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Head and Neck Cancer

Patterns of Neck Nodal Metastasis from Oral Cavity Carcinoma

Nitin Khunteta[1] Ayush Makkar[1] Jaspreet Singh Badwal[1] Prakhar Katta[1] Dinesh Choudhary[1] Mohinder Viswanath[1] Hemant Malhotra[2]

[1] Department of Surgical Oncology, Sri Ram Cancer Centre, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India
[2] Department of Medical Oncology, Sri Ram Cancer Centre, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India

Address for correspondence Nitin Khunteta, MBBS, MS, MCh, DNB, Department of Surgical Oncology, Sri Ram Cancer Centre, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur 302022, Rajasthan, India (e-mail: onconitin@yahoo.co.in).

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Abstract

Nitin Khunteta

Objectives The aim is to study the patterns of lymph node metastasis from various sites in oral cavity cancer and determine the risk factors for metastasis.

Materials and Methods It is a prospective observational study. The inclusion criteria were—245 patients of carcinoma buccal mucosa, anterior two-thirds of tongue, hard palate, oral surface of soft palate, floor of mouth, vestibule, and alveolus. The exclusion criteria were—patients who had received preoperative chemotherapy or radiotherapy and patients with recurrent disease.

Statistical Methods All data were analyzed using SPSS 18.0 and Graphpad prism 7 software for statistical analysis. Count data have been expressed as percentages (%). The χ^2 test was used for univariate analysis of the risk factors of cervical lymph node metastasis. The odds ratio value (with 95% confidence interval) was used to express the risk of cervical lymph node metastasis. p-Value of <0.05 was considered as the difference with statistical significance.

Results The most common site involved was buccal mucosa. Patterned lymph node metastasis was seen in 93.5% cases. Skip metastasis was seen in 4.31% cases. Level I b was the most common site of nodal involvement for all primary subsites of oral cavity cancer. The incidence of positive nodes on histopathological analysis was highest in cases of lower alveolus (63.15%), followed by tongue.

Conclusion In our study, patterns of lymph node metastasis for oral cavity cancer were comparable to other studies with large number of subjects. The incidence of skip metastasis or aberrant status was low. On multivariate analysis, depth of invasion of tumor, pathologic grade, pathologic T stage, and morphologic type of growth were found to be independent predictors of risk for metastasis.

Keywords

- patterns of lymph node metastasis
- oral cavity cancer
- risk factors for metastasis
- regional lymph node
- skip metastasis
- cervical lymph node

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Introduction

Oral cavity cancers are the most prevalent cancers in Indian population, particularly in the male population and are on rising trends. This is in large part because of ill habits of tobacco chewing, smoking, and alcohol intake.[1–3] These cancers particularly spread to lymph nodes in neck in an orderly manner.[1] Various investigations are done to know the status of neck nodes before commencing treatment for oral cavity cancer such as ultrasonography (USG) of neck, CT scan, MRI scan, PET scan, and USG-guided FNAC from the neck nodes. In various studies, it has been found that subsites of oral cavity behave differently, as far as the anatomical patterns of lymphatic spread and tumor biology are concerned.[4–11] Most of the literature available so far is from western world where oral cancer is less prevalent than our country. This study is an attempt to collect information on oral cavity cancers with respect to the tumor factors such as subsite, T stage, depth, histological differentiation, etc. and their relation to incidence and pattern of nodal metastases in neck.

Material and Methods

This study was conducted in the Department of Surgical Oncology and Department of Pathology at a tertiary care cancer hospital of northwest India. It is a prospective observational study.

The *inclusion criteria* were—245 patients of carcinoma buccal mucosa, anterior two-thirds of tongue, hard palate, oral surface of soft palate, floor of mouth, vestibule, and alveolus.

The *exclusion criteria* were—patients who had received preoperative chemotherapy or radiotherapy and patients with recurrent disease.

Patients of both sexes, all ages, presenting with carcinoma of oral cavity who were subsequently planned for treatment were included in the study. Data were evaluated with respect to subsite, T stage of cancer, tumor grading, lymphovascular and perineural invasion by preoperative clinical findings, radiological findings, and histopathological evaluations of the resected specimen and correlated with nodal spread in neck with respect to number of nodes, level of spread, and size of nodes.

All the patients underwent required hematological and radiological investigations and the resected specimen was processed for histopathological analysis. All the data was then entered in a performa designed for the study.

Method of Surgery

All the patients underwent oncological resection which includes wide local excision and neck dissection. The extent of neck dissection was dictated by spread of disease as appreciable by preoperative clinical findings and radiological findings and was based on existing protocols for management of oral cavity cancers.

All the levels of nodal spread as defined anatomically were removed separately and sent for histopathological examination as separate specimens.

Specimen of resected tumor and nodal dissection was histopathologically evaluated by Department of Pathology. Correlation was made between the tumor stage (T stage), tumor characteristics, and pattern of nodal spread in neck with respect to number, size, and level of nodal involvement.

Statistical Methods

All data were analyzed using SPSS 18.0 and Graphpad prism 7 software for statistical analysis. Count data have been expressed as percentages (%). The χ^2 test was used for univariate analysis of the risk factors of cervical lymph node metastasis. The odds ratio value (with 95% confidence interval) was used to express the risk of cervical lymph node metastasis. p-Value of <0.05 was considered as the difference with statistical significance.

Results

In the present study of 245 cases, the most common age group of the patients suffering from oral cancer (37.5%) was 41 to 50 years, with median age for males and females being 45 years. Age group <40 years comprised approximately 30% of the patients, while patients older than 50 years comprised approximately 33% of the population. Male to female ratio was 3.8:1. Out of 245 patients, 226 (92.2%) were using tobacco in some form. With regard to the presence of premalignant conditions, 33 patients suffered from preoperative submucous fibrosis, 16 from leukoplakia, and there was one case of erythroplakia. Of particular importance is the distribution of subsites within oral cavity, as each subsite is known to have different rates of metastasis and different patterns of spread to regional lymph nodes. As this is the primary subject of this present paper, the topic will be discussed in detail in the following comments. Among the 245 patients, 116 (47.3%) had history of smokeless tobacco, while 54 (22.04%) had history of beedi smoking. In patients with history of beedi smoking, the most common primary site of primary tumor was buccal mucosa, the next most common being floor of mouth, tongue, palate and lower alveolus, in descending order of frequency. Similarly, in patients presenting with history of smokeless tobacco, the most common sites of primary disease were buccal mucosa, lower alveolus, tongue, palate, and floor of mouth in descending order of frequency.

Buccal mucosa was the most common subsite of involvement in oral cavity followed by tongue, with 113 (46.12%) patients having their primary lesion in buccal mucosa and 58 (23.67%) in tongue, respectively. The next most common sites were lower alveolus, floor of mouth, retromolar trigone, and palate in descending order of frequency. Patients having pathological positive nodes were highest among patients with primary subsite at lower alveolus (63.15%), followed by tongue (50%). Though buccal mucosa was the most common primary site in oral cavity cancers, pathologically positive nodes were found only in 33% of the patients. This difference in nodal metastasis as per subsite was highly significant (Chi-square = 19.410, degrees of freedom/df = 5, $p = 0.0002$).

Patients were staged according to the 8th edition of AJCC staging system. The stage distribution of disease was

contrary to what is found in western countries. Majority of cases presented in Stage IVa ($n = 90$; 36.7%); rest in Stage II ($n = 67$; 24.8%), Stage I ($n = 56$; 22.8%) and Stage III ($n = 38$; 15.5%) in descending order of frequency.

Among 94 patients with pathologically positive nodes, 22 (23.40%) had no node on clinical examination (clinically occult metastases). All the patients with clinically occult metastases, had nodal involvement above or at level III. Out of 139 patients with clinically positive nodes, 5% of the patients had nodal involvement below level III, i.e., either level IV or VB.

Patterned nodal metastasis was seen in 93.5% (130/139 patients who underwent modified radical neck dissection) of the patients, with initial involvement of level IB/IIA, followed by level III and subsequent involvement of level IV and V. Patterned metastasis was seen in 96% of the patients when patients who underwent supraomohyoid neck dissection, were considered. Only nine (6.47%) patients had aberrant/skip metastasis with three patients having isolated level III and six patients having level IV and level V involvement without level III involvement. Level IB involvement was seen as the most common site of nodal metastasis in cases of oral cavity squamous cell carcinoma. It was involved in 73 (52.51%) cases followed by level IIA which was involved in 31 (22.30%) cases. Level IA was involved in five patients (3.59%) only. Level IV involvement was seen in four (2.87%) patients with two having patterned and two having skip metastasis. Level V was involved in five (3.59%) patients, one having isolated VA involvement, rest having skip metastasis to level VB. One (0.71%) patient had both level IV and VB involvement simultaneously. Subsite of primary carcinoma in oral cavity affected the level of nodal involvement significantly (Chi-square = 22.69, df = 12, $p = 0.03$, significant).

Pattern of Cervical Node Metastases "Subsite Wise"

Amongst the 245 patients, 2.04% had involvement of lymph nodes at level Ia, 29.79% showed involvement of level Ib, 12.65% at level IIa, 1.22% at level IIb, 5.30% at level III, 1.63% at level IV, and 2.04% at level V.

A. Buccal Mucosa

Out of 43 cases level IB was the most common site of involvement, being involved in 33 (76.74%) patients with cancer of buccal mucosa. All the patients had a systematic pattern of lymph node metastasis. None of the patients with buccal mucosa cancer had level IV or V involvement.

B. Tongue

Of 39 cases, none of the patients had involvement of level IIB. One patient had isolated level III positive lymph node. Involvement of level IV was seen in three patients with two patients having patterned metastasis with involvement at level IIA and III simultaneously. One patient had aberrant metastasis with involvement at level IB and skip metastasis to level IV. Aberrant metastasis to level V was seen in three patients. One showing isolated metastasis to level VA and one showing simultaneous metastasis to level IB and VB. The third case also had level IV involvement along with level IB and level VB. One patient had poorly differentiated tumor with involvement at level IV.

C. Lower Alveolus

Among 31 cases, Level IB was involved in 16 patients (51.61%) and eight patients (25.80%) had level IIA involvement. Skip metastasis to level IV was seen in one patient (3.22%) who also had pathological positive lymph node at level IB. Skip metastasis to level V was seen in two (6.45%) patients with one patient having positive lymph node at level IA and other at level IB simultaneously.

D. Floor of Mouth

Among 10 cases, level IB involvement was seen in six patients (60%) with carcinoma at floor of mouth and level IIA was involved in one patient (10%). One (10%) of the patients with carcinoma floor of mouth had isolated spread to level III.

E. Retromolar Trigone

Of 10 cases, level IB metastasis was seen in four patients (40%) with three patients (30%) having metastasis in level IIA. One patient (10%) showed isolated involvement of level III.

Pathological "T" Stage versus Pathological "N" Stage

Most of the patients had pathological T2 stage. Patients with pathological T4 stage had maximum percentage of patients with pathological positive cervical node metastases as well as maximum percentage of patients with multiple positive cervical node metastases. When pathological "T" stage was correlated to pathological "N," there was a trend toward increase in "N" stage with increasing "T" stage and it was statistically significant (Chi-square = 10.424 with four degrees of freedom; $p = 0.03$).

Pathological "T" Stage versus Cervical Node Metastases

A total of 33.3% of the patients with early stage (pathological T1/T2) had pathological positive lymph node metastases. 50.7% of the patients with late stage (pathological T3/T4) had pathological positive lymph node metastases. This difference was statistically significant (Chi-square 5.721, df = 1, $p = 0.01$).

Tumor Characteristics

1. *Depth of invasion*: Depth of invasion affected rate of cervical node metastasis significantly (Chi-square 7.895; $p = 0.02$). Incidence of metastasis increased with increasing depth of invasion.
2. *Pathological grade*: A total of 71.4% of patients with poorly differentiated/undifferentiated pathological positive nodes were identified. For grade I and II tumors, 37.3% of patients exhibited pathological positive lymph nodes. The difference was statistically significant. Further, it was observed that only one patient out of seven having grade I/II tumors had nodal involvement below level III. The difference was not statistically significant (Chi-square = 6.834; $p = 0.04$).
3. *Pathological T stage*: 33.3% of patients with early stage (pT1/pT2) disease had pathological positive lymph node

metastasis. Of patients staged as pT3/pT4, 50.7% had positive lymph nodes. This difference was statistically significant (Chi-square = 5.721; df = 1; p = 0.01).

4. *Morphological type of growth (ulceroproliferative versus ulceroinfiltrative)*: 29.4% of patients with ulceroproliferative growth and 36.6% of patients with ulceroinfiltrative lesions had pathological positive lymph nodes. The difference was statistically significant (Chi-square = 18.515; df = 2; p <0.001).

Multivariate Cox proportional hazards analysis showed that depth of invasion, pathologic grading, pathological T stage , and morphological type of growth are independent predictors for regional cervical lymph node metastasis.

Discussion

The present study involved 245 patients with primary squamous cell carcinoma of oral cavity. Patients who underwent neoadjuvant chemotherapy or had recurrent disease, were excluded from the study. All patients underwent wide excision of primary lesion with neck dissection and appropriate reconstruction. The resections and neck dissections were done as per existing protocols in available literature.[4–11] A total of 139 patients underwent MRND while 106 underwent SOHND, according to level and number of lymph nodes involved clinically and intraoperatively. Of 245 patients, 99 had free flap reconstructions. Rest of the patients underwent reconstruction by local/pedicled flaps/split skin grafting or primary closure.

In our study cohort of 245 patients, 96% of patients had a systematic spread with initial metastasis to level I or systematic spread with initial metastasis to level I or level IIa, followed by metastasis to level III and below. The most common site of metastasis was level Ib (73 patients, 29.79%), followed by level IIa (31 patients, 12.65%). Level IIb metastasis was seen in three (1.22%) patients only and level III metastasis was seen in 13 patients (5.30%). Patterned nodal metastasis was seen in 93.5% of (130 out of 139) patients who underwent Modified Radical Neck Dissection. Nine patients (6.47%) exhibited aberrant or skip metastasis. Metastasis to level IV was seen in four patients, all having clinically N+ and pathological N2b disease, with two having patterned and two exhibiting skip metastasis. Level V metastasis was seen in five patients, one showing isolated level Va involvement, rest having skip metastasis to level Vb (four patients exhibiting infrahyoid involvement). One patient had metastasis to both level IV and Vb simultaneously. So approximately 5% of the patients had cervical nodal involvement below level III. It reaches 7.3% when clinically *N* positive necks are taken into consideration. None of the patients with clinically *N*0 neck had nodal involvement below level III.

In a study by Shah et al,[12] among a total number of 501 patients undergoing 516 radical neck dissections, 357 were male (71%) and 144 female patients (29%), such that the sex ratio was 2.4: 1. The age of patients ranged from 17 to 95 years, with mean and median age of 60 years. Oral tongue was the common site of involvement (36%), followed by floor of the mouth (33%). The incidence of clinically negative lymph nodes confirmed as positive on histopathologic examination was 34%. Metastasis to level IV was seen in 3% of the patients with clinically N0 neck. However, in clinically node positive patients, cervical nodal involvement below level III was present in 15 to 16% of the patients. Metastasis to level V was confirmed only in floor of mouth and gum primaries (6% in each). In our study, amongst a cohort of 245 patients, male to female ratio was 3.8:1. This can be related to the fact that females in India are comparatively less prone to tobacco usage. The age ranged from 41 to 50 years, the median age being 45 years. Thus, the median age is much younger compared with western population. An appropriate corollary can be drawn to explain this fact, that exposure to tobacco begins at a much younger age in Indian population. The most common site of involvement was buccal mucosa (46.12%) followed by tongue (23.67%). This is due to prevalence of addiction to smokeless tobacco which is kept in the buccogingival sulcus for hours together, thus justifying the name "Indian Oral Cancer" for cancer of gingivobuccal sulcus. The incidence of clinically negative nodes confirmed as pathologically positive on histopathologic examination was 23.40%. This was lesser compared with the results from western studies. This can be related to difference in histopathological techniques in American centers, where serial sectioning of nodes is done more commonly. Level IV was involved in 2.87% of patients which was comparable to study by Shah et al.[12] Level V was involved in 3.59% of our patients which was comparatively much lesser. It was possibly due to higher prevalence of tongue cancer in the compared study, which is known to metastasize more aggressively.

In a study by Woolgar,[13] all primary sites except tongue showed patterned metastasis, with jugulo-omohyoid nodes and/or other deep cervical nodes at level IV positive in 20% of the patients. The primary tumor was located on tongue or base of tongue in all except two of the 24 patients with level IV disease. These two exceptions had tumors in anterior floor of mouth. Level IV was positive due to a regular progression (overflow) of metastatic disease in 42% of 26 sides of neck with level IV disease. In six of these, positive nodes were also found at level V. An erratic pattern of metastatic spread accounted for positive level IV nodes in remaining 15 neck dissections (peppering, i.e., histological involvement of nodes at multiple levels in the absence of macroscopic metastatic focus, seven necks; skip metastasis in eight necks). The increased prevalence of peppering in European and American studies could again be possibly due to employment of serial sectioning technique. In another study by Woolgar,[14] levels I and II were the most common levels to be involved in metastasis. Level IV was involved in 9% of patients and level III in 16% patients. Such high level of metastasis to level IV can be ascribed to higher incidence of oral tongue cancer in these studies. Metastasis in typical pattern, as mentioned in previous literature, was seen in 67% of the patients, with skip metastasis in 10% of the patients. A single micrometastasis was seen in 14% patients, with contralateral metastasis in one patient and peppering in 2% of the patients.

In a study by Shukla et al,[15] 93% of patients had a patterned nodal involvement above level III, which was

comparable to our study. This shows similarity of trends in incidence amongst patients presenting at centers of North India. In another study by Mishra and Sharma,[16] metastasis to level IV was seen in 9% of patients with clinically N+ disease and was not detected in any case with clinically N0 disease. Hence, though the rate of nodal involvement below level III is very low in clinically N0 patients, it rises in patients with clinical N+ disease.

It is well known that the rate of metastasis for oral cancer is directly related to tumor size and infiltration depth. In a meta-analysis by Huang et al,[17] a cut-off value of 4 mm for tumor infiltration depth was defined as a predictor for cervical metastasis in metastasized cancers of oral cavity. In our study, rate of metastasis increased with increasing depth of invasion. Similarly, Li et al[18] presented their results of 161 patients suffering from oral squamous cell carcinoma, in relation to T stage, depth of invasion, and pathologic differentiation. Rate of metastasis was found to increase with increasing pathologic grade of tumor, being established as an independent predictor on multivariate analysis. In our study, rate of metastasis increased with increasing pathologic grade of tumor. Poorly differentiated tumors had a higher rate of nodal spread as compared with moderately or well differentiated tumors. Haksever et al[19] have reported similar findings.

In our study, the rate of nodal metastasis increased with increase in T stage. 33.3% of patients with early stage (pT1/pT2) disease had pathological positive lymph node metastasis. Of patients staged as pT3/pT4, 50.7% had positive lymph nodes. This difference was statistically significant (Chi-square $= 5.721$; d$f = 1$; $p = 0.01$). These results are similar to those obtained by Sharma et al,[20] who showed that incidence of metastasis increased with increasing T stage. Also, in the present study, the rate of metastasis was correlated with morphological type of growth. 29.4% of patients with ulceroproliferative growth and 36.6% of patients with ulceroinfiltrative lesions had pathological positive lymph nodes. The difference was statistically significant (Chi-square $= 18.515$; d$f = 2$; $p < 0.001$). Khwaja et al,[21] Dissanayaka et al,[22] and Siriwardena et al[23] have confirmed similar findings.

Conclusion

In our study average age of patients suffering from squamous cell carcinoma of oral cavity was a decade earlier than the age reported in literature, probably due to early age exposure to tobacco. The most common site involved was buccal mucosa. Patterned lymph node metastasis was seen in 93.5% cases. Skip metastasis was seen in 4.31% cases. Level I b was the most common site of nodal involvement for all primary subsites of oral cavity cancer. The incidence of positive nodes on histopathological analysis was highest in cases of lower alveolus (63.15%), followed by tongue.

Authors' Contributions

N.K. and A.M. participated in the conception and design of the manuscript, drafting of manuscript, and literature search. J.S.B., P.K., D.C., M.V., and H.M. participated in the drafting of manuscript and literature search.

Conflict of Interest

None declared.

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