ORIGINAL ARTICLE

Immunomorphological patterns of cervical lymph nodes in oral squamous cell carcinoma

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ABSTRACT

Context: Squamous cell carcinoma (SCC) comprises 80% of the cancers of the oral cavity. Metastases to the cervical lymph nodes affects prognosis. Studying lymph node reactivity may help to understand host immune reaction against the tumor and thus influence prognosis. **Aims:** This study observed patterns of lymph node reactivity, metastases and grades of metastases in cervical lymph nodes and compared them with the histopathology of the primary tumor. **Materials and Methods:** Lymph nodes from 30 patients of oral squamous cell carcinoma (OSCC) were taken. 10 of these were well-differentiated SCC (WDSCC), 10 moderately differentiated SCC (MDSCC) and 10 poorly differentiated SCC (PDSCC). Four immunomorphological patterns were observed: lymphocyte predominance, germinal centre predominance, mixed pattern (sinus histiocytosis) and unstimulated pattern. **Statistical Analysis Used:** Chi square test. **Results:** The predominant lymph node reactive patterns were germinal centre predominance (79.27%), unstimulated pattern (14.63%) and lymphocyte predominance (6.10%). Positive nodes showed invasion in the form of islands (57.14%), cords (39.29%) and total replacement pattern (3.57%). Tumor involvement in positive nodes showed grade 3 invasion, (53.57%), grade 2 invasion (26.79%), grade 4 invasion (17.86%) and grade 1 invasion (1.79%). Statistically significant association was found between:

- Lymph node reactive pattern and histopathological grade of primary tumor. Higher numbers of germinal centre predominance lymph nodes were found in WDSCC and MDSCC
- Histopathological grade of primary tumor and the grade of lymph node invasion.

Conclusions: Immuno-morphological assessment of draining lymph nodes reflects the immune status of the patient with respect to metastases. This may facilitate identification of high and low risk patients and help in planning appropriate therapy for the high-risk patients.

Key words: Cervical lymph node metastasis, germinal centre, immunomorphology, lymphocyte predominant, oral squamous cell carcinoma

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common head and neck cancer, accounting for more than 90% of total cases. The incidence of OSCC has increased over the past decades, as has its mortality.[1]

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Globally, oral cancer is the sixth most common cancer. In developing countries like India it is a major public health problem accounting for 40% of all malignancies.[2]

It accounts for 3% of all cancers in men and 2% in women. It ranks as the sixth most common cancer in men and twelfth in women. The current male/female incidence ratio is approximately 1.8:1.[3]

Prognosis of patients with OSCC is difficult to predict, despite the diagnosis and therapeutic progress in the field of oncology. Currently, almost half the patients afflicted die within the first 2 years of diagnosis. There are various factors which influence prognosis such as patient factors (age, sex etc.) and tumor

factors (size, site, histopathological grade and metastasis). Among all the factors development of lymphatic metastasis is considered the single most important factor influencing the outcome of the patient with OSCC. The 5-year survival rate of patients with squamous cell carcinoma (SCC) of the upper aerodigestive tract is reduced by almost 50% with the development of cervical metastases.[4]

It has been recognized that the microscopic pattern of a regional lymph node can represent the immunologic reactivity in that node. Based on this, several investigators have attempted to formulate morphologic-immunologic analysis of lymph nodes draining a variety of malignant tumors based on the knowledge of the distribution of lymphoid cells of different classes in the nodes.

In the literature there are several studies reported based on these criteria on the carcinomas of the cervix[8,9], lung[10,11], breast[12] and larynx.[13] They have found that lymphocyte predominance pattern was common in patients with high survival rates and lymphocyte depletion was common in patients with the lowest survival rates. The germinal centre predominance and unstimulated patterns were associated with survival rates intermediate between the two.[5]

There are few studies describing the lymph node reactive patterns of OSCC.[5,14-16] This study is an attempt to document the immunomorphology of the draining cervical lymph nodes, the extent and pattern of metastatic deposits of OSCC and to correlate them with the clinical findings as well as the histopathology of the primary tumor.

SUBJECTS AND METHODS

The sole selection criterion was all excision cases of primary OSCC with neck dissection. 30 such specimens were obtained from the archives of the Dept. of Oral and Maxillofacial Pathology and from the archives of Department of Pathology. All the surgically excised lymph nodes of the patient were taken for the study.

Tissue sections of 4–6 µm thickness stained with haematoxylin and eosin were evaluated and the primary tumor grade was categorized as well-differentiated, moderately differentiated and poorly differentiated.

Lymph nodes evaluated for the study were from submental and submandibular (Level I), upper jugular (Level II), mid jugular (Level III), lower jugular (Level IV) and posterior triangle (Level V).

To assess patient immune response in the regional lymph nodes the criteria used was based on a standardized system of reporting human lymphnode morphologic characteristics in relation to immunologic function. There are five patterns:[16]
- Lymphocyte predominance [Figure 1]
- Germinal centre predominance [Figure 2]

- Mixed pattern (predominantly sinus histiocytosis)
- Unstimulated [Figure 3] and
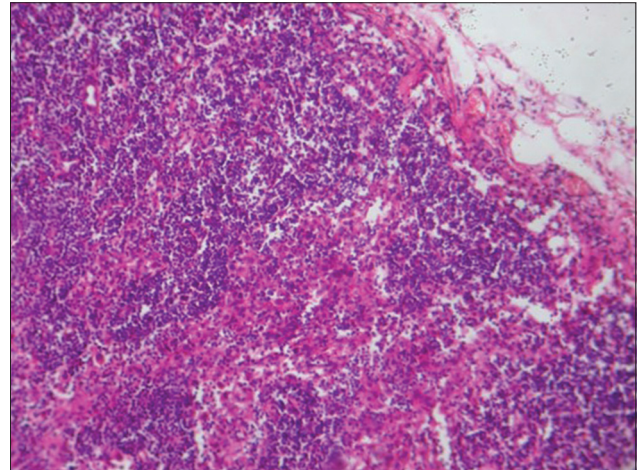- Lymphocyte depletion.

Figure 1: Lymphocyte predominant immunomorphologic pattern of lymph node (H&E stain, x40)
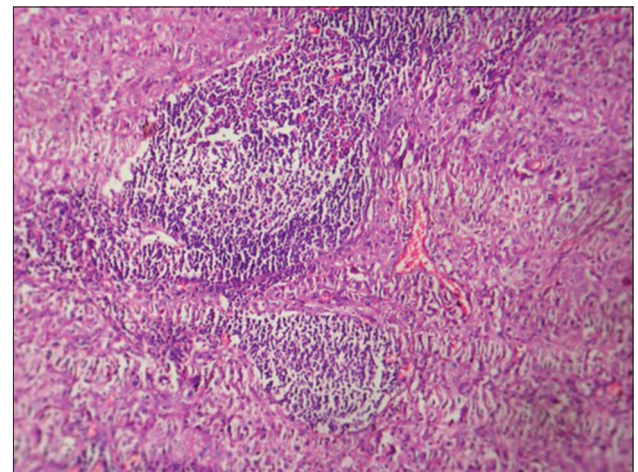

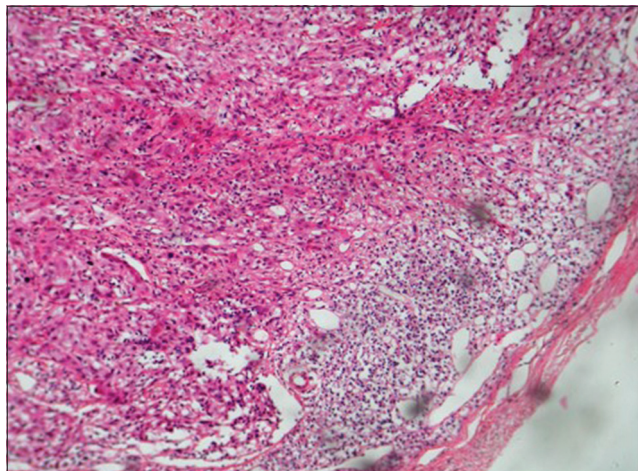**Figure 2:** Germinal centre predominant immunomorphologic pattern of lymph node (H&E stain, x40)

Figure 3: Unstimulated immunomorphologic pattern of lymph node (H&E stain, x40)

For the great majority of cases, most or all lymph nodes from an individual patient showed the same type of reaction pattern. Only infrequently did the several lymph nodes of an individual patient show substantial evidence of more than one type of reaction pattern. When this did occur, however, the predominant pattern was usually readily discernible.

In addition, each metastatic lymph node was evaluated for pattern of invasion. They were then grouped as follows:
- Total replacement [Figure 4]
- Invasion in the form of islands [Figure 5]
- Invasion in the form of cords [Figure 6].

The degrees of tumor involvement within the lymph nodes were evaluated using the following grading system.[6]

Grade 1: Micrometastasis
Grade 2: Less than 50% involvement
Grade 3: Greater than 50% involvement
Grade 4: Extracapsular spread.

The mode of invasion of the primary tumor was also classified into three types according to the pattern of tumor cell invasion at the tumor host interface.[7]

Type W: Well-defined borderline
Type M: Groups of tumor cells with no distinct borderline
Type D: Small aggregates with finger-like projections or diffuse invasion without forming nests of tumor cells.

The results obtained were statistically analysed using Chi-square test.

RESULTS

Of the 30 cases studied, 10 were well differentiated, 10 were moderately differentiated and 10 cases were of poorly differentiated SCC. Of these 21 patients were males and 9 were females. The age ranged from 35–70 years. We obtained a total of 82 lymph nodes from all the cases. Of these, 56 were positive for metastatic deposits. All 82 lymph nodes were assessed for the pattern of lymph node reactivity, but only the 56 positive nodes were assessed for the other parameters (pattern of invasion and grade of invasion) to evaluate whether these features could be helpful in assessing the immunological status of the patient and thereby the prognosis of the patient.

In the analysis of lymph node immunomorphology, we observed that 65 nodes (79.27%) showed germinal centre predominance, 12 nodes (14.63%) showed unstimulated pattern and 5 nodes (6.10%) showed lymphocyte predominance pattern [Figure 7].

The predominant grade of invasion among 56 lymph nodes showed 30 nodes (53.57%) with grade 3 invasion, 15 nodes (26.79%) with grade 2 invasion, 10 nodes (17.86%)
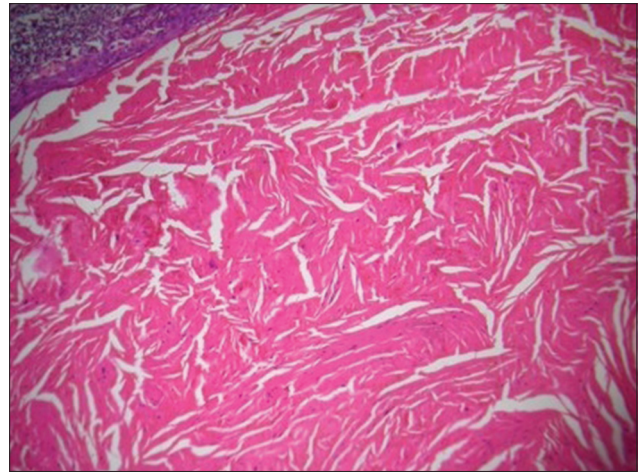

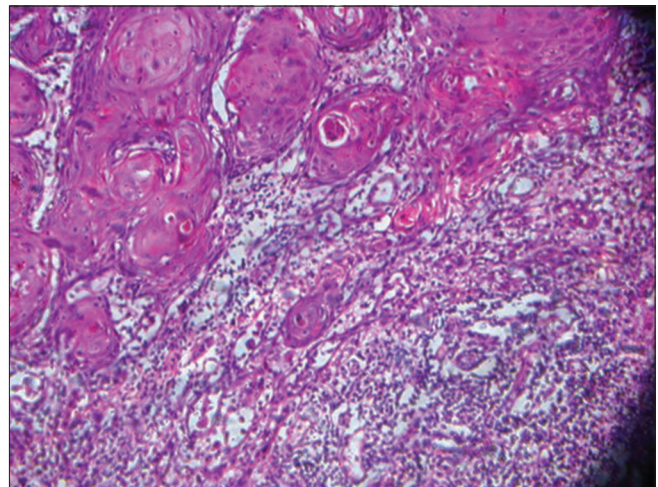**Figure 4:** Total replacement of lymph node by OSCC (H&E stain, x40)

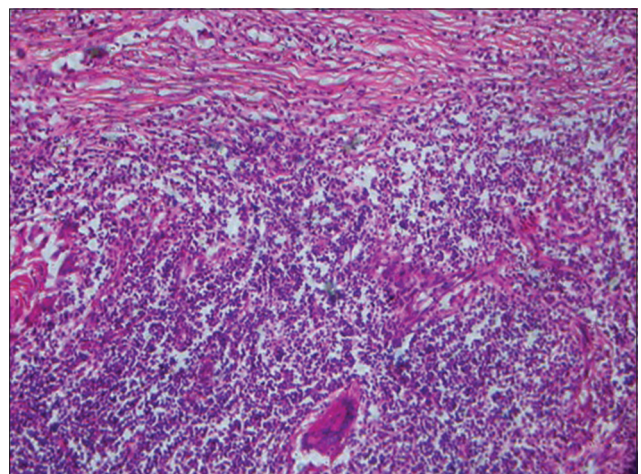**Figure 5:** Invasion of lymph node by islands of OSCC (H&E stain, x100)

Figure 6: Invasion of lymph node by strands & cords of OSCC (H&E stain, x40)

with grade 4 invasion and 1 node (1.79%) with grade 1 invasion [Figure 8].

The predominant pattern of invasion in 56 positive lymph nodes showed 32 lymph nodes (57.14%) with invasion in the form of islands, 22 lymph nodes (39.29%) with invasion in the form of cords and 2 lymph nodes (3.57%) with total replacement pattern [Figure 9].

While correlating the histopathological grade of the primary tumor with lymph node reactive pattern we found that lymphocyte predominance was highest in well-differentiated SCC (WDSCC) (11.11%) followed by moderately differentiated SCC (MDSCC) (6.45%). Germinal centre predominance was highest in WDSCC (85.19%) followed by MDSCC (83.87%) and poorly differentiated SCC (PDSCC) (66.67%). Unstimulated pattern was seen to be highest in PDSCC (33.33%) followed by MDSCC (9.68%) and WDSCC (3.7%) [Figure 10].

We observed that there is a statistically significant association between lymph node reactive pattern and H/P grade ($P < 0.01$). Higher numbers of germinal centre predominance lymph nodes are found in WDSCC and MDSCC.
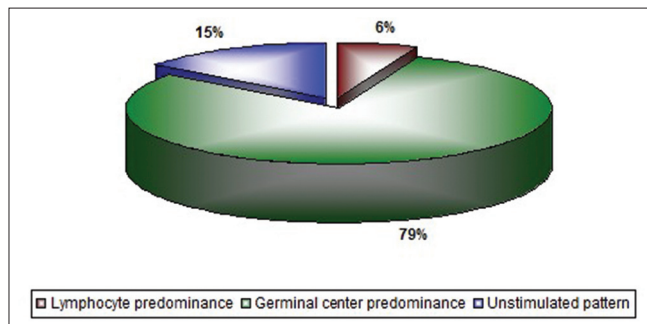

Figure 7: Distribution of lymph node immunomorphological patterns in the study sample

Correlating the histopathological grade of primary tumor with pattern of lymph node invasion we found that the highest percentage of invasion in the form of islands was seen in WDSCC (73.9%) followed by MDSCC (50%) and PDSCC (40%). Pattern of invasion in the form of cords was seen in PDSCC (60%) followed by MDSCC (44.4%) and WDSCC (21.7%) [Figure 11].

Correlation between histopathological grade of primary tumor with grade of invasion in lymph nodes showed highest percentage of grade 3 type of invasion in MDSCC (87.5%) followed by PDSCC (47.1%) and WDSCC (34.8%). Highest percentage of grade 4 type of invasion was seen in PDSCC (52.9%) followed by MDSCC (6.3%). Highest percentage of grade 2 type of invasion was seen in WDSCC (60.9%) followed by MDSCC (6.3%) [Figure 12].

This correlation was statistically significant ($P < 0.001$). More samples were found in grade 3 type of invasion with moderately differentiated histopathological grade.

Correlating mode of invasion of primary tumor with the lymph node reactive pattern, germinal center predominance was seen more in type W (100%), followed by type M (81%) and type D (71.45). Unstimulated pattern was seen more in type D (19%) followed by type M (13.8%) [Figure 13].

DISCUSSION

SCC comprises approximately 80% of the cancers of the oral cavity. Despite optimal treatment, the prognosis of advanced SCC remains poor. This is primarily due to high rate of loco-regional failure and secondarily due to distant metastasis. Incidence of lymph node metastasis in head and neck cancer is high and is the most important prognostic factor.[14] The incidence of neck metastasis in OSCC is relatively high, at 34–50%.[7]
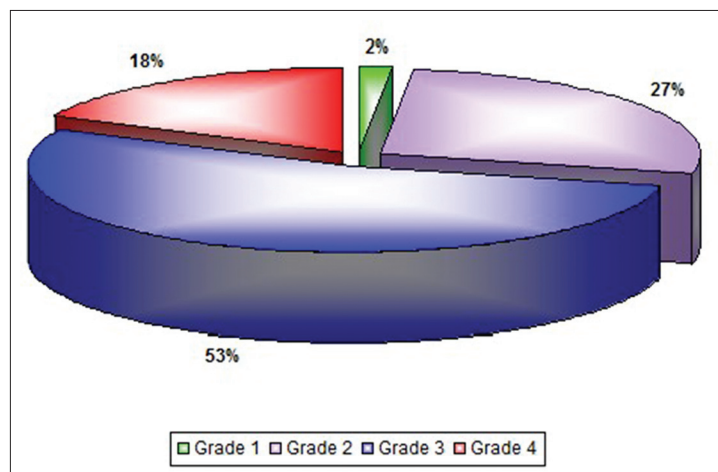

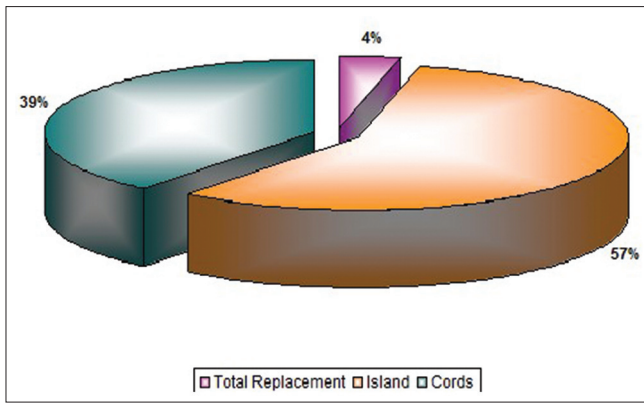**Figure 8:** Distribution of grade of invasion in positive nodes

Figure 9: Distribution of pattern of invasion in positive nodes

Figure 10: H/P grade of primary tumor vs. immunomorphological pattern of lymph node
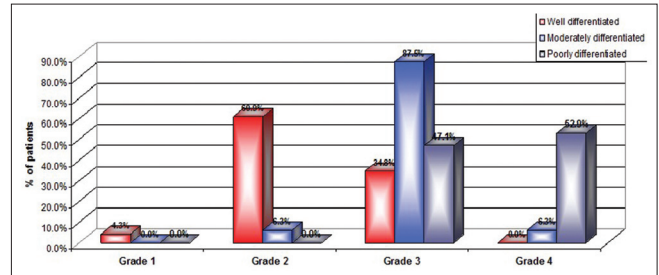
Figure 12: H/P grade of primary tumor vs. grade of invasion in lymph nodes
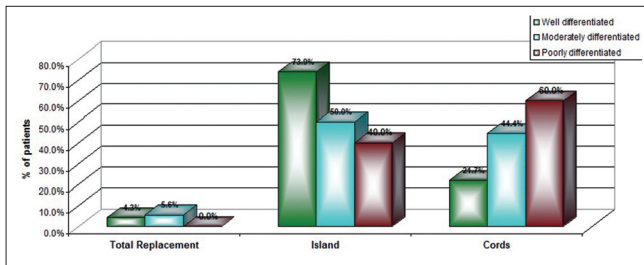

Figure 11: H/P grade of primary tumor vs. pattern of invasion in lymph nodes

Regional lymph nodes are considered to have their primary function not merely as anatomic barriers to the systemic dissemination of tumor cells but also as immunologic surveillance outposts. The histologic lymph node reactive pattern has been studied in various types of cancers for prognostic significance, but there are very few studies in OSCC.

This study included lymph nodes from 30 patients diagnosed with OSCC. Four histologic patterns were seen out of the described five[5]: Lymphocyte predominance, germinal centre predominance, sinus histiocytosis and unstimulated pattern.

The predominant lymph node reactive patterns seen were germinal centre predominance (79.27%), followed by unstimulated pattern (14.63%) and lymphocyte predominance pattern (6.10%). Similar results were obtained by Tsakraklides V *et al*., in uterine cervical cancer. They found germinal centre predominance more common in metastatic cases and frequently in cases with few and small metastases. The overall 5-year survival rate of cases with this pattern is somewhat higher than unstimulated pattern but lower than lymphocyte predominance. These findings suggest a relation between germinal centre predominance and the establishment of metastases in lymph nodes.[8]

Similar observations were made by Malicka in patients with cancer of the larynx and by Carter and Gershon and Edwards *et al*.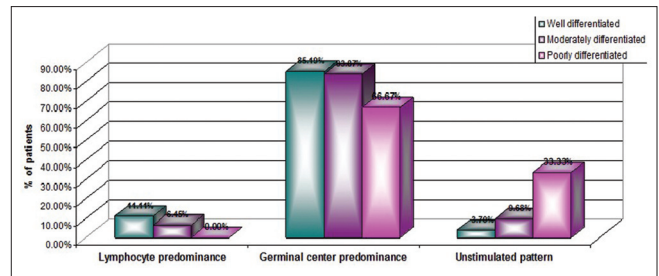, in experimental tumors. Several investigators have found that germinal centres are found early in the humoural response to antigenic stimuli and that they are largely related to the production of plasma cells and humoural antibodies. Thus, these data support the hypothesis that lymph nodes with germinal centre predominance pattern are responding to antigenic stimulation with the production of humoural antibodies.[8]

The distribution of grade of invasion in positive nodes showed grade 3 invasion (53.57%) followed by grade 2 (26.79%), grade 4 (17.86%) and grade 1 (1.79%). Very few studies have been done on this nodal metastasis parameter. Paladini *et al*., in SCC of vulva found node related parameters were strongly correlated with survival. The five actuarial survival was 83% in patients with metastases occupying less than 5% of the node (grade I invasion) and 17% in patients with metastases involving more than 50% of the node. Five-year survival was 51% in patients with intracapsular metastases; even if one node showed extracapsular metastatic involvement 5-year survival dropped to 15%. Five-year survival was 46% for patients with two or three nodes involved, and 23% for patients with more than three nodes involved.[9]

There are no studies reported in literature regarding pattern of invasion in lymph nodes. In our study we observed that the predominant pattern of invasion in the lymph nodes was invasion in the form of islands.

There was a statistically significant association between lymph node reactive pattern and histopathological (H/P) grade (*P* < 0.01). Higher numbers of germinal centre predominance lymph nodes are found in WDSCC and MDSCC.
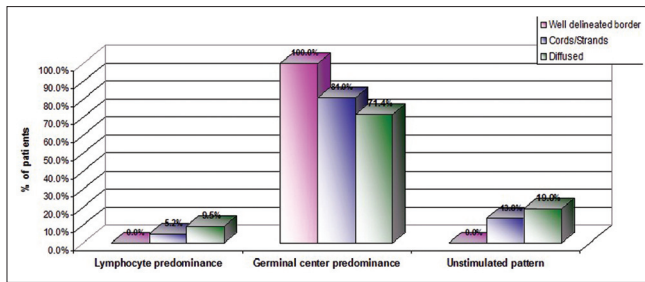
Figure 13: Mode of invasion of primary tumor vs. immunomorphological pattern of lymph node

Tsakraklides *et al*., in their study of uterine cervical cancer correlated lymph node histology with grade of the primary tumor and survival and found that Grade I (well-differentiated) patients survived longer and their predominant pattern was lymphocyte predominant. In Grade II (moderately differentiated) and Grade III (poorly differentiated) patient survival was less and the predominant pattern was germinal centre predominance and unstimulated pattern respectively.[8]

In contrast our study showed higher numbers of germinal centre predominance in WDSCC and MDSCC. We could not correlate lymph node reactive pattern with the survival of the patient in our study as there was no consistent follow up of the patients. However there are studies showing germinal centre predominance associated with better prognosis and longer survival.[5]

Statistically significant association was found between H/P grade of primary tumor and the grade of invasion in lymph nodes ($P < 0.001$). More samples were found showing grade 3 type of invasion in MDSCC. As already mentioned Paladini *et al*. in SCC of vulva found node related parameters were strongly correlated with survival. Histopathologically, these findings suggest that these patients should be categorized as high-risk patients.

Based on published studies, it appears that the node related parameters such as number of positive nodes, nodal immune response, percentage of the node replacement and extracapsular spread represent significant prognostic indicators. There are reports on uterine cervical cancer, SCC of vulva and other cancers where these nodal parameters have proved to be of statistical significance.[8,9] In the literature there are very few reports on OSCC regarding pathologic parameters of lymph node invasion.[14-16] These parameters have seldom been analysed in detail.

Since most of our patients were lost to follow-up, our study could not include the prognosis of these patients. We believe that the node related parameters should be assessed for every OSCC patient and according to the findings, the patients should be categorized into the relevant risk categories. Assessment of these parameters would help the pathologist send the referring surgeon a more informative report for assessing patient prognosis and formulating a more comprehensive treatment protocol. Further studies with larger sample sizes have to be done on lymph node related pathologic parameters to assess their prognostic significance with greater certainty.

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