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Original Article

Association between nodal metastasis and histopathological factors in postoperative gingivo–buccal complex squamous cell carcinoma: A Retrospective Study

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Abstract

Objective: To evaluate association between histopathological factors and cervical lymph node metastasis in postoperative gingiva–buccal complex squamous cell carcinoma.

Methods: We retrospectively analyzed 98 postoperative gingiva buccal complex squamous cell carcinoma patients' clinical and histopathological findings. The variables assessed were age, sex, tumour site, tumour size, degree of differentiation (grade), depth of invasion (DOI), lymphovascular invasion (LVI), perineural invasion (PNI) and extracapsular extension (ECE) and their relation with nodal metastasis.

Result: Out of 98 patients, 76 patients were pathologically node positive (pN+), including 39 of the 53 patients who were classified as cN0 (clinically node negative). The prevalence of occult neck metastasis was 73.5 %. Various parameters like tumour size, LVI, PNI, ECE and Grade showed statistically significant association with lymph node metastasis (p value: 0.029, 0.007, 0.003, 0.001 and 0.001 respectively) on bivariate analysis. Depth of invasion increases incidence of nodal metastasis but was not statistically significant (p value: 0.166). On multivariate logistic regression analysis male gender and presence of PNI were found as independent predicting factors for nodal metastasis (Odds Ratio 7.0826 to 8.65 respectively) while poorly differentiated carcinoma grade appeared non–inferior factor paradoxically (Odds Ratio 0.1033, overall 82.65 % cases were correctly classified by this model and area under ROC curve (AUC) was 0.794 of the model.

Conclusion: Male gender, poorly differentiated carcinoma and presence of PNI were found as independent predicting factors for nodal metastasis. Male gender and PNI were found risk factors while poorly differentiated carcinoma grade appeared non–inferior factor (protective) paradoxical.

Keywords: Histo–pathological factors, Gingivo buccal complex, Squamous cell carcinoma, Oral cavity

Introduction

Head and neck cancers comprise of a diverse group of malignancies encompassing the region from the level of the base of skull to the clavicles. It forms 30 % load of India's cancer burden with 2, 00,000 new head and neck cancer cases per year.

Among all variants, squamous cell carcinoma of head and neck is the most common type and is the sixth most common malignancy globally, with more than half a million new cases diagnosed each year. (1)

In head and neck cancers, nearly two thirds of these are located in the gingivo–buccal complex. The gingivobuccal complex is comprised of buccal mucosa, gingivobuccal sulcus, gingival/alveolus, retromolar trigone. It is most common site for oral cancer in the Indian subcontinent due to the habit of chewing tobacco.

Squamous cell carcinoma of gingivo–buccal complex is an aggressive malignancy, with greater propensity for

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invasion into the surrounding tissues and metastasis to the cervical lymph node. [2]

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. [3,4] There might also be an association between these factors and cervical lymph node involvement.

As involvement of cervical lymph node greatly impacts the treatment protocol and the prognosis of squamous cell carcinoma of gingiva–buccal complex.

Therefore, the purpose of the study is to evaluate the association between histopathological factors and cervical lymph node metastasis.

Material and Methods

98 patients with postoperative gingivo–buccal complex squamous cell carcinoma were enrolled in our retrospective study from January 2017 to June 2017.

Inclusion Criteria:

Postoperative cases of Carcinoma Buccal Mucosa, Gingiva, Alveolus and Retromolar trigone (pT1 – pT4a, pN0 – pN3), histopathology–proven squamous cell carcinoma, Age > 18 years to < 70 years, WHO Performance Status 0 – 1

Exclusion Criteria:

Primary site of tongue, floor of mouth, maxilla, History of previous radiotherapy or chemotherapy, Histopathology other than Squamous cell carcinoma, Presence of metastatic disease, Recurrence / Second Primary.

All eligible patients fulfilling inclusion and exclusion criteria were approached and their detailed socio–demographic and clinical history were recorded. Preoperative assessment of neck lymph node metastasis was based on physical examination and pre – operative imaging (CT scans or MRI).

All patients involved in the study underwent surgery which was followed by radiotherapy and /or chemotherapy based on histopathological findings.

The excised specimens were sent routinely to the histopathology department for assessment. The variables assessed were tumour site, tumour size, degree of differentiation, depth of invasion (DOI), lymphovascular invasion (LVI), perineural invasion (PNI) and extracapsular extension (ECE). The presence or absence of occult cervical lymph node metastasis was also extracted from the final histopathology report.

The data were analysed for associations between histopathological factors and neck node metastasis

Statistical Analysis:

Data was entered in MS Excel sheet to prepare master sheet and transported to statistical software for calculations. Continuous variable was summarized as mean and standard deviation whereas nominal variable as proportion.

Bivariate analysis was done using chi–square and Fischer exact test to identify associated factor of nodal metastasis.

Significant associated factor found in bivariate analysis along with other possible independent factor were put into regression model and stepwise logistic regression analysis was done keeping probability of inclusion of < 0.05 and of exclusion of 0.1.

P–value < 0.05 was considered significant Medcal 16.4 version software was used.

Results

Patient and treatment characteristics:

A total 98 patients were retrospectively analysed. In current study mean age was 49.1 years (minimum age = 26 years and maximum age = 72 years). Study showed male predominance, 88.78% (n = 87) were male and 11.2 % (n = 11) were female. Most commonly involved site was buccal mucosa (n = 56), followed by alveolus (n = 19), retromolar trigone (n = 17) and gingivobuccal sulcus (n = 6).

Out of 98 patients, tumour size of 55 patients were reported as pT1/ pT2 and 43 patients were reported as pT3/ pT4. Tumours were well differentiated (W/D) in 30 cases, moderately differentiated (M/D) in 57 cases and poorly differentiated (P/D) in 11 cases. Lymphovascular invasion (LVI) and perineural invasion (PNI) was present in 41.84 % (n = 41) and 45.92 % (n = 45). Extracapsular extension was seen in 26.53 % (n = 26)

In present study, 98 patients were categorized based on depth of invasion as < 4 mm (n = 1), 4–10 mm (n = 57) and >10 mm (n = 40). See Table 1.

On clinical examination, 45 patients were node positive (cN+) and 53 were node negative (cN0). Whereas in postoperative histopathology report, 76 patients were pathologically node positive (pN+), including 39 of the 53 patients who were classified as cN0. The prevalence of occult neck metastasis was 73.5 %. See Table 2.

	No.	%
Age group (Years)		
≤40	22	22.45
41–50	29	29.59
51–60	35	35.71
>60	12	12.24
Sex		
Male	87	88.78
Female	11	11.22
Site		
Alveolus	19	19.39
BM	56	57.14
GBS	6	6.12
RMT	17	17.35
Type of Neck Dissection		
MRND	90	91.84
SOHND	8	8.16
Size		
T1&T2	55	56.12
T3&T4	43	43.88
LVI		
Absent	57	58.16
Present	41	41.84
PNI		
Absent	53	54.08
Present	45	45.92
ECE		
Absent	72	73.47
Present	26	26.53
Depth of Invasion		
<4 mm	1	1.02
4mm–10mm	57	58.16
>10mm	40	40.82
Grade		
W/D	30	30.61
M/D	57	58.16
P/D	11	11.22

Table 1. Patients' Characteristics

	pN0	pN+	Total
cN0	14	39	53
cN+	8	37	45
Total	22	76	98

Table 2. Pre–operative vs Post–operative N status

Various parameters such as age, sex, grade, site, type of neck dissection, tumour size, LVI, PNI, ECE, depth of invasion, and grade of differentiation were included in bivariate analysis using chi–square and Fischer exact test to identify association with nodal metastasis. Of these parameters, tumour size, LVI, PNI, ECE and degree of differentiation were found to be significant (p value < 0.05). See Table 3.

Multivariate logistic regression analysis was done by using stepwise method to identify independent factors for nodal metastasis. Age, sex, grade, site, depth of invasion (DOI), lymphovascular invasion (LVI), Perineural invasion (PNI), extracapsular extension (ECE) were put into the model and the probability of retaining in model was kept < 0.05.

Male gender, poorly differentiated carcinoma and presence of PNI were found as independent predicting factors for nodal metastasis. Male gender and PNI were found as risk factors (Odds Ratio 7.0826 to 8.65 respectively) while poorly differentiated carcinoma grade appeared non–inferior factor paradoxically (Odds Ratio 0.1033, overall 82.65% cases were correctly classified by this model (using Hosmer & Lemeshow test) and area under ROC curve (AUC) was 0.794 of the model). See Table 4 and 5.

Discussion

Squamous cell carcinoma of gingiva–buccal complex is an aggressive malignancy. The most common oral cavity subsite in present study is buccal mucosa (57.14%) followed by alveolus (19.39%). In India, the gingival–buccal complex (alveolar ridge, gingival– buccal sulcus, buccal mucosa) forms the most common subsite for cancer of the oral cavity, in contrast to cancer of the tongue that is more common in the western world. [5] The difference in subsite is because of the prevalent culture practice of chewing tobacco in South Asia. Recent local studies have also shown that squamous cell carcinoma appears to be more aggressive compared with the other subsites of oral cavity. [6, 7]

Lymph node metastasis occur in about 40% of patients with oral cancer and their clinical manifestation are hidden in rate of 15 to 34 %.[8, 9] The status of cervical lymph node at presentation is the single most important

prognostic factor for patients with oral squamous cell carcinoma, and the presence of metastatic lymph nodes decreases survival rate by more than 50 %.[3, 10]

PARAMETERS	pN0		pN+		P value
	N	%	n	%	
AGE					
≤40	3	13.64	19	86.36	0.779
41–50	7	24.14	22	75.86	
51–60	10	28.57	25	71.43	
>60	2	16.67	10	83.33	
SEX					
Male	17	19.54	70	80.46	0.117
Female	5	45.45	6	54.55	
SITE					
Alveolus	2	10.53	17	89.47	0.732
BM	14	25.00	42	75.00	
GBS	2	33.33	4	66.67	
RMT	4	23.53	13	76.47	
TYPE OF NECK DISSECTION					
MRND	20	22.22	70	77.78	1.000
SOHND	2	25.00	6	75.00	
SIZE					
T1&T2	17	30.91	38	69.09	0.029
T3&T4	5	11.63	38	88.37	
LVI					
Absent	7	12.28	50	87.72	0.007
Present	15	36.59	26	63.41	
PNI					
Absent	18	33.96	35	66.04	0.003
Present	4	8.89	41	91.11	
ECE					
Absent	22	30.56	50	69.44	0.001
Present	0	0.00	26	100.00	
DEPTH OF INVASION					
<4 mm	1	100.00	0	0.00	0.166
4mm–10mm	13	22.81	44	77.19	
>10mm	8	20.00	32	80.00	
GRADE					
W/D	7	23.33	23	76.67	0.001
M/D	8	14.04	49	85.96	
P/D	7	63.64	4	36.36	

Table 3. Results of Bivariate Analysis: Association between Nodal Metastasis and Various Parameters

Therefore, neck dissection should always be performed when there is an obvious clinically– detectable lymph node in patient with squamous cell carcinoma of oral cavity. But in patients with clinically negative neck or with early stage (T1/T2 N0), treatment of neck remains controversial.

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 disadvantage of the morbidity of a second surgery, neck dissection might destroy the natural tumour barrier. [11]

In the present study, neck was addressed in all the cases (n = 98), MRND (n = 90) and SOHND (n = 8, in case of clinically early staged diseases). The rate of occult metastasis in our study was 73.5%. The incidence of occult metastases to the neck can range from 15% to 60% depending on different prognostic factors according to published data. [12]

Association between various parameters and cervical lymph node metastasis:

In the present study, bivariate analysis was done using Chi Square and Fischer Exact test. Age, subsite and type of neck dissection were not statistically significant with p values: 0.779, 0.732 and 1.000 respectively. Incidence of lymph node metastasis was seen higher in males compared to females, although results were not significant on bivariate analysis (p value: 0.117).

Whereas tumour size, LVI, PNI, ECE and Grade showed statistically significant association with lymph node metastasis (p value: 0.029, 0.007, 0.003, 0.001 and 0.001 respectively) on bivariate analysis.

Variable	Odds ratio	95% CI
Sex=1 (male)	7.0826	1.2953 to 38.7261
Grade=3 (poorly differentiated)	0.1033	0.0217 to 0.4928
PNI=1 (Present)	8.6593	2.0474 to 36.6237

Table 4. Results of Multivariate Logistic Regression Analysis: Association between Nodal Metastasis and Various Parameters (Odds Ratios and 95% Confidence Intervals)

Area under the ROC curve (AUC)	0.794
Standard Error	0.0521
95% Confidence interval	0.700 to 0.869

Table 5. ROC curve analysis

In the present study, it was also observed that the deeper the invasion, the more likelihood of lymph node metastasis to occur. However, it didn't show significant relation with bivariate analysis (p value: 0.166).

On multivariate logistic regression analysis, male gender, poorly differentiated carcinoma and presence of PNI were found as independent predicting factors for nodal metastasis. Male gender and PNI were found as risk factors (Odds Ratio 7.0826 to 8.65 respectively) while poorly differentiated carcinoma grade appeared protecting factor paradoxically (Odds Ratio 0.1033, overall 82.65% cases were correctly classified by this model and the area under ROC curve (AUC) was 0.794 of the model.

Various studies have observed that of the different variables that are related to neck metastasis, the most important is depth of invasion [13 – 15]. Depth of invasion is extension of tumour beneath the epithelial surface, where epithelium is destroyed. However, this was not observed in present study.

Alkaisi et al., concluded that tumour depth ($p < 0.001$) followed by pattern of invasion ($p < 0.01$), tumour site ($p = 0.003$), degree of differentiation ($p = < 0.001$), tumour size ($p = 0.004$) and lymphoplasmacytic infiltration ($p = 0.004$) are reliable factors in predicting nodal metastasis and tumour depth of 4 mm can be considered as cut–off number in staging and management of early oral squamous cell carcinoma. Also, no significant correlation was seen with patient's age and sex with cervical lymph node metastasis. [16] While in present study male gender was found as independent predicting factor for nodal metastasis by multivariate logistic regression analysis (Odds ratio: 7.0826, 95 % CI: 1.2953 to 38.7261).

Haksever et al. found that there is no significant association between neck node metastasis and both tumour size and lymphoplasmacytic infiltration which was consistent with our study. [17]

In a study by Ahmed et al. it was observed that with every 10 years increase in age, the risk of neck node metastasis in buccal squamous cell carcinoma increases by 1.84 times (odds ratio 1.06, 95 % CI 1.01–1.12, $p = 0.027$). Also risk of neck node metastasis in buccal squamous cell carcinoma decreases by 0.58 times for each centimetre decrease in tumour size (odds ratio: 0.58, 95 % CI: 0.40–0.82), $p = 0.002$). [18] However, our study did not show any significant association between age and tumour size.

Perineural invasion (PNI) is the process of neoplastic invasion of nerves and under–recognized route of metastatic spread. PNI is a marker of poor outcome and a sign of decreased survival. Perineural invasion in SCC of the oral cavity and oropharynx was associated with an increased incidence of cervical nodal metastasis which was consistent with our study. [19]

In our study, it was observed that poorly differentiated histological grade was significantly associated with the lower prevalence of neck metastasis compared to well and moderately differentiated tumors on multivariate analysis. However, 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 patients with well–differentiated tumors.[20] Fukano et al found no significant association between the degree of tumor differentiation and pN0 and pN+ status.[14] Hakshever et al. concluded that prevalence of neck lymph node metastasis in patients with squamous cell carcinoma of the oral cavity increases as the tumor depth increases and as the degree of tumor differentiation decreases from well to poor, risk of nodal metastasis increases.[17] These results were contradictory to the results of present study.

Conclusion

In conclusion, the rate of occult metastasis in our study was 73.5%. The incidence of occult metastases to the neck can range from 15% to 60% depending on different prognostic factors according to various published data. Therefore, elective neck dissection should be attempted in clinically N0/ early staged disease.

Various parameters like tumour size, LVI, PNI, ECE and Grade showed statistically significant association with lymph node metastasis (p value: 0.029, 0.007, 0.003, 0.001 and 0.001 respectively) on bivariate analysis. While it was observed that the deeper the invasion, the more likelihood of lymph node metastasis to occur. However, it didn't show significant relation with bivariate analysis (p value: 0.166).

On multivariate logistic regression analysis, male gender and presence of PNI were found as independent predicting factors for nodal metastasis (Odds Ratio 7.0826 to 8.65 respectively) while poorly differentiated carcinoma grade appeared non–inferior factor paradoxically.

Further studies are needed to understand the heterogeneous nature of tumour and other associated risk factors increasing incidence of nodal metastasis in gingiva–buccal complex squamous cell carcinoma to achieve appropriate treatment benefit.

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