Original Research Article

Assessment of histological parameters indicative of occult metastasis in oral cavity cancers

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Abstract

Objective: It is well established fact that in squamous cell carcinoma cases of oral cavity ,the presence of lymph node metastasis decreases the 5 year survival rate by 50%. Therefore, it is imperative to identify patients who are at greatest risk for occult cervical metastasis. This study aimed to identify various histological parameters which are predictive for occult metastasis. **Design and subject:** This is a retrospective study which includes all cases which are clinically cT1N0M0 and cT2N0M0 in a tenure of previous 2 years (2021 and 2020) and excludes all other cases which have clinically nodes palpable and have imaging findings suggestive of metastasis. **Methods:** The histological parameters of 24 cases of Oral cavity cancers (which includes tongue,buccal mucosa and hard palate cancers) with cT1N0M0 and cT2N0M0 as the stage and without prior radiotherapy and chemotherapy were considered. All radical specimens of oral cavity cancers were fixed in formalin and were subjected to processing and staining by Hematoxylin and Eosin. The sections obtained were microscopically examined by two pathologist individually. The histological parameters were recorded that includes tumor grade, invading front ,depth of invasion perineurial invasion , inflammatory response and lymph node metastasis. **Results and conclusion:** A total of 7 cases were found with positive occult nodal metastasis. On performing univariate analysis, the histolological parameters which were found to be significant were Perineurial invasion(p=0.001), Tumor inflammatory response(p=0.01) and Invading tumor front (p= 0.01). Hence histopathological assessment of the primary tumor specimen continues to provide information that is central to guide clinical management, particularly in cases of occult nodal metastasis.

Keywords: Occult, Metastasis, Oral cavity Cancer.

Introduction

Squamous cell carcinoma (SCC) is the most common histological type in oral cavity cancer. It forms nearly 95% of all malignant lesions found in the oral cavity[1]. Early detection and diagnosis of Oral cancers are crucial in order to get successful outcome in treatment of these cancers[2]. The most important and well-known prognostic factor of oral cavity squamous cell carcinoma (OCSCC) is the tumor-node-metastasis (TNM) system[3].

Treatment protocol of positive nodal metastasis is well standardized, however there is no clear agreement of management of occult nodal metastasis. Incidence of Occult nodal metastasis is relatively high[4,5,6] and histopathological examination is the only gold standard to look for subclinical metastasis to lymph nodes in early stage oral cancers.

About 80 percent of the patients without nodal metastasis undergo lymph node dissection in early stage oral cancers without any benefit. This study is performed to identify various histopathological parameters indicative of Occult metastasis thus allowing treatment decisions and also providing accurate indicator of patient outcome[2].

Materials and methods

The Present study was carried out in Gupta Diagnostic Laboratory in collaboration with Silverline Hospital Bhopal.

A total of 24 cases of oral cavity cancers with inclusion criteria of Oral cavity carcinoma as the site, cT1N0M0 /T2N0M0 as the stage and without prior radiotherapy and chemotherapy were considered.

All those cases in which the radiological and clinical assessment showed nodes positive are excluded from the study. The preoperative clinical AJCC/UICC TNM stages were 6 cT1N0M0 and 18 cT2N0M0 patients.

An average of 14 nodes per case with total of 336 nodes were obtained in entire study. 336 nodes were obtained in entire study.

All Glossectomy, Mandibulectomy and Buccal mucosa excision specimens along with neck nodes are fixed in formalin and 5µmthick sections were obtained. the hematoxylin and eosin stained sections were then subjected to microscopic examination.

Histological parameters

The histological parameters which were analyzed include Tumor Grade, Depth of invasion, Pattern of invasion, Lymphovascular emboli, Perineurial invasion and Inflammatory response. The head and Neck specimens were examined for positive occult nodal metastasis.

Grading of tumor was done using border criteria. The invading tumor front was grouped in to Pattern 1, 2, 3, 4 and 5. Pattern 1 was defined as broad, pushing margin of tumor with a smooth outline. Pattern 2 was defined as broad, pushing finger-like projection. Pattern 3 represents invasive tumor islands with >15 cells per island. Pattern 4 represents invasive tumor islands with less than 15 cells per island. Pattern 5 was defined by the presence of tumor island outside the main tumor at a distance of >1 mm[7].Depth of invasion is measured from adjacent normal mucosa to deepest point of invasion. Host inflammatory response was graded as mild, moderate and severe. Perineurial invasion is considered as infiltration of the perineurial space of nerves.

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Results

On performing univariate analysis, histopathological parameters that were found to be statiscally significant were Perineurial invasion(P value- 0.001) , Pattern of invasion (P value- 0.01),tumor infiltrating lymphocytes(P value- 0.01) and Level 1b nodal metastasis with T2 stage cancers(P value -0.00001).

The parameters which were not found to be significant were Depth of invasion, Lymphovascular emboli and Grade of tumor. A total of seven cases were found to have nodal metastasis. (Fig.1)

There were 19 males and 5 females. the age range varies from 32 to 63 years, with a maximum number of patients in 4th and 5th decade. Maximum number of patients with nodal metastasis were seen in Level Ib followed by rest of levels.

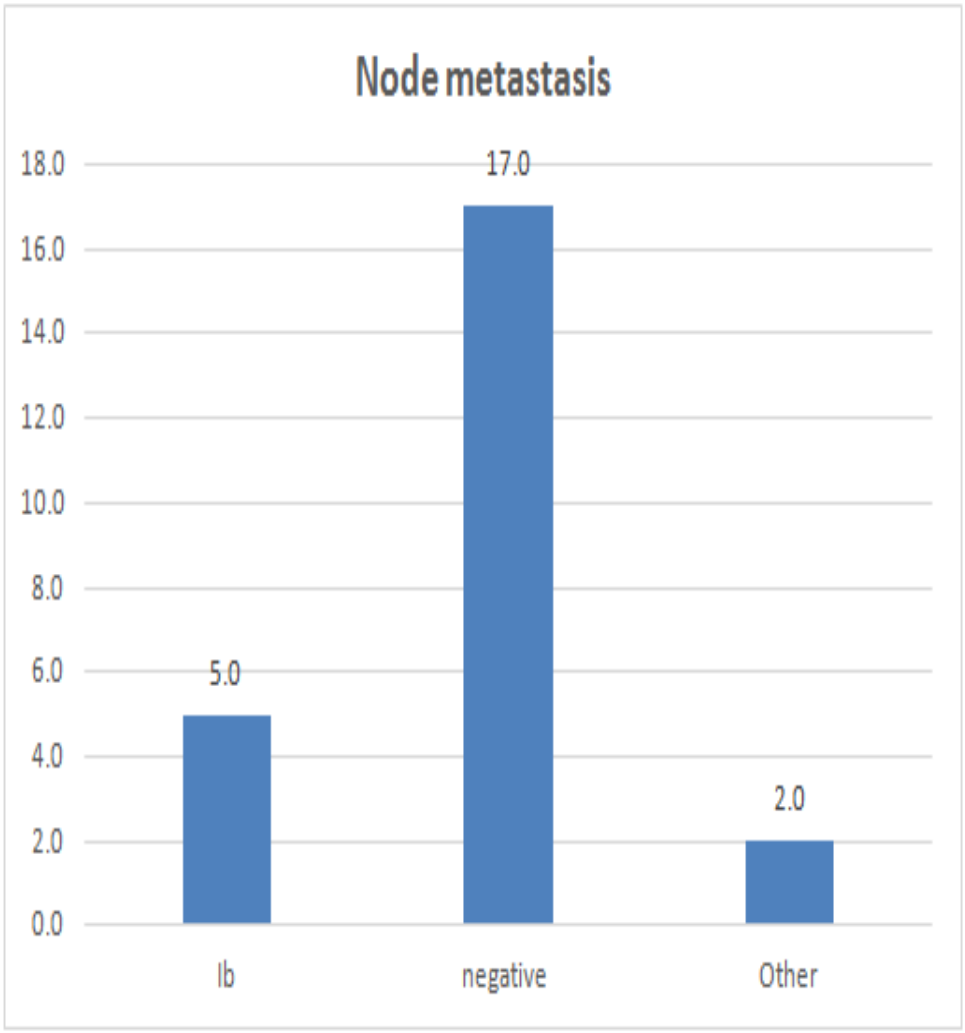


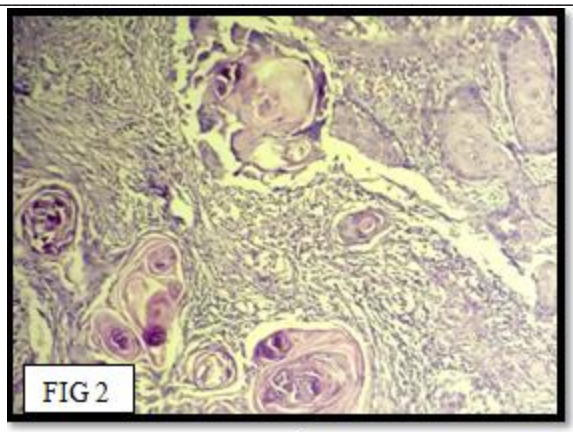
Fig. 1: Level IB and rest of MND- NODE positive

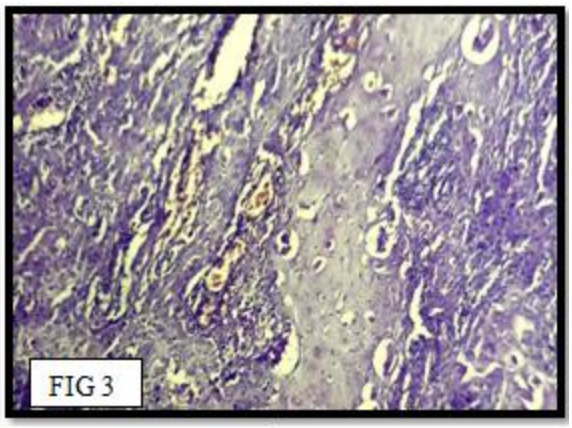
In this study there were 15 cases in Grade I that is Well differentiated Squamous cell carcinoma, Eight cases(Fig 2) in Grade II Moderately differentiated Squamous cell carcinoma(Fig 3) and 1 case on Grade III that is Poorly Differentiated Squamous cell carcinoma(Fig 4) . Tumor grade was statistically analyzed and was to be nonsignificant with a p value of 0.14 using Pearson Chi-square Test.(Table 1)

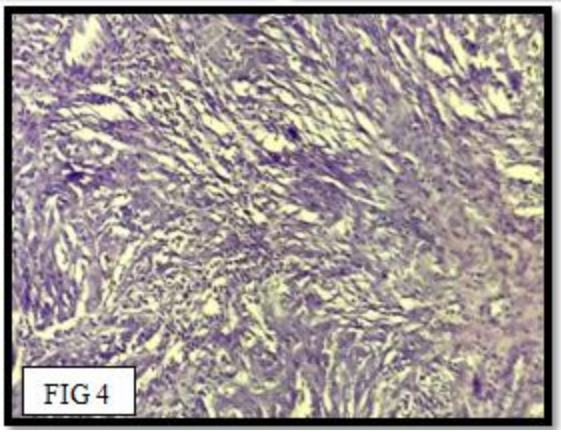
Table 1: Pearson chi-square test for tumor grade

Group	Tumor Grade			Total
	Grade 1	Grade 2	Grade 3	
Positive	3	4	0	7
Negative	12	4	1	17
				24

P VALUE 0.14







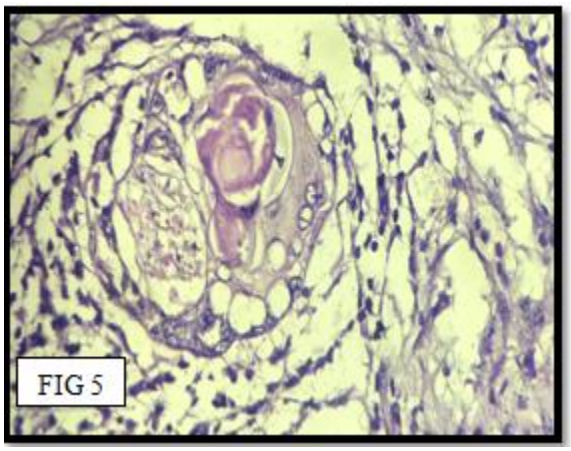
Well Differentiated Squamous Cell Carcinoma-Fig. 2; **Moderately Differentiated Squamous Cell Carcinoma- Fig. 3**; **Poorly Differentiated Squamous Cell Carcinoma- Fig. 4**

Lymphovascular emboli was not seen in any of the cases neither in node positive cases and node negative cases.
Perineurial invasion was seen in 5 cases of Node Positive biopsy group compared to 1 case in node negative biopsy group. Perineurial invasion was statistically analyzed and was to be significant with a p value of 0.001 using Pearson Chi-square Test.(Table 2, Figure 5)

Table 2: Pearson chi-square test for perineurial invasion

Group	YES	NO	TOTAL
Positive	5(83.3%)	1(16.6%)	6(100%)
Negative	2(11.1%)	16(88.8%)	18(100%)
Total	7(29.1%)	17(70.8%)	24

P VALUE 0.001



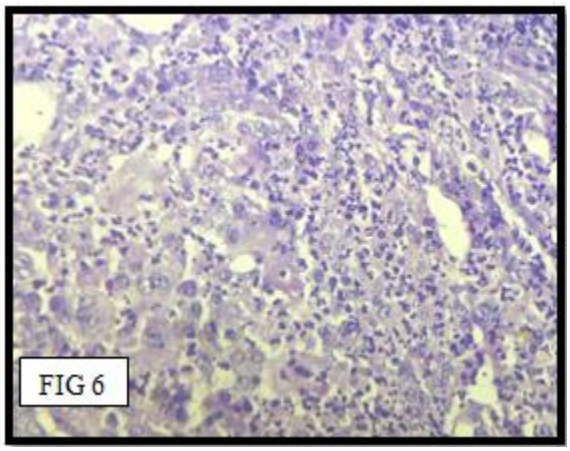


Fig. 5: Perineurial Invasion at 40x **Fig. 6 Dense inflammation at 40x**

Tumor infiltrating lymphocytes i.e. Host inflammatory response was found to be significant with a p value 0.01. Node negative cases have mild response in 4 cases, moderate response in 8 cases and severe response in 4 cases. Node positive cases have mild response in 5 cases and 1 case with moderate response and 1 case with no inflammatory response. Node negative cases were found to be significantly correlated with inflammatory response compared to node positive cases.(Table 3, FIGURE 6)

Table 3: Pearson chi-square test for tumor infiltrating lymphocytes

Group	Mild	Moderate	Severe	Not seen	Total
Positive	5(71.4%)	1(14.2%)	0(0%)	1(14.2%)	7(100%)
Negative	4(23.5%)	8(47%)	4(23.5%)	1(5.8%)	17(100%)
Total	9(37.5%)	9(37.5%)	4(16.6%)	2(8.3%)	24(100%)

P VALUE 0.01

Depth of invasion was not found to be significantly correlated with Node positive and node negative cases.(Table 4)

TABLE 4: Pearson chi-square test for depth of invasion

Group	0-5 mm	5-10mm	10-15mm	TOTAL
Positive	4(57.1%)	1(14.2%)	2(28.5%)	7(100%)
Negative	7(41.1%)	9(52.9%)	1(5.8%)	17(100%)
Total	11(45.8%)	10(41.6%)	3(12.5%)	24(100%)

P VALUE 0.25

The tumor front in positive node group was found to be pushing in 6 cases(46.1%), infiltrative front in 7 cases (53.8%) and in node negative group 11 cases was found to have pushing tumor front. None of the node negative cases have infiltrative front. Tumor invasive front was found to be significant using Pearson Chi Square test with P value 0.01 (Table 5)

TABLE 5: Pearson chi-square test for invasive front of tumor

Group	Pushing	Infiltrative	Total
Positive	06(46.1%)	07(53.8%)	13(100%)
Negative	11(100%)	0(0%)	11(100%)
Total	17(70.8%)	07(29.1%)	24(100%)

P VALUE

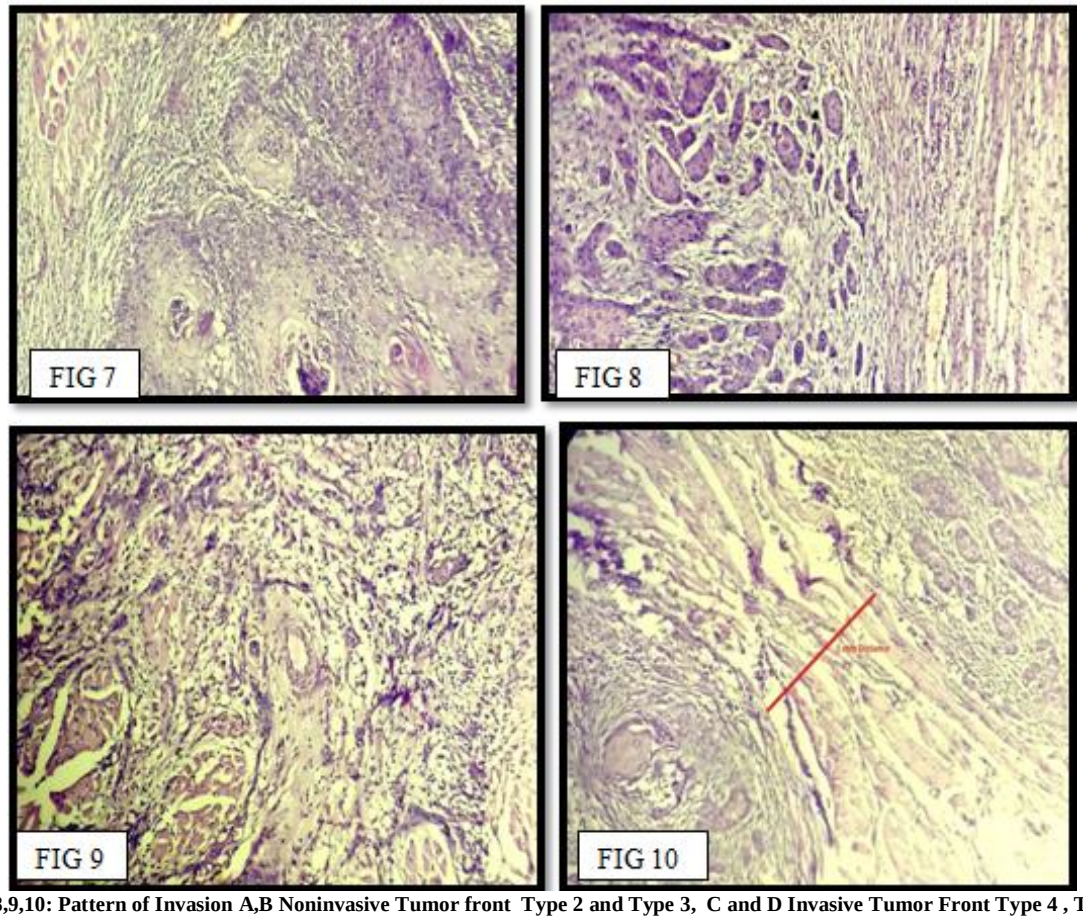


Fig.7,8,9,10: Pattern of Invasion A,B Noninvasive Tumor front Type 2 and Type 3, C and D Invasive Tumor Front Type 4 , Type 5

Discussion

Prevalence of Occult nodal metastasis depend primarily on tumor site. There are few studies regarding occult tumor metastasis to node[8]. In 2007 Blanco and chao explained prevalence of occult metastasis to neck: 60% Tongue cancer, 26% Floor of mouth,36% Tonsils, Retromolar trigone 20% and 15% Hard palate and alveolus respectively.

Many studies conform 5 year survival rate decreases by 50% once nodal metastasis is present. [9]

Presence of lymph node metastasis correlate with disease recurrence in primary site as well as with distant metastasis[10]. Hence detection of nodal metastasis imperative to maximize the potential of successful outcome.

The treatment protocol for positive nodal disease is well standardized but variations do exists in management of node negative cases. At present there is no accurate method to stage N0 cases as there is no clear agreement of occult nodal metastasis cases.

One approach is to treat 20% Occult nodal metastasis cases but in this way 80 % cases without metastasis needs to undergo neck dissection without benefit[4].

In our study a total of 24 cases of oral cavity cancers ,T1-T2 N0 included were subjected to modified neck node dissection. Various histological parameters such as tumor grade, Invading front, depth of tumor, Perineurial invasion and inflammatory response were assessed. The nodal status is correlated with histological parameters.

In this study, there were 15 cases of Grade I tumor, 8 cases of Grade II and One case of Grade III. Tumor grade was statistically analyzed between the positive and negative nodal group using Pearson Chi square test and was found to be not significant. The Percentage positive lymph node cases in grade I was 42.8%, in Grade II 57.1%nd 0 cases in Grade III 0%. The prognostic values of different grading classification were studied. Statistical analysis failed to detect any relationship between Broders grade and Lymph node metastasis[11].

The tumor front in the positive lymph node group was found to be invasive in all 7 node positive cases (100%) compared to node negative cases which have noninvasive front. So invasive tumor front was found to be strong predictor to asses occult nodal metastasis and found to be statiscally significant using Pearson Chi square test (Table 5)

Depth of invasion in positive lymph node group was distributed as 4 cases in 0-5mm , 1 case in 5-10mm and 2 cases with >10mm. In the node negative cases, maximum cases were in 5-10mm group. Therefore Depth of invasion was found to be statistically insignificant using Pearson Chi square test p value 0.25) However there are many studies which showed tumor thickness as strong predictor for occult nodal metastasis[12].

Perineurial invasion was seen in 71.4 % cases in positive lymph node group compared to 14.2 % in negative lymph node group. There was statistical significance using Pearson Chi square test with a p value 0.001 as summarized in table 2. Similar results were seen in many studies like in study by Fagan et al[13,14] where Perineurial invasion of small nerves effect the patient outcome with squamous cell carcinoma of upper aero digestive tract.

The inflammatory response in the positive node group was mild in 5 cases, moderate in 1 case and not seen in 1 case compared to node negative group which showed mild and severe response in 4 cases each. This tumor infiltrating lymphocyte parameter was found to be statistically significant using Pearson Chi square test with a p value of 0.01 shown i table 3. Hiratsuka et al performed univariate and multivariate analyses in their study for occult nodal metastasis . They found lymphocytic infiltrate to be one of the factor predicting occult nodal metastasis[15].

Effective management of patient of squamous cell carcinoma depends upon the accurate staging which in turn depends upon histology analyses of the resected specimen. The stage of the disease depends highly on the status of regional cervical lymph nodes at the risks of metastasis from the primary tumor.

Conclusion

Clinically evident cervical metastasis are found in approximately 30% of patients whereas occult nodal metastasis occur in 20-30% of patients without any evidence of regional disease. The accuracy of currently available means of detecting nodal disease such as radiology and imaging modalities has limitations. Therefore, histopathological assessment of the primary tumor specimen continues to provide information that is central to guide clinical management ,particularly in cases of occult nod al metastasis.

Conflict of Interest: Nil Source of support: Nil

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