Prognostic Significance of Lymph-Node Ratio in Patients with Oral Squamous Cell Carcinoma

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Abstract:

Background: The aim of this study was to assess the prognostic significance of lymph node ratio (LNR) in patients diagnosed with oral squamous cell carcinoma (OSCC).

Methods: This retrospective study included 82 patients with oral squamous cell carcinoma (OSCC) with positive nodal disease, who underwent surgical treatment for primary OSCC & received adjuvant treatment at the Clinical Oncology & Nuclear Medicine Department, Mansoura University Hospital, between January 2010 and June 2022. Patients' data were analyzed using log-rank statistic, univariate and multivariate data analyzes, and p values, for prediction of significance of lymph node ratio on overall and disease-free survival.

Results: Prognostic thresholds were determined at a cutoff value of 0.073% for LNR. LNR < 0.073 was a significant predictor of longer OS. LNR <0.073 was a significant predictor of longer OS (72 months vs 14 months in those with LNR < 0.073), while patients with LNR whether < 0.073 or ≥ 0.073 demonstrated nearly the same median DFS (39 months vs 37 months, respectively). Multivariate analysis revealed that lymph node ratio (LNR), neck dissection, lymphovascular embolization (LVE), perineural invasion and adjuvant treatment were confirmed as independent prognostic factors for OS.

Conclusion: Lymph node ratio (LNR) is a prognostic factor for survival in patients with oral squamous cell carcinoma (OSCC), who underwent surgical treatment for primary OSCC.

Keywords: lymph node ratio; oral squamous cell carcinoma, staging; survival analysis.

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Introduction:

Oral squamous cell carcinoma (OSCC) constitutes nearly 90% of all malignancies in the oral cavity, with a global incidence exceeding 350 000 cases [1].

In the Middle East, including Egypt, there has yet to be much research that shows the extent or etiology of HNC. Prior hospital-based research in Egypt revealed that HNC accounts for between 17 and 20 percent of all cancers [2].

Conway and colleagues describe oral cavity cancer sites as including the inner lip, parts of the tongue apart from the base and lingual tonsil, gingiva, floor of the mouth, palate, and “other unspecified parts of the mouth.” [3].

Common risk factors for oral cancer are tobacco use [4], alcohol consumption [5], older age [6], and HPV infection [7].

The gold standard for curative treatment is surgical resection with negative margins and neck dissection. In spite of significant advances in medical care, the prognosis for OSCC has not markedly improved over the past decades, maintaining a 5-year overall survival (OS) rate of approximately 60% [8].

Remarkably, the cervical lymph nodes status emerges as the most important prognostic factor, with nearly 40% incidence of lymph node metastases (LNMs) in OSCC patients [9]. Consequently, radical neck management is essential for both local control and survival [10].

With the introduction of lymph node ratio (LNR), it is the ratio between the number of affected lymph nodes and number of excised lymph nodes as a diagnostic tool in solid cancers, such as breast [11,12], gastric, endometrioid, and colorectal cancer [13].

Interest has been directed to the importance of nodal ratio in oral cavity squamous cell carcinoma (OSCC), in a retrospective study which included

242patients diagnosed with OSCC and cervical lymph node metastases, there is evidence for its prognostic value in oral cavity SCC, where LNR was identified as an independent risk factor, referring to OS and disease free survival (DFS) [14].

Aim of Work: The purpose of this study was to evaluate to evaluate LNR as a prognostic indicator in OSCC.

Patients and Methods:

The institutional review board of the Mansoura Faculty of Medicine gave ethical approval for the study (R.240.927.90).

Study Design

This is a retrospective analysis for the data base of 82 patients with oral squamous cell carcinoma with positive nodal disease who underwent primary surgery including neck dissection and presented to the Department of clinical Oncology and Nuclear Medicine, Mansoura University Hospital for continuation of treatment, between January2010 and June 2022.

Electronic based patients Data examined were: age and sex; tumor location, stage, size, and grade; neck lymph node status; histological factors [vascular, lymphatic, perineural invasion, extracapsular spread of lymph nodes]; resection margin; number of positive lymph nodes; LNR and use of adjuvant therapy (postoperative adjuvant radiotherapy or chemoradiotherapy). Descriptive statistics were computed for each variable.

Study Sample

The study population included 82 of 122 patients who met the criteria, 40 patients were excluded due to missing data and loss of follow up, with oral squamous cell carcinoma with positive nodal disease who were treated by resection of the primary tumor combined with uni or bilateral ND and presented at the Department of clinical oncology and nuclear medicine, Mansoura University Hospital for adjuvant treatment.

Inclusion criteria:

-Adult Patients.

-Male or female gender.

-histopathologic diagnosis of oral SCC with positive nodal disease and surgical treatment of the primary tumor with or without adjuvant radiotherapy or chemoradiotherapy.

Exclusion criteria:

-histological findings other than SCC.

-distant metastasis before neck dissection (ND).

Follow-up:

patients were followed up for at least 2 years.

Statistical analysis

Data were collected and were analyzed using SPSS software (SPSS 26 Inc., Chicago, IL). Qualitative data will be presented as number and percent, Quantitative data will be tested for normality by Shapiro-Wilk test then described as mean and standard deviation for normally distributed data and median and range for non-normally distributed. Univariate Cox regression analysis was used for each variable, Multivariate Cox regression analysis was used for each predictor variable, p value of < 0.05 is identified as significant. Kaplan-Meier survival analysis was conducted for both OS and DFS, and survival differences between groups were assessed using log-rank tests. Overall survival (OS) and disease-free survival (DFS) were used to evaluate the prognostic significance of the LNR.

Results:

As shown in table 1, the median age of the patients was 58 years (36-81), patients were divided into 2 age groups, <57 years (40/82) and ≥ 57 years (42/82). The included patients were predominantly male (44/82) and the majority of the tumors were localized at the tongue (46/82) , Table 1.

The cutoff value for LNR (0.073%) was determined using ROC curve analysis, which identified this threshold as the optimal point for distinguishing between high-risk and low-risk patients. LNR, was presented in patients as follow: LNR ≥ 0. 073 in (58/82) whereas LNR < 0. 073 was detected in (24/82), LNR distribution in patients ' groups is shown also in Table 1.

The majority of patients are smokers either current or former (current: 46/82, former: 12/82). Most of the patients underwent unilateral LN dissection 62/82 lymph node dissection from level I to level IV were detected in (60/82) patients, while 20 out of 82 patients had neck dissection from level I to level III , negative margins were detected in the majority of patients (72/82).

T2 and N2 tumors was the commonest TN staging (58, 42/82 respectively), grade II was the commonest grade (44/82), and stage VI was also the commonest stage (44/82).

Adjuvant CCRT was the commonest treatment modality received (40/82).

As shown in Figure 1 ,2, overall survival (OS) and disease-free survival (DFS) were used to evaluate the prognostic significance of the LNR. The Kaplan-Meier curve for OS indicated a significant difference in survival between patients with LNR ≥ 0.073 and those with LNR < 0.073 (log-rank P = 0.001). LNR <0.073 was a significant predictor of longer OS (72 months vs 14 months in those with LNR < 0.073), while patients with LNR whether < 0.073 or ≥ 0.073 demonstrated nearly the same median DFS (39 months vs 37 months, respectively). The 5 –year OS was 56% in patients LNR <0.073 vs 18% in those with LNR ≥ 0.073. The corresponding Kaplan–Meier curves are displayed in Figure 1,2.

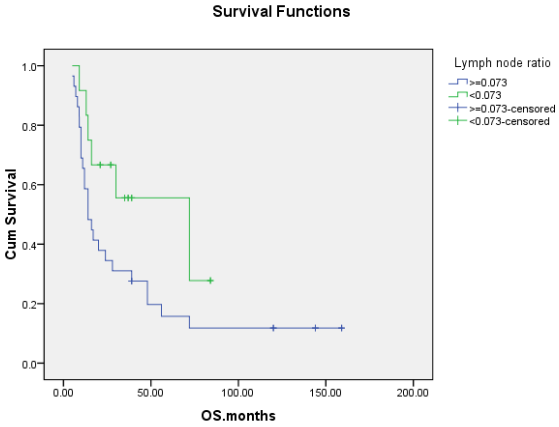

Figure (1): Kaplan-Meier survival curve for overall survival (OS)

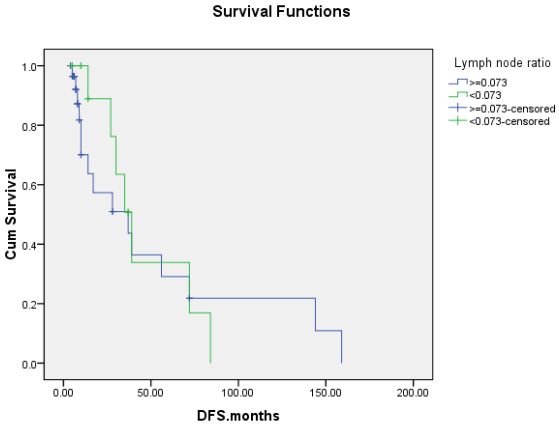

Figure (2): Kaplan-Meier curve for disease-free survival (DFS)

As shown in table 2,3, univariate analysis of OS showed that LNR, neck dissection, stage, LVE, perineural invasion and adjuvant treatment were significant prognostic factors.

Whereas ,in multivariate analysis , LNR, HR :1.94 (95% CI: 1.63-5.93) ,neck dissection, HR 5.77(95% CI :2.05-16.25) ,LVE ,HR: 9.22 (95% CI :1.89-45.11), perineural invasion, HR: 0.034(95% CI 0.007-0.166) and adjuvant treatment ,HR : 2.82 (95% CI :1.20-6.59) were confirmed as independent prognostic factors for OS, while only stage was no longer significant in multivariate analysis, emphasizing its independent impact on OS ,Table 2,3.

As shown in table 3, patients with LNR ≥ 0.073 had a hazard ratio of 1.94 (95% CI: 1.63-5.93), indicating that these patients were nearly twice as likely to die compared to those with LNR <0.073. This result is statistically significant, as the confidence interval does not include 1, suggesting a meaningful clinical impact.

As shown in table 4,5, regarding DFS, univariate analysis revealed that tumor grade, stage, ECS LVE, perineural invasion and adjuvant treatment were significant prognostic factors.

Whereas, in multivariate analysis revealed that only adjuvant treatment, HR: 5.89(95% CI:1.58-21.89) was confirmed as the independent prognostic factor for DFS, but tumor grade, stage, ECS LVE and perineural invasion were no longer significant in multivariate analysis, emphasizing the independent impact of these variables, Table 4,5

Discussion:

More than 90% of oral cancers are squamous cell carcinomas (OSCCs), constituting about 30% of all head and neck cancers. Surgical resection is considered the gold standard treatment for locally advanced disease. cervical lymph nodes involvement is one of the most significant independent prognostic factors in OSCC [15–17].

Generally, nodal involvement is associated with poor outcome in head & neck cancers [18–21]. Nodal stage, resection margins and ECS are significant prognostic factors for both loco-regional recurrence and survival [22].

This study was conducted to evaluate LNR as a prognostic factor in OSCC, using a cutoff value of 0.073.

The number of involved LN has been registered as a survival prognostic factor in OSCC patients in comparison to the AJCC N-staging [23]. As limited LN dissection might lead to nodal minimization, other evaluation parameters have been recommended, including lymph node yield (LNY) and LNR [24, 25].

The LNR has been considered as a significant prognostic factor in OSCC [26, 27]. A meta-analysis revealed that a high LNR was significantly associated with shorter OS and DFS [28]. In a study by Patel et al., reported that LNR less than 0.07 was associated with better loco-regional control, and DFS. Moreover, Patel & colleagues claimed that a new LNR-based TNM staging system is superior to the traditional staging system in evaluating OS, DSS, and locoregional control [29]. Talmi and colleagues concluded that to apply the importance of LNR into treatment modification, precise, prospective randomized trials are needed [30].

The current retrospective study revealed that LNR <0.073 was a significant predictor of longer OS (72 months vs 14 months in those with LNR < 0.073), the current results are in accordance with most of the previous trials, while patients with LNR whether < 0.073 or ≥ 0.073 demonstrated nearly the same median DFS (39 months vs 37 months, respectively).

Table (1): Clinicopathological features and lymph node ratio distribution among the studied cases

Risk factors	Total	LN ratio		Test of significance
		≥0.073 N=58	<0.073 N=24	
Age / years				
<57	40	30(75.0)	10(25.0)	χ^2=0.687
≥57	42	28(66.7)	14(33.3)	P=0.407
Sex				
Male	44	32(72.7)	12(27.3)	χ^2=0.183
Female	38	26(68.4)	12(31.6)	P=0.669
Smoking history				
Non smokers	24	22(91.7)	2(8.3)	χ^2=8.25
Ex-smokers	46	30(65.2)	16(34.8)	P=0.016*
Smokers	12	6(50.0)	6(50.0)	
Site				
Tongue	64	48(75.0)	16(25.0)	χ^2=14.37
buccal	8	4(50.0)	4(50.0)	P=0.002*
alveolar	4	0	4(100.0)	
Mouth floor	6	6(100.0)	0	
Dissection				
unilateral	62	40(64.5)	22(35.5)	χ^2=4.74
bilateral	20	18(90.0)	2(10.0)	P=0.029*
Levels of neck dissection				
I, II, III	22	12(54.5)	10(45.5)	χ^2=3.81
I to IV	60	46(76.7)	14(23.3)	P=0.051
Grade				
I	24	18(75.0)	6(25.0)	χ^2=0.418
II	44	30(68.2)	14(31.8)	P=0.811
III	12	8(66.7)	4(33.3)	
T				
T1	12	10(83.3)	2(16.7)	χ^{2MC}=5.82
T2	58	38(65.5)	20(34.5)	P=0.121
T3	4	2(50.0)	2(50.0)	
T4	8	8(100.0)	0	
N				
N1	38	14(36.8)	24(63.2)	χ^{2MC}=39.28
N2	42	42(100)	0	P=0.001*
N3	2	2(100)	0	
Staging				
III	34	12(35.3)	22(64.7)	χ^2=39.67
IV	44	44(100.0)	0	P=0.001*
ECS				
yes	26	24(92.3)	2(7.7)	χ^2=11.67
no	28	20(71.4)	8(28.6)	P=0.003*
unknown	28	14(50.0)	14(50.0)	
LVE				
yes	34	26(76.5)	8(23.5)	χ^2=1.73
no	32	20(62.5)	12(37.5)	P=0.421
unknown	16	12(75.0)	4(25.0)	
Perineural invasion				
yes	26	20(76.9)	6(23.1)	χ^2=1.97
no	38	24(63.2)	14(36.80	P=0.374
unknown	18	14(77.8)	4(22.2)	
Adjuvant TT				
CCRT	40	26(65)	14(35)	χ^2=2.72
RT	20	14(70)	6(30)	P=0.436
none	18	14(77.8)	4(22.2)	
Chemotherapy	4	4(100)	0	
Margins				
negative	72	52(72.2)	20(27.8)	χ^2=0.634
positive	10	6(60.0)	4(40.0)	P=0.468

x^2=Chi-Square test, *statistically significant, LNR: lymph node ratio, ECS: extracapsular spread, LVE: lymphovascular embolization, CCRT: concurrent chemoradiotherapy, RT: radiation therapy

Table (2): Univariate analysis of factors affecting overall survival

	Median overall survival (95%CI)	Log rank χ^2	P value
LN ratio			
≥0.073	14(10.27-17.73)	6.38	0.02*
<0.073	72(27.86-116.14)		
Age / years			
<57	20(3.85-36.15)	0.802	0.371
≥57	14.0(12.09-15.90)		
Sex			
Male	20(5.32-34.68)	1.37	0.243
Female	14(11.74-16.26)		
Smoking history			
No	13(10.6-15.4)	4.99	0.082
Ex-smokers	24(9.82-38.18)		
Smokers	30(10.48-49.52)		
Site			
tongue	16.0(12.08-19.92)	4.85	0.183
buccal	48.0(6.72-89.28)		
alveolar ridge	16.0(16.0-16.0)		
mouth floor	10.0(7.74-12.26)		
Dissection			
unilateral	20(11.12-28.88)	5.29	0.02*
bilateral	10(6.71-13.29)		
Levels			
I, II, III	30(8.55-51.45)	1.08	0.300
I to IV	16(10.31-21.69)		
Grade			
I	24(8.39-39.60)	2.23	0.328
II	14(10.75-17.25)		
III	14(10-45.91)		
T			
T1	30.0(10.2-70.74)	5.92	0.115
T2	16.0(14.14-17.86)		
T3	7.0(7.0-7.0)		
T4	6.0(5.0-29.65)		
N			
N1	One category have all cases censored	22.48	<0.001*
N2			
N3			
Staging			
III	72(39.58-104.42)	12.94	<0.001*
IV	14(11.44-16.56)		
ECS			
yes	9.0(7.75-10.25)	57.46	<0.001*
no	72(48.41-95.59)		
unknown	17(7.42-26.57)		
LVE			
yes	12(10.29-13.71)	17.06	<0.001*
no	56(29.94-82.06)		
unknown	20(12.16-27.84)		
Perineural			
yes	9(7.13-10.87)	54.58	<0.001*
no	56(38.25-73.75)		
unknown	17(14.93-19.07)		
Adjuvant			
CCRT	30.0(13.31-46.68)		
RT	12.0(8.71-15.29)	20.86	<0.001*
None	16.0(11.87-20.13)		
chemotherapy	5.0(5.0-5.0)		
Margins			
Negative	20(5.67-34.33)	2.32	0.128
positive	16(9.93-22.07)		

Table (3): Multivariate Cox regression for overall survival predictors

	β	P value	HR (95%CI)
LN ratio			
≥0.073 (R)	0.664	0.04*	R
<0.073			1.94(1.63-5.93)
Dissection			
unilateral (R)	1.72	0.001*	R
bilateral			5.77(2.05-16.25)
N			
N1	7.57	0.921	undefined
N2	8.12	0.913	
N3 (R)			
Staging			
III (R)	0.634	0.485	R
IV			1.89(0.318-11.17)
ECS			
yes	0.905	0.271	0.543(0.183-1.61)
no	-0.611	0.99	UNDEFINED
unknown (R)			R
LVE			
yes	0.654	0.290	1.92(0.572-6.47)
no	2.22	0.006*	9.22(1.89-45.11)
unknown (R)			R
Perineural			
yes	0.300	0.580	1.35(0.466-3.91)
no	-3.38	0.001*	0.034(0.007-0.166)
unknown (R)			R
Adjuvant			
CCRT (R)			R
RT	1.036	0.017*	2.82(1.20-6.59)
NONE	0.408	0.372	1.50(0.614-3.68)
Chemotherapy	-0.992	0.174	0.371(0.089-1.55)

R: reference group

Table (4): Univariate analysis of factors affecting disease free survival

	Median DFS (95%CI)	Log rank χ^2	P value
LN ratio			
≥0.073	37(11.85-62.15)	0.127	0.722
<0.073	39(31.35-46.65)		
Age / years			
<57	72(42.9-101)	0.863	0.353
≥57	30(8.39-51.60)		
Sex			
Male	37(28.25-45.75)	0.015	0.902
Female	39(15.48-62.52)		
Smoking history			
No	17(15-46.62)	0.595	0.743
Ex-smokers	35(27.75-42.25)		
Smokers	37(26.67-47.32)		
Site			
Tongue	35(24.6-45.4)	2.12	0.548
buccal	39(37.88-57.12)		
alveolar ridge	30(30-30)		
Mouth floor	10(8.22-38.8)		
Dissection			
Unilateral	35(27.32-42.6)	2.18	0.140
Bilateral	37(6.62-67.3)		
Levels			
I, II, III	30(21.88-38.12)	0.844	0.358
I to IV	39(30.97-47.03)		
Grade			
I	39(30.67-47.33)	7.79	0.02*
II	27(13.16-40.84)		
III	56(11.54-100.46)		
T			
T1	72(12.41-131.59)	11.02	0.012*
T2	35(24.88-45.12)		
T3	7(7-7)		
T4	37(37-37)		
N			
N1	39(18.15-59.85)	8.60	0.014*
N2	14(10.43-17.56)		
N3	39(39-39)		
Staging			
III	39(10.96-67.03)	5.75	0.017*
IV	28(5.87-50.13)		
ECS			
yes	10(8.64-11.36)	28.44	<0.001*
no	72(54.66-89.34)		
unknown	27(18.13-35.87)		
LVE			
yes	17(11.80-22.19)	8.78	0.012*
no	56(33.23-78.77)		
unknown	30(18-31.93)		
Perineural			
yes	14(11.02-16.97)	17.79	<0.001*
no	39(22.65-55.35)		
unknown	17(9.59-24.41)		
Adjuvant			
CCRT	35(26.64-43.35)	12.51	0.006*
RT	39(39-39)		
NONE	56(7.31-104.69)		
Chemotherapy	5(5-5)		
Margins			
negative	37(30.45-43.55)	2.04	0.153
positive	17(11.17-18.04)		

Table (5): Multivariate Cox regression for disease free survival predictors

	β	P value	HR (95%CI)
Grade			
I (R)	0.668	0.425	1.95(0.378-10.04)
II	1.82	0.089	6.19(0.757-50.74)
III			
T			
T1	0.560	0.611	1.76(0.199-15.65)
T2	-0.702	0.328	0.496(0.121-2.02)
T3	…	1.0	UNDEFINED
T4(R)	…		R
N			
N1	2.46	0.979	UNDEFINED
N2	8.12	0.903	UNDEFINED
N3(R)			R
Staging			
III	5.38	0.936	UNDEFINED
IV (R)			R
ECS			
yes	0.369	0.562	1.48(0.396-5.51)
no	-1.35	0.094	0.259(0.053-1.25)
unknown (R)			R
LVE			
yes	0.589	0.516	1.80(0.305-10.65)
no	-0.831	0.248	0.435(0.106-1.78)
unknown (R)			R
Perineural			
yes (R)			R
no	0.467	0.337	1.5(0.615-4.14)
unknown	0.678	0.504	1.97(0.269-14.41)
Adjuvant			
CCRT (R)			
RT	1.77	0.008*	5.89(1.58-21.89)
NONE	1.76	0.004*	5.82(1.73-19.59)
Chemotherapy	1.93	0.170	6.88(0.439-108.01)

R: reference group

Univariate analysis of OS showed that LNR, neck dissection, stage, LVE, perineural invasion and adjuvant treatment were significant prognostic factors, whereas, multivariate analysis Cox regression analysis revealed that LNR, neck dissection, LVE, perineural invasion and adjuvant treatment were confirmed as independent prognostic factors for OS, which also goes in line with other trials.

Regarding DFS , univariate Cox regression revealed that tumor grade, stage, ECS LVE, perineural invasion and adjuvant treatment were significant prognostic factors, whereas, multivariate analysis revealed that only adjuvant treatment was confirmed as the independent prognostic factor for DFS, The lack of a significant association between LNR and DFS reported in the current study was in contrast to other trials may be attributed to the significant difference in between the 2 groups of LNR as (LN dissection ,LN stage and ECS) in our cohort, the missing data and the small sample size which may have mitigated the effect of lymph node involvement on disease recurrence.

In line with our findings, a multi-institutional study conducted by Patel et al., included 4254 patients from 11 medical centers, reported LNR of 7% as a significant prognostic factor [29]. Our findings are consistent with those of Patel et al., who reported that LNR below 0.07 was associated with improved survival outcomes in OSCC. However, our study provides a more precise cutoff of 0.073%, which may better reflect the clinical characteristics of our cohort.

Furthermore, Gil et al. and Sayed et al. identified that a LNR below 6% in patients with OSCC was associated with better survival outcomes [31,32]. This was in accordance with our results. However, some studies determined higher cutoff values for LNR. For example, Shrime et al. found that only a LNR of ≥13% was significantly associated with lower OS and disease-specific survival (DSS) in a retrospective cohort of

OSCC patients [25], the poor OS with high LNR was in line with our findings, however, it was different regarding DFS.

In a retrospective trial, 163 patients with OSCC who underwent radical surgery were included. Survival endpoints were disease progression for disease-free time (DFT), freedom from loco-regional recurrence (FLR), and freedom from distant metastasis (FDM), and death from any cause for OS. Patients with a lower LNR were associated with superior DFT (LNR < 14%, P < 0.001), FLR (LNR <14%, P < 0.001), FDM (LNR <16%, P = 0.004), and OS (LNR <7%, P = 0.004) in comparison to patients with a higher LNR. LNR is a significant prognostic factor of survival and recurrence in OSCC [31], similar to our results, LNR had a prognostic significance on OS, but the current trial did not find that LNR is a significant prognostic factor for DFS.

In a meta-analysis by Huang et al. (2019), which included 19 studies. He showed that LNR is a prognostic factor in OSCC for OS, DFS, and DSS [28]. Our results were in accordance with this meta-analysis as regard OS, while regarding DFS, our study did not identify prognostic significance of LNR on DFS.

In a trial by Sporel et al, LNR was reported to significantly predict outcome in OSCC patients with a median cutoff (0.055), as in the current study. The 5-year OAS was 54.1% in patients with a low LNR, in comparison to 5-year OAS of 33.3% (p < 0.001) in patients with high LNR. comparable results were found in our study where, the 5 –year OS was 56% in patients with LNR <0.073 vs 18% in those with LNR ≥ 0.073.

LNR was shown to be an independent prognostic factor for outcome of OSCC in a population-based cohort by uni and multivariate analyses. Where LNR ≥ 0.055 predicted a shorter OAS and RFS [10].

Based on our findings, LNR could be considered as an additional prognostic factor which may be considered in treatment making decisions in multidisciplinary teams and could be incorporated into future classification systems for better risk stratification. Patients with LNR ≥ 0.073 may benefit from more intense adjuvant therapy and should be monitored for close follow up.

Conclusion:

This study showed that the lymph node ratio (LNR) is a predictive factor for survival in patients with oral squamous cell carcinoma (OSCC), however, prospective large-scale trials are essential to assure the significance of LNR.

Limitations in this study, its retrospective design and the small number of patients.

The retrospective design of this study introduces potential biases, including selection bias, and the relatively small sample size limits the generalizability of our findings. Additionally, incomplete follow-up data for some patients may have affected the accuracy of our survival estimates.

Recommendations:

Future studies of prospective trials with larger cohorts may confirm prognostic significance of LNR.

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