Is an Elective Neck Dissection Needed in Squamous Cell Carcinoma of the Maxillary Alveolus and Hard Palate?

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ABSTRACT

Background

Squamous cell carcinoma (SCC) of the maxillary alveolus and hard palate is a rare site for oral cavity carcinoma. Much controversy is there regarding the management of this site and elective neck dissection due to rarity and complex lymphatic drainage.

Objective

To estimate the prevalence of neck nodal metastasis in squamous cell carcinoma of maxillary alveolus and hard palate and the factors influencing the nodal metastasis.

Method

This retrospective cohort study includes patients diagnosed with squamous cell carcinoma of maxillary alveolus and hard palate and who underwent surgical intervention between March 2017 and March 2022.

Result

The study included 53 patients among them majority were men (73.6%). Prevalence of neck nodal metastasis was 36.6% and occult nodal metastasis was noted in 16%. On multivariate analysis, clinical nodal positivity increases the odds of pathological nodal positivity by 9.4 times compared to no nodal involvement (95% CI 2.07–42.57, $p \leq 0.004$). A depth of invasion (DOI) of more than 10 mm increases risk by 7.4 times for pathological nodal positivity compared to less than 10 mm invasion (95% CI 1.53–35.27, p=0.013).

Conclusion

Squamous cell carcinoma of maxillary alveolus and hard palate has a high risk of nodal metastasis. Depth of invasion is an important predictor for nodal metastasis. Due to the high risk of nodal metastasis elective neck dissection would be recommended in advanced stages. Squamous cell carcinoma of maxillary alveolus and hard palate with nodal metastasis has a poor survival.

KEY WORDS

Hard palate, Lymph node metastasis, Neck dissections, Squamous cell carcinoma

INTRODUCTION

Oral cancer has a diverse geographical distribution, incidence, and prevalence in different parts of the world. It is very widespread in India due to the uncontrolled use of tobacco products. Cancer of the oral cavity accounts for approximately 2% of all malignant diseases. In 2020, the global incidence of lip and oral cancer was 10.2 per 100,000.[1]

Much research has been published on various subsites of oral cancer, with little mention of the maxillary alveolus and hard palate tumors due to lower incidence.

The maxilla is thought to have limited lymphatic drainage compared to the abundant lymphatic vessels in other parts of the oral cavity, and tumors of the oral cavity of the maxilla are biologically like maxillary tumors arising in the sinonasal cavity, where elective treatment of the neck is still a debate.[2]

Previously, it was believed that recurrence due to malignancy in this subsite was most likely to be local. But it has now been shown that nodal recurrence is also high, the same would affect survival.[3]

This study mainly focuses on the prevalence of nodal metastasis in squamous cell carcinoma(SCC) of maxillary alveolus and hard palate, the factors influencing nodal metastasis, and its impact on survival.

METHODS

This retrospective cohort analysis included patients who were diagnosed to have SCC of maxillary alveolus and hard palate in the Department of Head and Neck Surgery for a period of 5 years (March 2017 to March 2022). The study was approved by institutional ethical review board (IRB Approval number 14573). All patients included in the study underwent multidisciplinary tumor board discussion before curative procedure. Patients underwent surgery with a minimum of 1 cm gross tumor margin along with neck dissection especially for advanced stage tumors. Adjuvant therapy (Radiotherapy/Chemoradiotherapy) was given when indicated. The objective of study was to know prevalence of nodal metastasis in squamous cell carcinoma(SCC) of maxillary alveolus and hard palate and the factors influencing the same. To know the impact of nodal metastasis on survival.

We included patients with SCC of maxillary alveolus and hard palate operated with a curative intention. Patients with SCC epicenter in nose and paranasal sinuses, those who underwent previous radiotherapy for head and neck region and patients presenting with second malignancy were excluded from the study. Electronic charts review of patients who meet the inclusion criteria were considered.

The sample size of the study was calculated using study by Joosten et al. with 9% precision, 5% desired confidence interval we expected to enrol 58 subjects.[4]

We have included various demographic parameters includes age, sex, comorbidities, and habits. Clinical parameters included were tumors extending to buccal mucosa, trismus, site of origin, tumor crossing midline, clinical skin involvement, clinical T staging, clinical tumor size, clinical nodes and number of nodes. Radiological parameter includes involvement of orbit, pterygoid muscle, pterygoid plate, pterygopalatine fossa, sinus involvement and widening of skull base foramen. Pathologic parameters includes grade of SCC, size, depth of invasion (DOI), perineural invasion (PNI), lymphovascular invasion (LVI), Worst pattern of invasion (WPOI), presence of pathological node, margin, extranodal extension (ENE) and pathological stage. Occult metastases is defined as the metastasis that are not detected during initial clinicoradiological examination but are identified with further pathological evaluation.[5] Disease free interval (DFS) was calculated as the period between the date of surgery and date of last follow up.

For continuous data, the descriptive statistics, mean, SD and for non-normally distributed data median, IQR was presented. All categorical variables were represented as numbers and percentages. The chi-square and Fisher's exact test were applied to find association between categorical variables. To identify the independent risk factors that were associated with the nodal metastasis logistic regression was used to build up the models and adjust for confounders. Multivariate analysis was also done using multivariate Cox regression to know their predictive value for positive nodal involvement. The Kaplan Meier curve was used to estimate survival time. All tests will be two-sided at alpha (α) = 0.05 level of significance. All analyses were done using STATA software version 16.0.

RESULTS

The study included 53 patients. Majority (92%) of patients were above the age of 45 years. Mean age of the study population was 60 years. Men were commonly affected (Male: Female was 2.7:1). Majority of our patients (72%) were tobacco users. Maxillary alveolus was commonly involved site (71.70%) with majority presenting in advanced stage (60.4%). Tumor extending into adjacent upper gingivobuccal sulcus(GBS) was noted in 35.85% (Table 1).

Neck dissection was performed in 83% of the patients among them 15% patient underwent MRND and the rest underwent a selective neck dissection of ipsilateral levels level I-III. There was no contralateral neck node dissection. Among the patient who underwent neck dissection 16 patients (36.36%) had pathologically proven metastatic lymph node (pN+/cN0: 4/25 (16%); pN+/cN+: 12/19

Table 1. Univariate analysis of parameters influencing nodal metastasis

Parameter	Variable	No. of Patients N=53 (%)	No. of patients with pathological nodes N=16(%)	P value
Demographic and clinical parameters				
Age	≤ 45 years	4(7.55)	0(0)	NA
	> 45 years	49(92.45)	16(100)	
Sex	Female	14(26.42)	4(25)	0.87
	Male	39(73.58)	12(75)	
Comorbidities	Absent	27(50.94)	6(37.50)	0.2
	Present	26(49.06)	10(62.50)	
Tobacco consumption	Absent	15(28.30)	2(12.5)	0.1
	Present	38(71.70)	14(87.50)	
Gingivobuccal extension	Involved	34(64.15)	9(56.25)	0.4
	Not Involved	19(35.85)	7(43.75)	
Trismus	Absent	46(86.79)	14(87.50)	0.9
	Present	7(13.21)	2(12.50)	
Site of origin	Palate	15(28.30)	4(25)	0.72
	Maxillary alveolus	38(71.70)	12(75)	
Tumor crossing midline	Absent	52(98.11)	15(93.75)	0.3
	Present	1(1.89)	1(6.25)	
Clinical skin involvement	Present	3(5.66)	0	NA
	Absent	50(94.34)	16(100)	
Clinical Tumor Staging	cT1+cT2	21(39.62)	6(37.5)	0.83
	cT3+cT4	32(60.38)	10(62.5)	
Clinical tumor size in mm	≤20	16(30.19)	4(25)	0.85
	20-40	18(33.96)	7(43.75)	
	>40	19(35.85)	5(31.25)	
Clinically significant node	Absent	34(64.15)	4(25)	**0.0001**
	Present	19(35.85)	12(75)	
No of clinically significant palpable nodes	Absent	34(64.15)	4(25)	**0.001**
	Single	15(28.30)	9(56.25)	
	Multiple	4(7.55)	3(18.75)	
Pathological parameters				
Pathological tumor size in mm	≤ 20	16(30.19)	3(18.75)	0.76
	21-40	18(33.96)	7(43.75)	
	>40	19(35.85)	6(37.5)	
Grade	Well differentiated	18(33.96)	5(31.25)	0.4
	Moderate differentiated	31(58.49)	11(68.75)	
	Poorly differentiated	4(7.55)	0	
Depth of invasion in mm	≤5	25(47.17)	4(23.53))	**0.03**
	6 to 10	16(30.19)	5(29.41)	
	>10	12(22.64)	8(47.06)	
Perineural invasion	Absent	43(81.13)	11(68.75)	0.13
	Present	10(18.87)	5(31.25)	
Worst pattern of invasion	1,2,3	23(43.40)	5(31.25)	0.24
	4,5	30(56.60)	11(68.75)	
Lymphovascular invasion	Absent	45(84.91)	11(68.75)	**0.04**
	Present	8(15.09)	5(31.25)	
Bone invasion	Present	26(49.06)	5(31.25)	**0.06**
	Absent	27(50.94)	11(68.75)	
Staging Pathological T stage	pT1/pT2	30(56.60)	6(33.5)	**0.07**
	pT3/T4	23(43.40)	10(62.5)	
Pathological nodes	Absent	37(69.81)		NA
	Present	16(30.19)		
Margin	Negative	18(33.96)	6(37.50)	0.14
	Close	24(45.28)	5(31.25)	
	Positive	11(20.75)	5(31.25)	
Extracapsular extension	Absent	44(83.02)	7(43.75)	NA
	Present	9(16.98)	9(56.75)	
Radiological Parameters				
Involvement of orbit	Present	3(5.66)	15(93.75)	0.9
	Absent	50(94.34)	1(6.25)	
Pterygoid plate involvement	Absent	46(86.79)	15(93.75)	
	Present	7(13.21)	1(6.25)	
"Perygopalatine fossa involvement	Absent	38(71.70)	11(68.75)	0.75
	Present	15(28.3)	5(31.25)	
Widening of skull base foramen	Absent	51(96.23)	16(100)	NA
	Present	2(3.77)	0(100)	
Pterygopalatine fossa	Absent	48(90.57)	16(100)	NA
	Present	5(9.43)	0(0)	
Sinus involved	Absent	22(41.51)	6(37.50)	0.69
	Present	31(58.49)	10(62.50)	
Other Parameters				
Neck dissection	Done	44(83.02)	16(100)	NA
	Not done	9(16.98)	0	
Adjuvant Radiotherapy	Given	43(81.13)	15(93.75)	0.8
	Not given	10(18.87)	1(6.25)	
Adjuvant Chemoradiotherapy	Given	14(26.42)	8(50)	0.9
	Not given	39(73.58)	8(50)	
Recurrence	Present	22(41.51)	12(75)	**0.002**
	Absent	31(58.49)	4(25)	
Recurrence Type	Local	14(63.64)	7(58.33)	**0.003**
	Regional	6(27.27)	3(25)	
	Distant	2(9.09)	2(16.67)	

NA:Not Applicable.

(63.16%). Thus, the prevalence of pathological positive nodes was 36.6% (Table 1). Incidence of occult nodal metastasis is 16% while considering 44 patients with neck dissection. Among the patients who did not undergo neck dissection, none had nodal recurrence. Detection of significant node using clinicoradiological parameters had a sensitivity and specificity of 75% (Table 2).

Table 2. Diagnostic utility of clinicoradiological parameters for detection of metastatic nodes in oral SCC of maxillary alveolus and hard palate in patients undergoing neck dissection

Clinicoradiological Parameters suggesting nodal metastasis (cN) [n (%)]	Metastatic node on histopathology (pN)	
	Positive (pN+) [n(%)]	Negative (pN0) [n (%)]
Positive (cN+)	True Positive	False Positive
19(43.18)	12(75)	7(25)
Negative (cN0)	False Negative	True Negative
25(56.81)	4(25)	21 (75)
	Value (%)	**95% CI**
Sensitivity	75.00	47.62-92.73
Specificity	75.00	55.13-89.31
Positive Likelihood Ratio	3.00	1.49-6.05
Negative Likelihood Ratio	0.33	0.14-0.80
Disease prevalence	36.36	22.41-52.23
Positive Predictive Value	63.16	45.95-77.56
Negative Predictive Value	84.00	68.63-92.65
Accuracy	75.00	59.66-86.81

Though not statistically significant lymph node metastasis was more common in patients with tobacco usage (87% vs 13%). About 80% of patients received adjuvant therapy in which 26% received adjuvant chemoradiotherapy. With a median follow up of 24 months 41.5% developed recurrence. Majority of recurrence was in the primary site (63%) (Table 1).

Among the demographic, clinical, radiological, pathological parameters analyzed, univariate analysis showed significant association of nodal metastasis with clinically significant neck nodes (p=0.0001) and multiple number of neck nodes palpable (p=0.001). Among pathological factors there was significant association noted with DOI (p=0.03) and LVI (p=0.04). Though not statistically significant WPOI > 3 (33% Vs 21.7%), bone invasion (40.7% Vs 19.2%) and advanced pathological tumor stage (43.5% Vs 20%) appeared to have association with nodal metastasis (Table 1).

Table 3. Multivariate analysis of significant univariate factors influencing pathological nodes in patients with SCC of maxillary alveolus and hard palate

Pathological nodes	Odds Ratio	Std. Err	z	P>|z|	95% Conf. Interval	
					Lowest	Highest
Clinical nodes (present)	9.40	7.24	2.91	**0.004**	2.07	42.57
Lymphovascular inva-sion (present)	2.43	2.40	0.90	0.369	0.35	16.93
Depth (> 10 mm)	7.35	5.88	2.49	**0.013**	1.53	35.27
6-10 mm	2.38	1.83	1.13	0.257	0.53	10.73

Multivariate analysis of significant univariate factors predicting nodal metastasis noted detecting a clinically significant neck node had 9.4 times increased risk for pathological nodal metastasis (95%CI: 2-42.5; p = 0.001) and depth of invasion greater than 10 mm had a 2.49 times increased risk of nodal metastasis (95%CI: 1.53-35.27; p=0.013) (Table 3). The presence of pathological nodes had a significant reduction in survival (HR, 6.6; 95%CI: 2.7-16.05; p = 0.001) (Fig. 1).

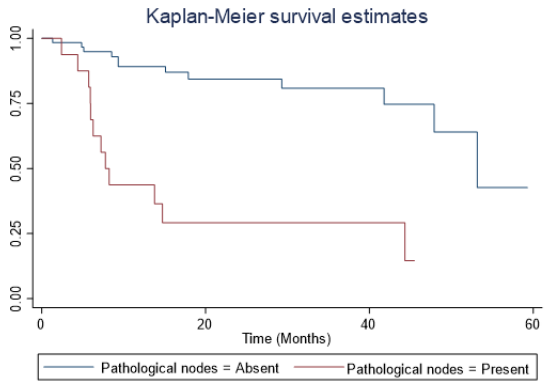

Figure 1. Kaplan -Meier survival curve showing comparison of disease free survival among pathological nodes positive and negative SCC of maxillary alveolus and hard plate (P value = 0.001).

DISCUSSION

The number of new cases of oral cavity and lip cancer worldwide is 377,713 and the number of deaths is 177,077 in the year 2020. One-third of global cases and one-half of oral cancer-related deaths are, from Southeast Asia.[6] Incidence of oral cancer is common in the age group over 45 years and the mean age of our affected population was 60 years, which was similar to our study.[7,8]

It is well known that occurrence of oral cancer is related to consumption of tobacco products especially tobacco chewing, betel-quid chewing, tobacco smoking, reverse smoking.[9] Majority of our patients had history if tobacco products consumption (71.70%). In India, the gingivo-buccal complex (alveolar ridge, gingival-buccal sulcus, buccal mucosa) forms the most common sub-site for cancer of the oral cavity, in contrast to the tongue and floor of the mouth that is prevalent in the western world, which can be mainly attributed to consumption of smokeless tobacco products.[10] Involvement of maxillary alveolus carcinoma (71.7%) was more common than hard palate in our study.

Study by Doll et al. compared carcinoma of buccal mucosa and current subsite of interest, noted DOI predicted pathological nodal metastasis (mean 10.3 mm ± 6.9 versus mean 6.1 mm ± 4.9; p = 0.02).[11] Similar result was observed in our study with DOI more 10 mm acted as an independent predictor of nodal metastasis (HR:2.49, 95%CI: 1.53-35.27; p=0.013). We noticed 56% of patients with disease extension to upper gingivobuccal sulcus (GBS) had nodal metastasis compared with 44% with no upper GBS involvement (p=0.4). It appears that involvement of upper GBS has increased risk of nodal metastasis. It was

also noted that presence of clinical parameters denoting an advanced disease like trismus and skin involvement was not significantly associated with nodal metastasis.

Studies have shown that patients with advanced histological T-stage (T3 and T4) showed an increased probability of the development of pathological nodes.[12] Similarly in our study 62.5% of patients who had nodal metastasis were classified to have an advanced pathological tumor stage.

Study done by Jones et al. showed there was a high incidence of LVI identified in the primary tumour of patients with cervical metastases (51%).[13] Though similar findings (38.5%) were noted in univariate analysis (p = 0.04) it was not significant in multivariate analysis. The presence of LVI might predict for cervical metastases as invasion of the lymphatics is the first step in the development of a metastatic focus.[14]

Van den Brekel et al. estimated that computer tomography imaging can miss up to 28% of metastatic cervical nodes and that the best predictor of lymph nodal metastases are multiple radilogical factors combined together.[15] We noted clinicoradiological parameters had a sensitivity of 75% and specificity of 75% (Table 2).

A study done by Yorozu et al. noted a nodal recurrence of 21% in patients with no metastatic disease who were treated with radiotherapy for SCC of the hard palate.[3] We noted 41% of our patient had recurrence, among them local recurrence was the majority (26.41%) nodal recurren ce was noted in 11.3% of patients.

Pathological node positivity was noted in 30% our study population. It is well known that oral SCC patients with a 20% rate of occult cervical metastasis will benefit from management of the N0 neck.[16] Kim et al. showed 13.5% risk of occult metastasis in patients at the time of primary resection in maxillary alveolus and palate carcinoma.[17] A study by Dubal et al. demonstrated that the risk as high as 22.2% of occult metastasis in malignancies of maxillary sinus and alveolus, which is also criteria for performing END.[18] In our study 16 patients had a histologically proven metastatic lymph. Besides being therapeutic, neck dissection will play's an important role in pathological correlation of disease stages. Consequently, having a positive neck node in histopathological specimen might advance the stage of tumors, necessitating adjuvant therapy. Four patients out of 25 (16%) clinicoradiologically negative node had a positive pathological node (pN+/cN0: 4/25) and 12 patient out of 19 (63.16%) clinicoradiologically positive nodes had pathological node pN+/cN+: 12/19. Thus risk of occult metastasis is 16% in our study which stands against elective neck dissection for SCC of maxillary alveolus and palate. Being said we have a high node positivity of 30% and presence of neck node significantly affects survival. Observation of neck needs to be relooked especially in advanced diseases.

As the standard of neck dissection has evolved over ages we need to relook the arbitrary value for neck dissection on patients perspective and provide a better care.

For oral cavity squamous cell carcinoma, sentinel lymphnode biopsy or the primary tumor depth of invasion is currently the best predictor of occult metastatic disease and can be used to guide decision-making.[19] Recent randomized trial evidence supports the effectiveness of elective neck dissection in patients with oral cavity cancers greater than 3 mm in depth of invasion for oral tongue.[20] We noticed that 23.5% of the node positive cases had DOI less than 5 mm and it acted as independent predictor of nodal metastasis.

Study by Obayemi Jr et al. on 1,830 patients with hard palate and upper gingival cancers noted performing elective neck dissection in a clinically node negative neck improve the overall survival.[21] Majority of our patients underwent elective neck dissection. The negative impact of node positivity on DFS can be well noted in figure 1. Local recurrence was the major cause of failure rather than nodal involvement in our study. We would still consider elective neck dissection for SCC of maxillary alveolus and palate especially in those with advanced disease. This is because most patients will not accept 20% cut-off value as elective neck dissection when explained and survival trends to be poor in those who has nodal involvement or recurrence. The occult nodal metastasis in our group is close to 20%. Further neck dissection acts as an diagnostic, therapeutic and prognostic tool.

Limitations of our study includes the following. We were not able to reach the target sample i.e, 58 patients one of the main reason being the COVID19 pandemic. So the number of patients enrolled was slightly less (53 patients compared to sample size 58) to firmly conclude our results. Also, the results were driven from a single institution and retrospective. This being said the current study is one of the largest for this rare subsite and elaborates probable need for elective neck dissection especially in advanced stage malignancy. The limitations can be solved through future studies such as multi-center prospective research. Ability of SLN biopsy to avoid elective neck dissection, for SCC of hard palate and maxillary alveolus needs further research.

CONCLUSION

The independent predictors of pathological nodes in SCC of the hard palate and maxillary alveolus were the presence of clinically significant neck nodes and depth of invasion greater than 10 mm. SCC of the hard palate and maxillary alveolus has high risk of nodal metastasis and nodal involvement has a significant influence on disease free survival. Elective neck dissection can be recommended for advanced tumours arising from this subsite. There needs to be research on the role of SLN biopsy in SCC of the hard palate and maxillary alveolus.

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