Original Article

Positive lymph node ratio predicts adverse prognosis for patients with lymph nodes metastatic hypopharyngeal squamous cell carcinoma after primary surgery

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Background: Positive lymph node ratio (LNR) is associated with the prognosis of many cancers. However, its prognostic value in patients with hypopharyngeal squamous cell carcinoma (HSCC) is unclear due to the rarity of HSCC. This study aimed to investigate the prognostic value of LNR in HSCC using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Data spanning 2004 to 2015 of eligible HSCC patients were retrospectively retrieved from the SEER database. Clinicopathological data, including age at diagnosis, race, gender, marital status, primary tumor site, tumor size, tumor grade, Tumor-Lymph Node-Metastasis (TNM) stage, surgical type, postoperative adjuvant therapy (POAT) record, the number of lymph nodes (LNs) examined, the number of positive LNs, survival time, and death classification were collected and dichotomized through the receiver operating characteristic (ROC) curve. The LNR was defined as the ratio of positive LNs to the total number of LNs examined. The Kaplan-Meier method and Cox regression models were used to assess the association between LNR vs. cancer-specific survival (CSS) and overall survival (OS).

Results: The 5-year CSS and OS rates of the 391 patients were 44% and 33.7%, respectively. The median LNR was 0.083 [interquartile range (IQR), 0.043–0.179], and the optimal cut-off value of LNR was 0.23. Kaplan-Meier curves showed that patients with LNR ≥0.23 had significantly shorter CSS and OS than LNR <0.23. In multivariable analysis, large tumor size [hazard ratio (HR): 1.012, P=0.016], N3 stage (HR: 2.113, P=0.040), M1 stage (HR: 2.458, P=0.041), with POAT (HR: 0.559, P=0.001), and LNR ≥0.23 (HR: 1.795, P=0.001) independently predicted CSS, while old age (HR: 1.019, P=0.009), large tumor size (HR: 1.012, P=0.006), M1 stage (HR: 3.422, P=0.001), with POAT (HR: 0.610, P=0.001), and LNR ≥0.23 (HR: 1.667, P=0.001) independently predicted OS. The subgroup analysis showed that patients with LNR ≥0.23 shared worse CSS and OS in either N2 or N3 subgroups than those with LNR <0.23. Furthermore, POAT provided an independent protective factor in the LNR ≥0.23 group, while it had no significant effect in the LNR <0.23 group.

Conclusions: This study demonstrates a strong association between LNR and prognosis in patients with LNs metastatic HSCC. Further, it provides an alternative tool for providing supplemental information regarding prognosis.

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Keywords: Hypopharyngeal cancer; lymph node ratio (LNR); cancer-specific survival (CSS); overall survival (OS); postoperative adjuvant therapy (POAT)

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Introduction

Hypopharyngeal squamous cell carcinoma (HSCC) is a rare malignant tumor, accounting for about 2–6% of head and neck cancers (1). However, the prognosis of HSCC patients is poor, with an estimated 5-year overall survival rate (OS) of about 30–35% (2,3). The rich lymph network near the cancer area and the submucosal extension promotes LNs metastasis, thus leading to an extremely low survival rate. Previous studies have shown that almost 60–70% of HSCC patients have lymph nodes (LNs) metastasis at diagnosis. Moreover, the risk of recurrence in LNs metastatic HSCC is high (4,5). Nodal staging for HSCC patients is primarily based on the size and laterality of positive LNs, with less value placed on the absolute number of positive LNs and surgically-removed LNs (6).

Most studies have analyzed the relationship between positive LNs and prognosis in HSCC patients (7-9). Moreover, the number of positive LNs is closely related to the number of LNs removed during surgery. However, the burden of positive LNs cannot reflect the true status of the nodal condition if there is a limited number of LNs dissected. Besides, the number of LNs removed during surgery can significantly affect prognosis in HSCC patients (10,11). In recent years, positive lymph node ratio (LNR) has been used as an independent prognostic factor in many malignancies (12-16). Besides the information on the burden of LNs metastasis, it infers the number of LNs dissected during surgery. Furthermore, recent studies have suggested that LNR is better than the Tumor-Lymph Node-Metastasis (TNM) staging and the absolute number of positive LNs in predicting the postoperative cancer-specific survival (CSS) rate of patients with bladder, laryngeal, and lung cancers (14,17,18). The HSCC patients with higher LNR are associated with worse survival (19-22). However, those studies were single-center analyses with limited sample sizes (~41–121 patients). Besides, the studies had an unknown number of LNs harvested, and those with an insufficient number of LNs harvested during surgery could have caused risk overestimation. As a result, this study aimed to investigate the prognostic value of LNR in patients with LNs metastatic HSCC after primary surgery. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1740/rc).

Methods

Study cohort

The study was a retrospective analysis of HSCC patients based on data from the Surveillance, Epidemiology, and End Results (SEER) database, containing about 28% of the U.S. population. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Detailed descriptions of the data were obtained from the official SEER website (https://seer.cancer.gov/data/). A total of 6,798 hypopharynx patients (TNM 7/CS v0204 + Schema = 'Hypopharynx') were obtained from January 2004 to December 2015. Inclusion criteria were: (I) patients who underwent primary surgery; (II) patients with pathologically confirmed HSCC; and (III) patients with positive LNs examined. Exclusion criteria were: (I) patients with <10 LNs examined; (II) patients with unknown number of positive LNs or LNs examined; (III) patients who survived less than three months after surgery; (IV) patients with incomplete clinic and prognostic data. The inclusion and exclusion flowchart is shown in *Figure 1*.

Data collection

The age at diagnosis, race (recorded as "white" or "others"), gender, marital status ("unmarried" or "married"), primary tumor site (recorded as "pyriform sinus" or "others"), tumor size, tumor grade, TNM stage (6th edition), surgical type (recorded as "local tumor resection", "pharyngectomy", or "pharyngectomy with laryngectomy"), radiotherapy record, chemotherapy record, the number of LNs examined, the number of positive LNs, survival time, and death classification, were retrieved for further analysis. Patients who received either chemotherapy or radiotherapy were recorded as "with POAT". Otherwise, they were recorded

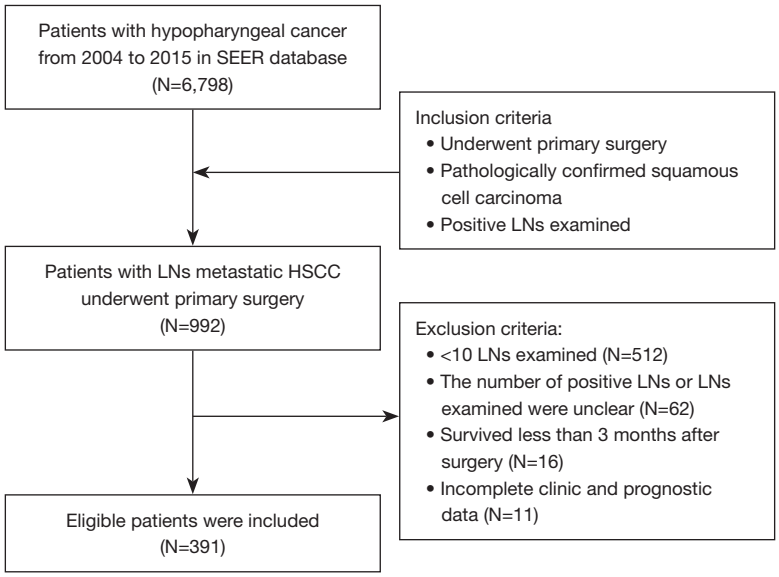

Figure 1 Summary of our study cohort and flow chart of inclusion and exclusion criteria. HSCC, hypopharyngeal squamous cell carcinoma; LN, lymph node; SEER, Surveillance, Epidemiology, and End Results.

as "without POAT". LNR (positive LNs density) was defined as the ratio of the number of positive LNs to the total number of LNs examined.

CSS was identified as the primary endpoint, and it was defined as the period from the date of diagnosis to cancer-specific death. The OS was regarded as the second endpoint, and it was defined as the period from the date of diagnosis to death of all causes.

Statistical analysis

The receiver operating characteristic (ROC) curve associated with cancer-specific death was used to determine the optimal cut-off value of LNR. This study also compared the clinicopathological characteristics of low and high LNR. The normally distributed continuous variables were recorded as mean and standard deviation (SD) and compared using student's *t*-test. Otherwise, they were reported as medians and interquartile range (IQR) and compared using Mann-Whitney U test. Categorical variables were expressed as frequency count and percentage and compared using the Chi-square test. The Kaplan-Meier method was used to estimate the CSS and OS and compared using log rank-test. The univariate Cox proportional hazards regression model was used to assess the association between LNR *vs.* CSS and OS. Multivariate Cox proportional hazards regression model was used to assess the prognostic value of LNR adjusted for other clinicopathological characteristics. The results were summarized using a hazard ratio (HR) and 95% confidence interval (CI). The univariate and multivariate Cox proportional hazards regression models were used to analyze the interaction effect of the LNR group and clinicopathological factors on CSS and OS.

Statistical analysis was performed using SPSS version 22 (IBM Corp, Armonk, NY, USA) and plotting done in GraphPad Prism version 8 (GraphPad Software Inc., San Diego, CA, USA). All tests were two-sided, and P<0.05 was considered statistically significant.

Results

Clinicopathological characteristics

This study identified 391 patients with LNs metastatic HSCC [median age: 61 years (IQR, 55–69 years), and 330 (84.4%) patients were males]. All patients had received primary surgery and neck LNs dissection. The medians of the examined LNs, positive LNs, and LNR were 37 (IQR, 23–55), 3 (IQR, 1–6), and 0.083 (IQR, 0.043–0.179), respectively. Most patients (N=312, 79.8%) received postoperative adjuvant therapy (POAT) after surgery. The Median follow-up duration was 30 months (IQR, 15–59 months). A total of 218 (55.8%) cancer-specific deaths with estimated 3- and 5-year CSS rates of 52.7%

and 44%, respectively, were reported during the follow-up. Besides, 292 (74.7%) all-cause deaths with estimated 3- and 5-year OS rates of 45.3% and 33.7%, respectively, were reported.

This study selected a cut-off value at 0.23 using the ROC curve area and the Youden Index for dichotomization since there is no widely recognized cut-off value for LNR. Patients with LNR ≥0.23 were associated with advanced N and M stages than LNR <0.23 (*Table 1*). However, other clinicopathological parameters were similar between the two groups. Besides, patients with LNR ≥0.23 had significantly shorter CSS and OS than those with LNR <0.23 (P<0.001, *Figure 2*).

Prognostic predictors

The univariable and multivariable Cox regression models predicting CSS for HSCC patents are shown in *Table 2*. The tumor size (HR: 1.013, P=0.001), advanced T stage (HR: 1.559, P=0.004), advanced N stage (N2, HR: 1.536, P=0.021; N3, HR: 2.505, P=0.003), M1 stage (HR: 2.512, P=0.018), POAT (HR: 0.699, P=0.029), and LNR ≥0.23 (HR: 2.037, P<0.001) in the univariable model were associated with CSS. Moreover, large tumor size (HR: 1.012, P=0.016), N3 stage (HR: 2.113, P=0.040), M1 stage (HR: 2.458, P=0.041), with POAT (HR: 0.559, P=0.001), and LNR ≥0.23 (HR: 1.795, P=0.001) in the multivariable model independently predicted CSS. Besides, age (HR: 1.020, P=0.003), tumor size (HR: 1.011, P=0.002), advanced T stage (HR: 1.342, P=0.021), M1 stage (HR: 3.060, P=0.001), surgical type (HR: 1.468, P=0.031), with POAT (HR: 0.686, P=0.008), and LNR ≥0.23 (HR: 1.820, P<0.001) in the univariable model were associated with OS (*Table 3*). The old age (HR: 1.019, P=0.009), large tumor size (HR: 1.012, P=0.006), M1 stage (HR: 3.422, P=0.001), with POAT (HR: 0.610, P=0.001), and LNR ≥0.23 (HR: 1.667, P=0.001) in the multivariable model independently predicted OS. This study set the cut-off point of LNR using a quartile to validate the prognostic value of LNR further. Patients with LNR ≥0.179 in the Cox regression model independently predicted worse CSS (HR: 1.531, P=0.013) and OS (HR: 1.392, P=0.024).

The value of LNR in different subgroups

The subgroup analysis showed that N2 patients with LNR <0.23 had a better CSS and OS than those with LNR ≥0.23 (P=0.004 and 0.002, respectively, *Figure 3A,3B*). Similarly, the N3 patients with LNR <0.23 had a better CSS and OS than those with LNR ≥0.23 (P=0.027 and 0.043, respectively, *Figure 3C,3D*). This study further compared "with POAT" and "without POAT" in LNR <0.23 and LNR ≥0.23 groups to determine the value of POAT for patients with different LNR subgroups. Patients with and without POAT had similar CSS and OS in the LNR <0.23 group (P=0.235 and 0.092, respectively, *Figure 4A,4B*). However, patients with POAT had significantly better CSS and OS than those without POAT in the LNR ≥0.23 group (P=0.004 and 0.002, respectively, *Figure 4C,4D*). The multivariate analysis showed that POAT was an independent protective factor for CSS (HR: 0.489, P=0.037) and OS (HR: 0.459, P=0.016) in patients with LNR ≥0.23 group. However, POAT had no significant effect on CSS and OS in patients with LNR <0.23 (Tables S1,S2).

Discussion

The study investigated the relationship between LNR and prognosis of LNs metastatic HSCC patients using SEER databases. The results showed that patients with LNR ≥0.23 were associated with advanced N and M stages and shorter CSS and OS than patients with LNR <0.23. Multivariable analysis showed that besides age, tumor size, TNM stage, and POAT, LNR was an independent predictor of CSS and OS. Subgroup analysis showed that N2 and N3 patients with LNR <0.23 had a better prognosis than those with LNR >0.23. Furthermore, POAT was an independent protective factor for patients with LNR ≥0.23, while it had no significant effect in patients with LNR <0.23.

Currently, Tumor-Lymph Node-Metastasis (TNM) staging is the most commonly used prognostic model for HSCC patients. The nodal stage is based on the number, size, and laterality of positive neck LNs (6). However, it does not evaluate LNs metastasis burden. Several studies have reported that the absolute number of positive LNs is associated with the prognosis for HSCC patients (7,8). For instance, Choi *et al.* (8) investigated 141 consecutive patients with HSCC and found that the number of positive LNs was strongly associated with disease-free survival (DFS) and OS outcomes (P<0.01). Ho *et al.* (7) also retrospectively analyzed 8,351 cases (largest series) and found that mortality risk increases as the number of metastatic LNs increases, with the hazard per node (HR: 1.19; 95% CI: 1.16–1.23; P<0.001) being most pronounced up to five positive LNs. Besides, they proposed a novel nodal stage, which exhibited greater concordance with survival than the TNM staging

Table 1 Demographics and characteristics of patients separated by lymph node ratio

Variables	Total cohort (N=391)	LNR <0.23 (N=317)	LNR ≥0.23 (N=74)	P
Age, years, median [IQR]	61 [55–69]	61 [55–68]	65.5 [56–71]	0.143
Gender				0.217
Male	330 (84.4)	271 (85.5)	59 (79.7)	
Female	61 (15.6)	46 (14.5)	15 (20.3)	
Race				0.270
White	309 (79.0)	254 (80.1)	55 (74.3)	
Others	82 (21.0)	63 (19.9)	19 (25.7)	
Marital status				1.000
Unmarried	207 (52.9)	168 (53.0)	39 (52.7)	
Married	184 (47.1)	149 (47.0)	35 (43.7)	
Primary site				0.138
Pyriform sinus	256 (65.5)	202 (63.7)	54 (73.0)	
Others	135 (34.5)	115 (36.3)	20 (27.0)	
Tumor size, cm, median [IQR]	3.6 [2.5–5.0]	3.8 [2.5–5.0]	3.5 [2.5–4.2]	0.070
Tumor grade				0.797
G1 + G2	191 (48.8)	156 (49.2)	35 (47.3)	
G3 + G4	200 (51.2)	161 (50.8)	39 (52.7)	
T stage				0.492
T1–T2	125 (32.0)	104 (32.8)	21 (28.4)	
T3–T4	266 (68.0)	213 (67.2)	53 (71.6)	
N stage				<0.001
N1	81 (20.7)	80 (25.2)	0 (0)	
N2	289 (73.9)	227 (71.6)	62 (83.8)	
N3	21 (5.4)	10 (3.2)	12 (16.2)	
M stage				0.025
M0	381 (97.4)	312 (98.4)	69 (93.2)	
M1	10 (2.6)	5 (1.6)	5 (6.8)	
Surgical type				0.987
Local tumor resection	55 (14.1)	45 (14.2)	10 (13.5)	
Pharyngectomy	57 (14.6)	46 (14.5)	1 (14.9)	
Pharyngectomy with laryngectomy	279 (71.4)	226 (71.3)	53 (71.6)	
POAT				0.337
Without	79 (20.2)	61 (19.2)	18 (24.3)	
With	312 (79.8)	256 (80.8)	56 (75.7)	

IQR, interquartile range; LNR, lymph node ratio; POAT, postoperative adjuvant therapy.

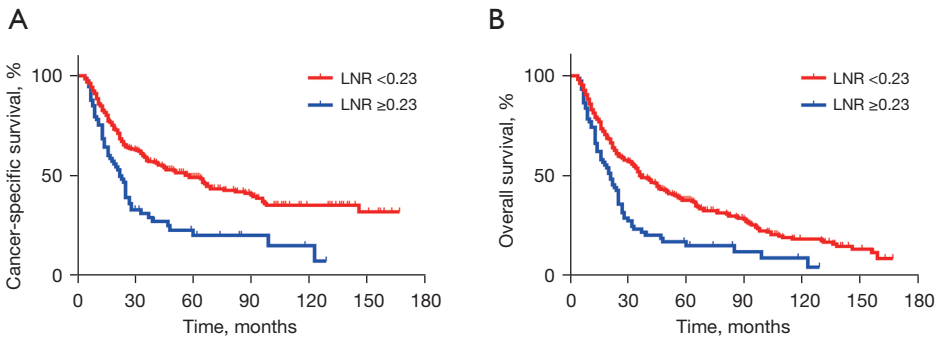

Figure 2 Kaplan-Meier curve demonstrating cancer-specific survival (CSS) and overall survival (OS) for our study cohort separated by LNR <0.23 and LNR ≥0.23. Survival curves for: (A) CSS, log-rank P<0.001; (B) OS, log-rank P<0.001. LNR, positive lymph node ratio.

Table 2 Univariable and multivariable Cox regression model for predictors of cancer-specific survival in patients with lymph nodes metastatic hypopharyngeal squamous cell carcinoma after primary surgery

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Age, years	1.015	0.999–1.030	0.064			
Gender						
Male	Ref.					
Female	1.236	0.874–1.748	0.231			
Race						
White	Ref.					
Others	1.117	0.806–1.548	0.506			
Marital status						
Unmarried	Ref.					
Married	0.859	0.658–1.122	0.264			
Primary site						
Pyriform sinus	Ref.					
Others	1.011	0.764–1.339	0.938			
Tumor size, cm	1.013	1.006–1.021	0.001	1.012	1.002–1.022	0.016
Tumor grade						
G1 + G2	Ref.					
G3 + G4	0.917	0.703–1.196	0.522			
T stage						
T1–T2	Ref.			Ref.		
T3–T4	1.559	1.154–2.106	0.004	1.323	0.896–1.953	0.160

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
N stage						
N1	Ref.			Ref.		
N2	1.536	1.067–2.212	0.021	1.500	0.992–2.267	0.055
N3	2.505	1.365–4.598	0.003	2.113	1.037–4.306	0.040
M stage						
M0	Ref.			Ref.		
M1	2.512	1.174–5.373	0.018	2.458	1.039–5.815	0.041
Surgical type						
Local tumor resection	Ref.					
Pharyngectomy	1.123	0.658–1.915	0.671			
Pharyngectomy with laryngectomy	1.495	0.995–2.246	0.053			
POAT						
Without	Ref.			Ref.		
With	0.699	0.507–0.963	0.029	0.559	0.394–0.793	0.001
LNR (dichotomized by ROC)						
<0.23	Ref.			Ref.		
≥0.23	2.037	1.497–2.773	<0.001	1.795	1.256–2.565	0.001
LNR (dichotomized by quartiles)*						
<0.179	Ref.			Ref.		
≥0.179	1.664	1.247–2.220	0.001	1.531	1.093–2.144	0.013

*, separate model with the inclusion of LNR (dichotomized by quartiles) and exclusion of LNR (dichotomized by ROC). CI, confidence interval; HR, hazard ratio; LNR, lymph node ratio; POAT, postoperative adjuvant therapy; ROC, receiver operating characteristic.

system. To the best of our knowledge, the scope of LNs dissection and the number of LNs harvested during surgery can also significantly affect the number of positive LNs. Furthermore, researchers have also found that the number of LNs dissected can affect prognosis even in patients with negative LNs, suggesting that the burden of metastatic LNs and the surgical performance (the number of LNs removed) affect HSCC prognosis (10). Therefore, LNR may have a greater prognostic value than the absolute number of positive LNs since it involves two factors, the number of positive LNs and the extent of surgical treatment (number of LNs removed).

High LNR is associated with adverse prognosis in many malignancies (12-18). Moreover, Suzuki *et al.* (19) demonstrated that LNR is a prognostic factor for HSCC patients with positive LNs. However, the study had a small sample size of only 46 patients, and thus further studies are necessary. Hua *et al.* (20) also analyzed 81 patients from a single center and found that LNR <0.1 is associated with significantly longer survival than LNR >0.1, even in the N1 and N2 subgroups. Two studies from South Korea also showed high LNR can independently predict adverse prognosis for HSCC patients (21,22). This study also suggested that high LNR can independently predict CSS and OS. This study also found that LNR could conduct further risk stratification for patients in the same N2 or N3 stages. Although high LNR was correlated with poor prognosis, the cut-off value was different across various studies. For instance, in the Suzuki *et al.* (19) and Hua *et al.* (20), the cut-off value of LNR were 0.09 and 0.1,

Table 3 Univariable and multivariable Cox regression model for predictors of overall survival in patients with lymph nodes metastatic hypopharyngeal squamous cell carcinoma after primary surgery

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Age, years	1.020	1.007–1.034	0.003	1.019	1.005–1.034	0.009
Gender						
Male	Ref.					
Female	1.193	0.880–1.618	0.257			
Race						
White	Ref.					
Others	1.153	0.868–1.531	0.325			
Marital status						
Unmarried	Ref.					
Married	0.820	0.651–1.033	0.093			
Primary site						
Pyriform sinus	Ref.					
Others	0.988	0.775–1.260	0.921			
Tumor size, cm	1.011	1.004–1.018	0.002	1.012	1.003–1.021	0.006
Tumor grade						
G1 + G2	Ref.					
G3 + G4	0.931	0.740–1.171	0.539			
T stage						
T1–T2	Ref.			Ref.		
T3–T4	1.342	1.045–1.724	0.021	1.122	0.797–1.580	0.510
N stage						
N1	Ref.					
N2	1.309	0.971–1.764	0.077			
N3	1.694	0.979–2.931	0.060			
M stage						
M0	Ref.			Ref.		
M1	3.060	1.615–5.801	0.001	3.422	1.647–7.111	0.001
Surgical type						
Local tumor resection	Ref.			Ref.		
Pharyngectomy	1.201	0.763–1.890	0.429	1.050	0.628–1.757	0.851
Pharyngectomy with laryngectomy	1.468	1.035–2.081	0.031	1.028	0.653–1.618	0.905

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
POAT						
Without	Ref.			Ref.		
With	0.686	0.520–0.906	0.008	0.610	0.450–0.826	0.001
LNR (dichotomized by ROC)						
<0.23	Ref.			Ref.		
≥0.23	1.820	1.374–2.410	<0.001	1.667	1.218–2.283	0.001
LNR (dichotomized by quartiles)*						
<0.179	Ref.			Ref.		
≥0.179	1.407	1.084–1.825	0.010	1.392	1.045–1.855	0.024

*, separate model with the inclusion of LNR (dichotomized by quartiles) and exclusion of LNR (dichotomized by ROC). CI, confidence interval; HR, hazard ratio; LNR, lymph node ratio; POAT, postoperative adjuvant therapy; ROC, receiver operating characteristic.

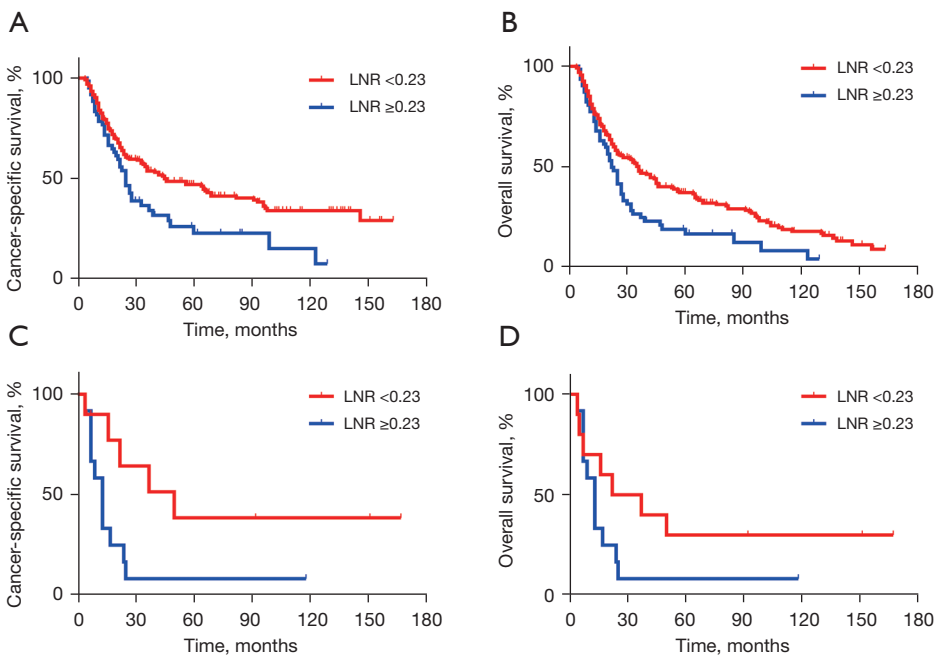

Figure 3 Kaplan-Meier curve demonstrating cancer-specific survival (CSS) and overall survival (OS) for N2 and N3 patients separated by LNR <0.23 and LNR ≥0.23. Survival curves for: (A) CSS in N2 patients, log-rank P=0.004; (B) OS in N2 patients, log-rank P=0.002; (C) CSS in N3 patients, log-rank P=0.027; (D) OS in N3 patients, log-rank P=0.043. LNR, positive lymph node ratio.

respectively, which is relatively lower than that in this study. The difference could be due to the different inclusion criteria among various studies. For instance, this study excluded patients with negative LNs and those with less than 10 LNs examined. It only focused on the positive LNs population with sufficient LNs dissected. Therefore, LNR can provide supplemental information for the prognosis of patients with positive LNs.

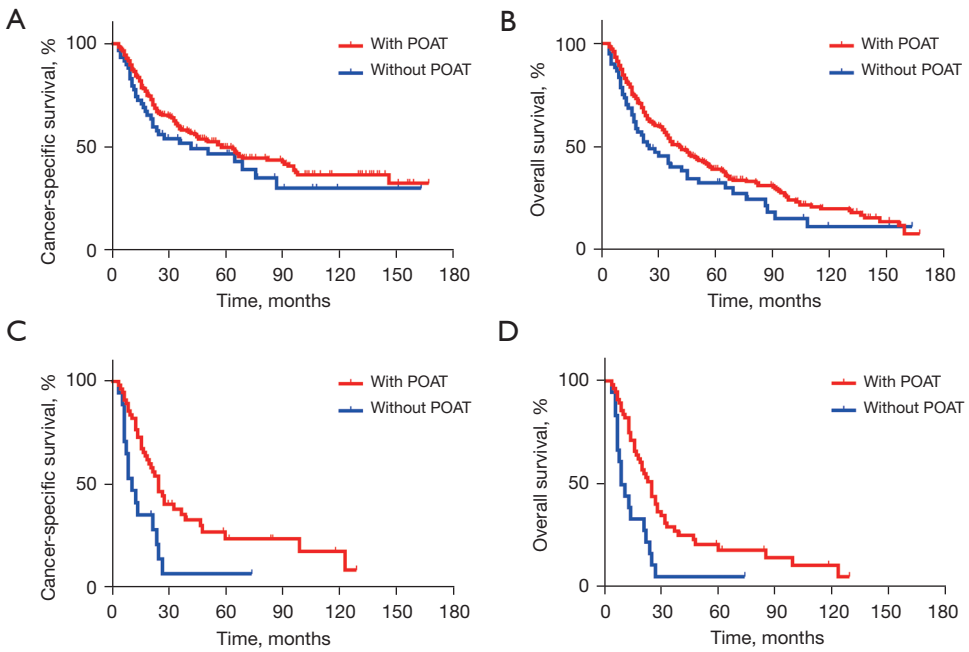

Figure 4 Kaplan-Meier curve demonstrating cancer-specific survival (CSS) and overall survival (OS) for LNR <0.23 and LNR ≥0.23 patients separated by postoperative adjuvant therapy (POAT). Survival curves for: (A) CSS in LNR <0.23 patients, log-rank P=0.235; (B) OS in LNR <0.23 patients, log-rank P=0.092; (C) CSS in LNR ≥0.23 patients, log-rank P=0.004; (D) OS in LNR ≥0.23 patients, log-rank P=0.002. LNR, positive lymph node ratio.

The optimal treatment modalities for HSCC patients are unknown due to the poor oncologic outcomes. Moreover, non-surgical treatment, including definitive chemoradiotherapy (CRT) and radiotherapy after induction chemotherapy (RT), has been used to treat HSCC patients in recent years (3). Surgery combined with POAT is the optimal choice for patients in the advanced stage (23). However, POAT can severely damage the normal tissue, and thus generating different degrees of radiation-induced cutaneous and mucous reactions (24,25). Therefore, high-risk patients should be identified before POAT. The NCCN guidelines indicate that POAT can treat patients with a positive margin and extranodal extension. However, recent evidence has shown that margin status and extranodal extension cannot identify patients suitable for POAT (9). Besides, stratification via metastatic LNs numbers can characterize a very high-risk patient cohort suitable for POAT (9). Herein, LNR was used to stratify patients' risk, and the results showed that those who received POAT had a significantly better survival outcome than those without POAT for the LNR ≥0.23 subgroup. However, the patients with or without POAT had a similar survival outcome in the LNR <0.23 subgroup. Another research also showed that POAT can benefit patients with high LNR (26). Therefore, LNR can help clinicians decide which patients could benefit from POAT among patients with LNs positive.

However, this study has some limitations. First, LNR was substantially affected by the quality of neck dissection achieved by the surgeon and the quantity of LNs harvested and examined by the pathologist. The above data could not be unified in the SEER database, thus generating information bias. However, this study excluded the patients with less than 10 LNs examined to ensure the quality of neck dissection and minimize the information bias. Second, the SEER database lacked the information on POAT and thus could affect the prognosis for HSCC patients. The SEER database did not also have the follow-up scheme, thus leading to potential bias. Third, TNM stage data in the SEER database are limited to only the 6th edition from 2004 to 2015, and thus the latest 8th edition TNM stage manual, commonly used in current clinical practice, could not be obtained.

Conclusions

In conclusion, this study showed that LNR is associated with the prognosis in patients with LNs metastatic

HSCC, providing supplemental information on prognosis. However, more prospective studies are needed to confirm the prognostic role of LNR in HSCC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1740/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Univariable and multivariable Cox regression model for predictors of cancer-specific survival in patients with LNR <0.23 and LNR ≥0.23

Variable	LNR <0.23				LNR ≥0.23			
	Univariate		Multivariate		Univariate		Multivariate	
	HR	P	HR	P	HR	P	HR	P
Age, years	1.010	0.285			1.017	0.301		
Gender								
Male	Ref.				Ref.			
Female	1.354	0.145			0.757	0.414		
Race								
White	Ref.				Ref.			
Others	1.041	0.839			1.254	0.469		
Marital status								
Unmarried	Ref.				Ref.			
Married	0.794	0.143			1.153	0.602		
Primary site								
Pyriform sinus	Ref.				Ref.			
Others	1.004	0.981			1.307	0.364		
Tumor size, cm	1.014	0.001	1.011	0.049	1.018	0.047	1.016	0.068
Tumor grade								
G1 + G2	Ref.				Ref.			
G3 + G4	0.926	0.625			0.769	0.338		
T stage								
T1–T2	Ref.		Ref.		Ref.			
T3–T4	1.510	0.019	1.254	0.316	1.642	0.124		
N stage								
N1	Ref.				NA	NA	NA	NA
N2	1.393	0.087			Ref.		Ref.	
N3	1.268	0.622			2.201	0.022	1.931	0.083
M stage								
M0	Ref.		Ref.		Ref.			
M1	3.756	0.010	2.995	0.062	1.261	0.699		
Surgical type								
Local tumor resection	Ref.				Ref.			
Pharyngectomy	1.136	0.687			1.005	0.993		
Pharyngectomy with laryngectomy	1.457	0.118			1.790	0.160		
POAT								
Without	Ref.				Ref.		Ref.	
With	0.795	0.240			0.423	0.006	0.489	0.037

HR, hazard ratio; LNR, lymph node ratio; NA, not available; POAT, postoperative adjuvant therapy.

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Table S2 Univariable and multivariable Cox regression model for predictors of overall survival in patients with LNR <0.23 and LNR ≥0.23

Variable	LNR <0.23				LNR ≥0.23			
	Univariate		Multivariate		Univariate		Multivariate	
	HR	P	HR	P	HR	P	HR	P
Age, years	1.016	0.046	1.019	0.019	1.028	0.073		
Gender								
Male	Ref.				Ref.			
Female	1.250	0.220			0.846	0.585		
Race								
White	Ref.				Ref.			
Others	1.077	0.659			1.350	0.293		
Marital status								
Unmarried	Ref.				Ref.			
Married	0.789	0.077			0.990	0.967		
Primary site								
Pyriform sinus	Ref.				Ref.			
Others	0.988	0.928			1.240	0.437		
Tumor size, cm	1.011	0.004	1.012	0.003	1.018	0.037	1.015	0.075
Tumor grade								
G1 + G2	Ref.				Ref.			
G3 + G4	0.966	0.794			0.733	0.220		
T stage								
T1–T2	Ref.				Ref.			
T3–T4	1.299	0.068			1.422	0.220		
N stage								
N1	Ref.				NA	NA		
N2	1.195	0.261			Ref.			
N3	0.988	0.976			1.853	0.068		
M stage								
M0	Ref.		Ref.		Ref.			
M1	3.866	0.003	3.569	0.013	1.940	0.160		
Surgical type								
Local tumor resection	Ref.				Ref.			
Pharyngectomy	1.284	0.334			0.883	0.812		
Pharyngectomy with laryngectomy	1.396	0.098			1.911	0.094		
POAT								
Without	Ref.				Ref.		Ref.	
With	0.761	0.096			0.417	0.003	0.459	0.016

HR, hazard ratio; LNR, lymph node ratio; NA, not available; POAT, postoperative adjuvant therapy.

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