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Original Article

Controversies on Tumor Thickness Versus Nodal Metastasis in Oral Squamous Cell Carcinomas Revealed: A Histopathologist's Perspective

Vandana Reddy, Vijay Wadhwan, Munish Reddy, Arvind Venkatesh

Departments of Oral Pathology and Microbiology, Orthodontics and Dentofacial Orthopedics and Pathology and Microbiology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh, India

Abstract

Background: Cervical metastasis has a tremendous impact on prognosis in patients with head and neck squamous cell carcinomas (HNSCCs). However, to date management of clinically negative neck in HNSCC is still a controversial subject. Tumor thickness (TT) is a strong predictor for lymph node involvement in oral squamous cell carcinomas (SCCs). However, controversy exists about the optimal TT cutoff point for a clinically relevant risk to the neck. **Aim and Objectives:** The aim is to evaluate the relationship between TT and the risk of cervical lymph node involvement and to determine optimal TT cutoff point for prompting prophylactic neck management. **Materials and Methods:** The clinical files and histological sections of 35 SCC (T1/T2) at buccal mucosa site from clinically determined N0 patients were retrospectively analyzed who underwent surgical treatment of their primary lesion with simultaneous neck dissection. An ocular micrometer was used to measure the TT both in exophytic and ulcerated lesions. Chi-square contingency tables were used to correlate TT and other clinicopathological parameters with metastasis in the neck. **Results:** Clinically, negative necks turned out pathologically positive in 42.8% (n = 15/35). In the group in which tumor depth exceeded 1.5 mm, the metastatic rate was 86.7% (13/15). In contrast, when the depth of invasion was <1.5 mm, the incidence of cervical metastasis was 13.3% (2/15) irrespective of the 2 stages. **Conclusion:** TT is a highly significant, objectively measurable prognostic factor in early stage oral cancers and elective neck therapy is indicated for tumors exceeding 1.5 mm invasion.

Keywords: *Elective neck therapy, metastasis, oral squamous cell carcinoma*

Introduction

Oral squamous cell carcinoma (OSCC) is the most frequent head and neck cancer.[1] In contrast to other sites of oral cancer, the incidence of the buccal carcinoma is increasing, especially in the younger age group which is related to the widespread practice of betel nut chewing placed along the buccal mucosa to induce a feeling of euphoria.[2] The metastatic dissemination of these tumors usually occurs through the lymphatic system, and level I and II neck lymph nodes are the most commonly involved.[3] The incidence of occult metastasis in neck lymph nodes in patients with clinical stages I and II squamous cell carcinoma (SCC) of the mouth ranges from 27% to 40%.[4] The presence of cervical lymph node metastasis is consistently a strong determinant of survival in patients with SCC of the oral cavity (OSCC).[5]

The high incidence of occult lymph nodal metastasis is a strong argument for the indication of elective neck dissection (END) in clinical Stages I and II oral cancers. END may be both diagnostic and therapeutic.[6] END provides pathologic information on the status of neck nodes thus helping to determine the need for additional therapy, and can also remove undetectable cancer cells lodged in the lymph vessels. However, there is a high percentage of patients who do not have metastasis in the pathological exam (pN_0). Furthermore, it does have an associated morbidity and may remove or destroy a natural barrier to cancer spread.[7] The identification of factors associated with the risk of lymph node metastasis may be useful for the proper selection of patients to END.

In 1970s, Breslow established a strong link between tumor thickness (TT) and both tumor-free survival and metastasis in patients with cutaneous melanoma.[8] Mohit-Tabatabai *et al*. and Spiro *et al*. first applied Breslow's hypothesis regarding the link between lymph node involvement and

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Address for correspondence:
Dr. Vandana Reddy, Department of Oral Pathology and Microbiology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh, India. E-mail: drvandanareddy@rediffmail.com

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TT to oral SCC.[9,10] Most studies have suggested that TT, which can be considered an objective parameter of the depth of invasion within the connective tissue is a strong predictor for lymph node involvement in oral SCC.[11] Although, in regard to the critical level of tumor thickness for predicting cervical metastasis, there were variable results which ranged from 1.5 to 5 mm; controversy still exists about the optimal TT cutoff point for a clinically relevant risk to the neck of harboring microscopic disease.[12,13]

The aim of this study was to evaluate the demographic, clinical, and pathological factors associated with the risk of occult metastasis and prognosis in patients with clinical stages I and II SCC of the buccal mucosa and to evaluate relationship between TT and the risk of cervical lymph node involvement and to determine optimal TT cutoff point for prompting prophylactic neck management.

Materials and Methods

This is a retrospective study performed by retrieving the records from pathology archives of cases reported between 2010 and 2014. Only patients diagnosed as SCC (8070/3) with $cT_1N_0M_0/cT_2N_0M_0$ at cheek mucosa (C06.0) who had primarily surgical treatment without radiotherapy or chemotherapy were recruited. Patients with carcinoma of other sites of the oral cavity were excluded from the study. All patients received removal as the primary treatment and patients had END. The tumor types were classified into superficial, exophytic, and ulcerative. Histological sections from each patient were analyzed by a single pathologist to reconfirm the initial diagnosis of SCC and to examine the type of differentiation of the tumor. Measurements for TT were made at step sections of 1–2 mm for maximum thickness. The optical micrometer was used to measure the distance (to the nearest mm) from an imaginary line reconstructing the basement membrane of the healthy mucosa to the deepest point of tumor invasion, in superficial, exophytic, and ulcerated lesions [Figure 1]. TT measured was categorized as <1.5 mm, 1.6–3 mm, and >3 mm. All levels of nodes stained with hematoxylin and eosin were re-examined microscopically for tumor invasion [Figure 2]. Chi-square test was used to correlate clinical and histopathologic parameters with lymph node metastasis. Values of $P < 0.05$ were considered to be statistically significant.

Results

The results of the present study show a total of 35 patients were eligible for the study, 30 (85.7%) were male and 5 (14.28%) female. The patient's age ranged from 24 to 85 years (mean, 52 years). A total of 7 (20%) were clinical stage I and 28 (80%) clinical stage II. With regard to the macroscopic type, 6 (17.14%) were exophytic, 28 (80%) were ulcerative, and 1 (2.85%) was superficial type lesion. Of the 35 patients whose histologic grade was observable, 19 (54.2%) were classified as Grade I, 16 (45.7%) as Grade II, and 0 (0%) as Grade III.

Of the 35 patients who underwent END metastasis (overall occult cervical metastatic rate) in lymph nodes was found in 15/35 (42.8%). When all the clinicopathological parameters were correlated with lymph node metastases only TT correlated with nodal metastases (0.032). In the group in which TT exceeded 1.5 mm, the metastatic rate was 37% (13/35). In contrast, when the TT was equal or <1.5 mm, the incidence of occult cervical nodal metastases was 5.7% (2/35). However, cervical metastases did not correlate with age, gender, T classification, the degree of differentiation, and tumor type [Table 1].

Discussion

SCC of the mouth is characterized by a high potentiality of local invasion and metastasis to neck lymph nodes, which diminishes the rates of locoregional control of the disease and the survival of these patients.[1] By the use of TNM classification of malignant tumours (TNM) staging system, there is no significant difference in the risk of subclinical nodal metastasis, local recurrence, and survival between T1

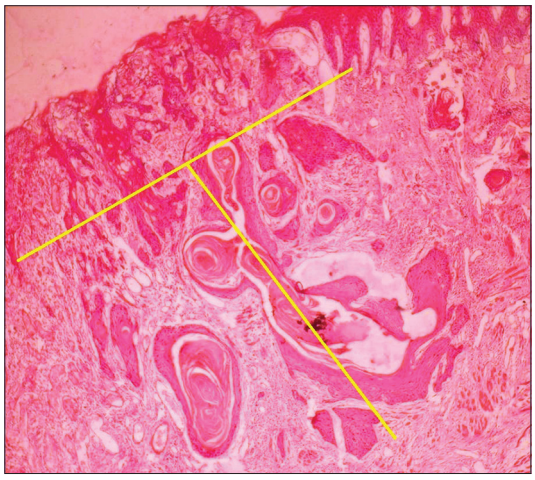

Figure 1: Tumor thickness to the nearest 0.1 mm is determined with an ocular micrometer

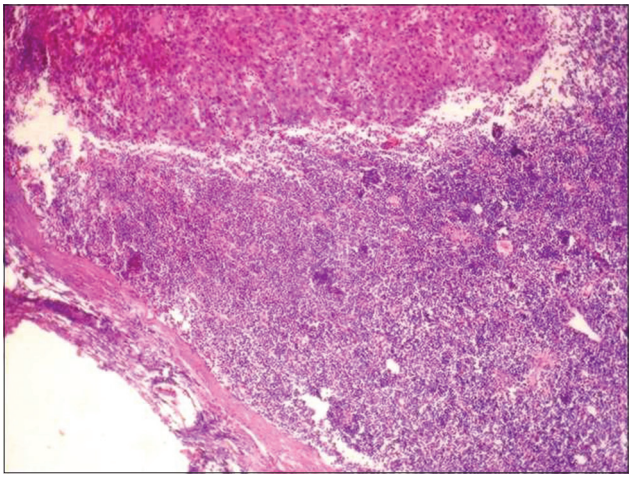

Figure 2: Tumor invasion within the lymph node

Table 1: Correlation of demographic and clinico-pathological parameters with occult metastasis

Variables	Total number (*n*=35), *n* (%)	Positive nodes (pN+) (*n*=15), *n* (%)	Negative nodes (pN−) (*n*=20), *n* (%)	*P*
Sex				
Male	30 (85.7)	13 (43.33)	17 (56.67)	0.081
Female	5 (14.28)	2 (40)	3 (60)	
Age				
≤39	4 (11.42)	1 (25)	3 (75)	0.319
40-59	26 (74.2)	12 (46.15)	14 (53.8)	
≥60	5 (14.28)	2 (40)	3 (60)	
T stage				
T1	7 (20)	1 (14.28)	6 (85.7)	0.096
T2	28 (80)	14 (50)	14 (50)	
Tumor morphology				
Exophytic	6 (17.14)	2 (33.33)	4 (66.67)	0.212
Ulcerative	28 (80)	13 (46.42)	15 (53.57)	
Superficial	1 (2.85)	0	1 (100)	
Differentiation				
Well	19 (54.2)	5 (26.31)	14 (73.68)	0.276
Moderate	16 (45.7)	10 (62.5)	6 (37.5)	
Poorly	0	0	0	
Depth of invasion				
<1.5	22 (62.8)	2 (9.09)	20 (90.9)	0.032
1.6-3.5	13 (37.1)	13 (100)	0	
>3.6	0	0	0	

pN – Pathological nodes

and T2.[12] A better prognostic evaluation system is therefore necessary to guide the clinical management, particularly in the prediction of subclinical nodal metastasis.

An important aspect of this study is to demonstrate that TT is an appropriate factor to predict cervical metastasis of primary SCC of the buccal mucosa. In addition, we evaluated other demographic, clinical, and histopathological factors with respect to their relevance in predicting lymph node metastasis.

The incidence of occult metastasis to cervical nodes has been commonly reported as 20%–30%.[13] The present study indicates subclinical lymph node metastasis of 5.7% was found in the tumors <1.5 mm of depth and 37% in the tumor depth that exceeded 1.5 mm. In the study presented here the rate of occult metastasis was seen in 42.8% of cases. A significant association was only observed for TT with nodal metastases in the present study. Thus, tumor depth is useful for predicting the occult cervical lymph node metastasis. Our results were in keeping with those of other investigators.[9,10]

Mohit-Tabatabai *et al*. reported that patients with lesion of <1.5 mm had a cervical metastasis rate of 2%. This incidence increased to 33% when the lesion was 1.6–3.5 mm in thickness and to 60% for lesions thicker than 3.6 mm.[9] Furthermore, according to Spiro *et al*. the risk of cervical metastases for lesions of more than 2 mm in thickness approached 40%.[10] The present study indicates that the prognosis is excellent in patients with a thin oral tumor (1.5 mm/less).

This can be explained as increasing depth of invasion, and the microvascular proliferation caused by neoplastic growth might determine proximity to blood vessels and lymphatics, thus facilitating tumor's ability to metastasize. Moreover, it has been observed that it is more difficult for tumor emboli to form in small-caliber lymphatics of superficial areas than in the wider lymphatics of deeper tissue.[14]

The female to male ratio of PN (−) to PN (+) was 0.4 (2/5) to 0.43 (13/30) respectively. Regarding age distribution, the proportion of young adults (younger than 50 years) was higher in the PN (−) group (62.5%) than the PN (+) group (41.67%). The sex and age distribution had no statistical significance with regard to cervical metastasis.[15] In some previous studies, relation between differentiation grade and lymph node metastasis was established by Rasgon[16] and Mendelson *et al*.[17] The study results differ from this observation as the majority of our cases are classified as well-differentiated type. Rasgon *et al*. and Byers *et al*. noted that T stage did not correlate with cervical lymph node metastasis. The study results are in agreement with their findings.[16,18] Shintani *et al*. reported significant relationship of tumor shape and neck metastasis.[19] In this study, there was no significant correlation of exophytic or endophytic pattern of growth with subclinical nodal metastasis.

Although most authors substantially agree that TT is a significant parameter for predicting nodal metastasis development and for survival the cutoff thickness is quiet variable, ranging from 1.5 to 10 mm.[20] Differences in

results could be attributable to the imprecise definition of TT used between studies. Several ways of defining TT have been used in the previous studies and summarized by Pentenero *et al*. as follows: (a) From surface/base of the ulcer to deepest point of invasion (b) from adjacent intact mucosa to deepest point of invasion (c) from basal membrane to deepest point of invasion [Figure 3][20] Moore *et al*. found that survival correlated better with TT when measured from a theoretical construction of a basement membrane through the tumor than from the surface of the tumor.[21]

Earlier studies have shown different values due to imprecise definition of TT used between studies and as summarized by Pentenero *et al*.[12,13,20] As mentioned in the present study measurements for TT were made using an optical micrometer by measuring the distance from an imaginary line reconstructing the basement membrane of the healthy mucosa to the deepest point of tumor invasion.

The value of 1.5 mm was taken as cutoff because 37% of cases showed metastases beyond this thickness. This may be attributed to the methodology (measurement technique) we have considered. The thickness cutoff can be more if the type of measurement technique is different like from the adjacent intact mucosa and the deepest point of invasion/from surface/base of the ulcer to the deepest point of invasion.

Alternately, some studies related the critical thickness to the site, but to date, there is no agreement about this.[20] In the present study, all the patients were with tumor in the gingival buccal site. Woolgar and Scott reported different cutoff values for TT as related to the tumor site. A possible explanation might be related to the difference in the depth and caliber of the lymphatics at the two sites.[22] O'Brien *et al*. found no difference among 145 cancers from different oral cavity sites, with a median TT that was similar for the tongue, the floor of the mouth and other sites.[23]

The drawback of using the TT parameter include the absence of mucosa in some samples, the tangential cutting of some tissue sections and samples that are inadequate to allow measurement of the maximum tumor depth.[24] Surgical excision of the primary tumor and measurement of the depth of invasion by frozen section may provide additional useful information for determining the need for neck dissection in the clinically N_0 patient.[15]

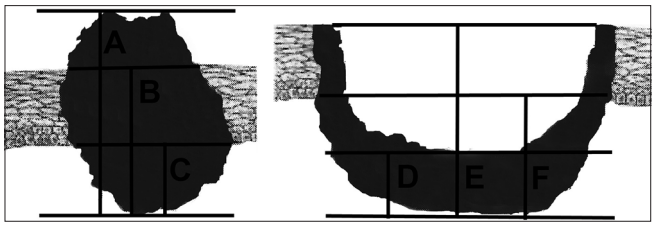

Figure 3: Methods of measuring Tumor thickness (A-D) tumor surface/base of the ulcer-deepest point of invasion (B-E) adjacent intact mucosa-deepest point of invasion (C-F) basal membrane-deepest point of invasion

Conclusion

As evident from above study the optimal cutoff point for TT is 1.5 mm for oral cavity tumors in buccal mucosa site, and for tumors thicker than 1.5 mm prophylactic neck management is recommended. Although there is substantial agreement among authors despite the lack of comparable study groups, of measurement techniques, and cutoff values paradoxically enforced its reliability. Further studies are clearly awaited to reach a consensus on the topic to develop therapy protocols that are also based on this parameter by incorporating into clinical TNM staging system.

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Conflicts of interest

There are no conflicts of interest.

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