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Evaluation of Incidence of Premalignant and Malignant Lesions by Mirror Image Biopsy in Oral Squamous Cell Carcinoma

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Abstract

Background: Oral Squamous Cell Carcinoma (OSCC) cancer arises due genetic and epigenetic changes caused by added infliction of various carcinogens including alcohol, smoking, tobacco, chronic injury. Patients treated with primary OSCC are more prone to develop multiple premalignant and malignant lesions in aero digestive tract compared to healthy individuals, due to existing field defects. Our study was conducted to histopathologically evaluate the apparently normal looking mirror image mucosa from contralateral anatomic site in unilateral, single, untreated and histopathologically diagnosed oral cancer patients to detect the incidence of premalignant and malignant lesions.

Methods: A cross-sectional observational study was carried out in Oral and Maxillofacial Surgery Department, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. About 44 consecutive eligible patients aged between 28 to 76 years diagnosed with primary, solitary, unilateral and untreated OSCC were subjected to mirror image biopsy and histopathologic examination from corresponding contralateral intraoral anatomic locations.

Results: Among 44 patients, 16 patients displayed dysplasia in oral mucosa at mirror image site, among which 12 had mild dysplasia and 4 had moderate dysplasia. Dysplasia was found higher in patients with pan with betel nut chewers plus tobacco chewers followed by paan with betel nut chewers and smokers. It was observed that buccal mucosa and gingivobuccal sulcus displayed more premalignant changes.

Conclusion: This study has demonstrated that clinically normal-looking mucosa from oral cancer patient's exhibit premalignant dysplastic changes in significant proportions. Hence, the mirror image biopsy would be an important diagnostic tool for early detection dysplastic changes in apparently normal mucosa preconditioned with field effect, to prevent further progression to cancer.

Keywords: Field cancerization; Metachronous tumors; Erythroleukoplakia; Primary cancer; Aerodigestive tract

Introduction

Oral cancer in early stages is often ignored by society mainly due to its asymptomatic nature. Usually, such cancer gets discovered when it has metastasized to other locations, especially to the lymph nodes. The prevalence of above cancer is increasing worldwide and throughout the world, oral cancer ranks 6th among the malignant diseases [1]. Oral cancer among of the head and neck malignancies constitutes 85% prevalence [2]. It is more prevalent in western countries and Southeast Asian countries [3]. The 5-year survival rate of such disease is 75% if diagnosed early, but in cases where metastasis has already taken place it comes to 35%, with an average 5-year survival rate of 50% [4]. Alcohol, tobacco chewing, smoking, betel quid chewing, trauma and HPV viruses are implicated as the predisposing factors of OSCC.

These agents on repeated infliction bring about DNA mutation promoting proto-oncogenes to oncogenes and interfere tumor suppressor genes which result in uncontrolled cell growth and proliferation signaling mechanisms [5]. Even after complete primary tumor excision up to histopathologically negative margins and

subjecting to multimodality treatment therapy such as radiotherapy and chemotherapy, it may recur or manifest as second primary tumors within months to years. As Slaughter discovered satellites of epithelial dysplasia near the primary tumor, he proposed the concept of field cancerization [6]. The hypothesis of metacentric neoplasia is explained by this concept [7]. Oral cavity including the upper aero digestive tract is described as the preferential site for occurrence of multiple primary tumors [8].

Second primary tumors are identified by Warren and gates criteria which describe them as an arising topographically separate lesion, must be malignant and of the same histopathological type as that of index tumor and probability of being a metastasis should be ruled out [9]. The cancer field may not be progressing in a concentric fashion, but it can develop into one or more of the three processes; the sub mucosal spread of initially formed clone, implantation of the cancer cells via saliva and development of a new clone independently [10]. The presence of second primary tumor lowers the survival rate of cancer patients, and loco regional management of primary also does not prevent the risk of appearance of second synchronous and metachronous tumors [11]. The present study was undertaken with the aim to identify premalignant and malignant changes in mirror image biopsy from contralateral normal looking anatomic sites in patients

histologically diagnosed with solitary, unilateral, non-metastatic squamous cell carcinoma.

Methods

The study was conducted from March 2015 to September 2016 in the Oral and Maxillofacial Surgery Department, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. After getting approval from the institutional review board and obtaining informed consent from the patients', this cross-sectional observational study was done in 44 consecutive patients who met the selection criteria. Patients with solitary, unilateral, previously untreated, non-metastatic and histopathologically diagnosed with squamous cell carcinoma were included in the study. Those having recurrent, midline, bilateral or multiple and metastatic lesions were excluded from the study. Standardized data collection sheet was used to record patient's clinical history, detailed habits, such as betel quid chewing, smoking, drinking and precise locations of the primary tumor and mirror image site.

The data was taken only from the patients who were later surgically treated in the department. After the patients were anesthetized for the surgical procedure, an incisional biopsy was taken from two sites maintaining all aseptic precautions. The first site was from the primary tumor and second from the healthy appearing mirror image contralateral site, and both the biopsies harvested by the same operator. Biopsy samples were standardized in terms of size and orientation. The biopsy samples from the both sites were fixed in 10% buffered neutral formalin in separate hard glass test tubes, labeled and sent for histopathological evaluation to the department of pathology BSMMU.

Findings from the primary lesion were tabulated as well differentiated, moderately differentiated, poorly differentiated and anaplastic. The findings from mirror image site were recorded for dysplasia, carcinoma in situ and frank malignancy. The morphological features like erythroplakia, leukoplakia were also recorded, however dysplasia, carcinoma in situ and frank malignancy were considered as primary study variables.

Results

Our study included 44 patients of ages from 28 to 76 years with single, unilateral, histopathologically confirmed oral squamous cell cancer. The mean age range of all patients was 55 ± 10.71 years. Out of total patients, 20 (45.5%) were males and 24 (54.5%) were females; with the male female ratio of 0.8:1.28 (63.6%) of the total patients were older than 50 years whereas 16 (36.6%) were equal or below 50 years of age.

Among the older age group, higher incidence of oral cancer was in females. The overall incidence of OSCC was more on the left side of oral cavity accounting 28 (63.6%) of the total cases (Table 1).

Sex	Male		Female	
	20 (45.5%)		24 (54.5%)	
Age	≤ 50 years		>50 years	
	Male	Female	Male	Female
	10 (22.7%)	6 (13.6%)	10 (22.7%)	18 (40.9%)
Laterality	Right sided		Left sided	
	16 (13.6%)	28 (63.6%)		

Table 1: Demography (n = 44) of oral squamous cell cancer.

Table 2 presents dysplastic changes in relation to age, sex, duration of exposure, habits, sites, primary tumor histology and TNM staging. In total 10 (22.7%) females and 6 (13.6%) males exhibited dysplasia. Around 11 (25.0%) patients older than 50 years showed dysplastic changes.

Those who were exposed to the carcinogens for 20-40 years had 9 (20.4%) carcinogenic changes while those with 5-20 years of exposure had only 7 (15.9%) changes.

Pan with betel nut chewers plus tobacco chewers had highest dysplastic changes in oral mucosa, which was in 10 (22.7%) subjects. Among intraoral sub sites, buccal mucosa displayed highest dysplastic changes 8 (18.1%) followed by gingivobuccal sulcus 4 (9.0%).

Primary tumors that were well differentiated had maximum premalignant changes. The oral mucosa of TNM stage IV cancer patients had 8 (18.1%) dysplastic changes.

Characteristics		Mild dysplasia	Moderate dysplasia
Sex	Male (20)	6 (13.6%)	0
	Female (24)	6 (13.6%)	4 (9.0%)
Age	≤ 50 years (16)	4 (9.0%)	1 (2.2%)
	>50 years (28)	8 (18.1%)	3 (6.8%)
Duration of exposure	5-20 years (20)	6 (13.6%)	1 (2.2%)
	21- 40 years (24)	6 (13.6%)	3 (6.8%)
Habits	Only Smokers (1)	0	0
	Only paan with betel nut chewers (1)	1 (2.2%)	0
	Paan with betel nut chewers + tobacco chewers (25)	6 (13.6%)	4 (9.0%)

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	Paan with betel nut chewers + smokers (13)	4 (9.0%)	0
	Paan with betel nut chewers + smokers+ tobacco chewers (4)	1 (2.2%)	0
Sites	Buccal mucosa (24)	7(15.9%)	1 (2.2%)
	Upper alveolus (2)	0	0
	Lower alveolus (1)	0	0
	Gingivobuccal sulcus (8)	3 (6.8%)	1 (2.2%)
	Retromolar trigone (2)	0	1 (2.2%)
	Tongue (6)	2 (4.5%)	1 (2.2%)
	Floor of mouth (1)	0	0
Primary tumor histology	Well-differentiated (35)	10 (22.2%)	3 (6.8%)
	Moderately differentiated (8)	1 (2.2%)	1 (2.2%)
	Poorly differentiated (1)	1 (2.2%)	0
TNM staging	Stage I (2)	0	1 (2.2%)
	Stage II (6)	2 (4.5%)	1 (2.2%)
	Stage III (23)	6 (13.6%)	1 (2.2%)
	Stage IV (13)	4 (9.0%)	4 (9.0%)

Table 2: Premalignant Changes (n = 44) with respect to age, sex, duration of exposure, habits, sites, primary tumor histology and TNM staging.

Discussion

Our present study has quantified the incidence and the type of field change that occurred in the clinically normal-looking oral mucosa of patients presenting with single primary oral squamous cell carcinoma with the help of histological evaluation of 'mirror image' biopsies taken from the contralateral anatomical site. Head and neck cancer is not the regional mucosal disease, can affect any part of aero digestive tract with different predilection rates for different sub sites and one site involvement rate independent of other [12].

Though the incidence of second field tumors is at the rate of 3.6% per year in aero digestive tract), neither precise nature of genetic alterations nor the structural changes leading to the development of carcinoma are until well established [1,8]. Our present study goes in favor with the study done by Tabor, et al. in 2001 who demonstrated loss of heterozygosis in non-contiguous mucosa biopsies by microsatellite markers on chromosomes 9p, 3p and 17p [13].

The study group consisted of 44 unilateral, single, histologically confirmed primary oral squamous cell carcinoma patients, out of which 45.5% were males and 54.5% were females with the male to female ratio being 0.8:1. This M: F ratio is not consistent with the Rahman, et al. (2014) who demonstrated the ratio to be 1.5:1 in oral SCC patients attending a tertiary hospital in Bangladesh, and 3.4:1 by Maria, et al. in 2001 in oropharyngeal cancer in American population [14,15]. Our finding that M:F ratio of 0.8:1 is unique because that study did not account for betel nut chewing habits of oral cancer patients.

The age of the patients ranged from 28 to 76 years, with the mean age being 55.09 + 10.71 years' standard deviation. In the present study, 28 (63.6%)s of the subjects was above the age of 50 years and 16 (36.6%) were equal to or below 50 years, which supports the fact that oral cancer is a disease of increasing age. Our findings of the incidence of premalignant changes follow increasingly with the age as evidenced by 13 (29.5%)s of patients more than 50 years of age displayed dysplasia whereas the only 7 (15.7%) under or equal to the age of 50 years had such changes. These findings were consistent with the similar study by Hebbale, et al. [16]. The Higher rate of oral cancer has been found between the 30-54-year-old group and the 55-69-year-old group according to a study by National cancer institutes the USA [17,18].Our finding also complies with the findings of this study but with higher incidences in the latter group.

The longer the duration of exposure, the more the occurrence of cancer and the more dysplastic changes as evidenced by 9 (20.4%) dysplasias in exposure group of 21-40 years and 7 (15.8%) in the age group 5-20 years. Llewellyn, et al. found greater or equal to 21 years of exposure to tobacco pose the highest risk factor for oral cancer in a prospective study after analysis of the risk factors for oral cancer [19].

In the current study, the site of occurrence of oral cancer was found the highest in buccal mucosa 24 (54.5%), followed by GBS 8 (18.1%), tongue 6 (13.6%). Dysplastic changes were more in buccal mucosa in 8 (18.1%) followed by gingivobuccal sulcus in 4 (9.0%). Our findings were consistent with the study by Hebbale, et al. but differed in a study by Thomson, where he found more dysplastic changes in tongue and floor of the mouth in oral cancer and precancer patients [16,1]. The difference would be due to the trend of placement of betel quid in buccal vestibule leading to more occurrences of dysplastic changes in betel nut chewing population of our study.

Pan with betel nut and tobacco combination consumption has the more potential to cause dysplastic changes as evidenced by 10 (22.7%) dysplastic changes in our study followed by pan with betel nut chewers

and smokers. These findings are near to the study by Hebbale, et al. [16].

Most cases of cancer at presentation were at well-differentiated stage and clinical TNM staging of stage III in our study. Dysplasia was found more in well-differentiated carcinoma groups and TNM stage IV groups. In the study by Hebbale, et al. most of the patients had well-differentiated SCC but the correlation between histological grading and TNM staining to field cancerization is unique to our study [16].

The mirror imaged mucosa in our study revealed 16 (36.3%) dysplasias, mild to moderate dysplasia in a ratio of 1:4 in total 44 biopsies from 7 different intraoral subsites. Epithelial dysplasia is the histologic characteristic feature of pre cancer and acts as predictive of an increased rate of transformation to squamous cell carcinoma [20]. A per Al-Dakkak, et al. the mean transformation rate of dysplasia to carcinoma was 12.1% and time to malignant transformation 4.3% in a randomized control study [21]. Dysplasia represents the precancerous condition of oral mucosa which may present clinically as leukoplakia, erythroplakia or erythroleukoplakia. In our study, also we encountered four cases of leukoplakia where two of them were also associated with dysplasia.

Thomson in his study revealed histological features of chronic mucosal irritation, dysplasia or pre malignancy in clinically normal-looking mucous membrane from mirror image site in oral cancer patients and established that floor of mouth and tongue happen to be more vulnerable to premalignant changes, but in our study premalignant changes were predominantly limited to buccal mucosa and gingivobuccal sulcus [1]. Hence it demands that further research is needed to establish preferential oral sub sites prone to dysplasia. Wright and Shear demonstrated oral squamous cell carcinomas to be surrounded by areas of leukoplakia to support that a field defect extends peripherally from the neoplasm as demonstrated by dysplastic features [22]. These features can also appear at distant site inflicted by carcinogens as proved by exfoliating cytological studies in smears prepared from contralateral mucosal sites in oral cancer patients in the form of nuclear cytoplasmic asynchrony and decrease in cytoplasmic areas [22].

The second field tumors are difficult to predict but affect negatively in survival rate and quality survival of remaining life. Lund reported the death of many patients due to second primary squamous cell malignancies in the aero-digestive tract of those previously diagnosed and treated for index tumors [23]. It appears here that mirror image biopsy is an indispensable histological tool to identify high-risk subjects to develop second primaries at the earliest.

Conclusion

From our study, it can be concluded that clinically normal appeared mirror image oral mucosa in oral cancer patients may already have developed dysplasia which has the potential to turn to malignancy due course of time. Mirror image biopsy could be valuable and cost effective diagnostic tool to detect these changes at the earliest, which can be helpful for taking necessary measures to digress the malignant transformation. Those patients were presented with dysplasia, recommended to avoid the predisposing factors and be remaining under regular follow up.

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