

# Evaluation of immunomorphological patterns of cervical lymph nodes in oral squamous cell carcinoma

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## Abstract

**Background:** The Immunomorphological patterns of Lymph Nodes indirectly assess the host immune response facing a malignant tumor. These patterns also help us predict the susceptibility of the patient to Lymph Node Metastasis.

**Aims and Objectives:** To evaluate the Immunomorphological patterns of Lymph Nodes in Oral Squamous Cell Carcinoma and to correlate them with the histopathological subtype of Oral Squamous Cell Carcinoma, TNM staging and the degree of tumor involvement within the Lymph Nodes.

**Methodology:** A total of 40 subjects were taken for the study. Individuals who were clinically and histopathologically diagnosed as cases of Squamous Cell Carcinoma, who had undergone Radical or Elective Neck dissection were considered. The excised Lymph Nodes along with the primary tumor were collected stained with Hematoxylin and Eosin. The Lymph Nodes were assessed for Metastasis and Immunomorphological patterns. Statistical Correlation was done between the Immunomorphological pattern of Lymph Nodes and (a) Size of the tumor, (b) TNM stage of the tumor, (c) Histopathological Grade of the primary tumor, (d) Metastasis of the Lymph Node and (e) Grade of the Metastasis of Lymph Node. Statistical Correlation was done between the Metastasis of the Lymph Node and (a) Size of the tumor and (b) TNM stage of the tumor.

**Results and Conclusion:** Statistically, a significant association was observed between TNM staging and Immunomorphological patterns of Lymph Node ( $P < 0.01$ ). The relationship between histopathological grade of primary tumor of Squamous Cell Carcinoma and the Immunomorphological patterns was statistically significant ( $P < 0.01$ ). Statistically, a significant association was observed between Sinus Histiocytosis pattern and decreased occurrence of nodal metastasis ( $P < 0.01$ ).

**Keywords:** Immunomorphological patterns, lymph node, metastasis, oral squamous cell carcinoma, tumor node metastasis staging

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## INTRODUCTION

Squamous cell carcinoma (SCC) accounts for more than 90% of oral malignancies.<sup>[1]</sup> The incidence of oral

SCC (OSCC) differs widely in various parts of the world and ranges from 2 to 10/100,000 persons per year. It forms about 45% of all cancers in India.<sup>[2]</sup>

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The origin of this host response against the tumor is the reticuloendothelial system, primarily, the lymph nodes which constitute the primary immune monitoring of the body. The first line of tumor surveillance is the host response manifested in the form of inflammatory cell infiltrate.<sup>[3]</sup> The correlation of host immune system and prognosis of patients with malignant tumors is proven.<sup>[4]</sup> The analysis of this interaction determines the tumor outcome.<sup>[5]</sup> The assessment of the immunomorphological patterns of lymph node is thus, a reliable method to evaluate the host immune status.

Immunomorphological patterns of lymph nodes were established following a previous proposal for a standardized system of reporting human lymph node morphological characteristics in relation to immunological function given by the World Health Organization (WHO). Furthermore, it has been recognized that the microscopic pattern of a regional lymph node can be represented as an indicator of the immunologic reactivity in that node.<sup>[6]</sup> The immunohistological patterns of lymph nodes indirectly assess host immune response facing a malignant tumor. These patterns also help us to predict the susceptibility of the patient to lymph node metastasis.<sup>[7]</sup>

Metastasis is an innate tendency of malignancy.<sup>[8]</sup> Lymphatic metastasis is one of the most important mechanisms in the spread of head and neck SCC and is the primary determinant of the stage of the tumor. The incidence of lymph node metastasis depends mainly on the size and site of the primary tumor. Survival decreases by 50%, with the presence of regional lymphadenopathy.<sup>[6]</sup>

Few studies are describing the immunomorphological patterns of lymph nodes in OSCC.<sup>[9]</sup> This study is an attempt to document the immunomorphological patterns of the draining cervical lymph nodes, the extent and pattern of metastatic deposits of malignant cells and to correlate them with the clinical findings as well as the histopathology of the primary tumor. Increase in the size of the tumor, higher grade and stage are likely to show a decrease in a number of reactive lymph nodes and increase in number of metastatic lymph nodes.<sup>[8]</sup>

The assessment of immunomorphological patterns of lymph nodes would help to elucidate the immunological host-tumor relationship and provide additional information on patient prognosis by helping in earlier detection of tumors showing preponderance to metastasis.

### Aim of the study

This study aims to evaluate the immunohistological patterns of cervical lymph nodes in OSCC and to

correlate them with tumor node metastasis (TNM) staging, histopathological subtype of OSCC, and the degree of tumor involvement within the lymph nodes.

### METHODOLOGY

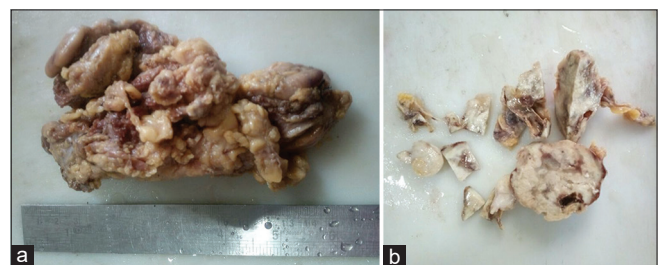
A total of 40 individuals were considered for the study. The sole selection criterion was excision cases of diagnosed primary OSCC with radical or elective neck dissection. Detailed clinical history was taken from the patients with ulcers or ulceroproliferative lesion visiting the oral medicine and radiology department and peripheral cancer hospitals in and around Visakhapatnam. The American Joint Committee on Cancer/Union for International Cancer Control, TNM staging system for OSCC is based on primary tumor size (T); quantification of nodal metastases according to size, number and distribution (N); and the presence of distant metastases (M). TNM Classification was used for the clinical staging of OSCC. A biopsy was done to confirm the diagnosis.

For each case, the slide containing the primary tumor was used for histopathological grading, and each case was graded according to Broder's classification.

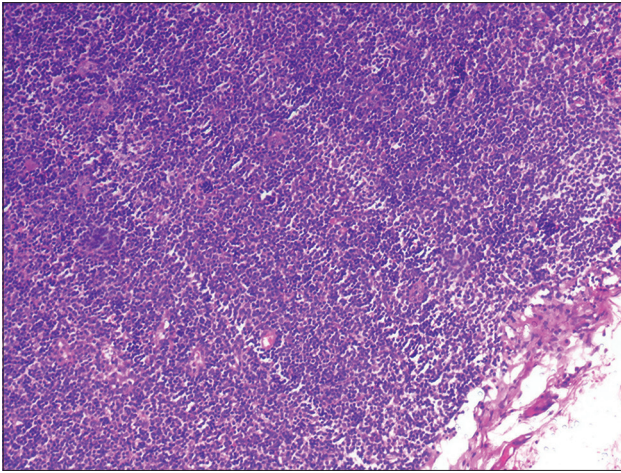
Patients were referred to the surgical oncology departments of peripheral cancer hospitals in and around Visakhapatnam for radical or modified neck dissection with the consultation of surgical oncologist. The excised lymph nodes [Figure 1] along with the primary tumor were collected from the surgical oncology department of peripheral cancer hospitals in and around Visakhapatnam after obtaining ethical clearance from the institution and written consent from the patient.

Lymph nodes and primary tumor were evaluated in each of the cases of diagnosed OSCC by fixing in 10% formalin, processing and preparation of paraffin blocks. Then, 4  $\mu$ m thick sections were done and stained with routine Hematoxylin and Eosin.

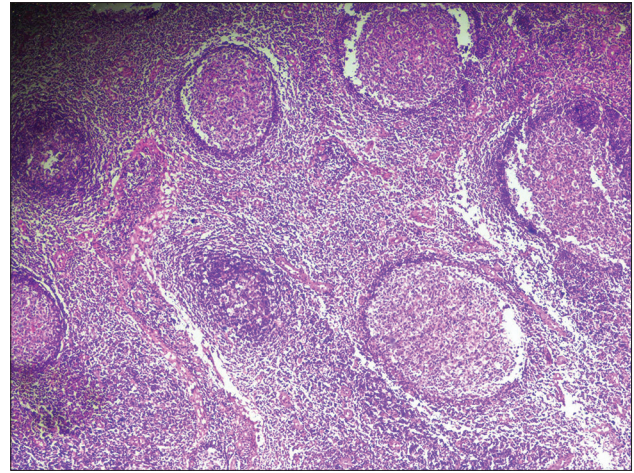
Immunomorphological patterns of lymph nodes were established in accordance with a previous proposal for



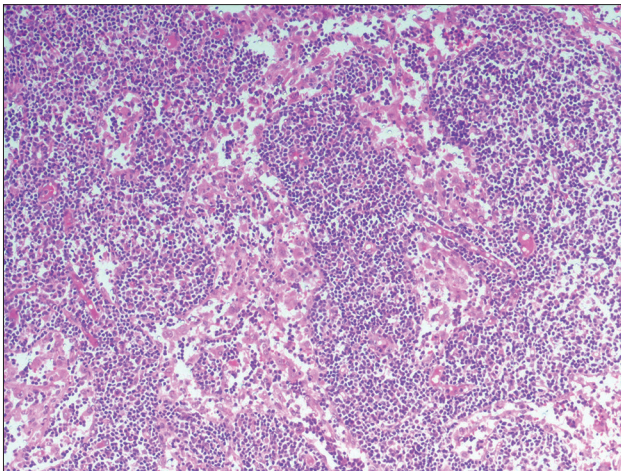
**Figure 1:** (a) Grossing images of excised lymph nodes. (b) Separated lymph nodes



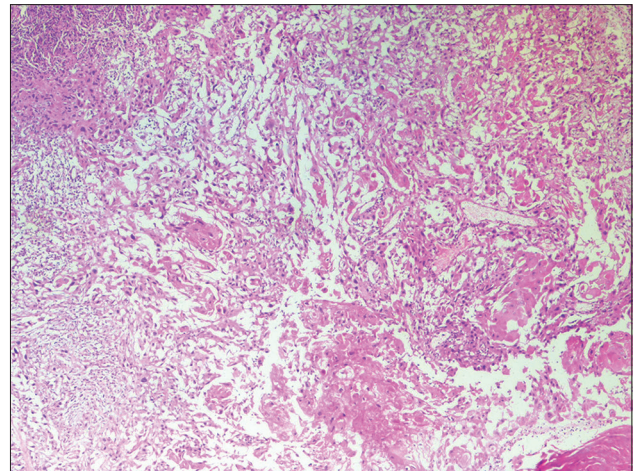
**Figure 2:** Lymphocyte predominance pattern (x10 view)



**Figure 3:** Germinal center predominance pattern (x10 view)



**Figure 4:** Sinus histiocytosis pattern (x10 view)



**Figure 5:** Lymphocyte-depleted pattern (x10 view)

a standardized system of reporting human lymph nodes morphological characteristics in relation to immunological function given by the WHO.<sup>[5,10]</sup>

The patterns of lymph nodes reactivity were accordingly categorized as:

1. Lymphocytic predominance [Figure 2]
2. Germinal center predominance [Figure 3]
3. Sinus histiocytosis [Figure 4]
4. Lymphocytic depleted [Figure 5]
5. Unstimulated lymph node.

Lymph nodes showing more than one reactivity patterns were classified into the most predominant pattern present within the lymph nodes.

The observation was carried out for the presence or absence of metastasis within the nodes. The degrees of tumor involvement within the lymph nodes were evaluated using the following grading system.

- Grade 1: Micrometastasis
- Grade 2: <50% involvement [Figure 6]
- Grade 3: >50% involvement [Figure 7]
- Grade 4: Extracapsular spread [Figure 8].

Statistical analysis was done for the following parameters.

Correlation was done between the immunomorphological pattern of lymph nodes and

- Size of the tumor
- TNM stage of the tumor
- Histopathological grade of the primary tumor
- Metastasis of the lymph nodes
- Grade of the metastasis of lymph nodes.

## RESULTS

The present study showed a maximum number of OSCC cases in 4, 5, and 6<sup>th</sup> decades. In this study, 92.5% of the patients were in the age group range of 40–69 years, indicating a trend toward an increase in the incidence

of the malignancy in older age group. The present study observed the occurrence of OSCC predominantly in males (55%) compared to females (45%). The increased occurrence of OSCC in men could be attributed to the

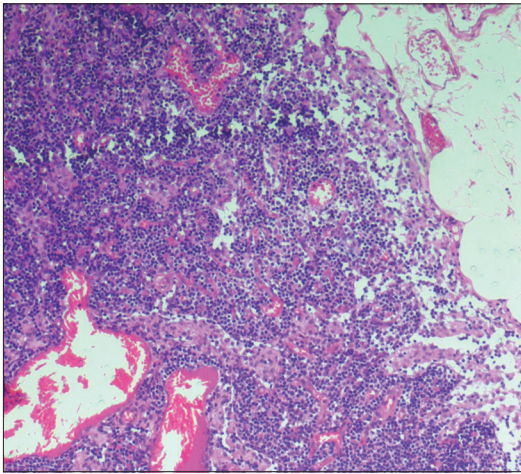


Figure 6: Grade 2 metastasis of lymph node (x10 view)

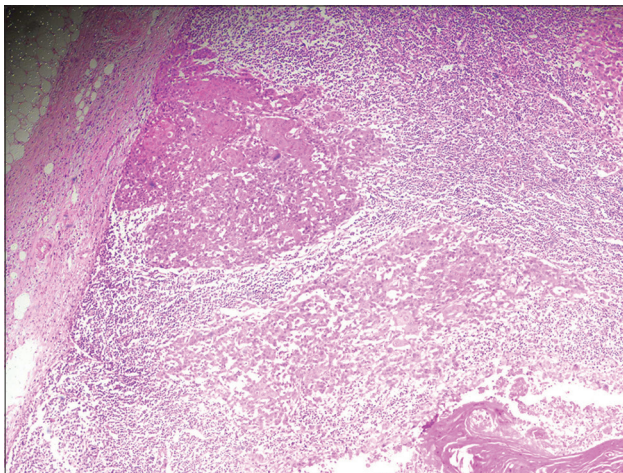


Figure 7: Grade 3 metastasis of lymph node (x10 view)

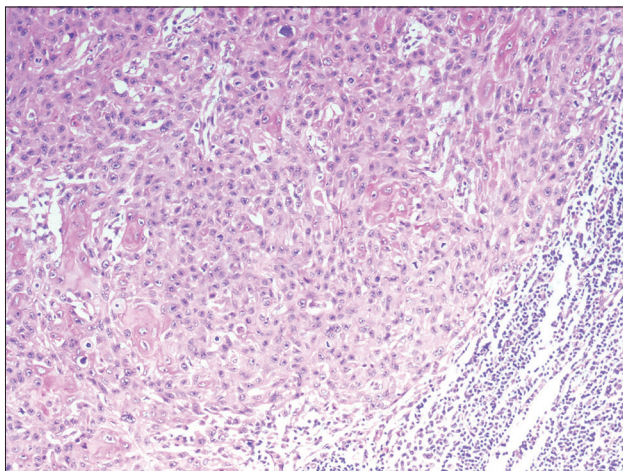


Figure 8: Grade 4 metastasis of lymph node (x20 view)

high consumption of tobacco. Regarding the distribution of site in this study, the highest number of cases were observed in the palate (35%) followed by tongue (30%), buccal mucosa (25%), the floor of the mouth (7.5%) and lip (2.5%). Based on the clinical staging of OSCC (TNM Staging), the highest number of cases were observed in Stage 2 (50%), followed by Stage 3 (27.5%) and Stage 1 constituted 22.5%. In this study population, well-differentiated SCC, moderately differentiated SCC and poorly differentiated SCC accounted for 42.5%, 30% and 27.5%, respectively.

In the lymph nodes exhibiting immunomorphological patterns, 166 lymph nodes showed lymphocyte predominance pattern (38.43%). One hundred and twenty-two lymph nodes exhibited germinal center predominance pattern (28.24%). One hundred and twenty-five lymph nodes showed sinus histiocytosis pattern (28.93%). Lymph nodes exhibited lymphocyte depleted pattern (4.40%).

Of a total number of 40 cases, 40% exhibited lymphocyte predominance, 30% exhibited germinal center predominance and 30% exhibited sinus histiocytosis pattern.

Of 40 cases of OSCC, 17 cases (42.5%) exhibited cervical lymph node metastasis. In this present study, out of a total number of 432 lymph nodes from 40 individuals, only 15.5% exhibited nodal metastasis. The number of lymph nodes that exhibited Grade 2 metastasis was 39; Grade 3 metastasis was 23 and Grade 4 metastasis was 5 which accounted for 58.21%, 34.33% and 7.46%, respectively.

In this present study, lymphocyte predominance pattern was highest in the cases of size <2 cm. Sinus histiocytosis pattern was greater in the cases of size between 2 cm and 4 cm. Germinal center predominance pattern was higher in the cases of size more than 4 cm. Statistically, a significant association was observed [Table 1].

Lymphocyte predominance pattern is highest in the cases of TNM Stage 1 of OSCC. Sinus histiocytosis pattern is highest in the cases of TNM Stage 2 of

Table 1: Statistical association between size and immunomorphological pattern

Size	LP (%)	GCP (%)	SH (%)	LD (%)	US (%)	Total (%)
2 cm or <2 cm	8 (50)	1 (8)	0 (0)	0 (0)	0 (0)	9 (23)
>2 cm but <4 cm	3 (19)	5 (42)	12 (100)	0 (0)	0 (0)	20 (50)
>4 cm	5 (31)	6 (50)	0 (0)	0 (0)	0 (0)	11 (28)

$\chi^2$ : 24.03,  $P < 0.01$  (highly significant). LP: Lymphocytic predominance, GCP: Germinal Center Predominance, SH: Sinus Histiocytosis, LD: Lymphocytic Depleted, US: Unstimulated

OSCC. Germinal Center Predominance is highest in the cases of Stage 3 of OSCC. Statistical analysis was done using the Chi-square test. *P* value was <0.01. The association between TNM stage of the primary tumor and the immunomorphological patterns was statistically significant [Table 2].

Lymphocyte predominance pattern was highest in cases of well-differentiated SCC. Germinal center predominance pattern was highest in cases of poorly differentiated SCC. Sinus histiocytosis pattern was highest in cases of moderately differentiated SCC. The association between histopathological grade of the primary tumor of SCC and Immunomorphological pattern was statistically significant [Table 3].

A statistical correlation was done between individual immunomorphological pattern and metastasis of lymph node [Table 4 and Graph 1]. In 16 cases with lymphocyte predominance, only five cases exhibited nodal metastasis [Figure 9].

In 12 cases with germinal center predominance, 9 cases exhibited nodal metastasis. Statistical analysis was done,

**Table 2: Statistical association between tumor-node-metastasis staging and immunomorphological pattern**

Stages	LP (%)	GCP (%)	SH (%)	LD (%)	US (%)	Total (%)
Stage 1	8 (50)	1 (8)	0 (0)	0 (0)	0 (0)	9 (23)
Stage 2	3 (19)	5 (42)	12 (100)	0 (0)	0 (0)	20 (50)
Stage 3	5 (31)	6 (50)	0 (0)	0 (0)	0 (0)	11 (28)
Stage 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

$\chi^2$ : 24.03, *P*<0.01 (highly significant). LP: Lymphocytic predominance, GCP: Germinal center predominance, SH: Sinus histiocytosis, LD: Lymphocytic depleted, US: Unstimulated

**Table 3: Statistical association between histopathological grade of primary tumor and immunomorphological pattern**

Grading	LP (%)	GCP (%)	SH (%)	LD (%)	Us (%)
Well	16 (100)	1 (8)	0 (0)	0 (0)	0 (0)
Moderately	0 (0)	0 (0)	12 (100)	0 (0)	0 (0)
Poorly	0 (0)	11 (92)	0 (0)	0 (0)	0 (0)
T	16 (100)	12 (100)	12 (100)	0 (100)	0 (100)

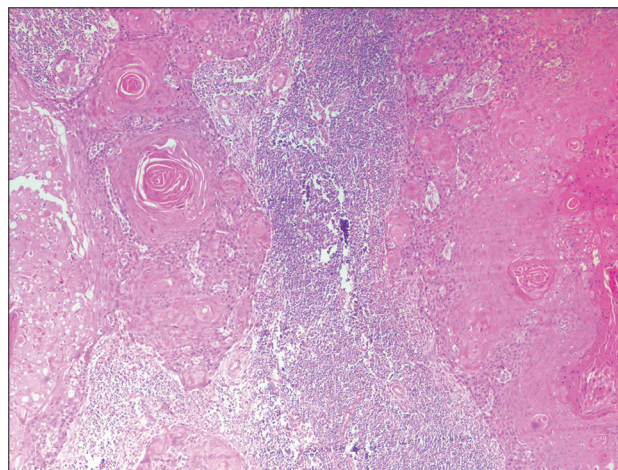
$\chi^2$ : 74.51, *P*<0.01 (highly significant). LP: Lymphocytic predominance, GCP: Germinal center predominance, SH: Sinus histiocytosis, LD: Lymphocytic depleted, US: Unstimulated

**Table 4: Statistical association between immunomorphological pattern and metastasis of lymph node**

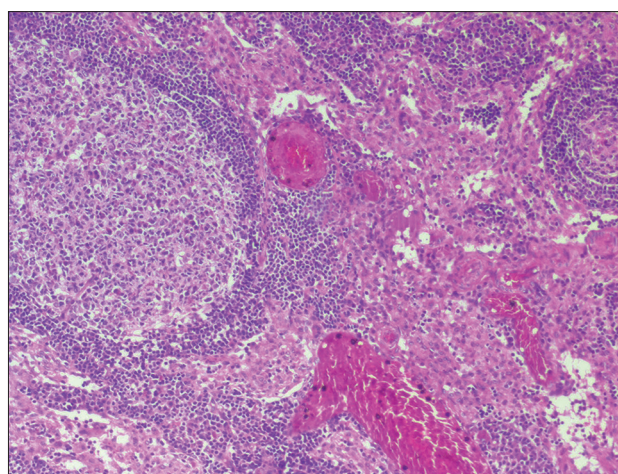
Pattern	Metastasis (%)	Nonmetastasis (%)	<i>P</i>
LP	5 (29.41)	11 (47.83)	0.240
GCP	9 (52.94)	3 (13.04)	0.140
SH	3 (17.65)	9 (39.13)	0.000
LD	0	0	-
US	0	0	-
Total	17 (100.00)	23 (100.00)	

LP: Lymphocytic predominance, GCP: Germinal Center Predominance, SH: Sinus Histiocytosis, LD: Lymphocytic Depleted, US: Unstimulated

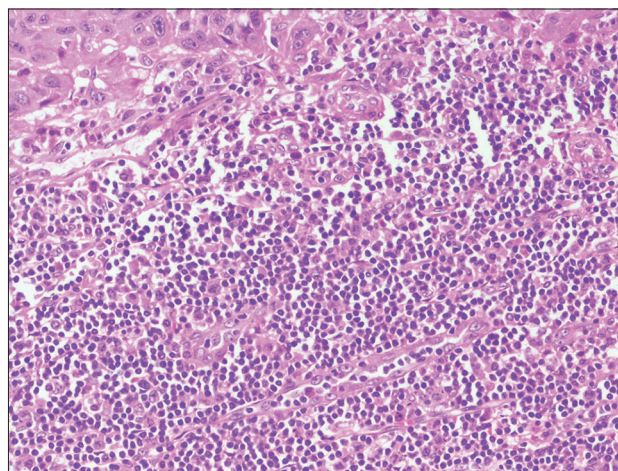
revealing a nonsignificant association between germinal center predominance and occurrence of nodal metastasis [Figure 10].



**Figure 9:** Lymphocyte predominance and metastasis (x10 view)



**Figure 10:** Germinal center predominance and metastasis (x20 view)

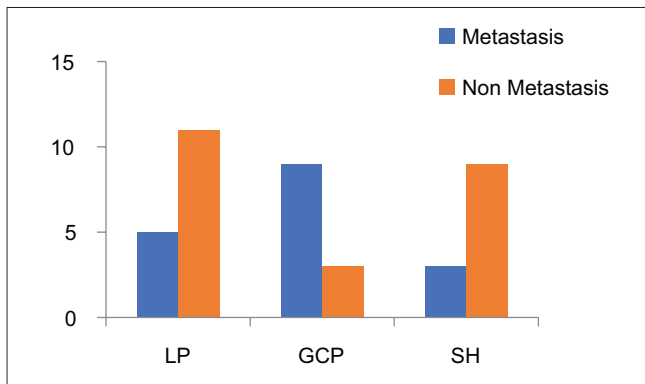


**Figure 11:** Sinus histiocytosis and metastasis (x20 view)

**Table 5: Immunomorphological pattern and grade of lymph node metastasis**

Metastasis grade	LP	GCP	SH	LD
Grade 1	0	0	0	0
Grade 2	15	21	3	0
Grade 3	8	15	0	0
Grade 4	0	5	0	0

$\chi^2$ : 5.70,  $P=0.22$  NS. NS: Not significant, LP: Lymphocytic predominance, GCP: Germinal Center Predominance, SH: Sinus Histiocytosis, LD: Lymphocytic Depleted



**Graph 1: Immunomorphological pattern and metastasis of lymph node**

In 12 cases with sinus histiocytosis, only 3 cases exhibited metastasis [Figure 11]. Statistical analysis was done, revealing a significant association between sinus histiocytosis pattern and occurrence of nodal metastasis.

In this study, a statistical correlation was done between immunomorphological pattern and grade of lymph node metastasis [Table 5]. Grade 1 Metastasis was not observed in this study. In cases exhibiting Grade 2 Metastasis, the majority were of germinal center predominance followed by lymphocyte predominance and sinus histiocytosis, respectively. In cases showing Grade 3 metastasis, the majority were of germinal center predominance followed by lymphocyte predominance. Cases exhibiting Grade 4 were entirely germinal center predominance. Statistical analysis revealed no significant association between grade of metastasis and the immunomorphological pattern shown by the lymph node.

## DISCUSSION

The prognosis of OSCC is hard to predict, despite the diagnosis and therapeutic progress in the field of oncology. Currently, almost half of the patients affected die within the first 2 years of diagnosis. There are various factors which influence prognosis such as patient factors (age and gender) and tumor factors (size, site, histopathological grade and metastasis). Among all the factors, the development of lymphatic metastasis is considered as the single most

important factor influencing the outcome of the patient with OSCC. The 5-year survival rate of patients with SCC of the upper aerodigestive tract is reduced by almost 50% with the development of cervical metastases.<sup>[9]</sup>

The development of head and neck SCC is strongly influenced by the immune system of the host. In the 1950s, Burnet and Thomas proposed the concept of immune surveillance of cancer.<sup>[11]</sup>

Regional lymph nodes in OSCC are considered as vital organs participating in the primary immunological defense mechanism against tumors. The most decisive evidence of the existence of an immune response in the lymph nodes that drain the tumor is the increase in size as a consequence of the increase in the number of lymphoid cells, indicating the immunity as a host defense mechanism. These changes of cellular organization within a draining lymph node suggest altered immune status and a possible defense mechanism on the part of the host.<sup>[12]</sup>

T-cell response characterizes lymphocyte predominance pattern. The pattern is the reaction of changes relate germinal center predominance pattern is characterized by efficient B-cell response and hyperplasia of germinal centers.<sup>[13]</sup> The accumulation of macrophages in sinus histiocytosis pattern was thought to ward off the tumor and was the first morphological response of the host immune system toward the tumor.<sup>[14]</sup> A predominance of sinuses distinguishes the histological pattern of sinus histiocytosis, which can occur in isolation or together with lymphocyte predominance and germinal center predominance patterns.<sup>[10]</sup> Lymphocyte-depleted pattern includes lymph nodes without germinal centers showing depleted lymphocytes, fibrosis and hyalinized deposits.<sup>[15]</sup>

Invasion and metastasis are the most insidious and life-threatening aspects of cancer. The involvement of lymph nodes by metastasis indicates that, through the succession of molecular changes, the neoplastic cells have acquired phenotypes that enable them to invade, colonize and disseminate. OSCC is typically diagnosed at advanced stages with evident locoregional and distant metastases. The prevalence of metastatic lesions directly correlates with poor patient outcome, resulting in high patient mortality rates after metastasis.

For most carcinomas, transport of cancer cells through lymphatic vessels is the most common pathway, following routes of natural drainage, because the lymphatic system seems to have more advantages over blood circulation for

cancer dissemination. The cytoplasm of the endothelium of the lymphatic vessels is highly attenuated. Fewer tight junctions are observed in the endothelium of lymphatic vessels than that of blood vessels, and this may be the cause of their greater permeability.<sup>[16]</sup>

With tumor progression, cancer cells secrete lymphangiogenic cytokines, which result in the formation of lymphatic vessels around or within the tumor. Then, the cancer cells dissociate from the primary tumor and invade the extracellular matrix. Following the chemotactic gradient of chemokines in tissue, cancer cells move toward lymphatic vessels. After attaching to lymphatic endothelium, they cross the endothelial cell barrier and enter into the lymphatic lumen. Then, the cancers cells in lymphatic vessels, singly or clusters, are drained into sentinel lymph nodes within the lymphatic stream.<sup>[17]</sup>

Statistical correlation was done between individual immunomorphological pattern and metastasis of lymph node, revealing a nonsignificant association between lymphocyte predominance and occurrence of nodal metastasis. In consistency with our findings, Berlinger *et al.* found that the lymphocyte predominance pattern experienced less incidence of metastases, i.e., 31% in their study on patients with head and neck carcinoma.<sup>[18]</sup> They attributed this to the lymphoblastic activity which occurred in the deep cortex.

In this study, it was found that humoral immunity, as evidenced by germinal center predominance, facilitated nodal invasion. The exact mechanism by which humoral immunity promotes nodal invasion is unclear. The appearance of a humoral immune response may favor the metastatic spread through the lymph nodes by blocking or inhibiting the histiocytes and T-lymphocyte cytotoxic activity.<sup>[19]</sup> Raj *et al.*<sup>[20]</sup> found that patients with recurrence of the tumor had germinal center predominance pattern, which indicated that neoplastic cells had reached the lymph node indicating a worse prognosis. In the study conducted by Yadav *et al.*,<sup>[5]</sup> it was found that metastases to the cervical lymph node occurred twice more frequently in patients showing germinal center predominance than in patients with lymphocyte predominance pattern, where they observed a statistically significant association. Tsakraklides *et al.* observed the same results, in their study on patients with cervical and breast cancer<sup>[21,22]</sup> and Di Giorgio *et al.*, in their study on lung carcinoma.<sup>[23]</sup> Similar observations were made by Cernea C *et al.* in patients with pathologic negative node squamous cell carcinomas of the oral cavity.<sup>[24]</sup> Di Giorgio hypothesized that, “Cellular immune activity may prevent Lymph Node invasion, whereas, the humoral

response may facilitate metastases” in patients with lung carcinoma.<sup>[23]</sup> This hypothesis was also supported by other studies by Tosi *et al.*, in bronchogenic carcinoma and Hunter *et al.* in mammary carcinoma. The relation between the development of a humoral response and lymph node metastatic growth remains unclear. Nevertheless, the appearance of a humoral immune response seems to favor the metastatic spread through the lymph nodes by block or inhibition of the histiocytes and T-lymphocyte cytotoxic activity, which indicates cellular response against tumor cells.<sup>[5]</sup>

Statistical analysis revealed a significant association between sinus histiocytosis pattern and occurrence of nodal metastasis. In the study conducted by Yadav *et al.*,<sup>[5]</sup> lower percentage of metastases was associated with sinus histiocytosis pattern, which was statistically not significant. This study results correlated with other studies done by Patt *et al.*, in laryngeal Carcinoma,<sup>[25]</sup> Silverberg *et al.*, in mammary Carcinoma<sup>[26]</sup> and Tosi *et al.*, in lung carcinoma.<sup>[27]</sup>

In most of the studies, lymph node immunoreactivity was correlated with the survival of the patient, but in this present study, the survival rate was not taken into consideration due to inconsistent follow-up and short duration.

The cases with unstimulated pattern and lymphocyte depleted pattern as the predominant pattern were not observed in any of the cases of this present study. However, a higher percentage of metastases associated with the unstimulated pattern was seen in studies by Tsakraklides *et al.*, on cervical and breast cancer<sup>[21,22]</sup> and Berlinger *et al.*, in head and neck cancer.<sup>[18]</sup> The unstimulated pattern was always associated with poor prognosis and shorter survival rate.<sup>[24]</sup>

## CONCLUSION

In spite of limited sample size and inadequate period for the assessment of survival rate, the present study showed positive results. However, further elaborated studies with larger cross-section of population and posttreatment survival period should be included, so that, in near future changes in immunomorphological patterns of excised lymph nodes could be taken into account as a prognostic indicator of individual with OSCC.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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