Original Article

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The Role of Lymph Node Ratio in Predicting Survival in Patients with Esophageal Squamous Cell Carcinoma

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Abstract

Background: This study aimed to evaluate the role of lymph node ratio (LNR) in the prediction of Overal Survival (OS) of patients with Esophageal Squamous Cell Carcinoma (ESCC).

Methods: Patients with ESCC who underwent radical esophagectomy and radical lymph node dissection were entered into the study. The survival rate of patients was determined using the Kaplan–Meier estimator. Also, the effect of LNR and other variables on the OS of patients was assessed applying COX proportional hazards regression model. Based on its mean, LNR was divided into two groups of ≤0.25 and >0.25.

Results: In total, 116 patients were entered into the study. The univariate and multivariate analyses showed that LNR was an independent prognostic factor for the prediction of the OS of patients with ESCC. An increase of LNR more than 0.25 led to an increase in the mortality risk by 1.57 times. Also, the five-year survival of patients was 26% with LNR≤0.25 and 5% with LNR>0.25.

Conclusion: LNR can be used as an independent prognostic factor in determining and predicting the OS of patients with ESCC. There was a relationship between the increase of this factor and the worsening of patients' OS.

Keywords: Esophageal squamous cell carcinoma, Lymph node ratio, Survival

Introduction

Esophageal Cancer (EC) is one of the most prevalent cancers with an annual mortality rate of above 500,000 deaths worldwide (the 6th highest mortality rate among cancers) (1). Esophageal cancer belt is the region where the prevalence of EC is higher than other parts of the world and a specific area of Iran (North of Iran) is part of this belt. In these areas, 90% of cases of EC are diagnosed with Esophageal Squamous Cell Carcinoma (ESCC) (2). After gastric cancer, EC is the major cause of cancer-related mortality among gastrointestinal cancers in Iran (3). Esophagectomy and Lymph Node Dissection (LND) are essential part of treatment for patients with ESCC; also, they can be effectively used in the accurate staging of patients, prediction of survival, and treatment selection (4). One of the important prognostic factors in patients with ESCC undergoing surgery is lymphatic metastasis. Therefore, the proper classification of metastatic lymph nodes in determining post-surgical treatment protocols is of paramount importance (5).

In 2010, the American Joint Committee on Cancer (AJCC) divided the N category of patients based on the number of involved lymph nodes for the first time in its seventh edition of EC staging (6). Meanwhile, the N category was divided merely based on the presence or absence of pathological lymph nodes in the previous edition (7). This change in staging is indicative of the importance of the number of pathological lymph nodes in the staging of patients, which affects the survival rate and determines the treatment protocols of these individuals.

Physical conditions of each person, different skills of surgeons, and various hospital equipment for large surgeries might lead to an insufficient number of dissected lymph nodes. This in return results in metastatic lymph nodes, reduction of N category, and underestimation of disease severity in patients, thereby depriving patients of the proper treatment and increasing the risk of recurrence or mortality (8).

To solve this problem, a new factor known as Lymph Node Ratio (LNR) is defined as the number of pathological lymph nodes divided into the number of dissected lymph nodes. This new prognostic factor has been effective in predicting patient survival not only in ESCC cases but also in other cancers such as head and neck squamous cell carcinoma (9), cutaneous melanoma (10,11), gastric cancer (12), and cervical cancer (13). It seems that various analytical analyses and differences in the inclusion criteria have led to a controversial optimal cut-off value for LNR in ESCC (14).

With this background in mind, this study aimed to determine whether LNR is an independent prognostic factor in predicting the Overall Survival (OS) of patients with ESCC or not.

Materials and Methods

Patients and data collection

This retrospective cohort study was conducted on patients with ESCC, referred to our institution during 2005-2012. Patients with this cancer, who underwent radical esophagectomy and LND, were entered into the study. However, patients who lost to follow-up or had distant metastasis when cancer was diagnosed or received neoadjuvant treatment were excluded from this study. The patient staging was carried out based on the 7th edition of AJCC (6), and the duration of the OS was estimated from the time of diagnosis to death or the last follow-up. Based on the LND pathologic report, LNR was calculated (LNR = number of metastatic lymph nodes/ number of total dissected lymph nodes).

Statistical analysis

At first, the analysis of the descriptive data was performed, followed by the application of the Kaplan–Meier estimator to estimate the OS of patients with ESCC. Also, the log-rank test was applied to compare the survival function. Moreover, the effect of variables on the OS of patients was evaluated by using the univariate and multivariate COX proportional hazards regression models. Based on its mean, the LNR variable was divided into two groups of ≤ 0.25 and >0.25. The variables with a p-value less than 0.2 in the univariate analysis were entered into the multivariate analysis. In addition, a p-value < 0.05 was considered statistically significant with a 0.95 confidence interval. Data were entered into SPSS v23 (IBM Inc, USA) to perform data analysis.

Results

In total, 116 patients were entered into the study. The median duration of follow-up was 19 months and

82.8% of patients died in the follow-up time. Patients' characteristics are shown in table 1. To evaluate the effect of the factors on patients' OS, the univariate analysis was used (Table 2), where the factors including age, sex, adjuvant therapy, N, and LNR with a p-value of ≤0.2 were entered into the multivariate analysis. N and LNR had similarities and demonstrated interferences in multivariate analysis. Therefore, two analysis models were planned separately.

According to the results, the LNR is an independent prognostic factor for predicting OS in ESCC patients (Table 2). An increase of LNR more than 0.25 led to an increase in the mortality risk by 1.57 times (p-value=0.036; CI 95%:1.03-2.38). Also, the risk of death in patients with N3 was 4 times higher than patients with N0 (p-value:0.005; HR: 4.65; CI 95%: 1.58-13.72). The Kaplan-Meier curve showed that OS differences between groups of LNR were significant (Figure 1). Five-year OS of patients with LNR≤ 0.25 and LNR> 0.25 was 26% and 5%, respectively.

Discussion

The precise staging of cancer is an important step in determining the patients' OS and appropriate treatment. The number of positive lymph nodes, which determines the pN category based on AJCC, is one of the key parts in the 7the edition of AJCC. However, an important issue in pN category is that the number of metastatic lymph nodes is affected by the number of dissected lymph nodes. The possibility of stage migration increases in the case of lack of adequate LND. Moreover, AJCC cannot provide a standard criterion for adequate LND in patients with ESCC (6); nevertheless, various studies have proposed different values for LND (15-17). Finally, in addition to the controversial nature of this issue, the difference in surgeons' skills, the physical condition

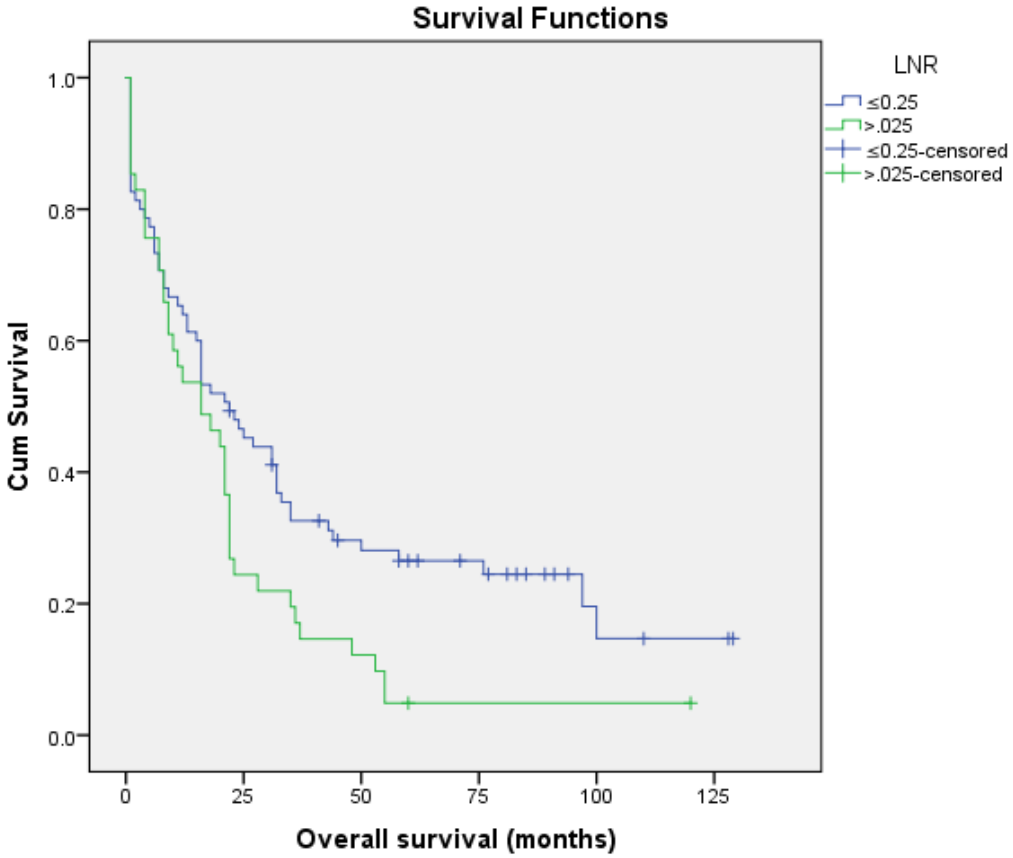

Figure 1. Kaplan-Meier curves estimating the overall survival for each LNR category, log-rank test for LNR, p-value= 0.023.

Table 1. Baseline Characteristics of 116 Patients with Esophageal squamous cell carcinoma

Variables		Frequency (n (%))
Age	≤60	47 (40.5%)
	>60	69 (59.5%)
Sex	female	71 (61.2%)
	male	45 (38.8%)
Lymphovascular invasion	Negative	41 (39.8%)
	Positive	62 (60.2%)
Grade	Well differentiated	35 (32.7%)
	Moderately differentiated	60 (56.1%)
	Poorly differentiated	12 (11.2%)
Dissected lymph node (Mean ±SD)		7.47± 6.6
Type of surgery	Hiatal	50 (49%)
	thoracic	52 (51%)
T	T1/T2	31 (29%)
	T3/T4	76 (71%)
Adjuvant therapy	No	63 (56.8%)
	Yes	48 (43.2%)
N	N0	60 (51.7%)
	N1	30 (25.9%)
	N2	22 (19.0%)
	N3	4 (3.4%)
Lymph node ratio (LNR)	A: ≤ 0.25	75 (64.7%)
	B: > 0.25	41 (35.3%)

Table 2. Univariate & multivariate Cox regression of prognostic factors

Variables	UVA			MVA 1			MVA 2		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age ≤60 >60	Ref 2.29	1.49-3.53	<0.001	Ref 1.97	1.22-3.16	0.005	Ref 2.06	1.26-3.39	0.004
Sex Female Male	Ref 1.64	1.09-2.46	0.017	Ref 1.44	0.93-2.22	0.099	Ref 1.46	0.95-2.25	0.086
Type of surgery Hiatal Thoracic	Ref 1.07	0.70-1.63	0.768						
Grade Well differentiated Moderately differentiated Poorly differentiated	Ref 0.90 0.95	0.57-1.42 0.46-1.97	0.650 0.901						
T ≤T2 >T2	Ref 1.15	0.72-1.84	0.546						
Adjuvant therapy No Yes	Ref 0.67	0.44-1.02	0.059	Ref 0.77	0.50-1.19	0.774	Ref 0.75	0.48-1.19	0.753
LVI Negative Positive	Ref 1.19	0.77-1.84	0.436						
Dissected lymph nodes	1.01	0.98-1.04	0.546						
N N0 N1 N2 N3	Ref 1.30 1.41 3.29	0.81-2.10 0.82-2.42 1.16-9.35	0.282 0.213 0.025				Ref 1.12 1.34 4.65	0.68-1.83 0.75-2.40 1.58-13.72	0.658 0.325 0.005
LNR A: LNR≤ 0.25 B: LNR> 0.25	Ref 1.58	1.05-2.39	0.029	Ref 1.57	1.03-2.38	0.036			

*Ref: reference; UVA: univariate analysis; MVU: multivariate analysis; HR: hazard ratio; CI: confidence interval; LVI: lymphovascular invasion; LNR: lymph node ratio.

of each patient, and the various hospital facilities for large surgeries can result in different numbers of dissected lymph nodes. To solve this problem and to prevent the under-staging of patients, a new factor called LNR was used in this study to predict the OS of patients.

In 2008, Mariette *et al* divided 536 patients into two groups of ≤0.2 and >0.2 based on LNR, demonstrating that LNR could be used as an independent prognostic factor for predicting the survival of patients with EC. The results showed that regardless of lymphadenectomy extension and neoadjuvant therapies, LNR is able to predict patient survival (18). However, in our study, patients who had received neoadjuvant therapy were excluded because it could affect the number of pathologic lymph nodes.

In another study by Wang *et al* conducted on 209 EC patients, 0.2 was considered as the cutoff for LNR. The multivariate analysis demonstrated that the risks of death and recurrence were respectively 1.70 and 1.86 times higher in patients with LNR ≥0.2 than in patients with LNR <0.2. This result shows that LNR is an independent prognostic factor in EC patients (19). In another study by Liu *et al* conducted on 1,325 ESCC patients, LNR was divided into three categories of >0.50, 0.25-0.50, and <0.25, in which the five-year OS was 8.9%, 14.6%, and 47.53%, respectively, and the difference between the rates was significant ($p<0.01$)(20).

In the current research, the prognostic effect of LNR on OS was assessed. Besides, the cutoff used in the present study was different from other conducted studies. Considering previous studies, it seems that LNR is an independent prognostic factor in predicting the OS of patients diagnosed with ESCC. However, their cutoff is controversial, which might be due to different inclusion criteria and the population assessed in each research, and the difference in the criteria in LND. The main limitations of the current study were its retrospective and single-centered nature. To overcome these problems, a prospective multi-center study with a larger sample is crucial to assist in predicting the OS of these patients more accurately.

Conclusion

In conclusion, LNR can be used as an independent prognostic factor in determining and predicting the OS of patients with ESCC. According to the results, there was a relationship between the increase of this factor and the worsening of patients' OS.

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The study was reviewed and approved by the Ethics Committee of Vice-Chancellor in Research Affairs at Tehran University of Medical Sciences (Ethics code: IR.TUMS.VCR.REC.1398.939).

Conflict of Interest

Authors declare that they have no conflict of interest.

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