

# Prognostic Significance of Lymph Node Pattern in Oral Squamous Cell Carcinoma (OSCC)

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## ABSTRACT

**Background:** Assessment of lymph node reactivity pattern is an important indicator of the host response status and prognosis of oral squamous cell carcinoma (OSCC).

**Aim:** To assess the prognostic significance of lymph node reactivity patterns in OSCC.

**Settings and Design:** This is a cross-sectional study aimed correlating host status and prognosis of OSCC.

**Materials and Method:** Morphological patterns of lymph nodes received from 30 histologically proven cases of OSCC were analyzed. Five different patterns of the lymph node reaction were categorized (lymphocytic predominance, germinal center predominance, sinus histiocytosis, normal lymph node and lymphocytic depleted) and compared with the prognosis of OSCC.

**Statistical Analysis Used:** TNM, Histological grading parameters and Lymph node reactivity pattern were compared with the event of recurrence of OSCC and death of patient using Fisher's Exact test. Survival of the patients was analyzed for association with lymph node patterns using Log rank test.

**Results:** Recurrence of the tumour was seen in association with all the patterns, with higher rates of mortality seen in patients with sinus histiocytosis of lymph node.

**Conclusion:** Morphological pattern being an aid in predicting prognosis, cannot be used as a lone predictor. An attempt is made to identify and discuss the possible pathogenesis for the reaction patterns.

**Keywords:** Lymphocytic predominance, Germinal center Predominance, Sinus histiocytosis, Lymphocytic depletion

## INTRODUCTION

The various systems used in grading of OSCC along with their various modification have stressed upon the host response, to the tumour as a vital prognosticator [1]. Metastasis is the innate tendency of malignancy. Tumour cells at the invasive front attain motility and are exposed to sustained stimulation to growth by the growth factors produced by itself (autocrine stimulation) or by the cancer associated peritumouralstroma leading to the migration and metastasis. The first line of defence/ tumour surveillance is the host response manifested as an inflammatory cell infiltrate [2]. We must remain cognizant that the origin of this host response is the reticulo-endothelial system, primarily from the series of lymph nodes which guard the human body. There exists a proven positive correlation of host immune system and prognosis of patients with malignant tumours [3]. The analysis of this interaction determines the tumour outcome [4]. Much in advance of the invasion of lymph nodes, the lymph node reacts to the numerous molecules produced by and in response to the tumour. Assessment of the patterns of reactivity of the lymph nodes is thus, a reliable method to evaluate the host immune status, as well as an indicator of, the potential of the cancer cells to invade. World Health Organization (1976) proposed a protocol for uniform assessment and reporting of lymph node reactivity patterns which were sub-categorised as Lymphocyte Predominance, Germinal Center Predominance, Mixed Pattern and Unstimulated Pattern [5].

The present study is aimed at the assessment of the regional lymph node status and its corresponding correlation with the prognosis of OSCC.

## MATERIALS AND METHODS

A total of 96 archival cases of OSCC with a three year follow-up were retrieved for the study. The selected cases satisfied the inclusion criteria of having margins free of tumour, no prior radiotherapy and a minimum follow-up of 3 years after surgery. Age, gender, TNM staging (UICC) were also noted from the patient records.

Lymph nodes from levels 1 to 3 (made available after neck dissection) were evaluated in each of the OSCC cases by taking 5 µm thick sections which were stained with routine Hematoxylin and Eosin (H& E). Lymph node reactivity patterns were established in accordance with a previous proposal for a standardized system of reporting human lymph node morphological characteristics in relation to immunological function given by WHO [5].

The patterns of lymph node reactivity were accordingly categorised as:

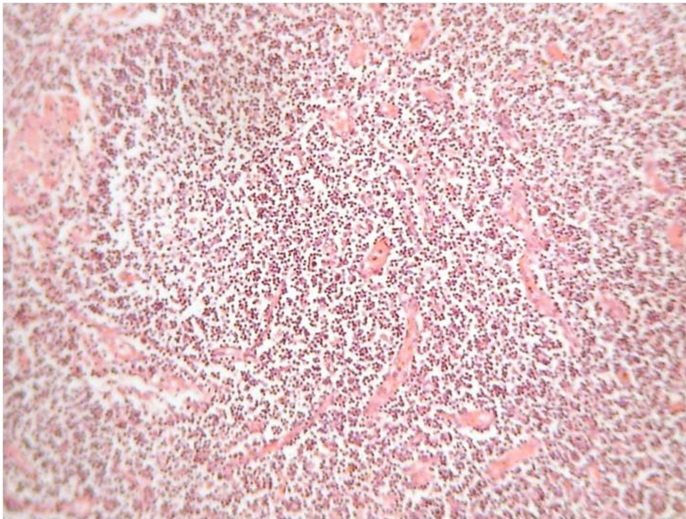
1. **Lymphocytic Predominance:** lymph node cortex showing lymphoid follicles without germinal centers and expanded paracortical area (with high endothelial blood vessels) [Table/Fig-1].
2. **Germinal Center Predominance:** lymph node cortex showing germinal centers with large lymphoid cells and mitotic figures [Table/Fig-2].
3. **Sinus Histiocytosis (SH):** lymph node with distended lymphatic sinuses. Sinuses are engorged with histiocytes [Table/Fig-3].
4. **Normal lymph node:** lymph node without any significant changes in architecture and cell distribution [Table/Fig-4].
5. **Lymphocytic depleted:** lymph node without germinal center showing depleted lymphocytes, fibrosis and hyalinized deposits [Table/Fig-5].

Lymph nodes showing more than one reactivity patterns were classified into the most predominant pattern present in the lymph node [4].

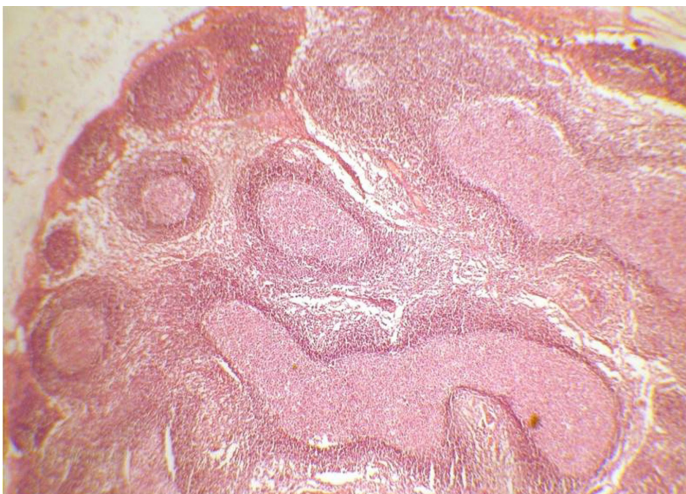
H&E-stained tissue sections of tumour proper were graded according to the "New Malignancy grading" given by Anneroth et al., and divided into 3 groups based on the total score [6].

## RESULTS

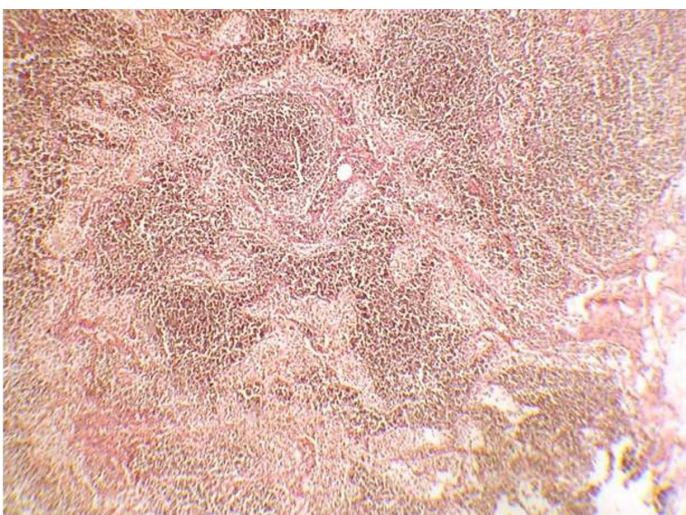
Of the 30 patients, 20 were male and 10 female. The age ranged from 28 to 80 years with an average of 55 years. Recurrence occurred in 13 patients resulting in the death of 5 of them. All the



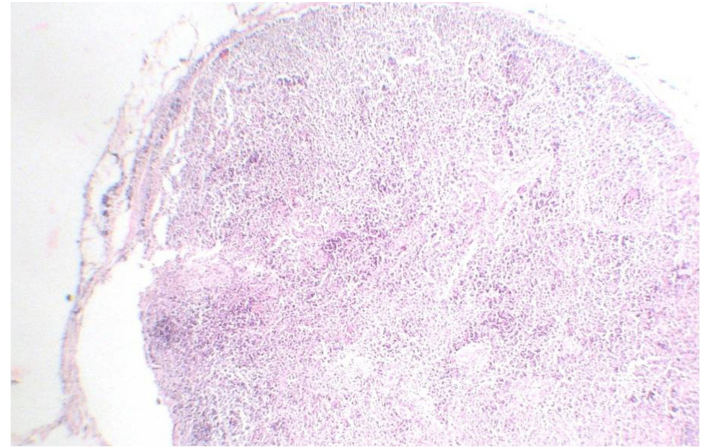
**[Table/Fig-1]:** Lymph node with High endothelial blood vessels (Lymphocytic predominance)



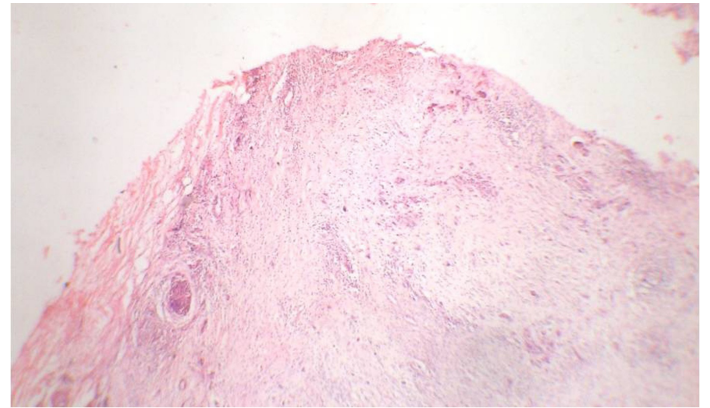
**[Table/Fig-2]:** Lymph node with Prominent germinal center (germinal center predominance)



**[Table/Fig-3]:** Lymph node with enlarged sinus with histiocytes (sinus histiocytosis)



**[Table/Fig-4]:** Normal lymph node



**[Table/Fig-5]:** Lymph node showing fibrosis (Lymphocytic depletion)

Among the 30 patients, 14 exhibited Germinal Center Predominance, 13 showed Lymphocytic Predominance and only 3 patients had Sinus Histiocytosis. Lymphocytic depletion and unstimulated lymph nodes were not found in any of our patients [Table/Fig-7 and 8]. No statistically significant value was derived, upon comparison of the observed morphological pattern of lymph node and recurrence and mortality of patients with OSCC. [Table/Fig-6 and 7] No significant value was observed when the lymph node pattern was correlated with tumour staging ( $p=0.802$ ) or grading ( $p=0.299$ ) [Table/Fig-9].

Conditional binary logistic regression analysis was performed to compare the event of recurrence with the lymph node pattern of all the available lymph nodes in various levels. GCP and LP showed the highest association with the event of recurrence with Odds ratio of 1.96 and 1.84, respectively, though it was not statistically significant [Table/Fig-10].

Patients with GCP and LP had a mean survival of 24 months and 23 months respectively, while those with SH had the least mean survival of 15 months. Log rank test performed to determine the survival rate showed an association of poor survival with sinus histiocytosis [Table/Fig-11].

## DISCUSSION

Regional lymph nodes are the first components of the immune system to react to tumour cells and their products. Microscopic examination of these draining lymph nodes is important to understand the immune system which controls the path and outcome of the malignant cells [7]. It is a well-known fact that patients exhibiting varied morphological patterns of lymph nodes have differing reactive response towards the tumour [1,4,8].

Among the various patterns of lymph node response, Germinal Center Predominance is considered thymus-independent and Lymphocytic Predominance and Sinus Histiocytosis are considered thymus-dependant [2]. In this series of 30 patients, 14 patients (46.7%) had Germinal Center Predominance, 13 patients (43.3%)

obtained data was tabulated and subjected to statistical analysis using SPSS software version 19.

The age and gender distribution of the various prognostic parameters are tabulated in [Table/Fig-6]. No significant difference was observed upon comparison of the tumour stage with event of recurrence or survival of patients. Grading of OSCC showed a statistically significant positive association only with the recurrence of tumour ( $p=0.041$ ) and not with the survival of the patients [Table/Fig-7 and 8].

had Lymphocytic Predominance and only 3 patients (10%) showed Sinus Histiocytosis, all of which increased from stage I to stage IV of the TNM stages. This indicates that the lymph node reactivity is good in most of the cases but in higher stages of tumour, the activity increases. This observation is well-supported by studies which observed germinal center predominance in the patients suffering from gastric carcinoma and Cernea et al., recorded 13 out of 30 patients with OSCC had GCP [4]. However, DiGiorgio et al., in their study observed more of Sinus Histiocytosis in patients suffering from lung cancer [7].

Parameter		Male (N=20)	Female (N=10)
Age	Mean age in years (standard deviation)	52.9 (12.949)	61.4 (10.069)
Recurrence	No recurrence	11	6
	Recurrence	9	4
Age	Mean time in months (standard deviation)	19.75 (14.52)	21.5 (15.981)
Lymph node Metastasis	Metastasis	11	7
	No metastasis	9	3
3 Year Survival	Alive	17	8
	Dead	3	2
Pattern of Lymph node	GCP	10	4
	LP	7	6
	SH	3	0
TNM	Stage I	1	1
	Stage II	3	0
	Stage III	4	6
	Stage IV	12	3

[Table/Fig-6]: Gender distribution among various parameters

Parameter		Recurrence free	Recurrence	Total %	Fishers exact value	P-Value
Staging	Stage I	1	1	6.7%	0.638	1.000
	Stage II	2	1	10.0%		
	Stage III	6	4	33.3%		
	Stage IV	8	7	50.0%		
Anneroth Grading	WELL	5	0	16.7%	5.175	0.041
	MODERATE	11	10	70.0%		
	POOR	1	3	13.3%		
Lymph Node Architecture	SH *	1	2	10.0%	1.137	0.663
	GCP †	9	5	46.7%		
	LP ‡	7	6	43.3%		

[Table/Fig-7]: Primary Tumour and Lymph Node Characteristics correlated with Recurrence

\* - sinus histiocytosis, † - Germinal center predominance, ‡ - Lymphocytic predominance

Parameter		Alive	Dead	Total %	Fishers exact value	p-value
Staging	Stage I	2	0	6.7%	0.888	1.000
	Stage II	3	0	10.0%		
	Stage III	8	2	33.3%		
	Stage IV	12	3	50.0%		
Anneroth Grading	WELL	5	0	16.7%	1.526	0.435
	MODERATE	16	5	70.0%		
	POOR	4	0	13.3%		
Lymph Node Architecture	SH	2	1	10.0%	1.173	0.618
	GCP	12	2	46.7%		
	LP	11	2	43.3%		

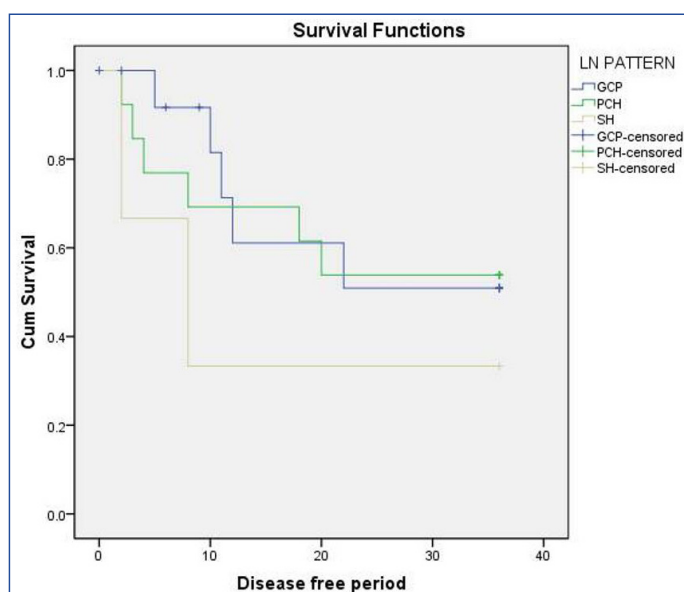
[Table/Fig-8]: Primary Tumour and Lymph Node Characteristics correlated with survival

Lymph node pattern		GCP	LP	SH	Fisher exact test value	p-value
Staging	Stage I	1	1	0	3.887	0.802
	Stage II	1	1	1		
	Stage III	5	5	0		
	Stage IV	7	6	2		
grading	Well	2	3	0	4.479	0.299
	Moderately	9	10	2		
	Poorly	3	0	1		

[Table/Fig-9]: Comparison of lymph node pattern with staging and grading

	Odds ratio	95% C.I.for EXP(B)		Sig.	adjusted odds ratio	95% C.I.for EXP(B)		Sig.
		Lower	Upper			Lower	Upper	
GCP	1.667	0.388	7.153	0.492	1.960	0.389	9.883	0.415
LP	1.500	0.325	6.918	0.603	1.844	0.310	10.967	0.501
SH	0.714	0.119	4.297	0.713	1.086	0.136	8.658	0.938

[Table/Fig-10]: Comparison of prevalence of lymph node pattern with recurrence



[Table/Fig-11]: Overall survival of the patient (Log rank test)

The results obtained by us and therefore mentioned researchers may not seem to be in direct agreement owing to the differential reactivity of lymph nodes at each anatomical region and level (even in the same individual) and therefore at greater distance from the inciting stimulus/tumour antigens/tumour metabolic products. Thus, it is prudent to observe the reactivity of all the nodes received from the patients. It is appropriate to state that the pattern of the sentinel node draining the site of the OSCC might be the best prognosticator.

Binary logistic regression analysis revealed that GCP and LP occurred twice more commonly in patient with recurrence (Odds ratio 1.96). [Table/Fig-4] Patients with GCP and LP have 1.9 times and 1.8 times respectively greater chances of exhibiting recurrence. These results echo those obtained by Manfro et al., (2010) [9] and indicate that GCP and LP are the best patterns of reactivity exhibited to the tumour which shows infiltrative and invasive pattern. The infiltrative tumour may interact with the stroma with the release of factors/antigens/proteins (either by the tumour or the stroma) which are able to traverse to the respective lymph nodes and cause these reactivity patterns.

In the present analysis, patients with recurrence of tumour had predominantly GCP and LP. This indicates that these tumour clones have reached the lymph node causing reactivity thus, GCP and LP, are good indicators of proximity to lymph nodes indicating worst prognosis.

The mean survival period of patients with OSCC who exhibited GCP and LP was noted to be higher (24 and 23 months respectively) than those with SH of lymph nodes (15 months). Likewise, the former groups also displayed a better overall prognosis in relation to mortality, findings substantiated by studies by Bennet et al., [1] (larynx or hypopharynx carcinoma), Cernea et al., (oral squamous cell carcinoma) and Tsakraklides et al., (cervical carcinoma) [1,4,8]. It can be interpreted in two ways, either the tumour is a silent progressor, meaning it invades without leaving any protein or antigenic foot prints, thus showing low reactivity or the host has weak immunity, thus not exhibiting reactivity (GCP or LP).

The present observation can be explained by the fact that lymph nodes with lymphocytic predominance pattern may reflect an active cell-mediated immune response [3,9]. Germinal centers formed in lymph nodes with Germinal Center Predominance indicate a humoral response to antigenic stimuli that is largely related to the production of plasma cells and humoral antibodies. These mechanisms may ward off tumour distant to the lymph nodes [3, 9]. Both type of lymph node reactivity showed to be a better prognostic factor [7].

There have been conflicting reports pertaining to prognostic value of sinus histiocytosis in lymph node of patients with gastric carcinoma, breast carcinoma and OSCC [10,11]. In the present study, patients exhibiting sinus histiocytosis in their lymph nodes had a poor prognosis with mean survival of 15 months. Similar results were obtained by Cernea et al., in oral squamous cell carcinoma, Bennet et al., in larynx or hypo pharynx carcinoma and Tsakraklides et al., in cervical carcinoma [1,4,8].

SH has a predominance of macrophages and histiocytes, not specific to any type of immune response. A school of thought suggests that accumulation of macrophages in sinus histiocytosis was thought to ward off tumour and was believed to be the first morphological response of the host immune system against the tumour [12,13]. Nagata et al., (2004) in an experimental study of reactivity patterns in carcinoma induced in rats showed that follicular hyperplasia and lymphocyte proliferation were induced earlier than sinus histiocytosis in response to carcinoma [12]. This evidence that sinus histiocytosis develops only during the late stages of tumour growth in experimental animals, supports the fact that the presence of SH indicates more advanced stage of carcinoma thus correlating with the poorer patient prognosis [1, 12].

Attempt to derive an association between the pattern of lymph node reactivity and the recurrence of the tumour, showed a very homogeneous distribution between the types of reactivity, having no statistically significant association in this analysis. Presence of sinus histiocytosis indicate poor prognosis in patients with OSCC.

The morphological and immunological patterns of lymphocyte predominance and sinus histiocytosis, are known to reflect the active response of the thymus-dependent cells linked to cellular immunity. The pattern of germinal center predominance, indicates an active response in the thymus-independent germinal centers related to humoral immunity. Thus, the reactivity patterns indicate the immune status of the patient. This also helps us predict the susceptibility of

the patient to lymph node metastasis which has worse prognosis with lower 5-year survival. Secondary chemo or radiation therapy could be planned following the primary surgical excision, in case predominantly lymphocyte depleted or sinus histiocytosis pattern is present [14].

## CONCLUSION

Patients with lymph node showing germinal center predominance and lymphocytic predominance have a better overall survival rate compared to nodes exhibiting sinus histiocytosis owing to better immune responses. Presence of Sinus histiocytosis may indicate a more advanced stage of carcinoma or complete lack of immune stimulation thus having a fatal outcome. This fact emphasizes the need for earlier detection of the tumours showing preponderance to metastasis. The histopathological lymph node pattern may serve as a surrogate marker in predicting the metastasis and survival of the patients.

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