A RETROSPECTIVE CASE REVIEW OF SOFT TISSUE ORAL MALIGNANCIES AND ASSOCIATED CLINICOPATHOLOGIC FEATURES (1991-2016)

by

Madawi Faisal Alkeheli

B.D.S, King Abdulaziz University, 2013

Submitted to the Graduate Faculty of

The School of Dental Medicine in partial fulfillment

of the requirements for the degree of

Master of Dental Sciences

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

SCHOOL OF DENTAL MEDICINE

This thesis was presented

by

Madawi Faisal Alkeheli

It was defended on

December 14, 2017

and approved by

Mark Mooney, PhD, Professor, Department of Oral Biology

Elia Beniash, PhD, Professor, Department of Oral Biology

Anitha Potluri, DMD, Associate Professor, Department of Diagnostic Sciences

Thesis Director: Elizabeth Ann Bilodeau, DMD, MD, Associate Professor, Departments of Diagnostic Sciences and Oral Biology

A RETROSPECTIVE CASE REVIEW OF SOFT TISSUE ORAL MALIGNANCIES AND ASSOCIATED CLINICOPATHOLOGIC FEATURES (1991-2016)

Madawi Alkeheli, B.D.S, M.S.

University of Pittsburgh, 2017

Intraoral soft tissue masses can clinically present as benign, premalignant, or malignant lesions. Variability in presentation of soft tissue masses bear the possibility of misdiagnosis not only by general dentists but also by specialists. After a differential diagnosis is formulated, histopathologic evaluation is essential for establishing a definitive diagnosis.

Neoplastic oral lesions in their early stages are subtle, which can make diagnosis challenging. Dentists play a vital role in the prevention of oral malignancy by early detection, and a thorough understanding of the diagnostic features. However, as most intraoral pathology is benign, clinicians frequently do not include malignancy in their differential diagnosis for soft tissue masses.(1) The aim of this study is to emphasize the need for histologic diagnosis of seemingly benign soft oral lesions as the clinical impression may not be accurate.(2-6)

We hypothesize that there will be a large number (~5%) of false negative diagnoses. These are cases in which the initial clinical diagnosis is a benign entity (e.g. fibroma or pyogenic granuloma) may change, upon histologic confirmation, to a pathologic diagnosis of a soft tissue malignancy. We will also identify which clinical features (i.e. size, color, or clinical differential diagnoses) that were most commonly diagnostic pitfalls. The purpose of the study is to elucidate the features most commonly associated with malignancy.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

My deep gratitude goes to my supervisor, my mentor, my role model, and my friend Dr. Elizabeth Bilodeau who made everything possible, and guided me through all. I'm so grateful for the great support she has been to me, and I'm thankful for the opportunity she gave me to work with her, and learn from her.

I would like to dedicate this to my husband, my two beautiful angles, and to my mom and dad in Saudi Arabia who I wish I can return some of their hard work they devoted for me.

My special thanks go to the smartest, kindest, and most humble person Dr. Mark Mooney for his guidance, and support. It has been a great pleasure knowing him.

I would like to thank my committee members, Dr. Elia Beniash who I'm blessed to be taught by him, all the knowledge he gave was precious. Special thanks to Dr. Anitha Potluri.

I would like to thank Dr. Shah for his assistance and guidance in the statistical analysis.

I'm thankful for the oral pathology department, Dr. Summersgill, and all faculty members and co-residents. As well as the oral biology department, faculty and friends.

1.0 BACKGROUND

Intraoral soft tissue masses can clinically present as benign, premalignant, or malignant lesions. Variability in presentation of soft tissue masses create the possibility of misdiagnosis not only by general dentists but also by dental specialists. After a clinical differential diagnosis is formulated, histopathologic evaluation is essential for establishing a definitive diagnosis.

Neoplastic oral lesions in their early stages are subtle, which can make diagnosis challenging. Dentists play a vital role in the management of oral malignancy by the detection of premalignant lesions and early detection of cancer with routine head and neck examinations. However, as most intraoral pathology is benign, clinicians frequently do not include malignancy in their differential diagnosis for soft tissue masses.(1) The aim of this study is to emphasize the need for histologic diagnosis of seemingly benign soft oral lesions as the clinical impression may not be accurate.(2-6)

We hypothesize that there will be a significant number (~5%) of false negative clinical diagnoses. These are cases in which the clinical impression is a benign entity (e.g. fibroma or pyogenic granuloma) but, upon histologic evaluation the pathologic diagnosis is of a malignant soft tissue mass. We will also identify which clinical features (i.e. size, color, or clinical differential diagnoses) are most common diagnostic pitfalls. The purpose of the study is to elucidate the features most commonly associated with malignancy.

Each year, in the United States, approximately 49,670 new oral cancers are diagnosed with 9,700 estimated deaths, making oral cancer the sixth most common cause of cancer mortality.(7) The majority of oral cancers are squamous cell carcinoma (SCC) which accounts for over 95% of all oral malignancies. Premalignant dysplastic epithelial lesions precede oral SCC. Other less common malignancies are seen in the oral cavity. Lymphomas comprise 3% of oral tumors.(8) Sarcomas originate from mesenchymal cells and compose 1% of oral and maxillofacial malignancies.(4) Metastasis to the oral cavity is rare, accounting for 1% of all oral malignancies.(5, 6) The rarity of these malignancies further increases the difficulty of diagnosis, with variable

clinical features associated with different malignancies.

Malignant soft tissue masses in the oral cavity pose diagnostic difficulties. General dentists, who serve as the first line of patient contact, may not have substantial experience with oral cancer. The non-specific clinical presentation of these malignant masses may contribute to misdiagnosis, delayed, or improper treatment. The lesion may have a variable non-specific appearance as a flat white or red patch, an ulcer, or an exophytic mass. Intraoral soft tissue masses can clinically present as benign, premalignant or malignant lesions. (1)

Evidence suggests that routine examination for potential oral malignancies by trained health care providers will lead to diagnosis at a lower pathologic stage at diagnosis.(9) Comprehensive oral examination, cervical lymph node palpation, as well as immediate referrals are essential components in early detection of malignancy, and reduction of mortality rates.(10, 11) Routine dental examination at time of bi-annual dental prophylaxis provides an opportunity to detect early asymptomatic cancer lesions.(9) Effective oral screening requires a knowledge of the risk factors, pathogenesis, and clinical behavior of malignant lesions. Upon identifying a lesion arising in the oral cavity, clinicians formulate a detailed description of the lesion, classifying it into the appropriate category based on salient features (e.g white lesion that is easily wiped off, red lesion, or an ulcer). Subsequently, based on the signs and symptoms and knowledge of the incidence of each entity, a prioritized differential diagnosis is created.(10) The priority ranking of differential diagnoses accounts for incidence, relative frequency, age, gender, race, and anatomical location of the lesion.

We hypothesize that there will be a significant number of cases in which the clinical diagnosis is a common benign entity (e.g. fibroma or pyogenic granuloma) but, upon histologic evaluation the pathologic diagnosis is of malignancy.

1.1 SQUAMOUS CELL CARCINOMA

Pain is one of the main presenting symptom in advanced stages of oral SCC as nerves or muscles are infiltrated, and it varies from mild to severe in intensity.(12) Therefore, early lesions are painless, asymptomatic, or associated with a vague discomfort, but not overt pain. However, tongue and floor of mouth lesions present with pain earlier.(12)

An association between the primary tumor size and the existence of ulceration, bleeding and lymphadenopathy has been found. Central ulceration and ill-defined borders are observed in mature lesions.(13) Large oral malignant lesions are easier to diagnose than small lesions, misdiagnosis is associated with lesions presenting with seemingly innocent alterations such as color change or ulcers misdiagnosed as aphthae.(9) Ulcers in oral SCC manifest an irregular margin with elevation.

SCC can range from few millimeters to several centimeters in size. Tumor thickness alters the clinical appearance of malignancies in the oral cavity. With time and growth of tumor, the gross morphology will show a thickened mucosa, or an exophytic mass. Thick tumors are frequently ulcerated, with a low propensity of presenting erosions or plaques. Whereas, premalignant lesions are more likely to be thin.(14)

Mortality is higher among lesions located in the retromolar trigone, and large tumors (T3-T4), as well as positive lymph nodes (N2a- N2b)(12). Early oral SCC mostly present as a relatively well-demarcated erythroleukoplakia, with slight surface roughness. In the anatomic location of the buccal mucosa and gingiva, tumors involving the tongue and retromolar trigone are associated with higher risk of cervical metastasis.(15)

Soft tissue changes include loss of elasticity and induration upon palpation. Classic features of advanced stages include fixation to tissue, and induration. Other less common presentations include delayed healing after tooth extraction in an otherwise healthy individual, numbness of the chin, or a lump with increase vascularity.

The oropharynx consists of the soft palate, lateral walls of pharynx, tonsils fossa, and the base of the tongue.(16) Clinically, oropharyngeal SCC presents with dysphagia,

odynophagia and otalgia. The tissue structure and lymphatic drainage of the oropharynx, which is unique to this anatomic site, permits the malignant cells to more easily travel, resulting in a faster progression, with patients more commonly presenting with advanced tumor stage (III, or IV).(17) Human papilloma virus is the most significant factor in the prognosis of oropharyngeal SCC. The process of carcinogenesis is related to "*viral oncoproteins, E6 and E7, which bind and inactivate tumor suppressors, p53 and pRb, respectively. Deficiency of p53 and Rb results in loss of cell cycle checkpoints and physiologic apoptosis*."(17) Young men are mostly affected by HPV oropharyngeal SCC, and primary sites are small, if present, with increased nodal involvement.(17) Primary base of tongue lesion, tonsillar, or nasopharyngeal SCC present with a 5% rate of cervical lymph node involvement with no clinically apparent oral lesion.(12) HPV status of oropharyngeal SCC is prognostically important, as patients have a 50% lower risk of death compared to HPV-negative SCC.(18)

While conventional SCC is the most common variant of SCC, other variants exist that are clinically relevant, including papillary SCC and verrucous carcinoma. Papillary SCC demonstrates an exophytic mass with a broad base attached to the mucosa, or a projected by a stalk. The finger-like projections dominate an infiltrative, endophytic growth.(16) Verrucous carcinoma is a slow growing tumor that appears clinically as a broad plaque that is distinct from the mucosa. It demonstrates a thickened texture with gray-white projections. Clinically, both of these variants of SCC behave more indolently, with verrucous carcinoma having a very low rate of metastases to the lymph nodes allowing surgeons to forgo neck dissection.(16)

1.2 SALIVARY MALIGNANCY

While most salivary pathology is benign, malignancies are more likely to arise as tumors in minor glands.(19) Salivary gland tumors exhibiting rapid growth, pain and firmness prompt increased clinical consideration of a malignant lesion. Lack of pain is not always a sign of a benign entity.(20) Of the major salivary glands tumors, malignancy of the parotid gland is the most common.(21) Partial or complete facial nerve palsy, is an indicator of an infiltrating parotid gland malignancy.(22, 23) However, adenoid cystic carcinoma is seen mostly in minor

salivary glands. (19) The incidence of malignancies occurring in the minor salivary glands of the palate and submandibular gland are similar which are 40-60%. However, the incidence increases to 90 % in the tongue, floor of mouth, and sublingual glands.(24, 25)

1.3 LYMPHOMA

Representing 3% of oral malignancy, lymphoma is the third most common malignant tumor of the oral cavity after SCC, and salivary gland malignancies. Lymphomas of the oral cavity are present initially as an asymptomatic pink-blue, nodules or soft swelling with a predilection for the tonsils, palate and buccal mucosa. 50% of oral lymphomas may mimic infection as their first manifestation.(8) However, if continued growth exerts pressure on adjacent tissue, including nerves, pain may develop. Lymphomas are difficult to identify clinically as it mimics periodontal diseases, and osteomyelitis. 50% of oral lymphoma may present as an infection as their first manifestation.(8) Since oral manifestations may appear as the first clinical evidence of lymphoma, an accurate detection is essential.

1.4 ORAL METASTASIS.

Oral metastases accounts for 1% of oral malignancies.(5, 6) In 30% of cases, oral metastasis is the initial presentation of underlying disease. Gnathic bone is more often involved than oral soft tissue. The gingiva and alveolar mucosa accounts for 54.8% of oral soft tissue metastases followed by the tongue in 27.4% of cases.(26) Metastases to the gingiva may resemble a reactive lesion such as pyogenic granuloma. Although oral metastasis can be a challenge to diagnose accurately, clinical signs may include a rapidly growing lesion, tendency to bleed, a necrotic appearance, or ulceration. Changes in the patient’s systemic health such as weight loss, fatigue, and malaise may be important signs and symptoms. Metastatic tumors to the oral tissue in males are mainly from the lung, kidney and prostate. In contrast, females exhibit breast, ovarian, and kidney metastatic tumors into the oral cavity.(27)

2.0 MATERIAL AND METHODS

This is a retrospective study using data collected from the Oral Pathology Biopsy Service at the School of Dental Medicine, University of Pittsburgh. Cases of malignant soft tissue masses diagnosed between 1991 and 2016 are included. The patient demographics, anatomic site, clinical description, clinical history, risk factors, clinical impression of the dentist, and the histopathologic diagnosis rendered by the pathologists are recorded. This study is performed utilizing the Text Information Extraction System (TIES), a University of Pittsburgh Medical Center pathology database containing de-identified surgical pathology reports for retrieving data and identifying tissue. This system uses a natural language search strategy.

The inclusion criteria are all malignancies of the oral cavity diagnosed by the University of Pittsburgh Oral Pathology Biopsy Service including SCC, papillary SCC, lymphoma, salivary malignancy, sarcoma, and verrucous carcinoma. The exclusion criteria (420 cases) are cases without a clinical history, bone malignancies, non-malignant lesions (cases with the diagnosis of dysplasia, carcinoma-in-situ, or suspicious for SCC), and University of Pittsburgh Medical Center cases (rather than the University of Pittsburgh Oral Pathology Biopsy Service).

Classification by location is performed; cases with malignancy of the lip, gingiva, hard palate, soft palate, buccal mucosa, floor of mouth, tongue, maxillary tuberosity, retromolar trigone, and mucosa of the alveolar ridge are identified and included. Cases involving intraosseous malignancy are excluded, as this was a study of soft tissue pathology.

Histopathological reports and clinical information are analyzed for each case, information regarding demographic data (age, gender), risk factors (alcohol, tobacco), clinical history (duration, pain, bleeding, neuropathy, increase in size, tooth mobility, treatment, history of malignancy). The clinical appearance of the lesion such as (color, size, ulceration, texture) is recorded from the patients' surgical pathology report.

Texture was divided into two categories (i.e. verrucous/papillary/roughened or smooth). Clinical density on palpation was divided into two categories (i.e. firm/hard/indurated or soft). The gross description including the size and shape of the specimen was recorded. The dentists' clinical impression (1^{st} and 2^{nd} differential diagnosis) and the definitive histopathologic diagnosis are collected.

2.1 STATISTICAL ANALYSIS

The relation between clinicians' misdiagnosis of the oral lesions and all recorded variables (gender, age, color, duration, increase in size, history of malignancy, ulceration, texture and site) was assessed using univariate logistic regression (see Table 1), odds ratio (OR), and 95% confidence interval were estimated. Furthermore, a multivariable regression analysis (see Table 2) was performed to further explore the factors most affecting misdiagnosis. A reduced model (see Table 3) was conducted to analyze and remove statistically insignificant variables. All statistical analyses were conducted utilizing the STATA14 software. A P-value of $\leq$ 0.05 was considered significant.

3.0 RESULTS

Our analysis of 25 years (1991-2016) of biopsies submitted by dentists for histologic examination supported our hypothesis of a high rate of false negatives exists (i.e. that clinicians identify oral soft tissue malignancy as benign clinical entities at a high rate).

3.1 DEMOGRAPHIC FEATURES

This study sample consists 485 oral malignancies with a 1.14 to 1 male to female ratio (258 male, 226 female). The mean and median patient age was 66 (22 to 90 range.) The majority of oral malignancies are observed in individuals 45 years- and older (see Figure 1). Univariate analysis showed that gender (male) and age (younger patients) have a statistically significant greater likelihood of the lesion being clinically misdiagnosed, with an odds ratio (1.56 (1.01-2.41), 0.98 (0.97-1.00) and p-value (0.044, 0.047) respectively. See Table 1 for all variables assessed.

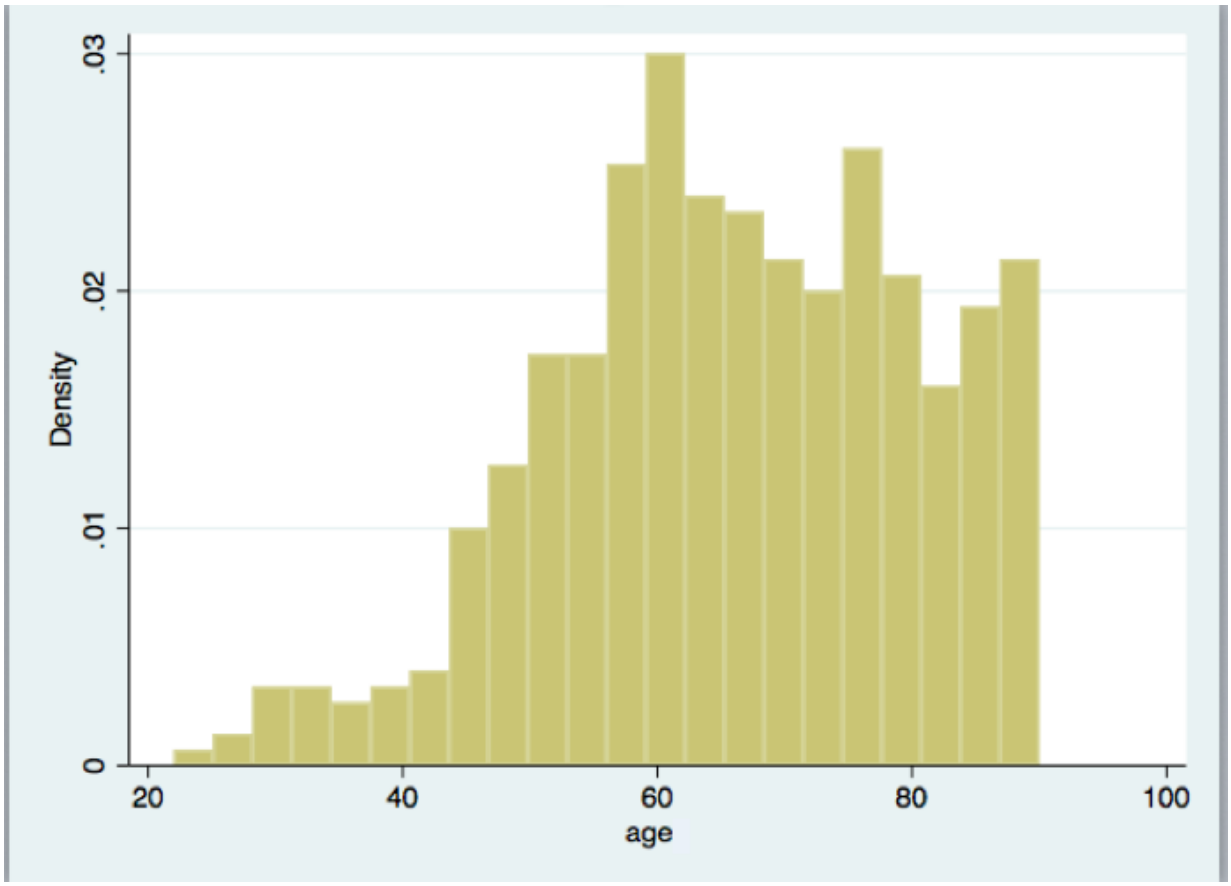

Figure 1. *Summary of Demographic Data*

The above density histogram demonstrates the distribution of patients age in the sample. The data spread is from 22 to 90 years old with the peak of data occurring at 60 years old. The density represents the area of the bar; the sum of the areas of all bars is equal to 1.

3.2 CLINICAL FEATURES

The results of this study confirm that tumors with leukoplakia are associated with higher risk of misdiagnosis. It was found that leukoplakic tumors (white tumors) have a 2.4 odds of misdiagnosis compared to mixed (red-white) tumors. We found that the odds of misdiagnosing SCC with an erythroplakic (red) component is less by 4%. Less common clinical appearance, including lesions with colors such as tan, brown, blue, yellow and gray, have a 1.9 higher chance of being misdiagnosed.

The clinical duration in months, and clinical history of prior malignancy were statistically insignificant with a p-value of 0.577, and 0.134 respectively.

The data confirmed that for every 1 cm increase in the size of oral tumor, the odds of misdiagnosis decrease by 43%, suggesting that smaller lesions were more likely to be missed. Therefore, clinicians tend to consider small lesions as being benign rather than malignant.

We found a relationship between lack of ulceration and the risk of misdiagnosis. Clinicians are often thought to associate lesions presenting as a non-healing ulcer as potential malignancy, on the other hand, lesions lacking ulceration are thought to be benign in nature. Of 485 cases, 105 had a history of ulceration, 7 had no history of ulceration, and for the majority, 373 cases, 76.9%, this variable was not reported (see Table 1). Oral tumors with ulceration have a 67% reduced odds of misdiagnosis, suggesting that non-ulcerated lesions were likely to be missed.

Table 1. Univariate Analysis of Odds of SCC Misdiagnosis

Variable	Odds Ratio (95% CI)	p-value
Gender (female baseline)	1.56 (1.01-2.41)	0.044
Age	0.98 (0.97-1.00)	0.047
Color (baseline: mixed)		0.047
Other	1.92 (0.85-4.33)	
Red	0.96 (0.45-2.05)	
White	2.42 (1.16-5.05)	
Duration (months)	1.01 (0.98-1.03)	0.577
Increase in size (cm)	0.62 (0.47-0.82)	0.001
History of malignancy	0.60 (0.31-1.17	0.134
Ulcerated	0.36 (0.21-0.61)	<0.001
Verrucous	0.89 (0.28-2.82)	0.842
Firm-hard-indurated	0.33 (0.12-0.96)	0.042
Site (baseline: Buccal		0.44

Mucosa)		
Mandible	0.71 (0.23-2.15)	
Maxilla	0.47 (0.10-2.27)	
Other	0.55 (0.28-1.33)	
Palate	0.41 (0.09-1.94)	
Tongue	0.85 (0.35-2.08)	

Table 2. Odds of SCC Misdiagnosis Multivariable Analysis

Variable	Adjusted Odds Ratio (95% CI)	p-value
Gender (female baseline)	1.97 (0.92-4.20)	0.080
Age	0.97 (0.94-1.00)	0.044
Color (baseline: mixed)		0.493
Other	1.44 (0.53-3.95)	
Red	0.65 (0.24-1.77)	
White	1.31 (0.52-3.30)	
Increase in size (cm)	0.62 (0.44-0.89)	0.008
Ulcerated	0.25 (0.08-0.73)	0.011

Table 3. Odds of SCC Misdiagnosis Multivariable Analysis Reduced Model

Variable	Adjusted Odds Ratio (95% CI)	p-value
Gender (female baseline)	1.47 (0.82-2.65)	0.198
Age	0.98 (0.96-1.00)	0.076
Increase in size (cm)	0.57 (0.42-0.77)	<0.001
Ulcerated	0.33 (0.16-0.65)	0.002

Among the recorded consistencies of oral lesions, clinically, the lesion was described as hard or indurated to palpation in 34 of 485 cases (451 cases had no data of this consistency). Lesions lacking this characteristic were less likely to be correctly clinically diagnosis (Odd ratio 0.33 (0.12-0.96), p=0.042.

The most common anatomic sites presenting with a malignancy in descending order were tongue (32 %), floor of mouth (11 %), buccal mucosa (10 %), lip (9%), gingiva (8 %), mandible (8 %), palate (7 %), alveolar ridge (5 %), retromolar pad (4%), maxilla (4%), vestibule (1 %), pharynx (1%) (see Figure 2).

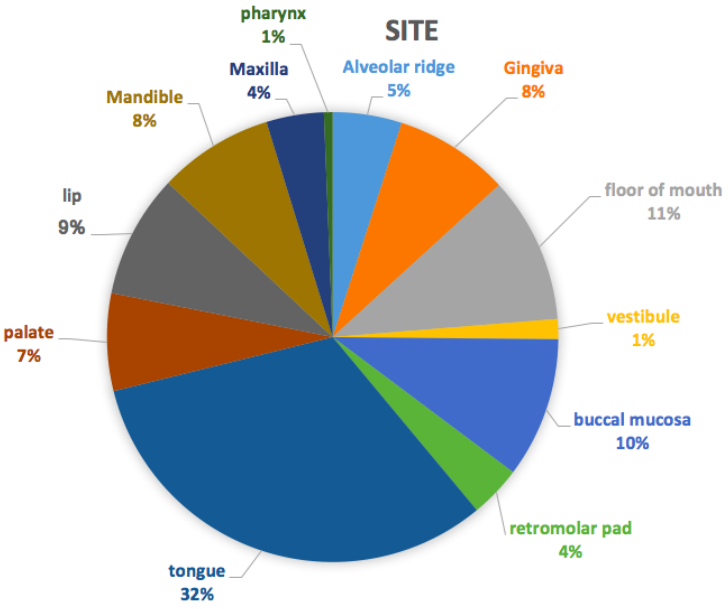

Figure 2. *Distribution of Anatomic Site*

We observed a consistent significance in both size increase and ulcerated lesions following the multivariable model as well as the reduced model with the odds ratio of 0.57 (0.42-0.77), 0.33 (0.16-0.65), and a p-value (<0.001, 0.002) respectively.

Based on the factors in our model, there is a 71% chance we can differentiate between a random correct diagnosis and a random misdiagnosis (see Figure 3).

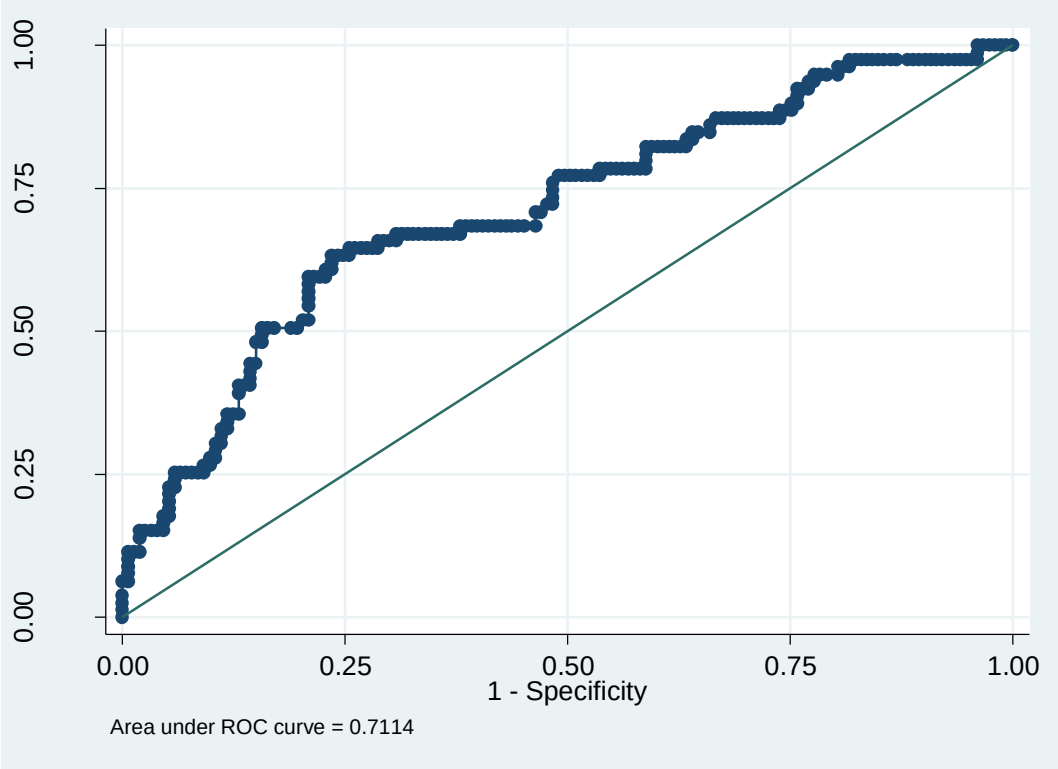

Figure 3. *ROC Curve*

3.3 EXPOSURE TO RISK FACTORS

Data on tobacco exposure was available for 142 patients, of these 3 had a history of previous tobacco usage, 86 were tobacco users, and 53 patients had no history of tobacco usage. 23 had a history of alcohol exposure with 113 having concomitant alcohol and tobacco risk factor.

3.4 PATHOLOGIC DIAGNOSIS

The most common oral malignancy was SCC (78.5%) with conventional SCC being most common (381/485 cases). Variants of SCC were less common, verrucous carcinoma accounted for 5.3 % of the lesions, and 3.2 % were papillary SCC, 1.6% were spindle cell SCC, and 0.4% were keratoacanthoma-type SCC. 5.7 % of the malignancies were salivary gland tumors. 3.2% were histologically diagnosed as lymphoma, 1.6 % were metastases to the oral cavity. Malignant melanoma of the oral cavity accounted for 0.6 % of lesions. 2% were categorized as other malignancies such as chondrosarcoma.

Our data demonstrated that 38% of SCC were clinically misdiagnosed. A benign clinical impression was considered in both primary and secondary clinical diagnosis. However, 29% of malignant lesions had a premalignant diagnosis of (epithelial dysplasia or epithelial atypia) in their clinical impression. Univariate results showed that gender (p-value 0.044), age (p-value 0.047), color (p-value 0.047), increase in size (p-value 0.001), ulceration (p-value <0.001), and firm-hard-induced texture (p-value 0.042) are statistically significant.

Many of the clinical impressions include benign entities (see Table 4).

Table 4. Summary of Clinical Impressions

Clinical impression	No. of cases	Percent of total (485)
Chronic inflammation	8	1.6 %
Dysplasia	22	4.5 %
Fibroma	17	3.5 %
Actinic keratosis	3	0.6 %
Epithelial Atypia	10	2.0 %

Mucocele	6	1.2 %
Lichen planus	9	1.8 %
Granulation tissue	8	1.6 %
Hyperkeratosis	17	3.5 %
Papilloma	14	2.8 %
Pleomorphic adenoma	6	1.2 %
Pyogenic granuloma	15	3.0 %
TUGSE	7	1.4 %
Ulcer	9	1.8 %

4.0 DISCUSSION

Recognition of clinical features, signs, and symptoms of malignant lesions challenge clinicians in correctly detecting, diagnosing, and preventing the progression of oral malignancies. (28) Early malignant lesions of the oral mucosa are: asymptomatic; comprise a tendency toward maintaining their size; exhibit surface changes, and; show no response to treatments. With continued growth, oral tumors develop an exophytic growth adopting an irregular appearance, or demonstrating an endophytic growth that present frequently a dispirited ulcer showing a raised, and everted border.(29)

Our study finds that oral malignancy was not correctly clinically identified in cases with a small anatomic size of the lesion (e.g. lesions less than 0.5 cm in size). Clinically, tumor size is the greatest surface dimension of the lesion. Pathologically, it is the greatest diameter of the specimen. (30) The maximum dimension and correlated lymph node metastasis of 155 oral SCCs were analyzed. It was concluded that tumors of 2 cm and smaller demonstrated metastasis to lymph nodes, with a good prognosis. In malignant tumors measuring more than 2 cm, the growth in size is not associated with an increased risk of nodal metastasis, except in large tumors that demonstrate infiltration. (31) Rate of metastases in oral SCC is mainly dependent on tumor size and differentiation. T1 and T2 are associated with high metastases. (32),(15) In the tumor-node-metastasis (TNM) clinical staging system (where T is the size of the primary tumor, N is the involvement of regional lymph node, and M is distant metastasis) , T is a prognostic factor for survival. (34) A study showed that T3/T4 classification are associated with a significantly higher rate of mortality. (33) Smaller tumor size does not exclude the presence of SCC but it may be clinically asymptomatic in early stages. Oral SCCs can range from few millimeters to a number of centimeters at presentation. In a series of 102 asymptomatic oral SCCs, 17% of SCCs were reported to be less than 2 cm. (34) Large malignant lesions imply lymph node metastasis, and raise the incidence of local failure.(35) Specifically, tumor thickness or depth has been a

significant indicator of subclinical lymph node metastasis and a prognostic factor. A 3-mm thick tumor has 8% nodal metastasis, 0% recurrence, and 100% 5-year survival. Tumors that are more than 3-mm to 9-mm thick have a 44% rate of nodal metastasis, 7% recurrence, and 76% 5-year survival.(36) Our data demonstrates that clinician's struggle in diagnoses most in lesions less than 0.5cm.

Interestingly, our data suggests that men are more likely to be misdiagnosed. Oral cancers are high among men compared to female. (37), (38), (39) It is well established in the literature (40), (41) that male patients are less likely to seek medical care. Male patients' health behavior includes poor oral hygiene and fear of physicians, young males are more likely associated with smoking and extreme alcohol consumption. (42) Males have a known increased risk for oral cancer (37), (38), (39) but we hypothesize on presentation, they may minimize their symptoms by less expression of symptoms to care providers. Perhaps due to a greater risk of malignancies seen in male population, male patients with SCC are seen by dental practitioners earlier age than women (38) which may result in presenting with early lesions. Conversely, female patients may be more vocal about clinical symptoms, whereas male patients minimize these symptoms.

As might be expected; our data suggest oral SCC in young individuals are prone to be misdiagnosed by clinicians. However, due to a higher incidence of HPV driven oropharyngeal SCC, younger individuals carry a higher risk of distant metastasis. It is well established that HPV related oropharyngeal SCC presents in a younger patient population than conventional SCC. Young females have a higher proportion of recurrence rate of tongue cancer. (43) Thus, as the demographics of SCC shift (because of the epidemic of HPV driven oropharyngeal SCC), clinicians must be aware of the increasing incidence in younger patients. SCC has a wide range of presentation with a myriad of risk factors. Many dental practitioners are more familiar with conventional SCC and its risk factors, only in the last decade or two has the increase in HPV related SCC come to the forefront. Newer studies on SCC in young individuals (<45 years old) show a mean age of 32.5 with a male predilection, and tongue predisposition. (44) It is suggested that young patients diagnosed with oral SCC possess a more aggressive, and higher-grade tumor when compared to old patients. However, younger patients exhibit a significantly higher survival rate.

The most established feature of oral SCC is the presence of ulceration (12) as non-healing ulcers are frequently seen with oral SCC. However, the presence of an ulcer is not among the

initial signs of a developing SCC. (45) Our data showed that lesions lacking an ulcer had a greater chance of misdiagnosis, if clinicians assume that oral SCCs usually present with non-healing ulceration. A superficial ulcer is seen in a more advanced cancer, its features usually include irregular floor with slight raised margins, and with time, firmness to palpation is encountered. (12) If an ulcer occurs on the vermilion border it is frequently concealed with a crust. (46) The most common oral mucosal site for ulcers are the lower lip, the tongue, and the floor of mouth.(46) In our study, 1.6 % of malignant lesions had traumatic ulcer in their differential diagnosis. Clinicians are required to ensure the resolution of ulcers malignancy is in the differential. (47) SCC in the micro-invasive stage is an early thin tumor that does not invade deep tissue. Micro-invasive tumors carry unique characteristics, they are featured regularly as patches or erosions rather than discrete ulcers.(14)

Early SCCs frequently arises as red, white, or mixed lesions. As the lesion progress an ulcer is developed. With more time, a fungating mass grows, or an endophytic growth is shown featuring a rolled, raised border.(48) One of the features of SCCs developing in the oral cavity is the change in the color of the mucosa. Leukoplakia is defined by the World Health Organization as "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.(49)" Therefore, leukoplakia is a clinical term and is not utilized as a microscopic diagnosis.(50) The term leukoplakia is under constant improvement. White patches that are secondary to local irritation rarely demonstrate dysplastic changes or malignant transformation. Such as hyperkeratotic lesions on edentulous alveolar ridges are usually a protective, reactive phenomenon.(51) Likewise, morsiactio buccarum or morsicatio linguarum that evolve from chronic check or tongue biting should be categorized separately as they are not premalignant lesions, thus, should not be considered as leukoplakia.(48) Leukoplakia remains a suspicious lesion and require a conventional biopsy. Even non-carcinomatous leukoplakia may harbor a future malignancy. The malignant transformation in oral leukoplakia ranges from 15.6 % to 39.2%. (50, 52-54) Similarly, erythroplakia is a red patch which cannot be diagnosed clinically as any other lesion(49).

Erythroplakia showed higher tendency toward carcinoma. In 65 cases of erythroplakia, all exhibited dysplasia, and 51% presented with invasive SCC.(48) Although leukoplakic lesions are more common, erythroplakia are more worrisome. The most common oral locations affected by erythroplakia are the floor of mouth, soft palate, retromolar trigone, and the lateral surface of

the tongue. Clinicians recognize that erythroplakic lesions are high risk lesions and a greater likelihood of correct diagnosis were associated with red lesions with OR 0.96 (0.45-2.05).

As the duration of the oral lesion had no effect on the clinical diagnosis in this study. We found the average length of duration of malignant lesions is 7.75 months which indicates the necessity to educate patients regarding the added value of oral cancer screening as a component of periodic oral examination in conjunction with dental prophylaxis. Delays in the diagnosis of oral malignancies from the time of recognition of symptoms to the onset of professional diagnosis is frequent. The asymptomatic early SCC attribute to delay in diagnosis. A median of 30 of days is the time until clinical diagnosis of oral malignancies with a range of 14 days to 2 years.(55, 56) Age is not a contributing factor to diagnostic delay.(55-58) Lethal delays are associated with clinical evaluation that are not referred to follow-up for investigation.(59)

Although a malignant neoplasm in the patients' medical history had little impact on the accuracy of clinicians' differential diagnosis in this study, a prevalence of 10% to 24 % development of second malignancy tumors following a primary cancer(60-63), and 8.0 % incidence rate of a secondary neoplasm arising within 10 years after the primary tumor (64), with a lower 5-year survival rate. Our study comprised 13 % of patients with a complain of a previous malignant neoplasm from variable sites within the body such as the lung, larynx, esophagus, colon, breast, prostate, and liver. Past malignancy of the oral, head and neck region accounted for 2.6%.

Texture and consistency of oral lesions is one of the essential parameters to consider during diagnosis. Lesions of the oral mucosa presenting with non-homogeneous texture warrant precancerous dysplastic changes. Homogenous lesions present on the floor of mouth and tongue exhibit a higher rate of dysplastic changes. (65) Firmness is among the strong indicators of oral malignancies, when firmness is increased upon palpation, infiltration is considered.

Studies regarding the association between risk factors (i.e. tobacco and alcohol consumption) and oral SCC are well established.(66, 67) Yet, in our oral pathology reports that are obtained from the clinicians, most commonly Oral and Maxillofacial surgeons, the history of smoking and alcohol was often not included as either a pertinent positive or negative factor.

Consistent with previous studies(48, 68, 69), the tongue and floor of mouth in our study represented the most common anatomic sites (32%, 11%) respectively. All oral mucosa is susceptible to the development of cancer, but some areas bear a higher risk of malignancy.

Interestingly, the site of the originating tumor was disregarded by clinicians even though it is well known that the floor of mouth and tongue possess a greater malignant potential due to factors such as the histology of these areas; comprising a thin, non-keratinized epithelium which minimally protects against carcinogens, and; the presence of carcinogens within the saliva which stay for long periods in the floor of the mouth and can have harmful effects(70).

The association between the location of the neoplasm and survival depends upon lymph node metastasis.(43) Malignant neoplasms of the tongue are more likely to metastasis compared to gingival and buccal tumors.(15) Approximately 55 % to 70 % of SCCs presenting in the tongue, occur between the middle and posterior thirds of the lateral border.(71, 72) SCC of the base of tongue accounts for one third of tongue SCCs, and less likely to present with symptoms, thus, usually present with more advanced stage at the time of diagnosis.(72, 73) Primary tumors of the tongue accounts for 66% of neck metastasis at the initial time of diagnosis due to its extensive blood support and lymphatic drainage.(74) Malignant lesions occurring in the retromolar area, posterior buccal mucosa, and hard palate raise the possibility of invading the anatomically complex masticator space.(43) Limited margins resection and rapid failure are observed in individuals diagnosed with stage T4b oral cancer which have poor prognosis. However, patients with negative cervical lymph node metastasis, or one positive lymph node metastasis without nerve invasion will demonstrate positive outcomes from surgery, as well as patients diagnosed with a malignancy located underneath the mandibular notch.(43)

In this study, the gingiva accounted for 8% of tumors. Malignancies of the gingiva have been studied in depth. In a study investigating the clinical and histologic appearance of SCC of the gingiva in 519 cases, it was reported that the majority of lesions were present in the posterior mandibular gingiva (69%).(75) The duration until the onset of diagnosis was less than 6 weeks in 75% of cases compared to floor of mouth and tongue SCC.(75) The most frequent symptom in gingival SCC is a mass-like lesion as well as ulceration. Diagnosis delay in gingival SCC is very common due to the similarity to benign lesions such as gingival inflammatory growth.(75) In 13% of cases, tooth extraction is an identifying gingival SCC. Atypical periodontal disease, or aggressive appearing gingival lesion also evoke the possibility of malignancy. (75) Tumors of the buccal mucosa are frequently associated with the utilization of tobacco products. SCC of the buccal area bear a poor prognosis and show recurrence within 1-2 years.(76)

The different parameters that play a role in the identification process of malignant tumors (e.g. loosening of teeth, bleeding, and pain) can be related to misdiagnosis, however, the low sample size due to missing data in these variables, prevented us from including it in the regression model, thus, analyses of these variables should be further investigated.

Non-palpable, asymptomatic carcinomas with negative lymphadenopathy remain ambiguous to diagnose but with intensifying sites at high risk, and acknowledging early presentations of oral SCC this will contribute to early diagnosis. (77)

5.0 CONCLUSION

Our results support our hypothesis. We have found that a majority of oral malignancies, especially SCCs, were clinically misdiagnosed. Clinical misdiagnosis is significantly associated with male gender, young individuals, smaller size neoplasms, and lack of ulceration. Although factors such as a history of malignancy, tobacco and alcohol use, and the location of the tumor had a minor influence on clinical diagnosis in this study, these factors are highly associated with increasing risk of oral malignancies.

Early detection of malignant signs impact overall prognosis. Dentists play a vital role in the prevention of oral malignancy by early detection, and a thorough understanding of the diagnostic features. They are "first line of defense" for both the symptomatic and asymptomatic signs of cancer(78-80). While clinicians perform well-established screening practices, most intraoral pathology is benign, and it is advisable for clinicians to include malignancy in their differential diagnosis for soft tissue masses. Clinicians are also advised to correlate between clinical and histological diagnosis. (81, 82) Our data suggest that this is especially true for small lesions in younger patients, where the risk of malignant potential may not be considered.

While clinical impression is important, histologic diagnosis is the gold standard for providing care for patients.

BIBLIOGRAPHY

1. Gonsalves WC, Chi AC, Neville BW. Common oral lesions: Part II. Masses and neoplasia. Am Fam Physician. 2007;75(4):509-12.
2. Abidullah M, Raghunath V, Karpe T, Akifuddin S, Imran S, Dhurjati VN, et al. Clinicopathologic Correlation of White, Non scrapable Oral Mucosal Surface Lesions: A Study of 100 Cases. J Clin Diagn Res. 2016;10(2):ZC38-41.
3. Munoz M, Monje F, Alonso del Hoyo JR, Martin-Granizo R. Oral angiosarcoma misdiagnosed as a pyogenic granuloma. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 1998;56(4):488-91.
4. Lopez-Jornet P, Garcia G, Camacho-Alonso F. Isolated gingival metastasis from lung carcinoma. N Y State Dent J. 2011;77(1):27-8.
5. Ramon Ramirez J, Seoane J, Montero J, Esparza Gomez GC, Cerero R. Isolated gingival metastasis from hepatocellular carcinoma mimicking a pyogenic granuloma. Journal of clinical periodontology. 2003;30(10):926-9.
6. Owosho AA, Xu B, Kadempour A, Yom SK, Randazzo J, Ghossein RA, et al. Metastatic solid tumors to the jaw and oral soft tissue: A retrospective clinical analysis of 44 patients from a single institution. Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery. 2016;44(8):1047-53.
7. Society AC. American Cancer Society. Cancer Facts & Figures 2017. Cancer Facts & Figures 2017. 2017.
8. Silva TD, Ferreira CB, Leite GB, de Menezes Pontes JR, Antunes HS. Oral manifestations of lymphoma: a systematic review. Ecancermedicalscience. 2016;10:665.
9. Seoane J, Warnakulasuriya S, Varela-Centelles P, Esparza G, Dios PD. Oral cancer: experiences and diagnostic abilities elicited by dentists in North-western Spain. Oral Dis. 2006;12(5):487-92.
10. Epstein JB, Guneri P, Boyacioglu H, Abt E. The limitations of the clinical oral examination in detecting dysplastic oral lesions and oral squamous cell carcinoma. Tex Dent J. 2013;130(5):410-24.
11. Brandizzi D, Gandolfo M, Velazco ML, Cabrini RL, Lanfranchi HE. Clinical features and evolution of oral cancer: A study of 274 cases in Buenos Aires, Argentina. Med Oral Patol Oral Cir Bucal. 2008;13(9):E544-8.
12. Bagan J, Sarrion G, Jimenez Y. Oral cancer: clinical features. Oral Oncol. 2010;46(6):414-7.

13. Kademani D. Oral cancer. Mayo Clin Proc. 2007;82(7):878-87.
14. Pentenero M, Navone R, Motta F, Marino R, Gassino L, Broccoletti R, et al. Clinical features of microinvasive stage I oral carcinoma. Oral Dis. 2011;17(3):298-303.
15. Woolgar JA, Rogers S, West CR, Errington RD, Brown JS, Vaughan ED. Survival and patterns of recurrence in 200 oral cancer patients treated by radical surgery and neck dissection. Oral Oncol. 1999;35(3):257-65.
16. Bishop JA, Sciubba JJ, Westra WH. Squamous Cell Carcinoma of the Oral Cavity and Oropharynx. Surg Pathol Clin. 2011;4(4):1127-51.
17. Clump DA, Bauman JE, Ferris RL. Cancer of the oropharynx. Surg Oncol Clin N Am. 2015;24(3):509-20.
18. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. Int J Cancer. 2007;121(8):1813-20.
19. Kruse AL, Gratz KW, Obwegeser JA, Lubbers HT. Malignant minor salivary gland tumors: a retrospective study of 27 cases. Oral Maxillofac Surg. 2010;14(4):203-9.
20. Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L. Major and minor salivary gland tumors. Crit Rev Oncol Hematol. 2010;74(2):134-48.
21. Parkin DM WS, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Volume VIII. IARC Sci Publ. 2002(155):1-781.
22. Hocwald E, Korkmaz H, Yoo GH, Adsay V, Shibuya TY, Abrams J, et al. Prognostic factors in major salivary gland cancer. Laryngoscope. 2001;111(8):1434-9.
23. Lima RA, Tavares MR, Dias FL, Kligerman J, Nascimento MF, Barbosa MM, et al. Clinical prognostic factors in malignant parotid gland tumors. Otolaryngol Head Neck Surg. 2005;133(5):702-8.
24. Waldron CA, el-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. Oral Surg Oral Med Oral Pathol. 1988;66(3):323-33.
25. Lopes MA, Kowalski LP, da Cunha Santos G, Paes de Almeida O. A clinicopathologic study of 196 intraoral minor salivary gland tumours. J Oral Pathol Med. 1999;28(6):264-7.
26. Hirshberg A, Leibovich P, Buchner A. Metastases to the oral mucosa: analysis of 157 cases. J Oral Pathol Med. 1993;22(9):385-90.
27. Murillo J, Bagan JV, Hens E, Diaz JM, Leopoldo M. Tumors metastasizing to the oral cavity: a study of 16 cases. J Oral Maxillofac Surg. 2013;71(9):1545-51.
28. Shugars DC, Patton LL. Detecting, diagnosing, and preventing oral cancer. Nurse Pract. 1997;22(6):105, 9-10, 13-5 passim.
29. Nicolás Bolesina FnLF, Silvia A. López de Blanc, Rosana A. Morelatto and María Alicia Olmos. Oral Squamous Cell Carcinoma Clinical Aspects. Oral Cancer. 2012;10.5772/32968.
30. Jadhav KB, Gupta N. Clinicopathological prognostic implicators of oral squamous cell carcinoma: need to understand and revise. N Am J Med Sci. 2013;5(12):671-9.
31. Moore C, Flynn MB, Greenberg RA. Evaluation of size in prognosis of oral cancer. Cancer. 1986;58(1):158-62.
32. Sagheb K, Blatt S, Rahimi-Nedjat RK, Eigenbrodt S, Al-Nawas B, Walter C. Cervical metastases behavior of T1-2 squamous cell cancer of the oral mucosa. Clin Oral Investig. 2017;21(3):931-5.

33. Rivera C, Gonzalez-Arriagada WA, Loyola-Brambilla M, de Almeida OP, Coletta RD, Venegas B. Clinicopathological and immunohistochemical evaluation of oral and oropharyngeal squamous cell carcinoma in Chilean population. Int J Clin Exp Pathol. 2014;7(9):5968-77.
34. Mashberg A, Merletti F, Boffetta P, Gandolfo S, Ozzello F, Fracchia F, et al. Appearance, site of occurrence, and physical and clinical characteristics of oral carcinoma in Torino, Italy. Cancer. 1989;63(12):2522-7.
35. Shaha AR, Spiro RH, Shah JP, Strong EW. Squamous carcinoma of the floor of the mouth. Am J Surg. 1984;148(4):455-9.
36. Yuen APW. PROGNOSTIC FACTORS OF CLINICALLY STAGE I
AND II ORAL TONGUE CARCINOMAĐA COMPARATIVE STUDY OF STAGE, THICKNESS, SHAPE, GROWTH PATTERN, INVASIVE FRONT MALIGNANCY
GRADING, MARTINEZ-GIMENO SCORE, AND PATHOLOGIC FEATURES. Wiley interScience. 2001;24(2002):513-20.
37. Kuriakose M, Sankaranarayanan M, Nair MK, Cherian T, Sugar AW, Scully C, et al. Comparison of oral squamous cell carcinoma in younger and older patients in India. Eur J Cancer B Oral Oncol. 1992;28B(2):113-20.
38. Funk GF, Karnell LH, Robinson RA, Zhen WK, Trask DK, Hoffman HT. Presentation, treatment, and outcome of oral cavity cancer: a National Cancer Data Base report. Head Neck. 2002;24(2):165-80.
39. Rosebush MS, Rao SK, Samant S, Gu W, Handorf CR, Pfeffer LM, et al. Oral cancer: enduring characteristics and emerging trends. J Mich Dent Assoc. 2012;94(2):64-8.
40. Perry DA, Freed JR, Kushman JE. Characteristics of patients seeking care from independent dental hygienist practices. J Public Health Dent. 1997;57(2):76-81.
41. Doyal L NS. Why dentists should take a greater interest in sex and gender. Br Dent J. 2010;209(7):335-7.
42. Vaisanen JA, Syrjala AM, Pesonen PR, Pukkila MJ, Koivunen PT, Alho OP. Characteristics and medical-care-seeking of head and neck cancer patients: a population-based cross-sectional survey. Oral Oncol. 2014;50(8):740-5.
43. Al-Swiahb JN, Chen CH, Chuang HC, Fang FM, Tasi HT, Chien CY. Clinical, pathological and molecular determinants in squamous cell carcinoma of the oral cavity. Future Oncol. 2010;6(5):837-50.
44. Muller S, Pan Y, Li R, Chi AC. Changing trends in oral squamous cell carcinoma with particular reference to young patients: 1971-2006. The Emory University experience. Head Neck Pathol. 2008;2(2):60-6.
45. Jainkittivong A, Swasdison S, Thangpisityotin M, Langlais RP. Oral squamous cell carcinoma: a clinicopathological study of 342 Thai cases. J Contemp Dent Pract. 2009;10(5):E033-40.
46. Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic Features of Common Oral Ulcerative Lesions: An Updated Decision Tree. Int J Dent. 2016;2016:7278925.
47. Sloan P. Squamous cell carcinoma and precursor lesions: clinical presentation. Periodontol 2000. 2011;57(1):10-8.
48. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin. 2002;52(4):195-215.
49. Kramer IR, Lucas RB, Pindborg JJ, Sobin LH. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. Oral Surg Oral Med Oral Pathol. 1978;46(4):518-39.

50. Shafer WG, Waldron CA. A clinical and histopathologic study of oral leukoplakia. Surg Gynecol Obstet. 1961;112:411-20.
51. Axell T, Pindborg JJ, Smith CJ, van der Waal I. Oral white lesions with special reference to precancerous and tobacco- related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18-21 1994. International Collaborative Group on Oral White Lesions. J Oral Pathol Med. 1996;25(2):49-54.
52. Banoczy J, Csiba A. Occurrence of epithelial dysplasia in oral leukoplakia. Analysis and follow-up study of 12 cases. Oral Surg Oral Med Oral Pathol. 1976;42(6):766-74.
53. Feller L AM, Slabbert H. Pre-malignant lesions of the oral mucosa in a South African sample: A clinicopathologic study. J Dent Assoc South Africa. 1991;46:261-26.
54. Pindborg JJ, Renstrup G, Poulsen HE, Silverman S, Jr. Studies in Oral Leukoplakias. V. Clinical and Histologic Signs of Malignancy. Acta Odontol Scand. 1963;21:407-14.
55. Jovanovic A, Kostense PJ, Schulten EA, Snow GB, van der Waal I. Delay in diagnosis of oral squamous cell carcinoma; a report from The Netherlands. Eur J Cancer B Oral Oncol. 1992;28B(1):37-8.
56. Pitiphat W, Diehl SR, Laskaris G, Cartsos V, Douglass CW, Zavras AI. Factors associated with delay in the diagnosis of oral cancer. J Dent Res. 2002;81(3):192-7.
57. Elwood JM, Gallagher RP. Factors influencing early diagnosis of cancer of the oral cavity. CMAJ. 1985;133(7):651-6.
58. Guggenheimer J, Verbin RS, Johnson JT, Horkowitz CA, Myers EN. Factors delaying the diagnosis of oral and oropharyngeal carcinomas. Cancer. 1989;64(4):932-5.
59. Kantola S, Jokinen K, Hyrynkangas K, Mantyselka P, Alho OP. Detection of tongue cancer in primary care. Br J Gen Pract. 2001;51(463):106-11.
60. Cianfriglia F, Di Gregorio DA, Manieri A. Multiple primary tumours in patients with oral squamous cell carcinoma. Oral Oncol. 1999;35(2):157-63.
61. Hashibe M RB, Le AD, Li G, Sankaranarayanan R and Zhang ZF. Radiotherapy for oral cancer as a risk factor for second primary cancers. . Cancer Lett. 2005;220:185-95.
62. Liao CT, Kang CJ, Chang JT, Wang HM, Ng SH, Hsueh C, et al. Survival of second and multiple primary tumors in patients with oral cavity squamous cell carcinoma in the betel quid chewing area. Oral Oncol. 2007;43(8):811-9.
63. Schwartz LH, Ozsahin M, Zhang GN, Touboul E, De Vataire F, Andolenko P, et al. Synchronous and metachronous head and neck carcinomas. Cancer. 1994;74(7):1933-8.
64. Li YD, Ma X, Han YL, Peng LW. Clinical features of multiple primary carcinomas of the oral cavity. Exp Ther Med. 2017;13(2):634-8.
65. Fatima Dost B, MPhil, Kim-Anh Lê Cao, Pauline J. Ford, BDentSt, Camile S. Farah. A retrospective analysis of clinical features of oral malignant and potentially malignant disorders with and without oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116(725-733).
66. Mahapatra S, Kamath R, Shetty BK, Binu VS. Risk of oral cancer associated with gutka and other tobacco products: a hospital-based case-control study. J Cancer Res Ther. 2015;11(1):199-203.
67. Motgi AA CM, Diwan NN, Chowdhery A, Channe PP, Shete MV. Assessment of cytogenic damage in the form of micronuclei in oral epithelial cells in patients using smokeless and smoked form of tobacco and non-tobacco users and its relevance for oral cancer. J Cancer Res Ther. 2014;10:165-70.

68. Watkinson JC GM, Wilson JA. Tumors of the lip and oral cavity In: Stell and Maran's Head & Neck surgery Butterworth-Heinemann, Oxford. 2000;275–318.
69. Rivera H, Nikitakis NG, Correnti M, Maissi S, Ponce JG. Oral and oropharyngeal cancer in a Venezuelan population. Acta Odontol Latinoam. 2008;21(2):175-80.
70. Jovanovic A, Schulten EA, Kostense PJ, Snow GB, van der Waal I. Tobacco and alcohol related to the anatomical site of oral squamous cell carcinoma. J Oral Pathol Med. 1993;22(10):459-62.
71. Krupala JL, Gianoli GJ. Carcinoma of the oral tongue. J La State Med Soc. 1993;145(10):421-2, 5-6.
72. Gorsky M, Epstein JB, Oakley C, Le ND, Hay J, Stevenson-Moore P. Carcinoma of the tongue: a case series analysis of clinical presentation, risk factors, staging, and outcome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98(5):546-52.
73. Spiro RH, Strong EW. Surgical treatment of cancer of the tongue. Surg Clin North Am. 1974;54(4):759-65.
74. Ho CM, Lam KH, Wei WI, Lau SK, Lam LK. Occult lymph node metastasis in small oral tongue cancers. Head Neck. 1992;14(5):359-63.
75. Fitzpatrick SG, Neuman AN, Cohen DM, Bhattacharyya I. The clinical and histologic presentation of gingival squamous cell carcinoma: a study of 519 cases. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(4):509-15.
76. Ghoshal S, Mallick I, Panda N, Sharma SC. Carcinoma of the buccal mucosa: analysis of clinical presentation, outcome and prognostic factors. Oral Oncol. 2006;42(5):533-9.
77. Mashberg A, Samit A. Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers. CA Cancer J Clin. 1995;45(6):328-51.
78. Gutmacher Z, Teich S, Lin S, Ghantous Y, Abu El-Naaj I. Practitioners' challenges in diagnosing oral and maxillofacial tumors. Quintessence Int. 2016;47(7):603-8.
79. Rethman MP CW, Cohen EEW, et al. . Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. J Am Dent Assoc. 2010;141:509–20.
80. Rethman M CW, Cohen E, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. Texas Dent J. 2012;129:491–507.
81. Kondori I, Mottin RW, Laskin DM. Accuracy of dentists in the clinical diagnosis of oral lesions. Quintessence Int. 2011;42(7):575-7.
82. Patel KJ DSH, Tong DC, Love RM. Concordance between clinical and histopathologic diagnoses of oral mucosal lesions. . J Oral Maxillofac Surg 2011;69:125–33.