

Original Article

Clinicopathologic Parameters Associated with Regional Lymph Node Metastasis in Oral Squamous Cell Carcinoma: A Retrospective Study

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ABSTRACT

Background and Objective: Oral cancer accounts for less than 3% of all cancers. Despite recent improvement in diagnostic and treatment methods, the overall survival of the disease is unfavorable. Several studies have been performed to assess factors influencing lymph node metastasis and prognosis. The aim of this study was to evaluate some clinical and pathological factors influencing lymph node metastasis in oral squamous cell carcinoma (SCC).

Materials and Methods: In this retrospective study, 111 cases of oral SCC registered from 1991 to 2001 were retrieved from the archive of the Department of Pathology of Cancer Institute. Cases were divided into two groups based on the presence of lymph node metastasis. Patients' pathological reports and medical records were reviewed and variables such as age, gender, occupation, disease duration, site and greatest diameter of tumor and histopathologic grade were compared between metastatic and non-metastatic groups. Data were analyzed using SPSS package and t, chi square, Mann-Whitney and Fisher's exact test with $p < 0.05$ as the limit of significance.

Results: Among the studied factors, patients' gender (female), the disease duration (more than 12 months) and tumor size based on T₁-T₄ category were significantly related to lymph node metastasis. Other factors failed to show any correlation with lymph node metastasis.

Conclusion: Based on the results of this study, women with large tumors lasting more than 12 months might be of greater risk for lymph node metastasis.

Key words: Mouth neoplasm, Squamous cell carcinoma, Lymph node metastasis, Clinicopathological parameter

Received: 5 March 2008

Accepted: 30 April 2008

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Introduction

Oral cancer accounts for less than 3% of all cancers in the United States and is the sixth most common cancer in males and twelfth in women. However in some countries like India, it is the most common cancer (1). Death due to oral and oropharyngeal cancer represents approximately 2% of the total in men and 1% of the total in women (2). The trend in survival of patients with this malignancy has been rather disappointing during the past several decades and the overall survival rate of all patients with oral cancer is about 50% (2). The prognosis for survival from oral cancer depends on various factors. The most important indicator of prognosis is the clinical stage of the disease. Once metastasis to cervical nodes has occurred, the 5-year survival rate is reduced by approximately half (2). Several studies have been performed in order to determine factors influencing and predicting lymph node metastasis. Many clinical, pathological and molecular parameters have been investigated but the results were different and controversial (3-15). In our country, information on prognosis and metastasis of oral cancer are limited and data on survival is lacking due to the absence of patients' follow up. Thus, the aim of this study was to evaluate some clinical and pathological factors influencing lymph node metastasis in oral squamous cell carcinoma (SCC) retrospectively.

Materials and Methods

In this retrospective study, the archive of the Department of Pathology, Cancer Institute was the source of data collection. All cases of oral SCC registered between 1991 and 2001 were retrieved and cases with complete resection of the primary tumor and radical neck dissection were selected. Patients' pathological reports and medical records were reviewed and information regarding age, gender, occupational status, history of smoking, disease duration, site and greatest diameter of tumor as well as histopathologic grading were recorded. As the study was restricted to intraoral SCC, cases of lip were excluded from the final analysis. Tumors with unknown origin, lesions involving the skin, sinuses, salivary glands, tumors with margin involvement as well as patients with recurrent tumors and those receiving radio- and/or chemotherapy were also excluded from the study.

Cases were divided into two groups regarding lymph

node metastasis based on microscopic examination of pathologic slides. Variables were compared between two groups and data was analyzed using SPSS package (version 9) and t, chi-square, Mann-Whitney and Fisher's exact tests. A p value less than 0.05 was considered as the limit of significance.

Results

From a total of 826 cases of oral SCC, 204 cases had complete resection of the primary tumor along with radical neck dissection. Considering the exclusion criteria, 111 cases remained for final analysis. Out of these, 61 cases (55%) were men and 50 cases (45%) were women. The mean age was 59 ± 13.7 years (with a range of 18 – 85 years) in all cases, 57.7 ± 13 years in men, and 61.6 ± 14 years in women. This difference was not statistically significant ($p=0.15$). In addition, 49.5% of cases were lymph node-positive and 50.5% was negative. Meanwhile, 25 cases (41%) of men and 30 cases (60%) of women had lymph node metastasis. This difference was statistically significant ($p=0.046$). The mean age for metastatic cases was 59.7 ± 14.7 years as compared to 59.2 ± 12.9 years for non-metastatic which this difference was not statistically significant ($p=0.1$). Regarding occupation, 43.3% of cases were housewife, 19.2% farmer, 16.2% employee, 11.1% self-employed and 10.1% worker. No statistical difference was observed between metastasis and non-metastasis group with respect to patient's occupational status.

In cases with lymph node metastasis, the mean tumor thickness was 1.96 ± 1.4 cm compared with 2.08 ± 1.2 cm in non-metastatic group. This difference was not statistically significant ($p=0.86$). The disease duration was evaluated with 5 and 12 months cut off. Considering 5 months cut off, no statistically significant difference was observed between the two groups ($p=0.53$). In addition, 42.5% of cases with a maximum disease duration of 12 months had lymph node metastasis whereas 100% of cases with disease duration more than 12 months had metastasis and the difference was significant ($p=0.01$).

The average of greatest tumor diameter was 3.35 ± 1.5 cm and 2.96 ± 2.7 cm in metastasis and non-metastasis groups respectively which was not statistically different ($p=0.41$). Tumor size classified by T₁-T₄ category was accessible in 85 patients and is shown in Table 1. The distribution of cases by tumor location in the studied groups is shown in Table 2. T category was

significantly correlated with lymph node metastasis ($p=0.02$). No statistical relation was found between the site of primary tumor and lymph node metastasis ($p=0.58$). The clinical presentation of lesions was recorded in 107 cases as ulcerative, exophytic or

both which was not different between the two groups ($p=0.22$). Descriptive pathologic grading was applied and no statistical relationship was observed for lymph node metastasis ($p=0.59$).

Table 1: The relationship between tumor location and lymph node metastasis

Lymph node status Tumor location	Positive		Negative		Total	
	No	(%)	No	(%)	No	(%)
Floor of mouth	8	47.1	9	52.9	17	100
Tongue	27	50	27	50	54	100
Gingiva*	10	47.6	11	52.4	21	100
Buccal mucosa	7	70	3	30	10	100
Mandible	2	28.6	5	71.4	7	100
Maxilla	1	100	--	--	1	100
Retromolar pad	--	--	1	100	1	100

* All cases involved lower gingiva

Table 2: The relationship between T stage and lymph node metastasis

Metastasis Tumor size	Positive		Negative		Total	
	No	(%)	No	(%)	No	(%)
T ₁	3	20	12	80	15	100
T ₂	28	56	22	44	50	100
T ₃	1	25	3	75	4	100
T ₄	11	68.8	5	31.2	16	100

Discussion

Lymph node metastasis significantly decreases the survival rate of oral squamous cell carcinoma, thus establishing predictors of metastasis is of critical importance. This study was designed in an attempt to evaluate the relation between the most accessible patients' characteristics and lymph node metastasis.

Out of all studied factors, female gender, disease duration more than 12 months and T₄ tumors were significantly related with lymph node metastasis. No statistical relationship was observed between age, occupational status, clinical presentation, tumor location, histopathologic grade and lymph node metastasis. Maddox and Urist reported a poor prognosis for men (3). Bansberg et al stated that the

age of patient is one of the most important factors related to survival and older age at the time of diagnosis increased the risk of death (4). In other studies poor prognosis was observed in young patients (5;6). Recent studies failed to show any relationship of age and gender with lymph node metastasis and prognosis (7-10). These differences might be attributed to several factors mainly geographic and environmental ones. In addition, differences in sampling and study design must be considered.

In the present study, T stage showed a significant correlation with metastasis. This was in accordance with several studies (4;5;8;11-13). In contrast, other studies failed to demonstrate such relationship (10;14;15). Some investigators emphasized the role of tumor thickness instead of tumor size (16-19).

Others included both the size and thickness of tumor as prognostic factors (20). In our study, we did not observe any relationship between tumor thickness and lymph node metastasis. This difference is related to the method and accuracy of tumor thickness measurement. In our study, tumor thickness was retrieved from macroscopic observation in pathologic reports. Studies in which the tumor thickness is measured microscopically and with 0.1 mm accuracy are more reliable. In addition, some investigators reported that incomplete excision of the primary tumor is a limitation in the evaluation of prognostic value of tumor thickness because the true depth of tumor is not reachable (21). Our study was restricted to cases with complete resection to overcome this limitation.

In the present study, disease duration was considered with 5 and 12 months cut offs. Our findings showed that tumors lasting more than 12 months were at higher risk for metastasis. Few studies have considered the delay and metastasis separately. In addition, the disease duration and delay are not the same, thus direct comparison of our results was not possible. Kerdpon et al (12) reported that patients with 4 to 6 months delay in referral and treatment as compared to those with 1 month delay were at higher stages of the disease. Tumor primary site was investigated in several studies. Our findings were in accordance with Rasgon et al (22) but some studies reported that tongue lesions are at higher risk for metastasis as compared to other parts of oral cavity (23-25). In our study, in order to achieve better and more accurate results, we excluded lip lesions because the true origin of lesions (skin or mucosa) was not clear. In addition, cases involving adjacent structures as well as marginal involvement were excluded from final analysis.

Also, it must be mentioned that jaw SCCs are not common and may be cases reported as primary intraosseous SCCs are simply tumoral invasion from primary gingival lesions reported as jaw tumors.

The influence of histopathologic grading on prognosis is controversial. Some studies have correlated Broder's system with lymph node metastasis (10;14-17;26-28) while others did not show any relationship (3;4;8;16;22;29). In our study, we recorded the descriptive system which is a modification of Broder's classification and did not observe any relationship with metastasis. Broder's system and similar systems consider the tumor as a whole and only one characteristic of tumor (differentiation) is evaluated.

Oral SCCs are composed of heterogeneous population of cells with different differentiation grades (4;29;30). Considering the limitation of these systems, several multifactorial grading systems were introduced and evaluated clinically. Most of studies have shown a correlation between those classifications and prognosis (11;31;32). Yazdi and khalili conducted a study to assess the relationship between several grading systems and lymph node metastasis. Their findings showed that Broder's system and the modified classification were not related to metastasis whereas a modification of Bryne system showed a significant correlation with lymph node metastasis (30). Their study was focused on histopathologic grading systems in a limited and selected sample of tongue SCC whereas in our study we aimed to evaluate several factors respectively based on patients' reports with larger sample from all parts of the oral cavity. It is obvious that grading systems based on different tumor characteristics are more accurate but they are not widely accepted in routine practice and their reproducibility and inter-observer agreement is not easily achieved. Studies regarding prognosis in oral SCCs lack a standard and established methodology, thus findings vary depending on several parameters such as source of data collection, sample size and sampling methods, type of study, inclusion and exclusion criteria and length of follow up period. But the most important factor is the difference in the definition of the oral cavity. In some studies, oral cavity is considered from the vermilion border including major and minor salivary glands (30), whereas in others the area is limited to the mouth cavity excluding soft palate and tonsils (27). In addition, the evaluation of prognosis is different in studies and may be based on survival or other well-known prognostic indicators such as lymph node metastasis and can be evaluated retrospectively or prospectively.

In our country, data on follow up and patients' recall are rare, thus design of studies considering true prognosis and survival is very difficult if not impossible. In addition, today several prognostic molecular and biological markers are introduced but they are not widely and routinely used. This study is a preliminary report on the most easily accessible factors related to lymph node metastasis. By excluding some possible confounding and confusing cases we tried to

achieve a more homogenous sample but this study is not apart from other retrospective archive based ones and before mentioned limitations must be considered while interpretation of our findings.

Conclusion

Based on our findings, women with large tumors lasting more than 12 months are at higher risks for lymph node metastasis in oral SCC. Prospective studies with molecular and biological markers are recommended to achieve better understanding of prognostic factors in our sample.

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