Original Article

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

Varuni Iyer[1], Kiran Kumar[1], Kaveri Hallikeri[1], Anil Kumar Desai[2], Niranjan Kumar[2], Srikant Natarajan[3]

[1]Department of Oral Pathology and Microbiology, SDM College of Dental Sciences and Hospital, A Constituent Unit of Shri Dharmasthala Manjunatheshwara University, [2]SDM Craniofacial Surgery and Research Centre, A Constituent Unit of Shri Dharmasthala Manjunatheshwara University, Dharwad, [3]Department of Oral Pathology and Microbiology, Manipal College of Dental Sciences, Mangalore, A Constituent Unit of Manipal Academy of Higher Education, Manipal, Karnataka, India

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 ($P \leq 0.001$). 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.

Keywords: Locoregional recurrence, log odds of positive lymph nodes, lymph node ratio, oral squamous cell carcinoma, overall survival

Address for correspondence: Dr. Kiran Kumar, Department of Oral and Maxillofacial Pathology, SDM College of Dental Sciences and Hospital, A Constituent Unit of Shri Dharmasthala Manjunatheshwara University, Sattur, Dharwad - 580 009, Karnataka, India.
E-mail: kirankumarop@gmail.com

Submitted: 18-Mar-2020, **Revised**: 05-Aug-2020, **Accepted:** 13-Aug-2020, **Published:** 09-Jan-2021

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

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.JOMFP_110_20

How to cite this article: Iyer V, Kumar K, Hallikeri K, Desai AK, Kumar N, Natarajan S. Log odds of positive lymph nodes as an independent predictor of overall survival in oral squamous cell carcinoma. J Oral Maxillofac Pathol 2020;24:576.

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 ed.ition), 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: Log ([number of positive lymph nodes + 0.5]/[total number of resected lymph nodes − number of positive lymph nodes + 0.5]). The obtained data were expressed as a percentage and mean ± standard deviation.

Data and Statistical analysis

Statistical analyses were performed using SPSS software package (version 21.0. Armonk, NY, USA). $P \leq 0.05$ 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: Demographic and clinicopathological characteristics of study cases

Parameters	Category	Frequency (%)
Age	Mean±SD	48.9±11.6
	Median	50.00
Gender	Male	160 (82.5)
	female	34 (17.5)
Habits	Smokeless tobacco	112 (57.7)
	Smoking tobacco	17 (8.8)
	Smokeless+smoking tobacco	28 (14.4)
	Alcohol+tobacco (smokeless/smoke)	16 (8.2)
	No habits	21 (10.8)
Site (primary)	Buccal mucosa	88 (45.4)
	Buccalmucosa + others	74 (38.1)
	Tongue + others	32 (16.5)
TNM staging (AJCC, 7th edition)	Stage I	4 (2.1)
	Stage II	9 (4.6)
	Stage III	110 (56.7)
	Stage IVa	71 (36.6)
Histopathology grading (broder's)	Well differentiated	132 (68.0)
	Moderate differentiated	58 (29.9)
	Poorly differentiated	4 (2.1)
PNI	Absent	156 (80.4)
	Present	38 (19.6)
PVI	Absent	180 (92.8)
	Present	14 (7.2)
Lymphnode metastasis	Present	96 (49.5)
	Absent	98 (50.5)
ECS	Absent	169 (87.7)
	Present	25 (12.3)
Margin status	Free	180 (92.8)
	Positive	14 (7.2)
Treatment	Surgery only	45 (23.19)
	Surgery + radiotherapy	115 (59.27)
	Surgery + radiotherapy + chemotherapy	34 (17.52)
Survival	Alive	92 (47.4)
	Dead	102 (52.6)
Recurrence	No	138 (71.1)
	Yes	56 (28.9)

ECS: Extracapsular spread, PVI: Perivascular invasion, PNI: Perinueral invasion, TNM: Tumor-node-metastasis, AJCC: American Joint Committee on Cancer, SD: Standard deviation

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]

Survival analysis

Kaplan–Meier curve and Log–rank (Mantel-Cox) test

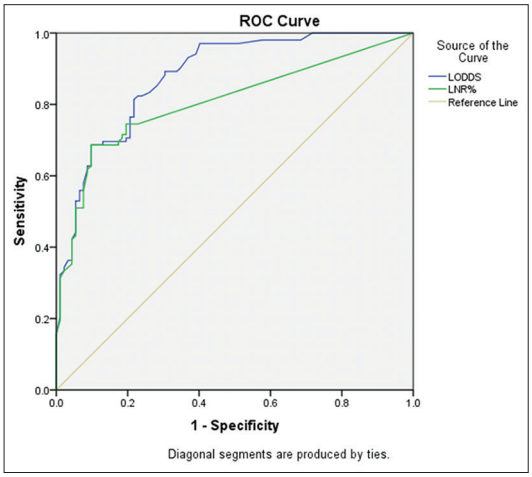

Figure 1: Receiver operating curve analysis for finding the cut-off of log odds of positive lymph nodes and lymph node ratio %

Area Under the Curve					
Test result variable (s)	Area	SE[a]	Asymptotic significanct[b]	Asymptotic 95% CI	
				Lower bound	Upper bound
LODDS	0.880	0.024	0.000	0.833	0.927
LNR%	0.807	0.032	0.000	0.745	0.869

The test result variable(s): LODDS, LNR% has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a]Under the nonparametric assumption, [b]Null hypothesis: true area=0.5. CI: Confidence interval, LNR: Lymph node ratio, LODDS: Log odds of positive lymph nodes

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].

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, $P \leq 0.001$, 95% confidence interval 3.947–27.525) [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).

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

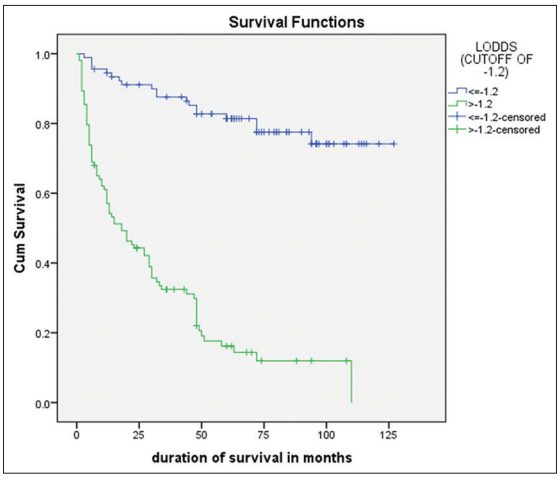

Figure 2: Kaplan–Meier curve and log-rank (mantel-cox) test survival estimate showed log odds of positive lymph nodes >−1.2 had significantly lower mean survival of 32.08 months compared to log odds of positive lymph nodes ≤1.2 having a survival of 105.19 months with $P \leq 0.001$

Means and medians for survival time								
LODDS (cut-off of −1.2)	Mean[a]				Median			
	Estimate	SE	95% CI		Estimate	SE	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
≤−1.2	105.199	4.460	96.458	113.940	.	.	.	.
>−1.2	32.080	3.640	24.946	39.214	18.000	4.249	9.673	26.327
Overall	67.465	4.037	59.553	75.377	50.001	7.840	34.634	65.366

[a]Estimation is limited to the largest survival time if it is censored. CI: Confidence interval, LODDS: Log odds of positive lymph nodes, SE: Standard error

Overall comparisons			
	Chi-Square	df	Significance
Log rank (mantel-cox)	88.736	1	0.000

Test of equality of survival distributions for the different levels of LODDS (cutoff of -1.2)

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

Table 2: Lymphnode data of study cases

Parameter	Mean±SD	Median	Minimum	Maximum
TNOD	16.9±7.69	16.00	0	43
PNOD	1.99±3.21	0.50	0	23
LNR	0.15±0.22	0.034483	0	1.00
LNR (%)	15.11±22.43	1.72	0	100
LODDS	−0.96±0.69	−1.13	−1.93	1.23

LNR: Lymph node ratio, SD: Standard deviation, LODDS: Log odds of positive lymph nodes, PNOD: Positive lymph nodes, TNOD: Total Lymph nodes resected

Table 3: Univariable and multivariable Cox regressions analysis of risk factors affecting the overall survival in oral squamous cell carcinomas

Parameters	Parameter coding	Univariate					Multivariate				
		HR	SE	95.0% CI for HR		*P*	HR	SE	95.0% CI for HR		*P*
				Lower	Upper				Lower	Upper	
Age	Age	1.001	0.008	0.985	1.017	0.92	1.01	0.01	0.991	1.03	0.313
Gender	Female versus male	1.54	0.25	0.943	2.514	0.084	1.576	0.325	0.833	2.98	0.162
Habits	5=No habits	Reference category					Reference category				
	1=Alcohol + Tob (chew/smoke)	0.974	0.505	0.362	2.619	0.958	0.83	0.443	0.349	1.978	0.675
	2=Smokeless tobacco	1.477	0.358	0.732	2.977	0.276	0.753	0.532	0.266	2.137	0.595
	3=Smoke and smokeless tobacco	1.426	0.414	0.634	3.209	0.391	1.084	0.582	0.346	3.394	0.89
	4=Smoking tobacco	1.069	0.486	0.412	2.772	0.891	0.392	0.607	0.119	1.288	0.123
Site	1=Buccal mucosa	Reference category					Reference category				
	2=Buccal mucosa + others	0.887	0.219	0.578	1.362	0.585	0.872	0.322	0.464	1.639	0.672
	3=Tongue	0.881	0.289	0.5	1.552	0.661	0.608	0.351	0.305	1.209	0.156
TNM staging	1=STAGE I	0	0	0	0	0.039	0	0	0	0	0.435
(AJCC, 7th	2=STAGE II	0.489	0.765	0.109	2.189	0.349	0.996	0.861	0.184	5.381	0.996
edition)	3=STAGE III	0.646	0.598	0.2	2.086	0.465	0.73	0.662	0.199	2.674	0.635
	4=STAGE IVa	1.12	0.597	0.347	3.61	0.85	1.108	0.678	0.293	4.184	0.88
Histopathology	1=Well differentiated	Reference category					Reference category				
grading	2=Moderately differentiated	1.264	0.213	0.832	1.92	0.273	1.173	0.256	0.71	1.939	0.533
	3=Poorly differentiated	3.332	0.592	1.044	10.627	0.042	8.631	0.69	2.231	3.397	0.057
PNI	PNI	1.332	0.238	0.836	2.121	0.228	1.163	0.282	0.669	2.021	0.593
PVI	PVI	1.338	0.35	0.674	2.655	0.405	0.602	0.458	0.246	1.477	0.268
Positive nodes	>5 nodes (ref ≤5 nodes)	4.485	0.249	2.756	7.299	0	1.818	0.301	1.008	3.279	0.047
ECS	ECS	3.618	0.249	2.219	5.9	0	1.763	0.311	0.957	3.246	0.069
Margin status	Margin positive compared to negative	1.472	0.35	0.742	2.921	0.269	1.491	0.401	0.679	3.274	0.319
Treatment	Surgery	Reference category					Reference category				
	Surgery + radiotherapy	0.811	0.247	0.5	1.315	0.396	0.69	0.285	0.395	1.206	0.193
	Surgery + radiotherapy + chemotherapy	1.456	0.284	0.835	2.542	0.186	0.714	0.356	0.355	1.436	0.345
LNR (cutoff 4)	LNR% ≤4 reference	6.229	0.235	3.932	9.866	<0.001	0.841	0.445	0.351	2.015	0.698
LODDS	LODDS (≤−1.2 as reference)	8.231	0.262	4.922	13.764	<0.001	10.423	0.495	3.947	27.525	<0.001
Recurrence	Recurrence status 10	1.281	0.207	0.853	1.923	0.232	0.821	0.253	0.5	1.349	0.437

ECS: Extracapsular spread, PVI: Perivascular invasion, PNI: Perinueral invasion, TNM: Tumor-node-metastasis, AJCC: American Joint Committee on Cancer, SD: Standard deviation, SE: Standard error, CI: Confidence interval, LNR: Lymph node ratio

Table 4: Comparison of clinicopathological and lymph node characteristics of recurred and nonrecurrent Oral squamous cell carcinoma groups in study cases

Parameter	*n*	Locoregional recurrence status				Chi square test	*P*
		No recurrence		Recurred			
		Count	Column, *n* (%)	Count	Column, *n* (%)		
Gender							
Female	34	26	18.80	8	14.30	0.572	0.45
Male	160	112	81.20	48	85.70		
Habits							
Alcohol + tob (chew/smoke)	16	11	8.00	5	8.90	0.49	0.974
Smokeless tobacco	112	80	58.00	32	57.10		
Smoke and smokeless tobacco	28	20	14.50	8	14.30		
Smoking tobacco	17	13	9.40	4	7.10		
No habits	21	14	10.10	7	12.50		
Site							
Buccal mucosa	88	59	42.80	29	51.80	1.468	0.48
Buccal mucosa + others	74	56	40.60	18	32.10		
Tongue	32	23	16.70	9	16.10		
TNM staging (AJCC, 7th edition)							
Stage I	4	2	1.40	2	3.60	2.011	0.57
Stage II	9	6	4.30	3	5.40		
Stage III	110	82	59.40	28	50.00		
Stage IVa	71	48	34.80	23	41.10		
Histopathology Grading							
Well	132	93	67.40	39	69.60	1.658	0.436
Moderate	58	41	29.70	17	30.40		
Poor	4	4	2.90	0	0.00		
Margin +ve							
Free	180	132	95.70	48	85.70	5.876	0.015
Positive	14	6	4.30	8	14.30		
PNI							
Absent	156	116	84.10	40	71.40	4.034	0.045
Present	38	22	15.90	16	28.60		
PVI							
Absent	180	130	94.20	50	89.30	1.438	0.23
Present	14	8	5.80	6	10.70		
ECS							
Absent	169	121	87.70	48	85.70	0.137	0.711
Present	25	17	12.30	8	14.30		
LODDS (Cutoff of -1.2)							
≤−1.2	91	74	53.60	17	30.40	8.658	0.003
>−1.2	103	64	46.40	39	69.60		
LNR% (Cutoff of 4)							
≤4	100	80	58.00	20	35.70	7.901	0.005
>4	94	58	42.00	36	64.30		
Treatment							
Surgery	45	34	24.60	11	19.60	0.561	0.756
Surgery + radiotherapy	113	79	57.20	34	60.70		
Surgery + radiotherapy + chemotherapy	36	25	18.10	11	19.60		

ECS: Extracapsular spread, PVI: Perivascular invasion, PNI: Perinueral invasion, TNM: Tumor-node-metastasis, AJCC: American Joint Committee on Cancer, SD: Standard deviation, SE: Standard error, CI: Confidence interval, LNR: Lymph node ratio

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

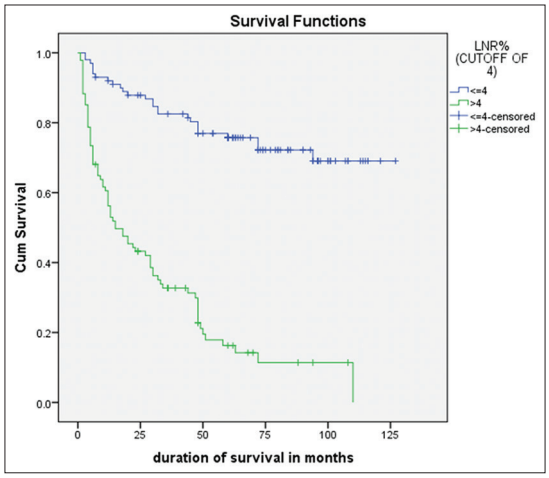

Figure 3: Kaplan–Meier curve and log-rank (mantel-cox) test survival estimate showed lymph node ratio % >4 had significantly lower mean survival of 31.68 months compared to lymph node ratio % ≤4 having a survival of 99.33 months with $P \leq 0.001$

Means and medians for survival time

LNR% (cutoff of 4)	Mean[a]				Median			
	Estimate	SE	95% CI		Estimate	SE	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
≤4	99.334	4.678	90.166	108.502	.	.	.	.
>4	31.687	3.798	24.243	39.132	15.000	4.356	6.461	23.539
Overall	67.465	4.037	59.553	75.377	50.001	7.840	34.634	65.366

[a]Estimation is limited to the largest survival time if it is censored. CI: Confidence interval, SE: Standard error, LNR: Lymph node ratio

Overall comparisons

	χ^2	df	Significant
Log rank (mantel-Cox)	78.209	1	0.000

Test of equality of survival distributions for the different levels of LNR% (Cutoff Of 4). LNR: Lymph node ratio

Table 5: Comparison of age and duration of survival and total nodes among recurred and nonrecurrent oral squamous cell carcinoma groups in study cases

	Recurrence status	*n*	Mean±SD	Independent '*t*'-test	df	*P*
Age	No recurrence	138	50.230±10.827	2.312	88.436	0.023
	Recurred	56	45.730±12.827			
Duration of survival in months	No recurrence	138	44.410±35.450	−0.049	192	0.961
	Recurred	56	44.680±32.005			
Total nodes	No recurrence	138	17.890±7.817	2.848	192	0.005
	Recurred	56	14.480±6.857			

SD: Standard deviation

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.

Financial support and sponsorship

Study is approved for studentship by ICMR (ICMR-STS 2019, Short term studentship program) Reference ID: 2019-05917

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Joshi P, Dutta S, Chaturvedi P, Nair S. Head and neck cancers in developing countries. Rambam Maimonides Med J 2014;5:e0009.
2. Vigneswaran N, Williams MD. Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral Maxillofac Surg Clin North Am 2014;26:123-41.
3. Safi AF, Kauke M, Grandoch A, Nickenig HJ, Drebber U, Zöller J, *et al*. The importance of log odds of positive lymph nodes for locoregional recurrence in oral squamous cell carcinoma. Oral Oncol 2017;72:48-55.
4. Wang B, Zhang S, Yue K, Wang XD. The recurrence and survival of oral squamous cell carcinoma: A report of 275 cases. Chin J Cancer 2013;32:614-8.
5. Shah JP, Gil Z. Current concepts in management of oral cancer–surgery. Oral Oncol 2009;45:394-401.
6. Lee CC, Lin YS, Kang BH, Chang KP, Chi CC, Lin MY, *et al*. Incorporation of log odds of positive lymph nodes into the AJCC TNM classification improves prediction of survival in oral cancer. Clin Otolaryngol 2017;42:425-32.
7. Yildiz MM, Petersen I, Eigendorff E, Schlattmann P, Guntinas-Lichius O. Which is the most suitable lymph node predictor for overall survival after primary surgery of head and neck cancer: PN, the number or the ratio of positive lymph nodes, or log odds? J Cancer Res Clin Oncol 2016;142:885-93.
8. Patel SG, Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, *et al*. Lymph node density in oral cavity cancer: Results of the international consortium for outcomes research. Br J Cancer 2013;109:2087-95.
9. González-García R, Naval-Gías L, Román-Romero L, Sastre-Pérez J, Rodríguez-Campo FJ. Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: A retrospective analytic study of 500 patients. Head Neck 2009;31:1168-80.
10. Ong W, Zhao R, Lui B, Tan W, Ebrahimi A, Clark JR, *et al*. Prognostic significance of lymph node density in squamous cell carcinoma of the tongue. Head Neck 2016;38 Suppl 1:E859-66.
11. Iocca O, Farcomeni A, De Virgilio A, Di Maio P, Golusinski P, Malvezzi L, *et al*. Prognostic significance of lymph node yield and lymph node ratio in patients affected by squamous cell carcinoma of the oral cavity and oropharynx: Study protocol for a prospective, multicenter, observational study. Contemp Clin Trials Commun 2019;14:100324.
12. Lemieux A, Kedarisetty S, Raju S, Orosco R, Coffey C. Lymph node yield as a predictor of survival in pathologically node negative oral cavity carcinoma. Otolaryngol Head Neck Surg 2016;154:465-72.
13. Lee CC, Ho HC, Su YC, Lee MS, Hung SK, Chen YL. The prognostic ability of log odds of positive lymph nodes in oral cavity squamous cell carcinoma. Medicine (Baltimore) 2015;94:e1069.
14. Subramaniam N, Balasubramanian D, Kumar N, Murthy S, Vijayan SN, Nambiar A, *et al*. Lymph node staging systems in oral squamous cell carcinoma: A comparative analysis. Oral Oncol 2019;97:92-8.
15. Divi V, Chen MM, Nussenbaum B, Rhoads KF, Sirjani DB, Holsinger FC, *et al*. Lymph node count from neck dissection predicts mortality in head and neck cancer. J Clin Oncol 2016;34:3892-7.
16. Ebrahimi A, Clark JR, Amit M, Yen TC, Liao CT, Kowalski LP, *et al*. Minimum nodal yield in oral squamous cell carcinoma: Defining the standard of care in a multicenter international pooled validation study.

Ann Surg Oncol 2014;21:3049-55.
17. Shrime MG, Bachar G, Lea J, Volling C, Ma C, Gullane PJ, *et al*. Nodal ratio as an independent predictor of survival in squamous cell carcinoma of the oral cavity. Head Neck 2009;31:1482-8.
18. Gil Z, Carlson DL, Boyle JO, Kraus DH, Shah JP, Shaha AR, *et al*. Lymph node density is a significant predictor of outcome in patients with oral cancer. Cancer 2009;115:5700-10.
19. Künzel J, Mantsopoulos K, Psychogios G, Agaimy A, Grundtner P, Koch M, *et al*. Lymph node ratio is of limited value for the decision-making process in the treatment of patients with laryngeal cancer. Eur Arch Otorhinolaryngol 2015;272:453-61.
21. Muttagi SS, Patil BR, Godhi AS, Arora DK, Hallikerimath SR, Kale AD. Clinico-pathological factors affecting lymph node yield in Indian patients with locally advanced squamous cell carcinoma of mandibular Gingivo-Buccal sulcus. Indian J Cancer 2016;53:239-43.
20. Helliwell T, Woolgar J. Dataset for Histopathology Reporting of Nodal Excisions and Neck Dissection Specimens Associated with Head and Neck Carcinomas. Available from: http://www.rcpath.org. [Last accessed on 2011 Dec 07].
22. Liao CT, Hsueh C, Lee LY, Lin CY, Fan KH, Wang HM, *et al*. Neck dissection field and lymph node density predict prognosis in patients with oral cavity cancer and pathological node metastases treated with adjuvant therapy. Oral Oncol 2012;48:329-36.
23. Sayed SI, Sharma S, Rane P, Vaishampayan S, Talole S, Chaturvedi P, *et al*. Can metastatic lymph node ratio (LNR) predict survival in oral cavity cancer patients? J Surg Oncol 2013;108:256-63.
24. Arslan NC, Sokmen S, Canda AE, Terzi C, Sarioglu S. The prognostic impact of the log odds of positive lymph nodes in colon cancer. Colorectal Dis 2014;16:O386-92.
25. Lee CC, Su YC, Hung SK, Chen PC, Huang CI, Huang WL, *et al*. Recommendation for incorporation of a different lymph node scoring system in future AJCC N category for oral cancer. Sci Rep 2017;7:14117.