brush Test was introduced in 1999 as a way to investigate innocuous-looking oral lesions for dysplasia or cancer that would not otherwise have been biopsied due to a lack of suspicious clinical features (Table 1) (Bocking et al., 2011). The biopsy kit consists of a specially designed sterile stiff bristle brush, a glass slide, a fixative (alcohol/polyethylene glycol), and a container and form for sending samples to the OralCDx laboratory (Sciubba, 2010).

Indications	Contraindications
Red or white spots, chronic ulcers, mucosal lesions with abnormal epithelial surface lesions	Lesions with intact normal epithelium
Common benign and small abnormalities that have been routinely seen and not suspicious enough to warrant for biopsy	Mucoceles, hemangiomas, fibromas, submucosal masses, pigmented lesions
Harmless looking lesions	Highly suspicious lesions
Precancerous lesions	Lesions with obvious etiology (herpes, aphthous ulcers, traumatic ulcers)

Brush Biopsy Technique

The OralCDx® Brush Test is relatively simple and does not require extensive training. A free online course is available on the CDx Laboratories website and an instructional video is also supplied when requesting a kit.

The major advantage of the test is that it does not require topical or local anesthetic and causes minimal or no bleeding and pain. The brush instrument has two cutting surfaces, the flat end of the brush and the border of the brush and either surface may be used to obtain the sample. Important in the use of the brush is learning how much pressure to apply and how many rotations are required. The cutting edge of the brush is placed against the lesion and while maintaining firm pressure, rotated in clockwise fashion. Applying enough pressure is critical to ensure cells are captured from the entire thickness of the epithelium. The brush should be repeatedly rotated in most cases about 5-15 times. Some lesions such as red lesions and ulcerations require little pressure and few rotations while white lesions, which are typically keratinized, require more pressure and rotations. The presence of reddening or pinpoint bleeding is a good indication that the basement membrane has been penetrated and thus a complete transepithelial sample has been achieved.

After obtaining the sample, the cellular material on the brush needs to be transferred to the glass slide that is provided. The surface of the brush is rotated on the glass slide from one end to another. A thin film of material should be observed on the glass slide if held up to the light. If not evident, additional samples must be obtained from the patient's lesion utilizing the same brush.

Once the transfer is complete, the glass slide is flooded with the fixative that is supplied. The slide is then set aside to dry and after approximately 15-20 minutes, the slide is ready to be placed into the slide holder that is supplied. A one-page form is completed and submitted with the specimen, which provides information on the patient history and clinical description of the lesion. The test slide is placed back into the same slide holder which it was shipped and together with the form, are shipped to the CDx® Laboratory.

Laboratory Analysis and Results

The high accuracy of OralCDx® is due to the fact that analyses of oral brush biopsies are accomplished with the assistance of sophisticated computers and advances in image recognition. The computer does not make the final diagnosis but presents potentially abnormal cells to the

pathologist on a high-resolution computer monitor to aid in diagnosis. With the aid of the specialized system, the pathologist can detect as few as one or two abnormal individual cells in a brush biopsy specimen.

Results can be reported as one of four findings (Casparis et al., 2014). A "negative" result implies there is no evidence of dysplasia or carcinoma in the specimen. Such a result should be expected since harmless appearing lesions are being tested, and most oral lesions that appear benign will prove to be negative. Lesions with a negative result must be followed and those that remain unchanged should be retested in 6 months. If cellular abnormalities are detected, then the clinician receives a report of either "positive", which means there is evidence of dysplasia or carcinoma, or "atypical", which means there are abnormal cells that require further investigation to identify their significance. Both "atypical" and "positive" results require incisional biopsy for definitive diagnosis (Naghipur, 2013). Lastly, an "inadequate" finding indicates that there was an incomplete transepithelial specimen and retesting is required.

The OralCDx® Brush Test has been extensively studied and a strong body of evidence exists supporting its use in clinical settings. In every study in which the same lesion was simultaneously tested with both a brush and scalpel biopsy, OralCDx® was shown to have a sensitivity and specificity exceeding 90% (Mehrota et al., 2009). As some authors have pointed out, however, in some of these studies, scalpel biopsy was performed after brush biopsy of lesions with high-risk clinical features, but not after brush biopsy of innocuous-looking lesions (Lingen et al., 2008). Therefore, the sensitivity and specificity values must be interpreted with a degree of caution. Additionally, more studies need to be completed in low-risk populations with benign-appearing oral lesions, as there is concern with reduced accuracy and increased rate of false positives (Fedele, 2009).

CONCLUSION

The CDx® brush biopsy can be a useful diagnostic aid in the detection of oral cancers by oral health professionals. One of the largest drawbacks of this test appears to be the time delay before the incisional biopsy, as authors have found an average delay of over 100 days before the diagnosis of a malignant lesion (Greenberg, 2002). Nevertheless, the test can be useful in certain clinical scenarios. For example, it may be beneficial in the patient with multiple oral lesions where it is unlikely that the patient would readily consent to multiple scalpel biopsies. Similarly, it may be useful in the non-compliant patient who is unlikely to come back for a follow-up exam or accept an immediate referral to an oral surgeon.

There has been an effort to improve the technique and increase its sensitivity by combining it with molecular analyses (Trullenque-Eriksson et al., 2009). This may permit the identification of genomic anomalies such as mutations of the tumor suppressing gene p53, epigenic alterations, genomic instability, and microsatellite instability (MSI), among others (Acha et al., 2005). However, these methods are in their infancy and need to be investigated by further studies.

REFERENCES

1. Acha, A., Ruesga, M.T., Rodriguez, M.J., Martinez de Pancorbo, M.A., Aguirre, J.M. (2005). Applications of the oral scraped (exfoliative) cytology in oral cancer and precancer. Medicina Oral, Patologia Oral, Cirugia Bucal, 10(2), 95-102.
2. Bocking, A., Sproll, C., Stocklein, N., Naujoks, C., Depprich, R., Kubler, N.R., Handschel, J. (2011). Role of brush biopsy and DNA cytometry for prevention, diagnosis, therapy and followup care of oral cancer. Journal of Oncology, https://doi.org/10.1155/2011/875959.
3. Casparis, S., Borm, J.M., Tomic, M.A., Burkhardt, A., Locher, M.C. (2014). Transepithelial brush biopsy–Oral CDx®–A noninvasive method for the early detection of precancerous and cancerous lesions. Journal of Clinical and Diagnostic Research for Doctors, 8(2), 222-6.
4. Fedele, S. (2009). Diagnostic aids in the screening of oral cancer. Head & Neck Oncology, 1(5). doi:10.1186/1758-3284-1-5.
5. Greenberg, M.S. (2002). The "brush" controversy. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, 93(3), 217-8.
6. Jemal, A., Siegel, R, Xu, J., Ward, E. (2010). Cancer statistics. CA: A Cancer Journal for Clinicians, 60(5), 277-300.
7. Lingen, M.W., Kalmar, J.R., Karrison, T., Speight, P.M. (2008). Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncology, 44(1): 10–22.
8. Mehrotra, R., Hullmann, M., Smeets, R., Reichert, T.E., Driemel, O. (2009). Oral cytology revisited. Journal of Oral Pathology and Medicine, 38(2), 161-6.
9. Naghipur, S. (2013). A review of diagnostic aids for oral cancer screenings in general practice dentistry. International Dental Journal of Student's Research, 2(2):10-16.
10. Naya, F.S., Carnicero, T.G., Vila, P.G., Folgueiras, E.C., Pérez, S.M., Vila, R.G. (2011). Applications of OralCDx® methodology in the diagnosis of oral leukoplakia. Medicina Oral, Patologia Oral, Cirugia Bucal, 17(1), e5-9.
11. Parkin, D.M., Bray, F., Ferlay, J., Pisani, P. (2001). Estimating the world cancer burden: Globocan 2000. International Journal of Cancer, 94(2), 153–6.
12. Platz, H., Fries, R., Hudec, M. (1985). Retrospective DÖSAK study on carcinomas of the oral cavity: results and consequences. Journal of Oral and Maxillofacial Surgery, 6(6), 320-8.
13. Sciubba, J.J. (1999). Improving detection of precancerous and cancerous oral lesions. Computer-assisted analysis of the oral brush biopsy. U.S. Collaborative OralCDx Study Group. Journal of the American Dental Association, 130(10), 1445-57.
14. Trullenque-Eriksson A., Munoz-Corcuera, M., Campo-Trapero, J., Cano-Sanchez, J., Bascones- Martinez, A. (2009). Analysis of new diagnostic methods in suspicious lesions of the oral mucosa. Medicina Oral, Patologia Oral, Cirugia Bucal, 14(5), E210-6.
15. Warnakulasuriya, S. (2009). Global epidemiology of oral and oropharyngeal cancer. Oral Oncology, 45(4- 5), 309–16.