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The Predictive Value of Tumor Depth for Cervical Lymph Node Metastasis in Oral Squamous Cell Carcinoma; Prospective and Retrospective Study in Iraq

Amera Alkaisi[1]*, Husham A Zaidan[2] and Ikbal AH Al Kabtan[3]

[1]*Department of Oral and Maxillofacial Surgery, University of Anbar, Iraq*
[2]*Department of Oral and Maxillofacial Surgery, College of Dentistry, University of Baghdad, Iraq*
[3]*Department of Pathology, College of Medicine, University of Baghdad, Iraq*

Abstract

Many histopathologic parameters in head and neck squamous cell carcinoma have been identified as predictive factors for cervical metastasis. Several studies focused on tumor thickness, and the depth of invasion was suggested to have a relationship to the occurrence of cervical metastasis, therefore the aim of this study was to determine the relationship between tumor depth and clinically suspicious neck, as well as occult neck disease, and to determine the cutoff point for metastasis in Iraqi population, in addition, the study intended to identify further predictive factors for cervical metastasis in squamous cell carcinoma of the oral cavity.

Methods: The medical records of 80 patients operated on with oral squamous cell carcinoma between 1991 and 2000 were reviewed; each patient, age, sex, tumor location, tumor size, degree of differentiation, pattern of invasion; lymphoplasmocytic infiltration and tumor depth were evaluated. All slides were examined by the same pathologist, chi-square test was used to compare the impact of these parameters on nodal metastasis in the neck.

Results: In multivariate analysis the most important factors was tumor depth followed by pattern of invasion, tumor site, degree of differentiation, tumor size, and lymphoplasmocytic infiltration. Univariate analysis indicates that tumor depth is important predictive factor in cervical metastasis for oral squamous cell carcinoma $P<0.001$.

Conclusion: Tumor depth is a reliable factor to predict nodal metastasis and tumor depth of 4 mm can be considered as a suggested standard Iraqi cutoff number in staging and management of early oral squamous cell carcinoma.

Keywords: Oral squamous cell carcinoma; Tumor depth; Lymphatic metastases

Introduction

Oral cancer is 95% refer to oral squamous cell carcinoma of the oral mucosa. It is estimated to be the sixth most common cancer which accounts for 0.6% to 5% of all cancers in Europe, United States, and Australia respectively, but up to 45% of cancers in India. It is mostly affect males with incidence of 75% patients over age 60 years old, but its incidence is growing among females [1-3]. The most common causative factors associated with squamous cell carcinoma of the oral cavity are alcohol and tobacco abuse. Betel nut and tobacco chewing are responsible for the high incidence in the Indian subcontinent. It may appear in any area of the oral cavity, but there are certain areas, in which it is found more frequently, the oral tongue and floor of the mouth represent about 90% of all oral cavity malignancies [4,5]. Lymphnode metastasis occur in about 40% of patients with oral cancer and their clinical manifestations are hidden in rate of 15% to 34% [6,7]. The status of cervical lymph nodes at presentation is the single most important prognostic factor for patients with oral squamous cell carcinoma, and the presence of metastatic lymph nodes decrease survival rate by more than 50% [8-10]. According to the published data, the incidence of occult metastases to the neck can range from 15% to 60% depending on different prognostic factors [11]. Currently the treatment dilemma that most head and neck oncology surgeons face is the treatment of the N0 neck in oral cavity squamous cell carcinoma [12]. Watchful waiting until patients with clinically negative neck develop detectable neck disease has been shown to significantly decrease survival [13], therefore the challenge of caring in identifying who is at risk for developing lymph node metastasis in order to treat them prophylactically and decrease the risk of failure in the neck. The basic rule for prophyloctic treatment of N0 neck is to treat any patient whose risk of occult lymph node metastasis is 20% or higher [12]. Unfortunately, the methods of detecting occult disease are not reliable or accurate, but several new methods are promising. Oral squamous cell carcinoma is unpredictable lesion; the marked variation in prognosis is probably a function of many variables related to biological behaviors of primary lesion. A number of studies have been reported on the predictive factors for cervical lymph node metastasis in oral cancer, the prediction for neck node metastasis in these studies was made on the basis of modern diagnostic modalities such as computed tomography (CT), magnetic resonance imaging (MR) positron emission tomography (PET), lymphoscintigraphy (LS), ultrasonography (USG) and USG-guided fine-needle aspiration cytology are recommended to increase the efficacy of the neck evaluation in patients with oral carcinoma, or on the basis of histopathologic parameters [7,12,14-17]. The fact that not all tumors and metastases can be detected by

***Corresponding author:** Amera Alkaisi – BDS, MSc, PhD, Lecturer in College of Dentistry, Oral & Maxillofacial Surgery, University of Anbar, P.O.Box 55, Al-Anbar, Iraq, Tel: 009647815845276; E-mail: ameraalkaisi@gmail.com

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such technique demonstrated the need for alternatives [18]. Many clinical and histopathologic parameters were used as a predictive factor for regional metastasis include size of the primary tumor, site, T stage, grade, depth of invasion, biological tumor markers, perineural invasion and patient compliance [5,19]. The TNM classification of oral squamous cell carcinoma [20] provides a reliable basis for patient prognosis and therapeutic planning, but, it does not completely efficient, many patients dies despite the fact that their primary neoplasms were considered clinically to be detected or small undetectable or early cases (Stage I or stage II) and were treated accordingly [21,22]. Since 1986 the depth of the primary tumor increasingly has become recognized as an important in determining prognosis. Investigations of this parameter and other 4 primary tumor characteristics have become more intense in an effort to better define the probability of metastasis. Multiple factors can affect the rate of cervical metastasis and survival from oral cavity cancer include size of the primary tumor, site, T stage, grade, depth of invasion, biological tumor markers, perineural invasion and patient compliance [12,19]. It is important for the head and neck oncologic surgeon to be familiar with these factors to be able to plane appropriate treatment modalities. Several studies focused on tumor depth as new parameter predict regional metastasis [8,23-27], therefore the aim of this study was to assess the relationship between the tumor depth and the risk of cervical lymphnode involvement as well to determine the optimal tumor depth cutoff point for nodal metastasis in Iraqi population, furthermore additional 4 clinical parameters (patient sex and age, tumor site and size) and 3 pathological parameters (degree of differentiation, pattern of invasion and lymphoplasmocytic infiltration) were evaluated for nodal metastasis.

Materials and Methods

Patients

The study protocol was approved by the human ethics committee University of Baghdad with the consent of the patients. For prospective study, from maxillofacial centers in Baghdad (AL-Shaheed Adnan Khairalla, AL-Kark and Alwasty Hospitals), 20 patients who underwent surgical excision of primary oral cancer and neck dissection were taken. We prepared a specially designed case sheet included social, familial and medical history, risk behaviors (tobacco and alcohol usage), history of head and neck radiotherapy, familial history of head and neck cancer and present history of cancer and we included examination, investigation and treatment modality 5 of the present cancer. We follow the basis of clinical staging system proposed by American Joint Committee on cancer AJCC 1993 for tumor staging. All resected primary tumor specimens were taken from operation theaters fixed with 10% formalin solution and transferred for histopathologic examination. The maximum diameters of the lesion were considered after measuring two dimensions by mean of an ordinary ruler. Sections of 0.5 cm were taken from three areas (one central and 2 lateral), the cuts were done vertically from the upper most surface to the lowest end of the specimen, several slides (obtained from central and lateral areas) were prepared, all slides were oriented perpendicular to the tumor surface. The slides were stained with hematoxilin-eosin in a usual manner. For retrospective study; from the archive of oral pathology department, College of Dentistry, University of Baghdad and Teaching Laboratories (Medical City). Histopathological reports of 60 patients with relatively complete information's, which were continued from patients charts in the original hospitals where the patients treated for their oral squamous cell carcinomas by, surgery alone or combination of chemotherapy and or irradiation in the years between 1991 and 2000, we have chosen only those patients who had documented follow up for at least 2 years and those who underwent neck dissection with a known histopathologic status of cervical lymph nodes. All available information‘s were taken from hospital charts and histopathological reports, loaded in our specially designed case sheet. The original biopsy slides and/or paraffin blocks of primary oral squamous cell carcinoma were available for 40 patients. All tangential cuts were recut from original tissue blocks. Pathological Reports, slides of all primary tumors were submitted to a single pathologist who had no knowledge of the clinical course of the patients to reconfirm the initial diagnosis of squamous cell carcinoma and to evaluate all our histopathologic parameter (maximum tumor depth, degree of differentiation, pattern of invasion, and lymphoplasmocytic infiltration).

Clinical and pathological data

Our main parameter was depth of tumor invasion, we added 4 clinical parameters and 3 histopathological, aiming to discover an additional predictive parameters for cervical nodes metastasis. The clinical parameters, tested were patient‘s sex, age, location of primary tumor and tumor size. The histopathological parameters tested were, tumor depth, degree of differentiation, pattern of invasion and lymphoplasmocytic infiltration. For pathological parameters we followed Anneroth et al. [21], grading system. Degree of differentiation based on the degree of keratinization & degree of nuclear pleomorphism as well-differentiated, moderately differentiated and poorly differentiated squamous cell carcinoma. Pattern of invasion graded as, grade I: pushing, well-delineated borders, grade II solid cords, bands, and strands, grade III: small group of cells or thin infiltration cords, the number cells, in each group not being less than 15, grade IV marked diffuse, widespread cellular invasion of the neoplasm in single neoplastic cells or in small groups of cells where the corresponding number of cells does not exceed 15. Lymphoplasmocytic Infiltration, this parameter is considered to reflect the immunologic reaction to the neoplasm, the occurrence of infiltrate of plasma cells and lymphocytes in close relation to invasive neoplastic cells were considered, grade I- marked, grade II- moderate and grade III- slight. Tumor depth was measured microscopically by two methods; first method by using the microscope rulers on the stage of microscope. The second method by the use of ocular micrometer, the distant form the most superficial after excluding keratin layer and site of ulceration to the deepest layer of invasion by malignant cells was measured.

Statistical analysis

The impact of the clinical and histopathalogical parameters of primary tumor site on pathologic cervical lymph node status was assessed by Pearson Chi-square test (multivariate and univariate).

Results

Clinical tumor staging, of 80 patients results were; stage I, 21 patients (26.25%), Stage II, 32 patients (40%), Stage III, 21 patients (27.5%) and Stage IV, 6 patients (6.25%), (Table 1). Regional metastasis, was mostly to level I, II, and III, the most frequent first involved lymph nodes in oral cancer. In the clinically negative node group 21 of 58 (36.20%) pathologically proven to be positive node. In clinically palpable nodes group 19 of 22 (86.36%) proven to be pathologically positive nodes. No distant metastasis was diagnosed.

Clinical parameters, the most common site for oral cancer was oral tongue (Table 2). Histopathological parameters, well differentiation squamous cell carcinomas, Pattern of invasion grade III and Lymphoplasmocytic infiltration grade III, were the commonest. Tumor depth was ranged from 0.2 to 2 cm (Table 3) (Figures 1-3).

Tumor size	N0	N1	N2	Total
T1	21	3	-	24
T2	32	9	1	42
T3	3	6	-	9
T4	2	1	2	5
Total	58	19	3	80

Table 1: Clinical staging of the present oral squamous cell carcinoma of 80 patients Nodal status.

carcinoma and its correlation with lymph node metastasis **Clinical parameters**	**Groups**	**Frequency**	**PN+**
Patients sex	Male Female	54 26	25 15
Patients age/years	< or=29 40-80	6 74	4 36
Tumor site	Floor of the mouth Anterior 2/3of the tongue Buccal mucosa Alveolar ridge Hard palate Lips	4 27 14 15 7 13	3 20 7 7 2 1
Tumor size	T1 T2 T3 T4	24 42 9 5	5 24 7 4

PN+ = Positive lymphnod

Table 2: Characteristic clinical feature for patient with oral squamous cell.

cell carcinoma and its correlation with lymph node metastasis **Pathological parameters**	**Groups**	**Frequency**	**PN+**
Degree of differentiation	Well differentiated Moderately differentiated Poorly differentiated	41 14 25	12 12 16
Pattern of invasion	Pushing Strands Groups Single	13 13 35 19	0 8 17 15
Lymphoplasmocytic infiltration	Marked Moderate Slight	19 19 42	4 7 29
Tumor Depth in mm	≤ 4 mm >4 mm	33 47	0 40

Table 3: Characteristic pathological feature for patient with oral squamous.

Cervical lymphnode metastasis, in relation with lymph node metastasis (Tables 2 and 3), factors significantly predicting the risk of neck metastasis were (Table 4). Tumor depth (P<0.001), pattern of invasion (P<0.001), Tumor Site (P=0.003), degree of differentiation (P<0.001), Tumor Size (P=0.004), Lymphoplasmocytic infiltration (P=0.004). No significant correlation was shown between patient‘s age and sex with cervical lymph node metastasis. With accuracy of 90% tumor depth was selected with other parameters (7 parameters) for potential inclusion in 2 models (classification function). Factors considered in addition to tumor depth were, patient‘s sex and age, tumor site and size, degree of differentiation, pattern of invasion and lymphoplasmocytic infiltration. The resulting 2 models (equations) can be used to predict the probability of nodal metastasis given information on the 8 factors included in these models. One equation represents pathologically node positive (N+) and the other one represent pathologically node negative (N-), the result (status of cervical lymph nodes) will be toward the higher value of the two equations and we will computerize these models. N (+) = - 37.162 + 9.767 X1 + 0.397 X2 + 2.506 X3 + 0.699 X4 + 9.436 X5 + 1.641 X6 + 3.213 X7 + 3.559 X8 N (-) = - 31.009 + 9.806 X1 + 0.447 X2 + 1.870 X3 + 1.366 X4 + 1.366 X5 + 0.353 X6 + 2.912 X7 + 2.823 X8. X1 = Patients sex, X2 patients age, X3 tumor size, X4 tumor site, X5 tumor depth, X6 degree of differentiation, X7 pattern of invasion, X8 lymphoplasmocytic infiltration (Fiugres 1-3).

Discussion

Thorough treatment of oral cancer based on treatment of primary lesion & the neck. Typically, T1-T2 lesions are often associated with a risk of regional metastasis, 10% to 30 respectively, while T3-T4 lesions have a significantly higher risk [3,28-30]. In general, management of the neck, especially using elective neck dissection (END) is recommended when the risk of cervical lymphnode involvement is greater than 15%-20% [31,32]. END may be both diagnostic and therapeutic, provides pathological information on the status of neck nodes, thus helping to determine the need for adjuvant therapies. As well, it removes any clinically undetectable metastases, however; a significant number of

Parameters	**Statistical Analysis**		
	X^{2o}	**X^2**	**P- Value**
Depth (≤ 4:>4 mm)	56.170	6.63	<.001 (S)
Pattern of invasion 1,2,3,4	21.061	11.3	<.001 (S)
Tumor Site1,2,3,4,5,6	17.919	15.1	.003 (S)
Degree of differentiation (1: 2,3)	14.459	6.63	<.001 (S)
Tumor Size (T1, T2, T3, T4)	13.602	11.3	.004 (S)
Lymphoplasmocytic infiltration (1: 2,3)	8.352	6.63	.004 (S)
Patients Sex	.912	6.63	.340 (NS)
Patients Age (< =39 yr.: >=40 yr.)	.721	6.63	.396 (NS)

X^2 Pearson Chi Square, S=Significant result

Table 4: Statistical analysis (Chi-Square test).

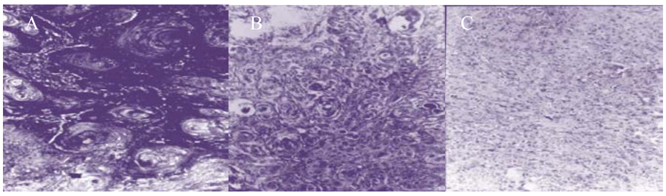

Figure 1: Degree of differentiation; A well; B, Moderate and C Poor.

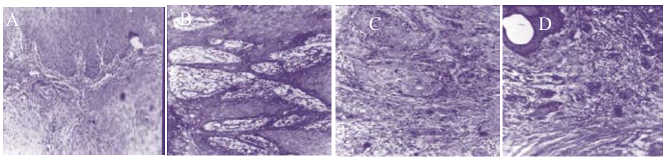

Figure 2: Mode of invasion; A, Pushing ; B, strands ; C, groups and D, Single cells.

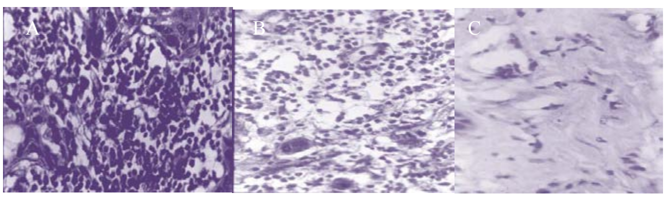

Figure 3: Lymphoplasmocytic infiltration; A, Marked ; B, Moderate and C Slight

patients undergone END will have no evidence of regional lymphnode metastases and may be subjected to the potential morbidity of a neck dissection. Since cervical lymphnode status is the most important prognostic factor in patients with head and neck carcinoma [8,9,33], prediction of nodal metastasis become important factor and identifying a reliable parameters that predict the risk of cervical lymphnode involvement is of great value. After assessing tumor depth with several factors relating to clinical and pathological determination of the oral squamous cell carcinoma attempting to determine which of these factors would predict the presence of occult node disease, the result revealed that factors predicting the risk of neck metastasis are tumor depth, Pattern of invasion, tumor site, degree of differentiation, tumor size and lymphoplasmocyic infiltration. This results is in agreement with several studies [9,15,16,34-38], however, Haksever et al. disagree with us, they found that there is no significant association between neck node metastasis and both tumor size and lymphoplasmocyic infiltration. In this study we found that the cutoff point is most strongly associated with neck metastasis when tumor depth categorized greater than 4 mm, in conversion N0-N1 group, tumor depth exceeding 4 mm was noted in 100% (n=21 patients out of 21), thus, tumor depth may be useful for predicting the occult cervical lymphnode metastasis [8,24-26,39-42]. Several studies have shown a clear correlation between increasing tumor thickness and an increased risk of cervical metastasis, However, controversy exists about the optimal tumor thickness cutoff point for the presence of nodal metastasis [28,29,42], There is no optimal cutoff point for tumor depth to predict clinical risk of cervical lymphnode involvement, Previous studies have suggested a cutoff point of between 3 mm to 6 mm [24,43-46]. Menezes et al., found that, tumor thickness is an important prognostic factor in carcinomas of the oral cavity and the treatment of tumors smaller than 3 mm might need to be less aggressive than if the tumor is larger than 5 mm. Shao, et al. concluded that the optimal cutoff point is 4 mm for consideration of neck management, this coincides with our study and the majority of previous studies [28,47-56], that patients with tumor depth ≤ 4 mm can be spared from subsequent END. The association of tumor depth with lymphnode metastasis is believed to reflect the aggressiveness of tumor growth [57] and/or is an objective indicator for the proximity of the tumor to lymphovascular structures [8]. Another theory for the positive relationship between tumor thickness and the presence of lymphnode involvement is that tumor emboli may be more difficult to form in the small-caliber lymphatics of superficial areas than in the wider lymphatics of deeper tissue [8]. Several studies had shown that the TNM staging system is not a sensitive indicator for the occurrence of lymphnode involvement in OSCC [25,38,44,50,57], tumor thickness, as the—third dimension of a tumor, has been shown to be a strong independent predictor for cervical lymphnode metastasis in many studies, several authors have suggested combining tumor thickness (TT) with the pathological TNM staging system to obtain a modified pT classification [30,57-59]. An interesting finding in this study is that the surgeons may be able to identify patients with occult nodal diseases preoperatively accurately. To our knowledge the value of tumor depth in prediction of cervical lymph node metastasis in Iraq has not been studied before. According to our study 8 parameter could be developed in to two models for the predication of nodal metastasis tumor depth, pattern of invasion, tumor site, degree of differentiation, lymphoplasmocytic infiltration, patients sex and age. This models will predict 90% chance of occult nodal involvement and useful for identifying a subset of patients who are likely to have nodal involvement. Our study shows increased number of patient under the age of 40 due to socioeconomic factors as poverty increased and malnutrition in our country due to blockage impressed on Iraq, also immune deficiency as a sequence of mal nutrition. In Iraq there was a shift in the age distribution of cancer cases towards younger age group due to the effect of depleted uranium [60].

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