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The Prevalence of Lymph Node Metastasis in Clinically Negative Necks in Oral Squamous Cell Carcinoma Patients

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ABSTRACT

Objective: To assess the prevalence of cervical lymph node metastasis in Oral squamous cell carcinoma (OSCC) patients with clinically negative necks (Cn0).

Study Design: Cross-sectional study.

Place and Duration of study: Armed Forces Institute of Dentistry Rawalpindi, Pakistan from Jan to Dec 2024.

Methodology: A total of fifty biopsy-proven oral squamous cell carcinoma patients with clinically negative necks who had undergone tumor resection along with elective neck dissections were included in the study. Their post-operative histopathology reports were analyzed to assess cervical metastasis. Data was collected, entered, and analyzed through SPSS version 26.

Results: Out of 50 patients 16(32.0%) patients had histopathologically confirmed cervical metastasis despite CNo status. The frequency of cervical metastasis was reported in 32.0% of total patients selected for study. The highest frequency of metastasis was observed in buccal mucosa tumors 8(50.0%) out of 16 patients, Alveolus 6(37.5%) out 16 patients followed by tongue 2(12.5%) out 16 patients who had metastasis. No cervical metastasis was recorded for lip tumors.

Conclusion: Overall higher prevalence was recorded in Oral Squamous cell carcinoma with clinically negative necks, which necessitates Elective Neck Dissections in high risk sites of oral cavity like buccal mucosa, alveolus and tongue even with clinically negative necks.

Keywords: Cervical Metastasis, Elective Neck Dissections, Neck Dissections, Occult Metastasis, Oral Cancer.

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is still one of the most prevalent malignancies of the head and neck area, posing a serious global health problem because of its vigorous biological behavior and unfavorable prognosis in advanced cases.[1,2] Cervical lymph node metastasis is an important prognostic factor in OSCC, as nodal metastasis decreases survival by about 50%.[3] Although the clinical examination and imaging tests like ultrasonography, CT, and MRI are now used as a matter of course for staging, there is a subgroup of cN0 patients who have occult metastases that are not detected preoperatively.[5] This poses a real problem for surgical decision-making in the context of early-stage OSCC, especially in the context of elective neck dissection.[6]

Oral squamous cell carcinoma (OSCC) is still a serious health problem, especially in South and South-East Asia, where age-standardized incidence rates (ASR) were 13.2 to 30.2 per 100,000 among males in Pakistan, India, and Taiwan.[7] Fatima *et al*., examined 168 OSCC cases reported that 63% of tumors were moderately or poorly differentiated, which was associated with much lower disease-free survival ($p< 0.05$).[8] Al-Jamaei *et al*., reported 18,963 OSCC cases, with increasing incidence specifically among the 20–34 year olds, substantiating efforts to target epidemiological patterns outside the usual risk groups.[9] Hashmi *et al*., identified areca nut use in 59.6% of OSCC patients in Pakistan and noted significant correlation with nodal metastasis and advanced tumor characteristics.[10] These findings establish a sizeable baseline risk of occult nodal disease even in clinically negative necks, particularly when high-risk behavior and tumor subsite are taken into account.

In spite of the increasing number of publications, a lack of regional data on the incidence and distribution of lymph node metastasis in clinically negative necks in OSCC patients, especially in populations with high-risk habits of areca nut chewing, exists. Although reports from outside

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countries give pooled estimates, these may not be representative of the pathological and epidemiological patterns in the local situation. This disparity restricts the formulation of disease-specific surgical protocols and evidence-based neck treatment protocols. Thus, the current study seeks to establish the occurrence and pattern of lymph node metastases among cN0 OSCC patients in our population, as well as clinicopathological correlations, to guide surgical practice and enhance patient prognostication.

METHODOLOGY

This cross-sectional study was carried out in the Department of Oral and Maxillofacial Surgery, Armed Forces Institute of Dentistry (AFID) Rawalpindi, Pakistan from January 2024 to December 2024. All the patients who reported during study period (January 2024 to December 2024) were enrolled through purposive sampling.

Inclusion Criteria: Both male and female patients of all ages, clinically and radiologically free of cervical metastasis, suitable for surgery after pre-anesthesia evaluation and acceptance for surgery, and accessible of pre- and post-operative computed tomographic (CT) images or radiographs.

Exclusion Criteria: Recurrent OSCC patients, who previously had undergone pre-operative chemotherapy or radiotherapy, in whom differentiation between clinically negative and positive necks was not possible pre-operatively and were not willing to have surgery were excluded.

Following institutional Ethical Review Committee approval (Ref No: 918/Trg, dated 13 May 2020), informed written consent was obtained from all participants. Data were collected prospectively with a pre-formatted questionnaire. The questionnaire captured demographic variables: age, sex, occupation, lifestyle variables: smoking history, tobacco consumption and tumor factors: size (T-stage) and location (buccal mucosa, tongue, alveolus, hard palate, lip).

Patients eligible for study were subjected to surgical tumor resection along with elective neck dissection (level I–III or IV depending on the tumor site). Cervical lymph nodes that were resected were examined histopathologically to ascertain the presence or absence of metastasis. Histopathology results were the gold standard for diagnosis of cervical metastasis. The cN0 status was clinically and radiologically (CT scan or MRI) established. All biopsy-proven OSCC cases were discussed in a multidisciplinary head and neck oncology conference with maxillofacial surgeons, ENT surgeons, plastic and reconstructive surgeons, radiation oncologists, and histopathologists.

All data were imported into the Statistical Package for the Social Sciences (SPSS) version 26. Frequency and percentage were used for descriptive statistics of categorical variables (such as gender, tumor site, and metastasis present). Chi-square test were used to analyze associations between categorical variables; a p-value ≤0.05 was considered statistically significant.

RESULTS

A total of 50 biopsy-proven OSCC and clinically negative neck (cN0) patients were studied among the patients with a mean age of 54.83±9.79 years. 28(56%) patients were male and 22(44%) patients were female indicating a higher prevalence of OSSC among males compared to females in this study. The most common primary site was the buccal mucosa (44%), followed by the tongue (20%) and alveolus (18%). These less common primary sites were maxilla and palate (12%), floor of mouth (4%), and lip (2%). Almost half of them were presented as T2 tumors (46%), then T3 (30%), T4 (16%), and T1 (8%). Histopathological examination showed that 48% of the tumors were well differentiated, 28% moderately differentiated, and 24% poorly differentiated. Metastasis in the cervical lymph node was histopathologically confirmed in 16 patients (32%), and 34 patients (68%) were free from nodal metastasis. Supraomohyoid neck dissection (SOND) was most frequently carried out (60%), while 40% of them had extended SOND. In the patients with positive nodes, most had metastasis at level I (28%), whereas only 4% had level 2 (Table-I).

Metastasis to cervical lymph nodes was most seen in buccal mucosa tumors (50%) and alveolus (37.5%). Tongue lesions exhibited metastasis in 12.5% of the cases, while metastasis was not seen in maxilla and palate, lip, or floor of the mouth tumors. A higher percentage of metastases was found in alveolar tumors, nevertheless the association between cervical lymph node metastasis and tumor site was not statistically significant (p=0.079) (Table-II).

Overall, poorly differentiated tumors had the highest (50%) and well-differentiated tumors the lowest (25%) incidence of cervical lymph node metastasis. Up to 25% of the moderately differentiated

tumors exhibited metastasis. The association between histopathological grade and cervical metastasis was statistically significant (p=0.010), which showed that poorer differentiation was associated with greater probability of nodal spread. The largest percentage of cervical metastasis was in T2 tumors (75%), followed by T3 (18.75%) and T4 (6.25%). There were no instances of metastasis among T1 tumors. The association between tumor stage and cervical metastasis was statistically significant (p=0.036), indicating that T2 tumors in this group had a greater chance of having occult nodal disease than other stages (Table-III).

Table-I: Clinicopathological Characteristics of Oral Squamous Cell Carcinoma Patients with Clinically Negative Necks (n=50)

Variable(s)	Category	n (%)
Site of Tumor	Buccal mucosa	22(44%)
	Tongue	10(20%)
	Alveolus	9(18%)
	Maxilla and palate	6(12%)
	Lip	1(2%)
	floor of mouth	2(4%)
Tumor stage	T1	4(8%)
	T2	23(46%)
	T3	15(30%)
	T4	8(16%)
Histopathological grades	Well differentiated	24(48%)
	Moderately differentiated	14(28%)
	Poorly differentiated	12(24%)
Cervical Metastasis	Absent	34(68%)
	Present	16(32%)
Level of Neck dissection	SOND	30(60%)
	Extended SOND	20(40%)
Lymph nodes involved	None	34(68%)
	level 1	14(28%)
	level 2	2(4%)

Table-II: Association between Primary Tumor Site and Presence of Cervical Lymph Node Metastasis (n=50)

Tumor Site	Cervical Metastasis		p-value
	Absent n=34	Present n=16	
Buccal mucosa n(%)	14(41.18%)	8(50.00%)	0.079
Tongue n(%)	8(23.53%)	2(12.50%)	
Alveolus n(%)	3(8.82%)	6(37.50%)	
Maxilla and palate n(%)	6(17.65%)	0(0.00%)	
Lip n(%)	1(2.94%)	0 (0.00%)	
Floor of mouth n(%)	2(5.88%)	0 (0.00%)	

DISCUSSION

In this study's cN0 OSCC cohort (n=50), occult cervical metastasis occurred in 32%, with greatest frequency of positive nodes in level I, and less frequently, level II. Cervical metastasis was significantly associated with worse histologic grade (p=0.010) and greater T stage (p=0.036). Site-wise variation was close to significance (p=0.079) with the alveolus having a higher rate of nodal positivity. These findings justify elective neck management in well-selected early-stage OSCC.

Table-III: Association between Histopathological Grade and Tumor Stage with Presence of Cervical Lymph Node Metastasis (n=50)

Variable(s)	Cervical Metastasis n(%)		p-value
	Absent n=34	Present n=16	
Histopathological Grades			0.010
Well differentiated	20(58.82%)	4(25.00%)	
Moderately differentiated	10(29.41%)	4(25.00%)	
Moderately differentiated	4(11.76%)	8(50.00%)	
Tumor Stage			
T1	4(11.76%)	0(0%)	0.036
T2	11(32.35%)	12(75.00%)	
T3	12(35.29%)	3(18.75%)	
T4	7(20.59%)	1(6.25%)	

Our results concur with global and regional statistics. The ASCO clinical practice guideline, on the basis of pooled analysis, expresses a rate of 20–30% occult metastasis in early-stage OSCC that has led to the recommendation of elective neck dissection.[11] Likewise, Bittar *et al*., quotes occult metastasis rates of 23% to 37%, and most commonly, in mid-oral subsites such as tongue and floor of mouth.[12] The rate of 32% in the present study is within this range and resonates with the 30% prevalence reported by Cell OS (2018) as a realistic threshold for surgical treatment.[13] A statistically significant difference in the incidence of occult cervical metastasis between female and male OSCC patients was not observed among patients in the present study. This is consistent with the results of Lin *et al*., who found there were significant differences between genders in age at diagnosis, subsites of the tumor, and exposure to lifestyle, but there were no significant differences in survival or pathological characteristics such as rates of nodal metastasis once OSCC was present.[14] Similarly, Thoenissen *et al*., analyzing lymph node involvement in head and neck squamous cell carcinomas, including oral cavity

cancers, indicated no noteworthy sex disparity in nodal metastasis in those with positive nodes; number of positive nodes per patient and their levels were similar in men and women.[15]

Regionally, Haseeb *et al*. reported a 27% rate of occult metastasis in a Pakistani population, with the most affected subsites being tongue (31.7%) and buccal mucosa (29.4%),[16] replicating our subsite-specific data. They had attributed these rates to endemic areca nut and tobacco chewing in the region. Yamagata *et al*., found that poorly differentiated tumors were associated with a 50% occult metastasis rate versus 20% for well-differentiated tumors.[17] This corresponds to our finding of significantly increased nodal spread with decreasing differentiation. In addition, the dominance of occult metastasis in T2 tumors, as noted in our study (75%), is also in keeping with Yamagata *et al*., 's findings that those tumors of intermediate stage with moderate depth invasion frequently develop subclinical nodal spread below the detection power of imaging.

Consistent with our results, Mehta *et al*., performed a prospective observational study in 63 oral cavity cancer patients and observed an overall pathological nodal positivity rate of 52%, of which 48% were positive nodes at level I and 20% at level II,[18] closely paralleling our trend of overwhelmingly level I involvement and scarce higher-level spread. Almangush *et al*., also highlighted the key role of DOI, grade, and invasive growth patterns in OSCC staging and prognosis, supporting our finding that increased T stages (p=0.036) and poor differentiation increase metastatic potential.[19] Emmanuel *et al*., likewise reported that site-specific Depth of Invasion is a significant prognosticator of nodal spread, particularly in the alveolus and tongue—and mirroring our pattern of increased metastasis in alveolar tumors (37.5%).[20] Finally, Mermod *et al*.,'s multivariable prediction model illustrated that the integration of Depth of Invasion with histologic grading considerably increases predictive accuracy for occult lymph node metastasis, attesting to the need for a multi-factorial risk assessment approach rather than sole dependence on individual clinical parameters.[21] END should be performed for tumors with a Depth of Invasion > 4mm, especially in high-risk sites such as the buccal mucosa and tongue.[22] Supraomohyoid or extended neck dissection should be selected based on tumor size and level of nodal involvement. More advanced diagnostic tools should be explored to improve early detection and reduce overtreatment.[23]

LIMITATIONS OF STUDY

This study has some limitations that need to be considered. Firstly, the relatively small number of 50 patients from one tertiary care facility may restrict the generalizability of results to larger populations. Secondly, the purposive sampling method might lead to selection bias, as the patients were not sampled randomly. Third, even though cN0 status was established both clinically and radiologically, the sensitivity of imaging modalities to diagnose microscopic metastases is low, and inter-observer agreement in radiological interpretation was not tested. Fourth, the research did not control for the possible role of tumor biology, molecular markers, or depth of invasion, all of which have been reported to affect the risk of occult metastasis. Fifth, regional recurrence follow-up information was not available, which might have given a better reflection of long-term oncologic results. Lastly, as a cross-sectional study, no causality between tumor location, stage, and lymph node status could be determined.

CONCLUSION

This study emphasizes on the prevalence of occult cervical lymph node metastasis in OSCC patients with (CN0). The findings of this study highlight the importance of site and size of tumor in the decision of neck management. Given that 32% of CN0 patients had hidden metastases, relying solely on clinical and radiological assessments may lead to under-treatment. A more customized approach to neck dissection is required, balancing the need for tumor control with minimum surgical morbidity. By adopting these guidelines, OSCC treatment results can be significantly improved, ensuring better patient survival rates, decreasing morbidity and improving quality of life.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

TM & SK: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

AB & SIK: Data acquisition, data analysis, approval of the final version to be published.

MJ & AW: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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