Original Article

The effect of depth of invasion and tumour size on risk of neck node metastasis in squamous cell carcinoma of oral cavity: retrospective analysis

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DOI: 10.5455/jrmds.20153312

ABSTRACT

Background: oral carcinoma is considered to be loco regional disease which metastasizes to nodal and distant sites. Prognostic factors include size of tumor, nodal status, depth of invasion and various pathological factors. Depth of invasion has been suggestive to have a relationship with the occurrence of cervical metastasis.

Aim: To study effect of depth of invasion and tumour size on risk of node metastasis in squamous cell carcinoma of oral cavity.

Methods: We retrospectively analyzed the effects of three different variables-tumor size, degree of differentiation, and depth of invasion-on the risk of neck node metastasis in 196 adults who had been treated with surgery for primary squamous cell carcinoma of the oral cavity. Primary tumor depth and other pathologic features were determined by reviewing the pathology specimens.

Results: Preoperatively, 140 of the 196 patients were clinically N0; however, occult lymph node metastasis was found in 70 of these patients (36.1%). The prevalence of neck node metastasis in patients with T1/T2 and T3/T4 category tumors was 51.5 and 58.8%, respectively. The associations between the prevalence of neck node metastasis and both the degree of differentiation and the depth of invasion were statistically significant.

Conclusion: The prevalence of neck lymph node metastasis in patients with squamous cell carcinoma of the oral cavity increases as the tumour depth increases. It is interesting that tumor size, which is the most important component of the TNM system, was not significantly associated with neck node involvement**.**

Key words: Invasion, Tumour size, Metastasis, Squamous cell carcinoma

INTRODUCTION

Squamous cell carcinomas of the oral cavity are relatively common among the head and neck cancers. As they grow, they invade the surrounding tissue and metastasize to cervical lymph nodes. This is believed to occur as a result of the filtering effect of the rich lymphatic system on the tumor cells' route of drainage. The lymphatic system captures the cancer cells and prevents them from spreading to the other organs. Cervical lymph node metastasis is the single most important prognostic factor for patients with head and neck carcinoma [1,2,3,4]. Therefore, appropriate management of the neck is important.

During the evaluation of cancer patients, the TNM classification has traditionally been used as an objective, internationally accepted system. However, several studies have shown that many factors other than size, node involvement, and metastasis have varying degrees of influence on a particular patient's prognosis. These factors include histological grade, degree of differentiation, and depth of invasion, tumor thickness, perineural perivascular invasion, growth pattern, and epidemiologic factors such as age, sex, race, and alcohol and tobacco use [5, 6]. Since there are associations between these factors and prognosis, it is logical to think that there might also be an association between these factors and cervical lymph node involvement.

The prefixes c and p are used to designate clinical (preoperative) and pathologic (postoperative) tumor status, respectively. There is a consensus that large (cT3 or cT4) head and neck tumors and cN + neck disease necessitate treatment of the cervical lymph nodes. However, in patients with early-stage disease, there are many doubts as to which approach to the neck is best [5]. It is generally known that overall survival for patients with clinically negative lymph nodes is high. The main problem in the management of early-stage

cancers is node involvement as a result of undetectable subclinical node metastasis [6]. Despite advances in imaging techniques for the detection of lymph node spread, occult metastases are unidentified in 20 to 50% of lymph node-negative patients [7, 8]. These patients eventually develop a clinically evident cervical metastasis, usually within 2 years [9, 10]. While Kamer et al showed that local failure was the most important factor affecting the final outcome, survival among patients with neck node involvement is usually poor [11].

In this article, we describe our study to determine whether the prevalence of cervical lymph node involvement is influenced by tumor size, degree of differentiation, and depth of invasion.

MATERIALS AND METHODS

Eligibility criteria: We retrospectively identified a group of patients who had been admitted to Gujarat Cancer and Research Institute, Ahmedabad, Gujarat. Inclusion criteria for this study included Tl to T4 oral cavity cancer that was primarily treated with wide excision of the tumor and simultaneous bilateral or unilateral neck dissection, depending on the tumor location and the status of the neck. Surgery was followed by radiotherapy and/or chemotherapy if necessary. Patients who had been previously treated with radiotherapy or chemotherapy were excluded.

Preoperative assessments of neck lymph node metastasis were based on physical examination. Some patients' charts also included ultrasonography, computed tomography, and/or magnetic resonance imaging scans. Evaluations of distant metastases were based on chest x-ray findings and further imaging if needed. When a proven or suspected distant metastasis was detected, the patient was excluded from the study.

Our study population was made up of 196 patients who met our eligibility criteria. This group included 141 men and 55 women, aged 27 to 77 years (mean: 55 years); they had been seen between July, 2012, and December, 2012. Of the 196 tumors, 84 were located in the tongue, 20 in the oral floor, 44 in the gingiva, 16 in the retromolar trigone, 24 in the buccal mucosa, 4 in the hard palate and 4 of lip (Table 1).

Histopathologic examination: Surgical specimens were oriented and labeled by surgeons and fixed in 10% buffered formalin by pathologists. The specimens were then processed and examined under microscopic vision. Paraffin was applied 1 day after fixation. Information on the presence or absence of cervical lymph node metastasis, tumor size, degree of differentiation, and depth of invasion was obtained from the pathology reports. The depth of invasion was calculated as the distance between the basal membrane and the deepest point of the invaded stromal tissue.

Statistical analysis: The significance of lymph node metastasis with different variables was investigated by means of the Fisher exact test. A p value of <0.05 was considered to be statistically significant.

Table 1: Demographic variables and tumor site

Variable	No. (percentage)
Sex	
Male	141 (72)
Female	55 (28)
Age (Yrs)	
≤ 30 yrs	16 (08)
31-40	19 (10)
41-50	39 (20)
51-60	43 (22)
61-70	63 (32)
≥ 71 yrs	16 (08)
Tumor Size	
Tongue	84 (43)
Oral floor	20 (10)
Gingiva	44 (22)
Retromolar trigone	16 (08)
Buccal mucosa	24 (12)
Hard Palate	04 (02)
Lip	04 (02)

RESULTS

Tumor size: Evaluation of preoperative tumor size revealed that 59 patients were classified as cTl, 71 as cT2, 39 as cT3, and 27 as cT4 (table 2). For purposes of statistical analysis, we subclassified early- and late-stage tumors into two groups: T1/T2 (n =130) and T3/T4 (n = 66).

Degree of differentiation: Tumors were well differentiated in 103 cases, moderately differentiated in 69, and poorly differentiated in 24. (Table 2).

Depth of invasion: Depth of invasion was 5 mm or less in 39 patients, 5.1 to 10 mm in 59 patients, and more than 10 mm in 98 (table 2).

Neck node involvement: On preoperative examination, 55 patients were node-positive (cN+) and 141 were node-negative (cN0). On postoperative pathology, however, 106 patients were found to be pN+, including 51 of the 141 patients who had been classified as cN0.

Therefore, the prevalence of occult neck metastasis was 36.1% (table 2 and table 3).

Associations. The data were analyzed for associations between the presence of neck node metastasis and tumor size, differentiation, and depth of invasion.

Table 2: Disease characteristics

Characteristics	No. (percentage)
Tumor size	
cT1	59 (30)
cT2	71 (36)
cT3	39 (20)
cT4	27 (14)
Degree of differentiation	
Well differentiated	103(53)
Moderately differentiated	69 (35)
Poorly differentiated	24 (12)
Depth of invasion	
≤5mm	39 (20)
5.1 to 10 mm	59 (30)
>10.1 mm	98 (50)
Neck node involvement	
cN0	141(72)
cN+	55 (28)
pN0	90 (46)
pN+	106(54)

cT indicates the preoperative clinical classification of tumor size; cN0 indicates no clinically detected involvement of cervical lymph nodes preoperatively; cN+ indicates clinical detection of lymph nodes preoperatively; pN0 indicates absence of histologically detected lymph nodes metastasis postoperatively; pN+ indicates presence of of histologically detected lymph nodes metastasis postoperatively

Table 3: comparison of pre- and postoperative N status

	pN0	pN+	Total
cN0	90	51	141
cN+	00	55	55
Total	90	106	196

cT indicates the preoperative clinical classification of tumor size; cN0 indicates no clinically detected involvement of cervical lymph nodes preoperatively; cN+ indicates clinical detection of lymph nodes preoperatively; pN0 indicates absence of histologically detected lymph nodes metastasis postoperatively; pN+ indicates presence of of histologically detected lymph nodes metastasis postoperatively

Tumor size: Neck metastases (pN+) were found in 67 of the 130 T1/T2 patients (51.5%) and in 39 of the 66 T3/ T4 patients (58.8%). The difference was not statistically significant (table 4 and table 5).

Degree of differentiation: Neck node metastasis was present in 39 of 103 cases of well-differentiated squamous cell carcinoma (38.1%), in 30 of 69 moderately differentiated tumors (42.9%), and in 19 of 24 poorly differentiated tumors (80.0%). The association between increasing node involvement and the decreasing degree of differentiation from well to poor was statistically significant ($p < 0.05$) (table 4).

Table 4: Univariate analysis of associations between node involvement and three study parameters
NS: not statistically significant

Parameters	pN0	pN+	P value
Tumor size			
T1/T2	63	67	>0.05
T3/T4	27	39	
Degree of differentiation			
Well differentiated	64	39	
Moderately differentiated	39	30	<0.05
Poorly differentiated	05	19	
Depth of invasion			
<5 mm	23	16	
5-10 mm	35	24	P<0.05
>10 mm	31	67	

We also evaluated the prevalence of node metastasis according to differentiation among the 141 cN0 patients in whom differentiation was known. We found node involvement in 15 of 71 patients with well-differentiated carcinoma (21.4%), in 20 of 50 with moderately differentiated disease (40.0%), and in 15 of 20 cases with poorly differentiated cancer (75.0%). The association between node metastasis and the degree of differentiation in the cN0 group was statistically significant ($p<0.05$)

Depth of invasion: Node metastases were present in 16 of 39 patients with a depth of invasion of 5 mm or less (40.0%), in 24 of 59 patients whose depth of invasion was between5.1 and 10 mm (40.0%), and in 67 of 98 patients with invasion more than 10 mm (68.0%). There was a statistically significant association between a higher prevalence of lymph node metastasis and a greater depth of tumor ($p <0.05$) (table 4).

When we evaluated depth of invasion in the 36 cN0 cases, the corresponding rates of neck node metastasis were 22.2%, 35.7%, and 46.1%. The

association of node metastasis with the depth of invasion in the cN0 group was statistically significant (p = 0.05).

Table 5: Distribution of preoperative T and N categories

	cT1	cT2	cT3	cT4	Total
cN0	47	51	23	20	141
cN1	07	04	08	08	27
cN2a	00	08	00	00	08
cN2b	00	04	04	00	08
cN2c	00	04	00	00	04
cN3	04	00	04	00	08
Total	58	71	39	28	196

cT and cN indicate the preoperative clinical evaluation of tumor size and nodal status , respectively

DISCUSSION

Treatment of the neck should always be performed when there are obvious clinically detectable lymph nodes in a patient with squamous cell carcinoma of the oral cavity. But in patients with a clinically negative neck or with early-stage oral cavity carcinoma (T1/T2, N0), treatment of the neck remains controversial. The two options for managing the neck in these cases are elective neck dissection and a wait-and-see approach.

The advantages of elective neck dissection are that it can (1) provide accurate neck staging, (2) allow for the removal of any neck metastasis that might be present, and (3) help determine the need for radiotherapy. In addition to the obvious disadvantage of the morbidity of a second surgery, neck dissection might destroy the natural tumor barrier [12].

Considering the high rates of occult metastasis that have been reported by various authors, elective neck dissection has many proponents.[9,13] In our study, the rate of occult metastasis was 36.1%, which is about average for cases of upper aerodigestive tract squamous cell carcinoma. The implication of this finding is that a wait-and-see policy could miss a metastasis in about 1 of every 3 patients. On the other hand, one can find in the literature that some wait-and-see groups had better survival rates than did groups of patients who had undergone elective neck dissection [14, 15]. Yet despite the disadvantages of dissection and the advantages of watchful waiting, the preference in most cancer centers, and in our institution, is for elective treatment of the neck, especially in patients whose primary tumor is located on the tongue or oral floor.

Others have found that the surface size of a tumor does not correlate with the incidence of metastasis in oral squamous cell carcinoma [9, 16, 17]. Therefore, consideration of a patient's T category might not be sufficient for making optimal treatment decisions.

Of the different variables that are related to neck metastasis, two of the most important are depth of invasion and tumor thickness [3]. These two terms are sometimes used interchangeably, but their meanings are not the same. Depth of invasion is used to define the extension of tumor beneath the epithelial surface, where epithelium is destroyed. Tumor thickness is used to define the measurement of a tumor's vertical bulk; it encompasses both the exophytic and endophytic portions of the tumor [6].

Many studies have demonstrated that depth of invasion is an appropriate factor on which to base predictions of cervical metastasis in oral squamous cell carcinoma [6, 13, 18, 19]. Other studies have shown that there is a statistically significant association between depth of invasion and neck node metastasis in all patient groups, including clinically N0 groups. We believe that this association is most important in cN0 patients because of the controversy surrounding the need for neck dissection.

Hosal et al reported that patients with a tumor depth of less than 9 mm fared significantly better than those whose depth was greater than 9 mm ($p < 0.05$) [20]. Therefore, tumor depth should be taken into consideration when deciding on neck treatment. Hosal et al recommended that elective node dissection be performed only in those patients with a tumor depth greater than 9 mm to optimize cure rates and avoid surgical morbidity in those patients who are unlikely to develop a neck metastasis [20].

Likewise, Ambrosch et al reported that tumor depth was strongly correlated with node disease, but they found no such association with pathologic tumor size (pT) or histologic grade [16]. Their study showed that a depth of 2 mm was a valuable threshold for determining the risk of lymph node metastasis. Shaha et al reported that tumor thickness between 2 and 9 mm is associated with a 50% rate of node metastasis [21]. Fukano et al and Yuen et al recommended elective neck treatment for patients with a tumor depth of 5 and 3 mm, respectively[13,22]. Although there is no doubt about the importance of tumor depth, no consensus has yet been reached on a valid cutoff point [23]. The fact that different authors report different thresholds might be attributable to factors such as individual definitions of tumor depth and differences in oblique sectioning during the processing of surgical specimens.

Yuen et al also reported that of all the tumor parameters and predictive models that they

evaluated, tumor thickness was the only one that had a statistically significant predictive value for subclinical node metastasis, local recurrence, and survival [22].

We hope that future multicenter studies will include a large number of cases and standardized measurements of depth of invasion, which might lead to identification of an ideal cutoff value. But some important issues must be addressed. One is that the depth of invasion is usually measured postoperatively in a pathologic specimen. Most operations begin with neck dissection followed by tumor excision and, if possible, en bloc resection of the tumor and neck specimen together. So most of the time we do not know what the depth of invasion is preoperatively, so we obviously cannot use it as a basis for deciding whether or not to operate. We hope that in the future, with the use of radiologic techniques such as magnetic resonance imaging, preoperative tumor depth will be determined accurately and with a high degree of association with pathologic findings so that we can evaluate the neck before surgery, especially in N0 cases.

Another possible way of determining depth of invasion might be to study frozen sections of the primary tumor intraoperatively before deciding on neck treatment, but again, the problem here is that neck dissection is performed prior to tumor excision in most cases.

Another parameter that we used in our study was the histologic differentiation of tumor. We found that well-differentiated tumors were significantly associated with the lowest prevalence of neck metastasis and that poorly differentiated tumors were significantly associated with the highest prevalence. This finding was consistent with those of some other basic studies on oral cavity squamous cell carcinoma. For example, Chen et al studied 94 patients with tongue cancer and found that those with poor and moderately differentiated tumors had a higher rate of neck node involvement than did patients with well-differentiated tumors [18]. Likewise, Ann et al showed that tumor differentiation was correlated not only with neck node involvement but with regional recurrence, as well [24]. On the other hand, the study by Fukano et al found no significant association between the degree of tumor differentiation and pN0 and pN+ status [13].

Many authors who have studied differentiation have also evaluated other histopathologic factors, such as perineural invasion, lymphovascular permeation, and muscle invasion [13, 18]. These studies have also shown a significant association between node neck involvement and histopathologic factors.

In our study, we sub classified patients according to tumor size into two groups: T1/T2 and T3/T4. The prevalence of neck node metastasis in the two groups was 51.5 and 58.8%, respectively. Since this difference was not statistically significant, we conclude that as tumor size increases, the rate of node metastasis does not significantly increase. A similar result was reported by Chen et al [18]. On the other hand, it has been shown that T category tends to be more advanced in N+ groups [19]. These conflicting findings might be attributable to several histopathologic factors, such as depth of invasion, degree of differentiation, and type of growth pattern (i.e. exophytic or endophytic).

In conclusion, we found that two of the three variables we analyzed-degree of differentiation and depth of invasion-were significantly correlated with neck node metastasis. We find it relevant that tumor size was not correlated with metastasis, which is significant because the TNM system is so widely used to evaluate patients preoperatively. The drawback of such a great reliance on the TNM system is that other important variables- especially depth of invasion-might not be considered. Obviously, the reason for a failure to consider depth of invasion is that it is difficult to evaluate preoperatively. In the future, we hope that depth of invasion can be determined preoperatively by the use of imaging techniques or intraoperatively by the use of frozen-section analysis so that we can achieve more accurate staging.

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Date of Submission: 07/04/2015
Date of Acceptance: 18/06/2015

How to cite this article: Trehan S, Patel K, Shukla H, Tripathi U, Tadaiya M. The effect of depth of invasion and tumour size on risk of neck node metastasis in squamous cell carcinoma of oral cavity: retrospective analysis. J Res Med Den Sci 2015;3(3):1-6.

Source of Support: None
Conflict of Interest: None declared