ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2024; 10(4): 332-337

www.oraljournal.com
Received: 06-11-2024
Accepted: 08-12-2024

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Evaluation of mirror image biopsy technique for the detection field change in patient with squamous cell carcinoma of oral tongue

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DOI: https://doi.org/10.22271/oral.2024.v10.i4e.2081

Abstract
Background: Squamous cell carcinoma (SCC) of the tongue is rising globally, particularly among individuals under 45, possibly due to genetic or unidentified etiological factors. In 2020, Iraq's prevalence (1.6/100,000) was lower than neighboring and industrialized countries. The mirror image biopsy technique, based on "field cancerization," involves biopsying the area opposite a confirmed lesion to identify hidden malignancies and guide treatment, especially in alcohol or tobacco users.
Aim: To histopathologically evaluate mirror image biopsy findings in tongue SCC patients to detect abnormalities ranging from reactive changes to malignancy.
Methods: A prospective study was conducted from January 2022 to December 2023 at the Maxillofacial Department, Al Shaheed Ghazi Al Harrery. Twenty tongue SCC patients (any age or gender) were included, excluding those with extensive, bilateral, or posterior tongue tumors or who declined the biopsy. Contralateral normal-appearing mucosa was biopsied under general anesthesia during primary tumor excision and analyzed histopathologically. Patients received post-operative care and follow-up.
Results: Among 20 cases, 60% showed hyperplasia, and 40% dysplasia (mild: 5; moderate: 2; severe: 1). The mean age was 56.4 years, with no significant age or gender differences (P=0.852). Tumor grade (P=0.033) and size (P=0.016) significantly influenced results, while lymph node status (p=0.083) and tumor position did not.
Conclusion: Dysplastic changes in mirror biopsies were significantly associated with higher tumor grades and larger sizes, highlighting the field cancerization concept. Comprehensive histopathological assessments are critical in managing tongue SCC.

Keywords: Mirror image biopsy technique, detection, patient, squamous cell carcinoma, oral tongue

Introduction

Squamous cell carcinoma (SCC) of the tongue represents a growing concern globally, signifying a notable shift in the epidemiology of oral malignancies. Analyzing data from over 80,000 patients registered in 22 international cancer registries reveals alarming trends, with tongue SCC increasing across all demographics and regions. While this rise is evident in all groups, a dramatic surge is noted in younger individuals under 45, emphasizing the need to explore genetic or unidentified etiological factors in disease development. Interestingly, gender-based disparities are evident, as the incidence among women has risen more sharply in some countries, highlighting potential gender-specific etiologies [1]. In Iraq, the prevalence of oral cavity cancer in 2020 was estimated at 1.6 per 100,000, notably lower than neighboring countries such as Saudi Arabia (3.9), Iran (3.8), and Turkey (7), as well as industrialized nations like the United States (23.7), Canada (25.5), and the United Kingdom (29.9). These figures are sourced from the World Health Organization Cancer Registry 2020, demonstrating significant regional variability in SCC incidence [2]. The development of SCC is associated with mutations in key genes. Mutations in TP53, a gene encoding the "guardian of the genome", disrupt cell cycle arrest and apoptosis mechanisms, leading to uncontrolled cell growth. Similarly, alterations in CDKN2A (p16), PIK3CA, and EGFR contribute to dysregulation of cellular processes, fostering malignancy.

Human papillomavirus (HPV) oncoproteins, specifically E6 and E7, further inhibit tumor suppressors like p53 and Rb, enhancing carcinogenesis [3-5]. Environmental and behavioral risk factors also play critical roles. Chronic irritation from poorly fitting dentures or sharp teeth can trigger repeated cellular injury, promoting carcinogenesis. Tobacco use introduces carcinogenic compounds like polycyclic aromatic hydrocarbons and aldehydes, which damage DNA. Alcohol, while not inherently carcinogenic, increases mucosal permeability, potentiating the effects of tobacco-derived carcinogens. HPV infections, especially with types 16 and 18, contribute significantly to tongue SCC by disrupting cell cycle regulation and promoting unchecked proliferation [6, 7]. Premalignant conditions such as leukoplakia, erythroplakia, and lichen planus are associated with varying risks of malignancy. Leukoplakia, characterized by white patches, progresses to SCC in 1-5% of cases, while erythroplakia, a red velvety lesion, carries a higher malignancy risk, with up to 50% already displaying SCC at diagnosis. Lichen planus, although less aggressive, requires careful monitoring due to its potential for malignant transformation [8-10]. The clinical presentation of tongue SCC varies by tumor location, size, and metastatic spread. Early signs include persistent ulcers or white/red patches, progressing to pain, dysphagia, and unexplained weight loss. Macroscopic features include irregularly shaped ulcers with indurated bases, while microscopic examination reveals keratinization, cellular atypia, and tissue invasion. Investigations such as biopsies, imaging, and HPV testing are critical for staging and treatment planning [11, 12].

The "field cancerization" concept underpins the utility of mirror image biopsy, detecting premalignant or malignant changes in clinically normal mucosa contralateral to primary tumors. This approach emphasizes the widespread impact of carcinogens across oral tissues, necessitating ongoing monitoring and comprehensive histopathological evaluation [13, 14]. Addressing the complex biology and causative factors of tongue SCC requires a multidisciplinary approach and further research into prevention and treatment strategies. Aim of the Study: To evaluate mirror image biopsy taken from clinically normal mucosa at the contralateral anatomical site to the primary lesion in patients with oral squamous cell carcinoma to detect abnormal features in oral mucosa, such as reactive change, tissue proliferation, hyperkeratosis, cellular atypia, dysplasia, and histopatho.

Methods

This prospective study was conducted in the Maxillofacial Department at Al-Shaheed Ghazi Al-Hariri for Specialized Surgeries from January 2022 to December 2023. It involved 20 patients diagnosed with squamous cell carcinoma (SCC) of the oral tongue.

- **Ethical Considerations:** All patients provided informed consent, and their data was anonymized and encrypted for security. Ethical approval was obtained from the Council of the Iraqi Board of Medical Specialization and the Maxillofacial Department.
- **Inclusion and Exclusion Criteria:** Patients with tongue SCC of any age or gender were included. Exclusion criteria comprised extensive midline or bilateral tumors, posterior tongue lesions, radiotherapy recipients, and patients who declined mirror image biopsy.
- **Patient and Clinical Data:** Demographic details, lifestyle habits (e.g., smoking, alcohol use), and medical history were recorded from patient files. Clinical examination included inspecting the size, site, and extent of the primary lesion and lymph nodes.
- **Biopsy Procedure:** Under general anesthesia, the primary lesion was excised with a 1.5 cm margin, followed by neck dissection. A wedge-shaped biopsy of 0.5-1 cm from the contralateral, clinically normal mucosa was taken, avoiding cautery to preserve tissue integrity. The wound was closed with silk sutures, and the sample stored in 10% formalin for histopathology.

Histopathology

Samples were stained with hematoxylin and eosin to assess reactive alterations, hyperkeratosis, cellular atypia, dysplasia, or malignancy.

- **Postoperative Care and Follow-Up:** Postoperative care included antibiotics (ceftriaxone or azithromycin), analgesics (acetaminophen), oral hygiene instructions, and nasogastric tube use. Sutures were removed after seven days.
- **Statistical Analysis:** Data was analyzed using SPSS, with results presented as counts, percentages, means, and SDs. P-values <0.05 were considered statistically significant.

Results

The study included 20 cases. Mirror image biopsy showed features of hyperplasia in 12 cases (60%) and dysplasia found in 8 cases (40%), as shown in (Figure 1).

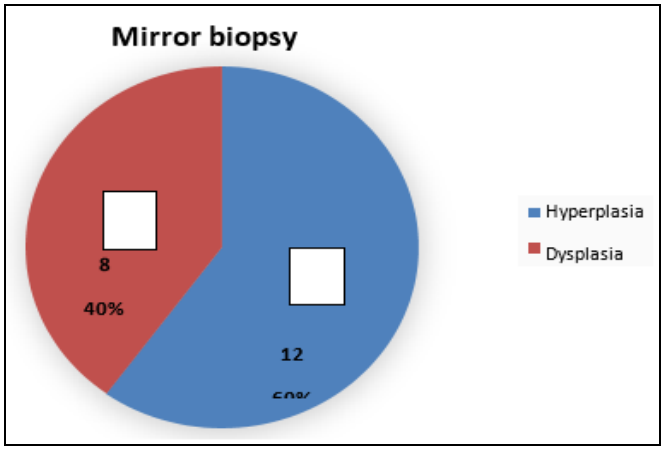

Fig 1: Hyperplasia and Dysplasia of Mirror Biopsy

The 8 cases of dysplasia were further divided according to the level of differentiation into 5 cases mild dysplasia, two cases moderately dysplasia, and one case was severe dysplasia, as shown in (Figures 2).

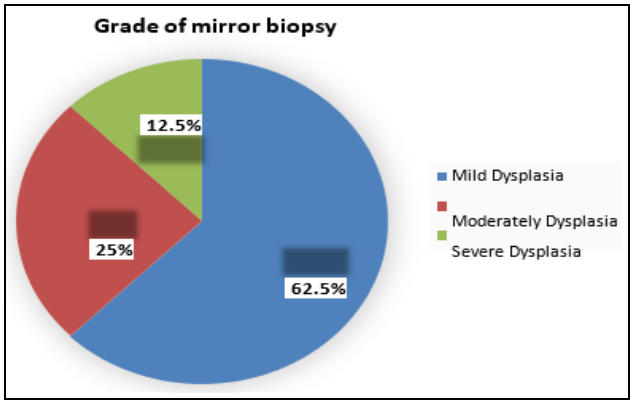

Fig 2: Grade of Dysplasia of Mirror Biopsy

Five male participants were found to have hyperplasia, or 41.7 percent of all the male participants. Three male subjects, or 37.5 percent of the total number of male participants, had dysplasia. Seven females, or 58.3% of the total female participants with this disease, had hyperplasia. Five women were found to have dysplasia, making up 62.5 percent of all the female participants. The p-value associated with the differences observed between males and females in this study was 0.852. This high p-value suggests that there is no statistically significant difference between the two genders in terms of the occurrence of hyperplasia or dysplasia when evaluated using the mirror image biopsy technique (Table 1).

Table 1: Relation between mirror biopsy result and gender

Variables		Hyperplasia	Dysplasia	P-Value
		No (%)	No. (%)	
Sex	Male	5 (41.7)	3 (37.5)	0.852
	Female	7 (58.3)	5 (62.5)	
Total		100%	100%	

Six people, or 50% of the total participants with tumor on the right side, showed signs of hyperplsia on the mirror biopsy. Three people 37.5 percent of the total participants with tumor on the right side showed dysplasia. Six people, or 50% of the total participants with tumor on the left side, were determined to have hyperplasia. Five people, or 62.5 with tumor on the left side, had dysplasia. The p-value associated with the observed differences between the right and left sites in this study was 0.582. This suggests that there is no statistically significant difference between the two sites in terms of the occurrence of hyperplasia or dysplasia when assessed using the mirror image biopsy technique. As shown in (Table 2).

Table 2: Distribution of the site of tumor and result of mirror biopsy

Variables		Dysplasia	Hyperplasia	P-Value
		No (%)	No. (%)	
Site	Right	3 (37.5)	6 (50)	0.582
	Left	5 (62.5)	6 (50)	
Total		100%	100%	

Six samples, or 30%, were deemed to be well differentiated and showed either hyperplasia or dysplasia. Five tissue samples, or 41.7 percent of the samples with well differentiated grade, had hyperplasia visible. One sample, or 12.5 percent of the samples in same grade, had dysplasia. Eight (or 40%) of the samples with intermediate differentiation exhibited hyperplasia or dysplasia. Six tissue samples, or 50% of the samples in moderately differentiated grade, showed signs of hyperplasia. Two samples, or 25% of the samples in this grade, had dysplasia, which was found. Six (or 30%) of the samples that were deemed to be poorly differentiated overall showed dysplasia or hyperplasia. One tissue sample, or 8.3% of the samples in this grade, contained hyperplasia. In 5 samples, or 62.5 percent of the samples in this grade, dysplasia was found. The p-value for this was 0.033. This shows that when employing the mirror image biopsy technique, there is a statistically significant variation in the incidence of hyperplasia and dysplasia across the various grades of differentiation. As shown in (Table 3).

Table 3: Distribution grade of primary tumor according to result of mirror biopsy

Variables		Hyperplasia	Dysplasia	P-Value
		No. (%)	No. (%)	
Grade	Well Differentiated	5 (41.7)	1 (12.5)	0.033
	Moderately Differentiated	6 (50)	2 (25)	
	Poorly Differentiated	1 (8.3)	5 (62.5)	
Total		100%	100%	

*P-Value <0.05 significant

Hyperplasia was observed in 3 tumor samples, representing 25% of the samples categorized as T_1. Dysplasia was not detected in any of the T_1 samples. Hyperplasia was present in 5 tumor samples, accounting for 41.7% of the samples within T_2 stage. Dysplasia was not noted in any of the T_2 samples. Hyperplasia was found in 3 tumor samples, which constitutes 25% of the samples in T_3 stage. Dysplasia was observed in 3 samples, making up 37.5% of the T_3 samples. Hyperplasia was detected in 1 tumor sample, representing 8.3% of the samples categorized as T_4. Dysplasia was noted in 5 samples, accounting for 62.5% of the T_4 samples. The p-value associated with these results was 0.016. This indicates a statistically significant difference in the occurrence of hyperplasia and dysplasia across different T stages when assessed using the mirror image biopsy technique. As shown in in (Table 4).

Table 4: Distribution of Tumor Size (T) according to the result of mirror biopsy

Variables		Hyperplasia	Dysplasia	P-Value
		No. (%)	No. (%)	
T	T_1	3 (25)	0 (0)	0.016
	T_3	3 (25)	3 (37.5)	
	T_4	1 (8.3)	5 (62.5)	
Total		100%	100%	

*p-value: <0.05 is significant

Hyperplasia was observed in 5 samples, representing 45.5% of the samples classified as N0. Dysplasia was detected in 7 samples, accounting for 87.5% of the No samples. Hyperplasia was present in 5 samples, constituting 45.5% of the samples within this N stage. Dysplasia was not noted in any of the N1 samples. Hyperplasia was found in 1 sample, which makes up 9.1% of the samples in this N stage. Dysplasia was observed in 1 sample, representing 12.5% of the N2 samples. The p-value associated with these findings was 0.083. While this indicates a trend towards significance, it does not meet the conventional threshold of 0.05 for statistical significance. Therefore, while there are differences in the occurrence of hyperplasia and dysplasia across different N stages when using the mirror image biopsy technique, these differences are not statistically significant, as shown in Table 5.

Table 5: Patient and tumor characteristics according to the result of mirror biopsy

Variables		Hyperplasia	Dysplasia	P-Value
		No. (%)	No. (%)	
N	N0	5 (41.7)	7 (87.5)	0.083
	N1	6 (50)	0 (0)	
	N2	1 (8.3)	1 (12.5)	
Total		100%	100%	

Of the males, 2 (25%) had biopsies from the right site, while a larger portion, 7 (58.3%), of females had biopsies from the same site. Overall, 9 (45%) of the biopsies were from the right site. In contrast, 6 (75%) of the males had biopsies from the left site, and 5 (41.7%) of females. This totals 11 (55%) biopsies from the left site. The p-value for a site based on gender is 0.142, which is not statistically significant. One (12.5%) male and 5 (41.7%) females were well differentiated. four (50%) males and 4 (33.3%) females were moderately differentiated. Three (37.5%) of males and 3 (25%) of females were poorly differentiated. The p-value for grade based on gender is 0.378, suggesting no significant difference between the genders. The distribution between males and females was as follows: T_1 was observed in 1 (12.5%) male and 2 (16.7%) females, totaling 3 (15%) samples; T_2 comprised 2 (25%) males and 3 (25%) females, summing up to 5 (25%); T_3 was identified in 3 (37.5%) males and 3 (25%) females, aggregating to 6 (30%) samples; and T_4 included 2 (25%) males and 4 (33.3%) females, totaling 6 (30%). A p-value of 0.937 suggests there's no statistically significant difference in the distribution of T stages between male and female patients. A total of 12 (63.2%) samples were categorized as N0. three (37.5%) males and 9 (81.8%) females showed no regional lymph node involvement. For N1 which makes up 5 (26.3%) of the samples. Equal representation was observed in males (3 or 37.5%) and females (2 or 18.2%). The total number of N2 cases was 2 (10.5%) samples. 2 (25%) males and no females were observed in this category. The p-value for N stage based on gender is 0.089, indicating a trend towards significance but not reaching the conventional threshold. As shown in Table 6.

Table 6: Distribution of data according to gender

Variables		Male	Female	P-Value
		No. (%)	No. (%)	
Site	Right	2 (25)	7 (58.3)	0.142
	Left	6 (75)	5 (41.7)	
Grade	Well Differentiated	1 (12.5)	5 (41.7)	0.378
	Moderately Differentiated	4 (50)	4 (33.3)	
	Poorly Differentiated	3 (37.5)	3 (25)	
T	T_1	1 (12.5)	2 (16.7)	0.937
	T_2	2 (25)	3 (25)	
	T_3	3 (37.5)	3 (25)	
	T_4	2 (25)	4 (33.3)	
N	No	3 (37.5)	9 (75)	0.089
	N1	3 (37.5)	3 (25)	
	N2	2 (25)	0 (0)	

Discussion:

The concept of *field cancerization* provides a robust framework to understand the histopathological changes observed in mirror biopsies of oral squamous cell carcinoma (OSCC) of the tongue. This study reinforces the concept, as all mirror biopsies showed abnormal results, including hyperplasia or dysplasia, even in early-stage tumors (T_1). Dysplasia was observed in 40% of cases, consistent with findings by Hebbale *et al.* [15] (48%) and slightly lower than Babu *et al.* [16], where all cases exhibited dysplasia. Differences may stem from variations in exposure to risk factors like tobacco, which was a significant factor in the Babu *et al.* study.

- **Age and Gender Distribution**: Age and gender did not significantly influence the histopathological outcomes of mirror biopsies. Previous studies, such as those by Yasin *et al.* [17], indicated a higher prevalence of tongue SCC in females (60%) compared to males (40%), but gender's impact on mirror biopsy outcomes remains unexplored.
- **Tumor Grade and Dysplasia**: Higher tumor grades were significantly associated with dysplasia in mirror biopsies. Ganly *et al.* [18] reported that higher tumor grades correlate with worse outcomes, aligning with our findings. The increased dysplasia rate near high-grade tumors can be attributed to several mechanisms, including field cancerization, clonal expansion, and micro environmental alterations induced by aggressive tumors. As suggested by Tabor *et al.* [19] and Petersen *et al.* [20], these mechanisms may involve the secretion of signaling molecules and genetic instability, which further predispose adjacent tissues to malignancy.
- **Tumor Size**: Larger tumors showed a greater association with dysplasia in mirror biopsies. This observation is supported by Liao *et al.* [21], who found that greater tumor burden correlates with larger zones of cancerization. Larger tumors may expand clonally, secreting growth factors and cytokines that disrupt adjacent tissue environments. Studies by Braakhuis *et al.* [22] and Hanahan *et al.* [23] further support the link between tumor size and the extent of carcinogenic influence, with increased angiogenesis and invasiveness exacerbating the genetic and epigenetic alterations in surrounding tissues.
- **Lymph Node Status**: Lymph node involvement showed no significant correlation with mirror biopsy results. This aspect has been poorly explored in the literature, leaving room for further investigation.
- **Implications for Diagnosis and Treatment**: The findings emphasize the need to reconsider diagnostic and

treatment approaches. Conventional imaging and sampling may fail to capture the full extent of the cancerization field. Enhanced detection methods could identify dysplastic or malignant changes earlier, improving outcomes [24]. Furthermore, surgical margins may need re-evaluation. Traditional margins might not encompass all affected tissues, as field cancerization suggests a broader zone of influence. Adjunctive therapies, such as chemotherapy or targeted treatments, may be necessary to address microscopic field changes [25].

- **Public Health Implications:** The association between dysplasia in mirror biopsies and exposure to carcinogens underscores the importance of public health interventions. Limiting exposure to risk factors like tobacco and alcohol is critical to preventing both primary tumors and secondary malignancies resulting from field cancerization [16]. This study underscores the significance of field cancerization in understanding tongue SCC progression and highlights the importance of comprehensive histopathological evaluation in clinically normal-appearing tissues for better disease management.

Conclusion

Substantial correlations have been identified between elevated tumour grades, increased tumour diameters (T_3 and T_4), and dysplastic alterations observed in mirror biopsies. The findings underscore the principle of field cancerisation and highlight the significance of thorough histopathological assessments in oral squamous cell carcinoma (OSCC). The study found no statistically significant disparities between genders in the progression of hyperplasia or dysplasia.

The absence of statistical significance in the age distribution of patients with hyperplasia or dysplasia highlights the broad applicability of mirror biopsy across different age demographics, thereby demonstrating its effectiveness in a variety of patient populations.

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Mashaan OA, Jameel N. Evaluation of mirror image biopsy technique for the detection field change in patient with squamous cell carcinoma of oral tongue. International Journal of Applied Dental Sciences. 2024;10(4):332-337.