

Lymph node ratio as a prognosis factor associated with tumoral recurrence in patients with oral cavity squamous cell carcinoma

Cociente ganglionar como factor pronóstico de recurrencia tumoral en pacientes con carcinoma escamoso de cavidad oral

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Abstract

Background: The lymph node ratio (LNR) is a recent tool, but its predictive value for recurrence is uncertain. **Objective:** The objective of this study was to evaluate LNR as a prognostic factor for disease-free survival (DFS) in patients with oral squamous cell carcinoma. **Methods:** This was retrospective observational study. Patients with oral squamous cell carcinoma undergoing resection and lymph node dissection. Chi-squared, Kaplan–Meier, log rank, and Cox regression tests were run; bilateral $p \leq 0.05$ determined statistical significance. **Results:** Eighty-eight patients were included, 45% ($n = 40$) men and 54% ($n = 48$) women, mean age of 60.42 (± 14.28) years. Main tumor location in tongue (75%); 61% in clinical stage I–III and 39% in clinical stage IV. Population was divided into $LNR < 0.06$ (58%) and $LNR \geq 0.06$ (42%). The median DFS was not reached for both groups ($p = 0.018$). Predictors of DFS were the LNR ($p = 0.024$; hazard ratio [HR]: 2.20; confidence interval of 95% [95% CI]: 1.11–4.39) and the clinical stage ($p = 0.004$; HR: 1.76; 95% CI: 1.19–2.59). In the multivariate analysis, predictors were not maintained ($p = 0.227$ and 0.191, respectively). **Conclusions:** Significant differences were observed in the DFS analysis; however, they were not predictive of local recurrence in the multivariate analysis.

Keywords: Oral squamous carcinoma. Node coefficient.

Resumen

Antecedentes: El cociente ganglionar (LNR) es una herramienta reciente, pero su valor predictivo de recurrencia es incierto. **Objetivo:** Evaluar el LNR como factor pronóstico de supervivencia libre de enfermedad (SLE) en pacientes con carcinoma oral de células escamosas. **Métodos:** Estudio retrospectivo observacional. Pacientes con carcinoma oral de células escamosas sometidos a resección y disección ganglionar. Se aplicaron las pruebas de ji al cuadrado, Kaplan–Meier, log rank y regresión de Cox; se consideró estadísticamente significativo $p \leq 0.05$ bilateral. **Resultados:** Fueron incluidos 88 pacientes, el 45% ($n = 40$) hombres y el 54% ($n = 48$) mujeres, con una edad media de 60.42 (± 14.28) años. La principal localización tumoral fue la lengua (75%); el 61% en etapa I–III y el 39% en etapa IV. Se dividió en $LNR < 0.06$ (58%) y $LNR \geq 0.06$ (42%). La mediana de SLE no fue alcanzada para ambos grupos ($p = 0.018$). Resultaron predictores de SLE el LNR ($p = 0.024$; hazard ratio [HR]: 2.20;

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intervalo de confianza del 95% [IC95%]: 1.11-4.39) y la etapa clínica ($p = 0.004$; HR: 1.76; IC95%: 1.19-2.59). En el análisis multivariado no se mantuvieron predictores ($p = 0.227$ y $p = 0.191$, respectivamente). **Conclusiones:** Se observaron diferencias significativas en el análisis de SLE, pero no se mantuvieron como predictoras de recurrencia local en el análisis multivariado.

Palabras clave: Carcinoma oral escamoso. Cociente ganglionar.

Introduction

Oral cancer is ranked eighth in world cancer incidence^{1,2}. Every year, approximately 11 out of every 100,000 adults are diagnosed with this type of cancer³⁻⁵. In Mexico, GLOBOCAN reported an incidence of 1.48 per 100,000 individuals in 2018⁶. At present, the eighth edition of the American Joint Committee on Cancer (AJCC) TNM classification system is used for head and neck squamous cell carcinoma staging and prognosis. Lymph node staging in this system is based on the number, location, and size of positive lymph nodes. Recent evidence suggests that, in addition to these factors, the number of positive lymph nodes and lymph node ratio or density (LNR or LND) are critical prognostic factors that were not included in TNM staging system⁷. Thus, an additional and emerging predictor for the outcome of patients with oral cavity cancer to be foreseen are LND or LNR, which is defined as the ratio of positive lymph nodes with regard to total number of resected lymph nodes⁸. In 2009, a cohort study was carried out with 201 patients diagnosed with aerodigestive squamous cell carcinoma who underwent surgery and lymph node dissection, in which the prognostic value of LND for overall survival, disease-free survival (DFS), and locoregional failure-free survival was determined. Median overall survival was found to be 40.70 months and 30.11 months in patients with $LNR \leq 0.06$ and > 0.06 , respectively. In addition, the authors conclude that a $LNR > 0.06$ is a significant prognostic factor for decreased overall survival in patients with oral cavity squamous cell carcinoma. Therefore, they recommend more intensive adjuvant treatments, such as chemotherapy with radiotherapy and short-term follow-up for those patients with $LNR > 0.06$ ⁹. Subsequently, in a study that included 386 patients with oral cavity cancer who underwent surgical treatment with or without adjuvant therapy, a median LNR of 0.06 was identified to be a relevant cutoff point, and it was concluded that LNR was significantly associated with overall survival (≤ 0.06 vs. 0.06 : 58 vs. 28%) and with disease-specific survival (≤ 0.06 vs. 0.06 : 65 vs. 34%). In addition, LNR was also found to be the only

significant outcome predictor in patients who received adjuvant radiotherapy. Given the high rates of recurrence and mortality of the disease in patients with oral cavity cancer, it is necessary to search for better predictors of survival and prognostic factors of recurrence¹⁰.

In this sense, various studies propose evaluating LNR as an independent prognostic factor for the risk of oral squamous cell carcinoma local, regional, or distant recurrence in patients undergoing neck dissection, while also evaluating the effect of other variables such as pathological stage, perineural invasion, lymphovascular invasion, surgical margin involvement, extranodal extension, oral cavity subsite, tumor thickness, adjuvant treatment, gender, and age on local, regional, or distant recurrence to rule out that the obtained results are caused by these variables¹⁰⁻¹⁴.

For this reason, the present study was developed, the purpose of which was to evaluate LNR as an independent prognostic factor associated with recurrence in patients with oral cavity squamous cell carcinoma undergoing tumor resection and neck dissection.

Methods

This was observational, retrospective study, with non-probability sampling. Patients diagnosed with oral squamous cell carcinoma undergoing resection and lymph node dissection during the period from January 2007 to December 2018 at the surgical oncology department of the Northeast Medical Center, High Specialty Medical Unit No. 25 of the Mexican Institute of Social Security were included in the study; patients with incomplete medical records were excluded from the study. To carry out the study, authorization was requested from the ethics and research committee of the center. Asking for informed consent was not necessary given the retrospective nature of the study. DFS was defined as the time from the date of surgery to the last date reported in the medical record.

For statistical analysis, the SPSS V.24 statistical package was used, with descriptive and inferential statistics being employed. The Chi-square test was

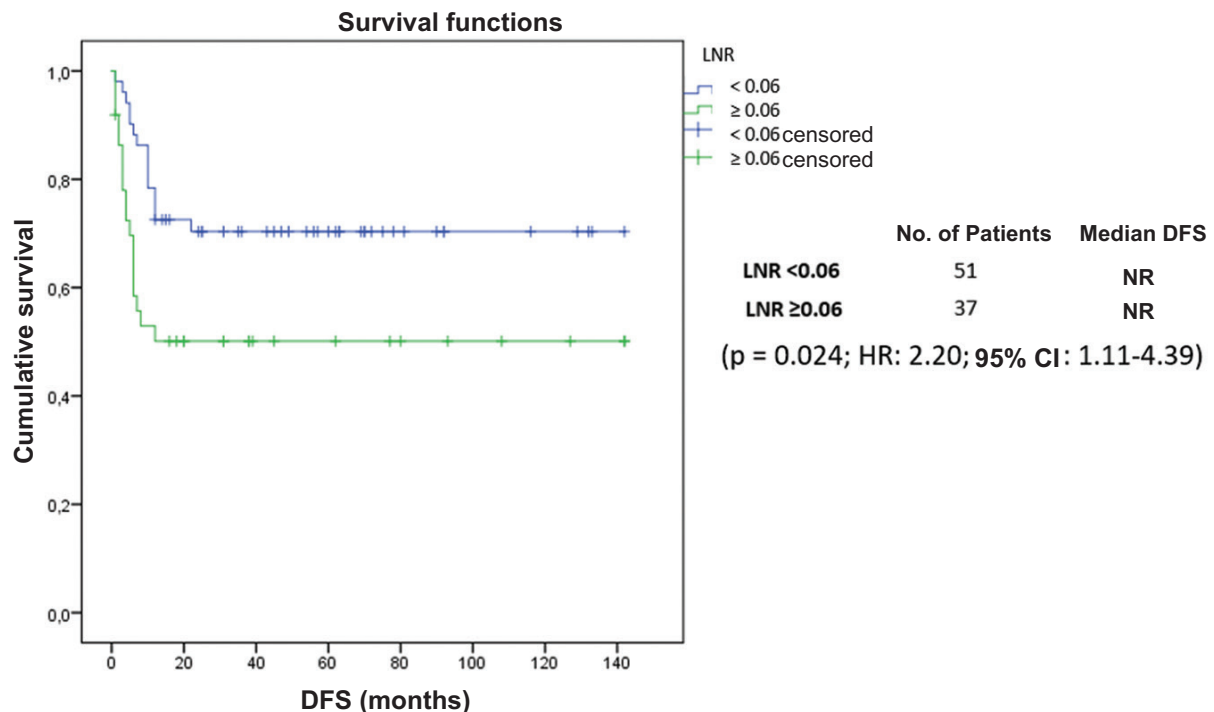


Figure 1. Disease-free survival analysis. CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; LNR: lymph node ratio; NR: not reached.

used to identify differences between the groups. Kaplan–Meier and log-rank tests were used for DFS analysis, and Cox regression for univariate and multivariate analyses. Statistical significance was established with a two-sided p-value ≤ 0.05 .

Results

Eighty-eight patients diagnosed with oral squamous cell carcinoma who underwent tumor resection and neck dissection were included for analysis. Of the entire group, 45% (n = 40) were men and 54% (n = 48) were women, with a mean age of 60.42 (± 14.28) years. The main site of tumor location was the tongue (75%), followed by the gums (13%). According to disease staging, 61% of cases were at early stages (I–III), and the remaining 39% were at clinical stage IV. As for disease stage, the predominant pathological T was T2 (36.8%, n = 32) and predominant N was N0 (46%, n = 40).

All 88 patients underwent surgical resection and lymph node dissection. Mean number of resected lymph nodes was 20.07 (± 12.55), with median positivity of 1.27 (1–8). LNR was < 0.06 in 58%, and ≥ 0.06 in the remaining 42%.

With regard to resection margins, 70% of cases had R0; in addition, negative lymphovascular and perineural invasion were observed in 77% and 91% of cases, respectively. As for the degree of differentiation, 76% (n = 67) were Grade 2. After surgical treatment, 72% received adjuvant treatment with chemotherapy with or without radiotherapy. No differences were found between the groups when the Chi-square test was carried out, except for the lymph nodes (N) (p = 0.001) and clinical stage (p = 0.001) (Table 1).

In the DFS analysis, median DFS was not reached in any of the groups, with statistically significant differences in the log-rank test (p = 0.018) (Fig. 1).

On univariate analysis, LNR (p = 0.024; hazard ratio [HR]: 2.20; 95% confidence interval [CI]: 1.11–4.39) and clinical stage (p = 0.004; HR: 1.76; 95% CI: 1.19–2.59) were found to be DFS predictors (Table 2). On the other hand, in the multivariate analysis, LNR and clinical stage were no longer predictors of recurrence, (p = 0.227 and p = 0.191, respectively; Table 2).

Discussion

Oral cancer is a public health problem, given that it is a major cause of morbidity and mortality² and is

Table 1. General characteristics and clinical outcomes

Clinical and demographic characteristics				
Characteristic	LNR < 0.06 (n = 51) n (%)	LNR ≥ 0.06 (n = 37) n (%)	Total (n = 88) n (%)	p
Gender				
Males	22 (43)	18 (49)	40 (45)	0.668
Females	29 (57)	19 (51)	48 (54.5)	
Age, years				
Mean	59	61.38	60.42	0.440
Standard deviation	15.32	12.85	14.28	
Location				
Tongue	38 (74)	28 (76)	66 (75)	0.703
Gums	6 (12)	5 (13)	11 (12)	
Oral cavity floor	4 (8)	4 (11)	8 (10)	
Lip	3 (6)	0 (0)	3 (3)	
Stage (T)				
T1	15 (27)	8 (21)	23 (25)	0.156
T2	22 (43)	10 (27)	32 (36)	
T3	9 (18)	14 (38)	23 (25)	
T4	6 (12)	5 (14)	11 (14)	
Lymph nodes (N)				
N0	40 (78)	0 (0)	40 (45)	0.001*
N1	9 (18)	11 (30)	20 (23)	
N2	1 (2)	25 (68)	26 (30)	
N3	1 (2)	1 (3)	2 (4)	
Clinical stage				
I	13 (26)	0 (0)	13 (15)	0.001*
II	15 (29)	0 (0)	15 (17)	
III	15 (29)	11 (30)	26 (29)	
IV	8 (16)	26 (70)	34 (39)	
Margins				
R0	36 (71)	26 (70)	62 (70)	0.961
R1	6 (12)	5 (13)	11 (13)	
R2	9 (17)	6 (17)	15 (17)	
Histological grade				
1	10 (20)	4 (11)	13 (16)	0.535
2	37 (72)	30 (81)	67 (76)	
3	4 (8)	3 (8)	7 (8)	
VI				
Negative	37 (72)	31 (84)	68 (77)	0.304
Positive	14 (28)	6 (16)	20 (23)	
PI				
Negative	48 (94)	32 (86)	80 (91)	0.273
Positive	3 (6)	5 (14)	8 (9)	
Lymph node number (mean)	20 (2-58)	20 (2-77)	20.07 (2-77)	0.577
Positive lymph nodes (median)	1 (0-8)	1 (0-5)	1 (0-8)	0.938
Adjuvant treatment				
Yes	33 (65)	30 (81)	63 (72)	0.102
No	18 (35)	7 (19)	25 (28)	
Recurrence				
Recurrence	15 (29)	18 (49)	33 (37)	0.078
No disease	36 (71)	19 (51)	55 (63)	

LNR: lymph node ratio; P: statistical significance value; PI: perineural Invasion; R0: no disease persistence; R1: microscopic disease persistence; R2: macroscopic disease persistence; and VI: vascular invasion.

*Statistical significance (p < 0.05).

Table 2. Multivariate analysis. Cox regression

Variables	Univariate		Multivariate	
	p	HR (95% CI)	p	HR (95% CI)
LNR ≥ 0.06	0.024*	2.20 (1.11-4.39)	0.548	1.27 (0.57-2.80)
Location	0.750	0.95 (0.743-1.24)	-	-
Clinical stage	0.004*	1.76 (1.19-2.59)	0.95	3.84 (0.72-18.72)
Grade 2	0.445	0.611 (0.17-2.16)	-	-
Margins	0.448	1.47 (0.55-3.75)	-	-
Vascular invasion	0.445	0.71 (0.29-1.72)	-	-
Perineural invasion	0.987	0.99 (0.30-3.24)	-	-
Adjuvant treatment	0.564	0.808 (0.39-1.66)	-	-

CI: confidence interval; HR: hazard ratio; LNR: lymph node ratio.

*Statistical significance ($p < 0.05$).

ranked eighth in world cancer incidence. In Mexico, in 2018, GLOBOCAN reported an incidence of 1.48 per 100,000 individuals⁶, with oral squamous cell carcinoma thus being the most common of all oral malignancies, accounting for at least 90% of all of them^{2,5,8}. After initial treatment, a significant number of patients suffer local and regional relapses; therefore, if an accurate prognostic factor could be identified, it would allow to offer more radical therapies and to monitor these patients more closely to early detect relapses, which would enable to rescue patients again with other cancer therapies and thereby reduce morbidity and mortality, as well as expenditure in treatments and palliative care generated by late detection of cases. Thus, LNR is an additional and emerging predictor of the outcome of patients with oral cavity cancer. Several retrospective studies have reported that LNR is predictive of overall survival^{12,13-20}, disease-specific survival¹³⁻¹⁸, DFS^{13,18,21}, and locoregional control^{16,19,21}. In the present study, significant differences were observed in DFS analysis ($p = 0.018$) between patients with LNR < 0.06 and those with LNR ≥ 0.06 .

Gil et al.⁹ evaluated the role of LNR in oral cavity carcinoma in a study that included 386 patients with oral cavity cancer. On multivariate analysis, LNR (cutoff point of 0.06) was shown to be the only independent predictor of locoregional failure. In the study by Prabhu et al.¹⁹, which included 350 patients, LNR was found to be significantly associated with locoregional recurrence when using a cutoff point of 0.2; thus, patients with a LNR higher than or equal to this value were at high risk of locoregional recurrence. Similarly, Lieng et al.²²⁻²⁴ determined the prognostic importance of LNR in 72 patients

with oral squamous cell carcinoma and positive lymph nodes. They found that patients with a LNR > 0.143 experienced a higher rate of regional recurrence.

In the present study, LNR and clinical stage were found to be DFS predictors. However, on multivariate analysis, LNR and clinical stage were no longer predictors of recurrence.

Our study has some limitations, such as its retrospective nature and sample size. Therefore, increasing the sample size and carrying out a study that includes an analysis by disease stage in relation to the type of resection and LNR is suggested.

Conclusions

The present study is highly useful because, although LNR did not persist as a single DFS predictor, it could be a tool that helps determining the risk of locoregional recurrence in patients with oral cavity carcinoma. For this reason, it would be necessary to expand the sample to improve the estimation and replicate the analysis including a subanalysis by clinical stage of the disease.

Conflicts of interest

The authors declare that they have no conflicts of interest relevant to this publication.

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The present investigation did not obtain any economic benefit.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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