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Log odds of positive lymph nodes as an independent predictor of overall survival in oral squamous cell carcinoma

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Abstract

Context: Log odds of positive lymph nodes (LODDS) have been recently demonstrated as a very promising staging model and have outperformed AJCC pN, lymph node ratio (LNR) category in major cancers. Literature is scarce concerning the prognostic ability of LODDS in oral squamous cell carcinoma (OSCC) patients. **Aims:** The present study was aimed to evaluate the importance of LODDS in predicting locoregional recurrence and overall survival (OS) in patients with OSCC compared to LNR. **Settings and Design:** The retrospective study was carried out on 194 patients with OSCC cases treated by surgery ± adjuvant therapy from 2008 to 2014 at our institution. **Subjects and Methods:** Demographical and clinicopathological details of study cases were recorded. LNR and LODDS were calculated and expressed as a percentage and mean ± standard deviation. **Statistical Analysis Used:** The OS analysis was done by the Kaplan–Meier curve followed by log-rank (mantel-cox) test. Univariate and multivariate survival analysis was done to analyze the prognostic ability of LNR% and LODDS after adjusting the clinicopathological parameters by the Cox proportional hazards model. **Results:** Patients with cut off values of LODDS >1.2 and LNR% >4 had significantly lower mean OS ($P = 0.001$). Multivariate analysis indicated that only mean LODDS >1.2 was significantly associated with poor OS. Although there was a correlation with locoregional recurrence, LODDS and LNR failed to be the independent predictors of locoregional recurrence. **Conclusions:** LODDS was an independent reliable prognostic indicator for patients with OSCCs than conventional staging systems and LNR.

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Full Text

Introduction

Head and neck squamous cell carcinomas (HNSCC) are the sixth most common cancer in the world. In India, 30%–40% of cancers involve the oral cavity.[1] Oral squamous cell carcinomas (OSCCs) in India are the most common cancer in men and the third most common cancer in women.[2] Despite recent advances in diagnostic and therapeutic strategies, the 5-year overall survival (OS) rate of patients with OSCC is below 50%.[3] The poor rate of OS of patients is mainly due to aggressive local invasion, locoregional recurrences, regional and distant metastasis which highlights the need for new approaches for diagnosis and treatment.[4]

Cervical lymph node assessment is a fundamental aspect of the staging system. It is considered as one of the major indicators for prognosis and helps in planning the treatment strategies in HNSCC.[5],[6],[7] A lot of studies have investigated the lymph node yield (LNY) and lymph node ratio (LNR) and proved them to be potential prognostic markers than the conventional nodal staging system.[8],[9],[10] LNY is defined as the number of lymph nodes retrieved after neck dissection and LNR is defined as the ratio of pathologically positive lymph nodes out of the total number of retrieved lymph nodes after neck dissection. It is suggested that a high LNY means that more potential, occult, pathological tissue has been removed and would have a favorable prognostic factor. Lower LNR may signify that few lymph nodes are positive out of the total removed resulting in a higher OS rate.[11] Although various optimal cut off values of LNY and LNR have been proposed in many retrospective studies, no definitive results have been drawn.[11]

Several studies have demonstrated limited prognostic importance of LNR as it might be confounded by a limited LNY as approximately 40% of patients with OSCC do not have positive neck lymph nodes.[6],[8],[12] Therefore, to prevent the under staging and stage migration, log odds of positive lymph nodes (LODDS) was introduced. LODDS is defined as the log of the ratio between the probability of being a positive lymph node and the probability of being a negative lymph node when one lymph node is retrieved.[3] LODDS discriminates patients without positive lymph nodes and better discriminates between cancer patients with few positive nodes or insufficient nodes retrieved.[6] The LODDS has outperformed AJCC pN, rN (LNR) category in major cancers, such as colon, gastric and pancreatic cancers.[6] For OSCC patients, there is a scarcity of literature concerning LODDS. Few studies have proved LODDS as an independent predictor of locoregional recurrence and accurate in predicting OS in OSCC cases.[3],[7],[13] There is only one recently published study on OSCC among the Indian population regarding prognostic importance of LODDS.[14] Hence, the present study was aimed to evaluate the importance of LODDS in predicting locoregional recurrence and OS in patients with OSCC compared to LNR.

SUBJECTS AND METHODS

The study was retrospective case–control type of study; the study was carried out by collecting demographic, clinicopathological and follow-up details of 194 OSCC cases treated from 2008 to 2014 at SDM Craniofacial surgery and research Centre. Ethical committee approval was obtained from the Institutional Review Board (IRB No. 2019/UG/OP/63) for the present study. Patients who have undergone radical neck dissection (RND) or modified RND for OSCC with or without adjunct radiotherapy or radiochemotherapy were considered for the study. The exclusion criteria's were neoadjuvant radiochemotherapy, perioperative death, patients who were having other malignancies, incomplete data or follow-up, distant metastasis and the

presence of N3 disease (because this may represent a mass of multiple matted nodes and the nodal number cannot be exactly determined).

Parameters such as age, gender, site, habit, TNM staging (AJCC, 7th edition), histopathological grade (Broders's), perivascular invasion (PVI), perineural invasion (PNI), surgical margin clearance, number of resected lymph nodes, number of positive lymph nodes, extracapsular spread (ECS), locoregional recurrence, postoperative radiochemotherapy and follow-up details were recorded.

Calculation of lymph node ratio and log odds of positive lymph nodes[7]

LNR was calculated as ratio between positive lymph nodes and the total number of resected lymph nodes. LODDS was estimated by: $\text{Log} \left(\frac{\text{number of positive lymph nodes} + 0.5}{\text{total number of resected lymph nodes} - \text{number of positive lymph nodes} + 0.5} \right)$. The obtained data were expressed as a percentage and mean \pm standard deviation.

Data and Statistical analysis

Statistical analyses were performed using SPSS software package (version 21.0. Armonk, NY, USA). $P = 0.05$ was considered statistically significant. Contingency tables were prepared and descriptive analysis was done for demographic, clinicopathological parameters, follow-up details and lymph node data of study cases.

OS was calculated from the date of surgery to date of death or last follow-up. Patients who died of causes other than OSCC were censored. The cut off values for LNR% and LODDS were obtained by constructing receiver operating characteristic (ROC) and Youden Index (Youden Index = Sensitivity + specificity - 1). The OS analysis was done by Kaplan–Meier curve followed by Log–rank (Mantel-Cox) test. Univariate and Multivariate OS analysis was done to analyze the prognostic ability of LNR% and LODDS after adjusting the clinicopathological parameters by Cox proportional hazards model.

Contingency tables, Chi-square test and Student's "t" test (unpaired) were performed to analyze the association between clinicopathological, lymph node characteristics with locoregional recurrence. Cox regressions analysis of risk factors was done to identify the independent predictor of the event of locoregional recurrence.

Results

Demographic and clinicopathological data

All inclusion and exclusion criteria's were met by 194 OSCC patients. The mean age of the study cases was 48.9 years and the majority of were male ($n = 160$, 82.5%). Most of the OSCCs were located in buccal mucosa associated with the habit of smokeless (chewing) tobacco (57.7%). Positive neck nodes were found in about 96 patients (49.5%) after primary surgery. Among the study cases, 38 (19.6%) cases had PNI and only 14 cases (14.2%) showed PVI. Positive neck nodes were found in about 96 patients (49.5%) after primary surgery and only 25 (12.3%) patients showed ECS. Fifty-six cases (28.9%) presented with locoregional recurrence with a mean age of recurrence of 6.19 months. About 92 patients were alive and a mean follow-up period was 44.5 months. The majority of the patients (59.27%) were treated with surgery followed by radiotherapy. [Table 1]{Table 1}

Lymph node data

The mean total lymph nodes resected from the study cases was 16.9 and mean positive lymph node was 1.99. The mean LNR and LNR% were 0.15 and 15.11, respectively. The mean LODDS was -0.96 with the maximum being 1.23 and the minimum being -1.93. The cut off values for LNR% and LODDS were obtained by constructing the ROC curve and you den index and was 1.2% and 4%, respectively. [Table 2] and [Figure 1]{Table 2}{Figure 1}

Survival analysis

Kaplan–Meier curve and Log–rank (Mantel-Cox) test survival estimate showed LODDS > -1.2 had a significantly lower mean OS period of 32.08 months compared to LODDS ≤ -1.2 $P < 0.001$ [Figure 2]. OS estimate showed LNR% > 4 had a significantly lower mean OS period of 31.68 months compared to LNR% ≤ 4 with $P < 0.001$ [Figure 3].{Figure 2}{Figure 3}

Univariable Cox regressions analysis of risk factors indicated that poorly differentiated grade, LODDS and LNR% were significantly associated with poor OS. However, multivariate analysis indicated that only mean LODDS > -1.2 was significantly associated with poor OS (hazard ratio 10.42, $P = 0.001$, 95% confidence interval 3.947–27.525) [Table 3].{Table 3}

Demographic, clinicopathological and survival analysis of recurrent cases compared to non-recurrent cases in the study group

The development of locoregional recurrence was significantly associated with margin positivity, PNI, LODDS > -1.2 and LNR% > 4 when clinicopathological and lymph node characteristics were compared [Tables 4]. Pair wise comparison ("t" test) showed a significant lower mean age of occurrence and lower means total nodes (LNY) in recurrent cases compared to nonrecurrent cases. However, there was no significant difference in mean OS period [Tables 5]. Multivariate analysis by Cox regressions analysis ruled out OS or any risk factors independently associated with the event of locoregional recurrence (Data not shown).{Table 4}{Table 5}

Discussion

In HNSCC, cervical lymph node status may be considered the main prognostic indicator.[11] OSCC patients with positive lymph nodes are staged as Stage III-IV according to widely used AJCC TNM staging system (7th edition) and are recommended for adjuvant radiotherapy or chemoradiotherapy. Due to shortcomings of the N category, the new updated version (8th edition) has incorporated extracapsular spread in the clinical and pathological N category.[6] However, in recent years, number of studies have pointed out a lack of accuracy of predicting prognosis by these conventional staging systems mainly because it does not consider the number of retrieved lymph nodes (nodal yield).[12],[13],[15] Ebrahimi et al. in 2014[16] demonstrated nodal yield as a strong independent prognostic indicator for patients with OSCC in a large multicentric international study on 1567 patients. They also concluded that resection of < 18 lymph nodes might be associated with understaging and stage migration. To overcome the limitation, another parameter LNR was developed. Some studies have shown that LNR as an independent predictor for OS in HNSCC.[16],[17] Patel et al.[8] in 2013 have shown LNR and number of positive lymph nodes (pN) as independent predictors OS in a multicenter study pooling data from 4254 patients with OSCC. Another retrospective single-center study by Gil et al. in 2009[18] with 386 patients has shown only LNR but not pN was the only independent predictor of OS. However, also few reports are concluding that LNR has limited value for decision-making process in the treatment of HNCC.[14],[19] Another important drawback of LNR is it is prognostic inability to differentiate between patients with pN0 classification, as it is equal to the conventional nodal staging system for this patient group (pN0 and LNR = 0%).[3] Our results confirm the major importance of LNR for patients with OSCC, as the Kaplan–Meier curve and log-rank (Mantel-Cox) test survival estimate showed LNR% > 4 had significantly poor OS compared to LNR% ≤ 4 . LNR% was also a significant predictive parameter for recurrence and survival in recurrent cases [Figure 3]. Although the Univariable Cox regressions analysis of risk factors indicated a significant association of LNR% with OS, the multivariate analysis failed to demonstrate LNR as an independent risk factor for survival [Table 5] and locoregional recurrence.

There is a wide variation that exists in the reports on cut off values of LNY and LNR% in the current literature mainly related to number of lymph nodes retrieved. Royal College of Pathologists has suggested RND yields 20 lymph nodes (range 10–30) in the absence of previous chemotherapy, radiotherapy or neck dissection.[20] In the present study, the mean total lymph nodes was low (16.9 ± 7.69) compared to other published LNY.[8],[16],[17],[18] A study on Indian patients with T3/T4 OSCC has shown mean LNY of 21.97.[21] The patients operated in the present study by selective neck dissection, which involves preservation of one or more lymph node groups could be one of the reasons for low LNY and LNR%. Apart from that, the surgical technique, role of pathologists, pathology technicians, method of handling the surgical specimen and the extent of training of these specialists have shown to influence the yield of lymph in turn affecting the overall LNY.[21] Our LNR% was close to Lio et al. in 2011[22] who reported a cut off value of 4.8% for 457 patients with OSCC, whereas

Sayed et al.[23] used a cut off value of 8.8% in 1408 patients with OSCC. In 2013, Patel et al.[8] determined a cut off value of 7% to analyze the influence of LNR on the prognosis of patients with OSCC and compared it with conventional nodal staging.

A more recent ratio-based nodal parameter is the LODDS. In colorectal, breast and gastric cancer, LODDS demonstrated to be superior to LNR and LNY in assessing the survival and locoregional recurrence.[3] LODDS avoids null values, by adding 0.5 to both the number of positive and to the number of negative lymph nodes, which can discriminate between patients without positive lymph nodes even when the total LNY is low.[7],[24] However, there is a lack of data concerning the importance of LODDS in patients with OSCC. Moreover, there are only one study published recently concerning prognostic importance of LODDS for OSCC among Indian population which highlights the importance of the present study.[14]

Yildiz et al.[7] in 2016 investigated the prognostic ability of LODDS in a study cohort of 225 patients with HNSCC. They concluded that LODDS predicts OS better than pN classification, LNR and number of positive cervical lymph nodes. However, only 35 suffered from oral cavity cancer in their study group. Lee et al. in 2015[13] in their retrospective study on 347 OSCC cases have shown prognostic superiority of LODDS compared with the AJCC pN classification and the LNR classification. Authors have shown patients with higher LODDS values had worst 5-year Disease specific survival (DSS) and OS. LODDS could better stratify OSCC patients and help to identify high-risk patients missed by the other systems in their study. In the present study, we also found similar results. LODDS was not only superior to TNM classification and LNR in predicting survival, but it also emerged as an independent predictive parameter for OS for OSCC [Table 5]. Lee et al.[6] in their series of research, have proposed and incorporated LODDS with AJCC pN and demonstrated better discriminatory and predictive ability than pathological TNM staging and help to identify high-risk patients for intense adjuvant therapy. However, a recent study by Subramaniam et al. 2019[14] reported contradicting finding to our study. They demonstrated that pN and LNR provided the most accurate prediction of OS and disease-free survival for patients with OSCC than LODDS. This discrepancy in the finding could be due to less number of patients (2.3%) with <18 nodes, no low-risk patients (LODDS <-1.68) and usage of different LNR ratio compared to ours and other studies.

In the present study, positive surgical margin, PNI, LNR% >4 and LODDS >-1.2 correlated significantly with locoregional recurrence [Table 3]. High LNR% and LODDS were significantly correlated with poor OS in recurrent cases [Figures 3], but failed to be the independent predictor of survival in the present study. Safi et al.[3] showed LODDS predicted locoregional recurrence better than conventional nodal staging system, LNR and the number of positive lymph nodes and they also proved LODDS as an independent predictor of recurrence. Whereas, Subramaniam et al. in 2019[14] demonstrated LNR better than LODDS in predicting recurrence. These contradicting findings could be due to number of study cases or use of different cut offs for LNR used in the studies.

Authors have used various cut-off values and classifications for LODDS ranging from -0.70 to -1.68.[3],[6],[7],[14],[25] in their study. This lack of uniformity could be due to wide variation in the number of lymph nodes retrieved, type of neck resection (unilateral/bilateral) or surgical technique of employed in neck dissection in the OSCC patients. However, the current guidelines recommend extensive removal of lymph nodes, without adverse damage to vessels and nerves, while performing neck dissection.[24]

Conclusions

LODDS was an independent reliable prognostic indicator for patients with OSCCs who have undergone surgery ± adjuvant radiochemotherapy. LODDS was superior and beyond conventional staging systems, LNR in predicting OS. LODDS had a limited value in predicting locoregional recurrence. LODDS is an easy and reliable method that can be used by clinical practitioners. Incorporation of LODDS into a prognostic model based on TNM classification in the future could help to identify high-risk patients who benefit from more intense adjuvant therapy. However, further studies to be conducted especially on larger cohorts, to evaluate our findings and to improve understanding of the influence of LODDS on prognosis.

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Conflicts of interest

There are no conflicts of interest.

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