

Prognostic Significance of Lymph Node Ratio in Predicting the Outcome of Oral Squamous Cell Carcinoma – A Retrospective Study

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Abstract

Introduction: The lymph node status is a very important prognostic factor in head-and-neck cancer. The presence of metastatic lymph nodes will reduce the overall survival by 50%. Lymph node ratio (LNR) is defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes dissected. The aim of the study was to investigate the prognostic value of LNR in oral squamous cell carcinoma (OSCC). **Materials and Methods:** Medical records of pathologically confirmed OSCC patients who reported with loco-regional recurrence from January 2017 to January 2022 were analysed. LNR and disease-free survival (DFS) were calculated for each patient. The endpoint of the study was disease-free survival. Spearman's correlation was used to establish a correlation between DFS and LNR. **Results:** A total of 33 patients were included in the study. DFS was calculated for all the patients. LNR was calculated in patients with pathological N+ neck. There was a negative significant moderate correlation between LNR and DFS (Spearman's rho = -0.593, $P < 0.001$). A higher LNR value of more than 0.01 was associated with a shorter DFS period. T4 tumour stage had significantly higher LNR. A positive significant moderate correlation was found between LNR and tumour stage (Spearman's rho = 0.703, $P = 0.01$). As the T stage increased, the LNR ratio also increased. In the present study, tumour subsite tongue was associated with significantly higher LNR ($P = 0.001$). **Discussion:** LNR can be considered an independent prognostic parameter for DFS in OSCC patients with cervical lymph node metastasis.

Keywords: Disease-free survival, lymph node ratio, oral squamous cell carcinoma, recurrence

INTRODUCTION

Head-and-neck cancer is the sixth-most common cancer in the world.^[1] Oral cavity cancers constitute about 30% of head & neck cancers and out of this 30%, 95% represent oral squamous cell carcinoma (OSCC).^[1-3] The mainstay of treatment of OSCC includes upfront surgical resection of the primary tumour with appropriate neck dissection, followed by post-operative radiotherapy (RT) with or without chemotherapy (CT) in the presence of adverse histopathological features. Pre-operative chemoradiation is given in cases of advanced stage tumours.^[4,5] Despite advancements in the treatment of OSCC, the prognosis is poor.

The lymph node status is a very important prognostic factor in OSCC. The presence of metastatic cervical lymph nodes will reduce the overall survival by 50%. Therefore, appropriate treatment of cervical metastasis is essential to achieve good loco-regional control of the disease.^[6,7]

Lymph node ratio (LNR) is defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes dissected.^[2,8] It has been proven to be an independent prognostic factor in breast, bladder and colorectal cancers.^[9-11] LNR is emerging as a valuable prognostic parameter by potentially predicting the outcome in OSCC patients after resection with curative intent.^[2,4]

The aim of our study is to investigate the prognostic value of LNR in OSCC patients reporting to our centre.

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MATERIALS AND METHODS

A retrospective study was conducted at a tertiary hospital in eastern Maharashtra. The ethical approval (PIMS/DR/RDC/2022/517) for the study was obtained from the institutional ethical committee. The study was conducted in accordance with the ethical standards given in the 1964 Declaration of Helsinki, as revised in 2013. Medical records of OSCC patients who reported loco-regional recurrence from January 2017 to January 2022 were analysed. The inclusion criteria included patients with loco-regional recurrence of OSCC, which was pathologically confirmed. These patients underwent surgery with curative intent in the past for the primary tumour with adequate margins and neck dissection with or without adjuvant chemoradiation. Patient consent was waived due to the nature of the study.

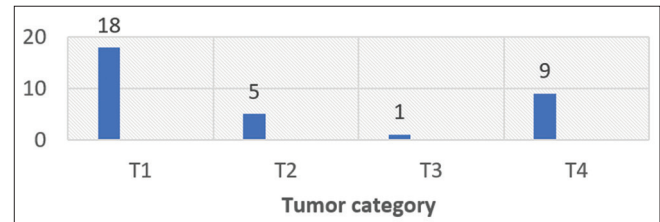
The variables that were recorded included age, sex, tumour, node, metastasis (TNM) stage, neck status and details of previous treatment of primary tumour, which included T stage of the primary tumour, type of primary tumour resection, type of neck dissection performed, total number of lymph nodes harvested, number of positive lymph nodes and adjuvant therapy (CT/RT) received. LNR was calculated for each patient, i.e., positive lymph nodes divided by the total number of lymph nodes. The end point of the study was disease-free survival (DFS). DFS is the length of time after the end of primary treatment of cancer till the patient develops signs and symptoms of cancer. It was calculated in months. The DFS period was calculated for every patient. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp. Results on continuous measurements were presented on mean \pm standard deviation (SD) (minimum–maximum) and categorical as frequency (percentage). The normality of the data was assessed using the Shapiro–Wilk test/Kolmogorov–Smirnov test. Inferential statistics such as Spearman’s correlation, Kruskal–Wallis and Mann–Whitney test was used to check the difference between the groups. The significance of the level adopted was 5%.

RESULTS

In total, 33 patients, 9 (27.2%) females and 24 (72.7%) males were included in this retrospective study. The mean age at the time of diagnosis of loco-regional recurrence was 53.1 years (range: 29–80).

All 33 patients at the time of diagnosis of loco-regional recurrence had histopathologically confirmed diagnosis of OSCC. Most patients were in the T1 category tumour (18 [54%]) [Graph 1] at the time of diagnosis and the most common site was buccal mucosa (11 [33%]) followed by the tongue (6 [18%]) [Graph 2]. In 23 (69.6%) patients, the loco-regional recurrence was on the same side as that of the primary tumour and in 10 (30.3%) patients, the loco-regional failure was on the opposite side. The median follow-up measured from the end of treatment until the last oncology-related follow-up was 20 months (range: 0–60 months). The average DFS period in the present study was 21.12 months (range: 2–124 months).

Most of the patients (12 [36.3%]) had a T3 primary tumour stage [Graph 3] and the most common primary tumour site was tongue (8 [24.2%]) followed by buccal mucosa (6 [18.1%]). All the patients received wide local excision and composite resection for the primary tumour. Adequate neck dissection (cN0 – levels 1–4 and cN+ – levels 1–5) was performed in all the patients, with a median of 17 nodes dissected. In the present study, 20 patients had pathological positive lymph nodes and 13 had pathological negative lymph nodes [Graph 4]. The median number of positive lymph nodes was 2, yielding a median LNR of 0.07. Most patients (16 [48.4%]) had an LNR of 10% or more, while six patients had an LNR <10% [Table 1]. The patients with pN+ ($n = 20$) received chemoradiation (adjuvant therapy comprised around 60 grey external beam RT and cisplatin-based CT). In the present study, patients with a higher LNR ($n = 20$) value of more than 0.01 had a shorter DFS period [Table 1]. According to Spearman’s rho, there was a negative significant moderate correlation between LNR and DFS [Table 2]. There

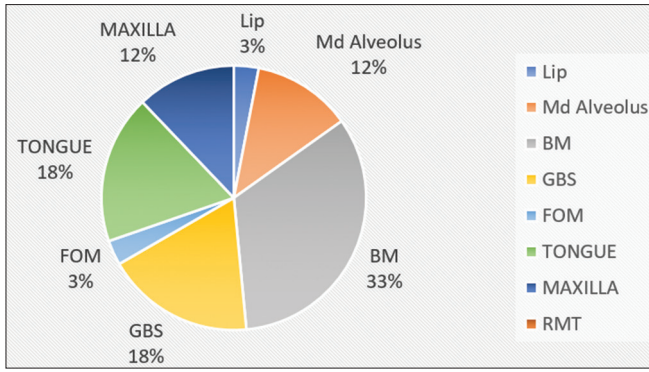


Graph 1: Patient distribution in T stage for loco-regional failure; X-axis – Tumour stages, Y-axis – number of patients

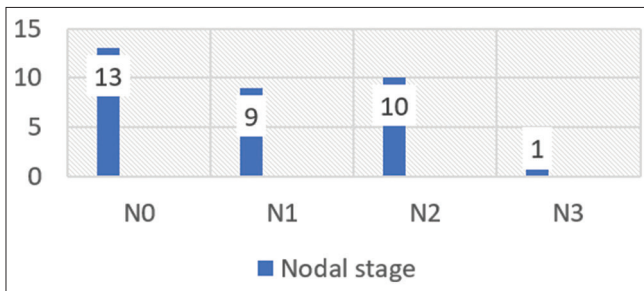
Table 1: pN+ patients - calculation of lymph node ratio and disease-free survival

| Serial number pN+ | Positive lymph nodes | Total number of lymph nodes | LNR | DFS (months) |
|-------------------|----------------------|-----------------------------|------|--------------|
| 1 | 3 | 15 | 0.2 | 17 |
| 2 | 7 | 24 | 0.29 | 5 |
| 3 | 5 | 21 | 0.23 | 3 1/2 |
| 4 | 6 | 25 | 0.24 | 2 1/2 |
| 5 | 2 | 9 | 0.22 | 3 1/2 |
| 6 | 5 | 23 | 0.21 | 4 1/2 |
| 7 | 3 | 12 | 0.25 | 7 |
| 8 | 6 | 19 | 0.31 | 4 |
| 9 | 5 | 21 | 0.23 | 3 |
| 10 | 1 | 14 | 0.07 | 3 1/2 |
| 11 | 3 | 13 | 0.23 | 5 |
| 12 | 6 | 23 | 0.26 | 3 |
| 13 | 1 | 23 | 0.04 | 5 |
| 14 | 3 | 18 | 0.16 | 8 |
| 15 | 4 | 14 | 0.28 | 8 |
| 16 | 3 | 11 | 0.27 | 4 |
| 17 | 1 | 24 | 0.04 | 31 |
| 18 | 3 | 15 | 0.2 | 121 |
| 19 | 1 | 15 | 0.06 | 7 |
| 20 | 7 | 23 | 0.3 | 12 |

LNR: Lymph node ratio, DFS: Disease-free survival



Graph 2: Patient distribution according to tumour subsite. BM: Buccal mucosa, GBS: Gingivo buccal sulcus, RMT: Retromolar trigone, FOM: Floor of mouth

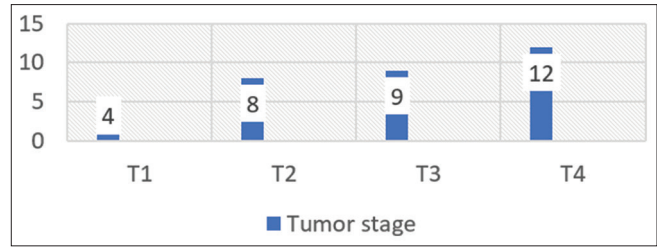


Graph 4: Patient distribution in N stage for primary tumour; X-axis – Nodal stages, Y-axis – number of patients

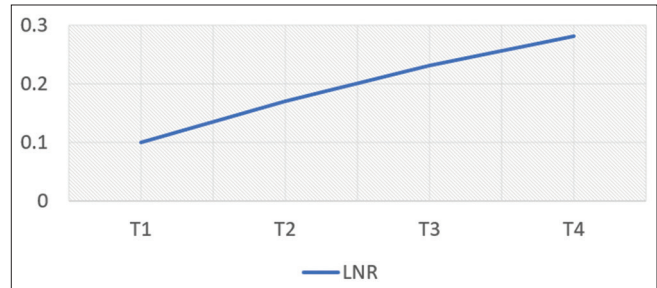
was a positive significant moderate correlation between LNR and tumour stage [Table 2 and Graph 5]. T3–T4 primary tumours were associated with higher LNR values. T4 had a significantly higher LNR mean \pm SD [Table 3]. In the present study, we found that the primary tumour site tongue was associated with a higher LNR value, followed by alveolus [Table 4]. Patients with LNR <0.01 ($n = 13$) had no statistical correlation with DFS and T stage.

DISCUSSION

Surgery is the mainstay treatment in OSCC, which includes surgical resection of the primary tumour with adequate margins for local control and neck dissection for neck control.^[12] Lymph node metastasis has been reported as one of the most important prognostic factors in OSCC. Therefore, the pathological neck nodal status is an essential aspect of current staging systems. Various characteristics of lymph node metastasis have prognostic significance, which include lymph node yield, total number of positive lymph nodes, extracapsular spread, level of lymph node involvement and size of the lymph node.^[13,14] The eighth edition of the American Joint Committee on Cancer (AJCC) staging manual recommends a lymph node yield of at least 15 nodes as adequate neck dissection, whereas some authors recommend a nodal yield of at least 18 lymph nodes in elective neck dissection for better prognosis of OSCC patients.^[15] In the present study, a median of 17 lymph nodes were dissected.



Graph 3: Patient distribution in T stage for primary tumour; X-axis – Tumour stages, Y-axis – number of patients



Graph 5: Correlation between lymph node ratio and T stage

Table 2: Correlation of lymph node ratio with disease-free survival and with tumour stage

| | Spearman's rho | P | Inference |
|----------------------|----------------|--------|----------------------|
| LNR and DFS | -0.593 | <0.001 | Negative correlation |
| LNR and tumour stage | 0.703 | 0.01 | Positive correlation |

DFS: Disease-free survival, LNR: Lymph node ratio

Table 3: Distribution of lymph node ratio values in T stage

| T stage | LNR (mean \pm SD) | P |
|---------|---------------------|------|
| T1 | 0.10 \pm 0.08 | 0.03 |
| T2 | 0.17 \pm 0.06 | |
| T3 | 0.23 \pm 0.02 | |
| T4 | 0.28 \pm 0.01 | |

LNR: Lymph node ratio, SD: Standard deviation

Table 4: Distribution of mean \pm standard deviation of lymph node ratio and subsite

| Subsite | LNR (mean \pm SD) | P |
|---------------|---------------------|-------|
| Tongue | 0.27 \pm 0.02 | 0.001 |
| Alveolus | 0.23 \pm 0.03 | |
| Buccal mucosa | 0.17 \pm 0.08 | |
| GBS | 0.21 \pm 0.10 | |
| Maxilla | 0.07 \pm 0.01 | |

LNR: Lymph node ratio, SD: Standard deviation, GBS: Gingivobuccal sulcus

LNR represents the number of lymph nodes being dissected and those that are positive for lymph node metastasis. The positive lymph nodes represent the tumour burden and the extent of the disease. In a study by Ho *et al.*, they found that

the mortality risk was proportional to the number of metastatic lymph nodes.^[16] The advantage of LNR is that it considers the differential extent of individual neck dissection. It is a simple ratio that can be calculated depending on the lymph node yield. However, in less extensive neck dissection, a falsely reported higher LNR can impair the outcome of the patient.^[17] de Ridder *et al.*, in their study, found that LNR was an unreliable parameter because the total number of lymph nodes harvested can be influenced by multiple factors such as differences in anatomy, surgical expertise type of neck dissection performed and specimen processing protocol.^[18] They believed that a number of positive lymph nodes is a more reliable parameter than LNR.

In the present study, higher LNR was associated with a short DFS period. Huang *et al.*, in their meta-analysis of 19 studies, found that higher LNR was significantly related to shorter DFS.^[2] Spoerl *et al.*, in their retrospective study on 717 patients, found that LNR was an independent prognostic factor in predicting the survival outcomes in OSCC. LNR value ≥ 0.055 predicted shorter recurrence-free survival.^[15] In the present study, we investigated LNR as a potential predictor of DFS in OSCC patients with lymph node metastasis. LNR value of ≥ 0.01 was associated with shorter DFS ($P < 0.001$).

Iftikhar *et al.*, in their cohort study of 130 patients, found that LNR > 0.012 had a poor DFS.^[19] Moratin *et al.*, in their study of 430 patients, found that LNR had better prognostic significance in oral cancer subsite tongue followed by an alveolar process.^[17] Similar findings were found in the present study. A higher value of LNR was associated with subsite tongue followed by alveolus. We also found that T3–T4 tumours were associated with higher LNR. The pattern of nodal metastasis and recurrence of diseases vary significantly between different subsites of the oral cavity. The LNR value is mainly affected by localisation of the tumour as this will affect the extent of cervical metastasis and the type of neck dissection performed.^[20]

All patients with pN+ received chemoradiation in the past. We did not find any significant correlation between chemoradiation therapy and LNR. This could be because of the small sample size.

CONCLUSION

Our results indicate the importance of LNR as an independent prognostic parameter for DFS in OSCC patients with lymph node metastasis. However, more prospective validation on a larger sample size would be needed. In addition to the AJCC TNM classification system, LNR may be useful in stratifying risk in patients with OSCC.

Limitations of the study include retrospective nature, small sample size and varying LNR values due to multiple factors like type of neck dissection performed, physical differences amongst patients and differences in specimen protocols amongst institutions.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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